

Plastic and Aesthetic Research

Day 1

Heterotopic prelamination

Pedicated lateral thoracic artery flap is wrapped
around tracheal segment



+

Heterotopic prefabrication

The construct is tunneled to the neck region to
avoid biting



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An overview of aesthetic surgery of the breast

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Aesthetic surgery for the breast is one of the common procedure performed by an aesthetic plastic surgeon today. The surgery is frequently performed for aesthetic as well reconstructive reasons. Breast itself is a uniquely important part of the female body and as such embodies in itself anatomical, physiological and aesthetic role. A proportionately developed breast is an important feminine feature, a sign for fertility and sexuality. It is not surprising that breasts are extremely important for women's self-confidence especially when their role in society has expanded immensely.

Aesthetic surgery for breast is not new and has been practiced for many years for reduction, enhancement and mastopexy. However, the introduction of implants by Cronin and Gerow in 1962, has given a new dimension to breast remodelling. Surgery for breast reduction, breast reconstruction, mastopexy and augmentation comprises the most common procedure performed today. Use of implant alone has increased exponentially in the second half of last century and breast augmentation for reshaping and remodelling alone has overtaken almost any other aesthetic procedure, including breast reduction, mastopexy and reconstruction. The safety of implants and choice of shape and volume has given a range of choices and predictability to patients for aesthetic and reconstructive reasons.

A variety of procedures are available for patients with inadequate breast development, breast hypertrophy, developmentally ptotic breasts, involution secondary to pregnancy, weight or age related changes or to correct breast asymmetry. Breast implants either alone or in combination has given versatility and predictability for a desirable breast shape, volume or positioning. Small volumetric enhancement or asymmetries can be corrected

using autologous fat grafting in selected cases. Advancement in imaging techniques has enable to provide better breast screening that can delineate suspicious breast lesions following use of breast implants or autologous fat grafting.

Augmentation mammoplasty alone using breast implants is the leading aesthetic procedure for breast remodelling. Safety of the implants paired with a high patient satisfaction has made this procedure very suitable and desirable in selected cases. Autologous fat grafting is becoming an increasingly used alternative for augmentation mammoplasty. The choice is especially useful for correction of breast asymmetries and for moderate size bilateral enhancement in selected cases. The use of autologous fat grafting is increasingly used for revision surgeries in aesthetic and reconstructive breast procedures alike.

Simultaneous mastopexy with augmentation is becoming more popular and staged procedure is broadly limited to selected cases. An abundant literature is available citing the efficacy of the combined procedure with acceptable revision rate. A variety of shape, size, profiles and filler materials are available with a choice of formed or expander prosthesis. Combination of desired implant along with choices for implant pockets, flap orientation for nipple elevation and selection of skin marking for envelope reduction has enabled surgeons to tailor make each surgery for each individual.

The use of synthetic mesh has shown more promising results in breast reconstructive, primary or secondary augmentation mammoplasty and augmentation mastopexy. Breast implant capsule flaps are more frequently used and various techniques have been described for its use in primary

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and secondary cosmetic and reconstructive surgeries with very good results.

We have a range of breast reconstruction procedures at our disposal today. Breast reconstruction can be achieved using autologous breast tissue as pedicle flaps with or without implants or free tissue transfers with a variety of options. The most popular being perforators based free tissue transfers. Skin sparing mastectomy can also be combined with acellular dermal matrix that has given a new dimension and scope to the oncological breast reconstruction.

As the Editor of Special Issue on Aesthetic Surgery of Breast, I would also like to thank the editorial team of *Plastic and Aesthetic Research* for the invitation and for their consistent

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Internal bra: a unifying solution for reconstructive and aesthetic breast surgery issues

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Dr. Richard A. Baxter has a special interest in revision breast surgery, internal bra concepts, and ultrasound in aesthetic medicine. In addition to his busy private plastic surgery practice in the Seattle area, he is engaged in clinical research, figure drawing, and learning Argentine tango.

ABSTRACT

The utility of the internal bra for breast support, reconstruction, and in revision breast surgery has been recognized and various materials have been introduced for this application. As clinical experience has grown and new products have been developed, the roles of these materials are becoming better defined. This paper reviews the use of the internal bra concept to date.

Key words:

Internal bra; acellular dermal matrix; alloderm; strattice; SERI surgical scaffold; GalaFLEX mesh; revision breast surgery; mastopexy

INTRODUCTION

Factors leading to revision breast implant surgery include capsular contracture, implant malposition, palpability, and animation deformity with subpectoral placement. These issues often occur in combination,^[1] for example lower or lateral fold malposition with rippling or animation deformity with fold malposition. Reoperation rates for breast implant procedures are high, and even higher for previous revision surgery.^[2] A comprehensive approach is needed if these numbers are to be improved.

There are certain commonalities underlying the issues

leading to revision breast surgery. Implant malposition and rippling are manifestations of thin tissue coverage, which can be thought of as periprosthetic atrophy. This in turn may relate to overly large implants, improper biodimensional planning, and saline implants as a result of fluid wave action. Aging, pregnancies, weight loss, and prior surgeries may contribute to weakening of the ligamentous support and soft tissue envelope of the breast. In combination, these patient-related and implant-related factors may multiply the severity of periprosthetic atrophy. Autologous material such as capsule flaps^[3,4] and fat grafting can be useful adjuncts in

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Table 1. Criteria for the ideal internal bra material

Criteria
No interference with mammography
Biocompatible
Bio-inductive: template for long-term host tissue replacement
Maintains strength until host tissue replacement
Handling characteristics: easy to template and suture
Easily stored and ready-to-use
Available in a range of sizes
Affordable
Natural feel

recreating a stable breast implant pocket, but are not always capable of providing a comprehensive solution.

Recognition of the potential benefit of non-autologous internal breast support was initially constrained by the lack of suitable materials [Table 1]. Most of the products were developed for hernia repair and general soft tissue support rather than for breast procedures specifically. These materials can be classified as first generation (nonresorbable synthetics), second generation (acellular dermal matrix), and third generation (slowly resorbable textiles) [Table 2]. The developing role of these products will be reviewed.

FIRST GENERATION INTERNAL BRA MATERIALS

The use of polypropylene mesh with reduction mammoplasty was reported in 1981,^[5] and more recently a three-dimensional pre-shaped polyester mesh was developed.^[6] Because Wise pattern/inverted T patterns rely on the skin envelope to shape the breasts, by offloading the support and shaping of the breast from the skin to the mesh, the role of short scar techniques expanded. Góes^[7] originally proposed the use of resorbable mesh with periareolar mastopexy but noted longer lasting results with a mixed mesh (40% polyester, 60% polyglactin). More recently, a titanium-coated mesh (TiLOOP® Bra) has been introduced in Europe.^[8] Nevertheless, concerns about biofilms and a permanent foreign body in the subcutaneous layer of the breast have limited the adoption of this approach.^[9] For these same reasons, non-resorbable meshes have had limited use in revision breast surgery although they helped establish proof of concept for the idea of an internal bra.

SECOND GENERATION MATERIALS

Duncan^[10] first reported the use of human-derived acellular

Table 2. Internal bra materials

First generation	Second generation	Third generation
Mixed mesh (polyester/polyglactin)	Human ADM	Silk fibroin mesh
Polypropylene mesh	• Alloderm	• SERI Scaffold
Polyester three-dimensional cone	• Dermamatrix	P4HB mesh
Titanium-coated polypropylene (TiLOOP® Bra)	• FlexHD	• GalaFLEX
	• AlloMax	• Phasix
	Porcine ADM	Mixed
	• Strattice	• TIGR® (Fast resorbing copolymer of lactide, glycolide and trimethylene carbonate; slow-resorbing copolymer of lactide and trimethylene carbonate)
	• Permacol	

ADM: acellular dermal matrix

dermal matrix (ADM) in revision breast surgery for correction of implant rippling. This was later expanded to include a variety of implant-related problems, with the common denominator being inadequate soft tissue support and/or coverage.^[11] Histologic analysis demonstrated integration and transformation into host tissue, with follow-up as long as 12 years.^[12] The ability of these materials to replace deficient or weakened tissue led to their widespread adoption in breast reconstruction and revision breast surgery and became the standard for many years.^[13] Host tissue response and long-term integration may be affected by decellularization and sterilization methods which can alter the architecture of the matrix.^[14]

ADM's have proven valuable in the setting of revision breast implant surgery, for both reconstructive and cosmetic cases.^[15-17] In primary reconstruction, they may allow for more rapid tissue expansion and higher initial fill volumes, though prospective studies on this are limited and inconsistent. Selection of an adequately sized piece is important.^[18] Direct-to-implant immediate reconstruction with skin-sparing mastectomy relies on the use of ADM's to offload the weight of the implant from the skin envelope and control pocket shape.^[19]

Further experience with ADM's revealed their resistance to radiation, of particular benefit to reconstruction patients.^[20] Another observation was a much lower than expected incidence of capsular contracture in reconstruction patients,^[21] leading to the use of ADM's in revision breast surgery for established capsular contracture.^[22,23] In this application, the material may afford protection against recurrent contracture, possibly related to altered inflammatory aspects of capsule formation.^[24] Importantly, ADM's serve to replace tissue support and implant coverage after capsulectomy. This ability to provide instant, predictable, and durable tissue thickness remains a primary advantage of ADM's. Porcine-derived ADM's, designed to offer a non-human source alternative, have found utility in this application. In general, porcine ADM's have more consistent thickness and less stretch than human-derived ADM's.

The use of ADM's has been mostly limited to the periprosthetic layer for creation of a stable pocket for implants, as a pectoral extension for post-mastectomy breast reconstruction and in revision aesthetic breast implant surgery. Use of an ADM internal bra in reduction

Table 3. Comparison of Internal bra materials

	Advantages	Disadvantages
First generation Polypropylene mesh; Mixed mesh	Durable; Affordable; Variety of sizes and shapes	Foreign body may be subject to biofilms/ infection/exposure; Possible interference with mammograms
Second generation Human-derived ADM	Potentially very long lasting; Elastic (facilitates tissue expansion); Extensive clinical record	Expensive; Potential for seromas; Need for long-term drains; Red breast syndrome; Limited sizes
Porcine-derived ADM	Potentially very long lasting; Inelastic; 1:1 correction for revision surgery; Instant thickness	Same as human-derived
Third generation SERI Scaffold, P4HB mesh	More affordable than ADM's; Variety of shapes and sizes; Slowly resorbing with induction of replacement by host tissue; Open weave may facilitate fluid egress and mesh integration	Limited clinical data for breast surgery

ADM: acellular dermal matrix

mammoplasty has been proposed,^[25] but the large pieces required can make it expensive. In the case of reconstruction, the concept of an internal bra is logical as the breast mound is entirely comprised of the implant; in the case of a breast augmentation, the concept is more limited because it supports the implant but not breast tissue unless placed in a more superficial layer. This would require placement in a subcutaneous layer, encompassing both implant and breast. ADM's are not generally suitable for this application without extensive meshing as with skin grafts.

Disadvantages of ADM's include cost,^[26] concerns about animal or cadaveric sourcing, the need for long-term suction drains,^[27] and complications such as red breast syndrome and seromas.^[28,29] Placement of fenestrations may ameliorate these issues to a degree.^[30] Another limitation is the inability to form an adherent capsule on textured implants, which may be desired in some cases to prevent rotation of form-stable implants.

THIRD GENERATION

As ADM's helped to propel the concept of an internal bra, the need for more versatile materials became evident. Slowly resorbing materials which induce formation of a strong and durable host tissue layer would have the versatility of permanent meshes and the biocompatibility of ADM's. SERI® surgical scaffold (Allergan, Inc.), comprised of purified fibroin silk, and meshes based on poly-4-hydroxybutyrate (GalaFLEX®, Tephamedical Devices) are the leading products in this category.

Silk-based scaffolds have been explored in various reconstructive surgery applications because of their potential to induce a host response characterized by site-specific tissue replacement.^[31] Raw silk consists primarily of

two proteins: fibroin, comprised of fibers with high tensile strength, and sericin, a glue-like substance which coats the fibroin strands but provokes an inflammatory response as an implant. Removal of the sericin component yields a biocompatible material that can be woven or knitted into various configurations.^[32] Experimentally, implantation is quickly followed by fibroblast migration, adherence, and proliferation.^[33] Early iterations of implantable fibroin-based scaffolds included anterior cruciate ligament^[34] and abdominal wall repair.^[35] Silk scaffolds seeded with specific cell lines or growth factors is an active area of research in tissue engineering.^[36]

SERI® surgical scaffold is a knitted multifilament implantable material derived from the cocoons of the silkworm *Bombyx mori*. It is easily cut without unraveling and suitable for a variety of applications in breast reconstruction, revision breast surgery, and some cases primary aesthetic breast surgery such as augmentation-mastopexy.^[37] In an ovine model of two-stage breast reconstruction, SERI scaffold demonstrated maintenance of burst strength greater than host fascia through 12 months, with histologic evidence of scaffold resorption and replacement by new tissue.^[38] Interim one-year data from an ongoing clinical trial of two-stage breast reconstruction shows low complication rates and high patient satisfaction.^[39] Early results from a European trial with SERI in direct-to-implant reconstruction after skin-sparing mastectomy showed good aesthetic outcomes and acceptable complication profile.^[40]

Poly-4-hydroxybutyrate is a bio-derived polymer produced by micro-organisms under specific conditions. P4HB is a monofilament used as a suture or knitted into a mesh, and is somewhat stiffer than SERI® scaffold. Clinical experience with P4HB meshes is extensive but only recently has it been applied to breast surgery.^[41] In a porcine model of abdominal

wall repair, PHASIX® knitted mesh (Tepha) demonstrated burst strength significantly greater than native tissue at all points up to one year.^[42] As with silk scaffolds, a variety of uses for constructs based on PHB have been explored, including heart valves.^[43] Clinical trial results for GalaFLEX® (P4HB mesh) in breast surgery have not yet been reported but a trial in mastopexy and reduction mammoplasty is ongoing.

A composite mesh comprised of fast-absorbing and slow-absorbing fibers has also been explored (TIGR® Matrix surgical mesh, Novus Scientific.) At an average follow-up of 16 months, a favorable complication rate was observed in a case series of breast reconstruction, revision implant surgery, and primary aesthetic procedures.^[44]

Because third generation meshes facilitate subcutaneous placement, mastopexy may be performed without parenchymal disruption or reliance on a tight skin envelope. For all internal bra materials, the ability to offload the weight of the breast during the transition from graft to host is critical. Quickly-resorbing materials lose support before host tissue can develop, so the ability of the material to induce or support ingrowth or replacement by host issue is an important variable. In practice, it is important to take advantage of the internal bra concept by adapting the skin envelope of the breast to the shape created by the material and close incisions under minimal tension. This may minimize the potential for would breakdown and exposure of the material. Minimal tension closure may reduce the potential for hypertrophic scarring as well. The ability to shape the breast mound as a composite unit of implant and parenchyma by wrapping in a subcutaneous internal bra may prevent long-term problems of differential implant or breast ptosis.

DISCUSSION

By restoring support due to attenuated or weak tissues, revision surgery for combination problems may find a unifying solution with the internal bra. Despite the paucity of robust long-term data for newer materials, they are finding a role in clinical practice. Each has its own limitations and advantages [Table 3]. Although there are general characteristics that are desirable across the category, different applications require specific mesh attributes. In revision surgery, elasticity and expandability may be disadvantages while they are plusses for tissue expansion. Placement in the subcutaneous layer is necessary for mastopexy, but placement too superficially may result in unacceptable palpability or risk of exposure, while in a deeper layer, non-take may be a concern because of less vascularity. The consequences of non-take for second and third generation materials include exposure, infection, and possible need for removal of both the material and implant. As application-specific characteristics such as pore size, fiber size, monofilament vs. multifilament, degradation profiles, and textile engineering become better understood, these materials will be better optimized. The introduction of fixation devices and 3-dimensionally shaped constructs may broaden the appeal of the internal bra.

CONCLUSION

The concept of an implantable internal bra continues to evolve. Third generation biomaterials designed to act as templates that resorb and initiate tissue neogenesis address many of the issues posed by non-resorbable materials and acellular matrices, but have only recently become widely available and less is known about complication rates and best practices. As indications become better defined and clinical experience grows, the use of these materials appears poised to usher in a new generation of regenerative surgery.

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REFERENCES

- Grewal NS, Fisher J. Why do patients seek revisionary breast surgery? *Aesthet Surg J* 2013;33:237-44.
- Forster NA, Künzi VV, Giovanoli P. The reoperation cascade after breast augmentation with implants: what the patient needs to know. *J Plast Reconstr Aesthet Surg* 2013;66:313-22.
- Wessels L, Murphy S, Merten S. The capsular hammock flap for correction of breast implant ptosis. *Aesthetic Plast Surg* 2014;38:354-7.
- Bogdanov-Berezovsky A, Silberstein E, Shoham Y, Krieger Y. Capsular flap: new applications. *Aesthetic Plast Surg* 2013;37:395-7.
- Johnson GW. Central core reduction mammoplasties and Marlex suspension of breast tissue. *Aesthetic Plast Surg* 1981;5:77-84.
- de Bruijn HP, Johannes S. Mastopexy with 3D preshaped mesh for long-term results: development of the internal bra system. *Aesthetic Plast Surg* 2008;32:757-65.
- Góes JC. Periareolar mastopexy: double skin technique with mesh support. *Aesthet Surg J* 2003;23:129-35.
- Dieterich M, Stubert J, Gerber B, Reimer T, Richter DU. Biocompatibility, cell growth and clinical relevance of synthetic meshes and biological matrixes for internal support in implant-based breast reconstruction. *Arch Gynecol Obstet* 2015;291:1371-9.
- Dixon JM, Arnott I, Schaverien MJ. Chronic abscess formation following mesh mastopexy: case report. *Plast Reconstr Aesthet Surg* 2010;63:1220-2.
- Duncan DI. Correction of implant rippling using allograft dermis. *Aesthet Surg J* 2001;21:81-4.
- Baxter RA. Intracapsular allogenic dermal grafts for breast implant-related problems. *Plast Reconstr Surg* 2003;112:1692-6.
- Baxter RA. Long-term follow-up with AlloDerm in breast reconstruction. *Plast Reconstr Surg Glob Open* 2013;1:1-2.
- Baxter RA. Acellular dermal matrices in breast implant surgery: defining the problem and proof of concept. *Clin Plast Surg* 2012;39:103-12.
- Boone MA, Draye JP, Verween G, Aiti A, Pirnay JP, Verbeken G, De Vos D, Rose T, Jennes S, Jemec GB, Del Marmol V. Recellularizing of human acellular dermal matrices imaged by high-definition optical coherence tomography. *Exp Dermatol* 2015;24:349-54.
- Spear SL, Sher SR, Al-Attar A, Pittman T. Applications of acellular dermal matrix in revision breast reconstruction surgery. *Plast Reconstr Surg* 2014;133:1-10.
- Pozner JN, White JB, Newman MI. Use of porcine acellular dermal matrix in revisionary cosmetic breast augmentation. *Aesthet Surg J* 2013;33:681-90.
- Maxwell GP, Gabriel A. Efficacy of acellular dermal matrices in revisionary aesthetic breast surgery: a 6-year experience. *Aesthet Surg J* 2013;33:389-99.
- Cayci C, Santner F, Jacobson SR. Impact and outcome of human acellular dermal matrix size for immediate and two-stage breast reconstruction. *Plast Reconstr Surg* 2013;132:11-8.
- Salzberg CA. Focus on technique: one-stage implant-based breast reconstruction. *Plast Reconstr Surg* 2012;130:S95-103.
- Topol BM. The use of human acellular dermal matrices in irradiated breast reconstruction. *Clin Plast Surg* 2012;39:149-58.
- Salzberg CA, Ashikari AY, Koch RM, Chabner-Thompson E. An 8-year experience of direct-to-implant immediate breast reconstruction using

- human acellular dermal matrix (AlloDerm). *Plast Reconstr Surg* 2011;127:514-24.
22. Namnoum JD, Moyer HR. The role of acellular dermal matrix in the treatment of capsular contracture. *Clin Plast Surg* 2012;39:127-36.
23. Hester TR Jr, Ghazi BH, Moyer HR, Nahai FR, Wilton M, Stokes L. Use of dermal matrix to prevent capsular contracture in aesthetic breast surgery. *Plast Reconstr Surg* 2012;130:S126-36.
24. Leong M, Basu CB, Hicks MJ. Further evidence that human acellular dermal matrix decreases inflammatory markers of capsule formation in implant-based breast reconstruction. *Aesthet Surg J* 2015;35:40-7.
25. Brown RH, Izaddoost S, Bullocks JM. Preventing the "bottoming out" and "star-gazing" phenomena in inferior pedicle breast reduction with an acellular dermal matrix internal brassiere. *Aesthetic Plast Surg* 2010;34:760-7.
26. Hartzell TL, Taghinia AH, Chang J, Lin SJ, Slavin SA. The use of human acellular dermal matrix for the correction of secondary deformities after breast augmentation: results and costs. *Plast Reconstr Surg* 2010;126:1711-20.
27. Israeli Ben-Noon H, Farber N, Weissman O, Tessone A, Stavrou D, Shabtai M, Maor Y, Haik J, Winkler E. The effect of acellular dermal matrix on drain secretions after immediate prosthetic breast reconstruction. *J Plast Surg Hand Surg* 2013;47:308-12.
28. Israeli R. Complications of acellular dermal matrices in breast surgery. *Plast Reconstr Surg* 2012;130:S159-72.
29. Michelotti BF, Brooke S, Mesa J, Wilson MZ, Moyer K, Mackay DR, Neves RI, Potochny J. Analysis of clinically significant seroma formation in breast reconstruction using acellular dermal grafts. *Ann Plast Surg* 2013;71:274-7.
30. Martin JB, Moore R, Paydar KZ, Wirth GA. Use of fenestrations in acellular dermal allograft in two-stage tissue expander/implant breast reconstruction. *Plast Reconstr Surg* 2014;134:901-4.
31. Kundu B, Rajkhowa R, Kundu SC, Wang X. Silk fibroin biomaterials for tissue regenerations. *Adv Drug Deliv Rev* 2013;65:457-70.
32. Wang Y, Rudym DD, Walsh A, Abrahamsen L, Kim HJ, Kim HS, Kirker-Head C, Kaplan DL. *In vivo* degradation of three-dimensional silk fibroin scaffolds. *Biomaterials* 2008;29:3415-28.
33. Acharya C, Ghosh SK, Kundu SC. Silk fibroin protein from mulberry and non-mulberry silkworms: cytotoxicity, biocompatibility and kinetics of L929 murine fibroblast adhesion. *J Mater Sci Mater Med* 2008;19:2827-36.
34. Horan RL, Toponarski I, Boepple HE, Weitzel PP, Richmond JC, Altman GH. Design and characterization of a scaffold for anterior cruciate ligament engineering. *J Knee Surg* 2009;22:82-92.
35. Clemens MW, Downey S, Agullo F, Leheldt MR, Kind GM, Palladino H, Marshall D, Jewell ML, Mathur AB, Bengtson BP. Clinical application of a silk fibroin protein biologic scaffold for abdominal wall fascial reinforcement. *Plast Reconstr Surg Glob Open* 2014;2:e246.
36. Kundu B, Rajkhowa R, Kundu SC, Wang X. Silk fibroin biomaterials for tissue regenerations. *Adv Drug Deliv Rev* 2013;65:457-70.
37. Bengtson B, Baxter RA, Clemens MW, Bates D. A 12-month survey of early use and surgeon satisfaction with a new highly purified silk matrix: SERI surgical scaffold. *Plast Reconstr Surg Glob Open* 2014;7:2:e182.
38. Gross JE, Horan RL, Gaylord M, Olsen RE, McGill LD, García-López JM, Biber K, Barnico K, Toponarski I, Altman G. An evaluation of SERI surgical scaffold for soft-tissue support and repair in an ovine model of two-stage breast reconstruction. *Plast Reconstr Surg* 2014;134:e700-4.
39. Fine NA, Leheldt M, Gross JE, Downey S, Kind GM, Duda G, Kulber D, Horan R, Ippolito J, Jewell M. SERI surgical scaffold, prospective clinical trial of a silk-derived biological scaffold in two-stage breast reconstruction: 1-year data. *Plast Reconstr Surg* 2015;135:339-51.
40. De Vita R, Buccheri EM, Pozzi M, Zoccali G. Direct to implant breast reconstruction by using SERI, preliminary report. *J Exp Clin Cancer Res* 2014;33:78.
41. Williams SF, Rizk S, Martin DP. Poly-4-hydroxybutyrate (P4HB): a new generation of resorbable medical devices for tissue repair and regeneration. *Biomed Tech (Berl)* 2013;58:439-52.
42. Deeken CR, Matthews BD. Characterization of the mechanical strength, resorption properties, and histologic characteristics of a fully absorbable material (poly-4-hydroxybutyrate-PHASIX Mesh) in a porcine model of hernia repair. *ISRN Surg* 2013;2013:238067.
43. Wu Q, Wang Y, Chen GQ. Medical application of microbial biopolyesters polyhydroxyalkanoates. *Artif Cells Blood Substit Immobil Biotechnol* 2009;37:1-12.
44. Becker H, Lind JG 2nd. The use of synthetic mesh in reconstructive, revision, and cosmetic breast surgery. *Aesthetic Plast Surg* 2013;37:914-21.

An analysis of underweight status on 30-day outcomes after breast reconstruction

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ABSTRACT

Aim: To examine the impact of underweight body mass index (BMI) values on breast reconstruction outcomes. **Methods:** The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database was retrospectively reviewed for all patients who underwent breast reconstruction between 2006 and 2011. Patients were first stratified by breast reconstruction modality into prosthetic or autologous cohorts, and second by BMI values into underweight (BMI < 18.5), normal to overweight (reference, BMI 18.5-29.99), moderate obesity (BMI 30-34.99), severe obesity (BMI 35-39.99), and morbid obesity cohorts. Multivariate logistic regression models were used to determine independent predictors of complications. **Results:** With regard to prosthetic breast reconstruction patients, obese patients demonstrated increased rates of surgical complications, while underweight patients did not have any differences on multivariable analysis. With respect to autologous reconstruction, risk-adjusted multivariate regression models showed a dose dependent response between obesity and risk for surgical complications and reoperation, but not for underweight patients. **Conclusion:** On multivariable analysis of over 4,600 patients, there were no significant differences in the rates of adverse events between underweight patients (BMI < 18.5) and their reference-weight counterparts, in spite of a significant increase in surgical and medical complication rates in underweight patients on univariate analysis.

Key words:

Breast reconstruction; underweight; complications; body mass index; obesity

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INTRODUCTION

Much has been published regarding the risks of obesity on medical outcomes. The prevalence of obesity among adults in the United States has been steadily increasing over the past several decades such that today over 1 in every 3 adults is obese [body mass index (BMI) > 30 kg/m²], and nearly 1 in every 10 adults is morbidly obese (BMI > 40 kg/m²).^[1,2] Obesity is a multi-system disease process which confers increased risk of medical comorbidities including hypertension (HTN), coronary artery disease, and diabetes mellitus (DM), and increases the risk of surgical morbidity.^[3,4] Similarly, extremes of underweight have recently been described as a risk factor for surgery.^[5-7] Several recent studies of critically and chronically ill patients,^[8-11] and of patients undergoing certain procedures^[12-15] suggest that overweight and obese patients may paradoxically have better outcomes than underweight patients, given an increased risk for death and catastrophic complications in the latter patients.

As many as 40% of women undergoing mastectomies in the USA, they are now seeking post-mastectomy breast reconstruction.^[16-19] While much recent literature has detailed an association between obesity and poor surgical outcomes,^[20-23] other studies have failed to demonstrate an increased risk of death or severe complications in these patients.^[24-26] Conversely, very little has been written about the risk of underweight patients undergoing breast reconstruction. Such studies have been compromised by small sample sizes, single-institutional bias, retrospective study design, limited patient follow-up, inconsistent definitions of underweight, types of surgical procedures included, and outcomes studied.^[27-30]

In an effort to better understand the influence of BMI on outcomes following breast reconstruction, we examined the National Surgical Quality Improvement Program (NSQIP) datasets. We aim to define and benchmark the

risks and outcomes associated with breast reconstruction in underweight patients. We hypothesized that patients who are at extremes of low BMI would have a higher risk of adverse outcomes.

METHODS

Patient population

All patients with “Plastics” recorded as their primary surgical team were isolated from the 2006-2011 NSQIP database. Patients were stratified into either “prosthetic” or “autologous” reconstruction cohorts, based on ACS-NSQIP classification. ACS-NSQIP tracks procedures based on Current Procedural Terminology (CPT) codes. Specific CPT codes used for each cohort include: 19340 (immediate breast reconstruction with implant), 19342 (delayed breast reconstruction with implant), 19357 (breast reconstruction with tissue expander), 19361 (breast reconstruction with latissimus dorsi flap), 19364 (breast reconstruction with free flap), 19367 [breast reconstruction transverse rectus abdominis musculocutaneous (TRAM) flap] and 19368 (breast reconstruction with TRAM flap, with microvascular anastomosis). Patients undergoing multiple types of reconstruction (e.g. latissimus dorsi flap + implant, or different types of reconstruction on each side) were excluded from analysis. Similarly, only patients with total breast reconstruction using the above-mentioned codes were included. Thus, patients undergoing breast reconstruction via fat grafting (CPT code 15770) or local flap closure (14301, 14302, 15734) were excluded from analysis. Breast reconstruction patients were further categorized into prosthetic and autologous reconstruction cohorts. Similar preoperative demographic and postoperative outcomes analyses were carried out separately in the prosthetic and autologous populations groups. Multivariate regression analysis was also conducted in similar fashion to the overall population.

Table 1: Prosthetic breast reconstruction patient clinical characteristics, stratified by body mass index, n (%)

	Underweight (< 18.5 , $n = 116$)	Normal to overweight ($18.5-29.99$, $n = 2,543$)	Moderate obesity ($30-34.99$, $n = 511$)	Severe obesity ($35-39.99$, $n = 229$)	Morbid obesity (≥ 40 , $n = 114$)
Age	48.12 \pm 12.04	51.43 \pm 11.55	53.988 \pm 10.58	54.60 \pm 10.92	52.54 \pm 10.56
Hypertension	9 (7.76)	474 (18.64)	204 (39.92)	125 (54.59)	56 (49.12)
Diabetes	2 (1.72)	71 (2.79)	57 (11.15)	37 (16.16)	18 (15.79)
COPD	2 (1.72)	16 (0.63)	4 (0.78)	7 (3.06)	2 (1.75)
Dyspnea	3 (2.59)	58 (2.43)	17 (3.33)	17 (7.42)	10 (8.77)
History of TIA or CVA	0 (0.00)	14 (0.59)	8 (1.57)	2 (0.87)	3 (2.63)
Prior PCI or PCS	0 (0.00)	21 (0.83)	8 (1.57)	4 (1.75)	0 (0.00)
Active smoking	20 (17.24)	344 (13.53)	62 (12.13)	25 (10.92)	16 (14.04)
Alcohol use	3 (2.59)	28 (1.10)	4 (0.78)	2 (0.87)	1 (0.88)
Chronic steroid use	0 (0.00)	22 (0.87)	2 (0.39)	3 (1.31)	4 (3.51)
Chemotherapy within 30 days	3 (2.59)	79 (3.11)	16 (3.13)	5 (2.18)	4 (3.51)
Radiation within 90 days	0 (0.00)	12 (0.47)	3 (0.59)	0 (0.00)	1 (0.88)
Wound infection within 30 days	1 (0.86)	36 (1.42)	6 (1.17)	1 (0.44)	0 (0.00)
Prior operation within 30 days	2 (1.72)	20 (0.79)	6 (1.17)	2 (0.87)	0 (0.00)
Outpatient cases	81 (69.82)	1,781 (70.03)	380 (74.36)	162 (70.74)	73 (64.04)
Emergent cases	1 (0.86)	14 (0.55)	3 (0.59)	1 (0.05)	1 (0.88)
Sum of relative value units	34.30 \pm 17.90	33.69 \pm 19.71	34.15 \pm 20.13	33.59 \pm 18.06	36.46 \pm 23.04
Operative time (h)	2.27 \pm 2.18	2.17 \pm 1.32	2.22 \pm 1.43	2.20 \pm 1.18	2.46 \pm 1.78

COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack; CVA: cerebrovascular accident; PCI: previous coronary intervention; PCS: previous cardiac surgery

Table 2: Autologous breast reconstruction patient clinical characteristics, stratified by body mass index, *n* (%)

	Underweight (<i>< 18.5, n = 20</i>)	Normal to overweight (<i>18.5-29.99, n = 706</i>)	Moderate obesity (<i>30-34.99, n = 281</i>)	Severe obesity (<i>35-39.99, n = 109</i>)	Morbid obesity (<i>≥ 40, n = 47</i>)
Age	48.42 ± 11.71	51.35 ± 10.05	52.08 ± 8.90	51.66 ± 9.15	50.81 ± 9.56
Hypertension	4 (20.00)	165 (25.31)	95 (33.81)	48 (44.04)	21 (44.68)
Diabetes	0 (0.00)	22 (3.37)	17 (6.05)	16 (14.68)	6 (12.77)
COPD	0 (0.00)	5 (0.77)	1 (0.36)	0 (0.00)	0 (0.00)
Dyspnea	1 (5.00)	15 (2.30)	7 (2.49)	4 (3.67)	3 (6.38)
History of TIA or CVA	0 (0.00)	7 (1.07)	1 (0.36)	1 (0.92)	1 (2.13)
Prior PCI or PCS	0 (0.00)	4 (0.61)	1 (0.36)	0 (0.00)	0 (0.00)
Active smoking	3 (15.00)	75 (11.50)	28 (9.96)	7 (6.42)	9 (19.15)
Alcohol use	0 (0.00)	6 (0.92)	2 (0.71)	0 (0.00)	1 (2.13)
Chronic steroid use	1 (5.00)	7 (1.07)	2 (0.71)	1 (0.92)	0 (0.00)
Chemotherapy within 30 days	1 (5.00)	29 (4.44)	14 (4.98)	3 (2.75)	0 (0.00)
Radiation within 90 days	0 (0.00)	6 (0.92)	2 (0.71)	2 (1.83)	0 (0.00)
Wound infection within 30 days	1 (5.00)	21 (3.22)	5 (1.78)	4 (3.67)	1 (2.13)
Prior operation within 30 days	0 (0.00)	22 (3.37)	7 (2.49)	3 (2.75)	2 (4.26)
Outpatient cases	2 (10.00)	75 (11.50)	22 (7.83)	5 (4.59)	7 (14.89)
Emergent cases	1 (5.00)	3 (0.46)	1 (0.36)	0 (0.00)	0 (0.00)
Sum of relative value units	48.02 ± 31.37	47.28 ± 24.73	48.79 ± 24.39	48.46 ± 26.30	47.14 ± 28.81
Operative time (h)	5.82 ± 2.42	6.09 ± 3.12	6.61 ± 3.41	6.38 ± 3.64	6.05 ± 3.63

TIA: transient ischemic attack; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; PCI: previous coronary intervention; PCS: previous cardiac surgery

Outcomes

Our primary outcomes of interest were: 30-day surgical complications, medical complications, reoperation, and mortality. Surgical complication was defined as having ≥ 1 of the following ACS-NSQIP post-operative adverse events: superficial surgical site infection (SSI), deep surgical site infection, organ/space surgical site infection, wound disruption/dehiscence, or graft/prosthesis failure. Medical complications included: pneumonia, unplanned intubation, pulmonary embolism (PE), failure to wean from ventilator, renal insufficiency, progressive renal failure, urinary tract infection, stroke, coma, peripheral neurologic deficiency, cardiac arrest, myocardial infarction, bleeding requiring a transfusion, deep venous thrombosis (DVT), and sepsis/septic shock.

Statistical analysis

Patients were stratified into BMI categories as follows: underweight, BMI < 18.5 ; normal to overweight, BMI 18.5-29.99; moderately obese, BMI 30-34.99; severely obese, BMI 35-39.99; and morbidly obese, BMI ≥ 40 . Patient demographics and clinical characteristics were tracked as potential cofounders. Chi-square analysis was used to compare categorical variables and one-way ANOVA tests were used to analyze continuous variables.

Multivariable logistic regression analysis was utilized to investigate the impact of BMI values on outcomes. Preoperative variables with ≥ 10 occurrences and $P \leq 20$ on bivariate screening were included in the analysis. All analysis was conducted using Statistical Product and Service Solutions (SPSS) version 21 (Chicago, IL). P values less than 0.05 were statistically significant. For statistical evaluation, the reference population was defined as the normal-weight cohort (i.e. BMI 18.5-29.99).

RESULTS

In review of the 25,346 plastic surgery patients extracted from the database, 4,676 patients met criteria for study inclusion. Three-fourths (3,513) of the reconstruction patients received prosthetic reconstruction and the remaining quarter (1,163) underwent autologous tissue based reconstruction. Rates of hypertension, diabetes, and dyspnea increased as BMI values increased in both prosthetic and autologous cohorts [Tables 1 and 2]. For statistical evaluation, the reference population was defined as the normal-weight cohort (i.e. BMI 18.5-29.99).

On univariate analysis, in the prosthetic patient population, adverse events (AE) increased from underweight, to reference, to obese patients [Table 3, Figure 1]. Total complications rose from 1.7%, 3.3%, to 11.4% in underweight, reference, and morbidly obese patients, respectively ($P < 0.001$). Similarly, surgical complications increased from 1.7%, 2.9%, to 11.4% as weight strata increased ($P < 0.001$). Medical complications were significantly increased in underweight and obese patients, compared to reference weight patients increased (1.7% for underweight, 2.4% for obese, and 0.8% for reference weight patients) ($P = 0.009$). Finally, reoperation rates increased as weight strata increased (0%, 3.6%, to 8.8%, respectively) ($P = 0.001$). There were no deaths in the prosthetic breast reconstruction cohort.

With respect to autologous reconstruction, complication rates increased when patients were at extremes of weight, whether underweight or overweight [Figure 2]. While the reference population (i.e. BMI 20-30) had a rate of total complications of 16.6%, underweight patients had a total rate of 20%, and overweight patients' complication rate increased to 40.43% ($P < 0.001$). Similarly, surgical complications increased from 6.9% to 15% and 29.79% in underweight and obese patients, respectively ($P < 0.001$).

Table 3: Postoperative complications following prosthetic breast reconstruction, stratified by body mass index, univariate analysis, *n* (%)

	Underweight (<i>< 18.5</i> , <i>n</i> = 116)	Normal to overweight (<i>18.5-29.99</i> , <i>n</i> = 2,543)	Moderate obesity (<i>30-34.99</i> , <i>n</i> = 511)	Severe obesity (<i>35-39.99</i> , <i>n</i> = 229)	Morbid obesity (<i>≥ 40</i> , <i>n</i> = 114)	<i>P</i>
Total complications	2 (1.72)	85 (3.34)	28 (5.48)	19 (8.30)	13 (11.40)	<i>< 0.001*</i>
Surgical complications	2 (1.72)	73 (2.87)	21 (4.11)	15 (6.55)	13 (11.40)	<i>< 0.001*</i>
Wound infection	2 (1.72)	57 (2.24)	18 (3.52)	15 (6.55)	10 (8.77)	<i>< 0.001*</i>
Superficial SSI	0 (0.00)	31 (1.22)	12 (2.35)	4 (1.75)	2 (1.75)	0.272
Deep SSI	0 (0.00)	16 (0.63)	3 (0.59)	6 (2.62)	2 (1.75)	0.006*
Organ/space SSI	2 (1.30)	12 (0.47)	3 (0.59)	5 (2.18)	6 (5.26)	<i>< 0.001*</i>
Dehiscence	0 (0.00)	19 (0.75)	3 (0.59)	2 (0.87)	4 (3.51)	0.02*
Prosthesis failure	0 (0.00)	4 (0.16)	2 (0.39)	1 (0.44)	1 (0.88)	0.384
Medical complications	2 (1.72)	20 (0.79)	12 (2.35)	5 (2.18)	1 (0.88)	0.009*
Pneumonia	0 (0.00)	1 (0.04)	0 (0.00)	1 (0.44)	0 (0.00)	0.17
Reintubation	0 (0.00)	1 (0.04)	0 (0.00)	0 (0.00)	0 (0.00)	0.976
PE	0 (0.00)	2 (0.08)	2 (0.39)	1 (0.44)	0 (0.00)	0.313
Ventilator > 48 h	0 (0.00)	0 (0.00)	1 (0.20)	0 (0.00)	0 (0.00)	0.209
Renal insufficiency	0 (0.00)	1 (0.04)	0 (0.00)	0 (0.00)	0 (0.00)	0.976
Acute renal failure	0 (0.00)	0 (0.00)	1 (0.20)	0 (0.00)	0 (0.00)	0.209
UTI	0 (0.00)	4 (0.16)	3 (0.59)	1 (0.44)	0 (0.00)	0.329
Stroke	0 (0.00)	1 (0.04)	0 (0.00)	0 (0.00)	0 (0.00)	0.976
Coma	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	-
Peripheral neuro deficiency	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	-
Cardiac arrest	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	-
Myocardial Infarction	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	-
Bleed requiring transfusion	0 (0.00)	4 (0.16)	5 (0.98)	0 (0.00)	0 (0.00)	0.013*
DVT	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.44)	0 (0.00)	0.006*
Sepsis/septic shock	1 (0.86)	6 (0.24)	3 (0.59)	1 (0.44)	1 (0.88)	0.646
Reoperation	0 (0.00)	91 (3.58)	20 (3.91)	18 (7.86)	10 (8.77)	0.001*
Death	0 (0.00)	0 (0.00)	1 (0.20)	0 (0.00)	0 (0.00)	0.209

*Denotes significant value, *P* < 0.05. SSI: superficial surgical site infection; PE: pulmonary embolism; DVT: deep venous thrombosis; UTI: urinary tract infection

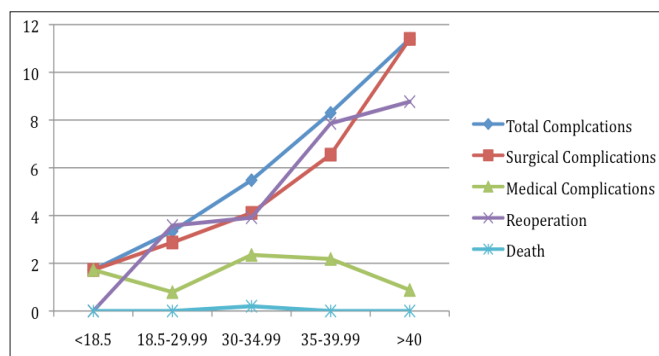


Figure 1: Incidence of adverse events vs. body mass index range, for prosthetic breast reconstruction cohort

In contrast, underweight patients had the lowest rate of medical complications (5%), compared to the reference population (11.2%), or obese patients (23.4%) (*P* = 0.005) [Table 4]. Reoperation rates also increased from 5%, 9%, to 29.79% in the underweight, reference, and obese populations, respectively (*P* < 0.001). There was one death in the autologous reconstruction cohort, in the reference weight subgroup (data not significant).

Multivariate regression analysis demonstrated a different picture. With respect to prosthetic reconstruction, only severely and morbidly obese patients had an elevated odds of having a surgical complication [Table 5]; the severely obese were also at risk for reoperation. Additionally, patients with moderate obesity had a 28.9% increase in their risk for incurring a medical complication. Interestingly, underweight patients appeared to have decreased risk of complications or reoperation, although

these numbers did not reach significance.

On multivariate analysis, a strong connection between BMI and autologous reconstruction outcomes was present. Specifically, there was a significant incremental increase in odds for surgical complications when transitioning from reference weight to morbid obesity (ranging from 1.35 to 3.31) [Table 6]. Individuals with a BMI over 35 also had significant risk for reoperation. Medical complications rose as BMI increased, although data did not reach significance. Similarly, underweight patients had an elevated risk of surgical complications; however this data did not reach significance (*P* = 0.062).

DISCUSSION

This study defines and benchmarks risks and outcomes at 30 days associated with breast reconstruction, utilizing a detailed stratification method, including a categorization of underweight patients. We found 4,676 patients who underwent breast reconstruction during this period, of whom 3,513 (75.1%) underwent prosthetic reconstruction, and 1,163 (24.9%) underwent autologous reconstruction. Of the total 4,676 patients, 136 (3%) were BMI < 18.5, 3,249 (69.5%) were BMI 18.5-30, 792 (16.9%) were BMI 30-34.99, 338 (7.2%) were BMI 35-39.99, and 161 (3.4%) were BMI > 40.

We found significant differences in the groups, with regard to preoperative variables. With regards to prosthetic reconstruction, underweight patients tended to be younger,

Table 4: Postoperative complications following autologous breast reconstruction, stratified by body mass index, univariate analysis, *n* (%)

	Underweight (<i>< 18.5</i> , <i>n</i> = 20)	Normal to overweight (<i>18.5-29.99</i> , <i>n</i> = 706)	Moderate obesity (<i>30-34.99</i> , <i>n</i> = 281)	Severe obesity (<i>35-39.99</i> , <i>n</i> = 109)	Morbid obesity (<i>≥ 40</i> , <i>n</i> = 47)	<i>P</i>
Total complications	4 (20.00)	117 (16.57)	64 (22.78)	40 (36.70)	19 (40.43)	<i>< 0.001*</i>
Surgical complications	3 (15.00)	50 (7.08)	33 (11.74)	21 (19.27)	14 (29.79)	<i>< 0.001*</i>
Wound infection	1 (5.00)	35 (4.61)	24 (8.54)	15 (13.76)	12 (25.53)	<i>< 0.001*</i>
Superficial SSI	1 (5.00)	19 (2.69)	19 (6.76)	10 (9.17)	7 (14.89)	<i>< 0.001*</i>
Deep SSI	1 (5.00)	14 (1.98)	5 (1.78)	2 (1.83)	3 (6.38)	0.353
Organ/space SSI	0 (0.00)	2 (0.28)	1 (0.36)	4 (3.67)	2 (4.26)	<i>< 0.001*</i>
Dehiscence	1 (5.00)	6 (0.85)	3 (1.07)	3 (2.75)	0 (0.00)	0.324
Flap failure	1 (5.00)	13 (1.84)	11 (3.91)	7 (6.42)	2 (4.26)	0.032*
Medical complications	1 (5.00)	79 (11.19)	43 (15.30)	23 (21.10)	11 (23.40)	0.005*
Pneumonia	0 (0.00)	2 (0.28)	0 (0.00)	1 (0.92)	0 (0.00)	0.592
Reintubation	0 (0.00)	4 (0.57)	1 (0.36)	2 (1.83)	0 (0.00)	0.471
PE	0 (0.00)	0 (0.00)	4 (1.42)	1 (0.92)	0 (0.00)	0.043*
Ventilator > 48 h	0 (0.00)	2 (0.28)	2 (0.71)	1 (0.92)	0 (0.00)	0.773
Renal insufficiency	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	-
Acute renal failure	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (2.13)	<i>< 0.001*</i>
UTI	0 (0.00)	6 (0.85)	2 (0.71)	0 (0.00)	1 (2.13)	0.677
Stroke	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	-
Coma	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	-
Peripheral neuro deficiency	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	-
Cardiac arrest	0 (0.00)	1 (0.14)	0 (0.00)	0 (0.00)	0 (0.00)	0.954
Myocardial infarction	0 (0.00)	1 (0.14)	1 (0.36)	9 (8.26)	9 (19.15)	0.923
Bleed requiring transfusion	1 (5.00)	63 (8.92)	28 (9.96)	17 (15.60)	6 (12.77)	0.226
DVT	0 (0.00)	4 (0.57)	5 (1.78)	1 (0.92)	0 (0.00)	0.388
Sepsis/septic shock	0 (0.00)	6 (0.85)	7 (2.49)	4 (3.67)	3 (6.38)	0.011*
Reoperation	1 (5.00)	63 (8.92)	35 (12.46)	21 (19.27)	14 (29.79)	<i>< 0.001*</i>
Death	0 (0.00)	1 (0.14)	0 (0.00)	0 (0.00)	0 (0.00)	0.954

*Denotes significant value, *P* < 0.05. SSI: superficial surgical site infection; PE: pulmonary embolism; DVT: deep venous thrombosis; UTI: urinary tract infection

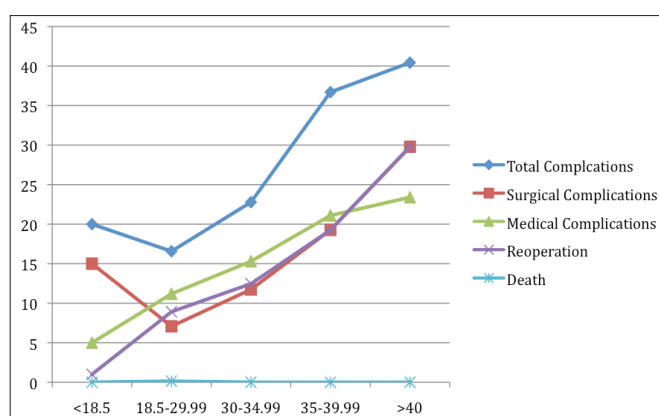


Figure 2: Incidence of adverse events vs. body mass index range, for autologous breast reconstruction cohort

while obese patients tended to be older (48.0 vs. 51.0 years) [Table 1]. With regards to underweight patients, there was a lower incidence of preoperative comorbidities, with the exception of active smoking (17% vs. 13.5%). With regards to overweight patients, nearly all comorbidities were increased, including hypertension, diabetes, chronic obstructive pulmonary disease (COPD), dyspnea, history of transient ischemic attack (TIA) or cerebrovascular accident (CVA), prior percutaneous coronary intervention (PCI) or previous cardiac surgery (PCS), and chronic steroid use. There was also a significant decrease in outpatient cases, and an increase in work relative value units (RVU) and operative time. These findings are all in accordance with previously published literature.^[24,25]

Preoperative variables in the autologous group paralleled

the prosthetic group [Table 2]. Underweight patients had lower incidence of nearly all comorbidities, with the exception of active smoking, steroid use, and wound infection. Underweight patients had similar percentage of outpatient cases, and decreased operative time. As expected, obese patients had an increased incidence of hypertension, diabetes, dyspnea, and wound infection in the prior 30 days.^[24,25] Significantly fewer obese patients were outpatient surgery, and operative time was significantly longer (6.09 h vs. 6.61 h).

While it has previously been found that underweight patients tend to utilize prosthetic breast reconstruction to a higher degree, and that obese patients utilize more autologous reconstruction, this is the first national evaluation of this trend.^[30] Ostensibly, this phenomenon is the result of the lack of donor-site availability in underweight (as opposed to overweight) patients. However, advanced microsurgical techniques, use of flap plus implant techniques, and double-free flap techniques have all contributed to increased the availability of autologous reconstruction for underweight patients.^[31,32]

In our study, we have opted to utilize a unique stratification method, to examine if different BMI categories result in different outcomes. In general, increasing obesity led to statistically increased rates of surgical complications, irrespective of reconstructive type. This is consistent with previous literature on this subject.^[33,34] Specifically, wound infection (superficial/deep/organ space), dehiscence, and prosthesis/flap failure all increased as patient BMI

Table 5: Body mass index as a predictor of outcomes following prosthetic breast reconstruction, multivariate analysis

BMI category	Surgical Complications				Medical Complications				Reoperation			
	OR	95% CI		P	OR	95% CI		P	OR	95% CI		P
< 18.5	0.53	0.07	3.93	0.54	0.46	0.06	3.36	0.44	0.57	0.26	1.33	0.25
18.5-29.99	Reference				Reference				Reference			
30-34.99	1.348	0.812	2.238	0.249	2.752	1.289	5.873	0.009*	0.983	0.585	1.653	0.949
35-39.99	2.032	1.113	3.71	0.021*	2.13	0.746	6.082	0.158	2.018	1.154	3.528	0.014*
> 40	3.308	1.709	6.403	< 0.001*	0.591	0.075	4.654	0.617	1.893	0.914	3.921	0.086

*Denotes significant value, $P < 0.05$. BMI: body mass index; OR: odds ratio; CI: confidence interval

Table 6: Body mass index as a predictor of outcomes following autologous breast reconstruction, multivariate analysis

BMI category	Surgical Complications				Medical Complications				Reoperation			
	OR	95% CI		P	OR	95% CI		P	OR	95% CI		P
< 18.5	2.48	0.85	6.88	0.07	0.66	0.23	2.33	0.44	0.72	0.17	3.14	0.68
18.5-29.99	Reference				Reference				Reference			
30-34.99	1.808	1.127	2.9	0.014*	1.203	0.787	1.839	0.394	1.319	0.835	2.082	0.235
35-39.99	3.357	1.902	5.925	< 0.001*	1.699	0.974	2.964	0.062	2.237	1.269	3.943	0.005*
> 40	5.552	2.748	11.218	< 0.001*	1.857	0.868	3.97	0.111	4.144	2.038	8.427	< 0.001*

*Denotes significant value, $P < 0.05$. BMI: body mass index; OR: odds ratio; CI: confidence interval

increased, although differences were more exaggerated in the autologous reconstruction group [Tables 3 and 4]. This finding was confirmed on both univariate and multivariate analysis.

Multiple medical complications increased as patient weight increased, in both reconstructive groups. Specifically, bleeding requiring transfusion and DVT were elevated in the prosthetic group; and PE, acute renal failure, and sepsis/septic shock were elevated in the autologous group. On multivariate analysis, while medical complication rates were elevated, data only reached significance for the prosthetic in moderate obesity group (OR 2.752, $P = 0.009$). Finally, reoperation rates were significantly elevated in both stratified obesity cohorts, with a stronger relationship in the autologous reconstruction group.

Previous literature has suggested that underweight patients suffer from elevated rates of surgical complications, and specific catastrophic medical complications (including death). While we found elevated rates of surgical complications in the autologous reconstruction group and medical complications in the prosthetic reconstruction group, we otherwise found a decreased incidence of surgical and medical complications, reoperation and death in underweight patients. However, none of these findings were significant on multivariate analysis. These findings suggest that, as with previous studies, patient groups may be too small to yield significant differences. Given the relatively small size of underweight breast reconstruction patients captured in NSQIP, it is not possible to discern between patients with lean muscle mass, versus those with chronic disease and multiple comorbidities. As the dataset continues to grow, it will be possible to separate these groups, thus increasing the value of data extracted from the dataset. However, at this time, our findings suggest that

all forms of breast reconstruction are safe in underweight patients. Additionally, there does not appear to be a role for the “obesity paradox” in breast reconstruction.

In conclusion, this study represents the only review to date of post-mastectomy breast reconstruction, using a weight-stratification system. Increasing obesity is associated with significantly increased risk of adverse events (AE's) in the first 30 days following breast reconstruction. The added risks translate into higher rates of overall morbidity, regardless of reconstructive modality. On multivariable analysis of over 4,600 patients, there were no significant differences in the rates of adverse events between underweight patients (BMI < 18.5) and their reference-weight counterparts, in spite of a significant increase in surgical and medical complication rates in underweight patients on univariate analysis. Based on the overall analysis, we conclude that while obese patients are at greater risk when undergoing breast reconstruction, with appropriate counseling breast reconstruction should continue to be offered to these patients.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. World Health Organization. Fact sheet No 311: Obesity and overweight. Geneva:World Health Organization. 2012.
2. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity in the United States, 2009-2010. *NCHS Data Brief* 2012;(82):1-8.
3. Russell GV, Pierce CW, Nunley L. Financial implications of obesity. *Orthop Clin North Am* 2011;42:123-7.
4. Arterburn, DE, Maciejewski ML Tsevat J. Impact of morbid obesity on medical expenditures in adults. *Int J Obes (Lond)* 2005;29:334-9.

5. Abedi NN, Davenport DL, Xenos E, Sorial E, Minion DJ, Endean ED. Gender and 30-day outcome in patients undergoing endovascular aneurysm repair (EVAR): an analysis using the ACS NSQIP dataset. *J Vasc Surg* 2009 Sep;50:486-91.
6. Mullen JT, Davenport DL, Hutter MM, Hosokawa PW, Henderson WG, Khuri SF, Moorman DW. Impact of body mass index on perioperative outcomes in patients undergoing major intra-abdominal cancer surgery. *Ann Surg Oncol* 2008;15:2164-72.
7. Mullen JT, Moorman DW, Davenport DL. The obesity paradox: body mass index and outcomes in patients undergoing nonbariatric general surgery. *Ann Surg* 2009;250:166-72.
8. Tremblay A, Bandi V. Impact of body mass index on outcomes following critical care. *Chest* 2003;123:1202-7.
9. O'Brien JM Jr, Phillips GS, Ali NA, Lucarelli M, Marsh CB, Lemeshow S. Body mass index is independently associated with hospital mortality in mechanically ventilated adults with acute lung injury. *Crit Care Med* 2006;34:738-44.
10. Curtis JP, Selter JG, Wang Y, Rathore SS, Jovin IS, Jadbabaie F, Kosiborod M, Portnay EL, Sokol SI, Bader F, Krumholz HM. The obesity paradox: body mass index and outcomes in patients with heart failure. *Arch Intern Med* 2005;165:55-61.
11. Galanos AN, Pieper CF, Kussin PS, Winchell MT, Fulkerson WJ, Harrell FE Jr, Teno JM, Layde P, Connors AF Jr, Phillips RS, Wenger NS. Relationship of body mass index to subsequent mortality among seriously ill hospitalized patients. SUPPORT Investigators. The Study to Understand Prognoses and Preferences for Outcome and Risks of Treatments. *Crit Care Med* 1997;25:1962-8.
12. Fleischmann E, Teal N, Dudley J, May W, Bower JD, Salahudeen AK. Influence of excess weight on mortality and hospital stay in 1346 hemodialysis patients. *Kidney Int* 1999;55:1560-7.
13. Fonarow GC, Srikanthan P, Costanzo MR, Cintron GB, Lopatin M; ADHERE Scientific Advisory Committee and Investigators. An obesity paradox in acute heart failure: analysis of body mass index and inhospital mortality for 108,927 patients in the Acute Decompensated Heart Failure National Registry. *Am Heart J* 2007;153:74-81.
14. Gruber L, Weissman NJ, Waksman R, Fuchs S, Deible R, Pinnow EE, Ahmed LM, Kent KM, Pichard AD, Suddath WO, Satler LF, Lindsay J Jr. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? *J Am Coll Cardiol* 2002;39:578-84.
15. Gurm HS, Brennan DM, Booth J, Tcheng JE, Lincoff AM, Topol EJ. Impact of body mass index on outcome after percutaneous coronary intervention (the obesity paradox). *Am J Cardiol* 2002;90:42-5.
16. Christian CK, Niland J, Edge SB, Ottesen RA, Hughes ME, Theriault R, Wilson J, Hergrueter CA, Weeks JC. A multi-institutional analysis of the socioeconomic determinants of breast reconstruction: a study of the National Comprehensive Cancer Network. *Ann Surg* 2006;243:241-9.
17. Alderman AK, Wilkins EG, Kim HM, Lowery JC. Complications in postmastectomy breast reconstruction: two-year results of the Michigan Breast Reconstruction Outcome Study. *Plast Reconstr Surg* 2002;109:2265-74.
18. Atisha DM, Alderman AK, Kuhn LE, Wilkins EG. The impact of obesity on patient satisfaction with breast reconstruction. *Plast Reconstr Surg* 2008;121:1893-9.
19. Chapman GW Jr, Mailhes JB, Thompson HE. Morbidity in obese and nonobese patients following gynecologic surgery for cancer. *J Natl Med Assoc* 1988;80:417-20.
20. Foley K, Lee RB. Surgical complications of obese patients with endometrial carcinoma. *Gynecol Oncol* 1990;39:171-4.
21. Jiganti JJ, Goldstein WM, Williams CS. A comparison of the perioperative morbidity in total joint arthroplasty in the obese and nonobese patient. *Clin Orthop Relat Res* 1993;175-9.
22. Stern SH, Insall JN. Total knee arthroplasty in obese patients. *J Bone Joint Surg Am* 1990;72:1400-4.
23. Vinton AL, Traverso LW, Jolly PC. Wound complications after modified radical mastectomy compared with tylectomy with axillary lymph node dissection. *Am J Surg* 1991;161:584-8.
24. Thomas EJ, Goldman L, Mangione CM, Marcantonio ER, Cook EF, Ludwig L, Sugarbaker D, Poss R, Donaldson M, Lee TH. Body mass index as a correlate of postoperative complications and resource utilization. *Am J Med* 1997;102:277-83.
25. Klasen J, Junger A, Hartmann B, et al. Increased body mass index and peri-operative risk in patients undergoing non-cardiac surgery. *Obes Surg* 2004;14:275-81.
26. Dindo D, Muller MK, Weber M, Clavien PA. Obesity in general elective surgery. *Lancet* 2003;361:2032-5.
27. Kim EK, Eom JS, Hwang CH, Ahn SH, Son BH, Lee TJ. Immediate transverse rectus abdominis musculocutaneous (TRAM) flap breast reconstruction in underweight Asian patients. *Breast Cancer* 2014;21:693-7.
28. Kroll SS. Bilateral breast reconstruction in very thin patients with extended free TRAM flaps. *Br J Plast Surg* 1998;51:535-7.
29. Lee JH, Lee PK, Oh DY, Rhie JW, Ahn ST. Subpectoral-subfascial breast augmentation for thin-skinned patients. *Aesthetic Plast Surg* 2012;36:115-21.
30. Kronowitz SJ, Robb GL, Youssef A, Reece G, Chang SH, Koutz CA, Ng RL, Lipa JE, Miller MJ. Optimizing autologous breast reconstruction in thin patients. *Plast Reconstr Surg* 2003;112:1768-78.
31. Figus A, Fioamonti P, Ramakrishnan V. Stacked free SIEA/DIEP flap for unilateral breast reconstruction in a thin patient with an abdominal vertical midline scar. *J Reconstr Microsurg* 2007;23:523-5.
32. Kitcat M, Molina A, Meldon C, Darhouse N, Clibbon J, Malata CM. A Simple Algorithm for Immediate Postmastectomy Reconstruction of the Small Breast-A Single Surgeon's 10-Year Experience. *Eplasty* 2012;12:e55.
33. Albornoz CR, Cordiero PG, Farias-Eisner G, Mehrara BJ, Pusic AL, McCarthy CM, Disa JJ, Hudis CA, Matros E. Diminishing relative contraindications for immediate breast reconstruction. *Plast Reconstr Surg* 2014;134:e363-9.
34. Nguyen KT, Hanwright PJ, Smetona JT, Hirsch EM, Seth AK, Kim JY. Body mass index as a continuous predictor of outcomes after expander-implant breast reconstruction. *Ann Plast Surg* 2014;73:19-24.

Commentary

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The association between body mass index (BMI) and surgical complications has been of great interest in recent years given the rise of obesity worldwide.^[1] Current evidence shows that there is a strong correlation between obesity and the rate of complications following breast reconstruction, such as wound dehiscence, superficial wound infection, and graft or flap loss.^[2] Although malnutrition has been identified as a risk factor for poor wound healing and the effects of reconstruction,^[3] no articles have examined the impact of low BMI on the outcomes of breast reconstruction.

The authors present a retrospective study involving 4,676 prosthetic or autologous breast reconstruction patients (136 of which were underweight) recorded on the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database between 2006 and 2011. The authors show that underweight patients undergoing autologous reconstruction have higher total and surgical complication rates, but lower reoperation and medical complication rates whereas, underweight patients undergoing prosthetic reconstruction have higher medical complication rates, but lower reoperation, total and surgical complication rates. However, none of these findings are statistically significant on multivariate analysis.

Despite the great efforts by the authors to answer the very important question of whether low BMI has impact on breast reconstruction, there are certain limitations that readers should consider when interpreting the results of this study. Firstly, the spectrum of breast cancer therapy

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produces a varied range in complication rates and types: simple mastectomy (4-5.72%),^[4,5] skin-sparing mastectomy (15.1-64.2%),^[6,7] and nipple-sparing mastectomy (12.4-22%).^[8,9] Each modality has benefits and short falls, and some of the complications might be enhanced by a low BMI and poor nutrition such as skin flap necrosis, with the rate reported as 0-6.3% for skin-sparing mastectomy,^[6] and 5.2-9.5% for nipple-sparing mastectomy,^[9,10] or nipple-necrosis with the rate reported as 4.4-9.2%^[8,9,11] in nipple-sparing mastectomy. Given the heterogeneity in complications rates, it would have been interesting to see if the effect of the type of mastectomy was a confounding factor in the results. Furthermore, breast conservation therapy (BCT) accounts for the majority of breast cancer treatment in the United States^[12] and the readers have to be mindful that the conclusions drawn by this article do not apply to partial breast reconstruction. Therefore, future research warrants inclusion and analysis of each type of breast cancer therapy modality.

Secondly, the stratification of patients into prosthesis and autologous categories does not take into account the heterogeneity of complications among the different types of breast reconstruction procedures. It is known that the rates of complications differ among patients who undergo pedicled flaps (58.5-67.9%) and those who undergo free flaps (17.7-26.9%).^[13,14] Furthermore, it is known that patients' BMI can have an impact on the rates of complications like skin flap necrosis, wound dehiscence, and graft and prosthesis loss.^[2,15] Even within each type of reconstruction, there is a variation among the selected flap. For example, a meta-analysis by Wang *et al.*^[1] revealed a lower rate of fat necrosis (RR 0.502) and a higher rate of abdominal hernias (RR 2.354) in muscle-sparing transverse rectus abdominis myocutaneous (TRAM) flap than in deep inferior epigastric perforator flap. Therefore, it is challenging to group pedicled flaps (e.g. latissimusdorsi, or TRAM) with free flaps (e.g. TRAM, muscle-sparing TRAM, DIEP), because variation in complication rates exists among them, and each complication may be affected differently by low BMI. Unfortunately, ACS-NSQIP does not allow distinguish between specific free flap procedures, since all free flap reconstructions are grouped under the same CPT code, making it impossible to perform subgroup analysis. These limitations restrict the authors' ability to accurately assess the impact of low BMI in breast reconstruction, since too much variation exists between breast reconstruction modalities. Therefore, future research warrants inclusion and analysis of each type of breast reconstruction modality. Most importantly, the authors omitted in the analysis, certain key complications like hematoma, seroma, fat necrosis, nipple necrosis, skin flap necrosis, and donor site complications, which are known issues of breast reconstruction procedures^[1,15,16] and whose incidence could be affected by the patient's BMI.^[17] The ACS-NSQIP dataset tracks certain complications for only 30 days and unfortunately does not include some very important and most relevant complications. A lack of data may have resulted in an under-reporting of complications in this study. Also, Epelboym *et al.*^[18] reported discordance in 27.3% of the time in complication reporting by the ACS-NSQIP including: missed complications, reported complications that did not

occur, and misclassification of postoperative events. Once again, readers have to be mindful of these significant limitations when drawing conclusions.

As illustrated by the authors, the small sample size confirms that breast reconstruction in patients with low BMI is not very common and an attempt to establish the etiology of being underweight unfortunately did not reach statistical significance. A patient with low BMI does not necessarily entail malnourishment. In fact, an obese patient may well be malnourished despite the high BMI. Studies have shown that malnourished patients often require longer hospitalizations, have more postoperative complications, and have delayed wound and fracture healing compared with well-nourished patients.^[19,20] For this reason, all patients regardless of their BMI should be evaluated for their nutritional status, and ensure adequate preoperative calorie, protein, vitamin, and mineral intake. This helps optimization of the patient's nutritional status and minimization of postoperative complications.

Low BMI is a poorly discussed topic and the limited number of eligible patients makes it challenging to obtain statistically significant results. We commend the authors for this study and we believe it provides a great starting point for debate. But because of the limitations (mostly dictated by the ACS-NSQIP data), we feel that definitive conclusions cannot be drawn from this study, but look forward to future research to evaluate the impact of low BMI in the varied spectrum of breast reconstruction.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Wang XL, Liu LB, Song FM, Wang QY. Meta-analysis of the safety and factors contributing to complications of MS-TRAM, DIEP, and SIEA flaps for breast reconstruction. *Aesthetic Plast Surg* 2014;38:681-91.
2. Fischer JP, Nelson JA, Kovach SJ, Serletti JM, Wu LC, Kanchwala S. Impact of obesity on outcomes in breast reconstruction: analysis of 15,937 patients from the ACS-NSQIP datasets. *J Am Coll Surg* 2013;217:656-64.
3. Arnold M, Barbul A. Nutrition and wound healing. *Plast Reconstr Surg* 2006;117:S42-58.
4. El-Tamer MB, Ward BM, Schiffner T, Neumayer L, Khuri S, Henderson W. Morbidity and mortality following breast cancer surgery in women: national benchmarks for standards of care. *Ann Surg* 2007;245:665-71.
5. De Blacam C, Ogunleye AA, Momoh AO, Colakoglu S, Tobias AM, Sharma R, Houlihan MJ, Lee BT. High body mass index and smoking predict morbidity in breast cancer surgery: a multivariate analysis of 26,988 patients from the national surgical quality improvement program database. *Ann Surg* 2012;255:551-5.
6. Kim Z, Kang SG, Roh JH, Park JH, Lee J, Kim S, Lim CW, Lee MH. Skin-sparing mastectomy and immediate latissimusdorsi flap reconstruction: a retrospective analysis of the surgical and patient-reported outcomes. *World J Surg Oncol* 2012;10:259.
7. Omranipour R, Bobin JY, Esouyeh M. Skin sparing mastectomy and immediate breast reconstruction (SSMIR) for early breast cancer: eight years single institution experience. *World J Surg Oncol* 2008;6:43.
8. Endara M, Chen D, Verma K, Nahabedian MY, Spear SL. Breast reconstruction following nipple sparing mastectomy: a systematic review

- of the literature with pooled analysis. *Plast Reconstr Surg* 2013;132:1043-54.
9. Colwell AS, Tessler O, Lin AM, Liao E, Winograd J, Cetrulo CL, Tang R, Smith BL, Austen WG Jr. Breast reconstruction following nipple-sparing mastectomy: predictors of complications, reconstruction outcomes, and 5-year trends. *Plast Reconstr Surg* 2014;133:496-506.
 10. Piper M, Peled AW, Foster RD, Moore DH, Esserman LJ. Total skin-sparing mastectomy: a systematic review of oncologic outcomes and postoperative complications. *Ann Plast Surg* 2013;70:435-7.
 11. Endara M, Chen D, Verma K, Nahabedian MY, Spear SL. The role of nipple-sparing mastectomy in breast cancer: a comprehensive review of the literature. *Plast Reconstr Surg* 2013;131:969-84.
 12. Kummerow KL, Du L, Penson DF, Shyr Y, Hooks MA. Nationwide trends in mastectomy for early-stage breast cancer. *JAMA Surg* 2015;150:9-16.
 13. Spear SL, Newman MK, Bedford MS, Schwartz KA, Cohen M, Schwartz JS. A retrospective analysis of outcomes using three common methods for immediate breast reconstruction. *Plast Reconstr Surg* 2008;122:340-7.
 14. Garvey PB, Buchel EW, Pockaj BA, Casey WJ 3rd, Gray RJ, Hernández JL, Samson TD. DIEP and pedicled TRAM flaps: a comparison of outcomes. *Plast Reconstr Surg* 2006;117:1711-9.
 15. Davies K, Allan L, Roblin P, Ross D, Farhadi J. Factors affecting post-operative complications following skin sparing mastectomy with immediate breast reconstruction. *Breast* 2011;20:21-5.
 16. Hanwright PJ, Davila AA, Hirsch EM, Khan SA, Fine NA, Bilimoria KY, Kim JY. The differential effect of BMI on prosthetic versus autogenous breast reconstruction: a multivariate analysis of 12,986 patients. *Breast* 2013;22:938-45.
 17. Kantak NA, Koolen PG, Martin C, Tobias AM, Lee BT, Lin SJ. Are patients with low body mass index candidates for deep inferior epigastric perforator flaps for unilateral breast reconstruction? *Plast Reconstr Surg* 2015;135:44-5.
 18. Epelboym I, Gawlas I, Lee JA, Schroppe B, Chabot JA, Allendorf JD. Limitations of ACS-NSQIP in reporting complications for patients undergoing pancreatectomy: underscoring the need for a pancreas-specific module. *World J Surg* 2014;38:1461-7.
 19. Jie B, Jiang ZM, Nolan MT, Zhu SN, Yu K, Kondrup J. Impact of preoperative nutritional support on clinical outcome in abdominal surgical patients at nutritional risk. *Nutrition* 2012;28:1022-7.
 20. Koval KJ, Maurer SG, Su ET, Aharonoff GB, Zuckerman JD. The effects of nutritional status on outcome after hip fracture. *J Orthop Trauma* 1999;13:164-9.

Bi-plane breast augmentation: a case series supporting its use and benefits

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ABSTRACT

Aim: Breast augmentation has traditionally been performed in either the subglandular or submuscular plane. Dual plane augmentation has been described before and captures the advantages of both of these techniques but reduces the trade-offs. The biplane muscle splitting technique adopts the similar advantages seen with the dual plane method without the need for extensive costal muscle fibre release at the infra-mammary fold. **Methods:** Thirty-five patients underwent bilateral breast augmentation using the biplanar technique from November 2007 to December 2008. All operations were performed by the senior author and followed up prospectively. **Results:** Follow up ranged from 9 months to 21 months. All of the patients achieved precise and reliable implant placement with no revisions or patient dissatisfaction. There have been no cases of implant misplacement/migration; synmastia, dynamic breast deformity, capsular contracture or infections. A single case of unilateral haematoma occurred early in the series. **Conclusion:** Our operative cases and early follow-up supports the use of this novel biplanar technique for breast augmentation. It optimizes the advantages of subglandular and submuscular breast augmentation with simpler dissection and less complications than other submuscular techniques. It can be used in a wide variety of breast types with predictable results.

Key words:

Biplane; dual-plane; breast augmentation; submuscular implants; muscle splitting augmentation

INTRODUCTION

The use of a dual plane for breast augmentation is not a new concept.^[1] Its use in primary breast augmentation is becoming more popular and can be performed through various different approaches.^[2] Indeed it is becoming a recognised method for the correction of established capsular contracture in secondary breast augmentation.^[3] The concept of the biplane muscle splitting technique was only introduced by Khan^[4] in 2007. It differs from the aforementioned dual plane technique as the implant is positioned both in front of and behind pectoral major simultaneously without the need of muscle release. Here

we present a case series of women who have all undergone bilateral breast augmentation using the same technique that Khan describes. This study supports and further reinforces the benefits and advantages of this novel technique.

METHODS

Thirty-five patients underwent bilateral breast augmentation using the biplanar technique from November 2007 to December 2008. All operations were performed by the

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senior author and followed up prospectively.

Surgical technique: Midline is drawn from sternal notch to xiphisternum as a reference point and inframammary incision is marked preoperatively with patient in standing position.

The procedure is performed in general anaesthetic with muscle relaxation with the patient in a supine position with their arms abducted. The marked mid-line is used for reference and future breast pocket is marked. Approximate positions of the origins of pectoralis major are marked and a line, extending between the junction of middle and lower third of sternum and anterior axillary fold is drawn, roughly level with the lower border of the areola. The line represents the level where the muscle splitting incision takes place. The infra-mammary incisions are made approximately 5 cm in length and positioned laterally to conceal them in the infra-mammary fold [Figure 1].

Dissection first takes place in the sub-glandular plane using cutting diathermy and continues superiorly up to the level of the nipple-areola complex superiorly and between the junction of middle and lower third of sternum medially going up and laterally to the anterior axillary fold [Figure 2].

The subpectoral pocket is accessed by separating the muscle fibres close to their origin at the previously marked level and the pocket is created by blunt dissection [Figure 3]. The medial two-thirds of pectoralis major are split in line with the muscle fibres maintaining the lateral portion of the muscle, which locks the implant and helps prevent lateral or

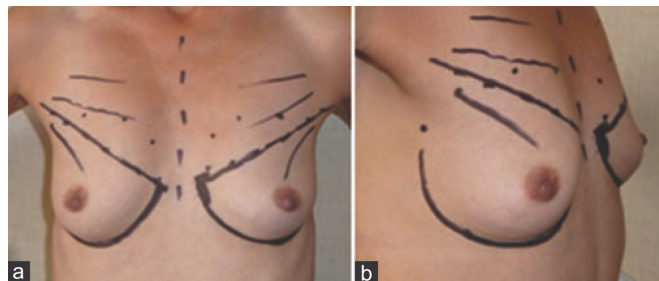


Figure 1: Preoperative skin markings

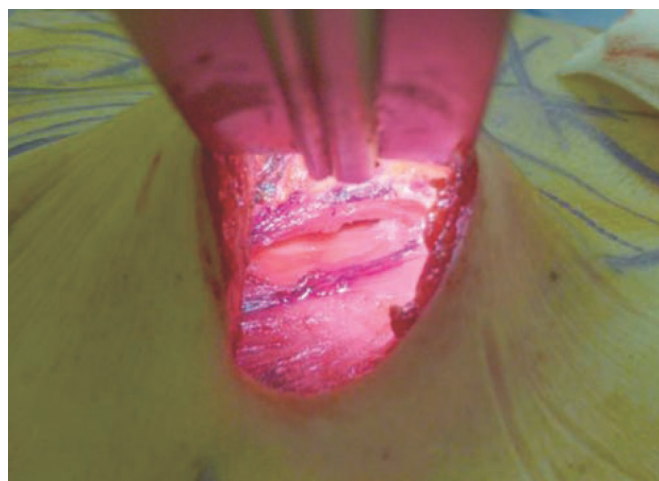


Figure 3: The muscle-splitting incision is made and access to the subpectoral pocket is gained

upward migration. The implant is inserted with the superior portion in the subpectoral plane and the incision closed occasionally with the placement of a drain.

RESULTS

Follow up ranged from 9 months to 21 months. All of the patients achieved precise and reliable implant placement with no revisions or patient dissatisfaction. There have been no cases of implant misplacement/migration; synmastia, dynamic breast deformity, capsular contracture or infections. A single case of unilateral haematoma occurred early in the series.

DISCUSSION

The use of a dual plane for breast augmentation has been well documented in the past by Tebbetts.^[1] Dual plane is an extension of partial sub muscular technique where muscle release is performed depending on the presence of the skin envelope. The bi-plane method, or muscle-splitting technique, has been described by Khan in 2007.^[4] The submuscular positioning of the implant offers less capsular contracture rate.^[5] This method involves splitting the pectoralis major



Figure 2: Arrows point to the level where the muscle-splitting incision is made and lower unmarked area represents the extent of subglandular pocket

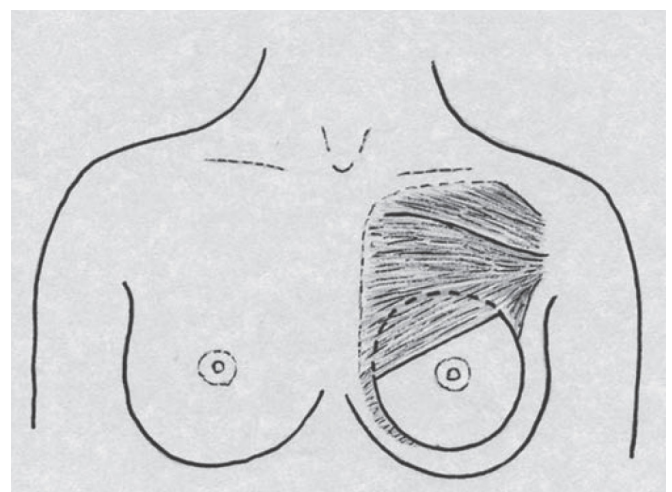


Figure 4: Anterior view showing position of the implant with the inferior portion anterior to pectoralis major. The subpectoral plane is accessed by splitting the muscle in the line of its fibres, lateral conjoint pectoralis prevents lateral and superior displacements

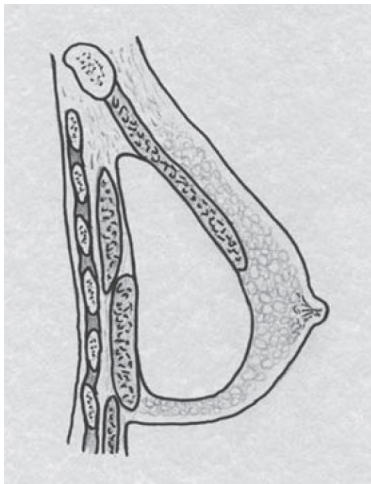


Figure 5: Sagittal view showing the prosthesis *in-situ*. Anterior to the implant is the superior portion of pectoralis major. Posterior to the implant lies pectoralis minor and the inferior portion of pectoralis major

in the line of its fibres to gain access to the submuscular plane as opposed to division of the pectoralis major along the infra-mammary fold [Figure 4]. The technique has been described for primary^[6-9] and secondary procedures.^[10-12] The technique not only reduces the dynamic deformity due to absence of muscle release but also has been described to correct dynamic deformity associated with partial submuscular or dual plane augmentation mammoplasty.^[13,14] In Muscle splitting Biplane, the pectoralis lies behind and in front of the implant at the same time and without the muscle release [Figure 5].

As Tebbetts has described, the use of a dual plane technique reduces the trade-offs commonly seen in subglandular or subpectoral implant placement. With subglandular placements there is an increased risk of a visible or palpable edge of the prosthesis, especially in the upper pole where there may be insufficient soft tissue coverage. There is also possibly an increased risk of capsular contracture leading to pain or breast deformity.

Although, historically, subpectoral breast implants have been reported as having lower incidences of capsular contracture,^[5] the technique is not without its disadvantages. There is a higher incidence of implant migration, dynamic breast deformity and less precise control of breast shape.^[1]

Use of the biplane technique compared with subglandular placement affords more adequate soft tissue coverage in the upper pole with a less stark transition between skin and implant. A long term review of a large study has shown a 6-7 fold reduction in the over rate of revision surgeries, when Muscle Splitting Biplane augmentation was compared with conventional sub glandular and partial submuscular augmentation mammoplasty.^[15] The submuscular positioning of implants in biplane also offers reduces incidence of capsular contracture.^[5] In our series there have been no cases of capsular contracture so far, however, a larger series with well monitored long term follow up will be required for an actual rate of capsular contracture.

The muscular attachment and portion of pectoralis major

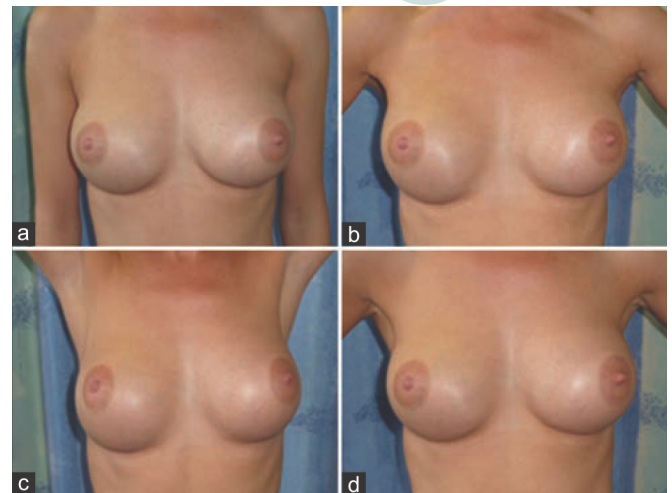


Figure 6: Postoperative anterior views of a young woman in (a) relaxed position; (b) hands on hips; (c) arms fully abducted; and (d) forced contraction of pectoralis showing no dynamic muscle deformity

used to cover the superior pole of the implant has not been shown to cause any significant muscle contraction associated deformities as may be the case with total submuscular or dual plane techniques [Figure 6]. In comparison with partial submuscular or dual plane implant positioning, where the muscle is released from the sternocostal margin, the biplane technique has the added advantage of less incidences of dynamic breast deformity due to absence of the release of the muscle.^[4,13,14] The muscle splitting technique does not require division of any of these fibres so that they are still available for functional use. The communication between the submuscular and sub glandular sections of the pocket allows one unit feel of the breast. The sub glandular position of the implant in the lower pole also allows a more natural and three-dimensional results with the implant covered by the muscle in the ever-changing upper part of the breast.

Intact sternal origin of the pectoralis muscle fibres acts as a fence preventing the implant pockets join over the sternum, thus, eliminating the risk of synmastia. When sternal margins of pectoralis are divided in conventional or dual plane pockets, the two pockets may communicate over the sternum resulting in synmastia. Subglandular positioning of implant with medial quadrant undermining may result in similar complication. The correction of sub glandular synmastia can be corrected by simply converting the pocket in to muscle splitting biplane.^[12] To date there have been no cases of synmastia and all of the patients have had an aesthetically pleasing cleavage.

As the muscle-splitting technique only divides the medial two-thirds of pectoralis major, this maintains the lateral portion of pectoralis major. The inferior retro-prosthetic portion conjoins with the superior pre-prosthetic portion of pectoralis major to locks the lateral part of the implant and helps prevent superior and lateral displacement [Figure 4]. There have not been any reported cases of implant displacement or migration in our series.

In comparison to submuscular implant placement, the biplane technique affords the same adequacy of soft tissue cover in the superior pole, but in addition better fill and

projection in the lower pole. This is especially true in thin women, patients with constricted lower poles or excessive skin envelopes. Conventional submuscular positioning of implants in such patients can lead to a double-bubble deformity. There have been no identifiable cases of this complication in our series. The biplane technique can be used in cases of grade I and II ptosis with satisfactory lower pole fill and projection. The senior author has not used this technique in more severe cases of ptosis.

In conclusion, our operative cases and early follow-up supports the use of this novel biplanar technique for breast augmentation. It optimizes the advantages of subglandular and submuscular breast augmentation with simpler dissection and less complications than other submuscular techniques. It can be used in a wide variety of breast types with predictable results.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Tebbetts JB. Dual plane breast augmentation: optimizing implant-soft-tissue relationships in a wide range of breast types. *Plast Reconstr Surg* 2001;107:1255-72.
2. Luan J, Mu D, Mu L. Transaxillary dual-plane augmentation mammoplasty: experience with 98 breasts. *J Plast Reconstr Aesthet Surg* 2009;62:1459-63.
3. Spear SL, Carter ME, Ganz JC. The correction of capsular contracture by conversion to "dual-plane" positioning: technique and outcomes. *Plast Reconstr Surg* 2003;112:456-66.
4. Khan UD. Muscle-splitting breast augmentation: a new pocket in a different plane. *Aesth Plast Surg* 2007;31:553-8.
5. Biggs TM, Yarish RS. Augmentation mammoplasty: a comparative analysis. *Plast Reconstr Surg* 1990;85:368-72.
6. Khan UD. Vertical scar mastopexy with cat's tail extension for prevention of skin redundancy: an experience with 17 consecutive cases following mastopexy and mastopexy with breast augmentation. *Aesthetic Plast Surg* 2012;36:303-7.
7. Khan UD. Augmentation mastopexy in muscle-splitting biplane: outcome of first 44 consecutive cases of mastopexies in a new pocket. *Aesth Plast Surg* 2010;34:313-21.
8. Khan U D. Multiplane technique for simultaneous submuscular breast augmentation and internal glandulopexy using inframammary crease incision in selected patients with early ptosis. *Eur J Plast Surg* 2010;34:337-43.
9. Lang Stumpfle R, Figueras Pereira-Lima L, Alves Valiati A, da Silva Mazzini G. Transaxillary muscle-Splitting breast augmentation: experience with 160 Cases. *Aesth Plast Surg* 2012;36:343-8.
10. Khan UD. Combining muscle-splitting biplane with multilayer capsulorrhaphy for the correction of bottoming down following subglandular augmentation. *Eur J Plast Surg* 2010;33:259-69.
11. Khan UD. Subglandular to Muscle Splitting Biplane Conversion for Revision Augmentation Mammoplasty. In: Mugea TT, Schiffmann MA, editors. *Aesthetic Surgery of the Breast*. 1st ed. Berlin: Springer; 2015. p. 535-41.
12. Khan UD. Correction of acquired synmastia with of with muscle-splitting biplane implant replacement. *Aesth Plast Surg* 2009;33:605-10.
13. Khan UD. Dynamic breasts: a common complication following partial submuscular augmentation and its correction using muscle-splitting biplane technique. *Aesth Plast Surg* 2009;33:353-60.
14. Khan UD. High transverse capsuloplasty for the correction of malpositioned implants following augmentation mammoplasty in partial submuscular plane. *Aesth Plast Surg* 2012;36:590-9.
15. Khan UD. Muscle-splitting, subglandular and partial submuscular augmentation mammoplasties: a 12-year retrospective analysis of 2026 primary cases. *Aesth Plast Surg* 2013;37:290-302.

A long term review of augmentation mastopexy in muscle splitting biplane

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ABSTRACT

Aim: Simultaneous or single stage mastopexy with augmentation is challenging, unique and commonly performed by a plastic surgeon. In this procedure pocket for implant placement, marking for envelope reduction and type of implants used can affect the outcome of the procedure. Muscle splitting pocket for mastopexy is a plane described by the author for implant placement with a short term follow up. The use and outcome of the technique is presented with a larger series and a long term follow up to evaluate the efficacy of the procedure. **Methods:** Retrospective data was collected. Augmentation was performed using muscle splitting technique and periareolar, vertical scar and wise pattern were used for skin reduction and mastopexy. A single surgeon performed all procedures. **Results:** In total 108 patients mastopexy with augmentation in muscle splitting technique. The mean age of the patient was 32.2 years (range: 18-67 years) with an average follow up of 4.5 years (range: 3 months to 10 years). All patients had round textured cohesive gel silicone implants with a mean size of 308 cc (range: 200-555 cc). Wound infection was seen in 4 (3.7%), wound breakdown in 7 (6.5%) patients. Drains were used in 25 (23.1%). All patients were treated as day cases and revision surgery was performed in 12 (11.1%). There was no hematoma, deep venous thrombosis (DVT) or nipple areolar complex in the series. **Conclusion:** Simultaneous augmentation mastopexy in muscle splitting pocket can be performed with good aesthetic results along with an acceptable revision rate.

Key words:

Augmentation mastopexy; muscle splitting mastopexy; muscle splitting augmentation; submuscular augmentation mammoplasty

INTRODUCTION

Augmentation mammoplasty for volume enhancement and mastopexy for ptosis correction is commonly performed as a simultaneous procedure by aesthetic plastic surgeons. In this procedure, envelope markings, type of implants and the pocket for implant placement can affect the outcome the result. Breast implants can be placed in front^[1] or behind^[2] the pectoralis muscle. Skin reduction is commonly performed using periareolar,^[3] wise pattern,^[4] vertical scar^[5] or its

modifications.^[6] The two procedures are totally independent of each other.^[7,8] A low complication rate is reported when each component performed separately. However when these two components are done as a simultaneous procedure, it was considered very challenging with a warning to surgeons.^[9] A revision rate of 16.7% was reported when the operation was performed as a single stage procedure

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than revision rates of 8.6% for mastopexy and 10.7% for augmentation mammoplasty performed separately.^[10,11] For this reason single stage augmentation mastopexy remains a very challenging procedure for surgeons and often done in stages. The use of muscle splitting submuscular technique for mastopexy with augmentation with earlier results has been described before.^[7] The current article includes a larger series with longer follow up to compare early and long term results and to evaluate the efficacy of the procedure.

METHODS

Retrospective data was collected using patient's charts. All patients who had simultaneous augmentation mastopexy in muscle splitting biplane using round cohesive gel textured silicone implants performed by author were selected.

All patients were operated under general anesthetic with full muscle relaxation and with their arms abducted and supported at an angle less than 90 degree. A single dose of intravenous cephalosporin was given to all patients at induction time. Periareolar, vertical or wise pattern scars were used for augmentation mastopexy depending on the preoperative measurements and wishes of the patient. Muscle splitting submuscular pocket was used for implant placement and procedure is performed as a day case. Drains were used in the earlier part of the study period. All patients wore support brassiere for three weeks as a routine.

Earlier complications related to wound infection, wound breakdown, haematoma, periprosthetic infection, use of drains and size of the implants were analyzed. Patients who had their implants placed in subglandular or partial submuscular pockets were excluded from the series.

RESULTS

Between 2005 and 2015 augmentation mastopexy was performed in 108 patients. Mean age of the patient was

32.2 years (range: 18-67 years) with an average follow up of 4.5 years (range: 3 months to 10 years). All patients had round textured cohesive gel silicone implants with a mean size of 308 mL (range: 200-555 mL). Mean size of implants in periareolar mastopexy, vertical scar and wise pattern mastopexy was 327 mL (range: 170-555 mL), 277 mL (range: 200-525 mL), 252 mL (range: 200-300 mL) respectively. Nipple-areolar complex (NAC) repositioning were predominantly performed using medially based flaps. Majority of the patient requiring mastopexy presented with varying degree of bilateral class A to C ptosis (66.7%) and a combination of ptosis (17.6%). Mean preoperative suprasternal notch (SN) to NAC distance was 24.3 cm (range: 19-31 cm). Mean neo NAC was marked at 21.4 cm (range: 18.5-25 cm) from suprasternal notch using inframammary crease (IMC) as a reference. Mean postoperative suprasternal notch to NAC distance was 20.8 cm (range: 18-24.5 cm). Mean preoperative NAC to IMC distance was 8.9 cm (range: 4.5-14 cm). Mean postoperative NAC to IMC distance 9.7 cm (range: 6.0-12.5 cm).

Mild to moderate wound infection noted in 4 (3.7%) and minor wound breakdown were seen in 7 (6.5%) patients respectively. Drains were used in 25 (23.1%) and there was no NAC necrosis, hematoma or DVT.

Revision surgery was performed in 12 (11.1%) patients. The most common reason for revision surgery was for redundant skin excision at lower pole (16.7%) and vertical scar touch up (16.7%).

Case I

A 31-year-old admin worker presented with a class C ptosis without a history of breast volume loss, weight loss or pregnancy. On examination her breast cup size was 34 D with a breast width of 15 cm each side. Her sternal notch to NAC distance was 24 cm and NAC to IMC distance of 9 cm respectively. She was interested in going bigger but

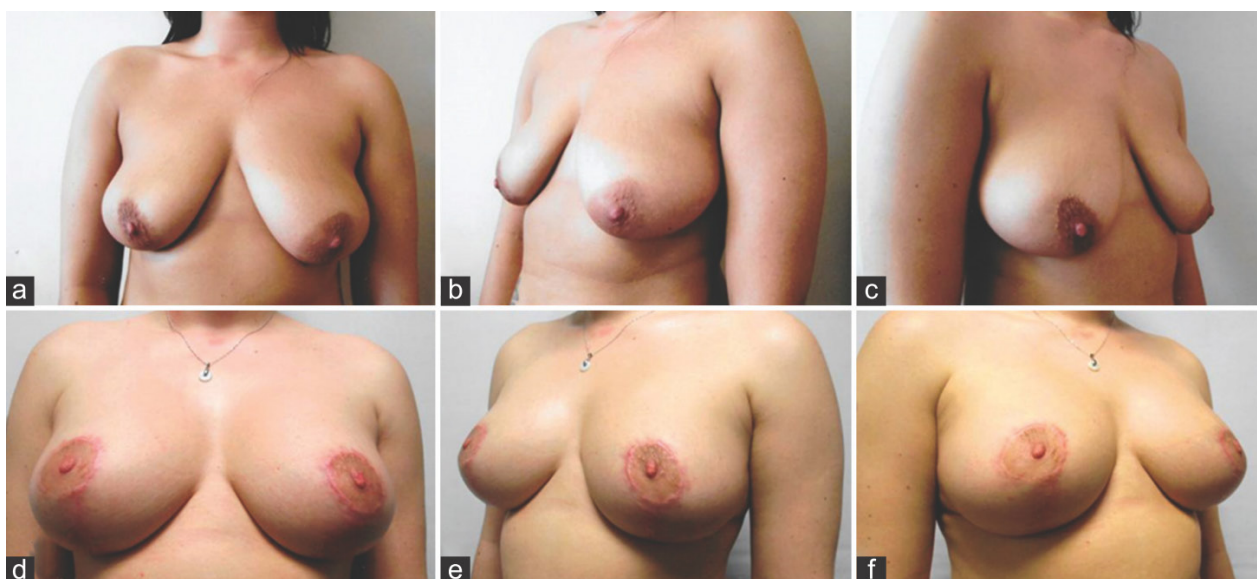


Figure 1: (a-c) Preoperative views of a 31-year-old patient with grade C ptosis; (d-f) four months' postoperative views showing results following vertical scar augmentation mastopexy with 250 mL moderate profile textured round cohesive gel silicone implants

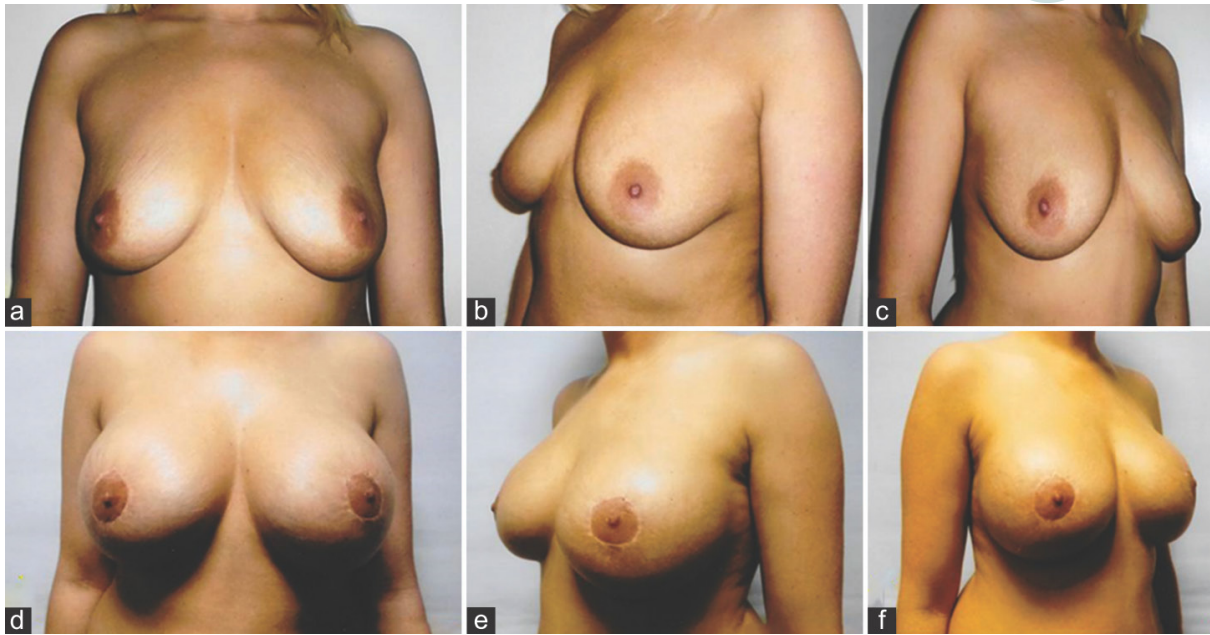


Figure 2: (a-c) Preoperative views of a 29-year old patient with grade B ptosis; (d-f) six months' postoperative views showing results following periareolar augmentation mastopexy with 400 mL high profile textured round cohesive gel silicone implants

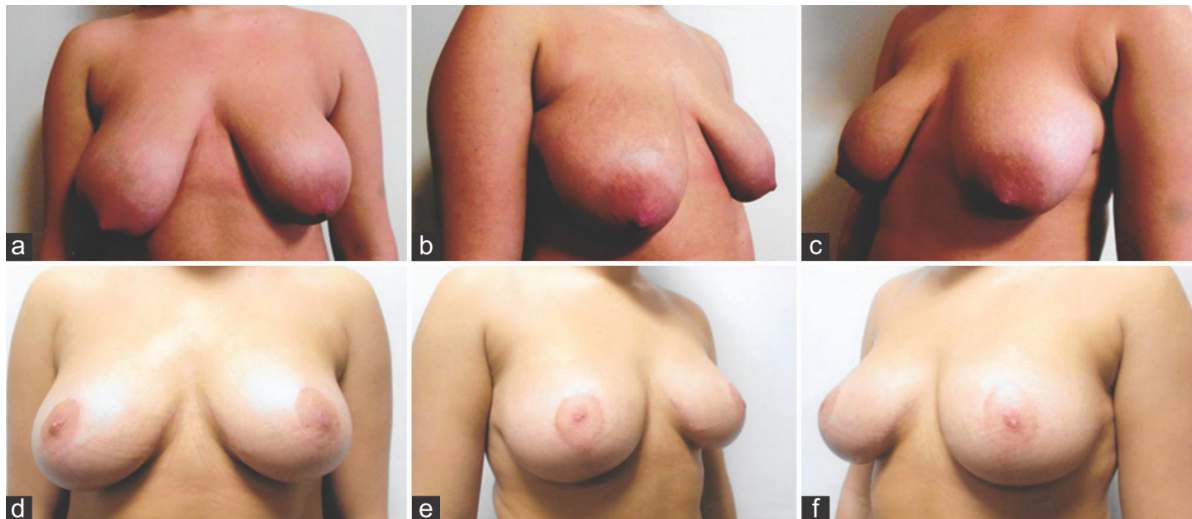


Figure 3: (a-c) Preoperative views of a 20-year old patient with severe grade C ptosis; (d-f) one year's postoperative views showing results following wise pattern augmentation mastopexy using 225 mL moderate profile textured round cohesive gel silicone implants

not more than a cup size and her main concern was the droopy looking breasts [Figure 1a-c]. A vertical scar cat's tail modification was selected for the NAC mobilization and envelope reduction and muscle splitting pocket was selected to place 250 mL Mentor Siltex Cohesive II Moderate profile implants. Her new NAC was marked 20 cm using IMC as the reference. Excised breast tissue weighed 63 g on her right and 69 g on her left side. Her one-year postoperative measurements showed a breast cup size of 34 DD and sternal notch to NAC and NAC to IMC distance of 19.5 cm and 10 cm respectively. Patient did develop bilateral hypertrophic scarring of NAC for which she was initially treated with silicone gel application and later with intra-lesional steroids injections [Figure 1d-f].

Case 2

A 29-year-old beautician and a mother of two children aged 12 and 7, booked a consultation for breast remodeling

surgery. Her breast cup size was measured 36 B along with Class B ptosis. Her preoperative SN to NAC measurements was 23 cm and nipple to IMC distance was measured 8 cm respectively. She used to be 36 DD prior to her pregnancies and was interested in regaining similar breast volume and cup size. To achieve desired cup size, 400 mL round extra high profile Allergan Natrelle INSPIRA TRX textured cohesive silicone implant were selected. Her grade B class ptosis with an adequate skin envelope and a reasonable nipple to inframammary crease position did not require skin envelope reduction; a moderate nipple elevation using periareolar markings was considered reasonable [Figure 2a-c]. Her new NAC was marked at 20.5 cm using IMC as the reference for an adequate new NAC position and projection. She had her breast implants placed in muscle splitting biplane submuscular pocket. Her one year postoperative cup size was 36 DD with sternal notch to NAC distance of 22 cm and NAC to IMC distance of 11 cm [Figure 2d-f].

Case 3

A 20-year-old young adult female was seen for a severe developmental ptosis along with a very noticeable breast size asymmetry. Patient has no history of childbirth or loss of weight or breast volume loss since puberty. She was wearing a 34 E brassiere and her sternal notch to NAC distance was measured 28 cm on her right and 26 cm on her left side with a breast width of 14 cm on both sides. Her NAC to IMC distance was measured 13 cm on her right and 10 cm on her left side respectively with a bilateral Class C ptosis [Figure 3a-c]. Patient was not interested in going any bigger than her current size. Mentor 225 mL Siltex cohesive II moderate profile implants were chosen to be placed in muscle splitting biplane pocket to replace the anticipated breast tissue reduction. Medially based flap with wise pattern markings were used to reduce preoperative inframammary mammary crease distance, NAC repositioning and envelope and breast reduction. New NAC was marked at 20 cm using IMC as a reference, 273 g of tissue was removed from right and 247 g tissue was excised from her left breast. Her ten month cup size was 34 DD with sternal notch to NAC distance of 20 cm, NAC to IMC distance of 9.5 cm bilaterally with good size symmetry [Figure 3d-f].

DISCUSSION

Selection of implant pocket, markings for breast envelope reduction and orientation of flap in simultaneous augmentation mastopexy are independent to each other and can be selected in any combination. The use of combination may affect the outcome with a variable rate of revision surgery.^[7] Despite the various safety issues encountered in the recent past,^[12] cohesive gel silicone breast implant remains the first choice for the volume replacement. In majority of the patients presenting with hypoplasia, requests for volume restoration in early type A ptosis, intended results are successfully achieved using breast implants with well-concealed scars. However more advanced ptosis necessitates the NAC repositioning with some sort of skin reduction. The NAC repositioning can be achieved using periareolar, vertical scar or wise pattern markings depending on the skin excess and degree of ptosis. In current series 66.7% of the patients presented with varying degree of class A to C ptosis and 17.6% of patients presented with varying combination of ptosis on

Table 1: Causes for mastopexy with augmentation in 108 patients

Cause for mastopexy	n (%)
Class A ptosis	6 (5.6)
Class B ptosis	22 (20.4)
Class C ptosis	35 (32.4)
Combination of A and C ptosis	2 (1.9)
Combination of A and B ptosis	3 (2.8)
Combination of B and C ptosis	14 (13)
Pseudoptosis	9 (8.3)
Loose skin	2 (1.9)
Tuberous breasts	2 (1.9)
Others	12 (11.2)

two sides [Table 1]. Selection of markings for skin reduction is paramount to achieve an aesthetically pleasing natural breast with normal breast morphometry, comparable to the results seen following augmentation mammoplasty with an implant alone.^[13] In authors' opinion, use of periareolar or vertical scar markings in patients presenting with excess IMC to NAC measurements are likely to end with bottoming out following simultaneous mastopexy with augmentation. Regardless of the degree of ptosis, type of skin markings for nipple elevation and mastopexy should ideally be based on the preoperative NAC to IMC measurements.^[13] When mastopexy is performed with vertical scar or wise pattern, the use of larger implant size selection may be restricted. Use of larger implant placements with these markings, is likely to result in complication namely skin and wound breakdown mainly due to pressure exerted by implant on reduced skin envelope. In current series, mean size of the implants used in the series is 308 mL but when looked into the mean size of the implants used in three types of mastopexies, the results were interesting. Mean size of the implants was considerably and significantly larger in periareolar mastopexies than the mean size of the implants used in vertical and wise pattern mastopexies [Table 2].

A high complication rate has been reported when the procedure is combined together as simultaneous mastopexy with augmentation.^[14] The author has reported a revision rate of 9% in an earlier report on mastopexy in muscle splitting biplane.^[7] The current series with long-term results have shown a revision rate of 11.1%, up by nearly 2% when compared with author's earlier series. The most common reason for revision being the excision of redundant skin in 2 patients (16.7%) and vertical scar touch up in 2 patients (16.7%) [Table 3]. The revision rate of 11.1% after 10 years follow-up is acceptable and comparable with the published revision rate of 16.7% in simultaneous mastopexy with augmentation and lower than 20% revision rate within five years following augmentation mammoplasty alone using saline-filled implants.^[10]

Table 2: Implants sizes used in three different types of mastopexies

Procedure	Implant Size		
	n	Range (mL)	Mean \pm SD (mL)
Periareolar	54	170-555	327 \pm 73.7
Vertical scar	45	200-525	277 \pm 62.7
Wise pattern	9	230-300	252 \pm 29.9

SD: standard deviation

Table 3: Reasons for revision surgery performed in mastopexy with augmentation

Reason for revision	n (%)
Dog ear bilateral	2 (16.7)
Dog ear unilateral	2 (16.7)
Areolar scar revision	2 (16.7)
Periareolar to vertical scar conversion	2 (16.7)
Nipple level asymmetry	1 (8.3)
Capsular contracture	1 (8.3)
Vertical scar revision	1 (8.3)
Bottoming out	1 (8.3)

The breast implant in augmentation mastopexy can be placed in front or behind the pectoralis muscle. Muscle splitting pocket, where implant lies in front and behind the muscle, has been described for augmentation mammoplasty and simultaneous mastopexy with augmentation.^[7,15] The pocket provides muscle cover to the implant in the upper part of the breast leaving lower split pectoralis behind the implant without being detached from the ribs. The advantages of this pocket are many and include undisturbed muscle origin that prevents animation deformity, implant gets locked up and laterally in between two split slips of pectoralis preventing implant's upward or lateral displacement. Intact skin and muscle interface in the upper part of the pocket maintain the vascular territories of the perforators arising from the internal mammary and thoracoacromial axis.^[7] These muscular perforators maintain undisturbed blood supply to the NAC flaps and are severed during subglandular pocket increasing vulnerability of NAC flaps. Medially based flap is the author's choice and to date there is no nipple areolar loss due to vascular compromise. The author has reported a revision rate of 1.2% in an earlier report when muscle splitting pocket was used for implant placement in muscle splitting augmentation when compared to 9.6% and 20% revision rate of silicone gel and saline implants respectively.^[10,16,17]

In a previously published article, author has suggested that periareolar mastopexy should best be limited to a breast where there is an inadequate skin envelope with NAC to IMC distance of less than 5 cm.^[13] Vertical scar selection for mastopexy is likely to give best aesthetic appearance when preexisting NAC to IMC distance is between 5-8 cm. In breasts where NAC to IMC distance is 9 cm or more, reduction of the vertical limb of the scars is essential for an acceptable NAC to IMC distance otherwise bottoming out is likely to result. Periareolar mastopexy can allow a larger implant to be placed due to the absence of vertical or vertical and transverse skin resection and can allow a far more freedom of implant size selection. However, periareolar mastopexy should be carefully selected, as it is a nipple elevation procedure rather than a skin reduction procedure. This type of mastopexy is best used in selected patients especially in smaller breasts with deficient lower pole skin regardless of the degree of ptosis or in patients with class A ptosis regardless of the skin envelope. Too ambitious use of periareolar markings in advanced ptosis along with skin excess may results in scar stretching associated with flattened nipple areolar complex and an inadequate skin envelope reduction. A high number of revision surgery is reported when periareolar mastopexy has been used for mastopexy with augmentation.^[10,18] Similarly when vertical mastopexy was used as "All-Season" markings, 28% skin redundancy and persistent ptosis was reported.^[11]

In conclusion, single stage mastopexy with augmentation in muscle splitting biplane pocket along with appropriate use of markings for skin reduction and careful implant size selection keep the complication and revision rate of the revision surgery within an acceptable range.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Biggs TM, Yarish R.S. Augmentation mammoplasty: A comparative analysis. *Plast. Reconstr Surg* 1990;85:368-372
2. Regnault P. Partially submuscular breast augmentation. *Plast Reconstr Surg* 1977;59:72-6.
3. Binelli L. A new periareolar mammoplasty: the "round block" technique. *Aesthetic Plast Surg* 1990;14:93-100.
4. Wise RL. A preliminary report on a method of planning the mammoplasty. *Plast Reconstr Surg* (1946) 1956;17:367-75.
5. Lejour M. Vertical mammoplasty and liposuction of the breast. *Plast Reconstr Surg* 1994;94:100-14.
6. Khan UD. Vertical scar mastopexy with cat's tail extension for prevention of skin Redundancy: an experience with 17 consecutive cases after mastopexy and mastopexy with breast augmentation. *Aesthetic Plast Surg* 2012;36:303-307.
7. Khan UD. Augmentation mastopexy in muscle-splitting biplane: outcome of first 44 consecutive cases of mastopexies in a new pocket. *Aesthetic Plast Surg* 2010;34:313-321.
8. Khan UD. Vertical scar with the bipedicle technique: a modified procedure for breast reduction and mastopexy. *Aesthetic Plast Surg* 2007;31:337-342.
9. Spear S. Augmentation/mastopexy: "Surgeon, beware". *Plast Reconstr Surg* 2003;112:905-6.
10. Stevens WG, Stoker DA, Freman ME, Quardt SM, Hirsch EM, Cohen R. Is one-stage breast augmentation with mastopexy safe and effective? A review of 186 primary cases. *Aesthet Surg J* 2006;26:674-81.
11. Swanson E. Prospective comparative clinical evaluation of 784 consecutive cases of breast augmentation and vertical mammoplasty, performed individually and in combination. *Plast Reconstr Surg* 2013;132:30e-45e.
12. Khan UD. Poly Implant Prothèse (PIP) incidence of device failure and capsular contracture: a retrospective comparative analysis. *Aesthetic Plast Surg* 2013;37:906-13.
13. Khan UD. Aesthetic surgery of the breast. In: Mugea TT, Shiffman MA, editor. Use of nipple-areolar to inframammary crease measurements to reduce bottoming out following augmentation mastopexy. Berlin: Springer; 2015. p. 649-56.
14. Spear SL, Low M, Ducic I. Revision augmentation mastopexy: indications, operations, and outcomes. *Ann Plast Surg* 2003;51:540-6.
15. Khan UD. Muscle-splitting breast augmentation: a new pocket in a different Plane. *Aesthetic Plast Surg* 2007;31:553-558.
16. Khan UD. Muscle-splitting, subglandular, and partial submuscular augmentation mammoplasties: a 12-year retrospective analysis of 2026 primary cases. *Aesthetic Plast Surg* 2013;37:290-302.
17. Calobrace MB, Herdt DR, Cothron KJ. Simultaneous augmentation/mastopexy: a retrospective 5-year review of 332 consecutive cases. *Plast Reconstr Surg* 2013;131:145-56.
18. Stevens WG, Freeman ME, Stoker DA, Quardt SM, Cohen R, Hirsch EM. One-stage mastopexy with breast augmentation: a review of 321 patients. *Plast Reconstr Surg* 2007;120:1674-9.

Augmentation mastopexy and augmentation mammoplasty: an analysis of 1,406 consecutive cases

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ABSTRACT

Aim: Simultaneous augmentation mastopexy is a challenging operation for esthetic plastic surgeons. Complication and revision rates following augmentation mammoplasty or mastopexy are less commonly seen when these two procedures are performed separately. However, when the two procedures are combined, the complication rate is reported exponentially higher when compared with its individual component carried out separately. The current retrospective chart review is a comparative analysis of the two procedures performed by a single surgeon. **Methods:** Retrospective data were collected using patient's charts. All patients who had augmentation mammoplasty (Group A) or simultaneous augmentation with mastopexy (Group B) in muscle splitting biplane using round cohesive gel textured silicone implants by a single surgeon were included. **Results:** A total of 1,406 patients had consecutive augmentation mammoplasty or simultaneous augmentation mastopexy. Augmentation mammoplasty (Group A) included 1,298 and simultaneous augmentation with mastopexy (Group B) had 108 patients, respectively. The mean age of the patients in Group A and B was 29.6 years and 32.2 years, respectively ($P = 0.006$). The mean size of the implants in Group A and B was 340 mL and 308 mL ($P = 0.001$), respectively. Wound infection in Group A and B was seen in 0.6% and 3.7%, respectively. Wound breakdown was seen in 1.1% in Group A as compared to 6.5% in Group B ($P = 0.001$). Revision surgeries were performed in 1.4% and 11.1% of Group A and B, respectively ($P = 0.001$). **Conclusion:** There was a statistically and clinically significant higher rate of complications and revision rate noted in simultaneous augmentation with mastopexy (Group B) as compared to augmentation mammoplasty alone (Group A). However, the rise in complications rate is sum of the complications of the two individual components performed and not exponential.

Key words:

Breast asymmetries, breast ptosis, muscle splitting augmentation, muscle splitting mastopexy, revision augmentation mammoplasty, revision augmentation mastopexy

INTRODUCTION

Augmentation mammoplasty and simultaneous augmentation mastopexy constitute a vast majority of the esthetic procedures.^[1] With the rise in a total number of procedure, a rise in total revisions is expected by a plastic surgeon.^[2] Earlier complications leading to revision

surgery following primary augmentation mammoplasty is generally low with a very high satisfaction rate.^[3] A 3-year revision rate following primary mammoplasty has been reported between 0%, 1.97%, and 15% for silicone and 13.2% for saline filled implants.^[3-6]

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In studies with a follow-up spanning between 6 and 12 years, revision rate has been reported between 0% and 1.2%.^[7,8] However, long-term 25 years study has shown a revision rate of 15.5% following primary augmentation mammoplasty.^[9] On the other hand, revision rate following simultaneous augmentation mastopexy is considerably higher. The reported revision rate may vary from 0%, 16.7%, and 25.8% respectively, depending on the duration of the study and follow-up.^[10-12] In both groups of patients, there is a noticeable time-dependent increase in the revision rate. The current article is an analysis of 10-year data in which 1,406 consecutive cases of augmentation mammoplasty and simultaneous augmentation mastopexy using single technique was reviewed for an early comparative complications and revisions rate. The results confirm that when augmentation mastopexy is carried out as a single procedure, it carries a higher rate of complication when compared with augmentation mammoplasty performed alone. However, the higher number of early complications seen in the combine procedure is the addition of the 2 distinctively individual procedures and not an exponential rise.

METHODS

Retrospective data were collected using patient's charts. All patients who had augmentation mammoplasty and simultaneous augmentation mastopexy in muscle splitting biplane using round cohesive gel textured silicone implants performed by author were selected. Patients were divided in Group A, which included augmentation mammoplasties alone, and Group B, who had simultaneous augmentation mastopexy.

All patients were operated under general anesthetic with full muscle relaxation and with their arms abducted and supported at an angle less than 90°. A single dose of intravenous cephalosporin was given to all patients at induction time. Augmentation mammoplasty is performed using inframammary incision, and periareolar, vertical or wise pattern scars were used for augmentation mastopexy depending on the preoperative measurements and wishes of the patient. Muscle splitting submuscular pocket was used for implant placement and procedure is performed as a day case. Drains were used in the earlier part of the study period. All patients wore support brassiere for 3 weeks as a routine.

Earlier complications related to wound infection, wound breakdown, hematoma, periprosthetic infection, use of drains, and size of the implants between the two groups were compared.

The data analysis was done. The results were given in the text as mean \pm standard deviation for quantitative/continuous variables and percentages for qualitative/categorical variables. Two-tailed independent t-test is used for statistical significance between groups for quantitative/continuous variables and Chi-square/Fischer exact test for qualitative/categorical variables between groups. In all

statistical analysis, only $P < 0.05$ is considered significant.

RESULTS

A total of 1,406 patients had augmentation mammoplasty and augmentation mastopexy in muscle splitting submuscular pocket by a single surgeon using round cohesive gel textured silicone implants. Group A included 1,298 augmentation mammoplasties, and Group B had 108 simultaneous augmentation mastopexy. The mean age of the patients in Group A and B was 29.6 ± 8.62 years (range: 18-67 years) and 32.2 ± 9.50 years (range: 18-67 years), respectively ($P = 0.006$). Mean follow-up was 4.5 years (range: 3 months to 10 years). Mean size of the implants in Group A and B was 340 ± 56.7 mL (range: 200-630 mL) and 308 ± 76.0 mL, respectively (range: 200-555 mL) ($P = 0.001$) [Table 1]. Wound infection in Group A and B was seen in 0.6% and 3.7%, respectively ($P = 0.010$). Wound breakdown was seen in 1.1% in Group A as compared to 6.5% in Group B ($P = 0.001$). Hematoma was seen in 0.9% and 0% in Group A and B, respectively. Drains were used in 5.5% and 23.1% of Group A and Group B, respectively ($P = 0.001$). Revision surgeries were performed in 1.4% and 11.1% of Group A and B patients, respectively ($P = 0.001$). Three patients developed late seromas in augmentation mammoplasty group, and all were treated conservatively without any recurrence. A total of 5 patients were treated for Grade IV capsular contracture, of these patients, 4 (0.32%) belonged to the augmentation mammoplasty and 1 (0.9%) from augmentation mammoplasty. There were no cases of deep venous thrombosis, pulmonary embolism, or death in the series.

DISCUSSION

Simultaneous augmentation mastopexy has been cited as a technically demanding procedure with unpredictable outcome with high nipple and skin flap necrosis, however, a later article by the same author reported satisfactory results.^[13,14]

Complications of augmentation mammoplasty and simultaneous augmentation mastopexy may require a planned or an unplanned theater visit for surgical intervention. Common early complications requiring surgical intervention are hematoma and periprosthetic infection. In current series, the hematoma in Group A was seen in 12 patients (0.9%). There were no hematomas seen in Group B when compared with a rate of 0.6% of hematoma in a large series of simultaneous mastopexy

Table 1: Relative age and implant size distribution between two groups

	Group A (1,298)	Group B (108)	P
Age (years) range, 18-67 (mean \pm SD)	29.6 ± 8.62	32.2 ± 9.50	0.006
Mean implant size (mL) range, (mean \pm SD)	200-630 (340 ± 56.7)	200-555 (308 ± 76)	0.001

SD: standard deviation

with augmentation mammoplasty.^[15]

Periprosthetic infection rate has been reported for primary and secondary mammoplasties, respectively.^[2,16] Wound breakdown of varying degree was less common in augmentation mammoplasty as compared to augmentation mastopexy [Figures 1 and 2, Table 2].

In current series, periprosthetic and wound infection were seen less commonly in augmentation mammoplasty when compared with augmentation mastopexy [Figure 3, Tables 2 and 3].

Implant size selection is an important part of the surgery, especially when a vertical scar or wise pattern markings are used for primary mastopexy augmentation [Table 1]. The skin envelope reductions in later two procedures limit the size of the implants in primary procedures and is due to the direct pressure and tension on newly sutured wounds exerted by expanded skin envelope.

The high number of complications or revision rate in combined augmentation with mastopexy is not exponential as reported in the past.^[15] The simple reason is that, in patients with augmentation mammoplasty alone, the known early complications are infection and hematoma [Table 4]. In this group, nipple areolar complex (NAC) size and level asymmetry, NAC level under or over positioning, ischemia and necrosis of nipple, loss of nipple sensation, skin and wound breakdown, and scar-related complications are not seen [Table 5]. Similarly, when a mastopexy alone is performed, capsular contracture, implant rupture, revision for size change, rippling, change for size, or other device-related complications are not the reason for revision surgeries. When the two are combined together, the incidence is likely to be higher than the single component performed separately. A long-term follow-up has shown a revision rate of 15.5% when silicone gel round textured implants were used alone,^[9] and a long-term tissue-related revision rate of 8.6% is reported when mastopexy alone was performed.^[11] A revision rate of 10% and 25.8% has been shown in simultaneous augmentation mastopexy.^[11,17] Although the revision rate in augmentation mastopexy is statistically significant, the increased rate of revision is simply the sum of the two individual components.

In a retrospective study performed by Calobrace, it was reported that tissue-related reoperation rate in combined procedures was 13.6% as compared to 10.2% for mastopexy alone. Whereas the implant-related reoperation rate was only 9.6% when the procedure was performed

alone as compared to 19.4% reoperation rate in Mentor 6 years core data.^[6,18]

Earlier concerns about the safety of the procedure with exponential complication and revision rate were further reviewed by Swanson in a prospective study in which consecutive cases of augmentation mammoplasty, simultaneous augmentation mastopexy, and mastopexy alone were analyzed. A single surgeon did all procedures, all implants were placed in a submuscular pocket, and all

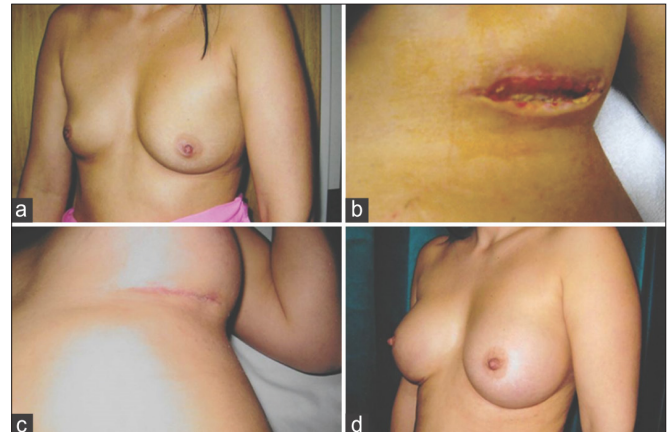


Figure 1: (a) Preoperative picture of a patient interested in augmentation mammoplasty; (b) postoperative picture showing left inframammary wound break down 4 weeks following augmentation mammoplasty when 300 mL round textured cohesive gel silicone implants were used; (c) completely healed wound following conservative treatment; (d) final result 3 months following augmentation mammoplasty



Figures 2: (a) Two weeks following simultaneous mastopexy with augmentation using 230 mL low profile round textured cohesive gel silicone implants showing left partial nipple necrosis; (b) right vertical scar breakdown in the same patient; (c) postoperative pictures taken 4 months following conservative treatment with regular change of dressings and wound cleansing

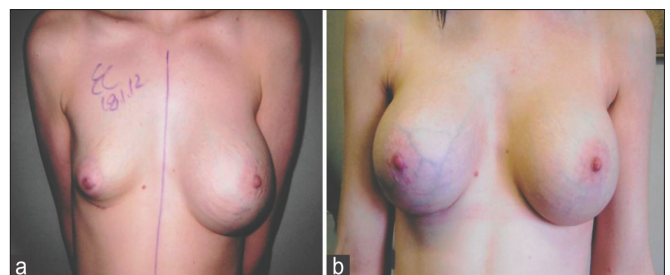


Figure 3: (a) Postexplantation picture of a patient who developed right periprosthetic infection following augmentation mammoplasty; (b) results following reimplantation using 360 mL round textured cohesive gel silicone implants 6 months after explantation

Table 2: Complications between the two groups

	Group A (1,298) (%)	Group B (108) (%)	P
Wound breakdown	14 (1.1)	7 (6.5)	0.001
Hematoma	12 (0.9)	0	-
Revision surgery	18 (1.4)	12 (11.1)	0.001
Grade IV capsular contractures	4 (0.3)	1 (0.92)	
Periprosthetic/wound infection	8 (0.6)	4 (3.7)	0.010

Table 3: Management of early complications

Procedure (n)	Hematoma		Periprosthetic/wound infection		Wound breakdown	
	Surgical	Conservative	Surgical	Conservative	Surgical	Conservative
Group A (1,298)	2	10	6	2	0	14
Group B (108)	0	0	0	4	0	7

Table 4: Reasons for revisions in augmentation mammoplasty group

Reason for revision	n (%)
Capsular contracture	4 (0.3)
Hematoma	3 (0.23)
Explantation and replantation later for infection	3 (0.23)
Debridement, curettage, lavage and immediate implant replacement for infection	3 (0.23)
Explantation without replacement	2 (0.15)
Bottoming out unilateral	1 (0.07)
Explantation with mastopexy	1 (0.07)
Bottoming out bilateral	1 (0.07)

Table 5: Reasons for revision surgery in mastopexy with augmentation

Reason for revision	n (%)
Dog ear bilateral	2 (16.7)
Dog ear unilateral	2 (16.7)
Areolar scar revision	2 (16.7)
Periareolar to vertical scar conversion	2 (16.7)
Nipple level asymmetry	1 (8.3)
Capsular contracture	1 (8.3)
Vertical scar revision	1 (8.3)
Bottoming out	1 (8.3)

mastopexies were performed using vertical scar with superomedial flaps. There was a revision rate of 20.5%, after augmentation mastopexy, 10.7% in augmentation, and 24.6% in mastopexy alone.^[19] Again the results support the argument for a combine procedure than to stage the procedure without an added risk of higher complication. When the procedure is staged, the second operation rate is 100%, with two visits to hospital, two costs of individual procedures, and two lots of recovery time from each procedure.

Late complications following simultaneous mastopexy with augmentation mammoplasty and augmentation mammoplasty are mostly implant-related and include capsular contracture, rippling, and device failure. The complications related to implants are not unique to each individual procedure and are shared between the two. The revision for capsular contracture being the most common reason for reoperation in both these groups [Figure 4]. In general, capsular contracture and device failures are time dependent and longer the follow-up, higher the incidence resulting in revision surgery.

Rippling in the lower pole is almost unavoidable and largely depends on the type of implant and existing breast envelope thickness. Breast augmentation in subglandular pocket, regardless of the preoperative tissue thickness, tends to have a higher revision rate for rippling due to the ever-changing breast envelope thickness.^[20] One very important tissue-related and avoidable complication following augmentation mastopexy is the siting of nipple and the choice of the markings. Choice of marking can vary from 65% areolar to 100% vertical scar markings.^[18,21] Inappropriate marking for

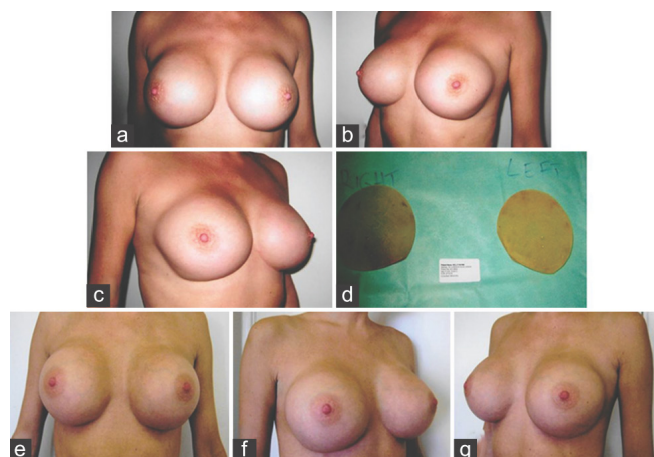


Figure 4: (a-c) A patient presenting with bilateral Grade IV capsular contracture following augmentation mammoplasty; (d) explanted implant showing bilateral fold flap failure; (e-g) three months postoperative pictures following bilateral capsulectomy and change of prosthesis using 460 mL textured round cohesive gel silicone implants

neo-NAC positioning, either too low or too high, also may result in persistent ptosis or bottoming out.^[21] In authors experience, use of periareolar markings should ideally be limited for unilateral mastopexy with asymmetrical nipple areolar level and with a difference of not more than 2 cm or patients presenting with early ptosis with an NAC at inframammary crease level. A breast with skin excess in horizontal excess, a breast with a wide base, or a breast with lower pole skin excess, periareolar skin excision from above the nipple does not address the tissue excess and result in less than optimal outcome. Bottoming out following mastopexy using vertical scars in patients presenting more than 9 cm distance from nipple to inframammary crease is a common observation. Nipple elevation to another few centimeters results in increased and above average nipple to inframammary crease length leading to bottoming out. Vertical scar markings selection for all mastopexies or augmentation mastopexies as all-season markings is a novel idea but should be used with caution. Lower pole redundancy or persistent ptosis has been reported in 28% of all the mastopexies when vertical scar mastopexy alone was used for all types of mastopexies.^[19] Other published studies also have shown that use of periareolar mastopexy or vertical scars markings was one of the leading cause for revision surgery in this group of patients.^[22,23]

The current article did not include authors own mastopexy alone revision rate and results. Therefore, based on the study design, our conclusion has limitation. However, previously published data of mastopexy alone has been used, and our data correlate with what has been published. Furthermore, there was no patient satisfaction survey included that would have indeed added strength to the outcome analysis.

In conclusion, there was a statistically and clinically

significant higher rate of complications and revision rate in simultaneous augmentation with mastopexy (Group B) as compared to augmentation mammoplasty alone (Group A). However, the overall revision rate in simultaneous augmentation with mastopexy was lower is actually a total sum of its two individual and distinct component and not exponential.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. The American Society for Aesthetic Plastic Surgery's Cosmetic Surgery National Data Bank: Statistics; 2013. Available from: <http://www.surgery.org/media/statistics>. [Last accessed on 2015 Oct 09].
2. Khan UD. Secondary augmentation mammoplasties and periprosthetic infection: a three-year retrospective review. *Aesthet Surg J* 2012;32:465-73.
3. Tebbetts JB. Achieving a zero percent reoperation rate at 3 years in a 50-consecutive-case augmentation mammoplasty premarket approval study. *Plast Reconstr Surg* 2006;118:1453-7.
4. Khan UD. The impact of preoperative breast implant selection on the 3-year reoperation rate. *Eur J Plast Surg* 2013;36:503-10.
5. Cunningham B. The mentor core study on silicone memorygel breast implants. *Plast Reconstr Surg* 2007;120:19S-29S.
6. Mentor Corporation. Saline Filled Breast Implant Surgery: Making an informed Decision. Mentor Corp, Santa Barbara, Calif. Available from: <http://www.mentorwwllc.com/pdf/finalinformedconsent.pdf>. [Last accessed on 2015 Sep 09].
7. Heden P, Bone B, Murphy DK, Slicton A, Walker PS. Style 410 cohesive silicone breast implants: safety and effectiveness at 5 to 9 years after implantation. *Plast Reconstr Surg* 2006;118:1281-7.
8. Khan UD. Muscle-splitting, subglandular and partial submuscular augmentation mammoplasties: a 12-year retrospective analysis of 2026 primary cases. *Aesthetic Plast Surg* 2013;37:290-302.
9. Handel N, Cordray T, Gutierrez J, Jensen JA. A long-term study of outcomes, complications, and patient satisfaction with breast implants. *Plast Reconstr Surg* 2006;117:757-67.
10. Khan UD. Vertical scar mastopexy with cat's tail extension for prevention of skin redundancy: an experience with 17 consecutive cases after mastopexy and mastopexy with breast augmentation. *Aesthetic Plast Surg* 2012;36:303-7.
11. Stevens WG, Stoker DA, Freeman ME, Quardt SM, Hirsch EM, Cohen R. Is one-stage breast augmentation with mastopexy safe and effective? A review of 186 primary cases. *Aesthet Surg J* 2006;26:674-81.
12. Discussion. A 15-year experience with primary breast augmentation. *Plast Reconstr Surg* 2011;127:1301-13.
13. Spear S. Augmentation/mastopexy: "surgeon, beware". *Plast Reconstr Surg* 2003;112:905-6.
14. Spear SL, Pelliery CV, Menon N. One-stage augmentation combined with mastopexy: aesthetic results and patient satisfaction. *Aesthetic Plast Surg* 2004;28:259-67.
15. Stevens WG, Macias LH, Spring M, Stoker DA, Chacón CO, Eberlin SA. One-stage augmentation mastopexy: a review of 1192 simultaneous breast augmentation and mastopexy procedures in 615 consecutive patients. *Aesthet Surg J* 2014;34:723-32.
16. Khan UD. Breast augmentation, antibiotic prophylaxis, and infection: comparative analysis of 1,628 primary augmentation mammoplasties assessing the role and efficacy of antibiotic prophylaxis duration. *Aesthetic Plast Surg* 2010;34:42-7.
17. Khan UD. Augmentation mastopexy in muscle-splitting biplane: outcome of first 44 consecutive cases of mastopexies in a new pocket. *Aesthetic Plast Surg* 2010;34:313-21.
18. Calobrace MB, Herdt DR, Cothron KJ. Simultaneous augmentation/mastopexy: a retrospective 5-year review of 332 consecutive cases. *Plast Reconstr Surg* 2013;131:145-56.
19. Swanson E. Prospective comparative clinical evaluation of 784 consecutive cases of breast augmentation and vertical mammoplasty, performed individually and in a combination. *Plast Reconstr Surg* 2013;132:30e-45e.
20. Khan UD. Selection of breast pocket using pinch test in augmentation mammoplasty: can it be relied in long term? *Aesthetic Plast Surg* 2009;33:780-1.
21. Spear SL, Boehmler JH 4th, Clemens MW. Augmentation/mastopexy: a 3-year review of a single surgeon's practice. *Plast Reconstr Surg* 2006;118:136S-47S.
22. Mugea TT, Schiffmann MA. *Aesthetic Surgery of the Breast*. 1st ed. Berlin, Heidelberg: Springer-Verlag; 2015. p. 649-56.
23. Stevens WG, Freeman ME, Stoker DA, Quardt SM, Cohen R, Hirsch EM. One-stage mastopexy with breast augmentation: a review of 321 patients. *Plast Reconstr Surg* 2007;120:1674-9.

Pathogenesis, presentation and classification of late autoinflation of the breasts: case report and literature search

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ABSTRACT

Aim: Autoinflation of the breast following mammoplasty using breast implants can be divided into early and late. Early autoinflation of the breast is commonly due to haematoma. Late autoinflation of the breast is an uncommon complication and its true incidence is not known due to the paucity of its reporting. **Methods:** A retrospective review was performed of the available charts for 2,772 consecutive bilateral primary, secondary augmentation mammoplasties and mastopexy with augmentation mammoplasties by the author between April 1999 and February 2015. Each breast was taken as a single unit for a total of 5,544 breasts. **Results:** There were 2,334 patients in primary augmentation mammoplasty, 258 in secondary augmentation mammoplasty and 180 in simultaneous mastopexy with augmentation mammoplasty. There were three autoinflation of breasts due to late seromas identified in the series. All patients presented at least six months following augmentation mammoplasty and all had textured implants place in muscle splitting submuscular pocket. There was no late seroma noted in secondary augmentation mammoplasty or simultaneous mastopexy with augmentation mammoplasty. All patients were treated conservatively without a recurrence. **Conclusion:** Late autoinflation of the breast due to seroma is an uncommon clinical complication and can be treated conservatively in the first instance.

Key words:

Anaplastic large cell lymphoma; autoinflation of the breast; haematoma; seroma of breast; anaplastic large cell lymphoma

INTRODUCTION

Since the introduction of implants in 1962, augmentation mammoplasty has become a widely accepted procedure for aesthetic and reconstructive reasons.^[1] An estimated five to 10 million women have breast implants worldwide.^[2] Early and late complications following mammoplasty are many. It is beyond the scope of this article to address all the arising complications. Intracapsular fluid is a common finding and has been reported with an incidence of 15%.

The accumulation of fluid was minimal and did not lead to swelling of the breast nor was it the reason for revision surgery.^[3,4]

Autoinflation of the breast is a clinical condition that can be defined as a sudden or spontaneous swelling of the breast following augmentation mammoplasty due to collection

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of fluid rather than the implant filler. The process may or may not proceed or follow with an incidence of trauma or injury. Early known causes of autoinflation of breast are infection, haematoma or seroma with a reported incidence of 0.5% and 0.7% respectively.^[5,6] Causes of late onset of autoinflation of breasts are many but these are not clearly defined on the basis of its aetiology, type of implants or site of accumulation of the fluid. Autoinflation of breasts may or may not be associated with implant rupture. Rupture of silicone implants is normally silent and rarely leads to loss of shape or consistency^[8] or axillary lymphadenopathy.^[9,10] Implant rupture may occasionally present as spontaneous autoinflation of the breast.^[11-13] In contrast saline implant can deflate following its rupture. Rarely a saline implant can present with autoinflation of the breast without a rupture or breach in the shell of the implant.^[14]

The presentation of anaplastic large cell lymphoma (ALCL) following augmentation mammoplasty also presents as an autoinflation of the breast. There is increasing awareness of ALCL which merits special attention.

The current article looks at the management and presentation of three patients. These patients presented with spontaneous autoinflation of the breasts due to late seroma. Also included is literature search to discuss various causes, locations and type of the texturing of the devices for the development of autoinflation of breast.

METHODS

A retrospective review was performed of the available charts for 2,772 consecutive bilateral primary, secondary augmentation mammoplasties and mastopexy with augmentation mammoplasties performed by the author between April 1999 and February 2015. Each breast was taken as a single unit for a total of 5,544 breasts.

RESULTS

There were 2,334 patients in primary augmentation mammoplasty, 258 in secondary augmentation mammoplasty and 180 in simultaneous mastopexy with augmentation mammoplasty groups. A total of 3 autoinflation of breasts due late seroma were identified in the series [Table 1]. All patients presented at least 6 months following augmentation mammoplasty and all had textured implants place in muscle splitting submuscular pocket. There was no autoinflation due to late seroma noted in secondary augmentation mammoplasty or simultaneous mastopexy with augmentation mammoplasty. All patients were treated conservatively without a recurrence.

Case 1

A 34-year-old mother of 2 children was interested in breast augmentation procedure. The augmentation mammoplasty was performed using 605 mL TRF Allergan Natrelle INSPIRA cohesive gel silicone textured round implants in muscle splitting pocket. She had an uneventful recovery.

Eight months following augmentation mammoplasty, she presented with spontaneous autoinflation of her right side. There was no recollectable history of trauma or injury. She was treated with antibiotics, cold compress, support garments and was followed up with regular intervals. The swelling gradually subsided within 2 months without surgical intervention and there was no recurrence for 8 years [Figure 1].

Case 2

A 25-year-old mother of 1 child showed interest in augmentation mammoplasty following the loss of volume of her breasts. Augmentation mammoplasty was carried out using 310 TRM Allergan Natrelle INSPIRA cohesive gel silicone textured round implants in muscle splitting pocket. She had an uneventful recovery and all settled well. Eight months following her surgery, she presented with quick onset autoinflation of her right breast. She was treated conservatively with antibiotics, cold compress and support garment. The swelling subsided in 8 weeks without surgical intervention and without recurrence for 6 years [Figure 2].

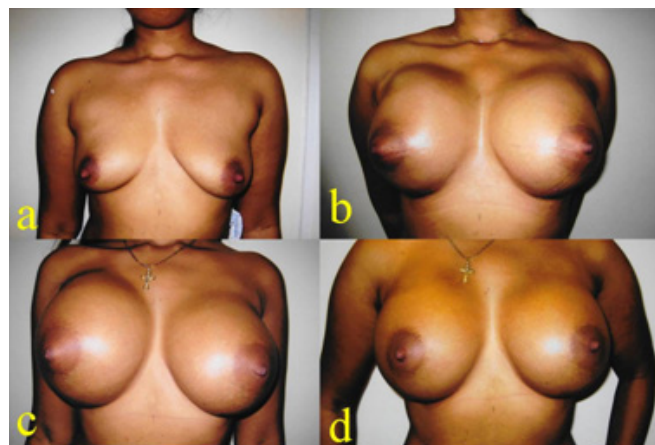


Figure 1: (a) Preoperative picture of a 34-year-old patient; (b) six weeks following augmentation mammoplasty with 605 TRF Allergan Natrelle textured implants; (c) the patient presented with massive right-sided swelling 8 months following mammoplasty; (d) two months following presentation with autoinflation due late seroma. The patient was treated conservatively

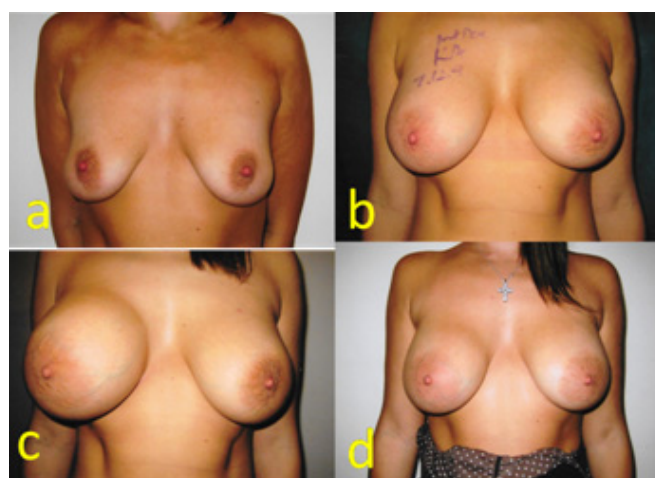


Figure 2: (a) Preoperative picture of a 25-year-old patient; (b) six weeks following augmentation mammoplasty with 310 TRM Allergan Natrelle textured implants; (c) the patient presented with right-sided spontaneous swelling 8 months following mammoplasty; (d) three months following presentation with autoinflation due to late seroma. The patient was treated conservatively

Case 3

A 19-year-old young female presented with asymmetrical breast along with right breast ptosis. She had her augmentation mammoplasty procedure using 275 mL on her right and 345 mL on her left side. Nagor GFX cohesive gel silicone textured implants were placed in muscle splitting pocket a right internal mastopexy was performed at the same time. Eight years later patient presented with an acute onset of right-sided autoinflation of breast. She was reassured and treated conservatively with antibiotics, cold compress and pressure garments successfully without any surgical intervention. Her swelling subsided with in 6 weeks and has been asymptomatic for the last 6 months [Figure 3].

DISCUSSION

Complications following augmentation mammoplasty though not very common can be early or late. Early complications are infection, haematoma and seroma and may require an urgent surgical intervention. Late complications are infrequent and may include capsular contracture, asymmetry, implant rupture, implant displacement, rippling and symmastia.^[5] Revision for these complications can be addressed on the basis of its presentation as an elective procedure. Autoinflation of the breast arising six months or later is an extremely rare presentation. Such autoinflation may have different causes and fluid collection can be intraprosthetic, intracapsular, extracapsular or a combination of the above. The fluid collection is equally seen in implants when silicone,

hydrogel or saline is used as filler. The implants can be textured, microtextured, smooth or polyurethane coated.^[3,4] However, there is a paucity in literature on the pathogenesis of this condition and is not comprehensively defined on the basis of aetiology, pathogenesis, anatomical location or type of implants.

Intraprosthetic collection of fluid presenting as autoinflation of breast

Intraprosthetic collection of fluid or sterile pus though not very common has been reported both in saline as well as silicone gel implants.^[11-14] However the process differs in the two instances. In saline implants, the shell allows passage of protein macromolecules, predominantly albumin that creates an osmotic gradient across the macroscopically intact silicone shell allowing body fluids to enter the prosthesis. The implants can gain a large volume of fluid and present as autoinflation of the breast. No extracapsular fluid collection has been reported with the process concerning saline implants.^[14] On the contrary, intraprosthetic collection of fluid in silicone gel implant is almost always associated with damaged or ruptured shell that may or may not be macroscopically visible and there is almost always intracapsular collection of fluid or sterile pus at the same time.^[11-13] The damaged shell allows intracapsular fluid to gain access to the inside of the damaged implant resulting in autoinflation of the breast.

Extracapsular fluid collection presenting as auto inflation of the breast

Extra capsular collection of fluid following augmentation mammoplasty leading to autoinflation of breast is uncommon. The extracapsular collection of fluid resulting in autoinflation of breast is usually associated with intracapsular collection of fluid. The presentation was noticed following the rupture of poly implant prothese (PIP). The defective silicone escaping into intracapsular and pericapsular spaces starts an inflammatory response that eventually result in large amount of creamy fluid or sterile pus collection leading to autoinflation of breast. The presentation was commonly observed with the rupture of PIP implants.^[11,13]

Polyacrylamide gel injections

The similar process of autoinflation of breast is also seen in breast injected with polyacrylamide gel (PAAG). Injection of PAAG does not always produce a distinct layer of capsule. The fluid collection can be in the periphery of the injected material or within injected PAAG. The combination of extra and intra-PAAG collection of fluid may also present as galactocele, seroma or haematoma.^[15] In PAAG injection



Figure 3: (a) Preoperative picture of a 19-year-old patient presenting with breast asymmetry; (b) eight months following augmentation mammoplasty with right internal mastopexy, patient had 275 mL GFX Nagor textured implant on her right and 345 mL GFX Nagor textured implant on her left side; (c) the patient presented with right-sided acute onset swelling 8 years following mammoplasty; (d) three weeks following presentation with autoinflation due to late seroma. The patient was treated conservatively

Table 1: Details of the cases presenting with late seromas in the series

No.	Age (years)	Implant make	Implant size (mL)	Implant surface characteristics	Time since surgery	Pocket of implant	Treatment
1	34	Allergan Natralle	605	Textured	8 months	Muscle splitting submuscular	Conservative
2	25	Allergan Natralle	310	Textured	8 months	Muscle splitting submuscular	Conservative
3	19	Nagor GFX	275	Textured	8 years	Muscle splitting submuscular	Conservative

the process of autoinflation is multifactorial, it has an inflammatory response resulting in sterile creamy pus like substance collection. Broken down PAAG products creates an osmotic gradient resulting in shift of body fluids into the injected PAAG resulting in autoinflation of the breast.^[16]

Intracapsular or periprosthetic fluid collection presenting as autoinflation of the breast

Intracapsular or periprosthetic fluid collection can be seen following augmentation mammoplasty, revision mammoplasty or breast reconstructive surgery using breast implants. The presence of fluid has been reported in 15% of the revision surgeries and the amount of fluid collected ranged from 0.2 mL to 20 mL. The fluid can be thick, mucinous, blood stained or serous.^[3,4] It is not surprising that collection of fluid in intracapsular space leading to autoinflation of the breast is the most common cause of the late autoinflation. Collection of thick mucinous creamy fluid, resembling like pus but with out positive bacterial culture, is uncommon and is possibly due to a chemical reaction in response to the leaked silicone.^[11-13] This type of collection is reported following PIP silicone and hydrogel implant ruptures^[11-13] and PAAG injections.^[15,16] The cause is the direct contact of the material with the body either through a rupture or following implantation or injection of PAAG.

Autoinflation of breast due to haematoma or blood stained fluid

This is not the most common form of intracapsular fluid collection presenting as autoinflation of the breast. This type of collection is seen following the separation of the adhered capsule from the textured surface of the implant following a physical force or trauma. These late blood stained fluid or haematomas are especially reported following the use of polyurethane coated implants, where disappearance of polyurethane coating results in inflammation and the implant starts behaving like a textured implant with a highly vascular internal lining of capsule rubbing against the textured surface of the implant.^[17]

Autoinflation of breast due to late seromas

The collection of serum in intracapsular space following breast implant surgery is the most common form of autoinflation. The causes can be mechanical, inflammatory, traumatic, hormonal and most importantly malignant (ALCL). Textured implants are more commonly involved and the possible mechanism is the separation of the capsule from the textured surface of the implant. The shearing of the textured surface of the implant on the raw internal vascular surface of the capsular lining starts an inflammatory process resulting in exudation of the fluid that may lead to autoinflation of breast.^[17,18]

Micro-movements between the micro-textured or smooth implants and capsule can result in synovial metaplasia of the capsular internal lining. The metaplastic lining continuously rubbing against the implant surface can trigger the process.^[19,20] Other less well defined possibilities are the presence of subclinical infection, biofilms, any generalised condition leading to low immune response, allergic

responses *etc.*^[19] These latter factors need to be investigated further using microbiological assessment of the serum present in the intracapsular fluid along with the chemical analysis of blood and intracapsular fluid samples.

Malignant effusion of the intracapsular space secondary to ALCL is the least common but most alarming cause of autoinflation of the breast. ALCL is a rare type of non-Hodgkin lymphoma, which is distinctly different from the primary breast lymphoma of breast. Primary breast lymphomas are overwhelmingly of B-cell as opposed to T-cell phenotype that is associated with breast implants.^[21] The incidence of primary breast lymphoma is less than 1% of all breast neoplasm as compared to an estimated 3 in 100 million women per year of ALCL reported. Implant related ALCL is reported in 34 cases out of estimated 5 to 10 million women with breast implants.^[2] These haemopoietic tumours of T-cell origin is extremely rare and the common factor appears to be the texturing of the implants suggesting a site and material specific chronic inflammatory cause. Other possible causes are genetic predisposition and Biofilm organism that may play a contributory role. The condition is not related to the implant fill material.^[22] Considering the extreme rarity of ALCL, it is likely that most physicians will never see a single case of ALCL in their career.^[2]

Following is the recommendations and algorithm as a useful guide to manage late autoinflation of the breast from Bengtson *et al.*^[23] Step 1: conservative treatment. Infection should be ruled out and antibiotics given when in doubt. Aspiration of fluid for culture and cytology when possible; Step 2: imaging ultrasound or magnetic resonance imaging (MRI). Ultrasound may also assist ultrasound-guided aspiration of fluid for culture and cytology; third step: if palpable or MRI evidence of a mass present or in case of refractory or recurrent seroma, surgical exploration is recommended. The procedure includes complete capsulectomy with or without implant replacement.

In the author's practice, the incidence of late seroma was noted in 0.05% which is much lower when compared to 0.88% and 1.68% incidence reported in other series.^[17,19] In the current series all three patients who presented with late seromas were treated conservatively using antibiotics and compression bandages. All responded to the treatment and there was no recurrence of autoinflation. One of the patient developed capsular contracture on the side of autoinflation due to late seroma.

In conclusion, implant working group recommendations are available and should be used a guideline for the treatment of late autoinflation of the breast. Late autoinflation of the breast on its own is uncommon and can be treated conservatively in the first instance.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Cronin TD, Gerow RM. Augmentation mamoplasty: new "natural feel" prosthesis. In: Translational of the third international congress of the plastic surgery. Amsterdam: Excerpta Medica International Congress; 1962. p. 41-9.
2. Eaves F 3rd, Nahai F. Anaplastic large cell lymphoma and breast implants: FDA report. *Aesth Surg J* 2011;31:467-8.
3. Ann CY, Ko CY, Wager EA, Wong RS, Shah WW. Clinical significance of intracapsular fluid in patients' breast implants. *Ann Plast Surg* 1995;35:455-7.
4. Ann CY, Ko CY, Wager EA, Wong RS, Shah WW. Microbial evaluation: 139 implants removed from symptomatic patients. *Plast Reconstr Surg* 1996;98:1225-9.
5. Khan UD. Breast augmentation, antibiotic prophylaxis and infection: comparative analysis of 1628 primary augmentation mammoplasties to assess the role and efficacy of length of antibiotic prophylaxis. *Aesth Plast Surg* 2010;34:42-7.
6. Khan UD. Muscle splitting, subglandular and partial submuscular augmentation mammoplasties. A twelve year retrospective analysis of 2026 primary cases. *Aesth Plast Surg* 2013;37:290-302.
7. Holmich LR, Vejborg IM, Conrad C, Sletting S, Hoir MM, Fryzek JP, McLaughlin JK, Kjoleer K, Wilk A, Friis S. Untreated silicone breast implant rupture. *Plast Reconstr Surg* 2004;114:204-14.
8. Pinchuk V, Tymofii O, Tkach O, Zamkovoy V. Implant rupture after augmentation mamoplasty. *Aesth Plast Surg* 2013;37:60-7.
9. Khan UD. Mondor's disease: a review of the literature and a case report. *Aesthetic Surg J* 2009;29:209-12.
10. Khan UD. Implant rupture and ante-grade excision of axillary silionoma through implant pocket. A case report and literature search. *J Muhamm Med Coll* 2010;1:56-60.
11. Khan UD. Breast autoinflation with sterile pus as a marker of implant rupture: single- stage treatment and outcome for five consecutive cases. *Aesth Plast Surg* 2009;33:58-65.
12. Khan UD. Left unilateral breast autoinflation and intraprosthetic collection of sterile pus: an unusual operative finding of silicone gel bleed with silicone lymphadenitis. *Aesth Plast Surg* 2008;32:684-7.
13. Khan UD. Poly implant prothese (PIP) incidence of device failure and capsular contracture: a retrospective analysis. *Aesth Plast Surg* 2013;37:906-13.
14. Robinson OG Jr, Benos DJ, Mazochi C. Spontaneous autoinflation of saline mammary implants: further studies. *Aesth Surg J* 2005;25:582-6.
15. Cheng NX, Zhang YL, Luo SK, Zhang XM, Hui L, Chen YL, Sheng SY, Wu DH, Wang HB, Li P. Late haematoma, seroma and galactocele in breast injected with polyacrylamide gel. *Aesthetic Plast Surg* 2011;35:365-72.
16. Kang GC, Ong YS. Large unilateral breast autoinflation after breastfeeding linked to polyacrylamide hydrogel injection augmentation mamoplasty. *Aesthetic Plast Surg* 2011;35:122-4.
17. Mazzochi M, Dessy LA, Corris F, Scuderi NA clinical study of late seroma in breast implantation surgery. *Aesthetic Plast Surg* 2012;36:97-104.
18. Park BY, Lee DH, Lim SY, Pyon JK, Mun GH, Oh KS, Bang SI. Is late seroma a phenomenon related to textured implants? A report of rare complication and a literature review. *Aesth Plast Surg* 2014;38:129-38.
19. Pinchuk V, Tymofii O. Seroma as a late complication after breast augmentation. *Aesth Plast Surg* 2011;35:303-14.
20. Raso DS, Green WB, Metcalf JS. Synovial metaplasia of a periprosthetic breast capsule. *Arch Pathol Lab Med* 1994;118:249-51.
21. Rupini A, Frame JD, Kamel D. Lymphomas associated with breast implants: a review of the literature. *Aesthet Surg J* 2015;35:533-44.
22. Brody G, Deapan D, Taylor CR, Printer-Brown L, House-Lighner SR, Anderson JS, Carlson G, Lechner MG, Epstein AL. Anaplastic large cell lymphoma in women with breast implants: analysis of 173 cases. *Plast Reconstr Surg* 2015;135:695-705.
23. Bengtson B, Brody GS, Brown MH, Glicksman C, Hammond D, Kaplan H, Maxwell GP, Oefelein MG, Reisman NR, Spear SL, Jewell ML; Late Periprosthetic Fluid Collection after Breast Implant Working Group. Managing late periprosthetic fluid collections (seroma) in patients with breast implants: a consensus panel recommendation and review of the literature. *Plast Reconstr Surg* 2011;128:1-7.

Cleavage classification: categorizing a vital feminine aesthetic landmark

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Breast cleavage is defined by the International Federation of Associations of Anatomists (IFAA), as the space present between a woman's breasts. The width of the inter-mammary cleft is defined by the distance between the points of attachment of the breast tissue to the periosteal tissue.^[1-3]

Cleavage is associated with femininity and its exposure to varying degrees by women across the world can be aimed to heighten both self-image and physical attractiveness.^[4,5] The use of Décolletage in dresses dates back to the 11th century, when an aesthetic cleavage was perceived as a sign of beauty, wealth and social stature.^[6,7] Corsets were later introduced in the 16th century and their use was primarily aimed at pushing the breasts upwards to give a fuller cleavage.^[8,9] In more recent times, specialized brassieres (push-up bras) with various forms of paddings (falsies) have become the more popular and comfortable option. Other conservative methods of making the cleavage more prominent include skin pulling techniques, taping, use of glued shapes, under bras, adhesive gels and the use of makeup.

Breast augmentation is the most commonly performed cosmetic procedure in the US, and in recent years a great increase has been reported in the number of these procedures performed annually.^[10] Women requesting breast augmentation often request a specific form of cleavage enhancement and it is common for potential patients to bring photographs of desired cleavage shapes and appearances. A plastic surgeon can be put in a

challenging position when the patient's expectations are not realistic; therefore a strong communication of ideas is necessary.^[11] Titration of the subjective expectations of the patients, while aiming for satisfactory aesthetic outcomes, becomes a dilemma for the surgeon.

It is therefore important to devise a more objective method of assessing the preoperative anatomy and classifying the postoperative expectations of a woman wanting an augmentation. Much work has been done to classify breasts based on their shapes, contours and sizes;^[12-15] however, despite cleavage being an equally important determinant of one's beauty, there has not been any reported efforts towards classification of cleavage.^[16]

Body postures, alternate postures, bras and garments can influence the appearance of the cleavage and hence during the assessment stage, a female patient's natural cleavage shape should be assessed in the "neutral" position with her arms by her sides and her hands on the back as she slightly leans forward. We identified different shapes of cleavage that women present with and classified them based on the "anterio-posterior" or "frontal" view (surgeon's perspective and patient's mirror view) as well as a "cranio-caudal" or "bird's eye" view (patient's direct visual perspective).

ANTERIOPOSTERIOR OR FRONTAL VIEW

From a frontal perspective, the shape of the cleavage has

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potential shapes based on the proximity of the breasts to each other and on the width of the cleavage at the inferior and superior poles. These can be classified as the “cocktail glass”, the “champagne glass”, the “hourglass” and the “hi-ball glass”.

The “cocktail glass” appearance, as the name suggests, is the shape of the cleavage where the breasts are in close proximity and there is no space between them in the inferior half of the cleavage. The superior part of the cleavage acutely curves away from the breasts in a relatively linear fashion

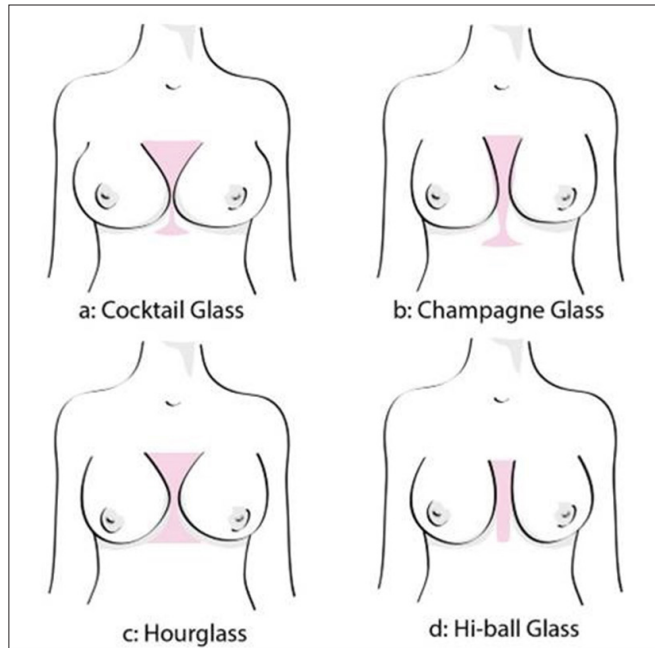


Figure 1: Cleavage classification based on anteroposterior point of view

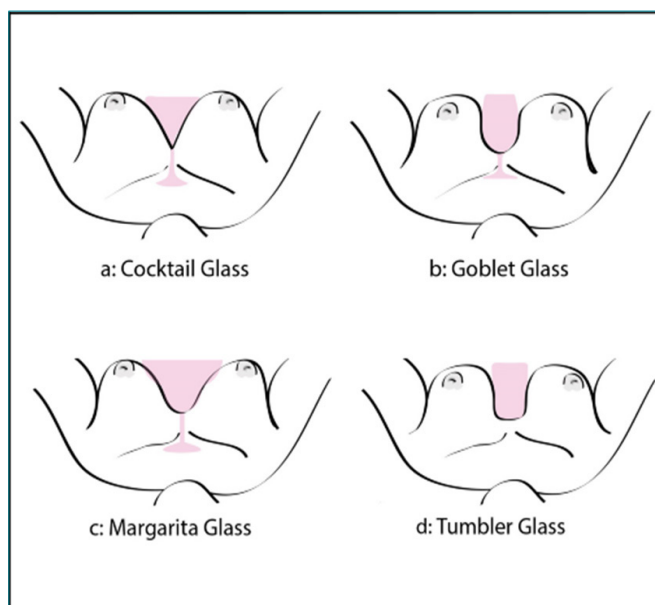


Figure 2: Cleavage classification based on craniocaudal point of view

leaving a wider, exposed region of the cleavage [Figure 1a].

A “champagne glass” appearance represents a cleavage in which though the breasts are in close proximity they are not in contact leaving a visible region between the breasts through the total length of the cleavage. The width in the inferior half remains short and constant, while that of the

superior part increases considerably and the contours bend away from the midline. This results in a wider cleavage in the superior half when compared to cocktail glass cleavage [Figure 1b].

The “hourglass” shape defines a cleavage in which the medial contours of the breast almost touch at a simple point of contact. When compared to the “cocktail glass” and “champagne glass” appearance, breasts with an hourglass cleavages have less proximity between them. The width of the cleavage is minimum at the midpoint between superior and inferior poles of the cleavage and increases almost symmetrically towards both these ends [Figure 1c].

The shape that defines a “hi-ball glass” cleavage is one where breasts are at a considerable distance from each other. The shape of this cleavage is such that the width of the cleavage stays considerably constant through its length [Figure 1d].

“CRANIOCAUDAL” OR “BIRD’S EYE”VIEW

To classify cleavages according to this view, the breasts and cleavage should be observed from above the head of a patient with the patient in a neutral position. From this view, the cleavage can be classified based on its width as well as the proximity of the breasts to each other into four shapes: the “cocktail glass”, “goblet glass”, “margarita glass” and “tumbler glass”.

The “cocktail glass” appearance is one in which the breasts are in close proximity to each other and there is a point in the cleavage where the breasts meet, leaving no visible gaps between the breasts. The breasts then curve antero-laterally in a relatively linear manner towards the areola. The shape formed by this cleavage is similar to a cocktail glass [Figure 2a].

Similarly there is the “goblet glass” appearance which is a result of a close proximity of the breasts to each other, while having no point of contact between them. The shape of the cleavage is such that it forms a curved shape in the center of the inter-mammary cleft which then curves antero-laterally towards the areola. When compared to the cocktail glass appearance the curves are more pronounced as compared to more linear ones in the earlier [Figure 2b].

The “margarita glass” cleavage is similar to both the cocktail glass and goblet glass cleavages with the exception that the width of the inter-mammary cleft is wider and the medial breast is more curvy and tapers antero-laterally more acutely [Figure 2c].

Lastly the “tumbler glass” appearance is one where the breasts are further apart leaving a greater space between them. The medial curves of the breasts descend postero-medially in a sharp manner and thus do not extend further towards the midline. This leaves a flat region in the cleavage representing the region superficial to the sternum that lacks breast tissue. The shape is such that instead of being curved the cleavage has a rectangular or “boxy” appearance [Figure 2d].

This classification system is applicable to all breast sizes. It is based on the appearance of the cleavage and takes in to account the width of the cleavage at the superior and inferior poles of the breast, and the midpoint between them. In women with smaller breasts the cleavage will be more pronounced, and different than that of women with fuller breasts. However, the authors believe that even in women with smaller breasts the shape of the cleavage should vary according to our classification system. In this cohort of patients the more prevalent classes would be the hour glass, and the hi-ball glass (anteroposterior view) and the margarita glass, and the tumbler glass (craniocaudal view). Similarly for women with larger breasts one would expect to observe cocktail glass and champagne glass (anteroposterior view) and cocktail and goblet glass (craniocaudal view).

Patient satisfaction after breast augmentation is variable and some studies have reported that not all patients are satisfied with their postoperative outcomes.^[5,10,17] It depends on multiple aspects of the appearance of the breasts including their shape, size, contours as well as the appearance of the cleavage. Patients are unique and any given cleavage may not necessarily fit one particular classification. However, this classification based on various everyday shapes of glasses, can be used by surgeons to help patients acquire an objective understanding regarding their expectations from surgery. Surgeons can use this classification system preoperatively to discuss the expectations of patients regarding the appearance of their cleavage in addition to their breasts. If patients desire a certain type of cleavage after their augmentation the surgeon can modify their choice of implants and their surgical technique accordingly. A breast augmentation procedure as well as the choice of implant may then be altered, taking into consideration not only the desired increase or decrease in breast size but also the desired modification of cleavage appearance.

Though the proposed classification is based on personal observations and the nomenclature of glasses, we believe that if used in conjunction with the existing practices of breast augmentation, it will result in an improved aesthetically pleasing outcome leading to better patient satisfaction with the results of the augmentation. Our proposed classification should be further explored by formal studies that analyze both preoperative and postoperative patient satisfaction. This analysis could be either a two-dimensional e.g. using photographs or three-dimensional analysis^[18,19] and lead to better understanding of role of preoperative and postoperative cleavage morphology in patient satisfaction.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

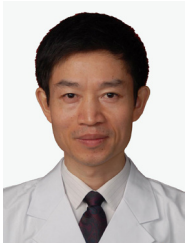
1. Oliver R. I'll boost your boobs or go bust! Plastic Surgery 101, 2007. Available from: http://plasticsurgery101.blogspot.com/2007_08_01_archive.html. [Last accessed on November 24, 2015]
2. West's federal supplement (First Series). Victoria, Minnesota: West Publishing Co; 1990. p. 994.
3. Eisenberg T, Eisenberg J. The scoop on breasts: a plastic surgeon busts the myths. 1st ed. Philadelphia: Incompra Press; 2012.
4. Hsu VM, Tahiri Y, Wes AM, Yan C, Selber JC, Nelson JA, Kovach SJ, Serletti JM, Wu LC. Does breast reconstruction impact the decision of patients to pursue cosmetic surgery? *Ann Plast Surg* 2014;73:S144-8.
5. Gladfelter J, Murphy D. Breast augmentation motivations and satisfaction: a prospective study of more than 3,000 silicone implantations. *Plast Surg Nurs* 2008;28:170-4.
6. Gernsheim A. Victorian and Edwardian Fashion: A Photographic Survey (Dover Fashion and Costumes). New York: Dover Publications, 1982.
7. Morris D. The naked woman: a study of the female body. Reprint edition. New York: St. Martin's Griffin; 2007.
8. Spooner C. Fashioning gothic bodies. Manchester: Manchester University Press; 2004. p. 28.
9. Condra J. The greenwood encyclopedia of clothing through world history. Westport, Connecticut: Greenwood Publishing Group; 2008. p. 152.
10. McCarthy CM, Cano SJ, Klassen AF, Scott A, Van Laeken N, Lennox PA, Cordeiro PG, Pusic AL. The magnitude of effect of cosmetic breast augmentation on patient satisfaction and health-related quality of life. *Plast Reconstr Surg* 2012;130:218-23.
11. Dini GM, Gozzano R, Ferreira RB, Faria M, Farinazzo M, Ferreira LM. Mirror, mirror on the wall, which breast is bigger of them all. *Plast Reconstr Surg Glob Open* 2014;2:e105.
12. von Heimburg D, Exner K, Kruff S, Lemperle G. The tuberous breast deformity: classification and treatment. *Br J Plast Surg* 1996;49:339-45.
13. India M. Breasts - structures and types. Available from: <http://www.medindia.net/patients/patientinfo/breasts-structures-and-types-breast-types.html>. [Last accessed on November 24, 2015]
14. Room H. Classify your breast. Available from: <http://www.herroom.com/breast-shape,336,30.html>. [Last accessed on November 24, 2015]
15. Chasan PE. A new breast shape classification. *Plast Surg Pract* 2011.
16. Kolker AR, Collins MS. Reply: tuberous breast deformity: classification and treatment strategy for improving consistency in aesthetic correction. *Plast Reconstr Surg* 2015;136:e269-70.
17. Young VL, Nemecek JR, Nemecek DA. The efficacy of breast augmentation: breast size increase, patient satisfaction, and psychological effects. *Plast Reconstr Surg* 1994;94:958-69.
18. Galdino GM, Nahabedian M, Chiaramonte M, Geng JZ, Klatsky S, Manson P. Clinical applications of three-dimensional photography in breast surgery. *Plast Reconstr Surg* 2002;110:58-70.
19. Kovacs L, Eder M, Hollweck R, Zimmermann A, Settles M, Schneider A, Udosc K, Schwenger-Zimmerer K, Papadopoulos NA, Biemer E. New aspects of breast volume measurement using 3-dimensional surface imaging. *Ann Plast Surg* 2006;57:602-10.

Modulation of Wnt/ β -catenin signaling affects the directional differentiation of hair follicle stem cells

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Prof. Bin Yang has engaged himself in practicing and researching cranio-maxillo-facial surgery for thirty years. He undertook successively more than ten scientific projects, including national and provincial priority projects supported by government fund. He possess national patent for invention of the head fixing frame for CT scanner. The project of surgical treatment of craniofacial malformations was awarded National and Provincial Scientific & Technological Advance Prize respectively in 1995 and 2008. He had published seven monographs, among two of those books he served as the editor-in-chief. He have had approximate 70 original articles, reviews and translations published on journals. He has 30-years experiences in treating craniomaxillofacial malformation. He has performed a lot of major surgical procedures on craniofacial deformities and gotten satisfactory results. Especially he used the distraction technique to treat Treacher-Collins syndrome, hemifacial microsomia, etc., having gotten both good appearance and physiologic function. His practice scope include craniomaxillofacial deformities, especially congenital craniofacial malformation, such as Crouzon syndrome and craniosynostosis (scaphocephalies, turriccephalies, brachycephalies, plagiocephalies, triangucephalies), orthognathic surgery, cleft lip and palate, scalp and skull defect, orbital hypertelorism, etc.

ABSTRACT

Aim: The differentiation of hair follicle stem cells (HFSCs) into hair follicle cells has potential clinical applications for cutaneous burns. However, the mechanisms regulating the differentiation of HFSCs into hair follicular papilla or epidermal cells are currently not clear. This study investigated the role of the Wnt/ β -catenin pathway and its crosstalk with other signaling components during this differentiation process. **Methods:** Lithium chloride (LiCl, 10 mmol/L) and keratinocyte growth factor (KGF, 10 μ g/L) were used to induce HFSC differentiation, validated by immunofluorescence analysis. The mRNA expression of β -catenin, adenomatous polyposis coli, glycogen synthase kinase-3 β (GSK-3 β), axin, and lymphoid enhancer factor-1 after 3, 5, 7, and 9 days were measured to evaluate the role of the Wnt/ β -catenin pathway. **Results:** During LiCl-induced HFSC differentiation into hair follicle cells, the Wnt/ β -catenin signaling pathway was activated and the expression of GSK-3 β , a vital component of the degradation compound, was inhibited. This led to increased cytoplasmic β -catenin expression, nuclear translocation, and subsequent target gene transcription. By contrast, KGF induced the differentiation of HFSCs into epidermal cells and did not affect the expression of β -catenin. This data indicates that LiCl and KGF distinctly regulate the differentiation of HFSCs into hair follicle and epidermal cells, respectively. Furthermore, the Wnt/ β -catenin signaling pathway is predominantly involved in hair follicle differentiation. **Conclusion:** these results demonstrate that LiCl can be used to differentiate HFSCs into hair follicle cells *in vitro*, which has important therapeutic applications for treating patients with cutaneous damage.

Key words:

Lithium chloride; keratinocyte growth factor; hair follicle stem cells; Wnt/ β -catenin signaling pathway

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INTRODUCTION

The discovery of hair follicle stem cells (HFSCs) and the development of methods to culture these cells *in vitro* have led to the possibility of developing new tissue engineering treatments for cutaneous damage caused by burns.^[1] HFSCs are highly proliferative multipotent stem cells with multi-lineage potential. They can differentiate into a range of distinct cell types including epidermal cells, hair follicle cells, and sebaceous cells.^[2] Both the proliferation rate and the differentiation capacity of HFSCs are influenced by autologous genes and external signals. The Wnt/ β -catenin signaling pathway plays a crucial role in the development of follicles and hair.^[3,4] During both embryonic development and tumorigenesis Wnt proteins bind to their receptors and activate Wnt/ β -catenin signaling, leading to β -catenin accumulation in the cytoplasm and subsequent nuclear translocation. β -catenin binding to lymphoid enhancer factor-1 (LEF1) activates target genes and accelerates the directional differentiation of HFSCs.^[3,4] Other factors, including chemicals (e.g. LiCl) and growth factors, influence cytoplasmic β -catenin levels in HFSCs, leading to HFSC differentiation.^[1] However, details of the mechanism require further investigation. The purpose of this study was to investigate how keratinocyte growth factor (KGF) and LiCl influence the function of the Wnt/ β -catenin signaling pathway and its interaction with other signaling components during human HFSC differentiation into dermal papilla and epidermal cells.

METHODS

Tissue harvest and cell isolation

Fresh scalp specimens were obtained under aseptic condition and HFSCs were isolated using previously established methods.^[1] Briefly, scalp skin from patients undergoing surgery was washed repeatedly with phosphate buffered solution (PBS) containing 5% penicillin and streptomycin (North China Pharmaceutical Corporation, China). After removing subcutaneous adipose tissue and impurities, the

skin was cut into 4 mm \times 2 mm pieces, placed in a centrifuge tube containing 0.25% Dispase (Shanghai Biological Technical Company, China), and digested overnight at 4 °C. The hair follicles were then gently pulled out in the direction of hair growth. The dissociated adipose tissue was then washed with PBS and hair follicles were added to a 60-mm petri dish containing 10% fetal bovine serum (FBS) in Dulbecco's Modified Eagle Media (DMEM; Hyclone, USA). Bulge areas were isolated from the hair follicles by incubation with 2.5 g/L trypsin and 0.04% EDTA for 10 min at 37 °C, followed by centrifugation and resuspension in K-SFM medium (Shanghai Biological Technical Company, Shanghai, China) at a density of 5×10^7 cells/L. Cells were incubated at 37 °C under 5% CO₂ in a humidified incubator. The culture medium was replaced every 3-4 days, and HFSCs were cultured and passaged three times prior to being used for all experiments.

Measuring the proliferation rate of HFSCs

To measure their rates of proliferation, HFSCs were seeded at the following four different densities: 1×10^3 , 1×10^4 , 1×10^5 , and 1×10^6 cells/mL of 24-well plate. Growth curves of the HFSCs were obtained by seeding 1×10^5 logarithmically growing cells in 1 mL medium into each well of a 24-well culture plate. A total of 36 wells were used. Hoechst 33258 DNA quantitation was performed every day after 7 days in culture.

Immunofluorescence assay

Immunofluorescence analysis was performed as previously described.^[5] Briefly, sterile glass coverslips were placed into 60 mm dishes, and approximately 2×10^4 cells/mL of 24-well plate were seeded into each dish. After 7 days in culture, adherent cells were stained for pan-cytokeratin, K19-Cy3, and β 1-integrin and analyzed by immunofluorescence microscopy.

Treatment with LiCl and KGF

To investigate the effects of specific compounds on HFSC differentiation, HFSCs were treated with LiCl (0.5, 1.5, 10, or 25 mmol/L) or KGF (10, 25, 50, or 100 μ g/L). After 7 days, Hoechst 33258 DNA quantitation was performed to compare

Table 1: Primer sequences and amplified fragments

Primer pairs	Sequences (5' to 3')	Denaturation temperature (°C)	Fragment size (bp)
β -catenin forward β -catenin reverse	TACCTCCCAAGTCCTGTATGAG TGAGCAGCATCAAAGTGTGTAG	56.0	180
APC forward APC reverse	TAAAGCAAGTTGAGGCACTG ACCGGCTTCCATAAGAACGGA	55.5	270
Axin forward Axin reverse	GCGGGACAGATTGATTCACCTT TGTGGACACCAGTTCTCCCT	57.0	190
GSK-3 β forward GSK-3 β reverse	ATTTCAGGGGATAGTGGTGT TCCTGACGAATCCTTAGTCCAAG	56.0	154
LEF1 forward LEF1 reverse	AATGAGAGCGAATGTCGTTGC GCTGTCTTTCTTTCCGTGCTA	56.5	137
GAPDH forward GAPDH reverse	TGTTGCCATCAATGACCCCTT CTCCACGACGTACTCAGCG	57.0	202

APC: adenomatous polyposis coli; GSK-3 β : glycogen synthase kinase-3 β ; LEF1: lymphoid enhancer factor-1; GAPDH: glyceraldehyde-3-phospho

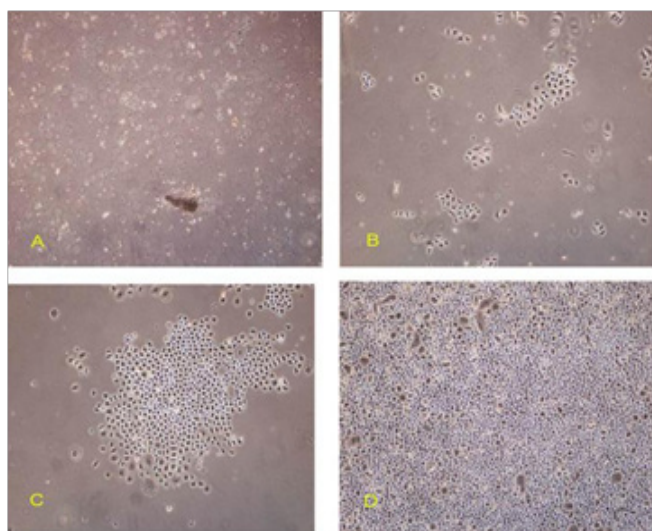


Figure 1: Primary culture of hair follicle stem cells (HFSCs). (A) Partial adherence of HFSCs (P0, 1 day); (B) adherent cell growth (P0, 3 days); (C) logarithmic cell growth (P0, 7 days); (D) cells reached 100% confluency (P0, 9 days). Magnification, $\times 40$

the effects of different incubation times on cell proliferation.

Reverse transcriptase-polymerase chain reaction analysis of mRNA expression

The reverse transcriptase-polymerase chain reaction (RT-PCR)^[6,7] was used to measure the expression of β -catenin, adenomatous polyposis coli (APC), axin, glycogen synthase kinase-3 β (GSK-3 β), and LEF1 mRNA at various time points following treatment with 10 mmol/L LiCl. HFSCs were resuspended in K-SFM medium (without fetal calf serum) and seeded into a 100-mm culture dish at a concentration of 1×10^5 cells/mL. LiCl was then added to the medium at a concentration of 10 mmol/L. RT-PCR was used to measure the expression of β -catenin, APC, axin, GSK-3 β , and LEF1 mRNA after 3, 5, 7, and 9 days in culture. An untreated group was included as a control. Similarly, following treatment with KGF, β -catenin, APC, axin, GSK-3 β , and LEF1 mRNA expression was measured on days 3, 5, 7, and 9. An untreated control group was included.

Isolation of total RNA: total RNA was isolated with TRIZOL using Superscript III (Invitrogen, CA, USA), according to the manufacturer's protocol.

Reverse transcription: template RNA (1 μ g) and 1 μ g Oligo (dT) 15 were added to RNase-free water (to a final volume of 5 μ L). After mixing well, the reaction was incubated at 70 $^{\circ}$ C for 5 min, chilled on ice for 5 min, and then 13.5 μ L RNase-free water, 4 μ L 5 \times RT Buffer, 1 μ L dNTPs, 1 μ L RNAase inhibitor and 1 μ L MMLV RNase were added. The reaction was incubated at 36 $^{\circ}$ C for 10 min, 42 $^{\circ}$ C for 60 min, and then inactivated at 70 $^{\circ}$ C for 10 min, cooled on ice, and stored.

Primer design and synthesis: primer design was based on the target DNA sequences. To avoid contamination of genomic DNA, primer pairs were designed to amplify across an intron [Table 1]. Primers were synthesized by Shanghai Sango Biotech Co. Ltd. (Shanghai, China).

RT-PCR reagents: RT-PCR reagents contained 1 μ L template

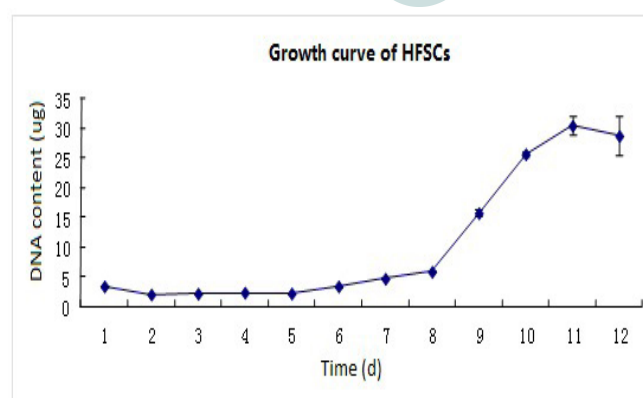


Figure 2: Growth curves of primary culture cells from scalp follicular bulge. HFSCs: hair follicle stem cells.

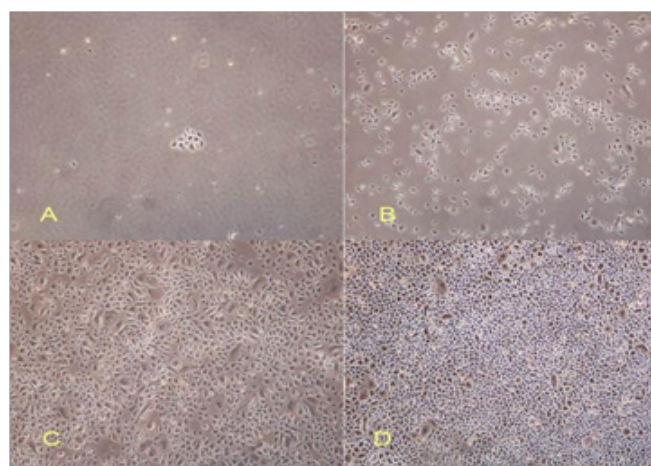


Figure 3: The effect of seeding density on cell growth. Cells were seeded at densities of 1×10^3 cells/mL (A), 1×10^4 cells/mL (B), 1×10^5 cells/mL (C), or 1×10^6 cells/mL (D). Cell proliferation and cells morphology were assessed after 3 days in subculture. Magnification, $\times 40$.

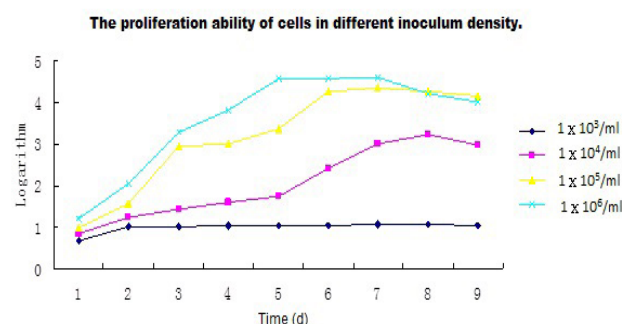


Figure 4: Proliferation of primary culture cells at different seeding densities

RNA, 1.5 μ L of 25 mmol/L MgCl₂, 4 μ L 5 \times PCR buffer, 1 μ L dNTPs, 1 μ L each primer, 0.5 μ L Taq DNA polymerase, and 9.5 μ L RNase-free water. RT-PCR were subjected to an initial denaturation for 3 min at 94 $^{\circ}$ C, and then 35 cycles of 94 $^{\circ}$ C for 45 s, 56 $^{\circ}$ C for 30 s, and 72 $^{\circ}$ C for 1 min. A final extension for 5 min at 72 $^{\circ}$ C was performed before the reaction was stored at 4 $^{\circ}$ C. Reaction products were analyzed by electrophoresis. Primers and annealing temperatures are shown in Table 1.

Statistical analysis

All data were analyzed using SPSS10.0. Statistical significance

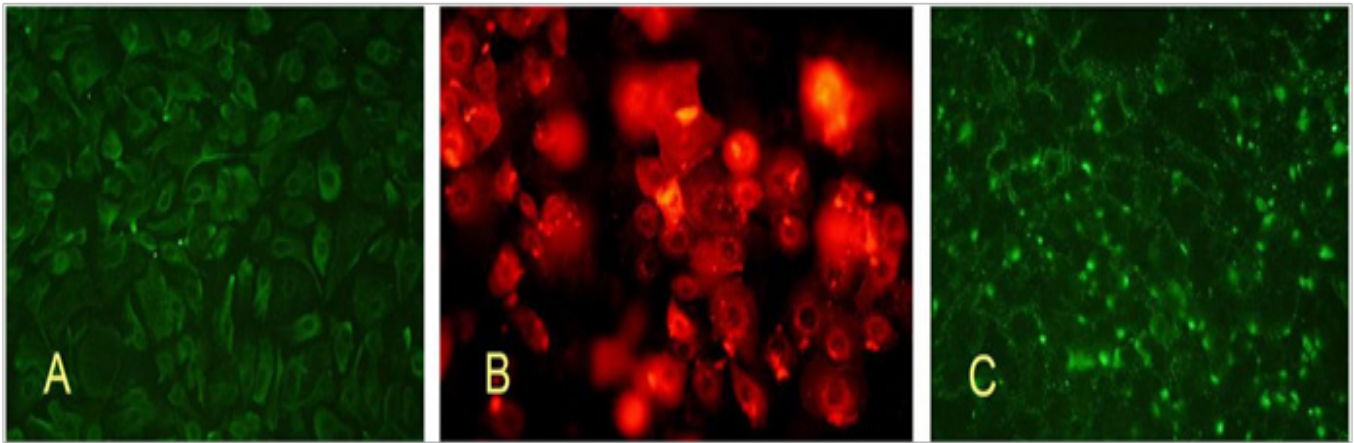


Figure 5: Hair follicle stem cells morphological observation and protein expression. Cells have round or oval nuclei and a high nucleus and cytoplasm ratio. Immunofluorescence staining of pan-cytokeratin (A), K19 (B), and β 1-integrin (C). Magnification, $\times 200$

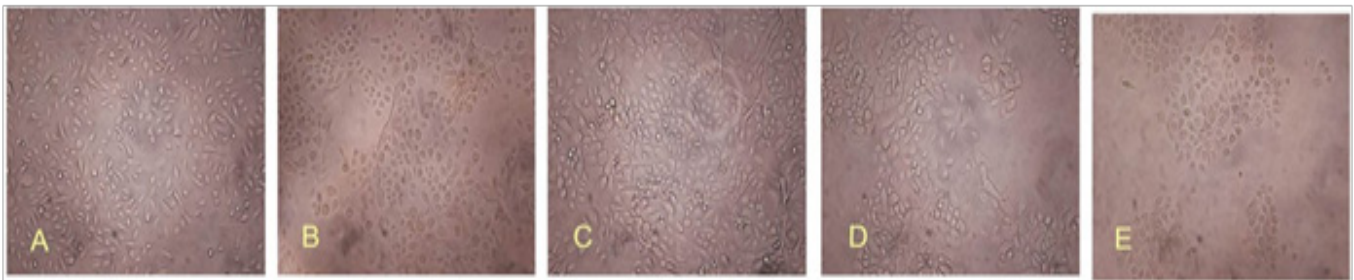


Figure 6: Effect of different LiCl concentrations on hair follicle stem cells proliferation. Cells were assessed 3 days after treatment of LiCl at different concentrations. (A) after treatment with 0 mmol/L LiCl, cells have grown well and display a cobblestone-like appearance; (B) after treatment with 0.5 mmol/L LiCl, cells have become rounded, or occasionally an elongated spindle shape, and show a tendency to aggregate; (C) after treatment with 1.5 mmol/L LiCl, in general, cells have become larger. Occasionally, cells have developed protuberances, which may be related to cell migration; (D) after treatment with 10 mmol/L LiCl, cell morphology has changed. Cells have become highly aggregated and cell density is reduced; (E) after treatment with 25 mmol/L LiCl, cell density has significantly decreased. Both the cytoplasm and nuclei show various morphological changes. The proliferation rate has also decreased. Magnification, $\times 100$

was set at $P < 0.05$; $P < 0.01$ indicates that the difference between experimental groups was significant; $P > 0.05$ indicates no difference between experimental groups.

RESULTS

HFSC growth characteristics

Primary cells derived from the hair follicle bulge were spheroid, small, and evenly sized. Live cells were optically transparent with a clear boundary and clusters of undissociated cells could be seen [Figure 1]. Trypan blue staining showed that 95% of cells were alive. At the initial stage of culture, cell adhesion and activity were weak. After culture in serum-free K-SFM containing epidermal growth factor (EGF) for 1-3 days, a few human HFSCs were observed to adhere

to culture vessel, although most remained in suspension [Figure 1A and B]. After 4-6 days in culture, a few single cells or cell clusters had attached to the culture dish; these had a cobblestone-like appearance, an orderly arrangement, and were highly refractive. Cell numbers increased with increasing culture time [Figure 1C and D]. After 2 weeks in culture, a small number of aging cells were observed.

Dynamics of cell growth

Growth curves [Figures 1 and 2] show that the cell growth rate was slow on days 1-3. On days 4-6, cells grew faster and were in the logarithmic phase. After this point, cell growth became slower and aging cells appeared.

Cell proliferation varied according to seeding density [Figures 3 and 4]. At seeding densities of 1×10^3 and 1×10^4 , a few cells showed clonal growth but cells proliferated slowly and most died after a short time in culture. When the seeding density was increased to 1×10^5 cells/mL, cells proliferated well and showed adherent growth at early time points. Cells seeded at a density of 1×10^6 cells/mL rapidly formed clusters and underwent contact inhibition following rapid nutrient depletion. These cells showed signs of aging.

Identification of HFSCs and characteristics of HFSC protein expression

Pan-cytokeratin expression: adherent pan-cytokeratin-labeled HFSCs showed that the cytoplasm of these cells

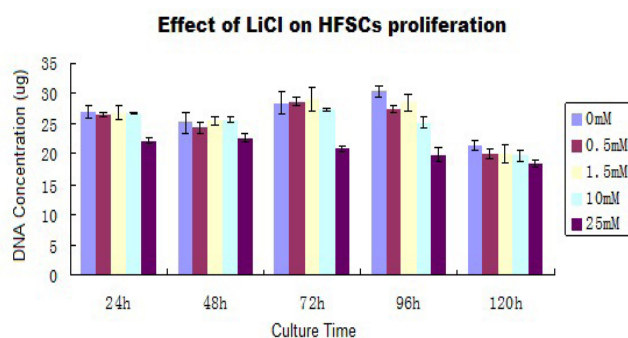


Figure 7: Effect of LiCl on hair follicle stem cells (HFSCs) proliferation

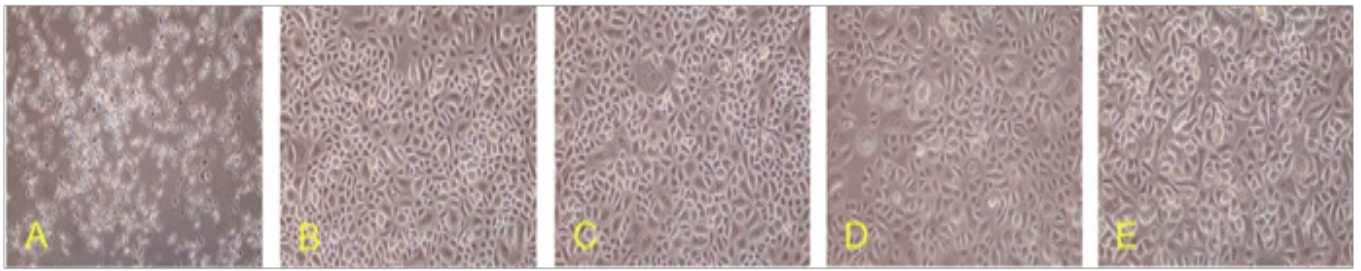


Figure 8: Effect of different keratinocyte growth factor (KGF) concentrations on hair follicle stem cells proliferation. Cells were assessed 3 days after treatment. (A) the KGF 0 µg/L group shows cells have grown well and display a cobblestone-like appearance; (B) the KGF 10 µg/L group shows cell density has increased. A small number of enlarged cells have appeared; (C) the KGF 25 µg/L group shows differentiated cells with enlarged nuclei and enriched cytoplasm can be seen; (D) the KGF 50 µg/L group shows the proportion of differentiated cells increased, and the cell density decreased; (E) the KGF 100 µg/L group shows the proportion of differentiated cells increased, cell aging was observed. Magnification, ×100.

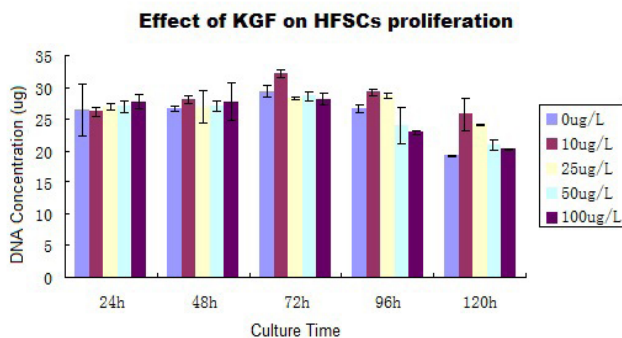


Figure 9: Effect of keratinocyte growth factor (KGF) on hair follicle stem cells (HFSCs) proliferation

were positive for pan-cytokeratin [Figure 5A]. Cytokeratin is a defining feature of HFSCs.^[5,8]

K19-Cy3 expression: isolated keratin 19 (K19)-labeled HFSC clusters were positive for cytoplasmic K19 [Figure 5B]. K19 is a specific cytoplasmic marker for HFSCs.^[5,9]

β1-integrin expression: HFSCs showed a high rate of β1-integrin expression, as shown in Figure 5C. Positively stained cells grew in clusters. Previous studies have confirmed that β1-integrin is a membrane marker for HFSCs.^[5,8]

The influence of LiCl on HFSC proliferation

There were no significant differences between the proliferation rates of HFSCs treated with lower doses of LiCl and that of the control group; there was an inverse correlation between dose and proliferation rate at higher concentrations of LiCl than 10 mmol/L [Figures 6 and 7]. LiCl concentrations less than 10 mmol/L had no effect on the proliferation rate; moreover, treatment with 0-10 mmol/L LiCl did not markedly affect cell proliferation, especially for culture times greater than 72 h ($P > 0.05$). However, the proliferation rate decreased at a LiCl concentration of 25 mmol/L; there was a clear difference between treated and control cells at each time point ($P < 0.05$).

After 24 h of culture, DNA quantitation in the 25 mmol/L group compared with 0 mmol/L group, $P < 0.05$, as compared with other groups, $P > 0.05$; after 48 h of

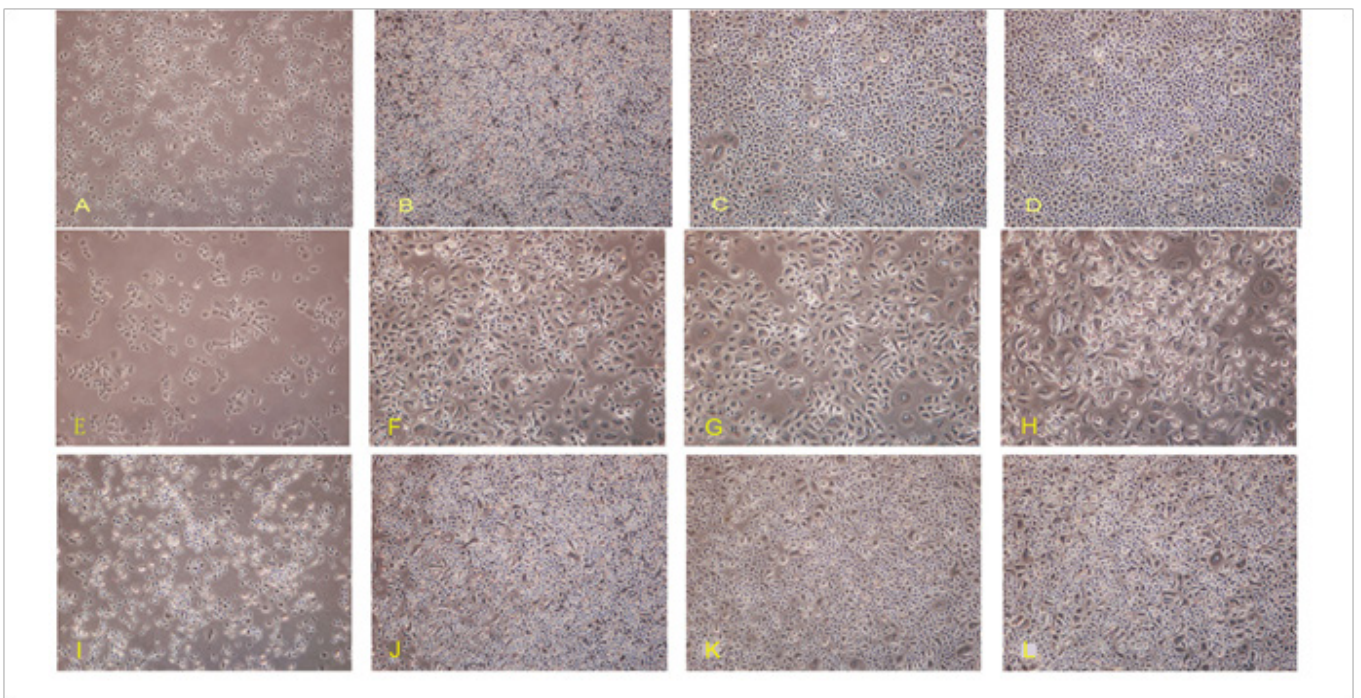


Figure 10: Untreated hair follicle stem cells (HFSCs). Cells morphological features of negative controls (HFSCs subculturing without intervention) after 3 (A), 5 (B), 7 (C), and 9 (D) days in culture. HFSC treated with 10 mmol/L LiCl. Cells morphological features shown after 3 (E), 5 (F), 7 (G), and 9 (H) days in culture. HFSCs treated with 10 µg/L KGF. Cells morphological features shown after 3 (I), 5 (J), 7 (K), and 9 (L) days in culture. Magnification, ×40.

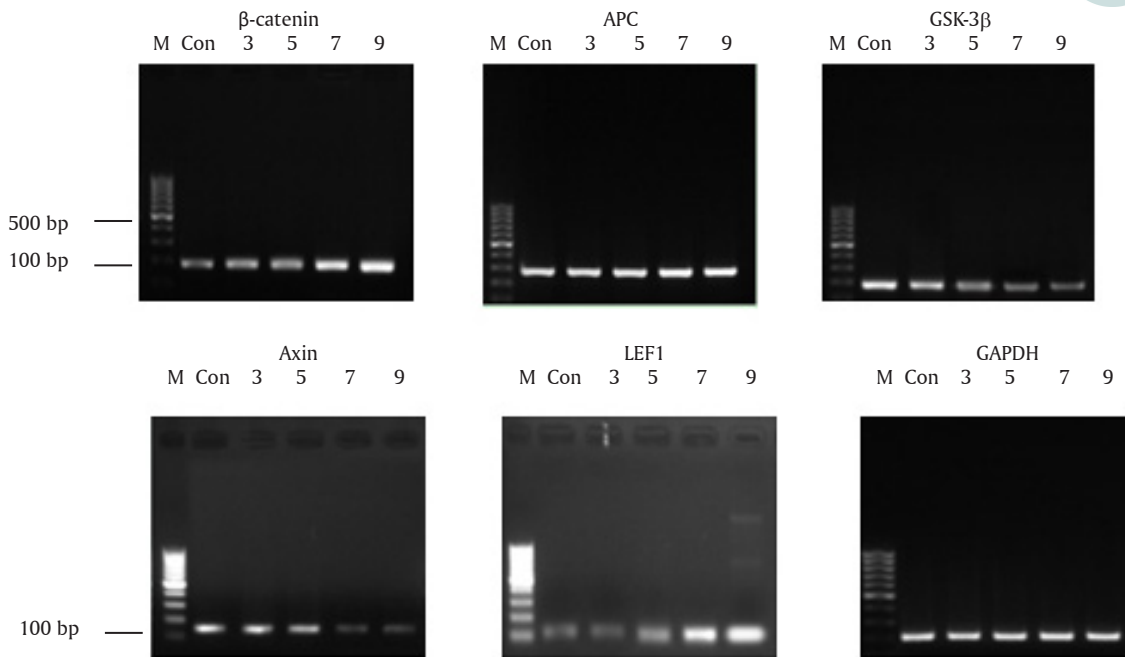


Figure 11: Effect of 10 mmol/L LiCl on β -catenin, APC, GSK-3 β , axin, and LEF1 mRNA expression. APC: adenomatous polyposis coli; GSK-3: glycogen synthase kinase-3 β ; LEF1: lymphoid enhancer factor-1.

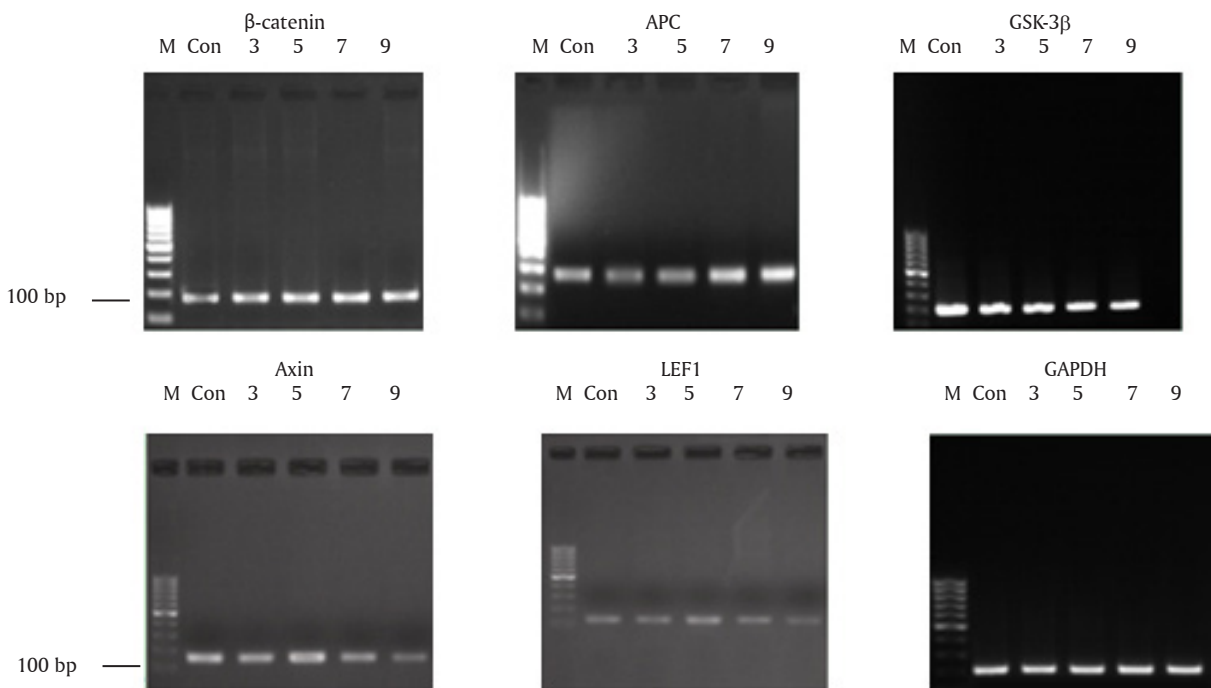


Figure 12: Effect of 10 μ g/L KGF on β -catenin, APC, GSK-3 β , axin, and LEF1 expression. KGF: keratinocyte growth factor; APC: adenomatous polyposis coli; GSK-3: glycogen synthase kinase-3 β ; LEF1: lymphoid enhancer factor-1.

culture, DNA quantitation in 25 mmol/L group compared with 0 mmol/L group, $P < 0.05$, as compared with other groups, $P > 0.05$; after 72 h of culture, DNA quantitation in 25 mmol/L group compared with 0 mmol/L group, $P < 0.01$, as compared with other groups $P > 0.05$; after 96 h of culture, DNA quantitation in 25 mmol/L group compared with 0 mmol/L group, $P < 0.01$, as compared with other groups, $P < 0.05$, also representing a significant difference; after 120 h of culture, DNA quantitation in 25 mmol/L group compared with 0 mmol/L group $P < 0.05$, as compared with other groups $P > 0.05$.

Effect of KGF on HFSC proliferation

The proliferation rate of HFSCs increased following KGF treatment, with a direct correlation between KGF dose and HFSC proliferation rate being observed [Figures 8 and 9]. HFSCs proliferated well at KGF concentrations less than 50 μ g/L. By contrast, at very high KGF concentrations HFSCs proliferated well at early time points, but died prematurely at later time points. At KGF concentrations of 10-25 μ g/L, cells proliferated well and showed no signs of premature aging at later time points.

Statistical analyses showed that after 24 h of culture, there were no significant differences between the KGF-dose

treatment groups and the control group.

After 48 h of culture, the KGF 10 $\mu\text{g/L}$ treatment group was significantly different as compared with the control group ($P < 0.05$), but there was no difference between the control group and the other KGF-dose treatment groups. After 72 h of culture, the KGF 10 $\mu\text{g/L}$ treatment group showed a significant increase in proliferation when compared with the control group ($P < 0.01$). However, there was no observed difference between the control group and the other KGF-dose treatment groups. After 96 h of culture, the 10, 25, and 100 $\mu\text{g/L}$ KGF treatment groups showed a significant increase in proliferation when compared with the control group ($P < 0.01$). However, there was no significant difference between the control group and the 50 $\mu\text{g/L}$ KGF treatment group. After 120 h of culture, all doses of KGF had significantly increased the proliferation of HFSCs compared with the control group ($P < 0.05$).

Effects of LiCl and KGF on HFSC differentiation and morphology.

There were obvious differences in cell morpho-differentiation, adhesion, and proliferation between the 10 mmol/L LiCl and 10 $\mu\text{g/L}$ KGF treatment groups and the control group [Figure 10A-D]. The LiCl 10 $\mu\text{g/L}$ treatment group showed a significant increase in proliferation [Figure 10E-H]. By contrast, the proliferation rate of KGF-treated cells initially increased in a dose-dependent manner. However, cell proliferation decreased with aging and vacuoles formed within the cells at later time points [Figure 10I-L].

Effects of LiCl and KGF on the mRNA expression of components of the Wnt/ β -catenin signaling pathway.

Following treatment with 10 mmol/L LiCl, the mRNA expression of β -catenin was increased when compared with control cells. There was also an increased expression of APC and LEF1 mRNA, but a gradual reduction in axin and GSK-3 β mRNA expression [Figure 11].

Following treatment with 10 $\mu\text{g/L}$ KGF, the expression of β -catenin mRNA did not change markedly compared with control cells; however, GSK-3 β and LEF1 mRNA expression gradually declined [Figure 12].

DISCUSSION

HFSC differentiation is regulated by multiple factors,^[1] which interact to form an intricate regulatory system.^[1,2] The main intrinsic regulatory factors affecting HFSC proliferation and differentiation are Wnt, β -catenin and the Notch and exit domain A (EDA) signaling pathways.^[1,10-12] Extrinsic signals primarily include mitogens, intercellular interactions, cell growth factors [e.g. basic fibroblast growth factor (bFGF) and EGF], and some chemical substances (e.g. LiCl).^[13-15] These signals constitute the external microenvironment of proliferation and differentiation of HFSCs. KGF is a member of the FGF superfamily, which regulates the proliferation and differentiation of various cell types. KGF expression in matrix cells is sharply upregulated when skin is injured.^[13]

KGF also facilitates HFSC proliferation. In this study, HFSCs were isolated from the hair follicle bulge and the effects of different concentrations of LiCl and KGF on HFSC proliferation and differentiation were explored.

LiCl, a crucial Wnt signaling agonist, inhibits the activity of GSK-3 β .^[11] GSK-3 phosphorylation at serine-9 prevents GSK-3 β from degrading β -catenin, thus elevating β -catenin expression.^[14] This study found that low LiCl concentrations (0-10 mmol/L) not only induce β -catenin expression but also slightly increase HFSCs proliferation. However, proliferation decreased as the LiCl concentration was increased. LiCl treatment also led to a reduction in cell adhesion and caused HFSCs to grow in dispersed clusters. This is a result of LiCl inhibiting intracellular E-cadherin expression, which weakens cell adhesion and facilitates cell migration.^[15] This phenomenon may result from E-cadherin transposition caused by β -catenin up-regulation. These data suggest that changes in β -catenin expression can change cell adhesion, which has an important role in promoting cell proliferation.

In the current study, β -catenin expression directly correlated with the β -catenin-axin-APC-GSK-3 β complex, but inversely correlated with GSK-3 β and axin levels. Axin, a critical negative regulator of the Wnt signaling pathway, is a key component of the β -catenin degradation complex. It has several protein-protein interaction domains and functions as scaffolding protein in various protein complexes. Axin brings GSK-3 β in close proximity to β -catenin and regulates the degradation of phosphorylated β -catenin. This study demonstrated that LiCl suppresses the expression of GSK-3 β mRNA and thus inhibits the formation of the axin complex, which indirectly elevates the level of β -catenin.

As a downstream transcription factor in the Wnt signaling pathway, LEF1 activates the transcription of specific genes. According to recent reports,^[7,8,16] endogenous LEF1 synergizes with Wnt signaling. It is widely accepted that β -catenin activates downstream target genes through a complex formation with LEF1. Cofactor ALY, enhancer TCR α , and LEF1 cooperatively form a higher-order nucleoprotein complex that enhances the synergistic activation of β -catenin/LEF1 and thus transcriptional activity.^[16] This study found that LiCl treatment increased the levels of β -catenin and LEF1 mRNA along with the course induce. It is likely that increased protein levels of β -catenin complex with LEF1. These results are identical with those of the above-mentioned mechanisms of the Wnt signaling pathway, and indicate that activations of the β -catenin and LEF1 signaling pathways are involved in HFSC's differentiation.

Numerous studies have shown that β -catenin functions by forming a complex with LEF1 in the Wnt signaling pathway.^[17-20] Zhu *et al.*^[17] transfected keratinocytes with retrovirus and found that mutant LEF1 expressed in the basal lamina of transgenic mice cannot interact with β -catenin. Thus, hair formation is prevented and adult basal epidermal cells are transformed into pluripotent embryonic-like ectoderm. LEF1 is an essential transcriptional factor for the normal development of hair follicles. LEF1 expression stimulates the stem cell to develop into hair, facilitates differentiation of both hair matrix cells and hair

follicles, and participates in the formation of the root sheath.

In an attempt to improve our understanding of the role of β -catenin in HFSC proliferation and differentiation, this study investigated whether KGF treatment stimulates these processes via the Wnt signaling pathway. The results indicate that adding KGF to serum-free culture medium containing EGF stimulated HFSC proliferation. Although this effect was not apparent in the first 48 h of culture, for incubation times more than 48 h, there was a marked difference in DNA content between the 10 μ g/L KGF treatment group and control cells. The reduction in DNA content indicates that KGF maintains cell proliferation and postpones keratinocyte differentiation.

Richardson *et al.*^[6] observed repression of hair follicle induction by KGF and EGF in cultured mice embryo skin. They found that Wnt signaling plays a role in the initial formation of hair follicles, and that the latter stages of follicle formation are dependent on the Shh signal. Formation of the hair follicle is usually caused by activation of Wnt signaling and upregulation of β -catenin mRNA. The Shh activating signal also elevates Gli1 mRNA. Nuclear LEF1 expression occurs at the initial stages and increases after 24 h. However, epidermal cells induced by KGF or EGF contain high nuclear LEF1 expression at all time points. KGF and EGF noticeably inhibited several important signaling molecules produced by hair follicles, including Wnt (LEF1, DKK4), Shh single pathway, and delayed HFSC differentiation. Recently, Andreadis *et al.*^[21] using a skin equivalent model system, demonstrated that KGF significantly facilitates the proliferation of epidermal cells inoculated in a cellular dermal matrix, which is associated with induced expression of α 5 β 1 integrins and delayed keratin-10 expression. In the present study, HFSCs were observed to exhibit a low proliferation rate in the first 72 h after KGF treatment, especially in the 10 μ g/L treatment group. When the culture time was longer than 72 h, DNA measurements showed that KGF treatment postponed apoptosis, but that high KGF concentrations accelerated cell aging. This may be related to excessive nutrient consumption in the *in vitro* culture medium. In cells treated with 10 μ g/L KGF β -catenin expression increased slightly and GSK-3 β expression decreased on day 7, as HFSCs underwent differentiation. LEF1 levels, however, declined at an early stage. How KGF switches the Wnt/ β -catenin pathway from an activated state to an inhibited state is unclear. However, this data suggest that KGF concentration inversely correlates with LEF1 expression and represses HFSC differentiation and the formation of hair follicles. This result supports a direct association of KGF with the Wnt signaling pathway through reducing LEF1 levels. These data are consistent with the results of Richardson *et al.*^[6] However, some of the links that mediate KGF regulation of the Wnt signaling pathway are not yet clear and require further investigation.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Yang B, Xiang MJ. Regulation of Wnt signaling pathway involved in the differentiation of hair follicle stem cells induced by lithium chloride. *Zhongguo Zuzhi Gongcheng Yanjiu yu Linchuang Kangfu* 2011;15:9202-6.
2. Taylor G, Lehrer MS, Jensen PJ, Sun TT, Lavker RM. Involvement of follicular stem cells in forming not only the follicle but also the epidermis. *Cell* 2000;102:451-61.
3. Waikel RL, Kawachi Y, Waikel PA, Wang XJ, Roop DR. Deregulated expression of c-Myc depletes epidermal stem cells. *Nat Genet* 2001;28:165-8.
4. DasGupta R, Kaykas A, Moon RT, Perrimon N. Functional genomic analysis of the Wnt-wingless signaling pathway. *Science* 2005;308:826-33.
5. Michel M, Török N, Godbout MJ, Lussier M, Gaudreau P, Royal A, Germain L. Keratin 19 as a biochemical marker of skin stem cells *in vivo* and *in vitro*: keratin 19 expressing cells are differentially localized in function of anatomic sites, and their number varies with donor age and culture stage. *J Cell Sci* 1996;109:1017-28.
6. Richardson GD, Bazzi H, Fantauzzo KA, Waters JM, Crawford H, Hynd P, Christiano AM, Jahoda CA. KGF and EGF signalling block hair follicle induction and promote interfollicular epidermal fate in developing mouse skin. *Development* 2009;136:2153-64.
7. Mullis KB, Faloona FA. Specific synthesis of DNA *in vitro* via a polymerase-catalyzed chain reaction. *Methods Enzymol* 1987;155:335-50.
8. Watt FM. Epidermal stem cells: markers, patterning and the control of stem cell fate. *Philos Trans R Soc Lond B Biol Sci* 1998;353:831-7.
9. Commo S, Gaillard O, Bernard BA. The human hair follicle contains two distinct K19 positive compartments in the outer root sheath: a unifying hypothesis for stem cell reservoir. *Differentiation* 2000;66:157-64.
10. Widelitz RB. Wnt signaling in skin organogenesis. *Organogenesis* 2008;4:123-3.
11. Lapébie P, Gazave E, Ereskovsky A, Derelle R, Bézac C, Renard E, Houliston E, Borchellini C. Wnt/ β -catenin signaling and epithelial patterning in the homoscleromorph sponge oscarella. *PLoS One* 2009;4:1-6.
12. Lowell S, Jones P, Le Roux I, Dunne J, Watt FM. Stimulation of human epidermal differentiation by delta-notch signaling at the boundaries of stem-cell clusters. *Curr Biol* 2000;10:491-500.
13. Marchese C, Chedid M, Dirsch OR, Csaky KG, Santanelli F, Latini C, LaRochelle WJ, Torrisi MR, Aaronson SA. Modulation of keratinocyte growth factor and its receptor in reepithelializing human skin. *J Exp Med* 1995;182:1369-76.
14. Wexler EM, Geschwind DH, Palmer TD. Lithium regulates adult hippocampal progenitor development through canonical Wnt pathway activation. *Mol Psychiatry* 2008;13:285-92.
15. Rao AS, Kremenevskaja N, Resch J, Brabant G. Lithium stimulates proliferation in cultured thyrocytes by activating Wnt/beta-catenin signalling. *Eur J Endocrinol* 2005;153:929-38.
16. Hsu SC, Galceran J, Grosschedl R. Modulation of transcriptional regulation by LEF-1 in response to Wnt-1 signaling and association with beta-Catenin. *Mol Cell Biol* 1998;18:4807-18.
17. Zhu AJ, Watt FM. Beta-catenin signaling modulates proliferative potential of human epidermal keratinocytes independently of intercellular adhesion. *Development* 1999;126:2285-98.
18. DasGupta R, Rhee H, Fuchs E. A developmental conundrum: a stabilized form of beta - catenin lacking the transcriptional activation domain triggers features of hair cell fate in epidermal cells and epidermal cell fate in hair follicle cells. *J Cell Biol* 2002;158:331-44.
19. Nguyen H, Rendl M, Fuchs E. Tcf3 governs stem cell features and represses cell fate determination in skin. *Cell* 2006;10:171-83.
20. Fathe C, Wilson L, Shah K, Kim B, Hocking A, Moon R, Isik F. Wnt signaling induces epithelial differentiation during cutaneous wound healing. *BMC Cell Biol* 2006;7:4.
21. Andreadis ST, Hamoen KE, Yarmush ML, Morgan JR. Keratinocyte growth factor induces hyperproliferation and delays differentiation in a skin equivalent model system. *FASEB J* 2001;15:898-906.

Reconstruction of the anterior skull base with radial forearm free tissue transfer: case series and literature review

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ABSTRACT

Aim: Reconstruction of the anterior skull base offers an especially complex challenge as the impermeable separation of the dural space and the upper aerodigestive tract must be maintained. We propose the use of the radial forearm free flaps (RFFF) as a superb method of re-establishing integrity in anterior skull base defects. **Methods:** Literature review and retrospective analysis of 4 single-institution cases of anterior skull base defects reconstructed with a RFFF. Data were collected on successful and unsuccessful defect repairs, complication rates, and length of hospitalization. **Results:** The indications for surgery were pneumocephalus, recurrent brain abscesses, recurrent frontal sinus mucocoeles, and cerebrospinal fluid leak. Of the 4 cases, 1 was complicated by a small dehiscence of the craniotomy site, 1 developed infection, and 2 required further surgery. **Conclusion:** The use of RFFF is an excellent option for reconstruction of defects in the anterior skull base, especially those complicated by radiation, prior surgery, or infections. Patients with skull base defects are inherently at high risk for post-surgical complications. The RFFF transfers healthy, viable, well-vascularized tissue to prevent further infections and provides a reliable barrier between the dural and sinonasal spaces. This can reduce the need for repeat neurosurgical operations and hospitalizations.

Key words:

Anterior skull base; defect; reconstruction; plastic surgery; free flap; radial forearm free flap

INTRODUCTION

The use of free tissue transfer for reconstructing the anterior skull base has become a well-established treatment for the rehabilitation of patients with life-threatening and disfiguring defects resulting from craniofacial resections. Defects of the anterior skull base are intrinsically complex with an irregular serrated surface separating the dura from the sinonasal space, and are often complicated further by radiation, multiple prior surgical interventions, and repeat

infections.^[1-4] Patients with these defects are generally quite ill with poor nutritional status and a weakened immune system. They are at risk for multiple life-threatening conditions including meningitis, encephalitis, brain abscess, persistent cerebrospinal fluid (CSF) leak, pneumocephalus, and even herniation of brain tissue.^[1-3] Thus it is paramount that reconstruction of anterior skull base defects be

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complete, reliable, and reconstruct a “water tight” barrier between the intracranial cavity and the physiologically contaminated upper aerodigestive tract.

In 1966, Ketcham *et al.*^[5] first attempted the use of a split thickness skin graft to cover exposed dura in a patient who had undergone resection of a tumor located in the anterior skull base, but this procedure resulted in a persistent CSF leak. Since this time, many other surgical reconstructive methods have been utilized because surgeons realized the importance of using well-vascularized tissue in reconstructing a dural seal including regional flaps such as the temporalis, muscle pericranial grafts, and galea-frontalis-myofascial flaps.^[6-8] In cases where local flaps have already failed or are otherwise not possible due to destructed wound beds, the use of pedicled flaps such as the pectoralis major, sternocleidomastoid, trapezius, and latissimus dorsi have been popular.^[6,9] The drawbacks typically observed with these pedicled flaps are related to their distance limitations and bulkier size. The sternocleidomastoid flap is additionally challenging due to its segmental blood supply.^[4] The endoscopically performed pedicled nasoseptal flap is a newer method gaining popularity within the otolaryngology community.^[10] Weber *et al.*^[11] described success in using a variety of free tissue transfer for both skull base defects and craniofacial reconstruction with exposed dura for anterior, middle and posterior skull defects combined. Other novel efforts to repair these complex defects have been reported, including a sandwiched or folded free fasciocutaneous flap, and titanium mesh bolstered free tissue flaps.^[12,13]

The last two decades have brought the increasing popularity of free tissue transfer for defects in this region.^[14-16] As noted by Neligan *et al.*,^[9] the use of distant free flaps is associated with a lower overall complication rate (33.5%) than both local pedicled flaps (38.8%), and regional flaps/grafts (75%). Due to their exceptional vascularity, ability to fill irregular spaces with a thin but sturdy fascial layer, and overall decreased rate of complication, the authors hypothesized that the use of radial forearm free flaps (RFFF) for the reconstruction of especially complex anterior skull base defects would offer an ideal reconstructive option. The authors present a case series of four patients to have reconstruction of the anterior skull base with radial forearm free tissue transfer.

METHODS

Four patients presented to our institution with complex anterior skull base defects, complicated by infections, pneumocephalus, and CSF leaks. All four were treated with RFFF for closure of the communicating spaces. Retrospectively, the patient scenarios, surgical management, and outcomes were reviewed. Data collected included flap survival, complications requiring non-operative management, the need for reoperation, length of hospital stay, and donor site morbidity. Patient diagnosis, age, nutritional status, medical history, social history, flap size, and recipient vessels were also reviewed.

The radial forearm flaps were usually taken from the non-dominant hand after Allen’s test confirmed collateral flow.

The superficial temporal vessels were also palpated and assessed with Doppler bilaterally to determine the best place for inset keeping in mind previous scars from operations, radiation, and/or infections to select the best side for vessel dissections. The flap was first de-epithelialized prior to elevation [Figure 1]. The neurosurgical team gained access to the anterior skull base and debrided any non-viable tissue, including infected and devascularized bone, as necessary [Figure 2]. Most often, the superficial temporal vessels were used and dissected proximally until encountering a curvature



Figure 1: Radial forearm flap de-epithelialized and raised in this left-hand dominate patient

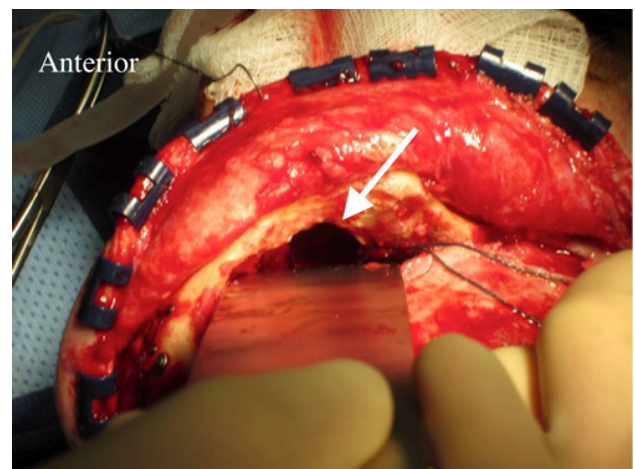


Figure 2: Anterior skull base defect after debridement. Arrow denotes the defect

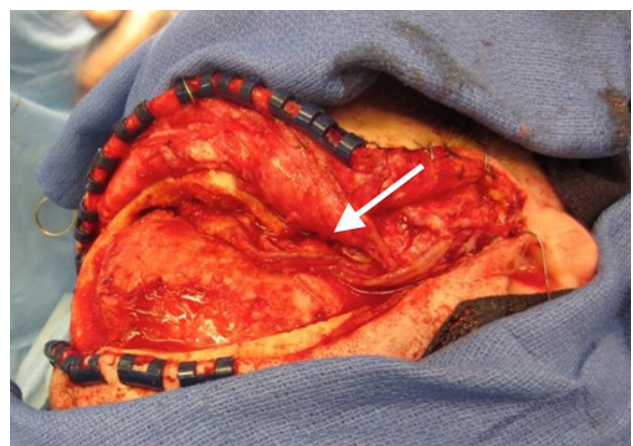


Figure 3: Radial forearm free flap filling the anterior skull base defect. Arrow denotes the pedicle

of the vessels where they dive deep; the more proximal area of the vessels were less damaged from previous radiation. Using the microscope, the recipient vessels were dissected free and prepared for microvascular anastomosis. The radial artery was hand-sewn to the superficial temporal artery with interrupted 9-0 nylon suture and a venous coupler was used for the venous anastomosis. The flap was then introduced into the defect to ensure adequate filling of the dead space [Figure 3]. Skin was closed primarily over the anastomosis. The donor site was first reduced in size by bringing in the tissue flaps and suturing directly to the deeper structures in the forearm, which allowed for a smaller skin graft to be taken. The forearm was then splinted to protect the skin graft. We did not use intracranial monitoring devices or drains. Patients were monitored in the surgical intensive care unit for three days with Doppler checks distal to the anastomosis every hour.

All research was reviewed and approved by the University of California Irvine Office of Research Institutional Review Board (HS# 2013-9374).

RESULTS

All of the patients with anterior skull base defects were males, between the ages of 51 to 63 years. Three of the patients had prior operative interventions performed for malignancy involving the anterior skull base, while the fourth patient had undergone repeated craniotomies for recurrent frontal sinus mucocoeles. Although all patients had a normal or near-normal body mass index (range 20.6-26.7), most also had suboptimal nutrition status with an albumin below 3.0 g/dL. Half of the patients had a remote smoking history, and all but one had a prior diagnosis of diabetes requiring control of hyperglycemia [Table 1].

All 4 patients had prior surgical intervention ($n = 4$), including pericranial flaps, but no patient had a previous free tissue transfer. In addition to surgically altered anatomy, all patients had wound beds further complicated

by a combination of recurrent infection ($n = 3$), radiation ($n = 2$), or persistent CSF leak ($n = 1$). In three patients the recipient vessels were the superficial temporal artery and vein. The facial artery and a branch of the external jugular vein were used for anastomosis in one patient. The average total hospital stay was 22.5 days (range 5-38) and average post operative stay was 16 days (range 4-27) [Table 2].

Infection was the most common postoperative complication, affecting three patients (75%) and requiring surgical debridement and/or drainage in two. These affected the same patients who had recurrent infections prior to the RFFF coverage. Patient 1 presented with chronic osteomyelitis which was discovered at the time of the RFFF surgery. The patient later developed a CSF leak with an epidural abscess and a wound breakdown at the craniotomy site, requiring drainage and repair, respectively. Patient 3 presented initially with recurrent abscesses, and although postoperatively the patient developed bacteremia, this resolved with IV antibiotics, and there has been no abscess recurrence at ten months follow up. Patient 4 developed a subgaleal infection requiring washout, and a subdural empyema requiring drainage, but his reconstruction remained free of infection at 22 months follow up. Importantly, despite these infective complications, no patients required reoperation on the flap.

All flaps were viable at the conclusion of the study as demonstrated by Doppler flow, and were successful based on clinical exam. Only one patient had a donor site morbidity, which resolved with Integra placement (LifeSciences, Plainsboro, New Jersey), combined with sub-atmospheric pressure therapy. No other major donor site morbidity was noted.

DISCUSSION

Anterior skull base defects are complex surgical problems and further they are associated with patients who have many comorbidities. They are prone to re-hospitalization and repeated neurosurgical operations given their high risk for life-threatening complications, including

Table 1: Patient demographics

Patient	Age, years	BMI	Albumin	Co-morbidities	Tobacco
1	51	23.2	2.6	CVA, seizures	No
2	62	20.6	2.3	Diabetes, hypertension, hyperlipidemia	Yes
3	61	26.7	Not available	Diabetes	No
4	63	22.2	2.4	Diabetes, hypertension, hyperlipidemia	Yes

BMI: body mass index; CVA: cerebrovascular accident

Table 2: Patient outcomes following reconstruction of anterior skull base with radial forearm free tissue transfer

Patient	Presenting condition	Indication for free tissue transfer	Flap size	Hospital length of stay (days)	Complications	Follow up time (months)
1	Squamous cell cancer of the maxillary sinus	Pneumocephalus	9 cm × 11 cm	15	CSF leak Epidural abscess	12
2	Esthesio-neuroblastoma of anterior skull	Recurrent brain abscesses	7 cm × 11 cm	9	Recurrent seizures Recurrent seizures	13
3	Recurrent frontal sinus mucocoele	Pneumocephalus	Not available	5	none	14
4	Recurrent meningioma of frontal and ethmoidal sinuses	CSF leak	5 cm × 7 cm	36	Subdural empyema Meningitis	22

CSF: cerebrospinal fluid

Table 3: Free tissue transfer alternatives for reconstruction of anterior skull base defects

	Benefits	Disadvantages
Radial forearm free flap	Versatile, reliable donor site anatomy, long pedicle length, size is appropriate for most anterior skull base defects	Visible donor site scar. Cannot cover very large skull base defects. Shorter hospital stays compared to other free tissue transfers
Latissimus dorsi muscle free flap	Consistent vascular pedicle and its large muscle	Larger donor site defect, greater risk of seroma, may result in redundant bulky tissue in an anterior skull base defect
Vertical rectus abdominis muscle free flap	Consistent vascular pedicle and its large muscle	Larger donor site defect, may result in redundant bulky tissue in an anterior skull base defect
Serratus anterior muscle free flap	Longer pedicle, versatile size	Can only reliably cover small skull defects
Temporoparietal fascial flaps	Thin and pliable, can be tailored to fit many defect sizes	May not provide long-term durable coverage. Less able to obliterate dead space. Limited rotation, can only provide coverage for anterior defects
Omental free flap	Minimal donor site scar, can be tailored to fit many defect sizes	Can thin over time and may not provide long-term durable coverage
Pedicled trapezius flap	Less complex operation without risk of vascular anastomoses	Only appropriate for low or inferior defects; pedicle length is limited
Pedicled latissimus dorsi	Less complex operation without risk of vascular anastomoses	Only appropriate for low or inferior defects; pedicle length is limited

meningitis, persistent CSF leak, herniation of brain tissue, pneumocephalus, encephalitis, and brain abscess.^[2,3] Patients with malignant tumors of the anterior skull base are prone to even higher rates of complication post-resection.^[17] As described by Bentz *et al.*,^[4] even in patients without confounding complications, the 5-year disease specific survival rate for patients undergoing anterior skull base resection for malignancy is 57%. Those patients with anterior skull base defects whose courses are complicated by prior surgical intervention, radiation, chronic infection, or fistula formation are at even greater risk for death and complications, and often suffer extended hospitalization and repetitive attempts at surgical correction.^[2]

The impact of prior treatment on overall survival of these complicated patients is significant. As noted by Jackson *et al.*^[18] in a series of 155 patients with tumors affecting the anterior skull base (malignant and non-malignant), survival was 85% for patients with no prior treatments, but only 48% for patients with prior intervention. Dos Santos *et al.*^[19] reported in a review of 81 patients who underwent skull base surgery that prior surgical treatment was a pre-operative factor that affected survival significantly. As reported by Teknos *et al.*,^[1] patients with skull base defects who have received prior radiation have a significant increase in hospital stay, with an average stay of 17.7 days versus 12.4 days in un-radiated patients. It is therefore important to choose the treatment with the highest chance of success, whether it is the initial repair or a revision of previous failed operations. With this goal, the reliable and well-vascularized RFFF is a reasonable treatment for correction of anterior skull base defects in complex wound beds, especially those weakened by prior interventions.^[20]

The RFFF is robust, predictable, and well-vascularized, yet lacks the bulkiness of muscle or myocutaneous flaps and is able to fill dimensionally intricate spaces. Compared to other pedicled or free tissue transfers, the radial forearm free flap's reliability and predictability make it an excellent option for infected, radiated buried anterior skull base reconstruction in complex patients who have received previous treatment [Table 3]. Our patients presented with prior surgical

intervention ($n = 4$), recurrent infection ($n = 3$), radiation ($n = 2$), persistent CSF leak ($n = 1$), or a combination of these. In our experience with these complex patients with prior therapeutic interventions, we demonstrate improved outcomes compared to previously published results, including 100% flap survival. For example, we noted an average post operative hospital stay of 16 days (range 4-37), compared to an average hospital stay of 26.4 days reported previously in the literature for cranial base reconstruction with free tissue transfer.^[17] To maximize the quality of life of patients with anterior skull base defects, it is essential to minimize their time spent in the hospital and minimize or eliminate the need for any further operations. To this end, we feel that anterior skull base reconstruction with the well-vascularized and highly reliable RFFF is an excellent option for the ill or complex patient who has received prior anterior skull base radiation or surgical intervention.

This case series demonstrates in four patients the successful reconstruction of anterior skull base with radial forearm free tissue transfer. Our flaps were successful in damaged, inhospitable wound beds and the authors are confident that this should be considered as an early reconstructive option in this patient population. Debridement of infected tissue is of upmost importance in these patients, Weber *et al.*^[11] described flap loss secondary to purulent material found at the time of initial free tissue transfer which persisted and occluded the pedicle after one week, despite aggressive antibiotic usage. Califano *et al.*^[2] reported a lower complication rate with free tissue transfer when compared to local flaps, even with more complex resections occurring in the free tissue transfer group. He further reported major complications with 35% of local tissue transfer and only 31% with free tissue transfer.^[2] This data combined with our experience with the RFFF suggests that free tissue transfer is a reasonable first choice reconstructive option in anterior skull base defects. Due to the moderate success of local flaps, it is reasonable to utilize these flaps before resorting to a RFFF, since they also do not prevent later anastomosing the radial artery to the superficial temporal artery. For secondary reconstruction or salvage operations, the RFFF should be considered after local flaps or other interventions have failed.

It is important for the plastic surgeon to have a familiarity with anterior skull base defects and the reconstructive possibilities. Fortunately, this defect is not seen everyday, but this means further case series will need to be conducted in order to amass statistically significant data for radial forearm free tissue transfer to anterior skull base defects.

In conclusion, patients with skull base defects are inherently at risk for post-surgical complications. The RFFF is a reliable reconstructive option with the aim of reducing repeat neurosurgical operations and extended hospitalizations. Due to the authors' success with the use of the RFFF, we suggest considering this flap as an early option for reconstruction of anterior skull base defects in those complex patients that have received prior radiation or failed other interventions for soft tissue coverage.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Teknos TN, Smith JC, Day TA, Nettekville JL, Burkey BB. Microvascular free tissue transfer in reconstructing skull base defects: lessons learned. *Laryngoscope* 2002;112:1871-6.
2. Califano J, Coraeiro PG, Disa JJ, Hidalgo DA, DuMornay W, Bilsky MH, Gutin PH, Shah JP, Kraus DH. Anterior cranial base reconstruction using free tissue transfer: changing trends. *Head Neck* 2003;25:89-96.
3. Ganly I, Patel SG, Singh B, Kraus DH, Cantu G, Fliss DM, Kowalski LP, Snyderman C, Shah JP. Craniofacial resection for malignant tumors involving the skull base in the elderly: an international collaborative study. *Cancer* 2011;117:563-71.
4. Bentz BG, Bilsky MH, Shah JP, Kraus D. Anterior skull base surgery for malignant tumors: a multivariate analysis of 27 years of experience. *Head Neck* 2003;25:515-20.
5. Ketcham AS, Hoye RC, Van Buren JM, Johnson RH, Smith RR. Complications of intracranial facial resection for tumors of the paranasal sinuses. *Am J Surg* 1966;112:591-6.
6. Kadlub N, Shin JH, Ross DA, Della Torre T, Ansari E, Persing JA, Ariyan S. Use of the external pectoralis myocutaneous major flap in anterior base skull reconstruction. *Int J Oral Maxillofac Surg* 2013;42:453-7.
7. Scher RL, Cantrell RW. Anterior skull base reconstruction with the pericranial flap after craniofacial resection. *Ear Nose Throat J* 1992;71:210-2, 215-7.
8. Costa H, Cerejo A, Baptista A, Vaz R, Gonçalves M, Guimarães A, Amarante J, Cruz C, Guimarães F. The galea frontalis myofascial flap in anterior fossa CSF leaks. *Br J Plast Surg* 1993;46:503-7.
9. Neligan PC, Mulholland S, Irish J, Gullane PJ, Boyd JB, Gentili F, Brown D, Freeman J. Flap selection in cranial base reconstruction. *Plast Reconstr Surg* 1996;98:1159-66; discussion 1167-8.
10. Hadad G, Bassagasteguy L, Carrau RL, Mataza JC, Kassam A, Snyderman CH, Mintz A. A novel reconstructive technique after endoscopic expanded endonasal approaches: vascular pedicle nasoseptal flap. *Laryngoscope* 2006;116:1882-6.
11. Weber SM, Kim JH, Wax MK. Role of free tissue transfer in skull base reconstruction. *Otolaryngol Head Neck Surg* 2007;136:914-9.
12. Largo RD, Schaefer DJ, Krueger J, Harschnitz O, Zimmerer S, Jaquiéry C, Haug MD, Mariani L, Kunz C. Intracranial application of free fasciocutaneous flaps in a novel sandwich technique for skull base reconstruction. *Int J Oral Maxillofac Surg* 2011;40:931-7.
13. Biron VL, Gross M, Broad R, Seikaly H, Wright ED. Radial forearm free flap with titanium mesh sandwich reconstruction in complex anterior skull base defects. *J Craniofac Surg* 2012;23:1763-5.
14. Valentini V, Fabiani F, Nicolai G, Torroni A, Gennaro P, Marianetti TM, Iannetti G. Use of microvascular free flaps in the reconstruction of the anterior and middle skull base. *J Craniofac Surg* 2006;17:790-6.
15. Chepeha DB, Wang SJ, Marentette LJ, Thompson BG, Prince ME, Teknos TN. Radial forearm free tissue transfer reduces complications in salvage skull base surgery. *Otolaryngol Head Neck Surg* 2004;131:958-63.
16. Burkey BB, Gerek M, Day T. Repair of the persistent cerebrospinal fluid leak with the radial forearm free fascial flap. *Laryngoscope* 1999;109:1003-6.
17. Ganly I, Patel SG, Singh B, Kraus DH, Bridger PG, Cantu G, Cheesman A, De Sa G, Donald P, Fliss D, Gullane P, Janecka I, Kamata SE, Kowalski LP, Levine P, Medina LR, Pradhan S, Schramm V, Snyderman C, Wei WI, Shah JP. Complications of craniofacial resection for malignant tumors of the skull base: report of an International Collaborative Study. *Head Neck* 2005;27:445-51.
18. Jackson IT, Marsh WR, Hide TA. Treatment of tumors involving the anterior cranial fossa. *Head Neck Surg* 1984;6:901-13.
19. Dos Santos LR, Cernea CR, Brandao LG, Siqueira MG, Vellutini EA, Velazco OP, Cruz OL, Morais-Besteiro J, Freitas CA. Results and prognostic factors in skull base surgery. *Am J Surg* 1994;168:481-4.
20. Chang DW, Langstein HN, Gupta A, De Monte F, Do KA, Wang X, Robb G. Reconstructive management of cranial base defects after tumor ablation. *Plast Reconstr Surg* 2001;107:1346-55; discussion 1356-7.

Utility of multi-detector row computed tomography angiography versus Doppler in localization of perforators of anterolateral thigh flaps

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ABSTRACT

Aim: Anterolateral thigh (ALT) flap is widely used in reconstruction of various defects. Preoperative imaging facilitates perforator mapping, overcoming intraoperative uncertainty. The purpose of this study was to investigate the utility of multi-detector row computed tomography angiography (MDCTA) and a handheld Doppler in locating ALT perforators. **Methods:** Twenty patients were randomized into two groups. Group 1 patients received MDCTA and Doppler studies whereas Group 2 received only a Doppler study. The number, location, course, and source of all cutaneous and sizable perforators were compared with intraoperative findings. Surgeons' stress levels during flap harvest and flap harvest time were compared. **Results:** MDCTA findings correlated well with intraoperative findings for perforator type and segmental distribution with 100% concordance. Doppler alone had a 52% rate of concordance. The sensitivity and specificity for MDCTA in demonstrating the presence of perforators were 85.71% and 97.22%, respectively; whereas for Doppler alone the sensitivity and specificity were 80% and 87.91%, respectively. In demonstrating perforator source, MDCTA showed a sensitivity of 100% and specificity of 91.66%, with 100% accuracy. Sensitivity and specificity for sizable perforators were 90% each, with 88.88% accuracy. Doppler studies were unable to provide this information. Comparison of surgeon stress levels showed no differences between the two groups, although the time for flap harvest was significantly shorter in Group 1. **Conclusion:** MDCTA compared to Doppler is more sensitive, specific, and accurate with respect to location, course, and source of perforators.

Key words:

Anterolateral thigh; multi-detector row computed tomography angiography; perforator

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INTRODUCTION

The anterolateral thigh (ALT) flap has become an increasingly popular reconstructive option due to its versatility of design, ability to be thinned and minimal donor site morbidity. The major limitation of this flap is the uncertainty in predicting perforator anatomy due to variability in perforator size and course.^[1] Formal analysis of these variations has not been adequately explored. Many authors have described the common location of ALT perforators as a tool in guiding flap harvest, but few have highlighted the inconsistencies.^[1] To improve operative planning, preoperative imaging is being increasingly utilized. In the past, Doppler ultrasound has been used for perforator mapping, with most studies demonstrating high sensitivity but poor accuracy and high interobserver variability. Despite improvements in ultrasound technology, this technique has been frequently abandoned, and there are trends toward performing no preoperative localization at all.^[2] Multi-detector row computed tomography angiography (MDCTA) has become a powerful noninvasive alternative to conventional digital subtraction angiography in preoperative imaging.^[3-5] The utility of MDCTA for preoperative planning in comparison with Doppler and effectiveness of the ABC system in preoperative perforator localization has not been studied in an adequate number of patients in the Indian population. The present randomized controlled study was designed to investigate the utility of preoperative imaging in the localization of perforators and design of the skin paddle. Flap harvest time, surgeon's stress levels, and operative outcome were also assessed.

METHODS

Patients

In patients undergoing free ALT flaps, the goals were (1) to compare the number, location, course, and source of cutaneous perforators with the use of preoperative MDCTA and a handheld Doppler device, with intraoperative observation as the gold standard; and (2) to compare the subjective stress levels of the surgeon during perforator dissection and flap harvest time in patients who had preoperative MDCTA versus those who did not.

The pilot study done between January and December 2011 included all patients who required a free ALT flap. Patients with a documented history of significant atherosclerotic disease with blockage at the level of the infrarenal aorta, lower limb infections, scars, prior surgery to the thighs, and preexisting renal disease, diabetes, or cardiovascular disease were excluded.

Handheld Doppler localization

All patients underwent preoperative perforator localization using a handheld audible Doppler probe (Huntleigh Healthcare, 8 MHz, Cardiff, UK) performed by an independent assessor who was blinded to the MDCTA findings. The patient was placed in the supine position with the leg straight in a neutral position. A line was drawn

connecting the anterior superior iliac spine (ASIS) to the superolateral corner of the patella (hereafter referred to as the AP line). The distance between these two points were measured, and the AP line was divided into 10 equal parts (hereafter referred to as segments) for the purpose of standardization between individuals and comparison. The Doppler signals were assessed at three main sites with a radius of 3 cm. A signal at the midpoint of the AP line corresponded to segment 5, while the others 5 cm proximal and distal to midpoint corresponded to segments 4 and 6, respectively. The most audible signals were marked each time by the same observer in all patients. The distance of the Doppler signals from the AP line were plotted on the X-axis (horizontal) and from a perpendicular drawn at the midpoint of the AP line, on the Y-axis.

Randomization into two groups

Following Doppler assessment, patients were randomized into two groups using computer-generated random numbers. Blocks of four were used to aid adequacy in randomization. In the first group (Group 1), preoperative mapping of location, number, source vessel, and course of all perforators of the ALT using an MDCTA was performed. In the second group (Group 2), no preoperative MDCTA was performed.

MDCTA

MDCTA was performed using a 64-detector row computed tomography scanner with the following parameters: 120 kVp, 80-120 mA, gantry rotation time 0.4 s, detector configuration 16 mm × 1 mm, 23 mm table travel per rotation, 512 × 512 matrix, and 180-240 field of view. All scans were performed with intravenous (IV) administration of 100 mL of nonionic iodinated contrast medium with a concentration of 300 mg/mL and injected at a rate of 4 mL/s through an 18-gauge IV catheter inserted into an antecubital vein. A bolus tracking technique was employed to obtain images from the point of bifurcation of the abdominal aorta to the level of the knee joint. The volumetric data acquired was then retrospectively used to reconstruct images with a slice thickness of 2 mm and a reconstruction interval of 0.75 mm in a soft tissue kernel. Ten radio-opaque markers (1 cm diameter plastic buttons) were placed at equal intervals along the AP line to depict each segment that assisted in accurate localization of perforators on preoperative MDCTA, which were plotted on the X-axis and Y-axis + or – symbols were used to depict the distances as plotted on the graph keeping the midpoint of intersection of AP line as (0, 0). These were then compared to the intraoperative findings.

Operative technique

All patients underwent harvest of a free ALT flap using the anterior approach as described by Song *et al.*^[6] and Koshima *et al.*^[7] Seven out of 10 patients in Group 1 and 9 out of 10 patients in Group 2 underwent subfascial dissection while suprafascial dissection was performed in the remainder of cases. During flap harvest, the location of each cutaneous perforator was marked with a needle at a specified distance from the perforator through the fascia

into the skin. A mark was then made on the skin paddle at this site. This point was then plotted on the X- and Y-axis after resuturing the skin paddle (subtracting the specified distance) to eliminate the obliquity of perforator entrance secondary to flap retraction/sagging. Care was taken to identify all perforators to the skin paddle which were preserved until the very end before committing to base the flap on the sizable perforators.

Surgeons' stress level

Surgeon's perceived (subjective) stress level during flap harvest was scored on a four-point visual analog scale (VAS) and recorded as follows:

- Grade 1 = no stress (preoperative perforator location matched intraoperative findings with only minor discrepancies (< 2 cm) in perforator location);
- Grade 2 = mild stress (discrepancy measured more than 2 cm in perforator location between preoperative and intraoperative findings);
- Grade 3 = moderate stress (gross difference in the perforator location, source, and course); and
- Grade 4 = severe stress (no perforator was present, or inadvertent perforator injury occurred during dissection).

Time taken for flap harvest and surgical outcome were also noted.

Statistical analysis

Statistical Package for the Social Science, version 19, IBM (2010) was used. The Kolmogorov-Smirnov test was applied to determine the distribution of data, and if data was skewed, Mann-Whitney test was applied. For comparison of categorical data, the Fischer exact and Chi-squared tests were applied. Kappa inter-rater agreement was applied to determine agreement between the preoperative findings of MDCTA versus Doppler using intraoperative findings as the gold standard.

RESULTS

A total of 20 patients over a period of 1 year who underwent free ALT flap coverage at our hospital were allocated randomly into two groups.

Patient demographics

In Group 1, the mean age of patients was 37.5 years \pm 11.49 years, and in Group 2, it was 43 years \pm 14.29 years ($P = 0.35$). There was a total of six patients with post head and neck cancer resection defects (3 in each group) while one patient in the Group 1 had invasive aspergillosis of the maxillary sinus. Eight patients had lower limb traumatic defects (5 in Group 1 and 3 in Group 2), and five patients had upper limb traumatic defects (1 in Group 1 and 4 in Group 2). Traumatic limb defects accounted for 65% of cases while nontraumatic defects accounted for 35%.

Anterolateral thigh flap characteristics

Four cutaneous ALT flaps (3 in Group 1 and 1 in Group 2),

ten fasciocutaneous flaps (4 in Group 1 and 6 in Group 2), five musculocutaneous (MC) flap (2 in Group 1 and 3 in Group 2), and one vastus lateralis muscle flap (in Group 1) were performed. Skin paddle size varied between 63 cm² and 264 cm² in Group 1 and between 90 cm² and 220 cm² in Group 2 with a mean of 173.78 cm² and 170.10 cm², respectively ($P = 0.89$).

Perforator number and type

MDCTA picked up all seven septocutaneous (SC) perforators, 4/7 MC perforators of which 1/4 were semi-septocutaneous (SSC). There were no differences between MDCTA and intraoperative findings for the distribution of type of perforators ($P = 0.68$).

Perforator source

Perforators were compared based on their source vessel: descending branch of the lateral circumflex femoral artery (DBLCFA), anteromedial thigh (AMT) perforator arising from the DBLCFA, the transverse branch of the lateral circumflex femoral artery (TBLCFA), or the oblique branch of the lateral circumflex femoral artery (OBLCFA). MDCTA accurately detected 8 out of 9 perforators arising from the DBLCFA and 3 of the 4 perforators arising from the TBLCFA. Two AMT perforators were identified intraoperatively (both in Group 2). There were no differences between preoperative MDCTA and intraoperative findings for the source vessel and origin of the perforators ($P = 0.832$).

Sizable perforators

In our study, any perforator over 0.8 mm was considered to be sizable.^[8] MDCTA detected all sizable SC perforators, 4/5 sizable MC perforators of which 1/2 was SSC. Doppler signals localized sizable perforators accurately in only 2 of 9 patients in Group 1 and 4 of 11 patients in Group 2. Sizable perforators were further compared based on their source vessel, i.e. DBLCFA, DBLCFA-AMT, TBLCFA, or OBLCFA. MDCTA localized all sizable perforators arising from the DBLCFA and TBLCFA. Overall sensitivity and specificity of MDCTA in demonstrating the sizable perforator in segments 4 and 5 was 90% and had an accuracy of 88.88% with a kappa value of 0.78 (good agreement) for each segment.

Concordance of MDCTA versus Doppler for perforator localization

A difference of more than 2 cm between preoperative localization and intraoperative findings was considered to be discordant. In Group 1, MDCTA had a concordance level of 100% (12/12) while Doppler had concordance of 46% (6/13). Overall concordance of Doppler was only 52% (13/25). This further establishes the accuracy of MDCTA in localization of perforators. The Bland-Altman plot [Figure 1] was used to depict the inter-rater agreement between the two variables (MDCTA with intraoperative findings in the first plot and Doppler with intraoperative findings in the second plot) by plotting the average of the distance of perforators noted by both the variables against its difference from the mean. This demonstrates that the values were

closer to the mean in the MDCTA-intraoperative plot, indicating a good agreement in the locations of the perforators as compared to the Doppler-intraoperative plot which was dispersed away from the mean.

Surgeons' stress levels

A VAS was used to record the level of stress experienced by the surgeon during flap harvest. The difference

between the mean VAS of Group 1 (2.1) and Group 2 (2.5) was not statistically significant ($P = 0.63$). The difference between mean flap harvest time of Group 1 (87.5 min) and Group 2 (117.5 min) was not statistically significant ($P = 0.28$). However, operator bias cannot be ruled out. Surgeon A (chief surgeon) performed an equal number of surgeries (five) in each group, of which two cases in each group required an intramuscular perforator dissection for perforators arising from the DLBCFA. The difference between mean flap harvest time for Surgeon A in Group 1

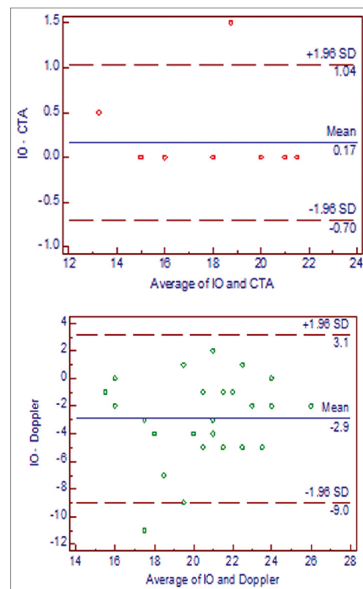


Figure 1: Bland-Altman plot for determining agreement between multi-detector row computed tomography angiography, Doppler, and intraoperative perforator location. IO: intraoperative; SD: standard deviation

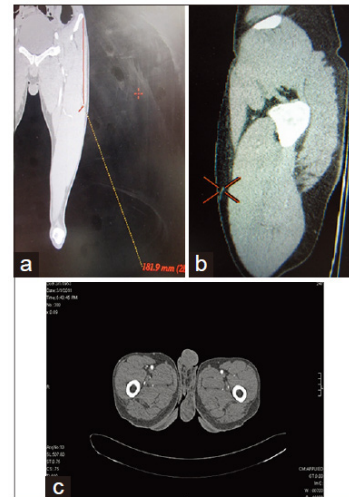


Figure 2: (a-c) Case 9: MDCTA coronal, sagittal, and axial section showing TBLCFAP-s 18 cm from ASIS. MDCTA: multi-detector row computed tomography angiography; ASIS: anterior superior iliac spine; TBLCFAP-s: septocutaneous perforator from transverse branch of lateral circumflex femoral artery through spectrum

Table 1: Perioperative details

Patient	Diagnosis	Group	Perforator		Concordance		Sizable Perforator	VAS	Time (min)
			Type CTA	Type IO	Doppler	MDCTA			
1	Grade 3B fracture lower one-third leg	1	No perforator	No perforator	No	Yes	VL muscle	4	115
2	Carcinoma buccal mucosa	1	MC	MC, SC, SC	Yes, yes	Yes	TBLCFAP-vl	3	80
3	Carcinoma buccal mucosa	1	SC	SC, SC	Yes, yes	Yes	DBLCFAP-s	1	60
4	Type 3A maxillectomy defect (invasive aspergillosis)	1	SC, SC	SC	No, no	Yes, yes	DBLCFAP-s	3	100
5	Carcinoma buccal mucosa	1	MC	MC	Yes	Yes	DBLCFAP-vl	1	75
6	Traumatic sole defect	1	SC	SSC	Yes	Yes	OBLCFAP-vl	2	115
7	Forearm electrical burns	1	MC, SC	MC, SSC	No	Yes	DBLCFAP-vl	2	100
8	Heel unstable scar	1	SC	SC	No	Yes	TBLCFAP-s	2	55
9	Traumatic heel defect	1	SC	SC	No	Yes	TBLCFAP-s	2	110
10	Traumatic heel defect	1		SSC	No	Yes	DBLCFAP-vl	1	65
11	Carcinoma buccal mucosa	2	NA	MC	No	NA	DBLCFAP-vl	1	85
12	Traumatic elbow defect	2	NA	SSC, SC	No, yes	NA	TBLCFAP-vl	4	95
13	Grade 3B fracture lower 1/3 leg	2	NA	MC, MC	No	NA	DBLCFAP-s	3	85
14	Type 4 maxillectomy defect (carcinoma maxillary sinus)	2	NA	MC	Yes	NA	DBLCFAP-vl+AMTP	4	125
15	Grade 3B fracture lower 1/3 leg	2	NA	MC, SC	No	NA	DBLCFAP-vl	1	105
16	Hand degloving	2	NA	MC, SC (AMT)	Yes	NA	DBLCFAP-s	4	180
17	Open wrist joint and hand defect	2	NA	SC	Yes, no	NA	TBLCFAP-vl	4	215
18	Grade 3 B fracture mid 1/3 leg	2	NA	SC	Yes	NA	DBLCFAP-s	2	95
19	Carcinoma buccal mucosa	2	NA	SC	Yes	NA	DBLCFAP-s	1	85
20	Forearm contour correction	2	NA	SC	Yes	NA	DBLCFAP-s	1	105

AMTP: anteromedial thigh perforator; MDCTA: multi-detector row computed tomography angiography; DBLCFAP-s: descending branch lateral circumflex femoral artery perforator through septum; DBLCFAP-vl: descending branch lateral circumflex femoral artery perforator through vastus lateralis; IO: intraoperative; MC: musculocutaneous; NA: not applicable; OBLCFAP-vl: oblique branch lateral circumflex femoral artery perforator through vastus lateralis; SC: septocutaneous; SSC: semi-septocutaneous; TBLCFAP-vl: transverse branch lateral circumflex femoral artery perforator through vastus lateralis; TBLCFAP-s: transverse branch lateral circumflex femoral artery perforator through septum; VAS: visual analog scale; VL: vastus lateralis; AMT: anteromedial thigh

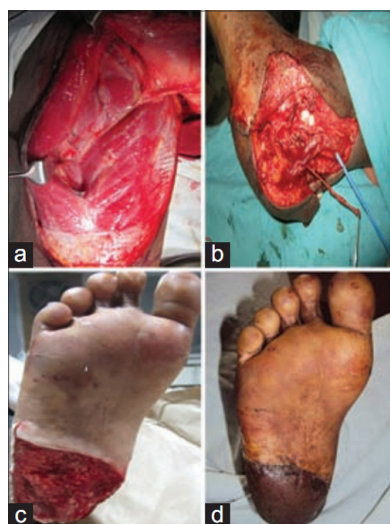


Figure 3: Case 9: (a) Sensate ALT flap, LCFN included; (b) intraoperative sizable septocutaneous perforator (TBLCFAP-s) was 18 cm from ASIS as determined preoperatively by MDCTA; (c) 8 weeks postoperative showing well settled sensate ALT flap; (d) posttraumatic heel defect with exposed calcaneus. ALT: anterolateral thigh; LCFN: lateral cutaneous femoral nerve; ASIS: anterior superior iliac spine; MDCTA: multi-detector row computed tomography angiography; TBLCFAP-s: septocutaneous perforator from transverse branch of lateral circumflex femoral artery through spectrum

(71 min) and Group 2 (95 min) was statistically significant ($P = 0.046$). Perioperative details are shown in Table 1. Figures 2 and 3 are representative of case 9, and Figure 4 is representative of case 4.

DISCUSSION

The vascular basis of the ALT flap has been extensively studied since its introduction by Song *et al.*^[6] 30 years ago. Although anatomy of the lateral circumflex femoral source vessel is quite consistent, the perforators to the skin territory can have multiple variations.^[9] Various imaging modalities have been used to predict the course and location of the perforators, of which MDCTA has been found to be the most consistent.^[9]

Perforator(s) number and type

In the current study, MDCTA did not affect the choice of limb (whether right or left side) for flap harvest as compared to a study by Rozen *et al.*^[11] The current study demonstrated an average of 1.45 perforators per limb, with 51.75% (15/29) SC and 48.25% (14/29) MC perforators. There were no perforators in 5% (one) of the patients. These findings differed from those published by Kimata *et al.*,^[10] in which 81.9% of the perforators were MC, 18.9% were SC, and there was no perforator in 5% of the patients. In the current study, SSC comprised 37.1% (5/14) of the total number of MC perforators, which differs from the study of Kim *et al.*,^[9] which showed SSC in 4.6% of patients. However, MDCTA failed to accurately label the SSC perforator in 2 patients and instead identified them as SC. This is consistent with the observation that more careful evaluation is required for identification of SSC perforators.^[9]

Perforator source

There was no difference between MDCTA and intraoperative findings for the source of perforators, indicating the efficacy of MDCTA. One patient had a

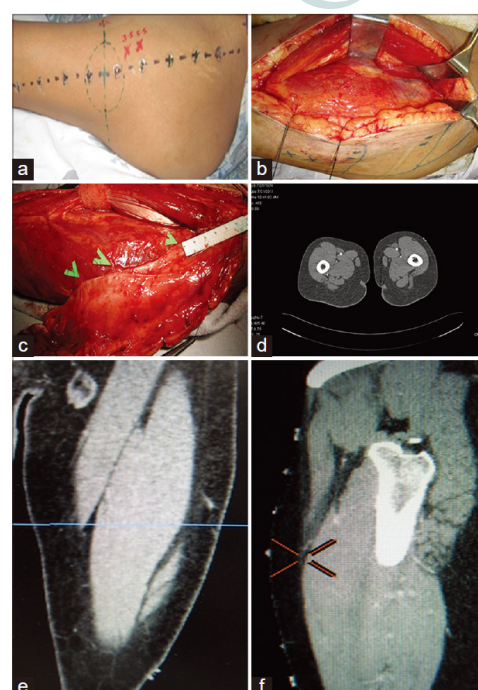


Figure 4: Case 4: (a) "X" denotes Doppler signal, "•" denotes MDCTA preoperative perforator localization; (b) plastic buttons at segments of thigh along AP line. Doppler signal at 3.5 cm and 5.5 cm above midpoint of AP line; (c) MDCTA axial section showing TBLCFAP; (d) sizable semi-septocutaneous perforator (TBLCFAP-ssc) 15 cm from ASIS and two other septocutaneous perforators DBLCFAP-s which correlated with preoperative MDCTA; (e) and (f) same TBLCFAP seen in coronal and sagittal sections. MDCTA: multi-detector row computed tomography angiography; TBLCFAP-ssc: semi-septocutaneous perforator arising from transverse branch of lateral circumflex femoral artery; DBLCFAP-s: septocutaneous perforator arising from descending branch of lateral circumflex femoral artery

perforator arising from an OBLCFA (a branch of DBLCFA), which on MDCTA was thought to be an intramuscular perforator arising from the DBLCFA. This was similar to the study by Wong *et al.*,^[11] in which the oblique branch predominantly arises from the DBLCFA.

Segmental distribution of perforators

Most of the perforators in this study were concentrated in segments 4 and 5 (24/29) [Table 2], which differed from the study by Kim *et al.*,^[9] in which perforators were concentrated in segments 5 and 6. There was no difference in the segmental distribution of perforators when comparison was made between MDCTA and intraoperative findings. However, the difference was statistically significant when compared to findings with Doppler localization ($P = 0.034$) [Table 2]. When the intraoperative segmental distributions of perforator types were analyzed, it was noted that both SC ($n = 8$) and MC ($n = 7$) perforators were concentrated in segment 5. However, SSC perforators were localized in proximal segments 3 ($n = 2$) and segment 4 ($n = 2$). This differed from the study by Lin *et al.*,^[12] in which the SC perforators were located in more proximal segments than the MC perforators. When the perforator quadrant was mapped in consistent with similar study by Yu *et al.*,^[12] MDCTA was independent of body mass index (BMI).

Sensitivity, specificity, accuracy of MDCTA in segments 4 and 5 on the right and left thighs, most of perforators were

found in the upper outer quadrant of the thigh, as opposed to the study of Kim *et al.*,^[9] which showed perforators primarily in the lower outer quadrant of the thigh.

Sensitivity, specificity, accuracy of Doppler versus MDCTA in localization

Yu *et al.*,^[12] in 2006, evaluated the accuracy of handheld Doppler and found it to be overly sensitive, poorly specific, and inaccurate in locating perforators. The current study showed an overall sensitivity of 74% and specificity of 80.86% for Doppler in the demonstration of the presence of a perforator. Lin *et al.*,^[12] conducted another study in 2011 in which MDCTA demonstrated a sensitivity of 74% and specificity of 90% in 16 patients. The current study showed a sensitivity and specificity for MDCTA of 85.71% and 97.22% in demonstrating the presence of a perforator [Table 3], while that for Doppler alone was 80% and 87.91%, respectively in Group 1 [Table 4]. MDCTA was superior to Doppler in accurate localization of the perforators in segments 3, 4, and 6. However, no difference was seen in segment 5. Doppler showed less accuracy in localizing perforators when the BMI increased.

Perforator source

The sensitivity of MDCTA in the detection of the source of the perforators decreased from proximal to distal while the specificity remained high in all segments, similar to a study by Garvey *et al.*,^[13] Perforators appeared to be better visualized when surrounded by subcutaneous fat, which decreases from proximal to distal in the thigh. MDCTA had 100% sensitivity, 91.66% specificity, and 100% accuracy in demonstrating the source of perforators in

segments 4 and 5 arising from the TBLCA and in segment 5 for perforators arising from the DBLCA. Our study showed an overall kappa value of 1 (very good agreement) for MDCTA in demonstrating the source of perforators, similar to the study by Garvey *et al.*,^[13] The Doppler was unable to provide any information regarding source vessel, course, and size of perforators.

Surgeons' stress levels

This study attempted to objectively classify the stress level of a surgeon during flap harvest and perforator dissection. Taylor *et al.*,^[3,14] used the retrograde VAS to assess the surgeons' stress levels during deep inferior epigastric artery perforator (DIEP) dissection. This was subjectable to recall bias and hence unreliable. In our study, the surgeon's operative stress score was analyzed prospectively. The difference in mean scores of the surgeon's stress level during flap harvest was not statistically significant, likely secondary to the small number of cases. However, the mean flap harvest time for Surgeon A was significantly less in Group 1 ($P = 0.046$). No similar studies have been reported in literature.

Complications

This study found no significant differences in flap survival or donor site complications in patients who underwent MDCTA versus those who did not ($P = 0.26$). This is in contrast to other studies of the DIEP flap, where preoperative MDCTA significantly decreased the incidence of marginal necrosis and donor site morbidity.^[14] However, it would probably be incorrect to extrapolate data obtained from an abdominal donor site and compare it to a thigh donor site. In the current study,

Table 2: Segmental distribution of perforators

Perforator segment	Intraoperative				Preoperative		P	
	Group 1		Group 2		MDCTA	Doppler	MDCTA	Doppler
	n	Percentage	n	Percentage	n	n		
3	1	7.14	2	13.33	1	0		
4	5	35.71	4	26.66	6	2		
5	7	50.00	8	53.33	4	22	0.666	0.034
6	1	7.14	1	6.33	0	4		
7	0	0.00	0	0.00	0	1		

MDCTA: multi-detector row computed tomography angiography

Table 3: Sensitivity, specificity, and accuracy of MDCTA to demonstrate the presence of a perforator in Group 1

Segment	Sensitivity %	95% CI	Specificity %	95% CI	Accuracy %	κ
3	100	5.46-100	100	71.65-100	100	NA
4	100	46.29-100	88.89	50.67-99.4	92.8	0.85
5	57.14	20.23-88.19	100	56.09-100	78.5	0.78
6	NA	NA	100	71.66-100	92.8	NA
Overall	85.71		97.22			

CI: confidence interval; NA: not applicable; MDCTA: multi-detector row computed tomography angiography

Table 4: Sensitivity, specificity, and accuracy of handheld Doppler to demonstrate the presence of a perforator in Group 1

Segment	Sensitivity %	95% CI	Specificity %	95% CI	Accuracy	κ
4	40	7.26-82.96	100	62.88-100	78.87	0.46
5	100	56.01-100	71.43	30.25-94.89	85.71	0.71
6	100	54.6-100	92.31	62.08-99.60	92.85	0.63
Overall	80		87.91			

CI: confidence interval

2 flaps in Group 2 underwent complete necrosis. Minor complications including marginal flap necrosis (2 cases) and infection (one case) were noted in Group 1 and were managed conservatively.

Prudent observations and surgical outcomes of this study

- The largest skin paddle harvested measured 264 cm² and survived. However, two flaps underwent complete necrosis (Group 2). In one, the MC perforator was injured, while in the other patient, the AMT perforator was dominant, but eccentric to the skin paddle designed which was based on a false localization by the Doppler signal. There was no perforator from the DBLCFA and the skin paddle had to be shifted proximally to include the TBLCFA perforator (TBLCFAP), which in turn had a tortuous intramuscular course and was inadvertently injured. Preoperative MDCTA could have picked up this anomaly, allowing the flap to be based on the AMT perforator. A thoraco-umbilical flap was performed as a salvage flap in this case. Two flaps had marginal necrosis (Group 1), one of which occurred secondary to a problem with the anastomosis. The recipient vessel posterior tibial artery had three episodes of vasospasm despite revision of the anastomosis. This was attributed to the subacute phase of injury. One patient in Group 2 with a defect of the upper and middle third of the leg had his anastomosis performed in the subacute phase of injury and distal to the zone of injury without any complications
- One patient in Group 1, who was diabetic, had delayed total flap loss after 2 weeks due to a necrotizing soft-tissue infection. This is a very rare complication which has not yet been reported
- In one patient in Group 2, the skin paddle was shifted 6 cm proximally as a sizable perforator was noted arising from the TBLCFA, which was more proximal than the proposed signal given by Doppler
- Three patients in Group 1 underwent intramuscular perforator dissection as opposed to only one patient in Group 2, as MDCTA provided a roadmap of the course and source vessel of a sizable perforator
- In one patient who required a sensate ALT flap for reconstruction of a heel defect, the skin paddle was planned based on the TBLCFAP through the septum, which was sizable SC perforator as shown on MDCTA, though there was also a sizable MC perforator (DBLCFA perforator-vastus lateralis) which was found more distally. The skin paddle was therefore designed proximally to include the lateral cutaneous femoral nerve of the thigh. MDCTA in this case significantly influenced preoperative planning
- MDCTA of one patient did not show any sizable perforators in one thigh, which was consistent with intraoperative finding. However, the Doppler gave a good audible signal in the same thigh, and an ALT flap was planned. When no perforator was identified, vastus lateralis muscle only flap was done. This was the index case in Group 1
- In one patient with a Type 3A maxillectomy defect following invasive aspergillosis, a flap with two skin paddles was initially planned, one for the palate and cheek based on the DBLCFA through septum and the other for the nasal lining based on the TBLCFAP through septum as noted on MDCTA.

Hence, MDCTA was useful in planning the reconstruction of complex defects requiring multiple paddles, similar to the study done by Garvey *et al.*^[13]

In conclusion, preoperative MDCTA as compared to Doppler was more sensitive, specific, and accurate with respect to the location, course, and source vessel of all perforators. This study demonstrates that preoperative MDCTA provides us with all the information required to make a choice regarding design of the skin paddle and also reduces the flap harvest time which was statistically significant. Our study showed that preoperative MDCTA lowered the surgeons' stress level during perforator dissection. Further studies with large number of patients are required to reach statistically significant conclusions. The trends shown toward the benefits of performing preoperative MDCTA are nonetheless encouraging.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Rozen WM, Ashton MW, Pan WR, Kiil BJ, McClure VK, Grinsell D, Stella DL, Corlett RJ. Anatomical variations in the harvest of anterolateral thigh perforators: a cadaveric and clinical study. *Microsurgery* 2009;29:16-23.
2. Yu P, Youssef A. Efficacy of the handheld Doppler in preoperative identification of the cutaneous perforators in the anterolateral thigh flap. *Plastic Reconstr Surg* 2006;118:928-33.
3. Taylor GI, Doyle M, McCarten G. The Doppler probe for planning flaps: anatomical study and clinical applications. *Br J Plast Surg* 1990;43:1-16.
4. Rosson GD, Williams CG, Fishman EK, Singh NK. 3D CT angiography of abdominal wall vascular perforators to plan DIEAP flaps. *Microsurgery* 2007;27:641-6.
5. Hamdi M, Van LK, Van HE. Advances in autogenous breast reconstruction: the role of preoperative perforator mapping. *Ann Plast Surg* 2007;58:18-26.
6. Song YG, Chen GZ, Song YL. The free thigh flap: a new free flap concept based on the septocutaneous artery. *Br J Plast Surg* 1984;37:149-59.
7. Koshima I, Fukuda H, Utunomiya R, Soeda S. The anterolateral thigh flap; variations in its vascular pedicle. *Br J Plast Surg* 1989;42:260-2.
8. Koshima I, Nanba Y, Tsutsui T, Takahashi Y, Itoh S, Fujitsu M. Minimal invasive lymphaticovenular anastomosis under local anesthesia for leg lymphedema: is it effective for stage III and IV? *Ann Plast Surg* 2004;53:261-6.
9. Kim EK, Kang BS, Honget JP. The distribution of the perforators in the anterolateral thigh and the utility of multidetector row computed tomography angiography in preoperative planning. *Ann Plast Surg* 2010;65:155-60.
10. Kimata Y, Uchiyama K, Ebihara S, Nakatsuka T, Harii K. Anatomic variations and technical problems of the anterolateral thigh flap: a report of 74 cases. *Plast Reconstr Surg* 1998;102:1517-23.
11. Wong CH, Wei FC, Fu B, Chen YA, Lin JY. Alternative vascular pedicle of the anterolateral thigh flap: the oblique branch of the lateral circumflex femoral artery. *Plast Reconstr Surg* 2009;123:571-7.
12. Lin SJ, Rabie A, Yu P. Designing the anterolateral thigh flap without preoperative Doppler or imaging. *J Reconstr Microsurg* 2010;26:67-72.
13. Garvey PB, Selber JC, Madewell JE, Bidaut L, Feng L, Yu P. A prospective study of preoperative computed tomographic angiography for head and neck reconstruction with anterolateral thigh flaps. *Plast Reconstr Surg* 2011;127:1505-14.
14. Rozen WM, Anavekar NS, Ashton MW, Stella DL, Grinsell D, Bloom RJ, Taylor GI. Does the preoperative imaging of perforators with CT angiography improve operative outcomes in breast reconstruction? *Microsurgery* 2008;28:516-23.

Hyperbaric oxygen therapy improves outcome of snake envenomation: tertiary center experience

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ABSTRACT

Aim: Snakebite injuries of the extremities are common in tropical India among those involved in farming and outdoor activities. These injuries often complicated by cellulitis, gangrene, regional lymphadenopathy, compartment syndrome, bleeding abnormalities, septicemia, hypotension, and disseminated intravascular coagulation, resulting in significant morbidity and mortality. The purpose of the study is to share our experience of hyperbaric oxygen (HBO) therapy in the management of snakebite injuries. **Methods:** All patients who were treated for snakebite injuries in our department between October 2012 and October 2013 were included in the study. **Results:** Out of a total 395 patients, 174 patients treated with anti-snake venom with a mortality of 17 posttreatment. Forty-four out of the 174 patients was in the pediatric age group. Out of the patients referred to our department, 23 presented with cellulitis, 7 with compartment syndrome and 17 for the management of soft tissue cover over the extremities. Of the 47 patients, 30 involved the lower extremity and rest involved the upper extremity. All patients were subjected to HBO therapy as an adjunct. Six patients required flap cover: cross finger flap ($n = 2$), anterolateral thigh free tissue transfer ($n = 1$), lateral supramalleolar flap ($n = 1$), groin flap ($n = 1$), and dorsal metacarpal artery flap ($n = 1$). There was no need for fasciotomy among the patients who suffered impending compartment syndrome. **Conclusion:** HBO therapy may reduce the incidence of fasciotomy and increase the effectiveness of plastic surgical modalities if administered early and may be used as a useful adjunct in the management of snake envenomation injury.

Key words:

Hyperbaric oxygen therapy; snake bite injury; soft tissue reconstruction; upper and lower extremity

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INTRODUCTION

Snakebite injuries of the extremities are common in India, among those involved in farming and outdoor activities. There are approximately 400 poisonous species among 2,000 species of snakes known worldwide. These species belong to the families of Elapidae, Viperidae,

Hydrophiidae, and Colubridae.^[1] Viper bites are the most common poisonous bites sustained by humans.^[2,3] Russell's viper (*Viperarusselli*) is the most common species in South Asia and considered as an occupational hazard in the farming community. The World Health Organization has estimated that approximately 125,000 deaths occur from 250,000 poisonous snake bites worldwide every year. India alone accounts for 10,000 deaths.^[4,5] These snake bites involve predominantly young, healthy, and the able-bodied working population in rural areas. Children and the elderly are most susceptible to mortality.^[5,6] Most of these injuries involve the extremities. This results in pain and swelling of the bitten region, leading to cellulitis and compartment syndrome, in addition to systemic toxicity. The main cause of mortality is the lack of a systematic approach or protocol for the management of such injuries. The purpose of the study is to share our experience of multidisciplinary approach in the management of snakebite injuries of the extremities with various treatment modalities including hyperbaric oxygen (HBO) therapy, surgical debridement, and skin grafting, local or distant flaps to provide a treatment for effective management of such injuries from a plastic surgeon's perspective.

METHODS

All patients who were treated for snakebite injuries in our department between October 2012 and October 2013 were included in the study. All patients received tetanus toxoid. The snakebites were assessed by an emergency physician who classified them into poisonous and nonpoisonous snakebites clinically. Anti-snake venom (ASV) was administered accordingly. Antibiotics, diuretics, and blood products were administered as indicated. Patients were initially admitted to the Departments of Medicine or Pediatrics. They were only subsequently referred to the plastic surgery department if cellulitis, compartment syndrome or soft tissue loss was suspected. The treatment of soft tissue complications was done only after critical stabilization of the patient. Patients with cellulitis and compartment syndrome were subjected to HBO therapy. Administration of HBO therapy was done in a monoplace chamber where a single patient is placed in a chamber that is then pressurized to 1.8-2.4 atmospheres with 100% oxygen. HBO therapy was administered in 6 daily sessions, with each session lasting 90 min. The sessions were extended according to the clinical progress of the disease judged by the clinician. The daily treatment sessions were extended another week if insufficient softness of the tissue was attained. The regimen for pediatric patients was identical, although parents were allowed to accompany the child in the chamber. Patients

who presented with soft tissue necrosis were subjected to surgical debridement prior to 6 sessions of HBO therapy. The patients were followed up for the effects and complications of the treatment.

RESULTS

Of a total 395 patients, 174 patients treated with ASV with a mortality of 17 posttreatment. Forty-four out of the 174 patients were in the pediatric age group [Table 1]. Of the patients referred to our department, 23 presented with cellulitis, 7 with compartment syndrome, and 17 for the management of soft tissue cover over the extremities. Of the 47 patients, 30 involved the lower extremity and rest involved the upper extremity. All patients were subjected to HBO therapy as an adjunct. Six patients required flap cover: cross finger flap ($n = 2$), anterolateral thigh free tissue transfer ($n = 1$), lateral supramalleolar flap ($n = 1$), groin flap ($n = 1$), and dorsal metacarpal artery flap ($n = 1$) [Tables 2 and 3]. There was no need for fasciotomy among patients who suffered impending compartment syndrome.

Case 1

A 5-year-old boy was admitted with a snakebite injury to the lower third of his right leg. He presented with compartment syndrome of the right leg and foot [Figure 1a and b]. HBO therapy was administered for six sessions following admission. The patient recovered from the syndrome without any surgical intervention [Figure 1c].

Case 2

An 8-year-old boy was admitted with a snakebite injury to the dorsum of his right foot. He presented with compartment syndrome and discoloration at the bite site [Figure 2a]. HBO therapy was administered for six sessions following admission, and sequential evaluation was performed [Figure 2b-d]. After demarcation of the nonviable tissue, debridement, and skin grafting was done [Figure 2e].

Case 3

A 45-year-old male presented with soft tissue loss measuring 8 cm × 7 cm × 2 cm over the lower third of his right leg and lateral aspect of his ankle [Figure 3a]. Wound debridement was performed, and the resultant soft tissue defect was covered with a left anterolateral thigh flap [Figure 3b]. Six sessions of HBO therapy was performed postoperatively.

DISCUSSION

Snake envenomations have the highest incidence in Asian countries resulting in gross morbidity and mortality. Males are more commonly affected than females, as they are mostly involved in farming and outdoor activities. The predominant age group affected is those between 20 and 40 years.^[3] The most common symptoms are pain and swelling of the bitten region. Systemic signs include

Table 1: The admission of patients with snakebite injuries during the period of October 2012-October 2013

Year	Month	In patient snake bite		ASV given	Death	Referred to plastic surgery	
		Adult	Pediatrics			Pediatrics	Adult
2012	October	23	3	10	1	1	4
2012	November	16	2	8	2	0	1
2013	December	15	5	5	1	1	1
2013	January	10	1	3	1	0	2
2013	February	16	2	9	2	0	4
2013	March	9	4	7	2	0	1
2013	April	11	7	10	1	1	4
2013	May	44	8	34	3	1	5
2013	June	119	2	22	0	1	4
2013	July	22	2	20	0	0	4
2013	August	27	1	20	2	1	5
2013	September	19	3	15	0	0	2
2013	October	20	4	11	2	1	3
Total	13 months	351	44	174	17	7	40
Number of patients		395				47	

ASV: anti-snake venom

Table 2: The number of pediatric and adult patients referred to plastic surgery department with snake bite injuries

	Cellulitis		Compartment syndrome		Surgery	
	Upper limb	Lower limb	Upper limb	Lower limb	Upper limb	Lower limb
<i>n</i>	6	17	2	5	7	10
Paediatrics	1	1	0	1	1	2
Adult	5	16	2	4	6	8
Total	23		7		17	

bleeding, hypotension, cardiotoxicity, and nephrotoxicity that require immediate medical attention. Local signs such as tissue edema, compartment syndrome, and tissue necrosis increases the morbidity and may result in fasciotomy or amputation of the involved extremity.^[7,8]

ASV administration can reduce progression of the initial tissue damage, but it cannot reverse local tissue damage such as tissue edema, inflammation, compartment syndrome, and necrosis.^[7] Although inflammation induced by snake envenomation often mimics infection, true bacterial cellulitis is uncommon, and only affects 3% of snakebites.^[9] Tissues at the point of envenomation may be nonviable regardless of intervention. The adjacent zone consists of variably injured tissues that may recover if the process of inflammation is reduced. Most therapeutic maneuvers are focused on this penumbra of tissue, in an attempt to maximize recovery of the injured marginal tissue. Finally, an outer zone of minimally injured tissues that are not subject to primary injury may be at risk from the processes of secondary injury resulting from the delayed, physiological inflammatory responses to snake bite injury. Occasionally, the quantity of tissue loss and destruction caused by secondary injury can dwarf the actual loss from the primary snakebite. Hence, there is a need for modalities that impede the progress of inflammation, preserve marginal tissue at risk, and prevent ischemic advancement of the injured tissue.

When compartment syndrome occurs in snakebite injuries, there is controversy as to whether or not fasciotomy is required. Snakebite injuries can produce pain, swelling, induration, paresthesias, color changes, absent pulses,



Figure 1: (a) Compartment syndrome right leg and foot lateral view; (b) compartment syndrome right leg and foot medial view; (c) six sessions following hyperbaric oxygenation therapy

and tenderness in the envenomated extremity, mimicking the initial signs of compartment syndrome. However, true compartment syndrome is much less common.^[10] In a case series conducted by Tanen *et al.*,^[11] only 8/236 (3.4%) of patients received a fasciotomy or digital dermatomy for compartment syndrome. Measurement of compartment pressures prior to fasciotomy is always recommended. Recent literature indicates that an increase of intracompartmental pressures of up to 30-45 mmHg is an absolute indication for fasciotomy.^[12,13] Unfortunately, measurement of intracompartmental pressure is not always possible in a number of medical centers in India, and most of the diagnoses of compartment syndrome are made on clinical grounds alone. Anz *et al.*^[14] reported that 21.2% of all poisonous snake bites involve fingers. Fingers have small compartments with its small diameters, and the elastic limit of the skin can be rapidly reached. Compartment pressure measurement may not be feasible in cases of digital envenomation, and the diagnosis of compartment syndrome can only be made on clinical grounds.^[15] Some authors support early fasciotomy in the treatment of all cases of snake bite envenomation.^[15,16] Fasciotomies are not without complication, and may result in disfiguring scars, contractures, nerve damage, leading to significantly lengthening of treatment.^[7]

Table 3: The number of pediatric and adult patients referred to plastic surgery department with snake bite injuries subjected to surgical intervention

Age (years)/ gender	Upper limb		Lower limb		Surgery
	Pediatric	Adult	Pediatric	Adult	
22/male		Right thumb			Terminalization
28/female		Right-hand dorsum			Debridement and groin flap cover
32/male		Right index finger			Terminalization
8/male			Right foot dorsum		Debridement and skin grafting
50/male				Right second toe	Terminalization
45/male				Right leg lower 3rd lateral aspect	Debridement and ALT free tissue transfer
25/male				Left 4th toe	Terminalization
7/male	Left middle finger				Terminalization
32/female		Right index finger MPX level			Debridement and cross finger flap
10/male			Left foot dorsum		Debridement and skin grafting
26/male				Right foot dorsum	Debridement and skin grafting
34/female		Right ring fingertip region			Debridement and cross finger flap
35/female				Right foot dorsum	Debridement and lateral supramalleolar flap cover
22/male				Left foot great toe	Terminalization
47/male				Left leg middle 3rd lateral aspect	Debridement and skin grafting
32/male				Left foot little toe	Terminalization
27/female		Right thumb dorsal aspect			Debridement and FDMA flap

ALT: anterolateral thigh; MPX: middle phalanx; FDMA: first dorsal metacarpal artery



Figure 2: (a) Day 1 following snake bite injury; (b) day 2 following hyperbaric oxygenation therapy; (c) day 3 following hyperbaric oxygenation therapy; (d) day 5 following hyperbaric oxygenation therapy; (e) wound following debridement and grafting

HBO therapy may reduce the penumbra of cells at risk for delayed necrosis and secondary ischemia in snakebite injury patients with early compartment syndrome.^[15] breathing of 100% oxygen under increased ambient pressure prevents reperfusion injury, reduces tissue edema, and reverses sublethal tissue damage.^[15,16] Vasoconstriction reduces edema and tissue swelling while ensuring adequate oxygen delivery in snakebite wounds.

In our series, 23 patients were treated for cellulitis and 7 patients for compartment syndrome. In our experience, HBO therapy is a helpful tool when there is an impending compartment syndrome that may require a fasciotomy



Figure 3: (a) Soft tissue defect right leg and ankle region; (b) anterolateral thigh free tissue transfer done for the soft tissue defect

later. We did not experience any complications related to HBO therapy in our series. It is difficult to be certain whether in the absence of HBO our patients treated with snake envenomation injuries would have progressed to compartment syndrome or tissue necrosis.

As the degree of cellulitis and its severity varied from patient to patient as did the timings of the referrals, there was no standardized starting point for HBO therapy. Six sessions are minimum given to attain a tangible decrease in swelling. Assessment of sensory loss may not be possible in small children, and hence we determine the treatment endpoint based on the decrease in girth of the limb and also the movement of the toes. HBO therapy after surgical debridement, skin grafting or flap reduces edema of the inflamed operation site. Hence, we

prefer administering HBO therapy for at least six sessions in postoperative patients if they can afford it. Prior to the use of HBO therapy, the general surgeon, who used glycerine magsulf dressings, treated the majority. If this did not improve, this often led to fasciotomies. The exact incidence of fasciotomies is not known. A course of hyperbaric treatment for 6 days is more expensive than fasciotomy, surgical charges, postsurgical dressings and extending patient care combined. As an adjunct to ASV, antibiotics, and surgery, HBO therapy can significantly decrease costs and complications.^[17] No studies controlled studies exist that prove the utility of HBO to date. HBO therapy may possibly work by preventing tissue damage that is not frankly necrotic. HBO therapy and debridement have their own roles to play in such injuries. Considering the high incidence of snakebites in the Asian population, further studies into the effectiveness of HBO therapy for this clinical condition is warranted.

In conclusion, snakebite injuries of the extremities are more common in Asian countries. Immediate medical care is almost always necessary. The majority of the patients with snakebite injuries of the extremity present with cellulitis, compartment syndrome, and tissue necrosis. Various treatment modalities including HBO therapy, fasciotomy, surgical debridement, skin grafting, local, and distant flaps may be required to provide an effective management of such injuries. HBO therapy as an adjunct is effective in the treatment of snakebite injuries.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Al Qahtani MA, Altheaby A, Al Anazi T, Al Saad K, Binsalih S, Al Helail

- M. Snake bite complicated by acute kidney injury secondary to necrotizing glomerulonephritis. *Saudi J Kidney Dis Transpl* 2014;25:1259-62.
2. Halesha BR, Harshavardhan L, Lokesh AJ, Channaveerappa PK, Venkatesh KB. A study on the clinic-epidemiological profile and the outcome of snake bite victims in a tertiary care centre in Southern India. *J Clin Diagn Res* 2013;7:122-6.
3. Singh V, Digra SK, Slathia SS, Kakkar T. Hemothorax following snakebite. *Indian Pediatr* 2012;49:242-3.
4. Bhalla G, Mhaskar D, Agarwal A. A study of clinical profile of snake bite at a tertiary care centre. *Toxicol Int* 2014;21:203-8.
5. Harshavardhan L, Lokesh AJ, Tejeshwari HL, Halesha BR, Metri SS. A study on the acute kidney injury in snake bite victims in a tertiary care centre. *J Clin Diagn Res* 2013;7:853-6.
6. Bosak AR, Ruha AM, Graeme KA. A Case of neurotoxicity following envenomation by the Sidewinder rattlesnake, *Crotalus cerastes*. *J Med Toxicol* 2014;10:229-31.
7. Gold BS, Dart RC, Barish RA. Bites of venomous snakes. *N Engl J Med* 2002;347:347-56.
8. Laloo DG, Theakston RD. Snake antivenoms. *J Toxicol* 2003;41:277-90.
9. Lavonas EJ, Ruha AM, Banner W, Bebart A, Bernstein JN, Bush SP, Kerns WP 2nd, Richardson WH, Seifert SA, Tanen DA, Curry SC, Dart RC; Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority. Unified treatment algorithm for the management of crotaline snakebite in the United States: results of an evidence-informed consensus workshop. *BMC Emerg Med* 2011;11:2.
10. Tanen D, Ruha A, Graeme K, Curry S. Epidemiology and hospital course of rattlesnake envenomations cared for at a tertiary referral center in Central Arizona. *Acad Emerg Med* 2001;8:177-82.
11. Tanen DA, Danish DC, Grice GA, Riffenburgh RH, Clark RF. Fasciotomy worsens the amount of myonecrosis in a porcine model of crotaline envenomation. *Ann Emerg Med* 2004;44:99-104.
12. Schexnayder SM, Schexnayder RE. Bites, stings, and other painful things. *Pediatr Ann* 2000;29:354-8.
13. Lykissas MG, Koulouvaris P, Kostas-Agnantis I, Gkiatas I, Milionis HJ, Mavrodontidis AN. Snakebites of fingers or toes by Viperidae family members: an orthopaedic approach. *Acta Orthop Belg* 2011;77:246-51.
14. Anz AV, Schweppe M, Halvorson J, Bushnell B, Sternberg M, Andrew Koman L. Management of venomous snakebite injury to the extremities. *J Am Acad Orthop Surg* 2010;18:749-59.
15. Rainer PP, Kaufmann P, Smolle-Juettner FM, Krejs GJ. Case report: hyperbaric oxygen in the treatment of puff adder (*Bitis arietans*) bite. *Undersea Hyperb Med* 2010;37:395-8.
16. Bhutani S, Vishwanath G. Hyperbaric oxygen and wound healing. *Indian J Plast Surg* 2012;45:316-24.
17. Sahni T, Hukku S, Jain M, Prasad A, Prasad R, Singh K. Recent advances in hyperbaric oxygen therapy. *Med Update* 2004;14:632-9.

Penoscrotal defect: a functional, esthetic, and psychological challenge

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ABSTRACT

Aim: Penoscrotal defects may be caused by a variety of events. Reconstruction of the penoscrotal region is required not only for aesthetic appearance but also for functional and psychological reasons. Numerous techniques have been described for penoscrotal reconstruction reflecting the challenge and complexity of the region involved. This suggests that no single method is satisfactory for all types and degrees of tissue defects. This prospective study was conducted in a tertiary care hospital in India, over a period of 5 years. **Methods:** Eighteen patients with penoscrotal defects of varying etiology were included in the study and underwent different surgical techniques. Age of the patients ranged from 20 to 60 years. The etiology of penoscrotal defect was Fournier's gangrene in 12 cases, trauma in 4 cases, and burn in 2 cases. The patients with Fournier's gangrene were initially treated by debridement, drainage, and antibiotics. The penoscrotal defects were treated with local flap advancement with skin grafting ($n = 7$), pedicled anterolateral thigh flap ($n = 4$), gracilis muscle flap with split skin grafting ($n = 4$), and medial thigh flap ($n = 3$). **Results:** There was complete healing in 16 patients with minor complications in the form of partial skin graft loss ($n = 1$) and wound dehiscence ($n = 1$). Results were highly satisfactory in 6 patients, satisfactory in 8 patients, and not satisfactory in 4 patients. Scarring at the donor site was limited and acceptable. **Conclusion:** The vast arsenal of options for penoscrotal defect coverage ranges from skin grafting to flaps, and every case needs a customized approach with regard to its feasibility, outcome, and complication rate. Flaps should be the preferred choice over the skin grafts because of the superior functional and aesthetic results and better compliance.

Key words:

Anterolateral thigh flap; gracilis muscle flap; penoscrotal defect

INTRODUCTION

Penoscrotal defects can be caused by road traffic accidents, assaults, burns, animal bites, infection/gangrene of the region (Fournier's gangrene), postfilarial surgeries, penoscrotal construction for congenital agenesis, and gender reassignment surgeries.^[1] Reconstruction of the penoscrotal region after a

complete loss of the overlying skin is a challenging problem.^[2] The difficulty in the reconstruction of the scrotum lies in the fact that the blood supply to the scrotal skin is destroyed when the skin and dartos muscle are avulsed or infected.^[3] Bacterial flora of the perineum, difficulty of immobilization, and contour of penis and testes makes the task of

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peno-scrotal coverage difficult.^[4] Reconstruction of the scrotum is required not only for cosmetic but also for functional and psychological reasons as well. Various surgical options have been described for penoscrotal reconstruction including split skin grafting (SSG), burying testis underneath the medial thigh skin, tissue expansion of adjacent tissues, use of local fasciocutaneous or musculocutaneous flaps, and free flaps. The aim of this study was to evaluate various reconstructive procedures for penoscrotal defects.

METHODS

A prospective study was conducted in a tertiary care hospital over a period of 5 years from March 2009 to February 2014. The operated patients were reviewed on a regular basis in context to the outcome of the procedures, complications, and further need for any intervention. Patients with penoscrotal defects of varying etiology and who had been operated using different reconstructive techniques were included in the study. Patients with uncontrolled diabetes were excluded from the study. Demographics, etiology, reconstructive technique, complications, and patient satisfaction were identified.

Patients with Fournier's gangrene were initially treated by debridement, drainage, and antibiotics. The penoscrotal defects were treated with local flap advancement with skin grafting, pedicled anterolateral thigh (ALT) flap, gracilis muscle flap with skin grafting, and medial thigh flap. Local flaps from remaining scrotal skin and adjacent medial thigh were advanced to cover the exposed testes. Any remaining defect was skin grafted. Lateral thigh flaps were raised based on the lateral circumflex femoral artery branch of the femoral artery to cover the defect [Figure 1a and b]. The donor area was primarily closed [Figure 1c and d]. Medial thigh flaps based on the medial circumflex femoral artery branch of the femoral artery was raised in the relatively bloodless subfascial plane. Gracilis muscle was separated from the distal

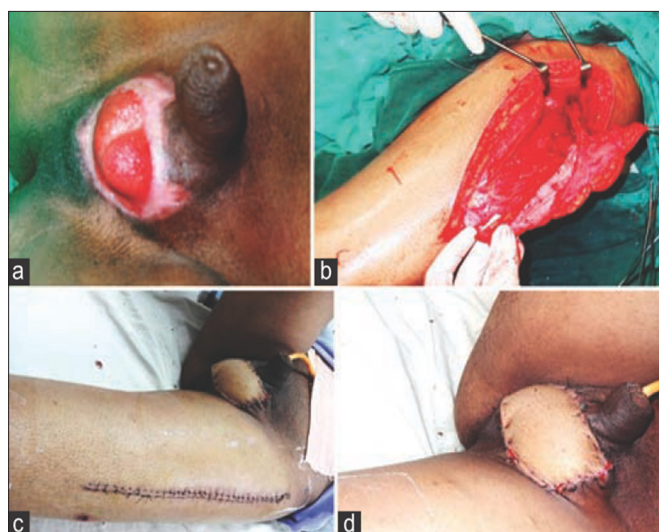


Figure 1: (a) A 28-year-old male with a history of road traffic accident presented with a penoscrotal soft tissue defect and exposed testes; (b) raised anterolateral thigh flap; (c) the bridging segment was de-epithelized, and the flap was tunneled; the defect was covered, and the donor area was primarily closed; (d) 10 days postoperative result

end after dissection with preservation of the vascular pedicle present at the proximal part [Figure 2a-c]. The dissected muscle was transferred over the defect and passed through a subcutaneous tunnel [Figure 2d]. The transferred muscle was skin grafted, and the harvested site was closed primarily [Figure 2e and f]. The operated patients were followed in our hospital at a regular interval and were asked about the improvement on a global scale of 1-10, ranging from not satisfied to highly satisfied. The penoscrotal defect etiology was Fournier's gangrene in 12 cases, trauma in four cases, and burn in two cases.

RESULTS

A total of 18 patients were identified, with a mean age of 45 years ranging from 20 to 60 years. The etiology included: 12 (66.6%) cases of Fournier's gangrene, 4 (22.2%) cases of traumatic injury, and 2 (11.2%) cases of burn injury. The defects were treated with local flap advancement with SSG ($n = 7$) (40%), pedicled ALT ($n = 4$) (22%), gracilis muscle flap with SSG ($n = 4$) (22%), and medial thigh flap ($n = 3$) (16.5%). The patients were followed on a regular basis with the mean of 8.7 months [Table 1].

Local flap advancement in combination with SSG was performed in 7 cases (5 cases following Fournier's gangrene, 1 case following trauma, and 1 case following burn injury). ALT flap was performed in 4 cases (3 cases following Fournier's gangrene and 1 case following trauma). Gracilis muscle flap in combination with SSG was performed in 4 patients (2 cases following Fournier's gangrene, 1 case following trauma, and 1 case following burn patient). See Table 1 for a summary of the patient included in the study. Medial thigh flap was performed in 3 patients (2 cases following Fournier's gangrene and 1 case following trauma).

A total of 6 patients developed complications. Three patients developed a postoperative wound infection and three developed wound dehiscence. Wound infection was present in 3 of the Fournier's gangrene cases, 2 of which underwent local flap advancement in combination with SSG, and 1 case underwent with ALT flap. Wound dehiscence was present in 1 case of Fournier's gangrene operated with local flap advancement and SSG, in 1 case of trauma operated with local flap advancement with SSG, and in 1 case of burn operated with gracilis muscle flap with SSG. Pedicled thigh and medial thigh flaps were associated with no complications.

Results were highly satisfactory in 6 patients, satisfactory in 8 patients, and not satisfactory in 4 patients. In patients with local flap advancement with SSG, 4 patients were satisfied, and 3 patients were not satisfied. In patients with ALT flap, 3 cases were satisfied, and 1 case was not satisfied. In patients operated with gracilis muscle flap, 3 cases were highly satisfied, and 1 case was satisfied. In patients with medial thigh flap, 2 cases were highly satisfied, and 1 case was satisfied. Scarring at the donor site was limited and acceptable. Patient compliance with

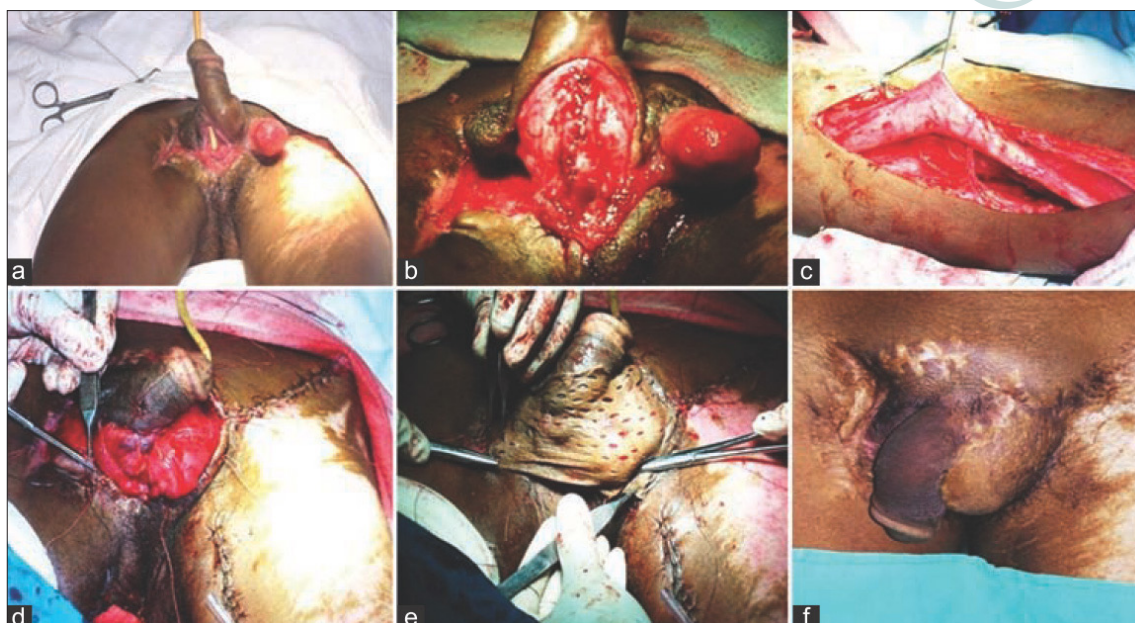


Figure 2: (a) A 30-year-old male with a history of road traffic accident presented with penoscrotal defect, exposed testes, and urethral injury; (b) debridement and urethroplasty were performed; (c) pedicled gracilis muscle flap was harvested; (d) the gracilis muscle flap was insetted; (e) split skin grafting over the muscle flap; (f) 1-year postoperative result

Table 1: Details of the patients included in the study

Age (years)	Etiology	Affected side	Time of reconstruction	Procedure done	Follow-up (postoperative)	Complications
45	Fournier's gangrene	B/L	27 days	Local flap advancement with SSG	8 months (satisfactory)	-
56	Fournier's gangrene	B/L	20 days	Local flap advancement with SSG	12 month (satisfactory)	Wound infection
58	Fournier's gangrene	B/L	31 days	Local flap advancement with SSG	6 months (highly satisfactory)	-
51	Fournier's gangrene	B/L	18 days	ALT flap	8 month (satisfactory)	-
48	Fournier's gangrene	B/L	2 months	Local flap advancement with SSG	10 months (unsatisfied)	Wound infection
42	Fournier's gangrene	B/L	28 days	Gracilis muscle flap with SSG	9 months (highly satisfactory)	-
47	Fournier's gangrene	B/L	1.5 months	Local flap advancement with SSG	15 months (unsatisfied)	Dehiscence
52	Fournier's gangrene	B/L	38 days	ALT flap	6 months (satisfactory)	-
55	Fournier's gangrene	B/L	26 days	Medial thigh flap	12 months (highly satisfactory)	-
47	Fournier's gangrene	B/L	2 months	ALT flap	5 months (unsatisfi ed)	Wound infection
57	Fournier's gangrene	B/L	2 months	Medial thigh flap	8 months (satisfactory)	-
51	Fournier's gangrene	B/L	1 month	Gracilis muscle flap with SSG	9 months (highly satisfactory)	-
32	Trauma	B/L	4 days	Gracilis muscle flap with SSG	6 months (highly satisfactory)	-
35	Trauma	B/L	3 days	Medial thigh flap	12 months (highly satisfactory)	-
30	Trauma	B/L	12 days	ALT flap	11 months (satisfactory)	-
38	Trauma	B/L	Immediate	Local flap advancement with SSG	7 months (unsatisfi ed)	Dehiscence
34	Burns	B/L	2 months	Gracilis muscle flap with SSG	6 months (satisfactory)	Dehiscence
42	Burns	B/L	1 month	Local flap advancement with SSG	8 months (satisfactory)	-

SSG: split skin grafting; B/L: bilateral; U/L: unilateral; ALT: anterolateral thigh

regional and muscle flaps were superior in comparison to the local flap advancement with SSG. This study did not include the assessment of sexual function, and further studies are needed.

DISCUSSION

SSG for scrotal avulsion injuries was first advocated by Millard and subsequently by Maguina.^[4-6] In cases of complete loss of penile and scrotum skin, grafting may be the most successful and simplest option in the closure

of these defects.^[4] The spermatic cord can be partially retracted up into the inguinal canals, and testicles should be sutured together to minimize motion and maximize graft take. Long-term success with skin grafting for scrotal injury is excellent, and only 20% of patients require significant revisions or reconstructions. However, SSG may have certain disadvantages such as technical difficulty at recipient site, poor graft take, contraction and distortion, lack of protective sensation, and less acceptable cosmetic results. An SSG does not take if the testes have been stripped of the tunica vaginalis. SSG is a better option for

old or debilitated patients, while young patients benefit from flap coverage.

Several locoregional cutaneous and fasciocutaneous flaps from thigh, perineal, and groin areas have been described to reconstruct the penoscrotal region. Local flap advancement provides a faster and simpler option of coverage, but the aesthetic appearance may not be pleasant to the younger patients.

The ALT flap provides excellent closure for extensive defects of the penoscrotal region because it is easy to rotate over the defect and provides excellent aesthetic results. Further thinning may be required as they are inherently bulky flaps though supra-thin flaps have also been described.

The fasciocutaneous flap of the inner thighs has excellent vascularization because of the presence of the branches of the femoral artery (internal and circumflex pudendal arteries), making the flap very safe even in diabetic and vasculopathic patients.^[7,8]

Many myocutaneous flaps have been described, including the rectus abdominis myocutaneous flap, the gracilis myocutaneous flap, and composite gastric seromuscular and omental pedicled flaps.^[9-11] These procedures produce acceptable cosmetic results, and the flaps take readily even in the contaminated environment. Limitations of muscle flaps include loss of functioning muscle, poor sensation, and scarring on thighs and lower abdomen.

Perforator-based flaps include the medial thigh flap, paraumbilical perforator-based cutaneous island flap, medial circumflex femoral artery perforator flap, and pedicled deep inferior epigastric perforator flap.^[11,12] These flaps are thin, which is aesthetically and functionally ideal for scrotum replacement. However, these flaps are technically difficult, and their blood supply is less predictable.

In conclusion, reconstruction of the penoscrotal region is

challenging because it not only affects the physical and esthetic appearance but also has a major psychological and social impact to the patient. Every case needs a customized approach. The choice depends upon the surgeon's preferences, condition of the patient, and ability to achieve the best reconstructive results with the least morbidity.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Kolehmainen M, Suominen S, Tukiainen E. Pelvic, perineal and genital reconstructions. *Scand J Surg* 2013;102:25-31.
2. Lee SH, Rah DK, Lee WJ. Penoscrotal reconstruction with gracilis muscle flap and internal pudendal artery perforator transposition. *Urology* 2012;79:1390-4.
3. Chen SY, Fu JP, Chen TM, Chen SG. Reconstruction of scrotal and perineal defects in Fournier's gangrene. *J Plast Reconstr Aesthet Surg* 2011;64:528-34.
4. Millard DR Jr. Scrotal construction and reconstruction. *Plast Reconstr Surg* 1966;38:10-5.
5. Maguina P, Palmieri TL, Greenhalgh DG. Split thickness skin grafting for recreation of the scrotum following Fournier's gangrene. *Burns* 2003;29:857-62.
6. Ellabban MG. Single stage muscle flap reconstruction of major scrotal defects. *Burns* 2004;30:505.
7. Yang J, Ko SH, Oh SJ, Jung SW. Reconstruction of a perineoscrotal defect using bilateral medial thigh fasciocutaneous flaps. *Arch Plast Surg* 2013;40:72-4.
8. Ferreira PC, Reis JC, Amarante JM, Silva AC, Pinho CJ, Oliveira IC, da Silva PN. Fournier's gangrene: a review of 43 reconstructive cases. *Plast Reconstr Surg* 2007;119:175-84.
9. Karsidag S, Akcal A, Sirvan SS, Guney S, Ugurlu K. Perineoscrotal reconstruction using a medial circumflex femoral artery perforator flap. *Microsurgery* 2011;31:116-21.
10. Parkash S, Gajendran V. Surgical reconstruction of the sequelae of penile and scrotal gangrene: a plea for simplicity. *Br J Plast Surg* 1984;37:354-7.
11. Gencosmanoğlu R, Bilkay U, Alper M, Gürlü T, Çağdaş A. Late results of split-grafted penoscrotal avulsion injuries. *J Trauma* 1995;39:1201-3.
12. Monteiro E, Carvalho P, Costa P, Ferraro A. "Inner thigh lift flap" for Fournier gangrene of the scrotum. *Plast Reconstr Surg* 2002;110:1372-3.

Painful scar neuropathy: principles of diagnosis and treatment

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Dear Editor,

We read with interest the article entitled “Painful scar neuropathy: principles of diagnosis and treatment” (Plast Aesthet Res Vol 2, Issue 4, Jul 15, 2015) where Tos *et al.*^[1] presented a literature review of treatment approaches to peripheral nerve scar neuropathy and the outcomes of neurolysis-associated procedures.

We would like to contribute our treatment experience of neuropathic pain with autologous fat grafting.

Autologous fat grafting is a safe technique that has been used to treat various pathologic conditions in reconstructive surgery. We applied its regenerative properties to treat burn^[2] and hypertrophic scars^[3] and have achieved issue release and quality improvement.

Using Coleman’s technique, we harvested adipose tissue

from the flank or abdominal region. The fat is then processed by centrifugation at 3,000 rpm for 3 min and re-injected with an 18-gauge hypodermic needle into the scar.

We have used fat grafting for the treatment of neuropathic pain conditions such as post mastectomy pain syndrome.^[4] This is a chronic neuropathic syndrome characterized by persistent pain in the anterior side of the thorax, axilla, and may include the upper half of the arm that begins after mastectomy or quadrantectomy. We observed statistically significant pain reduction when autologous fat grafting was used to treat this, evaluated on a visual analog scale scale.

We also performed autologous fat grafting for the treatment of another neuropathic pain condition, Arnold neuralgia.^[5] Arnold neuralgia is a chronic headache of cervical origin caused by scar entrapment of the great

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occipital nerve.

We postulate that our results are due to the induction of architectural remodeling and regeneration, neovascularization and improved hydration by fat grafting. This leads to the release of scar entrapment and anatomical remodeling.

We further evaluate the effect of autologous fat grafting on nerve function in our recent case report^[6] where we describe the case of a 45-year-old male patient who presented with a retracted and painful scar in the nasolabial fold. This scar of traumatic origin was associated with partial motor impairment of the muscles of the mouth. We observed complete restoration of movement with two cycles of autologous fat grafting at the one year follow-up.

The presence of mesenchymal multipotent stem cells in the adipocyte cell fraction of the graft have been demonstrated histologically. These are cells that are responsible for scar remodeling through engraftment and differentiation. Their presence induces fat and loose connective tissue regeneration that leads to increased scar softness and neurolysis.

Furthermore, we hypothesize that autologous fat graft could induce molecular changes in the microenvironment of the post-traumatic scar. This environment is otherwise hostile to nerve regeneration due to the presence of intrinsic

inhibitory factors expressed by the extracellular matrix.

Based on our experience, we consider autologous fat grafting as an innovative solution for neuropathic pain syndromes that are related to scar retraction. The low complication rate and good results indicate that it should be considered as an effective treatment option.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Tos P, Crosio A, Pugliese P, Adani R, Toia F, Artico S. Painful scar neuropathy: principles of diagnosis and treatment. *Plast Aesthet Res* 2015;2:156-64.
2. Klinger FM, Vinci V, Forcellini D, Caviggioli F. Basic science review on adipose tissue for clinicians. *Plast Reconstr Surg* 2011;128:829-30.
3. Klinger M, Lisa A, Klinger F, Giannasi S, Veronesi A, Banzatti B, Bandi V, Catania B, Forcellini D, Maione L, Vinci V, Caviggioli F. Regenerative Approach to Scars, Ulcers and Related Problems with Fat Grafting. *Clin Plast Surg* 2015;42:345-52.
4. Caviggioli F, Maione L, Forcellini D, Klinger F, Klinger M. Autologous fat graft in postmastectomy pain syndrome. *Plast Reconstr Surg* 2011;128:349-52.
5. Gaetani P, Klinger M, Levi D, Bussone G, Giannasi S, Caviggioli F, Marazzi M, Broggi G. Treatment of chronic headache of cervical origin with lipostructure: an observational study. *Headache* 2013;53:507-13.
6. Klinger M, Lisa A, Caviggioli F, Maione L, Murolo M, Vinci V, Klinger FM. Autologous Fat Grafting Improves Facial Nerve Function. *Case Rep Surg* 2015;2015:520746.

Biomaterials for facial aging

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Fountain of youth has always been the dream of mortals since the ancient time. Since ages ago, mortals have always been searching for ways to stay and look young. In the new millennia, retaining a youthful appearance is no longer a dream beyond reach. The advancement in medical technology, especially in the dermatological technology, has made the dream of youth possible.

The signs of aging often begin with the largest organ of human body, i.e. the skin. Facial wrinkles are the prominent sign of aging caused by facial volume loss under the skin, which will lead to skin sagging. The key to retain youth rely thus on prevention and treatment of wrinkles. As minimally invasive treatment, the emergence of intradermal fillers has excited the plastic surgeons. The injectable dermal fillers can be injected into the sagging skin to fill in the lost volume to rejuvenate facial appearance.

These intradermal fillers are divided into three categories which are biodegradable/non-permanent fillers, semi-permanent fillers, and permanent fillers. Biodegradable/non-permanent fillers include bovine collagen, porcine

collagen, human collagen, hyaluronic acid and autologous fat and are often used to treat nasolabial folds. They are mainly from animal source and will degrade upon time (3-12 months) and thus can only be used as temporary filler. Semi-permanent fillers include poly-L-lactic acid and calcium hydroxylapatite. These fillers are biocompatible and do not show significant adverse effect when tested on patients. They will gradually degrade *in vivo* upon the formation of replacement tissues. Permanent fillers, e.g. the most frequently used silicone, is often used to treat severe facial volume loss. They are very advantageous for prosthetic reconstruction that requires excessive surgical intervention and low maintenance.

With the increase in demand for non-surgical dermatological enhancement, the world has placed a lot of focus in search of various intradermal fillers that can suite the patients' demand. Young adult need it for youthful feature enhancement, middle aged adult need it for early prevention or volume restoration, while the mature need it for the delay and maintenance of aging related syndrome.

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Research is carried on progressively to search for optimal fillers that fulfil the requirement in effectiveness in treating facial aging, durability, no adverse effect on human body and cost effectiveness. Due to this ever increasing demand for better fillers, new formulation are created from time to time in short interval. Hybrid formulation that combines two or more fillers from different categories seems to be the trend of near future owing to its synergistic effects upon combination. Extra gadget such as radiofrequency devices also beneficial in enhancing the

treatment efficiency, by prolonging the duration and reduce the number of injection. Minimally invasive treatment of facial aging using intradermal fillers is on its way!

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Conflicts of interest

There are no conflicts of interest.

Intradermal fillers for minimally invasive treatment of facial aging

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ABSTRACT

The ever-increasing interest in retaining a youthful physical appearance has facilitated the development of various minimally invasive dermatological techniques. The use of intradermal fillers can be incorporated into dermatological practices with minimal overhead costs. This strategy addresses facial volume loss and dynamic lines, which are the main features of facial aging. Moreover, intradermal fillers provide an array of flexible treatment options for a balanced and holistic result to dermatological practitioners. This paper reviews the different intradermal fillers categorized by biodegradable and non-permanent fillers including collagen based materials, hyaluronic acid and autologous fat, semi-permanent fillers including poly methyl methacrylate, poly-L-lactic acid and calcium hydroxyapatite microspheres, and permanent fillers including silicone. A discussion is provided of the commercial products made of these materials and their clinical efficacy in the treatment of facial aging.

Key words:

Intradermal fillers; facial aging; volumization; biodegradable and non-permanent fillers; semi-permanent fillers; permanent fillers

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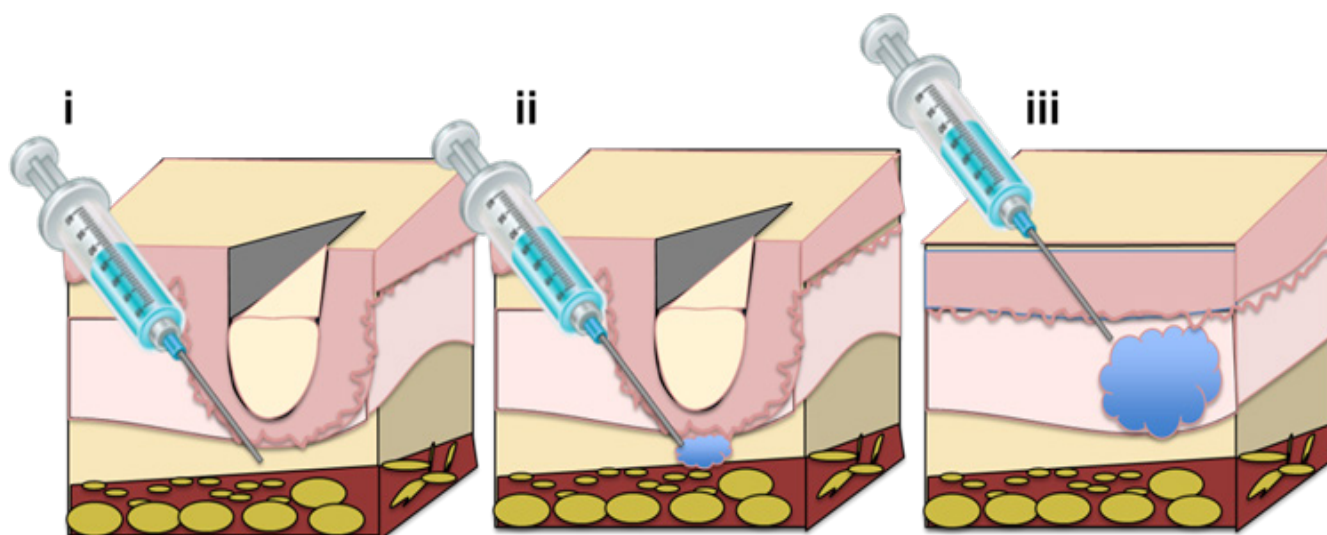


Figure 1: Procedure protocol for injection of intradermal fillers for the treatment of facial aging. (i) The depth of needle insertion ranges from superficial to mid-dermis and is dependent on both wrinkle type and filler type; (ii) release of intradermal fillers through the needle; (iii) filler insertion results in smoothed wrinkles and the effect is long-lasting^[1]

INTRODUCTION

A youthful face is characterized by fullness, balance, smoothness, and the absence of facial lines or wrinkles. During the aging process, the outer shell of the human body changes its appearance. These skin alterations are often narrowly focused on facial wrinkles, one of the most visible signs of the aging process. Therefore, the majority of approaches intending to reverse skin-aging signs target the treatment of wrinkles.^[1] However, it has recently become more evident that the treatment of wrinkles alone is not sufficient to restore a youthful facial appearance. As aging continues, the subcutaneous fat pads shrink, leading to the loss of structural support which in turn creates sagging of the overlying skin. The loss of facial volume beneath the skin (e.g. subcutaneous fat, muscle) is thus considered to be the major contributor to the appearance of advanced age.^[1]

A number of minimally invasive dermatological techniques have been developed for facial rejuvenation. Injectable dermal fillers can be injected through a needle into the upper layers of the dermis to treat superficial fine wrinkles or injected into the deep dermis or subcutaneous space for facial volume augmentation^[2] [Figure 1]. Dermal fillers are deposited in a slow and steady manner and fill central folds, resulting in a natural, long-lasting outcome. Crease depth, desired outcome, and the patient's financial situation are factors which need to be taken into account when deciding the amount of product to be used.

This paper focuses on intradermal fillers, chosen due to their ability to alleviate aging-related conditions and their ability to be easily incorporated into the armamentarium of outpatient cosmetic procedures with minimal overhead costs.

TYPES OF INTRADERMAL FILLERS

Intradermal fillers can be roughly divided into three categories depending on their durability: (1) biodegradable

and non-permanent agents [e.g. bovine collagen, porcine collagen, human collagen, hyaluronic acid (HA) and autologous fat]; (2) semi-permanent agents [e.g. poly methyl methacrylate (PMMA) microspheres, poly-L-lactic acid (PLA) and calcium hydroxyapatite (CaHA)]; (3) permanent agents (e.g. silicone). The commercial products, their materials, and their clinical efficacy are summarized in Table 1.

Biodegradable and non-permanent fillers

Bovine collagen

Bovine collagen has been in use for over 20 years as intradermal filler. It is extracted from bovine tendon, dermis and bone.^[3] Once injected it has the ability to form a rigid structure composed of fibrils, with an axial periodicity of native collagen which stays intact to help correct facial defects.^[4] Since its approval by the Food and Drug Administration (FDA) in 1981, highly purified bovine collagen products have been used as fillers in more than 2 million patients.^[5] Different forms of bovine collagen are currently available, including Zyderm® I and II (Inamed Aesthetics, Santa Barbara, CA, USA), composed of 3.5% or 6.5% bovine dermal collagen suspended in a phosphate buffer solution, respectively. Both are used for the correction of superficial lines including scars, peri-orbital lines and crow's feet.^[6] Similarly, Zyplast® (Inamed Aesthetics), is composed of 3.5% collagen with the addition of 0.0075% glutaraldehyde, which helps to strengthen the collagen fibers and prolong the duration of action.^[6] Zyplast® is primarily used to treat deeper scar tissue including acne scars and the vermilion border of the lip.^[6]

Various distinctive studies have demonstrated the efficacy of Zyderm® in the cosmetic industry including a study conducted by Nicolle,^[7] which showed the effectiveness of Zyderm® II in 350 patients treated for various facial contour defects including acne, glabellar frown lines, peri-orbital lines and naso-labial folds. Eighty percent of the patients treated were satisfied with their results although 5 patients showed signs of a positive localized reaction to the test dosage of Zyderm® II.^[7] Additionally, a clinical

Table 1. Commercially available facial fillers

Filler	Function	Uses	Pros	Cons
Biodegradable and non-permanent fillers				
Bovine collagen (Zyderm® I and II, Zyplast®)	Extracted from bovine tendons, dermis and bones; injected to correct facial defects	Forms a rigid structure composed of fibrils, with an axial periodicity of native collagen that stays intact	Optimal correction is usually found to last between 4-6 months for rhytids and 6-9 months for scars regardless of which product is used	Can cause adverse immune reactions
Porcine collagen (Evolence™, TheraFill®)	Extracted from porcine tendons, dermis and bones; injected to fill wrinkles	Volume enhancer (nasolabial)	Less immunogenic than bovine collagen	May elicit immunogenic reaction, although it may not be considered adverse
Human collagen (Cosmoderm®, Cosmoplast®, Cymetra®)	Derived from human dermis to treat wrinkles and scars	FDA-approved for deep scars, superficial and deep wrinkles	Skin testing is not required before use	May cause adverse reactions
HA (Restylane®, Juvederm 30™, Juvederm Ultra™, Juvederm Ultra Plus™, Perlane®, Hylaform®, Hylaform Plus®)	Very commonly found substance; usually derived from either bacteria or rooster combs	Volume and contouring (nasolabial, forearm, etc.)	Skin testing is not required before use	Usually associated with short-lived side effects
Autologous fat (Radiesse®)	Used for soft tissue augmentation	Facial volume augmentation and wrinkle reduction	Can use large volume without immunoreaction.	Fat needs to be first extracted from another source and grafted fat may be inconsistent quality.
Semi-permanent fillers				
PMMA microspheres (Arteplast®, Artecoll®, Artefill®, Dermalive®)	Non-biodegradable, biocompatible, synthetic polymer	Volume and contouring (nasolabial, radial upper lip lines, glabella lines, corner of mouth lines)	Can be easily fabricated to 30 to 40 µm in diameter, small enough to pass through the needles but big enough to avoid phagocytosis; inexpensive, readily accessible and simple to apply	Some immediate adverse reactions mainly associated with the development of lumps or nodules
PLA (Sculptra/Fill®)	Biodegradable; usually derived from renewable sources; injected into either the deep dermis or subcutaneous layer.	Restoration of facial fat loss (nasolabial folds, labiomentalar creases, marionette lines, upper lip, etc.)	Assists with volume restoration while simultaneously increasing dermal thickness in the face; reduced safety concerns; very good risk-benefit profile for HIV patients and for cosmetic purposes	Volumization disappears within a few months; dermal fibroplasia; Results not immediate (more than 2 years)
CaHA (Radiesse®)	CaHA microspheres acting as a scaffold for new collagen formation	Correction of moderate-to-severe wrinkles and folds; volumization of facial soft-tissue; correction of the signs of facial lipoatrophy	Biocompatible; skin testing is not required before use	Side effects more common; may be unsafe to use for glabellar or periorbital lines
Permanent fillers				
Silicone (Silikon 1,000 and AdatoSil 5,000)	Oil injected as microdroplets	Volume and contouring; injected into the deep dermis or subdermal plane	Low maintenance and cost; permanent	Adverse complications; cannot be removed after implantation

FDA: Food and Drug Administration; HA: hyaluronic acid; PMMA: poly(methyl methacrylate); PLA: poly-L-lactic acid; CaHA: calcium hydroxyapatite

study by Bailin and Bailin^[8] in which 8 patients were treated with Zyplast® and Zyderm® I and II for surgical scars, acne scars and rhytids or a combination of these found that both products were effective. Results lasted between 4-6 months for rhytids and 6-9 months for scars regardless of which product was used.^[8]

Skin testing is essential for patients undergoing treatment with bovine collagen because it is extracted from an animal source and may provoke a reaction. Generally, two skin tests spaced 2 or 4 weeks apart are recommended. The skin test is performed by intradermal injection of 0.1 mL of collagen onto the volar forearm to detect any pre-existing allergy to Zyderm® or its counterparts.^[9] It is suggested

that the occurrence of local sensitive reaction ranges from 3% to 5%. Various clinical tests and studies have shown that Zyderm® and Zyplast®, if not used effectively, can cause adverse reactions.^[9] These reactions are often classified as immune responses to the foreign material being injected into the body.^[9] In general, Zyplast® and Zyderm® may elicit adverse reactions such as hypersensitivity, herpes virus reactivation, bacterial infection, bruising, and local necrosis. Therefore, it is crucial to follow strict procedures regarding the skin testing protocol, as well as to compare it to other fillers to determine which one if appropriate for use.

Porcine collagen

Porcine collagen is extracted from porcine tendon, dermis

and bone. In recent years, porcine collagen has been marketed as an intradermal filler under the brand name of Evolence™ (ColBar LifeScience Ltd., Herzliya, Israel). Studies involving human medical devices have shown that porcine collagen is less immunogenic than bovine collagen, although the amount of published data regarding its potential as intradermal filler is still relatively insignificant.^[10] In a phase I clinical trial with 12 patients receiving treatment for nasolabial folds, both Evolence™ and Zyplast® were found to be safe and effective.^[10] The degree of improvement in wrinkles, graded by blinded examiners, was observed to be much greater for Evolence™ at both the 6-month and 18-month visiting periods.^[11] A larger randomized, double-blinded trial found no significant difference in effectiveness between Evolence™ and NASHA (Restylane®) in the treatment of nasolabial folds at the 6-month assessment. Although there were no positive skin tests against porcine collagen, 6.1% of patients developed IgG antibodies to porcine collagen. Although there were immunogenic reactions, it is important to note that none of them were considered to be adverse in nature.^[12]

Another study was conducted comparing the safety and efficacy of TheraFill®, a porcine collagen filler, to a bovine collagen filler for the treatment of nasolabial folds. In total 61 patients were evaluated in this randomized, double-blinded and split-face study over a 12-month period. The Wrinkle Severity Rating Scale (WSRS) rating of TheraFill® was shown to be higher than that of bovine collagen filler by a small margin, although not enough to be considered statistically significant. Both fillers were similarly effective and safe without eliciting severe adverse reactions, suggesting that TheraFill® could suitably replace bovine collagen filler.^[13]

Many studies have been performed which assess the efficacy of bovine and porcine dermal fillers. The aforementioned studies discuss the adverse/allergic responses and the efficacy of treatment provided by these fillers.^[14,15] More comparative studies have been done between bovine or porcine and other fillers to choose the safest and most preferred treatment.^[16] With the advent of new technology, the cosmetic industry has moved on to various other types of intradermal fillers including human collagen, smooth gel hyaluronic acid, poly-L-lactic acid (PLA), poly(methyl methacrylate) (PMMA) microspheres, etc., which have proven to be better alternatives to bovine and porcine fillers. These are discussed in detail below.

Human collagen

Collagen has traditionally been extracted from animal sources or cadavers. Recently researchers have proposed obtaining human collagen from other sources including adipose tissue obtained after liposuction^[17] and from yeast or bacteria used for the production of recombinant human collagen.^[18] Moreover, human collagen can now also be synthesized in the lab as discovered by Raines.^[19] Cosmoderm® and Cosmoplast® (Inamed Aesthetics) are some of the currently available products made of human collagen; both contain lidocaine and have received FDA approval. The collagen content is produced from a single human dermal fibroblast cell line. Cross-linking between lysine residues on collagen

and glutaraldehyde makes Cosmoplast® less prone to degradation. Cosmoplast® is used for the treatment of deeper wrinkles and deep scars whereas Cosmoderm® is used for the treatment of superficial wrinkles, both with effects lasting for 3-7 months.^[20] The Inamed clinical study of human collagen immunogenicity concluded with a 95% upper confidence interval that the probability of a hypersensitivity reaction from either Cosmoplast® or Cosmoderm® is less than 1.3%.^[21]

AlloDerm is a sheet derived from human dermis that requires a multi-step treatment to ensure optimal efficacy. Cymetra® (LifeCell Corp., Branchburg, NJ, U.S.A.) is an injectable form of AlloDerm.^[22] Very few trials have been conducted comparing human-derived collagen with other types of fillers. A randomized trial comparing Zyplast® (bovine collagen) and Cymetra® (human collagen) injections to the upper lip showed that Cymetra® had a much higher post-treatment value than Zyplast® by the 12-month visit, with bruising being the most commonly observed adverse effect for both fillers.^[23] Because Cymetra® is of human origin, skin testing is not required prior to use.

Although collagen treatment is beneficial for most individuals, it has its limitations. Patients who are sensitive to bovine collagen must instead use human collagen, which is typically more expensive. Individuals with autoimmune diseases should completely avoid the use of foreign collagen. Finally, the results typically last for a short period of time as the body absorbs external collagen naturally.

Hyaluronic acid

HA is a very commonly found substance which is usually derived from either bacteria or rooster combs for use as an intradermal filler.^[24] Although several products containing HA-related proteins have shown a theoretical risk of hypersensitivity, there is no requirement for skin testing prior to use.^[24]

Restylane®, a type of non-animal stabilized hyaluronic acid (NASHA), is a stable, partially cross-linked form of HA. It is fermented by bacteria and has a long track record of safety (over 10 years) as an intradermal filler. Due to rapid degradation of hyaluronic acid in the skin, cross-linking is required in order to produce a hydrophilic HA polymer. Because no anesthetic is associated with Restylane®, topical anesthesia or a nerve block may be administered prior to its use. Narins *et al.*^[25] conducted a double-blinded, randomized, and longitudinal comparison study between Restylane® and Zyplast® for treatment of the nasolabial fold. In the study involving 138 patients, the Wrinkle Severity Rating Scale (WSRS) (with 1 being the lowest and 5 being the most severe) and Global Aesthetic Improvement Scale (GAIS) (on a scale of 5 ranging from “worse” to “very much improved”) were used at 2, 4, and 6 months after baseline. Both groups showed similar improvements with 90% of patients exhibiting improvement by 1 or 2 scores according to the WSRS rating. At 6 months, more patients showed improvement with Restylane® (56.9% for WSRS; 62% for GAIS) than with Zyplast® (9.5% for WSRS; 8% for GAIS). Reactions (e.g. swelling, tenderness, bruising, redness and

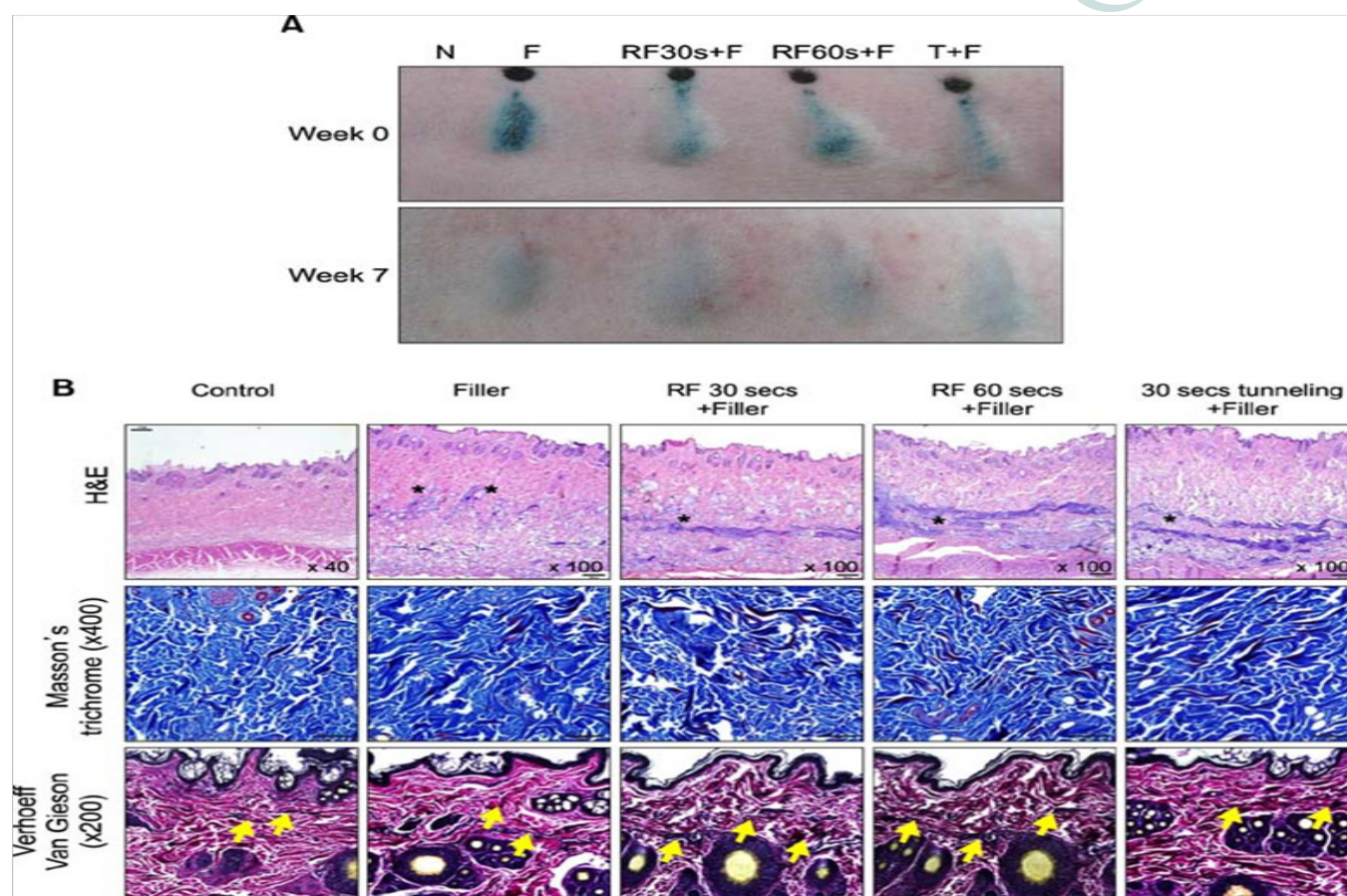


Figure 2: (A) Filler injections after radiofrequency (RF) treatment results in volumization. N: normal; F: Glytone 3 filler injection; RF30s+F: RF treatment for 30 s, RF60s+F: RF treatment for 60 s, both before filler injections through tunneling method; T+F: filler injected after tunneling without RF treatment for 30 s. (B) “*” sign indicates areas injected with fillers. Extracellular matrix components stained with Masson's trichrome show the treatment with both filler and RF enhances collagen bundle deposition (blue) and fibroplasia (red) Dermis stained with Verhoeff-Van Gieson shows that RF treatment resulted in shorter elastin fibers (“arrow” sign). Image used with permission.^[5]

pain) were observed in 93.5% of Restylane®-treated sites and 90.6% of Zyplast®-treated sites, and lasted for 7 days at most. Reactions were also observed after 14 days or more in 12 patients, with 10 reactions in Restylane®-treated sites and 11 reactions in Zyplast®-treated sites. Local erythema was the most common delayed reaction. All reactions spontaneously subsided without treatment and were not considered to be hypersensitivity reactions. A similar study was conducted comparing three formulations of HA filler (Juvederm 30™, Juvederm Ultra™ and Juvederm Ultra Plus™, Allergan) with Zyplast® for the treatment of nasolabial folds. This study also concluded that the effect of HA fillers was much longer-lasting than that of bovine collagen.^[16]

A Scandinavian double-blinded, randomized, longitudinal comparison study with 68 patients was conducted between Perlane® (a form of NASHA produced by Medicis Aesthetics, Scottsdale, AZ, USA) and Zyplast® for the treatment of nasolabial folds.^[26] Using the GAIS rating, both showed “much or very much improved” effects (89.7% for Perlane® and 86.8% for Zyplast®) at the baseline period (2 weeks after injection). Perlane® consistently had higher WSRS ratings during the 9-month follow-up period. Reactions were found at the injection sites for both (17.6% for Perlane® and 30.9% for Zyplast®). Three patients showed delayed reactions but none were considered to be hypersensitivity reactions.

A recent study regarding the use of NASHA showed that it

stimulates the production of new collagen in human skin. In this study, each of 11 volunteers received 3 filler injections into one forearm and 3 isotonic saline vehicle injections into the contralateral forearm. Tissue biopsies results taken 4 and 13 weeks after injection revealed increased collagen deposition around the filler, higher type I procollagen marker staining, upregulation of type I and II procollagen expression, and elongated fibroblast morphology at the injection site. Various mechanisms have been proposed in an attempt to elucidate the *de novo* collagen production, including mechanical fibroblast stretching, growth factor stimulation, and inhibition of collagen degradation. Inhibition of collagen degradation was proposed after observing the expression of matrix metalloproteinases and their regulators in skin treated using NASHA.^[27]

Double-blinded, randomized studies have also been conducted with Hylaform® (Inamed Aesthetics), an FDA-approved HA that is extracted from rooster combs. Hylaform® had similar efficacy compared to Zyplast® for up to 4 months in 300 patients treated for nasolabial folds, with few adverse effects and no allergic reactions.^[28] A small randomized longitudinal study was also conducted with Hylaform Plus®, which contains bigger cross-linked molecules with a larger average particle size than its Hylaform® counterpart. The study was conducted in comparison to Restylane® for the treatment of nasolabial folds and examiners were blinded during evaluation. At 3, 4.5, and 6 months, Restylane®

was found to have a significantly lower WSRS rating than Hylaform Plus®.^[29]

A randomized, split-face study was conducted for 12 months to assess the efficacy and safety of three HA formulations: HA-1 (Belotero Basic/Balance), HA-2 (Restylane), and HA-3 (Juvéderm Ultra 3/Juvéderm Ultra Plus XC) in the treatment of nasolabial folds.^[30] Participants were randomly assigned to one of two study groups, each with twenty participants. Each participant in group 1 received HA-1 on one side and HA-2 on the other, whereas participants in group 2 received HA-1 on one side and HA-3 on the other. Fillers were administered at the baseline visit, which took place during the initial phase, with follow-up injections at months 1, 6, 9, and 12. All three of the HA formulations showed minimal adverse reactions, the most common of which was erythema. The mean pre-treatment and post-treatment nasolabial fold severity ratings did not show statistically significant differences between the groups.^[30]

HA is the most widely used filler yet has a relatively short duration of action, resulting in the need for constant maintenance with frequent injections for optimal treatment.^[31] Recently, HA has been combined with radiofrequency (RF) devices to prolong the duration of action of HA, reducing the need for maintenance injections.^[31,32] RF treatment has been found to play a crucial role in collagen remodeling, skin tightening, and collagen deposition, but has a limited capacity to restore lost volume.^[32] Combination therapy in which RF is used immediately prior to treatment with a HA can compensate for both products' limitations while providing better treatment. Combination therapy was evaluated in both animal and human clinical studies where RF was delivered through an intradermal needle to create tunnel-like setting inside the dermis and hypodermis. This theoretically acts as a barrier to external oxygen radicals and contains the HA filler, restricting its spread.^[31] The results of the animal study showed that RF treatment could increase procollagen production with time. The total volume was substantially increased with the RF treatment as compared to HA filler injections alone [Figure 2]. Specifically, in the areas injected, small filler particles were observed in the dermis. At sites injected with fillers following RF treatment, linear continuous filler distribution was observed in the mid-dermis, and in the lower dermis of sites treated with the tunneling method [Figure 2B]. The ECM components and dermis were stained with Masson's trichrome and Verhoeff-Van Gieson, respectively. Enhancement of collagen bundle deposition and fibroplasia was observed with Masson's trichrome while the formation of short elastin fibers was observed with Verhoeff-Van Gieson staining [Figure 2B]. It is thus believed that the combination therapy of HA filler injection with RF is a biocompatible and long-lasting improvement in skin rejuvenation.

Although HA has shown excellent biocompatibility and efficacy in facial volumization, it has side effects including erythema, bruising, induration and edema. More importantly, they are all short-lived and therefore are of limited use in patients looking for longer lasting solutions.

Autologous fat

For more than a century, autologous fat transfer has been utilized for soft tissue secondary to its advantages including the absence of immune reaction and the feasibility in using large volumes. However, it suffers from various drawbacks including prior fat extraction from another source, and the inconsistent quality of fat due to the extraction technique.

A retrospective clinical study conducted by Kanchwala *et al.*^[33] examined facial volume augmentation and wrinkle reduction in 976 patients who received autologous fat, Restylane®, Hylaform® or Radiesse®. Patients were followed at least 1 year from the time of injection for an assessment of infection rate, revision rate, and overall longevity. In this study, 378 patients had their nasolabial folds treated with autologous fat. Self-limited bruising and swelling were observed 2-3 days after fat injection. Ten percent of patients required a second treatment 6-12 months following the first treatment, and the overall longevity was shown to be greater than 12 months. Forty-one and twenty-six patients received treatment of their nasolabial folds with Restylane® and Hylaform®, respectively. Although only minimal complications were observed, they lasted for, on average, 4.5 and 3 months for Restylane® and Hylaform®, respectively. One hundred and two patients were treated with Radiesse® for their nasolabial folds, and mild-to-moderate swelling was found at the injection sites for 24 h maximum. Twenty percent of patients required a second treatment at the same injection site less than 3 months following the first injection, and longevity was 11 months on average. Significant swelling and bruising that lasted for 1-2 weeks were noted in 87 patients who received autologous fat for lip augmentation, with nearly 30% of them requiring a second injection within 6 months secondary to variable resorption. Overall longevity was greater than 12 months. Twenty-four patients received Restylane® for lip augmentation with effects lasting for 4.5 months, while 17 patients received Hylaform® with 3-month longevity and slightly more swelling for 1-3 days. Twenty percent of patients required a second injection 3 months following the first injection.^[33]

Biodegradable and non-permanent fillers last only for a few months, which is suboptimal in cases where maintenance and cost are issues. This problem gave rise to the advent of semi-permanent fillers as discussed in the next section.

Semi-permanent fillers

Polymethyl methacrylate microspheres

PMMA is a non-biodegradable, biocompatible, synthetic polymer used in various medical devices. Bovine collagen injections on the human face have been found to last only for 3 to 6 months, giving rise to the use of PMMA microspheres as intradermal fillers.^[34] The main advantage of microspheres is their size of 30-40 µm in diameter, which is small enough to pass through a needle but still large enough to avoid phagocytosis.^[35]

Arteplast®, the first mixture which contained 20% PMMA and 80% bovine collagen, was noted to give rise to foreign body reactions due to the presence of a number of microspheres less than 20 µm which made them prone to phagocytosis.^[35]

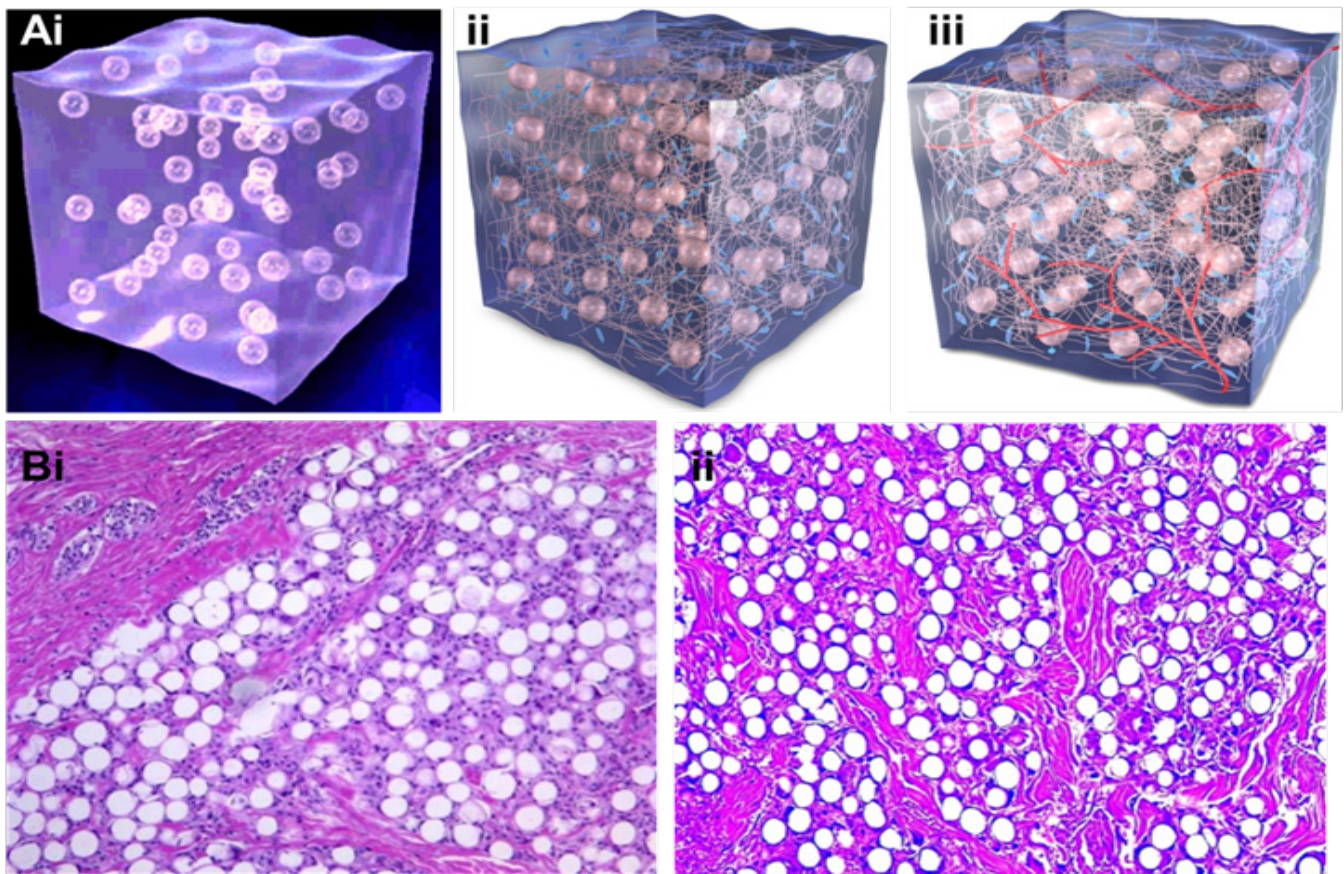


Figure 3: (Ai) ArteFill® composed of 20% PMMA microsphere (30-50 μm) and 80% denatured bovine collagen; (Aii) tissue growth stimulated due to collagen maintaining the viscosity of microspheres; (Aiii) the presence of blood vessels is observed and bovine collagen has been replaced with autologous connective tissue; (Bi) histological image of ArteFill® at month 3: capillaries are present in the implant and have been integrated into the patient's body ($\times 40$); (Bii) histological image taken 10 years after implantation of Artecoll®: connective tissues are mature, characterized by active fibroblasts, microsphere encapsulation, ingrown capillaries, and an absence of immune reaction ($\times 40$). Image modified with permission.^[35]

The formulation was later improved with the restriction of microsphere size to 30-50 μm to avoid phagocytosis, which in turn decreased the rate of granuloma formation.^[36-38] Either bovine collagen (Artecoll® or Artefill®; Artes Medical, San Diego, CA, USA) or HA (Dermalive®; Dermatech, Paris, France) can be used to suspend PMMA microspheres in order to facilitate the deposition of collagen in the surrounding region. It is important to note that unlike other injectable fillers, Artefill® stimulates the patient's own collagen while keeping the microspheres well-dispersed secondary to their viscosity [Figure 3A].^[35] When the collagen is resorbed, the microspheres persist and become encapsulated by connective tissue, resulting in a bulking effect.^[35] As demonstrated in Figure 3B, fibroblasts and collagen fibers have completely enveloped the PMMA microspheres three months following injection with Artefill® [Figure 3B].^[35] Allergy testing is required prior to use since the collagen contained in the product is of bovine origin.

Cohen and Holmes^[39] compared 123 patients treated with bovine collagen with 128 patients treated with Artecoll® for the treatment of 1,334 wrinkles (nasolabial folds, radial upper lip lines, glabella lines, and corner of mouth lines). One month after injection, only glabellar lines showed noticeable improvement, and collagen achieved better results. By month 3, the nasolabial folds and corner of the mouth lines treated with Artecoll® also showed significant improvements. Six months following injection, Artecoll® demonstrated a

superior improvement in nasolabial folds when compared to collagen and also had fewer adverse effects, although these differences were not statistically significant. In another study in which 950 patients were surveyed about their experience with Artecoll® for the long lasting correction of wrinkles, 515 surveys were returned. 29% of the respondents felt that the treatment was very good, 38% felt that it was good, 23% found it satisfactory, and 8% reported no difference. 91% of the respondents indicated their willingness to repeat the treatment.^[40] Carvalho Costa *et al.*^[41] carried out a study in which PMMA injections were administered to 266 patients (154 women, age: 17-72 years), with each patient receiving from 1-4 injections over an interval of 40 to 60 days. The average number of sessions required was four, with 8 mL of PMMA used per session. While 90% of the patients reported satisfactory results while the remaining 10% reported mild improvements, 20% of the patients experienced temporary adverse effects including swelling, bruising and erythema with no late complications.^[41]

Overall, PMMA-based fillers are inexpensive, readily accessible and simple to use. Although immediate adverse reactions have been reported in many of the studies, these primarily consist of lumps or nodules which may appear immediately following injection and in some cases several years later.

Poly-L-lactic acid

As a biodegradable thermoplastic polymer, PLA is extracted

from renewable sources and has been commercially available as Sculptra/Fill® (Sanofi Aventis, Paris, France). It is injected into either the deep dermis or subcutaneous layer and immediately fills the space, restoring facial fat loss.^[42] Once injected, the material creates immediate volumization secondary to the properties associated with the product's microparticles.^[43,44] However, the volumization effect disappears within a few months as the microparticles degrade and the material is metabolized, resulting in dermal fibroplasia.^[43] This degradation results in the formation of connective tissue or neocollagenesis.^[43,45] It is important to understand that PLA is a bio-stimulatory agent which benefits from the host system.^[46] The results associated with this product therefore are not immediate and are instead gradual, lasting for at least 2 years.^[45,47] It is approved in Europe for the treatment of scars and wrinkles, and in the United States for the treatment of facial lipoatrophy in patients diagnosed with human immunodeficiency virus (HIV) lipodystrophy syndrome. The injection technique is of crucial importance given the risk of papule and nodule formation.^[43,45,48] This product is overall very advantageous because it provides volume restoration while simultaneously increasing the dermal thickness.^[45,47] Other advantages include reduced safety concerns because it provides temporary results, and its very good risk-benefit profile in both HIV+ and cosmetic patients.^[42]

PLA was first approved for use in Europe in 1999. Subsequently, many studies have been performed to determine the best method for use and the potential benefits. A preclinical study was conducted in 1993 by Gogolewski *et al.*^[44] in which PLA solids were implanted into mice. There were no signs of abscess formation, acute inflammatory response, or cytotoxic effects at the site of implantation. Another study was conducted with 300 patients who underwent treatment with PLA between 1999 and 2004. In total, 819 injections were administered for treatment of the nasolabial folds, labiomental creases, temples, upper lip, cheeks, chin, and marionette lines. Improvements were noted in most patients with effects lasting for 12-24 months.^[49] Ten percent of patients who received treatments between 1999 and 2002 reported subcutaneous papules, which lasted for 12-24 months and resolved without further intervention. Papules can also be treated with intralesional triamcinolone (10 mg/mL) and/or intralesional 5-fluorouracil with resolution within 3 months. Since 2002, the reported rate of granuloma formation is less than 1%. This low rate is attributed to pre-treatment of PLA with 3 mL of sterile water 36-48 h prior to treatment, followed by adding 2 mL of 1% lidocaine immediately prior to injection. This creates a dilution of 5 mL, whereas previously 3 mL of sterile water only was added 2-12 h prior to use. Injection was administered into subcutaneous fat instead of the deep dermis.

A study was conducted by Valantin *et al.*^[50] in 2003 evaluating 50 patients who received four sets at day 0 and 2 mL, 4 mL, 6 mL, maximum 4 mL of PLA per cheek, monitored for 96 weeks with valuations at 6 weeks, 24 weeks, 48 weeks, 72 weeks and 96 weeks. Substantial improvement of at least 40% in cutaneous thickness from baseline was demonstrated in over 40% of patients. Total cutaneous thickness at the

onset of the trial was 2.9 mm without the presence of underlying facial fat. The increases in Cutaneous thickness increased at weeks 6, 24, 48, 72 and 96 to 5.1, 6.4, 7.2, 7.2 and 6.8 mm, respectively. Minimal and localized edema was observed in most patients but resolved spontaneously within 48 h. Fifteen out of fifty patients developed minimal ecchymosis which resolved within 3 days.^[50] Patients were compliant with their injections despite the side effects; the feasibility of using PLA for facial lipoatrophy treatment was clearly demonstrated. Moyle *et al.*^[51] conducted an open label study to evaluate the effect of immediate vs. delayed PLA injections for 24 weeks. Patients in the immediate treatment group received PLA treatments on day 1, as well as 2 and 4 weeks after the initial treatment. Patients in the delayed treatment group received PLA injections at weeks 12, 14, and 16.^[51] The study was limited to three injections per side and found similar improvements in 24 patients by both subjective assessment and ultrasound.^[51] Interestingly, by week 12, patients in the immediate treatment group scored significantly higher on the visual analogue scale and had lower levels of anxiety than their delayed treatment counterparts.^[51] Overall, it was concluded that PLA injection remained efficacious for more than 18 weeks.^[51]

Although many studies have examined the safety of PLA, its use is continually refined.^[46-48,51] While the above studies investigated the optimal treatment times and methods of application, additional studies have been conducted regarding injection in the periorbital and perioral regions,^[52] the use of conservative injection volumes^[53], and appropriate dilution volumes.^[53,54]

Calcium hydroxylapatite

CaHA and its derivatives are naturally found in human bone and dental enamel.^[55] Due to the structural similarity of the CaHA to the mineral portion of bone and its composition of calcium and phosphate ions, it is very biocompatible and therefore does not require skin testing. Radiesse® (Bioform Medical, Inc., San Mateo, CA, USA) consists of CaHA microspheres suspended in an aqueous carboxymethylcellulose gel carrier and is primarily used for the correction of moderate to severe wrinkles and folds and volumization of facial soft-tissue.^[1] It is also used for correction of facial lipoatrophy secondary to the human immunodeficiency virus.^[1] The microspheres present in Radiesse® are thought to act as a scaffold for new collagen formation. CaHA microspheres (25-45 µm in diameter) are suspended in a carboxymethylcellulose gel carrier in a ratio of 30% microspheres to 70% gel by volume.^[56] The gel base helps to evenly distribute the microspheres at the injection site, providing immediate volume restoration.^[56] After the gel degrades in 2-3 months, the microspheres promote the formation of new tissue formation by collagen deposition.^[57] Results typically last for 12-18 months^[58-60] leaving behind calcium and phosphate ions after undergoing the phagocytosis process by the macrophages.^[57] A study conducted by Marmur *et al.*^[57] evaluated the histologic and electron microscopic structural changes observed following CaHA injection at 1 and 6 months. Standard light microscopy imaging of tissue specimens at 1 month post-injection demonstrated no inflammatory cell response or fibrosis,

whereas light microscopy sections at 6 months post-injection showed tight aggregates of microspherules surrounded by thick collagen and histiocytes. Multinucleated giant cells surrounding each microspherule were also observed. All treated subjects reported high satisfaction levels at 6 months, and there were no reports of adverse reactions.

Another pivotal study testing the efficacy of Radiesse® for the treatment of nasolabial folds involved 117 subjects with a random split-face design. Radiesse® was injected on one side and collagen was injected on the other.^[61] Radiesse® was found to be superior to collagen in 79% of the folds after 6 months, and required almost half of the volume that was used with collagen.^[61] The long-term safety and efficacy of Radiesse® was also tested in the treatment of nasolabial folds by extending the previous study and offering re-treatment between 6 and 12 months.^[60] Out of a total of 117 subjects, 102 patients enrolled and were evaluated at 39 months after the last injection.^[60] At 30 months following the last treatment with Radiesse®, improvement was still observed in 40% of the folds, and no adverse events were reported.^[60] Safety and efficacy has also been tested for an injectable implant in which where researchers at two different treatment centers injected CaHA into 113 subjects.^[5] 75 patients received single injections and 38 had multiple sessions, with most patients receiving 1 mL per session.^[5] The results suggested a very favorable safety profile with a very high patient satisfaction rating (over 90% indicated that their results were “good” or “very good”) and only 7 minor adverse events which resolved within one month.^[5]

Although the majority of studies did not show any adverse effects, side effects of Radiesse® may include edema, erythema and transient lumpiness.^[63] Radiesse® is not recommended for lip injection because of the frequent occurrence of mucosal nodules.^[58] Radiesse® may not be suitable for the treatments of periorbital and glabellar rhytids secondary to safety concerns regarding embolism and necrosis. A case was reported in which a 35-year-old woman experienced nausea, vomiting, headache, ptosis and periorbital pain ten minutes following CaHA injection into the nasal tip and dorsum. The symptoms worsened and resulted in sudden monocular vision loss.^[62] Although many of the fillers discussed may be associated with very mild temporary reactions, the injector must remain alert to the risk of more serious adverse reactions.

Permanent fillers

Silicone

A primary consideration in the choice of filler is the degree of maintenance that is required. Some advantages associated with permanent fillers include low maintenance as a regular schedule for re-treatment is not required, and a lower overall cost because the procedure is performed only once.

Liquid injectable silicone, commonly available as Silikon 1000 and AdatoSil 5000, is classified as a permanent filler for soft tissue augmentation. The chemical composition of the material is predominantly dimethyl polysiloxane, which is available as fluid with variable levels of viscosity. It is injected into either the deep dermis or subcutaneous fat

with the aim of inducing fibroplasia and volumization.^[63] Moreover, it is characterized as a clear, colorless fluid with general physiological inertness and resistance to decomposition under extreme temperatures.^[63] If the product is inadvertently injected into the blood stream, it behaves very much like injections of air; small doses of the material are distributed throughout the body, while large doses can cause various severe complications including emboli and cellulitis.^[63] This product is overall very advantageous in the correction of facial defects, and other intradermal treatments that previously required excessive surgical intervention.^[63]

Injectable silicone oils for augmentation of the facial tissues were approved by the FDA in the early 1960s.^[64] In spite of the tremendous criticism that silicone has received due to its adverse complications, it has been shown to be very effective in facial augmentation.^[64] A clinical study conducted by Hevia^[65] demonstrated the efficacy of silicone oil in soft tissue augmentation. In total 916 patients were treated with PDMS-1000 (purified polydimethylsiloxane), an FDA approved silicone oil, over a six year period during which only 1% showed adverse granulomatous reactions.^[65] All treatments were performed with a serial puncture technique, which is well-suited for the injection of silicone oil.^[65] Narins and Beer^[64] note that the oil must be injected into the immediate subdermal plane or deeper to avoid dermal erythema and ridging. The volume should be limited to no more than 0.5 mL for small areas including the nasolabial fold, and 2.0 mL for larger areas as seen in facial lipotrophy.^[64]

Another study by Jones *et al.*^[66] evaluated the injection of liquid silicone into HIV patients with facial lipotrophy. In this study, 77 patients received either Silikon® 1000 (Alcon Inc., Fort Worth, TX, USA) or VitreSil® 1000 (Richard James Inc., Peabody, MA, USA). Less than 2 mL of silicone oil was repeatedly injected at intervals of at least a month until a state of “prelipotrophy” was achieved. Most patients developed erythema and edema following injection which resolved within 3 days. Patient satisfaction in this study was reported to be high although specific details were not provided.

Although many studies have shown the efficacy of silicone oil, an equal number of studies have highlighted adverse reactions secondary to misuse.^[9] The improper use of silicone oils including incorrect dosage, improper technique, and impurity of materials has resulted in serious repercussions including cellulitis, product migration, and death.^[9] A report by Requena *et al.*^[67] presents 4 cases in which patients experienced moderate to severe complications following silicone injections.

All 4 patients were diagnosed with orofacial granulomatosis after 8-12 months of treatment.^[56] It was suggested that the histological appearance of the odemas be studied as they give direct information regarding the form and purity of silicone used, including solid elastomer silicone and oil/gel silicone.^[56] The proper use of liquid silicone, i.e. small volumes, high purity, and the microdroplet technique, is

believed to have a rate of complications of less than 1%.^[67] Granulomas may develop weeks or even years following treatment, and can be managed using oral or intralesional corticosteroids and antibiotics.

The extent to which volume loss and fat atrophy affect facial aging is evident by the large variety of existing intradermal fillers. Intradermal fillers are not as strictly regulated as prescription drugs, as most fillers fall under the category of a medical device rather than that of a pharmaceutical agent. While intradermal fillers are considered to be inert, many of them elicit immunogenic reactions and granulomas. In addition, some fillers induce neo-collagenesis. Temporary fillers generally persist for 3-6 months. While permanent fillers may be advantageous in terms of their longevity, a permanent dermatological procedure may eventually become unnatural as it is unable to accommodate the patient's aesthetic needs over time due to the dynamic nature of facial aging.

Other fillers

Apart from the fillers mentioned above, a combination of two or more fillers have been shown to be very effective in facial volumization. A 6-month comparison study examined the efficacy and safety profiles of plain CaHA and CaHA mixed with lidocaine for the treatment of nasolabial folds.^[68] In this study, 16 patients with moderate-to-deep wrinkle ratings were recruited. A visual analog pain scale was used to assess the patients' pain perception. A blinded injector and an independent observer determined the efficacy of treatment over a period of 24 weeks. There were no significant adverse events and very few local adverse events. Both of the groups reported satisfaction with the treatment and much less pain when CaHA was mixed with lidocaine as compared to plain CaHA.^[68] Intradermal fillers have also been used with other anti-aging chemicals including BOTOX®. A study by Coleman and Carruthers^[69] showed that in younger subjects with glabellar frown lines, treatment with BOTOX® alone did not show positive results, but when combined with intradermal fillers such as HA gave an immediate resting result and made it last twice as long. Similarly, melomental folds in the perioral region can be effectively treated with the combination of BOTOX® to remove the muscular depressor action of the lower face and intradermal filler to volumize the mouth corners, giving an overall youthful appearance.^[69]

CONCLUSION

The field of cosmetic dermatology has been expanding globally. With the ever increasing popularity of nonsurgical enhancement and an increasing number of patients who have been treated, the demand for fillers continues to rise. Research articles, long-term clinical experience, peer reviewed publications and regulatory approvals have all demonstrated the safety and efficacy of various fillers. Fillers appeal to various age demographics including young adults for the enhancement of youthful features, middle-aged adults for early prevention and volume restoration, and the older individuals for delay and maintenance of age-related symptoms. All of the injectable fillers discussed above have

their own advantages and disadvantages, and generally do not have any adverse reactions. The optimal filler is determined by the case, cost associated with treatment, and the physician's experience. Research continues to be conducted on formulations, clinical trials, and comparative studies between fillers. Optimal results in treating dynamic lines and volume loss are achieved with combination therapy. It is crucial that patients have realistic expectations as multiple treatments may be required, and each filler has its limitations. More comparative studies and literature reviews are required to provide the layperson with a summary of the many options and their risks and benefits, thereby allowing patients to choose the filler most suitable to their needs.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Luebberding S, Alexiades-Armenakas M. Facial volume augmentation in 2014: overview of different filler options. *J Drugs Dermatol* 2013;12:1339-44.
2. Maddern G. The Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S) assesses new surgeries. *Aust Health Rev* 2004;28:143-4.
3. Silvipriya KS, Kumar KK, Bhat AR, Kumar BD, John A, Lakshmanan P. Collagen: animal sources and biomedical application. *J App Pharm Sci* 2015;5:123-7.
4. Ottani V, Raspanti M, Ruggeri A. Collagen structure and functional implications. *Micron* 2001;32:251-60.
5. Sadick NS, Katz BE, Roy D. A multicenter, 47-month study of safety and efficacy of calcium hydroxylapatite for soft tissue augmentation of nasolabial folds and other areas of the face. *Dermatol Surg* 2007;33:S122-6; discussion S126-7.
6. Baumann L, Kaufman J, Saghari S. Collagen fillers. *Dermatol Ther* 2006;19:134-40.
7. Nicolle FV. Correction of age- and disease-related contour deficiencies of the face. *Aesthetic Plastic Surg* 1985;9:159-62.
8. Bailin MD, Bailin PL. Correction of surgical scars, acne scars, and rhytids with zyderm and zyplast implants. *J Dermatol Surg Oncol* 1988;14:31-3.
9. Zeide DA. Adverse reactions to collagen implants. *Clin Dermatol* 1986;4:176-82.
10. Struck H. Immunological investigations of antigenicity and specificity of soluble collagen fractions. IV. Anaphylaxis and allergy experiments. *Eur Surg Res* 1976;8:243-9.
11. Monstrey SJ, Pitaru S, Hamdi M, Van Landuyt K, Blondeel P, Shiri J, Goldlust A, Shoshani D. A two-stage phase I trial of Evolence30 collagen for soft-tissue contour correction. *Plast Reconstr Surg* 2007;120:303-11.
12. Narins RS, Brandt FS, Lorenc ZP, Maas CS, Monheit GD, Smith SR, McIntyre S. A randomized, multicenter study of the safety and efficacy of Dermicol-P35 and non-animal-stabilized hyaluronic acid gel for the correction of nasolabial folds. *Dermatol Surg* 2007;33:S213-21; discussion S221.
13. Lee JH, Choi YS, Kim SM, Kim YJ, Rhie JW, Jun YJ. Efficacy and safety of porcine collagen filler for nasolabial fold correction in Asians: a prospective multicenter, 12 months follow-up study. *J Korean Med Sci* 2014;29:S217-21.
14. Brongo S, Moccia LS, Nunziata V, D'Andrea F. Keratoacanthoma arising after site injection infection of cosmetic collagen filler. *Int J Surg Case Rep* 2013;4:429-31.
15. Tumerdem B, Aydin A, Kesim SN. An unusual case of self-injected bovine fat in liquid form to the face for cosmetic reasons. *Aesthetic Plastic Surg* 2005;28:251-3.
16. Baumann LS, Shamban AT, Lupo MP, Monheit GD, Thomas JA, Murphy DK, Walker PS; JUVEDERM vs. ZYPLAST Nasolabial Fold Study Group. Comparison of smooth-gel hyaluronic acid dermal fillers with cross-linked bovine collagen: a multicenter, double-masked, randomized, within-subject study. *Dermatol Surg* 2007;33:S128-35.
17. Kim BS, Choi JS, Kim JD, Yoon HI, Choi YC, Cho YW. Human collagen isolated from adipose tissue. *Biotechnol Prog* 2012;28:973-80.

18. Báez J, Olsen D, Polarek JW. Recombinant microbial systems for the production of human collagen and gelatin. *Appl Microbiol Biotechnol* 2005;69:245-52.
19. Raines RT. Stronger and (now) Longer Synthetic Collagen. *Adv Exp Med Biol* 2009;611:xcv-xcvi.
20. Bauman L. CosmoDerm/CosmoPlast (human bioengineered collagen) for the aging face. *Facial Plastic Surg* 2004;20:125-8.
21. Sclafani AP, Romo T 3rd. Collagen, human collagen, and fat: the search for a three-dimensional soft tissue filler. *Facial Plastic Surg* 2001;17:79-85.
22. Stolman LP. Human collagen reactions. *Dermatol Surg* 2005;31:1634.
23. Sclafani AP, Romo T 3rd, Jacono AA. Rejuvenation of the aging lip with an injectable acellular dermal graft (Cymetra). *Arch Facial Plast Surg* 2002;4:252-7.
24. Lowe NJ, Maxwell CA, Lowe P, Duick MG, Shah K. Hyaluronic acid skin fillers: adverse reactions and skin testing. *J Am Acad Dermatol* 2001;45:930-3.
25. Narins RS, Brandt F, Leyden J, Lorenc ZP, Rubin M, Smith S. A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. *Dermatol Surg* 2003;29:588-95.
26. Lindqvist C, Tveten S, Bondevik BE, Fagrell D. A randomized, evaluator-blind, multicenter comparison of the efficacy and tolerability of Perlane versus Zyplast in the correction of nasolabial folds. *Plast Reconstr Surg* 2005;115:282-9.
27. Wang F, Garza LA, Kang S, Varani J, Orringer JS, Fisher GJ, Voorhees JJ. *In vivo* stimulation of *de novo* collagen production caused by cross-linked hyaluronic acid dermal filler injections in photodamaged human skin. *Arch Dermatol* 2007;143:155-63.
28. Monheit GD, Coleman KM. Hyaluronic acid fillers. *Dermatol Ther* 2006;19:141-50.
29. Beer K. A randomized, evaluator-blinded comparison of efficacy of hyaluronic acid gel and avian-sourced hylan B plus gel for correction of nasolabial folds. *Dermatol Surg* 2007;33:928-36.
30. Prager W, Wissmueller E, Havermann I, Bee EK, Howell DJ, Zschocke I, Simon J. A prospective, split-face, randomized, comparative study of safety and 12-month longevity of three formulations of hyaluronic acid dermal filler for treatment of nasolabial folds. *Dermatol Surg* 2012;38:1143-50.
31. Kim H, Park KY, Choi SY, Koh HJ, Park SY, Park WS, Bae IH, Kim BJ. The efficacy, longevity, and safety of combined radiofrequency treatment and hyaluronic acid filler for skin rejuvenation. *Ann Dermatol* 2014;26:447-56.
32. Choi SY, Lee YH, Kim H, Koh HJ, Park SY, Park WS, Bae IH, Park KY, Kim BJ. A combination trial of intradermal radiofrequency and hyaluronic acid filler for the treatment of nasolabial fold wrinkles: a pilot study. *J Cosmet Laser Ther* 2014;16:37-42.
33. Kanchwala SK, Holloway L, Bucky LP. Reliable soft tissue augmentation. *Ann. Plas. Surg.* 2005;55:30-5.
34. Lemperle G, Ott H, Charrier U, Hecker J, Lemperle M. PMMA microspheres for intradermal implantation: Part I. Animal research. *Ann Plast Surg* 1991;26:57-63.
35. Vent J, Lemperle G. Prevention and treatment of complications after polymethylmethacrylate-microspheres injections. *Facial Plast Surg* 2014;30:628-34.
36. Lemperle G, Knapp TR, Sadick NS, Lemperle SM. ArteFill permanent injectable for soft tissue augmentation: I. Mechanism of action and injection techniques. *Aesthetic Plastic Surg* 2010;34:264-72.
37. Lemperle G, Sadick NS, Knapp TR, Lemperle SM. ArteFill permanent injectable for soft tissue augmentation: II. Indications and applications. *Aesthetic Plastic Surg* 2010;34:273-86.
38. Cohen SR, Berner CF, Busso M, Clopton P, Hamilton D, Romano JJ, et al. Five-year safety and efficacy of a novel polymethylmethacrylate aesthetic soft tissue filler for the correction of nasolabial folds. *Dermatol Surg* 2007;33:5222-30.
39. Cohen SR, Holmes RE. Artecoll: a long-lasting injectable wrinkle filler material: Report of a controlled, randomized, multicenter clinical trial of 251 subjects. *Plast Reconstr Surg* 2004;114:964-76; discussion 977-9.
40. Lemperle G, Gauthier-Hazan N, Lemperle M. PMMA-Microspheres (Artecoll) for long-lasting correction of wrinkles: refinements and statistical results. *Aesthetic Plastic Surg* 1998;22:356-65.
41. Carvalho Costa IM, Salero CP, Costa MC. Polymethylmethacrylate facial implant: a successful personal experience in Brazil for more than 9 years. *Dermatol Surg* 2009;35:1221-7.
42. Donofrio L, Weinkle S. The third dimension in facial rejuvenation: a review. *J Cosmet Dermatol* 2006;5:277-83.
43. Bartus C, William Hanke C, Daro-Kaftan E. A decade of experience with injectable poly-L-lactic acid: a focus on safety. *Dermatol Surg* 2013;39:698-705.
44. Gogolewski S, Jovanovic M, Perren SM, Dillon JG, Hughes MK. Tissue response and *in vivo* degradation of selected polyhydroxyacids: polylactides (PLA), poly(3-hydroxybutyrate) (PHB), and poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHB/VA). *J Biomed Mater Res* 1993;27:1135-48.
45. Vleggaar D, Bauer U. Facial enhancement and the European experience with Sculptra (poly-L-lactic acid). *J Drugs Dermatol* 2004;3:542-7.
46. Fitzgerald R, Vleggaar D. Facial volume restoration of the aging face with poly-L-lactic acid. *Dermatol Ther* 2011;24:2-27.
47. Burgess CM, Quiroga RM. Assessment of the safety and efficacy of poly-L-lactic acid for the treatment of HIV-associated facial lipoatrophy. *J Am Acad Dermatol* 2005;52:233-9.
48. Schierle CF, Casas LA. Nonsurgical rejuvenation of the aging face with injectable poly-L-lactic acid for restoration of soft tissue volume. *Aesthet Surg J* 2011;31:95-109.
49. Woerle B, Hanke CW, Sattler G. Poly-L-lactic acid: a temporary filler for soft tissue augmentation. *J Drugs Dermatol* 2004;3:385-9.
50. Valantin MA, Aubron-Olivier C, Ghosn J, Laglenne E, Pauchard M, Schoen H, Bousquet R, Katz P, Costagliola D, Katlama C. Polylactic acid implants (New-Fill) to correct facial lipoatrophy in HIV-infected patients: results of the open-label study VEGA. *AIDS* 2003;17:2471-7.
51. Moyle GJ, Lysakova L, Brown S, Sibtain N, Healy J, Priest C, Mandalia S, Barton SE. A randomized open-label study of immediate versus delayed polylactic acid injections for the cosmetic management of facial lipoatrophy in persons with HIV infection. *HIV Med* 2004;5:82-7.
52. Lowe NJ, Maxwell CA, Lowe P, Shah A, Patnaik R. Injectable poly-L-lactic acid: 3 years of aesthetic experience. *Dermatol Surg* 2009;35:344-9.
53. Palm MD, Woodhall KE, Butterwick KJ, Goldman MP. Cosmetic use of poly-L-lactic acid: a retrospective study of 130 patients. *Dermatol Surg* 2010;36:161-70.
54. Rossner F, Rossner M, Hartmann V, Erdmann R, Wiest LG, Rzyany B. Decrease of reported adverse events to injectable polylactic acid after recommending an increased dilution: 8-year results from the Injectable Filler Safety study. *J Cosmet Dermatol* 2009;8:14-8.
55. Hobar PC, Pantaloni M, Byrd HS. Porous hydroxyapatite granules for alloplastic enhancement of the facial region. *Clin Plast Surg* 2000;27:557-69.
56. Pavicic T. Calcium hydroxylapatite filler: an overview of safety and tolerability. *J Drugs Dermatol* 2013;12:996-1002.
57. Marmur ES, Phelps R, Goldberg DJ. Clinical, histologic and electron microscopic findings after injection of a calcium hydroxylapatite filler. *J Cosmet Laser Ther* 2004;6:223-6.
58. Moers-Carpi M, Vogt S, Santos BM, Planas J, Valve SR, Howell DJ. A multicenter, randomized trial comparing calcium hydroxylapatite to two hyaluronic acids for treatment of nasolabial folds. *Dermatol Surg* 2007;33:S144-S151.
59. Jacovella PF. Use of calcium hydroxylapatite (Radiesse) for facial augmentation. *Clin Interv Aging* 2008;3:161-74.
60. Bass LS, Smith SL, Busso M, McClaren M. Calcium hydroxylapatite (Radiesse) for treatment of nasolabial folds: long-term safety and efficacy results. *Aesthet Surg J* 2010;30:235-8.
61. Smith S, Busso M, McClaren M, Bass LS. A randomized, bilateral, prospective comparison of calcium hydroxylapatite microspheres versus human-based collagen for the correction of nasolabial folds. *Dermatol Surg* 2007;33:S112-21; discussion S21.
62. Chou CC, Chen HH, Tsai YY, Li YL, Lin HJ. Choroid vascular occlusion and ischemic optic neuropathy after facial calcium hydroxyapatite injection- a case report. *BMC Surg* 2015;15:21.
63. Aronson RB. Observations on the use of silicone in the face. *Arch Otolaryngol* 1965;82:191-4.
64. Narins RS, Beer K. Liquid injectable silicone: a review of its history, immunology, technical considerations, complications, and potential. *Plast Reconstr Surg* 2006;118:775-84S.
65. Hevia O. Six-year experience using 1,000-centistoke silicone oil in 916 patients for soft-tissue augmentation in a private practice setting. *Dermatol Surg* 2009;35:1646-52.
66. Jones DH, Carruthers A, Orentreich D, Brody HJ, Lai MY, Azen S, Van Dyke GS. Highly purified 1000-cSt silicone oil for treatment of human immunodeficiency virus-associated facial lipoatrophy: an open pilot trial. *Dermatol Surg* 2004;30:1279-86.
67. Requena C, Requena L, Alegre V, Serra C, Lombart B, Nagore E, Guillén C, Sanmartín O. Adverse reaction to silicone simulating orofacial granulomatosis. *J Eur Acad Dermatol Venereol* 2015;29:998-1001.
68. Narins RS, Baumann L, Brandt FS, Fagien S, Glazer S, Lowe NJ, Monheit GD, Rendon MI, Rohrich RJ, Werschler WP. A randomized study of the efficacy and safety of injectable poly-L-lactic acid versus human-based collagen implant in the treatment of nasolabial fold wrinkles. *J Am Acad Dermatol* 2010;62:448-62.
69. Coleman KR, Carruthers J. Combination therapy with BOTOX and fillers: the new rejuvenation paradigm. *Dermatol Ther* 2006;19:177-88.

Advances in the research of autologous fibroblast injections for aging skin

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ABSTRACT

With the development of autologous stem cells transplantation, the application of autologous fibroblast graft has been an important therapy in defect repair. In the past decade, amounts of studies have reported favorable treatment effect and safety about the therapy. The material has the ability to produce human collagen *in vivo*. This article details recent scientific work of the cases, effect, injection technique, complications and safety of autologous fibroblast injection treatment.

Key words:

Autologous fibroblast; injection; aging skin

INTRODUCTION

Wrinkles can be corrected by using various treatment methods like lasers, soft tissue fillers, Botox for dynamic wrinkles, and so on. The most common therapy is dermal fillers like hyaluronic acid. However, dermal fillers are typically degradable or semipermanent, and liable to allergic reaction or other side reactions like skin necrosis, visual impairment.^[1] Autologous materials have been used for more than a century for soft tissue augmentation. Autologous fat has always been the first choice of autologous graft. However, the high rate of graft resorption and unpredictable degree of volume loss in some degree reduced the enthusiasm for the use of adipose grafts in soft tissue augmentation.^[2] With the development of autologous stem cells transplantation, the application of autologous fibroblast graft has been an important therapy in defect repair.^[3-7] Fibroblasts are the main functional cells in dermis and autologous fibroblasts injection may be more beneficial than other therapies in facial rejuvenation.^[8] Autologous fibroblasts injection is not

a common kind of dermal filler, that is to say, it is not volume filler. As a result, it's very important to notify patients that the therapy does not take effect in a short time. Fibroblasts show mitigating improvement after about 3 serial treatment processes and living cells keep vigorous growth that may lead to greater persistence than other fillers.^[9] Autologous cultured fibroblasts have been used effectively for dermal and subcutaneous deficiencies since 1995.^[10] Autologous fibroblast transplantation first received approval from the US Food and Drug Administration in June 2011 to improve moderate or severe nasolabial fold wrinkles.

CASES AND TREATMENT OUTCOME

In the past decade, amounts of studies have reported favorable treatment effect and safety about the therapy.^[11-13] Clinical researches for autologous fibroblast therapy have been carried on since 2001. Cultured autologous fibroblasts

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have been utilized effectively to treat various wrinkles, depressed scars, acne irregularities,^[14] wounds^[15] and atrophy.^[16,17]

In 2007, Weiss *et al.*^[18] in America reported a double-blind, randomized comparison on autologous fibroblast injection and placebo for facial contour defects treatment. Results showed that autologous fibroblasts generated statistically significantly greater improvements in dermal deformities and acne scars than did placebo. The difference between fibroblast injections and placebo obtained statistical significance at 6 months ($P < 0.0001$). Patients treated with autologous fibroblasts continuously show benefit at 9-month and 12-month follow-up. There were no serious treatment-related adverse events in this study.

In 2012, Smith *et al.*^[19] reported a multicenter, double-blind, placebo-controlled trial of autologous fibroblast therapy to treat nasolabial fold wrinkles. A large sample including 372 subjects was enrolled in this trial. There were comparisons between subjects treated with cultured autologous fibroblast and placebo. The results showed at least 1-point improvement on both subject and evaluator assessment after 6 months ($P < 0.001$).

In 2012, in a South American study, Eça *et al.*^[20] published the results of their search about the safety and efficacy of dermal regeneration with the injection of young autologous fibroblasts obtained from patients themselves. With 4 injections given at 15-day intervals after 60 days, periorbital tonicity had improved obviously. Nevertheless, there was little improvement in surface lines and no improvement at all in deeper wrinkles.

In 2013, Munavalli *et al.*^[12] in America reported a randomized multicenter, prospective, double-blind, placebo-controlled clinical trial about the treatment of bilateral moderate to severe acne scars using autologous fibroblasts. Ninety-nine subjects underwent three intradermal injection sessions at 14-day intervals. They were injected autologous fibroblast suspension on one cheek and cell culture medium on the other cheek. The outcome showed that autologous fibroblast had significantly greater efficacy than vehicle control (cell culture medium).

INJECTION TECHNIQUE

Different anesthesia forms are provided at the discretion of the investigator. A topical anesthetic cream containing 4% lidocaine may be applied. The areas of treatment are swabbed with an antiseptic before injections.

Autologous fibroblast suspension or placebo is injected using a 1-mL syringe and a 29- or 30-G needle. A retrograde linear threading technique is utilized. The suspension is placed into the superficial papillary dermis. Create a wheal and transient blanching of the skin surface with each injection. The current injection dose is 0.1 mL of suspension with a concentration of $(1.0-2.0) \times 10^7$ cells/mL. During the

injection, doctors should pay attention to the following points:

- No lidocaine or epinephrine is mixed to the cell suspension before injection to avoid the negative impact on the viability of the cells.
- No massage or other manipulation of the areas is performed to avoid damaging or altering the cells.
- No soaps, cosmetics, or any other products are used to the injection sites for 72 h after operation. Limited short-term indirect application of ice to the treatment area was allowed but not recommended.^[19]

Injections can be given in the forehead wrinkles, perioral wrinkles, nasolabial fold, chin, and periorbital wrinkles with a minimal interval of 15 days between each session. The injection technique has no obvious difference among these different injected sites.

COMPLICATIONS AND SAFETY

There is no record in the scientific literature of any case of tumor formation resulting from the stem cell injection since the first transplants of adult stem cells from bone marrow in the 1960s^[21] and the transplant of adult stem cells from umbilical cord blood in 1988.^[22]

Autologous fibroblast therapy has been considered to be safe and well tolerated in amounts of researches. The wrinkle improvement during this treatment is different from most dermal fillers. The product results in the accumulation of new collagen but not direct volume replacement. Consequently, it has a more gradual onset of effect than which has been seen immediate correction from other dermal fillers.^[19]

Autologous fibroblast therapy has adverse events including: local redness, bruising, swelling, bleeding, pain or irritation, erythema, developing nodules, nausea, headache and so on. The most common adverse events reported were redness, swelling, and bruising in and around the treatment areas. The severity of majority of adverse events is mild to moderate and probably related to the process of injection.

CONCLUSION

Autologous fibroblast treatment is a novel therapeutic method for treating dermal defects. The material has the ability to produce human collagen *in vivo*. In sum, autologous fibroblasts injection has the following characteristics: (1) it's not a volume filler; (2) injection level is more superficial; (3) need a period of time (about 6 months) to take effect; (4) treatment effect on fine lines like nasolabial wrinkles is better; (5) need additional costs and processes for harvesting and culturing fibroblasts before injection; and (6) adverse reactions are minimal and comparable with other common injection. Although the favorable outcomes have been obtained from various studies, the specific cellular and molecular biologic mechanism remains unknown. They may take effect through single or several signal pathways that could

cause direct synthesis of increased amounts of collagen and elastin, proliferation of fibroblasts and the deposition of cofactors.^[23] This may be the long-term goal of the autologous fibroblast transplantation research.

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There are no conflicts of interest.

REFERENCES

- Carruthers JD, Fagien S, Rohrich RJ, Weinkle S, Carruthers A. Blindness caused by cosmetic filler injection: a review of cause and therapy. *Plast Reconstr Surg* 2014;134:1197-201.
- Illouz YG. Present results of fat injection. *Aesthetic Plast Surg* 1988;12:175-81.
- You HJ, Han SK, Rhie JW. Randomised controlled clinical trial for autologous fibroblast-hyaluronic acid complex in treating diabetic foot ulcers. *J Wound Care* 2014;23:521-2, 524, 526-30.
- Milinkovic I, Aleksic Z, Jankovic S, Popovic O, Bajic M, Cakic S, Lekovic V. Clinical application of autologous fibroblast cell culture in gingival recession treatment. *J Periodontol Res* 2015;50:363-70.
- Morimoto N, Ito T, Takemoto S, Katakami M, Kanda N, Tada H, Tanaka S, Teramukai S, Kawai K, Nakamura Y, Kasai Y, Masayuki Y, Maekawa T, Shimizu A, Suzuki S. An exploratory clinical study on the safety and efficacy of an autologous fibroblast-seeded artificial skin cultured with animal product-free medium in patients with diabetic foot ulcers. *Int Wound J* 2014;11:183-9.
- Pichler R, Klima G, Richter E, Marksteiner R, Mayr V, Skradski V, Horninger W, Oswald J. Autologous fibroblast transplantation at the vesico-ureteral junction as potential reconstructive cell replacement in an animal model. *World J Urol* 2013;31:169-74.
- Malecki M. Improved targeting and enhanced retention of the human, autologous, fibroblast-derived, induced, pluripotent stem cells to the sarcomeres of the infarcted myocardium with the aid of the bioengineered, heterospecific, tetravalent antibodies. *J Stem Cell Res Ther* 2013;3:pii138.
- Martin I, Baldomero H, Bocelli-Tyndall C, Slaper-Cortenbach I, Passweg J, Tyndall A. The survey on cellular and engineered tissue therapies in Europe in 2009. *Tissue Eng Part A* 2011;17:2221-30.
- Weiss RA. Autologous cell therapy: will it replace dermal fillers? *Facial Plast Surg Clin North Am* 2013;21:299-304.
- Boss WK Jr, Usal H, Fodor PB, Chernoff G. Autologous cultured fibroblasts: a protein repair system. *Ann Plast Surg* 2000;44:536-42.
- Shevtsov MA, Galibin OV, Yuditceva NM, Blinova MI, Pinaev GP, Ivanova AA, Savchenko ON, Suslov DN, Potokin IL, Pitkin E, Raykhtsaum G, Pitkin MR. Two-stage implantation of the skin- and bone-integrated pylon seeded with autologous fibroblasts induced into osteoblast differentiation for direct skeletal attachment of limb prostheses. *J Biomed Mater Res A* 2014;102:3033-48.
- Munavalli GS, Smith S, Maslowski JM, Weiss RA. Successful treatment of depressed, distensible acne scars using autologous fibroblasts: a multi-site, prospective, double blind, placebo-controlled clinical trial. *Dermatol Surg* 2013;39:1226-36.
- Jin Z, Wu YG, Yuan YM, Peng J, Gong YQ, Li GY, Song WD, Cui WS, He XY, Xin ZC. Tissue engineering penoplasty with biodegradable scaffold Maxpol-T cogenerated autologous fibroblasts for small penis syndrome. *J Androl* 2011;32:491-5.
- Munavalli GS, Smith S, Maslowski JM, Weiss RA. Successful treatment of depressed, distensible acne scars using autologous fibroblasts: a multi-site, prospective, double blind, placebo-controlled clinical trial. *Dermatol Surg* 2013;39:1226-36.
- Morimoto N, Kakudo N, Valentin Notodihardjo P, Suzuki S, Kusumoto K. Comparison of neovascularization in dermal substitutes seeded with autologous fibroblasts or impregnated with bFGF applied to diabetic foot ulcers using laser Doppler imaging. *J Artif Organs* 2014;17:352-7.
- Zhao Y, Wang J, Yan X, Li D, Xu J. Preliminary survival studies on autologous cultured skin fibroblasts transplantation by injection. *Cell Transplant* 2008;17:775-83.
- Milinkovic I, Aleksic Z, Jankovic S, Popovic O, Bajic M, Cakic S, Lekovic V. Clinical application of autologous fibroblast cell culture in gingival recession treatment. *J Periodontol Res* 2015;50:363-70.
- Weiss RA, Weiss MA, Beasley KL, Munavalli G. Autologous cultured fibroblast injection for facial contour deformities: a prospective, placebo-controlled, phase III clinical trial. *Dermatol Surg* 2007;33:263-8.
- Smith SR, Munavalli G, Weiss R, Maslowski JM, Hennegan KP, Novak JM. A multicenter, double-blind, placebo-controlled trial of autologous fibroblast therapy for the treatment of nasolabial fold wrinkles. *Dermatol Surg* 2012;38:1234-43.
- Eça LP, Pinto DG, de Pinho AM, Mazzetti MP, Odo ME. Autologous fibroblast culture in the repair of aging skin. *Dermatol Surg* 2012;38:180-4.
- Thomas ED, Lochte HL Jr, Cannon JH, Sahler OD, Ferrebee JW. Supralethal whole body irradiation and isologous marrow transplantation in man. *J Clin Invest* 1959;38:1709-16.
- Gluckman E, Broxmeyer HA, Auerbach AD, Friedman HS, Douglas GW, Devergie A, Esperou H, Thierry D, Socie G, Lehn P. Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling. *N Engl J Med* 1989;321:1174-8.
- Lamme EN, Van Leeuwen RT, Brandsma K, Van Marle J, Middelkoop E. Higher numbers of autologous fibroblasts in an artificial dermal substitute improve tissue regeneration and modulate scar tissue formation. *J Pathol* 2000;190:595-603.

Materials to facilitate orbital reconstruction and soft tissue filling in posttraumatic orbital deformities

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ABSTRACT

Posttraumatic orbital reconstruction has been a challenging mission for decades in craniomaxillofacial surgery. Complications like enophthalmos, diplopia and gaze obstacles emerge when orbital trauma occurs, affecting people's daily life as well as their appearance. Advances in technology and research gained through years of experience has provided us with a greater understanding of the changes following trauma, as well as providing us with a variety of filling materials that we can choose from to handle the deformities. However, the best type of material for repair of orbital deformities remains controversial. This paper reviewed approximately 60 articles discussing materials used in orbital reconstruction or soft tissue defect filling in the past years, with the aim of giving a comprehensive overview of the advantages and disadvantages of materials used in this field so as to help surgeons to make a better choice.

Key words:

Orbital reconstruction; soft tissue filling; materials; enophthalmos

INTRODUCTION

Orbital fracture is common in facial trauma. Its incidence ranges from 18% to 50% of all craniomaxillofacial traumas, considering the difference of the geographic region, injury mechanism and study population.^[1] Although the

eye is well protected by the strong orbital rim, the thin orbital floor, and the medial wall that acts as a shock absorber, there is a high chance of associated ocular injuries after orbital trauma, ranging from 22% to 76%.^[2]

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If the traumas are not diagnosed or well treated in a timely fashion, patients can suffer from functional and aesthetic sequelae.

In 1889, Lang^[3] was first to recognize that traumatic enophthalmos is caused by fracture of the orbital wall and the associated orbital tissue abnormality. Significant progress has been made in the field of orbital reconstruction. It's commonly believed that orbital deformities occur because of two main causes: first, the anatomic changes behind the eyeball that may consist of an inferior dislocation of the orbital floor or a transversal expansion of the orbit which contributes to the defect;^[4] second, once soft tissue within the socket is affected, the whole socket can be influenced. Thus, we are supposed not only to repair the orbital fracture, but also find the appropriate filling materials to restore the volume of orbit, avoiding bothersome sequelae, and restore ocular functions.

Orbital fractures occur with bothersome complications like enophthalmos and constant diplopia. Among 55 studies performed on orbital reconstruction, it was found that the indication for surgery was based on diplopia in 18.3% of cases and on preoperative enophthalmos in 29.8% of cases.^[5] The goal of orbital reconstruction is to repair trauma defects, to correct the anatomical position of the eye, to accurately restore the volume of the orbit, to avoid sequelae such as enophthalmos, and to restore ocular function. Orbital fractures can occur alone or with other craniomaxillofacial fractures, which may complicate the reconstruction. It's reported that the medial wall and the orbital floor fractures are the most frequent type. The medial wall of the orbit consists of the maxilla, lacrimal, ethmoid and sphenoid bones, and it is the most vulnerable and most complicated to repair due to its anatomical structure. Small defects may heal alone by the formation of scar tissue, whereas larger defects, especially those associated with enophthalmos and hypoglobus, need material of a sufficient strength to support the orbital contents and restore the contour of the orbit.^[6]

In terms of operation, we should consider three pivotal questions. When is the best timing to perform the operation? How to perform the operation? What materials should be used? This review aims to give a comprehensive overview of the advantages and disadvantages of materials used to repair orbital fractures or used for soft tissue defect filling, with the goal of assisting surgeons to make a better choice.

THE IDEAL IMPLANT MATERIAL FOR ORBITAL FRACTURE RECONSTRUCTION

It's very difficult to determine which material is the ideal implant for orbital fracture reconstruction. The ideal characteristics of the material used as an orbital implant include: (1) ability to bend into an anatomical shape; (2) radiopacity; and (3) permanent stability.^[5] For smaller defects, the strength of the implant holds limited relevance for a successful outcome, and the choice of implant is more dependent on biocompatibility.^[7] In larger fractures,

mechanical properties, biocompatibility, and the contour or form factor needs special attention.^[8] A recent article argues that the ideal implant should be discussed in seven points: (1) stability and fixation; (2) contouring and handling; (3) biological behavior; (4) drainage; (5) donor site morbidity; (6) radiopacity; and (7) availability and cost-effectiveness.^[5]

First of all, the ideal material is expected to be strong enough to support the orbital content, to be stable, to maintain its shape over time, and to fix itself to surrounding structures. Second, it should be malleable with a smooth surface. A desirable implant needs to be of high biocompatibility, chemically inert, non-allergenic and non-carcinogenic to ensure a decrease in rates of infection/extrusion/migration/foreign body reaction. It must allow high tissue incorporation with minimal resorption. Furthermore, spaces within the implant should be present to allow drainage of orbital fluid. Materials that are radiopaque facilitate postoperative evaluation. Lastly, it should be readily available, in sufficient quantities, and have an acceptable cost to ensure easy popularization.

BIOMATERIALS

Biological materials including autografts, allografts, and xenografts, are defined as grafts harvested from the same body, from cadavers or from animals. Generally speaking, autologous grafts are characterized by cost-effectiveness but limited availability, variable resorption rates resulting in unpredictable orbital volume that may lead to enophthalmos, associated donor site morbidity (pain, scarring, infection, haematoma), as well as an increased surgical time. Autologous bone was the first material used to reconstruct the orbit and remains popular today. Since the 18th century, it has been the "gold standard" biomaterial for the reconstruction of craniofacial bony defects.^[9,10] The major donor sites include crista iliaca, calvarium, maxilla and mandible.^[11-14] Autologous bone graft is applied in orbital reconstruction because of its strength, rigidity, biocompatibility, vascularization potential, and incorporation into the orbital tissue with minimal acute and chronic immune reactivity. The advantages mentioned above make it a significant role in the stage of orbital



Figure 1: Multiple small plates of calvarial bone and screws were used to re-create the normal contour of the orbit. Adapted from Gunarajah and Samman^[6]

reconstruction. However, its poor malleability, donor site morbidity and fluctuant resorption rates may be problematic [Figure 1]. The unpredictable resorption rates of autologous bone especially iliaca can even reach 80%, which increase the risk of complications.^[13] Resorption may be decreased by fixating of the graft, which promotes revascularization and osteoconduction.^[15]

Another option is cartilage graft, which compared to the “gold standard” bone graft is easier to harvest, is more malleable, and has less resorption.^[16] The nasal septum, conchal cartilage and costal cartilage are the common donor sites. The nasal septum is advantageous owing to the rapid harvest time and the minimal cosmetic and functional morbidity.^[17,18] Bayat *et al.*^[19] performed a randomized clinical trial and found a superior effect for nasal cartilage compared to conchal cartilage with respect to the incidence of enophthalmos at the 3-6 months follow-up point. Whereas, the autologous cartilage still cannot avoid donor site morbidity and is limited in quantity.

Allograft is transplanted tissue from human cadaver. Lyophilized dura mater, demineralized human bone, lyophilized cartilage, irradiated fascia lata are types of harvested tissues. The advantages of allograft include a decreased surgical time, preoperative customizability, absence of donor site morbidity (only in cadavers), and abundant availability. Lyophilized dura (Lyodura) was once the standard for the repair of smaller orbital defects.^[20] However, it became controversial after a report of Creutzfeldt-Jakob prion disease in a patient who received dura.^[21] The disadvantages of allograft include a resorption rate substantially higher than that of autologous tissue, the necessity for immunosuppressive pharmacotherapy, and potential risk of viral transmission.^[22-24]

Xenograft mainly includes collagen membrane, porcine sclera, porcine skin gelatin/gelfilm, bovine bone or sclera. It is only rarely used for the repair of orbital fractures because of the association with disease transmission, immunological transplant rejection, and unpredictable and high resorption rates in spite of a reduction in operative time and lack of donor site morbidity.^[25]

METALS

Studies have shown that titanium and cobalt alloys used to be active in the stage of orbital skeleton repair.^[26] Cobalt alloys seem not that gratifying because of its poor performance in orbital surgery and have gradually been

replaced by titanium.

Titanium mesh has been approved by the Food and Drug Administration since 1984, and now is accepted throughout the world to be used in the craniomaxillofacial surgery, especially in large defects. Titanium is chemically similar to calcium which makes it physiologically inert, and tissue tolerant. Titanium has a high corrosion resistance due to the spontaneously forming thin oxide layers on the surface. This guarantees that the material behaves passively in order not to provoke toxic nor allergic reactions [Figure 2].^[27] Computer-assisted designed and manufactured titanium implants have enabled optimal reconstructive surgery, with the protection of vital structures such as the optic nerve.^[28] However, it is costly and may have irregular edges that may impinge on soft tissue. Furthermore, fibrous tissue will incorporate the mesh-holes, which can make implant replacement technically difficult.^[29]

POLYMERS

Polymers are large molecules comprising of multiple repeated subunits, and can be categorized into absorbable and non-absorbable (permanent), or porous and non-porous types.

Since 1990s, porous ultra-high-density polyethylene (PE, medpor) sheets have been widely used in smaller orbital floor defects [Figure 3]. It's non-absorbable and easily malleable into shapes. The smooth surface of medpor allows tissues within the orbit to move around freely.^[26] Connective tissue and vascular components can grow into the pores which provides great biocompatibility. Medpor is reported to be able to achieve similar outcomes and lower infection rates than autologous bone.^[8]

Non-porous, non-absorbable materials include silicone,^[30] polytetrafluoroethylene (teflon), nylon foil. Silicone is cheap, flexible and easy to handle. However, it has unacceptable high rates of extrusion, cyst formation, and infections. Teflon is biologically and chemically inert, non-antigenic with minimal foreign body reaction, sterilizable, and easily moldable.^[31] However, with the proven reliability of porous materials, nonporous materials such as polytetrafluoroethylene are not used as frequently. Nylon has been used since 1965 by Browning and Walker with a lot of complications.^[32] Recent studies utilize fixation of the implant to the inferior orbital rim in blow-out fractures, demonstrating a complication rate as low as 1.7%.^[33]

As for absorbable implants like PLA/PGA, PDS, they have been used in the field of surgery for years with more predictable absorption rates as well as higher level of control than biomaterials. They provide temporary support leaving fibrotic tissues. Generally, they are not encouraged to be used in orbital reconstruction considering their unsatisfactory effect and high incidence of complications.^[13]

BIOLOGICAL CERAMICS

Hydroxyapatite (HA), which is chemically and crystallographically similar to bone mineral, has been

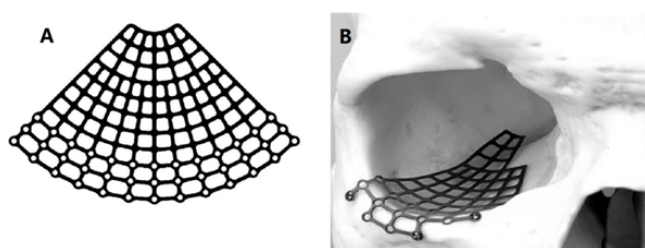


Figure 2: (A) Titanium to be used in orbital reconstruction, especially for large defect; (B) titanium mesh placed in the orbit. Adapted from Ellis and Messo^[27]

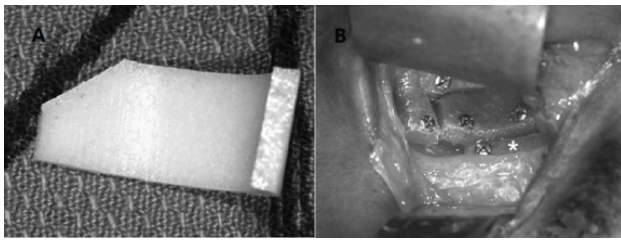


Figure 3: Example of polyethylene for reconstruction of internal orbital defect. (A) Shaped and sized polyethylene; (B) material in the orbit with bone screwed intraoperatively. Adapted from Ellis and Messo^[27]

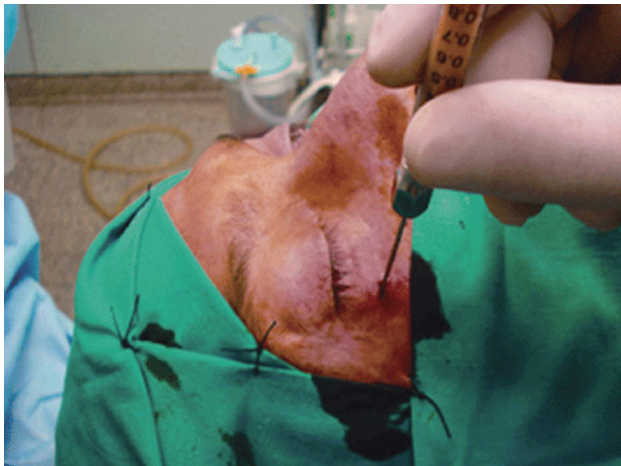


Figure 4: Minimally invasive autologous fat injection: atraumatic suction, purification, and reinjection in the orbit using a cannula. Adapted from Cervelli *et al.*^[50]

available for craniofacial surgery since the 1990s. As opposed to porous polyethylene, HA is more fragile, more expensive, and not as easily shaped intraoperatively.^[34] HA appears to have a higher risk of postoperative enophthalmos than medpor.^[35] Bioactive glasses (BAGs) are synthetic blocks or granules that bond chemically to bone. Despite the fact that BAGs are of brittle nature and hard to mould and shape, they are osteoinductive and osteoconductive.^[36-38] They can prompt the repair of bone with minimal foreign body reaction, infection, extrusion and resorption.^[39]

COMPOSITES

Composites are an interesting attempt to utilize the advantages of one selected material while reducing its disadvantages with another material. An example is the titanium-reinforced PE. Titanium mesh offers the advantages of high strength and stability, easy contouring, and radiopacity in postoperative imaging, while PE implants have a smooth surface allowing free movement of orbital tissue.^[40]

SOFT TISSUE FILLING MATERIALS

As mentioned above, repairing only the fracture is not sufficient. Even if repaired perfectly, many patients may suffer from late sequelae such as enophthalmos due to soft tissue abnormality within the orbit. It's claimed that alterations like atrophy or herniation of soft tissue have a decisive part in the enophthalmos after orbital reconstruction.^[41] Thus, we must act to prevent late sequelae by using soft tissue filling materials.

These materials are aimed to replace the abnormal soft tissue and to restore volume of the orbit, to finally restore ocular function as well as aesthetic appearance. They can also be divided into many autologous grafts, allografts, xenografts and alloplastic grafts.

As the “gold standard” of craniofacial reconstruction, autologous bone graft should be the first to be used in this process. However, the rigidity of bone (especially cranium) is relative to the increase of intraocular pressure that might influence the movement of eye and the optic nerve. Furthermore, the donor site morbidity is inevitable.

Silicone oil was one of the first injectable materials placed into the orbit for volume augmentation. Since 1960s, silicone oil has been used for volume augmentation.^[42] It's cheap but its outcome is not satisfactory and it needs multiple injections. Many authors have reported complications like extrusion, immigration of implants and infections.^[43]

Autologous fat graft (either as free fat or dermal fat graft) has been used since the end of the 19th century to handle various soft-tissue defects. Lipofilling, also known as autologous fat transplantation, has been investigated for a long time, especially as a natural implant for aesthetic and reconstructive purposes. Neuber^[44] first used fat autografting to correct facial defects in 1893. He reported a 20% to 90% graft absorption rate, so these defects require multiple injections to obtain a satisfactory target. In 1970s, dermal fat transplants were used to fill the orbit. Similarly to other autologous implants, they have outstanding high biocompatibility with minimal infection rate. However, the risk of operation and the donor site morbidity still exist.

In 1980s, collagens injectable became more popular. High resorption grade of non cross-linked collagen gives unsatisfactory results. The use of cross-linked collagen (Zyplast) in the orbital region has a documented risk of blood vessels occlusion, which can lead to a severe visual damage.^[45]

In the last decade, Hunter and Baker^[46] described the use of autologous fat in the orbit for the correction of posttraumatic enophthalmos. The outcome was not good for most of their patients and needed a second injection. Coleman^[47,48] reported his technique, defined as atraumatic liposuction with injection of purified fat, for fat transfer: harvesting, purification by centrifugation, and injection. This technique indeed improved the survival rate of fat. Hardy *et al.*^[49] obtained good results in a retrospective study of 12 patients with anophthalmic and enophthalmos; a further injection was necessary in only 1 case. Autologous fat seems to be the ideal filling material for soft tissue defect. Autologous fat is an ideal filler because of its excellent biocompatibility as a living graft, which is easily harvested and incorporated into the surrounding tissues with no hypersensitivity potential and minimal chance of infection. It is readily available in large quantities at low cost, and grafted fat gives a natural consistency with excellent volume augmentation. It is potentially permanent and the regenerative ability of fat is believed to improve the overlying skin quality. Autologous fat

transfer is minimally invasive, making it more acceptable for patients [Figure 4].^[50] At present, the greatest inconvenience is the unpredictable long term outcome of the graft, related to the extremely variable rate of fat resorption.^[51-53] Many animal models have been tried to find the best process of lipofilling.^[54-56] However, among the animal models, there is no useful posttraumatic model. Further studies are needed in this field.

We also can choose injectable filler, such as CaHA (Radiesse) or polyacrylamide gel (Aquamid), to treat the soft tissue defect in the orbit. Lately, a patient who received CaHA injection complained of soft tissue swelling.^[57] Both of them are reported to be effective in volume augmentation with minimal infections. However, they share the risk of anterior migration of filler.^[58-60] We have to take this disadvantage into consideration when choosing the filling material.^[61]

CONCLUSION

The controversy about the ideal material for orbital reconstruction and soft tissue defect filling will continue because it's hard to reach consensus due to the limited number of RCTs and studies. New materials emerge often and more studies are needed. We can safely conclude that there is a worldwide trend for surgeons to prefer minimally invasive techniques and alloplastic grafts are becoming increasingly popular.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Chen CT, Chen YR. Update on orbital reconstruction. *Curr Opin Otolaryngol Head Neck Surg* 2010;18:311-6.
- Kelley P, Crawford M, Higuera S, Hollier LH. Two hundred ninety-four consecutive facial fractures in an urban trauma center: lessons learned. *Plast Reconstr Surg* 2005;116:e42-9.
- Lang W. Traumatic enophthalmos with retention of perfect acuity of vision. *Trans Ophthalmol Soc UK* 1889;9:41.
- Ramieri G, Spada MC, Bianchi SD, Berrone S. Dimensions and volumes of the orbit and orbital fat in posttraumatic enophthalmos. *Dentomaxillofac Radiol* 2000;29:302-11.
- Dubois L, Steenen SA, Gooris PJ, Bos RR, Becking AG. Controversies in orbital reconstruction-III. Biomaterials for orbital reconstruction: a review with clinical recommendations. *Int J Oral Maxillofac Surg* 2016;45:41-50.
- Gunarajah DR, Samman N. Biomaterials for repair of orbital floor blowout fractures: a systematic review. *J Oral Maxillofac Surg* 2013;71:550-70.
- van Leeuwen AC, Ong SH, Vissink A, Grijpma DW, Bos RR. Reconstruction of orbital wall defects: recommendations based on a mathematical model. *Exp Eye Res* 2012;97:10-8.
- Wajih WA, Shaharuddin B, Razak NH. Hospital Universiti Sains Malaysia experience in orbital floor reconstruction: autogenous graft versus medpor. *J Oral Maxillofac Surg* 2011;69:1740-4.
- Schlickewei W, Schlickewei C. The use of bone substitutes in the treatment of bone defects - the clinical view and history. *Macromol Symp* 2007;253:10-23.
- Tessier P, Woillez M, Lekieffre M, Asseman R. Posttraumatic diplopia and osseous grafts. Observations. *Bull Mem Soc Fr Ophtalmol* 1960;73: 271-91. (in French)

- Kosaka M, Matsuzawa Y, Mori H, Matsunaga K, Kamiishi H. Orbital wall reconstruction with bone grafts from the outer cortex of the mandible. *J Craniomaxillofac Surg* 2004;32:374-80.
- Lee HH, Alcaraz N, Reino A, Lawson W. Reconstruction of orbital floor fractures with maxillary bone. *Arch Otolaryngol Head Neck Surg* 1998;124:56-9.
- Kontio RK, Laine P, Salo A, Paukku P, Lindqvist C, Suuronen R. Reconstruction of internal orbital wall fracture with iliac crest free bone graft: clinical, computed tomography, and magnetic resonance imaging follow-up study. *Plast Reconstr Surg* 2006;118:1365-74.
- Ilankovan V, Jackson IT. Experience in the use of calvarial bone grafts in orbital reconstruction. *Br J Oral Maxillofac Surg* 1992;30:92-6.
- Zins JE, Whitaker LA. Membranous versus endochondral bone: implications for craniofacial reconstruction. *Plast Reconstr Surg* 1983;72:778-85.
- Castellani A, Negrini S, Zanetti U. Treatment of orbital floor blowout fractures with conchal auricular cartilage graft: a report on 14 cases. *J Oral Maxillofac Surg* 2002;60:1413-7.
- Lai A, Gliklich RE, Rubin PA. Repair of orbital blow-out fractures with nasoseptal cartilage. *Laryngoscope* 1998;108:645-50.
- Baranov IV, Devdariani DSh, Kulikov AV, Aleksandrov AB, Bagnenko AS. Surgical treatment of posttraumatic deformity of the orbital floor. *Vestn Khir Im I I Grek* 2011;170:63-5. (in Russian)
- Bayat M, Momen-Heravi F, Khalilzadeh O, Mirhosseni Z, Sadeghi-Tari A. Comparison of conchal cartilage graft with nasal septal cartilage graft for reconstruction of orbital floor blowout fractures. *Br J Oral Maxillofac Surg* 2010;48:617-20.
- Luhr HG, Maerker R. Transplantation of homologous dura in reconstruction of the orbital floor. *Trans Int Conf Oral Surg* 1973;4:340-4.
- Centers for Disease Control (CDC). Rapidly progressive dementia in a patient who received a cadaveric dura mater graft. *MMWR Morb Mortal Wkly Rep* 1987;36:49-50, 55.
- Chowdhury K, Krause GE. Selection of materials for orbital floor reconstruction. *Arch Otolaryngol Head Neck Surg* 1998;124:1398-401.
- Aho AJ, Hirn M, Aro HT, Heikkilä JT, Meurman O. Bone bank service in Finland. Experience of bacteriologic, serologic and clinical results of the Turku Bone Bank 1972-1995. *Acta Orthop Scand* 1998;69:559-65.
- Campbell DG, Li P. Sterilization of HIV with irradiation: relevance to infected bone allografts. *Aust N Z J Surg* 1999;69:517-21.
- Baino F. Biomaterials and implants for orbital floor repair. *Acta Biomater* 2011;7:3248-66.
- Sullivan PK, Smith JF, Rozzelle AA. Cranio-orbital reconstruction: safety and image quality of metallic implants on CT and MRI scanning. *Plast Reconstr Surg* 1994;94:589-96.
- Ellis E 3rd, Messo E. Use of nonresorbable alloplastic implants for internal orbital reconstruction. *J Oral Maxillofac Surg* 2004;62:873-81.
- Lieger O, Richards R, Liu M, Lloyd T. Computer-assisted design and manufacture of implants in the late reconstruction of extensive orbital fractures. *Arch Facial Plast Surg* 2010;12:186-91.
- Schubert W, Gear AJ, Lee C, Hilger PA, Haus E, Migliori MR, Mann DA, Benjamin CI. Incorporation of titanium mesh in orbital and midface reconstruction. *Plast Reconstr Surg* 2002;110:1022-30; discussion 1031-2.
- Lipshutz H, Ardizzone RA. The use of silicone rubber in the immediate reconstruction of fractures of the floor of the orbit. *J Trauma* 1963;3:563-8.
- Polley JW, Ringle SL. The use of teflon in orbital floor reconstruction following blunt facial trauma: a 20-year experience. *Plast Reconstr Surg* 1987;79:39-43.
- Browning CW, Walker RV. Polyethylene in posttraumatic orbital floor reconstruction. *Am J Ophthalmol* 1961;52:672-7.
- Park DJ, Garibaldi DC, Iliff NT, Grant MP, Merbs SL. Smooth nylon foil (SupraFOIL) orbital implants in orbital fractures: a case series of 181 patients. *Ophthal Plast Reconstr Surg* 2008;24:266-70.
- Bae YC, Choi SJ, Moon JS, Nam SB. Comparison of the postoperative outcome in pure medial orbital fracture among three groups: using porous polyethylene or hydroxyapatite through subciliary approach and transnasal endoscopic correction. *Ann Plast Surg* 2007;59:287-90.
- Nam SB, Bae YC, Moon JS, Kang YS. Analysis of the postoperative outcome in 405 cases of orbital fracture using 2 synthetic orbital implants. *Ann Plast Surg* 2006;56:263-7.
- Peltola M, Kinnunen I, Aitasalo K. Reconstruction of orbital wall defects with bioactive glass plates. *J Oral Maxillofac Surg* 2008;66:639-46.
- Heikkilä JT, Aho HJ, Yli-Urpo A, Happonen RP, Aho AJ. Bone formation in rabbit cancellous bone defects filled with bioactive glass granules. *Acta Orthop Scand* 1995;66:463-7.
- Aitasalo K, Kinnunen I, Palmgren J, Varpula M. Repair of orbital floor fractures with bioactive glass implants. *J Oral Maxillofac Surg* 2001;59:1390-5; discussion 1395-6.

39. Amato MM, Blyden SM, Scribbick FW Jr, Belden CJ, Shore JW, Neuhaus RV, Kelley PS, Holck DE. Use of bioglass for orbital volume augmentation in enophthalmos: a rabbit model (*Oryctolagus cuniculus*). *Ophthalm Plast Reconstr Surg* 2003;19:455-65.
40. Zhang L, Fay A. Composite implants in oculoplastic surgery. *Semin Ophthalmol* 2010;25:303-8.
41. Grant MP, Iliff NT, Manson PN. Strategies for the treatment of enophthalmos. *Clin Plast Surg* 1997;24:539-50.
42. Chasan PE. The history of injectable silicone fluids for soft-tissue augmentation. *Plast Reconstr Surg* 2007;120:2034-40; discussion 2041-3.
43. Laiseca A, Laiseca D, Laiseca J, Laiseca J Jr. Correcting superior sulcus deformities. *Adv Ophthalmic Plast Reconstr Surg* 1990;8:229-42.
44. Neuber GA. Fett transplantation. *Verh Dtsch Ges Chir* 1893;22:66.
45. Cahill KV, Burns JA. Volume augmentation of the anophthalmic orbit with cross-linked collagen (Zyplast). *Arch Ophthalmol* 1989;107:1684-6.
46. Hunter PD, Baker SS. The treatment of enophthalmos by orbital injection of fat autograft. *Arch Otolaryngol Head Neck Surg* 1994;120:835-9.
47. Coleman SR. Long-term survival of fat transplants: controlled demonstrations. *Aesthetic Plast Surg* 1995;19:421-5.
48. Coleman SR. Facial recontouring with lipostructure. *Clin Plast Surg* 1997;24:347-67.
49. Hardy TG, Joshi N, Kelly MH. Orbital volume augmentation with autologous micro-fat grafts. *Ophthalm Plast Reconstr Surg* 2007;23:445-9.
50. Cervelli D, Gasparini G, Moro A, Grussu F, Boniello R, Pelo S. Retrobulbar lipofilling to correct the enophthalmos. *J Craniofac Surg* 2011;22:1918-22.
51. Coleman SR. Structural fat grafting: more than a permanent filler. *Plast Reconstr Surg* 2006;118:108-20.
52. Smith P, Adams WP Jr, Lipschitz AH, Chau B, Sorokin E, Rohrich RJ, Brown SA. Autologous human fat grafting: effect of harvesting and preparation techniques on adipocyte graft survival. *Plast Reconstr Surg* 2006;117:1836-44.
53. Moseley TA, Zhu M, Hedrick MH. Adipose-derived stem and progenitor cells as fillers in plastic and reconstructive surgery. *Plast Reconstr Surg* 2006;118:121-8.
54. Cakir B, Aygit AC, Omur-Okten O, Yalcin O. Retro-orbital intraconal fat injection: an experimental study in rabbits. *J Oral Maxillofac Surg* 2012;70:242-50.
55. Lee JY, Lee KH, Shin HM, Chung KH, Kim GI, Lew H. Orbital volume augmentation after injection of human orbital adipose-derived stem cells in rabbits. *Invest Ophthalmol Vis Sci* 2013;54:2410-6.
56. Brown M, Lee M, Zwiebel S, Adenuga P, Molavi S, Gargasha M, Varghai D, Guyuron B. Augmentation of intraorbital volume with fat injection. *Plast Reconstr Surg* 2014;133:1098-106.
57. Rauso R. A unique late complication with the use of calcium hydroxylapatite filler in facial lipotrophy rehabilitation. *Plast Aesthet Res* 2014;1:122.
58. Vagefi MR, McMullan TF, Burroughs JR, Georgescu D, McCann JD, Anderson RL. Orbital augmentation with injectable calcium hydroxylapatite for correction of postenucleation/eversion socket syndrome. *Ophthalm Plast Reconstr Surg* 2011;27:90-4.
59. da Silva AL, Bredemeier M, Gebrim ES, Moura Eda M. Intraorbital polyacrylamide gel injection for the treatment of anophthalmic enophthalmos. *Ophthalm Plast Reconstr Surg* 2008;24:367-71.
60. Buchanan AG, Holds JB, Vagefi MR, Bidar M, McCann JD, Anderson RL. Anterior filler displacement following injection of calcium hydroxylapatite gel (Radiesse) for anophthalmic orbital volume augmentation. *Ophthalm Plast Reconstr Surg* 2012;28:335-7.
61. Vagefi MR. Minimally invasive approaches to orbital volume augmentation. *Int Ophthalmol Clin* 2013;53:67-86.

An update review on recent skin fillers

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ABSTRACT

Facial rejuvenation has changed over the last decade, evolving from the rhytidectomy to an approach that focuses on revolumization, due to a more complete understanding of the changes to bone and soft tissue that occur with the aging face. Soft tissue augmentation using various injectable filler agents has gained popularity due to their nonsurgical, non-invasive procedures, instant cosmetic outcomes and limited recovery time. The skin filler market is booming and the variety of available skin fillers is increasing, providing the plastic surgeons many choices. Nonpermanant, biodegradable, resorbable agents may induce little complications, but they will normally disappear soon after injection. Semipermanant, biodegradable, biostimulatory, nonresorbable fillers may induce a bit more complications, but they will normally disappear spontaneously in a few months. Permanent, nonresorbable fillers usually give rise to severe complications or reactions which may not disappear spontaneous. They may appear several years after the injection, and treatment is often insufficient. Unfortunately, the ideal filler with lasting effect but without any complication has not been discovered yet. In this review, we give an update on currently available skin filler agents, and what is new in recent 5 years.

Key words:

Skin fillers; revolumization; biodegradable; biostimulatory; nonresorbable; bovine collagen; hyaluronic acid; polyacrylamide

INTRODUCTION

The past decade has seen an evolution in the filler market for meaningful volume restoration in the aging face. There are now over 35 major filler product companies worldwide.^[1] In 2014, there were 2.3 million soft-tissue filler procedures in the United States, an increase of 3% from 2013.^[2] The days of treating a nasolabial fold with single skin filler injection is gone, and a new era of more sophisticated approach of thoughtful, restrained,

and effective filler injection has come. Deep-volume increase, combinational approaches, natural looking outcomes, and safety measures are the most important considerations for filler use.

Skin fillers on the market today are categorized into transitory biodegradable or resorbable within months and years respectively, and permanent or nonresorbable fillers. Biodegradable agents can be divided into

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two categories: (1) nonpermanent fillers, also named replacement fillers (collagen, hyaluronic acid and biological fillers), which has a short duration with typical lengths of several months to one year and are eventually reabsorbed through macrophage activation; (2) semipermanent fillers, or stimulatory fillers (polylactic acid and calcium hydroxylapatite), which have a longer duration of aesthetic improvements lasting up to years with minimal side effects. They will typically result in a foreign body reaction that elicits fibroblast activation and collagenesis at the site of injection. Permanent implants (polymethylmethacrylate, silicone and hydroxyethylmethacrylate) could provide long-lasting revolumization results and could also induce fibrogenesis and collagen production, but with higher potential risk of complications. The skilled hands of the experienced plastic surgeons/dermatologists are required for injection.^[3-5]

BIODEGRADABLE FILLERS

Biodegradable fillers are impermanent agents than can last for a limited time of volume augmentation, from months up to 12 months, but will eventually metabolized by the body. Some of the volume effect is due to a transient inflammatory response to skin fillers with associated edema. However, these volume effects will diminish soon after injection.^[6,7] Subsequent fibroblast activation and neocollagenesis can be another two factors for volume augmentation, but they only result in partial filler engraftment into the surrounding tissue.^[8-10] Current biodegradable fillers stimulate neocollagenesis for more sustained aesthetic improvements and carry a low risk of adverse events or serious complications. Although permanent agents offer significant clinical benefits, short-term of volume effect, ease of correction and often reversible in the event of adverse effects make biodegradable fillers attractive to patients and plastic surgeons worldwide.

Generally, biodegradable filler spread on the market currently includes: hyaluronic acid (HA), bovine collagen, calcium hydroxylapatite (CaHA) and injectable poly-L-lactic acid (PLLA).

Bovine collagen

Bovine collagen is a resorbable filler. Bovine collagen was the first facial filler approved by the Food and Drug Administration (FDA) for the correction of contour irregularities in the USA,^[11,12] which has been used as an injectable filler for almost 30 years. Originally, Bovine collagen was injected into the dermis and subcutaneous tissue to correct viral pockmarks, depressed acne scars, lipoatrophy, deep nasolabial folds, rhytides, and soft tissue augmentation. The duration of the augmentation effect is usually less than 6 months.^[13,14]

Histopathologically, bovine collagen fibers are much thicker than human collagen, have a homogeneous appearance nearly devoid of spaces between them, with fewer fibroblasts, and fail to refract polarized light. Skin tests are required before the injection of bovine collagen products. Rare hypersensitive reactions, including foreign body

granulomas and palisading granulomas to bovine collagen have been reported. Rare systemic complications include flulike symptoms, paresthesias or difficulty breathing, and severe anaphylactic shock have been reported after injections of bovine collagen.^[15,16]

The requirement for skin testing before injection to identify patients at risk for allergic reactions and its short duration of effect, particularly in more mobile areas of the face have restricted the popularity of Bovine collagen's usage as a skin filler.^[17] Although human-based collagen was subsequently developed to lessen the chance of hypersensitivity reaction, the demand for collagen rapidly declined in the face of emerging products that offered long-lasting effects with few side effects.

Human-derived bioengineered collagen implants

Human-based collagen implants have been developed in recent years, to avoid allergic reactions to bovine collagen. Autologen (Collagenesis, Beverly, MA) is an injectable autologous human tissue matrix primarily composed of intact collagen fibrils that are processed from the patient's own skin and harvested during elective surgery.^[18,19] Human collagen implants are also obtained from human donor tissues that undergo extensive screening for infectious disease and the material is irradiated before use. The cosmetic effect lasts about 4 to 7 months, depending on the area of treatment, injection technique, and amount of injected collagen.^[17] No skin test for hypersensitive reactions is required for human-derived collagen products. Local adverse reactions include bruising, erythema, and swelling at the site of injection. Granulomatous reaction at the site of the injection has also been reported in few cases.^[20]

HA

Crosslinked animal or non-animal derived HA fillers have been introduced to the market for more than 20 years in the USA and even longer in different countries around the world. Today, HA-based dermal fillers are the fastest non-invasive esthetic procedure in the USA,^[21] which still remains the most popular dermal filler^[22] despite the new injectable fillers with different innovative compounds continues to expand.

HA was first discovered by Karl Meyer, who is considered the father of glycosaminoglycan chemistry, and his assistant John Palmer.^[23] HA is a glycosaminoglycan disaccharide, which exists naturally in the body. Approximately 50% of total HA is found in the skin, and it is produced by dermal fibroblasts, endothelial cells, synovial cells, adventitial cells, smooth muscle cells, and oocytes, and is released into the surrounding extracellular space. The half-life of HA is three days or less.^[4]

Injections of HA are used for correction the wrinkles of the face, for soft tissue augmentation, and for filling all types of defects. HA has become the most popular skin filler agent, and reached a high patient satisfaction with a low incidence of serious complications. The highly charged nature of HA

provides its high solubility and high water binding affinity, which also contributes to volume augmentation.^[23] HA may also stimulate neocollagenesis which is another reason for volume augmentation.^[8,24,25] The injected HA is eventually degraded and cleared by hepatic metabolism as thus the effect diminished.

HA has no organ or species specificity, and therefore in theory there is no risk of an allergic reaction. Very few adverse hypersensitivity reactions secondary to injections of HA used as filler have been reported; in histology, they consisted of a granulomatous foreign body reaction, with abundant multinucleated giant cells surrounding an extracellular basophilic amorphous material, which was the injected hyaluronic acid gel. One favorable character of HA is that it can be easily dissolved with hyaluronidase if there is an undesired or adverse effect. The duration of action averages 6 months with a residual effect lasting up to 2 to 3 years.^[26] The short longevity is the primary limitation of HA.

Currently available HA dermal fillers, depending on HA concentration, cross-link density, and manufacturing process, has different hydration capacity at equilibrium. Below are some of the favorable HA products by the plastic surgeons and dermatologist.

(1) Restylane® was FDA-approved in December of 2003, which is now the most popular dermal filler. Restylane® has been proven to be safe and effective in the treatment of nasolabial folds in a pivotal multicenter, double-blind clinical study.^[27] Perlane® is a more viscous version of Restylane®, which was FDA-approved in 2007. Both Restylane® and Perlane® are produced by Q-Med AB in Sweden and distributed in the USA by Medicis Pharmaceutical Corporation. They are based on “nonanimal stabilized hyaluronic acid” and produced from cultures of *Streptococcus equi* via a proprietary process crosslinked with 1,4-butanediol diglycidyl ether giving a final concentration of 20 mg/mL. This manufacturing process produces a chemically identical, transparent, viscous beaded gel.^[28]

(2) Juvéderm™ Ultra and Juvéderm™ Ultra Plus, FDA-approved in September, 2006, are new injectable HA dermal fillers, which are distributed by Allergan, Inc. The FDA has granted a label extension for Juvéderm™ Ultra and Juvéderm™ Ultra Plus in June, 2007 (Allergan, Inc. 2007). Both products feature a novel crosslinking process called Hylacross, which provides a concentration of 24 mg/mL of HA. Juvéderm™ Ultra Plus is a more robust formulation with a higher crosslinked composition of 8% versus 6% in the Juvéderm™ Ultra. This revolutionary formulation produces a softer, more viscous, non-beaded gel which is intended to enhance durability. The clinical data demonstrates that the effects with a single treatment of Juvéderm™ Ultra or Juvéderm™ Ultra Plus may last for up to 12 months.^[22,29,30]

(3) Eleveess™ is the latest HA approved by the FDA, in July 2007, which was manufactured by Anika Therapeutics, MA, USA, and was based on chemically modified non-animal HA proprietary technology which incorporates 0.3% lidocaine hydrochloride as a component of the treatment syringe. The concentration of HA in this product is the highest available

at 28 mg/mL.^[22,29,30]

(4) The HA dermal fillers on the horizon are Puragen, Puragen Plus, Prevelle, Prevelle Plus, Belotero, and Teosyal family of products. Puragen and Puragen plus are based on double crosslinked (DXL™) technology with non-animal HA chains. DXL™ technology increases the resistance to degradation once the product is implanted Hyaluronic acid dermal fillers to come and not yet available in the USA.

Despite its great popularity and satisfying aesthetic outcome, there are some adverse reactions of HA injection. Nonallergic local side effects at the sites of injections are frequent, including pain, bruising, and transient edema, but they disappear in a few days and usually do not need any treatment.^[31] Too superficial placement of HA fillers or an uneven distribution of the injected product can lead to visible, pale nodules in the skin. Uncommon additional nonallergic reactions include bacterial infections, herpes reactivation, generalized scleromyxedema,^[32] aseptic abscess,^[33] scar sarcoidosis,^[34] and interferon-induced systemic sarcoidosis in patients with chronic hepatitis C, who also developed sarcoidal granulomas around the injected HA filler^[35] and necrosis and livedoid pattern after accidental arterial embolization.^[36] Blood vessels-embolism by HA injection is the most severe complications, which may lead to organ necrosis, such as blindness, stroke, which sometimes could be irreversible.

Platelet-rich plasma

Platelet-rich fibrin matrices (Selphyl System; Aesthetic Factors, LLC, Princeton, N.J.), derived through the collection and centrifugation of blood, is approved by the FDA as a medical device designed for the safe and rapid preparation of autologous platelet-rich plasma (PRP) for use in orthopedic surgery. For cosmetic applications, PRP is injected into the face to stimulate cell proliferation via the release of growth-promoting proteins.^[37] Histological examination shows activated fibroblasts and new collagen deposition at the site of injection.^[38] Injection is an office-based procedure used to fill scars and rhytides with only minor transient ecchymosis and edema.^[31,37] Additional studies are required to evaluate the efficacy and safety of platelet-rich fibrin matrices for soft-tissue augmentation.^[3]

PLLA

Injectable PLLA is biocompatible, biodegradable, biostimulatory, synthetic filler that must be injected into the reticular dermis or subcutaneous fat. Polylactic acid as Sculptra® was licensed by FDA in July, 2009.^[39,40] Sculptra® effects by stimulating neocollagenesis through fibroblast activation,^[41] thus becomes popular as soft-tissue augmentation filler. Animal studies have revealed that PLLA are able to stimulate the proliferation of dermal fibroblasts with subsequent endogenous production of collagen.^[41,42] Histological studies in humans have shown gradual dissolution of the injected PLLA and dermal in-growth of type I collagen over 8 to 30 months after injection.^[43,44] PLLA is gradually degraded by nonenzymatic hydrolysis into water and carbon dioxide over approximately 9 to 24

months.^[45,46] However, the augmentation effect lasts for at least 24 months due to the neocollagenesis.^[47]

Short-term adverse events, including swelling, bruising, erythema, pain, inflammation, and pruritus, are frequently, but they usually disappear in a few days. The rate of granuloma formation of Sculptra® has been reported as high as 44%.^[48] The formation of granuloma greatly influences patient's appearance. Treatment of granulomas includes surgical excision and intralesional injection of corticosteroids.^[49] Surgical excision is not recommended except as a last resort. The corticosteroids used to treat granulomas need to be injected repeatedly.^[50,51] There are also severe systemic adverse effects, which is very rare, with only one case reported as an anaphylactic reaction necessitating treatment interruption.^[52]

CaHA

CaHA is a biocompatible, biodegradable, resorbable and biostimulatory filler that contains microspheres which can stimulate the endogenous production of collagen. The product has a texture resembling native soft tissue and migration is minimal.^[53] Histopathologically, microspheres of CaHA stimulate almost no foreign body reaction and they appear bluish in color and round or oval in shape. It is suggested that the microspheres of this implant are degraded by enzymatic breakdown rather than phagocytosis. The microspheres appear packed together, with bluish color, round or oval shape, 25 to 40 µm in size, and surrounded by some fibrin fibers but little cellular infiltrate.

Initial augmentation is afforded by the implant itself, but in a few months the palpable implant diminishes further in size and has disappeared clinically at 9 to 12 months. When macrophages begin to degrade the implant, new collagen may form around the CaHA microspheres.^[54]

Injectable microspheres of CaHA have been successfully used for correction of lipoatrophy of HIV patients receiving antiprotease treatment and for smoothing moderate wrinkles.^[55-59] When this agent is injected in the lips, it tends to induce a high incidence of nodules.^[60] Migration to a distant location from the injection site, a foreign body granulomatous reaction, seen as blue-gray microspheres in the extracellular matrix or within multinucleated giant cells has also been reported.^[61]

Polycaprolactone-based dermal filler

A promising new biodegradable collagen stimulatory filler, composed of 70% aqueous carboxymethylcellulose (CMC) gel carrier (Ellans é™, Aqtis Medical, a Sinclair Company; Utrecht, The Netherlands) and 30% synthetic polycaprolactone (PCL) microspheres has recently been introduced to the market. Its unique tuneable longevity gives the dermal filler variable durations for up to 4 years [Ellans é™-S (1 year), Ellans é™-M (2 years), Ellans é™-L (3 years) and Ellans é™-E (4 years)] and is therefore ideal for those seeking long-lasting results.^[62]

The PCL-based dermal filler is proved to be safe and durable in use in facial treatment and in hand rejuvenation in a clinical trial.^[63,64] Furthermore, PCL-based dermal filler could

induce neocollagenesis in rabbit tissue.^[65] In Kim-Jongseo's study, the PCL-based dermal filler was injected intra-dermally in the temporal area in human tissue. The results revealed that PCL-based filler is capable of inducing neocollagenesis for up to 13 months after injected intra-dermally in human tissue. However, further clinically study and safety study should be introduced before it could be finally used as a biostimulatory filler in human.^[62]

Cross-linked CMC

Five-eight chemically cross-linked CMC is now available as skin filler for the correction of facial defects and imperfections. It was first used in the pharmaceutical industry since the 1960s as an excipient and for drug delivery. A commercially available product based on cross-linked CMC is Erelle™ (Total Action, Bioitech Italy Ltd, Rome, Italy). It consists of a non-particulate, viscoelastic, monophasic gel based on cross-linked CMC in isotonic saline solution. One study of CMC injection in 350 patients with 3-year follow-up revealed that CMC could effectively and durably correct nasolabial wrinkles for 9-12 months.^[66] Product reapplication over a 36-month period did not lead to an increase in adverse effects, which always remained rare and of little clinical significance, usually consisting of bruising and redness.^[67] However, further safety studies and clinical trials should be conducted be finally published in the market.

Autologous fat

Fat grafting is revolutionizing plastic surgery by providing methodologies to less invasively transfer fatty tissue. The initial attempts at soft-tissue augmentation revolved around the surgical use of autologous fat to reconstruct facial scars in 1893.^[68] It then were largely used for nasolabial folds injection, forehead augmentation, temporal augmentation, breast augmentation, mid face lift. PRP^[69] and cell-assisted lipotransfer using adipose-derived stem cells have recent been developed to enhance the survival rate of fat grafting.^[70] There is certain inconsistent reabsorption rate and longevity lasts once the fat survives.^[71-75] Adverse effects include prolonged edema and ecchymosis which will fade several days after injection. There is also a risk of necrosis and infection.^[76] There are also vascular complications, which may lead to vision loss and stroke after injection of fat into the glabella and nasolabial folds have been reported.^[77,78] Proper injection technique is critical for fat injection.

PERMANENT FILLERS

Permanent fillers include polymethyl-methacrylate (PMMA), silicone, polyacrylamide hydrogel, polyvinylpyrrolidone-silicone suspension, polyalkylimide gel, polyvinylhydroxide microspheres suspended in polyacrylamide gel and others. Permanent fillers are non-resorbable and could provide long-lasting revolumization results. They could also induce fibrogenesis and collagen production, but complications such as granulomas are more frequent in subcutaneous injection with such filler.^[79]

Paraffins

Paraffins were initially used for aesthetic procedures to

restore facial volume and contours, but complications such as granulomas and paraffinomas years after treatment have restricted their use for aesthetic treatment.

Silicone

No silicone product for soft tissue augmentation has been approved by FDA. The major indication for FDA-approved products is retinal detachment with removal of the material after reattachment. In soft tissue augmentation, removal of silicone is not performed. The use of liquid silicon is off label.^[80] For decades, horrendous complications have been reported from silicone injections into breasts, and its use has been banned by many authorities. Adverse effects have also been noted after use for facial tissue augmentation.^[81-83] After illegal silicone injection, the silicone embolism syndrome has been observed with potential fatal outcome in 24% of patients. Symptoms and signs of the “silicone syndrome” include dyspnea, fever, cough, hemoptysis, chest pain, hypoxia, alveolar hemorrhage, and altered consciousness.^[84] They have almost been abandoned nowadays.

PMMA

PMMA is rigid, transparent and colorless, thermoplastic permanent skin filler with low cost, easy accessibility, and potential to achieve lasting results. PMMA has been used as an injectable filler to treat hollows and reduce rhytids. PMMA injections have been associated with several side effects; especially they may lead to some undesirable effects in the eyelids and periocular region.

First-generation polymerized PMMA microspheres are purified with diameter greater than 20 μm , which may produced foreign body granulomas; Lemperle *et al.*^[85,86] postulate that larger PMMA microspheres (30 to 50 μm) may resist phagocytosis. However, Bachmann *et al.*^[87] demonstrated that a giant cell reaction still occurs with larger PMMA microspheres. Complications of PMMA injection were classified as nodular masses, inflammation, allergies and skin hypopigmentation. The most affected sides were the lips (46%), followed by periocular, nasolabial folds, forehead, and cheeks. PMMA injection to the periocular region may be lead to erythema, hardening of the local tissues, edema, and formation of nodules and eyelid malposition, which are associated with fibrotic nodules, giant cell inflammation. The best treatment for these PMMA injection complications remains uncertain. Corticosteroid injection may have limited efficacy while surgical debulking may achieve favorable results.^[88]

Aquamid (polyacrylamide hydrogel)

Aquamid has been used extensively for soft tissue augmentation and body contouring for 2 decades.^[89] Aquamid is a biocompatible and nonabsorbable hydrogel consisting of 97.5% water and 2.5% cross-linked polyacrylamide (PAAG). The gel is manufactured through polymerization of the acrylamide monomers and N, N'-methylenbisacrylamide.^[89] Aquamid is currently approved in several countries in Europe, European Conformity marked in Europe in 2001 for facial augmentation and minor body contouring, PAAG is available in more than 40 countries worldwide (Europe,

Asia, the Middle East, and Latin America) and awaiting FDA approval.

After injection, the implant is encapsulated and surrounded by fibroblasts and macrophages, theoretically preventing migration. Many studies have supported the usage of Aquamid for the treatment of various rhytides, facial contouring, and correction of HIV lipoatrophy. PAAG has been evaluated in clinical trials for facial contouring, deep rhytides and folds,^[90-92] and the correction of facial lipoatrophy^[93,94] with efficacy similar to nonanimal stabilized hyaluronic acid and duration of at least 1 year when used for the treatment of nasolabial folds.^[95-98]

For the past decade, Aquamid has gained popularity as injectable filler. Similar to other facial fillers, there have been reported cases of inflammation, nodule and granuloma formation, and delayed hypersensitivity reactions. Histologic analysis of Aquamid injected into the subcutaneous layer revealed bioactive product that underwent cell infiltration and integration into tissues between weeks 1 and 8.^[99] In some instances, surgical extraction of the polyacrylamide product was necessary to correct the adverse event of nodule formation. Careful attention to injection technique and sterile precautions are necessary to minimize unwanted reactions. In addition, there have been recent recommendations for the usage of prophylactic antibiotics to minimize complications from bacterial injections and biofilm formation when injecting Aquamid.^[100,101]

Polyvinylpyrrolidone-silicone suspension

This is a permanent filler comprised of particles of polymerized silicone elastomer, 100-600 μm in size, dispersed in a carrier of polyvinylpyrrolidone (Bioplastique; Uroplasty BV, Geleen, The Netherlands). The suspension has been mostly used for lip augmentation and the correction of facial rhytids. It should be injected in the subcutaneous tissue. They usually remain at the injected site and could avoid from being phagocytosed by macrophages due to the large size of the silicone particles. They would produce a local foreign body reaction and fibrosis, which contributes to the filling effect.^[102] Local side effects include induration, swelling, and granuloma formation.^[103-105]

Histopathologically, granulomas secondary to this filler consist of irregularly shaped cystic spaces containing translucent, jagged “popcorn” nonbirefringent particles of varying size dispersed in a sclerotic stroma surrounded by abundant multinucleated foreign body giant cells.^[102-105]

Polyalkylimide gel

Polyalkylimide gel is a permanent hydrophilic translucent gel filler composed of a hydrophilic biopolymer with 96% sterile water and 4% polyalkylimide polymer (Bio-Alcamid; Polymekon, Brindisi, Italy), and different from polyacrylamide. It has been used to increase volume in the cheeks in HIV patients with facial lipoatrophy related to antiretroviral therapy and for gluteal augmentation, correction of irregularities after liposculpture, scar depressions, and posttraumatic subcutaneous atrophy and

filling of pectus excavatum or other malformations of the skeleton. Complications secondary to this filler include edema, bruising, nodules, and infections, but no granulomas have been described. Histopathologically, this filler appears as basophilic amorphous material with granular appearance surrounded by sparse numbers of epithelioid histiocytes, foreign body multinucleated giant cells, neutrophils, and red cells.^[106-110]

Polyvinylhydroxide microspheres suspended in polyacrylamide gel

This is a permanent filler composed of composed of a suspension of 6 polyvinylhydroxide microspheres suspended in 2.5% polyacrylamide gel (Evolution; ProCytech SA), and has been used mostly for lip augmentation. This is a rarely used filler, and there are not descriptions of adverse reactions to this filler, other than the observation made by Lemperle *et al.*^[49] who, in their comparative paper on fillers, injected Evolution (and later excised it from the first author's forearm) and found the filler to give little local reaction and diminish slowly over 9 months.^[4]

CONCLUSION

Although dermal fillers have been used for decades in aesthetic medicine, the ideal filler is still missing, because all of them known today may cause adverse reactions. Patients' safety is hampered by nonlicensed products and users. These side effects tend to be less severe after injection with non-permanent or semi-permanent biodegradable skin fillers, which will mostly disappear spontaneously within a few months. Unfortunately, however, after injection with slowly or nonbiodegradable permanent fillers, severe adverse reactions may appear and need active treatment. Follow-up of patients by trained physicians is necessary to reduce risks and initiate early treatment in case of complications. Careful selection of patients and particular selection of products, matching particular needs, and skilled injector is the best way to perform safe three-dimensional rejuvenation and achieve high patient's satisfaction. In the future, individualized, specifically tailored filler with long-lasting effect but with fewer complications might become available.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Pak CS, Lee J, Lee H, Jeong J, Kim EH, Jeong J, Choi H, Kim B, Oh S, Kim I, Heo CY. A phase III, randomized, double-blind, matched-pairs, active-controlled clinical trial and preclinical animal study to compare the durability, efficacy and safety between polynucleotide filler and hyaluronic acid filler in the correction of crow's feet: a new concept of regenerative filler. *J Korean Med Sci* 2014;29 Suppl 3:S201-9.
- 2014 Complete Plastic Surgery Statistic Report. American Society of Plastic Surgeons. Available from: <http://www.plasticsurgery.org/news/plastic-surgery-statistics/2014-plastic-surgery-statistics.html>.
- Carruthers J, Carruthers A, Humphrey S. Introduction to fillers. *Plast Reconstr Surg* 2015;136 Suppl 5:S120-31.
- Requena L, Requena C, Christensen L, Zimmermann US, Kutzner H, Cerroni L. Adverse reactions to injectable soft tissue fillers. *J Am Acad Dermatol* 2011;64:1-34.
- Christensen L, Breiting V, Janssen M, Vuust J, Hogdall E. Adverse reactions to injectable soft tissue permanent fillers. *Aesthetic Plast Surg* 2005;29:34-48.
- De Boulle K. Management of complications after implantation of fillers. *J Cosmet Dermatol* 2004;3:2-15.
- Bertossi D, Sbarbati A, Cerini R, Barillari M, Favero V, Piccozzi V, Ruzzenente O, Salvagno G, Guidi GC, Nocini P. Hyaluronic acid: *in vitro* and *in vivo* analysis, biochemical properties and histological and morphological evaluation of injected filler. *Eur J Dermatol* 2013;23:449-55.
- Wang F, Garza LA, Kang S, Varani J, Orringer JS, Fisher GJ, Voorhees JJ. In vivo stimulation of a de novo collagen production caused by cross-linked hyaluronic acid dermal filler injections in photodamaged human skin. *Arch Dermatol* 2007;143:155-63.
- Turlier V, Delalleau A, Casas C, Rouquier A, Bianchi P, Alvarez S, Josse G, Briant A, Dahan S, Saint-Martory C, Theunis J, Bensafi-Benaouda A, Degouy A, Schmitt AM, Redoulès D. Association between collagen production and mechanical stretching in dermal extracellular matrix: *in vivo* effect of cross-linked hyaluronic acid filler. A randomised, placebo-controlled study. *J Dermatol Sci* 2013;69:187-94.
- Watson W, Kaye RL, Klein A, Stegman S. Collagen: a clinical overview. *Cutis* 1983;31:543-6.
- Klein AW, Rish DC. Dermatology: bovine injectable collagen. *West J Med* 1985;143:231.
- Knapp TR, Kaplan EN, Daniels JR. Injectable collagen for soft tissue augmentation. *Plast Reconstr Surg* 1977;60:389-405.
- Stegman SJ, Chu S, Bensch K, Armstrong R. A light and electron microscopic evaluation of Zyderm collagen and Zyplast implants in aging human facial skin: a pilot study. *Arch Dermatol* 1987;123:1644-9.
- Douglas RS, Donsoff I, Cook T, Shorr N. Collagen fillers in facial aesthetic surgery. *Facial Plast Surg* 2004;20:117-23.
- Mullins RJ, Richards C, Walker T. Allergic reaction to oral, surgical and topical bovine collagen. Anaphylactic risk for surgeons. *Aust N Z J Ophthalmol* 1996;24:257-60.
- Siegle RJ, McCoy JP, Schade W, Swanson NA. Intradermal implantation of bovine collagen. humoral immune responses associated with clinical reactions. *Arch Dermatol* 1984;120:183-7.
- Sclafani A, Romo T, Jacono AA, McCormick SA, Cocker R, Parker A. Evaluation of acellular dermal graft in sheet (Alloderm) and injectable (micronized Alloderm) forms for soft tissue augmentation: clinical observations and histologic findings. *Arch Facial Plast Surg* 2000;2:130-6.
- Fagien S. Facial soft-tissue augmentation with injectable autologous and allogenic human tissue collagen matrix (autologen and dermalogen). *Plast Reconstr Surg* 2000;105:362-73.
- Moody BR, Sengemann RD. Self-limited adverse reaction to human-derived collagen injectable product. *Dermatol Surg* 2000;26:936-8.
- Wise JB, Greco T. Injectable treatments for the aging face. *Facial Plast Surg* 2006;22:140-6.
- Lupo MP. Hyaluronic acid fillers in facial rejuvenation. *Semin Cutan Med Surg* 2006;25:122-6.
- Termeer C, Benedix F, Sleeman J, Fieber C, Voith U, Ahrens T, Miyake K, Freudenberg M, Galanos C, Simon JC. Oligosaccharides of hyaluronan activate dendritic cells via toll-like receptor 4. *J Exp Med* 2002;195:99-111.
- Mansouri Y, Goldenberg G. Update on hyaluronic acid fillers for facial rejuvenation. *Cutis* 2015;96:85-8.
- Turlier V, Delalleau A, Casas C, Rouquier A, Bianchi P, Alvarez S, Josse G, Briant A, Dahan S, Saint-Martory C, Theunis J, Bensafi-Benaouda A, Degouy A, Schmitt AM, Redoulès D. Association between collagen production and mechanical stretching in dermal extracellular matrix: *in vivo* effect of cross-linked hyaluronic acid filler. A randomised, placebo-controlled study. *J Dermatol Sci* 2013;69:187-94.
- Quan T, Wang F, Shao Y, Rittiti L, Xia W, Orringer JS, Voorhees JJ, Fisher GJ. Enhancing structural support of the dermal microenvironment activates fibroblasts, endothelial cells, and keratinocytes in aged human skin *in vivo*. *J Invest Dermatol* 2013;133:658-67.
- Duranti F, Salti G, Bovani B, Calandra M, Rosati ML. Injectable hyaluronic acid gel for soft tissue augmentation. A clinical and histological study. *Dermatol Surg* 1998;24:1317-25.
- Narins RS, Brandt F, Leyden J, Lorenc ZP, Rubin M, Smith S. A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. *Dermatol Surg* 2003;29:588-95.
- Palm MD. Filler frontier: what's new and heading West to the US market. *Semin Cutan Med Surg* 2014;33:157-63.
- Brandt FS, Cazzaniga A. Hyaluronic acid gel fillers in the management of facial

- aging. *Clin Interv Aging* 2008;3:153-9.
30. Mansouri Y, Goldenberg G. Update on hyaluronic acid fillers for facial rejuvenation. *Cuti* 2015;96:85-8.
31. Pollack SV. Some new injectable dermal filler materials: Hylaform, Restylane and Artecoll. *J Cutan Med Surg* 1999;Suppl 4:S27-35.
32. Rongioletti F, Cattarini G, Sottofattori E, Rebora A. Granulomatous reaction after intradermal injections of hyaluronic acid gel. *Arch Dermatol* 2003;139:815-6.
33. Shafir R, Amir A, Gur E. Long-term complications of facial injections with Restylane (injectable hyaluronic acid). *Plast Reconstr Surg* 2000;106:1215-6.
34. Dal Sacco D, Cozzani E, Parody A, Rebora A. Scar sarcoidosis after hyaluronic acid injection. *Int J Dermatol* 2005;44:411-2.
35. Descamps V, Landry J, Frances C, Marinho E, Ratzliff V, Chosidow O. Facial cosmetic filler injections as possible target for systemic sarcoidosis in patients treated with interferon for chronic hepatitis C: two cases. *Dermatol* 2008;217:81-4.
36. Schanz S, Schipper W, Ulmer A, Rassner G, Fierlbeck G. Arterial embolization caused by injection of hyaluronic acid (Restylane). *Br J Dermatol* 2002;146:928-9.
37. Grossman KL. Hyaluronic acid gel fillers: hypersensitivity reactions. *Aesthet Surg J* 2005;25:403-5.
38. Leonard JM, Lawrence N, Narin RS. Angioedema acute hypersensitivity reaction to injectable hyaluronic acid. *Dermatol Surg* 2005;31:577-9.
39. Schierle CF, Casas LA. Nonsurgical rejuvenation of the aging face with injectable poly-L-lactic acid for restoration of soft tissue volume. *Aesthet Surg J* 2011;31:95-109.
40. Ladewig K, Abbott K, Andrea J O'Connor. Designing *in vivo* bioreactors for soft tissue engineering. *J Biomater Tissue Engineering* 2012;2:1-13.
41. Gogolewski S, Jovanovic M, Perren SM, Dillon JG, Hughes MK. Tissue response and *in vivo* degradation of selected poly-hydroxyacids: polylactides (PLA), poly(3-hydroxybutyrate) (PHB) and poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHB/VA). *J Biomed Mater Res* 1993;27:1135-48.
42. Lam SM, Azizzadeh B, Graivier M. Injectable poly-L-lactic acid (Sculptra): technical considerations in soft-tissue contouring. *Plast Reconstr Surg* 2006;118:S55-63.
43. Vleggaar D. Facial volumetric correction with injectable poly-L-lactic acid. *Dermatol Surg* 2005;31:1511-7.
44. Vleggaar D, Bauer U. Facial enhancement and the European experience with Sculptra (poly-L-lactic acid). *J Drugs Dermatol* 2004;3:542-7.
45. Athanasiou KA, Niederauer GG, Agrawal CM, Landsman AS. Applications of biodegradable lactides and glycolides in podiatry. *Clin Podiatr Med Surg* 1995;12:475-95.
46. Spenlehauer G, Vert M, Benoit JP, Boddaert A. *In vitro* and *in vivo* degradation of poly(D, L-lactide/glycolide) acid microspheres made by solvent evaporation method. *Biomater* 1989;10:557-63.
47. Vleggaar D. Soft-tissue augmentation and the role of poly-L-lactic acid. *Plast Reconstr Surg* 2006;118:S46-54.
48. Valantin MA, Aubron-Olivier C, Ghosn J, Laglenne E, Pauchard M, Schoen H, Bousquet R, Katz P, Costagliola D, Katama C. Polylactic acid implants (New-Fill) to correct facial lipatrophy in HIV-infected patients: results of the open-label study. *AIDS* 2003;17:2471-7.
49. Lempereur G, Rullan PP, Gauthier-Hazan N. Avoiding and treating dermal filler complications. *Plast Reconstr Surg* 2006;118:S92-107.
50. Alijotas-Reig J, Fernández-Figueras MT, Puig L. Inflammatory, immune-mediated adverse reactions related to soft tissue dermal fillers. *Semin Arthritis Rheum* 2013;43:241-58.
51. Fan M, Liao J, Guo Q, Ding Q, Yang Y, Luo F, Qian Z. Dexamethasone-loaded poly (D,L-lactic acid) microspheres/poly (ethylene glycol) = poly (epsilon-caprolactone) – poly (ethylene glycol) micelles composite for skin augmentation. *J Biomed Nanotechnol* 2014;10:592-602.
52. Lafaurie M, Dolivo M, Porcher R, Rudant J, Madeline I, Molina JM. Treatment of facial lipatrophy with intradermal injections of polylactic acid in HIV-infected patients. *J Acquir Immune Defic Syndr* 2005;38:393-8.
53. Tzikas TL. Evaluation of the radiance FN soft tissue filler for facial soft tissue augmentation. *Arch Facial Plast Surg* 2004;6:234-9.
54. Marmur ES, Phelps R, Goldberg DJ. Clinical, histologic and electron microscopic findings after injection of a calcium hydroxylapatite filler. *J Cosmet Laser Ther* 2004;6:223-6.
55. Broder KW, Cohen SR. An overview of permanent and semipermanent fillers. *Plast Reconstr Surg* 2006;118:75-145.
56. Silvers SL, Eviatar JA, Echavez MI, Pappas AL. Prospective, open-label, 18-month trial of calcium hydroxylapatite (Rad-iesse) for facial soft-tissue augmentation in patient with human immunodeficiency virus-associated lipatrophy: one-year durability. *Plast Reconstr Surg* 2006;118:S34-45.
57. Sklar JA, White SM. Radiance FN: a new soft tissue filler. *Dermatol Surg* 2004;30:764-8.
58. Jansen DA, Graivier MH. Evaluation of calcium hydroxylapatite based implant (Radiessse) for facial soft-tissue augmentation. *Plast Reconstr Surg* 2006;118:S22-30.
59. Ahn MS. Calcium hydroxylapatite: Radiessse. *Facial Plast Surg Clin North Am* 2007;15:85-90.
60. Duffy DM. Complications of fillers. Overview. *Dermatol Surg* 2005;31:1626-33.
61. Beer KR. Radiessse nodule of the lips from a distant injection site: report of a case and consideration of etiology and management. *J Drugs Dermatol* 2007;6:846-7.
62. Kim JA, Van Abel D. Neocollagenesis in human tissue injected with a polycaprolactone-based dermal filler. *J Cosmet Laser Ther* 2015;17:99-101.
63. Moers-Carpi MM, Sherwood S. Polycaprolactone for the correction of nasolabial folds: a 24-month, prospective, randomized, controlled clinical trial. *Dermatol Surg* 2013;39:457-63.
64. Figueiredo VM. A five-patient prospective pilot study of a polycaprolactone based dermal filler for hand rejuvenation. *J Cosmet Dermatol* 2013;12:73-7.
65. Nicolau PJ, Marijnissen-Hofsté J. Neocollagenesis after injection of a polycaprolactone based derma filler in a rabbit. *Eur J Aesthet Med Dermatol* 2013;3:19-26.
66. Leonardis M, Palange A. New-generation filler based on cross-linked carboxymethylcellulose: study of 350 patients with 3-year follow-up. *Clin Interv Aging* 2015;10:147-55.
67. Leonardis M, Palange A, Dornelles RF, Hund F. Use of cross-linked carboxymethyl cellulose for soft-tissue augmentation: preliminary clinical studies. *Clin Interv Aging* 2010;5:317-22.
68. Neuber F. Fettersplantation. *Chir Kongr Verhandl Dtsch Gesellsch Chir* 1893;22:66.
69. Cervelli V, Palla L, Pascali M, De Angelis B, Curcio BC, Gentile P. Autologous platelet-rich plasma mixed with purified fat graft in aesthetic plastic surgery. *Aesthetic Plast Surg* 2009;33:716-21.
70. Sterodimas A, De Faria J, Nicaretta B, Papadopoulos O, Papalambros E, Illouz YG. Cell-assisted lipotransfer. *Aesthet Surg J* 2010;30:78-81.
71. Ersek RA. Transplantation of purified autologous fat: a 3-year follow-up is disappointing. *Plast Reconstr Surg* 1991;87:219-27.
72. Coleman SR. Long-term survival of fat transplants: controlled demonstrations. *Aesthetic Plast Surg* 1995;19:421-5.
73. Fulton JE, Suarez M, Silverton K, Barnes T. Small volume fat transfer. *Dermatol Surg* 1998;24:857-65.
74. Fournier PF. Fat grafting: my technique. *Dermatol Surg* 2000;26:1117-28.
75. Kanchwala SK, Bucky LP. Facial fat grafting: the search for predictable results. *Facial Plast Surg* 2003;19:137-46.
76. Cheng JT, Perkins SW, Hamilton MM. Collagen and injectable fillers. *Otolaryngol Clin North Am* 2002;35:73-85.
77. Carruthers JD, Fagien S, Rohrich RJ, Weinkle S, Carruthers A. Blindness caused by cosmetic filler injection: a review of cause and therapy. *Plast Reconstr Surg* 2014;134:1197-201.
78. Hong DK, Seo YJ, Lee JH, Im M. Sudden visual loss and multiple cerebral infarction after autologous fat injection into the glabella. *Dermatol Surg* 2014;40:485-7.
79. Yamauchi PS. Emerging permanent filler technologies: focus on aquamid. *Clin Cosmet Investig Dermatol* 2014;7:261-6.
80. Peters W, Fornasier V. Complications from injectable materials used for breast augmentation. *Can J Plast Surg* 2009;17:89-96.
81. Altmeyer MD, Anderson LL, Wang AR. Silicone migration and granuloma formation. *J Cosmet Dermatol* 2009;8:92-7.
82. Schwartzfarb EM, Hammett JM, Romanelli P, Ricotti C. Foreign body granuloma formation secondary to silicone injection. *Dermatol Online J* 2008;14:20.
83. Ficarra G, Mosqueda-Taylor A, Carlos R. Silicone granuloma of the facial tissues: a report of seven cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002;94:65-73.
84. Schmid A, Tzur A, Leshko L, Krieger BP. Silicone embolism syndrome: a case report, review of the literature, and comparison with fat embolism syndrome. *Chest* 2005;127:2276-81.
85. Vent J, Lempereur G. Prevention and treatment of complications after polymethylmethacrylate-microspheres injections. *Facial Plast Surg* 2014;30:628-34.
86. Lempereur G, Nacul AM, Fortes FB. Can injection of PMMA-microspheres cause hypercalcemia? *Clin Cases Miner Bone Metab* 2015;12:82-3.
87. Bachmann F, Erdmann R, Hartmann V, Becker-Wegerich P, Wiest L, Rzyan B. Adverse reactions caused by consecutive injections of different fillers in the same facial region: risk assessment based on the results from the injectable filler safety study. *J Eur Acad Dermatol Venereol* 2011;25:902-12.
88. Limongi RM, Tao J, Borba A, Pereira F, Pimentel AR, Akaiishi P, Velasco E Cruz AA. Complications and management of polymethylmethacrylate (PMMA) injections to the midface. *Aesthet Surg J* 2016;36:132-5.

89. Christensen LH, Breiting VB, Aasted A, Jørgensen A, Kebuladze I. Long-term effects of polyacrylamide hydrogel on human breast tissue. *Plast Reconstr Surg* 2003;111:1883-90.
90. Breiting V, Aasted A, Jørgensen A, Opitz P, Rosetzsky A. A study on patients treated with polyacrylamide hydrogel injection for facial corrections. *Aesthetic Plast Surg* 2004;28:45-53.
91. Von Buelow S, Von Heimburg D, Pallua N. Efficacy and safety of polyacrylamide hydrogel for facial soft-tissue augmentation. *Plast Reconstr Surg* 2005;116:1137-46.
92. Von Buelow S, Pallua N. Efficacy and safety of polyacrylamide hydrogel for facial soft-tissue augmentation in a 2-year follow-up: a prospective multicenter study for evaluation of safety and aesthetic results in 101 patients. *Plast Reconstr Surg* 2006;118:S85-91.
93. De Santis G, Jacob V, Baccarani A, Pedone A, Pinelli M, Spaggiari A, Guaraldi G. Polyacrylamide hydrogel injection in the management of human immunodeficiency virus-related facial lipoatrophy: a 2-year clinical experience. *Plast Reconstr Surg* 2008;121:644-53.
94. Negredo E, Puig J, Aldea D, Medina M, Estany C, Pérez-Alvarez N, Rodríguez-Fumaz C, Muñoz-Moreno JA, Higuera C, Gonzalez-Mestre V, Clotet B. Four-year safety with polyacrylamide hydrogel to correct antiretroviral-related facial lipoatrophy. *AIDS Res Hum Retroviruses* 2009;25:451-5.
95. Wolters M, Lampe H. Prospective multicenter study for evaluation of safety, efficacy, and esthetic results of crosslinked polyacrylamide hydrogel in 81 patients. *Dermatol Surg* 2009;35 Suppl 1:338-43.
96. Mole B, Gillaizeau F, Carbonnel E, Pierre I, Brazille P, Grataloup C, Mercier S, Duracinsky M, Weiss L, Piketty C. Polyacrylamide hydrogel injection in the management of human immunodeficiency virus-related facial lipoatrophy: results of the LIPOPHILL open-label study. *AIDS Res Hum Retroviruses* 2012;28:251-8.
97. Lafaurie M, Dolivo M, Girard PM, May T, Bouchaud O, Carbonnel E, Madelaine I, Loze B, Porcher R, Molina JM; ANRS 132 SMILE study group. Polylactic acid vs. polyacrylamide hydrogel for treatment of facial lipoatrophy: a randomized controlled trial [Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS) 132 SMILE]. *HIV Med* 2013;14:410-20.
98. Narins RS, Coleman VPP 3rd, Rohrich R, Monheit G, Glogau R, Brandt F, Bruce S, Colen L, Dayan S, Jackson I, Maas C, Rivkin A, Sclafani A, Spivak JC. 12-Month controlled study in the United States of the safety and efficacy of a permanent 2.5% polyacrylamide hydrogel softtissue filler. *Dermatol Surg* 2010;36 Suppl 3:1819-29.
99. Fernández-Cossío S, Castaño-Oreja MT. Biocompatibility of two novel dermal fillers: histological evaluation of implants of a hyaluronic acid filler and a polyacrylamide filler. *Plast Reconstr Surg* 2006;117:1789-96.
100. Christensen L, Breiting V, Bjarnsholt T, Eickhardt S, Høgdall E, Janssen M, Pallua N, Zaat SA. Bacterial infection as a likely cause of adverse reactions to polyacrylamide hydrogel fillers in cosmetic surgery. *Clin Infect Dis* 2013;56:1438-44.
101. Nygart JF, Nygart VA, Borggren M, Tvede M. Effect of prophylactic antibiotics on polyacrylamide gel safety in facial augmentation. *J Drugs Dermatol* 2014;13:571-3.
102. Ersek RA, Beisang AA 3rd. Bioplastique: a new texture copolymer microparticle promises permanence in soft tissue augmentation. *Plast Reconstr Surg* 1991;33:693-702.
103. Rudolph CM, Soyer HP, Schuller-Petrovic S, Kerl H. Bioplastiquegranulom. *Hautarzt* 1997;48:749-52.
104. Hoffmann C, Schuller-Petrovic S, Soyer HP, Kerl H. Adverse reactions after cosmetic augmentation with permanent biologically inert implant materials. *J Am Acad Dermatol* 1999;40:100-2.
105. Rudolph CM, Soyer HP, Schuller-Petrovic S, Kerl H. Foreign body granulomas due to injectable aesthetic microimplants. *Am J Surg Pathol* 1999;23:113-7.
106. Margolis DM. Treatment for lipoatrophy: facing the real costs. *AIDS* 2007;21:1819-20.
107. Nelson L, Stewart KJ. Experience in the treatment of HIV-associated lipodystrophy. *J Plast Reconstr Aesthet Surg* 2008;61:366-71.
108. Karim RB, De Lint CA, Van Galen SR, Van Rozelaar L, Nieuwkerk PT, Askarizadeh E, Hage JJ. Long-term effect of polyalkylimide gel injections on severity of facial lipoatrophy and quality of life of HIV-positive patients. *Aesthetic Plast Surg* 2008;32:873-8.
109. Mallewa JE, Wilkins E, Vilar J, Mallewa M, Doran D, Back D, Pirmohamed M. HIV-associated lipodystrophy: a review of underlying mechanisms and therapeutic options. *J Antimicrob Chemother* 2008;62:648-60.
110. Hönig J. Cheek augmentation with Bio-Alcamid in facial lipoatrophy in HIV seropositive patients. *J Craniofac Surg* 2008;19:1085-8.

Collagen membrane for reconstruction of soft tissue defects after surgery of oral cancer and precancer: a brief review

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ABSTRACT

There are some surgeries after which a temporary cover for raw wounds is required to ensure healing. Some of those circumstances are loss of tissue due to burns, trauma, amputation, chronic ulcer, leprosy, and skin graft sites. Although the body initiates regeneration mechanisms, however the time taken for complete healing of wounds is unpredictable. Also, there is a tendency for long standing wounds to undergo infection and scarring. Oral mucosa is no exception to scarring and infection of wounds and there has always been a search for new materials that can be used for coverage of oral defects. Xenogenous collagen is one such grafting material. Over the years collagen implant solutions for a number of clinical applications include general surgery, burn surgery, neurosurgery, plastic and reconstructive surgery, oral surgery, and peripheral nerve and tendon surgery. This paper aims to focus on collagen as an effective option of wound closure in plastic and reconstructive surgery of the head and neck, especially after loss of soft tissue following resection of oral malignancies.

Keywords: Collagen; oral mucosa; grafting; oral submucous fibrosis; oral cancer

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INTRODUCTION

Oral mucosa is predisposed to a variety of pathologies such as leukoplakia, oral submucous fibrosis, oral squamous cell carcinoma; the treatment of which may lead to significant soft tissue loss that may not be amenable to primary closure. According to Ashley's principles of plastic surgery, covering the raw wound is necessary to prevent infection, tissue contracture and scarring.^[1] A variety of approaches have been used in the past, including split and full-thickness skin grafts, oral mucosa free grafts, oral connective tissue grafts, the latest being tissue engineered grafts.^[2] For larger defects, pedicled local and distant flaps or free microvascular grafts have been tried with variable success rates.^[2]

Non-vascularized free graft materials like split thickness skin graft, human amniotic membrane, palatal mucosa, buccal mucosa and collagen are easy to obtain, but each material has its own limitations.^[1,3-5] One of these materials is collagen, which is in extensive use as temporary dressing material in a lot of surgical fields. This paper aims to highlight the various types of collagen, its manipulation and applications in the field of oral cancer and precancer.

COLLAGEN AS A BIOMATERIAL IN PLASTIC AND RECONSTRUCTIVE SURGERY

Collagen is the major insoluble protein (fibrous protein) in the extra-cellular matrix and in connective tissues. More than 80% of the skin is composed of collagen. It is also the main component of the ligaments and tendons. In the early 1970's, John F. Burke and Ioannis Yannas developed a bio-compatible collagen matrix to improve wound healing. It is commonly used in the management of burns,^[6] diabetic foot ulcer,^[7,8] toxic epidermal necrolysis,^[9] chronic wounds, *etc.*^[10-12] This versatile material also finds its application in the field of plastic surgery, oral and maxillofacial surgery and dentistry for various purposes e.g. as an interpositional graft material during palatoplasty;^[13] for guided bone regeneration during maxillary sinus lift;^[14] for inducing bone formation along with/without certain medicaments like gusuibu;^[15,16] bone augmentation of posterior atrophic mandibular ridge for placement of dental implants;^[17] as a reconstructive material for orbital floor fractures;^[18] in treatment of localized gingival recession;^[19] as a scaffold in tissue engineering to generate dental pulp;^[20] for coverage of small intraoral soft tissue defects of the oral cavity^[21] and much more. Collagen also has use as a medium for culturing cells such as osteoblasts.^[22]

Biological dressings are the logical best candidate for the management of wounds since they create the most physiological interface between the wound surface and the environment.^[23] Collagen is a biological skin substitute, i.e. natural, easily available, ready to use, non-immunogenic, and non-pyrogenic. Today, a variety of collagen sheets are available with or without carriers, e.g. gels, pastes, polymers, oxidized regenerated cellulose, and ethylene diamine tetraacetic acid. This collagen may be derived from bovine, porcine, equine, or avian sources, which is purified to make it nonantigenic. Collagen dressings are

made of either type I (native) or denatured collagen and they can come in a variety of pore sizes and surface areas. Many collagen dressings contain an antimicrobial agent to control pathogens within the wound.^[24]

According to Lazovic *et al.*^[7] the physical properties of collagen sheet can be divided into two categories, i.e. biological, physiological. The biological properties include its non-inflammatory nature, low antigenicity, no toxicity and minimal biodegradation. It facilitates migration of fibroblasts and microvascular cells and helps in the synthesis of neodermal collagen matrices. Collagen sheet also helps in minimizing scarring. The physiological properties of collagen are its non-permeability to bacterial migration, modulation of fluid flux from the wound, elasticity, softness and suppleness, good tear strength, good suturing characteristics and enough strength to be peeled off the wound. Collagen sheet has been found to be well tolerated in clinical trials.^[7] There have been no reports of clinically significant immunological or histological responses to the implementation of collagen sheet that could cause its rejection.^[7]

Research shows that some collagen-based dressings can produce a significant increase in the fibroblast production; can promote fibroblast permeation by the virtue of their hydrophilic nature; can cause increased deposition of oriented and organized collagen fibers by attracting fibroblasts and causing a directed migration of cells; can help in the uptake and bioavailability of fibronectin; can cause preservation of leukocytes, macrophages, fibroblasts, and epithelial cells; and assist in the maintenance of the chemical and thermostatic microenvironment of the wound.^[24]

Collagen makes large areas of ulcerated skin pain free. The use of collagen dressing has been found to inhibit the action of metalloproteinases, hence it is useful in treating chronic wounds.^[25] Collagen is a biomaterial that encourages wound healing through deposition and organisation of freshly formed fibres and granulation tissue in the wound bed, thus creating a good environment for wound healing.^[26] Cutaneous lesions can bleed due to shearing of the gauze dressings. Application of collagen sheet to such wounds, not only promote angiogenesis, but also aid in body's repair mechanisms.^[7,27] Collagen sheets act as a mechanical support, reduce oedema and loss of fluids from the wound site, facilitate the of migration of fibroblasts into the wound, thus enhancing the metabolic activity of the granulation tissue.^[27-29] This fact is of particular importance in treating painful and bleeding ulcers of the mucosal surfaces of the body such as buccal cavity, nasal cavity, conjunctiva, urethra, vagina, and anal canal.

COLLAGEN FOR COVERAGE OF SOFT TISSUE DEFECTS OF ORAL MUCOSA SECONDARY TO RESECTION OF PRECANCEROUS AND CANCEROUS LESIONS

Cancer is one of the main causes of death in all societies, its relative position varying with age and sex.^[30] Globally, oral cancer is the sixth most common cause of cancer related-death, although many people are unaware of its existence.^[30]

In the International Classification of Diseases [9th revision-World Health Organization (WHO)], oral cancer is classified under the rubrics 140 (lip), 141 (tongue), 143 (gingiva), 144 (floor of the mouth), and 145 (other parts of the mouth). Oral precancer is distinguished by WHO into “precancerous lesions” (e.g. leukoplakia, erythroplakia) and “precancerous conditions” (e.g. oral sub mucous fibrosis, lichen planus).^[31] The treatment of these suspicious precancerous lesions involve wide excision followed by grafting of the surgical sites. Depending on the status of metastasis of established malignancies, resection of affected area and radical neck dissection followed by adjuvant radiotherapy with or without chemotherapy may be required. In the surgery of oral submucous fibrosis (OSMF), bilateral fibrotic bands are excised with or without bilateral coronoidectomy or temporalis myotomy.

In all such cases, wounds left uncovered are prone to infection, contraction, and scarring with other clinical complications. Raw wounds of the oral cavity, like any other wounds, heal by epithelialization and granulation. However, in the oral cavity the healing of raw wounds presents some special problems. The environment is always moist with contamination from salivary secretion and food ingestion. This, compounded by poor oral hygiene and constant movements of the cheek and tongue and masticatory forces, may interfere with graft adherence and acceptance. The risk of infection in the oral cavity is also quite high, which may result in scarring and contraction. The oral cavity is highly sensitive to any residual scarring, which may undergo ulceration and could be a constant source of irritation to patients wearing dentures. Hence, a need arises to use a biologic cover to prevent these complications.^[32]

Free split-skin graft and free mucosal graft have been used to cover raw wounds in the oral cavity. The use of these grafts required a separate surgical procedure with associated technical difficulties. The color and texture of skin do not conform totally to the oral cavity. Also seen is the growth of adnexal structures such as hair and sweat glands. In elderly persons the skin is atrophic and inelastic, making it unsuitable. Mucosal grafts offer the best solution because they come nearest to fulfilling the requirements of an ideal graft material, which include the ability to replace lost structures and the ability to induce the formation of such tissues. Donor sites for mucous graft are limited, and there is always morbidity associated with donor-site healing. The oral environment and its constant movements are impediments to graft acceptance.^[32] Other reconstructive options which have been used in the past include nasolabial flaps, transposition of the buccal pad of fat, dorsal tongue flap, radial forearm flaps, flaps of the temporalis fascia/muscle or both, palatal island flaps to cover surgical defects, each having their own advantages and shortcomings.^[33,34] Use of island palatal flap has limitation such as its involvement with fibrosis and second molar tooth extraction is required for flap cover without tension. Bilateral palatal flaps leave a large raw area on palatal bones. Sometimes the defect created may be large and local flaps may not be able to cover the entire defect. A nasolabial flap is too short to cover the defect and causes visible scarring on the face and requires division at second stage. Tongue flaps have been used to cover the buccal defects but were found to be bulky and needed additional surgery for detachment. Bilateral tongue flaps can cause severe dysphagia and disarticulation and carry the risk of postoperative

aspiration. Pindborg *et al.*^[1] found an incidence of 38% tongue involvement in OSMF, which precludes its use. Bilateral free radial artery forearm free flaps require micro vascular expertise, the flaps are hairy and 40% of patients require secondary debulking procedures. Extraction of third molar tooth is required to avoid flap inclination between teeth.

Chemically, bovine collagen is very similar to the human form. This is crucial, as the human immune system will reject everything that deviates too much from its own proteins. For these reasons, collagen sheets are well qualified for use as an effective wound cover.^[7] Bovine collagen contain mostly type I and III collagen, packed in a neutral glass vial of sterile preservative mixture of isopropyl alcohol and water sterilized with ethylene oxide and are available in different sizes for clinical application. The freeze-dried form of collagen is also available so that there is no need to treat the membrane in normal saline before application. Meshed collagen membrane in wet form, porous collagen dressing and collagen film dressings are also available.^[6] Wet collagen membrane comes in varying in dimensions of 10 cm × 10 cm, 10 cm × 25 cm and 25 cm × 25 cm with thickness of 0.6 mm.^[35]

Collagen covers sensitive nerve endings, thereby diminishing degree of pain in raw wounds. Initially collagen adheres due to fibrin collagen interaction and later by fibrovascular ingrowth into the collagen. All collagen membranes, with time, slowly undergo collagenolysis and get eventually sloughed off.^[1]

The advantages of collagen sheet as a wound dressing material in surgery precancerous and cancerous lesions of oral soft tissues include the easy availability of collagen sheet, convenience of application, good tolerance of oral tissue, no adverse effects of the use of this membrane, obviation of second surgery to obtain graft or detachment of the pedicle, there is no morbidity associated with the use of grafts, and there are no problems associated with donor site healing.^[34,36] No threat of human immunodeficiency virus or hepatitis infections is associated with collagen, as the bovine material is obtained from countries free of bovine spongiform encephalopathy and has a long shelf-life under normal storage conditions.^[7]

OSMF is an insidious chronic disabling disease involving oral mucosa, oropharynx and rarely larynx characterized by juxtaepithelial inflammatory reaction followed by progressive fibrosis of the lamina propria and deeper connective tissues with concomitant muscle degeneration. Although vesicle formation is an early sign, patient's usual complaint will barely be burning sensation and inability to have hot and spicy food. In the later stages, it shows a tendency for progressive fibrosis, leading to gradual reduction in mouth opening which hinders the function.^[37,38] Management of trismus in OSMF is extremely challenging because of the nature of the disease, making the oral mucosa prone to contraction causing a significant reduction in the interincisal opening that was achieved with surgery. Nataraj *et al.*^[1] performed a study in which collagen was used to cover surgical defects of OSMF in 15 cases and in other 15 cases, buccal pad of fat was used for the same. They found that the use of collagen membrane following excision of fibrotic bands in the management of oral submucous fibrosis, though statistically not significant gave better results with respect to post operative mouth opening

as seen with a 6-month follow up. Pradhan *et al.*^[33] also in a similar study found a significant difference in the postoperative mouth opening, an insignificant difference for post surgical morbidity and higher grades of surgical convenience in using collagen sheet as a wound dressing material as compared to buccal pad of fat. Reddy *et al.*^[39] found good results in cases of OSMF when they impregnated dexamethasone in the collagen graft after excision of fibrous bands.

MANIPULATION OF COLLAGEN

Though it has not been mentioned in literature, we have observed that most surgeons find it difficult to handle the wet collagen sheet in the oral cavity once it is taken out from its sterile packing. Even after washing away the preservative medium by immersing the material in sterile solution for 5-10 min, the tendency of the collagen to coil in itself does not go away. In our opinion, it can be attributed to its minimal thickness, elasticity and cohesiveness. So, the technique of using a “tie-over” bolster dressing (as used with skin grafts)^[40] can be tried to secure collagen membrane to the recipient site. However, if the surgeon does not desire to keep the gauze or sponge dressing tied to the collagen graft, we suggest an easy technique that not only reduces the difficulty in manipulating collagen, but also provides perfect adaptation of the graft to the recipient site in oral cavity.

The method involves spreading the wet collagen sheet over a thick moistened gauze ball [Figure 1] after removing the preservative from collagen by immersing in saline for 10 min. The size of graft and gauze depends on the size of the surgical defect. This gauze along with the graft is then taken to the surgical site and placed there with collagen facing the recipient site. With the gauze still in place, the accessible portion of collagen sheet underneath the gauze can be sutured to the wound margin [Figure 2]; choice of the suture depends on the surgeon. Next, the gauze can be slightly lifted over the portion of graft situated adjacent to the sutured collagen and another couple of stay sutures can be placed as required [Figure 3]. For example, if a buccal mucosa defect has to be grafted, the first suture can be placed anteriorly and lifting the gauze pad can proceed from anterior to posterior region. Thereafter, using this same technique, the whole circumference of the wound can be



Figure 1: Picture demonstrating the placement of wet collagen sheet over a thick, moistened gauze



Figure 2: Placing the first suture through the accessible portion of graft to the surgical site, while the gauze is stabilized over the graft with a finger rest or an instrument

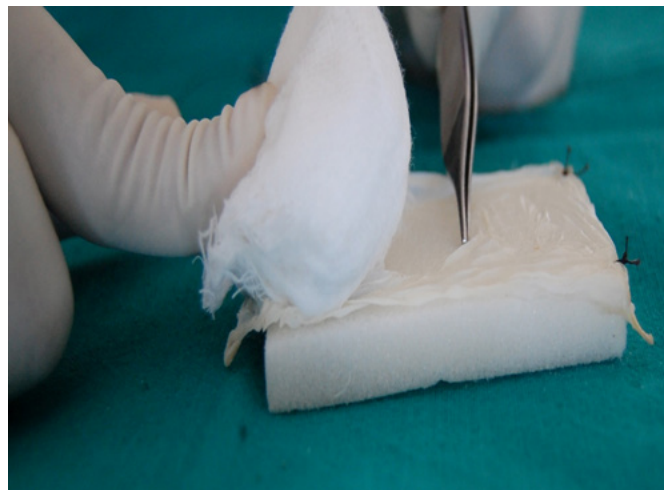


Figure 3: The gauze is slowly mobilized/ rolled, but not removed completely from the graft surface so that more area of the graft is accessible for suturing without much warping of the graft. Simultaneously, an instrument tip can be used to stabilize the graft



Figure 4: The collagen graft in place after suturing; the gauze is removed just before placing the last suture

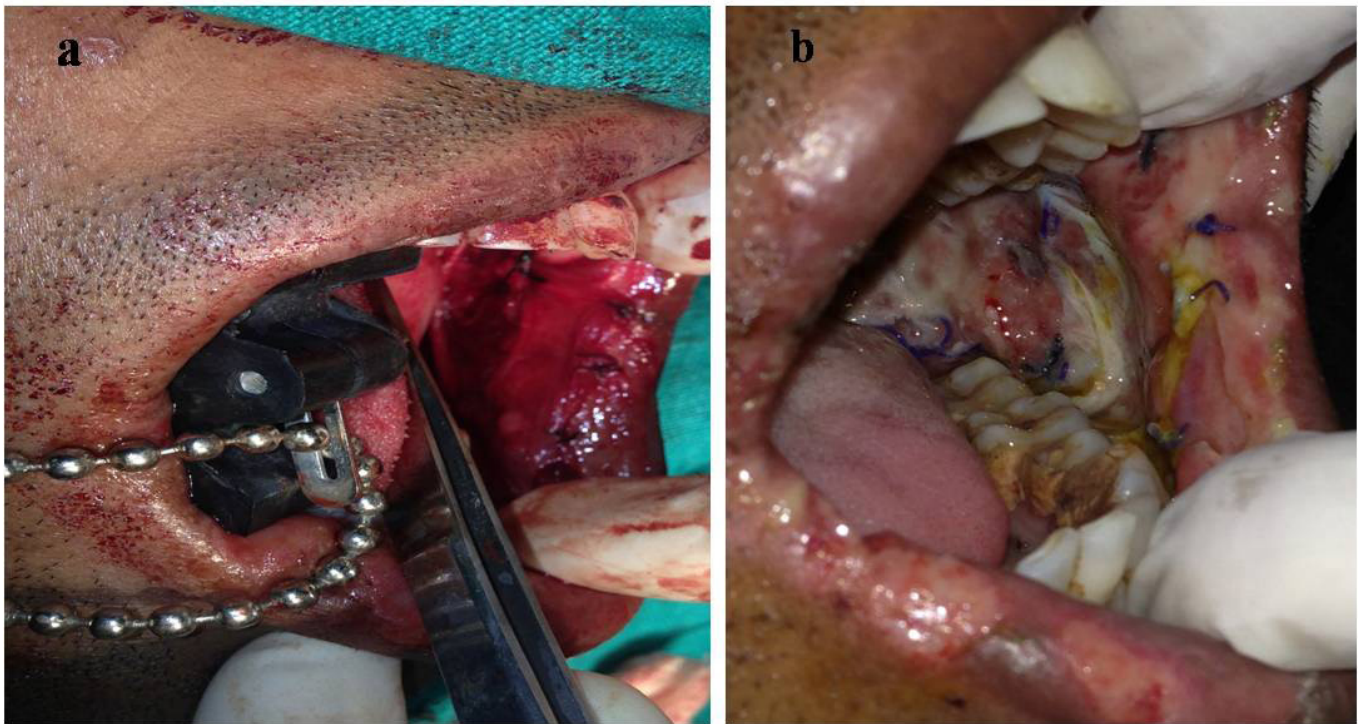


Figure 5: (a) Collagen membrane secured on buccal mucosa in a case of oral submucous fibrosis following excision of buccal fibrous bands; (b) photograph of the 7th postoperative day showing partial healing of buccal mucosa and partial sloughing of collagen

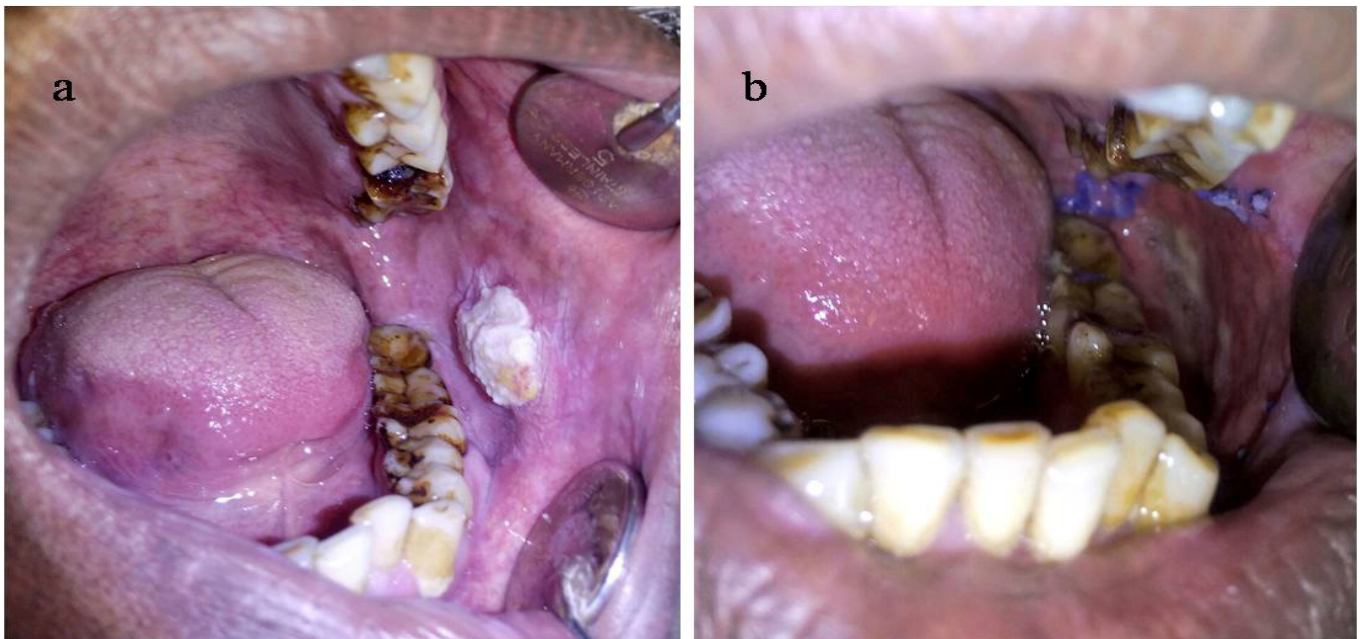


Figure 6: (a) Preoperative photograph showing verrucous carcinoma of left buccal mucosa; (b) photograph of the 7th postoperative day showing almost complete take up of collagen graft by the defect made by wide excision of lesion

covered with the graft by sutures [Figure 4]. It is important to note that the gauze should be removed only before the last suture remains to be given to secure the graft in proper adaptation. After the gauze is removed, a well-adapted collagen can be seen which is not amenable to the problem of mobility and rolling of the material during suturing; making the placement of additional sutures (if required) very easy. A dressing may or may not be placed over the graft, depending on the choice of surgeon. We prefer to snugly fit a thick, removable, moistened gauze dressing over the graft at least for two days, to avoid graft contamination and to prevent the collection of fluid between graft and recipient site that could predispose the site to infection, thus jeopardizing

the successful take-up of graft. If the surgical defects are multiple or bilateral, we advocate placement of a Ryle's tube for 3-4 days so that immediate oral intake after the surgery can be avoided, yet nutrition is maintained. Clinical appearance of collagen grafted in OSMF and oral squamous cell carcinoma can be seen in Figures 5 and 6 respectively.

CONCLUSION

Oral and maxillofacial surgeons treat various pathologies in and around the oral cavity. The commonest protocol of treatment for all pathologies is the surgical excision, rendering postoperative

wounds prone to infection and scarring, unless they are covered using some kind of a graft. Various materials like skin, buccal mucosa, buccal pad of fat, tongue, palatal mucosa and xenografts have been used in the past for this purpose, each having its own advantages and shortcomings. Collagen is one such biomaterial that can be safely and effectively used for coverage of oral defects following surgery of oral cancer and precancer owing to a number of benefits such as its free availability, no additional donor site morbidity, economic, non-allergenic, biocompatibility, good epithelization with less contraction, etc. It is of particular value in cancer surgeries if one wants to safeguard autogenous grafts for future use, should a second resective surgery be required.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Nataraj S, Guruprasad Y, Shetty JN. A comparative clinical evaluation of buccal fat pad and collagen in surgical management of oral submucous fibrosis. *Arch Dent Sci* 2011;2:17-24.
- Bagheri SC, Bell RB, Khan HA. Current therapy in oral and maxillofacial surgery. Philadelphia: Elsevier Saunders; 2011.
- Shevale VV, Kalra RD, Shevale VV, Shringarpure MD. Management of oral submucous fibrosis: a review. *Indian J Dent Sci* 2012;4:107-14.
- Mokal NJ, Raje RS, Ranade SV, Prasad JS, Thatte RL. Release of oral submucous fibrosis and reconstruction using superficial temporal fascia flap and split skin graft- a new technique. *Br J Plast Surg* 2005;58:1055-60.
- Lai DR, Chen HR, Lin LM, Huang YL, Tsai CC. Clinical evaluation of different treatment methods for oral submucous fibrosis. A 10-year experience with 150 cases. *J Oral Pathol Med* 1995;24:402-6.
- Mariappan N. Collagen dressing for thermal burns. *Sch J App Med Sci* 2015;3:58-61.
- Lazovic G, Colic M, Grubor M, Jovanovic M. The application of collagen sheet in open wound healing. *Ann Burns Fire Disasters* 2005;18:151-6.
- Holmes C, Wyrobel JS, MacEachern MP, Boles BR. Collagen-based wound dressings for the treatment of diabetes-related foot ulcers: a systematic review. *Diabetes Metab Syndr Obes* 2013;6:17-29.
- Bhattacharya S, Tripathi HN, Gupta V, Nigam B, Khanna A. Collagen sheet dressings for cutaneous lesions of toxic epidermal necrolysis. *Indian J Plast Surg* 2011;44:474-7.
- Singh O, Gupta SS, Soni M, Moses S, Shukla S, Mathur RK. Collagen dressing versus conventional dressings in burn and chronic wounds: a retrospective study. *J Cutan Aesthet Surg* 2011;4:12-6.
- Shankar N, Eligar R, Ramesh H, Hebsur NI. A comparative study of collagen granule dressing versus conventional dressing in deep wounds. *IOSR J Dent Med Sci* 2015;14:23-8.
- Rai R, Sudarshan SH, Dsouza R, Saldhana E, Aithala PS. Collagen dressing versus heparin dressing in burn wound management. *J Evol Med Dent Sci* 2013;2:9124-30.
- Hudson JW, Pickett DO. A 5-year retrospective review of primary palatoplasty cases utilizing an acellular collagen interpositional graft. *J Oral Maxillofac Surg* 2015;73:1393.e1-3.
- Li X, Chen SL, Zhu SX, Zha GQ. Guided bone regeneration using collagen membranes for sinus augmentation. *Br J Oral Maxillofac Surg* 2012;50:69-73.
- Wong RW, Rabie AB. Effect of gusuibu graft on bone formation. *J Oral Maxillofac Surg* 2006;64:770-7.
- Ferreira AM, Gentile P, Chiono V, Ciardelli G. Collagen for bone tissue regeneration. *Acta Biomater* 2012;8:3191-200.
- Block MS, Kelley B. Horizontal posterior ridge augmentation: the use of a collagen membrane over a bovine particulate graft: technique note. *J Oral Maxillofac Surg* 2013;71:1513-9.
- Birkenfeld F, Flörke C, Behrens E, Rohnen M, Kern M, Gassling V, Wiltfang J. Mechanical properties of collagen membranes modified with pores - are they still sufficient for orbital floor reconstruction? *Br J Oral Maxillofac Surg* 2015;53:957-62.
- Babu HM, Gujjari SK, Prasad D, Sehgal PK, Srinivasan A. Comparative evaluation of a bioabsorbable collagen membrane and connective tissue graft in the treatment of localized gingival recession: a clinical study. *J Indian Soc Periodontol* 2011;15:353-8.
- Prescott RS, Alsanea R, Fayad MI, Johnson BR, Wenckus CS, Hao J, John AS, George A. In vivo generation of dental pulp-like tissue using human pulpal stem cells, a collagen scaffold and dentin matrix protein 1 following subcutaneous transplantation in mice. *J Endod* 2008;34:421-6.
- Sowjanya NP, Rao NM, Satya Bhushan NVVS, Krishnan G. Versatility of the use of collagen membrane in oral cavity. *J Clin Diagn Res* 2016;10:ZC30-3.
- Wiesmann HP, Nazer N, Klatt C, Szuwart T, Meyer U. Bone tissue engineering by primary osteoblast-like cells in a monolayer system and 3-dimensional collagen gel. *J Oral Maxillofac Surg* 2003;61:1455-62.
- Chvapil M, Kronenthal L, Van Vinkle W Jr. Medical and surgical applications of collagen. *Int Rev Connect Tissue Res* 1973;6:1-61.
- Brett D. A review of collagen and collagen-based wound dressings. *Wounds* 2008;20:347-56.
- Veves A, Sheehan P, Pham HT. A randomized, controlled trial of promogran (a collagen/oxidized regenerated cellulose dressing) vs. standard treatment in the management of diabetic foot ulcers. *Arch Surg* 2002;137:822-7.
- Nataraj C, Ritter G, Dumas S, Helfer FD, Brunelle J, Sander TW. Extra cellular wound matrices: Novel stabilization and sterilization method for collagen-based biologic wound dressings. *Wounds* 2007;19:148-56.
- Park SN, Lee HJ, Lee KH, Suh H. Biological characterization of EDC-crosslinked collagen-hyaluronic acid matrix in dermal tissue restoration. *Biomaterials* 2003;24:1631-41.
- Nagata H, Ueki H, Moriguchi T. Fibronectin: localization in normal human skin, granulation tissue, hypertrophic scar, mature scar, progressive systemic sclerotic skin, and other fibrosing dermatoses. *Arch Dermatol* 1985;121:995-9.
- Motta G, Ratto GB, De Barbieri A, Corte G, Zardi L, Sacco A, Castagnola M. Can heterologous collagen enhance the granulation tissue growth? An experimental study. *Ital J Surg Sci* 1983;13:101-8.
- Shah JP, Johnson NW, Batsakis JG. Oral cancer. London: Taylor and Francis Group; 2003.
- Kramer IR, Lucas RB, Pindborg JJ, Sobin LH. World Health Organization Collaborating Center for oral precancerous lesions. Definition of leukoplakia and related lesions: an aid to studies on oral precancer. *Oral Surg Oral Med Oral Pathol* 1978;46:518-39.
- Rastogi S, Modi M, Sathian B. The efficacy of collagen membrane as a biodegradable wound dressing material for surgical defects of oral mucosa: a prospective study. *J Oral Maxillofac Surg* 2009;67:1600-6.
- Pradhan H, Gupta H, Sinha V, Gupta S, Shashikanth M. Two wound-covering materials in the surgical treatment of oral submucous fibrosis: a clinical comparison. *J Oral Biol Craniofac Res* 2012;2:10-4.
- Borle RM, Nimmonkar PV, Rajan R. Extended nasolabial flaps in the management of oral submucous fibrosis. *Br J Oral Maxillofac Surg* 2009;47:382-5.
- Rahman A, Packiaraj I, Genmorgana, Alagavelrajan, Kandasamy. Role of collagen membrane: a comprehensive review. *J Adv Med Dent Sci Res* 2015;3:95-7.
- Paramhans D, Mathur RK, Newaskar V, Shukla S, Sudrania MK. Role of collagen membrane for reconstruction of buccal defects following fibrotic band excision and coronoidectomy in oral submucous fibrosis. *MP Soc Otolaryngol Waent* 2010;3.
- Borle RM, Borle SR. Management of oral submucous fibrosis: a conservative approach. *J Oral Maxillofac Surg* 1991;49:788-91.
- Pillai R, Balaram P, Reddiar KS. Pathogenesis of oral submucous fibrosis: Relationship to risk factors associated with oral cancer. *Cancer* 1992;69:2011-20.
- Reddy YR, Srinath N, Nandakumar H, RajiniKanth M. Role of collagen impregnated with dexamethasone and placetrin in patients with oral submucous fibrosis. *J Maxillofac Oral Surg* 2012;11:166-70.
- Reus WF, Mathes SJ. Plastic Surgery: Principles and Practice. In: Jurkeiwicz MJ, Krizek TJ, Mathes SJ, Ariyan S, editors. Wound closure. St. Louis: Mosby; 1990. p. 20-2.

Blood lipid profiles following nonfocused ultrasonic treatment for noninvasive body contouring

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ABSTRACT

Aim: Blood lipid profiles changed following nonfocused ultrasound treatments for body contouring. The present study elucidates clinical effects of these devices on adipose tissue. **Methods:** Ultrasound treatments for 5 males and 5 females in a supine position, ages 37-67 years, were applied at 20 KHz and 3.0 W/cm² in modulated emission. Whole abdomen was treated by an ultrasound handpiece for 30 min followed by a 6-min lymphatic drainage. Waist circumferences at the level of the umbilicus and body weight were measured before and immediately after treatment. Blood lipid profiles including total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride (TG), nonesterified fatty acid (NEFA) and lipoprotein-a were measured at baseline, every 10 min during treatment, and 15, 30, 45, 60, 75, and 90 min after treatment completion. **Results:** NEFA showed statistically higher values after 10 min following treatment initiation. Subsequent values remained high despite some fluctuation, reaching a maximum at 90 min. In contrast, TG gradually decreased in concentration until the last measurement, especially for the first 30 min, with statistically significant reduction. Changes in other lipid profiles and lipoprotein-a were not significant. **Conclusion:** Changes in NEFA concentration were significant following ultrasound treatment, and suggest that metabolism of TGs stored within the adipocytes occurred immediately after treatment initiation.

Key words:

Noninvasive body contouring; MC1 device; nonfocused ultrasound; cavitation; blood lipid profiles

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INTRODUCTION

Nonsurgical body contouring devices, including cryolipolysis, low-level laser therapy, radiofrequency instruments, and external ultrasound devices, are widely used noninvasive procedures for body contouring and fat reduction. In a clinical environment, the most effective treatments for noninvasive fat reduction involve ultrasound, using either focused or nonfocused waves depending on how ultrasonic energy is delivered to the tissue.^[1-4]

The MC1 instrument (General Product S.r.l., Montespertoli, Italy) uses nonfocused ultrasound, and is designed to induce stable cavitation while reducing adipose tissue volume in treated tissue.^[2,5,6]

Despite its apparent clinical efficacy, biological mechanisms reducing adipose tissue are not fully understood. Adipose cell cavitation induced focal alterations of the plasma membrane and lipid leakage during *in vivo* porcine studies.^[5] Bani *et al.*^[6] reported that ultrasound cavitation induced a statistically significant reduction in the size of adipocytes, the appearance of micropores, and triglyceride (TG) leakage.

The primary objective of this study was to document blood lipid profile changes following nonfocused ultrasound treatments for body contouring, elucidating clinical and biochemical effects of these devices on adipose tissue.

METHODS

Device

The MC1 device consists of ultrasound and drainage handpieces. The ultrasound handpiece delivers a dualinclined nonfocused beam of 20 to 60 KHz on a 1 MHz carrier wave, capable of creating a weakly focused ultrasound field within subcutaneous fat tissue at the point where the beams overlap [Figure 1].

The draining handpiece is used during both pre- and post-treatments. The former is to open the main lymph nodes to facilitate the flow of excess fluids and facilitate their removal. The latter promotes immediate lymphatic drainage of treated areas, stimulating metabolic processes that lead to natural elimination of the fat waste.

Study objectives and methods

Five males and five females (37-67 years old) in supine position were exposed to ultrasound at 20 KHz and 3.0 W/cm² in modulated emission. Whole abdomens were treated by continuously moving an ultrasound handpiece for 30 min, followed by a 6-min lymphatic drainage.

Waist circumferences at the level of the umbilicus and body weight were measured before and immediately after treatment. Blood lipid profiles including total cholesterol, low-density lipoprotein, high-density lipoprotein (HDL), TG, nonesterified fatty acid (NEFA) and lipoprotein-a were analyzed at baseline, every 10 min during treatment, and 15, 30, 45, 60, 75, and 90 min after completion of treatment.

A paired *t*-test was performed for each group to determine the presence or absence of significant differences between baseline and post-treatment for weight, body mass index (BMI), and circumference reduction. Subjects provided written informed consent prior to participation in the study.

RESULTS

Ten subjects (5 males, 5 females) with an average age of 45



Figure 1: MC1 device. The MC1 device has an ultrasound and a zonal massage handpiece. The ultrasound handpiece with angled, nonfocused emitters deliver 1 MHz ultrasound. In modulated emission mode, the nonfocused beams create a slightly focused ultrasound field within the tissue at the point where the beams overlap

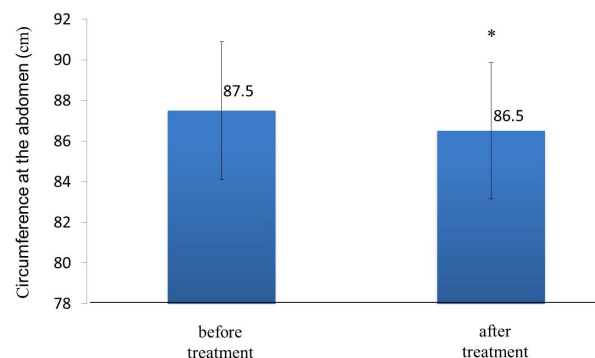


Figure 2: Summary of abdominal circumference. The circumference at the abdomen was significantly reduced (**P* < 0.003) from baseline measurements

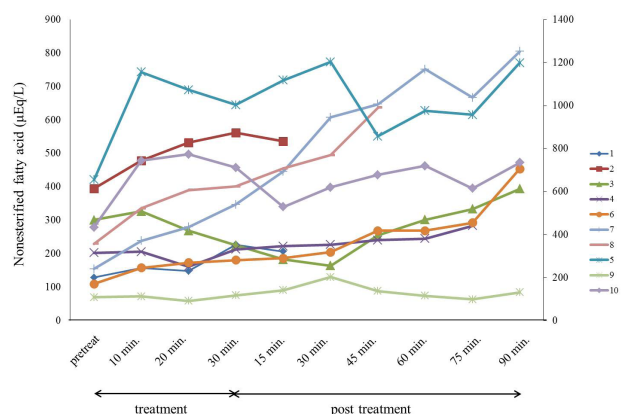


Figure 3: Blood NEFA changes in 10 subjects. Most subjects displayed increased blood NEFA levels from the early phase and had higher values at termination of the experiments. NEFA: nonesterified fatty acid

Table 1: Baseline data and post-treatment changes

	Weight (kg)	BMI (kg/cm ²)	Somatic fat rate (%)	Circumference at the abdomen (cm)
Before	70.95 ± 18.42	25.82 ± 3.49	27.99 ± 4.05	88.85 ± 10.73
After	70.75 ± 18.54	25.75 ± 3.51	27.99 ± 4.09	88.12 ± 10.58

The body weight, body mass index (BMI), and somatic fat rate showed slight decreases from the baseline, but they were statistically insignificant

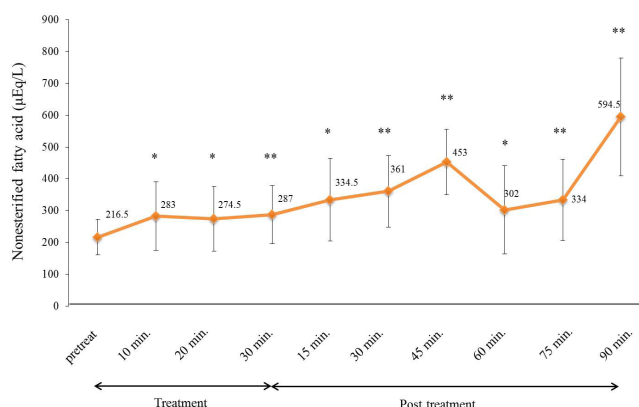


Figure 4: Summary of blood NEFA levels. Statistically significant increases from baseline NEFA were observed at any points during the study period, and showed the highest values at 90 min (* $P < 0.05$, ** $P < 0.02$). NEFA: nonesterified fatty acid

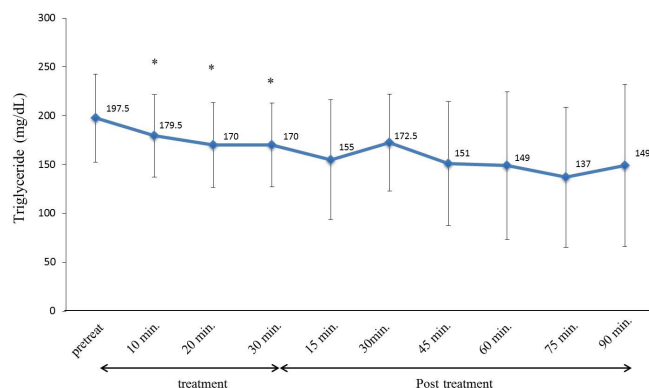


Figure 5: Summary of mean blood TG levels. TG levels up to 30 min from the beginning of the study were significantly lower, and continued to decline thereafter, albeit at a statistically insignificant level (* $P < 0.02$). TG: triglyceride

(range 37-68 years) and an average BMI of 25.8 (range 21.3-29.8 kg/cm²) were treated, with all subjects completing the treatments. Serial blood samples were obtained until 90 min after completion of the treatment from 6 subjects, until 75 min from 1 subject, until 45 min from 1 subject, and until 15 min from 2 subjects.

Circumference of the abdomen was significantly reduced ($P < 0.003$) from baseline measurements following treatment [Figure 2], whereas weight and BMI showed no statistically significant differences before and after treatment [Table 1].

While NEFA showed noticeable changes in most patients [Figure 3], other parameters did not predictably change. NEFA and TG were subsequently examined in greater detail since they appeared to have more pivotal roles in fat reduction for body contouring.

Although 2 subjects exhibited transient decreases in blood NEFA, the remaining 8 subjects demonstrated higher values at the 90 min drawing than at baseline, and concentrations

were significantly higher ($P < 0.05$) throughout the periods of measurement for this cohort [Figure 4].

TG conversely showed significantly lower values ($P < 0.02$) at 10, 20, and 30 min. A gradual decline persisted, but was not statistically significant [Figure 5].

DISCUSSION

The biological mechanisms of liporeductive effects following exposure to high-intensity focused ultrasound (HIFU) has been previously reported by many authors. HIFU, when focused within subcutaneous adipose tissue, raises the regional temperature resulting in coagulative necrosis and instantaneous cell death within the targeted area without damage to the surrounding tissue. Lipids are subsequently released from disrupted adipose tissue, and then cleared by fat metabolic pathways, and the lesion gradually heals.^[7,8] Almost all the disrupted adipocytes were resorbed within 18 weeks after treatment, resulting in an overall reduction in local fat volume without evidence of significant increases in plasma lipids.^[9] Jewell *et al.*^[10] reported that clinical laboratory tests did not reveal any abnormalities with regard to lipid profiles obtained before HIFU treatment, 1 h after treatment, and at weeks 1, 4, 8, and 12.

Brown *et al.*^[11] exploited another novel technology platform utilizing nonthermal focused ultrasound. The energy from the device was delivered as cavitation followed by mechanical destruction of cells. The term cavitation refers to a range of complex phenomena that involve the creation, oscillation, growth, and collapse of bubbles within a medium to subsequently produce mechanical energy. Little is known about the mechanism of action of nonfocused external ultrasound reducing adipose tissue.

Garcia and Schafer^[5] treated pigs with the MCI instrument and concluded that adipose tissue was reduced by ultrasound cavitation inducing focal alterations of the plasma membrane, and lipid leakage into interstitial space and lymphatic vessels without cell necrosis. The blood lipid profiles obtained prior to the treatments and approximately 25 to 30 min post-treatment did not show statistically significant changes in serum cholesterol, TG, or HDL.

Bani *et al.*^[6] concluded that lipid discharge from adipocytes was not accompanied by morphological signs of adipocyte death and disruption, or interstitial inflammation in both *ex vivo* and *in vivo* experiments; moreover, ultrasound-induced cavitation caused selective adipose cell reduction without injury to skin, vessels, nerves, or connective tissue.

Although both authors noted TG changes following ultrasonic cavitation, there was no reference to NEFA levels in blood samples. Plasma NEFA levels significantly increased

from baseline at all posttreatment times until 90 min after completion of the treatments.

Elevation of blood NEFA levels suggests that nonfocused ultrasound metabolized TG within fat cells to glycerol and NEFA, followed by release of NEFA into the blood stream through the lymphatic system. While lymphatic drainage manipulation might shift NEFA in the lymphatic system to adipose tissue via blood circulation, blood NEFA levels increased before application of lymphatic drainage procedures. Given the half-life of NEFA of 1.7-3.0 min, such shifts of NEFA from lymphatics to the blood circulation is unlikely to maintain the high levels of NEFA until 90 min after drainage. It might be possible for the TG in the blood vessels within the adipose tissue being a source; however, blood vessels in adipose tissues are sparse. It is more likely that the NEFA originated from the abundant TG in the adipocytes within the adipose tissue.

There is no definitive evidence that TG can be released into inter-cellular spaces due to increased permeability of adipocyte membranes, and then degraded to NEFA and glycerol-3-phosphate in transit to the blood stream. An alternative involves lipolysis activation within adipocytes resulting in elevation of blood NEFA. TG may be metabolized within adipocytes by ultrasonic stimulations, mimicking a photochemical mechanism. The body contouring mechanism of low-level laser treatment may involve activation of cyclic adenosine monophosphate in mitochondria within adipocytes, and subsequent activation of hormone-sensitive lipases resulting in metabolism of TG in adipocytes.^[12,13]

The current study suggests nonfocused ultrasound metabolizes TGs immediately after treatment, but it is unclear whether this involves intra- or extra-cellular spaces of adipocytes. Since there was no control group in the current study, but given the short half-life of NEFA, the significant elevation of blood NEFA must be due to the effects of activated lipolysis within the adipose tissue induced by ultrasound-induced cavitation.

Given the paucity of clinical or biochemical evidence for mechanisms of nonfocused ultrasound reduction of adipose

tissue, further study in this field is warranted.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Mulholland RS, Paul MD, Chalfoun C. Noninvasive body contouring with radiofrequency, ultrasound, cryolipolysis, and low-level laser therapy. *Clin Plast Surg* 2011;38:503-20.
- Honda T, Suzuki T, Tanaka I, Goto H, Kure K, Hishiyama J, Isago T. Clinical analysis of noninvasive body contouring by nonfocused ultrasound device. *J JSAPS* 2014;3:10-20. (in Japanese)
- Teitelbaum SA, Burns JL, Kubota J, Matsuda H, Otto MJ, Shirakabe Y, Suzuki Y, Brown SA. Noninvasive body contouring by focused ultrasound: safety and efficacy of the Contour I device in a multicenter, controlled, clinical study. *Plast Reconstr Surg* 2007;120:779-89.
- Jewell ML, Solish NJ, Desilets CS. Noninvasive body sculpting technologies with an emphasis on high-intensity focused ultrasound. *Aesth Plast Surg* 2011;35:901-12.
- Garcia O, Schafer M. The effects of nonfocused external ultrasound on tissue temperature and adipocyte morphology. *Aesthetic Surg J* 2013;33:117-27.
- Bani D, Quattrini A, Freschi G, Russo GL. Histological and ultrastructural effects of ultrasound-induced cavitation on human skin adipose tissue. *Plast Reconstr Surg Glob Open* 2013;1:e41.
- Haar GT, Coussios C. High intensity focused ultrasound: physical principle and devices. *Int J Hyperthermia* 2007;23:89-104.
- Gadsden E, Aguilar MT, Smoller BR, Jewell ML. Evaluation of a novel high-intensity focused ultrasound device for ablating subcutaneous adipose tissue for noninvasive body contouring: safety studies in human volunteers. *Aesthetic Surg J* 2011;31:401-10.
- Fatemi A. High-intensity focused ultrasound effectively reduced adipose tissue. *Semin Cutan Med Surg* 2009;28:257-62.
- Jewell ML, Baxter RA, Cox SE, Donofrio LM, Dover JS, Glogau RG, Kane MA, Weiss RA, Martin P, Schlessinger J. Randomized sham-controlled trial to evaluate the safety and effectiveness of a high-intensity focused ultrasound device for noninvasive body sculpting. *Plast Reconstr Surg* 2011;128:253-62.
- Brown SA, Greenbaum L, Shtukmaster S, Zadok Y, Ben-Ezra S, Kushkuley L. Characterization of nonthermal focused ultrasound for noninvasive selective fat cell disruption (lysis): technical and preclinical assessment. *Plast Reconstr Surg* 2009;124:92-101.
- Avci P, Nyame TT, Gupta GK, Sadasivam M, Hamblin MR. Low-level laser therapy for fat layer reduction: a comprehensive review. *Lasers Surg Med* 2013;45:349-57.
- McRae E, Boris J. Independent evaluation of low-level laser therapy at 635 nm for non-invasive body contouring of the waist, hips, thighs. *Lasers Surg Med* 2013;45:1-7.

Self-esteem and rhinoplasty: a case-control study

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ABSTRACT

Aim: Self-esteem is one's attitude towards oneself. It is one of the most important psychological aspects of rhinoplasty, a common aesthetic operation. Prior studies have indicated an improvement in patients' self-esteem after this operation. The aim of current study was to preoperatively compare self-esteem in patients seeking aesthetic rhinoplasty with that of functional rhinoplasty patients. **Methods:** A total of 42 patients completed the validated Rosenberg Self-Esteem Scale preoperatively (21 aesthetic surgery patients and 21 functional surgery patients). Those with both aesthetic and functional purposes were categorized regarding their primary objective. The *t*-test for independent groups was used for analysis of the data, and Cohen's *d* was calculated as a measure of effect size. **Results:** The mean level of self-esteem in the aesthetic surgery group was significantly lower than that of the functional surgery group ($P < 0.05$). Age, gender, socio-economic status, and educational backgrounds were analyzed and comparative analysis of each showed no significant difference between the two groups. The value of effect size measure was very high ($d = 1.04$). **Conclusion:** The findings of the present study showed that aesthetic rhinoplasty patients had lower self-esteem in comparison with functional rhinoplasty patients.

Key words:

Cosmetic surgery; aesthetic rhinoplasty; functional rhinoplasty; self-esteem

INTRODUCTION

Beauty is admired by everyone, and facial beauty is the most important component of beauty among humans. Several studies have suggested that the perception of facial attractiveness is relatively independent of culture.^[1,2] Attractive faces activate reward centers in the brain,^[3] motivate sexual behavior and the development of same-

sex alliances,^[4,5] and elicit positive treatment in various settings.^[6] As a result, it is not surprising that philosophers and scientists have long puzzled over what makes a face more attractive and why we have specific preferences.^[7]


The nose plays a significant role in facial beauty.^[8] Awareness of its role in facial beauty and the emphasis on beauty by

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mass media have made aesthetic rhinoplasty one of the most frequently requested aesthetic operations worldwide. Aesthetic rhinoplasty carries tremendous potential for contouring, improving harmony, and improving the proportions of a patient's facial aesthetics, but patients occasionally demand too much of the rhinoplasty procedure.

Aesthetic plastic surgery deals with the psychosocial problems of patients in addition to their medical condition. In the past several decades, researchers have begun to explore the psychology underlying cosmetic surgeries. This aspect of cosmetic surgeries has two major aspects, the surgeons' viewpoints and the patients' points of view. The opinions of surgeons on this subject vary and have not been studied comprehensively. For patients, the strongest motivation for undergoing cosmetic surgery is body dissatisfaction, as their physical appearance constitutes an important part of their self-esteem.^[9] Body image refers to the way people perceive their bodily appearance^[10] and consists of several components. Sarwer *et al.*^[11] introduced a theoretical model of the association between body image and aesthetic surgery in which the two basic parts of body image, valence and body image value, play a crucial role.^[12] Body image valence refers to the importance of body image to one's self-esteem, whereas body image value describes the extent to which one is satisfied with her/his physical appearance. According to this model, those whose self-esteem highly depends on their appearance and those who have significant body dissatisfaction levels will consider cosmetic surgery.

Self-esteem is one of the psychological aspects of aesthetic surgery which has received increased attention in the past few decades.^[13] Self-esteem refers to how much people value or accept themselves for whom and what they are. It has also been defined as one's attitude towards oneself or one's opinion or evaluation of oneself, which may be positive, neutral, or negative.^[14] It has been shown that satisfaction with one's own appearance (positive body image) and self-esteem are relatively strongly correlated, especially in women.^[15]

Empirical studies support the notion that aesthetic rhinoplasty patients show low levels of self-esteem.^[16,17] This study aimed to compare the mean score of self-esteem between aesthetic rhinoplasty candidates as cases and functional rhinoplasty patients as the control group.

METHODS

Participants

A total of 42 surgical patients (28 females and 14 males) were recruited for this study using the convenience sampling method from a surgical clinic in Tehran, Iran. All patients had been scheduled to undergo plastic surgery in winter 2012. Approval from the ethics committee of the Rhinology Research Society and Tehran University of Medical Sciences and informed consent were obtained. Twenty-one patients who needed functional rhinoplasty surgery were recruited as the control group while 21 cases of aesthetic rhinoplasty were included as the study group. The deformities included:

dorsal hump, supratip nasal deformity, septal deviation, and dorsal irregularities. No congenital deformities were present in the cases. Secondary rhinoplasty patients were excluded given the greater risk of issues with self-esteem and body image. Those with both functional and aesthetic complaints ($n = 7$) were asked about their main objective and were categorized accordingly.

Measures

Demographics

A questionnaire consisting of information about the patient's age, gender, marital status, educational background, and subjective socio-economic status (SES) was used as the demographic questionnaire.

Rosenberg Self-Esteem Scale

Global self-esteem was measured by the Rosenberg Self-Esteem Scale^[18] which contains 10 items to be scored on a four-point Likert scale. Higher scores correspond to more positive levels of self-esteem. Scores can range between 10 and 40, with scores below 21 indicating low self-esteem.^[19] Response options were provided ranging from "strongly disagree" to "strongly agree" and were coded from 1 to 4. Therefore, the maximum and minimum scores were 40 and 10 respectively. Cronbach's alpha in the current study was 0.86.

Procedure

All participants from both groups completed the questionnaires preoperatively. Informed consent letters were also collected prior to administration of tests.

Statistical analysis

Data entry and analysis were performed in a blinded fashion by personnel who were not involved in the process of data collection. All tests were 1-tailed due to the hypothesis and $P < 0.05$ was considered statistically significant. Additionally, Levene's test was performed for assessment of equality of variances. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) software.

RESULTS

Twenty-one patients seeking aesthetic rhinoplasty and 21 patients seeking functional rhinoplasty participated in this study. The mean age in the functional rhinoplasty group was 27.48 years ($SD = 10.40$) and that of the aesthetic rhinoplasty group was 25.57 years ($SD = 7.06$). No significant difference was observed between means ($P > 0.05$). The demographic information is summarized in Table 1.

Using the *t*-test for independent groups, analysis of the data demonstrated that the mean self-esteem score in the aesthetic surgery group was significantly lower than that of the functional surgery group ($P < 0.01$). Age, gender, SES, and educational backgrounds were analyzed and no significant differences were found between the two groups ($P > 0.05$). Moreover, the Levene's test for equality of variances was not significant ($P > 0.05$). Independent *t*-test details are presented in Table 2.

Table 1. Demographic characteristics of cases and controls

Characteristics	Aesthetic rhinoplasty patients	Functional rhinoplasty patients
n (%)	21 (50%)	21 (50%)
Mean age	25.27	27.48
Gender		
Male	5	9
Female	16	12
Marital status		
Single	11	14
Married	9	6
Separated	1	1
Educational level		
Low	9	8
Medium	11	12
High	1	1
Socio-Economic Status		
Low	2	3
Medium	15	15
High	4	3

Table 2. Independent t-test details between aesthetic and functional groups

Group	Mean	SD	t-test statistic	P value	Cohen's d
Aesthetic	29.667	3.954	3.911	$P < 0.01$	1.04
Functional	34.095	3.360			

DISCUSSION

The objective of this study was to compare self-esteem between candidates applying for aesthetic rhinoplasty and patients seeking functional nasal surgery. Both groups were evaluated for other variables including age, gender, SES, and education, and no significant differences were found.

Findings from statistical analyses suggest that cosmetic rhinoplasty candidates have lower levels of self-esteem in comparison with functional patients. Results are consistent with prior studies suggesting that aesthetic rhinoplasty patients have lower scores in self-esteem and body-image measures.^[16,17] It has also been reported that women with higher self-esteem have less interest in cosmetic surgery, and that a negative body-image is associated with lower self-esteem.^[9] Results of the present study are in line with these findings. The magnitude of effect size in the present study shows that there is a clinically meaningful difference in self-esteem between aesthetic rhinoplasty patients and functional rhinoplasty patients.

The findings of the present study are limited to behavioral manifestations prior to surgery. Other studies have evaluated the long-term outcomes of cosmetic surgery, and have demonstrated that aesthetic surgery can statistically improve self-esteem, depression, and anxiety.^[20] However, only a small effect size ($d = 0.15$) has been reported for an improvement in self-esteem prior to and 6 months after aesthetic surgery.^[21] Other psychological variables including depression and anxiety have also shown improvement following aesthetic surgery.^[22] The findings of the current study are consistent with another study which reported high scores of depression among aesthetic rhinoplasty

patients.^[23,24] This study also supports the notion that an interest in aesthetic rhinoplasty is associated with a negative body image.^[25]

The present study shows that aesthetic rhinoplasty patients are more likely to have low levels of self-esteem. Some limitations of the study are worth noting. First, the utilized instrument could have been more comprehensive by including more aspects of self-esteem. Second, two patients in the aesthetic group showed extremely low levels of self-esteem, which lowered this group's mean score. It is recommended for future research to evaluate the differences using various psychometric instruments by more accurate sampling methods.

In conclusion, the current findings indicate that evaluation of the psychological condition of aesthetic rhinoplasty candidates is of great value. Therefore, cosmetic surgeons might screen patients with psychometric instruments^[26] and/or consider cooperating with psychologists. Moreover, cosmetic surgeons can gain skills to recognize potential psychologically problematic patients. In this respect, it is crucial for cosmetic surgeons to be familiar with the psychology of cosmetic surgery and related disorders.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Cunningham MR, Roberts AR, Barbee AP, Druen PB, Wu CH. Their ideas of beauty are, on the whole, the same as ours: consistency and variability in the crosscultural perception of female physical attractiveness. *J Personal Soc Psychol* 1995;68:261-79.
2. Langlois JH, Kalakanis L, Rubenstein AJ, Larson A, Hallam M, Smoot M. Maxims or myths of beauty? A meta-analytic and theoretical review. *Psychol Bull* 2000;126:390-423.
3. Aharon I, Etcoff NL, Ariely D, Chabris CF, O'Connor E, Breiter HC. Beautiful faces have variable reward value: fMRI and behavioral evidence.

- Neuron 2001;32:537-51.
4. Berscheid E, Reis HT. Attraction and close relationships. In: Gilbert DT, Fiske ST, Lindzey G, editors. *The Handbook of Social Psychology*. 4th ed. Oxford: Oxford University Press; 1998. p. 193-281.
5. Rhodes G, Simmons L, Peters M. Attractiveness and sexual behaviour: does attractiveness enhance mating success? *Evol Hum Behav* 2005;26:186-201.
6. Hosoda M, Stone-Romero EF, Coats G. The effects of physical attractiveness on job related outcomes: a meta-analysis of experimental studies. *Pers Psychol* 2003;56:431-62.
7. Etcoff N. *Survival of the Prettiest: The Science of Beauty*. New York: Anchor/Doubleday; 1999.
8. Amodeo CA. The central role of the nose in the face and the psyche: review of the nose and the psyche. *Aesthet Plast Surg* 2007;31:406-10.
9. Sarwer DB, Wadden TA, Pertschuk MJ, Whitaker LA. The psychology of cosmetic surgery: a review and conceptualization. *Clin Psychol Rev* 1998;18:1-22.
10. Cash TF. Body image: past, present, and future. *Body Image* 2004;1:1-5.
11. Sarwer DB, Whitaker LA, Pertschuk MJ, Wadden TA. Body image concerns of reconstructive surgery patients: an underrecognized problem. *Ann Plast Surg* 1998;40:403-7.
12. Cash TF, Pruzinsky T. *Body image: a handbook of theory, research and clinical practice*. New York, NY: The Guilford Press; 2002.
13. Figueroa C. Self-esteem and cosmetic surgery: is there a relationship between the two? *Plast Surg Nurs* 2003;23:21-4.
14. Colman AM. *Oxford dictionary of psychology*. Oxford: Oxford University Press; 2009.
15. Feingold A. Good-looking people are not what we think. *Psychol Bull* 1992;111:304-41.
16. Phillips KA, Pinto A, Jain S. Self-esteem in body dysmorphic disorder. *Body Image* 2004;1:385-90.
17. Pecorari G, Gramaglia C, Garzaro M, Abbate-Daga G, Cavallo GP, Giordano C, Fassino S. Self-esteem and personality in subjects with and without body dysmorphic disorder traits undergoing cosmetic rhinoplasty: preliminary data. *J Plast Reconstr Aesthet Surg* 2010;63:493-8.
18. Rosenberg M. *Society and the adolescent self-image*. Princeton, NJ: Princeton University Press; 1965.
19. Rosenberg M. *Conceiving the self*. New York: Basic Books, Inc.; 1979.
20. Moss TP, Harris DL. Psychological change after aesthetic plastic surgery: a prospective controlled outcome study. *Psychol Health Med* 2009;14:567-72.
21. Von Soest T, Kvalem IL, Roald HE, Skolleborg KC. The effects of cosmetic surgery on body image, self-esteem, and psychological problems. *J Plast Reconstr Aesthet Surg* 2009;62:1238-44.
22. Sarwer DB, Gibbons LM, Magee L, Baker JL, Casas LA, Glat PM, Young VL. A prospective, multi-site investigation of patient satisfaction and psychosocial status following cosmetic surgery. *Aesthet Surg J* 2005;25:263-9.
23. Naraghi M, Atari M. Comparison of patterns of psychopathology in aesthetic rhinoplasty patients versus functional rhinoplasty patients. *Otolaryngol Head Neck Surg* 2015;152:244-9.
24. Naraghi M, Atari M. A comparison of depression scores between aesthetic and functional rhinoplasty patients. *Asian J Psychiatr* 2015;14:28-30.
25. Atari M, Akbari-Zardkhaneh S, Mohammadi L, Soufiabadi M. The factor structure and psychometric properties of the Persian version of body appreciation scale. *Am J Appl Psychol* 2015;3:62-6.
26. Wildgoose P, Scott A, Pusic AL, Cano S, Klassen AF. Psychological screening measures for cosmetic plastic surgery patients: a systematic review. *Aesthet Surg J* 2013;33:152-9.

The forehead flap: a valuable option in resource depleted environment

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ABSTRACT

Aim: Reconstruction of orofacial soft tissue defect is often challenging and this is more difficult in resource challenged environment. This retrospective study highlights our experience with the use of forehead flap to overcome some of the challenges of orofacial reconstruction in a resource depleted environment. **Methods:** A 23-year retrospective analysis of all patients who had orofacial defect reconstruction using forehead flap in our department was undertaken. Information was sourced from patient's case notes and operating theatre records. Data was analyzed using Statistical Package for Social Sciences (SPSS) version 16 (SPSS Inc., Chicago, IL, USA) and Microsoft Excel 2007 (Microsoft, Redmond, WA, USA). **Results:** A total of 43 patients were managed within the period reviewed and consisted of 31 (72.1%) males and 12 (27.9%) females. Trauma 24 (55.8%) accounted for most defect and the lip was the commonest site of defect. Complete forehead flap was used in 31 (72.1%) of cases and when timing of defect repair is considered, delayed reconstruction was the preferred method. Postoperative complications was observed in 8 (18.6%) patients and consisted of failed flap in 2 (25.0%) patients, tumor recurrence in reconstructed site in 2 (25.0%) patients and tumor occurrence in forehead flap donor site in 1 (12.5%) patient. **Conclusion:** The forehead flap remains a reliable option in orofacial soft tissue defect reconstruction. It is easy to raise and can provide coverage for wide defects as far as the paramandibular and submandibular regions. Moreover, it does not require patient repositioning.

Key words:

Orofacial; soft tissue defect; forehead flap; delayed reconstruction

INTRODUCTION

Tissues in the orofacial region contribute significantly to the functional, aesthetic and psychological wellbeing of an individual.^[1,2] Similarly, individuals place a high value on facial

aesthetics such that alterations in facial appearance may cause severe disability, psychological morbidity, and huge economic loss to the victim(s).^[3] Defects in the orofacial region may involve

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soft tissues, hard tissues or a combination of both and may be congenital or acquired in origin.^[4] Congenital defects include cleft lip/palate, maxillary and mandibular hypoplasia. Acquired defects may result from trauma, surgery or infections. Generally, the main etiological factor in acquired orofacial defects varies from one environment to another.

Reconstruction of orofacial tissue defects may be undertaken as an immediate or delayed procedure. Traditionally, the reconstructive ladder approach has been advocated in soft tissue defect reconstruction and this allows a stepwise option from the simplest to the most complex procedures. These procedures are healing by secondary intention, primary closure, skin grafting and use of local, regional and free flaps techniques. However, recently the concept of reconstructive escalator or elevator has been advocated since reconstruction should be individualized to each patient and not based on a rigid approach.^[5,6]

Despite advances in soft tissue reconstruction using free flaps, pedicle flaps are still relevant in functional and aesthetic rehabilitation of patients.^[7] Free flaps provide enough volume of tissue for reconstruction; they are more resistant to radiation injury (which is important cancer patients requiring radiotherapy); allow for unrestricted flap repositioning, and achieve optimal reconstruction with resultant reduction in the cost and morbidity often associated with repeat surgeries due to failure of suboptimal reconstructions using locoregional flaps.^[8] However, use of free flaps is technique sensitive, involves prolong procedure, require extensive postoperative monitoring, may be relatively contraindicated in some patients with co-morbid conditions, and there may be aesthetic problems such as flap bulkiness, colour and texture mismatch.^[9,10] Locoregional flaps have reduced vulnerability to infection and thrombosis; they are much easier to raise and transfer when compared to free flaps, and usually provide excellent colour match. Limited reach of locoregional flaps, difficulty in achieving three-dimensional reconstruction or cover extensive tissue defects, and occasional need for multistage procedure are some of its limitations.^[11] Moreover, locoregional flaps frequently have complications in irradiated fields and may require specific patient positioning to raise.^[9]

In current practice, locoregional flaps are still important for head and neck reconstruction in environment where microvascular free tissue transfer is not feasible. In technologically developed environment, they are used as rescue flaps following free flap failure and in patients with relative contraindications for free flap transfer such as the presence of co-morbid medical conditions.^[12]

The forehead region over the years has remained the best donor site for nasal reconstruction, having the advantage of textural, thickness and colour match.^[13] Different types of forehead flaps with axial or random pattern blood supply have been described.^[14] The aim of this study therefore is to review the use of forehead flap in orofacial reconstruction, highlighting our experience in the management of forty-three cases.

METHODS

All patients who had orofacial reconstruction using forehead flap at a regional teaching hospital from April 1991 to June 2014 were

retrospectively studied. Information was sourced from patient's case notes and operating theatre register. Information retrieved included age, gender, indication for surgical reconstruction, type of forehead flap, duration of hospital stay and complications. All patients agree with this publication and use of photographs.

Preoperative planning

The superficial temporal artery was assessed preoperatively by palpatory method only. This involved the identification of its outline and feeling the strength of its pulsation. The position of other axial vessels of the forehead was planned based on established anatomical guidelines. Presence of significant scars along established axial vessels of the forehead which may indicate vascular compromise were also excluded. Patients for complete forehead flap raising were instructed to shave their hair but preserve the hairline.

Surgical procedure

Reconstruction was carried out as a two or three (if debulking is necessary) stage procedure involving initial flap raising and transfer, followed by flap division usually after a period of three weeks, and finally debulking of the reconstructed site. When complete forehead flap was raised, split thickness skin graft from the thigh was used to cover the flap donor site either intraoperatively or 24-48 h postoperatively (to reduce operating time or allow for adequate hemostasis) on the dental chair, secured with sutures and a pressure dressing applied on the forehead to prevent hematoma collection under the skin graft.

The critical aspect in successfully raising a complete forehead flap is the plane of dissection close to its base to avoid damage to the nutrient vessels. The key is to initially raise the flap supraperiosteally from one end of the forehead until the temporalis fascia is encountered on the contralateral side. Once the temporalis fascia is encountered on the contralateral side, dissection with scissors should follow a connective tissue plane above the fascia to preserve the nutrient vessels of the flap.

Classification

Forehead flap was classified as either complete (if the whole forehead tissue between hairline and supraorbital rim was mobilized from a point perpendicular to the lateral canthal region on one side to the corresponding point or beyond on the contralateral side) or partial (if only a part of the forehead tissue was mobilized), while timing of flap division was classified as early (less than 16 days), conventional (between 16-28 days) or delayed (greater than 28 days). Reconstruction was classified as immediate (if done within 24 h following defect formation) or delayed (if done after 24 h following defect formation), and two stage (initial flap raising and flap division later) or three stage (initial flap raising, flap division and secondary debulking of recipient site).

Data retrieved was analyzed using Statistical Package for Social Sciences (SPSS) version 16 and Microsoft Office Excel 2007. Findings from descriptive statistics were represented in the form of graphs, tables and charts.

Table 1: Site of orofacial defect

Site	Frequency
Lip	15
Nose	13
Cheek	9
Eyelid	7
Perimandibular/submandibular region	3

Table 2: Timing of forehead flap division in 19 patients

Time of flap division	Number of patients
Less than 16 days	-
16-28 days	8
Greater than 28 days	11

Table 3: Complications noted following use of forehead flap

Complication	Frequency
Total flap failure	2
Epidemolysis	1
Infection	4
Tumor recurrence in flap recipient site	2
Tumor occurrence in flap donor site	1

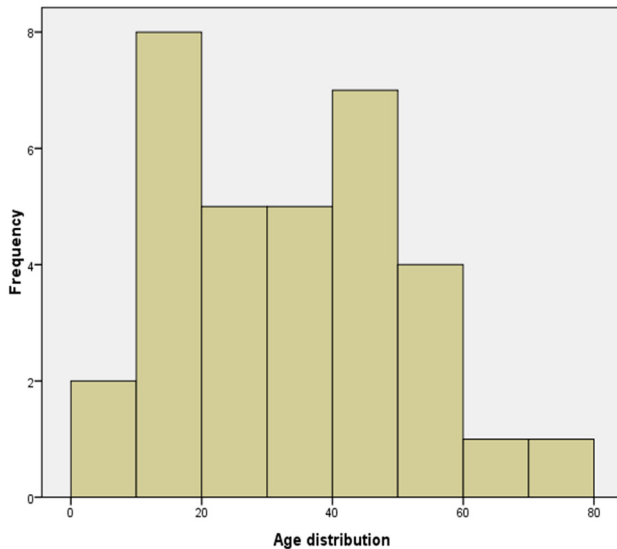


Figure 1: Age distribution

RESULTS

A total of 43 patients had orofacial reconstruction using forehead flap under general anesthesia within the period reviewed and this consisted of 31 (72.1%) males and 12 (27.9%) females, giving a male to female ratio of 2.6:1. Patients' ages ranged from 4 to 75 years [Figure 1] with a mean of 33.9 ± 16.3 years. The aetiology of soft tissue defect was trauma in 24 (55.8%) cases, tumor resection in 13 (30.2%) cases, and infection in 6 (14.0%) cases [Figure 2]. Road traffic crashes accounted for 11 (45.8%) of 24 cases of trauma associated soft tissue defects, while malignant tumor excision accounted for 11 (84.6%) of 13 cases associated with tumor excision. All soft tissue defects arising from orofacial infection were as a result of cancrum oris. When site of defect is considered, the lip 15 (31.91%) had the highest frequency [Table 1].

Complete forehead flap was used in 31 (72.1%) of cases while

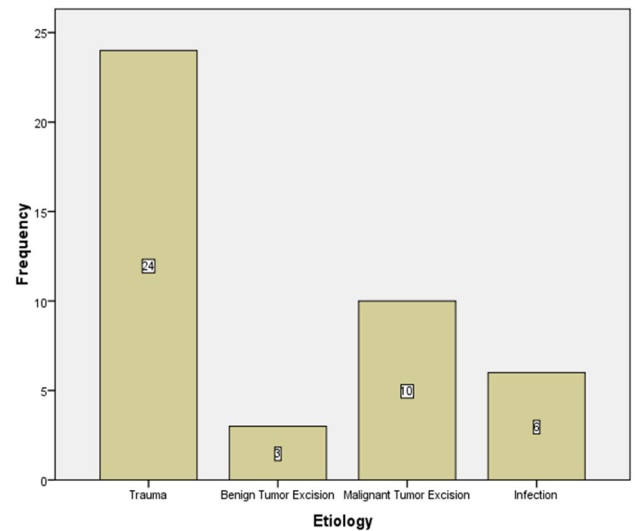


Figure 2: Etiology of orofacial defect

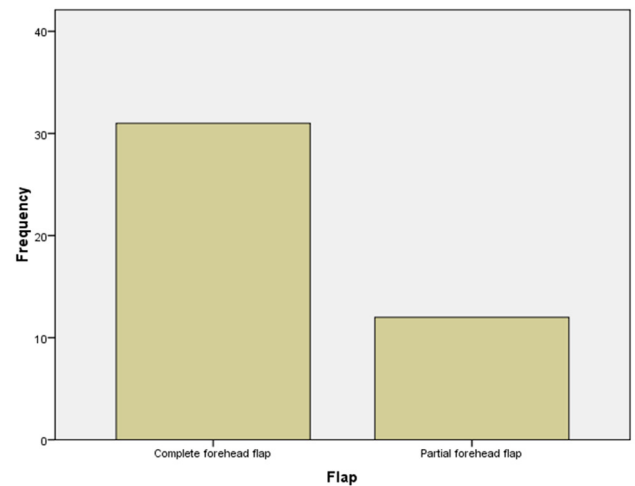


Figure 3: Types of forehead flap used

partial forehead flap was used in the remaining 12 (27.9%) cases [Figure 3]. Immediate soft tissue reconstruction was performed in 7 (16.3%) cases and all were secondary to tumor excision. The remaining 36 (83.7%) patients had delayed reconstruction. Timing of flap division was documented only in 19 (44.2%) of the 43 patients reviewed and this ranged from 20 to 65 days with a mean of 35.8 ± 11.9 days. Of these, 11 (57.9%) had delayed flap division, 8 (42.1%) had conventional flap division. No patient had early division [Table 2]. All flaps were divided under general anesthesia.

Of the 43 patients reviewed, 23 had documentation on the duration of hospital stay and this ranged from 19 to 146 days with a mean of 66.9 ± 31.0 days. Postoperative complications [Table 3] was observed in 8 (18.6%) patients and consisted of failed flap in 2 (25.0%) patients, tumor recurrence in reconstructed site in 2 (25.0%) patients and tumor occurrence in forehead flap donor site in 1 (12.5%) patient.

DISCUSSION

Axial pattern forehead flaps include both partial (such as median, para-median and lateral) and complete flaps. These flaps are

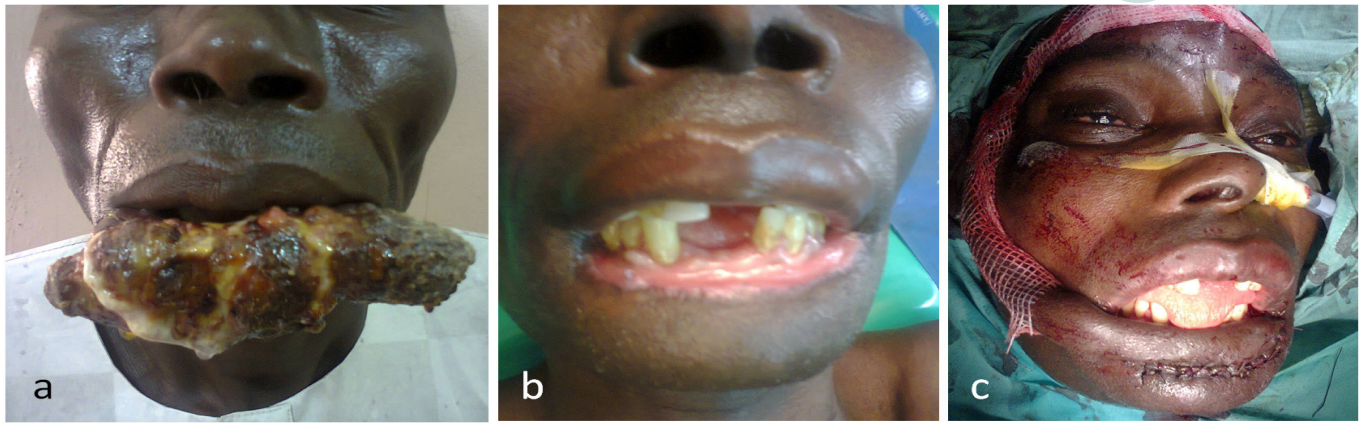


Figure 4: Forehead flap reconstruction of lower lip defect post squamous cell carcinoma excision. (a) Preoperative view; (b) delayed reconstruction to ensure tumour free margins; (c) forehead flap reconstruction

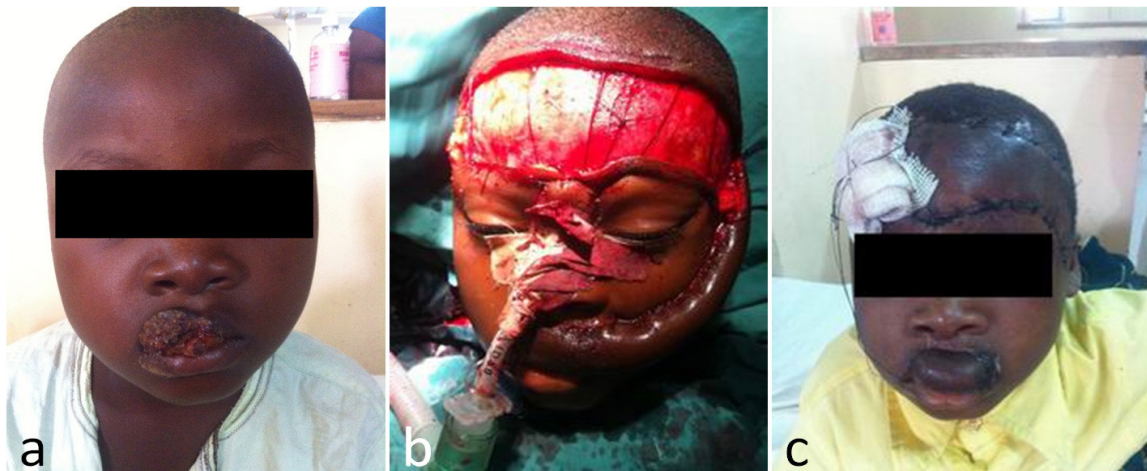


Figure 5: Forehead flap reconstruction of upper lip defect post squamous cell carcinoma excision. (a) Preoperative view; (b) immediate forehead flap reconstruction; (c) patient prior to flap debulking

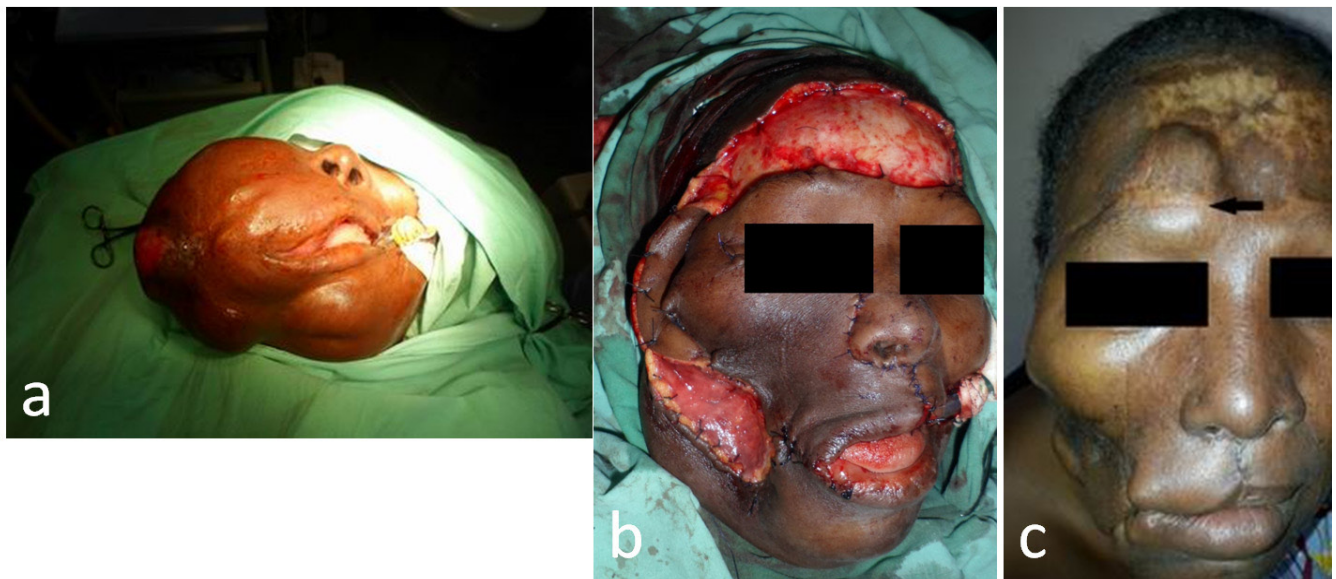


Figure 6: Tumour occurrence in forehead flap donor site. (a) Preoperative view of patient with mucoepidermoid carcinoma of the cheek; (b) tumour excision and immediate forehead flap reconstruction; (c) tumour occurrence in forehead (black arrow) 1 year postoperative

raised with the patient in supine position, thus eliminating the need to reposition and redrape patient as obtainable with other flaps such as the latissimus dorsi.

Majority (72.1%) of patients reconstructed in the present

study were males. Males in our environment are generally less concerned with aesthetics when compared to females. It is likely that these male patients were motivated as a result of functional limitations such as speech and feeding rather than aesthetics. The age of the patients ranged from 4-75 years

and this highlight the wide range of patient age group that can be successfully reconstructed using this flap. Healing is usually excellent in children following use of forehead flap and this has been attributed to the non sebaceous quality of their forehead skin.^[15]

Trauma (mainly road traffic crash) was the main aetiological factor for orofacial defect, followed by neoplasia. Delayed reconstruction was used in most patients and this may be related to the aetiological factors. Most road traffic crash soft tissue injuries in our environment present as class III or IV surgical wounds and require meticulous wound care to become clean before reconstruction can be undertaken. This fact has been highlighted in studies from this environment.^[16,17]

Complete forehead flap was the most common type of flap used, accounting for 72.1% of all forehead flaps in our study. This is in contrast to other studies^[18,19] that reported partial forehead flaps as the most common type used. This difference may be related to the site [Table 3] and size of the soft tissue defect. About 57.4% of orofacial defects in our study were in the lower third and inferior half of the middle-third of the face [Figures 4 and 5]. Thus, the need for increased flap width and length to enable a wider arc of rotation in addition to adequate defect coverage favored our use of complete forehead flap. From our experience, the flap can be used to cover defects as low as the inferior border of the mandible and can provide tissue for both internal (mucosal) lining and external (skin) cover when folded along its long axis. The complete forehead flap is based on the frontal branch of the superficial temporal artery (FBSTA). The FBSTA enters the forehead at varying transverse levels at the lateral orbital rim vertical plane and anastomose with the supraorbital and supratrochlear arteries on one side, and the FBSTA on the contralateral side. However, in 74% of cases, the FBSTA entered the forehead at the junction between the middle and inferior transverse thirds of the forehead.^[14]

Of the partial forehead flaps, the median forehead flap which is based on supratrochlear artery bilaterally and the angular artery, offers the shortest distance of rotation. In contrast, the paramedian flap which is based on the supratrochlear artery on one side with contributions from the angular and supraorbital artery (depending on the width of the flap) offers a wider arc of rotation and thus increased cover of the defect.^[14]

With regard to the timing of flap division, majority of the cases had delayed flap division (greater than 28 days). This is in contrast to other reports^[13,20] in which the flap was divided at 3 weeks or less. Factors responsible for the long waiting period prior to flap division noted in this study include; inability of patients to pay for flap division procedure, inadequate operating slots and disruption of medical services by health workers as a result of industrial disputes. Traditionally, forehead flaps are divided 3 weeks post transfer. During this period, patient experience some discomfort such partial obstruction of vision or an inability to use prescribed eye glasses due to bulging of the flap trunk.^[21] To shorten this period, different technique both in animal models and human subjects have been suggested and these include ischemic preconditioning, use of hyperbaric oxygen, perfusion fluorometry, laser Doppler flowmetry and near-infrared laser angiography.^[22-26] Early division of forehead flaps as at 4-6 days

has been documented with minimal complications. However, it is recommended that early flap division should not be undertaken in active smokers and in patients with bleeding disorders to avoid complications.^[21,27]

Documented disadvantages of the forehead flap include facial disfiguring and bulkiness of flap. Complications noted in this study are shown in Table 3. Infective complications were observed only in patients who were reconstructed using complete forehead flap. This increased tendency for infection with complete forehead flap may be related to the large surface area of the flap exposed.

Total flap failure was recorded in 2 cases (1 complete and 1 partial forehead flap). Failure of the median forehead flap occurred post division despite a timing period of 36 days prior to division. It is likely that excessive pressure was applied to the distal part of the flap during division or the patient had some underlying systemic abnormalities. Tumor occurrence at the donor [Figure 6] site one year after complete forehead flap division was documented in 1 case with mucoepidermoid carcinoma. The main presentation was swelling in the region of the forehead tissue that was previously returned back to the donor site following flap division. This was confirmed histologically to be mucoepidermoid carcinoma. Occurrence of tumor in flap donor site has been previously documented in the pectoralis major myocutaneous and deltopectoral flap donor sites.^[28,29]

To the best of our knowledge, this is the first report of tumor occurrence in the forehead flap donor site. Two mechanisms are possible: implantation of tumor cells in the donor site during flap raising, and invasion of the distal end of pedicle flap by residual tumor cells in the recipient site which are subsequently transferred to the donor site following flap division. The possibility of this occurrence without the knowledge of the surgeon is further increased by the absence of frozen section technique in our environment to determine tumor free margins. Measures to decrease this avoidable and devastating complication such as the use of different sets of gloves, gowns and instruments from those used for tumor excision have been highlighted in some studies.^[30] In addition, we recommend that where available, frozen section of the distal end of pedicle flaps should be obtained after flap division before returning it to the donor site. During follow-up review, attention should not be focused only on the recipient site; the flap donor site should also be regularly examined.

In conclusion, the forehead flap remains a reliable option in orofacial soft tissue defect reconstruction. It is easy to raise, can provide coverage for wide defects as far as the paramandibular region, it does not require patient repositioning and provides good textural, thickness and colour match when compared with the recipient site tissues.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Ellis E III, Scott K. Assessment of patients with facial fractures. *Emerg Med Clin North Am* 2000;18:411-48.
- Aziz SR, Zichard VB, Borah G. A current therapy: complications associated with rigid internal fixation of facial fractures. *Compend Contin Educ Dent* 2005;26:565-71.
- De Sousa A. Psychological issues in acquired facial trauma. *Indian J Plast Surg* 2010;43:200-5.
- Cawood JJ, Stoelinga PJW. International academy for oral and facial rehabilitation-consensus report. *Int J Oral Maxillofac Surg* 2006;35:195-8.
- Ng W. Reconstructive options in head and neck surgery. *Hong Kong Med Diary* 2007;12:14-6.
- Janis JE, Kwon RK, Attinger CE. The New reconstructive ladder: modifications to the traditional model. *Plast Reconstr Surg* 2011;127:S205-12.
- Asamura S, Kakizaki H, Mori K, Matsunaga K, Wada M, Isogai N. The pectoralis major myocutaneous pedicled flap revisited. *Surg Sci* 2013;4:380-4.
- Chim H, Salgado CJ, Seselgyte R, Wei FC, Mardini S. Principles of head and neck reconstruction: an algorithm to guide flap selection. *Semin Plast Surg* 2010;24:148-54.
- Hunt JP, Buchmann LO. The supraclavicular artery flap for lateral skull and scalp defects: effective and efficient alternative to free tissue transfer. *J Neurol Surg Rep* 2014;75:e5-10.
- Rinaldo A, Shaha AR, Wei WI, Silver CE, Ferlito A. Microvascular free flaps: a major advance in head and neck reconstruction. *Acta Otolaryngol* 2002;122:779-84.
- Baliarsing AS, Thorat TS, Gupta A, Bhat U, Garg S, Bhattacharyya D. Flap selection in head and neck cancer reconstruction. *Int J Otorhinolaryngol Clin* 2013;5:63-76.
- Colletti G, Autelitano L, Tewfik K, Rabbiosi D, Biglioli F. Autonomized flaps in secondary head and neck reconstructions. *Acta Otorhinolaryngol Ital* 2012;32:329-35.
- Yavuzer R, Ayhan S, Cavusoglu T, Latifoglu O, Ozmen S. A workhorse for nasal reconstruction: the forehead flap. *Gazi Med J* 2001;12:107-11.
- Kleintjes WG. The vascular anatomy of the forehead related to forehead flaps and its application in plastic and reconstructive surgery. Dissertation presented for the degree of Doctor in Philosophy, Faculty of Health Sciences at the University of Stellenbosch, 2007.
- Burget GC. Preliminary review of pediatric nasal reconstruction with detailed report of one case. *Plast Reconstr Surg* 2009;124:907-18.
- Akinyoola AL, Ako-Nai AK, Dosumu O, Aboderin AO, Kassim OO. Microbial isolates in early swabs of open musculoskeletal injuries. *Niger Postgrad Med J* 2006;13:176-81.
- Kigera JWM, Shamim M. Antibiotic prescription patterns in the management of open fractures at Mulago Hospital in Kampala. *East Cent African J Surg* 2012;17:47-50.
- Bhatt Y, Vyas K, Nakade D, Zade M. Reconstruction of nasal defects our three years experience. *Indian J Otolaryngol Head Neck Surg* 2006;58:51-6.
- Rao J, Deora H. Surgical excision with forehead flap as single modality treatment for basal cell cancer of central face: single institutional experience of 50 cases. *J Skin Cancer* 2014;2014:320792.
- Shaikh MI, Rajput F, Khatoon S, Shaikh MA. Forehead flap for reconstruction of maxillofacial region defects. *JLUMHS* 2014;13:61-6.
- Somoano B, Kampp L, Gladstone HB. Accelerated takedown of the paramedian forehead flap at 1 week: indications, technique, and improving patient quality of life. *J Am Acad Dermatol* 2011;65:97-105.
- Halim AS, Kamal WS, Noor NM, Abdullah S. Effects of ischemic preconditioning of different intraoperative ischemic times of vascularized bone graft rabbit models. *Arch Plast Surg* 2013;40:687-96.
- Richards L, Lineaweaver WC, Stile F, Zhang J, Zhang F. Effect of hyperbaric oxygen therapy on the tubed pedicle flap survival in a rat model. *Ann Plast Surg* 2003;50:51-6.
- Furnas DW, Lamb RC, Achauer BM, Turpin IM, Black KS. A pair of five-day flaps: early division of distant pedicles after serial cross-clamping and observation with oximetry and fluorimetry. *Ann Plast Surg* 1985;15:262-7.
- Cheng MH, Chen HC, Wei FC, See LC, Lee HY, Wang CJ. Combined ischemic preconditioning and laser doppler measurement for early division of pedicled groin flap. *J Trauma* 1999;47:89-95.
- Liu DZ, Mathes DW, Zenn MR, Neligan PC. The application of indocyanine green fluorescence angiography in plastic surgery. *J Reconstr Microsurg* 2011;27:355-64.
- White JB, Macht SD. Two-stage nasolabial flaps for facial reconstruction: revisiting the Three Week Rule for pedicle division. *Laryngoscope* 2010;120:S109.
- Vasu RC, Vijayakumar M, Sabitha K.S, Chris DA, Mahesh K, Jagadish S. Pectoralis major myocutaneous (PMMC) flap donor site recurrence in a case of buccal mucosal cancer: a case report. *Int J Health Sci Res* 2013;3:55-7.
- Ashok BC, Cherian MT, Ashok H. Secondaries at deltopectoral flap donor site. *Indian J Cancer* 2002;39:149-50.
- Robbins KT, Woodson GE. Chest wall metastasis as a complication of myocutaneous flap reconstruction. *J Otolaryngol* 1984;3:13-4.

Treatment of chronic recurrent dislocation of temporomandibular joint by autologous blood injection

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ABSTRACT

Aim: The aim of this study was to evaluate the efficacy of autologous blood injection in the management of recurrent temporomandibular joint (TMJ) dislocation. **Methods:** A total of 11 patients, 4 males, 7 females, mean age of 58.6 years and suffering from recurrent dislocation of TMJ, were included in the study. In all the patients the procedure included anesthesia- local or sedation, arthrocentesis which was followed by autologous blood injection in the upper joint cavity. The peri-articular tissues were also infiltrated with autologous blood. Post procedure advice included restricted mouth activity and liquid diet for a month. **Results:** The results indicate that success rate of treatment of recurrent dislocation of TMJ is 72.8% which can be considered as impressive. The recurrence was noticed in 27.2% cases after one year follow up. **Conclusion:** Autologous blood injection is an effective, simple, non-invasive, and safe procedure for treatment of recurrent dislocation of TMJ and can be performed on outpatient basis.

Key words:

Subluxation; recurrent dislocation; arthrocentesis; temporomandibular joint; autologous blood

INTRODUCTION

Sometimes during normal opening of the mouth the condylar head of the mandible moves forward anterior to the articular eminence but still remains within the capsule of the joint. This is termed as dislocation which may be classified as acute, chronic and recurrent. Recurrent dislocation of temporomandibular joint

(TMJ) may require professional help for reduction or occasionally it may be self reducing. This condition is characterized by inability to close the mouth once mouth is wide open. When this is self reducible or self reducing - it is referred to as subluxation. In contrast, luxation or dislocation is a condition requires professional help to return the joint to its normal position.

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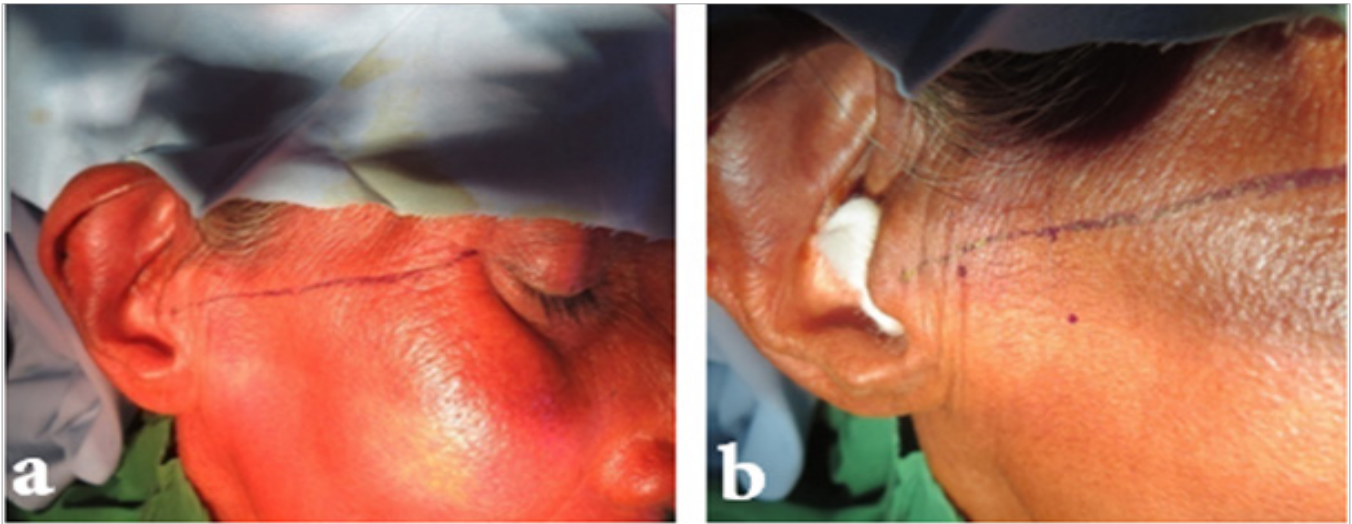


Figure 1: (a) Showing markings for canto-tragal line; (b) two points marking for double puncture arthrocentesis followed by blood injection at the posterior mark

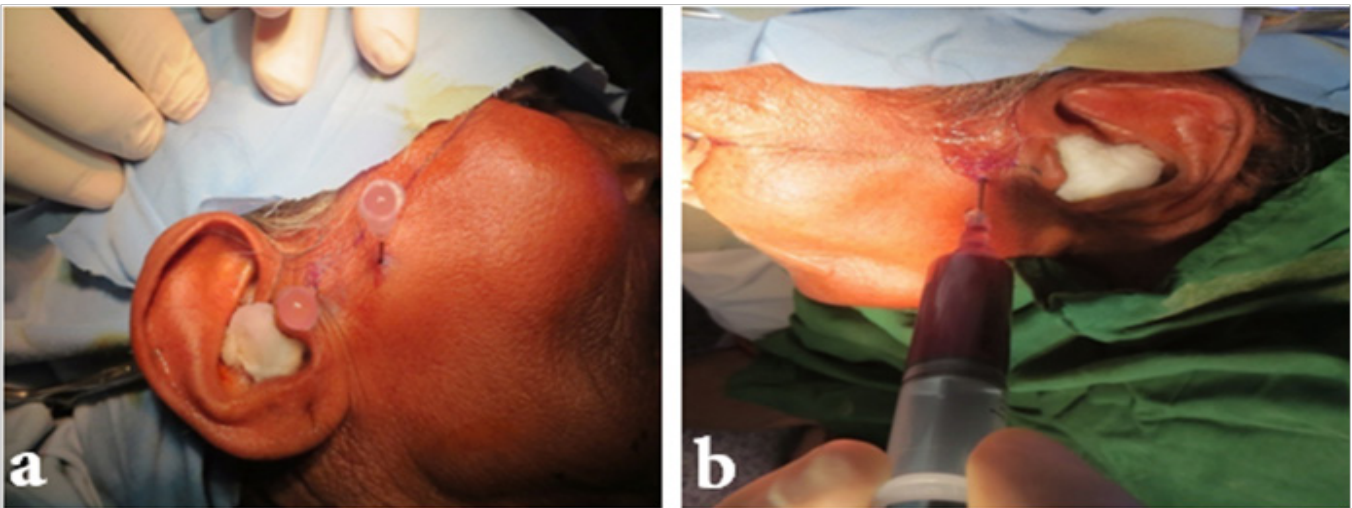


Figure 2: (a) Arthrocentesis using two point puncture in temporomandibular joint technique; (b) autologous blood injection

Table 1: Age, gender, duration of disease, frequency and treatment outcome

No.	Age	Gender	Duration of disease in months	Frequency of dislocation per week	Average frequency per week	History of previous treatment	Period of follow up in months	Post treatment recurrence
1	43	M	12	3-4	4.2	-	24	No
2	45	F	6	3-5	-	-	18	No
3	48	F	12	4-6	-	-	24	No
4	51	M	24	2-3	4.4	Yes, bandage to restrict mouth opening	12	No
5	53	F	5	5-6	-	-	16	Yes
6	55	M	36	3-4	-	Yes, IMF, medications	18	No
7	52	F	18	4-6	-	-	26	Yes
8	56	F	12	5-6	-	Yes, medications, bandage to restrict mouth opening	24	No
9	62	F	36	3-4	4.3	-	18	No
10	67	F	12	4-6	-	-	20	No
11	73	M	48	Innumerable	-	Yes, injections and medications	24	Yes

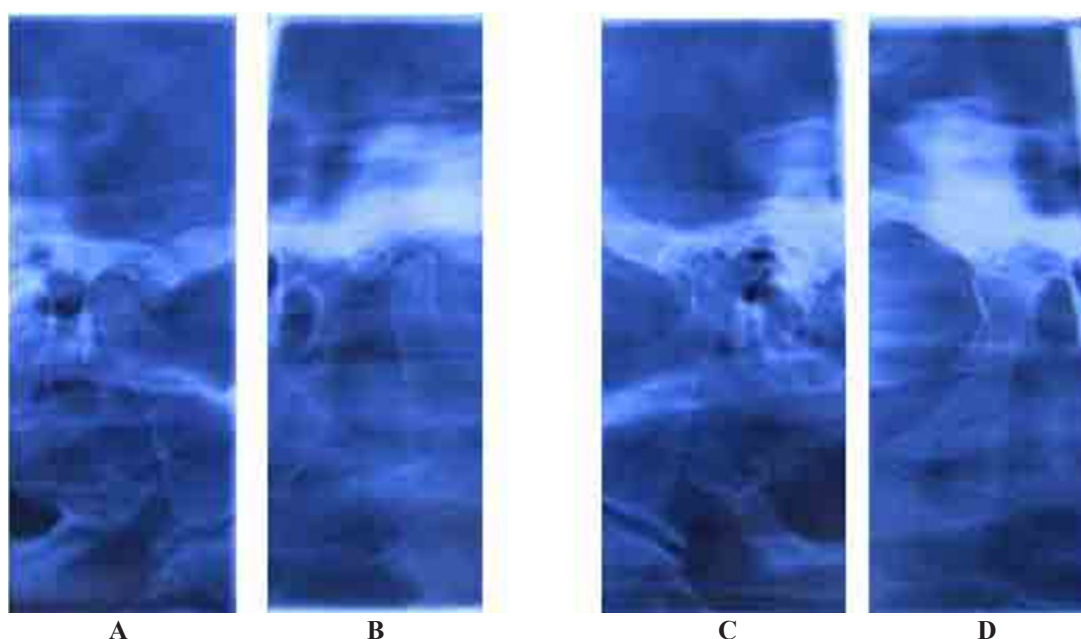
IMF: intramaxillary fixation

Chronic recurrent dislocation of TMJ (RTMJJD) may occur as results of routine activity of life, like excessive yawning, laughing loudly, vomiting or opening mouth too wide for eating, due to trauma

like blow on the chin while mouth is open, injudicious use of mouth gag during general anesthesia or excessive pressure on the mandible during dental extraction, and is characterized

Table 2: Showing recovery after treatment and complications

No.	Maximum mouth opening preoperative in mm	Episodes of dislocation during period of observation						Maximum mouth opening in mm	Complications
		1st and 2nd week	3rd week	1st month	3rd month	6th month	1 year		
1	38	-	-	-	-	-	-	38	Mild pain
2	39	Yes	-	-	-	-	-	38	-
3	42	-	-	1	1	-	-	40	-
4	39	-	-	-	-	-	-	38	Mild pain
5	40	Yes	Yes	Yes	Yes	Yes	Lost follow up	-	-
6	39	-	-	-	-	-	-	36	-
7	37	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Recurrence
8	38	-	-	-	-	-	-	34	-
9	39	-	-	-	-	-	-	36	Mild pain
10	42	-	-	-	-	-	-	40	-
11	46	Yes	Yes	Yes	-	-	Treated by surgical means	-	Recurrence
Mean mouth opening (preoperative) 39.9								Mean mouth opening 37.2 mm (postoperative)	


Figure 3: Temporomandibular joint view showing pre and post autologous injection radiographs. A: Pre-injection left side; B: post autologous blood injection; C: pre-injection right side; D: post autologous blood injection

by gagging of molar teeth, anterior open bite or long face appearance. The etiology of recurrent dislocation is not known, however, the pathogenesis involves soft tissues or bone. Involvement of tissues is related with weakness of ligaments or laxity of capsule.^[1] At bone level, abnormal size of eminence or shallow glenoid fossa, may another contributing factor. Certain systemic diseases like Parkinson's disease, epilepsy, Ehler Danlos syndrome and antipsychotic drugs which may cause extra pyramidal reactions, have also been attributed as predisposing factors.

Recurrent dislocation induces traumatic effects on all the structures of joint including disc, ligament and capsule. Various surgical and non-surgical and surgical treatments have been employed to treat chronic recurrent dislocations of TMJ but none has received universal approval,^[2-4] thus attempts are still on finding an amicable treatment of this problem.

Among conservative, nonsurgical treatment intra articular

injections of sodium psyllate, sodium murrehoate and sodium decyl sulphate^[5] have been used with limited success. Brachmann^[6] was first to use intrarticular injection of autologous blood for treatment of RTMJD. Schulz^[7] re-described the technique for the treatment with good results. However, still very little is known about the use of autologous blood in this condition, we decided to document our experiences of intrarticular injections of autologous blood in RTMJD. This technique is simple, non-invasive, and safe and can be performed under local anesthesia or intravenous sedation on outpatient basis.

METHODS

A total of 11 patients (4 males, 7 females) with age range between 43-73 years (mean age 58.6 years) who attended the OPD of Department of Oral and Maxillofacial Surgery, Dr. Ziauddin Ahmed Dental College and Hospital, Aligarh Muslim University, Aligarh, India with chief complaint of inability to close the mouth which very often remained open during routine activity of the

mouth. The problem was either reduced by patient themselves, or required some professional help or was self reducing. They all had undergone conservative treatment for the condition but no significant improvement was noticed. The clinical diagnosis was confirmed by lateral view of TMJ in open and closed mouth position. In all cases, the head of condyle was found to be anterior to the articular eminence in wide open mouth position. To all the patients various treatment options were presented and only those patients who consented for intra-articular autologous blood injection (IABI) were included in the study. IABI was given by two point puncture technique as described by Schulz.^[7]

Technique

The procedure was planned to be performed under local anesthesia using lignocaine 2% with adrenaline. The patient was asked to lie in supine position. After preparing the site with antiseptic and draping, an auriculotemporal nerve block was given on either side using. A line from middle of tragus to lateral canthus of eye was drawn on either side and a point was marked at articular fossa which was located 10 mm anterior and 2 mm inferior to this line. Second point was marked 20 mm anterior and 10 mm inferior to this canthotragal line and this line corresponds to the peak of eminence [Figure 1a and b]. Then an 18-gauge 1.5-inch long needle was inserted at the first point up to a depth of 1 inch and stabilized. Another 18-gauge 1.5-inch long needle was inserted at the second mark corresponding to articular eminence. After insertion of needle at the two points, joint lavage (arthrocentesis) was done using 10 mL of normal saline solution [Figure 2]. After lavage of the joint second needle was withdrawn and 4 mL of blood was taken from patients cubital vein and 3 mL was injected in the articular fossa through first needle. Then the needle was withdrawn slightly outward for 1 cm and another 1 mL of blood was injected around pericapsular tissue. The same procedure was done for the opposite side also [Figure 3]. After this an elastic bandage was applied for one week and all the patients were advised to restrict their mouth opening and to take liquid diets only. Anti-inflammatory analgesic (aceclofenec 100 mg) was prescribed for 3 days. Subsequent follow up was done at 1 week, 1 month and 6 months period and clinical outcomes and maximal mouth opening were noted during follow-up period.

The composition of patients and various observations pertaining to study have been shown in Tables 1 and 2.

RESULTS

The results of study indicate that success rate of treatment of recurrent dislocation of temporomandibular joint is 72.8% which can be considered as impressive. After follow up period of one year, only 3 patients suffered from recurrence (27.2%).

DISCUSSION

We have performed autologous blood injection in eleven patients of recurrent dislocations. The results of study have been summarized in Tables 1 and 2. At a follow up period of one year and only 3 of them suffered from recurrence. Their average maximal mouth opening also reduced from 39.9 mm preoperatively to 37.2 mm postoperatively.

Blood is injected into two regions, in the articular fossa and pericapsular tissue. The blood injection causes fibrosis and scarring in the areas of injection which stops the dislocation of condyles from recurring. However, we feel that limited mouth in initial first week is important for the success of treatment. This limitation can be achieved by TMJ bandage or intermaxillary fixation,^[1] or asking the patient to take liquid or semi solid diet with efforts of not to open wide. We have used elastic bandaging for three weeks and kept the patients exclusively on liquid diets in the first week and then soft and semisolid diet for the next two weeks to restrain the mandibular movements. After three weeks patients were advised to start mandibular physiotherapy to maintain functional mouth opening. Some workers have shown their concern about development of ankylosis and degeneration of articular cartilage after performing autologous blood injection.^[1,2] In our study, no such complications were found at whole period of follow-up. We have opinion that there is no chance of ankylosis after IABI. Chances of ankylosis are always there wherever the joint is traumatized to extent that structures within the joint capsule are damaged and there is intrarticular bleeding. Exogenous bleeding (intra-articular injection) doesn't have same effect as endogenous bleeding. The blood simply pushes the condylar head in posterior position and helps in maintaining the position. The periarticular fibrosis, which results due to autologous blood injection supplements the forward translation of condyle which is further aided by elastic bandage, restricting the mouth opening.^[8,9]

The disadvantage of the procedure is that it is a blind procedure, even then it is safe and complication free. In our study, pain was only reported complication which could be easily managed by anti-inflammatory analgesics.

Results of our study support the findings of Daif^[10] who performed a comparative study of autologous blood injection in the superior joint space alone vs. superior joint space and pericapsular tissues and found higher success rate in the combined injection than the same in superior joint space alone. However, we performed clinical study using combined injection technique as it appeared much sound. Using combined technique we found success rate of 89.1% at a follow-up period of 1 year.

Various means to restrict mandibular movement have been applied.^[11,12] We used elastic bandage for one month and soft diet in our cases. It was convenient, comfortable to patient and easily adjustable.

There is no predictive indicator for success of treatment by non surgical means including autologous blood injection. However, the cases who don't respond positively in the initial 3 weeks of treatment should be considered as failure case. In such condition surgical methods should be opted.

We did not find any appreciable complications in the study. Only 3/11 (27.3%) patients complained of mild pain which was controlled by tablet aceclofenac 100 mg in twice daily doses and did not affect the routines of the patients. These results are in slight contrast to study of Candirli^[13] in which, 14 patients were treated with autologous blood injection and found no complications. The only serious complication was recurrence which could be noticed in 2/11 cases (18.9%). In other words, the success rate is

89.1%. However, in other studies, 80-85% success rate has been documented. This difference may be due to difference in sample size. Further, personal application of technique may be also an important factor. Hence further study with large sample size and long term follow-up is needed to see the actual success rate with autologous blood injection. In our study, the mouth opening after was slightly reduced which is statistically insignificant and can be clinically considered as unchanged.

In conclusion, autologous blood injection is a simple, noninvasive, cost-effective, short duration and safe procedure which can be performed under local anesthesia/IV sedation in an outpatient basis. However, the results of the present study are of limited value because of the scarce amount of patients in the series and because the technique does not allow a direct visualization of the intra-articular space of the joint.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Sharma R. Modifications to Norman's procedure for hypermobility of the TMJ. *Med J Armed Forces India* 2012;68:231-5.
- Costas López A, Monje Gil F, Fernandez Sanromán J, Goizueta Adame C, Castro Ruiz PC. Glenotemporal osteotomy as a definitive treatment for recurrent dislocation of the jaw. *J Craniomaxillofac Surg* 1996;24:178-83.
- Bakardjiev A. Treatment of chronic mandibular dislocations by bone plates: two case reports. *J Craniomaxillofac Surg* 2004;32:90-2; discussion 93.
- Kummoona R. Surgical managements of subluxation and dislocation of the temporomandibular joint: clinical and experimental studies. *J Craniofac Surg* 2010;21:1692-7.
- Rowe NL, Williams JL. Row and Williams Maxillofacial Injuries. London: Churchill Livingstone; 1994. p. 352-5.
- Brachmann F. Autologous blood injection for recurrent hypermobility of the temporomandibular joint. *Dtsch Zahnarztl Z* 1964;15:97-102. (in German)
- Schulz S. Evaluation of periarticular autotransfusion for therapy of recurrent dislocations of the temporomandibular joint. *Dtsch Stomatol* 1973;23:94-8. (in German)
- Ungor C, Atasoy KT, Taskesen F, Cezairli B, Dayisoylu EH, Tosun E, Senel FC. Short-term results of prolotherapy in the management of temporomandibular joint dislocation. *J Craniofac Surg* 2013;24:411-5.
- Zhou H, Hu K, Ding Y. Modified dextrose prolotherapy for recurrent temporomandibular joint dislocation. *Br J Oral Maxillofac Surg* 2014;52:63-6.
- Daif ET. Autologous blood injection as a new treatment modality for chronic recurrent temporomandibular joint dislocation. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010;109:31-6.
- Machon V, Abramowicz S, Paska J, Dolwick MF. Autologous blood injection for the treatment of chronic recurrent temporomandibular joint dislocation. *J Oral Maxillofac Surg* 2009;67:114-9.
- Kato T, Shimoyama T, Nasu D, Kaneko T, Horie N, Kudo I. Autologous blood injection into the articular cavity for the treatment of recurrent temporomandibular joint dislocation: a case report. *J Oral Sci* 2007;49:237-9.
- Candirli C, Yüce S, Cavus UY, Akin K, Cakir B. Autologous blood injection to the temporomandibular joint: magnetic resonance imaging findings. *Imaging Sci Dent* 2012;42:13-8.

Angioleiomyoma: a rare diagnosis of a painful subcutaneous nodule in the hand

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ABSTRACT

Angioleiomyoma of the hand is a rare differential diagnosis of painful soft tissue nodule in the extremity. It arises from smooth muscle of the blood vessels and the most common symptom is pain. Imaging with magnetic resonance imaging shows characteristic features like a hypodense peripheral capsule with linear or branching internal hyperdensities on T2-weighted images, and post-contrast diffuse homogenous enhancement with a vessel leading up to the lesion. Histopathological examination shows well circumscribed fascicles of mature smooth muscle cells surrounding vascular lumina, lined by normal appearing endothelium without elastic lamina present. These cells stain positive for smooth muscle actin, desmin, vimentin, type IV collagen and S100, but stain negative for HMB-45 and ER. Angioleiomyoma is amenable for surgical resection. We report a case of painful subcutaneous nodule of hand, with radiological and histopathological findings suggestive of angioleiomyoma. We outline the clinical, radiological and histopathological features of this rare diagnosis for painful nodule of extremity.

Key words:

Hand; tumor; angioleiomyoma; histopathology; excision; biopsy



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Figure 1: Preoperative picture. Note the bulge over the thenar eminence



Figure 2: MRI showing well defined lesion in the thenar area. MRI: magnetic resonance imaging



Figure 3: Intraoperative view showing a blood vessel from the palmar arch in close proximity to the tumor

INTRODUCTION

Angioleiomyoma is a unique form of soft tissue tumor, which arises from the smooth muscle of blood vessels.^[1] This tumor can appear in different parts of the body, and the most

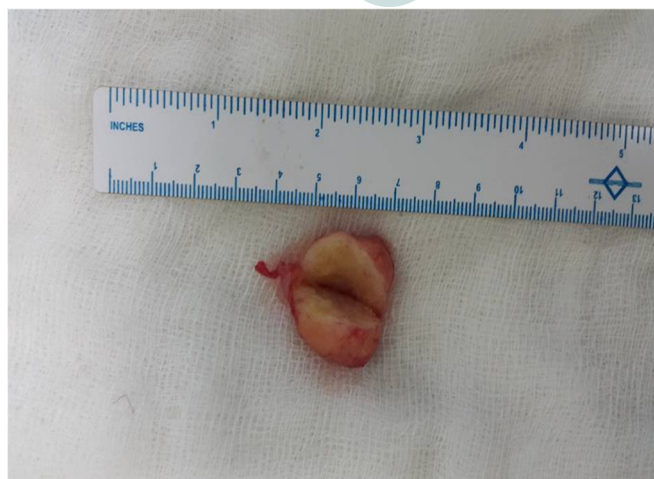


Figure 4: Gross cut section

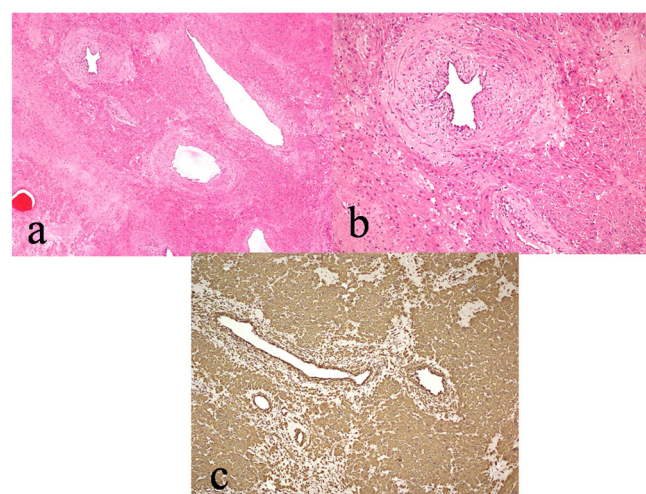


Figure 5: (a) Photomicrographs showing a tumor composed of bundles of smooth muscles with intervening blood vessels (HE, $\times 100$); (b) higher magnification showing bland nature of the smooth muscles and intervening thick muscular blood vessel (HE, $\times 200$); (c) the tumor cells show strong positivity for smooth muscle actin (IP, $\times 100$)

common presenting complaint is pain. Since this lesion is a rare occurrence and the list of differential diagnoses for painful mobile subcutaneous mass is extensive, a case report and literature review of angioleiomyoma is presented.

CASE REPORT

A 36-year-old man presented with a 2-year history of a slow-growing, mildly painful mass in the palmar aspect of the thenar eminence of the right hand. There was no history of trauma. On examination, a 3 cm \times 2 cm firm, mobile mass was palpated on the thenar eminence of the right hand. The lesion did not extend to the underlying bone and tendon. The overlying skin could be easily pinched from the lesion and did not show ulceration or discoloration. Temperature and sensation of the overlying skin was normal. Thus, a clinical diagnosis of soft tissue tumor was made [Figure 1].

Magnetic resonance imaging (MRI) of the hand revealed a well-defined 2.5 cm \times 2.8 cm lesion in the first web space of the right hand infiltrating adjacent musculature. The lesion was heterogeneously hyperdense on T2, and isodense on T1. Prominent feeders were seen from arterial branches of the palmar arch. No

early draining veins were seen [Figure 2].

Excision of the lesion was performed under brachial block. A single 2 cm in diameter spherical mass was identified [Figure 3]. The outer surface was smooth and whitish in color. It was well encapsulated [Figure 4]. Histopathology revealed a well-circumscribed tumor, composed of multiple thick-walled blood vessels with thickened smooth muscle coating. The smooth muscles were arranged in form of interlacing fascicles. Neither mitosis nor necrosis was seen. Tumor cells were positive for smooth muscle actin and desmin, but they were negative for Bcl-2 and CD34. The features were consistent with angioleiomyoma or vascular leiomyoma [Figure 5].

The patient was kept on regular follow-up. Six months following surgery, there are no signs of recurrence.

DISCUSSION

Angioleiomyomas are rare benign subcutaneous or deep dermal tumors of smooth muscle and vessels. They are also called angiomyomas or vascular leiomyomas. They are common among females in 30-60 years of age.

Angioleiomyomas present as slow growing painful solitary nodules of extremities.^[2-5] Other rare sites have also been reported in the literature including the labia majora, nipple, hard palate,^[6] pinna, and sella.^[7] The most common presenting symptom is pain, found in up to 60% of cases.^[8] This is attributed to stretching of nerves in tumor or capsule, or release of mediators from mast cells.

Differential diagnoses to be considered in cases of painful nodules in extremities are glomus tumor, traumatic neuroma, eccrine spiradenoma and angiolipoma.^[1,9] All are treated by surgical excision and they do not reoccur. The gross appearance is firm and spherical nodule that is grayish white to brown in color, and usually 2 cm or less in diameter.

MRI features characteristic to angiomyomas include a hypodense peripheral capsule with linear or branching internal hyperdensities on T2-weighted images, and postcontrast diffuse homogenous enhancement, with a vessel leading up to the lesion in the majority of cases. These features were also seen in our case.

Histopathological examination showed well-circumscribed fascicles of mature smooth muscle cells surrounding vascular lumina,^[10] lined by normal appearing endothelium without elastic lamina. There are subtypes described in literature: (1) solid type-closely compacted smooth muscle bundles; (2) venous type-vessels have thick muscular walls that merge with smooth muscle bundles; and (3) cavernous type-dilated vascular channels with minimal smooth muscle that merges with smooth muscle bundles. The venous type is observed more in males, and in the region of the head and neck. The solid type is more common in women, and in the lower extremities.

They may have foci of cartilaginous or adipose metaplasia. Rarely, they might have calcification.^[11] Hemorrhage, necrosis, mitotic activity, vasculitis or fibromuscular dysplasia are not encountered.

Morphologically they have moderate or sparse cellularity. They are composed of bundles of smooth muscles arranged in varying size fascicles admixed with varying amount of collagen with intervening vascular structures. Occasional macrophages, fat cells and ganglion-like cells are seen. Angiomyolipoma is a histological differential diagnosis. This lesion usually contains adipose tissue in addition to smooth muscle and vascular components. Angioleiomyoma cells stain positive for smooth muscle markers like alpha smooth muscle actin, desmin, myosin, trichrome, HHF-35, calponin and h-caldesmon. These cells are also positive for vimentin, type IV collagen and variably for S100. They stain negative for HMB-45 and estrogen receptor.

To conclude, angioleiomyoma of the hand is a rare differential diagnosis of a painful subcutaneous nodule in the extremities and has to be kept in mind during such clinical presentation.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Ohtsuka H. Angioleiomyoma of the pulp. *J Plast Surg Hand Surg* 2014;48:285-6.
- Mok JC, Fan KY, Lui TH. A huge angioleiomyoma of the finger. *Hand Surg* 2015;20:310-2.
- Nishio J, Aoki M, Tanaka Y, Iwasaki H, Naito M. Painless angioleiomyoma of the first web space of the hand. *In Vivo* 2013;27:519-22.
- Ogura K, Goto T, Nemoto T. Painless giant angioleiomyoma in the subfascia of the lower leg. *J Foot Ankle Surg* 2012;51:99-102.
- Raval A, Schuller M, Al-Atassi S. Neurosurgical management of a painful subcutaneous nodule of the knee: angioleiomyoma. *Neurosurgery* 2014;75:E190-4.
- Eley KA, Alroyayamina S, Golding SJ, Tiam RN, Watt-Smith SR. Angioleiomyoma of the hard palate: report of a case and review of the literature and magnetic resonance imaging findings of this rare entity. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012;114:e45-9.
- Xu Y, Jing Y, Ma S, Ma F, Wang Y, Ma W, Li Q. Primary angioleiomyoma in the sellar region: a case report and literature review. *Clin Neuropathol* 2010;29:21-5.
- Hachisuga T, Hashimoto H, Enjoji M. Angioleiomyoma. A clinicopathologic reappraisal of 562 cases. *Cancer* 1984;1;54:126-30.
- Lee HH, Park SH, Choi HY, Park HK. Eccrine spiradenoma arising in the breast misdiagnosed as an epidermal inclusion cyst. *Korean J Radiol* 2011;12:256-60.
- Shafi M, Hattori Y, Doi K. Angioleiomyoma of distal ulnar artery of the hand. *Hand (NY)* 2010;5:82-5.
- Onishi M, Takahashi K, Watabe D, Onodera H, Akasaka T. A case of angioleiomyoma with epithelioid granuloma. *Case Rep Dermatol* 2011;3:170-4.

State of the art in the management of oral squamous cell carcinoma

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When considering the last report by the World Health Organization in 2014, oral squamous cell carcinoma (OSCC) represents the seventh cause of cancer worldwide and causes 529,000 new cases per year. In addition to its considerable frequency, death by this entity may overcome in approximately 50% of the patients, even after aggressive multi-modality treatment. Although surgery followed or not by radiotherapy is the main treatment option, many factors may influence overall outcome in terms of survival, including patient-related, tumor-related and treatment-related factors.

A myriad of articles has been published in the literature concerning "oral cancer" and "squamous cell carcinoma of the oral cavity and oropharynx". Although several high-quality papers are advised, the heterogeneity of the studies in terms of methodology, treatment protocols, and inclusion/exclusion criteria makes direct comparison among series and institutions challenging. However, some main guidelines may guide the clinician into the best treatment modality for each patient, while an effort in terms of classifying patients who may benefit from one or other treatment option has been made in the last decade.

The present editorial is an introductory paper to a special issue composed of eleven manuscripts focusing on particular aspects about the state of the art in OSCC under the light of current knowledge. While strict criteria for systematic reviewing concerning Cochrane database recommendations have not been followed due to the heterogeneity of the revised series, an effort has been made to selectively approach particular aspects of OSCC management, while selecting the most prominent series within the last 15 years. Some of the incoming works have made a special effort in trying to include and systematically analyze more relevant works according to a predetermined search, inclusion and exclusion criteria, with a particular PICO question and a flow chart, while others have made a general review according to subjective criteria based on authors' own experience in selecting more relevant works. While the more systematically approach is more relevant in the evidence-based scale, reviews by selected experts still have a relevant role in the field of surgery.

The approached items were: (1) the role of human

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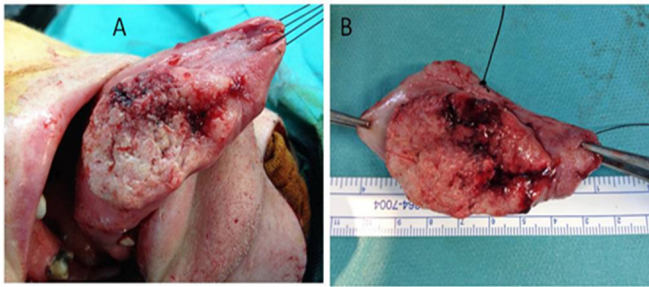


Figure 1: Oral squamous cell carcinoma (OSCC) of the tongue. (A) Intraoral view of the tumor; (B) immediate intraoperative tissue shrinkage following resection of OSCC by a partial glossectomy

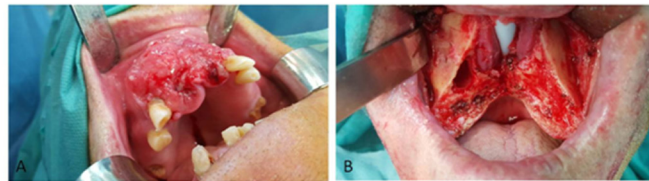


Figure 3: Oral squamous cell carcinoma of the upper maxilla. (A) Intraoral view of the tumor; (B) intraoperative view of the remnant maxilla following anterior partial maxillectomy

papillomavirus (HPV) in OSCC; (2) the role of sentinel node biopsy in the treatment of OSCC; (3) the influence of surgical resection margins in OSCC; (4) the role of radiotherapy in OSCC; (5) the role of elective neck dissection in early-staged OSCC; (6) the role of elective neck dissection in OSCC of the upper maxilla; (7) the role of contralateral neck dissection in OSCC; (8) the role of salvage surgery in recurrent OSCC; (9) the reliability of the combined-triangular full-thickness skin graft for covering the radial forearm free flap donor-site; (10) the prognosis and quality of life in head and neck cancer; and (11) last but not least a special article about the current role of the facial allograft transplantation. This last paper is performed by one of the first and more experienced surgical teams in performing facial allograft transplantation worldwide.

Electronic literature search was conducted mostly in Medline, but also Embase and Cochrane databases were used in some of the articles in the present issue. The abstracts of yielded results were reviewed and the full text of those with apparent relevance was obtained. The references of identified articles were crosschecked for unidentified articles, and only those in English language were selected. In most of the articles in the present issue, exclusion criteria concerning the type of articles to be included were established, thus excluding case reports and technical notes, letters to Editors, expert opinions, animal or *in vitro* studies, review articles, and repetitive data from series of the same authors or institutions. Qualitative systematic reviews or non-systematic reviews were performed, while two articles, one concerning elective neck dissection in OSCC of the upper maxilla, and the other dealing with salvage surgery for OSCC, analyzed data from features in the selected articles to infer new results as meta-analysis. Two additional articles are dealing with special reconstructive surgical procedures that were developed and put in practice by the authors' surgical teams, being the facial allograft transplantation and the covering of the radial forearm free flap donor-site by the

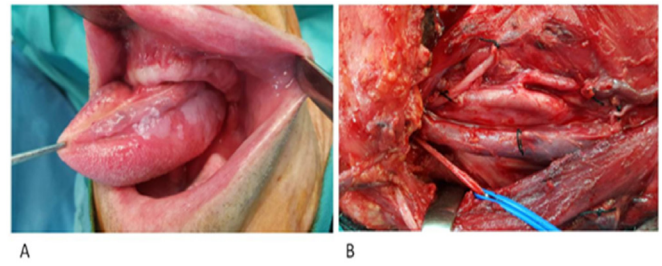


Figure 2: Selective supraomohioid neck dissection involving cervical levels I to III in a T1 oral squamous cell carcinoma of the tongue. (A) Intraoral view of the tumor; (B) intraoperative view of the dissected neck



Figure 4: Contralateral modified type III radical neck dissection in an oral squamous cell carcinoma of the mandible involving the right parasymphiseal region. Detail of levels II to V left neck dissection

elsewhere named “Iberic graft”, a new technique consisting on the use of full-thickness skin grafts obtained from the volar side of the forearm skin.

Some strong conclusions can be obtained from the reading of the reviewing works included in this special issue, which may move the reader closer to the current knowledge about OSCC, or at least may provide a baseline from which the reader can deep into a more specific and advanced knowledge. These conclusions are: (1) HPV is increasingly being associated to OSCC, usually diagnosed at a younger age, mainly in the oropharynx, while HPV⁺ OSCC patients have an increased survival, better treatment response and lower recurrence rates; (2) the sentinel node biopsy is a reliable staging method in early-stage OSCC as an alternative to elective neck dissection for staging N0-neck, with a reasonable false-negative rate while decreasing morbidity associated to selective neck dissection if performed by an experienced multidisciplinary team; (3) tissue shrinkage on surgical margins of resection in OSCC is a tangible phenomenon, being the highest percentage of retraction occurring at the time of resection, which leads the surgeon into a major therapeutic role, as involved or closed margins in the histologic report may determine the administration of complementary treatments such as post-operative radiotherapy and/or chemotherapy [Figure 1]; (4) both external radiotherapy and brachytherapy play a determinant role in the treatment of OSCC, alone in early stages or combined with surgery and/or chemotherapy in advanced ones; (5) if routine strict follow-up using ultra-sonography fine needle aspiration cytology (USgFNAC) by a well-trained ultrasonographer cannot be assured in clinically N0-neck,

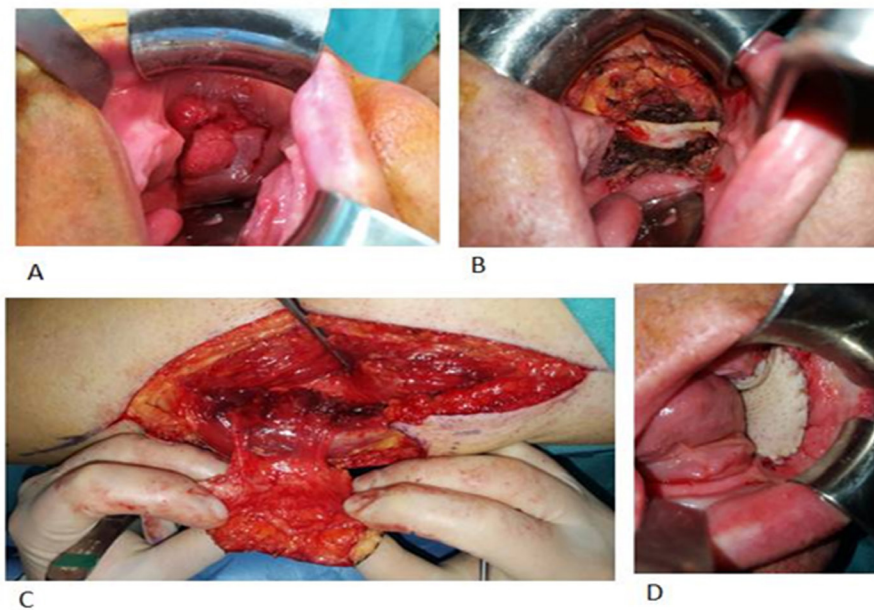


Figure 5: Recurrent oral squamous cell carcinoma of the buccal mucosa. (A) Intraoral view of the tumor; (B) intraoperative view of the resection; (C) reconstruction with an antero-lateral thigh flap; (D) intraoperative view of the reconstructed defect

elective neck dissection is advised by a supraomohyoid neck dissection as an effective method to control cervical metastases [Figure 2]; (6) the rate of metastases in patients with OSCC of the upper maxilla is high and comparable with metastases from other sites of the oral cavity, thus elective neck dissection should be routinely performed in T3/T4 tumors of the upper maxilla [Figure 3]; (7) with a variable reported contralateral lymph neck node metastases rate in OSCC ranging from 0.9% to 36%, surgeons should take into account the detailed and individual study of risks and potential benefits of elective neck dissection for contralateral N0 neck [Figure 4]; (8) from a meta-analysis of 13 eligible series comprising 1,692 recurrent OSCC patients, recurrence appeared in up to 26% of primarily treated patients. With a mean 5-year overall survival rate of 40.2%, salvage surgery is the first treatment option for recurrent OSCC patients [Figure 5]; (9) the “Iberic graft”, consisting on a combined full-thickness skin graft obtained from the volar forearm skin, is a reliable method for closing most of radial forearm free flap donor-site defects, as it provides excellent color match and pliability, while obviates the need for a second surgical site; (10) although prognosis of OSCC has improved, further studies are necessary to understand the behaviour in every case and determine how the impact on the quality of life can be a useful tool to individualize therapies; and (11) although clinical experience has demonstrated the facial transplantation viability, it is still considered an experimental procedure in which we have much to learn to define its true role in the current reconstructive surgery and resolve major

technical, medical and ethical problems involved.

In summary, these and several other conclusions can be highlighted from the reviews of this special issue. OSCC represents a challenge for the clinician as mortality and morbidity still remain high in advance-stage patients, despite recent advances in therapies and reconstructive options. Surgery still plays the major role in controlling the disease and provides the highest overall and specific-disease survival rates, although advanced-stage disease may require the administration of postoperative radiotherapy with or without chemotherapy.

This is the reason why a multidisciplinary approach with surgeons, radiotherapy oncologists, medical oncologists and others is mandatory to obtain the highest standards in terms of survival and quality of life, with the Head and Neck Surgeon leading this team. The acquisition of new knowledge in relation to OSCC may add new weapons to the armamentarium of the clinician. This and other compendiums of current knowledge about the disease may establish the baseline for further goals and achievements in the battle against oral cancer.

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There are no conflicts of interest.

The role of human papillomavirus in oral squamous cell carcinoma

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ABSTRACT

Aim: The causative role of human papillomavirus (HPV) has been established into the aetiology of oral squamous cell carcinoma (OSCC). Some authors believe that HPV can determinate the prognosis and module treatment response from this kind of malignancies. **Methods:** Articles published in the last 10 years, focusing on the role of HPV in the development, molecular biology, prognosis and treatment of OSCC were reviewed. **Results:** Thirty-nine articles from 252 were selected, highlighting 4 meta-analysis, 3 prospective and 2 retrospective studies. According to its role in the development of cervical cancer, HPV is classified into a high risk for malignant lesions subtype and a low-grade malignant lesions subtype. Epidemiology and prevalence of HPV varies according to the published data: large studies tend to have lower rates of HPV (< 50%) than smaller ones (0-100%). Interestingly, HPV+ patients are usually diagnosed at a younger age, mainly those with oropharyngeal tumours. There is a predilection for the oropharynx and Waldeyer ring tumours. Regarding prognosis, OSCC HPV+ patients tend to have better outcome and treatment response. **Conclusion:** HPV divides OSCC in two types of tumours with different prognostic and therapeutic implications, with increased survival, better treatment response rates and lower risk of death and recurrences.

Key words:

Papillomavirus infections; carcinoma squamous cell; mouth

INTRODUCTION

Squamous cell carcinoma (SCC) is the most common malignant lesion of the oral cavity and oropharynx. It is characterized by a multifactorial aetiology,^[1-5] where the causative role of papillomavirus (HPV) has been

established.^[6] It is sexually acquired,^[7] usually described in the tonsillar area,^[8-10] affecting younger, non-drinkers and non-smokers patients.^[11-13] DNA from most oncogenic risk HPV is detected in approximately 26% of all oral

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Figure 1: The case of a 70-year-old and ex-smoker female patient with a human papillomavirus+ head and neck squamous cell carcinoma. We can see an exophytic lesion three years of evolution on the left floor of the mouth, surpassing the midline, with a progressive growth. The patient has no dysphagia or dyspnea. We decide to take biopsies, obtaining the diagnosis of squamous cell carcinoma

squamous cell carcinoma (OSCC) throughout the world.^[14]

The appearance of this kind of tumours has changed among the last decades. Some genotypes have been suggested as the most likely causative agents of human papillomavirus, whose carcinogenic effect in oropharynx was first proposed by Syrjänen *et al.*^[15] in 1983 according to common morphological characteristics of HPV and immunohistochemistry. Later, this was confirmed by using new techniques such as "Southern Blot Hybridization".^[16,17] HPV has been proposed as a major risk factor for oropharyngeal squamous cell carcinoma (OPSCC),^[7,18] with a strong association in subjects with or without the established risks of smoking and alcohol.^[7]

The oncogenic potential of certain high-risk HPV genotypes is related to its ability of integrating DNA fragments (E5, E6 and E7) in the host cell, annulling the function of tumour suppressor factors such as p21, p53 and pRb routes.^[19] However, there are many ethno-geographical differences between the examined groups, with detection ranges from 0 to 100%.^[18,20-24] Virus detection is also affected by the sensitivity of the diagnostic test and the location of the lesion, which difficult the clarification of the role of HPV and its carcinogenic potential.^[7,25]

Some authors not only involve the virus in the pathogenesis of OSCC, but also believe that it can determine the prognosis and module treatment response.^[26] The first type of HPV isolated in OSCC was HPV16 in the palatine tonsil, made by Niedobitek *et al.*^[27] in 1990. However, this is not the only subtype identified, varying according to the analysed population sample.^[28] Recently this type of HPV-positive tumours in the oral cavity was described as an entity with different molecular, clinical, etiologic, pathological and prognostic characteristics.^[6,20-23,29-32]

METHODS

A review of articles published in the last ten years (since February 29, 2016 until January 1, 2005) in the database of medical literature MEDLINE via PubMed search engine was performed. The following descriptors obtained from "DeCS" were used as keywords: "Papillomavirus Infections", "Carcinoma, Squamous Cell" and "Mouth". All possible associations between them were used.

The main objective was to study the role of HPV in the development, molecular biology, prognosis and treatment of OSCC. We also provided special attention to detection and sampling techniques, risk factors, epidemiology, relationship with other non-malignant lesions and history of the virus.

Inclusion criteria were: (1) studies published between the dates indicated; (2) English language; (3) both observational and experimental studies; (4) reviews and meta-analyses; and (5) items that although published at an earlier date than the cut-off, are cited in the main revised. Exclusion criteria were: (1) publications that do not appear in the set date range and which are not mentioned in any of the included; (2) any type of non-English language; (3) studies lacking internal or external validity; (4) editorials and case reports; (5) studies with a sample size lower than 30, or if it is not mentioned by any of the included; and (6) articles that do not contain information on the main search object.

RESULTS

We preliminarily found 252 articles, of which only 39 were included and reviewed. Among these, 9 publications were highlighted: 4 meta-analysis,^[14,33-35] 3 prospective studies^[32,36,37] and 2 retrospective studies.^[38,39] Main results from these

Table 1: Nine highlighted publications

Author	Year	Study	Objective	Number	Results
Miller and Johnstone ^[33]	2001	Meta-analysis	To determine the significance of the relationship of HPV in the progressive development of oral cancer	4,680	HPV is detected with increased frequency in oral dysplastic and carcinomatous epithelium in comparison with normal oral mucosa
Kreimer <i>et al.</i> ^[14]	2005	Meta-analysis	To describe the prevalence and type distribution of HPV by anatomic cancer site	5,046	Tumor site-specific HPV prevalence was higher among studies from North America compared with Europe and Asia
Ragin and Taioli ^[35]	2007	Meta-analysis	To study the overall relationship between HPV infection and OS and DFS in HNSCC	3,151	The improved OS and DFS for HPV+ HNSCC patients is specific to the oropharynx; these tumours may have a distinct etiology from those tumours in non-oropharyngeal sites
Jayaprakash <i>et al.</i> ^[34]	2011	Meta-analysis	To provide a prevalence estimate for HPV-16/18 in OPD	458	HPV-16/18 were 3 times more common in dysplastic lesions (OR, 3.29; 95% CI, 1.95-5.53%) and invasive cancers (OR, 3.43; 95% CI, 2.07-5.69%), when compared to normal biopsy
Rosenquist <i>et al.</i> ^[32]	2007	Prospective	To evaluate the influence of different risk factors for recurrence or the appearance of new second primary in the OSCC	128	High-risk HPV cases have a higher risk of recurrence/second primary tumours, but lower risk of death in intercurrent disease, compared with HPV-
Fakhry <i>et al.</i> ^[36]	2008	Prospective	To evaluate the association between tumour HPV status with the therapeutic response and survival	96	HPV+ HNSCC respond better to QT and RT-QT, with better overall survival rate at two years and reduced risk of disease progression than HPV-
Rischin <i>et al.</i> ^[37]	2011	Prospective	To determine the prognostic significance of p16 and HPV in patients with OPC	185	HPV+ OPC is a distinct entity with a favorable prognosis (when compared with HPV-). When it is treated with cisplatin-based chemotherapy
Ang <i>et al.</i> ^[38]	2010	Retrospective	To study the association between tumor HPV status and survival in stage III and IV OPD	743	Among patients with OPC, tumor HPV status is a strong and independent prognostic factor for survival
Lassen <i>et al.</i> ^[39]	2014	Retrospective	To test the hypothesis that the impact of HPV/p16 also extends to non-OP tumours	1,294	The prognostic impact of HPV- associated p16-expression may be restricted to OPC only

Nine highlighted publications are summarized because of their high number of patients, recent date of publication, good study design and highly cited in the literature, including 4 meta-analysis,^[14,33-35] 3 prospective studies,^[32,36,37] and 2 retrospective studies.^[38,39] HPV: human papillomavirus; OPD: oropharyngeal dysplasias; OP: oropharyngeal; OPC: oropharyngeal cancer; HNSCC: head and neck squamous cell carcinoma; OS: overall survival; DFS: disease free survival; QT: chemotherapy; RT: radiotherapy; OSCC: oral squamous cell carcinoma; OR: odds ratio; CI: confidence interval

studies are summarized in Table 1.

DISCUSSION

There is much written literature about the relationship of HPV virus and OSCC. Due to the great disparity of published data, it is very difficult to establish rightly the role HPV plays and its etiopathological, clinical and prognostic considerations. This can be related to differences in study populations (genetic, social and cultural factors) and the methodology of study and detection of virus.

There are many HPV genotypes identified, within which, over 130 are related to skin and mucosal lesions.^[40] The first to propose the pathogenic relationship of this type of virus with OSCC was Syrjänen *et al.*^[15] in 1983. And the first type identified in head and neck was HPV16 in palatine tonsil carcinomas.^[27] Since then, there have been many published studies on detection and about its role in OSCC.

HPV molecular biology

HPV belongs to a heterogeneous group corresponding to the "Papillomaviridae" family.^[41] It is characterized as a DNA-double stranded virus. It has a diameter of 50 µm and it is covered by an icosahedral capsid consisting of 72 capsomeres, without casing^[42,43] and presents a particular tropism by keratinocytes, being the synthesis and expression of their genes linked to

the level of their differentiation.^[44]

There are different routes of infection, mainly sexual, vertical and self-inoculation; they all share the need for close contact to occur.^[45,46] Transmission from non-primates to humans is unknown to occur.^[47,48]

To active the infection, the virus must reach the epithelial basal layer, where the specific integrin alpha 6 receptor is present.^[33] Once the infection becomes productive, cytopathic effects can appear, first of all koilocytosis.^[44] To make this happen, the patient's immune response plays an important role. During infection, viral antigen presentation is minimal and thus the infection can persist until years.^[33] In immunocompetent patients lesions usually regress spontaneously, while in immunodeficient the incidence and persistence of them is usually higher.^[49]

Regarding the oncological potential of the virus, there is much controversy about the true role played by the integration of viral DNA into human epithelial cells. Several authors have investigated its pathogenesis in OSCC. According to its role in the development of cervical cancer, HPV is classified into a high risk for malignant lesions subtype (HPV 16, 18, 31, 33, 35, 45, 51, 52, 56, 58, 59, 68, 73 and 82) and low-grade malignant lesions subtype but related to benign lesions (HPV 6, 11, 13, 32, 42, 43, 44).^[33,50]

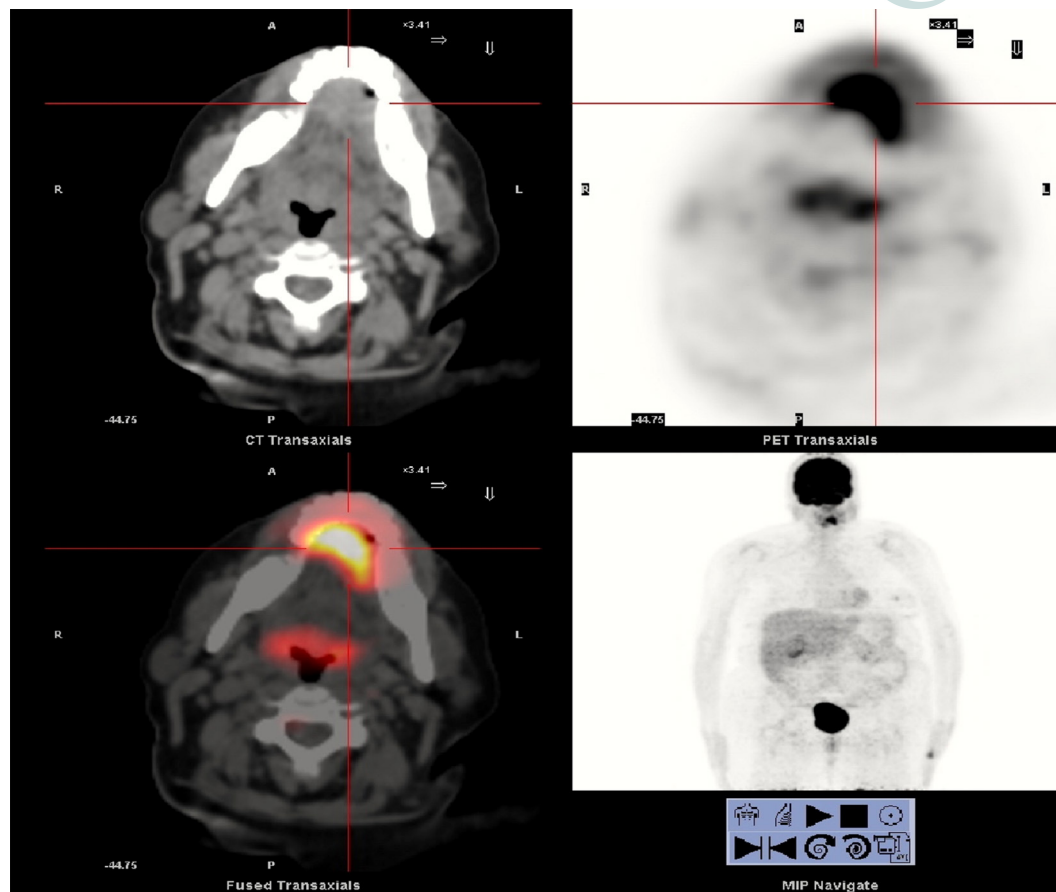


Figure 2: Positron emission tomography-computed tomography shows a mass in the left region of the anterior mouth floor, with marked increase glucose metabolism, about 3 cm in diameter and high probability of malignancy. The other cervical structures have normal glucose metabolism, showing no other hypermetabolic neoplastic involvement

The HPV genome is divided into about eight open reading frames (ORFs) divided into three regions:^[2,33] (1) early region (E): it is required for replication, cell transformation and control of viral transcription; (2) late region (L): it encodes structural proteins; and (3) long control region (LCR): it is required for replication and transcription of viral DNA.

In E, three proteins are encoded, which are often described as involved in the carcinogenesis related to the virus: pE7, pE6 and pE5.^[2,33,44] PE5 stimulates proliferation and inhibits apoptosis, while pE7 and pE6 act as oncogenes.^[2,33,47,48,51,52]

The final result is an induced and unregulated cell proliferation, with consequent immortality of the keratinocyte^[19] due to the integration and expression of the viral genome into the host cell. Chromosome aberrations and excessive production of viral DNA^[53,54] all occur due to inhibition of tumor suppressor factors (p21, p53 and pRb roads).^[19]

However, although the involvement of inhibition of tumor suppressor gene p53 in the carcinogenic effect of HPV seems to be clear, there are some publications that question the relationship of p53 polymorphism with the risk of oral cancer,^[55] suggesting that HPV does not play an important role oral lesions due to low detection in their analysed.^[56-59] This could be justified by population differences, sample size, detection techniques and tumor location. Some studies suggest that in HPV+ OSCC, p53 mutation is conditioned by tumor localization and expression of E6 and E7 viral genes, appearing a mutated p53 when the tumor is HPV+ but it does

not express these genes (mainly oropharynx), or when the tumor is HPV-.^[60,61]

Epidemiology and prevalence

Epidemiology and prevalence of HPV infection associated with OSCC varies according to the published data. Large studies tend to have lower rates of HPV (< 50%) than smaller studies (0-100%).^[25,62] Miller and Johnstone^[33] in a meta-analysis about 4,680 patients with OSCC from 94 reports reported that HPV was present in 46.5% of the cases (95% CI, 37.6-55.5%). However, the oral cavity was not the most often location, being surpassed by the oropharynx.^[63,64]

Kreimer *et al.*^[14] in a meta-analysis from 60 publications in 2005 (5,046 patients) reported that the overall prevalence of HPV in OSCC was 25.9% to 34.5%.^[14,25] The prevalence of OSCC ranges from < 2% to 100%^[10,25,57,65] and it may be because some studies do not differentiate between Paraffine Embedded and Fresh Frozen biopsies or different classification criteria, including incorrectly OPSCC within the OSCC, making an overestimation.^[25]

There is an association between the presence of HPV and age; patients older than 60 years have a lower HPV+ prevalence (29.4%) compared to patients under that age (77.8%).^[66] Within the OPSCC HPV+, HPV16 is higher in patients younger than fifty years.^[67,68] In relationship to sexual behaviour, the risk of oral cancer increases in male patients with decreasing age of first intercourse, with increasing numbers of partners and history of genital warts.^[69]

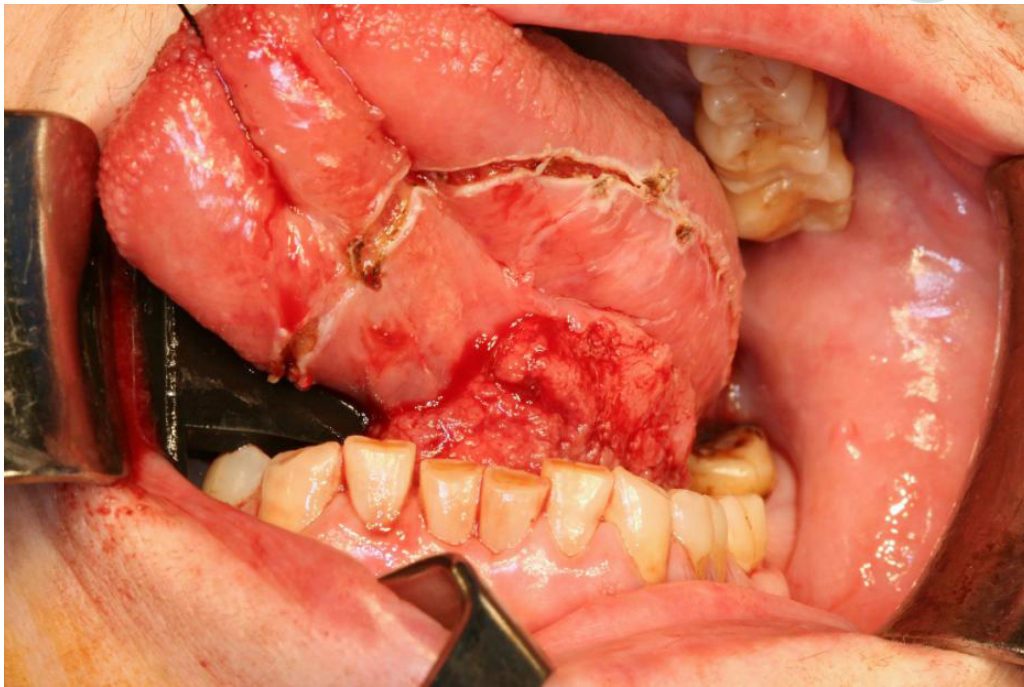


Figure 3: Intraoperative image. After performing tracheotomy, double functional bilateral neck dissection, excision of the lesion with macroscopic margins above the centimeter and subsequent reconstruction with radial forearm flap was performed. Histological results reveals a pT3N0M0 human papillomavirus 16+ squamous cell carcinoma, with close resection margins, 6 mm thickness, with no vascular or perineural infiltration. After surgery, the patient received adjuvant radiotherapy. She is currently without signs of loco-regional recurrence

Regarding to etnogeographical differences, some authors suggest that Japanese studies tend to have the highest rate of HPV,^[70,71] while Africans tend to have the lowest rate.^[59] Kreimer *et al.*^[14] established that HPV+ prevalence was higher among studies from North America compared with those from Europe and Asia. In 2016, Mehanna *et al.*^[72] conducted a prospective study of 801 patients with head and neck cancers. They established the geographic variability (differences between continents) as an independent risk factor for HPV+ prevalence of OPSCC. It is most prevalent in Western Europe, when compared to Eastern Europe (37%, 155 of 422 vs. 6%, 8 of 144; $P < 0.0001$) and Asia (37% vs. 2%, 4 of 217; $P < 0.0001$).

Regarding the genotype, the most prevalent is HPV16 (68.2-90%)^[14,33,66] [Figures 1-3] followed by HPV18 (34.1%).^[14,73] But this varies depending on the series analysed and the techniques used, and that proportion may be reversed, being higher HPV18.^[28,59] Although the association between HPV and OSCC is described,^[32,62,68,74-77] it is important to note that high-risk genotypes HPV16 have been detected in normal oropharyngeal mucosa,^[78,79,62] questioning this causal relationship. In 2001, Mork *et al.*^[80] defined HPV infection as a risk factor for OSCC, whose exposure may precede the occurrence of OPSCC in 10 years and older.

In the oropharynx there is no hard evidence linking HPV with alcohol or tobacco use, and the absence of synergism is the most accepted hypothesis,^[81] suggesting two ways for the development of OPSCC, one derived from smoking with or without alcohol and another derived from the HPV induced genomic instability.^[31]

Most frequent location

HPV has a predilection for the oropharynx and the Waldeyer ring.^[14,24,59] It is estimated that the most frequent location

for detecting papillomavirus DNA is the palatine tonsil and the base of the tongue, with a strong causal association,^[14,82] independently of the influence of smoking or alcohol. Oropharyngeal HPV+ tumours appears in up to six times more often than in other tumours of the head and neck.^[6] Snijders *et al.*^[83] were the first to suggest the amygdala is linked with the HPV, in 1992.

Detection, diagnosis and typing techniques

Molecular assays are the gold standard for HPV identification,^[84] mainly polymerase chain reaction (PCR),^[85] specifically the reverse transcription PCR (RT-PCR) to measure viral mRNA E6 and E7 in fresh tissue.^[86] It has a high sensitivity.^[80,85-88] It is even able to detect latent infections. Other tests that have been used for detection of HPV are “Southern Blot” (less sensitivity than PCR)^[89] and *in situ* hybridization (ISH) (less sensitive and less expensive than PCR). Some authors have proposed the combination of PCR with ISH, combining the advantages of the two tests: the high sensitivity of PCR and the ability of ISH to identify and localize genomic sequences linked to HPV in this kind of tumours.^[90,91]

P16 is a protein used by some authors as a biomarker for HPV infection, which can be expressed when viral DNA is integrated into the host cell. It reflects the functional effects derived from the inactivation of pRb, induced by E7. It is detected by immunohistochemistry staining and it can be used as a predictor of HPV infection in OPSCC, even being proposed by some authors the detection of p16INK4A as an initial test, followed by the detection of HPV in which are positive for this.^[92-94]

Regarding to the sample being sent for testing, the most commonly accepted it is taking biopsies or tumour specimen analysis [Figure 1]. This allows not only molecular analysis

but also morphological analysis of the piece, including all cell layers where the virus may be latently.^[95] As a method of screening for epidemiological studies, Lawton *et al.*^[96] reported that mouthwash is the technique of choice, although higher performance by combining different sampling techniques is obtained.

Virus relationship with other oral lesions

Since the early 1980s some authors have reported the presence of HPV not only in cancerous lesions of the oral cavity, but also in premalignant lesions.^[15,97,98] Recently, the presence of HPV has been identified as an independent prognostic factor for survival in patients with OPSCC.^[38] Miller and Johnstone^[33] indicate that HPV (low and high risk serotypes) are 2-3 times more detected in precancerous mucosa and almost 5 times more detected in carcinoma than in non-neoplastic mucosa: (1) 22.2% in benign leukoplakia; (2) 26.2% in intraepithelial neoplasias; and (3) 46.5% in OSCC, with a detection probability of high-risk ones 2.8 times higher than low risk.

Jayaprakash *et al.*^[34] published in 2011 a meta-analysis about 458 oropharyngeal dysplasias, estimating that the prevalence of HPV16/18 is 24.5%. They reported that HPV16/18 were 3 times more common in dysplastic lesions (OR, 3.29; 95% CI, 1.95-5.53%) and invasive cancers (OR, 3.43; 95% CI, 2.07-5.69%), when compared to normal biopsies. In addition, they found these two genotypes are at least 2.5 times more common in men than in women. Within oral leukoplakia, proliferative verrucous leukoplakia is believed to have a stronger relationship with HPV^[44] mainly 16, with a range of onset between 10% and 85%,^[99,100] and higher rate of malignant transformation.^[101] Some authors have also reported a relationship between lichen planus and HPV, ranging from 0 to 100%,^[102] which indicates the existing controversy about this association.

Many publications are studying virus connection with benign lesions or even in normal mucosa, varying its prevalence depending on the technique used, many times no PCR techniques are used, which may underestimate measurements. As a summary:

Appearance in normal mucosa: varies between 0 and 81%.^[78,103] It may appear subclinical or latent,^[104] being detected by the extreme sensitivity of the PCR and may be or not related to the emergence of a future lesion.

Squamous papilloma: clinically often indistinguishable from common warts. HPV genotypes 6 and 11 are most frequently associated, detected by ISH.^[105]

Condyloma accuminatum: it is a sexually transmitted infection and it is usually related to HPV 6 and 11 infection, varying its positivity between 75% and 85% in oral lesions.^[106,107] Furthermore it is also related to the HPV 16.^[108,109] It is usually present in HIV+ patients.^[110]

Common wart (verruca vulgaris): oral lesions usually result from autoinoculation from the fingers. It usually occurs in children. The HPV 2 is described as the most frequently related, followed by HPV 57,^[106,111] detected most of the time

with no PCR techniques between 80% and 90%. Other authors with more recent publications detected more frequently HPV2 and 4.^[109]

Focal epithelial hyperplasia (Heck's disease): they usually occur in children and young adults. There is usually genetic predisposition.^[112] HPV13 (20%) and HPV32 (60%) are related to those lesions.^[113-115]

Prognosis and treatment

There is much controversy about the role that infection by the HPV plays in the prognosis and treatment of patients with OSCC. Most of the published studies are retrospective. But they do generally conclude that the presence of HPV divides these tumours in two different entities with different prognostic and therapeutic implications. The most commonly accepted is that patients with OPSCC HPV+ have a better prognosis due to increased survival, showing better treatment response rates.^[36,38,63,116-118]

The most cited paper in the literature is the one published by Fakhry *et al.*^[36] in 2008. They conducted a prospective phase 2 study of 96 patients with oral, oropharyngeal and laryngeal SCC. All patients received two cycles of induction chemotherapy with paclitaxel and carboplatin followed by concurrent weekly paclitaxel and radiotherapy. They detected HPV (types 16, 33 and 35) with PCR and ISH in 40% of all patients. They compared their response to treatment with HPV-: OSCC HPV+ have better respond to chemotherapy (82% vs. 55%, difference = 27%, 95% CI, 9.3-44.7%; $P = 0.01$) and chemo-radiotherapy (84% vs. 57%, difference = 27%, 95% CI, 9.7-44.3%; $P = 0.007$).

Patients with OSCC HPV + have a better overall survival rate at two years [95% (95% CI, 87-100%) vs. 62% (95% CI, 49-74%), (difference = 33%, 95% CI, 18.6-47.4%; $P = 0.005$, log-rank test)] and a lower risk of disease progression than HPV- [Hazard Ratio (HR), 0.27; 95% CI, 0.10-0.75%].

In 2007, Ragin and Taioli^[35] performed a meta-analysis of 37 studies, which conclude that patients with OSCC HPV+ had a lower risk of death (HR = 0.85 target; 95% CI, 0.7-1.0) and lower risk of recurrence (HR = 0.62 target; 95% CI, 0.5-0.8) than in HPV-. Regarding OPSCC they conclude that HPV+ had a reduced risk of death of 28% (Target HR 0.72; 95% CI, 0.5-1.0) compared with HPV- with a similar result for disease-free survival (Meta HR, 0.51; 95% CI, 0.4-0.7).

In the same year, Rosenquist *et al.*^[32] conducted a prospective study of cases and controls over 128 Swedish patients with OPSCC to evaluate the influence of different risk factors for recurrence or appearance of new second primaries in the first 3 years after the diagnosis. They found, unlike other published studies that high-risk HPV+ cases had a higher risk of recurrence/second primary tumour, but lower risk of death in intercurrent disease, compared with HPV- ones.

In 2008, Worden *et al.*^[119] conducted a study about the response to treatment of 66 patients with OPSCC. They found that the presence of HPV was significantly associated with response to chemotherapy ($P = 0.001$), chemo-radiotherapy (P

= 0.005), with better overall survival ($P = 0.007$) and disease-free survival ($P = 0.008$). They conclude that chemotherapy followed by chemo-radiation therapy is an effective treatment especially in patients with HPV + OPSCC.

In 2010, Ang *et al.*^[38] conducted a retrospective study of the association between tumor HPV status and survival among 743 patients with stage III or IV OPSCC who were enrolled in a randomized trial comparing treatment with accelerated-fractionation RT+ cisplatin vs. standard-fractionation RT+ cisplatin. Among 323 OPSCC, 63.8% were HPV+, which presented better 3-year rates of overall survival (82.4% vs. 57.1% among patients with HPV- negative tumours; $P < 0.001$ by the log-rank test) and they also had a 58% reduction in the risk of death (HR, 0.42; 95% CI, 0.27 to 0.66). They concluded that among patients with OPSCC, tumor HPV status is a strong and independent prognostic factor for survival.

Some authors have studied the prognostic influence of some biomarkers related to HPV infection in OSCC. One of the most studied biomarkers is p16, being observed that p16+ and HPV+ patients have a better overall survival compared with HPV- or HPV+ but p16-.^[93] This was corroborated in the prospective phase III study of concomitant chemotherapy published in 2011 by Rischin *et al.*^[37] In a sample of 465 patients with OPSCC stage III or IV, 172 were analysed with evaluable HPV and p^{16INK4A} status, and 185 with eligible p16 status. They randomized RT+ cisplatin with or without tirapazamine, concomitantly. They found that p16+ tumours compared to p16- presented: (1) higher rates of overall survival at 2 years (91% vs. 74%; HR, 0.36; 95% CI, 0.17-0.74; $P = 0.004$); (2) higher rates of relapse-free survival (87% vs. 72%; HR, 0.39; 95% CI, 0.20-0.74; $P = 0.003$); and (3) lower loco-regional recurrence and death rates from other causes. They also observed a trend in favour of tirapazamine group in terms of improved loco-regional control disease in p16- patients (HR, 0.33; 95% CI, 0.09-1.24; $P = 0.13$). They concluded that OPSCC HPV+ have a favourable prognosis when treated with cisplatin-based chemotherapy, compared to HPV-.

In 2014, Lassen *et al.*^[39] published a retrospective study among 1,294 Danish patients with advanced stage OPSCC. They observed that p16 positivity was significantly higher in oropharyngeal than non-oropharyngeal SCC ($P < 0.0001$). OPSCC p16+ presented a statistically significant improvement in loco-regional disease control with primary RT [HR (95% CI), 0.38 (0.29-0.49)], free survival events [HR (95% CI), 0.44 (0.35-0.56)] and overall survival [HR (95% CI), 0.38 (0.29-0.49)], unlike in non-OP.

Future therapeutic lines

HPV+ OSCC response to RT, chemotherapy and the combination of both are topics widely approached in the literature and specialized forums. However, little or nothing is known about immunotherapy techniques and their effectiveness. In 2015, Rosenthal *et al.*^[120] published a retrospective assessment of the IMCL-9815 study, trying to find if there were any differences in treatment patients with RT alone vs. RT+ cetuximab, in a series of 182 OSCC patients, in relation to the presence or absence of HPV and p16. They concluded that the addition of cetuximab to RT improved

clinical outcomes regardless of p16 or HPV positivity. They also indicated that p16 does not predicted response to cetuximab.

Unlike cervical cancer, regarding OSCC there is not much literature on the use of HPV vaccines to treat these tumours. The effectiveness of the HPV vaccine against OSCC is not yet proven.

In conclusion, there is much controversy about the carcinogenic potential of HPV. Its mechanism usually involves the pE7 and pE6 proteins, which can delete p53, p21 and pRb routes.

HPV+ patients are usually diagnosed at a younger age, mainly those with oropharyngeal tumours, presenting positivity first of all for HPV16 > HPV18, although it varies depending on the population and the test used to detect the infection.

For more diagnostic performance, the most advisable is to use the combination of several techniques. P16 positivity needs to be mentioned in special attention as a predictor of HPV infection in the OPSCC for their prognostic and therapeutic considerations.

HPV can appear in normal mucosa, benign and precancerous lesions.

The most commonly accepted is that the presence of HPV divides OSCC, mainly oropharyngeal, in two types of tumours with different prognostic and therapeutic implications.

Despite the great controversy in prognosis, most studies tend to indicate that HPV+ OSCC have an increased survival, better treatment response rates, lower risk of death and lower risk of recurrence [Figure 3].

The oropharyngeal region should be analysed separately. OPSCC HPV+ tend to respond better to radio-chemotherapy treatments, considering the HPV positivity as a strong and independent survival prognostic factor. In addition, if p16+, these tumours tend to have better survival and loco-regional disease-control.

Future research should evaluate the possibility of new treatments.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Scully C, Field JK, Tanzawa H. Genetic aberrations in oral or head and neck squamous cell carcinoma (SCCHN): I. Carcinogen metabolism, DNA repair and cell cycle control. *Oral Oncol* 2000;36:256-63.
2. Syrjänen S, Lodi G, von Bültzingslöwen I, Aliko A, Arduino P, Campisi G, Challacombe S, Ficarra G, Flaitz C, Zhou HM, Maeda H, Miller C, Jontell M. Human papillomavirus in oral carcinoma and oral potentially malignant disorders: a systematic review. *Oral Dis* 2011;17 Suppl 1:58-72.
3. Pande P, Soni S, Kaur J, Agarwal S, Mathur M, Shukla NK, Ralhan R.

- Prognostic factors in betel and tobacco related oral cancer. *Oral Oncol* 2002;38:491-9.
4. Franceschi S, Levi F, La Vecchia C, Conti E, Dal Maso L, Barzan L, Talamini R. Comparison of the effect of smoking and alcohol drinking between oral and pharyngeal cancer. *Int J Cancer* 1999;83:1-4.
 5. La Vecchia C, Tavani A, Franceschi S, Levi F, Corrao G, Negri E. Epidemiology and prevention of oral cancer. *Oral Oncol* 1997;33:302-12.
 6. Gillison ML, Koch WM, Capone RB, Spafford M, Westra WH, Wu L, Zahurak ML, Daniel RW, Viglione M, Symer DE, Shah KV, Sidransky D. Evidence for causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst* 2000;92:709-20.
 7. D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, Westra WH, Gillison ML. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med* 2007;356:1944-56.
 8. Hammarstedt L, Lindquist D, Dahlstrand H, Romanitan M, Dahlgren LO, Joneberg J, Creson N, Lindholm J, Ye W, Dalianis T, Munck-Wikland E. Human papillomavirus as a risk factor for the increase in incidence of tonsillar cancer. *Int J Cancer* 2006;110:2620-3.
 9. Mellin H, Friesland S, Lewensohn R, Dalianis T, Munck-Wikland E. Human papillomavirus (HPV) DNA in tonsillar cancer: clinical correlates, risk of relapse, and survival. *Int J Cancer* 2000;89:300-4.
 10. Paz IB, Cook N, Odom-Maryon T, Xie Y, Wilczynski SP. Human papillomavirus in head and neck cancer: an association of HPV 16 with squamous cell carcinoma of Waldeyer's tonsillar ring. *Cancer* 1997;79:595-604.
 11. Shiboski CH, Schmidt BL, Jordan RC. Tongue and tonsil carcinoma: increasing trends in the US population ages 20-44 years. *Cancer* 2005;103:1843-9.
 12. Canto MT, Devesa SS. Oral cavity and pharynx cancer incidences rates in the United States, 1975-1998. *Oral Oncol* 2002;38:610-7.
 13. Frisch M, Hjalgrim H, Jaeger AB, Biggar RJ. Changing patterns of tonsillar squamous cell carcinoma in the United States. *Cancer Causes Control* 2000;11:489-95.
 14. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinoma worldwide: a systematic review. *Cancer Epidemiol Biomarkers Prev* 2005;14:467-75.
 15. Syrjänen K, Syrjänen S, Lamberg M, Pyrhönen S, Nuutinen J. Morphological and immunohistochemical evidence suggesting human papillomavirus (HPV) involvement in oral squamous cell carcinogenesis. *Int J Oral Surg* 1983;12:418-24.
 16. Franceschi S, Muñoz N, Bosch XF, Snijders PJ, Walboomers JM. Human papillomavirus and cancers of the upper aerodigestive tract: a review of epidemiological and experimental evidence. *Cancer Epidemiol Biomarkers Prev* 1996;5:567-75.
 17. Lönging T, Ikenberg H, Becker J, Gissmann L, Hoepfer I, zur Hausen H. Analysis of oral papillomas, leukoplakias, and invasive carcinomas for human papillomavirus type related DNA. *J Invest Dermatol* 1985;84:417-20.
 18. Tran N, Rose BR, O'Brien CJ. Role of human papillomavirus in the etiology of head and neck cancer. *Head Neck* 2007;29:64-70.
 19. Ragin CC, Modugno F, Gollin SM. The epidemiology and risk factors of head and neck cancer: a focus on human papillomavirus. *J Dent Res* 2007;86:104-14.
 20. Gillson ML. Human papillomavirus-associated head and neck cancer is a distinct epidemiologic, clinical and molecular entity. *Semin Oncol* 2004;31:744-54.
 21. Dahstrand H, Dahlgren L, Lindquist D, Munck-Wikland E, Dalianis T. Presence of human papillomavirus in tonsillar cancer is a favourable prognostic factor for clinical outcome. *Anticancer Res* 2004;24:1829-35.
 22. Sanderson RJ, Ironside JA. Squamous cell carcinomas of the head and neck. *BMJ* 2002;325:822-7.
 23. Gillison ML, Lowy DR. A causal role for human papillomavirus in head and neck cancer. *Lancet* 2004;365:1488-9.
 24. Miller CS, White DK. Human Papillomavirus expression in oral mucosa, premalignant conditions, and squamous cell carcinoma: a retrospective review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996;82:57-68.
 25. Termine N, Panzarella V, Falaschini S, Russo A, Matranga D, Lo Muzio L, Campisi G. HPV in oral squamous cell carcinoma vs. head and neck squamous cell carcinoma biopsies: a meta-analysis (1988-2007). *Ann Oncol* 2008;19:1681-90.
 26. Charfi L, Jouffroy T, de Cremoux P, Le Peltier N, Thioux M, Fréneaux P, Point D, Girod A, Rodriguez J, Sastre-Garau X. Two types of squamous cell carcinoma of the palatine tonsil characterized by distinct etiology, molecular features and outcome. *Cancer Lett* 2008;260:72-8.
 27. Niedobitek G, Pitteroff S, Herbst H, Shepherd P, Finn T, Anagnostopoulos I, Stein H. Detection of human papillomavirus type 16 DNA in carcinomas of the palatine tonsil. *J Clin Pathol* 1990;43:918-21.
 28. Soares RC, Oliveira MC, de Souza LB, Costa Ade L, Pinto LP. Detection of HPV DNA and immunohistochemical expression of cell cycle proteins in oral carcinoma in a population of Brazilian patients. *J Appl Oral Sci* 2008;16:340-4.
 29. El-Mofty SK, Lu DW. Prevalence of human papillomavirus type 16 DNA in squamous cell carcinoma of the palatine tonsil, and not the oral cavity, in young patients: a distinct clinicopathologic and molecular disease entity. *AM J Surg Pathol* 2003;27:1463-70.
 30. El-Mofty SK, Patil S. Human papillomavirus (HPV)-related oropharyngeal nonkeratinizing squamous cell carcinoma: characterization of a distinct phenotype. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;101:339-45.
 31. Chen SF, Yu FS, Chang YC, Fu E, Nieh S, Lin YS. Role of human papillomavirus infection in carcinogenesis of oral squamous cell carcinoma with evidences of prognostic association. *J Oral Pathol Med* 2012;41:9-15.
 32. Rosenquist K, Wennerberg J, Annerz K, Schildt EB, Hansson BG, Bladström A, Andersson G. Recurrence in patients with oral and oropharyngeal squamous cell carcinoma: human papillomavirus and other risk factors. *Acta Otolaryngol* 2007;127:980-7.
 33. Miller CS, Johnstone BM. Human papillomavirus as a risk factor for oral squamous cell carcinoma: a meta-analysis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001;91:622-35.
 34. Jayaprakash V, Reid M, Hatton E, Merzianu M, Rigual N, Marshall J, Gill S, Frustino J, Wilding G, Loree T, Popat S, Sullivan M. Human papillomavirus types 16 and 18 in epithelial dysplasia of oral cavity and oropharynx: a meta-analysis, 1985-2010. *Oral Oncol* 2011;47:1048-54.
 35. Ragin CC, Taioli E. Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: review and meta-analysis. *Int J Cancer* 2007;121:1813-20.
 36. Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, Forastiere A, Gillison ML. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst* 2008;100:261-9.
 37. Rischin D, Young RJ, Fisher R, Fox SB, Le QT, Peters LJ, Solomon B, Choi J, O'Sullivan B, Kenny LM, McArthur GA. Prognostic significance of p16INK4A and human papillomavirus in patients with oropharyngeal cancer treated on TROG 02.02 phase III trial. *J Clin Oncol* 2010;28:4142-8.
 38. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP, Gillison ML. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010;363:24-35.
 39. Lassen P, Primdahl H, Johansen J, Kristensen CA, Andersen E, Andersen LJ, Evensen JF7, Eriksen JG8, Overgaard J8; Danish Head and Neck Cancer Group (DAHANCA). Impact of HPV-associated p16-expression on radiotherapy outcome in advanced oropharynx and non-oropharynx cancer. *Radiother Oncol* 2014;113:310-6.
 40. De Villiers EM. Papillomavirus and HPV typing. *Clin Dermatol* 1997;15:199-206.
 41. Van Regenmortel MHV FC, Fauquet CM, Bishop DHL, Carsten EB, Estes MK, Lemon SM, Maniloff J, Mayo MA, McGeoch DJ, Pringle CR, Wickner RB. Virus taxonomy: classification and nomenclature of viruses. Seventh report of the International Committee on Taxonomy of Viruses. New York, San Diego: Academic Press; 2000.
 42. Howley PM. Role of the human papillomaviruses in human cancer. *Cancer Res* 1991;51:S5019-22.
 43. Cobb MV. Human papillomavirus infection. *J Am Acad Dermatol* 1990;22:547-66.
 44. Campsini G, Panzarella V, Giuliani M, Lajolo C, Di Fede O, Falaschini S, Di Liberto C, Scully C, Lo Muzio L. Human papillomavirus: its identity and controversial role in oral oncogenesis, premalignant and malignant lesions (Review). *Int J Oncol* 2007;30:813-23.
 45. Cason J, Kaye J, Pakarian F, Raju KS, Best JM. HPV-16 transmission. *Lancet* 1995;345:197-8.
 46. Mindel A, Tideman R. HPV transmission - still feeling the way. *Lancet* 1999;354:2097-8.
 47. Hiller T, Iftner T. The human papillomavirus. In: Prendiville W, Davies P, editors. Human papillomavirus and cervical cancer. The Health Professional's HPV Handbook. London and New York: Taylor & Francis; 2004. p. 11-26.
 48. Antonsson A, Forslund O, Ekburg H, Sterner G, Hanson BG. The ubiquity and impressive genomic diversity of human skin papillomavirus suggest a commensal nature of these viruses. *J Virol* 2000;74:11636-41.
 49. Chang F. Role of papillomaviruses. *J Clin Pathol* 1990;43:269-76.
 50. World Health Organization; International Agency for Research on Cancer (IARC). Human papillomavirus. *IARC Monogr Eval Carcinog Rsk Hum* 2007;90:47-79,113-7.
 51. De Villiers EM, Gunst K. Characterization of seven novel human papillomavirus types isolated from cutaneous tissue, but also present in mucosal lesions. *J Gen Virol* 2009;90:1994-2004.
 52. De Villiers EM, Faquet C, Broker TR, Bernard HU, Zur Hausen H. Classification of papillomaviruses. *Virology* 2004;324:17-27.

53. Munger K, Werness BA; Dyson N, Phelps WC, Harlow E, Howley PM. Complex formation of human papillomavirus E7 proteins with the retinoblastoma tumor suppressor gene product. *EMBO J* 1989;8:4099-105.
54. Werness BA, Levine AJ, Howley PM. Association of human papillomavirus types 16 and 18 E6 proteins with p53. *Science* 1990;248:76-9.
55. Saini R, Tang TH, Zain RB, Cheong SC, Musa KI, Saini D, Ismail AR, Abraham MT, Mustafa WM, Santhanam J. Significant association of high-risk human papillomavirus (HPV) but not of p53 polymorphisms with oral squamous cell carcinomas in Malaysia. *J Cancer Res Clin Oncol* 2011;137:311-20.
56. Ishibashi M, Kishino M, Sato S, Morii E, Ogawa Y, Aozasa K, Kogo M, Toyosawa S. The prevalence of human papillomavirus in oral premalignant lesions and squamous cell carcinoma in comparison to cervical lesions used as a positive control. *Int J Clin Oncol* 2011;16:646-53.
57. Khvidhunkit SP, Buajeeb W, Sanguansri S, Poomsawat S, Weerapradist W. Detection of human papillomavirus in oral squamous cell carcinoma, leukoplakia and lichen planus in Thai patients. *Asian Pacific J Cancer Prev* 2008;9:771-5.
58. Rivero ER, Nunes FD. HPV in oral squamous cell carcinomas of Brazilian population: amplification by PCR. *Braz Oral Res* 2006;20:21-4.
59. Boy S, Van Rensburg EJ, Engelbrecht S, Dreyer L, van Heerden M, van Heerden W. HPV detection in primary intra-oral squamous cell carcinomas-commensal, aetiological agent or contamination? *J Oral Pathol Med* 2008;35:86-90.
60. Wiest T, Schwartz E, Enders C, Flechtenmacher C, Bosch FX. Involvement of intact HPV16 E6/E7 gene expression in head and neck cancers with unaltered p53 status and perturbed pRb cell cycle control. *Oncogene* 2002;21:1510-7.
61. van Houten VM, Snijders PJ, van den Brekel MW, Kummer JA, Meijer CJ, van Leeuwen B, Denkers F, Smele LE, Snow GB, Brakenhoff RH. Biological evidence that human papillomaviruses are etiologically involved in a subgroup of head and neck squamous cell carcinomas. *Int J Cancer* 2001;93:232-5.
62. Cox M, Maitland N, Scully C. Human Herpes simplex-1 and papillomavirus type 16 homologous DNA sequences in normal, potentially malignant and malignant oral mucosa. *Eur J Cancer B Oral Oncol* 1993;29B:215-9.
63. Gillson ML, D'Souza G, Westra W, Sugar E, Xiao W, Begum S, Viscidi R. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. *J Natl Cancer Inst* 2008;100:407-20.
64. Pannone G, Santoro A, Papagerakis S, Lo Muzio L, De Rosa G, Bufo P. The role of human papillomavirus in the pathogenesis of head and neck squamous cell carcinoma: an overview. *Infect Agents* 2011;6:4.
65. Van Rensburg EJ, Engelbrecht S, Van Heerden WT, Raubenheimer EJ, Schoub BD. Human papillomavirus DNA in oral squamous cell carcinomas from African population sample. *Anticancer Res* 1996;16:969-73.
66. Cruz IB, Snijders PJ, Steenberg RD, Meijer CJ, Snow GB, Walboomers JM, van der Waal I. Age-dependence of human papillomavirus DNA presence in oral squamous cell carcinomas. *Eur J Cancer B Oral Oncol* 1996;32B:55-62.
67. Smith EM, Ritchie JM, Pawlita M, Rubenstein LM, Haugen TH, Turek LP, Hamsikova E. Human papillomavirus seropositivity and risks of head and neck cancer. *Int J Cancer* 2007;120:825-32.
68. Smith EM, Ritchie JM, Summersgill KF, Klussmann JR, Lee JH, Wang D, Haugen TH, Turek LP. Age, sexual behaviour and human papillomavirus infection in oral cavity and oropharyngeal cancers. *Int J Cancer* 2004;108:766-72.
69. Schwartz SM, Daling JR, Doody DR, Wipf GC, Carter JJ, Madeleine MM, Mao EJ, Fitzgibbons ED, Huang S, Beckmann AM, McDougall JK, Galloway DA. Oral cancer risk in relation to sexual history and evidence of human papillomavirus infection. *J Natl Cancer Inst* 1998;90:1626-36.
70. Zhang ZY, Sdek P, Cao J, Chen WT. Human papillomavirus type 16 and 18 DNA in oral squamous cell carcinoma and normal mucosa. *Int J Oral Maxillofac Surg* 2004;33:71-4.
71. Sugiyama M, Bhawal UK, Kawamura M, Ishioka Y, Shigeishi H, Higashikawa K, Kamata N. Human papillomavirus-16 in oral squamous cell carcinoma: clinical correlates and 5-year survival. *Br J Oral Maxillofac Surg* 2007;45:116-22.
72. Mehanna H, Franklin N, Compton N, Robinson M, Powell N, Biswas-Baldwin N, Pileri V, Hartley A, Fresco L, Al-Booz H, Junor E, El-Hariry I, Roberts S, Harrington K, Ang KK, Dunn J, Woodman C. Geographic variation in human papillomavirus-related oropharyngeal cancer: data from four multinational randomized trials. *Head Neck* 2016;38 Suppl 1:E1863-9.
73. Mathew A, Mody RN, Patait MR, Razooki AA, Varghese NT, Saraf K. Prevalence and relationship of human papilloma virus type 16 and type 18 with oral squamous cell carcinoma and oral leukoplakia in fresh scrapings: a PCR study. *Indian J Med Sci* 2011;65:212-21.
74. Hansson BG, Rosenquist K, Antonsson A, Wennerberg J, Schildt EB, Bladström A, Andersson G. Strong association between infection with human papillomavirus and oral and oropharyngeal squamous cell carcinoma: a population-based case-control study in southern Sweden. *Acta Otolaryngol* 2005;125:1337-44.
75. Herrero R, Castellsagué X, Pawlita M, Lissowska J, Kee F, Balam P, Rajkumar T, Sridhar H, Rose B, Pintos J, Fernández L, Idris A, Sánchez MJ, Nieto A, Talamini R, Tavani A, Bosch FX, Reidel U, Snijders PJ, Meijer CJ, Viscidi R, Muñoz N, Franceschi S; IARC Multicenter Oral Cancer Study Group. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. *J Natl Cancer Inst* 2003;95:1772-83.
76. Smith EM, Ritchie JM, Summersgill KF, Hoffman HT, Wang DH, Haugen TH, Turek LP. Human papillomavirus in oral exfoliated cells and risk of head and neck cancer. *J Natl Cancer Inst* 2004;96:449-55.
77. Dahlstrom KR, Adler-Storthz K, Etzel CJ, Liu Z, Dillon L, El-Naggar AK, Spitz MR, Schiller JT, Wei Q, Sturgis EM. Human papillomavirus type 16 infection and squamous cell carcinoma of the head and neck in never-smokers: a matched pair analysis. *Clin Cancer Res* 2003;9:2620-6.
78. Terai M, Hashimoto K, Yoda K, Sata T. High prevalence of human papillomaviruses in the normal oral cavity of adults. *Oral Microbiol Immunol* 1999;14:201-5.
79. Kurose K, Terai M, Soedarsono N, Rabello D, Nakajima Y, Burk RD, Takagi M. Low prevalence of HPV infection and its natural history in normal oral mucosa among volunteers on Miyako Island, Japan. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004;98:91-6.
80. Mork L, Lie AK, Glatte E, Hallmans G, Jellum E, Koskela P, Møller B, Pukkala E, Schiller JT, Youngman L, Lehtinen M, Dillner J. Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2001;344:1125-31.
81. Shanesmith R, Ilen RA, Moore WE, Kingma DW, Caughron SK, Gillies EM, Dunn ST. Comparison of 2 line blot assays for defining HPV genotypes in oral and oropharyngeal squamous cell carcinomas. *Diagn Microbiol Infect Dis* 2011;70:240-5.
82. Pintos J, Black MJ, Sadeghi N, Ghadirian P, Zeitouni AG, Viscidi RP, Herrero R, Coutlée F, Franco EL. Human papillomavirus infection and oral cancer: a case-control study in Montreal, Canada. *Oral Oncol* 2008;44:242-50.
83. Snijders PJ, Cromme FV, van den Brule AJ, Schrijnemakers HF, Snow GB, Meijer CJ, Walboomers JM. Prevalence and expression of human papillomavirus in tonsillar carcinomas, indicating a possible viral etiology. *Int J Cancer* 1992;51:845-50.
84. Zaravinos A, Mammas IN, Sourvinos G, Spandidos DA. Molecular detection methods of human papillomavirus (HPV). *Int J Biol Markers* 2009;24:215-22.
85. Giovannelli L, Lama A, Capra G, Giordano V, Arici P, Ammatuna P. Detection of human papillomavirus DNA in cervical samples: analyses of the new PGMV-PCR compared to the hybrid capture II and MY-PCR assays and a two-step nested PCR assay. *J Clin Microbiol* 2004;42:3861-4.
86. Chernock RD, El-Mofty SK, Thorstad WL, Parvin CA, Lewis JS Jr. HPV-related nonkeratinizing squamous cell carcinoma of the oropharynx: utility of microscopic features in predicting patient outcome. *Head Neck Pathol* 2009;3:186-94.
87. Venuti A, Badaracco G, Rizzo C, Mafera B, Rahimi S, Vigili M. Presence of HPV in head and neck tumours: high prevalence in tonsillar localization. *J Exp Clin Cancer Res* 2004;23:561-6.
88. Remmerbach TW, Brinckmann UG, Hemprich A, Chekol M, Kühndel K, Liebert UG. PCR detection of human papillomavirus of the mucosa: comparison between MY09/11 and GP5+/6+ primer sets. *J Clin Virol* 2004;30:302-8.
89. Mckaig RG, Baric RS, Olshan AF. Human papillomavirus and head and neck cancer: epidemiology. *Head Neck* 1998;20:250-65.
90. Koyama K, Uobe K, Tanaka A. Highly sensitive detection of HPV-DNA in paraffin sections of human oral carcinomas. *J Oral Pathol Med* 2007;36:18-24.
91. Uobe K, Masuno K, Fang YR, Li LJ, Wen YM, Ueda Y, Tanaka A. Detection of HPV in Japanese and Chinese oral carcinomas by *in situ* PCR. *Oral Oncol* 2001;37:146-52.
92. Pannone G, Rodolico V, Santoro A, Lo Muzio L, Franco R, Botti G, Aquino G, Pedicillo MC, Cagiano S, Campisi G, Rubini C, Papagerakis S, De Rosa G, Tornesello ML, Buonaguro FM, Staibano S, Bufo P. Evaluation of a combined triple method to detect causative HPV in oral and oropharyngeal squamous cell carcinomas: p16 Immunohistochemistry, Consensus PCR HPV-DNA, and *In Situ* Hybridization. *Infect Agent Cancer* 2012;7:4.
93. Schache AG, Liloglou T, Risk JM, Filia A, Jones TM, Sheard J, Woolgar JA, Helliwell TR, Triantafyllou A, Robinson M, Sloan P, Harvey-Woodworth C, Sisson D, Shaw RJ. Evaluation of human papilloma virus diagnostic testing in oropharyngeal squamous cell carcinoma: sensitivity, specificity, and prognostic discrimination. *Clin Cancer Res* 2011;17:6262-71.
94. Husnjak K, Grce M, Magdic L, Pavelic K. Comparison of five different polymerase chain reaction methods for detection of human papillomavirus in cervical cell specimens. *J Virol Methods* 2000;88:125-34.
95. Longworth MS, Laimins LA. Pathogenesis of human papillomavirus in

- differentiating epithelia. *Microbiol Mol Biol Rev* 2004;68:362-72.
96. Lawton G, Thomas S, Schonrock J, Monsour F, Frazer I. Human papillomaviruses in normal mucosa: a comparison of methods for simple collection. *J Oral Pathol Med* 1992;21:265-9.
97. Loning T, Ikenberg H, Becker J, Gissmann L, Hoepfer I, zur Hausen H. Analysis of oral papillomas, leukoplakias, and invasive carcinomas for human papillomavirus type related DNA. *J Invest Dermatol* 1985;84:417-20.
98. de Villiers Em, Weidauer H, Otto H, zur Hausen H. Papillomavirus DNA in human tongue carcinomas. *Int J Cancer* 1985;36:575-8.
99. Palefsky JM, Silverman S Jr, Abdel-Salaam M, Daniels TE, Greenspan JS. Association between proliferative verrucous leukoplakia and infection with human papillomavirus type 16. *J Oral Pathol Med* 1995;24:193-7.
100. Fettig A, Pogrel MA, Silverman SJr, Bramanti TE, Da Costa M, Regezi JA. Proliferative Verrucous leukoplakia of the gingiva. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000;90:723-30.
101. Hansen LS, Olson JA, Silverman S Jr. Proliferative verrucous leukoplakia. A long-term study of thirty patients. *Oral Surg Oral Med Oral Pathol* 1985;60:285-98.
102. Lodi G, Scully C, Carrozzo M, Griffiths M, Sugerman PB, Thongprasom K. Current controversies in oral lichen planus: report of an international consensus meeting. Part I. Viral infections and etiopathogenesis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005;100:40-51.
103. Terai M, Takagi M. Human papillomavirus on oral cavity. *Oral Med Pathol* 2001;6:1-12.
104. Castro TP, Bussoloti Filho I. Prevalence of human papillomavirus (HPV) in oral cavity and oropharynx. *Braz J Otorhinolaryngol* 2006;72:272-82.
105. Eversole LR, Laipis PJ. Oral squamous papillomas: detection of HPV DNA by *in situ* hybridization. *Oral Surg Med Oral Pathol* 1998;65:545-50.
106. Syrjänen S. Human papillomavirus infections and oral tumours. *Med Microbiol Immunol* 2003;192:123-8.
107. Chang F, Syrjänen S, Kellokoski J, Syrjänen K. Human papillomavirus (HPV) infections and their associations with oral disease. *J Oral Pathol Med* 1991;20:305-17.
108. Manganaro AM. Oral condilloma accuminatum. *Gen Dent* 2000;48:62-4.
109. Eversole LR. Papillary lesions of the oral cavity: relationship to human papillomaviruses. *J Calif Dent Assoc* 2000;28:922-7.
110. Resnik DA. Oral manifestations of HIV Disease. *Top HIV Med* 2006;13:143-8.
111. Padayachee A, Sanders CM, Maitland NJ. A polymerase chain reaction (PCR) investigation of oral verrucae which contain HPV types 2 and 57 by *in situ* hybridization. *J Oral Pathol Med* 1995;24:329-34.
112. Garcia-Corona C, Vega-Memije E, Mosqueda-Taylor A, Yamamoto-Furusko JK, Rodríguez-Carreón AA, Ruiz-Morales JA, Salgado N, Granados J. Association of HLA-DR4 (DRB1*0404) with human papillomavirus infection in patients with focal epithelial hyperplasia. *Arch Dermatol* 2004;140:1227-31.
113. Schwenger JU, Von Buchwald C, Lindeberg H. Oral focal epithelial hyperplasia. Any risk of conclusion with oral condylomas? *Ugeskr Laeger* 2002;164:4287-90.
114. Pfister H, Heitich J, Runnae U, Chliff GN. Characterization of human papillomavirus type 13 from focal epithelial Heck's lesions. *J Virol* 1983;47:363-6.
115. Beaudenon S, Praetorius F, Kremsdorf D, Lutzner M, Worsaae N, Pehau-Arnaudet G, Orth G. A new type of human papillomavirus associated with oral focal epithelial hyperplasia. *J Invest Dermatol* 1997;88:130-5.
116. Fakhry C, Gillson ML. Clinical implications of human papillomavirus in head and neck cancers. *J Clin Oncol* 2006;24:2606-11.
117. Schwartz SR, Yueh B, McDougall JK, Daling JR, Schwartz SM. Human papillomavirus infection and survival in oral squamous cell cancer: a population-based study. *Otolaryngol Head Neck Surg* 2001;125:1-9.
118. Weinberger PM, Yu Z, Haffty BG, Kowalski D, Harigopal M, Brandsma J, Sasaki C, Joe J, Camp RL, Rimm DL, Psyrri A. Molecular classification identifies a subset of human papillomavirus-associated oropharyngeal cancers with favorable prognosis. *J Clin Oncol* 2006;24:736-47.
119. Worden FP, Kumar B, Lee JS, Wolf GT, Cordell KG, Taylor JM, Urba SG, Eisbruch A, Teknos TN, Chepeha DB, Prince ME, Tsien CI, D'Silva NJ, Yang K, Kurnit DM, Mason HL, Miller TH, Wallace NE, Bradford CR, Carey TE. Chemoselection as a strategy for organ preservation in advanced oropharynx cancer: response and survival positively associated with HPV-16 copy number. *J Clin Oncol* 2008;26:3138-46.
120. Rosenthal DI, Harari PM, Giralt J, Bell D, Raben D, Liu J, Schulten J, Ang KK, Bonner JA. Association of human papillomavirus and p16 status with outcomes in the IMCL-9815 phase III registration trial for patients with locoregionally advanced oropharyngeal squamous cell carcinoma of the head and neck treated with radiotherapy with or without cetuximab. *J Clin Oncol* 2016;34:1300-8.

The role of sentinel node biopsy in oral squamous cell carcinoma

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ABSTRACT

Aim: The purpose of this study was to conduct a systematic review of the published literature to assess the state of the art of this procedure. Sentinel node biopsy (SNB) in oral squamous cell cancer (OSCC) is a novel and proven useful technique alternative to the neck dissection (ND) in the management of OSCC. **Methods:** The authors searched PubMed for literature in English published for the last five years, addressing this topic. Prospective studies articles were selected with at least thirty patients studied. **Results:** Of 235 studies found, 14 studies met the exclusion and inclusion criteria for this review. The studies selected focused on the role of the SNB in the OSCC, advantages compared to ND and its limitations, testing different solutions and innovations that could implement the conventional procedure. Meta-analysis studies and review articles were also selected in order to perform the introduction and support the discussion. Based upon these findings authors have tried to establish the state of the art of the SNB and authors have highlighted recent advances that improve the sentinel lymphatic node biopsy technique in the future. **Conclusion:** SNB is an excellent staging method in OSCC and an interesting alternative to ND. The authors show the most appropriate procedures recommended in the bibliography revised in a trend to depict the actual state of the art.

Key words:

Oral cavity; squamous cell cancer; sentinel node biopsy

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is predominantly a loco-regional disease. One of the most significant prognostic factors in management are the lymph node metastasis.^[1] Due to the high metastatic potential of

these tumors, the presence of tumors spread to a single regional lymph node can transform a small stage I tumor to an advanced stage III or even stage IV head and neck

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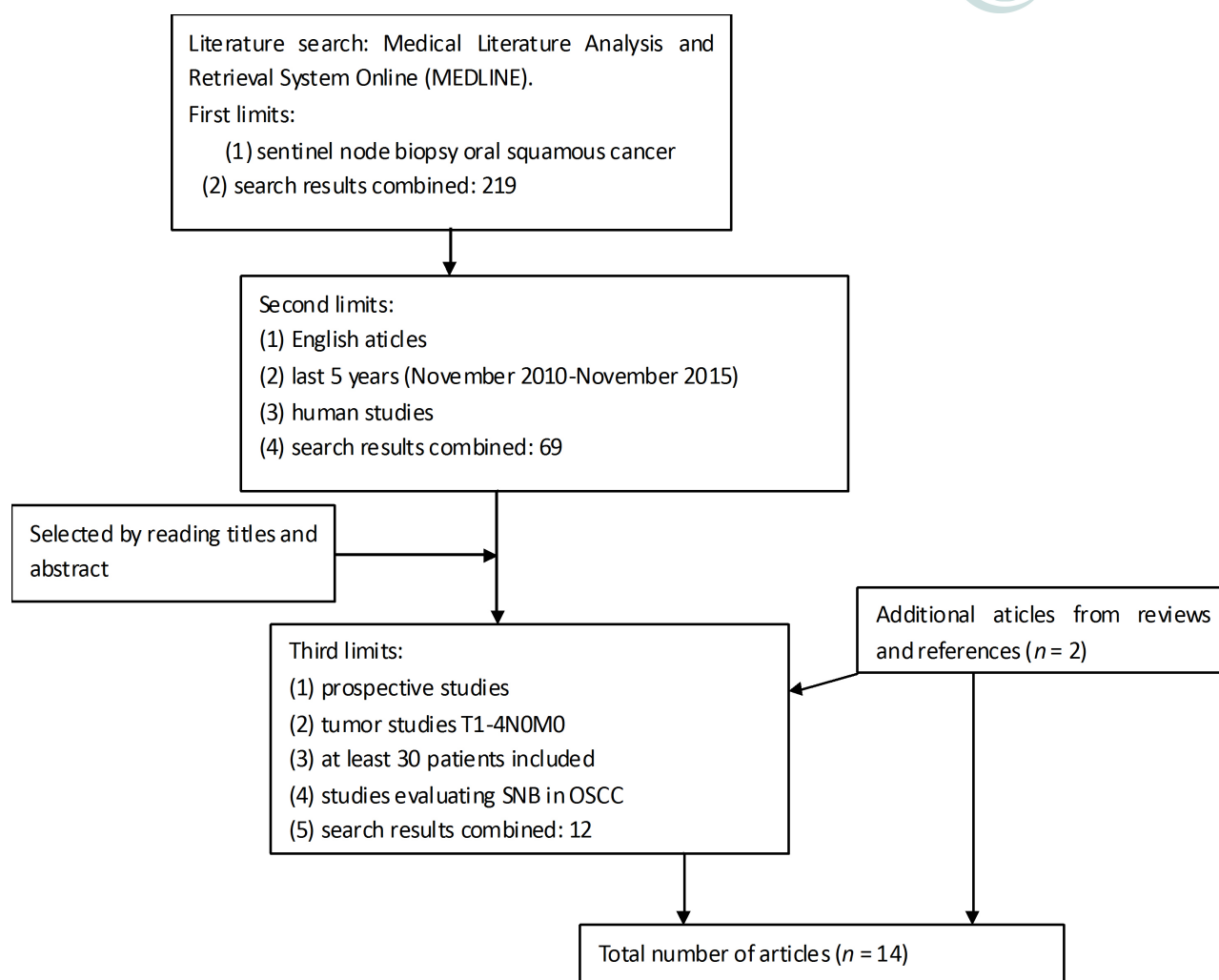


Figure 1: Literature search flow chart and selected studies from the literature according to inclusion criteria. SNB: sentinel node biopsy; OSCC: oral squamous cell cancer

cancer. The presence of a single positive lymph node can reduce disease free survival at 5 years by 50%. In order to perform an adequate treatment of the neck, a correct diagnosis and staging are crucial for determining prognosis.^[2]

OSCC frequently metastasizes to the cervical nodal basins, yet clinical staging with physical exam and imaging modalities [positron emission tomography-computed tomography (CT), CT scan, magnetic resonance imaging or ultrasound] usually cannot detect metastases less than 8 to 10 mm in size.^[3,4] Thus, for the last few years, the conventional procedure for the clinically node negative (N0) patient has been neck dissection (ND), which leads to increased loco-regional control and regional recurrence-free survival. However, ND is an aggressive procedure that represents overtreatment for approximately 70% of cN0 patients who are found to have a histological negative neck for metastases.^[5-7] ND is traditionally recommended when the tumor size and subsite confer at least a 15-20% risk of lymphatic spread.^[8] Nevertheless, in OSCC tumors that have 20% rate of nodal metastasis, the vast majority of these patients will undergo ND with no evidence of lymph node metastasis.^[1]

A conservative trend in the treatment of OSCC N0

patients has encouraged the application of sentinel node biopsy (SNB). SNB entails identifying and harvesting the initial node, to which the primary tumor drains, while limiting dissection and harm to vital structures. The advantages of implementing SNB instead of ND include decreased morbidity, operating room time, and length of postoperative stay.^[9]

SNB is a radio-isotopic technique that included: a peritumoral injection of adequate radiotracer that will be trapped by the regional lymphatic chains and echelons, an imaging technique capable depicting these, a radio guided surgical procedure for removing sentinel node (SN) and a pathological study of the node that allows to know the status of the node.^[10]

SNB as a staging procedure and decision tool to establish whether surgical treatment of the lymphatic area is to be performed or not, is now recognized as the gold standard in melanoma and breast cancer.^[10,11] Although the methodology of sentinel lymphatic node biopsy (SLNB) in OSCC has been well known for more than 10 years and many prospective studies with a significant number of patients have been published, it has not been accepted worldwide, where it is still considered investigational.^[2]

Table 1: The main features of the studies selected for this systematic review

Studies	Patients	Mean age	Staging	Injection	Tracer	MBq/ dose	Volume per dose	Imaging	Equipment	Surgery	Lymph nodes	Histological	SS	NPV
Salazar <i>et al.</i> ^[16] 2015	96	59	TX-N0	Peritumoral	Nanocoll	20	NA	Dynamic; static SPECT	Probe; portable camera	Tumorectomy* + SLNB + ND	NA	HE; SSS; INMH CTK	88	94
Farmer <i>et al.</i> ^[17] 2015	140	62	T1-2N0	Peritumoral	SulphColl	10	NA	Dynamic; static	Probe	Tumorectomy* + SLNB + ND	>4	NA	99	
Flach <i>et al.</i> ^[18] 2014	62	61	T1-2N0	Peritumoral	Nanocoll	27	NA	Dynamic; static	Probe; BLUE DYE	Tumorectomy** + SLNB + ND if SN+	2	HE; SSS; INMH CTK	80	88
Hernando <i>et al.</i> ^[19] 2014	73	66	T1-2N0	Peritumoral	Nanocoll	NA	NA	Dynamic; static	Probe	Tumorectomy* + SLNB + ND if SN+	2	HE; SSS; INMH CTK	94	96
Blumel <i>et al.</i> ^[20] 2014	23	58	T1-2N0	Peritumoral	Nanocoll	2.5 - 102	0.05-0.1 mL	Dynamic; static SPECT-CT	FHSPECT	Tumorectomy\$ + SLNB + ND if SN+	3.1	HE; SSS; INMH CTK	100	100
Alvarez <i>et al.</i> ^[21] 2014	63	57	T1-2N0	Peritumoral	Nanocoll	40-50	0.2 mL	Dynamic	Probe	Tumorectomy* + SLNB + ND if SN+	NA	HE; SSS; INMH CTK	100	86
Samant ^[12] 2014	34	61	T1-2N0	Peritumoral	SulphColl	25	0.1-0.3 mL	Dynamic	Probe; BLUE DYE	Tumorectomy* + SLNB + ND if SN+; / + RTX	4	HE; INMH CTK	94	93
Bell <i>et al.</i> ^[22] 2013	36	57	T1-2N0	Peritumoral	SulphColl	15	0.2-0.4 mL	Static	Probe	Tumorectomy* + SLNB + ND	NA	HE; SSS; INMH CTK	87.5	96
Melkane <i>et al.</i> ^[23] 2012	53	56	T1-2N0	Peritumoral	SulphColl	15	NA	Dynamic	Probe	Tumorectomy** + SLNB + ND	2	HE; SSS; INMH	95.2	95.2
Brogie <i>et al.</i> ^[24] 2013	111	61	T1-2N0	NA	NA	NA	NA	Dynamic; static SPECT-CT	Probe	Tumorectomy* + SLNB + ND if SN+	NA	NA	93	95
Chone <i>et al.</i> ^[25] 2013	46	55	T1-2N0	Peritumoral	SulphColl	12	0.5 mL/day	Static	Probe	Tumorectomy* + SLNB + ND	>1	HE; SSS; INMH CTK	92	98
Brogie and Stoeckli ^[26] 2011	79	60	T1-2N0	Peritumoral	NA	NA	NA	Dynamic; static SPECT-CT	Probe	Tumorectomy* + SLNB + ND if SN+	NA	NA	88	94
Ross <i>et al.</i> ^[23] 2002	48	59	TX-N0	Peritumoral	Nanocoll	37	NA	Dynamic; static	Probe; BLUE DYE	Tumorectomy* + SLNB + ND if SN+	NA	HE; SSS; INMH CTK	94	96
Ross <i>et al.</i> ^[23] 2004	125	58	T1-2N0	Peritumoral	Nanocoll; SulphColl	NA	NA	Static	Probe; BLUE DYE	Tumorectomy* + SLNB + ND if SN+	NA	HE; SSS; INMH CTK	93	96

Nanocoll: Tc99m-Nanocolloid; SulfColl: Tc99m-sulphure colloid; FHSPECT: free hand single photon emission computed tomography; Tumorectomy*: tumorectomy prior to SLNB; Tumorectomy**: tumorectomy after SLNB; Tumorectomy\$: sometimes prior to SLNB and sometimes after SLNB; HE: hematoxylin and eosin staining; SSS: serial step sectioning; INMH CTK: anti-cytokeratin immunohistochemistry; NA: not available; SLNB: sentinel lymphatic node biopsy; ND: neck dissection; SN: sentinel node; SS: sensitivity; SPECT-CT: single photon emission computed tomography-computed tomography; NPV: negative predictive value

Observation approach carries with it the risk that many patients with microscopic metastasis will be unsalvageable by the time their recurrence is detected. Hence, ND is commonly favored because of a lowered risk of uncontrolled disease. However, elective treatment in all comers has the disadvantage of unnecessary neck dissection in the majority of patients who are without microscopic cervical metastasis.^[12]

With the developments of imaging tomographic techniques like single photon CT (SPECT) and hybrid techniques combining SPECT with CT (SPECT-CT) the identification of sentinel nodes has improved compared to conventional scintigraphy.^[13]

In clinical trials on OSCC performed both in Europe and North America, SLNB has been shown to have predictably high accuracy in identifying occult metastasis. SN identification rates, as well as accuracy of staging of lymphatic spread, are comparable with those reported in melanoma and breast cancer, where this procedure is used routinely in patient care.^[14-16]

The purpose of this study was to conduct a systematic review of the published literature to assess the state of the art of this procedure focused on the role of the SNB in the OSCC. We have evaluated the advantages of SNB compared to ND and its limitations, testing different solutions and innovations that could implement the conventional

Table 2: Values of survival in terms of DFS, OS and DSS respect to the different histopathological findings in the articles cited

Stuides	Histological findings	DFS	OS	DSS
Broglie <i>et al.</i> ^[24]	Total	85	80	87
2013	Negative SLNB	96	88	96
	Positive SLNB	73	74	77
	ITC	80	80	80
	Micrometastases	69	75	75
	Macrometastases	62	62	73
Broglie and Stoeckli ^[26] 2011	Total	89	88	91
	Negative SLNB	98	98	95
	Positive SLNB	73	71	76
	ITC	75	89	75
	Micrometastases	71	71	66
	Macrometastases	67	67	65

SLNB: sentinel lymphatic node biopsy; ITC: isolated tumoral cells; DFS: disease free survival; OS: overall survival; DSS: disease specific survival

procedure in the best way.

METHODS

We searched the medical literature analysis and retrieval system online (MEDLINE), databases via OVID and Saludteca (Virtual Library of Extremadura Public Health System) for relevant studies published in English from January 2011 to January 2016, limited to human subjects. The combination of search terms used was the following: (1) sentinel node; (2) oral; and (3) squamous cell cancer. The abstracts were reviewed one by one and applying the inclusion criteria. The inclusion criteria were the following: (1) original studies; (2) prospective studies; (3) studies evaluating the role SLNB in OSCC in N0 patients; and (4) at least 30 subjects included in the study. Meta-analysis and review articles were collected in order to establish the introduction and support the data in the discussion of the article. The references of these latter works were examined and all interesting articles were included for the elaboration of this review.

Data extraction

For each study, we extracted data on the author's name, year, type of study, characteristics of patients, staging of the tumour, type of radiotracer, amount of activity and volume injected per dose of radiotracer, type of images acquired, method of analysis of images, types of radioguided surgery equipment employed, surgical technique employed, histological techniques for evaluating the SN, sensitivity (SS), negative predictive value (NPV), patients survival in terms of disease-free survival (DFS), overall survival (OS) and disease-specific survival (DSS).

All parameters involved in the SNB technique were examined in the articles; they were analyzed in order to determine which one would be the most reasonable and useful to establish the state of the art of the procedure.

RESULTS

The literature search yielded a total of 219 potential articles [Figure 1]. When we established the second limits (English articles, of the last 5 years and only human studies) we

excluded 150 articles. After screening the titles and abstracts of the remaining 69 articles, applying the third selection (prospective studies, TxN0, 30 patients at least) we selected 12 articles.^[12,16-26] Together with two additional prospective articles^[27,28] identified from reviews and references, a total of 14 articles were included in this systematic review. Table 1 summarizes all the studies included providing the details of the individual studies (full database available from author). Table 1 summarizes the pooled sensitivity and negative predictive values of the SNB. Six out of fifteen of these articles also include survival data [Table 2] in terms of OS, DFS and DSS. All articles studied OSCC T1-2N0 except two that included any T and N0.

Regarding the radio-isotopic technique employed, 7 authors used colloid sulfur radiolabeled with Technetium99m (Tc99m-colloidsulfur) and other 5 nanocolloid radiolabeled with Tcnetium99m (Tc99m-nanocolloid). One of this latter combined with immunoglobulins. In the two remaining studies these data were not available. All authors employed peritumoral injection. The activity injected was detailed in 12 articles and ranged between 10-80 MBq each dose (mean \pm 20 MBq). In 9 studies the dose ranged between 10 and 20 MBq. The volume of tracer injected per dose was only described in 6 articles and ranged between 0.05 and 0.5 mL (mean \pm 0.23 mL).

The imaging technique employed was detailed in 13 studies, performing dynamic images after tracer administration and static planar conventional images at 2 h in 6 cases. Three authors only performed static planar conventional images 2 h after tracer administration. One work included dynamic, static and SPECT images. Three studies carried out dynamic, static and hybrid SPECT-CT images. In 4 works blue dye was injected in the surgical room for improving the identification of the sentinel node according to their color and radioactivity.^[12,18,27,28]

For the intraoperative SN localization, the equipment employed was as follows: only radioguided probe in 8 cases, radioguided probe and blue dye colorant in 3 cases, combined radioguided probe and portable gamma-camera in 1 case and 1 work employed a novel detection system with intrasurgical free-hand SPECT (SurgicEye[®]).^[20]

Regard the surgical technique employed, in eleven works a tumorectomy was first performed and immediately a SNB. If the result of SNB showed any lymphatic node affected, a ND was carried out in 9 studies. In the remaining 5 studies, tumorectomy, SNB and ND was performed in all patients.

The number of biopsied nodes was detailed in 9 works, with a mean of 3 nodes per patient. The nodes was studied in 10 studies by mean of histological techniques that include hematoxylin-eosin (HE) staining, step serial section (SSS) and immunohistochemistry (IHC) analysis for cytokeratin AE1/AE3, in order to confirm the absence of metastatic lymph nodal disease. In 1 article only HE and IHC techniques were employed.^[12] In three works, these data were not available.

SS values ranged in all studies between 80% and 100% (mean

$\pm 94.2\%$). NPV were available in 13 studies reaching values between 88% and 100% (mean $\pm 94.4\%$).

In only 5 works, the survival data were displayed in terms of DFS, OS and DSS regard the SLNB results. These 5 works showed the data detailing the positivity or negativity of the nodes biopsied. In only 2 studies the terms of survival were also displayed depending of the type of node invasion, isolated tumoral cells (ITC), micrometastases or macrometastases.^[24,26] All type of node invasion showed significant differences in terms of DFS, OS and DSS respect to the absence of node invasion. The two works were published by Broglie *et al.*^[24,26] in 2011 and 2013 obtaining very similar values for DFS for the pathological results of SNB negative, ITC, micrometastases and macrometastases. Those results were: 96% and 98%, 80% and 75%, 69% and 71%, 62% and 67%, respectively. The values obtained for OS for the same pathological results were: 88% and 98%, 80% and 89%, 75% and 71%, 62% and 67%, respectively. Finally, the values obtained for DSS for those pathological results were: 96% and 95%, 80% and 75%, 75% and 66%, 73% and 65%, respectively [Table 2].

DISCUSSION

SNB is a well contrasted technique for the regional evaluation of tumor staging in breast cancer and melanoma included in international guidelines of management of these tumors.^[10,11] However, in OSCC it still remains with an investigational role. This procedure is very complicated in head and neck tumors because of the great wealth of lymphatic vessels and a great variability of regional lymphatic migration. We selected articles published in the last 5 years, as accumulated experience has induced some evolution in radioisotope procedures, imaging techniques and radio-surgery procedures. We included 2 interesting prospective papers published in 2002 and 2004 because they reach every required criteria, with high number of patients and included detailed data of survival respect to the histological findings of IHC.^[27,28]

We selected only prospective studies because they imply an approach and prior review of the different techniques used. In OSCC, the first studies have only been published since 1999, 7 years after the technique gained acceptance in breast and melanoma. This, combined with the reduced incidence of oral cancers compared to melanoma and breast cancer, necessarily results in a low number of studies with more than 30 patients, but it is similar to some meta-analysis reviewed.^[29]

Radiotracer

Seven studies employed Tc99m-nanocolloid as radiotracer and 6 used Tc99m-sulphur colloid [Table 1]. Values of SS and NPV ranged between 88-100% and 86-100% with Tc99m-nanocolloid, and between 80-95% and 93-98% with sulphur colloid. The number of studies is very low but there were no significant differences.

Several 99mTc-based agents have been used for radioguided SNB. The ideal radiotracer should show rapid transit to SNs with prolonged retention in the nodes. In general, the drainage, distribution, and clearance of radioactive colloids

by the lymphatic system may vary and are dependent on the size of the particles. Small particles are drained and cleared first; large particles are drained and cleared last and may be retained longer at the injection site. There is worldwide variation in radiopharmaceuticals used for lymphoscintigraphy. Tc-99m sulphur colloid is employed in the USA, with an average size ranging from 305 nm to 340 nm and Tc-99m-nanocolloid are used in Europe with size ranging from 5 nm to 100 nm.^[30] Studies have shown that the success rate of identification of SNs is not significantly affected by the particle size of the radiotracer.^[31-34] Thus, the selection of radiotracer is based more on local availability than on differences in sentinel lymph node (SLN) detection.

Recent developments in new tracers are coming, like the use of indocyanine green-Tc99m-nanocolloid, a hybrid tracer that is both radioactive and fluorescent. The addition of fluorescence imaging was shown to be of particular value when SNs were located in close proximity to the primary tumour.^[35]

Tilmanocept[®], is another novel receptor-targeted radiopharmaceutical, Tc99m-labeled non-particulate radiotracer with high affinity for the macrophages and dendritic cells, within the sentinel lymph node. Studies have been promising, with suggestions that tilmanocept may have improved clearance from the site of the primary tumor and enhanced retention within the sentinel node when compared to sulfur colloid.^[36]

Based upon the experience accumulated in SNLB in other tumors, consensus on the activity to be administered in a SNB procedure has not been reached. The investigated and suggested activities vary considerably. Activities as low as 3.7 MBq (0.1 mCi)^[37] and as high as 370 MBq (10 mCi)^[36] have been used. In our review, the doses ranged between 10 and 80 MBq, the adequate dose if the tracer administration is performed the day before surgery, especially if we are going to acquire SPECT-CT images that require greater tracer activity. These doses do not imply a significant radiation dose to the workers in the operation room. Note that between administration of the radiotracer and surgery usually pass at least 24 h. It means that an administered dose will become to 1/16 of the injected at the operation time, so that no specific radioprotection precautions are required.

Radiotracer administration

Respect to the volume of radiotracer injected, Chone *et al.*^[25] employed the largest volume per dose (0.5 mL) in an attempt to completely surround the tumor in its deep and lateral aspects at a sub-mucous level of normal mucous membrane that surrounds the tumor in a volume of approximately 1-2 mL. However, we did not find any significant difference in terms of SS or NPV. In breast cancer with peritumoral injections, larger volumes per dose (i.e. 0.5-1.0 mL) are preferred for the same reason.^[33] Perhaps the best option would be to try the peritumoral region completely surrounded by the radiotracer to avoid false negative results.

SN preoperative localization

The most common method to preoperatively localize SN included injecting a radioactive sentinel node tracer

followed by lymphoscintigraphy, without the use of blue dye. Its use may also facilitate SLN detection during surgery but there were no significant differences in terms of SS or NPV. It highlights the fact that the lowest value of SS was obtained in a job that used blue dye.^[18]

False-negatives can occur through multiple mechanisms, including incomplete or inadequate peritumoral injection, obscuring of the SN by shine-through of the radioactive signal at the primary tumor site, and lymphatic obstruction secondary to tumor-obstructed nodes resulting in redirection of lymphatic flow.^[14]

Nine authors employed dynamic images in a trend to identify the lymphatic migration to the sentinel nodes. To date; the predominant clinical experience with SNB has been with oral cavity tumors. There is still some debate in the literature regarding the accuracy of SNB for floor of mouth tumors compared to other oral locations.^[38-40] The argument by those who report a lower sensitivity and negative predictive value for floor of mouth tumors compared to other locations is that tumors in the floor of mouth lie in very close proximity to level I nodes leading to difficulty in identifying and harvesting SLNs.^[14,40] Antonio *et al.*^[2] state that the minimum treatment of the neck is probably dissection of the levels between the primary tumour and the level containing the SN(s).

This problem can be solved by means of tomographic imaging techniques that can separate tracer uptake of adjacent organs, especially the hybrid techniques such as SPECT-CT that by their much greater anatomical resolution and image quality are much more appropriate. It is noteworthy that only three authors use these techniques to help more accurately identifying lymph node stations in various forms, as well as its relations with adjacent structures.^[13]

Intraoperative procedure

In the surgical room, radioguided surgical probe was employed in 11 articles; one of them with a portable intraoperative gamma-camera added.^[16] When we use exclusively a probe it is recommended to previously identify the SN and its anatomical location based upon the images examination and labeling marks on the skin of the patient. For this, a close collaboration between the physicians of nuclear medicine and surgeons is recommended. In order to avoid or minimize the shine-through effect, the surgeon must perform a lumpectomy before the SNB. After lumpectomy, additional images can be acquired with portable gamma-camera and identify the SN of the regions close to the tumor that could be missed in the initial images.

Blumel *et al.*^[20] used a new detection system based on a freehand SPECT performed in the operating room before surgery and even intraoperatively after lumpectomy in a short period of time (less than 2 min) that eliminated the peritumoral tracer activity and improved the location of those lymphatic echelons close to the tumor and eliminating the shine-through effect.

There was no agreement in which would be the adequate number of SN biopsied. This fact remains controversial in OSCC because of the possibility of great number of SN, variability of different lymphatic echelons, frequent contralateral migration, *etc.* Perhaps it would be wise to excise at least, all hot cervical nodes found in the images.

Histological techniques

Histological techniques employed are a crucial point in the SNB process. All items with available data, except one, employed HE, SSS and IHC analysis for cytokeratin. All remarked the importance of the three techniques for reaching the highest accuracy. On the other hand, one of the biggest potential downsides to a strategy of SNB as compared with upfront elective ND is the need to return to the operating room on a separate occasion for a completion ND for a positive SLNB. Although immediate intraoperative frozen section can identify a significant proportion of patients with a positive SNB, there remains a subset of patients whose occult disease will only become apparent with SSS and IHC analysis.^[25] The increased morbidity, cost and delay in healing that comes from a second procedure are viewed by many as an obstacle to the implementation of SNB. Some authors attempted to develop a more efficient method for the intraoperative genetic detection of lymph node metastasis in head and neck squamous cell carcinoma using the one-step nucleic acid amplification (OSNA) method of cytokeratin-19.^[41]

Perspectives

The data founded showed that any type of neoplastic spread to the SN imply significant differences in terms of survival [Table 2]. The presence of micrometastases and macrometastases must be followed by ND in order to control the disease. This probably means that more survival specific studies are necessary to clarify the role of ITC in SN. According to the guidelines in early breast cancer, complete axillary lymph node dissection is recommended if SNB is positive except for ITCs.^[42] However, the reviewed studies suggested that the presence of even small tumor-cell deposits in lymph nodes reflects the potential of the primary tumor to metastasize and, for the time being, completion elective neck dissection should be performed irrespectively of the size of metastases.^[24,26]

Based upon this review, we can resume the protocol of SNB as follows: (1) close collaboration between the departments of maxillofacial surgery, oncology, radiology and nuclear medicine is recommended; (2) the selection of radiotracer is based more on local availability than on differences in SLN detection. In our mean, Tc99m-nanocolloid should be employed. In the future, attention must be focused on new tracers; (3) activity dose per injection will range between 37-74 MBq if surgery is performed the day after the tracer administration; (4) peritumoral injection will be performed trying to surround the lesion as much as possible to avoid false negative results; (5) the volume per dose recommended will reach 0.5 mL in a trend to completely surround the tumor in a total volume of 1-2 mL; (6) imaging techniques should include tomographic studies, especially hybrid SPECT-

CT techniques, if available, in a trend to avoid shine-through effect and identify SN in lymphatic echelons close to the tracer injection. Free-hand intraoperative SPECT technique will be an interesting choice in the future; (7) tumorectomy will be performed previous to SNB to avoid shine-through effect helping to identify SN in lymphatic spaces I and II; (8) SN will be studied with histological exhaustive techniques including HE, SSS and IHC to reach the highest accuracy to identify occult disease. In the future, OSNA techniques could be developed but more studies are necessary to evaluate these; and (9) if SN shows a positive result a ND will be mandatory. There are only doubts about the role of ITCs in SN, but the current data suggest that any neoplastic presence in SN recommend a ND.

In conclusion, SNB is a well-known powerful tool in the management of some tumors like breast cancer and melanoma. In early-stage oral cavity cancer, SNB is gaining acceptance worldwide as an effective alternative to elective neck dissection for staging the N0 neck. Nowadays, despite anatomical and functional differences of this region, the available evidence suggests that SNB accurately stages the neck with a reasonable false-negative rate.

False-negatives can occur through multiple mechanisms, including incomplete or inadequate peritumoral injection, obscuring of the SN by shine-through of the radioactive signal at the primary tumor site, and lymphatic obstruction secondary to tumor-obstructed nodes resulting in redirection of lymphatic flow. The use of adequate radiotracer and proper injection as well as the optimal employment of imaging procedures and surgical techniques can help solving this limitation.

Given the increased risk of morbidity with selective neck dissection or radiation therapy, and the decreased survival with watchful waiting, the SNB may provide a reasonable alternative when done by an experienced multidisciplinary group of surgeons, radiologists, oncologists and nuclear medicine physicians.

Recent advances are focused on the development of novel radiotracers imaging techniques and molecular assays, to improve the intraoperative identification of SN. They may help to overcome some of the obstacles to widespread implementation of SNB for OSCC N0.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

- Thompson CF, St John MA, Lawson G, Grogan T, Elashoff D, Mendelsohn AH. Diagnostic value of sentinel lymph node biopsy in head and neck cancer: a meta-analysis. *Eur Arch Otorhinolaryngol* 2013;270:2115-22.
- Antonio JK, Santini S, Politi D, Sulfaro S, Spaziante R, Alberti A, Pin M, Barzan L. Sentinel lymph node biopsy in squamous cell carcinoma of the head and neck: 10 years of experience. *Acta Otorhinolaryngol Ital* 2012;32:18-25.
- Ferris RL, Xi L, Seethala RR, Chan J, Desai S, Hoch B, Gooding W, Godfrey TE. Intraoperative qRT-PCR for detection of lymph node metastasis in head and neck cancer. *Clin Cancer Res* 2011;17:1858-66.
- Shoib T, Soutar DS, MacDonald DG, Camilleri IG, Dunaway DJ, Gray HW, McCurrach GM, Bessent RG, MacLeod TI, Robertson AG. The accuracy of head and neck carcinoma sentinel lymph node biopsy in the clinically N0 neck. *Cancer* 2001;91:2077-83.
- Kligerman J, Lima RA, Soares JR, Prado L, Dias FL, Freitas EQ, Olivatto LO. Supraomohyoid neck dissection in the treatment of T1/T2 squamous cell carcinoma of oral cavity. *Am J Surg* 1994;168:391-4.
- McGuirt WF Jr, Johnson JT, Myers EN, Rothfield R, Wagner R. Floor of mouth carcinoma. The management of the clinically negative neck. *Arch Otolaryngol Head Neck Surg* 1995;121:278-82.
- Taylor RJ, Wahl RL, Sharma PK, Bradford CR, Terrell JE, Teknos TN, Heard EM, Wolf GT, Chepeha DB. Sentinel node localization in oral cavity and oropharynx squamous cell cancer. *Arch Otolaryngol Head Neck Surg* 2001;127:970-4.
- Pillsbury HC, Clark M. A rationale for therapy of the N0 neck. *Laryngoscope* 1997;107:1294-315.
- Murer K, Huber GF, Haile SR, Stoeckli SJ. Comparison of morbidity between sentinel node biopsy and elective neck dissection for treatment of the n0 neck in patients with oral squamous cell carcinoma. *Head Neck* 2011;33:1260-4.
- Buscombe J, Paganelli G, Burak ZE, Waddington W, Maublant J, Prats E, Palmedo H, Schillaci O, Maffioli L, Lassmann M, Chiesa C, Bombardieri E, Chiti A; European Association of Nuclear Medicine Oncology Committee and Dosimetry Committee. Sentinel node in breast cancer procedural guidelines. *Eur J Nucl Med Mol Imaging* 2007;34:2154-9.
- Blumel C, Herrmann K, Giammarile F, Nieweg OE, Dubreuil J, Testori A, Audisio RA, Zoras O, Lassmann M, Chakera AH, Uren R, Chondrogianis S, Colletti PM, Rubello D. EANM practice guidelines for lymphoscintigraphy and sentinel lymph node biopsy in melanoma. *Eur J Nucl Med Mol Imaging* 2015;42:1750-66.
- Samant S. Sentinel node biopsy as an alternative to elective neck dissection for staging of early oral carcinoma. *Head Neck* 2014;36:241-6.
- Serrano-Vicente J, Rayo-Madrid JI, Domínguez-Grande ML, Infante-Torre JR, García-Bernardo L, Moreno-Caballero M, Medina-Romero F, Durán-Barquero C. Role of SPECT-CT in breast cancer sentinel node biopsy when internal mammary chain drainage is observed. *Clin Transl Oncol* 2016;18:418-25.
- Civantos FJ, Zitsch RP, Schuller DE, Agrawal A, Smith RB, Nason R, Petruzelli G, Gourin CG, Wong RJ, Ferris RL, El Naggar A, Ridge JA, Paniello RC, Owzar K, McCall L, Chepeha DB, Yarbrough WG, Myers JN. Sentinel lymph node biopsy accurately stages the regional lymph nodes for T1-T2 oral squamous cell carcinomas: results of a prospective multi-institutional trial. *J Clin Oncol* 2010;28:1395-400.
- Govers TM, Hannink G, Merks MA, Takes RP, Rovers MM. Sentinel node biopsy for squamous cell carcinoma of the oral cavity and oropharynx: a diagnostic meta-analysis. *Oral Oncol* 2013;49:726-32.
- Salazar-Fernandez CI, Gallana-Alvarez S, Pereira S, Cambill T, Infante-Cossio P, Herce-Lopez J. Sentinel lymph node biopsy in oral and oropharyngeal squamous cell carcinoma: statistical validation and impact of micrometastasis involvement on the neck dissection decision. *J Oral Maxillofac Surg* 2015;73:1403-9.
- Farmer RW, McCall L, Civantos FJ, Myers JN, Yarbrough WG, Murphy B, O'Leary M, Zitsch R, Siegel BA. Lymphatic drainage patterns in oral squamous cell carcinoma: findings of the ACOSOG Z0360 (Alliance) study. *Otolaryngol Head Neck Surg* 2015;152:673-7.
- Flach GB, Bloemena E, Klop WM, van Es RJ, Schepman KP, Hoekstra OS, Castelijns JA, Leemans CR, de Bree R. Sentinel lymph node biopsy in clinically N0 T1-T2 staged oral cancer: the Dutch multicenter trial. *Oral Oncol* 2014;50:1020-4.
- Hernando J, Villarreal P, Alvarez-Marcos F, Gallego L, García-Consuegra L, Junquera L. Comparison of related complications: sentinel node biopsy versus elective neck dissection. *Int J Oral Maxillofac Surg* 2014;43:1307-12.
- Blumel C, Herrmann K, Kübler A, Buck AK, Geissinger E, Wild V, Hartmann S, Lapa C, Linz C, Müller-Richter U. Intraoperative 3-D imaging improves sentinel lymph node biopsy in oral cancer. *Eur J Nucl Med Mol Imaging* 2014;41:2257-64.
- Alvarez J, Bidaguren A, McGurk M, Diaz-Basterra G, Brunsó J, Andikotxea B, Martín JC, Barbier L, Arteagoitia I, Santamaría JA. Sentinel node biopsy in relation to survival in floor of the mouth carcinoma. *Int J Oral Maxillofac Surg* 2014;43:269-73.
- Bell RB, Markiewicz MR, Dierks EJ, Gregoire CE, Rader A. Thin serial step sectioning of sentinel lymph node biopsy specimen may not be necessary to accurately stage the neck in oral squamous cell carcinoma. *J Oral*

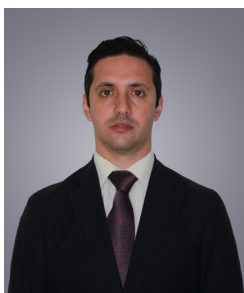
- Maxillofac Surg* 2013;71:1268-77.
23. Melkane AE, Mamelle G, Wycisk G, Temam S, Janot F, Casiraghi O, Lumbroso J. Sentinel node biopsy in early oral squamous cell carcinomas: a 10-year experience. *Laryngoscope* 2012 ;122:1782-8.
24. Broglie MA, Haerle SK, Huber GF, Haile SR, Stoeckli SJ. Occult metastases detected by sentinel node biopsy in patients with early oral and oropharyngeal squamous cell carcinomas: impact on survival. *Head Neck* 2013;35:660-6.
25. Chone CT, Aniteli MB, Magalhães RS, Freitas LL, Altemani A, Ramos CD, Etchebehere E, Crespo AN. Impact of immunohistochemistry in sentinel lymph node biopsy in head and neck cancer. *Eur Arch Otorhinolaryngol* 2013;270:313-7.
26. Broglie MA, Stoeckli SJ. Relevance of sentinel node procedures in head and neck squamous cell carcinoma. *Q J Nucl Med Mol Imaging* 2011;55:509-20.
27. Ross G, Shoaib T, Soutar DS, Camilleri IG, Gray HW, Bessent RG, Robertson AG, MacDonald DG. The use of sentinel node biopsy to upstage the clinically N0 neck in head and neck cancer. *Arch Otolaryngol Head Neck Surg* 2002;128:1287-91.
28. Ross GL, Soutar DS, Gordon MacDonald D, Shoaib T, Camilleri I, Robertson AG, Sorensen JA, Thomsen J, Grupe P, Alvarez J, Barbier L, Santamaria J, Poli T, Massarelli O, Sesenna E, Kovács AF, Grünwald F, Barzan L, Sulfaro S, Alberti F. Sentinel node biopsy in head and neck cancer: preliminary results of a multicenter trial. *Ann Surg Oncol* 2004;11:690-6.
29. Paleri V, Rees G, Arullendran P, Shoaib T, Krishnan S. Sentinel node biopsy in squamous cell cancer of the oral cavity and oral pharynx: a diagnostic meta-analysis. *Head Neck* 2005;27:739-47.
30. Wilhelm AJ, Mijnhout GS, Franssen EJ. Radiopharmaceuticals in sentinel lymph-node detection-an overview. *Eur J Nucl Med* 1999;26:S36-42.
31. Mariani G, Moresco I, Viale G, Villa G, Bagnasco M, Canavese G, Buscombe J, Strauss HW, Paganelli G. Radioguided sentinel lymph node biopsy in breast cancer surgery. *J Nucl Med* 2001;42:1198-215.
32. Clarke D, Khoni NL, Mansel RE. Sentinel node biopsy in breast cancer. ALMANAC trial. *World J Surg* 2001;25:819-22.
33. Bourgeois P. Scintigraphic investigations of the lymphatic system: the influence of injected volume and quantity of labeled colloidal tracer. *J Nucl Med* 2007;48:693-5.
34. Burak WE Jr, Agnese DM, Povoski SP. Advances in the surgical management of early stage invasive breast cancer. *Curr Probl Surg* 2004;41:877-936.
35. Van den Berg NS, Brouwer OR, Klop WM, Karakullukcu B, Zuur CL, Tan IB, Balm AJ, van den Brekel MW, Valdés Olmos RA, van Leeuwen FW. Concomitant radio- and fluorescence-guided sentinel lymph node biopsy in squamous cell carcinoma of the oral cavity using ICG-(99m)Tc-nanocolloid. *Eur J Nucl Med Mol Imaging* 2012;39:1128-36.
36. Sondak VK, King DW, Zager JS, Schneebaum S, Kim J, Leong SP, Faries MB, Averbook BJ, Martinez SR, Puleo CA, Messina JL, Christman L, Wallace AM. Combined analysis of phase III trials evaluating [99mTc]tilmanocept and vital blue dye for identification of sentinel lymph nodes in clinically node-negative cutaneous melanoma. *Ann Surg Oncol* 2013;20:680-8.
37. McCarter MD, Yeung H, Yeh S, Fey J, Borgen PI, Cody HS 3rd. Localization of the sentinel node in breast cancer: identical results with same-day and day-before isotope injection. *Ann Surg Oncol* 2001;8:682-6.
38. Tomifuji M, Shiotani A, Fujii H, Araki K, Saito K, Inagaki K, Mukai M, Kitagawa Y, Ogawa K. Sentinel node concept in clinically n0 laryngeal and hypopharyngeal cancer. *Ann Surg Oncol* 2008;15:2568-75.
39. Jeong HS, Baek CH, Son YI, Cho DY, Chung MK, Min JY, Ko YH, Kim BT. Sentinel lymph node radiolocalization with 99mTc filtered tin colloid in clinically node-negative squamous cell carcinomas of the oral cavity. *J Korean Med Sci* 2006;21:865-70.
40. Mozzillo N, Chiesa F, Caracò C, Botti G, Lastoria S, Longo F, Ionna F. Therapeutic implications of sentinel lymph node biopsy in the staging of oral cancer. *Ann Surg Oncol* 2004;11:S263-6.
41. Goda H, Nakashiro K, Oka R, Tanaka H, Wakisaka H, Hato N, Hyodo M, Hamakawa H. One-step nucleic acid amplification for detecting lymph node metastasis of head and neck squamous cell carcinoma. *Oral Oncol* 2012;48:958-63.
42. Carlson RW, Allred DC, Anderson BO, Burstein HJ, Carter WB, Edge SB, Erban JK, Farrar WB, Goldstein LJ, Gradishar WJ, Hayes DF, Hudis CA, Jahanzeb M, Kiel K, Ljung BM, Marcom PK, Mayer IA, McCormick B, Nabell LM, Pierce LJ, Reed EC, Smith ML, Somlo G, Theriault RL, Topham NS, Ward JH, Winer EP, Wolff AC; NCCN Breast Cancer Clinical Practice Guidelines Panel. Breast cancer. Clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2009;7:122-92.

The tissue shrinkage phenomenon on surgical margins in oral and oropharyngeal squamous cell carcinoma

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ABSTRACT

Aim: One of the most important factors associated with recurrence rate and overall survival is the status of surgical margin of resection free of disease. However, sometimes, the margins measured intra-operatively at the time of surgery differ of those measured by the pathologist in the histopathologic analysis. Faced with this dilemma, a literature review of the best available evidence was conducted in an attempt to determine how the phenomenon of tissue shrinkage may influence on the surgical margin of resection in patients undergoing oral and oropharyngeal squamous cell carcinoma (SCC). **Methods:** An electronic and manual search was conducted by one reviewer. A combination of controlled Medical Subjects Headings and keywords were used as search strategy. Inclusion and exclusion criteria were established. **Results:** Finally, after an exhaustive selection process, four articles fulfilled the inclusion criteria and were analyzed. All articles reported a decrease of surgical margin after resection. The tumor site and tumor stage seem to influence in degree of margin shrinkage. **Conclusion:** Tissue shrinkage on surgical margins of resection in oral SCC is a tangible phenomenon. There is a significant discrepancy between margins measured intraoperatively previous to resection and margins measured by pathologist after histologic processing. The highest percentage of retraction occurs at the time of resection. Margin shrinkage based on tumor site and tumor stage should be considered by any oncologic surgeon to ensure adequate margins of resection cleared of tumor.

Key words:

Squamous cell carcinoma; tissue shrinkage; surgical margin; retraction; oral cavity; oropharynx

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INTRODUCTION

According to the last report of World Health Organization in 2014, cancer of the oral cavity and pharynx constitute, in combination, the seventh most common cancer in the world and the ninth most common cause of death by cancer. Its annual incidence is estimated about 529,000 new cases/year.^[1] Two-thirds of these cases are described in developing countries.^[2] The squamous cell carcinoma (SCC), with a high morbidity and mortality, constitutes the most common entity in the upper aerodigestive tract in approximately 90% of cases. Its survival rate at 5 years, for most countries, is around 50%.^[2] Numerous clinical and histopathologic factors have been considered as prognostic at the SCC.^[3,4] Among them, one of the most relevant, with respect to the overall survival and recurrence rate, is the status of surgical margin of resection free of disease.^[5-8] However, although one goal in the oncologic surgery is the complete removal of the tumor with an appropriate margin of security and less aesthetic and functional impact; in the head and neck region, due to its three-dimensional characteristics and the presence of noble structures, the obtaining of appropriate limits of resection constitutes, on occasions, a real challenge for the surgeon.^[9,10]

Nevertheless, since 1978 when Looser *et al.*^[5] defined the term “positive surgical margin”, diverse concepts such as “close margins”, “involved margins” or “clear margins”, among others, have been introduced in the literature without a general consensus.^[10-13] In fact, even today, there are no universal guidelines that permit different pathologists to adopt the same histologic criteria regarding to surgical margin.^[5,14-17] This lack of agreement on what should constitute an “adequate” or “safe” margin of resection^[8,18] have led to each pathology department to classify surgical margins according to its own experience or internal guidelines, thereby hampering the comparison of the results obtained in the different studies and its extrapolation to the clinical practice.^[14] A recent systematic review concluded that a histopathologic margin of at least 5 mm is the minimum acceptable margin size that should be achieved in any oral SCC.^[19] Currently, following the surgical standard, it has been established that a macroscopic surgical margin of 1 to 2 cm obtained intra-operatively is enough extent to obtain a free-tumor margin (5 mm at present) in the oral cavity and oropharynx.^[3,19-21] Nevertheless, sometimes it happens that, despite surgical margins measured by the surgeon intra-operatively seem appropriate, a notable discrepancy is observed when are analyzed by the pathologist under the microscope. Faced with this dilemma, a review of the best available evidence in the literature regarding to the tissue shrinkage phenomenon observed on surgical margins of resection in patients with oral and oropharyngeal SCC was carried out.

METHODS

An electronic literature search was conducted by one reviewer (D.G.B) in Pubmed (Medline) database, up to January 2016. No language or date restrictions were applied.

The population, intervention, control and outcomes^[22] (PICO) question that guided this review was as follows: is the effect of tissue shrinkage phenomenon a factor to take into account in the surgical treatment of oral and oropharyngeal squamous cell carcinoma?

Search strategy

A combination of controlled terms Medical Subjects Headings (MeSH) and keywords were used as strategy of search. The search terms used, where “[mh]” represented the MeSH terms and “[tiab]” represented title and/or abstract, were: “carcinoma, squamous cell” [MeSH Terms] OR “mouth neoplasms” [MeSH Terms] OR “oropharynx neoplasm” [MeSH Terms] OR “oral cancer” [Title/Abstract] OR “oral neoplasm” [Title/Abstract] OR “oral tumour” [Title/Abstract] OR “oropharynx cancer” [Title/Abstract] OR “oropharynx tumours” [Title/Abstract] OR “squamous cell carcinoma” [Title/Abstract]) AND (“tissues” [MeSH Terms] OR “tissues” [Title/Abstract] OR “tissue” [Title/Abstract] OR “margin” [Title/Abstract] OR “surgical margin” [Title/Abstract] OR “resection margin” [Title/Abstract]) AND (shrinkage [All Fields] OR “retraction” [Title/Abstract] OR “shrink” [Title/Abstract]).

In addition, to identify supplementary articles, the related citations function of Pubmed was used. Likewise, a manual search based on an equivalent search strategy to that used in the Pubmed was performed. Some of the most relevant head and neck, oral and maxillofacial and plastic surgery-related journals were consulted, including: *International Journal of Oral and Maxillofacial Surgery*; *Journal of Oral and Maxillofacial Surgery*; *Journal of Craniomaxillofacial Surgery*; *Journal of Maxillofacial Surgery*; *British Journal of Oral and Maxillofacial Surgery*; *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology and Endodontology*; *Head and Neck*; *Oral Oncology and Journal of Plastic, Reconstructive and Aesthetic Surgery*.

Eligibility criteria

Articles were included in this systematic review if they met the following inclusion criteria: prospective and retrospective studies, cohort, cross-sectional and case-control studies or human clinical trials that discussed: (1) the phenomenon of retraction or tissue shrinkage on surgical margins of resection; (2) the difference between measurements taken in the operation room and those reported by the pathologist on the surgical specimen; or (3) the influence of histopathologic processing on resection margins of surgical pieces in patients underwent surgery for oral or oropharyngeal SCC.

On the contrary, single case reports, animal or *in vitro* studies, literature reviews, letters, editorial, correspondence or those studies in which phenomenon of shrinkage was not centered on surgical margin were excluded.

Screening process and data extractions

The screening process was conducted by one reviewer (D.G.B). The titles and abstracts were firstly analyzed. The second step consisted of a selection of those articles related with the PICO question. All articles selected were

carefully analyzed according to eligibility criteria for future data extraction. From each study included in the review the following information was extracted: first author, year of publication, study design, demographic data (age-range), number of subjects, tumor type, tumor site, tumor stage, margin identification, resection margin, surgical instrument used for resection, measuring instrument, pre-resection measurement, measuring time pre-post resection, mean shrinkage pre-post resection, measurement by stage and measurement by site.

RESULTS

Literature search

The initial search strategy yielded a total of 107 articles from Pubmed database, 9 articles obtained from related citations of Pubmed and 287 articles from hand- searching. In the first step, titles and abstracts of articles obtained in the strategy search were reviewed for elimination of irrelevant articles (376 articles). In the second step, those articles related with PICO question were analyzed for eligibility (27 articles).

Subsequently, a comprehensive and careful reading of the full-text of selected articles was carried out (6 articles). Finally, only 4 articles were included for final data extraction [Figure 1]. Due the heterogeneity of analyzed studies a qualitative synthesis of the data was performed.

Study characteristics

The characteristics of the studies included in this review are showed in Tables 1 and 2. One prospective study, one retrospective study and other two articles without a clear definition of the type of study design were included. The number of participants in the studies ranged from 35 to 95, and the average age was 59.32 years.

Three articles studied the discrepancy between “*in situ*” margins and “histopathologic” margins in patients underwent surgery for oral SCC, while one study analyzed the effect of tissue shrinkage on surgical margins of resection in patients operated for lip SCC. In all analyzed studies, the appropriate surgical margin of resection was defined as that margin located 1 cm from the tumor border; likewise, the resection margin was identified by mean of marking ink in

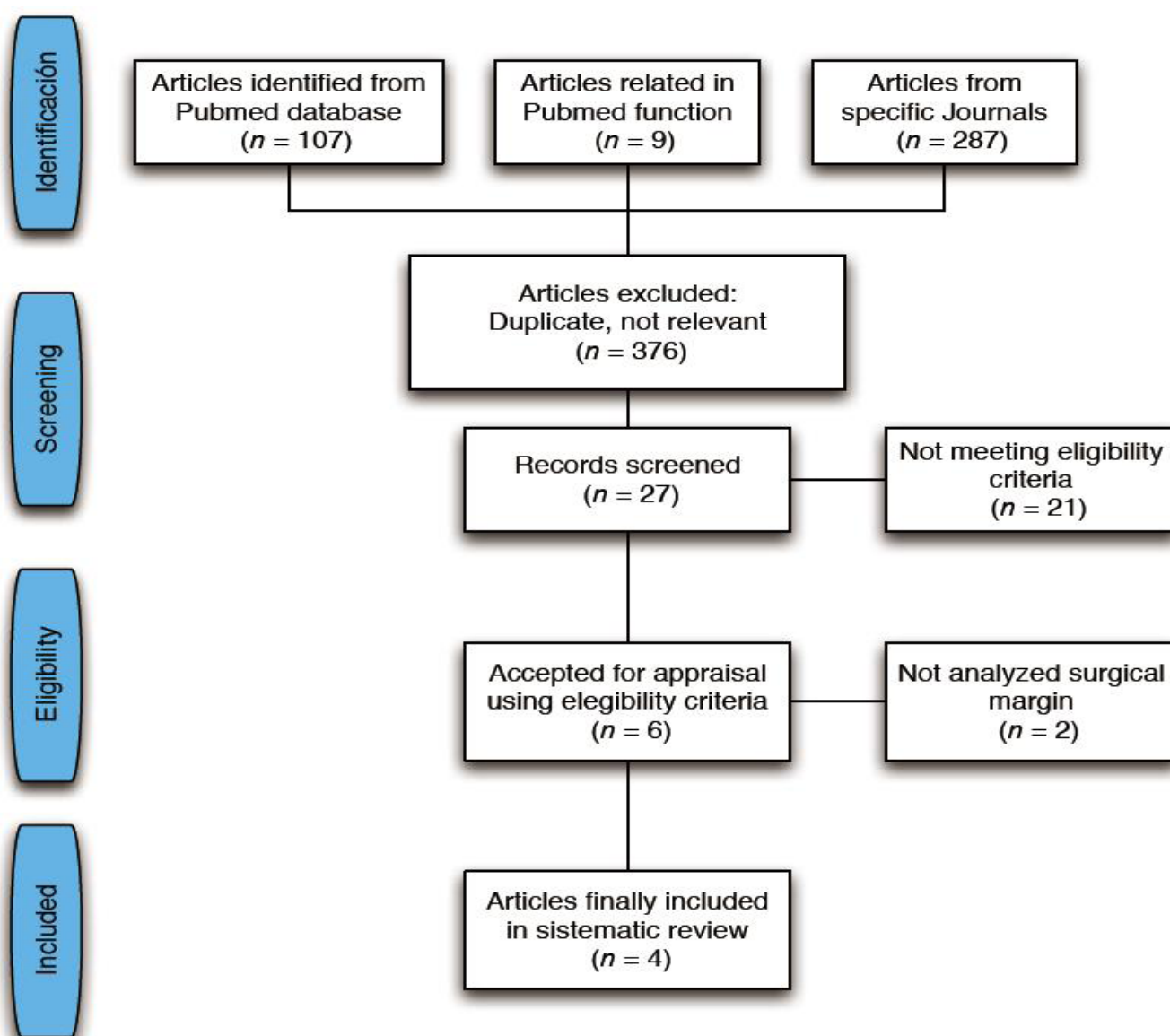


Figure 1: Flow chart (screening and selection process) used for the articles included in this review

Table 1: Summary of main characteristics of reviewed studies

Authors (year)	Study design	Demographic data (No. of subjects; gender; age range; mean age)	Tumor type	Location tumor and No. of patients	Tumor stage and No. of patients
El-Fole <i>et al.</i> ^[23] (2014)	Prospective	61 patients; 39 M (63.9%), 22 F (36.1%); 35-69 years; mean 51.6 years	Oral SCC	Tongue: 20; mucosa alveolar margin mandible: 13; buccal mucosa: 15; retromolar trigone: 6; floor of the mouth: 3; mucosa alveolar margin maxilla: 4	T1: 4; T2: 47; T3: 5; T4: 5
Egemen <i>et al.</i> ^[24] (2014)	NR	21 patients; 14 M (66.6%), 7 F (33.3%); 47-92 years; mean 71.1 years	Lip SCC	Lower lip: 15; Upper lip: 5; Commisure: 1	T1: 8; T2: 10; T3: 3
Cheng <i>et al.</i> ^[20] (2008)	NR	41 patients; 21 M (51%), 20 F (49%); 35-95 years; mean 67 years	Oral SCC	Group 1: buccal mucosa, mandibular Alveolar ridge and retromolar trigone - 21; Group 2: maxilar alveolar ridge and hard palate - 6; Group 3: oral tongue - 14	T1: 11; T2: 16; T3: 1; T4: 11; 2 patients excluded
Mistry <i>et al.</i> ^[16] (2005)	Retrospective	27 patients; 18 M (66.6%), 9 F (33.3%); 36-61 years; mean 47.6 years	Oral SCC	Oral tongue - 16; buccal mucosa - 11	T1: 11; T2: 11; T3: 3; T4: 2

M: male; F: female; NR: not reported; SCC: squamous cell carcinoma

Table 2: Summary of the measurements made in the analyzed studies

Authors (year)	Margin identification; surgical instrument; resection margin; measuring instrument	Surgical measurement	Measuring time, pre-post resection	Mean shrinkage	Shrinkage by site	Shrinkage by stage
El-Fole <i>et al.</i> ^[23] (2014)	Margin ink/sutures; electrocautery; 1 cm; metric ruler or caliper	<i>In situ</i> /pre-resection; immediately post-resection	NR	47.6% buccal mucosa; 33.3% tongue; 9.5% mandibular alveolus; 4.8% floor of mouth; 4.8% retromolar trigon	66.7% buccal mucosa; 35% tongue; 33.3% floor of mouth; 15.4% mandibular alveolus; 16.7% retromolar trigon	NR
Egemen <i>et al.</i> ^[24] (2014)	Margin ink; not indicated; 1 cm; metric ruler/water flooding	<i>In situ</i> /pre-resection; immediately post-resection	At 24 h and 48 h of fixation (volume, tumor length and distance); After 48 h of fixation - standardized fashion	41-47%; volume decrease 21.8%	NR	NR
Cheng <i>et al.</i> ^[20] (2008)	Margin ink; not indicated; 1 cm; metric ruler	<i>In situ</i> /pre-resection	NR	59.02%	71.90% Group 1; 53.33% Group 2; 41.14% Group 3	T1/T -51.48%; T3/T -75%
Mistry <i>et al.</i> ^[16] (2005)	Margin ink/sutures; electrocautery 1 cm; caliper	<i>In situ</i> /pre-resection	Half on hour post-resection	22.7 %	23.5% tongue; 21.2% buccal mucosa	T1-T2-25.6%; T3-T4-9.2%

NR: not reported

all examined articles and only 2 of them reported the use of sutures as an additional means of margins identification. Only 2 studies indicated the instrument utilized for resection (electrocautery). The extent of the tumor was, in all cases, determined by visual inspection and palpation. With regards to the measuring instruments used to assess the discrepancy between “*in situ*” margins and “histologic” margin, 3 studies reported the use of the metric ruler as measuring instrument, 1 study described the caliper as the instrument utilized in the measurements and 1 study informed the use of both instruments for measuring of the margins. All articles reported a measurement of surgical margin prior to the surgical resection, but only 2 of them indicated the time until the measurement recorded by the pathologist (one study at 24-48 h postresection and another study at half an hour after resection).

A statically significant discrepancy between margins

measured at the time of the surgery and margins measured after histopathologic processing was observed in all studies analyzed. Thus, Mistry *et al.*^[16] reported a mean shrinkage from the pre-resection to the post-resection measurement of 3.18 mm (22.7%) ($P < 0.011$). In their study, Cheng *et al.*^[20] informed a mean discrepancy between the *in situ* margins and the histopathologic margins for all patients of 59.02% ($P < 0.001$). However, El-Fol *et al.*^[23] described a mean discrepancy between intraoperative margins and histopathologic margins exclusively analyzing all close and positive margins. In this study, the mean discrepancy for buccal mucosa was 47.6%, 33.3% for the tongue, 9.5% for the mandibular alveolus, and 4.8% for both, retromolar trigon and floor of the mouth. Finally, the study of Egemen *et al.*^[24] based on the surgical margins of the resected lip specimens, reported a mean decrease of up to 41-47.5% in the length and of 21.8% in volume between measurements performed before the resection and those obtained in the histopatologic study.

Shrinkage depending on the tumor site

The degree of shrinkage based on the different tumor sites was analyzed by three studies. Mistry *et al.*^[16] published a study on 27 patients with oral SCC of the tongue and buccal mucosa of the oral cavity where examined the distances pre-resection and post-resection. They reported a greater discrepancy of the tongue margins (23.5%) than the buccal mucosa margin (21.2%) and a mean loss of 22.7%, however, these results were not statistically significant. In the study of Cheng *et al.*^[20] on 41 patients with diagnosis of oral SCC the amount of margin discrepancy between margins measured intraoperatively and those measured microscopically was quantified. The patients were grouped by locations obtaining the following statistically significant result: mean discrepancy for group 1 (buccal mucosa, mandibular alveolar ridge and retromolar trigone) 71.90%, 53.33% for group 2 (maxillary alveolar ridge and palate) and 42.14% for group 3 (oral tongue), with a *P* value corresponding to 0.0133. Likewise, El-Fol *et al.*^[23] measured the difference between the “*in situ*” margins and “histopathologic” margins of 61 patients that underwent resective surgery for oral SCC. A significant difference in the measurement of resection margin according to the anatomical site was obtained with a mean of discrepancy of 66.7% for buccal mucosa, a 35% for the tongue, a 33.3% for the floor mouth, a 16.7% for the retromolar trigone and a 15.4% for the mandibular alveolus.

Shrinkage depending on the tumor stage

The percentage of discrepancy in the different studies analyzed according to the tumor stage was described in only two studies.

The study of Mistry *et al.*^[16] compared the mean shrinkage of patients with lower stage tumors (T1 and T2) with the mean shrinkage in patients with higher stage tumors (T3 and T4). The difference between the two groups was statistically significant (*P* < 0.011), with a mean of 3.59 mm (25.6%) for T1/T2 tumors vs. 1.4 mm (9.2%) for T3/T4 tumors, respectively. However, these results were different to the study presented by Cheng *et al.*^[20] where the mean of discrepancy for T1/T2 tumor was 51.48%, and 75% for T3/T4 tumors (*P* = 0.0264).

DISCUSSION

One of the most important prognostic factors respect to overall survival and local recurrence rates is the status of surgical margins of resection.^[5,25] Indeed, the main goal of the resective surgery of the head and neck is the complete removal of the tumor with suitable margins of resection free of disease.^[23] However, even at the present day, there has not been consensus between researches on what constitutes tumor involvement at the resection margin (including mucosal dysplasia or carcinoma *in situ*) and what constitutes an “adequate” margin of resection.^[7,8,18] Though controversial, it seems reasonable to accept, based on studies, that 5 mm of healthy tissue around the tumor should be the minimum acceptable margin size for a clear surgical margin in any oral SCC.^[7,19]

Nevertheless, it sometimes happens that, the surgeon feels frustration when noticing that an appropriate surgical margin in the operation room presents a considerably decrease in size when is observed by the pathologist. In such cases, it is not surprising that a surgical margin that seems appropriate intra-operatively can be reported as positive or affected in the final histopathologic analysis. Diverse explanations have been considered in the literature. Thus, the invasive character of oral SCC can lead to occult microscopic margins, finger extensions or islands of tumor that extend beyond the clinically visible and palpable tumor, obtaining a margin that is closer than previously expected.^[20,23] Moreover, it should be kept in mind that malignant molecular changes may be present even when there are histopathologic normal margins.^[26] Nevertheless, it seems clear that the discrepancy observed between clinical and pathological margins is most often associated to shrinkage phenomenon after resection.^[23]

The aim of this literature review was to identify studies that discussed the tissue shrinkage phenomenon on surgical margins of resection in patients underwent surgery for oral and oropharynx SCC. Only four articles were finally included in this review according to our search strategy (one prospective, one retrospective and two articles not defined). All of them reported a discrepancy between surgical margins measured intra-operatively and those margins of resection measured by the pathologist after processing of the surgical piece. These findings are consistent with those reported by others authors that observed the phenomenon of margin shrinkage at other places of the body.

Thus, in a study by Silverman *et al.*^[27] on 199 cutaneous malignant melanoma reported of a shrinkage of a 15 to 25% on margins of surgical specimens depending on the patient's age. Likewise, Weese *et al.*^[28] observed in ten patients who underwent colonic resection that resected rectal margin could shrink up to 50% or more after processing histologic of surgical piece. Siu *et al.*^[29] noted in a study on esophagus carcinoma that exist a different degree of shrinkage of the entire specimen from its surgical resection to its final pathological study. The surgical specimen shrank a 40% following resection and another 10% after formalin fixation.

However, the first reference regarding to the study of tissue shrinkage on surgical margins of resection in oral cavity and oropharynx is attributed to Johnson *et al.*^[9] in 1997. In their experimental study on ten mongrel dogs they reported that a shrink of up to 30-50% may be expected in the specimens of oral cavity and oropharynx and the maximum shrinkage occurs immediately after the resection. These results are similar to those of the articles analyzed in this review of human study. In fact, a conclusion shared by all the authors is that specimens of oral SCC are significantly reduced after surgical resection.^[16,20,23,24]

Thus, Mistry *et al.*^[16] published a study on 27 patients with oral SCC of the tongue and buccal mucosa where analyzed the distances pre-resection and post-resection and reported a mean shrinkage of 3.18 mm (22.7%). However, El-Fol *et al.*^[23] described a mean discrepancy between intraoperative margins and

histopathologic margins exclusively analyzing all close and positive margins. In this study, the mean discrepancy for buccal mucosa was 47.6%, 33.3% for the tongue, 9.5% for the mandibular alveolus, and 4.8% for both, retromolar trigone and floor of the mouth.

In the study of Cheng *et al.*,^[20] the mean discrepancy between the *in situ* margins and the histopathologic margins for all patients was reported statistically significant at 59.02% ($P < 0.001$). One conclusion of the authors for these findings is that the specimens of the oral cavity retract significantly after resection and subsequently after pathologic processing.

Likewise, Egemen *et al.*^[24] in their study on surgical margins of the resected lip specimens, observed a mean decrease of up to 41-47.5% in length and of 21.8% in volume between measurements obtained before the resection and those reported in the histopathologic study. Moreover, they noted that the most significant step for shrinkage phenomenon was the excision step followed by the formalin fixation step and also noted that the duration of the fixation did not affect the shrinkage rate of surgical margins; however, the volume of the specimen was decreased in higher proportion at 48 h compared with 24 h of fixation.

An interesting fact to consider is whether the tumor site influences on the degree of tissue shrinkage. Certain

intrinsic factors, such as tissue composition, have been studied as responsible of different shrinkage percentages at different locations in the given specimen. It has been observed that intra-tumoral shrinkage is less as is compared to the shrinkage at surgical margins. Even if different surgical margins of a single specimen are from the same location of the oral cavity, shrinkage of each margin may vary. The reason, according to some authors, could be diverse: presence of varying number of tumor cells underneath surgical margin, cohesiveness of tumor cells, degree of keratinization, degree of inflammation, variable susceptibility of invasion or inclusive heterogeneous biology among other.^[20,30]

In this regard, Mistry *et al.*^[16] reported a greater discrepancy of the tongue margins (23.5%) that the buccal mucosa margin (21.2%), however, these results were not statistically significant. They concluded that factors like age, gender or site of tumor do not significantly affect the quantum of shrinkage. On the other hand, in the study of Cheng *et al.*^[20] where the patients were grouped by locations, the mean of discrepancy obtained for group 1 (buccal mucosa, mandibular alveolar ridge and retromolar trigone) was 71.90%, 53.33% for group 2 (maxillary alveolar ridge and palate) and 42.14% for group 3 (oral tongue), with a P value corresponding to 0.0133. Likewise, El-Fol *et al.*^[23] found a significant difference in the measurement of resection margin

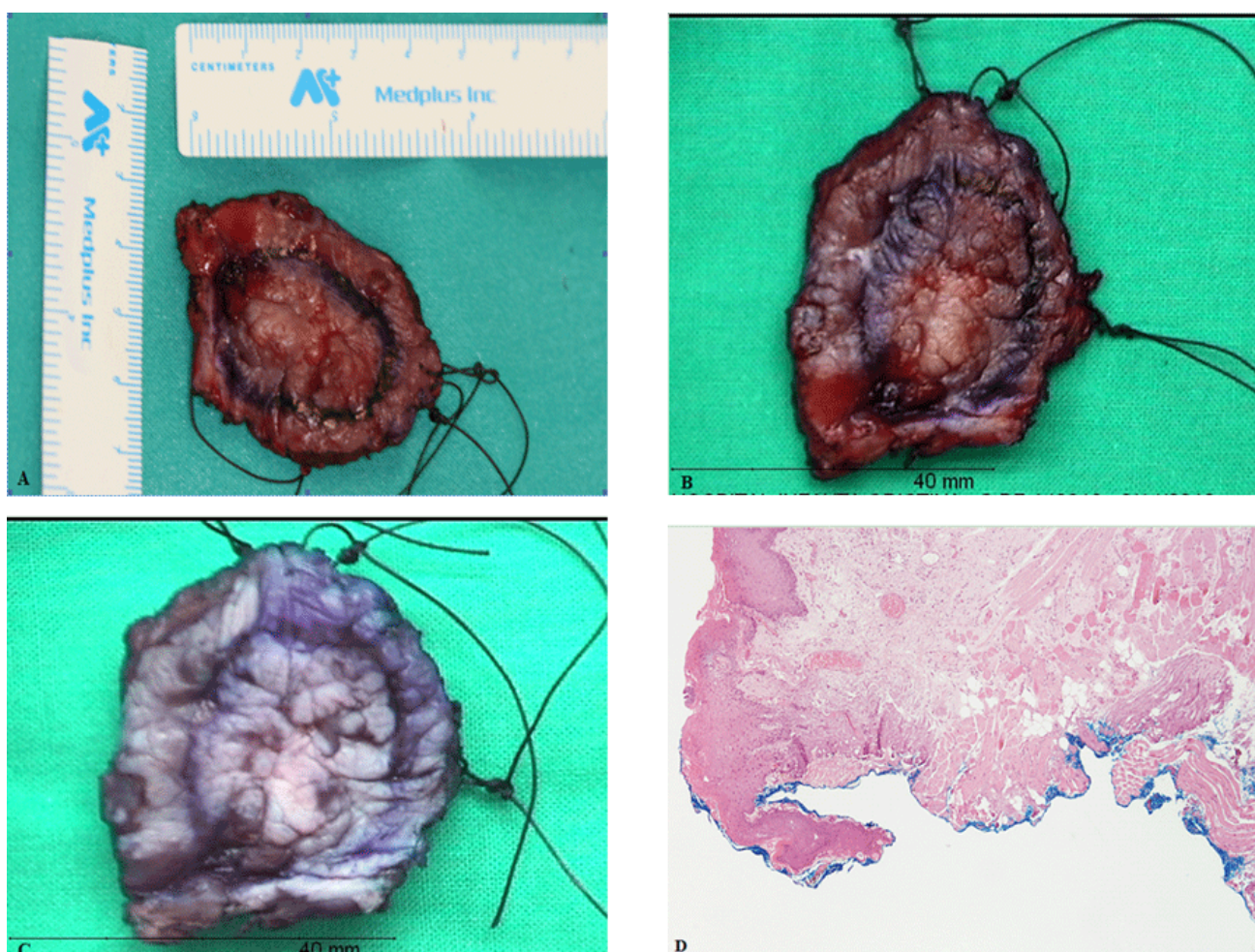


Figure 2: Brief summary of the measurements taken during the different phases of the study performed by the authors' team. (A) intraoperative measurement in fresh; (B) measurement in fresh by the pathologist; (C) measurement after fixation with formaldehyde; (D) measurement under microscope (C) in a patient with oral squamous cell carcinoma - T1N0M0

according to the anatomical site. In this study the mean of discrepancy observed for buccal mucosa was of 66.7%, 35% for the tongue, a 33.3% for the floor mouth, a 16.7% for the retromolar trigon and a 15.4% for the mandibular alveolus. Given these results, it seems appropriate to believe that knowing shrinkage of each margin according to its location instead of shrinkage of the specimen, is what should guide treatment guidelines.^[30]

When comparing margins discrepancies based on staging, Cheng *et al.*^[20] described a mean discrepancies in T1/T2 tumors of 51.48% and in T3/T4 tumors of 75% with a *P* value of 0.0264. These findings differed from those presented by Mistry *et al.*^[16] who observed a mean shrinkage of 3.59 mm (25.6%) for T1/T2 tumors and 1.4 mm (9.2%) for T3/T4 tumors with a difference statistically significant (*P* < 0.011). In this study, the authors hypothesized that late stage tumors may show a smaller discrepancy due to tumor related destruction of contractile elements surrounding cancer. However, Cheng *et al.*^[20] tried to explain this discrepancy alluding that late stage tumors result in a greater microscopic invasiveness and that the small number of cases presented by Mistry *et al.*^[16] could be considered an artifact. As we can see in view of the results obtained, the degree of discrepancy between the pre and post surgical resection margins based on tumor staging does not obtain extrapolated conclusions mainly because only two studies, whose tumor sites clearly differ from each other, were analyzed.

The results obtained in this review related to the phenomenon of tissue shrinkage on the surgical margin of resection in patients with oral SCC, coincide with the results observed by the author and his team. In our study, pending on its recent publication, patients diagnosed of oral and oropharyngeal squamous cell carcinoma and that underwent surgery with reconstruction by means of microsurgical techniques, the analysis of surgical resection margins was performed in several stages: pre-resection, immediately post-resection in the operating room, in fresh in the pathology department, after fixation by the pathologist and under microscope [Figure 2]. In anticipation of the results, only indicate that a large discrepancy between the margins intraoperatively measured and the margins microscopically analyzed was observed, with an average of 4.46 mm. The step in which a smaller reduction of surgical margins was observed coincide with that reported in this review, the step from formalin fixation to the microscope analysis, with an overall mean of 0.68 mm.

Study limitations

The author of this paper recognizes the limitations inherent to this review. The study is limited to one database (Pubmed) and only four articles were included in the final study according to our search strategy. The scarce number of patients observed by staging or by site in some articles, the variety of study designs, the absence of measurement post-resection immediately in the operation room in two of the studies, together to the fact that not all articles explain the surgical instruments used for tumor resection or how long was from resection of surgical specimen to the measurement by the pathologist after histopathologic processing, make that studies be quite heterogeneous as to obtain any type

of quantitative results. Therefore, the conclusions achieved have to be taken with caution before its application to clinical practice. Maybe, future studies involving a largest number of patients by stage or locations can provide more reliable information for application to clinical routine.

In conclusion, tissue shrinkage on surgical margins of resection in oral SCC is a tangible phenomenon. The highest percentage of retraction occurs at the time of resection. Tumor staging should be established intra-operatively and no following histopathologic processing when the tissue shrinkage phenomenon is already established. The surgeon should take the tissue shrinkage phenomenon into account when affording surgical resection, while his/her actuation must be based on tumor site and stage in order to provide adequate definitive tumor margins.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Stewart BW, Wild CP. World Cancer Report 2014. World Health Organization: Geneva; 2014.
2. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. *Oral Oncol* 2009;45:309-16.
3. Massano J, Regateiro FS, Januário G, Ferreira A. Oral squamous cell carcinoma: review of prognostic and predictive factors. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;102:67-76.
4. Spiro RH, Guillemondegui O Jr, Paulino AF, Huvos AG. Pattern of invasion and margin assessment in patients with oral tongue cancer. *Head Neck* 1999;21:408-13.
5. Looser K, Shah J, Strong E. The significance of "positive" margins in surgically resected epidermoid carcinomas. *Head Neck Surg* 1978;1:107-11.
6. Yahalom R, Dobriyan A, Vered M, Talmi YP, Teicher S, Bedrin L. A prospective study of surgical margin status in oral squamous cell carcinoma: a preliminary report. *J Surg Oncol* 2008;98:572-8.
7. Kurita H, Nakanishi Y, Nishizawa R, Xiao T, Kamata T, Koike T, Kobayashi H. Impact of different surgical margin conditions on local recurrence of oral squamous cell carcinoma. *Oral Oncol* 2010;46:814-7.
8. Hinni ML, Ferlito A, Brandwein-Gensler MS, Takes RP, Silver CE, Westra WH, Seethala RR, Rodrigo JP, Corry J, Bradford CR, Hunt JL, Strojjan P, Devaney KO, Gnepp DR, Hartl DM, Kowalski LP, Rinaldo A. Surgical margins in head and neck cancer: a contemporary review. *Head Neck* 2013;35:1362-70.
9. Johnson RE, Sigman JD, Funk GF, Robinson RA, Hoffman HT. Quantification of surgical margin shrinkage in the oral cavity. *Head Neck* 1997;19:281-6.
10. McMahon J, O'Brien CJ, Pathak I, Hamill R, McNeil E, Hammersley N, Gardiner S, Junor E. Influence of condition of surgical margins on local recurrence and disease-specific survival in oral and oropharyngeal cancer. *Br J Oral Maxillofac Surg* 2003;41:224-31.
11. Nason RW, Binahmed A, Pathak KA, Abdoh AA, Sándor GKB. What is the adequate margin of surgical resection in oral cancer? *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;107:625-9.
12. Woolgar JA, Triantafyllou A. A histopathologic appraisal of surgical margins in oral and oropharyngeal cancer resection specimens. *Oral Oncol* 2005;41:1034-43.
13. Brandwein-Gensler M, Teixeira MS, Lewis CM, Lee B, Rolnitzky L, Hille JJ, Genden E, Urken ML, Wang BY. Oral squamous cell carcinoma: histologic risk assessment, but not margin status, is strongly predictive of local disease-free and overall survival. *Am J Surg Pathol* 2005;29:167-78.
14. Tirelli G, Zacchigna S, Biasotto M, Piovesana M. Open questions and novel concepts in oral cancer surgery. *Eur Arch Otorhinolaryngol* 2015; Epub ahead of print.
15. Chiou WY, Lin HY, Hsu FC, Lee MS, Ho HC, Su YC, Lee CC, Hsieh CH, Wang YC, Hung SK. Buccal mucosa carcinoma: surgical margin less than 3 mm, not 5 mm, predicts locoregional recurrence. *Radiat Oncol* 2010;5:79.

16. Mistry RC, Qureshi SS, Kumaran C. Post-resection mucosal margin shrinkage in oral cancer: quantification and significance. *J Surg Oncol* 2005;91:131-3.
17. Loree TR, Strong EW. Significance of positive margins in oral cavity squamous carcinoma. *Am J Surg* 1990;160:410-4.
18. Weinstock YE, Alava I, Dierks EJ. Pitfalls in determining head and neck surgical margins. *Oral Maxillofac Surg Clin North Am* 2014;26:151-62.
19. Anderson CR, Sisson K, Moncrieff M. A meta-analysis of margin size and local recurrence in oral squamous cell carcinoma. *Oral Oncol* 2015;51:464-9.
20. Cheng A, Cox D, Schmidt BL. Oral squamous cell carcinoma margin discrepancy after resection and pathologic processing. *J Oral Maxillofac Surg* 2008;66:523-9.
21. Upile T, Fisher C, Jerjes W, El Maaytah M, Searle A, Archer D, Michaels L, Rhys-Evans P, Hopper C, Howard D, Wright A. The uncertainty of the surgical margin in the treatment of head and neck cancer. *Oral Oncol* 2007;43:321-6.
22. Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak* 2007;7:16.
23. El-Fol HA, Noman SA, Beheiri MG, Khalil AM, Kamel MM. Significance of post-resection tissue shrinkage on surgical margins of oral squamous cell carcinoma. *J Craniomaxillofacial Surg* 2015;43:475-82.
24. Egemen O, Bingöl D, Orman Ç, Sayilgan AT, Özkaya Ö, Akan M. Quantification of the surgical margin shrinkage in lip cancer: determining the relation between the surgical and histopathologic margins. *J Craniofac Surg* 2014;25:2152-5.
25. Ravasz LA, Slootweg PJ, Hordijk GJ, Smit F, van der Tweel I. The status of the resection margin as a prognostic factor in the treatment of head and neck carcinoma. *J Craniomaxillofac Surg* 1991;19:314-8.
26. van Houten VM, Leemans CR, Kummer JA, Dijkstra J, Kuik DJ, van den Brekel MW, Snow GB, Brakenhoff RH. Molecular diagnosis of surgical margins and local recurrence in head and neck cancer patients: a prospective study. *Clin Cancer Res* 2004;10:3614-20.
27. Silverman MK, Golomb FM, Kopf AW, Grin-Jorgensen CM, Vossaert KA, Doyle JP, Levenstein MJ. Verification of a formula for determination of preexcision surgical margins from fixed-tissue melanoma specimens. *J Am Acad Dermatol* 1992;27:214-9.
28. Weese JL, O'Grady MG, Ottery FD. How long is the five centimeter margin? *Surg Gynecol Obstet* 1986;163:101-3.
29. Siu KF, Cheung HC, Wong J. Shrinkage of the esophagus after resection for carcinoma. *Ann Surg* 1986;203:173-6.
30. Sarode SC, Sarode GS. A novel "microscopic method" of shrinkage calculation in the pursuance of shrinkage based histopathologic guidelines for interpretation of surgical margins. *Oral Oncol* 2012;48:15-6.

The role of radiotherapy in the treatment of oral cavity cancer

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ABSTRACT

Radiotherapy plays a critical role in the treatment of oral cavity squamous cell carcinoma as monotherapy in early stage cancer or combined with surgery and/or chemotherapy in advanced ones. Recent developments in the imaging of cancer and radiation technology have allowed developing more precise delivery of treatment with recent data demonstrating improvement in survival and lessening of adverse toxic effects of radiation. This review will focus in the recent advances and current state-of-the-art in radiation oncology both external beam radiotherapy and brachytherapy. As complexity of cancer treatments increases a close coordination between head-neck surgeons and radiation oncologist is needed due to a significant proportion of patients will be treated with combined modality therapy.

Key words:

Radiotherapy; intensity modulated radiation therapy; high dose rate; low dose rate; head neck cancer; brachytherapy

INTRODUCTION

Although surgery is the recommended treatment for oral cavity squamous cell carcinoma (OCSCC),^[1] radiotherapy (RT) plays a capital role in the treatment of OCSCC either exclusively or as adjuvant after surgery.

RT may be administered using two techniques, which, in turn, are likely to be combined together in the specific case of OCSCC: external beam radiotherapy (EBRT) and brachytherapy (BT). Usually patients with early stage disease are treated exclusively radical radiotherapy; however, patients with

unresectable or advanced disease will receive radiotherapy plus chemotherapy or targeted therapy with monoclonal antibodies against epidermal growth factor receptor (EGFR) in order to enhance the cytotoxic effect of radiation.

The present manuscript is a revision of most important manuscripts concerning a large and extended bibliography has been performed in order to elucidate the current role of RT in the treatment of patients with squamous cell carcinoma of the oral cavity.

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RADIOTHERAPY TECHNIQUES OVERVIEW

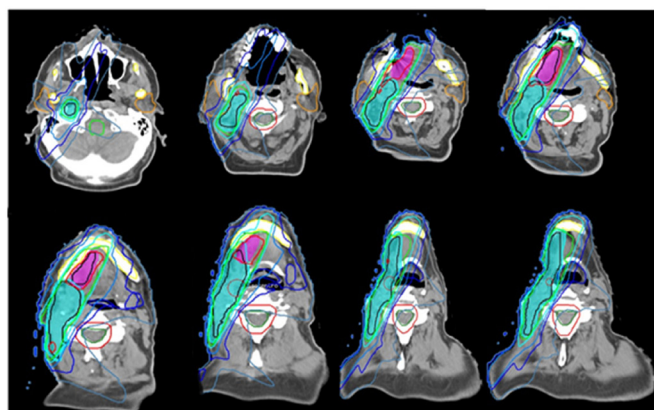


Figure 1: Postoperative intensity modulated radiation therapy plan for an oral tongue squamous cell carcinoma pT2 pN1 M0. High dose encompass risk volumes (blue: ipsilateral nodal bed, purple: tumor bed) while sparing healthy organ: parotids glands (orange) spinal cord (green) mandible and larynx (courtesy of Dr. Enrique Miragall from Fundación ERESA)

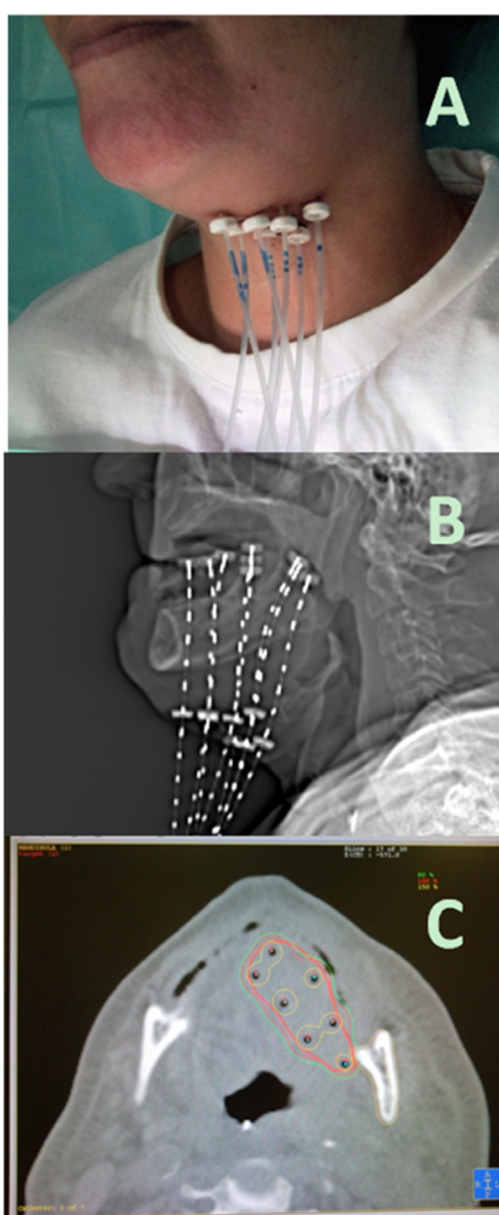


Figure 2: High dose rate brachytherapy for oral tongue carcinoma. (A) showing external outward appearance of percutaneous catheters for afterloading technique; (B) digital radiographic reconstruction of the implant for planning purposes; (C) computed tomography axial view showing high isodose lines covering tumor bed but sparing contralateral tongue, mandible and lips (courtesy of Dr. José Luis Guinot from Instituto Valenciano de Oncología)

Currently standard EBRT is based on the assessment of target volumes to irradiate and organs at risk to protect in 3D-computed tomography (CT) simulation plus multimodal images (e.g. positron emission tomography-CT, magnetic resonance imaging).^[2-6] Delivery of treatment should be based on intensity modulated radiation therapy^[7] (IMRT) which involves the use of multiple computer-aided beams of inhomogeneous radiation, allow dose shaping the spatial shape of treatment volume, improving the coverage of target area and the protection of healthy tissue [Figure 1]. When using IMRT different treatment volumes (e.g. macroscopic tumor vs. elective nodal levels) receive a different dosage during the same fraction, without increasing the number of RT sessions, so the intensity of treatment is adjusted to each volume of interest by dose gradients.^[8] IMRT compared with traditional 2D-EBRT has been shown to improve toxicity^[9] and survival^[10] in patients with head neck cancer.

Traditionally BT implant has been performed with low dose rate (LDR) by inserting iridium needles (¹⁹²Ir) mainly; this technique has been gradually displaced by the so-called high dose rate (HDR) BT [Figure 2] due to its advantages of radiation protection of medical personnel, better dose distribution and shorter duration of treatment.^[11] However, the accelerated treatment and high dose per fraction used in HDR could lead to a decrease in the therapeutic ratio because of the risk of complications in extreme cases.^[12] Liu *et al.*^[13] conducted a meta-analysis to compare HDR BT vs. LDR BT in the treatment of OCSCC. No statistically significant difference was found in the odds ratio (OR) between the group of patients treated with LDR or HDR in terms of local recurrence OR = 1.12, mortality OR = 1.01, and complications grade 3-4 OR = 0.86.

The equivalent fractionation and total dosing between LDR and HDR is unknown. Neither the Groupe Européen de Curiethérapie-European Society for Radiotherapy and Oncology (GEC-ESTRO)^[11] nor the American Brachytherapy Society^[14] came to publish a consensus, although they recommended not to exceed a dose 6 Gy per fraction. In the comparative meta-analysis of Liu *et al.*,^[13] the mean dose administered was 66.17 Gy in LDR group and 50.75 Gy in the HDR. Radiobiological studies suggest that the optimal dose for exclusive HDR is about 50 Gy^[15,16] consistent with data from Liu *et al.*^[13] GEC-ESTRO has published recommendations^[17] for the calculation of equivalent doses between different protocols and BT techniques.

The main indication for combining EBRT and BT is the need to irradiate the cervical lymph node chains when the risk of involvement is significant due to the primary site,^[18] tumor thickness greater than 4 mm^[19] and stage cT2-T3.

Stages I-II

In treating early OCSCC the best results were obtained when BT is part of the treatment, either exclusively or as tumor overdose after EBRT.^[11] Evidence supporting this practice is based entirely on retrospective series. Even with the advent of IMRT, BT administration is advantageous in terms of shaping and

Table 1: Radical brachytherapy for oral cavity squamos cell carcinoma only, not including other head and neck sites

Studies	No. of patients	Site	Technique	Radiotherapy schedule	5-year local control (%)	5-year survival (%)
Lau <i>et al.</i> ^[12] 1996	27	Tongue	HDR	BT only, 45.5 Gy @6.5 Gy	53	92
Leung <i>et al.</i> ^[22] 2002	19	Tongue	HDR	BT only, 45-63 Gy (median 55 Gy, ten fractions)	94.7 (4-year)	NS
Martínez-Monge <i>et al.</i> ^[23] 2009	8	Oral cavity	HDR	EBRT 45 + BT 16 Gy @4 Gy	86 (7-year)	52.3 (7-year)
Guinot <i>et al.</i> ^[24] 2010	33	Tongue	HDR	EBRT 55 + BT 18 Gy @3 Gy	79	74
Inoue <i>et al.</i> ^[28] 2001	17	Tongue	HDR	BT only 44 Gy @4 Gy		
	25	Tongue	HDR	BT only 60 Gy @6 Gy	87	
	26		LDR	BT only 70 Gy	84	
Yamazaki <i>et al.</i> ^[29] 2003	58	Tongue	HDR	BT only 60 Gy @6 Gy	84	
	341		LDR	BT only 70 Gy	80	
Yamazaki <i>et al.</i> ^[30] 2007	80	Tongue	HDR	EBRT 37 Gy + BT 36-60 Gy	85	
	217		LDR ²²⁶ Ra	EBRT 29 Gy + BT 59-94 Gy	74	
	351		LDR ¹⁹² Ir	EBRT 29 Gy + BT 59-94 Gy	72	
Kakimoto <i>et al.</i> ^[32] 2011	14	Tongue (T3)	HDR	EBRT 30 Gy + 60 Gy	71 (2-year)	
	61		LDR	EBRT 30 Gy + 72 Gy	62	
Akiyama <i>et al.</i> ^[33] 2012	17	Tongue	HDR	BT only 54 Gy @ 6 Gy	88	
	34			BT only 60 Gy @6 Gy	88	
Donath <i>et al.</i> ^[34] 1995	13	Oral cavity	HDR	BT only 45-50 Gy @4.5-5 Gy	92	
Inoue <i>et al.</i> ^[35] 1998	16	Floor or Mouth	HDR	EBRT 30-40 Gy + BT 36-48 Gy @6 Gy	94	
	41		LDR ¹⁹⁸ Au	EBRT 30-40 Gy + BT 65-85 Gy	69	
Matsumoto <i>et al.</i> ^[36] 2013	67	Tongue	HDR	EBRT 20 Gy + BT 50 Gy	94	88.7
Khalilur <i>et al.</i> ^[37] 2011	125	Tongue	LDR	70 Gy	86	
Vedasoundaram <i>et al.</i> ^[38] 2014	33	Buccal mucosa	HDR	BT only 38.5 Gy @3.5 Gy	92.3	
Lee <i>et al.</i> ^[39] 2014	16	Oral cavity	HDR	EBRT 50 Gy + BT 21 Gy @3.5 Gy		
				BT only 50 Gy @5 Gy	84 (3-year)	70
				EBRT 50 Gy + BT 35 Gy @5 Gy		
Tuček <i>et al.</i> ^[40] 2014	20	Tongue	HDR	BT only 54 Gy @3 Gy	85	75
Oota <i>et al.</i> ^[25] 2006	433	Tongue	LDR	BT only 70 Gy	85.6	
				EBRT 35 Gy + BT 60 Gy		
Pernot <i>et al.</i> ^[41] 1996	552	Tongue	LDR	BT only 66 - 75 Gy	90.5	71.5
	207	FOM				
Lefebvre <i>et al.</i> ^[42] 1994	429	OC	LDR	BT only 66 Gy	90	
Mazeron <i>et al.</i> ^[43] 1991	279	Tongue & FOM	LDR	BT only 60-70 Gy	87-93	
Marsiglia <i>et al.</i> ^[44] 2002	160	FOM	LDR		88-93	76
Dearnaley <i>et al.</i> ^[45] 1991	149	Tongue & FOM	LDR	BT only	90	
Fujita <i>et al.</i> ^[46] 1999	207	Tongue	LDR	EBRT 30 Gy + BT 50-60 Gy	82.2	
				BT only 65-70 Gy		
Bachaud <i>et al.</i> ^[27] 1994	94	Tongue & FOM	LDR	EBRT 48 Gy + BT 26 Gy	61	
				BT only 66 Gy		
Ihara <i>et al.</i> ^[47] 2005	117	Tongue	LDR	EBRT 30 Gy + BT 65 Gy	59.2	54
				BT only 70 Gy		

@: dose per fraction when HDR is used. LDR: low dose rate; HDR: high dose rate; EBRT: external beam radiotherapy; BT: brachytherapy; OC: oral cavity; FOM: floor of mouth; NS: no shown

uniformity of dose^[20] and tumor control.^[21] Table 1 summarizes the results of selected series of OCSCC patients treated with radical BT with or without EBRT.^[12,22-47] In the case of floor of mouth stage cT1 local control is 93-95% and 72-88% for stage cT2. Local control in cancer of mobile tongue is achieved in 79-97% for stage I and 65-95% for stage II.

Stages III-IV

Usually the treatment of advanced cancer of OCSCC has been included in the group of “advanced head and neck cancer” (AHNC) because of this the indications, techniques and results from clinical trials are fully applicable.

Radiotherapy alone

Modification of EBRT fractionation allows to intensify radiation dose by means of two way: (a) increase in the total dose with hyperfractionation; and (b) shorten the duration of

using accelerated fractionation radiotherapy.

Two meta-analyses of randomized trials^[48,49] comparing conventional fractionation EBRT (CF-EBRT) against modified fractionation EBRT (MF-EBRT) were published. Bourhis *et al.*^[48] analyzes all clinical trials for all locations of the head and neck (12.6% of cases OCSCC), however data are presented separately depending on location; Glennly *et al.*^[49] examined trials for oral cavity and oropharynx cancer only.

Bourhis *et al.*^[48] found a statistically significant benefit in terms of overall survival (OS) HR = 0.92 in favor of MF-EBRT as well as an improvement in locoregional control (LRC) HR = 0.82. Hyperfractionated EBRT was also significantly better in terms of OS than accelerated EBRT, with an absolute benefit of 8% at 5 years.

Table 2: Risk groups definition according multivariate analysis (recursive partitioning analysis) by Langendijk

RPA class	Definition	VUMC series		VUMC series	
		LRC 5-year	OS 5-year	LRC 5-year	OS 5-year
Class I (intermediate risk)	Free margins without ECE	92%	67%	82%	60%
Class II (high risk)	T1, T2, T4 tumors with close or positive surgical margins; One lymph node metastasis with ECE	78%	50%	82%	50%
Class III (very high risk)	T3 tumors with close or positive surgical margins; Multiple lymph node metastases with extranodal spread; N3 neck	58%	37%	63%	36%

RPA: recursive partitioning analysis; LRC: locoregional control; OS: overall survival; ECE: extracapsular extension

Table 3: Adjuvant brachytherapy for oral cavity squamous cell carcinoma

Studies	No. of patients	Site	Technique	RT schedule	5-year local control (%)	5-year-overall survival (%)
Goineau <i>et al.</i> ^[89] 2015	112	Tongue	LDR	EBRT: 60-66 Gy + BT 50-55 Gy	76	56
Petera <i>et al.</i> ^[90] 2015	30	Tongue FOM	HDR	BT only 54 Gy @3 Gy	85.4 (3-year)	73 (3-year)
Lapeyre <i>et al.</i> ^[91] 2004	82	Tongue FOM	LDR	EBRT 48 Gy + BT 24 Gy BT only 60 Gy	81	80
Pernot <i>et al.</i> ^[92] 1995	97	Tongue FOM	LDR	NS	84	79
Fietkau <i>et al.</i> ^[93] 1991	50	Tongue FOM	LDR	EBRT 55 Gy + BT 24.5 Gy	94 (crude)	84 (crude)

@: dose per fraction when HDR is used. RT: radiotherapy; LDR: low dose rate; HDR: high dose rate; EBRT: external beam radiotherapy; BT: brachytherapy; FOM: floor of mouth; NS: not shown

Table 4: Postoperative intensity modulated radiation therapy for oral cancer

Studies	No. of patients	Site	RT schedule	Loco-regional control	Overall survival
Chan <i>et al.</i> ^[94] 2013	180	Oral		83 (2-year)	65 (2-year)
Hoffman <i>et al.</i> ^[95] 2015	18	Oral cavity	66 Gy IMRT with SIB	78 (5-year)	77 (5-year)
Sher <i>et al.</i> ^[96] 2011	30	Oral	64.13 Gy IMRT secuencial boosting	91 (2-year)	85 (2-year)
Gomez <i>et al.</i> ^[97] 2011	35	Oral	60 Gy IMRT SIB	77 (3-year)	74 (3-year)
Chakraborty <i>et al.</i> ^[98] 2015	75	Oral	IMRT volumetric	88.9 (2-year)	80.5 (2-year)
Studer <i>et al.</i> ^[99] 2012	99 (R0-1) 17 (R2)	Oral (primary + recurrent)	70 Gy IMRT SIB	80 (4-year) 35 (4-year)	79 (4-year) 30 (4-year)
Collan <i>et al.</i> ^[100] 2010	40	Oral	58 Gy IMRT secuencial boosting	87.5 (5-year)	75 (5-year)
Geretschlager <i>et al.</i> ^[101] 2012	53	Oral	66 Gy IMRT secuencial boosting	79 (3-year)	73 (3-year)
Yao <i>et al.</i> ^[102] 2007	55 (5 p definitive RT)	Oral	66 Gy IMRT SIB	82 (3-year)	82 (3-year)
Daly <i>et al.</i> ^[103] 2011	37 (7 definitive RT)	Oral	66 Gy IMRT SIB	53 (3-year)	60 (3-year)

Most patients receive chemoradiation. Only include studies about oral cancer or mixed head and neck tumors reporting oral cancer results separately. RT: radiotherapy; IMRT: intensity modulated radiation therapy; SIB: simultaneous integrated boost

Glenny *et al.*^[49] reported that MF-EBRT, reduces overall mortality, HR = 0.86, and increased LRC HR = 0.79. Trials included as "purely hyperfractionated" also showed a significant gain in OS compared with the accelerated fractionation HR = 0.78.

Radiotherapy and chemotherapy combination

Pignon *et al.*^[50] performed a meta-analysis on benefit of chemotherapy (CMT) added to EBRT in head and neck cancer (MACH-NC). Overall improvement in OS was demonstrated when chemotherapy is added to radiation. Maximum benefit was found when CMT is administered concurrently with EBRT: 5-year OS 8% improvement. The benefit of CRT is applicable to all locations of the head and neck.^[51]

Two randomized trials have investigated whether the addition of chemotherapy to MF-EBRT is superior to CRT (CF-EBRT) or MF-EBRT alone.

The French Group of Radiation Oncology of Head and Neck Cancer (GORTEC)^[52] randomized patients into three arms: accelerated EBRT alone, CF-EBRT plus CMT or accelerated EBRT plus CMT. No statistically significant difference was found between the treatment groups at 3-year OS: 32.2% vs. 37.6% vs. 34.1%, nor distant metastasis (DM). However, both locoregional failure (LCF) (49.9% vs. 41.7% vs. 45.4%) and progression-free survival (PFS) (32.2% vs. 37.6% vs. 34.1%) were significantly lower in the accelerated EBRT arm. Mucosal acute toxicity and the need for feeding tube were significantly higher in patients treated with MF-EBRT.

In the second study by the Radiation Therapy Oncology Group (RTOG)^[53] patients were randomized to MF-EBRT alone or FM-EBRT plus CMT. No statistically significant difference was found in 8-year OS (48% in both arms) LRF (37% vs. 39%) PFS (42% vs. 41%) or DM (15% vs. 13%) No statistically significant differences in toxicity were found

either. In conclusion, no advantage in combining MF-EBRT and CMT have been proved so far.

Target therapy

EGFR over expression leads to decreased survival and increased risk of local and regional recurrence in head and neck cancer.^[54] The inhibition of EGFR by monoclonal antibodies (cetuximab) associated with EBRT in patients with non-operated AHNC showed an increase 5-year OS (46% vs. 36%) and LRC (47% vs. 34%) compared with EBRT alone.^[55] Notably in this trial did not include patients with OCSCE therefore clinical benefit in this group of patients is presently unknown.

Nowadays, the standard of treatment for non-operable AHNC, including OCSCE, is EBRT plus CMT despite the fact that its benefit in OS and LRC probability equals of the hyperfractionated-EBRT. The reasons that have led to this situation are basically two: (1) logistics, due to the consumption of resources and the drawbacks associated with treating patients twice a day, for 7-8 weeks; and (2) the development of high conformation techniques as IMRT, which allow to exploit the different sensitivity to radiation of the tumor and healthy tissues using a single fraction per day with a shorter overall time of treatment, usually 5-6 weeks.

Postoperative radiation therapy

Adjuvant EBRT

The value of postoperative radiotherapy (PORT) for AHNC, was established by Fletcher and Evers^[56] and Marcus *et al.*^[57] in 1970's. The evidence that proves the usefulness of PORT has been based on retrospective studies of large groups of patients. Due to the inherent bias in such kind of studies the survival benefit of PORT is not fully confirmed, although there are no doubts about the gain in LRC.

Lundahl *et al.*^[58] performed a retrospective, matched-pair analysis to compare surgery alone vs. surgery plus PORT. They found significant improvement in LRC and OS in the PORT group.

Lavaf *et al.*^[59] and Kao *et al.*^[60] analyzed patients with AHNC stage III-IV treated with surgery alone or surgery plus PORT from Surveillance Epidemiology End Results (SEER) data base. In multivariate analysis the survival benefit of PORT vs. surgery alone at 5-year was significant in both non-locally advanced tumors with lymph node metastasis (51.6% vs. 40.6%) as in the case of locally advanced tumors with lymph node metastasis (35.3 % vs. 25.2%). Overall PORT significantly improved OS by 11% and cancer-specific survival by 8.6%. They showed a greater reduction in the risk of death in stage N2b-N3 compared to N1-N2a (HR = 0.62, 0.78 and 0.82 respectively). The magnitude of the reduction was larger for tumors of the oropharynx, hypopharynx and larynx compared to oral cavity (HR = 0.72, 0.66 and 0.62 respectively) Patients with lymph node metastasis and any tumor sites, all benefited from the administration of PORT although the gain is greater in high-risk disease.

Whereas PORT is not routinely indicated in patients with HNSCC stage pT1-2 pN1^[61] because there is not definitive data supporting that approach. Moergel *et al.*^[62] published a meta-analysis of studies in order to elucidate the role

of PORT in patients pN1 with oral cavity and oropharynx primaries. Any firm conclusions could be drawn due to the heterogeneity of the studies, although it was evident more mortality (not significant) in the group treated with PORT (44% vs. 34%). Shrimel^[63] analyzed the benefit of PORT in patients with OCSCE pT1-2 pN1. PORT improved OS at 5 years [41.4% vs. 54.2% ($P < 0.001$)] of note PORT improved OS in T2 tongue and floor of mouth subgroup [52.3% vs. 37.9% ($P = 0.002$) and 39.9% vs. 17.7% ($P = 0.003$), respectively] but not significantly in T1 subgroup.

The hypothesis that early nodal metastases may express a more aggressive biology supports adjuvant therapy in stage III.^[64]

Risk factors for locoregional recurrence

Extracapsular extension (ECE) in cervical lymph node metastases and the involvement of surgical resection margins (ISRM) are the most important prognostic factors for risk of LRC and death.

RTOG^[65] stratified patients treated with PORT into 3 risk groups according to the presence of ECE, 2 or more lymph nodes with metastasis or ISRM. Group I were those with no more than 2 nodes affected without ECE; group II included patients with more than 2 positive lymph nodes or ECE, negative margins; group III comprised patients with ISRM. Significant difference was found in the rate of loco-regional recurrence at 5 years between groups I, II and III of 17%, 27% and 67% respectively and median OS at 5.6 years, 2 years and 1.5 years, respectively.

Langendijk *et al.*^[66] conducted a multivariate analysis to define different prognostic groups based on pathologic features a series of 801 patients with AHNC treated with PORT. The final model identified 6 prognostic factors and grouped the patients into 3 risk groups [Table 2]. This model was validated by the Dutch Head and Neck Oncology Cooperative Group (DHNOCC) in a multicenter study.^[67]

Nowadays, there is consensus^[68] to identify patients at high risk of recurrence after surgery who benefit from PORT: (1) major criteria: ECC or ISRM; and (2) minor criteria: inadequate surgical margins (< 5 mm), ≥ 2 lymph nodes metastases (N2b-N3), stage pT3-T4 even with negative margins, in primary oral cavity, metastases in levels IV and V, presence of PNI or LVI.

Perineural infiltration

One of most controversial point is the value of PORT when there is PNI but the absence of other factors associated with risk of recurrence. Neither in the analysis of Jonkman *et al.*^[66] or its further validation,^[67] PNI was found to be an independent prognostic factor. Bur *et al.*^[69] after a systematic review on the potential benefit of PORT in patients with PNI concluded that there is insufficient evidence to recommend PORT routinely in these cases. The author suggests that in case of infiltration of cranial nerves or multiple PNI, PORT might be justified. PNI is associated with increased risk of nodal recurrence, therefore it is recommended to treat the neck in this scenario.

Time factor in PORT

Evidence exists suggesting that the risk of LRC is higher in patients with AHNC when receiving PORT more than 6 weeks

after surgery,^[70] OR: 2.89. Further work^[71] confirmed elevated RR 1.28 on LRC and decrease in OS (RR: 1.16) per month of delay. The waiting list to start radiotherapy has negative effect on the prognosis according to a Dutch national study.^[72]

The accelerated repopulation during radiotherapy is a cause of treatment failure, that can be increased by the undue prolongation of radiation therapy.^[73] González Ferreira *et al.*^[74] found an loss in LRC of 1-1.2% per extra-day or 12-14% per extra-week. Prolongation of radiotherapy negatively interferes LRC and OS even in case of CRT.^[74]

Finally, the overall treatment time (OTT) from the day of surgery to the end of PORT showed prognostic significance for the LRC and OS in a randomized trial when the entire duration of treatment was greater than 13 weeks.^[75] No other randomized studies have been published that would confirm this finding, a retrospective series found no prognostic association in the OTT with LRC neither OS.^[76]

Intensification of adjuvant treatment

The value of dose escalation with PORT as a function of risk of recurrence has been explored in 2 prospective randomized trials. Peters and Withers^[77] showed the benefit of a dose of 63 Gy in 1.8 Gy fractions in patients with ECE, positive or inadequate surgical margins. Ang *et al.*^[75] published the results of a multicenter trial that randomized 151 patients with high-risk criteria (ECE and 2 or more additional criteria) between accelerated concomitant boost radiotherapy 63 Gy in 5 weeks or the same dose in conventional fractionation in 7 weeks. The accelerated treatment showed significantly improvement in LRC and OS when the interval between surgery and the start of PORT was not stretched or if the duration of the whole treatment (surgery plus PORT) no exceeded 13 weeks. Role of accelerated PORT is not firmly established, a confirmatory phase III Dutch trial (POPART CKTO 2003-11) is currently in recruitment period.

A meta-analysis^[78] on the benefit of postoperative CRT confirmed the reduction in RR of LRC (RR = 0.59) and death (RR = 0.80) and improvement in median survival (from 22-32 months to 40-72 months). The authors state that the patients included in those trials were under 70 years and with good performance status, so the impact of the CRT in patients aged 70 or older with associated co-morbidities is unknown.^[50,78] A pooled analysis^[79] of 2 phase III trials from RTOG^[80] and the European Organization for Research and Treatment of Cancer (EORTC)^[81] on the role of the postoperative CRT in adjuvant treatment of the SCCHN, confirmed that patients with ECE or ISMR were those who most benefit obtained with the administration of PORT chemoradiation in terms of risk reduction in LRC (48%) in time to progression (23%) and mortality (30%). Other pathological features commonly used to define patients at risk of relapse were not so decisive influencing LRC, OS, neither benefit of CRT. However a updating of the RTOG 9501 trial^[82] found no significant difference between patients treated with PORT alone and those treated CRT regarding LRC (28.8% vs. 22.3%, $P = 0.1$), DFS (19.1% vs. 20.1%, $P = 0.25$) or OS (27% vs. 29.1%, $P = 0.31$); an unplanned analysis on the subgroup of patients with ECE or ISMR showed that the combined treatment improved LRC (33.1% vs. 21%, $P = 0.02$) and DFS (12.3% vs. 18.4%, $P = 0.05$)

but not OS (19.6% vs. 27.1%, $P = 0.07$).

On the technical aspects of PORT

PORT administration is a particular challenge from the point of view of the radiation oncologist. Anatomy distortion due to tumor resection, the presence of reconstruction flaps, prosthetic material and the position of scars may influence routes of dissemination and hamper assessing volumes at risk to irradiate. Due the narrow conformation of dose to the target volume by IMRT, failure to design an adequate treatment volume will leave untreated areas of unrecognized risk; on the contrary excessively large volumes lead to higher radiation exposure of healthy tissue regions with consequent toxicity.^[83,84] Close collaboration between the radiation oncologist and head and neck surgeon is imperative when interpreting the pathological findings and surgical technique used; the engagement with radiologist and pathologist will be necessary in most cases. There is currently no international consensus on standard volumes for PORT irradiation in AHNC, but there are some guidelines published.^[85-88]

Adjuvant brachytherapy

In the specific case of OCSCC, PORT can be performed in fully or partly by BT reaching an equivalent dose of 60-66 Gy (LDR or HDR) on the tumor bed when surgical margins are infiltrated (stages pT1-T3) EBRT is administered alone when cervical nodes are at risk or primary surgical bed is not amenable for BT. Adjuvant BT results are summarized in [Table 3].^[89-93] While in early-stage OCSCC treated with radical RT adding BT plays a critical role in cure and local control, it is not the case of adjuvant setting (early nor advanced stage OCSCC) as either LRC and OS are equivalent between PORT-EBRT or PORT-BT. Table 4 shows recent published studies on patients with advanced OCSCC treated with PORT IMRT-based.^[94-103]

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Conflicts of interest

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REFERENCES

1. National Comprehensive Cancer Network. Fort Washington PA. c2015. NCCN Practice Guidelines in Oncology: Head and Neck Cancers, version 1. 2015 [updated 2015 Dec 05; cited 2016 Feb 22] Available from http://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf.
2. Unger K, Riaz N, Chen A, Lee NY. Oral Cavity Cancer. In: Lee NY, Liade JL, editors. Target Volume Delineation and Field Setup. A Practical Guide for Conformal and Intensity-Modulated Radiation Therapy. Berlin-Heidelberg: Springer-Verlag; 2013. P. 35-44.
3. Grégoire V, Ang K, Budach W, Grau C, Hamoir M, Langendijk JA, Lee A, Le QT, Maingon P, Nutting C, O'Sullivan B, Porceddu SV, Lengele B. Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. *Radiother Oncol* 2014;110:172-81.
4. Liu SH, Chao KS, Leu YS, Lee JC, Liu CJ, Huang YC, Chang YF, Chen HW, Tsai JT, Chen YJ. Guideline and preliminary clinical practice results for

- dose specification and target delineation for postoperative radiotherapy for oral cavity cancer. *Head Neck* 2015;37:933-9.
5. Leclerc M, Martigau E, Lacornerie T, Daisne JF, Kramar A, Grégoire V. Primary tumor delineation based on (18)FDG PET for locally advanced head and neck cancer treated by chemo-radiotherapy. *Radiother Oncol* 2015;116:87-93.
 6. Brouwer CL, Steenbakkers RJ, Bourhis J, Budach W, Grau C, Grégoire V, van Herk M, Lee A, Maingon P, Nutting C, O'Sullivan B, Porceddu SV, Rosenthal DI, Sijtsema NM, Langendijk JA. CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines. *Radiother Oncol* 2015;117:83-90.
 7. Chao KSC, Mohan R, Marinetti TD, Dong L. Intensity-Modulated Radiation Treatment Techniques and Clinical Applications. In: Halperin EC, Wazer DE, Perez CA, Brady LW, editors. *Perez and Brady's Principles and Practice of Radiation Oncology*. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2013. p. 221-45.
 8. Orlandi E, Palazzi M, Pignoli E, Fallai C, Giostra A, Olmi P. Radiobiological basis and clinical results of the simultaneous integrated boost (SIB) intensity modulated radiotherapy (IMRT) for head and neck cancer: a review. *Crit Rev Oncol Hematol* 2010;73:111-25.
 9. Marta GN, Silva V, de Andrade Carvalho H, de Arruda FF, Hanna SA, Gadia R, da Silva JL, Correa SF, Vita Abreu CE, Riera R. Intensity-modulated radiation therapy for head and neck cancer: systematic review and meta-analysis. *Radiother Oncol* 2014;110:9-15.
 10. Beadle BM, Liao KP, Elting LS, Buchholz TA, Ang KK, Garden AS, Guadagnolo BA. Improved survival using intensity-modulated radiation therapy in head and neck cancers: a SEER-Medicare analysis. *Cancer* 2014;120:702-10.
 11. Mazeron JJ, Ardiet JM, Haie-Méder C, Kovács G, Levendag P, Peiffert D, Polo A, Rovirosa A, Strnad V. GEC-ESTRO recommendations for brachytherapy for head and neck squamous cell carcinomas. *Radiother Oncol* 2009;91:150-6.
 12. Lau HY, Hay JH, Flores AD, Threlfall WJ. Seven fractions of twice daily high dose-rate brachytherapy for node-negative carcinoma of the mobile tongue results in loss of therapeutic ratio. *Radiother Oncol* 1996;39:15-8.
 13. Liu Z, Huang S, Zhang D. High dose rate versus low dose rate brachytherapy for oral cancer--a meta-analysis of clinical trials. *PLoS One* 2013;8:e65423.
 14. Nag S, Cano ER, Demanes DJ, Puthawala AA, Vikram B; American Brachytherapy Society. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for head-and-neck carcinoma. *Int J Radiat Oncol Biol Phys* 2001;50:1190-8.
 15. Petera J, Matula P, Paluska P, Sirák I, Macingova Z, Kasaova L, Frgala T, Hodek M, Vosmik M. High dose rate versus low dose rate brachytherapy in the treatment of tongue carcinoma - a radiobiological study. *Neoplasma* 2009;56:163-8.
 16. Yamazaki H, Inoue T, Yoshida K, Yoshioka Y, Furukawa S, Kakimoto N, Shimizutani K, Inoue T. Brachytherapy for early oral tongue cancer: low dose rate to high dose rate. *J Radiat Res* 2003;44:37-40.
 17. Van Limbergen E, Joiner M, Van der Kogel A, Dörr W. Radiobiology of LDR, HDR, PDR and VLDR Brachytherapy. In: Van Limbergen E, Pötter R, Hoskin P, Baltas D, editors. *The GEC ESTRO Handbook of Brachytherapy*. 2nd ed (ebook version 1 | 2/11/2015). Available from: <http://www.estro.org/search?type=Activities&q=radiobiology+ldr+hdr&alloptions=on>.
 18. Grégoire V, Coche E, Cosnard G, Hamoir M, Reyckel H. Selection and delineation of lymph node target volumes in head and neck conformal radiotherapy. Proposal for standardizing terminology and procedure based on the surgical experience. *Radiother Oncol* 2000;56:135-50.
 19. Huang SH, Hwang D, Lockwood G, Goldstein DP, O'Sullivan B. Predictive value of tumor thickness for cervical lymph-node involvement in squamous cell carcinoma of the oral cavity: A meta-analysis of reported studies. *Cancer* 2009;115:1489-97.
 20. Sresty NV, Ramanappa T, Raju AK, Muralidhar KR, Sudarshan G. Acquisition of equal or better planning results with interstitial brachytherapy when compared with intensity-modulated radiotherapy in tongue cancers. *Brachytherapy* 2010;9:235-8.
 21. Studer G, Brown M, Bredell M, Graetz KW, Huber G, Linsenmeier C, Najafi Y, Riesterer O, Rordorf T, Schmid S, Glanzmann C. Follow up after IMRT in oral cavity cancer: update. *Radiat Oncol* 2012;7:84.
 22. Leung TW, Wong VY, Kwan KH, Ng TY, Wong CM, Tung SY, Leung LC, O SK. High dose rate brachytherapy for early stage oral tongue cancer. *Head Neck* 2002;24:274-81.
 23. Martínez-Monge R, Gómez-Isturriaga A, Cambeiro M, Garrán C, Montesdeoca N, Aristu JJ, Alcalde J. Phase I-II trial of perioperative high-dose-rate brachytherapy in oral cavity and oropharyngeal cancer. *Brachytherapy* 2009;8:26-33.
 24. Guinot JL, Santos M, Tortajada MI, Carrascosa M, Estellés E, Vendrell JB, Muelas R, Chust ML, Mengual JL, Arribas L. Efficacy of high-dose-rate interstitial brachytherapy in patients with oral tongue carcinoma. *Brachytherapy* 2010;9:227-34.
 25. Oota S, Shibuya H, Yoshimura R, Watanabe H, Miura M. Brachytherapy of stage II mobile tongue carcinoma. Prediction of local control and QOL. *Radiat Oncol* 2006;1:21.
 26. Fujita M, Hirokawa Y, Kashiwado K, Akagi Y, Kashimoto K, Kiriu H, Matsuura K, Ito K. Interstitial brachytherapy for stage I and II squamous cell carcinoma of the oral tongue: factors influencing local control and soft tissue complications. *Int J Radiat Oncol Biol Phys* 1999;44:767-75.
 27. Bachaud JM, Delannes M, Allouache N, Benchalal M, Alzieu C, David JM, Serrano E, Daly-Schveitzer NJ. Radiotherapy of stage I and II carcinomas of the mobile tongue and/or floor of the mouth. *Radiother Oncol* 1994;31:199-206.
 28. Inoue T, Inoue T, Yoshida K, Yoshioka Y, Shimamoto S, Tanaka E, Yamazaki H, Shimizutani K, Teshima T, Furukawa S. Phase III trial of high- vs. low-dose-rate interstitial radiotherapy for early mobile tongue cancer. *Int J Radiat Oncol Biol Phys* 2001;51:171-5.
 29. Yamazaki H, Inoue T, Yoshida K, Yoshioka Y, Furukawa S, Kakimoto N, Shimizutani K, Inoue T. Brachytherapy for early oral tongue cancer: low dose rate to high dose rate. *J Radiat Res* 2003;44:37-40.
 30. Yamazaki H, Inoue T, Yoshida K, Yoshioka Y, Furukawa S, Kakimoto N, Shimizutani K. Comparison of three major radioactive sources for brachytherapy used in the treatment of node negative T1-T3 oral tongue cancer: influence of age on outcome. *Anticancer Res* 2007;27:491-7.
 31. Ihara N, Shibuya H, Yoshimura R, Oota S, Miura M, Watanabe H. Interstitial brachytherapy and neck dissection for Stage III squamous cell carcinoma of the mobile tongue. *Acta Oncol* 2005;44:709-16.
 32. Kakimoto N, Inoue T, Inoue T, Murakami S, Furukawa S, Yoshida K, Yoshioka Y, Yamazaki H, Tanaka E, Shimizutani K. Results of low- and high-dose-rate interstitial brachytherapy for T3 mobile tongue cancer. *Radiother Oncol* 2003;68:123-8.
 33. Akiyama H, Yoshida K, Shimizutani K, Yamazaki H, Koizumi M, Yoshioka Y, Kakimoto N, Murakami S, Furukawa S, Ogawa K. Dose reduction trial from 60 Gy in 10 fractions to 54 Gy in 9 fractions schedule in high-dose-rate interstitial brachytherapy for early oral tongue cancer. *J Radiat Res* 2012;53:722-6.
 34. Donath D, Vuong T, Shenouda G, MacDonald B, Tabah R. The potential uses of high-dose-rate brachytherapy in patients with head and neck cancer. *Eur Arch Otorhinolaryngol* 1995;252:321-4.
 35. Inoue T, Inoue T, Yamazaki H, Koizumi M, Kagawa K, Yoshida K, Shiomi H, Imai A, Shimizutani K, Tanaka E, Nose T, Teshima T, Furukawa S, Fuchihata H. High dose rate versus LDR interstitial radiotherapy for carcinoma of the floor of mouth. *Int J Radiat Oncol Biol Phys* 1998;41:53-8.
 36. Matsumoto K, Sasaki T, Shioyama Y, Nakamura K, Atsumi K, Nonoshita T, Ooga S, Yoshitake T, Uehara S, Hirata H, Honda H. Treatment outcome of high-dose-rate interstitial radiation therapy for patients with stage I and II mobile tongue cancer. *Jpn J Clin Oncol* 2013;43:1012-7.
 37. Khalilur R, Hayashi K, Shibuya H. Brachytherapy for tongue cancer in the very elderly is an alternative to external beam radiation. *Br J Radiol* 2011;84:747-9.
 38. Vadasoundaram P, Prasanna AK, Ks R, Selvarajan G, Sinnatamby M, Ramapandian S, Kandasamy S. Role of high dose rate interstitial brachytherapy in early and locally advanced squamous cell carcinoma of buccal mucosa. *Springerplus* 2014;3:590.
 39. Lee SU, Cho KH, Moon SH, Choi SW, Park JY, Yun T, Lee SH, Lim YK, Jeong CY. Clinical outcome of high-dose-rate interstitial brachytherapy in patients with oral cavity cancer. *Radiat Oncol* 2014;32:238-46.
 40. Tuček L, Petera J, Sirák I, Vošmik M, Doležalová H, Brokešová S, Hodek M, Kašáková L, Paluska P. Hyperfractionated high-dose rate brachytherapy in the treatment of oral tongue cancer. *Rep Pract Oncol Radiother* 2011;16:243-7.
 41. Pernot M, Hoffstetter S, Peiffert D, Aletti P, Lapeyre M, Marchal C, Luporsi E, Bey P, Nancy VL. Role of interstitial brachytherapy in oral and oropharyngeal carcinoma: reflection of a series of 1344 patients treated at the time of initial presentation. *Otolaryngol Head Neck Surg* 1996;115:519-26.
 42. Lefebvre JL, Coche-Dequeant B, Buisset E, Mirabel X, Van JT, Prevost B. Management of early oral cavity cancer. Experience of Centre Oscar Lambret. *Eur J Cancer B Oral Oncol* 1994;30B:216-20.
 43. Mazeron JJ, Simon JM, Le Péchoux C, Crook JM, Grimard L, Piedbois P, Le Bourgeois JP, Pierquin B. Effect of dose rate on local control and complications in definitive irradiation of T1-2 squamous cell carcinomas of mobile tongue and floor of mouth with interstitial iridium-192. *Radiother Oncol* 1991;21:39-47.
 44. Marsiglia H, Haie-Meder C, Sasso G, Mamelle G, Gerbaulet A. Brachytherapy for T1-T2 floor of mouth cancers: the Gustave-Roussy Institute experience. *Int J Radiat Oncol Biol Phys* 2002;52:1257-63.
 45. Dearnaley DP, Dardoufas C, A'Hearn RP, Henk JM. Interstitial irradiation for carcinoma of the tongue and floor of mouth: royal marsden hospital

- experience 1970-1986. *Radiother Oncol* 1991;21:183-92.
46. Fujita M, Hirokawa Y, Kashiwado K, Akagi Y, Kashimoto K, Kiriu H, Matsuura K, Ito K. Interstitial brachytherapy for stage I and II squamous cell carcinoma of the oral tongue: factors influencing local control and soft tissue complications. *Int J Radiat Oncol Biol Phys* 1999;44:767-75.
47. Ihara N, Shibuya H, Yoshimura R, Oota S, Miura M, Watanabe H. Interstitial brachytherapy and neck dissection for Stage III squamous cell carcinoma of the mobile tongue. *Acta Oncol* 2005;44:709-16.
48. Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J, Horiot JC, Le Maître A, Pajak TF, Poulsen MG, O'Sullivan B, Dobrowsky W, Hliniak A, Skladowski K, Hay JH, Pinto LH, Fallai C, Fu KK, Sylvester R, Pignon JP; Meta-Analysis of Radiotherapy in Carcinomas of Head and Neck (MACH) collaborative group. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet* 2006;368:843-54.
49. Glenny AM, Furness S, Worthington HV, Conway DI, Oliver R, Clarkson JE, MacLuskey M, Pavitt S, Chan KK, Brocklehurst P; CSROC Expert Panel. Interventions for the treatment of oral cavity and oropharyngeal cancer: radiotherapy. *Cochrane Database Syst Rev* 2010;(12):CD006387.
50. Pignon JP, le Maître A, Maillard E, Bourhis J; MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol* 2009;92:4-14.
51. Blanchard P, Baujat B, Holostenco V, Bourredjem A, Baey C, Bourhis J, Pignon JP; MACH-CH Collaborative group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. *Radiother Oncol* 2011;100:33-40.
52. Bourhis J, Sire C, Graff P, Grégoire V, Maingon P, Calais G, Gery B, Martin L, Alfonsi M, Desprez P, Pignon T, Bardet E, Rives M, Geoffrois L, Daly-Schweitzer N, Sen S, Tachais C, Dupuis O, Guerif S, Lapeyre M, Favrel V, Hamoir M, Lusinchi A, Temam S, Pinna A, Tao YG, Blanchard P, Aupérin A. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. *Lancet Oncol* 2012;13:145-53.
53. Nguyen-Tan PF, Zhang Q, Ang KK, Weber RS, Rosenthal DI, Soulieres D, Kim H, Silverman C, Raben A, Galloway TJ, Fortin A, Gore E, Westra VH, Chung CH, Jordan RC, Gillison ML, List M, Le QT. Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 trial: long-term report of efficacy and toxicity. *J Clin Oncol* 2014;32:3858-66.
54. Martinez-Useros J, Garcia-Foncillas J. The challenge of blocking a wider family members of EGFR against head and neck squamous cell carcinomas. *Oral Oncol* 2015;51:423-30.
55. Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, Raben D, Baselga J, Spencer SA, Zhu J, Yousoufian H, Rowinsky EK, Ang KK. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol* 2010;11:21-8.
56. Fletcher GH, Evers WT. Radiotherapeutic management of surgical recurrences and postoperative residuals tumors of the head and neck. *Radiology* 1970;95:185-8.
57. Marcus RB Jr, Million RR, Cassisi NJ. Postoperative irradiation for squamous cell carcinomas of the head and neck: analysis of time-dose factors related to control above the clavicles. *Int J Radiat Oncol Biol Phys* 1979;5:1943-49.
58. Lundahl RE, Foote RL, Bonner JA, Suman VJ, Lewis JE, Kasperbauer JL, McCaffrey TV, Olsen KD. Combined neck dissection and postoperative radiation therapy in the management of the high-risk neck: a matched-pair analysis. *Int J Radiat Oncol Biol Phys* 1998;40:529-34.
59. Lavaf A, Genden EM, Cesaretti JA, Packer S, Kao J. Adjuvant radiotherapy improves overall survival for patients with lymph node-positive head and neck squamous cell carcinoma. *Cancer* 2008;112:535-43.
60. Kao J, Lavaf F, Teng MS, Huang D, Genden EM. Adjuvant radiotherapy and survival for patients with node-positive head and neck cancer: an analysis by primary site and nodal stage. *Int J Radiat Oncol Biol Phys* 2008;71:362-70.
61. Hu KS, Quon H, Harrison LB. Management of the neck: radiation therapy and chemotherapy. In: Harrison LB, Sessions RB, Hong WK, editors. *Head and Neck Cancer. A Multidisciplinary Approach*. 3rd ed. Philadelphia: Lippincott-Williams & Wilkins; 2009. p. 204-31.
62. Moergel M, Meurer P, Ingel K, Wendt TG, Al-Nawas B. Effectiveness of Postoperative Radiotherapy in Patients with Small Oral and Oropharyngeal Squamous Cell Carcinoma and Concomitant Ipsilateral Singular Cervical Lymph Node Metastasis (pN1). *Strahlenther Onkol* 2011;187:337-43.
63. Shrimel MG, Gullane PJ, Dawson L, Kim J, Gilbert RV, Irish JC, Brown DH, Goldstein DP. The impact of adjuvant radiotherapy on survival in T1-2N1 squamous cell carcinoma of the oral cavity. *Arch Otolaryngol Head Neck Surg* 2010;136:225-8.
64. Leemans CR, Tiwari T, Nauta JJ, van der Waal L, Snow GB. Regional Lymph node involvement and its significance in the development of distant metastases in head and neck carcinoma. *Cancer* 1993;71:452-6.
65. Cooper JS, Pajak TF, Forastiere A, Jacobs J, Fu KK, Ang KK, Laramore GE, Al-Sarraf M. Precisely defining high-risk operable head and neck tumors based on RTOG #83-03 and #88-24: Targets for postoperative radiochemotherapy? *Head Neck* 1998;20:588-94.
66. Langendijk JA, Slotman BJ, van der Waal I, Doornaert P, Berkof J, Leemans CR. Risk group definition by recursive partitioning analysis of patients with squamous cell head and neck carcinoma treated with surgery and postoperative radiotherapy. *Cancer* 2005;104:1408-17.
67. Jonkman A, Kaanders JH, Terhaard CH, Hoebbers FJ, van den Ende PL, Wijers OB, Verhoef LC, de Jong MA, Leemans CR, Langendijk JA. Multicenter validation of recursive partitioning analysis classification for patients with squamous cell head and neck carcinoma treated with surgery and postoperative radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;68:119-25.
68. Expert Panel on Radiation Oncology-Head and Neck, Salama JK, Saba N, Quon H, Garg MK, Lawson J, McDonald MW, Ridge JA, Smith RV, Yeung AR, Yom SS, Beitler JJ. ACR appropriateness criteria® adjuvant therapy for resected squamous cell carcinoma of the head and neck. *Oral Oncol* 2011;47:554-9.
69. Bur AM, Lin A, Weinstein GS. Adjuvant radiotherapy for early head and neck squamous cell carcinoma with perineural invasion: a systematic review. *Head Neck* 2016;38 Suppl 1:E2350-7.
70. Huang J, Barbera L, Brouwers M, Browman G, Mackillop WJ. Does delay in starting treatment affect the outcomes of radiotherapy? a systematic review. *J Clin Oncol* 2003;21:555-63.
71. Chen Z, King W, Pearcey R, Kerba M, Mackillop WJ. The relationship between waiting time for radiotherapy and clinical outcomes: a systematic review of the literature. *Radiother Oncol* 2008;87:3-16.
72. van Harten MC, Hoebbers FJ, Kross KW, van Werkhoven ED, van den Brekel MW, van Dijk BA. Determinants of treatment waiting times for head and neck cancer in the Netherlands and their relation to survival. *Oral Oncol* 2015;51:272-8.
73. Peters LJ, Withers HR. Applying radiobiological principles to combined modality treatment of head and neck cancer - the time factor. *Int J Radiat Oncol Biol Phys* 1997;39:831-6.
74. González Ferreira JA, Jaén Olasolo J, Azinovic I, Jeremic B. Effect of radiotherapy delay in overall treatment time on local control and survival in head and neck cancer: review of the literature. *Rep Pract Oncol Radiother* 2015;20:328-39.
75. Ang KK, Trotti A, Brown BW, Garden AS, Foote RL, Morrison WH, Gera FB, Klotch DW, Goepfert H, Peters LJ. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2001;51:571-8.
76. Langendijk JA, de Jong MA, Leemans CR, de Bree R, Smeele LE, Doornaert P, Slotman BJ. Postoperative radiotherapy in squamous cell carcinoma of the oral cavity: the importance of the overall treatment time. *Int J Radiat Oncol Biol Phys* 2003;57:693-700.
77. Peters LJ, Goepfert H, Ang KK, Byers RM, Maor MH, Guillemondeguie O, Morrison WH, Weber RS, Garden AS, Frankenthaler RA, Oswald MJ, Brown BW. Evaluation of the dose for postoperative radiotherapy of head and neck cancer: first report of a prospective randomized trial. *Int J Radiat Oncol Biol Phys* 1993;26:3-11.
78. Winquist E, Oliver T, Gilbert R. Postoperative chemoradiotherapy for advanced squamous cell carcinoma of the head and neck: a systematic review with meta-analysis. *Head Neck* 2007;29:38-46.
79. Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, Ozsahin EM, Jacobs JR, Jassem J, Ang KK, Lefebvre JL. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of EORTC (#22931) and RTOG (#9501). *Head Neck* 2005;27:843-50.
80. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, Kish JA, Kim HE, Cmelak AJ, Rotman M, Machtay M, Ensley JF, Chao KS, Schultz CJ, Lee N, Fu KK; Radiation Therapy Oncology Group 9501/Intergroup. Postoperative concurrent radiotherapy and chemotherapy for high risk squamous cell carcinoma of the head and neck. *N Engl J Med* 2004;350:1937-44.
81. Bernier J, Dornge C, Ozsahin M, Matuszewska K, Lefebvre JL, Greiner RH, Giralt J, Maingon P, Rolland F, Bolla M, Cognetti F, Bourhis J, Kirkpatrick A, van Glabbeke M; European Organization for Research and Treatment of Cancer Trial 22931. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 2004;350:1945-52.

82. Cooper JS, Zhang Q, Pajak TF, Forastiere AA, Jacobs J, Saxman SB, Kish JA, Kim HE, Cmelak AJ, Rotman M, Lustig R, Ensley JF, Thorstad VW, Schultz CJ, Yom SS, Ang KK. Long-term follow-up of the RTOG 9501/Intergroup Phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys* 2012;84:1198-205.
83. Eisbruch A, Gregoire V. Balancing risk and reward in target delineation for highly conformal radiotherapy in head and neck cancer. *Semin Radiat Oncol* 2009;19:43-52.
84. Chen AM, Farwell DG, Luu Q, Chen LM, Vijayakumar S, Purdy JA. Marginal misses after postoperative intensity-modulated radiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys* 2011;80:1423-9.
85. Grégoire V, Eisbruch A, Hamoir M, Levendag P. Proposal for the delineation of the nodal CTV in the node-positive and the post-operative neck. *Radiother Oncol* 2006;79:15-20.
86. Liu SH, Chao KS, Leu YS, Lee JC, Liu CJ, Huang YC, Chang YF, Chen HW, Tsai JT, Chen YJ. Guideline and preliminary clinical practice results for dose specification and target delineation for postoperative radiotherapy for oral cavity cancer. *Head Neck* 2015;37:933-9.
87. Merlotti A, Alterio D, Vigna-Taglianti R, Muraglia A, Lastrucci L, Manzo R, Gambaro G, Caspiani O, Micciché F, Deodato F, Pergolizzi S, Franco P, Corvò R, Russi EG, Sanguineti G; Italian Association of Radiation Oncology. Technical guidelines for head and neck cancer IMRT on behalf of the Italian association of radiation oncology - head and neck working group. *Radiat Oncol* 2014;9:264.
88. Ko HC, Gupta V, Mourad WF, Hu KS, Harrison LB, Som PM, Bakst RL. A contouring guide for head and neck cancers with perineural invasion. *Pract Radiat Oncol* 2014;4:e247-58.
89. Goineau A, Piot B, Malard O, Ferron C, Lisbona A, Cassagnau E, Delamazure AS, Campion L, Bardet E. Postoperative interstitial brachytherapy for resectable squamous cell carcinoma of the tongue. *Brachytherapy* 2015;14:71-6.
90. Petera J, Sirák I, Laco J, Kašáková L, Tuček L, Doležalová H. High-dose-rate brachytherapy in early oral cancer with close or positive margins. *Brachytherapy* 2015;14:77-83.
91. Lapeyre M, Bollet MA, Racadot S, Geoffrois L, Kaminsky MC, Hoffstetter S, Dolivet G, Toussaint B, Luporsi E, Peiffert D. Postoperative brachytherapy alone and combined postoperative radiotherapy and brachytherapy boost for squamous cell carcinoma of the oral cavity, with positive or close margins. *Head Neck* 2004;26:216-23.
92. Pernot M, Aletti P, Carolus JM, Marquis I, Hoffstetter S, Maaloul F, Peiffert D, Lapeyre M, Luporsi E, Marchal C, Noël A, Bey P. Indications, techniques and results of postoperative brachytherapy in cancer of the oral cavity. *Radiother Oncol* 1995;35:186-92.
93. Fietkau R, Grabenbauer GG, Iro H, Müller RG, Farmand M, Atendorf-Hofmann A, Sauer R. Interstitial and percutaneous radiotherapy after limited surgery in carcinoma of the oral cavity. *Strahlenther Onkol* 1991;167:591-8.
94. Chan AK, Huang SH, Le LW, Yu E, Dawson LA, Kim JJ, Cho BC, Bayley AJ, Ringash J, Goldstein D, Chan K, Waldron J, O'Sullivan B, Cummings B, Hope AJ. Postoperative intensity-modulated radiotherapy following surgery for oral cavity squamous cell carcinoma: patterns of failure. *Oral Oncol* 2013;49:255-60.
95. Hoffmann M, Saleh-Ebrahimi L, Zwicker F, Haering P, Schwahofer A, Debus J, Huber PE, Roeder F. Long term results of postoperative Intensity-Modulated Radiation Therapy (IMRT) in the treatment of Squamous Cell Carcinoma (SCC) located in the oropharynx or oral cavity. *Radiat Oncol* 2015;10:251.
96. Sher DJ, Thotakura V, Balboni TA, Norris CM Jr, Haddad RI, Posner MR, Lorch J, Goguen LA, Annino DJ, Tishler RB. Treatment of oral cavity squamous cell carcinoma with adjuvant or definitive intensity-modulated radiation therapy. *Int J Radiat Oncol Biol Phys* 2011;81:e215-22.
97. Gomez DR, Zhong JE, Gomez J, Chan K, Wu AJ, Wolden SL, Pfister DG, Shaha A, Shah JP, Kraus DH, Wong RJ, Lee NY. Intensity-modulated radiotherapy in postoperative treatment of oral cavity cancers. *Int J Radiat Oncol Biol Phys* 2009;73:1096-103.
98. Chakraborty S, Patil VM, Babu S, Muttath G, Thiagarajan SK. Locoregional recurrences after post-operative volumetric modulated arc radiotherapy (VMAT) in oral cavity cancers in a resource constrained setting: experience and lessons learned. *Br J Radiol* 2015;88:20140795.
99. Studer G, Brown M, Bredell M, Graetz KW, Huber G, Linsenmeier C, Najafi Y, N Riesterer O, Rordorf T, Schmid S, Glanzmann C. Follow up after IMRT in oral cavity cancer: update. *Radiat Oncol* 2012;7:84.
100. Collan J, Lundberg M, Vaalavirta L, Bäck L, Kajanti M, Mäkitie A, Tenhunen M, Saarialhti K. Patterns of relapse following surgery and postoperative intensity modulated radiotherapy for oral and oropharyngeal cancer. *Acta Oncol* 2011;50:1119-25.
101. Geretschläger A, Bojaxhiu B, Crowe S, Arnold A, Manser P, Hallermann W, Aebbersold DM, Ghadjar P. Outcome and patterns of failure after postoperative intensity modulated radiotherapy for locally advanced or high-risk oral cavity squamous cell carcinoma. *Radiat Oncol* 2012;7:175.
102. Yao M, Chang K, Funk GF, Lu H, Tan H, Wacha J, Dornfeld KJ, Buatti JM. The failure patterns of oral cavity squamous cell carcinoma after intensity-modulated radiotherapy-the university of iowa experience. *Int J Radiat Oncol Biol Phys* 2007;67:1332-41.
103. Daly ME, Le QT, Kozak MM, Maxim PG, Murphy JD, Hsu A, Loo BW Jr, Kaplan MJ, Fischbein NJ, Chang DT. Intensity-modulated radiotherapy for oral cavity squamous cell carcinoma: patterns of failure and predictors of local control. *Int J Radiat Oncol Biol Phys* 2011;80:1412-22.

Elective neck dissection in early oral squamous cell carcinoma: necessary?

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ABSTRACT

Aim: The indication of neck dissection in oral squamous cell carcinoma (OSCC) is a problem of risk-benefit evaluation between probability of neck metastases, the problem of complications associated with neck dissection and the prognostic influence of delayed diagnosis of metastasis during follow-up. There is no consensus on the elective treatment of the neck in early oral cancer patients with a clinically N0 (cN0) neck. **Methods:** The author performed a search of PubMed articles with the words "elective neck dissection vs. observation", "node negative neck" and "early stage oral squamous cell carcinoma". The author selected those articles that studied the early OSCC (T1-T2), and elective neck treatment was compared with clinical observation. **Results:** Many studies have compared the outcome of elective neck dissection (END) to observation of the neck in early OSCC. The results of them are described. The biologic aggressiveness of oral cavity squamous cell carcinoma, particularly in the early stages, is reflected in its ability to metastasize to regional lymph node chains. Many pretreatment imaging techniques to diminish the incidence of occult metastases haven been studied, and comparative studies have shown ultrasound guided fine needle aspiration cytology (USgFNAC) to be the most accurate. **Conclusion:** A few non-randomized studies have shown no advantages of END when strict USgFNAC follow-up was employed. Thus, if routine strict follow-up using USgFNAC by a well-trained ultrasonographer cannot be assured, END is the safest strategy.

Key words:

Early stage; oral squamous cell carcinoma; negative lymph necknode; elective neck dissection versus observation

INTRODUCTION

Management of the clinically negative neck in patients with T1-T2 oral cancer remains controversial [Figure 1]. The single most important tumor-related prognostic factor in patients

with head and neck squamous cell cancer is the status of the cervical lymph node.^[1-5] Patients with lymph node metastases require treatment of the neck. When the neck

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Figure 1: Clinical Stage I (T1N0M0) squamous cell carcinoma of the tongue

needs to be entered for excision of the primary tumor or reconstruction of the surgical defect, a neck dissection needs to be performed.^[6-10] Currently, management of the clinically negative (cN0) neck in patients whose tumor can be resected transorally remains controversial.^[11-15] In general an elective neck dissection (END) is justified if the estimated risk of occult lymph node metastases exceeds 15-20%.^[16-20]

Although screening of clinically N0 neck by ultrasound, computed tomography (CT) magnetic resonance imaging (MRI), or positron emission tomography (PET) can help to detect some of these non-palpable nodal metastases, the recurrence rate in the observed N0 neck is 23.7-42%.^[21-25]

The indication of neck dissection in oral squamous cell carcinoma (OSCC) is a problem of risk-benefit evaluation between probability of neck metastases, the problem of complications associated with neck dissection and the prognostic influence of delayed diagnosis of metastasis during follow-up.^[26-30] Although END results in early treatment of occult lymph node metastases, the vast majority of these neck dissections harbors no metastases and was unnecessary.^[31-35] Moreover, these patients are subjected to morbidity such as shoulder morbidity, pain and sensibility disorders, which may have major impact on health-related quality of life.^[36-40] Furthermore, neck dissection may remove a barrier to cancer spread in case of local recurrence or second primary tumor.^[41-45] There is no consensus on the elective treatment of the neck in early oral cancer patients with a cN0 neck.^[46-50]

METHODS

We performed a search of PubMed articles with the words "elective neck dissection versus observation", "node negative neck" and "early stage oral squamous cell carcinoma": ("elective surgical procedures" [MeSH Terms] OR ("elective"[All Fields] AND "surgical" [All Fields] AND "procedures" [All Fields]) OR "elective surgical procedures" [All Fields]

OR "elective" [All Fields]) AND ("neck dissection" [MeSH Terms] OR ("neck" [All Fields] AND "dissection" [All Fields]) OR "neck dissection" [All Fields]) AND versus [All Fields] AND ("observation" [MeSH Terms] OR "observation" [All Fields]). Node [All Fields] AND negative [All Fields] AND ("neck" [MeSH Terms] OR "neck" [All Fields]). Early [All Fields] AND stage [All Fields] AND ("mouth" [MeSH Terms] OR "mouth" [All Fields] OR "oral" [All Fields]) AND ("carcinoma, squamous cell" [MeSH Terms] OR ("carcinoma" [All Fields] AND "squamous" [All Fields] AND "cell" [All Fields]) OR "squamous cell carcinoma" [All Fields] OR ("squamous" [All Fields] AND "cell" [All Fields] AND "carcinoma" [All Fields])).

We selected those articles that studied the early oral squamous cell carcinoma (T1-T2), and elective neck treatment was compared with clinical observation. We only included studies published in the English language and those dealing with "squamous cell carcinoma of the oral cavity".

The following technical bibliographic exclusion criteria were applied: (1) case reports; (2) technical reports; (3) animal or *in vitro* studies; (4) uncontrolled clinical studies; and (5) publications in which the same data were published by the same group of researchers.

RESULTS

Many studies^[4-6,10,15] have compared the outcome of END to observation of the neck. In the prospective study of O'Brien *et al.*^[4] management of the cN0 neck in T1-T4 oral cancer patients was based on clinical criteria such as T-classification and tumor site, which makes comparison of survival between treatment options difficult. Two studies showed statistical significant difference in disease specific survival or overall survival between END and observation.^[13,15] However, Huang *et al.*^[13] did not describe surveillance of the neck in the observation arm and if absent or merely clinical, this may have influenced

survival. The group of La Princesa University Hospital^[51] (Madrid, Spain) analyzed only END patients who were pN0, which obviously resulted in better overall survival in END patients. Three studies reported a significantly better disease-free survival in the END arm.^[6,13,15]

Fasunla *et al.*^[52] systematically reviewed the available literature and performed a meta-analysis on the existing randomized controlled clinical trials which compared END with observation (and therapeutic neck dissection only when lymph node metastasis were detected) in early OSCC patients. Only four randomized clinical trials with a total of 283 patients were eligible for inclusion in this meta-analysis. Although the data used in that meta-analysis were from different parts of the world, between study heterogeneity of the relative risk of disease specific death in the trials were tested and no statistically significant difference were found. This meta-analysis showed that END significantly reduced the risk of disease specific death: fixed-effects model $RR = 0.57$ [95% confidence interval (CI) 0.36-0.89; $P = 0.014$] and random-effects model $RR = 0.59$ (0.37-0.96; $P = 0.034$).^[52]

D'Cruz and Dandekar^[53] from Tata Memorial Center (Mumbai, India) performed a critical appraisal of this meta-analysis which revealed "some caveats that need careful consideration before the findings can be accepted". They pointed out the poor follow-up in one of the included studies that resulted in a large number of patients with advanced neck recurrences and low salvage rates. Finally, they emphasized the need for meticulous follow-up patients on the observation arm.^[53] The same group analyzed their series of 359 patients with early oral cancer, found no difference in disease specific survival between END and observation and elaborated the need for a large randomized controlled clinical trial (RCT).^[15] The Head and Neck Disease Management group of Tata Memorial Centre performed such a trial, enrolled 596 patients and reported the results of the first 500 patients. The conclusion was that among patients with early stage OSCC, END results in higher rates of overall and disease free survival than observation with therapeutic neck dissection in patients in whom lymph node metastases are detected during follow-up.^[54]

The group of the Tata Memorial Centre had chosen overall survival as primary endpoint and disease free survival as secondary endpoint for their RCT. END resulted in an improved 3-year overall survival rate (80%; 95% CI 74-86) as compared with observation and therapeutic neck dissection (68%; 95% CI 61-74): hazard ratio of death 0.64 (95% CI 0.45-0.92; $P = 0.01$). Patients in the END group had a higher disease free survival than those in the observation group (79% vs. 46%, $P < 0.001$).^[54] It is not surprising that END improves the regional control rate because development of lymph node metastases during observation of the neck should be taken into account as an inevitable consequence of the adopted strategy. Therefore, this disease free survival is a useful outcome measure of diagnostic work-up but not a reliable outcome measure in comparing END and observation of the neck.

Ganly *et al.*^[55] reported on a series on 216 cT1-T2N0 patients treated with or without END and found a 5-year disease specific, overall and disease free survival of 86%, 79% and 70%, respectively. Disease specific survival is probably the most clinically meaningful endpoint for measuring an eventual benefit of END, but

unfortunately is not reported in the RCT. As mentioned above, in the meta-analysis of Fasunla *et al.*^[52] END significantly reduces the risk of disease specific deaths.

Flach *et al.*^[11] presents a survival analysis of a large series of patients with T1-T2 cancer of the mobile tongue or floor of mouth with a wait and scan follow-up policy of the neck with regular ultrasound guided fine needle aspiration cytology (USgFNAC). The 5-year disease specific survival (DSS) and overall survival (OS) of "wait and scan" policy (W&S) patients were 94.2% and 81.6%, respectively, and these rates were comparable to those of END patients. The most important finding is that in W&S patients with delayed metastases the 5-year DSS and OS were similar to END patients with proven metastases in the neck dissection specimen: 80.0% and 62.8% to 81.3% and 64.2%, respectively. In order to justify an observation policy, survival rates of patients with delayed metastases in a W&S policy should not be worse than rates of END patients with nodal metastases in the neck dissection specimen. In the above mentioned series the patients who developed delayed metastases (27.8%) did not have worse survival rates (DSS 80.0%, OS 62.8%) as compared to END patients with nodal metastases in the neck dissection specimen (DSS 81.3%, OS 64.2%), also when corrected for confounding factors. Moreover, with regard to the total study groups after correction for confounding no significant difference in survival between W&S and END patients was found and survival rates were comparable to the reported rates in literature.^[14-6] Out of the W&S patients, 72.2% did not develop lymph node metastases during follow-up, meaning that they were saved from END with good survival rates (DSS 99.4%, OS 89.1%). Although, DSS in the W&S group was significantly different between pT1 and pT2 tumors, pT2 tumors still had a 5-year DSS of 88.6%, which resembles the survival rates of END patients.

Tsang *et al.*^[56] stated that "wait and scan" would not be effective in pT2 tumors, but that conclusion was based on a 5-year DSS of 46% for pT2 tumors. These authors assumed that the delayed lymph node metastases were missed by preoperative USgFNAC. In a "wait and scan" policy, the diagnostic method should be highly sensitive. This is dependent on the cut off level for aspiration and of the expertise of the radiologist.^[57-59] Almost all patients with delayed metastases underwent a modified radical neck dissection and 90.6% needed adjuvant radiotherapy. Since they also found metastases in level IV, they would recommend selective neck dissection of level I-IV in case of delayed lymph node metastases, although Wensing *et al.*^[60] suggested selective neck dissection of level I-III.

Borgemeester *et al.*^[57] compared the overall survival in head and neck squamous cell carcinoma patients with a clinically N0 neck who underwent END or close observation using regular USgFNAC during follow-up. Survival in the OSCC patients of the close observation group was not different from the END group: 90% and 81% after 3 years and 79% and 75% after 5 years, respectively. Nieuwenhuis *et al.*^[61] showed that by using USgFNAC pretreatment and during follow-up 79% of the delayed metastases could be salvaged resulting in a regional control rate of 88%.

Yuen *et al.*^[14] performed a prospective multicenter randomized trial in 71 T1-T2 oral cancer patients with cN0 necks

evaluated by USgFNAC and the patients were stratified for T-staging classification. Observation of the neck consisted of ultrasonographic examination every 3 months during the first 3-year follow-up, which strongly resembles our wait and scan follow-up policy. Although the sample size was limited, this study had the preferable study design to compare the outcome of elective neck treatment with observation. The reported 5-year disease-specific survival rates were not significantly different (observation arm 87%, END arm 89%).^[14]

In the study of Feng *et al.*^[16] total regional recurrence rate of the untreated N0 neck was found to be 19.2% for stage T1 (8/48, 16.7%) and stage T2 (6/25, 24.0%), respectively. 92.9% of them occurred in the early postoperative period (within 2 years). Of these regional recurrences, only 41.7% patients were successful salvaged due to advanced neck disease. In their department, observation policy for clinically N0 neck was more common in patients with the stage T1 tumours, so that the T1/T2 ratio for the randomized controlled study was unbalanced (T1/T2 ratio in "END vs. observation": 0.6 vs. 1.9). Although the patients from the observation group had a higher proportion of stage T1, They found that the patients from END group exhibited significantly better DSS rates than those from observation group. They further analysed the prognosis of subgroups (T1/T2) in each group, the results showed that the patients from the END group with stage T2 tumours had a higher survival rate than those from the observation group.^[16]

Weiss *et al.*^[3] suggested that END is necessary if the incidence of occult metastasis is greater than 20%. The proponents of wait and watch policy argue that 80% of patients with N0 neck would be over treated, and subjected to additional morbidity and costs. Though this argument may apply to most oral cavity tumors, the cancer of the tongue must be viewed as a separate entity. The incidence of nodal metastasis is higher for early cancer of the tongue when compared with other sites of the oral cavity.^[62,63] D'Cruz *et al.*^[15] found the incidence of nodal metastasis to be 37.5% in T1 lesions and 62.5% in T2 lesions of the oral tongue. Andersen *et al.*^[64] studied the results of neck failure following observation of N0 necks. They found that 60% of patients had N2 disease and 49% had extracapsular spread (ECS). Either or both these adverse prognostic factors were present at the time of surgery in 77% of patients.^[22,62-64]

Four RCTs have been performed to compare END with wait and watch policy. Two of the trials were conducted purely on early oral tongue cancers. Fakih *et al.*^[65] in a series on T1 and T2 lesions, compared END with observation. They found that there was no survival difference between the two groups. They found that a tumor depth of more than 4 mm was associated with higher rates of involved nodes and suggested that these set of patients may benefit from END. A more recent RCT from Hong Kong compared END versus observation for T1 and T2 lesions of the oral tongue. The authors had a robust follow-up protocol of clinical and ultrasonographic examination of the neck to detect recurrences. They were able to salvage all neck recurrences in the observational arm and thus found no survival differences between the two arms.^[14] All the above RCTs had small numbers and consisted of methodology flaws making their conclusions difficult to inculcate into clinical practice.

Vijayakumar *et al.*^[22] found that about 50% of patients with tongue tumor depth more than 4 mm had grade III and IV tumors. The incidence of occult metastasis was 62.2%, which is significantly higher than for other subsites of the oral cavity. Thirty eight (33.9%) patients with occult metastasis had ECS, which is a poor prognostic feature. Another poor prognostic indicator they detected was multiple levels of nodal involvement in 79 (70.5%) patients. As expected most of the lymph nodes were localized to levels I, II and III. But level IV was involved in 23 patients.^[22]

In the study of Huang *et al.*^[13] neck recurrence rate in the OBS group (28.6%) was significantly higher compared with that observed in the END group (12.7%, $P = 5.004$). Although contralateral regional metastases have been described in some series of patients with early stage tumors of the oral cavity,^[26,66] their data show that neck recurrence is mainly ipsilateral in patients treated with glossectomy alone. Among patients treated with END, 12.7% developed a regional recurrence. Contralateral level I lymph nodes were the most frequent site of regional recurrence. This finding was in line with previous data.^[66] It is posited that this phenomenon may be due to an afferent communicating pathway that drains from the floor of the mouth into the contralateral lymph nodes.^[67] This may also occur silently before surgery. The second most common site of regional recurrence was ipsilateral level I nodes. In their study, the 5-year cervical control rates was much better for patients treated by END compared with OBS. In addition, the 5-year OS in the END group was superior compared with patients who had a subsequent therapeutic neck dissection. These data are in line with previous studies in early-stage tongue cancer.^[65] It is thus posited that END might improve both neck control and OS. Indeed, application of this technique might improve the chance of clearance of micrometastasis that cannot be detected by histology or imaging. However, their data provide evidence that, in the group of patients treated by END, the incidence of skip metastasis to level IV in the absence of level I/II lesions is as low as 2.7% (1 case out of 37 patients). In the OBS group, the skip metastasis rate was 5.4% (3 of 56) in patients with regional recurrence who received salvage neck dissection. In their report the skip metastatic rate was lower compared with that reported in previous studies.^[68-71] However, in their study all patients were staged with the use of CT/MR imaging. In the light of our data, routine dissection of level IV lymph node alongside supraomohyoid neck dissection can provide little benefit to patients with early-stage tongue cancer. It is concluded that level IV nodes should not be routinely included in the neck dissection for patients with negative neck as assessed by CT/MRI scans.

In the study of Dias *et al.*^[6] analyzing the two groups of patients (resection of the primary tumor alone-RA and resection of the primary tumor "plus" elective neck dissection-RA+END) according to the incidence of regional recurrence, they found a 24% incidence in the RA group compared with a 4% incidence in the R+END group. The 20% difference between the two groups was statistically significant ($P = 0.03$). Differences between disease-free survival of 97% for the R+END group and of 74% for the RA group were also statistically significant ($P = 0.05$). These findings confirm the results of Kligerman *et al.*^[34] in

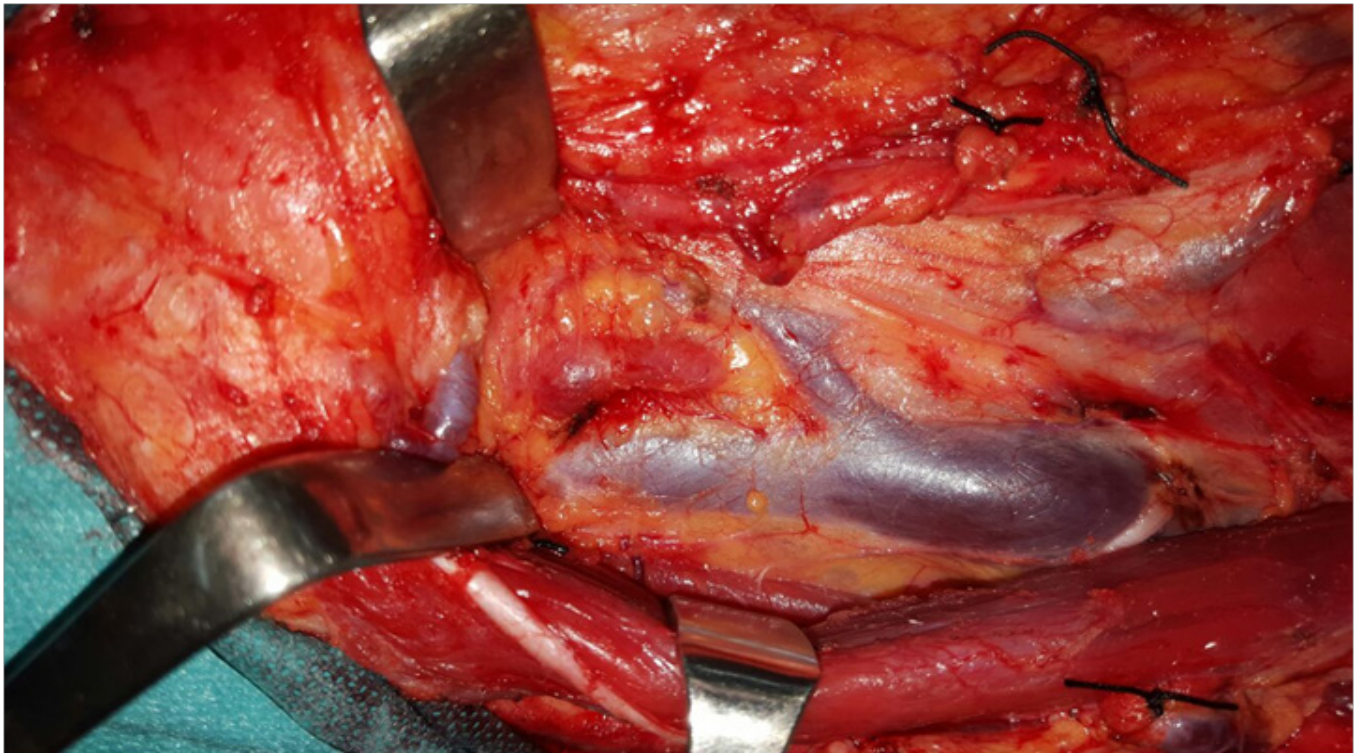


Figure 2: Right selective supraomohyoid neck dissection. Note the appearance of a 1-cm node in the jugulodigastric region (level II) intraoperatively, which was evident neither by palpation nor in the preoperative computed tomography scan. This otherwise not so uncommon situation may justify the performance of elective neck dissection even in T1 squamous cell carcinoma of the oral cavity and oropharynx

their comparative analysis of the outcome in patients treated with END versus observation in early oral cancers.

Most locoregional recurrences in oral cancer patients occur during the early postoperative follow-up period.^[23,24,34,38] Analyzing the patterns of regional recurrence in untreated N0 neck patients, they found involvement of multiple nodes of levels I to III, involvement of levels IV and V (2 cases), and involvement of bilateral lymph node metastases (2 cases). These observations clearly confirm the more aggressive behavior of the oral cancer when delayed cervical metastases have become clinically apparent.^[26-30]

Regional recurrence was the most important cause of failure after surgical treatment in their groups of patients. END, when used, reduced the initial regional recurrence rate and improved the disease-free survival time of patients. The overall 24.5% incidence of neck metastases allied with the poor rate of salvage in the case of regional recurrence (28.5%) found in this study strongly suggest the need for elective treatment of the neck in stage I squamous cell carcinoma of the tongue and floor of the mouth.^[6]

DISCUSSION

Cervical node metastasis in head and neck cancer is a poor prognostic feature and decreases the survival by 50%. It is obvious that patients with clinically involved nodes require treatment of the neck. However, controversy exists in the management of patients with early cancers and N0 neck.^[22,23]

The biologic aggressiveness of oral cavity squamous cell carcinoma, particularly in the early stages, is reflected in its

ability to metastasize to regional lymph node chains. Because of the rich lymphatic network of the tongue and floor of the mouth (FOM), the risk of development of lymph node metastases in these particular sites varies between 6% and 46%, even in the early stages.^[6,29-33] This metastatic disease is almost always subclinical or occult at the time of the diagnosis and treatment of early tongue and FOM cancers, thereby contributing to the controversy regarding elective treatment of the neck.

END for N0 neck has been increasingly performed for early oral carcinomas.^[23,26,33-35] The main reason for this aggressive therapeutic approach is the high index of occult^[33,34,36] metastases in association with poor salvage rates for recurrences at the neck.

Although palpation is the most practical means of staging the neck, it has a false-negative rate of about 40%.^[38,39] The use of CT may reduce the false negative rate of the staging to 22.7%.^[38] The use of MRI or PET scans can further improve detection rates for neck nodal metastases. A high incidence of neck recurrence has been reported in patients with T1-T2 cancer of the oral tongue treated by primary tumor excisions alone.^[40,41] Specifically, cervical lymph node metastases developed subsequently in 38% to 43% of such patients.^[41-43]

Management of the clinically negative neck in patients with T1-T2 oral cancer remains controversial. Although END can result in early treatment of occult lymph node metastases, the vast majority of these neck dissections turn out to be unnecessary. Moreover, these patients are subjected to morbidity such as shoulder morbidity, pain and sensibility disorders,^[44,45] which may have major impact on health-related quality of life.^[46,47] Furthermore, elective neck treatment may remove or destroy a barrier to cancer spread in case of local recurrence or second primary tumor which occur

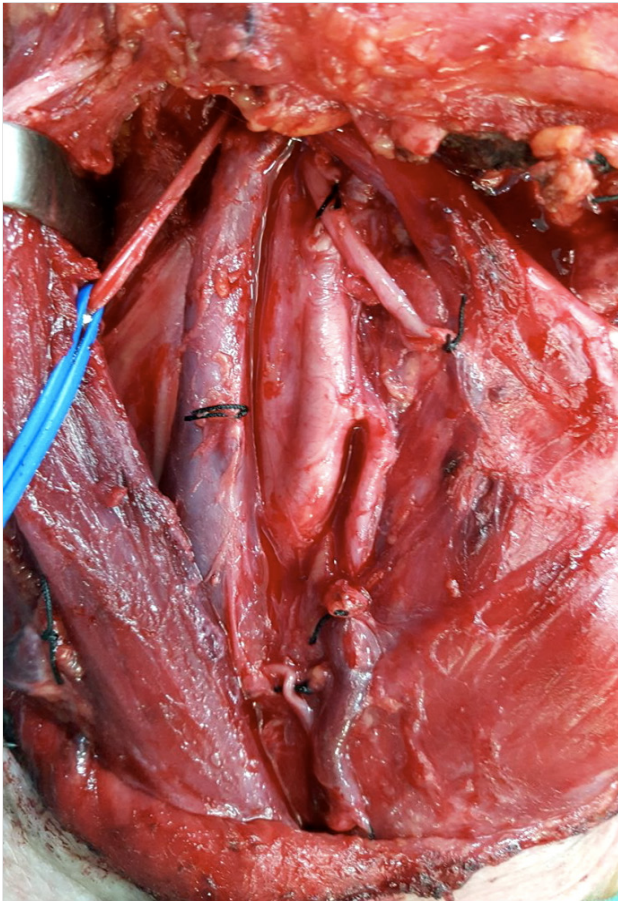


Figure 3: Completed selective supraomohyoid neck dissection, with extirpation of fibro-fatty tissue and lymph neck nodes from levels I to III, while preserving the sternocleidomastoid muscle, accessory spinalis nerve and internal jugular vein

frequently in head and neck cancer patients.^[48] Therefore, it is challenging to optimize management of the neck in T1-T2 oral cancer and tailor management in the individual patient.

Several articles have stated that tumor depth is an important factor contributing to neck lymph node metastasis.^[72-76] Other factors such as differentiation, DNA aneuploid, T stage, perineural invasion, infiltration pattern, and other molecular markers have also been proposed.^[35,77-79] In general, these studies agree that the depth of tumor invasion more than 4 to 5 mm will have higher risk of neck lymph node metastasis.

Because of the dense lymphatic interconnections of the tongue and FOM, bilateral and contralateral spread is not uncommon in early oral lesions of these anatomic sites.^[6,26,33,66] Contralateral regional metastases have been described in some series of early tumors of the oral cavity facing elective ipsilateral neck dissection.^[26,66]

These results are in accordance with the findings of Cunningham *et al.*^[39] in their analysis of cervical metastases in stage I and II squamous cell carcinoma (SCC) of the oral cavity. The possibility of metastatic spread to lower lymphatic levels at the neck (levels IV-V) or the development of the so-called “skip metastases” challenges selective supraomohyoid neck dissection as an effective therapeutic method of regional control in oral cancer patients.^[35,69] Byers *et al.*^[69] found a 15.8% incidence of level IV metastases as the only metastatic manifestation or involvement of level III without compromising

of levels I and II in 277 oral tongue cancer patients. Lydiatt *et al.*^[35] concluded that the inclusion of the lower jugular chain with the supraomohyoid neck dissection had increased the effectiveness of regional control by 20% to 24%.

Shah *et al.*^[68] found a 3.5% incidence of nodal metastases at levels IV and V and a 1.5% incidence of isolated level involvement, outside the supraomohyoid triangle (level I, II, or III) in their review of the patterns of cervical metastases in 192 squamous cell carcinoma of the oral cavity. These findings emphasize the effectiveness of selective supraomohyoid neck dissection when used electively to control cervical micrometastases [Figures 2 and 3].

Many pretreatment imaging techniques to diminish the incidence of occult metastases have been studied, and comparative studies have shown USgFNAC to be the most accurate. However, the sensitivity is only in the range of 50-65% and whether imaging should change the current management of the cN0 neck remains controversial. In early OSCC, sentinel node biopsy (SNB) has a sensitivity of 93% for the detection of occult lymph node metastases.^[62] This figure is probably even higher in the more experienced centers. Thus, SNB has a much higher sensitivity and can be used to better select candidates for neck dissection. Although the long-term follow-up results of the large European SENT study are not yet reported, several centers have already adopted sentinel node biopsy as an alternative to END. In the American National Comprehensive Cancer Network (NCCN) guidelines as well as the guidelines of the Dutch Head and Neck Society, sentinel node biopsy is already mentioned as an alternative for END. However, this technique does require experience and is currently recommended only for centers with the necessary facilities and expertise. The group of Tata Memorial Centre recently reported their experience in 51 early OSCC patients and found a sensitivity of only 71%. In spite of this low percentage, they concluded that SNB is a reliable method to detect occult metastases which has potential to replace END.^[63]

Sentinel node biopsy has been investigated in many cancer centres.^[80] Some authors postulate that SNB might replace END in the treatment of early, node-negative OSCC.^[81,82] Other studies, however, do not find such a high sensitivity for SNB, suggesting that this approach should primarily be considered for patients with T1 tumours and a low risk of occult metastases.^[83-85] In the future, we believe that SNB will play a vital role in classification for patients with T1 tumours who would benefit from END. Nevertheless, before further prospective studies confirm that SNB can actually replace END for T2 tumours, simultaneous neck dissection is still the most preferred recommended neck management choice for stage II OSCC.^[16]

In conclusion, a few non-randomized studies have shown no advantages of END when strict USgFNAC follow-up was employed. In these studies, the salvage rates were much higher and relapses were diagnosed earlier. However, it is a highly operator dependent investigation. It also requires additional manpower and time, thus making its routine use difficult in a high volume cancer center. Thus, if routine very strict follow-up using USgFNAC by a well-trained ultrasonographer cannot be assured,

END is the safest strategy. We emphasize the effectiveness of selective supraomohyoid neck dissection when used electively to control cervical micrometastases.

Therefore, it seems to not be practical to use the depth of tumor invasion or other pathologic parameters as a guideline to determine whether the patient should receive END or not. It will become two stages of surgery. Instead, it is proper to proceed with supraomohyoid neck dissection at the time of neck operation.

The next step in refinement of the choice to manage the cN0 neck with END or observation is to perform a RCT comparing END with close observation in OSCC patients with a cN0 neck based on sentinel node biopsy.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Flach GB, Tenhagen M, De Bree R, Brakenhoff RH, Van der Waal I, Bloemena E, Kuik DJ, Castelijns JA, Leemans CR. Outcome of patients with early stage oral cancer managed by an observation strategy towards the N0 neck using ultrasound guided fine needle aspiration cytology. No survival difference as compared to elective neck dissection. *Oral Oncol* 2013;49:157-64.
2. Leemans CR, Tiwari R, van der Waal I, Karim AB, Nauta JJ, Snow GB. The efficacy of comprehensive neck dissection with or without postoperative radiotherapy in nodal metastases of squamous cell carcinoma of the upper respiratory and digestive tracts. *Laryngoscope* 1990;100:1194-8.
3. Weiss MH, Harrison LB, Isaacs RS. Use of decision analysis in planning a management strategy for the stage N0 neck. *Arch Otolaryngol Head Neck Surg* 1994;120:699-702.
4. O'Brien CJ, Traynor SJ, McNeil E, McMahon JD, Chaplin JM. The use of clinical criteria alone in the management of the clinically negative neck among patients with squamous cell carcinoma of the oral cavity and oropharynx. *Arch Otolaryngol Head Neck Surg* 2000;126:360-5.
5. Kaya S, Yilmaz T, Gursel B, Sarac S, Sennaroğlu L. The value of elective neck dissection in treatment of cancer of the tongue. *Am J Otolaryngol* 2001;22:59-64.
6. Dias FL, Kligerman J, Matos de Sá G, Arcuri RA, Freitas E, Farias T, Matos F, Lima RA. Elective neck dissection versus observation in stage I squamous cell carcinomas of the tongue and floor of the mouth. *Otolaryngol Head Neck Surg* 2001;125:23-9.
7. Smith GI, O'Brien CJ, Clark J, Shannon KF, Clifford AR, McNeil EB, Gao K. Management of the neck in patients with T1 and T2 cancer in the mouth. *Br J Oral Maxillofac Surg* 2004;42:494-500.
8. Duvvuri U, Simental AA, D'Angelo G, Johnson JT, Ferris RL, Gooding W, Myers EN. Elective neck dissection and survival in patients with squamous cell carcinoma of the oral cavity and oropharynx. *Laryngoscope* 2004;114:2228-34.
9. Amaral TM, Da Silva Freire AR, Carvalho AL, Pinto CAL, Kowalski LP. Predictive factors of occult metastasis and prognosis of clinical stages I and II squamous cell carcinoma of the tongue and floor of the mouth. *Oral Oncol* 2004;40:780-6.
10. Keski-Säntti H, Atula T, Törnwall J, Koivunen P, Mäkitie A. Elective neck treatment versus observation in patients with T1/T2 N0 squamous cell carcinoma of oral tongue. *Oral Oncol* 2006;42:96-101.
11. Lim YC, Choi EC. Unilateral, clinically T2N0, squamous cell carcinoma of the tongue: surgical outcome analysis. *Int J Oral Maxillofac Surg* 2007;36:610-4.
12. Iype EM, Sebastian P, Mathew A, Balagopal PG, Varghese BT, Thomas S. The role of selective neck dissection (I-III) in the treatment of node negative (N0) neck in oral cancer. *Oral Oncol* 2008;44:1134-8.
13. Huang SF, Kang CJ, Lin CY, Fan KH, Yen TC, Wang HM, Chen IH, Liao CT, Cheng AJ, Chang JT. Neck treatment of patients with early stage oral tongue cancer: comparison between observation, supraomohyoid dissection, and extended dissection. *Cancer* 2008;112:1066-75.
14. Yuen AP, Ho CM, Chow TL, Tang LC, Cheung WY, Ng RW, Wei WI, Kong CK, Book KS, Yuen WC, Lam AK, Yuen NW, Trendell-Smith NJ, Chan YW, Wong BY, Li GK, Ho AC, Ho WK, Wong SY, Yao TJ. Prospective randomized study of selective neck dissection versus observation for N0 neck of early tongue carcinoma. *Head Neck* 2009;31:765-72.
15. D'Cruz AK, Siddachari RC, Walvekar RR, Pantavaidya GH, Chaukar DA, Deshpande MS, Pai PS, Chaturvedi P. Elective neck dissection for the management of the N0 neck in early cancer of the oral tongue: need for a randomized controlled trial. *Head Neck* 2009;31:1618-24.
16. Feng Z, Li JN, Li CZ, Guo CB. Elective neck dissection versus observation in the management of early tongue carcinoma with clinically node-negative neck: a retrospective study of 229 cases. *J Craniomaxillofac Surg* 2014;42:806-10.
17. Brugère JM, Mosseri VF, Mamelle G, David JM, Buisset E, Vallicioni J, Raucourt D, Szpirglas HJ, Asselain BJ. Nodal failures in patients with N0 N+ oral squamous cell carcinoma without capsular rupture. *Head Neck* 1996;18:133-7.
18. Khafif RA, Gelbfish GA, Tepper P, Attie JN. Elective radical neck dissection in epidermoid cancer of the head and neck. A retrospective analysis of 853 cases of mouth, pharynx, and larynx cancer. *Cancer* 1991;67:67-71.
19. Okamoto M, Nishimine M, Kishi M, Kirita T, Sugimura M, Nakamura M, Konishi N. Prediction of delayed neck metastasis in patients with stage I/II squamous cell carcinoma of the tongue. *J Oral Pathol Med* 2002;31:227-33.
20. De Bree R, Van den Brekel MW. Elective neck dissection versus observation in the clinically node negative neck in early oral cancer: do we have the answer yet? *Oral Oncol* 2015;51:963-5.
21. Kowalski LP, Sanabria A. Elective neck dissection in oral carcinoma: a critical review of the evidence. *Acta Otorhinolaryngol Ital* 2007;27:113-7.
22. Vijayakumar M, Burrah R, Sabitha KS, Nadimul H, Rajani BC. To operate or not to operate N0 neck in early cancer of the tongue? A prospective study. *Indian J Surg Oncol* 2011;2:172-5.
23. Teichgraber JF, Clairmont AA. The incidence of occult metastasis for cancer of the oral tongue and floor of the mouth: treatment rationale. *Head Neck Surg* 1984;7:15-21.
24. DiTroia JF. Nodal metastases and prognosis in carcinoma of the oral cavity. *Otolaryngol Clin North Am* 1972;5:333-41.
25. O'Brien CJ, Lahr CJ, Soong SJ. Surgical treatment of early-stage carcinoma of the oral tongue--wound adjuvant treatment be beneficial? *Head Neck Surg* 1986;8:401-8.
26. Yuen APW, Wei WI, Wong YM. Elective neck dissection versus observation in the treatment of early oral tongue carcinoma. *Head Neck* 1997;19:583-8.
27. Spiro RH, Strong EV. Epidermoid carcinoma of the oral cavity and oropharynx. *Arch Surg* 1973;107:382-4.
28. Spiro RH, Strong EV. Surgical treatment of cancer of the tongue. *Surg Clin N Am* 1974;54:757-65.
29. Lee JG, Litton WB. Occult regional metastases: carcinoma of the oral tongue. *Laryngoscope* 1972;82:1273-80.
30. Fu KK, Lichter A, Galante M. Carcinoma of the floor of the mouth: an analysis of treatment results and the sites and causes of failure. *Int J Radiat Oncol Biol Phys* 1976;1:829-37.
31. Whitehurst JO, Droulias CA. Surgical treatment of squamous cell carcinoma of the oral tongue. *Arch Otolaryngol* 1977;103:212-5.
32. Johnson JT, Leitzig B, Cummings CW. Management of T1 carcinoma of the anterior aspect of the tongue. *Arch Otolaryngol* 1980;106:249-51.
33. Ho CM, Lam KH, Wei WI. Occult lymph node metastases in small oral tongue cancers. *Head Neck* 1992;14:359-63.
34. Kligerman J, Lima RA, Soares JR, Prado L, Dias FL, Freitas EQ, Olivatto LO. Supraomohyoid neck dissection in the treatment of T1/T2 squamous cell carcinoma of oral cavity. *Am J Surg* 1994;168:391-4.
35. Lydiatt DD, Robins KT, Byers RM, Wolf PF. Treatment of stage I and II oral tongue cancer. *Head Neck* 1993;15:308-12.
36. Van den Brekel MWM, van der Waal I, Meijer CJ, Freeman JL, Castelijns JA, Snow GB. The incidence of micrometastases in neck dissection specimens obtained from elective neck dissections. *Laryngoscope* 1996;106:987-91.
37. Van den Brekel MWM, Castelijns JA, Stel HV, Golding RP, Meyer CJ, Snow GB. Modern imaging techniques and ultrasound-guided aspiration cytology for the assessment of neck node metastases: a prospective comparative study. *Eur Arch Otorhinolaryngol* 1993;250:11-7.
38. Snow GB, Patel P, Leemans CR, Tiwari R. Management of cervical lymph nodes in patients with head and neck cancer. *Eur Arch Otorhinolaryngol* 1992;249:187-94.
39. Cunningham MJ, Johnson JT, Myers EN, Schramm VL Jr, Thearle PB. Cervical lymph node metastasis after local excision of early squamous cell carcinoma of the oral cavity. *Am J Surg* 1986;152:361-66.
40. Beenken SW, Krontiras H, Maddox WA, Peters GE, Soong S, Urist MM. T1 and T2 squamous cell carcinoma of the oral tongue: prognostic factors and the role of elective lymph node dissection. *Head Neck* 1999;21:124-30.

41. Yii NW, Patel SG, Rhys-Evans PH, Breach NM. Management of the N0 neck in early cancer of the oral tongue. *Clin Otolaryngol Allied Sci* 1999;24:75-9.
42. Spiro RH, Strong EV. Discontinuous partial glossectomy and radical neck dissection in selected patients with epidermoid carcinoma of the mobile tongue. *Am J Surg* 1973;126:544-6.
43. Dijkstra PU, van Wilgen PC, Buijs RP, Brendeke W, de Goede CJ, Kerst A, Koolstra M, Marinus J, Schoppink EM, Stuiver MM, van de Velde CF, Roodenburg JL. Incidence of shoulder pain after neck dissection: a clinical explorative study for risk factors. *Head Neck* 2001;23:947-53.
44. El Ghani F, van den Brekel MW, de Goede CJ, Kuik DJ, Leemans CR, Smele LE. Shoulder function and patient well-being after various types of neck dissections. *Clin Otolaryngol Allied Sci* 2002;27:403-8.
45. Inoue H, Nibu KI, Saito M, Otsuki N, Ishida H, Onitsuka T, Fujii T, Kawabata K, Saikawa M. Quality of life after neck dissection. *Arch Otolaryngol Head Neck Surg* 2006;132:662-6.
46. Stuiver MM, van Wilgen CP, de Boer EM, de Goede CJ, Koolstra M, van Opzeeland A, Venema P, Sterken MW, Vincent A, Dijkstra PU. Impact of shoulder complaints after neck dissection on shoulder disability and quality of life. *Otolaryngol Head Neck Surg* 2008;139:32-9.
47. Braakhuis BJ, Tabor MP, Leemans CR, van der Waal I, Snow GB, Brakenhoff RH. Second primary tumors and field cancerization in oral and oropharyngeal cancer: molecular techniques provide new insights and definitions. *Head Neck* 2002;24:198-206.
48. Smith GI, O'Brien CJ, Clark J, Shannon KF, Clifford AR, McNeil EB, Gao K. Management of the neck in patients with T1 and T2 cancer in the mouth. *Br J Oral Maxillofac Surg* 2004;42:494-500.
49. Duvvuri U, Simental AA, D'Angelo G, Johnson JT, Ferris RL, Gooding W, Myers EN. Elective neck dissection and survival in patients with squamous cell carcinoma of the oral cavity and oropharynx. *Laryngoscope* 2004;114:2228-34.
50. Iype EM, Sebastian P, Mathew A, Balagopal PG, Varghese BT, Thomas S. The role of selective neck dissection (I-III) in the treatment of node negative (N0) neck in oral cancer. *Oral Oncol* 2008;44:1134-8.
51. Capote A, Escorial V, Munoz-Guerra MF, Rodriguez-Campo FJ, Gamallo C, Naval L. Elective neck dissection in early-stage oral squamous cell carcinoma – does it influence recurrence and survival? *Head Neck* 2007;29:3-11.
52. Fasunla AJ, Greene BH, Timmesfeld N, Wiegand S, Werner JA, Sesterhenn AM. A meta-analysis of the randomized controlled trials on elective neck dissection versus therapeutic neck dissection in oral cavity cancers with clinically node-negative neck. *Oral Oncol* 2011;47:320-4.
53. D'Cruz AK, Dandekar MR. Elective versus therapeutic neck dissection in the clinically node negative neck in early oral cavity cancers: do we have the answer yet? *Oral Oncol* 2011;47:780-2.
54. D'Cruz AK, Vaish R, Kapre N. Elective versus therapeutic neck dissection in node-negative oral cancer. *N Engl J Med* 2015;373:521-9.
55. Ganly I, Patel S, Shah J. Early stage squamous cell cancer of the oral tongue—clinicopathologic features affecting outcome. *Cancer* 2012;118:101-11.
56. Tsang RK, Chung JC, Howe To VS, Chan JY, Ho WK, Wei WI. Efficacy of salvage neck dissection for isolated nodal recurrences in early carcinoma of oral tongue with watchful waiting management of initial N0 neck. *Head Neck* 2011;33:1482-5.
57. Borgemeester MC, van den Brekel MW, van Tinteren H. Ultrasound-guided aspiration cytology for the assessment of the clinically N0 neck: factors influencing its accuracy. *Head Neck* 2008;30:1505-13.
58. Van den Brekel MW, Castelijns JA, Snow GB. The size of lymph nodes in the neck on sonograms as a radiologic criterion for metastasis: how reliable is it? *AJNR Am J Neuroradiol* 1998;19:695-700.
59. Van den Brekel MW, Reitsma LC, Quak JJ. Sonographically guided aspiration cytology of neck nodes for selection of treatment and follow-up in patients with N0 head and neck cancer. *AJNR Am J Neuroradiol* 1999;20:1727-31.
60. Wensing BM, Merks MA, de Wilde PC, Marres HA, van den Hoogen FJ. Assessment of preoperative ultrasonography of the neck and elective neck dissection in patients with oral squamous cell carcinoma. *Oral Oncol* 2010;46:87-91.
61. Nieuwenhuis EJ, Castelijns JA, Pijpers R, van den Brekel MW, Brakenhoff RH, van der Waal I, Snow GB, Leemans CR. Wait-and-see policy for the N0 neck in early-stage oral and oropharyngeal squamous cell carcinoma using ultrasonography-guided cytology: is there a role for identification of the sentinel node? *Head Neck* 2002;24:282-9.
62. Govers TM, Hannink G, Merks MA, Takes RP, Rovers MM. Sentinel node biopsy for squamous cell carcinoma of the oral cavity and oropharynx: a diagnostic meta-analysis. *Oral Oncol* 2013;49:726-32.
63. Chaturvedi P, Datta S, Arya S. Prospective study of ultrasound-guided fine-needle aspiration cytology and sentinel node biopsy in the staging of clinically negative T1 and T2 oral cancer. *Head Neck* 2015;37:1504-8.
64. Andersen PE, Cambronero E, Shaha AR, Shah JP. The extent of neck disease after regional failure during observation of the No neck. *Am J Surg* 1996;172:689-91.
65. Fakhri AR, Rao RS, Patel AR. Prophylactic neck dissection in squamous cell carcinoma of oral tongue: a prospective randomized study. *Semin Surg Oncol* 1989;5:327-30.
66. Kowalski LP, Medina JE. Nodal metastases: predictive factors. *Otolaryngol Clin North Am* 1998;31:621-37.
67. Ossoff RH, Sisson GA. Lymphatics of the floor of the mouth and neck: anatomical studies related to contralateral drainage pathways. *Laryngoscope* 1981;91:1847-50.
68. Shah JP, Candela FC, Poddar AK. The patterns of cervical lymph node metastases from squamous carcinoma of the oral cavity. *Cancer* 1990;66:109-13.
69. Byers RM, Weber RS, Andrews T, McGill D, Kare R, Wolf P. Frequency and therapeutic implications of "skip metastases" in the neck from squamous carcinoma of the oral tongue. *Head Neck* 1997;19:14-9.
70. Kowalski LP, Bagietto R, Lara JR, Santos RL, Silva JF Jr, Magrin J. Prognostic significance of the distribution of neck node metastasis from oral carcinoma. *Head Neck* 2000;22:207-14.
71. Woolgar JA. Histological distribution of cervical lymph node metastases from intraoral/oropharyngeal squamous cell carcinomas. *Br J Oral Maxillofac Surg* 1999;37:175-80.
72. Byers RM, El Naggar AK, Lee YY, Rao B, Fornace B, Terry NH, Sample D, Hankins P, Smith TL, Wolf PJ. Can we detect or predict the presence of occult nodal metastases in patients with squamous carcinoma of the oral tongue? *Head Neck* 1998;20:138-44.
73. Fukano H, Matsuura H, Hasegawa Y, Nakamura S. Depth of invasion as a predictive factor for cervical lymph node metastasis in tongue carcinoma. *Head Neck* 1997;19:205-10.
74. Lim SC, Zhang S, Ishii G, Endoh Y, Kodama K, Miyamoto S, Hayashi R, Ebihara S, Cho JS, Ochiai A. Predictive markers for late cervical metastasis in stage I and II invasive squamous cell carcinoma of the oral tongue. *Clin Cancer Res* 2004;10:166-72.
75. Asakage T, Yokose T, Mukai K, Tsugane S, Tsubono Y, Asai M, Ebihara S. Tumor thickness predicts cervical metastasis in patients with stage I/II carcinoma of the tongue. *Cancer* 1998;82:1443-8.
76. Kane SV, Gupta M, Kakade AC, D' Cruz A. Depth of invasion is the most significant histological predictor of subclinical cervical lymph node metastasis in early squamous carcinomas of the oral cavity. *Eur J Surg Oncol* 2006;32:795-803.
77. Sparano A, Weinstein G, Chalian A, Yodanis M, Weber R. Multivariate predictors of occult neck metastasis in early oral tongue cancer. *Otolaryngol Head Neck Surg* 2004;131:472-6.
78. Spiro RH, Huvois AG, Wong GY, Spiro JD, Gnecco CA, Strong EW. Predictive value of tumor thickness in squamous carcinoma confined to the tongue and floor of the mouth. *Am J Surg* 1986;152:345-50.
79. Hiratsuka H, Miyakawa A, Nakamori K, Kido Y, Sunakawa H, Kohama G. Multivariate analysis of occult lymph node metastasis as a prognostic indicator for patients with squamous cell carcinoma of the oral cavity. *Cancer* 1997;80:351-6.
80. O'Connor R, Pezier T, Schilling C, McGurk M. The relative cost of sentinel lymph node biopsy in early oral cancer. *J Craniomaxillofac Surg* 2013;41:721-7.
81. Alkureishi LW, Burak Z, Alvarez JA, Ballinger J, Bilde A, Britten AJ, Calabrese L, Chiesa C, Chiti A, de Bree R, Gray HW, Hunter K, Kovacs AF, Lassmann M, Leemans CR, Mamelle G, McGurk M, Mortensen J, Poli T, Shoaib T, Sloan P, Sorensen JA, Stoeckli SJ, Thomsen JB, Trifiro G, Werner J, Ross GL; European Association of Nuclear Medicine Oncology Committee, European Sentinel Node Biopsy Trial Committee. Joint practice guidelines for radionuclide lymphoscintigraphy for sentinel node localization in oral/oropharyngeal squamous cell carcinoma. *Ann Surg Oncol* 2009;16:3190-210.
82. Stoeckli SJ, Alkureishi LW, Ross GL. Sentinel node biopsy for early oral and oropharyngeal squamous cell carcinoma. *Eur Arch Otorhinolaryngol* 2009;266:787-93.
83. Keski-Säntti H, Kontio R, Leivo I, Törnwall J, Mätzke S, Mäkitie AA, Atula T. Sentinel lymph node biopsy as an alternative to wait and see policy in patients with small T1 oral cavity squamous cell carcinoma. *Acta Otolaryngol* 2008;128:98-102.
84. Keski-Säntti H, Kontio R, Törnwall J, Leivo I, Mätzke S, Suominen S, Leppänen E, Atula T. Sentinel lymph node biopsy or elective neck dissection for patients with oral squamous cell carcinoma? *Eur Arch Otorhinolaryngol* 2008;265:513-7.
85. Thiele OC, Seeberger R, Flechtenmacher C, Hofele C, Freier K. The role of elective supraomohyoid neck dissection in the treatment of early, node-negative oral squamous cell carcinoma (OSCC): a retrospective analysis of 122 cases. *J Craniomaxillofac Surg* 2012;40:67-70.

Elective neck dissection in oral squamous cell carcinoma of the upper maxilla: necessary?

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ABSTRACT

Aim: Surgical treatment of clinically negative neck in maxillary squamous cell carcinoma (SCC) of the upper jaw is controversial. The purpose of this systematic review was to define the incidence of cervical metastasis and to assess if elective neck dissection is justified when the neck is not primarily affected. **Methods:** An electronic literature search was conducted in several databases, including MEDLINE, EMBASE, and Cochrane Central databases, for articles written in English. **Results:** Twenty-eight articles were included in the review. The overall cervical metastases rate was 33% and the total initial cervical metastases rate was 16%. Interestingly, the author found that 71% of patients with cervical metastases from maxillary SCC carcinoma were T3/T4 stage. **Conclusion:** This review shows the need for a change in the management of the N0 neck in SCC arising in the maxillary alveolus and hard palate. Elective neck dissection should be performed in patients with T3/T4 tumours with clinic or radiographic negative necks (N0c).

Key words:

Elective neck dissection; maxilla squamous cell carcinoma; surgical treatment; cervical lymph node metastasis

INTRODUCTION

Squamous cell carcinoma (SCC) located in the maxillary gingiva and hard palate is relatively rare and less

frequent than SCC from other oral sites such as tongue, floor of mouth or retromolar region. Many studies^[1-5]

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Table 1: Studies included in the review about patients with squamous cell carcinoma of the upper maxilla

Author	Year	Country	No. of patients	Study	Nodal disease in T3/T4 (%)	Initial nodal disease (%)	Overall nodal disease incidence (%)	Follow-up (months)
Truitt <i>et al.</i> ^[23]	1999	USA	24	Retrospective	Unknown	17%	33%	60
Ogura <i>et al.</i> ^[14]	2003	Japan	21	Retrospective	Unknown	29%	67%	Unknown
Simental <i>et al.</i> ^[11]	2006	USA	26	Retrospective	Unknown	12%	35%	65
Zwetyenga <i>et al.</i> ^[35]	2006	France	34	Retrospective	91%	18%	32%	Unknown
Montes and Schmid ^[9]	2008	USA	14	Retrospective	50%	21%	43%	27
Lin and Bhattacharyya ^[22]	2009	USA	725	Cross-section	64%	14%	14%	Unknown
Kruse and Grätz ^[12]	2009	Switzerland	30	Retrospective	18%	13%	37%	Unknown
Mourouzis <i>et al.</i> ^[13]	2010	UK	17	Retrospective	100%	24%	35%	60
Montes <i>et al.</i> ^[16]	2011	USA	131	Retrospective	55%	24%	31%	1-180
Lubek <i>et al.</i> ^[18]	2011	USA	37	Retrospective	67%	5%	16%	49
Nicolai <i>et al.</i> ^[34]	2010	Italy	86	Retrospective	31%	9%	22%	Unknown
Wang <i>et al.</i> ^[36]	2010	Taiwan	79	Retrospective	100%	9%	22%	Unknown
Valentini <i>et al.</i> ^[25]	2010	Italy	19	Retrospective	Unknown	5%	11%	Unknown
Beltrami <i>et al.</i> ^[26]	2012	Italy	65	Retrospective	86%	12%	22%	43.3
Morris <i>et al.</i> ^[15]	2011	USA	139	Retrospective	71%	8%	31%	57
Brown <i>et al.</i> ^[10]	2013	UK	43	Retrospective	81%	7%	37%	94
Poeschl <i>et al.</i> ^[33]	2012	Austria	74	Retrospective	100%	Unknown	22%	6-130
Dalal and McLennan ^[30]	2013	UK	30	Retrospective	100%	27%	36%	60
Feng <i>et al.</i> ^[27]	2013	China	129	Retrospective	65%	0%	24%	Unknown
Eskander <i>et al.</i> ^[32]	2013	Canada	97	Cohort	53%	24%	41%	Unknown
Sagheb <i>et al.</i> ^[29]	2014	Germany	138	Retrospective	60%	38%	46%	43
Zhang <i>et al.</i> ^[37]	2015	China	100	Retrospective	79%	9%	34%	46
Philip <i>et al.</i> ^[24]	2014	UK	39	Retrospective	95%	33%	46%	38
Givi <i>et al.</i> ^[39]	2016	USA	199	Retrospective	50%	6%	22%	52
Berger <i>et al.</i> ^[40]	2015	Germany	171	Retrospective	78%	Unknown	44%	Unknown
Yang <i>et al.</i> ^[28]	2015	China	62	Retrospective	69%	15%	37%	37
Troeltzsch <i>et al.</i> ^[41]	2016	Germany	92	Retrospective	40%	16%	29%	42
Moreno-Sánchez <i>et al.</i> ^[42]	2016	Spain	20	Retrospective	100%	30%	45%	53

have evaluated the need for elective neck dissection in these intraoral common sites when there is no clinical or radiographic suspicious of lymphadenopathy.^[6-10] Controversies remain regarding the strategy of treatment for patients with maxillary SCC,^[11-15] including indications for unilateral or bilateral elective neck dissection and postoperative adjuvant treatment.^[16-20] Only a few authors^[21-25] have focused on the management of the neck in SCC of the maxillary gingiva, maxillary alveolus and hard palate.^[26-30]

Traditionally, when there is no clinical or radiographic suspicious of lymphadenopathy, management has been to watch and wait. However, in recent studies,^[31-35] it has been proven that a higher rate of occult cervical metastases in SCC of the maxilla has been found^[36-40] and elective neck dissection in these patients has been recommended in order to reduce recurrences.^[41-43]

A systematic review was conducted in order to clarify if elective neck dissection is necessary in management of SCC of the maxillary gingiva, maxillary alveolus and hard palate, and to identify the risk of cervical metastases in patients with maxillary SCC.

METHODS

An electronic literature search was conducted in several databases, including MEDLINE, EMBASE, and Cochrane Central databases, for articles written in English from their respective dates of inception to December 2015. The searching keywords were “cervical metastases” OR “cervical metastases” OR “neck metastases” AND “maxillary squamous cell carcinoma” OR “maxilla squamous cell carcinoma” OR “squamous cell carcinoma of upper maxilla” AND (limit to clinical trial OR randomized controlled trial).

The abstracts of yielded results were reviewed and the full text of those with apparent relevance was obtained. The references of identified articles were crosschecked for unidentified articles. These journals were *Journal of Oral and Maxillofacial Surgery*; *International Journal of Oral and Maxillofacial Surgery*; *Journal of Oral Surgery*; *British Journal of Oral and Maxillofacial Surgery*; *Head and Neck Surgery*; *Laryngoscope*; *Oral Oncology*; *Journal of Cranio-Maxillo-Facial Surgery*; *Oral Surgery*, *Oral Medicine*, *Oral Pathology and Oral Radiology*; and *Revista Española de Cirugía Oral y Maxilofacial*. The searches were limited to articles

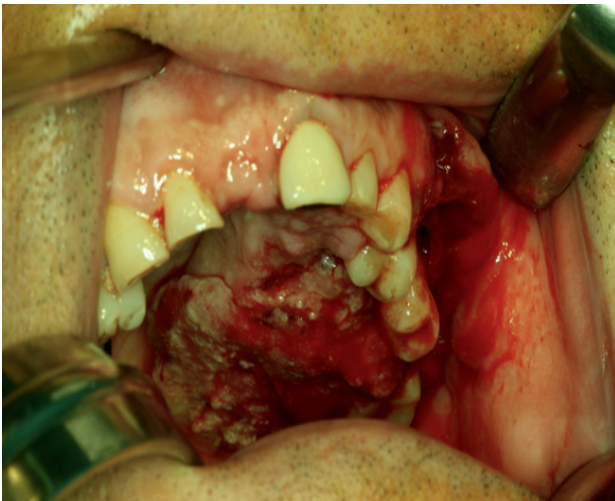


Figure 1: Intraoperative photograph of a patient with T4 squamous cell carcinoma of the hard palate with cervical metastases

published in English. The PICO question was as follows: is elective neck dissection necessary in oral squamous cell carcinoma of the upper maxilla?

The following exclusion criteria were applied: (1) case reports; (2) technical reports; (3) animal or *in vitro* studies; (4) review articles; (5) uncontrolled clinical studies; and (6) publications in which the same data were published by the same group of researchers. The authors carefully assessed the eligibility of all studies retrieved from the databases. From the included studies in the final analysis, the following data were extracted: authors, year of publication, country, study design, number of patients in the groups, initial nodal disease (%), and nodal disease in T3/T4 stage (%), overall nodal disease incidence (%) and follow-up period.

The selected articles were used to assess the rate of cervical metastases in patients with squamous cell carcinoma of the upper maxilla.

RESULTS

The electronic search resulted in 502 entries. Four additional articles were identified by manual searching. Of the 502 articles identified by electronic search, 305 were excluded because they were being retrieved in more than one search. After the initial screening of titles and abstracts, 169 articles were excluded because they were off topic. Thus, 28 articles were included in the review.

Of the 28 articles, 26 were retrospective studies, 1 was a cohort study, and 1 was a cross-sectional study. The studies included 2,641 cases in total [Table 1].

Rates of total cervical metastases

The rates of total cervical metastases were analysed in 28 articles [Table 1] in which metastases was confirmed by pathological examination. The overall metastases rate was defined as the ratio between the number of

pN+ cases and total cases. For the patients without neck dissection initially, those presenting with regional metastases or recurrence during the follow-up period would also be counted as pN+ cases. Several authors reported high rate of total cervical metastases. In a recent study, Berger *et al.*^[40] reported 44% of total cervical metastases in a series of 171 patients. Yang *et al.*^[31] observed a 37% of patients with cervical metastases during the follow-up in a series of 62 patients. Eskander *et al.*^[32] reported a total of 41% of cervical metastases in a well-structured study of a 97 patients. Montes and Schmidt^[9] reported a 42.9% rate of regional nodal disease in a series of 14 patients. Brown *et al.*^[10] reported a rate of 37.2% in a series of 43 patients.

We can conclude from our meta-analysis about these 28 studies including 2,641 patients that the overall cervical metastases from SCC of the upper maxilla are 33%.

Initial nodal disease

Initial nodal disease was defined as the patients with lymph neck node metastases from the physical and radiologic examination in the first examination and the overall initial metastases rate was defined as the ratio between the number of initial cN+ cases and total cases. This variable was analysed in 26 of the 28 articles [Table 1]. At the time of the primary diagnosis, in a series of 138 patients, Sagheb *et al.*^[29] observed 52 (38%) with cervical metastases whereas 53 (38%) patients that had a T3 ($n = 6$) or T4 ($n = 47$) tumour as well. Philip and James^[24] reported 33% (13) of patients with neck disease at presentation. Ogura *et al.*^[14] observed 28.5% of cervical metastases at presentation in their series of 21 patients with SCC of the upper maxilla. Dalal and McLennan^[30] reported a 27% of cervical metastases at initial diagnosis.

From our meta-analysis among 26 studies including 2,396 patients with SCC of the upper maxilla, we can conclude that the overall initial cervical metastases rate is 16%.

T3/T4 nodal rate

We also analysed the incidence of cervical metastases of maxillary SCC in advanced-stage (T3/4) disease, including 24 articles for this purpose. Interestingly, we observed that the probability of lymph node metastases increased with the size of the tumour. Brown *et al.*^[10] reported an 81% of cervical metastases in T3/T4 tumours in a series of 43 patients and Berger *et al.*^[40] observed a 78% of cervical metastases in patients with T3/T4 stage in a series of 171 patients. Philip and James^[24] observed a 95% of cervical metastases in T3/T4 tumours. Even authors such as Poeschl *et al.*^[33] or Dalal and McLennan^[30] reported that all the patients (100%) with advanced-stage (T3/T4) developed cervical metastases.

From our meta-analysis these 24 studies including 2,551 patients, we observed that 71% of patients with cervical

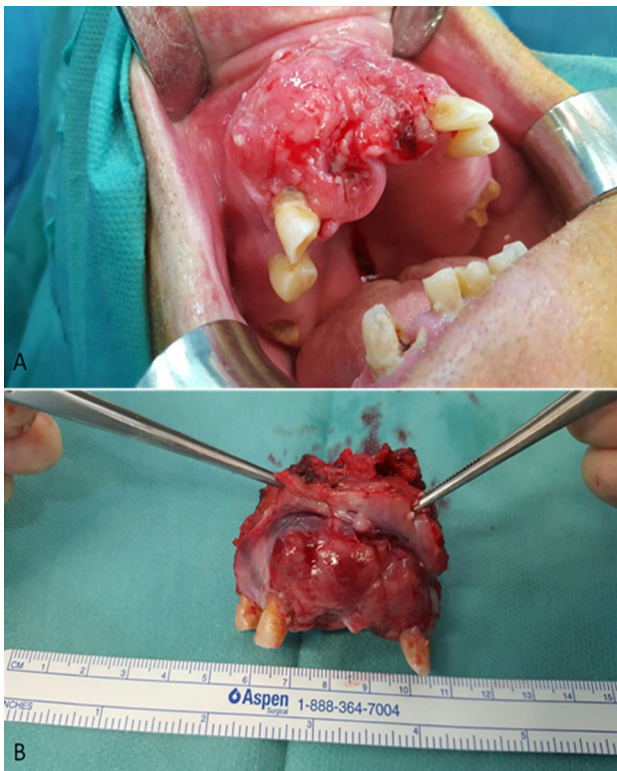


Figure 2: (A) Intraoperative photograph of a patient with T4 squamous cell carcinoma of the maxillary gingiva and bone invasion; (B) maxillary tumour was resected with wide surgical margins

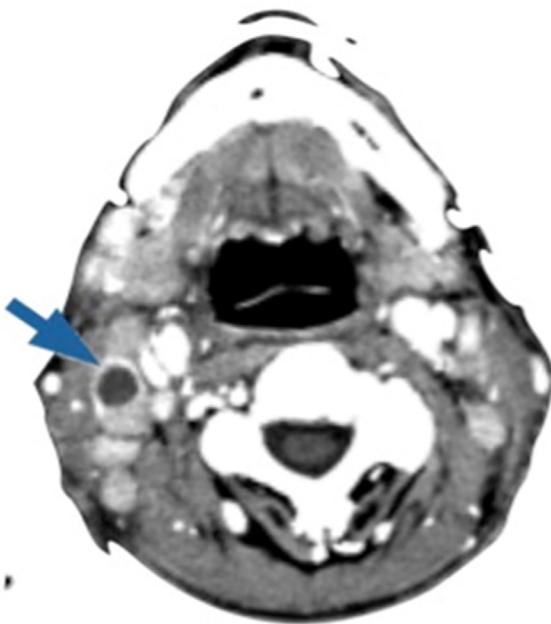


Figure 3: Computed tomography of the neck showing a cervical metastasis (arrow) of maxillary squamous cell carcinoma

metastases from maxillary SCC carcinoma were T3/T4 stage [Table 1].

DISCUSSION

In the last century, few studies have been focused

on cervical metastases from SCC of the maxilla. Nevertheless, cervical metastases from SCC of tongue or floor of mouth have been well studied, both sites presenting a high incidence, considering elective neck dissection necessary in patients.

Elective neck dissection is generally performed in patients with SCC of the oral cavity when there is a risk of occult metastases higher than 15%. It is made at the time of surgery of the primary tumour, since most cancers of the oral cavity are treated surgically.^[1-5] The risk of cervical metastases of maxillary gingival and hard palate SCC is considered lower than metastases of SCC in other primary sites, and management of clinical NO (cN0) patients is to “watch and wait”. The National Comprehensive Cancer Network proposed guidelines for treatment strategies for head and neck cancer, suggesting selective neck dissection for cN0 patients with SCC of the tongue, floor of the mouth, mandibular gingiva, and buccal mucosa.^[44] However, there is still no specific strategy for cN0 cases of maxillary SCC.

Recently, several studies reported that cervical metastases of maxillary SCC are much higher than expected and comparable to that of other primary oral sites. Montes and Schmidt^[9] reported a 42.9% rate of regional nodal disease in a series of 14 patients with SCC of the maxilla; Brown *et al.*^[10] reported a rate of 37.2% in a series of 43 patients; Simental *et al.*^[11] in a series of 26 patients with SCC of the maxillary alveolus and hard palate found cervical metastases in 34.6%, similar to that observed by Kruse and Grätz^[12] (33.6%) in a series of 30 patients. Mourouzis *et al.*^[13] reported a 23.5% incidence of cervical metastases at presentation with maxillary SCC in a series of 17 patients. These reported incidences of cervical metastases are comparable to those observed for SCC of tongue or floor of mouth. Ogura *et al.*^[14] reported a 28.5% incidence of cervical disease at presentation. Recently, Berger *et al.*^[40] reported an overall rate of 44% of cervical metastases in a series of 171 patients. In our series, we founded that 9 of the 20 (45%) patients with SCC involving the palate or the maxillary alveolus [Figures 1 and 2] developed cervical metastases [Figure 3] during disease.^[42]

In the 28 articles included in this systematic review, the initial nodal disease was 16% and cervical metastases rate ranged from 11% to 67% with an overall metastases rate of 33% in a total of 2,641 patients, which was similar to the cervical metastases from SCC of other oral sites, such as the tongue or floor of the mouth.

According to the tumour node metastasis classification system, T represents tumour size, depth of invasion, and relation with the surrounding tissue. The association between tumour site, size and grading and the risk of lymphatic metastases is well known for SCC of oral cavity and is not different for SCC of the maxilla.^[44]

It is very significant that most of cervical metastases from SCC of the maxilla in the analysed series (71%) corresponded with a tumour size larger than 4 cm (T3 and T4 tumours). This rate of cervical metastases from big-sized tumours may suggest performing elective neck dissection only in patients with advanced disease. This finding has been observed by an American multicenter study by Montes *et al.*^[16] about maxillary SCC, which reported a high percentage of cervical metastases in T3 and T4 tumours. Meng *et al.*,^[21] in their series of 78 patients with SCC of the maxilla, reported that rates for positive nodal metastases from T1 and T2 tumours were lower than 15%, whereas those for T3 and T4 tumours were higher than 40%. Zhang *et al.*,^[37] in a series of 100 patients, observed a 79% of cervical metastases in patients with T3/T4 SCC of the upper maxilla. Brown *et al.*^[10] reported an 81% of cervical metastases in T3/T4 tumours in a series of 43 patients, while Berger *et al.*^[40] in a series of 171 patients, observed a 78% of cervical metastases in patients with T3/T4 stage. Even others authors have reported that all the patients (100%) with advanced-stage (T3/T4) developed cervical metastases in some point during the study.^[13,30,33,42]

Within our meta-analysis, in 24 out of 28 articles, metastases in patients with T3/T4 tumours were analysed, founding a total of 71% of cervical metastases. These data could demonstrate a significant connection between T-stage and metastatic cervical status, and may suggest that patients with advanced-stage (T3/4) disease face a significantly higher risk of metastases.

It is a fact that most clinicians do not routinely perform elective neck dissection when the neck is clinically or radiographically negative. However, the results from our systematic review suggest that elective neck dissection should be performed in patients with locally advanced SCCs of the hard palate and maxillary alveolus, despite the fact that SCC of these sites has traditionally been believe to have a low rate of occult metastases.

In spite of the results observed from this meta-analysis, we believe that it is important to highlight that most of the analysed studies are retrospective, with their intrinsic limitations. Furthermore, several papers are limited by the small number of patients enrolled in the study. Therefore, prospective studies with larger series are necessary.

In conclusion, this systematic review shows the fact that the rate of metastases in patients with SCC of the upper maxilla is high and comparable with metastases from other oral cavity cancers. Thus, the authors believe in the need for a change in the management of the N0 neck in SCC arising in the maxillary alveolus and hard palate. Elective neck dissection should be performed in patients with T3/T4 tumours with clinic or radiographic negative necks (N0c). Prospective studies with a large

number of patients are necessary to confirm the results obtained from this study.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Shah JP, Candela FC, Poddar AK. The patterns of cervical lymph node metastases from squamous carcinoma of the oral cavity. *Cancer* 1990;66:109-13.
- Woolgar JA. Histological distribution of cervical lymph node metastases from intraoral/oropharyngeal squamous cellcarcinomas. *Br J Oral Maxillofac Surg* 1999;37:175-80.
- González-García R, Naval-Gías L, Román-Romero L, Sastre-Pérez J, Rodríguez-Campo FJ. Local recurrences and second primary tumors from squamous cell carcinoma of the oral cavity: a retrospective analytic study of 500 patients. *Head Neck* 2009;31:1168-80.
- Kowalski LP, Bagietto R, Lara JR, Santos RL, Tagawa EK, Santos IR. Factors influencing contralateral lymph node metastasis from oral carcinoma. *Head Neck* 1999;21:104-10.
- Weiss MH, Harrison LB, Isaacs RS. Use of decision analysis in planning a management strategy for the stage N0 neck. *Arch Otolaryngol Head Neck Surg* 1994;120:699-702.
- Capote A, Escorial V, Muñoz-Guerra MF, Rodríguez-Campo FJ, Gamallo C, Naval L. Elective neck dissection in early-stage oral squamous cell carcinoma-does it influence recurrence and survival? *Head Neck* 2007;29:3-11.
- Hiratsuka H, Miyakawa A, Nakamori K, Kido Y, Sunakawa H, Kohama G. Multivariate analysis of occult lymph node metastasis as a prognostic indicator for patients with squamous cell carcinoma of the oral cavity. *Cancer* 1997;80:351-6.
- Yuen AP, Ho CM, Chow TL, Tang LC, Cheung WY, Ng RW, Wei WI, Kong CK, Book KS, Yuen WC, Lam AK, Yuen NW, Trendell-Smith NJ, Chan YW, Wong BY, Li GK, Ho AC, Ho WK, Wong SY, Yao TJ. Prospective randomized study of selective neck dissection versus observation for N0 neck of early tongue carcinoma. *Head Neck* 2009;31:765-72.
- Montes DM, Schmidt BL. Oral maxillary squamous cellcarcinoma: management of the clinically negative neck. *J Oral Maxillofac Surg* 2008;66:762-6.
- Brown JS, Bekiroglu F, Shaw RJ, Woolgar JA, Rogers SN. Management of the neck and regional recurrence in squamous cell carcinoma of the maxillary alveolus and hard palate compared with other sites in the oral cavity. *Head Neck* 2013;35:265-9.
- Simental AA, Johnson JT, Myers EN. Cervical metastasis from squamous cell carcinoma of the maxillary alveolus and hard palate. *Laryngoscope* 2006;116:1682-4.
- Kruse AL, Grätz KW. Cervical metastases of squamous cellcarcinoma of the maxilla: a retrospective study of 9 years. *Head Neck Oncol* 2009;20:1-28.
- Mourouzis C, Pratt C, Brennan PA. Squamous cell carcinoma of the maxillary gingiva, alveolus, and hard palate: is there a need for elective neck dissection? *Br J Oral Maxillofac Surg* 2010;48:345-8.
- Ogura I, Kurabayashi T, Sasaki T, Amagasa T, Okada N, Kaneda T. Maxillary bone invasion by gingival carcinoma as an indicator of cervical metastasis. *Dentomaxillofac Radiol* 2003;32:291-4.
- Morris LG, Patel SG, Shah JP, Ganly I. High rates of regional failure in squamous cell carcinoma of the hard palate and maxillary alveolus. *Head Neck* 2011;33:824-30.
- Montes DM, Carlson ER, Fernandes R, Ghali GE, Lubek J, Ord R, Bell B, Dierks E, Schmidt BL. Oral maxillary squamous carcinoma: an indication for neck dissection in the clinically negative neck. *Head Neck* 2011;33:1581-5.
- Kermer C, Poeschl PW, Wutzl A, Schopper C, Clemens K, Poeschl E. Surgical treatment of squamous cell carcinoma of the maxilla and

- nasal sinuses. *J Oral Maxillofac Surg* 2008;66:2449-53.
18. Lubek J, El-Hakim M, Salama AR, Liu X, Ord RA. Gingival carcinoma: retrospective analysis of 72 patients and indications for elective neck dissection. *Br J Oral Maxillofac Surg* 2011;49:182-5.
 19. Haddadin KJ, Soutar DS, Oliver RJ, Webster MH, Robertson AG, MacDonald DG. Improved survival for patients with clinically T1/T2, N0 tongue tumors undergoing a prophylactic neck dissection. *Head Neck* 1999;21:517-25.
 20. Woolgar JA, Scott J. Prediction of cervical lymph node metastasis in squamous cell carcinoma of the tongue/floor of mouth. *Head Neck* 1995;17:463-72.
 21. Meng FY, Ko JY, Lou PJ, Wang CP, Yang TL, Chang CH, Chang YL, Chen TC. The determining risk factors for treatment outcomes in patients with squamous cell carcinoma of the hard palate. *Ann Surg Oncol* 2012;19:2003-10.
 22. Lin HW, Bhattacharyya N. Survival impact of nodal disease in hard palate and maxillary alveolus cancer. *Laryngoscope* 2009;119:312-15.
 23. Truitt TO, Gleich LL, Huntress GP, Gluckman JL. Surgical management of hard palate malignancies. *Otolaryngol Head Neck Surg* 1999;121:548-52.
 24. Philip J, James R. Maxillary squamous cell carcinoma: an 11-year retrospective study of one regional cancer centre. *Int J Oral Maxillofac Surg* 2014;43:1195-8.
 25. Valentini V, Terenzi V, Battisti A, Cassoni A, Anelli A, Priore P, Petrinca P. Management of clinically negative neck in maxillary carcinoma. *J Craniofac Surg* 2010;21:759-62.
 26. Beltrami GA, Massarelli O, Demarchi M, Copelli C, Cassoni A, Valentini V, Tullio A, Gianni AB, Sesenna E, Baj A. Is neck dissection needed in squamous-cell carcinoma of the maxillary gingiva, alveolus, and hard palate? A multicentre Italian study of 65 cases and literature review. *Oral Oncol* 2012;48:97-101.
 27. Feng Z, Li JN, Li CZ, Guo CB. Elective neck dissection versus observation for cN0 neck of squamous cell carcinoma primarily located in the maxillary gingiva and alveolar ridge: a retrospective study of 129 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2013;116:556-61.
 28. Yang X, Song X, Chu W, Li L, Ma L, Wu Y. Clinicopathological characteristics and outcome predictors in squamous cell carcinoma of the maxillary gingiva and hard palate. *J Oral Maxillofac Surg* 2015;73:1429-36.
 29. Sagheb K, Sagheb K, Taylor KJ, Al-Nawas B, Walter C. Cervical metastases of squamous cell carcinoma of the maxilla: a retrospective study of 25 years. *Clin Oral Investig* 2014;18:1221-7.
 30. Dalal AJ, McLennan AS. Cervical metastases from maxillary squamous cell carcinoma: retrospective analysis and review of the literature. *Br J Oral Maxillofac Surg* 2013;51:702-6.
 31. Yang Z, Deng R, Sun G, Huang X, Tang E. Cervical metastases from squamous cell carcinoma of hard palate and maxillary alveolus: a retrospective study of 10 years. *Head Neck* 2014;36:969-75.
 32. Eskander A, Givi B, Gullane PJ, Irish J, Brown D, Gilbert RW, Hope A, Weinreb I, Xu W, Goldstein DP. Outcome predictors in squamous cell carcinoma of the maxillary alveolus and hard palate. *Laryngoscope* 2013;123:2453-8.
 33. Poeschl PW, Seemann R, Czembirek C, Russmueller G, Sulzbacher I, Selzer E, Selzer E, Nuhic D, Ewers R. Impact of elective neck dissection on regional recurrence and survival in cN0 staged oral maxillary squamous cell carcinoma. *Oral Oncol* 2012;48:173-8.
 34. Nicolai G, Lorè B, Prucher G, De Marinis L, Calabrese L. Treatment of N in the upper maxillary tumors. *J Craniofac Surg* 2010;21:1798-800.
 35. Zwetyenga N, Miquel L, Garuet A, Ricard AS, Majoufre-Lefebvre C, Demeaux H, Siberchicot F. Treatment of squamous-cell carcinoma of the upper gum and the hard palate. *Rev Stomatol Chir Maxillofac* 2006;107:80-5.
 36. Wang TC, Hua CH, Lin CC, Tsou YA, Tseng HC, Tsai MH. Risk factors affect the survival outcome of hard palatal and maxillary alveolus squamous cell carcinoma: 10-year review in a tertiary referral center. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010;110:11-7.
 37. Zhang WB, Wang Y, Mao C, Guo CB, Yu GY, Peng X. Cervical metastasis of maxillary squamous cell carcinoma. *Int J Oral Maxillofac Surg* 2015;44:285-91.
 38. Binahmed A, Nason RW, Hussain A, Abdoh AA, Sándor GK. Treatment outcomes in squamous cell carcinoma of the maxillary alveolus and palate: a population-based study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008;105:750-54.
 39. Givi B, Eskander A, Awad M, Kong Q, Montero PH, Palmer FL, Xu W, De Almeida JR, Lee N, O'Sullivan B, Irish JC, Gilbert R, Ganly I, Patel SG, Goldstein DP, Morris LG. Impact of elective neck dissection on the outcome of oral squamous cell carcinomas arising in the maxillary alveolus and hard palate. *Head Neck* 2016;38 Suppl 1:E1688-94.
 40. Berger M, Grau E, Saure D, Ristow O, Thiele O, Hofele C, Hoffmann J, Seeberger R, Freier K. Occurrence of cervical lymph node metastasis of maxillary squamous cell carcinoma-A monocentric study of 171 patients. *J Cranio Maxillofac Surg* 2015;43:2195-9.
 41. Troeltzsch M, Knösel T, Woodlock T, Troeltzsch M, Pianka A, Probst FA, Mast G, Ehrenfeld M, Otto S. Are there clinical or pathological parameters of maxillary oral squamous cell carcinoma with an influence on the occurrence of neck node metastasis? An appraisal of 92 patients. *J Oral Maxillofac Surg* 2016;74:79-86.
 42. Moreno-Sánchez M, González-García R, González-Ballester D, Ruiz-Laza L, Moreno-García C, Monje F. What is the role of elective neck dissection in patients with squamous cell carcinoma of the upper jaw? *Rev Esp Cir Oral Maxillofac* 2016; doi:10.1016/j.maxilo.2016.02.003.
 43. Robbins KT, Clayman G, Levine PA, Medina J, Sessions R, Shaha A, Som P, Wolf GT; American Head and Neck Society; American Academy of Otolaryngology-Head and Neck Surgery. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American academy of Otolaryngology-Head and Neck Surgery. *Arch Otolaryngol Head Neck Surg* 2002;128:51-8.
 44. Webber C, Gospodarowicz M, Sobin LH, Wittekind C, Greene FL, Mason MD, Compton C, Brierley J, Groome PA. Improving the TNM classification: findings from a 10-year continuous literature review. *Int J Cancer* 2014;135:371-8.

Contralateral neck dissection in oral squamous cell carcinoma: when it should be done?

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ABSTRACT

Oral cavity squamous cell carcinoma (OSCC) has a high incidence of cervical micrometastases and sometimes metastasizes bilaterally because of the rich lymphatics in the submucosal plexus, which freely communicate across the midline. The presence of contralateral pathologic lymph nodes has been reported previously as a critical factor influencing the survival of patients. There are a few reports in the literature with regard to the rates of contralateral neck disease and the factors that may be involved in the risk with them. An elective ipsilateral neck treatment is generally recommended for initial treatment in all OSCC. However, no consensus exists whether or not to perform an elective contralateral neck dissection or radiation. In this study, a systematic review has been performed in order to evaluate the predictive value of clinical-histopathologic factors potentially related to contralateral occult lymph node metastasis in squamous cell carcinomas of the oral cavity to form a rational basis for elective contralateral neck management.

Key words:

Contralateral neck dissection; squamous cell carcinoma; oral cavity; oral cancer

INTRODUCTION

Head and neck cancer is the fifth most common type of cancer worldwide, among all neoplasms. Approximately

40% of them occur in the oral cavity. Squamous cell carcinoma (SCC) is the most common histological type, with a frequency of approximately 90%. The presence

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of neck lymph node metastasis is the most significant prognostic and survival factor in patients with oral cavity squamous cell carcinoma (OSCC). With the exception of thin early-stage tumours in the context of clinically and radiologically node negative necks, most patients with OSCC undergo neck dissection.^[1] This has the benefit of treating occult metastatic disease and providing pathological staging information to direct adjuvant therapy.^[2,3] The rich lymphatic connections in the head and neck makes oral cavity malignancies susceptible to spread across the midline.^[4] The SCC of the oral cavity presents a variable frequency of contralateral lymph neck metastases (CLNM) between 0.9% to 36%, reported in the literature.^[5,6] The presence of such metastases decreases the survival rate of the patients, generating a poor prognosis.^[7] Although elective treatment of the contralateral neck is accepted for OSCC approaching or crossing the midline, this is not routinely performed in lateralized cases. Few studies have analyzed rates of contralateral neck disease in oral cancer and the factors that may be involved with them. In terms of treatment decision-making, the use of elective contralateral neck dissection remains controversial for patients with OSCC that does not cross the midline.

The purpose of this review was to evaluate the incidence of CLNM and analyze the factors that may predict their appearance in OSCC to form a rational basis for elective contralateral neck management.

METHODS

To address the research purpose, the authors designed and implemented a systematic review of the literature. The electronic search was performed in the Cochrane Library, MEDLINE via Pubmed and EMBASE using the key terms “contralateral neck dissection”, “contralateral metastases”, “oral squamous cell carcinoma” and “oral cancer”. Some of these terms were searched in combination. The references of each article obtained were checked for additional relevant studies. Only articles published in English were included in this study. One reviewer screened all titles and abstracts. A total of 103 references were retrieved, of which 34 were screened. The exclusion criteria were: (1) date of publication before 1999; (2) articles written in a language different from English; (3) required data not available; and (4) type of article: abstracts, letters, comments, editorials, expert opinions or case reports.

THE ROLE OF CLNM IN OSCC

The contralateral metastasis propagation can occur in the head and neck carcinoma in different ways: firstly, by crossing afferent lymphatic vessels, by tumor spread along the midline, when ipsilateral lymph nodes are widely involved, and secondly, in certain anatomical areas where there is not a real barrier in the midline.^[7]

The OSCC has a high incidence of micrometastases and often bilaterally metastases due to the rich submucosal lymphatic plexus, that communicates freely crossing the middle line.^[8] It presents a variable incidence of CLNM between 0.9% to 36%, reported in the literature. Diverse factors can be held responsible for such differences, among them the diversity of the anatomic regions considered for study, problems in clinical staging, and exclusion of cases not considered eligible for treatment. Kowalski *et al.*^[6] found a rate of 36% of contralateral positive nodes after bilateral neck dissection. Kurita *et al.*^[5] observed an incidence of CLNM in early oral tongue SCC of 12.2%. In the paper reported by Koo *et al.*^[8] the overall rate of occult contralateral metastasis in OSCC was 11%, and the rate was 21% in cases of ipsilateral pathologic metastasis. In the study of Bier Laning *et al.*^[9] the incidence was 10%. This corresponds to the findings of Mukherji *et al.*^[10] who found that oral tongue and floor-of-mouth cancers had an expected drainage to contralateral lymph nodes in up to 9% of cases. On the other hand, Lim *et al.*^[11] in their study detected only a 4% rate of contralateral occult metastases in a series of early tongue carcinomas and did not recommend elective contralateral neck treatment. González-García *et al.*^[12] in a large series of 315 patients with oral squamous cell carcinoma of the oral cavity, reported an incidence rate of 5.7% for CLNM, which is similar to the 5-year CLNM rate of 4.1% reported by Feng *et al.*^[13] while another large cohort study by Huang *et al.*^[14] showed a 7.1% 5-year CLNM rate.

In relation to prognosis, it has been widely accepted that CLNM dramatically reduce the long-term survival and prognosis in these patients is described as extremely poor.^[6,8,15,16] Capote-Moreno *et al.*^[7] reported a decrease in the 5-year survival rate in patients with OSCC, from 70% in patients with negative contralateral lymph nodes to 41.2% in those with CLNM. These rates were similar to those found by other authors; for example, Koo *et al.*^[8] found a 5-year cause-specific survival rate of 43% in patients with contralateral disease compared with 73% in metastasis-free patients in a series of 173 cases with oral and oropharyngeal SCC, which emphasizes the prognostic importance of CLNM.

With respect to the time of appearance, most studies corroborate that CLNM mainly happens within two years postoperatively.^[17-20] For instance, González-García *et al.*^[20] in a series of 203 patients with oral squamous cell carcinoma of the tongue, with especial consideration in excluding those cases involving the midline or at a distance less than 1 cm, reported CLNM occurring within the first 2 years after surgery in 89.9% of the affected patients. Therefore, special effort should be paid early detecting nodal relapse in the cervical region, while a careful follow-up is mandatory during this period of time.

PREDICTIVE FACTORS

Several clinical and pathological factors have been proposed

to be correlated with the risk of contralateral lymph node metastasis as well as with patient survival. We consider it important to analyze these factors. It is currently unclear whether CLNM are underestimated in OSCC patients at initial presentation. Therefore, correct identification of risk factors associated with CLNM is paramount to improve the clinical outcome of this patient group, especially because ultrasound diagnostic imaging and computed tomography scannings are not sensitive enough to sufficiently detect occult disease. Prediction of tumors at high risk for contralateral involvement may determine a better therapeutic management of the contralateral neck and may improve OSCC prognosis [Table 1].

Tumor location

One of the factors that has been speculated as a determinant prognosticator for contralateral metastases is tumor location, although there is not a clear consensus about which location is of higher risk for cross-metastases.

The importance of tumor midline involvement had been already exposed by Martin *et al.*^[21] Risk increased to 16% in cases with tumors crossing the midline by less than 1 cm and reached 46% in those where the crossing was of more than 1 cm. In the same way, Koo *et al.*^[8] also demonstrated that the rate of contralateral occult neck metastasis was significantly higher in cases in which the primary lesion showed extension across the midline, compared with early-stage or unilateral lesions. In a series including 513 consecutive cases, Kowalski *et al.*^[6] testified that the risks of CLNM were significantly higher in cases of tumors extending to 1 cm or less of the midline or crossing such medial margin (relative

risk from 2.8 to 12.7). In the study of Kurita *et al.*,^[5] patients with tumors showing radiological evidence of extension crossing the midline were at a higher risk for CLNM (53.8%) than patients without an extension crossing the midline (10.3%).

In relation to the location of the primary tumor, a higher risk for CLNM in patients with tumors of the floor of the mouth and the anterior third of the tongue in detriment of the retromolar region or the lateral gum has been reported.^[6] Cross-drainage in the oral tongue and floor of mouth cancer is common, thereby placing both sides of the neck at risk for nodal metastases, as reported in the study by Mukherji *et al.*^[10] Califano *et al.*^[22] found a higher rate of contralateral involvement in the base of the tongue even in early tumors than in the body and the tip of the tongue and recommended prophylactic bilateral neck dissection in all tongue base carcinomas. The data of Olzowy *et al.*^[23] also showed that tumors of the base of tongue had a higher risk of contralateral metastases than that of tumors of the tonsillar fossa. Moreover, although not statistically significant, tumors of the soft palate and the pharyngeal walls also seemed to have a higher risk of CLNM. Capote-Moreno *et al.*^[7] observed a higher tendency for contralateral metastases in tumors located in the tongue base (31.4%) and the floor of the mouth (11%), with a lower frequency in the mobile tongue (7.2%) and the oropharynx (6.3%). However, in the study of Kurita *et al.*,^[5] the incidence of CLNM was higher in cases of lower gum carcinoma (25%) than in those with mobile tongue carcinoma (15.4%). They suggested that the direction of tumor invasion is a more important factor for CLNM than the original tumor location in patients with

Table 1: Chart review of the main articles that analyze risk factors for CLNM

Study	Year	Number	Mean age (years)	Male:female	Follow-up (months)	CLNM (number of patients)	Predictive factors
Kowalski <i>et al.</i> ^[6]	1999	513	56.4	437:76	-	38	TNM stage and ipsilateral metastases
Kurita <i>et al.</i> ^[5]	2004	126	66	74:55	21	19	T-stage, ipsilateral metastases, and histo-pathologic grading
Koo <i>et al.</i> ^[8]	2006	66	53	52:14	44	7	T-stage and ipsilateral metastases
González-García <i>et al.</i> ^[20]	2007	203	59	72:28	71	9	Histo-pathologic grading and peritumoral inflammation
González-García <i>et al.</i> ^[12]	2008	315	60	222:93	> 5 years	18	TNM stage, histopathologic grading, surgical margins, ipsilateral neck dissection and perineural invasion
Liao <i>et al.</i> ^[31]	2009	913	49	852:61	> 24	55	ECS, tumor location, ipsilateral metastases and histo-pathological grading
Capote-Moreno <i>et al.</i> ^[7]	2010	402	59	293:109	> 12	20	ECS, tumor location, ipsilateral metastases and histo-pathological grading
Olzowy <i>et al.</i> ^[23]	2011	352	56.8	274:78	-	75	Tumor location, T-stage and ipsilateral metastases
Lin <i>et al.</i> ^[38]	2012	683	> 50	624:59	-	36/676	Tumor location and histo-pathologic grading
Feng <i>et al.</i> ^[13]	2014	1,482	60	822:66	> 5 years	35/844	ECS
Habib <i>et al.</i> ^[33]	2016	481	64	288:193	160	14	Ipsilateral metastases and histo-pathologic grading

CLNM: contralateral lymph neck metastases; TNM: tumor node metastasis; ECS: extracapsular spread

carcinoma that has originated laterally in the oral cavity.

Tumor size

The literature reports a strong correlation between the size of the primary and the risk of CLNM.^[24-28] A significant correlation between the T-stage and the occurrence of CLNM was observed by Kurita *et al.*^[5] In this study, the incidence of CLNM for the T4 tumor (31.4%) was relatively high compared to that for the T1 (0%) as well as the T2 (12.2%) and T3 tumor (11.8%). In addition, CLNM in patients with the T2 and T3 tumor occurred only in cases of the mobile tongue, but not in other sites. Excluding cases of the tongue SCC, CLNM was unlikely in patients with T1 to T3 oral carcinoma that had arisen in the unilateral side. In a retrospective analysis of 66 patients with cancer of the oral cavity at N0-2 stage, Koo *et al.*^[8] showed that the rate of contralateral occult metastasis was 8% for T2, 25% for T3, and 18% for T4, whereas no metastasis was observed in the T1 cases.

Tumor thickness

Tumor thickness has been recognized as an histological prognostic factor of local recurrence, cervical nodal metastasis, and survival. Bier-Laning *et al.*^[9] found an approximately 5% increased risk of CLNM for every 1-mm increase in tumor thickness. They did not find cases of CLNM when the primary tumor had a thickness less than 3.75 mm. So, they recommended that consideration should be given to observation of the contralateral neck for tumors less than 3.75 mm, neck dissection to the contralateral neck for tumors more than 3.75 mm thick, and treatment of the contralateral neck with surgery and/or radiation therapy if the tumor is more than 9.5 mm thick. This is compatible with the findings of others, in which the risk of ipsilateral nodal metastasis is increased in tumors thicker than 4-5 mm.^[29,30] Other authors, as González-García *et al.*^[12] failed to show tumoral thickness greater than 2 mm as predictive for CLNM, which could be attributable to the insufficient sample size where 7.1% of the patients with tumor thickness greater than 2 mm developed CLNM in comparison with 0% of the patients with tumor thickness less than 2 mm.

Infiltration of the cervical lymph nodes

In relation to cervical affectation, ipsilateral lymph node metastasis has been referred to as a significant predictor in assessing the risk to the contralateral neck. According to the statistical results of Kurita *et al.*,^[5] no CLNM occurred in patients without ipsilateral lymph node metastasis. In addition, the incidence of CLNM was higher in patients with multinode involvement (50%) than in those with single node involvement (26.1%). The study reported by Capote-Moreno *et al.*^[7] supported these results, in which 21.6% of the cases with positive homolateral nodes showed positive CLNM whereas contralateral disease developed in only 6.4% of the cases with negative homolateral nodes. This prognostic

variable, together with tumor extension across the midline, was the most important risk factor in the logistic regression analysis performed in this report. Other studies have also shown a significant correlation between the presence of ipsilateral and CLNM.^[6,8] In the study of Olzowy *et al.*^[23] patients with two or more ipsilateral neck metastases showed significantly more bilateral metastases compared with patients with fewer than two positive ipsilateral lymph nodes.

In contrast to these previous studies, González-García *et al.*^[20] did not find an association between the presence of clinical and pathological positive node status on the ipsilateral side of the neck and a higher incidence of contralateral cervical metastasis in SCC of the lateral side of the tongue.

Extracapsular spread

Transcapsular infiltration of lymph node metastases is another important prognostic factor that, although it can be found in smaller lymph nodes, is generally associated with lymph nodes with a diameter of more than 2 cm. In a retrospective study performed by Feng *et al.*,^[13] they demonstrated that extracapsular spread (ECS) status was correlated with 5-year CLNM. In a series of 913 patients, Liao *et al.*^[31] also showed that the 5-year CLNM rate was significantly higher in patients with ECS (39%) than in those without (12%). Furthermore, the 5-year overall survival was 48% in patients without ECS, whereas it dropped to 16% in those with ECS.

However, other authors such as Koo *et al.*^[8] did not find a statistical association between ECS and the occurrence of CLNM.

Clinical tumor node metastasis stage

It has been reported that patients with advanced tumors are at a higher risk for CLNM in OSCC.^[5,6,12] In the multivariate analysis performed by Kowalski *et al.*,^[6] it became clear that the risk of CLNM for patients with clinical stage (CS) I and II tumors not involving the floor of the mouth was low, even though it crossed midline (< 1 cm). On the other side, CS IV tumors that were less than 1 cm away from midline had a high risk of metastasis, independent of tumor original site. Frequency of such metastases was 33% for stage T4, 15% for CS III and 32% for CS IV. Risk of contralateral metastases was over 20% in stage T1-3 N2a-3 and T4 N0-3 M0 tumors. González-García *et al.*^[12] found in their series that 6.7% of patients with staging IV in the tumor node metastasis (TNM) classification developed CLNM, whereas only 2.6% of patients with TNM staging I showed CLNM.

Surgical margins

In relation to surgical resection, the absence of wide enough margins in the excised primary tumor has been reported to be a predictor for CLNM. Particularly, the presence of 1 cm or more of non-affected tissue around the tumor was considered adequate, in contrast to

specimens with less than 1 cm of non-affected tissue around the tumor. Illustratively, only 4% of patients in the first group developed CLNM in contrast to 11.6% of patients in the last group.^[12] Nason *et al.*^[32] found that each 1-mm increase in clear surgical margin decreased the risk of death at 5 years by 8%. Other authors have also demonstrated that surgical margins had a statistical association with a higher risk of CLNM developing.^[7]

Grade of histological differentiation

Histopathological grading is also an important predictive factor for the occurrence of CLNM in head and neck SCC. For Kurita *et al.*^[5] the risk for CLNM increased as the degree of histopathological grading advanced. In another study, González-García *et al.*^[12] also demonstrated a statistically significant association between histological grading and the appearance of CLNM and found that 13.5% of the patients with poor-differentiated SCC developed CLNM, in comparison with 5.2% of patients with well-differentiated tumors. Other authors also have identified poor tumour differentiation as a significant predictor.^[5,20,31,33]

Tumor satellite distance

Tumor satellites can be defined as separate islands of tumor cells at the tumor and nontumor interface. Tumor satellite distance (TSD) is the distance from the main tumor to the most distant tumor satellite and reflects the spreading ability of tumor satellites. In the literature, microsatellite tumor spreading was reported to reach as far as 1.8 cm.^[34] Yang *et al.*^[35] reported that TSD is significantly associated with the survival of patients with tongue cancer in areas of endemic betel nut consumption. In addition, increased TSD is associated with a higher incidence of local recurrence, shorter intervals to neck recurrence, and a higher tendency to contralateral or bilateral neck metastasis.

Perineural and lymphovascular invasion

Perineural infiltration of the primary tumor has been shown to be highly predictive for CLNM, as it was illustrated in the series of González-García *et al.*^[12] by the appearance of pathologic contralateral lymph neck nodes in 17.02% of patients with perineural infiltration, in comparison with 4.1% of those patients without perineural involvement. In the study of Capote-Moreno *et al.*,^[7] perineural invasion also turned out to be a relevant factor for contralateral metastases. Kowalski *et al.*^[6] suggested the presence of lymphovascular involvement, as well as of perineural infiltration, were significantly associated to higher rates of risk of CLNM in OSCC.

Peritumoral inflammation

A statistically significant association between the absence of peritumoral inflammation and the appearance of CLNM has been observed. A possible explanation for this association could be that a low host immunological

response around the primary tumour could allow easier dissemination of cancer cells through lymphatic drainage.^[20]

Local-regional recurrence

Local recurrence has been defined as an independent risk factor for CLNM in the study of Liao *et al.*^[31] Specifically, the percentage of CLNM was 18% (17/132) in patients with LR, and 5% (38/781) in those without.

TREATMENT OPTIONS

The possibility of occult CLNM in the OSCC requires a challenging decision: whether the contralateral neck should be electively treated or not. No consensus has been reached on the need for contralateral neck dissection (CND) or radiotherapy. Implications of such treatment on the contralateral side include the advantage of treating subclinical disease on the one hand, but on the other hand, because these cases have a poor prognosis, treatment may lead to a significant increase in morbidity and even mortality without improvement.

Neck dissection

Appropriate management of cervical lymph nodes is an important aspect of the treatment of patients with OSCC. Although elective treatment of the contralateral neck is accepted for oral cancers approaching or crossing the midline, this is not routinely performed in lateralized cases. Unfortunately, even with the use of elective CND for ipsilateral tumors crossing the midline, approximately one-third of neck lymph node recurrences occur at the contralateral site. So, it is unclear whether the use of elective CND may reduce incidence of contralateral neck recurrences in this patient group.

Various studies have failed to show a benefit in the survival rate from elective treatment of the contralateral neck.^[11,13,36] The reduced survival in some patients with OSCC appears to reflect aggressive disease biology with regional and/or distant failure in spite of salvage therapy, suggesting that elective treatment of the contralateral neck is unlikely to improve their prognosis. So, some surgeons advocate an observation-only policy for the contralateral neck. For example, Lim *et al.*^[11] examined 54 patients with early stage SCC of the oral tongue. The goal of this study was to determine if there was an outcome difference between patients who underwent observation of the contralateral neck (29 patients) versus the 25 patients who underwent bilateral elective neck dissection (END). Notably, 7 patients in the “observation” group underwent radiation therapy that included the contralateral neck. The incidence of recurrence at any site in this study was 17/54 (31%), with no recurrences in the contralateral neck. There was only 1 of 25 (4%) CNDs that showed occult malignancy. There was no significant difference in the disease-free survival between those

who underwent observation of the contralateral neck and those who underwent contralateral END, even when those in the observation group who received radiation therapy were excluded.

Although the reason for these findings is unclear, it has been suggested that END, in conjunction with primary tumor resection, may predispose patients to aberrant migration of intransit carcinomatous cells to the opposite side of the neck.^[12] Chow *et al.*^[28] failed to show bilateral neck dissections reduced the contralateral neck relapse by statistical testing. Remarkably, only 1 of the 12 patients undergoing bilateral neck dissection as part of their definitive treatment developed contralateral nodal recurrence. In contrast, 8 of the 46 patients undergoing only ipsilateral neck dissection developed contralateral or bilateral nodal recurrence. In the same way, for González-García *et al.*^[12] unilateral cervical dissection was predictive for CLNM. In fact, only 1.8% of the patients that primarily underwent bilateral neck dissection developed CLNM, in comparison with 7.4% of those patients undergoing unilateral neck dissection. Remarkably, only 2 of 64 patients undergoing bilateral neck dissection as definitive treatment developed CLNM. In contrast, 14 of 149 patients undergoing ipsilateral neck dissection developed CLNM. However, despite these results, they stated that the low reported incidence of CLNM and the added morbidity supported recommendation for bilateral neck dissection in selected patients with tumors primarily arising in the midline.

Lanzer *et al.*^[4] did neither show a statistical benefit of elective CND in patients with contralateral clinically negative neck. Neither locoregional recurrence-free survival nor overall survival rates differed.

In another study, performed by Liao *et al.*,^[31] the independent risk factors for the 5-year CLNM rate were poor differentiation, perineural invasion, and level IV/V lymph node metastases. A prognostic scoring system was thus formulated by summing up the three significant factors identified by multivariate analysis. In order to reduce the incidence of CLNM, CND and adjuvant therapy were recommended in high-risk patients with tongue cancer [score 2-3, 5-year nonrenal clearance rate (CLNR) 40%]. In the intermediate-risk group (score 1, 5-year CLNR 15%), neck ultrasound examinations were recommended every 3 months until 24 months postoperatively. Observation should be considered sufficient for low-risk patients (score 0, 5-year CLNR 3%).

In a recent study by Fan *et al.*,^[37] all indications for contralateral END in oropharyngeal SCC were summarised as leading to: (1) tumours crossing the midline; (2) advanced staging (cT34); (3) primary tumour more than 3.75 mm thick; (4) multiple ipsilateral node involvement; and (5) tumours arising in the base of the tongue and floor of the mouth.

The location of the primary tumor plays an important role in other studies. The carcinoma of the base of tongue seems to have a high propensity to produce bilateral neck metastases. For Olzowy *et al.*,^[23] in the case of involvement of the base of tongue, the neck should be operated on bilaterally, independent of T classification of the primary. In carcinomas of the soft palate greater than T1, bilateral neck dissection should also be recommended because of a high frequency of bilateral metastases. For Lin *et al.*,^[38] prophylactic CND is suggested for primary oral tumors with mouth floor invasion or midline crossing, or at advanced tumor stage (> T3). This recommendation is not supported by most authors.

In summary, despite facing a high number of occult lymph node metastasis in the ipsilateral and contralateral neck in oral cancer, the locoregional recurrence rate seems to be low. Surgeons should take into account the detailed and individual study of risks and potential benefits of elective neck treatment for contralateral N0 neck while considering the small percentage of patients with oral carcinoma that finally develop CLNM.

Adjuvant radiotherapy

The alternative to the bilateral neck dissection is radiotherapy (RT) of the contralateral neck in the case of a relevant risk of bilateral metastases, particularly in patients receiving planned adjuvant RT postoperatively. In this way, Capote-Moreno *et al.*^[7] recommended bilateral treatment of the neck with surgery or RT in patients with several risk factors. On the other hand, Koo *et al.*^[8] showed that the patients who received adjuvant RT had a lower locoregional control and survival rate compared with those who did not receive adjuvant RT. However, this was attributed to the fact that the patients who received adjuvant RT were those who had an advanced-stage disease or worse prognosis, which would have affected the locoregional control and survival rate. Finally, they suggested elective contralateral neck management with surgery or RT in the treatment of OSCC patients with ipsilateral node metastasis and/or those with tumors either greater than stage T3 or crossing the midline.

The results of the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer trials have provided evidence that in patients with head and neck cancer surgery plus concomitant chemoradiation (CCRT) had a better impact on clinical outcome compared with surgery plus RT.^[39,40] The benefits of CCRT were especially evident in head and neck cancer patients with positive margins and ECS.^[40] In the study performed by Feng *et al.*,^[13] postoperative CCRT compared with surgery alone improved the 5-year disease-specific survival in these high-risk patients but did not decrease the 5-year CLNM rate. However, it is important to take in mind that the use of CCRT in the adjuvant setting, which is highly toxic, may cause immunosuppression.^[41] For these authors, whether high-risk patients benefit from

contralateral neck dissection plus adjuvant CCRT can only be answered in a prospective trial.

To come to conclusions, when RT is employed as the elective treatment modality, the threshold for treating the contralateral neck is low, taking in mind the difficulty of future treatment in cases of recurrence, and the relative low additional morbidity associated with the therapy. Thus, in patients at a moderate-high risk of developing CLNM, contralateral neck should be included in the radiation field.

CONCLUSION

The OSCC presents a variable incidence of CLNM, reported between 0.9% to 36% and it has been widely accepted that CLNM dramatically reduce long-term survival and prognosis. Several predictive factors have been proposed to be correlated with the risk of contralateral lymph node metastasis, such as tumor location, size or thickness, ipsilateral lymph node metastasis, ECS, TNM stage, surgical margins, grade of histological differentiation, tumor satellite distance, perineural and lymphovascular invasion, peritumoral inflammation and local recurrence.

It is important for clinicians to pay careful attention to these prognostic variables that must be globally considered for each individual case. Surgeons should take into account the detailed and individual study of risks and potential benefits of elective neck treatment for contralateral N0 neck while considering a small percentage of patients with oral carcinoma that finally develop CLNM.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Fasunla AJ, Greene BH, Timmesfeld N, Wiegand S, Werner JA, Sesterhenn AM. A meta-analysis of the randomized controlled trials on elective neck dissection versus therapeutic neck dissection in oral cavity cancers with clinically node-negative neck. *Oral Oncol* 2011;47:320-4.
2. Campana JP, Meyers AD. The surgical management of oral cancer. *Otolaryngol Clin North Am* 2006;39:331-48.
3. Jalisi S. Management of the clinically negative neck in early squamous cell carcinoma of the oral cavity. *Otolaryngol Clin North Am* 2005;38:37-46.
4. Lanzer M, Zemmann VV, Lubbers TH, Kruse A, Reinisch S. Do patients with oral and oropharyngeal squamous cell carcinoma benefit from elective contralateral neck dissection? A long-term analysis. *Head Neck Oncol* 2012;4:70-5.
5. Kurita H, Koike T, Narikawa J, Sakai H, Nakatsuka A, Uehara S, Kobayashi H, Kurashina K. Clinical predictors for contralateral neck lymph node metastasis from unilateral squamous cell carcinoma in the oral cavity. *Oral Oncol* 2004;40:898-903.
6. Kowalski LP, Bagietto R, Lara JR, Santos RL, Tagawa EK, Santos IR. Factors influencing contralateral lymph node metastasis from oral carcinoma. *Head Neck* 1999;21:104-10.
7. Capote-Moreno A, Naval L, Muñoz-Guerra MF, Sastre J, Rodríguez-Campo FJ. Prognostic factors in uncinct contralateral neck lymph node metastases in oral and oropharyngeal carcinoma. *J Oral Maxillofac Surg* 2010;68:268-75.
8. Koo BS, Lim YC, Lee JS, Choi EC. Management of contralateral N0 neck in oral cavity squamous cell carcinoma. *Head Neck* 2006;28:896-901.
9. Bier-Laning CM, Durazo-Arvizu R, Muzaffar K, Petruzzelli GJ. Primary tumor thickness as a risk factor for contralateral cervical metastases in T1/T2 oral tongue squamous cell carcinoma. *Laryngoscope* 2009;119:883-8.
10. Mukherji SK, Armao D, Joshi VM. Cervical nodal metastases in squamous cell carcinoma of the head and neck: what to expect. *Head Neck* 2001;23:995-1005.
11. Lim YC, Lee JS, Koo BS, Kim SH, Kim YH, Choi EC. Treatment of contralateral N0 neck in early squamous cell carcinoma of the oral tongue: elective neck dissection vs. observation. *Laryngoscope* 2006;116:461-5.
12. González-García R, Naval-Gías L, Rodríguez-Campo FJ, Sastre-Pérez J, Muñoz-Guerra MF, Gil-Díez Usandizaga JL. Contralateral lymph node metastasis of squamous cell carcinoma of the oral cavity: a retrospective analytic study in 315 patients. *J Oral Maxillofac Surg* 2008;66:1390-8.
13. Feng Z, Niu LX, Yuan Y, Peng X, Guo CB. Risk factors and treatment of contralateral neck recurrence for unilateral oral squamous cell carcinoma: a retrospective study of 1482 cases. *Oral Oncology* 2014;50:1081-8.
14. Huang SF, Wei FC, Liao CT, Wang HM, Lin CY, Lo S, Huang JJ, Chen IH, Kang CJ, Chien HT, Chen HH. Risk stratification in oral cavity squamous cell carcinoma by preoperative CRP and SCC antigen levels. *Ann Surg Oncol* 2012;19:3856-64.
15. Shingaki S, Takada M, Sasai K, Bibi R, Kobayashi T, Nomura T, Saito C. Impact of lymph node metastasis on the pattern of failure and survival in oral carcinomas. *Am J Surg* 2003;185:278-84.
16. Greenberg JS, El Naggar AK, Mo V, Roberts D, Myers JN. Disparity in pathologic and clinical lymph node staging in oral tongue carcinoma. *Cancer* 2003;98:508-15.
17. Jang WI, Wu HG, Park CI, Kim KH, Sung MW, Kim MJ, Choung PH, Lee JH, Chao JY. Treatment of patients with clinically lymph node-negative squamous cell carcinoma of the oral cavity. *Jpn J Clin Oncol* 2008;38:395-401.
18. Vandenbrouck C, Sancho-Garnier H, Chassagne D, Saravane D, Cachin Y, Micheau C. Elective versus therapeutic radical neck dissection in epidermoid carcinoma of the oral cavity: results of a randomized clinical trial. *Cancer* 1980;46:386-90.
19. Snow GB, Annas AA, van Slooten EA, Bartelink H, Hart AA. Prognostic factors of neck node metastasis. *Clin Otolaryngol Allied Sci* 1982;7:185-92.
20. González-García R, Naval-Gías L, Sastre-Pérez J, Rodríguez-Campo FJ, Muñoz-Guerra MF, Gil-Díez Usandizaga JL, Diaz-Gonzalez FJ. Contralateral lymph node metastasis of primary squamous cell carcinoma of the tongue: a retrospective analytic study of 203 patients. *Int J Oral Maxillofac Surg* 2007;36:507-13.
21. Martin H, Del Valle B, Ehrlich H, Cahan WG. Neck dissection. *Cancer* 1951;4:441-99.
22. Califano L, Zupi A, Mangone GM, Longo F, Coscia G, Piombino P. Surgical management of the neck in squamous cell carcinoma of the tongue. *Br J Oral Maxillofac Surg* 1999;37:320-3.
23. Olzowy B, Tsalemchuk Y, Schotten KJ, Reichel O, Harréus U. Frequency of bilateral cervical metastases in oropharyngeal squamous cell carcinoma: a retrospective analysis of 352 cases after bilateral neck dissection. *Head Neck* 2011;33:239-43.
24. Woolgar JA, Rogers S, West CR, Errington RD, Brown JS, Vaughan ED. Survival and patterns of recurrence in 200 oral cancer patients treated by radical surgery and neck dissection. *Oral Oncol* 1999;35:257-65.
25. Gallo O, Fini-Storchi I, Napolitano L. Treatment of the contralateral negative neck in supraglottic cancer patients with unilateral node metastases (N1-3). *Head Neck* 2000;22:386-92.
26. Woolgar JA. The topography of cervical lymph node metastases revisited: the histological findings in 526 sides of neck dissection from 439 previously untreated patients. *Int J Oral Maxillofac Surg* 2007;36:219-25.
27. Lim YC, Lee SY, Lim JY, Lim JY, Shin HA, Lee JS, Koo BS, Kim SH, Choi EC. Management of contralateral N0 neck in tonsillar squamous cell carcinoma. *Laryngoscope* 2005;115:1672-5.
28. Chow TL, Chow TK, Chan TT, Yu NF, Fung SC, Lam SH. Contralateral

- neck recurrence of squamous cell carcinoma of oral cavity and oropharynx. *J Oral Maxillofac Surg* 2004;62:1225-8.
29. Hayashi T, Ito J, Taira S, Katsura K. The relationship of primary tumor thickness in carcinoma of the tongue to subsequent lymph node metastasis. *Dentomaxillofac Radiol* 2001;30:242-5.
 30. Kurokawa H, Yamashita Y, Takeda S, Zhang M, Fukuyama H, Takahashi T. Risk factors for late cervical lymph node metastases in patients with stage I or II carcinoma of the tongue. *Head Neck* 2002;24:731-6.
 31. Liao CT, Huang SF, Chen IH, Chang JT, Wang HM, Ng SH, Hsueh C, Lee LY, Lin CH, Cheng AJ, Yen TC. Risk stratification of patients with oral cavity squamous cell carcinoma and contralateral neck recurrence following radical surgery. *Ann Surg Oncol* 2009;16:159-70.
 32. Nason RW, Binahmed A, Pathak KA, Abdoh AA, Sándor GK. What is the adequate margin of surgical resection in oral cancer? *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;107:625-9.
 33. Habib M, Murgasen J, Gao K, Ashford B, Shannon K, Ebrahimi A, Clark JR. Contralateral neck failure in lateralized oral squamous cell carcinoma. *ANZ J Surg* 2016;86:188-92.
 34. Brandwein-Gensler M, Teixeira MS, Lewis CM, Lee B, Rolnitzky L, Hille JJ, Genden E, Urken ML, Wang BY. Oral squamous cell carcinoma: histologic risk assessment, but not margin status, is strongly predictive of local disease-free and overall survival. *Am J Surg Pathol* 2005;29:167-78.
 35. Yang TL, Wang CP, Ko JY, Lin CF, Lou PJ. Association of tumor satellite distance with prognosis and contralateral neck recurrence of tongue squamous cell carcinoma. *Head Neck* 2008;30:631-8.
 36. Donaduzzi LC, De-Conto F, Kuze LS, Rovani G, Flores ME, Pasqualotti A. Occurrence of contralateral lymph neck node metastasis in patients with squamous cell carcinoma of the oral cavity. *J Clin Exp Dent* 2014;6:209-13.
 37. Fan S, Tang QL, Lin YJ, Chen WL, Li JS, Huang ZQ, Yang ZH, Wang YY, Zhang DM, Wang HJ, Dias-Ribeiro E, Cai Q, Wang L. A review of clinical and histological parameters associated with contralateral neck metastases in oral squamous cell carcinoma. *Int J Oral Sci* 2011;3:180-91.
 38. Lin TC, Tsou YA, Bau DT, Tsai MH. Factors influencing contralateral neck metastasis in oral squamous cell carcinoma. *Formosan J Surg* 2012;45:83-7.
 39. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, Kish JA, Kim HE, Cmelak AJ, Rotman M, Machtay M, Ensley JF, Chao KS, Schultz CJ, Lee N, Fu KK; Radiation Therapy Oncology Group 9501/ Intergroup. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous cell carcinoma of the head and neck. *N Engl J Med* 2004;350:1937-44.
 40. Bernier J, Dumenil C, Ozsahin M, Matuszewska K, Lefèbvre JL, Greiner RH, Giral J, Maingon P, Rolland F, Bolla M, Cognetti F, Bourhis J, Kirkpatrick A, van Glabbeke M; European Organization for Research and Treatment of Cancer Trial 22931. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 2004;350:1945-52.
 41. Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, Ozsahin EM, Jacobs JR, Jassem J, Ang KK, Lefèbvre JL. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC and RTOG. *Head Neck* 2005;27:843-50.

The role of salvage surgery in oral squamous cell carcinoma

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ABSTRACT

Aim: To select and analyze the most representative papers published in the literature concerning oral squamous cell carcinoma (OSCC), specifically dealing with salvage surgery following primary treatment by surgery with or without by postoperative radiotherapy, specifically focusing in the oral cavity and oropharynx locations. **Methods:** A bibliography search on MEDLINE and EMBASE databases for studies published from March 2000 to March 2016 was conducted. The authors only included studies published in the English language and those dealing with "squamous cell carcinoma of the oral cavity and/or oropharynx". The following technical bibliographic exclusion criteria were applied: (1) case reports; (2) technical report; (3) animal or *in vitro* studies; (4) review articles; (5) uncontrolled clinical studies; and (6) publications in which the same data were published by the same group of researchers. The abstracts of yielded results were reviewed and the full text of those with apparent relevance was obtained. **Results:** A total amount of 188 studies were found using the above reported searching parameters. Thirteen original papers were finally selected according to the inclusion and exclusion criteria. From 1,692 analyzed patients, overall recurrence rate was 26% (range: 15-41.7%), with a mean 47.3%, 35.1% and 10.9% local, regional and loco-regional recurrence, respectively. Mean 5-year overall survival rate was 40.2% (range: 37.5-42.9%). **Conclusion:** Salvage surgery is the best option for the treatment of recurrent OSCC, either local, regional or loco-regional, with the highest rates in terms of survival and with an acceptable morbidity.

Key words:

Salvage surgery; oral squamous cell carcinoma; recurrent oral cancer

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INTRODUCTION

Nowadays, recurrence in oral squamous cell carcinoma (OSCC) remains the main cause for failure in oral cancer patients, despite advances in surgical techniques and chemo-radiotherapy (CRT) protocols. In fact, treatment of OSCC with radical surgery followed by radiotherapy (RT) has been reported to be unsuccessful in 25% to 48% of the cases.^[1] This recurrence can be local-oral cavity or oropharynx-, regional- in the neck, ipsilateral, contralateral or both-, or loco-regional. Today, salvage surgery is generally considered to be the best choice for treating recurrent OSCC patients that have been previously irradiated, although cure rates are still poor. Also, when dealing with regional recurrences, primary treatment seems to determine overall outcome following salvage surgery, with poorer rates in previously irradiated and surgically treated necks.^[2]

Otherwise two conditions are mandatory for this subset of patients to undergo salvage surgery: (1) the recurrence has still to be resectable in terms of resectability criteria within the head and neck region; and (2) the patient has to be operable in terms of anesthesiologic criteria. Other eligible options are generally behind in terms of curative intention such as re-irradiation or CRT, while palliative chemotherapy and supportive care are reserved for non-curative patients.

In considering the treatment to be performed, especially for those patients with advanced recurrences, there is a trend to outweigh the importance of quality of life for the patient, even more than in the first approach to the disease, in which survival is far from any other consideration, such as function and aesthetic impairment. Moreover if one takes into consideration that many of these advanced recurrent patients may undergo a permanent tracheostomy and/or a gastrostomy, a realistic evaluation of the probability of cure versus the generated morbidity has to be evaluated and sincerely approached with the patient and his/her family before salvage surgery is to be offered for the recurrent patient.

The purpose of the present study was to select and analyze the most representative papers published in the literature concerning OSCC, specifically dealing with salvage surgery following primary treatment by surgery with or without by postoperative radiotherapy, specifically focusing in the oral cavity and oropharynx locations.

METHODS

A bibliography search on MEDLINE and EMBASE databases for studies published from March 2000 to March 2016 was conducted, with the searching terms: ("salvage therapy" [MeSH Terms] OR ("salvage" [All Fields] AND "therapy" [All Fields]) OR "salvage therapy" [All Fields] OR "salvage" [All Fields] AND ("surgery, oral" [MeSH Terms]

OR ("surgery" [All Fields] AND "oral" [All Fields]) OR "oral surgery" [All Fields] OR ("surgery" [All Fields] AND "oral" [All Fields]) OR "surgery, oral" [All Fields]) AND ("carcinoma, squamous cell" [MeSH Terms] OR ("carcinoma" [All Fields] AND "squamous" [All Fields] AND "cell" [All Fields]) OR "squamous cell carcinoma" [All Fields] OR ("squamous" [All Fields] AND "cell" [All Fields] AND "carcinoma" [All Fields])). References were explored to identify other articles.

A total amount of 188 studies were found using the above reported searching parameters. We only included studies published in the English language and those dealing with "squamous cell carcinoma of the oral cavity and/or oropharynx", excluding those exclusively referring to the larynx, hypopharynx or other sites of the head and neck, such as paranasal sinuses or salivary gland neoplasms. If an overall approach to multiple locations of the upper aero-digestive tract was performed in a particular study, only those locations referred to the oral cavity and/or oropharynx were taken into consideration regarding data output, if available. However, if no specific data was offered for "oral cavity" and "oropharynx" and only general data was offered, then the series was rejected for inclusion in the meta-analysis. Articles dealing with CRT as the salvage treatment of choice for recurrent tumors were also excluded from this review. Besides, articles specifically focusing on the reliability of the used reconstructive method or surgical technique were not considered if data referring to prognosis and/or survival analysis was not performed.

Then, a manual screening of articles' abstracts was performed in order to explore the role of salvage surgery in squamous cell carcinoma of the oral cavity and oropharynx from the ultimate complete 16 years. The following technical bibliographic exclusion criteria were applied: (1) case reports; (2) technical reports; (3) animal or *in vitro* studies; (4) review articles; (5) uncontrolled clinical studies; and (6) publications in which the same data were published by the same group of researchers. The abstracts of yielded results were reviewed and the full text of those with apparent relevance was obtained. The references of identified articles were crosschecked for unidentified articles. The author carefully assessed the eligibility of all studies retrieved from the databases. A total amount of 13 original papers were finally selected according to the provided inclusion and exclusion criteria.

RESULTS

Summary of results from the selected studies

From the review of the selected papers, several common weakness among them have to be highlighted, such as the difficulty in establishing prospective series of patients submitted for different treatment modalities, the variation in the series' size, and the lack of homogeneity

Table 1: Selected studies from systematic review and meta-analysis

	Recurrent patients' series size (n)	Overall series size (n)	Overall recurrence rate (%)	Local recurrence n (%)	Regional recurrence n (%)	Loco-regional recurrence n (%)	5-year overall survival after salvage surgery (%)
Schwartz <i>et al.</i> ^[3] 2000	38	135*	28%	-	-	-	21%
Kowalski ^[4] 2002	214	513	41.7%*	-	82 (38.3%)	-	31-36%
Lin <i>et al.</i> ^[1] 2004	56	191	29.3%*	-	-	-	38-60%
Agra <i>et al.</i> ^[5] 2006	246	-	-	154 (62.6%)	59 (24%)	33 (13.4%)	32%
Koo <i>et al.</i> ^[6] 2006	36	127	28%	15 (41.7%)	13 (36.1%)	3 (8.3%)	38%
Brown <i>et al.</i> ^[7] 2007	98	462	21%	48 (59.2%)	34 (34.7%)	16 (16.3%)	-
Liao <i>et al.</i> ^[8] 2008	272	953	28.5%	133 (48.9%)	139 (51.1%)	-	36%
Lim and Choi ^[9] 2008	16	76	21%	5 (31.2%)	8 (50%)	2 (12.5%)	36%
Zafereo <i>et al.</i> ^[17] 2009	434	1681	26%	199 (45.8%)	53 (12.2%)	-	28%
Kernohan <i>et al.</i> ^[10] 2010	117	533	22%*	39 (33.3%)	38 (32.5%)	-	50%
Sklenicka <i>et al.</i> ^[11] 2010	24	157	15%	11 (45.8%)	9 (37.5%)	1 (4.1%)	48%
Kostrzewa <i>et al.</i> ^[12] 2010	72	-	-	-	-	-	44%
Goto <i>et al.</i> ^[13] 2016	69	-	-	-	-	-	48-86%
Overall results^a (González-García, 2016)	1,692	-	26%	47.3%	35.1%	10.9%	40.2% (37.5-42.9%)

*Indirectly calculated by the author from data provided in respective publications; ^aOverall results from recalculation of variables in previous analyzed studies, considering only articles with available data in relation to each particular variable

for inclusion/exclusion criteria and treatment protocols among institutions. All these features make quantitative analysis of results difficult if bias wants to be dismissed. The following paragraphs in the results section will deal with the description of the main results provided by the authors of the 13 selected papers in a chronologic manner [Table 1]. Further qualitative analysis of these results will be individually approached in the discussion section.

Up in the beginning of the 21st century, Schwartz *et al.*^[3] in a retrospective study about 38 patients that had developed recurrence of oral cavity SCC, reported an overall recurrence rate of 28%, with a local recurrence of 58%, a loco-regional recurrence of 27% and an isolated regional recurrence of 16%. With an overall salvage cure rate of 21%, they found that those patients receiving surgery as salvage treatment modality significantly improved in terms of survival time with respect to those treated with chemotherapy and/or RT, while cure rate trended to signification ($P = 0.08$). Interestingly, primary tumor staging was predictive for improved survival time but not for improved cure rate, while recurrent tumor staging was not predictive for any of them. In a general approach, among patients with recurrence, those who had primary tumors stage I-II, those having recurred after 6 months of initial treatment and those being amenable to surgical resection had better prognosis.

Kowalski *et al.*^[4] in a series of 513 patients with OSCC, observed an overall recurrence rate of 41.7%, with 82 (16%) patients showing a regional recurrence. Only 36 (44%) patients were amenable to salvage surgery, with an overall survival after salvage surgery of 31% to 36%, depending on the location of the recurrence in the ipsi- or contra-lateral neck. The authors found that patient's previously undergoing treatment of the neck experimented a poorer

survival after recurrence than those not previously treated, and concluded that patients with neck recurrences have a poor prognosis despite salvage surgery.

In a series of 191 patients receiving curative intended surgery for SCC of the oral cavity, Lin *et al.*^[1] isolated 56 patients with recurrence, for whom salvage surgery was performed. By defining "early recurrence" as a localized tumor less than 4 cm, without bone invasion in the computed tomography (CT)-scan, and "late recurrence" as a tumor larger than 4 cm with bone invasion that presented as a lymph neck node or a diffuse invasion in the CT scan, they found a 5-year disease-free survival rate of 24%, with 32% of patients free of disease if an early recurrence was detected, in comparison to only 16% of patients free of disease if a late recurrence was treated. They also reported an acceptable overall 5-year survival rate of 60% for early recurrences, in contrast to 38% if recurrences were late.

Agra *et al.*^[5] in 2006, studied 246 patients with recurrent SCC of the oral cavity and oropharynx who underwent salvage surgery from a single institution. They found a statistical significant better 5-year overall survival in favor of: (1) early (I/II) (43.6%) versus late recurrent clinical tumor, node, and metastasis stages (III/IV) (29.1%), $P = 0.027$; (2) disease free interval more than 1 year (42.1%) versus less than one year (26.7%), $P = 0.023$; and (3) previous treatment by surgery alone (39.3%) versus surgery followed by RT (26.1%) or RT alone (25.3%), $P = 0.028$. There were no differences in relation to survival according to the period of admission, sex, age, type of recurrence, and status of surgical margins. Patients with recurrent cancer of the oral cavity showed a higher 5-year overall survival rate than patients with recurrent oropharyngeal cancer (33.6% vs. 25.6%), although this difference was not

statistically significant ($P = 0.226$). Similarly, Koo *et al.*,^[6] in a series about 127 patients with OSCC observed a 28% overall recurrence rate, with a 12% local recurrence, 13% regional recurrence, and 2% loco-regional. They reported a 5-year overall survival rate of 38% and the mean interval free of disease higher than in 18%.

In a well-known study by Brown *et al.*^[7] about a series of 462 patients with OSCC treated by surgery followed or not by postoperative RT, they found an overall recurrence rate of 21%, with a 10.4%, 7.35% and 3.46% of local, regional and loco-regional recurrence rates, respectively. They wanted to study the hypothetical benefit of post-operative RT in the group of patients at intermediate risk of recurrence, and observed that a significant higher proportion of patients undergoing adjuvant RT had loco-regional recurrence (24%) compared to those treated by surgery alone (15%). They also found an improved salvage rate for recurrent disease in the surgery alone group (53%) in comparison to the postoperative RT group (13%).

Liao *et al.*,^[8] in a series of 272 recurrent OSCC patients, found an overall recurrence rate of 28.5%, with a local recurrence of 48.9% and a regional recurrence of 51.1%. They observed that the cutoff point at 10 months from the initial treatment has the worst prognosis in terms of 5-year disease-specific survival (DSS) and overall survival (OS). They found that a late-relapse was associated with better survival than an early-relapse occurring within the first 10 months after primary treatment. Considering treatment in patients with early-relapsed OSCC, a significant benefit was demonstrated for salvage treatment (salvage surgery with or without RCT), in terms of both 5-year DSS and OS. Similarly, in patients with a late-recurrence OSCC, a significant improvement in both 5-year DSS and OS rates were observed for salvage therapy. It is interesting to note that salvage surgery was significantly better than salvage RCT for patients with late-relapsed OSCC but not for early-relapsed OSCC.

In 2008, Lim and Choi^[9] found recurrences of OSCC to appear in 21% of the patients with T1 and T2 tumors primarily treated with surgery alone, with 31% and 50% local and regional recurrence rates, respectively. They encountered a 36% OS rate for recurrent patients following salvage surgery. This recurrent rate is very similar to that reported by Brown *et al.*^[7] and also by Kernohan *et al.*^[10] with a 22% recurrence rate. These authors also reported a quite high OS of 50% for recurrent patients. Meanwhile, in a short series by Sklenicka *et al.*,^[11] in 2010, they found a 15% recurrence rate, with 67% of recurrent patients undergoing further salvage surgery and an estimated 5-year disease-free survival of 48% for the whole series.

Kostrzewa *et al.*,^[12] in a series of 72 recurrent OSCC patients that underwent salvage surgery, observed a 44% OS rate. These authors did not encounter a significant association

between OS following salvage surgery and restaging after recurrence or margin status following surgical salvage. Conversely, they demonstrated a significant association between survival and time to recurrence, showing that recurrences within the first 6 months from the primary treatment had a worse prognosis.

According to Goto *et al.*,^[13] in a series of 69 recurrent OSCC, the 5-year OS rate for those patients undergoing salvage surgery ranged from 86% in recurrent stage I or II to 48% in recurrent stage III or IV. Their multivariate analysis identified extra-capsular spread (ECS) as an independent prognostic factor for OS following salvage surgery, with patients presenting ECS at salvage surgery having a 37% 5-year OS rate, in contrast to 78% for those do not presenting ECS.

Overall results from the systematic review

Several articles in the primary literature search evaluated recurrence and overall survival rates in relation to “head and neck cancer” or “squamous cell carcinoma” of the “upper aerodigestive tract”, including oral cavity, oropharynx, hypopharynx and larynx subsites. As categorization was not always performed by the authors and results specifically dealing with OSCC were not either supported, these series were systematically excluded from our study. Thus, only those series specifically dealing with recurrence and overall survival at the oral cavity and/or oropharynx were selected and included for the analysis [Table 1].

From the finally analyzed 13 articles, a recalculation of the values within selected variables was performed. For their calculation, only those articles with available data in relation to a specific variable were selectively chosen. A total number of 1,692 patients with recurrent OSCC were included from the author’s selection, ranging from 16 patients corresponding to the lower series to 434 patients from the largest one. The recalculated overall recurrence rate from the meta-analysis was 26% (range: 15-41.7%), with a mean 47.3%, 35.1% and 10.9% of local, regional and loco-regional recurrences, respectively.

Except for a single paper, the 5-year OS rate was present in all selected papers. Regarding the survival expressed in terms of 5-year OS rate, a mean value of 40.2% (range: 37.5-42.9%) was obtained from the meta-analysis. Three particular series showed their results concerning survival in terms of categorization upon early stage (I/II) or advanced stage (III/IV), and thus two values for the variable 5-year OS rate were provided. This could explain the observed range of survival rates between 37.5% and 42.9%.

DISCUSSION

Survival of recurrent OSCC patients

Although some classical studies^[14,15] advocated for

the use of only palliative treatment in recurrent oral cancer, mainly in advanced cancer previously treated with surgery and radiotherapy, actually a main role for curative treatment is advocated, basically by means of salvage surgery. In a meta-analysis by Goodwin *et al.*,^[16] a 5-year overall survival rate of 43% was reported for recurrent SCC of the oral cavity, while a 26% was referred for recurrent SCC of the oropharynx. In the study by Agra *et al.*^[5] the overall 5-year survival rate was 32.3%, with a 33.6% for the SCC of the oral cavity and a 25.6% for SCC of the oropharynx. Even, for advanced clinical stage recurrences (rCS III/IV), an overall 29.1% 5-year overall survival was found. Zafereo *et al.*^[17] found a 3-year and 5-year OS rates for salvage surgery of 42% and 28%, respectively, being favorable patients for such a treatment: (1) youngers; (2) long disease-free interval after primary treatment; (3) small recurrent tumors for which is possible to obtain negative surgical margins; and (4) no recurrent neck disease. All these OS rates illustrate that, even for advance recurrent OSCC, salvage surgery is still an option with curative intention for many patients.

Prognostic factors for survival are not similarly considered in all the studies. While some authors^[3] did not find a relation between the clinical stage of the recurrence and survival, others have encountered a significant association among them. Agra *et al.*^[5] showed this association in the univariate as well as in the multivariate analysis. Goodwin *et al.*^[16] found that the clinical stage of the recurrent tumor was the most significant predictor of survival. Interestingly other authors^[13] have found the ECS as the most powerful prognostic factor for surveillance, even superior to the stage of the recurrence.

Also, recurrences before 1 year after primary treatment seem to have worse prognosis. This is somehow a common topic, as Liao *et al.*,^[8] in their series of 272 recurrent OSCC, have also checked that early recurrences before 10 months after primary treatment had a significant worse prognosis in terms of 5-year DSS and OS than late-relapsed OSCC. Similarly, Zafereo *et al.*,^[17] for recurrent SCC of the oropharynx, observed that a disease-free interval after primary treatment was a critical factor in predicting the success of salvage surgery. In concordance, Agra *et al.*^[5] showed that patients recurring less than a year before primary treatment had a significant worse prognosis.

While some authors^[3,15] have suggested that patients with advanced III/IV recurrent tumors that have received previous surgery followed by RT, based on poor prognosis, should only receive palliative treatment, this asseveration is no longer supported in the light of the results from the last decade. In fact, there are several studies^[5] which indicate from multivariate analyses that previous treatment is not a predictor of survival anymore, and so advanced recurrent OSCC patients cannot be excluded from salvage surgery if general conditions and

resectability criteria allows for it, as 5-year OS is higher than 30%. In the light of the results from the present meta-analysis, with a mean 5-year OS rate upper than 40%, if candidates, salvage surgery is strongly recommended for treating recurrent OSCC patients.

In concordance with several other studies, Liao *et al.*^[8] found that better prognosis was achieved for local recurrence in comparison to cervical recurrence. In concordance with it, Lim and Choi^[9] also observed that although good salvage was accomplished in local recurrences, a poor salvage rate was found in cases of cervical nodal recurrences, especially if being associated with a neck level IV recurrence. Goto *et al.*^[13] was coincident in asseverating that node involvement at levels IV or V was predictive for a decreased 5-year OS rate.

Besides several prognostic tumor-related factors, the influence of primary treatment modality in the outcome of recurrent OSCC patients has also been investigated. In relation to this, the study by Brown *et al.*^[7] demonstrated that the administration of postoperative RT negatively influenced prognosis and recurrence rate in patients at intermediate risk of recurrence that underwent further salvage surgery because of relapse. Goto *et al.*^[13] also demonstrated several prognostic factors being predictive for a worse 5-year OS after salvage surgery, such as advanced stages (III and IV) recurrent tumors, two or more positive cervical lymph nodes, positive cervical lymph nodes at levels IV or V, ECS, and disease-free interval from primary treatment minor than a year.

The role of salvage surgery

Traditionally, in relation to resectability criteria, many concerns about the possibility for real resection of recurrent oral SCC and related reconstructive options made salvage surgery scarcely indicated. Nowadays, advances in surgical approaches, technology, microsurgical reconstruction, and also surgeons' training have extended indications for salvage surgery, even for patients with advanced recurrent clinical stages III/IV.

As pointed out by Liao *et al.*^[8] salvage therapy is of benefit for patients with early-relapsed OSCC in terms of both 5-year DSS and OS. Interestingly, these authors could not find a significant difference for salvage surgery compared with salvage RCT, regardless of whether patients have a local or a regional recurrence. In contrast, the benefit of salvage surgery over salvage RCT was clearly stated for patients with late-relapsed OSCC, in which recurrence appeared 10 months later than primary treatment. In relation to the benefit of salvage surgery, Zafereo *et al.*^[17] revealed that patients who underwent salvage surgery had a significantly higher 3-year OS rate than patients who underwent non-surgical treatments (excluding patients who received supportive care), such as re-irradiation or brachytherapy or chemotherapy.

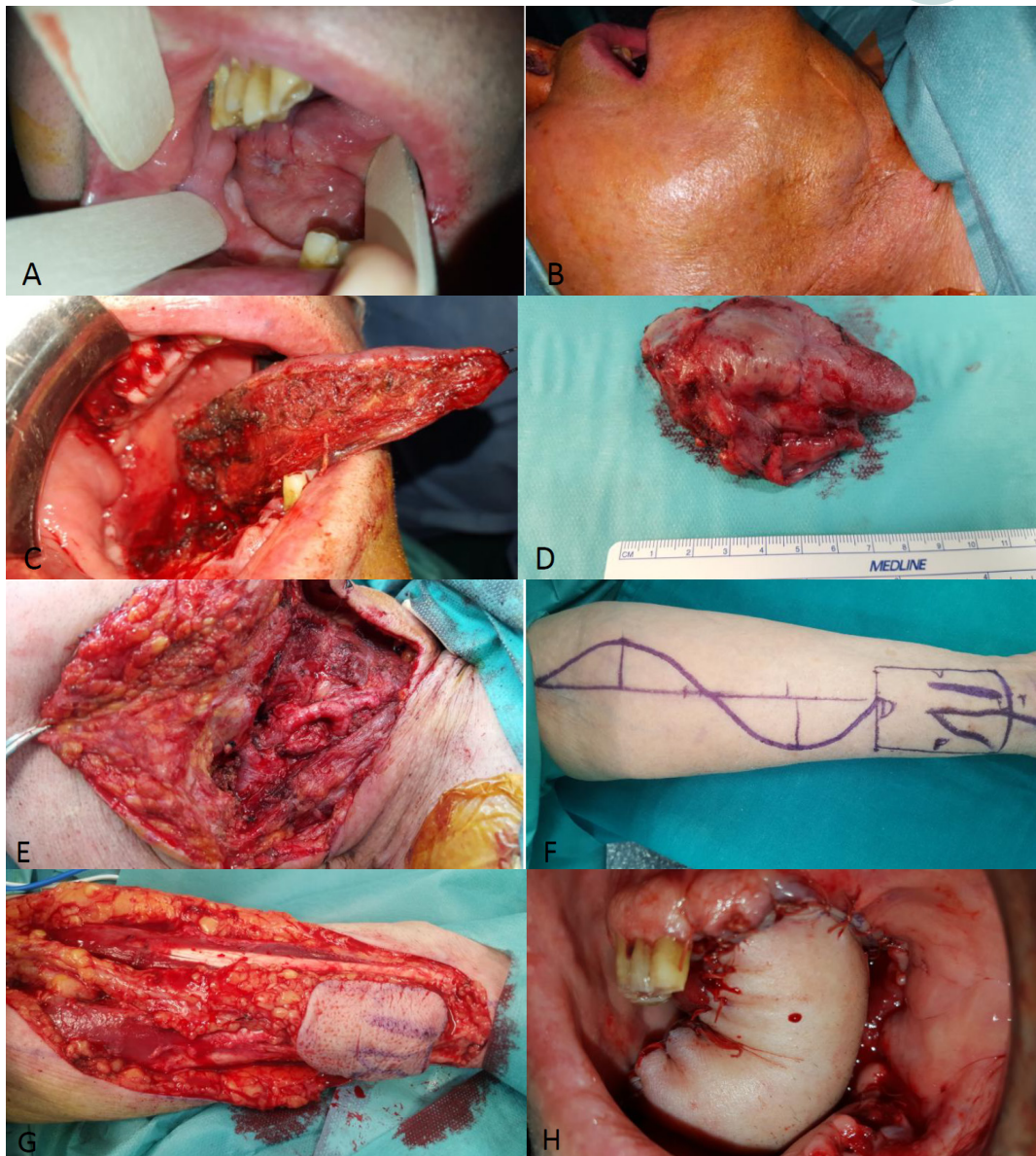


Figure 1: Recurrent oral squamous cell carcinoma (OSCC) patient 1. (A) Local recurrence of OSCC in the right side of the tongue; (B) regional recurrence in right cervical level II; (C) intraoperative hemi-glossectomy; (D) intraoperative view of the resected specimen; (E) classical radical neck dissection; (F) design of the "Iberic graft" technique for reconstruction of the defect with a radial forearm free flap (RFFF); (G) RFFF harvesting; (H) intraoral view of the reconstruction, with the RFFF showing arterial bleeding and viability

Actually, salvage surgery is being considered as the best treatment in recurrent OSCC, especially in those patients in which previous radiotherapy has been administered as part of the primary treatment, because of the toxicity of re-irradiation [Figure 1]. Re-irradiation in SCC of the aero-digestive tract has been reported to have an overall 5-year survival rate up to 20%, while chemotherapy is clearly discouraging.^[5] The real fact with many recurrent OSCC patients is that RT has already been administered as part of the primary treatment, in most of the cases as an adjuvant therapy to primary surgery, and re-irradiation with its inherent toxicity is not tolerated by the patient.

Besides, the main concern with respect to the use of RT is the increased morbidity, such as risk of osteo-radionecrosis and caries, worseness of speech and swallowing, and

xerostomia, among others. Considering that some authors^[7] have found a loco-regional recurrence rate of only 18% for patients at intermediate risk of recurrence [close surgical margins (> 1 mm and < 5 mm) and/or positive neck disease without ECS], and that 82% of them may not benefit from adjuvant RT, the clinician must reconsider the systematic administration of post-operative RT in those patients without cervical ECS or an involved margin (< 1 mm from the margin).

In our experience from a single institution (University Hospital Infanta Cristina, Badajoz, Spain) treating SCC of the oral cavity and oropharynx by surgery in a population area of one million and five hundred thousand inhabitants (Extremadura, Spain), salvage surgery is the best option for recurrent patients, even in

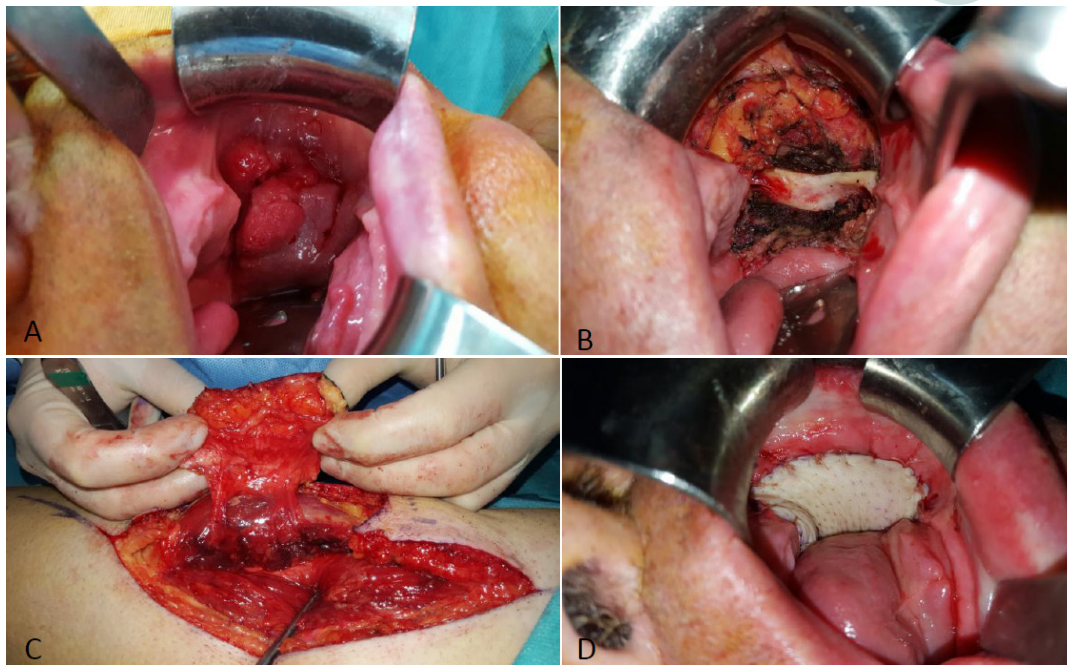


Figure 2: Recurrent oral squamous cell carcinoma (OSCC) patient 2. (A) Local recurrence of OSCC in the left buccal mucosa and retromolar trigone; (B) intraoral view of the defect after resection with margins; (C) harvesting of the anterolateral thigh flap; (D) intraoral view of the reconstruction with the anterolateral thigh flap covering defect in the buccal mucosa and retromolar trigone

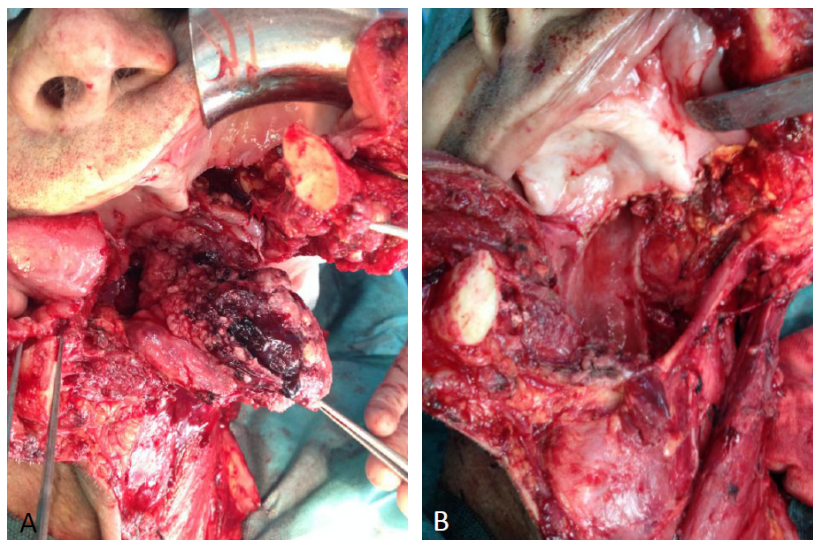


Figure 3: Recurrent oral squamous cell carcinoma (OSCC) patient 3. (A) Loco-regional recurrence of OSCC in the tongue. Intraoperative view of the resection and classical radical neck dissection; (B) intraoperative view following resection

advanced stages, if feasible [Figure 2]. We only reserve re-irradiation (if toxicity tolerated), chemotherapy or supportive care for those patients with unresectable or inoperable recurrent tumors, in whom a radical surgical surgery is not warranted and/or a general anesthetic procedure is an extremely risky intervention.

Complications following salvage surgery

One of the major concerns regarding performance of salvage surgery for the recurrent patients is the high rate of complications. Agra *et al.*^[5] reported a 37% overall complication rate and a mortality of 2% for salvage surgery, most of complications being wound

infection, wound dehiscence and/or flap necrosis, and oro-cutaneous fistulas. A major complication such as the rupture of the carotid artery was only observed in 0.5% of the cases. Lin *et al.*^[1] reported an overall complication rate of the salvage group of 60.7%, which was higher than that for patients primarily treated with surgery 30.4%. However, no significant differences in terms of major complications were observed. This consideration is based on a myriad of recurrent tumors, with early and late stages mixed together.

Considering that for these authors, early recurrent tumors did not involve bone and/or neck, it is my believing,

based on our own experience in treating advanced recurrent tumor with neck involvement, that the major complication rate may be significantly different when only a local recurrence is surgically treated or by contrast when a loco-regional or regional recurrence with neck involvement is managed [Figure 3]. Most of our recurrent patients have been previously treated by primary surgery with local excision and cervical neck dissection followed or not by loco-regional radiotherapy. The effect of prior operation and/or irradiation is determinant in the absence of anatomical layers or boundaries, which makes salvage surgery of the neck completely different from that performed in the primary treatment. Even, it is not uncommon among our recurrent patients to encounter advanced tumors in which diffuse invasion is present, with invasion of major vascular structures such as the internal jugular vein and surrounding musculature, which subsequently makes surgery much more difficult and hazardous, with potential severe complications such as massive bleeding from big cervical vessels.

Thus, based on previous series and on our own experience, we believe that: (1) overall complication rate for salvage surgery is higher than that for primary surgery; (2) major complications rate does not seem to be statistically different for salvage surgery; and (3) major complication rate and postoperative mortality from salvage surgery does not seem to differ from that observed for advanced stages III/IV primary OSCC, but this should not be extensible to early stage tumors (I/II) treated primarily by surgery, in which major complications are being expected in a lower rate.

Also, the influence of long-term radiation toxicity derived from its postoperative administration in the primary treatment and/or following salvage surgery may determine the appearance of xerostomia, osteo-radionecrosis of the jaws or restricted mouth opening and lingual movements, which may add its deleterious effects to those derived from surgery. Even, despite the performance of free flap reconstruction, up to 25-50%^[16] of the patients may require a permanent gastrotomy because of feeding impairment, although these considerations concerning sequelae are beyond the scope of the present paper.

In summary, with an overall 26% recurrence rate for OSCC despite primary treatment with surgery followed by post-operative radiotherapy, the clinician must be firmly aware of recurrence, which is mainly a local relapse in more than 47% of the cases, followed by a regional recurrence in 35% and a combined loco-regional relapse in almost 11% of the cases. While chemotherapy is clearly discouraging and radiotherapy has only been reported to be curative in no more than a 20%, salvage surgery is the best option for the treatment of recurrent OSCC patients, also for those with advanced disease, with a mean 5-year overall-survival rate of more than 40% of the cases, showing acceptable morbidity and good functional results if reconstructive

microsurgical techniques are used.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Lin YC, Hsiao JR, Tsai ST. Salvage surgery as the primary treatment for recurrent oral squamous cell carcinoma. *Oral Oncol* 2004;40:183-9.
2. Gleich LL, Ryzenman J, Gluckman JL, Wilson KM, Barrett WL, Redmond KP. Recurrent advanced (T3 or T4) head and neck squamous cell carcinoma: is salvage possible? *Arch Otolaryngol Head Neck Surg* 2004;130:35-8.
3. Schwartz GJ, Mehta RH, Wenig BL, Shaligram C, Portugal LG. Salvage treatment for recurrent squamous cell carcinoma of the oral cavity. *Head Neck* 2000;22:34-41.
4. Kowalski LP. Results of salvage treatment of the neck in patients with oral cancer. *Arch Otolaryngol Head Neck Surg* 2002;128:58-62.
5. Agra IM, Carvalho AL, Ulbrich FS, de Campos OD, Martins EP, Magrin J, Kowalski LP. Prognostic factors in salvage surgery for recurrent oral and oropharyngeal cancer. *Head Neck* 2006;28:107-13.
6. Koo BS, Lim YC, Lee JS, Choi EC. Recurrence and salvage treatment of squamous cell carcinoma of the oral cavity. *Oral Oncol* 2006;42:789-94.
7. Brown JS, Blackburn TK, Woolgar JA, Lowe D, Errington RD, Vaughan ED, Rogers SN. A comparison of outcomes for patients with oral squamous cell carcinoma at intermediate risk of recurrence treated by surgery alone or with post-operative radiotherapy. *Oral Oncol* 2007;43:764-73.
8. Liao CT, Chang JT, Wang HM, Ng SH, Hsueh C, Lee LY, Lin CH, Chen IH, Huang SF, Cheng AJ, Yen TC. Salvage therapy in relapsed squamous cell carcinoma of the oral cavity: how and when? *Cancer* 2008;112:94-103.
9. Lim YC, Choi EC. Surgery alone for squamous cell carcinoma of the oral cavity: survival rates, recurrence patterns, and salvage treatment. *Acta Otolaryngol* 2008;128:1132-7.
10. Kernohan MD, Clark JR, Gao K, Ebrahimi A, Milross CG. Predicting the prognosis of oral squamous cell carcinoma after first recurrence. *Arch Otolaryngol Head Neck Surg* 2010;136:1235-9.
11. Sklenicka S, Gardiner S, Dierks EJ, Potter BE, Bell RB. Survival analysis and risk factors for recurrence in oral squamous cell carcinoma: does surgical salvage affect outcome? *J Oral Maxillofac Surg* 2010;68:1270-5.
12. Kostorzewa JP, Lancaster WP, Iseli TA, Desmond RA, Carroll WR, Rosenthal EL. Outcomes of salvage surgery with free flap reconstruction for recurrent oral and oropharyngeal cancer. *Laryngoscope* 2010;120:267-72.
13. Goto M, Hanai N, Ozawa T, Hirakawa H, Suzuki H, Hyodo I, Kodaira T, Ogawa T, Fujimoto Y, Terada A, Kato H, Hasegawa Y. Prognostic factors and outcomes for salvage surgery in patients with recurrent squamous cell carcinoma of the tongue. *Asia Pac J Clin Oncol* 2016;12:141-8.
14. Cooney TR, Poulsen MG. Is routine follow-up useful after combined-modality therapy for advanced head and neck cancer? *Arch Otolaryngol Head Neck Surg* 1999;125:379-82.
15. Goodwin WJ Jr. Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means. *Laryngoscope* 2000;110:1-18.
16. Dziegielewska PT, Ho ML, Rieger J, Singh P, Langille M, Harris JR, Seikaly H. Total glossectomy with laryngeal preservation and free flap reconstruction: objective functional outcomes and systematic review of the literature. *Laryngoscope* 2013;123:140-5.
17. Zafereo ME, Hanasono MM, Rosenthal DI, Sturgis EM, Lewin JS, Roberts DB, Weber RS. The role of salvage surgery in patients with recurrent squamous cell carcinoma of the oropharynx. *Cancer* 2009;115:5723-33.

The reliability of the “Iberic graft” for covering of the radial forearm free flap donor site

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ABSTRACT

Aim: Traditional donor site closure from radial forearm free flap (RFFF) has been associated with esthetic and functional morbidity. To avoid complications, such as color mismatch and secondary donor site morbidity, a new technique named “Iberic graft” for covering the RFFF donor site was described previously by our team. **Methods:** A study of patients who underwent reconstruction of head and neck defects using a RFFF was conducted to assess postoperative complications of the RFFF donor site and also to evaluate the morbidity in terms of aesthetics and function following the use of the “Iberic graft”. The donor site was covered by the use of

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a combined local triangular full-thickness skin graft. Color match, quality of the scar, presence of necrosis, dehiscence of the suture or tendon exposure were recorded and analyzed. **Results:** One hundred and twenty-five consecutive patients undergoing RFFF harvesting were included. RFFF donor site defects ranged from 15 cm² to 70 cm²; 9 patients (7%) had small dehiscences of the forearm skin graft, whereas 2 cases (1.6%) presented tendon exposure. Otherwise, partial skin graft loss occurred in a few patients. In all cases, these sites healed secondarily by conservative management, with no final impairment of function. Assessment of the forearm donor site at 1 to 3 months after the primary surgical procedure showed complete defect coverage, good color match, and no scarring along the graft line. **Conclusion:** The “Iberic graft” is a reliable method for closing most of RFFF donor site defects as it provides excellent color match and pliability, while obviates the need for a second surgical site.

Key words:

Radial forearm free flap; donor site morbidity; full-thickness skin graft; “Iberic graft”

INTRODUCTION

Since its introduction in 1981 by Yang *et al.*^[1] the radial forearm free flap (RFFF) has been used extensively for reconstruction of head and neck defects after oncologic resection. However, many donor site complications have been described, such as partial loss of the skin graft, sensory disturbance, tendon exposure, and esthetic pitfalls.^[2-5] Direct closure is not often possible due to too-large defects or insufficient skin laxity.^[6-8]

Several techniques have been described for adequate closure of the donor site defect after RFFF harvesting, such as purse-string closure,^[9] split-thickness skin grafts (STSGs),^[10,11] full-thickness skin grafts (FTSGs),^[12-15] tissue expansion,^[16,17] closure with local flaps,^[18-20] cross-suturing,^[21] use of artificial dermis,^[22,23] and local fascial flaps.^[24] STSGs are most commonly used. FTSGs can be used to provide a thicker coverage of the defect; they are more resistant to contractures or trauma and provide better esthetics results. However, their main disadvantages are potential increased morbidity and occasional need for an STSG to close the second donor site.^[25] Those patients in whom the skin graft is harvested from the thigh can develop several other complications, such as pain, infection, and hypertrophic scar formation. Moreover, evident color mismatch is often present in relation to the surrounding forearm skin.^[26] In addition, avoiding a second surgical site might be a valuable aspect to consider to decrease postoperative complication rates.

To avoid complications at the donor site from RFFF harvesting, such as color mismatch and secondary donor site morbidity, a new technique named “Iberic graft” for covering the RFFF donor site based on the use of combined local FTSG triangles within a geometric model concept was described by the authors’ group in 2009.^[27]

Since its description, we have used this technique for covering the RFFF donor site in 125 patients. In this

article, we analyzed the results (esthetics and function) using the Iberic graft.

METHODS

As described by González-García *et al.*,^[27] the design of the RFFF begins by outlining the course of the dominant subcutaneous veins and the palpable pulse of the radial artery. The flap is elevated in a subfascial layer in a few cases and in a supra-fascial layer in other cases. The superficial branch of the radial nerve is preserved in all cases. The basis for the design of the Iberic graft is the geometric concept of the designed skin paddle and the local FTSGs. Thus, a quadrangular or rectangular radial forearm flap is outlined on the distal forearm. A double curvilinear line is outlined from the proximal portion of the RFFF to the proximal forearm to provide Access to the proximal portion of the neurovascular pedicle; this double curvilinear line allows the design of 2 opposed arcs. Then, 2 bowstrings are outlined within the concavities of the arcs. At the midpoint of each bowstring, a perpendicular dotted line is outlined to the midpoint of each arc. This perpendicular dotted line is half the width of the RFFF donor defect and no longer than 3.5 cm to allow direct closure of the forearm skin flaps. At this point, 4 isosceles triangles are depicted [Figure 1]. Subsequent triangular FTSGs are harvested and freed from the forearm. Silk sutures are used to join the FTSGs to the borders of the defect and resorbable sutures are used to join 1 skin triangle to another. Then, the FTSGs are covered with a sponge using a tie-bolster technique and dressed with regular gauzes with nitrofurazone (Furacin® 2 mg/g; LAB-SEID®, Barcelona, Spain) and protected in a forearm splint for 10 days.

RESULTS

One hundred and twenty-five consecutive patients underwent RFFF harvesting for head and neck reconstruction since the first case. Primary closure of

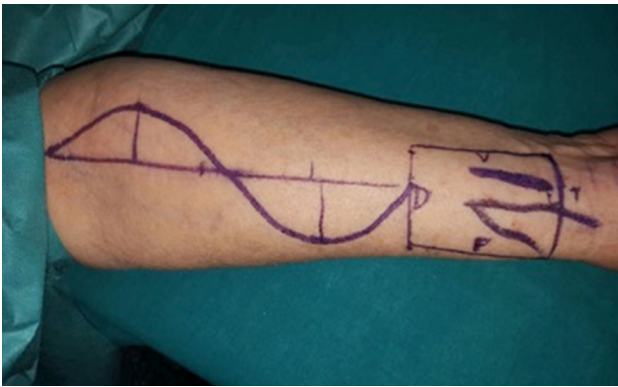


Figure 1: Design of the combined local triangular full-thickness skin graft based on 4 skin triangles for rectangular defects



Figure 2: Postoperative clinical views of donor site. Horizontal design with 4 triangles

the donor site was achieved in all cases using the Iberic graft technique.

This technique allows covering big-sized defects using skin grafts extracted from the donor site, obtaining the same color of it. In the series of 125 patients, the RFFF donor site defects ranged from 15 cm² to 70 cm² (mean \pm 24.5 cm²). Most patients underwent reconstruction with 4 skin triangles [Figure 2], whereas coverage of the RFFF donor site with 2 or 3 skin triangles was carried out for smaller defects [Figure 3]. The versatility of this technique allows using either triangle-shaped or crescent-shaped grafts, as convenient for a proper closure.

Concerning complications of the radial donor site, only a few patients developed partial necrosis of the FTSG [Figure 4] that was treated with local debridement and healed successfully by secondary intention. No patients developed complete necrosis of the graft. Only two cases presented tendon exposure. In all cases, these sites healed secondarily by conservative management, with no final impairment of wrist mobility. No acute ischemia or compartment syndromes were encountered using this technique.

Complete healing typically occurred for 2 to 3 weeks, with the longest healing time taking approximately 2 months. Although no specific functional tests were applied, no



Figure 3: Reconstruction of radial forearm free flap donor site defect with 3 triangles (vertical design)



Figure 4: Partial necrosis of the full-thickness skin graft

patients complained of symptoms related to motion or any other functional deficit. No prolonged hand swelling was found. Assessment of the forearm donor site at 1 to 3 months after the primary surgical procedure showed complete defect coverage, good color match, and no scarring along the graft line [Figures 5-7].

DISCUSSION

Several methods for closure of the RFFF donor site have been described, most of which are based on the use of an STSG or an FTSG.^[12] Because of its ease in harvesting and use, the STSG has been the most frequently used method of reconstruction, although several complications such as partial skin graft loss, flexor tendon exposure, and postoperative pain and discomfort have been reported.^[9]

The use of FTSG combined with a direct closure of the FTSG donor site has been reported to provide better pliability and promotion of the healing process, together with less postoperative pain and discomfort from the donor site, although it is more time-consuming and requires additional intraoperative processing of the graft.^[28-31] However, it is used for closure because it provides a thicker base to prevent wound breakdown and a superior esthetic result.^[32] This is the main reason for the use of this kind of grafting by the authors.



Figure 5: Good color match and esthetic outcome six months after surgery



Figure 6: Good color match and esthetic outcome two months after surgery

FTSGs harvested from the abdomen for donor site closure have been used and several complications have been observed, including hematomas, postoperative pain, delayed healing, poor esthetic results, and the need for a second surgical site.^[27] An FTSG from the inner arm has been used by other investigators, but they claim that additional time for removal of the tourniquet and further preparation and draping of the arm are required.^[33,34] Other authors have recently reported the use of FTSGs harvested from the upper inner arm or neck for closure of the RFFF donor site defect, leading to a robust coverage.^[35,36] Among 25 RFFFs used for soft tissue reconstruction, Kaltman *et al.*^[35] found donor site morbidity in only 1 case, which had a failed FTSG. They promoted the use of a technique similar to the one proposed by Avery *et al.*,^[14] which involves obtaining an FTSG from the inner arm to close the defect remaining from the RFFF harvesting. However, they also reported wound dehiscence at the medial arm donor site in 2 patients. Hanna *et al.*,^[36] in a series of 50 patients who underwent RFFF reconstruction with repair of the donor site using an FTSG harvested along the neck dissection incision, reported minor skin loss in 15 cases (30%), which was managed with local wound care until healing by secondary intention. None of the patients had recipient site infections. With this method, the need for this second surgical site was eliminated. However, this technique can be used only when the



Figure 7: Good color match three months after surgery

recipient vessels are in the neck (it is not possible to use when anastomosis is performed with temporal vessels in non-oncologic patients). In the authors' opinion, another drawback with the use of an FTSG from the arm or neck for RFFF donor site reconstruction is the color mismatch in relation to the forearm skin. Several investigators have reported good results in associated morbidity for the RFFF donor site.^[8,29,37,38] However, some reported methods for covering a donor site defect are limited by the size of the defect.

As we described in the first 100 cases,^[39] the Iberic graft technique using 2, 3, or 4 local FTSG triangles facilitates the development of a geometric model for the reconstruction of large RFFF donor site defects (70 to 80 cm²), because the alignment of triangles with bases measuring up to 3.5 cm covers defects up to 7 cm wide. The length of the defect is not usually a problem, because defects up to 10 cm in length can be easily covered by triangles measuring up to 5 cm in height, without the need for additional extension of the forearm incision. A limitation to consider in this technique was related to moderate skin laxity of the patients, because most were 55 to 60 years old and thus more likely to achieve good results in the defect closure than younger patients with mild skin laxity. Nonetheless, this surgical technique has shown optimal results in young patients.

During the 7 years since the first description of the technique in 2009, the Iberic graft technique has been performed by the authors in every single patient undergoing reconstruction with an RFFF. Interestingly, there has been an evolution of the adaptation of the skin triangles in the donor site defect from a rigid horizontal disposition of the triangles in the very beginning to a more adaptable and flexible adaptation of the triangle skin grafts, depending on the size, shape, and contour of the donor site defect, including a proximal-to distal disposition of the grafts in the wrist to an oblique or irregular disposition. This feature also illustrates the versatility of this evolving technique for closure of RFFF donor site defects.^[40]

In conclusion, the Iberic graft technique is a reliable method for closing RFFF donor site defects because

it provides several advantages compared with other methods: (1) it provides an easy and fast way for closure of the donor site defect; (2) it is a 1-stage procedure that does not need further revision or care; (3) it obviates a second surgical site and subsequent distant donor site complications or sequela; (4) it provides an excellent color match and pliability, similar to that of the surrounding skin, because it is an FTSG harvested from the neighboring forearm skin; and (5) it can be used to cover large defects of the donor site, ensuring an adequate amount of available skin and decreasing the risk for scarring tissue. More clinical series must be reported worldwide to support the suitability of this technique in the optimal covering of RFFF defects.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Yang GF, Chen PJ, Gao YZ, Liu XY, Li J, Jiang SX, He SP. Forearm free skin flap transplantation: a report of 56 cases. *Br J Plast Surg* 1981;50:162-5.
2. Soutar DS, Scherer LR, Tanner NS, McGregor IA. The radial forearm flap: a versatile method for intra-oral reconstruction. *Br J Plast Surg* 1983;36:1-8.
3. Soutar DS, McGregor IA. The radial forearm flap for intraoral reconstruction: the experience of 60 consecutive cases. *Plast Reconstr Surg* 1986;78:1-8.
4. Futran ND, Gal TJ, Farwell DG. Radial forearm free flap. *Oral Maxillofac Surg Clin North Am* 2003;15:577-91.
5. Swanson E, Boyd JB, Manktelow RT. The radial forearm flap: reconstructive applications and donor-site defects in 35 consecutive patients. *Plast Reconstr Surg* 1990;85:258-66.
6. Richardson D, Fisher SE, Vaughan ED, Brown JS. Radial forearm flap donor-site complications and morbidity: a prospective study. *Plast Reconstr Surg* 1997;99:109-15.
7. Chen CM, Lin GT, Fu YC, Shieh TY, Huang IY, Shen YS, Chen CH. Complications of free radial forearm transfers for head and neck reconstruction. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005;99:671-6.
8. Elliot D, Bardsley AF, Batchelor AG, Soutar DS. Direct closure of the radial forearm flap donor-site. *Br J Plast Surg* 1988;41:358-60.
9. Winslow CP, Hansen J, Mackenzie D, Cohen JI, Wax MK. Pursestring closure of radial forearm fasciocutaneous donor sites. *Laryngoscope* 2000;110:1815-8.
10. Sidebottom AJ, Stevens L, Moore M, Magennis P, Devine JC, Brown JS, Vaughan ED. Repair of the radial free flap donor site with full or partial thickness skin graft: a prospective randomized controlled trial. *Int J Oral Maxillofac Surg* 2000;29:194-7.
11. Boahene K, Richmon J, Byrne P, Ishii L. Hinged forearm split-thickness skin graft for radial artery fasciocutaneous flap donor site repair. *Arch Facial Plast Surg* 2011;13:392-4.
12. Sleeman D, Carton AT, Stassen LF. Closure of radial forearm free flap defect using full-thickness skin from the anterior abdominal wall. *Br J Oral Maxillofac Surg* 1994;32:54-5.
13. Liang MD, Swartz WM, Jones NF. Local full-thickness skin graft coverage for the radial forearm flap donor-site. *Plast Reconstr Surg* 1994;93:621-5.
14. Avery CM, Iqbal M, Orr R, Hayter JP. Repair of radial free flap donor site by full-thickness skin graft from inner arm. *Br J Oral Maxillofac Surg* 2005;43:161-5.
15. Kim TB, Moe KS, Eisele DW, Orloff LA, Wang SJ. Full-thickness skin graft from the groin for coverage of the radial forearm free flap donor site. *Am J Otolaryngol* 2007;28:325-9.
16. Berge SJ, Wiese KG, von Linderen JJ, Niederhagen B, Appel T, Reich RH. Tissue expansion using osmotically active hydrogel systems for direct closure of the donor defect of the radial forearm flap. *Plast Reconstr Surg* 2011;108:1-5.
17. Bonaparte JP, Corsten MJ, Odell M, Gupta M, Allen M, Tse D. Management of the radial forearm free flap donor site using a topically applied tissue expansion device. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2013;116:28-34.
18. Hui KC, Zhang F, Lineaweaver WC. Z-plasty closure of the donor defect of the radial forearm free flap. *J Reconstr Microsurg* 1999;15:19-21.
19. Akyurek M, Safak T. Direct closure of radial forearm free-flap donor sites by double-opposing rhomboid transposition flaps. *J Reconstr Microsurg* 2002;18:33-6.
20. Lane JC, Swan MC, Cassell OC. Closure of the radial forearm donor site using a local hatchet flap: analysis of 45 consecutive cases. *Ann Plast Surg* 2013;70:308-12.
21. Moazzam A, Gordon DJ. Cross-suturing as an aid to wound closure: a prospective randomized trial using the forearm flap donor site as a model. *Br J Plast Surg* 2003;56:695-00.
22. Sinha UK, Shih C, Chang K, Rice DH. Use of AlloDerm for coverage of the radial forearm free flap donor site. *Laryngoscope* 2002;112:230-4.
23. Wester JL, Pittman AL, Lindau RH, Wax MK. AlloDerm with split-thickness skin graft for coverage of the forearm free flap donor site. *Otolaryngol Head Neck Surg* 2014;150:47-52.
24. Lutz BS, Wei FC, Chang SC, Yang KH, Chen IH. Donor site morbidity after suprafascial elevation of the radial forearm flap: a prospective study in 95 consecutive cases. *Plast Reconstr Surg* 1999;103:132-7.
25. Rowe NM, Morris L, Delacure MD. Acellular dermal composite allografts for reconstruction of the radial forearm donor site. *Ann Plast Surg* 2006;57:305-11.
26. Ho T, Couch M, Carson K, Schimberg A, Manley K, Byrne PJ. Radial forearm free flap donor site outcomes comparison by closure methods. *Otolaryngol Head Neck Surg* 2006;134:309-15.
27. González-García R, Ruiz-Laza L, Manzano D, Moreno C, Maestre O, Serrano H, Villanueva L, Monje F. Combined local triangular full-thickness skin graft for the closure of the radial forearm free flap donor site: a new technique. *J Oral Maxillofac Surg* 2009;67:1562-7.
28. Karimi A, Mahy P, Reyhler H. Closure of the radial forearm free flap donor site defect with a local meshed full-thickness skin graft: a retrospective study of an original technique. *J Craniomaxillofac Surg* 2007;35:369-73.
29. Zuidam JM, Coert JH, Hofer SO. Closure of the donor site of the free radial forearm flap: a comparison of full-thickness graft and split-thickness graft. *Ann Plast Surg* 2005;55:612-6.
30. Lee JW, Jang YC, Oh SJ. Use of the artificial dermis for free radial forearm flap donor site. *Ann Plast Surg* 2005;55:500-2.
31. Pandya AN, Vadodaria S, Coleman DJ. Tissue expansion in the limbs: a comparative analysis of limb and non-limb sites. *Br J Plast Surg* 2002;55:302-6.
32. Gaukroger MC, Langdon JD, Whear NM, Zaki GA. Repair of the radial forearm flap donor site with a full-thickness graft. *Int J Oral Maxillofac Surg* 1994;23:205-8.
33. Médard de Chardon V, Balaguer T, Chignon-Sicard B, Riah Y, Ihrat T, Dannan E. The radial forearm free flap: a review of microsurgical options. *J Plast Reconstr Aesthet Surg* 2009;62:5-10.
34. van der Lei B, Spronk CA, de Visscher JG. Closure of radial forearm free flap donor site with local full-thickness skin graft. *Br J Oral Maxillofac Surg* 1999;37:119-22.
35. Kaltman JM, McClure SA, Lopez EA, Pedroletti F. Closure of the radial forearm free flap donor site defect with a full-thickness skin graft from the inner arm: a preferred technique. *J Oral Maxillofac Surg* 2012;70:1459-3.
36. Hanna TC, McKenzie WS, Holmes JD. Full-thickness skin graft from the neck for coverage of the radial forearm free flap donor site. *J Oral Maxillofac Surg* 2014;72:2054-9.

37. Shiba K, Iida Y, Numata T. Ipsilateral full-thickness forearm skin graft for covering the radial forearm flap donor site. *Laryngoscope* 2003;113:1043-6.
38. Jaquet Y, Enepekides DJ, Torquerson C, Higgins KM. Radial forearm free flap donor site morbidity: ulnar-based transposition flap vs. split-thickness skin graft. *Arch Otolaryngol Head Neck Surg* 2012;138:38-43.
39. Moreno-Sánchez M, González-García R, Ruiz-Laza L, Manzano Solo de Zaldivar D, Moreno-García C, Monje F. Closure of the radial forearm free flap donor site using the combined local triangular full-thickness skin graft. *J Oral Maxillofac Surg* 2016;74:204-11.
40. González-García R. Local full-thickness skin graft to cover the radial forearm free flap donor site. *Int J Oral Maxillofac Surg* 2016;45:132-3.

Current prognosis and quality of life following surgical treatment for head and neck squamous cell carcinoma

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ABSTRACT

Head and neck squamous cell carcinoma (HNSCC) is one of the most common cancers in the world with a close relation with some risk factor like, tobacco, alcohol consumption and more recently, with human papilloma virus infection. A review of the literature about actual prognosis and quality of life in HNSCC has been done analysing the results of surgical treatment and their impact on the quality of life of patients. Despite the elevated incidence of HNSCC, the survival rate has increased considerably over the last years thanks to the development of new surgical techniques, such as, microvascular reconstruction or transoral robotic surgery and the most accurate adjuvant radiochemotherapy. Even in bad prognosis cases, there are many options to take into account not only with curative expectation, even, keeping in mind the preservation of the quality of life of patients. Due to the improvement of the prognosis, the interest of surgeons has been focused on preserve the aesthetics, functional and psychosocial aspect of patients without a worsening of the main objective which is the curative result. Although prognosis of HNSCC has improved, further studies are necessary to understand the behaviour in every case and determine how the impact on the quality of life can be a useful tool to individualize the therapies.

Key words:

Carcinoma; squamous cell of the head and neck; head and neck neoplasms/mortality; quality of life; oral cancer

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INTRODUCTION

Squamous cell carcinoma (SCC) is one of the most common malignant neoplasms in the head and neck and the sixth cause of cancer worldwide. Approximately 600,000 cases are diagnosed every year. Although head and neck squamous cell carcinoma (HNSCC) includes salivary glands and paranasal sinuses tumours, their low incidence and different behaviour, have been made them be excluded from this study.^[1]

There are many risk factors associated to HNSCC, but, alcohol and tobacco consumption are the most important and they are related to the 75% total tumours. However, recent studies have demonstrated that the connection between the infection by oncogenic virus human papillomavirus (HPV) (specifically the serotype 16) and SCC is an established cause of oropharynx cancer, mainly located in tonsils and base of the tongue.^[2,3] Currently, the incidence of HPV-related HNSCC has been increased in the young population.

The survival rate of HNSCC among the last 20 years has increased considerably. The development of new methods of diagnosis, surgical techniques, radiotherapy (RT) and chemotherapy (CMT), are helpful tools that contributed to achieve the best results.^[4]

During the last decades, head and neck surgeons focused

their efforts on morbidity reduction, increased the quality of life and the functional status of the patients.^[5] The development of reconstructive surgical techniques such as microvascularized free flaps, led us transfer any kind of tissue (skin, muscle bone, nerves) to the surgical defect after resection.

Treatment choices depend on the neoplasm location, tumour stage and the oncologic free disease survival expectation. Surgery is still the main therapy, most of the time accompanied by postoperative RT. Although, some advanced cases need to be treated with CMT with cetuximab. The overall survival rate varies between 40-60% after 5 years of treatment.^[6]

METHODS

A qualitative review of the literature about actual prognosis and quality of life of oral squamous cell carcinoma has been done analysing the results of surgical treatment and their impact on the quality of life of patients. A bibliographic search on MEDLINE and EMBASE databases, with the key words: “carcinoma, squamous cell of the head and neck”; “head and neck neoplasms/mortality”; “quality of life”; “oral cancer” was conducted. After a manual selection of the abstracts, a total amount of 45 papers were selected from the literature and intensively reviewed.



Figure 1: Infiltrated skin with cervical infection in a recurrent tracheostomized head and neck squamous cell carcinoma patient

RESULTS CONCERNING PROGNOSIS

Every year, over 50,000 patients with HNSCC are diagnosed and, approximately 12,000 developed regional disease or distant metastases in United States. Almost 60% of patients are diagnosed since the first moment as III/IV stage.^[7] From 30% to 50% of them have locally advanced disease which will develop recurrences and 20-30% of them will exhibit distant metastases.

The treatment choices for patients with non-resectable metastases are reduced to palliative care therapy, while the main objective of patients with resectable tumours is curative, enhance the overall survival, get a better functional result and palliate the symptoms.

When, the aerodigestive tract is involved can determinate many complications like dysphagia, airway obstruction and speech impediments. The infiltrated skin generates chronic infections, painful and malodorous fistulae [Figure 1]. These are some of the reasons that determine the social and familiar isolation despite the lack on the quality of life (QOL).

The reason of the high incidence of recurrences is still unknown. While the rate of smokers is decreasing, the incidence of patients HPV+ is raising. It seems like cases HPV+ present a low rate of secondary tumours and is not related with the typical cancerization field. Anyway, is well known the connection between the high risk of recurrence and the development of radio-induced tumours with HPV+ cases during a long period of time.^[8-10]

Recurrences differ from primary tumour because they are typically more infiltrative and multifocal, it is very common to find disseminated tumours outside the radiated field and the surgically area.^[11] Despite the effort to find wide resection margins, the presence of fibrosis and the distortion of the anatomy make us very difficult to get free margins.

PROGNOSIS FACTORS OF RECURRENCES IN HNSCC

One of the most important criteria is determine the real curative expectation of patients. There are many studies published with ambiguous results because the heterogeneity of the data, the different location sites of the tumours and the therapies included.

Factors depending on the patient

Comorbidity of the patient is a determinant factor for the prognosis. An excessive loss of weight, high comorbid diseases, low cognitive level, lack of social support, the low quality of life and the continuing alcohol and tobacco abuse are some of the most frequent adverse prognosis factors.^[12,13]

Factors depending on the tumour

The most important factor is the stage of the recurrence.

Some studies reveal a significant difference up to 2 years of free disease survival without recurrences (67% for stage II, 33% for stage III and 22% for stage IV).^[14] Otherwise, a short interval without recurrences demonstrated an important negative impact factor.

Some studies included more than 500 patients, revealed 20% of differences of 5 years overall survival with a 9-month interval and considering a short period of free survival disease, probably the most important factor despite the tumour site.^[15]

Previous computed tomography-scan is considered a poor prognosis factor in patients with recurrences. Many patients showed a worst survival rate after recurrences (5 months mean rate vs. 25 months).^[14] Although the explanation for this result is already unknown, it seems like a good response after induction CMT anticipates a good response in the recurrence area. CMT can detect those patients with more aggressive recurrences. Alternatively, CMT could be a landmark for advances stages where more intense previous therapy is required but with poor prognosis.

Factors depending on tumour location

Comparing oropharynx with hypopharynx, the larynx tumours developed more early symptoms and could be detected in an early and more treatable stage. The drainage pathways are well established and the lymph dissemination is more predictable. These factors can be observed in cases of recurrences and total laryngectomy is already a curative therapy with a 5-year overall survival about 68-70%.^[16,17]

The favourable prognosis in patients with recurrent laryngeal disease is the reason why many groups propose a more conservative surgical treatment, such as, partial laryngectomy performed with transoral laser microsurgery or open partial laryngectomy. Ganly *et al.*^[17] referred that stages rT1-T2 enable to be surgically treated with partial laryngectomy have a 5-year overall survival of 89%, meanwhile, those who require a total laryngectomy due to a more aggressive tumour behaviour, the overall survival decrease to 50%. Obviously, patients with early stages show, not only, a better survival rate, also a better functional larynx preservation.

Sinclair *et al.*^[18] demonstrated that intelligible speech could be preserved in 66-71% of patients in which conservative larynx therapies were performed. It supposes a better QOL in this group of patients.^[18]

Oral recurrences are easier to detect, but the prognosis is poorer than other location, probably the reason is the different lymphatic drainage pathways, biological behaviour and the easy dissemination to many other areas of the oral cavity.

In contrast to laryngeal recurrences, the oral cavity recurrence occurs more frequently in distant sites. According to some studies, one of the determinant prognostic factor for long

disease-free survival is the tumour depth more than 10 mm and presence of neck metastases.^[19] Regarding the group of patients with recurrences after a long period of time free of disease, the overall survival rate is higher in the group where salvage surgery were performed than the group who receive RT/CMT (84% vs. 52% after 5 years).

Analysing the group of patients who presented a short period of free survival disease (FSD), the different survival after 5 years was lower, 38% vs. 31%; this result could be caused by an early recurrence and infiltrative feature of the tumour, which determine a more aggressive behaviour that hides an occult expansion more difficult to be eradicated. In conclusion, a short period of FSD is a negative prognosis factor.^[20,21]

Oropharyngeal recurrences are more common despite the prevalence of HPV and its high sensitivity to CMT/RT. The rates of regional and distant failure in patients with HPV+ disease were 14% and 9% respectively in the Radiation Therapy Oncology Group 0129 study.^[2] The survival after salvage surgery in recurrence cases is worse than for larynx and oral cavity neoplasms with a 5-year survivor of 13-28%.

The salvage surgery or reirradiation in oropharynx often results in high comorbidity including dysphagia, aspiration, dysarthria and permanent tracheostomy. The development of microsurgical reconstruction has led the possibility to perform salvage surgical treatment in more cases although the functional and QOL worsening are more controversial.

Many authors referred that the time needed to return to overall baseline health after a free flap reconstruction exceed the mean time of FSD before a second recurrence, despite the controversies, it is obvious that microvascular reconstruction demonstrates to be feasible and reliable, with low rate of complications and a better impact on patients.^[22] As well as in other tumours in oral cavity, the FSD until recurrence is one of the most important prognostic factor. Nevertheless, in that cases, salvage surgery whenever is possible, demonstrates

to be more effective than RT/CMT, despite the functional sequelae.

Recurrences in hypopharynx show worse survival and functional results than other location. Symptoms may be non-specific and diagnosis can be delayed when the disease is already advanced.

Lymphatic spread is extensive and invasion of unresectable structures can be affected, Salvage surgery such as pharyngo-laryngectomy has dramatic side effects and a high risk of postoperative complications. About 29% of patients present resectable recurrences at the moment of diagnosis, maybe this situation determine that a few cases could obtain benefits from salvage surgery.

Nevertheless, when surgery is possible, has demonstrated it is the best option to control the tumour. Some studies, showed how salvage surgery gets the same survival rates in patients previously treated with RT/CMT than patients who surgical treatment where done.

Regional recurrence is another bad prognosis factor, as well as the presence of distant metastasis. Even if, isolated neck nodule is easy to be resected compared to local recurrence, patients with regional recurrences have better free tumour margin control at the surgical moment (42% vs. 29%) rather than local recurrences. But, present a worse long term survival (26% vs. 42%). Also, overall survival decreases in operated necks than others where surgery was not performed (18% vs. 32%).^[23] Lim *et al.*^[24] found in rN2-rN3 stages that previous neck dissection and previous RT/CMT are the worst negative predictive factors.

RESULTS CONCERNING QOL

According to the World Health Organization, health-related quality of life (HRQOL) is defined as the self-perception of

Table 1: Commonly used tools to collect patient-reported QOL outcomes in patients with HNSCC

QOL instrument-specific measures for head and neck cancer	Description	Domains measured
EORTC QOL Head and Neck Version (EORTC QLQ-H&N35)	35-item, self-administered questionnaire to be administered along with EORTC QLQ-30	Pain swallowing, senses, speech, social eating, social contact and sexuality
Functional Assessment of Cancer Therapy-Head and Neck (FACT-H&N)	39-item, self-administered questionnaire 12 questions specific to head and neck cancer	General wellbeing questions (covering physical, social/family, emotional and functional parameters)
FACT-Head & Neck Symptom Index (FHNSI)	10-item, self-administered questionnaire, a subset of the FACT-H&N	General wellbeing questions (covering physical, social/family, emotional and functional parameters)
Liverpool Oral Rehabilitation Questionnaire	40-item, self-administered questionnaire	Eating, swallowing, dry mouth, saliva, speech, appearance, social life and interactions
MD Anderson Dysphagia Inventory (MDADI)	20-item self-administered questionnaire for patients with head and neck cancer	Oropharyngeal dysphagia
The University of Washington Quality of Life Instrument (UW-QOL)	10 domains, self-administered questionnaire	Pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder problems, taste, saliva and general health questions

QOL: quality of life; HNSCC: head and neck squamous cell carcinoma

patients in the cultural context and valuable systems where they live in relation with their expectations, standards and concerns.

HRQOL is the assessment of the effect of a disease or treatment of a patient's wellbeing and daily function.^[25] It is a multidimensional tool reflecting the self-perception of the patients.

Evaluating the HRQOL of patients can be a helpful tool for physicians before taking decisions about the effectiveness of treatments, clarifying and helping to decide according to the side effects, can be used as a prognostic factor to analyse symptoms and evolution, identifying factors which can interfere the survival of patients, useful to estimate cost-effectively of therapies, helping to organize and maintain the quality of therapies. It helps to develop new drugs and reveal patients priorities.^[26]

There are amounts of questionnaires used to determine the impact of cancer or treatments on patients. In contrast, just a few other surveys are designed specifically for patients with HNSCC [Table 1].

In our daily practice is common ask to the patient about how they feel but we do not usually spend time in complete questionnaires unless for some specific researches. Complete a survey means leave the patient alone in a proper environment without the influence of distractors to avoid bias or incorrect results. Many authors tried to solve the problem making online questionnaires, by this way we do not miss time and we let the patient a comfortable moment to do the questionnaire and value how the cancer affects them daily.

Specifically, patients' concerns about HNSCC can depend on individual factors such as age, comorbidity and psychosocial situation, stage and side effects. Motorization of the QOL can be a value tool to measure effectiveness of the treatment like how determine the intensity of chemotherapy. Information obtained from questionnaires could be useful to make decisions and management of patients, give priority to some important factors for their life such as pain, organ preservation, speech, physical appearance and their worries about recurrences.

The term QOL includes many factors related with life conditions, subjective reflection about the individual well-being rate. During the last years, a lot of studies have been published about QOL, which is consequence of the great response to the treatment. Professionals must be concerned not only about surgery, therapeutic treatment and complication rate, also about psychosocial aspect of people. For many authors QOL is an independent survival factor.^[27,28] Due to the subjectivity of the term and how difficult is to measure, value the QOL is challenging, that is why many questionnaires have been developed.

There are many questionnaires in the literature, such as

number of surveys just reflects that any of them is well validated, there are not common criteria, but all of them must be easy to understand and quickly to complete in no more than 10 min.

One of them is the University of Washington Quality of Life (UW-QOL), this questionnaire is short and easy to response and has been validated in many studies published. It includes 12 domains: pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder, taste, saliva, mood and anxiety. This questionnaire also added final global question where the patient could explain which factors secondary to the tumour affected mostly in their daily activity giving them the chance to add several aspects not asked before. Each domain has 5 possible answers, with the score ranging from 0 (worst) to 100 (best).^[29]

Some of the disadvantages that we find is due to most of studies are retrospective, and there are just a few prospective results. Visacri *et al.*^[30] elaborated a study including prospectively 32 patients who underwent RT/CMT and they evaluated the quality of life using UW-QOL questionnaire. There was a reduction in overall QOL that was significant after cycle 2 of chemotherapy and the sixth week of radiotherapy when compared with baseline. There was a significant improvement in some domains, such as pain and anxiety. The domain most affected after the start of treatment was taste.^[30]

Another study analysed the QOL in a group including 82 patients who completed the EORTC QLQ-H&N35 questionnaire in 4 different times: before starting the radiotherapy, in the middle (15th or 20th fraction the radiotherapy), at the end, at 1 month and at 6 months after the treatment. In the middle, at the end the radiotherapy, one and six-month after the treatment, compared to before starting the radiotherapy, all symptom scales of the quality of life were affected negatively. However, 6 months after radiotherapy, all of them show an improvement excepting, dental problems, dryness of the mouth and the viscosity of the saliva. According to the localization, stickiness of saliva and dry mouth were significantly more frequent in the tumours of the nasopharynx, the oral cavity and the oropharynx, compared to the tumours of the larynx area. Regarding age, groups over 65 years demonstrated better results than young people. Also, the group with high radiation was affected more in terms of shortage of social interaction, speech problems, eating in social environment, opening the mouth, sticky saliva, feeling sick, weight loss and additional nutrient intake.^[31]

Qiu *et al.*^[29] compared the impact in QOL of patients with HNSCC treated with surgery and adjuvant therapies versus those treated with radical RT alone. A total of 30 patients fulfilled the UW-QOL questionnaire at least after 1 year of follow up. According to the results, pain due to treatment recreation activities and shoulder weakness were well tolerated by most patients. But, chewing and taste were the domains with the worst scores in both groups. Significant



Figure 2: The reconstruction of mandibular oral squamous cell carcinoma with composite resection by the miocutaneous pectoralis major flap. Note differences in terms of color and possibility for scar contraction in the neck area

differences were found in the domains: appearance, shoulder and anxiety. Patients who underwent surgery and reconstruction were found to be more concerned about their appearance and complained about shoulder pain; whereas patients who were treated with radical radiotherapy were more anxious about their cancer. Finally, no significant differences were found according to the follow-up, it seems that do not interfere in the QOL.^[29]

Chewing is the function that was mostly impaired after HNSCC treatment, despite the location. Also, impaired chewing may lead to dysphagia and insufficient feeding. These are consequences not only of radiation and surgical damage of the salivary glands but also his disruption of the normal anatomy of the jaw. Thus, all efforts must be made to preserve vital structures and organ-function, the use of organ-sparing RT could be a good option because it predicts potential complications according to the dose of radiation and allows preservation of contralateral salivary glands.^[32,33]

The facial disfigurement after surgery is considered to be the most distressing aspect of HNSCC, although is well tolerated in patients who received RT. The surgery group, scars and the different colour of the flaps' skin paddle add serious discomfort to patients [Figure 2]. Another aspect to

be concerned is that anxiety was significantly higher in the group of radiotherapy, especially in women.^[29]

Among psychosocial issues, depression is the most prevalent in cancer patients, and it is the most common reason for referral to a mental health professional in oncology. In head and neck cancer, depression rates can reach 43% before treatment and 44% after treatment, which is particularly elevated compared with all oncology patients, in whom depression rates vary between 20 and 30% at any one time.^[34]

Depression is underdiagnosed and the consequence includes impaired quality of life, treatment noncompliance, and increased length of hospital stay, greater health care utilization, and suicide. Taking into account that HNSCC survivors rank among the top three cancers with the highest rates of suicide, after lung and stomach cancer, the main interest about target depression as a main QOL-outcome is the powerful to be prevented or treated using psychotherapy and/or pharmacologic therapy.^[35,36]

Moubayed *et al.*^[37] established a study including 209 patients with HNSCC and they analysed the results of a few questionnaires to determine the presence of depression and its impact in their quality of life. They identified 4 independent predictors of long-term depressive symptoms after controlling for all patient, tumour and treatment factors. They include the following pre-treatment factors: (1) having more than 3 medications; (2) smoking at diagnosis; (3) having more than 14 drinks per week; and (4) T3 or T4 tumour stages. These factors were used as independent risk factors in the creation of a depression predictive score, identify patients at risk for developing depressive symptoms and to be treated. In this study, they conclude that in presence of 2 risk factors, there is 82.3% of probability to identify depressive symptoms.^[37]

The development of new surgical techniques such as transoral robotic surgery (TORS) has let us to find not only the reduction of side effect; whereas it has demonstrated the same long-term results with better preservation of the quality of life. Choby *et al.*^[38] analysed in a retrospective study 34 patients who TORS was performed in oropharynx (tonsil and base of the tongue). They used the UW-QOL questionnaire in different times: at 1-month, 6-month, 12-month and 24-month postoperative visits. The results showed a tendency to improve throughout follow-up, specially the domains pain, swallowing, activity and chewing. Increasing recognition of the adverse effects of CRT and their negative effect on QOL has provided the rationale for TORS as a primary treatment modality option for some head and neck cancers. This study not only obtained an improvement in the QOL, whereas presents better results compared to the group of conventional surgery.^[38]

Other authors analysed 32 patients classified in 3 groups: surgery for resection, surgery and adjuvant RT and surgery and adjuvant RT/CMT. In this case, they apply the

UW-QOL modified questionnaire in which it is included a new item called overall well-being. Results showed that scores for all parameters were higher or at least equally high for group 2 compared to group 1. When asked to compare their pre- and post-therapeutic HRQOL, 21.9% of patients in group 1 stated that there were no differences, whereas 46.9% stated there was a moderate deterioration, and 31.3% stated that deterioration was marked. Furthermore, 53.1% of patients in group 2 and 56.3% of patients in group 3 reported a marked deterioration of their QOL after treatment. In fact, just 34.4% in group 2 and 53.1% in group 3 would consent to further RT/CMT if necessary during the follow up.^[39]

Herce-Lopez *et al.*^[40] elaborated a cross-sectional study including 60 patients treated for a head and neck cancer who survived over 5 years without recurrences. In this case, patients filled out the SF-36 questionnaire, which include 8 categories: physical functioning, role-physical, role-emotional, vitality, mental health, social function, pain and the social dimension. Regarding the impact of gender, in the male group, found statistically significant positive differences for the dimensions of vitality and general health; and significantly negative for the dimensions of role-physical, social functioning and pain. In the female group, statistically significant negative differences for the dimensions social functioning were observed. Respecting age, patients over 65 years showed statistically significant negative differences for social functioning and pain; and positive for vitality and general health status. Similar to previous results, T1-T2 stages had significant positive differences for general health and negative for role-physical, role-emotional, social functioning and pain. Also, T3-T4 showed statistically negative differences for social functioning and pain. The impact of surgical reconstruction showed that patients who underwent complex reconstruction referred worse social functioning and pain, whereas patients who did not receive this kind of surgical procedure they referred a better general health status unless worst role-physical, role-emotional, social functioning and pain.^[40]

Follow up length is still a controversial aspect, because every author obtained results according a short follow-up period. Nevertheless, Rogers *et al.*^[41] determined no differences respecting the QOL between patients after 1 year of treatment or 5 years. Although, other authors are not agree with this because patients consider themselves cured 5 years after treatment may significantly change their perception of the disease.

With regard to survival prediction from pre-treatment HRQOL data among HNSCC patients, few investigations with some extent of varied finding have been published. A significant predictive effect of HRQOL scores on survival has been detected, but noteworthy variations with regard to design, sample sizes, and use of HRQOL inventories exist.^[42-44] Osthus *et al.*^[45] determined the predictive potential of HRQOL scores in a heterogeneous cohort of patients with

newly diagnosed HNSCC. They used QLQ-C30 and QLQ-h&N35 questionnaires in a group of 106 patients, finding that high comorbidity is a risk factor especially cardiac disease. They did not find relation between tumour stage and tumour location, and, alcohol consumption supposes a predictive value of survival.^[45]

CONCLUSION

Over the last decades, the perspective and management of SCC in head and neck has changed, many disciplines have contributed to improve the prognosis not only surgeons. The advancement of reconstructive surgical techniques and adjuvant therapies such as RT/CMT made treatable an increased number of patients with many risk factors that otherwise would have been relegated to palliative care.

Regarding SCC prognosis, many factors have demonstrated to be influential but, high level tumour stage and short length of free survival disease time are the most important to predict the really expectation of therapies.

Despite de numerous studies published in the literature about the assessment of the quality of life in patients with HNSCC, the heterogeneity of the population and the lack of internal validity of studies, can explain why there is not a consensus about the accuracy of the questionnaires as a predictive tool to distinguish the bad prognosis cases and their capacity to choose the best therapeutic option in every situation.

Currently, data do not let us individualize patients' treatment, but this is the objective for the future and maybe new studies will show us the ways to identify how the QOL can modify the treatment choices.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Machiels JP, Lambrecht M, Hanin FX, Duprez T, Gregoire V, Schmitz S, Hamoir M. Advances in the management of squamous cell carcinoma of the head and neck. *Fl000Prime Rep* 2014;6:44.
2. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP, Gillison ML. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010;363:24-35.
3. Gillison ML. Human papillomavirus-associated head and neck cancer is a distinct epidemiologic, clinical, and molecular entity. *Semin Oncol* 2004;31:744-54.
4. Johnson-Obaseki S, McDonald JT, Corsten M, Rourke R. Head and neck cancer in Canada: trends 1992 to 2007. *Otolaryngol Head Neck Surg* 2012;147:74-8.
5. Ceccoli E, Bianchini C, Ciorba A, Candiani M, Riberti C, Pelucchi S, Pastore A. Reconstructive head and neck surgery: oncological and functional results. *Tumori* 2013; 99:493-9.
6. Gregoire V, Lefebvre JL, Licitra L, Felip E; EHNS-ESMO-ESTRO Guidelines Working Group. Squamous cell carcinoma of the head and

- neck: EHNS-ESMO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21:v184-6.
7. Miglani A, Patel VM, Stern CS, Weichman KE, Haigentz M Jr, Ow TJ, Garfein ES. Palliative reconstruction for the management of incurable head and neck cancer. *J Reconstr Microsurg* 2016;32:226-32.
 8. Morris LG, Sikora AG, Patel SG, Hayes RB, Ganly I. Second primary cancers after an index head and neck cancer: subsite-specific trends in the era of human papillomavirus-associated oropharyngeal cancer. *J Clin Oncol* 2011;29:739-46.
 9. Peck BW, Dahlstrom KR, Gan SJ, Caywood W, Li G, Wei Q, Zafereo ME, Sturgis EM. Low risk of second primary malignancies among never smokers with human papilloma virus-associated index oropharyngeal cancers. *Head Neck* 2013;35:794-9.
 10. van der Laan BF, Baris G, Gregor RT, Hilgers FJ, Balm AJ. Radiation-induced tumours of the head and neck. *J Laryngol Otol* 1995;109:346-9.
 11. Zbaren P, Nuyens M, Curschmann J, Stauffer E. Histologic characteristics and tumor spread of recurrent glottic carcinoma: analysis on whole-organ sections and comparison with tumor spread of primary glottic carcinomas. *Head Neck* 2007;29:26-32.
 12. Colevas AD. Chemotherapy options for patients with metastatic or recurrent squamous cell carcinoma of the head and neck. *J Clin Oncol* 2006;24:2644-52.
 13. Fury MG, Pfister DG. Current recommendations for systemic therapy of recurrent and/or metastatic head and neck squamous cell cancer. *J Natl Compr Canc Netw* 2011;9:681-9.
 14. Goodwin WJ, Jr. Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means? *Laryngoscope* 2000;110:1-18.
 15. Stell PM. Time to recurrence of squamous cell carcinoma of the head and neck. *Head Neck* 1991;13:277-81.
 16. Holsinger FC, Funk E, Roberts DB, Diaz EM Jr. Conservation laryngeal surgery versus total laryngectomy for radiation failure in laryngeal cancer. *Head Neck* 2006;28:779-84.
 17. Ganly I, Patel SG, Matsuo J, Singh B, Kraus DH, Boyle JO, Wong RJ, Shaha AR, Lee N, Shah JP. Results of surgical salvage after failure of definitive radiation therapy for early-stage squamous cell carcinoma of the glottic larynx. *Arch Otolaryngol Head Neck Surg* 2006;132:59-66.
 18. Sinclair CF, Rosenthal EL, McColloch NL, Magnuson JS, Desmond RA, Peters GE, Carroll WR. Primary versus delayed tracheoesophageal puncture for laryngopharyngectomy with free flap reconstruction. *Laryngoscope* 2011;121:1436-40.
 19. Liao CT, Chang JT, Wang HM, Ng SH, Hsueh C, Lee LY, Lin CH, Chen IH, Huang SF, Cheng AJ, Yen TC. Salvage therapy in relapsed squamous cell carcinoma of the oral cavity: how and when? *Cancer* 2008;112:94-103.
 20. Mucke T, Wagenpfeil S, Kesting MR, Holzle F, Wolff KD. Recurrence interval affects survival after local relapse of oral cancer. *Oral Oncol* 2009;45:687-91.
 21. Liu SA, Wong YK, Lin JC, Poon CK, Tung KC, Tsai WC. Impact of recurrence interval on survival of oral cavity squamous cell carcinoma patients after local relapse. *Otolaryngol Head Neck Surg* 2007;136:112-8.
 22. Kozrzewa JP, Lancaster WP, Iseli TA, Desmond RA, Carroll WR, Rosenthal EL. Outcomes of salvage surgery with free flap reconstruction for recurrent oral and oropharyngeal cancer. *Laryngoscope* 2010;120:267-72.
 23. Wong LY, Wei WI, Lam LK, Yuen AP. Salvage of recurrent head and neck squamous cell carcinoma after primary curative surgery. *Head Neck* 2003;25:953-9.
 24. Lim JY, Lim YC, Kim SH, Byeon HK, Choi EC. Factors predictive of successful outcome following salvage treatment of isolated neck recurrences. *Otolaryngol Head Neck Surg* 2010;142:832-7.
 25. Licitra L, Mesia R, Keilholz U. Individualised quality of life as a measure to guide treatment choices in squamous cell carcinoma of the head and neck. *Oral Oncol* 2016;52:18-23.
 26. Moriel G, Roscani MG, Matsubara LS, Cerqueira AT, Matsubara BB. Quality of life in patients with severe and stable coronary atherosclerotic disease. *Arq Bras Cardiol* 2010;95:691-7.
 27. Goldstein DP, Hynds Karnell L, Christensen AJ, Funk GF. Health-related quality of life profiles based on survivorship status for head and neck cancer patients. *Head Neck* 2007;29:221-9.
 28. Hammerlid E, Wirblad B, Sandin C, Mercke C, Edström S, Kaasa S, Sullivan M, Westin T. Malnutrition and food intake in relation to quality of life in head and neck cancer patients. *Head Neck* 1998;20:540-8.
 29. Qiu SS, Cambeiro M, Hontanilla B. Comparison of quality of life in head and neck stage IV squamous cell cancer patients treated with surgery and reconstruction versus radical radiotherapy. *Ann Plast Surg* 2014;73:205-9.
 30. Visacri MB, Ferrari GB, Dias P, Pimentel R, de Souza CM, Costa AP, de Carvalho Pincinato E, Lima CS, Mazzola PG, Moriel P. Quality of life of patients with squamous cell carcinoma of the head and neck receiving high-dose cisplatin chemotherapy and radiotherapy. *South Med J* 2015;108:343-9.
 31. Akkas EA, Yucel B, Kilickap S, Altuntas EE. Evaluation of quality of life in Turkish patients with head and neck cancer. *Asian Pac J Cancer Prev* 2013;14:4805-9.
 32. Rogers S, Lowe D. Screening for dysfunction to promote multidisciplinary intervention by using the University of Washington Quality of Life questionnaire. *Arch Otolaryngol Head Neck Surg* 2009;135:369-75.
 33. Dirix P, Nuyts S. Evidence-based organ-sparing radiotherapy in head and neck cancer. *Lancet Oncol* 2010;11:85-91.
 34. Haisfield-Wolfe ME, McGuire DB, Soeken K, Geiger-Brown J, De Forge BR. Prevalence and correlates of depression among patients with head and neck cancer: a systematic review of implications for research. *Oncol Nurs Forum* 2009;36:E107-25.
 35. Misono S, Weiss NS, Fann JR, Redman M, Yueh B. Incidence of suicide in persons with cancer. *J Clin Oncol* 2008;26:4731-8.
 36. Kendal WS. Suicide and cancer: a gender-comparative study. *Ann Oncol* 2007;18:381-7.
 37. Moubayed SP, Sampalis JS, Ayad T, Guertin L, Bissada E, Gologan OE, Soulières D, Lambert L, Filion E, Nguyen-Tan PF, Christopoulos A. Predicting depression and quality of life among long-term head and neck cancer survivors. *Otolaryngol Head Neck Surg* 2015;152:91-7.
 38. Choby GW, Kim J, Ling DC, Abberbock S, Mandal R, Kim S, Ferris RL, Duvvuri U. Transoral robotic surgery alone for oropharyngeal cancer: quality-of-life outcomes. *JAMA Otolaryngol Head Neck Surg* 2015;141:499-504.
 39. Mucke T, Koschinski J, Wolff KD, Kanatas A, Mitchell DA, Loeffelbein DJ, Deppe H, Rau A. Quality of life after different oncologic interventions in head and neck cancer patients. *J Craniomaxillofac Surg* 2015;43:1895-8.
 40. Herce-Lopez J, Rollon-Mayordomo A, Lozano-Rosado R, Infante-Cossio P, Salazar-Fernandez CI. Assessment of quality of life of oral cancer survivors compared with Spanish population norms. *Int J Oral Maxillofac Surg* 2013;42:446-52.
 41. Rogers SN, Hannah L, Lowe D, Magennis P. Quality of life 5-10 years after primary surgery for oral and oro-pharyngeal cancer. *J Craniomaxillofac Surg* 1999;27:187-91.
 42. Montazeri A. Quality of life data as prognostic indicators of survival in cancer patients: an overview of the literature from 1982 to 2008. *Health Qual Life Outcomes* 2009;7:102.
 43. Grignon LM, Jameson MJ, Karnell LH, Christensen AJ, Funk GF. General health measures and long-term survival in patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg* 2007;133:471-6.
 44. Meyer F, Fortin A, Gelinat M, Nabid A, Brochet F, Têtu B, Bairati I. Health-related quality of life as a survival predictor for patients with localized head and neck cancer treated with radiation therapy. *J Clin Oncol* 2009;27:2970-6.
 45. Osthus AA, Aarstad AK, Olofsson J, Aarstad HJ. Prediction of survival by pretreatment health-related quality-of-life scores in a prospective cohort of patients with head and neck squamous cell carcinoma. *JAMA Otolaryngol Head Neck Surg* 2013;139:14-20.

Current role in facial allograft transplantation: what have we learned?

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ABSTRACT

Face transplant (FT) has evolved enormously in the last 10 years since the successful completion of the first facial transplant. This procedure has become a new reconstructive option for complex facial deformities to restore the anatomy of patients with severely disfigured faces. The authors review the literature and discuss the main surgical, immunological, and ethical aspects as well as the results described in patients undergoing FT. To date there have been more than thirty FT worldwide. The main indication was post-traumatic deformity. In all cases a standard immunosuppression was performed with three drugs, although acute rejection episodes were observed, that could be controlled with conventional immunosuppressive regimen. Overall, functional and aesthetic results have been excellent at short-term and high satisfaction rate exceeded initial expectations, although long-term data are still scarce. Major complications were opportunistic infections. Five deaths that occurred have reopened the ethical debate about the potential complications and concerns of providing informed consent to recipients. Continuous progresses in microsurgical techniques and preoperative planning have promoted the evolution from partial to full FT. All these are on the basis of accurate and careful selection of well-motivated candidates. The next challenge will be getting new immunosuppressive treatment strategies. Although clinical experience has demonstrated the FT viability, it is still considered an experimental procedure in which we have much to learn to define its true role in the current reconstructive surgery and resolve major technical, medical and ethical problems involved.

Key words:

Face transplantation; composite tissue transplantation; facial allograft transplantation; facial reconstruction; outcomes and complications of face transplantation

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INTRODUCTION

Face transplant (FT) has evolved enormously in the last 10 years since the successful completion of the first facial transplant allograft (FAT) in November 2005 in Amiens (France).^[1] However, scientific community must be cautious because there are scarcely few selected cases in clinical follow-up after a decade of clinical experience. In a literature search in English from the PubMed/Medline data base (<http://www.ncbi.nlm.nih.gov/PubMed>), with the following search terms: “face”, “facial”, “transplant”, “transplantation”, “composite allotransplant tissue” and “vascularized composite allotransplant”, there have been reported clinical data from 31 patients to date [Figures 1 and 2].^[2,3] Although the comparative analysis of data reported in these early clinical cases shows that overall functional and aesthetic results in FT are encouraging, there are still many unresolved aspects of experimental research and clinical application to know the real extent and the true dimension of this procedure. This paper will review, point by point, major surgical, immunological, ethical, and clinical follow-up aspects on FAT published in the literature, from the analysis of the results reported by pioneer FT teams on patients operated to date.

SURGICAL CONSIDERATIONS

Preclinical models

The initial problem on the knowledge of FT is common to other body transplants: to provide a basis for the study of the surgical technique. That is why in recent years, worldwide FT transplant teams have developed different preclinical research in experimental surgery on animals and cadaveric models. The pioneer teams have emphasized the importance on this preclinical work prior to the completion of a successful clinical transplantation.^[4,5] FAT is a new field in reconstructive surgery that is still considered as an experimental and exceptional procedure. Therefore, it is imperative to establish a protocol and a previous training to achieve excellence in this demanding procedure, to know perfectly the anatomy of the allograft needed in each case, and to handle the tissues that compound the allograft.

The non-human primate model is the best suited since it provides tissues of anatomical size and texture very similar to humans.^[6-9] Other models used have been rats,^[10-14] rabbits and dogs,^[15,16] animals that are easy to use in a research center [Figure 3].^[17,18]

Preclinical studies on cadavers have sought to find the best way to recover soft and hard tissues, muscles, nerves and vessels of donor face while reducing tissue ischemia to the minimum. Studies on cadavers have been performed with recovery simulations of lower, middle and/or upper third face for FAT preparation^[19-23] and development either partial or total.^[4,5,24-26] Preclinical planning studies for implementation and validation of tools for planning, design and adaptation of allograft into recipients are other key

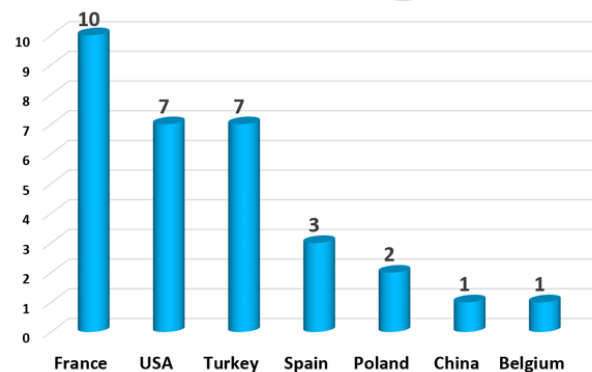


Figure 1: Countries in which a face transplant had been made in the last decade

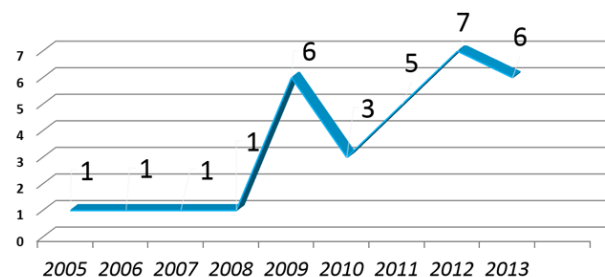


Figure 2: Evolution of the number of face transplant in the last decade

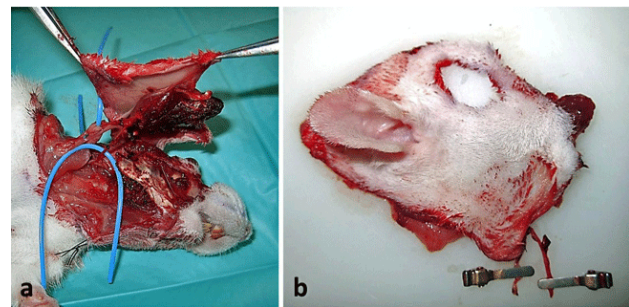


Figure 3: Design of a facial transplant allograft in a Wistar rat. (a) Allograft pedicled in the external jugular vein and common carotid artery; (b) external view of the allograft before anastomosis

aspects for anatomical structures of donors and recipients are consistent in size and configuration to allow a reasonable accommodation. Anthropometric study of facial soft and hard tissues both the donor and the recipient must be as accurate as possible to ensure the viability of the procedure and the proper insertion of the allograft into the defect,^[27-29] even including the preparation of preoperative surgical osteotomy guides.^[30-32]

Overall aspects on surgery

In FAT, microsurgical procedures are similar to those other complex reconstructive surgical procedures of the face.^[33,34] The crux here is based on the exact surgical planning and surgical execution considering to ensure the adequate perfusion and blood supply allograft, knowledge of angiosomes, and vascularity of facial tissues. Allografts are recovered from the donor in monobloc containing the facial osteomiocutaneous tissues with mimic muscles, vessels and motor and sensory

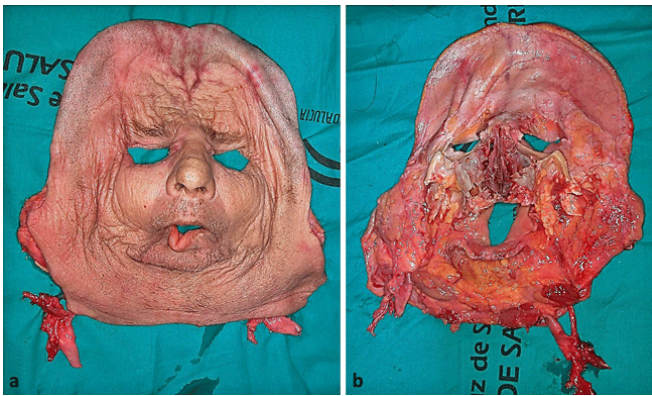


Figure 4: Experimental model of a full face transplant in cadaver. (a) External and (b) internal view of the allograft

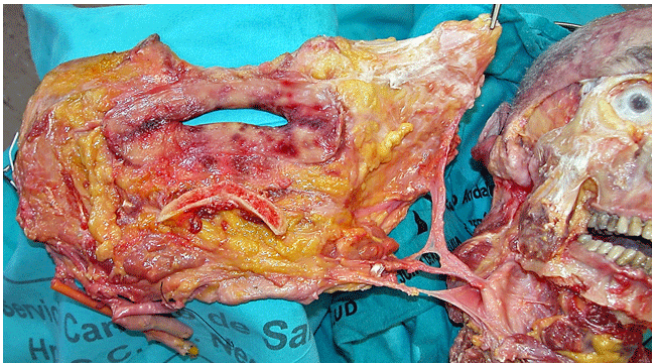


Figure 5: Experimental model of a partial face transplant in cadaver

nerves. This has ensured the full allograft vascularization by preserving muscle-cutaneous perforating vessels between facial muscles and skin component [Figure 4].^[35]

FAT design has varied depending on tissue components involved, which determines the extent of each surgical procedure.^[36] Most allografts included cheeks, nose, eyelids and lips, and in some cases the tongue and parotid glands have been transferred. At least half of them contained bone (maxilla and/or mandible, including teeth), which requires open osteosynthesis.^[37,38]

Despite the complexity of the procedure, surgical primary failure has not been documented, which can be explained by head and neck rich vascularisation and the capability of the teams involved in the procedures.^[39-41] A significant blood loss has been described during the procedure requiring transfusions.^[42]

The restoration of the circulation allograft is achieved with relatively few vascular anastomoses. Most anastomosis was performed in large diameter vessels to minimize the risk of thrombosis. Complete revascularization of the face has proved to be possible from the anastomosis of one vascular pedicle,^[43] and vascular viability of the maxilla, palate and mandible.^[34] Most teams opted for a bilateral connection of the external carotid or facial arteries. The venous drainage was mainly channeled through the connection of the external jugular, facial or thyrolinguofacial trunk

veins [Figure 5].^[44] Almost all anastomoses were performed using conventional end-to-end or end-to-side microsurgical techniques.

Regarding facial nerve neurorrhaphy, some teams have accessed to nerve via parotidectomy, performing the nerve connection at recipient main trunk also including the parotid glands in the allograft.^[21] Other teams have performed the anastomosis at peripheral facial nerve branches doing an intra-parotid nerve dissection^[45,46] connecting only distal branches to the parotid gland.^[1,47] Regarding sensory nerves, most teams connected infraorbital and mental nerves^[48-51] while the supraorbital nerve neurorrhaphy is preferably carried out in full FT.^[35,36,52,53]

PRE-TRANSPLANT CONSIDERATIONS

In all cases a brain death donor is required besides the consent of the family. Donors and recipients are matched on the basis of race, sex, blood type, human leukocyte antigen and skin color.^[54,55] A full psychological evaluation before including the recipient as a candidate on a FT program is essential.^[56] Evident contraindications are psychological disorders that impair the ability of the recipient to follow the immunosuppressive protocol. Informed consent prior to the FT requires a clear understanding of the risks of surgery, immunosuppressive therapy and potential allograft rejection.

Recovery strategy of allograft

The cold ischemia period since vascular disconnection of allograft from donor until reperfusion is one of the most important aspects as the rapid removal and transference into recipient is required. In the context of a multi-organ donation, most FT teams have removed “the face in the first place” after cardiac arrest and before organ removal. In worldwide experience to date, most of allografts have been removed from beating heart donors in brain dead. In order to reduce cold ischemia period if multiple organ donations, surgical teams prepared the removal procedure by dissecting most of allografts under maintenance of circulation before clamping.^[1,39,57-59] If recovery and insertion of allograft are performed in different hospitals, allograft transport should be done in a secure manner in an organ preservation solution, and as quickly as possible to limit the time of ischemia tissues.^[60,61]

FT indications

The most common indication was to restore the lower two thirds of the face, especially the perioral and periorbital central zone, including in some cases the forehead, eyelids and scalp, as well as maxilla, mandible and teeth.^[62] Inclusion criteria of patients in FT programs vary from one center to another. To date only those patients with extensive tissue damage in which conventional reconstruction procedures previously failed have been included.^[49,63,64]

Most frequent indications were severe burns (including

chemical and electrical burns), gunshot trauma, animal bites, plexiform neurofibromas of the trigeminal nerve in the context of neurofibromatosis type I, tumoral sequelae, severe side effects of radiotherapy, vascular tumors, and occupational traumas. However, it must be highlighted that since the first full FT performed in 2010,^[43] the spectrum of possible candidates has expanded. In general, patients with significant medical comorbidity, lack of guarantee for post-transplant monitoring, high risk of recurrent cancer under immunosuppression, and pregnancy are excluded.^[49] Protocols considered only stable psychological and immunologically patients as potential recipients.^[50,56]

Patients with plexiform neurofibromas associated with neurofibromatosis type 1 are possible candidates in the absence of viable reconstructive options. To date, 4 patients with neurofibromatosis have undergone FAT.^[40,51,55] However, this procedure should still be considered as an experimental option and consequently these patients as well as cancer patients must be carefully selected.

Evolution from partial to full FT

All FT had been partial before the first full FT which included different aesthetic units of the face (Barcelona, Spain, 2010).^[43,65] After the first full FT there was a change in the reconstructive paradigm because of adherence to the classical concepts of facial aesthetic to a FT. From that moment, most FT was complete. This full FT approach has proven effective and safe, and most teams have reported excellent anatomical and functional results.^[66-68] Moreover, the restoration of a full new anatomy of the face allowed conventional cosmetic procedures of refinement.

IMMUNOLOGY

The skin is the most important and largest component of FAT, and it is well known that the skin (and the mucosa) has a high immunogenicity, so it is inevitable that rejection episodes are triggered at different times:^[33,69] in the early period (hyper-acute rejection), within days or months after transplantation (acute rejection) or chronic rejection.^[55,70]

Hyper-acute graft rejection has not been reported so far. However, most recipients had acute rejection episodes in the first year, revealed as skin redness, swelling and nodules and papules.^[54,71,72] In FAT, episodes of mild rejection may be easier to treat than in solid organ transplantation due to immediate visibility of the skin and easy inspection. Episodes of acute rejection were usually reversible with corticosteroids (bolus treatment), supplemented in some cases by topical drugs (steroids and tacrolimus).^[1,55] Other treatments included the increased tacrolimus levels and topical drugs.^[39,50,51,73]

For monitoring rejection episodes after transplantation, clinical systematic follow up is required performing skin and/or oral mucosa biopsies.^[69,74] In some cases, a sentinel free flap has been transplanted into donor for carrying out

multiple biopsies and monitoring of clinical and pathological signs of graft rejection.^[1,48]

Prevention and treatment of rejection

Immunosuppressive therapy in patients with FT has been similar to the scheme used in solid organ transplantation.^[43,52,54,66,75] It consisted of an "induction" phase, which starts at an early stage of surgery, followed a "maintenance" phase. Most teams employed an induction therapy with polyclonal anti-thymocyte globulins, monoclonal antibody anti-interleukin-2 receptor as daclizumab and basiliximab, anti-CD3 monoclonal antibodies, mycophenolate mofetil, methylprednisolone, and tacrolimus (anti-calcineurin inhibitor).^[76] Maintenance and preventing rejection of allograft is based today on the use of a global immunosuppression induction, non-specific, by postoperative triple therapy consisting of the administration of mycophenolate mofetil, tacrolimus and prednisolone.^[77]

This immunosuppressive regimen should continue during the life of the patient, which carries risks of toxicity and complications like infections (opportunistic infections by cytomegalovirus, herpes, *etc.*), metabolic (diabetes), nephrotoxicity, hypertension and malignancies.^[54] Although theoretically there is a risk of chronic rejection, most teams have not reported evidence of chronic rejection over time.^[72,78,79] Recently there is a report of chronic rejection in a patient who left immunosuppression due to a malignant process.^[3]

New strategies of immunosuppression

Current research is focused on finding new immunosuppressive molecules that allow adjustment of known drugs and avoid the problems associated with allograft rejection. Research are mainly directed on antibodies anticell-T, the development of more selective molecules with less toxicity to organs (kidney, liver) and creating a state of hematopoietic chimerism. In addition, new immunosuppressant associations are being studied to reduce the doses of each. Some researchers have used bone marrow infusion, thymoglobulin, anti-IL-2 receptor antibody and irradiation of X-rays. Since the skin is the more antigenic portion of allograft, topical treatment with tacrolimus ointment and phototherapy has also been used.^[34,80]

RESULTS AND COMPLICACIONES

Functional and aesthetic results

FT aims to re-establish the functions of speaking, swallowing and mimic muscle mobility as well as to provide aesthetic improvements that allow patients to live a normal social life. Although a systematic analysis of all cases cannot be performed due to the unique characteristics of each patient, the results of the earliest FT, as a whole, are very convincing.^[81]

Unlike solid organ transplants, in which a metabolic

function after revascularization of the organ is immediately detected, the FAT is initially viable after reperfusion in the operating room, but facial motor activity and sensitivity are absent. Therefore, in the first months of follow up, nerve regeneration and muscle rehabilitation becomes a challenge as well as patient's ability to reintegrate allograft in sensory and motor cortex in the central nervous system. Between 6-9 months, patients recovered discriminative sensitivity of the face. The recovery of active and passive movements of the lips was obtained between 6 and 12 months, but results differed between full or partial FT.^[45,48,54,57] The functional improvements have been proportional to motor recovery, reaching even in some cases to restoration of near normal functional capacity.^[72]

The long-term results are yet to be assessed and reported by different FT teams and therefore a final assessment of the results cannot be offered now.^[82] Almost all patients have been able to breathing through the nose, smelling, chewing, swallowing, eating and speech and phonation recovering to a greater or lesser extent.^[50,55,63,82-84]

Psycho-social outcomes

Psychological long-term results are not known with accuracy because the novel nature of the procedure, although preliminary results have reported positive outcomes. In general, patients experienced an acceptable improvement of quality of life with social reintegration and meaningful changes for having recovered their body image, without psychological disorders.^[40,63] All patients have accepted their new face and some patients returned to work.^[45,53,72] The favorable outcome is probably a consequence of the strict preoperative selection with a psychiatric and psychological evaluation of motivated and compliant patients.^[85-87]

After the inset of the donor face on the recipient, no problems were detected with regard to identity transfer or change in body image in FT recipients. What is obtained is a mixture of both subjects, and due to differences in the characteristics of each facial bony structures, a new face is formed. Therefore, the initial concerns about appearance of feelings of depersonalization to the new face and the transfer or separation of the donor's identity have not been substantiated. According to donor families, recipients and transplant teams, the recipients do not resemble the donor.^[72,88,89]

Post-transplant revisions and refinements

To the extent that the number of FT has increased, various surgical refinements have been planned to optimize the aesthetic and functional results.^[30,90] The functional and aesthetic improvement can be supported in various secondary procedures as such as the re-alignment of the jaws, restoration of teeth, re-suspension of the soft tissues, fat injections and dermabrasion.^[91-95] These revisions did not seem to have caused major complications or affected in any way the immunological rejection.^[40]

Post-trasplant complications

Despite the complexity of the procedure, no cases of allograft loss by surgical failures, such as arterial or venous thrombosis or tissue damage by cold ischemia time, have been reported. The most important complications derived from immunosuppressive therapy and drug toxicity leading to metabolic disorders, opportunistic infections and increased incidence of malignancy. Tacrolimus, a potent calcineurin inhibitor, is well known for its severe nephrotoxicity.^[63] The majority of patients have suffered from opportunistic infections such as cytomegalovirus, herpes simplex, herpes zoster, candida albicans and bacterial infections, most of them have been treated successfully.^[55,75] Due to an increased risk of carcinogenesis in the context of a suppressed immune system, it was likely that a correlation between immunosuppressive medication and the appearance of tumors was established. In this sense, neurofibromatosis type 1 or post-oncological sequelae are indications that may be critically questioned. Finally, at least 5 deaths associated with the FT procedure have been collected so far caused by failure of the immunotherapeutic regime, sepsis, recurrent malignant tumor, multiple organ failure and suicide,^[34,96] which for some researchers reopens the question of risk versus benefit in the FT.^[3,97]

ETHICAL IMPLICATIONS

From the ethical point of view, a crucial issue widely discussed in the literature has been the obligation to subject individuals to immunosuppressive treatment during patient's life, leading to increased risk of developing complications,^[33] when it is not a procedure to "save lives", unlike solid organ transplant that often have an urgent indication to save a person life. From that point of view, the risks of immunosuppressive therapy may outweigh the benefits of the procedure due to recipients are exposing to the risks of immunosuppression. However, all transplant teams have reported that the reestablishment of the functional capabilities and the restoration of the face "have changed the lives of patients", and a significant improvement in patient's quality of life has occurred.^[45]

An ethical unsolved problem would arise if a total loss allograft occurs as a result of a surgical complication or irreversible rejection.^[55] Confronted with this catastrophic situation, very few reconstructive options would remain for that patient^[54] and hypothetically, patients would return to a starting situation much worse as consequence of the procedure FAT.

Informed consent is crucial before performing a FAT for the reasons discussed above. Moreover, the question has arisen whether consent can be truly informed if the candidate previously does not coexist with the facial disfigurement for some time. Something as outlined in breast reconstruction, where a period of post-mastectomy waiting gives the woman the opportunity to accept a complex reconstruction.^[98] Pediatric age creates an ethical

dilemma since it is linked to the difficulty of obtaining informed children consent, psychological instability during the years of growth, risk of cancer and complications of immunosuppression throughout a long life ahead. Another aspect to consider is the high economic costs of FT,^[54,99] both the procedure and the immunosuppressive lifetime therapy, preventing its widespread application and opens the discussion of opportunity-cost for countries with public health services.^[54,99]

FUTURE DIRECTIONS

From the first FT performed a decade ago, more than thirty FAT have been performed worldwide with promising immunological, functional, psychological and aesthetic results that have clearly demonstrated the feasibility of this demanding process. Unlike solid organ transplant that “potentially saved a life”, what FAT provides is a “change of life” to recipients. This substantial difference has created ethical concerns in society about the exposure of individuals (young and otherwise healthy) to potential immunological complications and the ability to provide informed consent. On the other hand, the incessant advance in microsurgical techniques and the computer assisted surgical planning, have progressively allowed a broader clinical application of this procedure, and have promoted the evolution from the first partial FT to full procedures of FT. All these are on the basis of accurate and careful selection of well-motivated candidates. There is a firm belief in the scientific community that, at present, surgical innovations in the field of FT have overcome to some extent immune, medical and ethical aspects. However, FT is still an experimental procedure in which we have much to learn. Next challenge will be getting new strategies for more effective immunosuppressive therapy and improved donor-specific tolerance. There are still unresolved problems and crucial aspects to define the true role of the FAT in the current reconstructive surgery.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Devauchelle B, Badet L, Lengelé B, Morelon E, Testelin S, Michallet M, D'Hauthuille C, Dubernard JM. First human face allograft: early report. *Lancet* 2006;368:203-9.
- Roche NA, Blondeel PN, Van Lierde KM, Vermeersch HF. Facial transplantation: history and update. *Acta Chir Belg* 2015;115:99-103.
- Wu L, Bueno E, Pomahac B. Facial transplantation: worth the risks? A look at evolution of indications over the last decade. *Curr Opin Organ Transplant* 2015;20:615-20.
- Siemionow M, Unal S, Agaoglu G, Sari A. A cadaver study in preparation for facial allograft transplantation in humans: part I. What are alternative sources for total facial defect coverage? *Plast Reconstr Surg* 2006;117:864-72.
- Meningaud JP, Paraskevas A, Ingallina F, Bouhana E, Lantieri L. Face transplant graft procurement: a preclinical and clinical study. *Plast Reconstr Surg* 2008;122:1383-9.
- Silverman RP, Banks ND, Detolla LJ, Shipley ST, Panda A, Sanchez RA, Azimzadeh AM, Pierson RN 3rd, Wang D, Rodriguez ED, Holton LH 3rd, Bartlett ST. A heterotopic primate model for facial composite tissue transplantation. *Ann Plast Surg* 2008;60:209-16.
- Barth RN, Bluebond-Langner R, Nam A, Stanwix M, Shipley S, Bartlett ST, Rodriguez ED. Facial subunit composite tissue allografts in nonhuman primates I. Technical and functional requirements for prolonged graft survival. *Plast Reconstr Surg* 2009;123:493-501.
- Kuo YR, Shih HS, Lin CC, Huang CC, Yang JC, Wu WS, Goto S, Chen CL, Lee WP. Swine hemi-facial composite tissue allotransplantation: a model to study immune rejection. *J Surg Res* 2009;153:268-73.
- Baek RM, Eun SC, Heo CY, Chang H. Experimental facial transplantation surgery. *J Craniofac Surg* 2010;21:648-51.
- Ulusal BG, Ulusal AE, Ozmen S, Zins JE, Siemionow MZ. A new composite facial and scalp transplantation model in rats. *Plast Reconstr Surg* 2003;112:1302-11.
- Landin L, Cavadas PC. The mystacial pad flap: a functional facial flap in rats. *Ann Plast Surg* 2005;56:107-8.
- Yazici I, Carnevale K, Klimczak A, Siemionow M. A new rat model of maxilla allotransplantation. *Ann Plast Surg* 2007;58:338-44.
- Landin L, Cavadas PC, Gonzalez E, Rodriguez JC, Caballero A. Functional outcome after facial allograft transplantation in rats. *J Plast Reconstr Aesth Surg* 2008;61:1034-43.
- Kulahci Y, Siemionow M. A new composite hemiface/mandible/tongue transplantation model in rats. *Ann Plast Surg* 2010;64:114-21.
- Liu Q, Li Q, Zheng S, Zheng D. Preservation of canine composite facial flaps using UW solution. *Arch Facial Plast Surg* 2010;12:263-8.
- Yu D, Li Q, Zheng S, Wang H, Liu Q. Some results of our research on composite tissue transplantation in dogs. *Transplant Proc* 2010;42:1953-5.
- Yazici I, Unal S, Siemionow M. Composite hemiface/calvaria transplantation model in rats. *Plast Reconstr Surg* 2011;118:1321-7.
- Ramirez AE, Lao WW, Wang YL, Cheng HY, Wei FC. Two-stage face transplantation: a new concept in vascularized composite allotransplantation. *Microsurgery* 2015;35:218-26.
- Siemionow M, Agaoglu G, Unal S. A cadaver study in preparation for facial allograft transplantation in humans: part II. Mock facial transplantation. *Plast Reconstr Surg* 2006;117:876-85.
- Lengelé BG. Current concepts and future challenges in facial transplantation. *Clin Plast Surg* 2009;36:507-21.
- Meningaud JP, Benjoar MD, Hivelin M, Hermeziu O, Toure G, Lantieri L. Procurement of total human face graft for allotransplantation: a preclinical study and the first clinical case. *Plast Reconstr Surg* 2010;126:1181-90.
- Gordon CR, Susarla SM, Peacock ZS, Cetrulo CL, Zins JE, Papay F, Kaban LB, Yaremchuk MJ. Osteocutaneous maxillofacial allotransplantation: lessons learned from a novel cadaver study applying orthognathic principles and practice. *Plast Reconstr Surg* 2011;128:465-79.
- Meningaud JP, Hivelin M, Benjoar MD, Toure G, Hermeziu O, Lantieri L. The procurement of allotransplants for ballistic trauma: a preclinical study and a report of two clinical cases. *Plast Reconstr Surg* 2011;127:1892-900.
- Gastman B, Djohan R, Siemionow M. Extending the Cordeiro maxillofacial defect classification system for use in the era of vascularized composite transplantation. *Plast Reconstr Surg* 2012;130:419-22.
- Baccarani A, Follmar KE, Erdmann D, Levin LS. Face transplantation surgical options and open problems in cadaveric models: a review article. *Microsurgery* 2013;33:239-46.
- Mohan R, Borsuk DE, Dorafshar AH, Wang HD, Bojovic B, Christy MR, Rodriguez ED. Aesthetic and functional facial transplantation: a classification system and treatment algorithm. *Plast Reconstr Surg* 2014;133:386-97.
- Rudman K, Hoekzema C, Rhee J. Computer-assisted innovations in craniofacial surgery. *Facial Plast Surg* 2011;27:358-65.
- Brown EN, Dorafshar AH, Bojovic B, Christy MR, Borsuk DE, Kelley TN, Shaffer CK, Rodriguez ED. Total face, double jaw, and tongue transplant simulation: a cadaveric study employing computer-assisted techniques. *Plast Reconstr Surg* 2012;130:815-23.
- Caterson EJ, Diaz-Siso JR, Shetye P, Junker JP, Bueno EM, Soga S, Rybicki FJ, Pomahac B. Craniofacial principles in face transplantation. *J Craniofac Surg* 2012;23:1234-8.
- Jacobs JM, Dec W, Levine JP, McCarthy JG, Weimer K, Moore K, Ceradini DJ. Best face forward: virtual modeling and custom device fabrication to optimize craniofacial vascularized composite allotransplantation. *Plast Reconstr Surg* 2013;131:64-70.
- Caterson EJ. Future directions for face transplantation. *J Craniofac Surg*

- 2014;25:3-5.
32. Fernandez-Alvarez JA, Infante-Cossio P, Barrera-Pulido F, Gacto-Sanchez P, Suarez-Mejias C, Gomez-Ciriza G, Sicilia-Castro D, Gomez-Cia T. Virtual reality AYRA software for preoperative planning in facial allotransplantation. *J Craniofac Surg* 2014;25:1805-9.
33. Petruzzo P, Kanitakis J, Badet L, Pialat JB, Boutroy S, Charpulat R, Mouly J, Gazarian A, Lanzetta M, Brunet M, Devauchelle B, Testelin S, Martin X, Dubernard JM, Morelon E. Long-term follow-up in composite tissue allotransplantation: in-depth study of five (hand and face) recipients. *Am J Transplant* 2011;11:808-16.
34. Shanmugarajah K, Hettiaratchy S, Clarke A, Butler PE. Clinical outcomes of facial transplantation: a review. *Int J Surg* 2011;9:600-7.
35. Pushpakumar SB, Barker JH, Soni CV, Joseph H, van Aalst VC, Banis JC, Frank J. Clinical considerations in face transplantation. *Burns* 2010;36:951-8.
36. Hui-Chou HG, Nam AJ, Rodriguez ED. Clinical facial composite tissue allotransplantation: a review of the first four global experiences and future implications. *Plast Reconstr Surg* 2010;125:538-46.
37. Smeets R, Rendenbach C, Birkelbach M, Al-Dam A, Gröbe A, Hanken H, Heiland M. Face transplantation: on the verge of becoming clinical routine? *Biomed Res Int* 2014;2014:907272.
38. Özel AŞ, Güçlü ZA, Gülşen A, Özmen S. The Importance of the condition of the donor teeth and jaws during allogeneic face transplantation. *J Craniofac Surg* 2015;26:1338-41.
39. Guo S, Han Y, Zhang X, Lu B, Yi C, Zhang H, Ma X, Wang D, Yang L, Fan X, Liu Y, Lu K, Li H. Human facial allotransplantation: a 2-year follow-up study. *Lancet* 2008;372:631-8.
40. Lantieri L, Meningaud JP, Grimbert P, Bellivier F, Lefacheur JP, Ortonne N, Benjoar MD, Lang P, Wolkenstein P. Repair of the lower and middle parts of the face by composite tissue allotransplantation in a patient with massive plexiform neurofibroma: a 1-year follow-up study. *Lancet* 2008;372:639-45.
41. Gomez-Cia T, Sicilia-Castro D, Infante-Cossio P, Barrera-Pulido F, Gacto-Sanchez P, Lagares-Borrego A, Narros-Gimenez R, Garcia-Perla A, Hernandez-Guisado JM, Gonzalez-Padilla JD. Second human facial allotransplantation to restore a severe defect following radical resection of bilateral massive plexiform neurofibromas. *Plast Reconstr Surg* 2011;127:995-6.
42. Hinojosa Pérez R, Porras López M, Escobedo-Ortega AM, Herruzo Avilés A, León A, Noval JA, Gómez-Cía T, Sicilia D, González Padilla JD. Severe rhabdomyolysis after allogeneic transplantation of facial structures: a case report. *Transplant Proc* 2010;42:3081-2.
43. Barret JP, Gavalda J, Bueno J, Nuviols X, Pont T, Masnou N, Colomina MJ, Serracanta J, Arno A, Huguet P, Collado JM, Salameiro P, Moreno C, Deulofeu R, Martínez-Ibáñez V. Full face transplant: the first case report. *Ann Surg* 2011;254:252-6.
44. Infante-Cossio P, Sicilia-Castro D, Gomez-Cia T. Comment on: "Two-stage face transplantation: a new concept in vascularized composite allotransplantation". *Microsurgery* 2015;35:419-20.
45. Pomahac B, Pribaz J, Eriksson E, Bueno EM, Diaz-Siso JR, Rybicki FJ, Annino DJ, Orgill D, Caterson EJ, Caterson SA, Carty MJ, Chun YS, Sampson CE, Janis JE, Alam DS, Saavedra A, Molnar JA, Edrich T, Marty FM, Tullius SG. Three patients with full facial transplantation. *N Engl J Med* 2012;366:715-22.
46. Khalifian S, Brazio PS, Mohan R, Shaffer C, Brandacher G, Barth RN, Rodriguez ED. Facial transplantation: the first 9 years. *Lancet* 2014;384:2153-63.
47. Cavadas PC, Ibáñez J, Thione A. Surgical aspects of a lower face, mandible, and tongue allotransplantation. *J Reconstr Microsurg* 2012;28:43-7.
48. Dubernard JM, Lengelé B, Morelon E, Testelin S, Badet L, Moure C, Beziat JL, Dakpé S, Kanitakis J, D'Hauthuille C, El Jaafari A, Petruzzo P, Lefrançois N, Taha F, Sirigu A, Di Marco G, Carmi E, Bachmann D, Cremades S, Giraux P, Burloux G, Hequet O, Parquet N, Francès C, Michallet M, Martin X, Devauchelle B. Outcomes 18 months after the first human partial face transplantation. *N Engl J Med* 2007;357:2451-60.
49. Pomahac B, Diaz-Siso JR, Bueno EM. Evolution of indications for facial transplantation. *J Plast Reconstr Aesthet Surg* 2011;64:1410-6.
50. Pomahac B, Pribaz J, Eriksson E, Annino D, Caterson S, Sampson C, Chun Y, Orgill D, Nowinski D, Tullius SG. Restoration of facial form and function after severe disfigurement from burn injury by a composite facial allograft. *Am J Transplant* 2011;11:386-93.
51. Sicilia-Castro D, Gomez-Cia T, Infante-Cossio P, Gacto-Sanchez P, Barrera-Pulido F, Lagares-Borrego A, Narros-Gimenez R, Garcia-Perla A, Hernandez-Guisado JM, Gonzalez-Padilla JD. Reconstruction of a severe facial defect by allotransplantation in neurofibromatosis type I: a case report. *Transplant Proc* 2011;43:2831-7.
52. Shanmugarajah K, Hettiaratchy S, Butler PE. Facial transplantation. *Curr Opin Otolaryngol Head Neck Surg* 2012;20:291-7.
53. Singhal D, Pribaz JJ, Pomahac B. The Brigham and Women's Hospital face transplant program: a look back. *Plast Reconstr Surg* 2012;129:e81-8.
54. Siemionow M, Ozturk C. Face transplantation: outcomes, concerns, controversies, and future directions. *J Craniofac Surg* 2012;23:254-9.
55. Infante-Cossio P, Barrera-Pulido F, Gomez-Cia T, Sicilia-Castro D, Garcia-Perla-Garcia A, Gacto-Sanchez P, Hernandez-Guisado JM, Lagares-Borrego A, Narros-Gimenez R, Gonzalez-Padilla JD. Facial transplantation: a concise update. *Med Oral Patol Oral Cir Bucal* 2013;18:e263-71.
56. Lantieri L. Face transplant: a paradigm change in facial reconstruction. *J Craniofac Surg* 2012;23:250-3.
57. Siemionow M, Papay F, Alam D, Bernard S, Djohan R, Gordon C, Hendrickson M, Lohman R, Eghesad B, Coffman K, Kodish E, Paradis C, Avery R, Fung J. Near-total human face transplantation for a severely disfigured patient in the USA. *Lancet* 2009;374:203-9.
58. Bueno J, Barret JP, Serracanta J, Arnó A, Collado JM, Valles C, Colominas MJ, Diez Y, Pont T, Salameiro P, Martinez-Ibáñez V. Logistics and strategy of multiorgan procurement involving total face allograft. *Am J Transplant* 2011;11:1091-7.
59. Gomez-Cia T, Infante-Cossio P, Sicilia-Castro D, Gacto-Sanchez P, Gonzalez-Padilla JD. Sequence of multiorgan procurement involving face allograft. *Am J Transplant* 2011;11:2261.
60. Pomahac B, Papay F, Bueno EM, Bernard S, Diaz-Siso JR, Siemionow M. Donor facial composite allograft recovery operation: Cleveland and Boston experiences. *Plast Reconstr Surg* 2012;129:e461-7.
61. Siemionow M, Ozturk C. An update on facial transplantation cases performed between 2005 and 2010. *Plast Reconstr Surg* 2011;128:e707-20.
62. Gordon CR, Susarla SM, Peacock ZS, Kaban LB, Yaremchuk MJ. Le Fort-based maxillofacial transplantation: current state of the art and a refined technique using orthognathic applications. *J Craniofac Surg* 2012;23:81-7.
63. Lantieri L, Hivelin M, Audard V, Benjoar MD, Meningaud JP, Bellivier F, Ortonne N, Lefacheur JP, Gilton A, Suberbielle C, Marty J, Lang P, Grimbert P. Feasibility, reproducibility, risks and benefits of face transplantation: a prospective study of outcomes. *Am J Transplant* 2011;11:367-78.
64. Iglesias M, Butrón P, Osuna-Leal AI, Abarca-Perez L, Sosa-Ascencio MJ, Moran-Romero MA, Cruz-Reyes AU, Pineda-Gutierrez FJ, Leon-Lopez DA, Garcia-Alvarez MN, Alberu J, Vilatoba M, Leal-Villalpando RP, Zamudio-Bautista J, Acosta-Nava VM, Gonzalez J. Is Mexico ready for face transplantation? *Transplant Proc* 2015;47:1998-2002.
65. Barret JP, Serracanta J, Collado JM, Garrido A, Salameiro P, Pont T, Masnou N, Arana E, Arno A, Garcia V, Sancho J, Ruiz M. Full face transplantation organization, development, and results-the Barcelona experience: a case report. *Transplant Proc* 2011;43:3533-4.
66. Bojovic B, Dorafshar AH, Brown EN, Christy MR, Borsuk DE, Hui-Chou HG, Shaffer CK, Kelley TN, Sauerborn PJ, Kennedy K, Hyder M, Brazio PS, Philosophie B, Barth RN, Scalea TM, Bartlett ST, Rodriguez ED. Total face, double jaw, and tongue transplant research procurement: an educational model. *Plast Reconstr Surg* 2012;130:824-34.
67. Pomahac B, Pribaz JJ, Bueno EM, Sisk GC, Diaz-Siso JR, Chandawarkar A, Westvik TS, Malin EW, Eriksson E. Novel surgical technique for full face transplantation. *Plast Reconstr Surg* 2012;130:549-55.
68. Pomahac B, Bueno EM, Sisk GC, Pribaz JJ. Current principles of facial allotransplantation: the Brigham and Women's Hospital experience. *Plast Reconstr Surg* 2013;131:1069-76.
69. Kanitakis J, Badet L, Petruzzo P, Beziat JL, Morelon E, Lefrançois N, Francès C, Claudy A, Martin X, Lengelé B, Testelin S, Devauchelle B, Dubernard JM. Clinicopathologic monitoring of the skin and oral mucosa of the first human face allograft: report on the first eight months. *Transplantation* 2006;82:1610-5.
70. Alam DS, Papay F, Djohan R, Bernard S, Lohman R, Gordon CR, Hendrickson M, Siemionow M. The technical and anatomical aspects of the World's first near-total human face and maxilla transplant. *Arch Facial Plast Surg* 2009;11:369-77.
71. Fischer S, Lian CG, Kueckelhaus M, Strom TB, Edelman ER, Clark RA, Murphy GF, Chandraker AK, Riella LV, Tullius SG, Pomahac B. Acute rejection in vascularized composite allotransplantation. *Curr Opin Organ Transplant* 2014;19:531-44.
72. Petruzzo P, Testelin S, Kanitakis J, Badet L, Lengelé B, Girbon JP, Parmentier

- H, Malcus C, Morelon E, Devauchelle B, Dubernard JM. First human face transplantation: 5 years outcomes. *Transplantation* 2012;93:236-40.
73. Siemionow MZ, Papay F, Djohan R, Bernard S, Gordon CR, Alam D, Hendrickson M, Lohman R, Eghesad B, Fung J. First U.S. near-total human face transplantation: a paradigm shift for massive complex injuries. *Plast Reconstr Surg* 2010;125:111-22.
74. Chaudhry A, Sosin M, Bojovic B, Christy MR, Drachenberg CB, Rodriguez ED. Defining the role of skin and mucosal biopsy in facial allotransplantation: a 2-year review and analysis of histology. *Plast Reconstr Surg* 2015;136:559-67.
75. BenMarzouk-Hidalgo OJ, Cordero E, Gómez-Cía T, Sánchez M, González-Padilla JD, Infante-Cossio P, Sicilia-Castro D, Hernández-Guisado JM, Pérez-Romero P. First face composite-tissue transplant recipient successfully treated for cytomegalovirus infection with preemptive valganciclovir treatment. *Antimicrob Agents Chemother* 2011;55:5949-51.
76. Whitaker IS, Duggan EM, Alloway RR, Brown C, McGuire S, Woodle ES, Hsiao EC, Maldonado C, Banis JC Jr, Barker JH. Composite tissue allotransplantation: a review of relevant immunological issues for plastic surgeons. *J Plast Reconstr Aesthet Surg* 2008;61:481-92.
77. Siemionow M, Madajka M, Cwykiel J. Application of cell-based therapies in facial transplantation. *Ann Plast Surg* 2012;69:575-9.
78. Wu S, Xu H, Ravindra K, Ildstad ST. Composite tissue allotransplantation: past, present and future-the history and expanding applications of CTA as a new frontier in transplantation. *Transplant Proc* 2009;41:463-5.
79. Unadkat JV, Schneeberger S, Horibe EH, Goldbach C, Solari MG, Washington KM, Gorantla VS, Cooper GM, Thomson AW, Lee WP. Composite tissue vasculopathy and degeneration following multiple episodes of acute rejection in reconstructive transplantation. *Am J Transplant* 2010;10:251-61.
80. Garrett GL, Beegun I, D'souza A. Facial transplantation: historical developments and future directions. *J Laryngol Otol* 2015;129:206-11.
81. Fischer S, Kueckelhaus M, Pauzenberger R, Bueno EM, Pomahac B. Functional outcomes of face transplantation. *Am J Transplant* 2015;15:220-33.
82. Westvik TS, Dermietzel A, Pomahac B. Facial restoration by transplantation: the Brigham and Women's face transplant experience. *Ann Plast Surg* 2015;74 Suppl 1:S2-8.
83. Lierde KM, Roche N, Letter MD, Corthals P, Stillaert F, Vermeersch H, Blondeel P. Speech characteristics one year after first Belgian facial transplantation. *Laryngoscope* 2014;124:2021-7.
84. Roche NA, Vermeersch HF, Stillaert FB, Peters KT, De Cubber J, Van Lierde K, Rogiers X, Colenbie L, Peeters PC, Lemmens GM, Blondeel PN. Complex facial reconstruction by vascularized composite allotransplantation: the first Belgian case. *J Plast Reconstr Aesthet Surg* 2015;68:362-71.
85. Johnson SE, Corsten MJ. Facial transplantation in a new era: what are the ethical implications? *Curr Opin Otolaryngol Head Neck Surg* 2009;17:274-8.
86. Siemionow MZ, Gordon CR. Institutional review board-based recommendations for medical institutions pursuing protocol approval for facial transplantation. *Plast Reconstr Surg* 2010;126:1232-9.
87. Soni CV, Barker JH, Pushpakumar SB, Furr LA, Cunningham M, Banis JC Jr, Frank J. Psychosocial considerations in facial transplantation. *Burns* 2010;36:959-64.
88. Coffman KL, Gordon C, Siemionow M. Psychological outcomes with face transplantation: overview and case report. *Curr Opin Organ Transplant* 2010;15:236-40.
89. Coffman KL, Siemionow MZ. Face transplantation: psychological outcomes at three-year follow-up. *Psychosom* 2013;54:372-8.
90. Dorafshar AH, Bojovic B, Christy MR, Borsuk DE, Iliff NT, Brown EN, Shaffer CK, Kelley TN, Kukuruga DL, Barth RN, Bartlett ST, Rodriguez ED. Total face, double jaw, and tongue transplantation: an evolutionary concept. *Plast Reconstr Surg* 2013;131:241-51.
91. Meningaud JP, Donsimoni JM, Lantieri L. Facial allograft transplantation and basal implantology (cortically anchored disk-design implants). *Rev Stomatol Chir Maxillofac* 2009;110:353-8.
92. Fisher M, Dorafshar A, Bojovic B, Manson PN, Rodriguez ED. The evolution of critical concepts in aesthetic craniofacial microsurgical reconstruction. *Plast Reconstr Surg* 2012;130:389-98.
93. Barret JP, Serracanta J. LeFort I osteotomy and secondary procedures in full-face transplant patients. *J Plast Reconstr Aesthet Surg* 2013;66:723-5.
94. Diaz-Siso JR, Parker M, Bueno EM, Sisk GC, Pribaz JJ, Eriksson E, Annino D, Tullius SG, Pomahac B. Facial allotransplantation: a 3-year follow-up report. *J Plast Reconstr Aesthet Surg* 2013;66:1458-63.
95. Mohan R, Fisher M, Dorafshar A, Sosin M, Bojovic B, Gandhi D, Iliff N, Rodriguez ED. Principles of face transplant revision: beyond primary repair. *Plast Reconstr Surg* 2014;134:1295-304.
96. Carty MJ, Hivelin M, Dumontier C, Talbot SG, Benjoar MD, Pribaz JJ, Lantieri L, Pomahac B. Lessons learned from simultaneous face and bilateral hand allotransplantation. *Plast Reconstr Surg* 2013;132:423-32.
97. Coffman KL, Siemionow MZ. Ethics of facial transplantation revisited. *Curr Opin Organ Transplant* 2014;19:181-7.
98. Gharb B, Rampazzo A, Hakki S, Madajka M, Cwykiel J, Stratton J, Siemionow MZ. Effectiveness of topical immunosuppressants in prevention and treatment of rejection in face allotransplantation. *Transplantation* 2013;95:1197-203.
99. Rüegg EM, Hivelin M, Hemery F, Maciver C, Benjoar MD, Meningaud JP, Lantieri L. Face transplantation program in France: a cost analysis of five patients. *Transplantation* 2012;93:1166-72.

Preface to special issue on “EuRePS Meeting”

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The present special issue collects the best papers from the “EuRePS” (European Residents in Plastic Surgery) Meeting, which was held in Favignana from 18th to 21st of June 2015. The scientific committee selected the best 5 presentations, to be published on *PAR* journal thanks to an agreement with the editorial board.

The 5 papers will be introduced by a letter by Dr. Carlo Melloni, a resident in Plastic Surgery at the University of Palermo, representing the Organizational Committee of the meeting. The first following paper is a letter from Dr. Giovanna Spino on her experience as a resident in India. The second paper by Dr. Margot den Hondt presents the outstanding twenty years of experience of her group in tracheal transplantation research on a rabbit model. The special issue continues with a clinical paper by Dr. Giuseppe Guarro on closed rhinoplasty and effects

and changes on voice and a paper by Dr. Mauro Barone on the application of regenerative medicine in treatment of acne scars. Finally, a case report on breast amyloidosis by Dr. Giulia Boscaini closes the special issue.

Thanks to all the authors and the reviewers for their contributions and to the editorial staff of *PAR* for hosting this special issue and for the precious and continuous support.

I hope you enjoy reading this special issue.

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Report on the European Residents in Plastic Surgery Meeting 2015

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As the chairman of the 2015 European Residents in Plastic Surgery (EuRePS) Meeting and on behalf of the organizing committee, it is a pleasure for me to describe the emotions that flew through that magic days.

The setting was Favignana, an enchanting, whimsical, harsh and welcoming island in the Mediterranean Sea. About 150 participants from all over Europe and beyond have invaded the venue of the meeting, an old tuna-fish factory called "Tonnara Florio".

Countdown to suspense and video with special effects introduced the EuRePS Meeting's opening, on 18th June 2015. The conference, entirely dedicated to European Residents in Plastic Surgery, has been organized by the School of Specialization in Plastic, Reconstructive and Aesthetic Surgery of the University of Palermo.

The enthusiasm is sky high and the focus is at the top. Off we go!

With their communications and high quality scientific works, the residents gave birth to four days of intense debate on the most advanced researches in plastic surgery.

Sharing knowledge and setting new collaborations were the main goals of the meeting. Attendants presented their works, both in podium and in poster presentation, and residents also had the opportunity to be moderators for one day tutored by the Directors of the Italian Schools of Plastic Surgery.

The poster session was one of the greatest innovations. With a fresh and informal format, the poster session was arranged as a short-oral-presentation during an aperitif. Speakers presented their works in three minutes enjoying

together with the attendant a glass of icy-white-wine.

The Keynote Lectures of the invited "Special Guest" such as Roy De Vita (Rome), Jaume Masia (Barcelona), Fabio Santanelli di Pompeo (Rome), Jan Vranckx (Leuven) and Salvatore D'Arpa (Gent) have enriched the scientific program with important practical information, charming the participants with their "ars oratoria".

The event ended on Sunday 21st with a space reserved for the projects of the Italian Society of Plastic, Reconstructive and Aesthetic Surgery (SICPRE) dedicated to residents and the awards for the best five works here published in *Plastic and Aesthetic Research Journal*.

The EuRePS Award for the best communication went to Margot Den Hondt, resident in Leuven (Belgium), who will have the opportunity to participate for free at the upcoming EuRePS meeting in Brussels in 2016.

In this way, four unforgettable days of science, friendship and fun come to the end: the perfect mix that made this event unique.

We are looking at the future; we are looking for a new way to arrange meetings in a different format: less formal, relaxed atmosphere and smart presentations with lots of tips and tricks messages to take home. The future is now!

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Conflicts of interest

There are no conflicts of interest.

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Incredible surgery in India

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I completed my Residency in Plastic and Reconstructive Surgery at Tata Memorial Hospital, in Mumbai, India. "Everybody has gone through something that has changed them in a way that they could never go back to the person they once were." My life changing experience happened in India.

The first time I stepped foot in India was the 26th of September 2014. My Professor, Giorgio De Santis, Chief of Plastic and Reconstructive Surgery Department at Policlinico di Modena, President in charge of the Italian Society of Plastic, Reconstructive and Aesthetic Surgery, gave all his residents the opportunity to spend six months of their residency abroad; I chose India.

Though I was excited to embark on this new adventure, I also had some fears about India. However, upon arriving many of my fears were quickly washed away.

I was a visiting doctor at Tata Memorial Hospital (TMH), the second largest cancer hospital in Asia and the national center for prevention, treatment, education and research in cancer. India is the oral cancer capital of the world; 80% of Indian patients come to consultancy with late or advanced stage malignancy. The major cause is "chewing tobacco", a smokeless tobacco product consumed by placing a portion of tobacco between cheek and gum or upper lip teeth and chewing. In particular in India the most common used is "paan", a preparation combining betel leaf with areca nut, tobacco, slaked lime (chunnam); it is an addictive and euphoria-inducing formulation.

At TMH every week about 15 free flaps were performed, mainly for head and neck reconstruction; free fibula flap was daily bread, along with free radial forearm or

anterolateral thigh flap; other flap performed weekly were pectoral mayor muscle cutaneous flap (about 5 per week), or latissimus dorsi (about 2 per week).

Deep inferior epigastric perforators flaps for breast reconstruction where performed once or twice a week and that's not including the larger number of breast cancer removals per week (approximately 20). Breast reconstruction is not a "trend" in India and this is basically due to the conservative way of thinking and religious beliefs; the female body is still considered a taboo and women often lack of self-confidence. Many women are unaware that it is even an option they could consider.

At TMH a normal surgery day was scheduled as following: patients arrived at the operating theater at 8 a.m.; after anesthesia induction, while the oncosurgeon started the demolition part, the plastic surgeons (one senior consultant and residents or fellows assisting him or performing surgery by themselves) performed the harvesting of the flap; the microscope time was always in the middle afternoon and most of the cases were completed for dinner time.

The senior consultants always trusted us as he would say, "Start, be confident, and if you have any problem, stop; I will guide you and help you". This is real teaching plastic surgery.

I spent the first month observing and trying to understand their entire system: the timing, the scrubbing, the instruments, the recording system, the tips and trick of surgery in India. After a month of observations, I started to scrub and to be part of the group. They welcomed

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me into their hospital and quickly I became part of their family of doctors.

At TMH I was able to hone the skills in which I had been trained at medical school. In India I had the opportunity to encounter, learn about, and treat a wide variety of diseases: sarcomas big as a soccer ball (to have a very realistic idea) or more, last stage melanomas, large ulcerations in the neck and cheek. Most of Indian population doesn't know that it is a tumor: at the beginning they try to tolerate, then they pray to their gods, they go to a guru, they use natural or ayurvedic methods and if all that fails they finally go to doctor for a checkup.

Patients come from the villages from all across India and sleep outside the TMH; some wait a week to be seen by a doctor. TMH is a hospital where different classes of people can still come and choose different levels of comfort during their recovery, from the beautiful suites to the common wards on the first floor with 30-40 beds. But all the patients in the operating room receive the same human treatment.

My life in India wasn't only confined to TMH. I scheduled one trip per month during the weekend: Goa, Agra (Taj Mahal), New Delhi, Kerala, Ajanta and Ellora, Rajasthan. This gave me the opportunity to understand, and still there's a lot to learn, a millenary and fascinated culture, made of colors, smiles, foods, traditions, gods, temples and all the ancient world mixed today with the fast and running progress that this developing country is brilliantly facing.

This experience changed my way of thinking, reacting, speaking, and living. I believe all residents should have an experience abroad in places like Europe, South America,

Asia, Australia, and there's always a lot to learn from other schools and mostly from other cultures.

I will always keep with me the tricks and tips learned in harvesting a fibula or other flaps, and why not at the last year of residency I learned other ways for better suturing. But the most important aspect of my professional experience was the lovely atmosphere of hospitality and kindness of people from the consultants to the residents, nurses and "chaiwalla", the boys employed to serve masala chai (Indian tea). In Veda, the sacred Sanskrit tests, is written: "Your mother, your father, your teacher and your guest must be treated as God by you."

Currently I am living in India with a goal to bridge my "western" experience with the expertise and knowledge I learned from my residency here. My hope is to educate women on the breast reconstruction options that are available to them.

I will always be grateful to my professor for giving me such an amazing opportunity to improve myself not only from the professional point stance but also from the human, social, and personal stance. I went to India to gain experience in my medical career and I gained that and so much more.

As you can see, spending six months in India was not as bad as most people would imagine.

Namaskar.

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Twenty years of experience with the rabbit model, a versatile model for tracheal transplantation research

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ABSTRACT

Pathologies comprising more than half the length of the trachea are a challenge to the reconstructive surgeon. Innovative tracheal transplantation techniques aim to offer the patient a curative solution with a sustained improvement in quality of life. This review summarizes the authors' experience with the rabbit as a versatile model for research regarding tracheal transplantation. Because of the segmental blood supply of the trachea, it is not feasible to transplant the organ together with a well-defined vascular pedicle. As such, the key element of successful tracheal transplantation is the creation of a new blood supply. This vascularized construct is created by prelaminating the rabbit trachea heterotopically, within the lateral thoracic fascia. After prelamination, the construct and its vascular pedicle are transferred to the orthotopic position in the neck. This model has become gold standard because of the advantages of working with rabbits, the anatomy of the rabbit trachea, and the reliability of the lateral thoracic artery flap. In this paper, the key elements of surgery in the rabbit are discussed, as well as the tracheal anastomosis and the harvest of the lateral thoracic artery flap. Practical tips and tricks are presented. The data described in this review represent the fundamentals of ongoing translational research in the center over the past twenty years.

Key words:

Trachea; transplantation; rabbit; lateral thoracic artery flap; prelamination; prefabrication

INTRODUCTION

Pathologies comprising more than half the length of the trachea are a challenge to the reconstructive surgeon. Innovative transplantation techniques aim to offer the

patient a curative solution with a sustained improvement in quality of life. In the nineties, Delaere *et al.*^[1] developed a rabbit model for orthotopic tracheal transplantation

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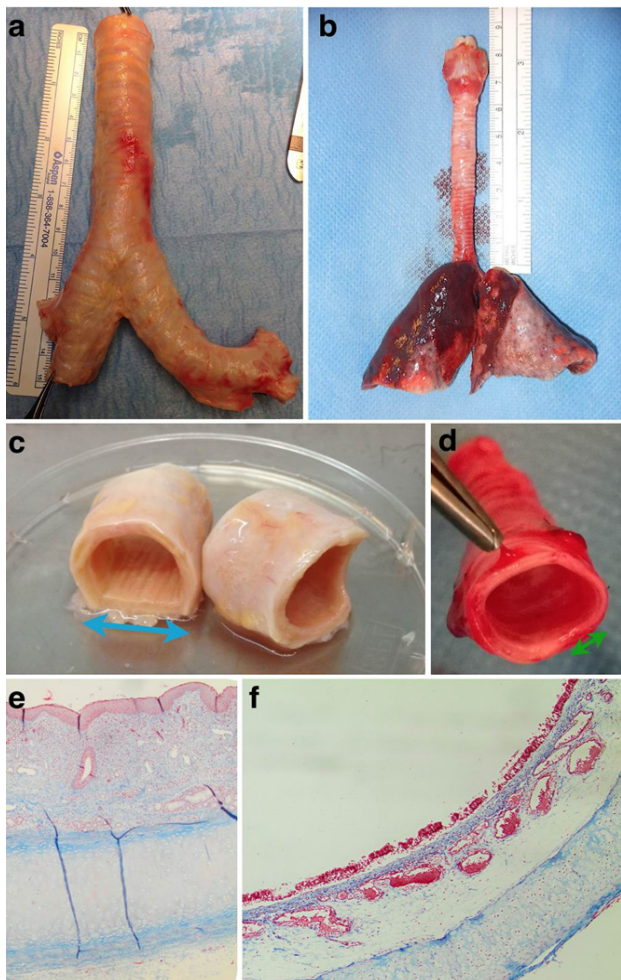


Figure 1: Human vs. rabbit trachea. (a) Human trachea measures 10 cm \pm 9 cm;^[10] (b) rabbit trachea measures on average 6.5 cm; (c) human cartilage rings comprise two-thirds of tracheal circumference vs. 90% in rabbits (d). The blue (c) and green (d) arrows represent the trachealis muscle; (e and f) Masson's trichrome stain: human trachea (e) contains more submucosal glands, compared to the better-developed submucosal capillaries in rabbits (f)

following a period of heterotopic revascularization in the lateral thoracic fascia. This animal model has become the gold standard of the authors for research regarding tracheal transplantation. As a result of this benchwork, the first human allogenic trachea was transplanted with withdrawal of immunosuppression in 2008.^[2] Since then, 5 more patients have been transplanted in our center.^[3,4] This clinical breakthrough, in addition to ongoing translational research in the rabbit model, has contributed to the authors' experience in the field. To date, over 200 tracheal transplantations in the rabbit have been performed. The authors wish to share their 20 years of experience with this versatile model by discussing the key elements of tracheal surgery in the rabbit, by reviewing key elements of the tracheal anastomosis and the harvest of the lateral thoracic artery flap, and by giving practical examples. The importance of proper revascularization of the construct is emphasized, as it is the authors' opinion that it is paramount in obtaining a successful tracheal transplantation.

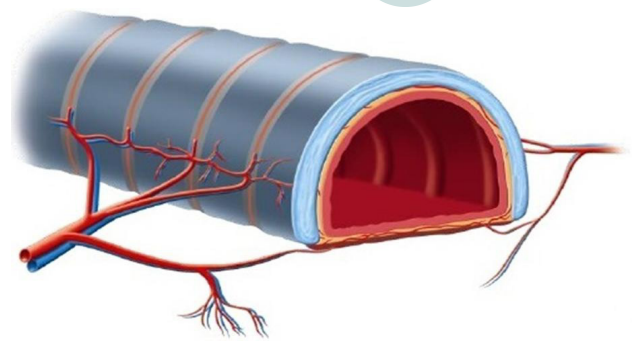


Figure 2: The tracheal blood supply is segmental.^[12] Branches from the inferior thyroid, subclavian, internal thoracic, innominate, superior and middle bronchial arteries form two lateral longitudinal anastomoses to supply the anterolateral trachea. These anastomoses give off transverse branches, which penetrate through the intercartilaginous ligaments to feed the submucosal capillary plexus. Cartilage is nourished via diffusion from this plexus. The posterior membranous trachea has an independent vascular supply derived from the oesophageal branches of the above-mentioned large neck vessels

Definitions

The term prelamination was defined by Pribaz and Fine^[5] to describe the implantation of tissue or another device into a vascular territory without manipulation of the blood supply. In a second stage, the construct with its blood supply can be transferred as a pedicled or free flap. As such, it is possible to create a multilayered, vascularized flap. Prelamination is not to be confused with prefabrication, introduced by Yao,^[6] which is the implantation of a vascular pedicle into a new territory. After neovascularization, tissue in this territory can be transferred based on the implanted pedicle.

Heterotopic placement of the trachea refers to the temporary placement of the tube in an anatomical location other than its normal position in the neck, for example in the lateral thoracic area. When the trachea is transplanted to its anatomically correct position in the neck, it is referred to as orthotopic position.

Why rabbits?

Numerous advantages are associated to working with rabbits. Rabbits have a long cervical trachea, allowing for easy access to the tube and segmental transplantation. Also, in contrast to larger animals such as pigs or sheep, rabbits are more readily accessible for research purposes and are more convenient to manage. Rabbit cell-surface markers for recognition by the immune system have been mapped out.^[7] These rabbits major-histocompatibility complexes are referred to as Rabbit Leukocyte Antigens. Rabbits are phylogenetically closer to primates and have a more diverse genetic background than inbred and outbred rodent strains.^[7-9] This makes the model a better overall approximation to humans, mimicking human genetic diversity more accurately. Moreover, the tracheal anatomy of humans resembles that of the rabbit closely. It is also possible to perform tracheoscopy as a monitoring tool following transplantation, and to obtain an adequate tracheal length for epithelial cell-cultivation.

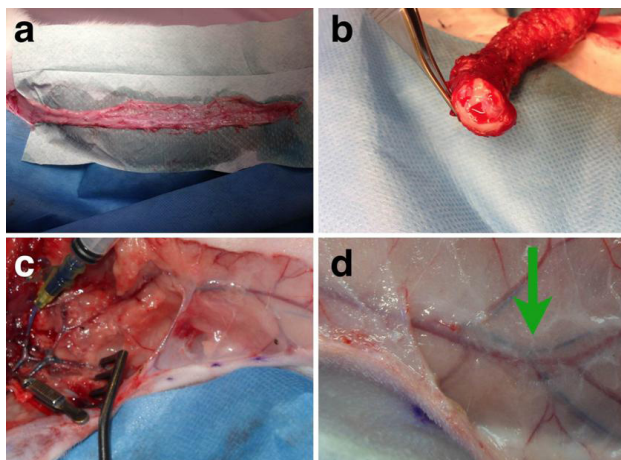


Figure 3: (a) Dissection of the lateral thoracic artery flap. The flap is isolated for 2 weeks within the donor area; (b) patent artery and vein after 2 weeks of flap isolation; (c) injection of silicone dye into the lateral thoracic artery; (d) patent artery with blue silicone dye up to distal from the bifurcation and anastomosis with the superficial inferior epigastric artery (green arrow)

Together with the relative cost-effectiveness compared to larger animal models, these characteristics make the rabbit our experimental model of choice.

TRACHEAL ANATOMY AND BLOOD SUPPLY

The rabbit trachea is approximately 6.5 cm in length and 0.5 cm in diameter [Figure 1].^[10] It is composed of cartilage rings connected by intercartilaginous ligaments anteriorly, and the trachealis muscle posteriorly. Both the cartilage and trachealis muscle contribute to the typical semi-rigid, semi-flexible characteristic of the trachea.

Hyaline cartilage is composed of an outer layer of highly-organized collagen type I and II fibrils, which provide strength to the construct.^[11] This outer layer surrounds a hydrated proteoglycan-core, which is able to resist compression. The rings are connected by fibroelastic ligaments, through which vessels penetrate to create a richly-anastomosing submucosal capillary network. The trachealis muscle shapes the posterior part of the circle. This smooth muscle alters luminal diameter, e.g. during coughing.

The intrinsic blood supply of the trachea is segmental [Figure 2].^[12] As such, unlike other solid organ transplants, a direct microvascular transfer of the organ together with its own vasculature is unfeasible. To solve this problem, the technique of indirect revascularization or prelamination is used.^[5,13] The trachea is wrapped with heterotopic tissue that is perfused by an identifiable vascular pedicle, such as the lateral thoracic fascia with the lateral thoracic artery and vein. In a second stage, the trachea and its new vascular pedicle are transferred to the orthotopic position in the neck.

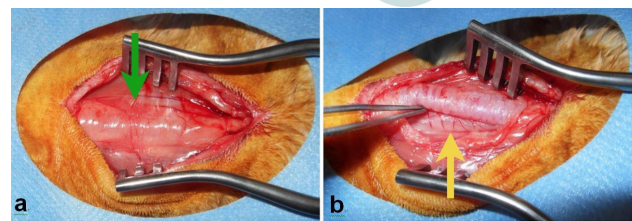


Figure 4: (a) Peroperative view on the pretracheal fascia with the thyroid gland (green arrow), after dividing the strap muscles; (b) image of posterior oesophageal branches (yellow arrow) after opening the pretracheal fascia

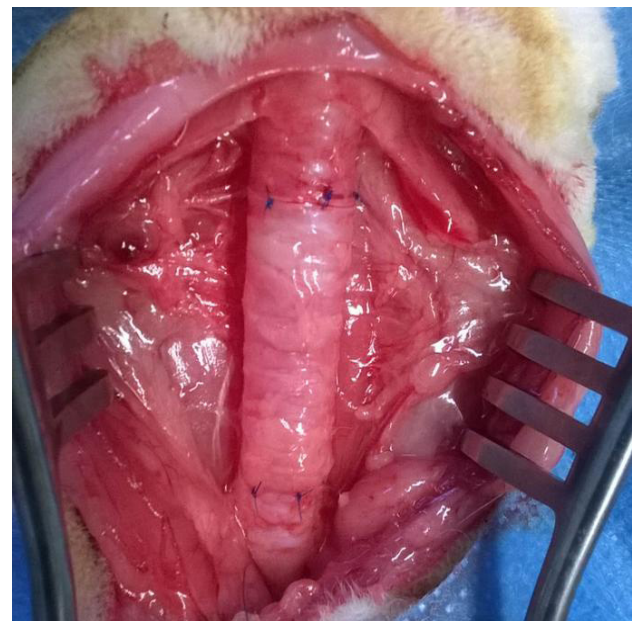


Figure 5: Peroperative image of autologous rabbit tracheal transplantation. Each anastomosis was closed with 6 points, using interrupted Prolène 6-0 sutures with external knots. The result shows no caliber mismatch

Lateral thoracic artery flap

The authors' workhorse flap for tracheal revascularization in humans is the free radial forearm flap. The counterpart in the rabbit is the pedicled lateral thoracic artery flap. The lateral thoracic artery flap is composed of subcutaneous fascia with a thin muscular layer, i.e. the panniculus carnosus.^[14] This striated muscle is particularly well developed in the trunk of rabbits. In humans, with the exception of remnants such as the platysma, it is almost entirely regressed.

The rabbit's lateral thoracic artery originates from the external thoracic artery.^[14] It travels caudally together with the lateral thoracic vein and nerve, deep to the pectoralis muscle. On the latero-inferior border of the muscle, the artery continues superficially within the thoracoabdominal panniculus carnosus. Around the second to third nipple, the artery anastomoses with secondary branches from the superficial inferior epigastric artery.^[15,16] One prominent lateral thoracic vein, which runs parallel to its artery, drains into the axillary vein.

The human lateral thoracic artery has a small caliber

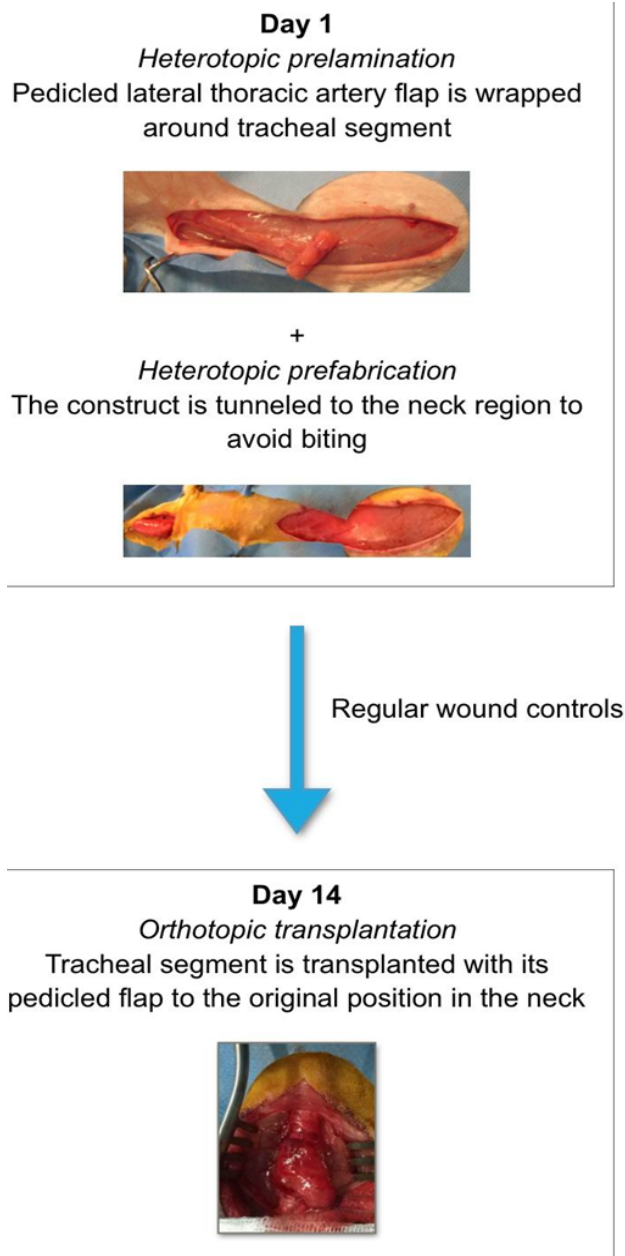


Figure 6: Timeline of tracheal revascularization and transplantation

and shows anatomical variations.^[17,18] Compared to the shorter, variable human lateral thoracic vessels, rabbit vessels in our series ($n > 200$) had a consistent, long course before anastomosing with the superficial inferior epigastric artery. As in humans, the caliber of the artery is small. Patency and course of the pedicle were demonstrated by isolating the flap for 2 weeks *in situ*, and by injecting silicone dye into the lateral thoracic artery (Microfil, Flow Tech, Inc., Massachusetts) [Figure 3].

RABBIT ANESTHESIA AND EUTHANASIA

Animal handling

All rabbits are treated according to the European Directive on the Protection of Animals. The Ethical Committee for

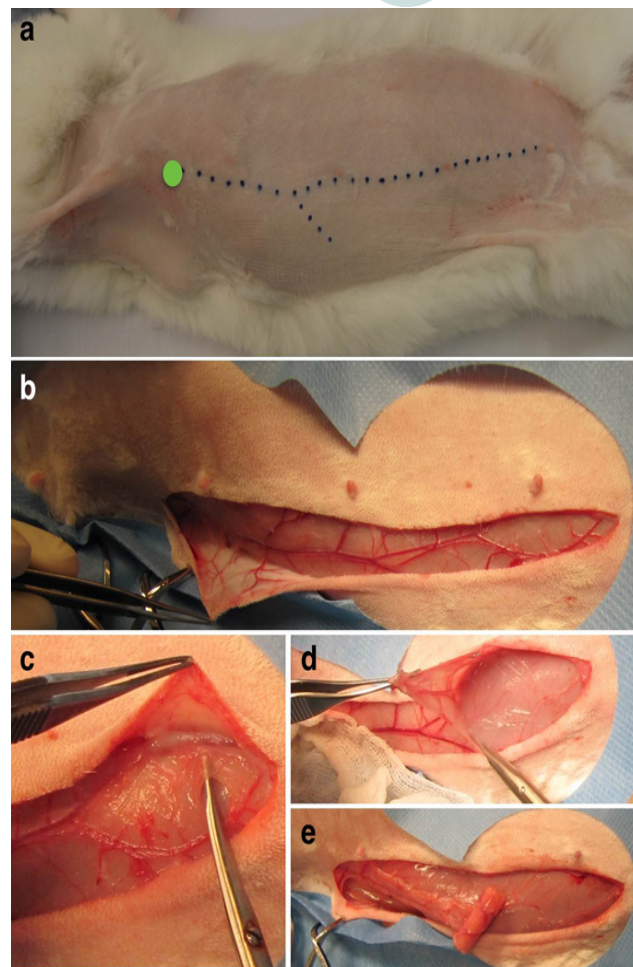


Figure 7: Harvest of lateral thoracic artery flap. The rabbit's head is located on the left. (a) The pedicle is visible throughout the skin after shaving. The pivot point of the flap (green circle) is situated at the latero-inferior border of the pectoralis muscle, where the lateral thoracic artery appears superficially; (b) view on the lateral thoracic artery and vein within the panniculus carnosus, coursing over the thorax (left) and abdomen (right). The lateral thoracic artery anastomoses with the superficial inferior epigastric artery at the level of the third nipple; (c) opening of fascia and panniculus carnosus distally; (d) elevation of the flap from the underlying muscles; (e) heterotopic prelamination of trachea within the lateral thoracic artery flap

Animal Experimentation of KU Leuven verifies each study protocol. As with any animal, it is important to handle rabbits with care. When lifting rabbits out of their cages, their lower legs are supported to prevent spinal cord injuries secondary to kicking.

Anesthesia

General anesthesia is performed by the researcher after having obtained adequate training skills and qualifications regarding laboratory animal science, the use of anesthetic agents, and monitoring tools.

Adult New Zealand white rabbits, weighing approximately 3 kg, are used in all studies. Rabbits are anesthetized by inhalation of isoflurane. Because of the particular smell of this gas, conscious rabbits will counteract its use. Moreover, induction with isoflurane may cause life-

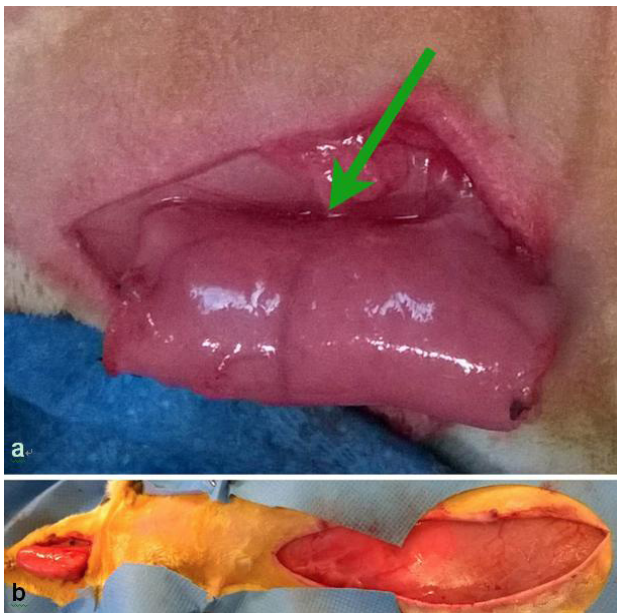


Figure 8: (a) Trachea wrapped within lateral thoracic artery flap, tunneled to cervical incision. The pedicle (green arrow) is oriented perpendicular to the longitudinal tracheal axis. The flap is fixed loosely to the local subcutaneous tissue to prevent dislocation; (b) lateral neck incision with tunneled construct (left) and lateral thoraco-abdominal incision (right), the flap donor site

threatening apnea in rabbits.^[19] Therefore, proper induction is carried out with the use of xylazine 6 mg/kg and ketamine 40 mg/kg intramuscularly, each injected into 1 gluteal region. The primary function of xylazine is sedation, while ketamine induces dissociative anesthesia. Analgesia is achieved by administering buprenorphine 0.05 mg/kg subcutaneously in the gluteal region. Additional doses are administered every 8 to 10 h, up to 72 h or as needed. Once proper induction is achieved, maintenance gas-anesthesia with isoflurane 1% to 2% supplemented with oxygen 1 L/min is administered by mask ventilation with spontaneous breathing. Rabbits are obligate nasal breathers, and as such, a mask firmly attached around the nose provides adequate inhalation of isoflurane. Rabbits are monitored with pulse oximetry. It is important to work in an adequately-equipped environment with proper ventilation and a scavenging system to minimize spills. Upon orthotopic transplantation, it is useful to have a sterile tube available in the operating field which can be inserted into the distal tracheal segment at the moment that the trachea is opened.

Euthanasia

Rabbits are euthanized by intravenous injection of a lethal dose of T61 0.3 mL/kg into the marginal auricular vein. When the trachea is used for transplantation or *in vitro* research, it is important to limit warm ischemia time.^[20,21] Therefore, opening of the neck is performed under general anesthesia. Only after exposure of the entire tracheal length, is the euthanizing agent administered and the trachea procured.

OPERATING TECHNIQUE

Tracheal surgery as well as flap dissection can be performed

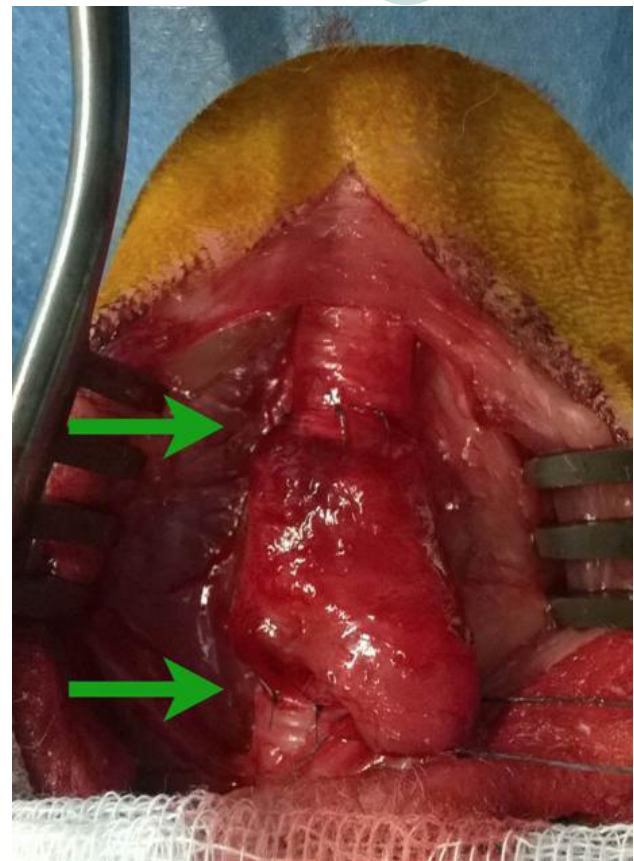


Figure 9. Orthotopic inset of trachea prelaminated within the left lateral thoracic artery flap (between green arrows)

with the rabbit in dorsal decubitus without the need to change position. After achieving proper sedation, the rabbit is shaved and the skin is disinfected with an alcoholic preparation. Both upper legs can be fixed in relaxed extension, taking care to avoid brachial plexus injury caused by overstretching of the limbs.

Tracheal surgery

The neck is opened via a vertical midline incision to expose the superficial investing fascia. Deep to this fascia, the paired sternocleidomastoid and strap muscles are divided via their connecting raphe, forming a bloodless plane at the midline. The raphe is opened from the thyroid cartilage to the sternal notch to expose the cervical trachea over its entire length. Upon approaching the sternal notch, the venous jugular arc is encountered, running deep to the distal part of the sternocleidomastoid muscles and crossing the midline. The branch is ligated and an orthostatic retractor is placed to provide adequate exposure [Figure 4]. The trachea is covered by pretracheal fascia. The thyroid gland is also incorporated into this fascia, and can be divided along the midline while opening the fascia longitudinally. The cervical trachea is then circularly detached from the surrounding tissue.

The recurrent laryngeal nerve travels within the tracheal-esophageal groove and enters the larynx on the posterior surface of the trachea.^[22] The nerve is identified and dissection is pursued close to the trachea to avoid vocal-cord paralysis.

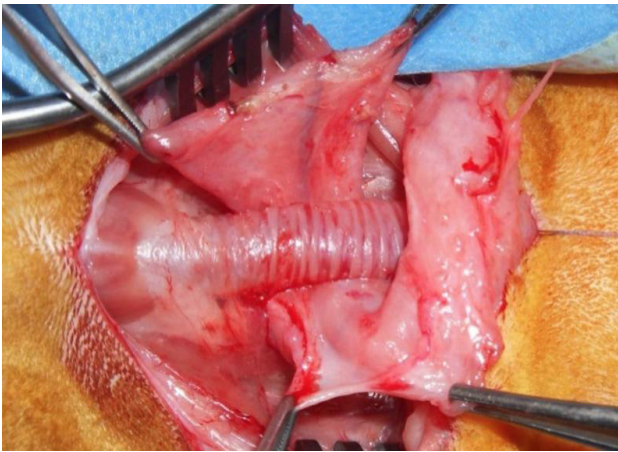


Figure 10: Wrapping of an orthotopic tracheal segment within the lateral thoracic artery flap. The native trachea is not manipulated until complete ingrowth of the flap, i.e. after two weeks. After prefabrication, the tracheal segment can be safely manipulated on its pedicle, without the risk of devascularization

The quality of the anastomosis depends on the degree of exposure, the presence of a bloodless field, and well-prepared tracheal ends. To control both segments, a retraction suture is placed proximal and distal to the segment that will be removed. The circularly-detached trachea is elevated and the desired tracheal length is procured. At this point, a sterile tube providing isoflurane can be placed into the distal native segment. A suctioning device is used to prevent blood from the submucosal capillary plexus of the tracheal ends from leaking into the tube.

Tracheal anastomosis

The tracheal anastomosis is performed under loop magnification with Prolène 6-0 interrupted sutures [Figure 5]. As with every anastomosis, careful approximation of both segments without overlap is important. To minimize the risk of stenosis, as few sutures as necessary are used to close the gap while preventing the leakage of air. On average, 6 to 7 points per anastomosis are used. If the caliber-difference is substantial, a short vertical incision is made in the narrowest segment to enlarge the diameter. To prevent secondary healing, it is important not to damage the mucosa. Microsurgical tissue handling techniques are used and grasping of the inner lumen with a forceps is avoided.

The first two interrupted sutures are placed posteriorly. Full-thickness bites are avoided by passing the suture from externally to the submucosal space. As such, the integrity of the fragile mucosa is preserved, and the risk of stenosis is diminished. Knots are tied externally, as intraluminal knots and suture ends will obstruct airflow. By suctioning the lumen, again without harming the mucosa, stasis of secretions or blood is prevented. Next, the remaining sutures are placed, progressing anteriorly. Once the tube is closed, a tracheoscopy can be performed to check the quality of the anastomosis from the luminal side.

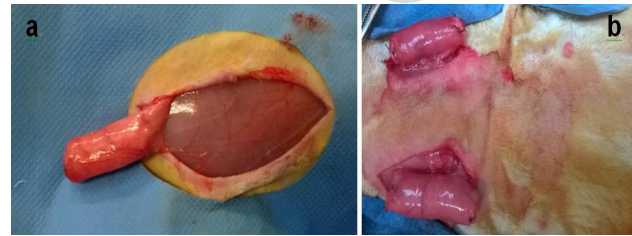


Figure 11: (a) Trachea wrapped with lateral thoracic artery flap, located within the lateral thoraco-abdominal area; (b) two constructs can be tunneled to two separate lateral neck incisions

Strap muscles and investing fascia are closed. Rabbits do not tolerate foreign material such as a Penrose drain to prevent possible air trapping. As a preventive measure, loose, interrupted sutures are placed, taking care not to impair flap vascularization. The distal part of the incision is left open for a distance of approximately one centimeter.

Flap dissection

Heterotopic prelamination

After the thoraco-abdominal region has been shaved, the lateral thoracic vessels are easily recognizable [Figures 6 and 7]. The vessels are palpable and visible through the skin. When in doubt, a handheld Doppler can be used to assist in marking the visible portion of the vessels. The point at which the vessels dive deeper to reach the axillary artery is the pivot point of the flap. The length from the pivot point to the native trachea is measured to ensure that the fabricated flap reaches the neck without tension. Extra length is added to the distal part of the flap for tracheal wrapping.

The skin overlying the vessels is incised and undermined between the dermis and subcutaneous fascia. Once the correct plane has been identified, dissection proceeds easily from distal to proximal. Operating clips or fine bipolar coagulation are used to divide branches to the skin. Once the length of the flap has been established, the pedicle is divided distally. It is important to preserve enough width of the flap to be able to wrap the desired tracheal length. The flap is elevated from the underlying muscles via the intervening bloodless plane. Elevation is continued towards the pivot point while leaving a cuff of tissue on each side of the pedicle. It is not necessary to skeletonize the pedicle proximally.

The flap is wrapped around the tracheal tube with its pedicle perpendicular to the longitudinal axis of the trachea to facilitate future orthotopic inset of the tube [Figure 8].

Rabbits tend to bite wounds in the trunk. To avoid trauma during prelamination, the construct is tunneled with its flap to a lateral neck incision [Figures 6 and 8]. This region is not accessible to biting and has an abundance of excess skin. The technique is a combination of prelamination and prefabrication. The trajectory from the lateral thoracic

incision to the neck incision is freed subdermally, creating enough width in the tunnel to prevent flap congestion. The flap is fixated in the neck to avoid dislocation. The incisions are closed with subcutaneous interrupted and intradermal running sutures with buried knots to prevent wound dehiscence secondary to biting.

Orthotopic transfer

Optimal revascularization of autologous trachea is achieved after fourteen days of heterotopic prelamination.^[23-25] At this point, the trachea and its flap can be transferred to their orthotopic position in the neck [Figure 9]. Upon inserting the construct, it is important to minimize the amount of tension placed on the flap. This tension can potentially create respiratory distress secondary to kinking of the tube. Proximal and distal anastomoses are performed as described earlier.

Postoperative care

Rabbits are awakened from anesthesia with extra oxygen via mask ventilation and kept warm. Adequate analgesia is provided postoperatively and enrofloxacin is administered in the drinking water upon indication. Tracheoscopy is performed weekly or in case of respiratory distress (2.9 mm, 0°, rigid endoscope, Karl Storz).

PRACTICAL EXAMPLES

Orthotopic prefabrication

To perform studies on vascularized autologous trachea, a native tracheal segment can be wrapped with lateral thoracic fascia prior to manipulation [Figure 10]. After two weeks of prefabrication, the autologous tracheal segment is vascularized and can be manipulated safely on the lateral thoracic pedicle.

Heterotopic prelamination

Regular wound controls are planned during heterotopic vascularization. Every three days the skin is opened and the construct is exposed under general anesthesia. As such, intraluminal tissue-ingrowth and mucus-accumulation are avoided, thereby preventing fibrosis and infection.

For ethical reasons, if orthotopic inset is not planned, two lateral thoracic artery flaps can be used per rabbit to minimize the number of animals used [Figure 11].

COMPLICATIONS AND LIMITATIONS

Complications

Minor complications such as seroma formation can be treated by aspiration of the region of fluctuance. Wound dehiscence is prevented by using intradermal running sutures with buried knots, and by transferring the construct to the neck during heterotopic revascularization. To date, no flap failures have been

observed. Three rabbits exhibited flap congestion, which could be corrected by widening the subcutaneous tunnel (1.5%, total $n = 200$).

Limitations

Although rabbit tracheal anatomy resembles human anatomy closely, the rabbit is not a large animal model. Rabbit trachea contains more submucosal vascular structures, as compared to the more glandular submucosa of human trachea [Figure 1]. Furthermore, the rabbit trachealis muscle encompasses only 10% of the tracheal circumference, in contrast to 30% in humans. Also, it is postulated that rabbits have better developed longitudinal anastomoses along the lateral tracheal wall, as is the case for cats and dogs.^[12] Another difficulty in the use of rabbits for study is the application of immunohistochemistry markers in rabbit tissue. Rabbits are commonly used to produce monoclonal antibodies against rodent or human epitopes. As a consequence, appropriate rabbit-specific antibodies are more difficult to find, as they are often produced in the rabbit itself. As in humans, a disadvantage of the rabbit's lateral thoracic artery is its routinely small caliber, which makes it more difficult for free flap transfer.

CONCLUSION

This review summarizes our experience with the rabbit as a versatile model for tracheal transplantation research. The advantages of working with rabbits, the anatomy of the rabbit trachea and the reliability of the lateral thoracic artery flap make this model the authors' gold standard. Additionally, the pedicled lateral thoracic artery flap can be used for various reconstructive procedures and prelamination studies. The data presented in this review represent the fundamentals of ongoing translational research in our center over the past twenty years. Because of the segmental blood supply of the trachea, it is unfeasible to transplant the organ together with a well-defined vascular pedicle. As such, the main challenge of successful tracheal transplantation is the creation of a new blood supply. In clinical practice, revascularization of human allotrachea in the radial forearm fascia was enhanced by making incisions in the intercartilaginous ligaments.^[3] To further enhance vascularization of transplanted tracheae, the authors are currently investigating pro-angiogenic strategies in their standardized rabbit model.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Delaere PR, Liu ZY, Hermans R, Sciort R, Feenstra L. Experimental tracheal allograft revascularization and transplantation. *J Thorac Cardiovasc Surg* 1995;110:728-37.
2. Delaere PR, Vranckx JJ, Verleden G, De Leyn P, Van Raemdonck D, Leuven Tracheal Transplant Group. Tracheal allotransplantation after withdrawal of immunosuppressive therapy. *N Engl J Med* 2010;362:138-45.
3. Delaere PR, Vranckx JJ, Meulemans J, Vander Poorten V, Segers K, Van Raemdonck D, De Leyn P, Decaluwé H, Doms C, Verleden G. Learning curve in tracheal allotransplantation. *Am J Transplant* 2012;12:2538-45.
4. Delaere PR, Vranckx JJ, Den Hondt M; Leuven Tracheal Transplant Group. Tracheal allograft after withdrawal of immunosuppressive therapy. *N Engl J Med* 2014;370:1568-70.
5. Pribaz JJ, Fine NA. Prelamination: defining the prefabricated flap - a case report and review. *Microsurgery* 1994;15:618-23.
6. Yao ST. Microvascular transplantation of prefabricated free thigh flap. *Plast Reconstr Surg* 1982;69:568.
7. Cockett NE, Kole C. Genome Mapping and Genomics in Domestic Animals. Berlin: Springer; 2009.
8. Graur D, Duret L, Gouy M. Phylogenetic position of the order Lagomorpha (rabbits, hares and allies). *Nature* 1996;379:333-5.
9. Bosze ZS, Houdebine LM. Application of rabbits in biomedical research: a review. *World Rabbit Sci* 2006;14:1-14.
10. Kamel KS, Lau G, Stringer MD. *In vivo* and *in vitro* morphometry of the human trachea. *Clin Anat* 2009;22:571-9.
11. Mankarious LA, Adams AB, Pires VL. Patterns of cartilage structural protein loss in human tracheal stenosis. *Laryngoscope* 2002;112:1025-30.
12. Salassa JR, Pearson BV, Payne WS. Gross and microscopical blood supply of the trachea. *Ann Thorac Surg* 1977;24:100-7.
13. Vranckx JJ, Den Hondt M, Delaere P. Prefabrication and prelamination strategies for the reconstruction of complex defects of trachea and larynx. *J Reconstr Microsurg* 2014;30:145-52.
14. Barone R. Comparative anatomy of domestic mammals. Volume 5, Angiology. 2nd ed. Paris: Vigot; 2012. (in French)
15. Delaere PR, Hardillo J. Tubes of vascularized cartilage used for replacement of rabbit cervical trachea. *Ann Otol Rhinol Laryngol* 2003;112:807-12.
16. Giessler GA, Friedrich PF, Shin RH, Bishop AT. The superficial inferior epigastric artery fascia flap in the rabbit. *Microsurgery* 2007;27:560-4.
17. Loukas M, du Plessis M, Owens DG, Kinsella CR Jr, Litchfield CR, Nacar A, Lu O, Tubbs RS. The lateral thoracic artery revisited. *Surg Radiol Anat* 2014;36:543-9.
18. Wei FC, Mardini S. Flaps and Reconstructive Surgery. 1st ed. Philadelphia: Saunders; 2009.
19. Flecknell PA, Roughan JV, Hedenqvist P. Induction of anaesthesia with sevoflurane and isoflurane in the rabbit. *Lab Anim* 1999;33:41-6.
20. Kushibe K, Tojo T, Sakaguchi H, Takahama M, Nishizaki K, Nezu K, Taniguchi S. Effects of warm ischemia and cryopreservation on cartilage viability of tracheal allografts. *Ann Thorac Surg* 2000;70:1876-9.
21. Kitamura Y, Shimizu N, Aoe M, Date H, Nagahiro I, Andou A. Allowable warm ischemic time to tracheal extraction for allotransplantation of cryopreserved trachea. *Jpn J Thorac Cardiovasc Surg* 2004;52:169-74.
22. Ryan S, McNicholas WT, O'Regan RG, Nolan P. Intralaryngeal neuroanatomy of the recurrent laryngeal nerve of the rabbit. *J Anat* 2003;202:421-30.
23. Delaere PR, Liu ZY, Pauwels P, Feenstra L. Experimental revascularization of airway segments. *Laryngoscope* 1994;104:736-40.
24. Hardillo JA, Vander Poorten V, Delaere PR. Transplantation of tracheal autografts: is a two-stage procedure necessary? *Acta Otorhinolaryngol Belg* 2000;54:13-21.
25. Delaere PR, Liu Z, Feenstra L. Tracheal autograft revascularization and transplantation. *Arch Otolaryngol Head Neck Surg* 1994;120:1130-6.

Closed rhinoplasty: effects and changes on voice - a preliminary report

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ABSTRACT

Aim: Effects of rhinoplasty were already studied from many points of view: otherwise poor is scientific production focused on changes of voice after rhinoplasty. This preliminary study analyzed objectively and subjectively these potential effects on 19 patients who underwent exclusively closed rhinoplasty. **Methods:** This preliminary evaluation was conducted from September 2012 to May 2013 and 19 patients have undergone primary rhinoplasty with exclusively closed approach (7 males, 12 females). All patients were evaluated before and 6 months after surgery. Each of them answered to a questionnaire (Voice Handicap Index Score) and the voice was recorded for spectrographic analysis: this system allowed to perform the measurement of the intensity and frequency of vowels ("A" and "E") and nasal consonants ("N" and "M") before and after surgery. Data were analysed with the Mann-Whitney test. **Results:** Sixteen patients showed statistically significant differences after surgery. It was detected in 69% of cases an increased frequency of emission of the consonant sounds ($P = 0.046$), while in 74% of cases the same phenomenon was noticed for vowel sounds ($P = 0.048$). **Conclusion:** Many patients who undergo rhinoplasty think that the intervention only leads to anatomical changes and improvement of respiratory function. The surgeon should instead accurately inform patients about the potential effects on the voice. This preliminary study reveals the significant effects of closed rhinoplasty on the human voice.

Key words:

Rhinoplasty; voice; handicap; score; spectrogram

INTRODUCTION

Closed rhinoplasty is nowadays one of the most requested aesthetic surgeries in occident. Many effects of this kind of procedure have already been studied from several points of view, otherwise in literature we found few works about the impact of exclusively closed rhinoplasty on individual and technical features of voice.^[1-3] The impact of surgery on the anatomy of the nasal cavity, the true resonance box of the phonatory system, was not deeply studied.^[4] Patients who use professionally their

voices can feel the relevance of these consequences.^[5] We conducted a preliminary evaluation to study these potential effects, considering that changes on the size of nasal cavity may let airflow resistance grow.^[6] We decided to study patients who underwent a surgical procedure like closed rhinoplasty, because it allows to solve many respiratory dysfunctions, but it is also a widely requested aesthetic procedure. A preliminary evaluation, conducted

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by our department, analyzed objectively and subjectively the potential changes brought by closed rhinoplasty on many characteristics of vocal pattern, such as frequency, tones and timbre.

METHODS

Our preliminary evaluation was conducted from September 2012 to May 2013. We studied 19 patients (7 males, 12 females), ranging in ages from 19 to 56 years (mean age was 29.3 years). All of them underwent exclusively closed rhinoplasty. An informed consent and an accurate clinical history were obtained from all patients, and every single step of our evaluation was carried on through the rules of the local medical ethic committee of Umbria, Italy. Our preliminary evaluation was obtained with an observational study. Both the objective and the subjective evaluation were realized with a time series study, through a chronological sequence of data points, consisting in several measures made over a 6 months time interval. All data were analyzed with the Mann-Whitney test. Inclusion criteria were the professional use of voice and the purely aesthetic request for the surgery. We excluded patients affected by chronic respiratory diseases; we also excluded secondary procedures. The study was approved by the local ethical committee under the World Medical Association Declaration of Helsinki guidelines. Of our patients, 24% used their voice professionally. All 19 patients were studied before and 6 months after surgery. The same surgeon performed the 19 operations. Authors always used the closed approach for the surgical procedures, performed under general anesthesia with the supplementary infiltration of a local anesthetic with vasoconstrictor (xylocaine 1% and epinephrine 1:100,000). The intercartilaginous incision starts the procedure, and after the dissection of vestibular skin, the operator reduces the dorsum. Lateral low-to-high osteotomies and the management of the tip, performed with a delivery approach, complete the procedure. Grafts or additional procedures were never used.

After 1 week, we removed nasal splints. This preliminary postoperative evaluation was performed 6 months after surgery (we will evaluate more patients for a longer period of time, for a stronger report). The study of the voice was performed with both objective and subjective methods. To compare the extracted data from preoperative and postoperative evaluations, the results were analyzed with the Mann-Whitney test. The objective analysis, conducted with the study on spectrograms, allowed to quantify the frequency levels of nasal consonants ("N" and "M") and vowels ("A" and "E") before and 6 months after surgery. It was conducted with a professional recording system and sounds were analysed using the PRAAT open source software. Voices were analyzed in frames of 3 s and for every single sound we extracted a spectrogram and studied it through a spectrographic analysis. Every recording was performed in a quiet room, using the

professional recording system at a constant distance from mouth (12 cm). All data, expressed as \pm standard deviation, were analyzed with the Mann-Whitney test and values were compared before and 6 months after the intervention. All data with a *P* value of 0.05 or less were considered statistically significant for the preliminary report.

The subjective evaluation, instead, was supported by a questionnaire, translated in Italian. The questionnaire was a modified version of the Voice Handicap Index Score^[7,8] and helped us to study the subjective changes. It is composed by 3 legs, technical, structural and perceptive: a greater handicap is reflected by a greater score. Technical leg is about effects of vocal pattern on work life. The structural leg is about any personal detected disorders. Perceptive leg comprises questions about the personal perception of the effects on voice after rhinoplasty. Patients answered this questionnaire before and 6 months after surgery. Results were compared in total score and separately for each area of questions.

RESULTS

The 19 patients enrolled for the study were observed before and 6 months after surgery (this is a preliminary report, we will continue with a long-term evaluation in future, with more patients). For the subjective evaluation, our modified version of Voice Handicap Index Scores helped us to evaluate several characteristics of the personal perception of voice. We separately scored and compared each area of the translated questionnaire.

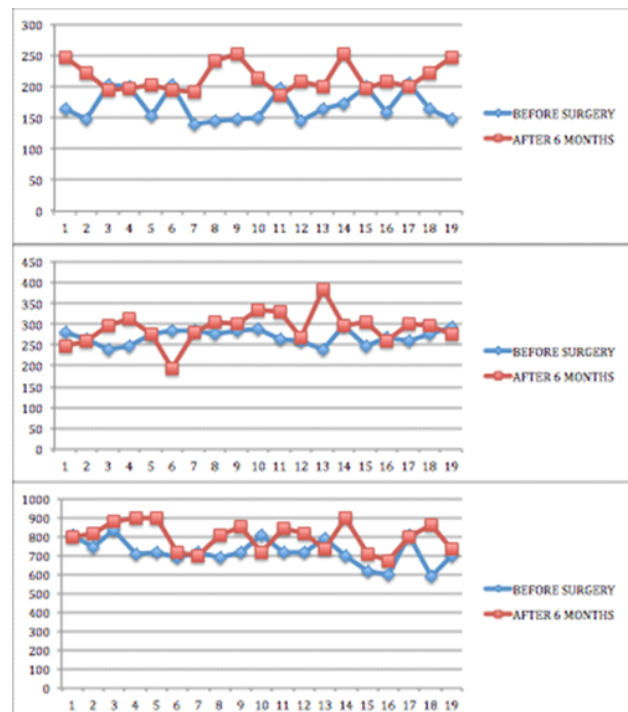


Figure 1: Frequencies of "M" consonant sound (top), "N" consonant sound (middle) and "A" vowel sound (bottom) before and 6 months after surgery. Data are expressed in Hertz

We noticed a statistically significant difference in data derived from the answers 6 months after surgery ($P = 0.047$). Patients noticed effects on voice not only in general, but also for every single area of questions. The increased score suggests that vocal features significantly change after closed rhinoplasty.

The objective evaluation was conducted with a spectrographic analysis for the 4 sounds (“A”/“E” vowels, “N” and “M” consonants), before and 6 months after surgery. The frequency of every single spectrogram (Hz) was the main considered parameter. We have to underline that data extracted from the spectrographic analysis of vowel sounds clearly show the improved vocal pattern in patients undergoing closed rhinoplasty. We found an increased frequency of emission of consonant sounds in 69% of cases ($P = 0.046$), and in 74% of cases for vowels ($P = 0.048$). The results of this analysis are shown in Figure 1. We didn’t detect major complications in the immediate postoperative period (2 weeks).

DISCUSSION

Changes on voice after closed rhinoplasty were the main target of this preliminary report: we found statistically significant effects on several vocal features.

In literature, we didn’t find any work about the impact of exclusively closed rhinoplasty on individual and technical features of voice.^[9-12] This preliminary evaluation begins from the principle that changes in nasal cavity volume may bring effects to the resonance system and frequency of several vocal sounds.^[13-16]

We conducted a preliminary report and enrolled 19 patients which underwent a closed primary rhinoplasty.

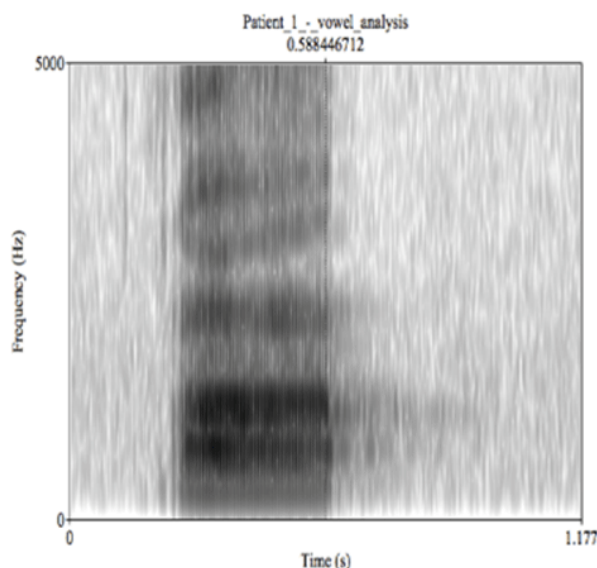


Figure 2: An example of a spectrogram analyzed in our preliminary report

We didn’t include open procedures because our target was an evaluation after a single and standardized surgery. Objective and subjective analyses supported this evaluation, the first one performed with a spectrographic study of vocal sounds frequencies (data expressed in Hertz) before and 6 months after surgery, the second one supported by the Italian version of the “Voice Handicap Index Score”.

The objective study, performed with an open source software and a professional recording system, helped us to notice effective changes on intensity and frequency of voice after surgery. This evaluation was performed again after 6 months. The Mann-Whitney test allowed us to analyze data. An example of a spectrogram from our study is shown on Figure 2.

Data extracted from the spectrographic analysis let us discover a statistically significant change of the frequency emission for the “A” and “E” vowels and the “N”/“M” consonants (results with data expressed in Hertz are summarized on Figure 1).

The subjective evaluation showed significant changes about the perception of voice after this kind of surgery ($P = 0.047$). This evaluation helped us to study the impact of these changes on the professional and everyday life of the 19 subjects. This result, although it represents the first and preliminary step of our evaluation, is statistically significant.

In our opinion, these changes could be caused by the lateral low-to-high osteotomies performed during the surgery.

Several characteristics of vocal pattern, according to our preliminary evaluation, can be statistically changed by this kind of surgery. The subjective analysis reveals how surgery can change the personal and ideal perception of voice. The objective evaluation helped us to notice differences in sound frequency and amplitude after surgery. Bringing the focus of our study to everyday life, we can say that every surgeon who performs a closed rhinoplasty should accurately talk to patients about potential changes on the quality of voice, first of all through the informed consent. Limitations of our study were the small series of patients and the relatively short period of evaluation. We will evaluate more patients for a longer period of time, in order to confirm the results of our preliminary report.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Brandt MG, Rotenberg BW, Moore CC, Bornbaum CC, Dzioba A,

- Glicksman JT, Doyle PC. Impact of nasal surgery on speech resonance. *Ann Otol Rhinol Laryngol* 2014;123:564-70.
2. Mora R, Jankowska B, Dellepiane M, Mora F, Crippa B, Salami A. Acoustic features of voice after septoplasty. *Med Sci Monit* 2009;15:CR269-73.
3. Behrman A, Shikowitz MJ, Dailey S. The effect of upper airway surgery on voice. *Otolaryngol Head Neck Surg* 2002;127:36-42.
4. Ozbal Koc EA, Koc B, Ercan I, Kocak I, Tadihan E, Turgut S. Effects of septoplasty on speech and voice. *J Voice* 2014;28:393.
5. Natour YS, Sartawi AM, Al Muhairy O, Efthymiou E, Marie BS. Emirati teachers' perceptions of voice handicap. *J Voice* 2016;30:378.e13-20.
6. Rosanowski F, Eysholdt U. Phoniatric aspects in cleft lip patients. *Facial Plast Surg* 2002;18:197-203.
7. Seifpanahi S, Jalaie S, Nikoo MR, Sobhani-Rad D. Translated versions of voice handicap index (VHI)-30 across languages: a systematic review. *Iran J Public Health* 2015;44:458-69.
8. Arffa RE, Krishna P, Gartner-Schmidt J, Rosen CA. Normative values for the voice handicap index-10. *J Voice* 2012;26:462-5.
9. Chen W, Woo P, Murry T. Vocal fold vibratory changes following surgical intervention. *J Voice* 2016;30:224-7.
10. Behlau M, Madazio G, Moreti F, Oliveira G, Dos Santos Lde M, Paulinelli BR, Couto Junior Ede B. Efficiency and cutoff values of self-assessment instruments on the impact of a voice problem. *J Voice* 2016;30:506.e9-18.
11. Behlau M, Hogikyan ND, Gasparini G. Quality of life and voice: study of a Brazilian population using the voice-related quality of life measure. *Folia Phoniatr Logop* 2007;59:286-96.
12. Datta R. Occupational hazards of the emerging voice professions. *J Laryngol Voice* 2013;3:1-2.
13. Faheem RS, Botros RR, Shoker SA, Azab SN. Voice acoustic changes after uvulopalatopharyngo-plasty surger. *J Laryngol Voice* 2014;4:53-7.
14. Desai V, Mishra P. Voice therapy outcome in puberphonia. *J Laryngol Voice* 2012;2:26-9.
15. Elmiyeh B, Dwivedi RC, Jallali N, Chisholm EJ, Kazi R, Clarke PM, Rhys-Evans PH. Surgical voice restoration after total laryngectomy: an overview. *Indian J Cancer* 2010;47:239-47.
16. Chirilă M, Țiple C, Dinescu FV, Mureșan R, Bolboacă SD. Voice rehabilitation with tragal cartilage and perichondrium after vertical partial laryngectomy. *J Res Med Sci* 2015;20:323-8.

Application of regenerative medicine in treatment of acne scars

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ABSTRACT

Aim: The aim of this study is to evaluate the efficacy of the protocol of nanofat and platelet-rich plasma (PRP) infiltration and fractional CO₂ laser resurfacing for face atrophic scars by acne and to analyse patient's satisfaction with the original questionnaire. **Methods:** From March 2014 to June 2015, 30 patients with acne scars on the cheeks were selected for this pilot study. Patients were evaluated pre- and postoperatively by a physical examination, photographs and ultrasound scan with a 22 MHz probe to measure subcutaneous tissue thickness. All patients were treated by infiltration of nanofat and PRP. The production of PRP was achieved by RegenLab THT tube® method. Subsequently, patients were randomly divided into two groups: group A, which also underwent a fractional CO₂ laser resurfacing at 15 W; and group B, which only underwent nanofat and PRP infiltration. The original questionnaire of quality of life questionnaire (QoL-Q) was also administered pre- and postoperatively to analyse satisfaction and aesthetical perception of the result. **Results:** Preoperative thickness of subcutaneous tissue of patients from group A was 0.532 mm, whilst preoperative thickness of subcutaneous tissue of patients from group B was 0.737 mm. Postoperative thickness of subcutaneous tissue was 1.201 mm in group A and 1.367 mm in group B. The improvement of thickness of subcutaneous tissue was 0.668 mm in group A and 0.630 mm in group B. The authors applied a *t*-test on unpaired data, comparing the difference in thickness obtained with the treatment both in group A and in group B, with a *P* = 0.7289 (not significant). All patients in both groups had a treatment benefit. **Conclusion:** Combined approach with nanofat, PRP and CO₂ laser seems to be effective to improve trophic scars, however, infiltration alone proved to significantly increase skin and subcutaneous tissue thickness. QoL-Q confirmed the impact of acne scars on the face in social life and relationships.

Key words:

Acne; scars; regenerative; laser; nano-fat

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INTRODUCTION

Acne is a chronic inflammatory disease of the pilosebaceous unit, characterised by the presence of polymorphic skin lesions such as blackheads, papules, pustules, nodules and cysts. As regards the pathogenesis of the disease, some typical conditions such as a sebaceous hypersecretion and a hyper keratinisation of the follicular ostium, usually contribute to the creation of an anaerobic environment which facilitates the bacterial growth and the subsequent development of an inflammatory reaction (i.e. *Propionibacterium acnes*). Despite numerous topical and systemic therapeutic weapons, nowadays available to the dermatologist, some forms of acne, especially those characterised by an inflammation extended to deep dermis (nodular cysts), hesitate in scars, which strongly impact on both the aesthetic and, above all, on the psychological side of the disease. The scarring process is most often the result of a severe inflammatory process that extends to

the dermis as it usually happens in nodulocystic acne; however, it may also derive from the manipulation of less severe acne lesions by the patients themselves. Two forms of scar are generally identified: hypertrophic and atrophic, such as icepick [Figure 1], rolling [Figure 2] and the most common boxcar [Figure 3]. The management of acne scars consists of different approaches: physical approach (laser, pulsed light, cryotherapy), surgical approach (dermabrasion, punch excision *etc.*), fillers and chemical peels.^[1] Up to now, none of these methods has been considered the gold standard for the treatment of scars from acne and or is enough for a good cosmetic outcome; moreover, there are no studies in the literature analysing patient's satisfaction after treatment. The aim of this study is to evaluate the efficacy of our protocol of nanofat and platelet-rich plasma (PRP) infiltration and fractional



Figure 1: Icepick scar



Figure 2: Rolling scar



Figure 3: Boxcar scar

Table 1: Thickness of subcutaneous tissue of the patients of group A

ID of patient	I preoperative thick (mm)	I postoperative thick (mm)	II preoperative thick (mm)	II postoperative thick (mm)
1	0.175	0.475	0.94	1.25
2	0.11	0.61	0.685	0.950
3	0.355	0.48	0.415	0.650
4	0.175	0.61	0.550	0.750
5	0.41	1.115	0.975	1.250
6	0.52	0.69	1.09	1.150
7	0.5	1.215	1.150	1.050
8	0.35	1.32	1.02	1.550
9	0.54	0.755	1.08	1.250
10	1.09	1.92	1.750	1.950
11	0.9	1.125	1.450	1.70
12	0.615	0.750	0.650	0.850
13	0.5	0.650	0.55	0.750
14	1.3	1.550	1.450	1.650
15	0.450	0.875	0.9	1.250

I postoperative control: 3 months; II postoperative control: 3 months from the second treatment

Table 2: Thickness of subcutaneous tissue of the patients of group B

ID of patient	I preoperative thick (mm)	I postoperative thick (mm)	II preoperative thick (mm)	II postoperative thick (mm)
1	0.335	0.930	1.48	1.650
2	0.36	0.450	0.445	0.550
3	1.03	1.4	1.175	1.350
4	0.98	1.3	1.275	1.650
5	1.02	1.450	1.770	1.990
6	0.545	0.760	0.880	1.3
7	0.46	0.650	0.890	1.2
8	0.9	0.9	1.1	1.240
9	0.985	0.99	1.125	1.275
10	0.350	0.780	0.880	0.9
11	1.3	1.550	1.750	1.950
12	0.7	0.920	1.150	1.370
13	1.1	1.550	1.750	1.980
14	0.450	0.880	0.9	1.2
15	0.550	0.750	0.88	0.9

I postoperative control: 3 months; II postoperative control: 3 months from the second treatment

Table 3: Patient's quality of life evaluated with QoL-Q

Thinking about the body part that you turned to the plastic surgeon:	Preoperatively (%) [*]	Postoperatively (%) [*]	P
How do you feel in your clothes?	8 (27)	27 (90)	0.0001†
How you feel when you're in the midst of the people?	5 (17)	28 (93)	0.0001†
How do you feel showing the part of the body?	1 (3)	29 (97)	0.0001†
Do you feel safe in working life?	15 (50)	24 (80)	0.002†
Do you feel safe in your private life?	11 (37)	26 (87)	0.065
Do you feel safe of the body part for which you have addressed to the plastic surgeon	1 (3)	26 (87)	0.0001†
Do you feel safe of your body?	18 (30)	25 (83)	0.068
Do you feel reassured?	7 (23)	25 (83)	0.0001†
Do you think your quality of life is good?	13 (43)	24 (80)	0.003†
Do you think to be successful in life?	12 (40)	22 (73)	0.004†
You think your body is beautiful?	6 (20)	19 (63)	0.0001†

†: statistically significant; *: raw score ≥ 2 ; QoL-Q: questionnaire of quality of life

CO₂ laser resurfacing for face atrophic scars by acne and to analyse patient's satisfaction with our original questionnaire. All related patients are consented and agree with this publication.

METHODS

From March 2014 to June 2015, 30 patients with acne scars on the cheeks were selected for this pilot study. Age ranged between 18 and 52 years old. Patients were evaluated pre- and postoperatively by a physical examination, photographs and ultrasound scan with a 22 MHz probe to measure subcutaneous tissue thickness. All patients were treated by infiltration of nanofat and PRP.^[2] The production of PRP was achieved by RegenLab THT tube[®] method.^[3,4] Subsequently, patients were randomly divided into 2 groups: group A, which also underwent a fractional CO₂ laser resurfacing at 15 W; and group B, which only underwent nanofat and PRP infiltration. Patients attended a 1 month, 3 months and 6 months follow-up after treatment. The difference in thickness obtained with the treatment in group A and in group B was compared through a *t*-test on unpaired data. Our original questionnaire of quality of life questionnaire (QoL-Q) was also administered pre- and postoperatively to analyse satisfaction and aesthetical perception of the

result. The pre- and postoperative module was comprised of 11 multiple-response questions. The questionnaire was conceived by the authors as a test of self-administration, only for patients candidate to undergo all type of cosmetic procedures. Questionnaires were filled out in an anonymous fashion. Preoperative surveys were completed during the initial consultation, and postoperative surveys were completed at the 6 months postoperative visit. This was a cross-sectional study and therefore the patients who filled out preoperative surveys may be different from those who filled out postoperative surveys. Because surveys were filled out anonymously, there was no way to identify those patients who filled out both the preoperative and postoperative surveys. Statistical analysis was performed using descriptive and summary statistics to identify a central tendency. An unpaired *t*-test was performed to examine the significance of changes in mean scores of satisfaction. Fisher's exact test was used to detect any significant differences between preoperative and postoperative satisfaction for a dichotomous outcome. A value of $P < 0.05$ was considered significant.

Inclusion criteria were: (1) patients from 18 to 40 years old in good health; and (2) patients with chronical acne scars on the cheeks.

Exclusion criteria were: (1) patients with diabetes, cancer, collagen disorders, deficiency status; (2) others acute or chronical dermatological disorders; (3) patients with coagulation defects and platelet count less than 150,000/mm³; (4) pregnancy status; (5) acute phase of acne; and (6) chronical assumption of anti-aggregants agents or non-steroidal anti-inflammatory drugs.

RESULTS

Preoperative thickness of subcutaneous tissue of patients from group A was 0.532 mm, whilst preoperative thickness of subcutaneous tissue of patients from group B was 0.737 mm. Postoperative thickness of subcutaneous tissue was 1.201 mm in group A and 1.367 mm in group B. The improvement of thickness of subcutaneous tissue was 0.668 mm in group A and 0.630 mm in group B. Preoperative and postoperative thickness values of group A and group B are displayed in Tables 1 and 2, respectively. The difference in thickness obtained with the treatment in group A and in group B was not statistically significant, with a $P = 0.7289$. Answers of QoL-Q pre-module and post-module questionnaires are reported in Table 3 and Figure 4, respectively.

DISCUSSION

Currently, we have many new treatments for acne scars,^[4-8] no gold standard has been officially identified yet. Historically, the most used treatments were: dermabrasion, a decade-old technique which employs the use of a motorised device equipped with an abrasive material to

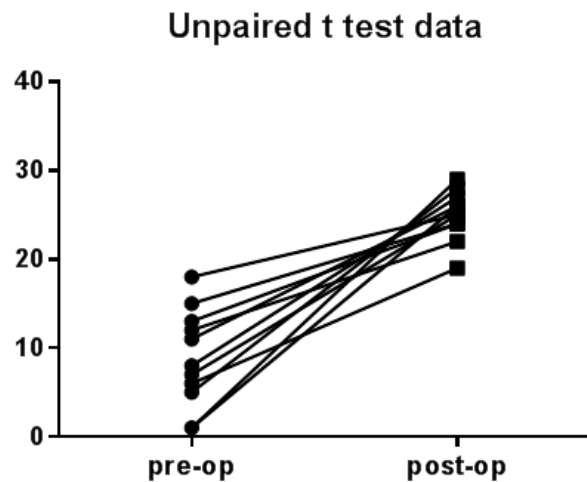


Figure 4: Student *t*-test for unpaired data. Pre-op: 8.818 ± 1.661 , $n = 11$; post-op: 25.00 ± 0.8421 , $n = 11$; $P < 0.0001$



Figure 5: The case of a 33-year-old woman with icepick scar treated with platelet-rich plasma and nanofat injection and laser CO₂. (A) preoperative situation; (B) 3 months after the second treatment

physically remove the superficial layers of the skin, thus inducing the wound-healing process with subsequent formation of new collagen;^[9] ablative lasers, which are effective in the treatment of atrophic scars;^[10] nonablative radiofrequency, which gives better results in the treatment of ice pick scars, compared to the use in more superficial scars;^[11] subcision, a more physically intensive technique useful for treatment of superficial atrophic acne scars;^[12] skin needling, also referred to as collagen induction therapy, which makes use of vertical needle punctures to treat rolling and boxcar scars;^[13] punch techniques, useful for treating deeper atrophic acne scarring, which are difficult to be treated otherwise;^[14] chemical peels, which traditionally employ acidic compounds to strip away the outer layers of skin at variable depths, depending on the concentration of the agent being applied;^[15] soft-tissue



Figure 6: The case of a 36-year-old woman with boxcar acne scars, treated with platelet-rich plasma and nanofat injection and laser CO₂. (A) preoperative situation; (B) 3 months after the second treatment



Figure 7: The case of a 41-year-old man with boxcar scars, treated with platelet-rich plasma and nanofat injection. (A) preoperative situation; (B) 3 months after the second treatment

augmentation, another effective treatment of superficial atrophic acne scars which is characterised by the injection of hyaluronic acid or calcium hydroxylapatite, poly-L-lactic acid, or even autologous fat to replace lost tissue volume while simultaneously inducing collagen production via stretching of dermal fibroblasts.^[16] The idea of our protocol came from the patients' request to search a satisfactory solution to the problem of atrophic scars of the face. These scars are not only the outcome of a devastating inflammatory disease for the patient's appearance, but in severe cases constitute the reason of relational and psychological problems. We think the atrophic acne scars should be treated as "dips" to fill and smooth. In fact, scars are found in the subcutaneous tissue, thus making a decisive surface treatment difficult to obtain. Scars need also a stimulation to maintain that volume. The best treatment is to fill the scars and



Figure 8: The case of a 28-year-old man with rolling scars treated with platelet-rich plasma and nanofat injection. (A) preoperative situation; (B) 3 months after the second treatment

stimulate the self-regeneration. The results obtained from the measurement of the thickness do not show evident differences in group A [Figures 5 and 6] and in group B [Figures 7 and 8], therefore the use of dermabrasion does not bring change in the aesthetic result. The surface treatment of atrophic scars is therefore not the best treatment to get good results. Into the 2 groups, we did not notice any difference between the various patients, nor according to the type of scars (icepick, boxcar or rolling), nor on the basis of the initial thickness of the scars. Indeed, we have calculated the differences of thicknesses obtained after treatment in group A and in group B and we applied a *t*-test for unpaired data with a non-significant result ($P = 0.7289$). All patients in both groups had a treatment benefit. Through our questionnaire we were able to know the patients' point of view, both before and after treatment and we could find in all a great improvement in the perception of its image. All patients were highly motivated to perform the treatment, both those with severe scars and those with milder scars. We report the results of the questionnaire into a single table because there was no difference between the 2 groups. The questionnaires which we administered to the patients were collected and processed in anonymous form so it was only possible to compare the responses obtained from each group of patients without being able to be divided into subgroups according to age, gender, type of scars. For the future, we would like to assess the stability of postoperative results with a longer follow-up and the effects of nano-fat plus PRP through histological analysis (cutaneous biopsies during the treatment) on a short and long time. Also, we would like to use 2 other comparison groups, one with the use of only nanofat and 1 only with the use of PRP to study the role of the nanofat and the PRP in the treatment of atrophic scars.

In conclusion, combined approach with nanofat, PRP and CO₂ laser seems to be effective to improve atrophic scars, however, infiltration alone proved to significantly increase skin and subcutaneous tissue thickness. QoL-Q confirmed the impact of acne scars on the face in social life and relationships. All patients, regardless of age, social class or educational level, are highly motivated to perform the treatment because they have not found a solution in previous treatments or have not performed any treatment yet.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Basta-Juzbašić A. Current therapeutic approach to acne scars. *Acta Dermatovenol Croat* 2010;18:171-5.
2. Tonnard P, Verpaale A, Peeters G, Hamdi M, Cornelissen M, Declercq H. Nanofat grafting: basic research and clinical applications. *Plast Reconstr Surg* 2013;132:1017-26.
3. Anitua E, Sánchez M, Orive G, Andía I. The potential impact of the preparation rich in growth factors (PRGF) in different medical fields. *Biomaterials* 2007;28:4551-60.
4. Barrientos S, Stojadinovic O, Golinko MS, Brem H, Tomic-Canic M. Growth factors and cytokines in wound healing. *Wound Repair Regen* 2008;16:585-601.
5. Phothong W, Wanitphakdeedecha R, Sathaworawong A, Manuskiatti W. High versus moderate energy use of bipolar fractional radiofrequency in the treatment of acne scars: a split-face double-blinded randomized control trial pilot study. *Lasers Med Sci* 2016;31:229-34.
6. Zhou BR, Zhang T, Bin Jameel AA, Xu Y, Xu Y, Guo SL, Wang Y, Permatsari F, Luo D. The efficacy of conditioned media of adipose-derived stem cells combined with ablative carbon dioxide fractional resurfacing for atrophic acne scars and skin rejuvenation. *J Cosmet Laser Ther* 2016;18:138-48.
7. Min S, Park SY, Yoon JY, Suh DH. Comparison of fractional microneedling radiofrequency and bipolar radiofrequency on acne and acnesar and investigation of mechanism: comparative randomized controlled clinical trial. *Arch Dermatol Res* 2015;307:897-904.
8. Seidel R, Moy RL. Improvement in atrophic acne scars using topical synthetic epidermal growth factor (EGF) serum: a pilot study. *J Drugs Dermatol* 2015;14:1005-10.
9. Frank W. Therapeutic dermabrasion. Back to the future. *Arch Dermatol* 1994;130:1187-9.
10. Alster TS, West TB. Resurfacing of atrophic facial acne scars with a high-energy, pulsed carbon dioxide laser. *Dermatol Surg* 1996;22:151-4.
11. Ramesh M, Gopal M, Kumar S, Talwar A. Novel technology in the treatment of acne scars: the matrix-tunable radiofrequency technology. *J Cutan Aesthet Surg* 2010;3:97-101.
12. Alam M, Omura N, Kaminer MS. Subcision for acne scarring: technique and outcomes in 40 patients. *Dermatol Surg* 2005;31:310-7.
13. Fabbrocini G, Annunziata MC, D'Arco V, De Vita V, Lodi G, Mauriello MC, Pastore F, Monfrecola G. Acne scars: pathogenesis, classification and treatment. *Dermatol Res Pract* 2010;2010:893080.
14. Johnson WC. Treatment of pitted scars: punch transplant technique. *J Dermatol Surg Oncol* 1986;12:260-5.
15. Lee JB, Chung WG, Kwahck H, Lee KH. Focal treatment of acne scars with trichloroacetic acid: chemical reconstruction of skin scars method. *Dermatol Surg* 2002;28:1017-21.
16. Wang F, Garza LA, Kang S, Varani J, Orringer JS, Fisher GJ, Voorhees JJ. In vivo stimulation of de novo collagen production caused by cross-linked hyaluronic acid dermal filler injections in photodamaged human skin. *Arch Dermatol* 2007;143:155-63.

Breast amyloidosis: a case report

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ABSTRACT

Amyloidosis is an uncommon disorder characterized by extracellular deposition of abnormal proteins. Breast involvement has rarely been reported and can clinically be misdiagnosed as breast cancer. A 60-year-old woman presented with a 3-mm diameter mass in the right breast close to a silicon implant positioned 20 years before. A core biopsy, performed to rule out breast cancer, showed amyloid deposit. Further exams confirmed a systemic amyloid light chain amyloidosis. After few months the mass increased causing breast volume and shape distortion. Since breast cancer may be the cause of amyloid deposits or be hidden by it, the patient underwent a bilateral skin sparing mastectomy and expander and fat grafting breast reconstruction. The resection specimens showed amyloid deposits only, no evidence of cancer. At 2 years follow-up, no breast amyloidosis recurrence was shown. Breast amyloidosis is rare but can occur in a plastic surgeon's practice. It is mandatory to rule out a comitant breast cancer or systemic amyloidosis.

Key words:

Amyloidosis; breast amyloidosis; breast cancer; breast reconstruction

INTRODUCTION

Amyloidosis is an uncommon disorder characterized by extracellular deposition of amorphous and insoluble proteins in an abnormal fibrillary configuration. Despite the various morphologic manifestations in tissue, staining for amyloid protein with Congo red reveals a characteristic apple-green birefringence under polarized light. The most common types of amyloidosis are amyloid light chain (AL) and amyloid A (AA). AL, caused by immunoglobulin light-chains [amyloid heavy chain (AH) is more rare and caused by heavy chains], is secondary to plasma cell dyscrasia (clonal plasma cell disorder secreting fibril-forming monoclonal immunoglobulin), while AA is reactive amyloidosis associated with chronic

inflammatory disease (rheumatoid arthritis, Reiter syndrome, *etc.*).^[1] The precise aetiology and pathogenesis of amyloidosis are unknown.

AL amyloidosis can be systemic, affect more than one organ or tissue (commonly involving heart, gastrointestinal tract and tongue), or less commonly localized, affecting individual organs.

Breast involvement by amyloidosis has rarely been reported in the literature, first by Fernandez and Hernandez^[2] in 1973. Breast amyloidosis can be part of a systemic amyloidosis disease or it may be limited to the breast and therefore be cause of misdiagnosis.

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In the vast majority of patients, breast amyloidosis is part of a systemic AL type disease (usually kappa light chain proteins). It can be associated with malignancies of the breast including invasive ductal or lobular carcinoma but mainly it is associated with hematologic malignancies.

Moreover, breast cancer may sometimes be the cause of amyloid, the so-called amyloid tumour of the breast but it is rare.^[3]

The typical clinical presentation of breast amyloidosis is a painless, solitary or multiple breast mass. Mammogram shows a mass of focal or diffuse density with or without calcification.

CASE REPORT

A 60-year-old woman presented in 2011 with a non-palpable 3-mm diameter mass visualized at ultrasound in the right breast close to a silicone implant imaging [Figure 1].

She had a bilateral breast augmentation with silicone gel implants 30 years before.

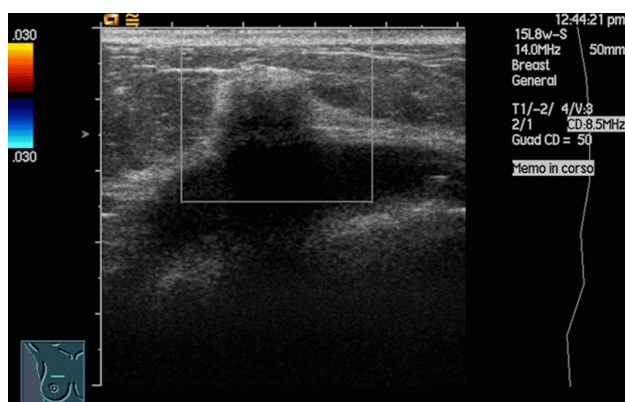


Figure 1: Right breast ultrasound imaging

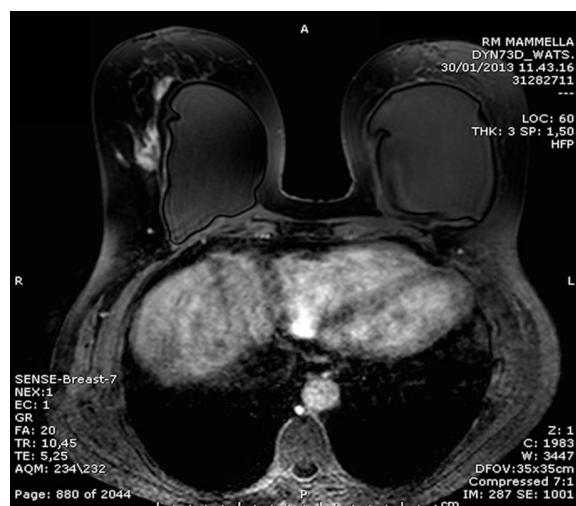


Figure 2: Magnetic resonance imaging of the breast: demonstrating a conglomerate coalescent mass in the superior right breast upon the implant

Comorbidities, on regular treatment, were hyperthyroidism, hypertension and heart failure.

Although the first mammogram did not suspect a malignant lesion, but only showed heterogeneously dense breast, the clinical suspicion was breast cancer or silicon leakage.

Magnetic resonance imaging (MRI) did not show implant rupture. A fine needle aspiration cytology was performed, which was negative for malignancy, and reported a non-specific inflammatory reaction only.

At 2 years follow-up, the mass size increased to 3 cm. An ultrasound guided core needle biopsy was performed and the histological examination showed amyloid deposits but no evidence of cancer. Amyloid deposits appeared as eosinophilic amorphous material with lymphocytes, plasma cells and multinucleated giant cells and showed characteristic staining with Congo Red (under fluorescence light and laser microdissection). Amyloid typing, performed by immunohistochemistry (immunoperoxidase staining on paraffin sections of the breast using antibodies), showed immunoglobulin-associated mixed light chains (kappa and lambda) and heavy chains.

Our first hypothesis was that amyloid deposits could be related to a local inflammation (silicon leakage) or could be due to a breast cancer or could be part of a systemic amyloidosis. Further investigations confirmed a systemic AL amyloidosis.

In a few months, the breast mass increased in volume and new nodules appeared causing breast volume and shape distortion. At ultrasound several masses were found in both breasts.

The MRI showed global replacement of normal parenchyma with mixed hyper and hypo echogenic masses that formed a conglomerate coalescent mass in the superior right breast close to the implant [Figure 2]. In accordance with the patient, a bilateral skin sparing mastectomy and implant removal was performed [Figure 3].



Figure 3: Pre operative pictures and surgical plan

The resection specimens of both breasts showed nodular amyloid deposits only, with no evidence of cancer or calcifications [Figure 4]. Multinucleated giant cells were present within and adjacent to the amyloid deposits. Focal aggregates of lymphocytes (B and T) and plasma cells were also found.

The patient opted for a bilateral reconstruction with fat grafting. Two 470 mL expanders were positioned under the pectoralis major muscle at the time of mastectomy and gradually inflated on an outpatient basis.

In three consecutive surgeries the expanders were gradually deflated and that volume replaced by fat grafts according to the Coleman technique.

At two years of follow-up, MRI did not show any breast amyloidosis recurrence [Figure 5].

The patient is satisfied with the reconstruction. No significant fat resorption was shown [Figure 6].

She is under follow-up for systemic amyloidosis and did not show involvement of other organs until now.

DISCUSSION

Röcken *et al.*^[4] and Charlot *et al.*^[5] reported that breast amyloidosis is associated with invasive cancer (ductal or lobular carcinoma or lymphoma). Other studies^[6,7] showed that comitant malignancies may be absent, as happened in our case.

Although breast amyloidosis is most commonly AL type, our patient had a systemic amyloidosis of the AH/AL type.

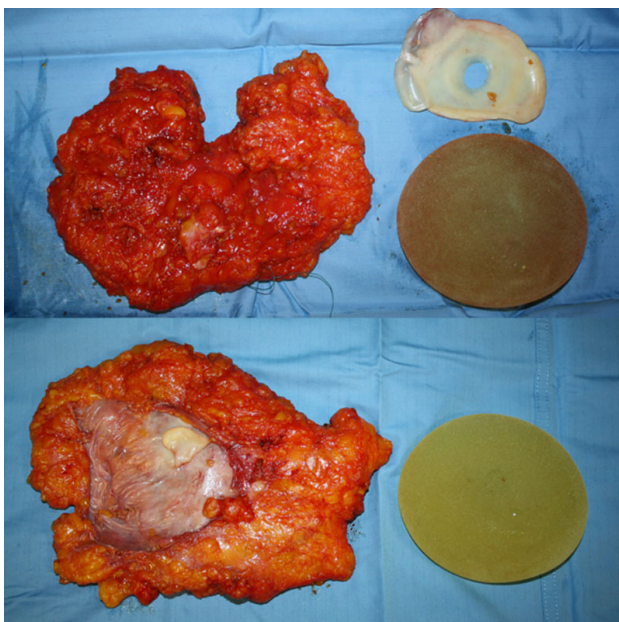


Figure 4: Resection specimens of the breasts



Figure 5: Magnetic resonance imaging of the breasts at 2 years of follow-up



Figure 6: Patient appearance at 2 years of follow-up

Breast amyloidosis doesn't have specific clinical or radiographic features. In the majority of cases it is not suspected clinically; instead, breast biopsies are usually done to rule out malignancy.

The pathogenesis of localized breast amyloidosis in the absence of a concomitant breast lymphoma or plasma cell dyscrasia is unknown, probably originating from local plasma cells secreting immunoglobulins. Plasma cell proliferation by itself is probably not sufficient to trigger amyloid deposition, and undetermined factors are needed for amyloid deposition.^[5]

Prosthetic breast implantation is one of the world's most popular aesthetic surgical operations.

The amyloid fibril proteins deposited in the breast of our patient were not of epithelial origin. Nevertheless, one may suggest a reaction link between leakage of silicon and deposition of amyloid deposits. The role of silicone gel in relation to connective tissue disease and amyloidosis has not been proved by current serologic, immunologic, or epidemiologic test. We found multinucleated giant cells within or adjacent to amyloid deposits; multinucleated giant cells may represent a

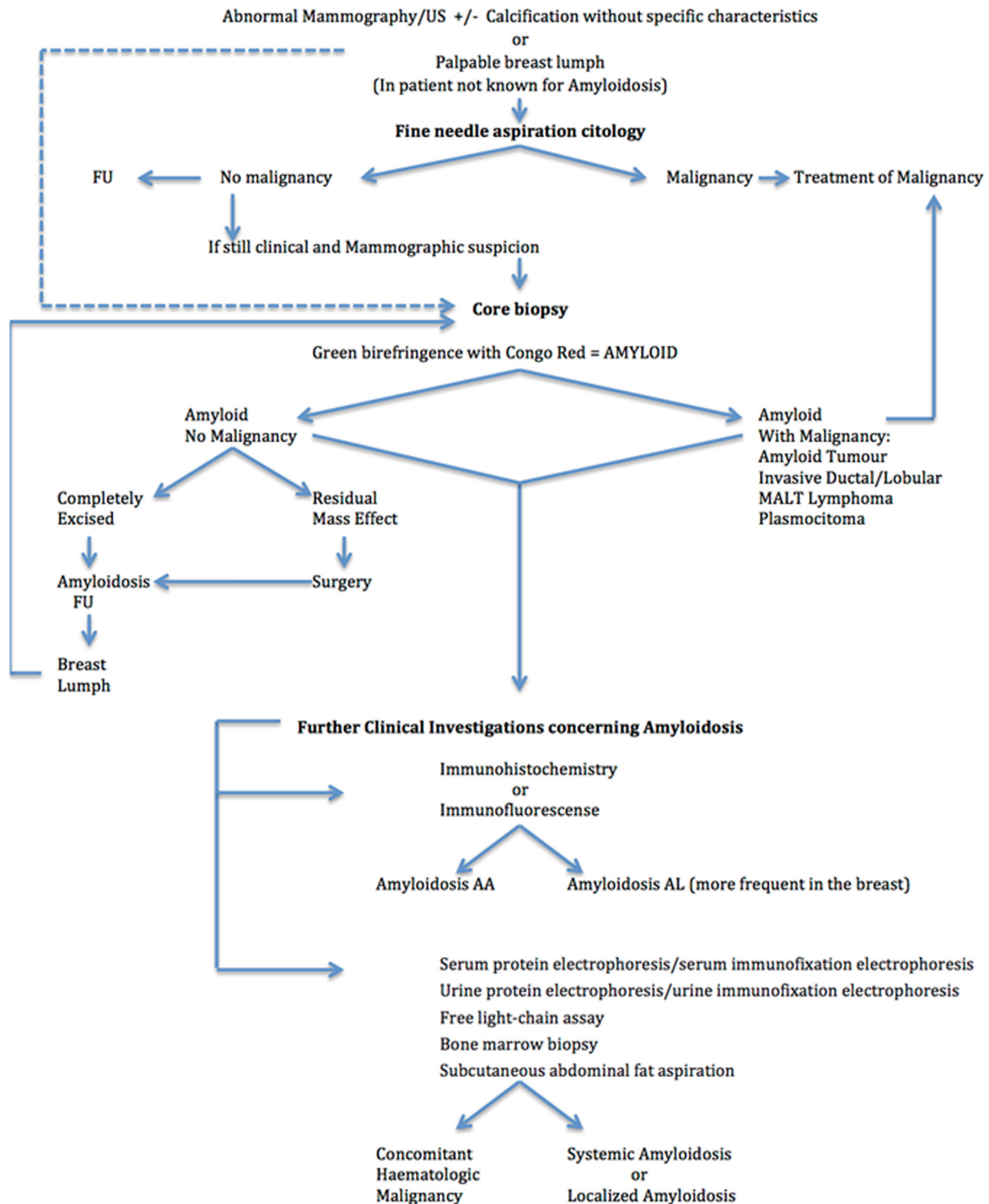


Figure 7: Flow chart for diagnosis of amyloidosis

tissue response but also they have been described in amyloidosis of the breast and they might be involved in the resorption of amyloid deposits by synthesized proteases.^[8]

In conclusion, breast amyloidosis is rare but can occur in a plastic surgeon's practice.

The surgical pathologist may miss amyloid deposits, especially if the deposits are very discrete. When diagnosis of amyloidosis is done, it is mandatory to rule out a concomitant breast cancer or a systemic amyloidosis. In Figure 7, we present a flow chart to guide clinicians in the diagnostic pathway.

Moreover, recognition and appropriate classification of amyloid deposits in biopsy specimens is mandatory, independently of whether amyloidosis is local, organ-limited or generalized to help diagnose concomitant conditions (i.e. B-cell or plasma cell proliferation for AL, chronic inflammatory diseases for AA as previously explained).^[1] Breast amyloidosis treatment options include conservative excision of the nodules or, in rare and diffuse cases such as the one presented, mastectomy can be considered.

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Conflicts of interest

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REFERENCES

1. Said SM, Reynolds C, Jimenez RE, Chen B, Vrana JA, Theis JD, Dogan A, Shah SS. Amyloidosis of the breast: predominantly AL type and over half have concurrent breast hematologic disorders. *Mod Pathol* 2013;26:232-8.
2. Fernandez BB, Hernandez FJ. Amyloid tumour of the breast. *Arch Pathol* 1973;95:102-5.
3. Deolekar MV, Larsen J, Morris JA. Primary amyloid tumour of the breast: a case report. *J Clin Pathol* 2002;55:634-5.
4. Röcken C, Kronsbein H, Sletten K, Roessner A, Bässler R. Amyloidosis of the breast. *Virchows Arch* 2002;440:527-35.
5. Charlot M, Seldin DC, O'hara C, Skinner M, Sancharawala V. Localized amyloidosis of the breast: a case series. *Amyloid* 2011;18:72-5.
6. Lamovec J, Jancar J. Primary malignant lymphoma of the breast. Lymphoma of the mucosa-associated lymphoid tissue. *Cancer* 1987;60:3033-41.
7. Gupta D, Shidham V, Zemba-Palko V, Keshgegian A. Primary bilateral mucosa-associated lymphoid tissue lymphoma of the breast with atypical ductal hyperplasia and localized amyloidosis. A case report and review of the literature. *Arch Pathol Lab Med* 2000;124:1233-6.
8. Wright JR, Ozdemir AI, Matsuzaki M, Binette P, Calkins E. Amyloid resorption: possible role of multinucleated giant cells. The apparent failure of penicillamine treatment. *Johns Hopkins Med J* 1972;130:278-88.

How we do it: the Running-X suture technique

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ABSTRACT

There are a myriad of suture techniques available to close incisions of the brow and forehead, each with their own advantages and disadvantages. The ideal suture technique would provide excellent cosmetic results, offer expedient wound closure, optimize skin eversion and wound edge apposition, and provide excellent cosmetic results. The authors describe a new suture technique, the Running-X suture, a running horizontal mattress suture that has successfully been used by the senior author for many years to re-approximate surgical wounds of the brow and forehead in an expeditious and aesthetic manner.

Key words:

Suture technique; running horizontal mattress suture; forehead incisions; eyebrow incisions

INTRODUCTION

The choice of suture technique used to close incisions depends on multiple variables which include anatomic location, thickness of skin, type of wound, and degree of tension. Of the various epidermal skin closure techniques used throughout the body, simple interrupted and simple running sutures are the most common because of the ease of placement and speed of closure.^[1,2] Although simple interrupted sutures are easy to place and have a lower potential to cause impaired cutaneous circulation, the major disadvantages are that the technique is more time consuming and produces minimal eversion. The main advantages of using a simple running suture are the rapid closure of wounds and its ability to simultaneously approximate the dermis and epidermis. However, its major disadvantage is poor control of inversion and eversion of the epidermal edges. Mattress sutures are

also widely used in epidermal closures because of their ability to produce eversion, compression of wound edges, and close wounds under moderate tension.^[3,4] One of the major disadvantages to mattress sutures, both vertical and horizontal, is they are more prone to become buried during the healing process, requiring a more tedious removal. Combining the advantages of mattress sutures with the time saved using a running technique has been widely described, although the wound edge apposition tends to be imprecise.^[2]

Herein, we describe the Running-X suture, a novel running horizontal mattress suture. This suture technique provides multiple advantages when compared to traditional running mattress sutures. The Running-X

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provides rapid wound closure, excellent skin eversion, precise wound edge apposition, ability to close wounds under tension, ease of suture removal, and most importantly excellent cosmesis in sensitive areas of the face such as the temporal brow and forehead.

TECHNIQUE

Anchoring stitch

The Running-X begins with a simple interrupted stitch. The initial throw is passed from the epidermis on the opposite side of the wound, through the wound, and then out of the epidermis. A knot is tied and the free end of the suture tail is cut leaving a small tail [Figure 1a].

Running-X

The needle is then picked up, reloaded and inserted in the epidermis on the opposite side of the anchoring knot approximately 4 mm from the initial stitch (far) and 2 mm from the wound edge. The needle is passed perpendicular to the wound edge, across the wound and through the epidermis on the same side as the anchoring knot [Figure 1a]. The suture is pulled through leaving a small loop between the anchoring knot and the entry point of the first throw. The needle is then thrown at the midpoint between the first throw and the anchoring stitch (near), inside the loop, starting on the opposite side of the anchoring knot 2 mm from the wound edge, with the needle passed perpendicularly through the wound, and ending through the epidermis on the same side as the anchoring knot [Figure 1b]. The next throw is

then started 4 mm from the first far throw starting on the opposite side of the anchoring knot [Figure 1c]. This will now produce what appears to be a “double-X” pattern over the wound. Following the second far throw, the next throw is placed midway between the first and second far throws inside the loop between the first near throw and the second far throw making this the second near throw [Figure 1d]. This pattern of far-near is repeated for the remainder of the wound.

End stitch

After the Running-X is used across the entire wound length, the suture is tied off using a final far throw. This final far throw is different from the previous far throws because it is placed only 2 mm from the previous far throw as opposed to 4 mm like the previous ones [Figure 1e]. The suture is secured with a knot created using the loop between the previous near exit site and entry of the final far throw, and the end of the suture. The tails are then cut short.

Suture material

We prefer to use polypropylene (Prolene, Ethicon, Somerville, NJ, USA). This suture material provides more elasticity and stretch than nylon. This is important because it allows for wound edema and decreases the risk of tissue strangulation and necrosis.^[3]

Time to removal

The Running-X suture is removed at the appropriate time interval for the specific anatomic locations to avoid track

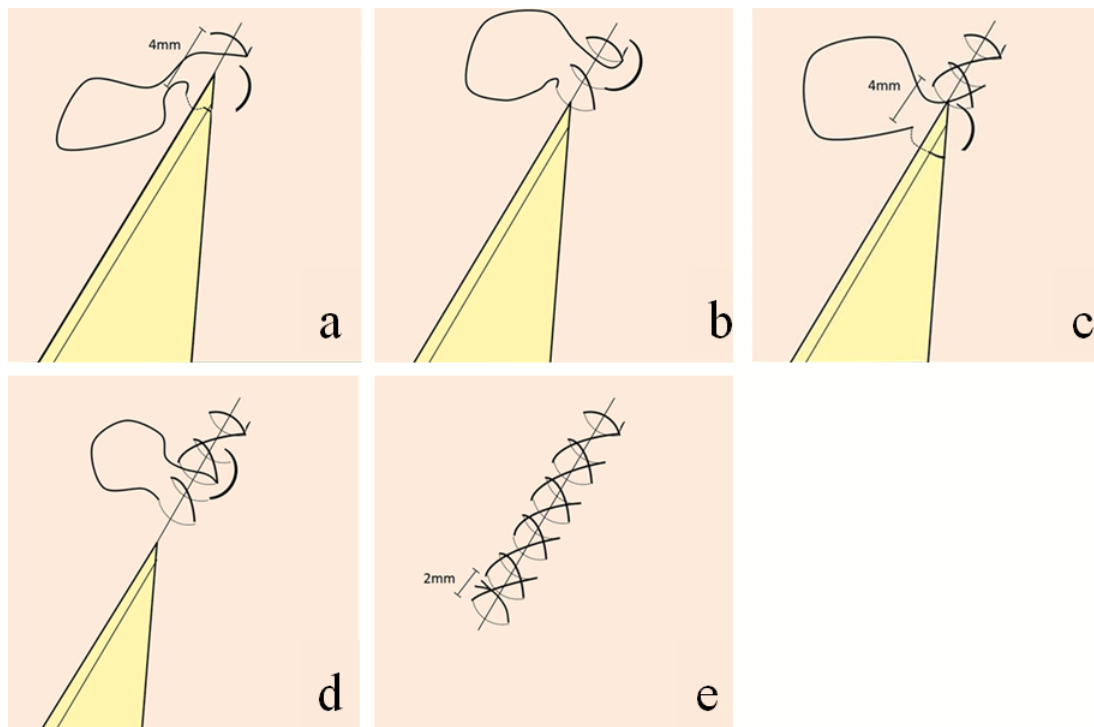


Figure 1: Running-X suture technique. (a) Anchor stitch and first far throw; (b) first near throw midway between anchor stitch and far throw; (c) second far throw 4 mm distal to first far throw; (d) second near throw midway between first and second far throw; (e) final far throw only 2 mm distal to penultimate far throw and secured to loop between the last near and last far throw with tails cut

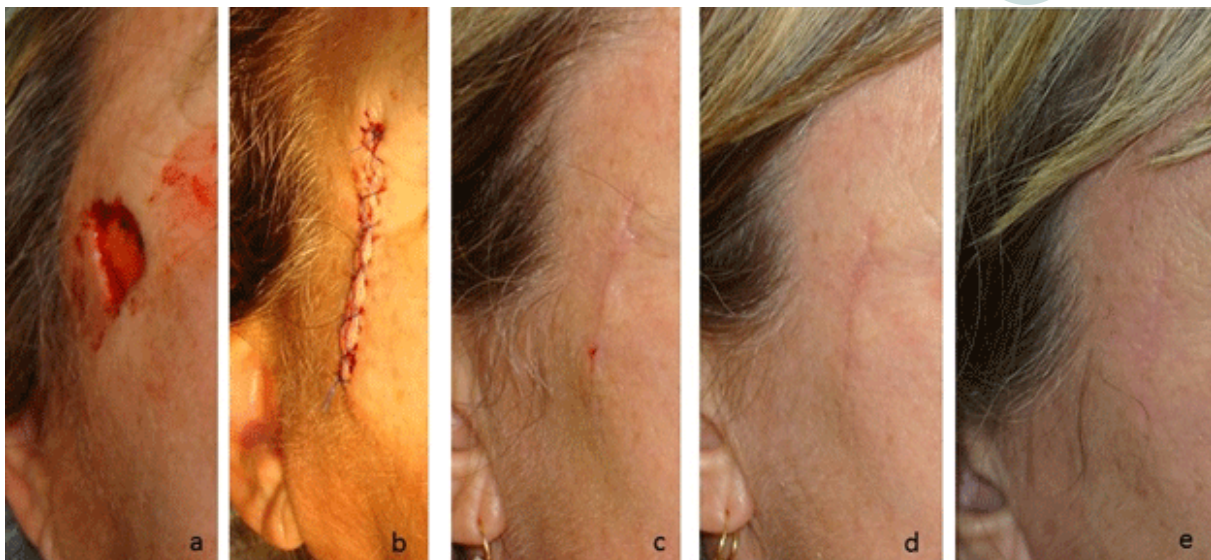


Figure 2: (a) Preoperative defect of the right temporal area following Mohs surgical excision of a Basal cell carcinoma, in a 58-year-old female with Fitzpatrick II skin type; (b) intraoperative appearance following dog ear excision and closure using the Running-X technique; (c) ten days postoperatively; (d) six weeks postoperatively; (e) twelve weeks postoperatively

marks. The authors in this report have primarily used this technique for brow and forehead wound closures. Therefore, the sutures were removed at 5 to 7 days from closure.

DISCUSSION

The senior author (Ronald Mancini) has successfully used this technique for many years to re-approximate surgical wounds of the brow, forehead and temporal area. Since the Running-X technique is continuous it allows for rapid wound closure. The needle is always thrown in the same direction, reducing the time to reload the needle compared to a running horizontal mattress suture which needs to be reloaded in opposing directions with each throw. This technique functions as a horizontal mattress specifically at the interval between the far and near throws. The horizontal and oblique forces placed across the wound at these intervals of the technique provide excellent skin eversion and precise wound edge apposition. The eversion is created in a similar fashion to running horizontal mattress sutures. However, it is superior to the running horizontal mattress because the "X"s created over the wound edges provide a leveling force for the epidermal edges. In addition, the Running-X is excellent for closure of wounds under tension because it provides added strength. A similar suture pattern has been described for epitendinous suture in tendon repairs, and when compared to a simple running suture, the similar patterned suture provided a 245% increase in tensile strength.^[5] Since this technique places suture strands over the wound, unlike traditional running mattress sutures, these strands can easily be divided at the time of suture removal with minimal patient discomfort. Finally, through a summation of the advantages of the

Running-X, this technique has provided the authors with excellent cosmetic results [Figure 2].

We do not recommend this suture technique for anatomic locations with thinner, fragile skin or distorted wound edges due to the increased risk of tissue strangulation and wound dehiscence. We also recommend against over tightening this suture in order to avoid tissue strangulation.

Despite our positive clinical experience with this technique, further studies are required to further define the limitations and tissue biomechanics of this technique and a prospective study comparing the Running-X suture technique with commonly used running and interrupted suture techniques is necessary before any definitive conclusions can be drawn.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Adams B, Levy R, Rademaker AE, Goldberg LH, Alam M. Frequency of use of suturing and repair techniques preferred by dermatologic surgeons. *Dermatol Surg* 2006;32:682-9.
2. Wong NL. Review of continuous sutures in dermatologic surgery. *J Dermatol Surg Oncol* 1993;19:923-31.
3. Kronic AL, Weitzul S, Taylor RS. Running combined simple and vertical mattress suture: a rapid skin-everting stitch. *Dermatol Surg* 2005; 31:1325-9.
4. Moy RL, Lee A, Zalka A. Commonly used suturing techniques in skin surgery. *Am Fam Physician* 1991;44:1625-34.
5. Kim PT, Aoki M, Tokita F, Ishii S. Tensile strength of cross-stitch epitendon suture. *J Hand Surg Br* 1996;21:821-3.

Use of negative pressure wound therapy in pediatric oncology patients: a single-center review of 66 patients

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ABSTRACT

Aim: Negative pressure wound therapy (NPWT) has been studied extensively in adult patients, but less is known about pediatric patients. This study assesses the efficacy and safety of vacuum-assisted closure® usage in pediatric oncology patients. **Methods:** Retrospective data on all patients treated with NPWT at a single pediatric oncology hospital were collected between April 2005 and September 2013. Details on pre-treatment factors, treatment course, and post-treatment events were collected. No control group was available for comparison. **Results:** Sixty-six patients were identified, with a total of 74 wounds. Median age at the time of NPWT application was 13 years (range, 10 months-23 years). Median duration of treatment was 21 days (range, 3-236 days). NPWT therapy was started with continuous high negative pressures (125 mmHg) in most patients. Sixty-nine percent of patients had their wounds healed without intervention, and 20% of patients required surgical closure. NPWT was discontinued temporarily secondary to skin maceration or cellulitis in 12% of patients. NPWT was used in a number of non-standard clinical situations, including primarily-closed incisional wound NPWT and bridging NPWT through adjuvant chemotherapy. **Conclusion:** In pediatric oncology patients, NPWT is safe, effective, and well-tolerated. Although this study is retrospective in nature, and there was no control group for comparison, these data are important for clinicians to guide therapy as device monitoring agencies and payors increasingly require outcomes data for the approval of therapeutic decisions.

Key words:

Pediatric; oncology; negative pressure wound therapy

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INTRODUCTION

Negative pressure wound therapy (NPWT) has fundamentally changed complex wound management, such that it is now considered an independent rung on the “reconstructive ladder.”^[1-4] NPWT therapy has been studied extensively in adults, where it has found applications in chronic wounds, open abdominal wounds, and open fractures, amongst others.^[5-8] Recent studies have showed that outcomes in the pediatric population are often equivalent to those reported in adults.^[9-12] However, no large studies have examined the use of NPWT in the pediatric oncology population, a group which is unique given the frequent utilization of extensive surgery, systemic chemotherapy, radiotherapy, and (in some cases) stem cell transplantation.^[13] In this study, we reviewed our single-center experience with NPWT in pediatric oncology patients and reported our outcomes with respect to efficacy, safety, and technical innovation in wound treatment.

METHODS

Records of patients treated with NPWT at a single center between April 2005 and September 2013 were reviewed. Approval for the study was obtained from the institutional review board of the respective institution. Patient data included demographics, diagnosis, and duration of NPWT, adjunctive treatment, wound size, definitive wound closure technique, complications, chemotherapy, radiation, recurrent disease, and general outcomes.

All NPWT systems used in this study were designed and manufactured by Kinetic Concepts, Incorporated (KCI Inc, San Antonio, TX, USA). The device includes a vacuum-assisted cosure® (VAC) dressing (wound VAC® dressing), consisting of a polyurethane or polyvinyl sponge placed directly over a wound site. The sponge is then sealed with plastic tape and connected to a negative pressure device with a tube. The vacuum pump in the device creates a sub-atmospheric negative pressure in the wound bed, and it is reported to reduce edema, increase local blood supply, increase the formation of granulation tissue, reduce bacterial colonization, improve patient tolerance, and accelerate wound healing overall.^[14,15]

RESULTS

Between April 2005 and September 2013, a total of 66 patients were identified for study inclusion. Seven patients required multiple wound VAC, or a wound VAC at multiple times, for a total number of 74 wounds treated with NPWT. Patient and wound characteristics at baseline are reported in Table 1. The median patient age was 13 years, with a range of 10 months to 18 years.

Table 1: Patient and wound characteristics at baseline (n = 66)

Patient characteristics	
Age at NPWT application, median (range)	13 years (10 months-18 years)
Gender	31 females; 35 males
Body mass index (kg/m ²), median (range)	21.5 (14.1-45.9)
Serum albumin (g/dL), median (range)	4.2 (2.5-4.8)
Patients using NPWT during chemotherapy	22
Patients receiving chemotherapy	56
Patients receiving radiation	24
Wound size (cm ²), median (range)	27 (4-250)
Time until wound closure (days), median (range)	21 (3-236)
Duration of wound NPWT (days), median (range)	21 (3-236)

NPWT: negative pressure wound therapy

Table 2: Pathologic diagnosis of primary tumors

Primary disease	Number of patients
Osteosarcoma	30
Ewing sarcoma	6
Retinoblastoma	2
Acute lymphoblastic leukemia	6
Acute myeloid leukemia	2
Adrenocortical carcinoma	1
Dermatofibrosarcoma protuberans	1
Epitheloid sarcoma	1
Glioma	1
Hodgkins lymphoma	1
Melanoma	2
Malignant fibrous histiocytoma	1
Malignant periphery nerve sheath tumor	2
Soft tissue high grade polyphenotypic sarcoma	1
Rhabdomyosarcoma	1
Sickle cell anemia	1
Synovial sarcoma	5
Malignant teratoma of the sacral bone	1
Thalamic glioblastoma	1

Our sample had 35 males to 31 females. The median body mass index (BMI) was 21.5 kg/m² (range, 14.1-45.9 kg/m²). Only 5 patients had serum albumin less than 3.4 mg/L, and only 1 patient had serum albumin less than 3.1 mg/L. There was no association between serum albumin level and adverse events ($P > 0.05$). Wounds were primary wounds in 62 patients, and recurrent in 4 patients.

Patient primary diagnoses are reported in Table 2. Fifty-six patients received chemotherapy at some point during their cancer therapy, and 22 of these patients had wounds requiring NPWT during chemotherapy. In these latter patients, NPWT was used for a range of 21-206 days. Twenty-four patients received radiation therapy at some point during their cancer treatment. Of these patients, the radiation dose was administered to the site of the wound in all but nine cases.

NPWT was used in total of 66 patients. Three patients

Table 3: Wound etiology in patients (n = 66)

Wound etiology	Number of patients
Trauma	2
Wound dehiscence	2
Post-surgical	56
Skin infection	1
Pressure sore	1
Sickle-cell/vascular disease	1
Cutaneous acute lymphoblastic leukemia	1
Purpura fulminans	1
Extravasation injury	1

Table 4: Indication for negative pressure wound therapy (n = 66)

Indication	Number of patients
Local wound care	44
Skin graft/Integra fixation	11
Brachytherapy	1
Support of primarily-closed incision	10

Table 5: Anatomic location of wounds, and exposed structures at wound base (wounds = 74)

	Number of wounds
Wound location	
Head and neck	4
Trunk	13
Upper extremity	10
Lower extremity	47
Exposed structures	
Bone	11
Fascia	4
Tendon	7
Nerve	3
Endoprosthesis	2
Skin (incisional wound VAC)	11
Muscle or fat	36

VAC: vacuum-assisted closure

Table 6: Outcomes of negative pressure wound therapy utilization (n = 66)

	Number of patients
Mechanism of closure in healed wounds	(n = 60)
Secondary intention	47
Skin graft/Integra	6
Local flap/tissue closure	4
Delayed primary closure	3
Characteristics of non-healing wounds	(n = 6)
Wound recurrence	2
Died of primary disease before wound closure	1
Died of necrotizing fasciitis	1
Amputation	2

had NPWT therapy twice: once before reconstruction and again for skin graft fixation. One patient had NPWT applied three times: first, for local wound care; second, for fixation of integra dermal regeneration template (Integra Life Sciences, Plainsborough, New Jersey, USA); and third, for skin graft fixation. Three patients had two

separate wounds, requiring two separate wound VACs. In total, NPWT was used 74 times in 66 patients.

Wound etiology is presented in Table 3. Fifty-six patients had surgically-created wounds. Two patients had traumatic wounds. Two patients had wound dehiscence requiring NPWT. One patient had pressure ulcer. There was one case of sickle-cell induced avascular skin necrosis. One case of cutaneous acute lymphoblastic leukemia resulted in full thickness skin loss. One patient with osteosarcoma who was treated with methotrexate developed a case of purpura fulminans that required debridement and NPWT. One wound resulted after debridement of a cutaneous infection. There was one wound that resulted after an extravasation injury. Three patients had amputations that required NPWT; 2 of them for open wounds and 1 for an incisional wound. NPWT was applied immediately in the event of surgically-created wounds, and it was delayed for a range of 1 to 21 days in the remaining patients.

NPWT indication is shown on Table 4. NPWT was used for local wound care in 44 patients, skin graft and/or integra fixation in 10 patients, local wound care in the setting of brachytherapy in one patient, and incisional support in 11 patients. With respect to incisional NPWT, 4 patients had previous external beam radiation therapy, and 2 patients had previous brachytherapy. There were 10 extremity wounds and 1 scalp wound that utilized incisional NPWT. All wounds were healed without complications at the time incisional NPWT was discontinued (5-7 days postoperatively).

Table 5 shows the anatomic distribution of wound NPWT usage. NPWT was used in the head and head/neck in three patients, trunk in 13 patients, upper extremity in 10 patients, and lower extremity in 40 patients. Eleven wounds had bone exposure in the wound bed; four had exposure of fascia; seven had tendon exposure; three had nerve exposure; and two patients had exposure of their endoprostheses. The remaining had either skin, fat, or muscle exposed.

The respective wounds ultimately healed in 60 patients [Table 6]. Wounds healed by secondary intention in 47 patients, skin grafting in four patients, adjacent tissue transfer in three patients, split-thickness skin graft (STSG) and Integra in two patients, local flap in one patient, and delayed primary closure in three patients. Wounds failed to heal in 2 patients who had recurrence of their wound at last follow up, in 1 patient who died of necrotizing fasciitis, in 1 patient who died of primary disease, and in 2 of the 3 patients who required amputation. No patients required free flap to reconstruct their wound.

At the time of their last follow-ups, 2 patients had died of their primary disease. One patient died secondary to necrotizing fasciitis. One patient had a below-knee



Figure 1: Right leg after limb-salvage procedure, with gastrocnemius muscle flap and skin graft coverage of central wound



Figure 2: Surgical site with wound vacuum-assisted closure in place



Figure 3: Surgical site after wound has healed

amputation secondary to intractable pain, unrelated to his wound. Three patients had above-knee amputations: 1 secondary to local tumor recurrence; 1 due to a failed free flap reconstruction; and 1 from implant failure.

NPWT was applied with a negative pressure of 125 mmHg, except in 1 scalp case in which the negative pressure was set to 75 mmHg. NPWT was used under continuous pressure except in 1 patient where intermittent pressure was used for a cheek wound. The regular black Granu-foam sponge was used in all but 11 cases. Silver-impregnated Granu-foam sponges were used in 7 cases, and 1 case used the White-foam sponge for an open abdominal wound. The average wound size was 36 cm²

(median, 27 cm²; range, 4-250 cm²). The average number of days to achieve wound closure was 39 days, with a median of 21 days and a range of 3 to 236 days.

In general, patients tolerated NPWT with minimal morbidity. One patient who had NPWT for fixation of STSG developed cellulitis under the sponge secondary to methicillin-resistant *Staphylococcus aureus*. The cellulitis resolved after the discontinuation of the NPWT and healed completely with no further interventions. Seven patients developed maceration of the skin under the wound VAC dressing, requiring temporary discontinuation of NPWT.

DISCUSSION

Wound issues are not uncommon in the oncology population due to various factors including radiation, chemotherapy, and decreased immunity.^[16-19] NPWT has showed some promising results in the pediatric population.^[12-15] Our study assesses the safety and efficacy of NPWT therapy in the pediatric oncology population.

NPWT therapy offers several advantages over traditional wound care. Because dressing changes are only done every two to three days, the often painful dressing change experience is less traumatic, simplifying wound care for both the patient and the provider. Drainage of the wound is contained in a transparent container, and wound leakage is far less likely compared to traditional wound care. These factors help improve compliance and reduce patient anxiety regarding wound care.

In this study, most wounds were managed successfully with NPWT. The wound VAC was applied in all our patients without any problems regardless of the patient's age or the location or size of the wound.

Of the total 66 patients treated with NPWT, 69% of the wounds healed completely with no intervention, and 20% required delayed surgical closure. NPWT was discontinued temporarily secondary to skin maceration or cellulitis in 12% of patients. Wound care was converted to traditional saline wetted gauze in those cases, and all wounds subsequently healed completely without surgical intervention. No problems of retained sponge material, device malfunction, or inability to apply the wound NPWT were reported in our study. Complications were seen in 12% of the patient population.

The indications for NPWT have expanded since its first introduction. We started using NPWT directly on primarily-closed incisions in the setting of previous radiation therapy, reoperation, and chronic steroid use in 2009. Initially described in patients with multiple comorbidities, this technique was met with moderate success and has resulted in the introduction of NPWT

systems specifically tailored for this use [Figures 1-3].^[20-22] In our study, no complications were reported with incisional wound NPWT. All wounds using the incisional NPWT system healed without issue, although use of the incisional NPWT was not randomized to establish a control group for comparison. However, from historical controls of similar patients, we would have expected a complication rate of 6-22%. In addition to wound care, our study shared the same favorable outcomes of previous studies in using vacuum assisted fixation of STSG and Integra with acceptable complication rates.^[23]

Another novel use of NPWT in our system involved using the VAC in patients with wound healing issues while undergoing concurrent chemotherapy. Specifically with regard to limb salvage patients, one of our protocols involved the use of bevacizumab (an angiogenesis inhibitor) and concurrent high-dose methotrexate. Post-surgical wound dehiscence or delayed wound healing in this population was not uncommon. Given the attendant myelosuppression in these patients, surgical wound closure frequently needed to be delayed. In such patients, wound care was often performed using NPWT for a prolonged period of time, with excellent results.

NPWT offers a safe and reliable alternative to traditional wound care. Our findings are equivalent to similar reports in other pediatric populations.^[6,10] Two cases did have severe complications in our series. In the first case the patient ultimately required a hemipelvectomy for definitive oncologic treatment; however, this complication was related to the nature of the wound rather than use of NPWT. The only wound-related mortality in our cohort was secondary to a case of *Streptococcus pyogenes* necrotizing fasciitis. The patient was a 9-year-old girl with acute lymphoblastic leukemia, status post allogeneic bone marrow transplant, and she was being treated with methotrexate and prednisone. She developed necrotizing fasciitis and underwent two rounds of surgical debridement of an abdominal wound before NPWT. She expired 3 days later. There was no evidence that the infection was due to the use of NPWT in this case. There was a reported case^[24] of necrotizing fasciitis in an adult paraplegic patient which occurred after NPWT for treatment of a debrided grade IV ischial pressure ulcer. The authors believed that the patient's underlying osteomyelitis and his prolonged wound VAC dressing change regimen (the dressing sponge was only changed every 5 days rather than the recommended 2 to 3 days regimen) may have contributed to the development of necrotizing fasciitis. There is no evidence in the literature that supports a correlation between the use of NPWT and an increased risk for the development of necrotizing fasciitis.

One of the limitations of our study is its retrospective nature. Because this study was observational, we lacked a control group to compare NPWT to traditional wound

management in pediatric oncology patients. Another weakness is the lack of patients below six months of age; this patient population may require different approaches and different settings for NPWT.^[25] Another issue which was not addressed in our study is the use of continuous versus intermittent negative pressure.^[26] All our patients except one had continuous NPWT. There is experimental evidence that intermittent vacuum therapy promotes more granulation tissue formation than continuous therapy.^[27] Regardless of these limitations, our study suggests that the use of NPWT is a viable and safe tool in this pediatric oncology population.

In conclusion, we have found NPWT to be a valuable tool for the management of open wounds, fixation of skin grafts, and as a dressing for incision sites in children who are undergoing chemotherapy or radiation therapy. NPWT complications in this patient population are acceptable and easily manageable.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Dedmond BT, Kortesis B, Pungner K, Simpson J, Argenta J, Kulp B, Morykwas M, Webb LX. Subatmospheric pressure dressings in the temporary treatment of soft tissue injuries associated with type III open tibial shaft fractures in children. *J Pediatr Orthop* 2006;26:728-32.
2. Canavese F, Gupta S, Krajchich JI, Emara KM. Vacuum-assisted closure for deep infection after spinal instrumentation for scoliosis. *J Bone Joint Surg Br* 2008;90:377-81.
3. Stannard JP, Volgas DA, Stewart R, McGwin G Jr, Alonso JE. Negative pressure wound therapy after severe open fractures: a prospective randomized study. *J Orthop Trauma* 2009;23:552-7.
4. McCord SS, Naik-Mathuria BJ, Murphy KM, McLane KM, Gay AN, Bob Basu C, Downey CR, Hollier LH, Olutoye OO. Negative pressure therapy is effective to manage a variety of wounds in infants and children. *Wound Repair Regen* 2007;15:296-301.
5. Bütter A, Emran M, Al-Jazaeri A, Ouimet A. Vacuum-assisted closure for wound management in the pediatric population. *J Pediatr Surg* 2006;41:940-2.
6. Caniano DA, Ruth B, Teich S. Wound management with vacuum-assisted closure: experience in 51 pediatric patients. *J Pediatr Surg* 2005;40:128-32.
7. Contractor D, Amling J, Brandoli C, Tosi LL. Negative pressure wound therapy with reticulated open cell foam in children: an overview. *J Orthop Trauma* 2008;22:S167-76.
8. Horn PL, Ruth B, Kean JR. Use of wound V.A.C. therapy in pediatric patients with infected spinal wounds: a retrospective review. *Orthop Nurs* 2007;26:317-22.
9. Baharestani MM. Use of negative pressure wound therapy in the treatment of neonatal and pediatric wounds: a retrospective examination of clinical outcomes. *Ostomy Wound Manage* 2007;53:75-85.
10. Mooney JF 3rd, Argenta LC, Marks MW, Morykwas MJ, DeFranzo AJ. Treatment of soft tissue defects in pediatric patients using the V.A.C. system. *Clin Orthop Relat Res* 2000;(376):26-31.
11. Shilt JS, Yoder JS, Manuck TA, Jacks L, Rushing J, Smith BP. Role of vacuum-assisted closure in the treatment of pediatric lawnmower injuries. *J Pediatr Orthop* 2004;24:482-7.
12. Doak J, Ferrick M. Nonoperative management of pediatric grade I

- open fractures with less than a 24hour admission. *J Pediatr Orthop* 2009;29:49-51.
13. Dedmond BT, Kortesis B, Pungner K, Simpson J, Argenta J, Kulp B, Morykwas M, Webb LX. The use of negative-pressure wound therapy (NPWT) in the temporary treatment of soft-tissue injuries associated with high-energy open tibial shaft fractures. *J Orthop Trauma* 2007;21:11-7.
 14. Argenta LC, Morykwas MJ. Vacuum-assisted closure: a new method for wound control and treatment: clinical experience. *Ann Plast Surg* 1997;38:563-76.
 15. Morykwas MJ, Simpson J, Pungner K, Argenta A, Kremers L, Argenta J. Vacuum-assisted closure: state of basic research and physiologic foundation. *Plast Reconstr Surg* 2006;117:S121-6.
 16. Feldmeier JJ. Problem wounds: the irradiated wound. In: Sheffield PJ, Fife CE, Smith AP, editors. *Wound care practice*. Flagstaff (AZ): Best Publishing Company; 2004. p. 369-88.
 17. Marx RE. Radiation injury to tissue. In: Kindwall EP, Whelan HT editors. *Hyperbaric medicine practice*. 2nd ed. Flagstaff (AZ): Best Publishing Company; 1999. p. 665-723.
 18. Rosenberg LA, Esther RJ, Erfanian K, Green R, Kim HJ, Sweeting R, Tepper JE. Wound complications in preoperatively irradiated soft-tissue sarcomas of the extremities. *Int J Radiat Oncol Biol Phys* 2013;85:432-7.
 19. Davidge KM, Wunder J, Tomlinson G, Wong R, Lipa J, Davis AM. Function and health status outcomes following soft tissue reconstruction for limb preservation in extremity soft tissue sarcoma. *Ann Surg Oncol* 2010;17:1052-62.
 20. Reddix RN Jr, Leng XI, Woodall J, Jackson B, Dedmond B, Webb LX. The effect of incisional negative pressure therapy on wound complications after acetabular fracture surgery. *J Surg Orthop Adv* 2010;19:91-7.
 21. Masden D, Goldstein J, Endara M, Xu K, Steinberg J, Attinger C. Negative pressure wound therapy for at-risk surgical closures in patients with multiple comorbidities: a prospective randomized controlled study. *Ann Surg* 2012;256:1043-7.
 22. Webster J, Scuffham P, Stankiewicz M, Chaboyer WP. Negative pressure wound therapy for skin grafts and surgical wounds healing by primary intention. *Cochrane Database Syst Rev* 2014;10:CD009261.
 23. Stiefel D, Schiestl C, Meuli M. The positive effect of negative pressure: vacuum-assisted fixation of Integra artificial skin for reconstructive surgery. *J Pediatr Surg* 2009;44:575-80.
 24. Citak M, Backhaus M, Meindl R, Muhr G, Fehmer T. Rare complication after VAC-therapy in the treatment of deep sore ulcers in a paraplegic patient. *Arch Orthop Trauma Surg* 2010;130:1511-4.
 25. Rentea RM, Somers KK, Cassidy L, Enters J, Arca MJ. Negative pressure wound therapy in infants and children: a single-institution experience. *J Surg Res* 2013;184:658-64.
 26. Lopez G, Clifton-Koeppel R, Emil S. Vacuum-assisted closure for complicated neonatal abdominal wounds. *J Pediatr Surg* 2008;43:2202-7.
 27. Malmström M, Gustafsson L, Lindstedt S, Gesslein B, Ingemansson R. The effects of variable, intermittent, and continuous negative pressure wound therapy, using foam or gauze, on wound contraction, granulation tissue formation, and ingrowth into the wound filler. *Eplasty* 2012;12:e5.

Meshed acellular dermal matrix: technique and application in implant based breast reconstruction

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ABSTRACT

Alloderm was the first acellular dermal matrix used and remains a popular choice among plastic surgeons. However, while the overall surgical outcome of breast reconstruction using alloderm has been a success, the economic burden on the health care system makes it a subject of frequent re-evaluations in cost-effectiveness. Prompted by the high price of \$3,700 USD for a 6 cm × 16 cm area, our group proposes the meshing of AlloDerm to decrease the total amount needed for breast reconstruction, while achieving comparable surgical outcomes as using unmeshed alloderm.

Key words:

Alloderm; acellular dermal matrix; breast reconstruction; meshing; breast cancer

INTRODUCTION

The use of acellular dermal matrices (ADM) in breast reconstruction has grown in popularity in the last decade, stemming from the increase in implant based reconstruction requiring adequate lower pole coverage.^[1] Our idea of meshing ADM originates from a common surgical technique used for skin grafting.

Skin grafts can be classified broadly into two groups: split-thickness grafts that contain a portion of the dermis, and full-thickness grafts that contain the entire dermis. An advantage of split-thickness grafts over full-thickness grafts is that they can survive in less vascular conditions, but are more prone to contracting.^[2] Split-

thickness grafts can be processed through meshing, therefore increasing promoting improved adherence to the wound. To date, there have been no reports in the literature on using meshed alloderm routinely for breast reconstruction surgery.

Alloderm is an acellular human tissue matrix derived from cadaveric tissue that exhibits regenerative properties.^[3] All donor cells and allergenic epitopes are removed, leaving a collagen scaffold, growth factor receptors, and vascular channels that aid in tissue regeneration with minimum scarring and fibrosis. The utility of alloderm is based on its ability to integrate and promote neovascularization

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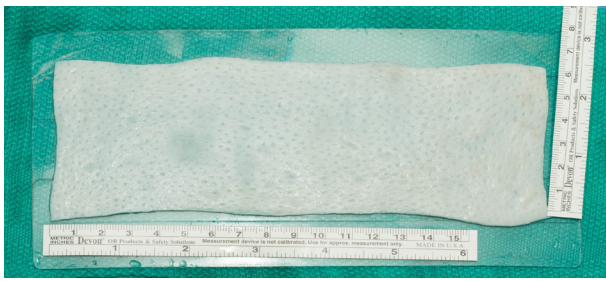


Figure 1: Native alloderm with dimensions of 6 cm × 17 cm = 102 cm² and having a thickness of 1.0 mm ± 0.2 mm (thin type)



Figure 3: Meshed alloderm with new dimensions of 9 cm × 17 cm = 153 cm²



Figure 2: AlloDerm (thin-type) is processed by the skin graft mesher

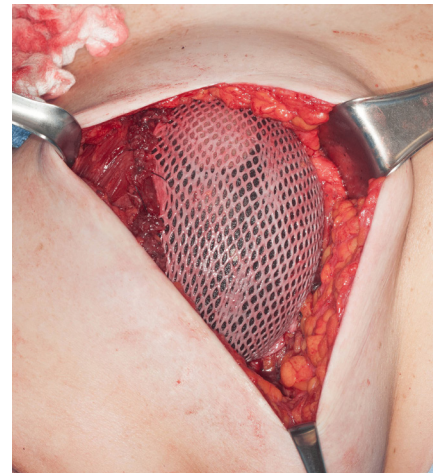


Figure 4: Meshed alloderm is sutured to the pectoralis muscle and the chest wall

in the wound bed.^[4] It follows the principles of skin graft healing and can therefore be easily incorporated into host tissue as a suitable alternative. These properties make alloderm an excellent support material for breast reconstruction.

Alloderm has been used since 2005.^[5] Lower pole coverage was achieved by suturing alloderm to the caudal aspect of the pectoralis major and at the level of the inferior and lateral mammary folds. The benefits of alloderm include reducing implant exposure, visibility and palpability, preventing window shading, better defined inframammary and lateral mammary folds, and allowing for a more natural breast shape.^[5]

TECHNICAL NOTE

AlloDerm was initially developed to solve problems with lower pole coverage. Depending on the size of the breast, the quantity of alloderm sheets per operation may vary, leading to increased costs. Meshing alloderm is a novel technique that increases the surface area of usable ADM while maintaining structural integrity.

A sheet of alloderm regenerative tissue matrix (LifeCell Corporation, Branchburg, NJ) measuring 6 cm × 17 cm = 102 cm² [Figure 1] and having a thickness of 1.0 mm ± 0.2 mm (thin type) was prepared in standard fashion by soaking in antibacterial solution and placed on the

skin graft carrier (Zimmer Dermacarrier, Zimmer Surgical Inc., Dover, OH). The tissue matrix was passed through the skin graft mesher (Zimmer Surgical Inc.) with a pre-installed roller blade size of 1.5:1 [Figure 2]. Once meshed, it measures 9 cm × 17 cm = 153 cm², an increase in surface area of 50% [Figure 3]. The meshed alloderm is then attached to the chest wall and pectoralis major muscle with PDS 2-0 sutures (Ethicon Inc.), with a tissue expander placed underneath [Figure 4].

DISCUSSION

The most widely used technique for breast reconstruction employs tissue expanders and implants.^[6] When first described, the expander or implant was inserted under the pectoralis major muscle to obtain complete sub-muscular coverage. If not feasible, the serratus anterior or rectus muscles would be raised to cover the lower pole of the breast. However, using the serratus anterior muscle would often times be associated with donor site morbidity. This includes shoulder pain, weakness and limitation of shoulder elevation due to serratus anterior palsy, in addition to other problems such as wound dehiscence, infection and hematoma formation at donor site closure.^[7] Therefore, the dual-plane technique was developed, where the expander or implant was covered by the pectoralis major superiorly and by the dermis of the breast inferiorly. This eliminated donor site morbidity,

but was associated with the pectoralis major migrating superiorly and causing window shading. In addition, as the inferior pole is covered solely by a thin skin flap, there is a risk of implant migration, poor visibility, palpability, and excessive ptosis. Window shading has since been corrected with marionette sutures to anchor the pectoralis major, while the development of alloderm helped with the problem of lower pole coverage.^[2]

Meshing of alloderm is an innovative idea that can decrease the costs of its use. A recent study looked at the effects of fenestrating ADMs.^[8] Their results showed that with fenestrations, the incidence of capsular contractures, infections and seroma formation were all decreased. Further, they described improved intra-operative fill volumes and expansion rate, as well as a decreased number of post-operative expansions.^[8] While not identical in technique to meshing alloderm, it does show potential further benefits for meshing alloderm. By employing a similar technique used with split thickness skin grafts, we were able to take a standard 6 cm × 17 cm sheet of alloderm and increase its area from 102 cm² to 153 cm², an increase of 50%. In our experience, with an increase of 50% more alloderm available for use, this amounted to savings of approximately 50% per sheet of alloderm. Intraoperative findings during the second stage (expander to implant exchange) show that the meshed alloderm integrates as well if not better than the standard unmeshed alloderm. This may be because the overall three-dimensional surface area of the ADM is increased, allowing for better integration and neovascularization. Further correlation with histological analysis and clinical follow up to

compare meshed versus un-meshed ADM is pending.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Gabriel A, Maxwell GP. Evolving role of alloderm in breast surgery. *Plast Surg Nurs* 2011;31:141-50.
2. Shimizu R, Kishi K. Skin graft. *Plast Surg Int* 2012;2012:563493.
3. Jansen LA, De Caigny P, Guay NA, Lineaweaver WC, Shokrollahi K. The evidence base for the acellular dermal matrix alloderm: a systematic review. *Ann Plast Surg* 2013;70:587-94.
4. Chauviere MV, Schutter RJ, Steigelman MB, Clark BZ, Grayson JK, Sahar DE. Comparison of alloderm and allomax tissue incorporation in rats. *Ann Plast Surg* 2014;73:282-5.
5. Glasberg SB, Light D. AlloDerm and strattice in breast reconstruction: a comparison and techniques for optimizing outcomes. *Plast Reconstr Surg* 2012;129:1223-33.
6. Wu C, Cipriano J, Osgood G, Tepper D, Siddiqui A. Human acellular dermal matrix (AlloDerm®) dimensional changes and stretching in tissue expander/implant breast reconstruction. *J Plast Reconstr Aesthet Surg* 2013;66:1376-81.
7. Dumont CE, Domenghini C, Kessler J. Donor site morbidity after serratus anterior free muscular flap: a prospective clinical study. *Ann Plast Surg* 2004;52:195-8.
8. Mowlds DS, Salibian AA, Scholz T, Paydar KZ, Wirth GA. Capsular contracture in implant-based breast reconstruction: examining the role of acellular dermal matrix fenestrations. *Plast Reconstr Surg* 2015;136:629-35.

The most compatible position of operator for mandibular right posterior teeth extraction

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Sir,

The positions of the dental chair, patient and operator are critical for successful completion of tooth extraction.^[1] Whilst, the proper positioning of the operator is very important to have good visibility and accessibility of the oral cavity, besides allowing the surgeon to have maximal control of the force that is being delivered to the patient's tooth through the forceps.^[1] Also, proper operating position and good posture reduces fatigue and physical strain and possibility of developing musculo-skeletal disorders.

For extraction of the mandibular right posterior teeth, a right-handed operator would usually stand at the right rear position (11 o'clock) or direct rear position^[2] (12 o'clock) [Figure 1]. These positions give good visibility and maximal accessibility to the oral cavity posteriorly as far as right first mandibular molar. However, a diminished accessibility is experienced by many operators when extracting the right second and third molars from these positions. It also results in unnecessary curvature of the spine or slumping of shoulders during the surgical procedure leading to physical strain [Figure 2].

With the intention to overcome this diminished accessibility and to enhance the effectiveness of the operator, the authors recommend positioning of a right-handed operator at the

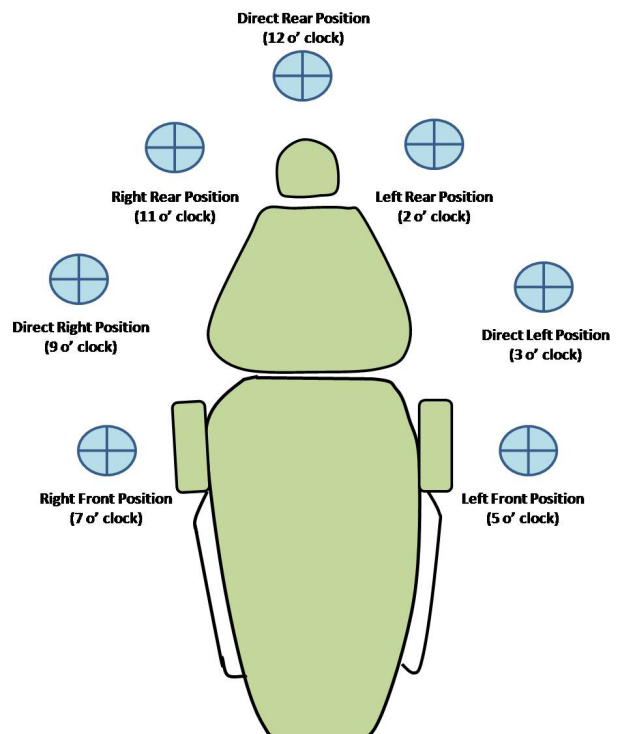


Figure 1: Operator positions for tooth extraction

left rear position (2 o'clock) for extraction of the mandibular right posterior teeth [Figure 3]. This compatible operator

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Figure 2: Diminished visibility and accessibility during extraction of mandibular right posterior teeth from right rear position

position provides a more balanced posture with increased visibility and accessibility to the oral cavity when extracting the mandibular right second and third molars.

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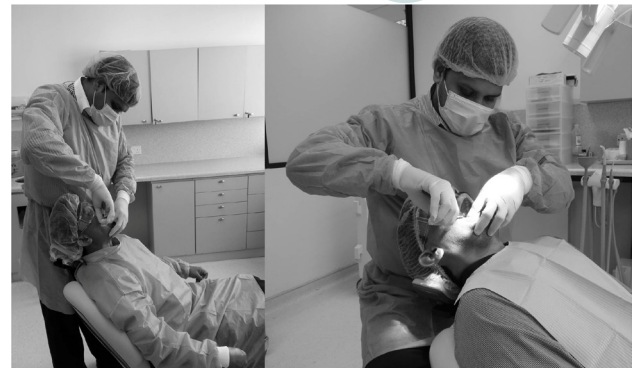


Figure 3: The most compatible operator position for mandibular right posterior teeth extraction

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Hupp JR. Principles of Routine Exodontia. In: Hupp JR, Ellis E, Tucker MR, editors. Contemporary Oral and Maxillofacial Surgery. 6th ed. St Louis, Missouri: Mosby Elsevier; 2014. p. 88-118.
2. Robinson PD. Tooth Extraction: a practical guide. 1st ed. Oxford: Wright; 2000. p. 34-5.

A propensity score matched analysis of obesity as an independent risk factor for postoperative complications in reduction mammoplasty

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ABSTRACT

Aim: Reduction mammoplasty is a commonly performed procedure for the treatment of symptomatic macromastia and is increasingly desired by the obese population. With the increasing prevalence obesity in the population, it is imperative to understand its effect on postoperative outcomes. The purpose of this study is to evaluate obesity as an independent risk factor for postoperative complications in breast reduction surgery using 1:1 patient matching through propensity scores between obese patients and non-obese controls. **Methods:** Between 2005 and 2013, the National Surgical Quality Improvement Program dataset identified a total of 6,016 patients as having undergone primary reduction mammoplasty with 30-day postoperative follow-up. Patients were divided into obese [body mass index (BMI) of 30 or more] vs. not obese (BMI below 30). Patients were initially analyzed using standard multivariable analysis. Using propensity scores obtained from a logistic regression model, patients were subsequently matched 1:1 according to preoperative and operative variables to truly isolate the effect of obesity on surgical outcomes. Outcomes were compared between the matched cohorts using McNemar's test and the Wilcoxon signed rank test. **Results:** In unmatched multivariable analysis, rates of overall complications (7.2% vs. 5.3%, $P = 0.0024$), wound complications (5.5% vs. 3.6%, $P = 0.0004$), superficial surgical site infection (4.1% vs. 2.8%, $P = 0.0050$), and wound dehiscence (0.3% vs. 1.1%, $P = 0.0005$) were found to be statistically different between obese vs. non-obese, respectively. However, when comparing 1:1 matched obese and non-obese patients, only wound complications (4.6% vs. 3.1%, $P = 0.0334$) were significantly increased in the obese cohort. **Conclusion:** Using the most robust statistical tools available, obesity was

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determined to affect wound complications after breast reduction without increased detriment on other major complications when compared to the non-obese. Obesity should be considered with other preoperative comorbidities, rather than an independent contraindication to surgery. Breast reduction appears to be safe in the obese patient who is otherwise healthy.

Key words:

Obesity; breast reduction; reduction mammoplasty; National Surgical Quality Improvement Program; propensity score

INTRODUCTION

Breast reduction surgery, or reduction mammoplasty, is a commonly performed procedure for the treatment of symptomatic macromastia. Over 101,000 breast reductions were performed in 2014.^[1] Patients seek relief from back and neck pain, intertriginous rashes, shoulder grooving, ill-fitting clothing, and dissatisfaction with breast appearance. Breast reduction has been shown to improve physical, psychosocial, and sexual well-being.^[2] Patients experience enhanced quality of life^[3] and are highly satisfied with the procedure.^[4,5]

The incidence of postoperative complications in reduction mammoplasty is relatively low, approximately 6%.^[6] Problems range from minor wound complications and infections to significant bleeding and thromboembolic events. Thorough preoperative assessment is imperative to patient safety and avoiding poor surgical outcomes.

Many women suffering from symptomatic macromastia are obese. Given the increasing number of obese patients in the general population, the role of body mass index (BMI) as a preoperative assessment factor remains of great interest to the surgical community. Obese patients are more likely to have medical comorbidities, including hypertension, diabetes, chronic respiratory disease and obstructive sleep apnea. They are 35% more likely to have an emergency department visit or hospital admission 30 days after outpatient surgery.^[7] Many surgeons require obese patients to lose weight prior to undergoing surgery, and certain insurance carriers use higher weights as refusal criteria for coverage.^[8] The role of obesity in postoperative complications following reduction mammoplasty is inconsistently defined in the literature. Some studies associate obesity with increased postoperative complications,^[9-13] whereas others find no statistically significant correlation.^[14-17]

In 2014, Nelson *et al.*^[6] studied obesity and reduction mammoplasty using the 2005-2011 American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP) datasets. NSQIP is a nationally-validated, risk-adjusted surgical outcomes database to measure and improve the quality of surgical care. The authors reported an increased rate of overall complications in the early 30-day postoperative period among obese patients

on multivariable analysis. However, no study to date has harvested the statistical power of the NSQIP dataset with the use of propensity score matching to evaluate the effect of obesity as an independent risk factor on breast reduction outcomes. Multivariable analysis attempts to control for heterogeneity between patient cohorts via advanced statistical techniques. Patient matching, however, eliminates heterogeneity between patient cohorts by 1:1 matching each experimental group patient with a control group patient with similar characteristics. The goal of this study is to isolate the effect of obesity on breast reduction outcomes using 1:1 patient matching.

METHODS

Data acquisition

Patients undergoing primary reduction mammoplasty were identified from the 2005-2013 ACS-NSQIP registry. Methods for data acquisition involved trained research nurses from participating institutions in the United States who collected data through systemic sampling of surgical procedures, as previously described.^[18] A total of 240 variables were collected for each case. Further information can be accessed via the ACS-NSQIP website at <http://www.acsnsqip.org/>. Data are depersonalized and Health Insurance Portability and Accountability Act compliant.

The NSQIP registry was queried using Current Procedural Terminology code 19318 to identify patients who had undergone reduction mammoplasty. Patients were then characterized according to the World Health Organization (WHO) classification of obesity: non-obese (BMI < 30 kg/m²), class I obesity (BMI 30-34.9 kg/m²), class II obesity (BMI 35-39.9 kg/m²), or class III (BMI ≥ 40 kg/m²). Inclusion criteria included primary bilateral breast reductions.

Outcome variables

Primary outcomes of interest were analyzed through several pre-defined NSQIP variables, including patient demographics and comorbidities, as well as early surgical complications, defined as adverse events occurring within 30 days after surgery. Demographics included race and age. Comorbidities included diabetes (further classified into insulin dependent and non-insulin dependent),

Table 1: Patient characteristics

	Overall		Complications	
	n	%	n	%
Overall	6,016		378	
Race				
White	2,773	46.1	154	40.7
Black	918	15.3	57	15.1
Hispanic	33	0.5	0	0.0
Other	53	0.9	1	0.3
Unknown	2,239	37.2	166	43.9
Age, years				
< 45	3,009	50.0	185	48.9
45-65	2,663	44.3	175	46.3
> 65	344	5.7	18	4.8
Diabetes				
None	5,736	95.3	350	92.6
Any diabetes	280	4.7	28	7.4
Insulin dependent	52	0.9	6	1.6
Non-insulin dependent	228	3.8	22	5.8
Active smoking	675	11.2	57	15.1
Alcohol use	40	0.7	5	1.3
Dependent functional status	16	0.3	1	0.3
Respiratory disease	169	2.8	17	4.5
Chronic obstructive pulmonary disease	40	0.7	4	1.1
Dyspnea	142	2.4	15	4.0
Hypertension	1,307	21.7	100	26.5
30-day prior wound infection	23	0.4	4	1.1
Heart disease	34	0.6	3	0.8
Previous cardiac surgery	31	0.5	2	0.5
History of angina	4	0.1	1	0.3
Recent weight loss	12	0.2	1	0.3
Bleeding disorder	28	0.5	3	0.8
Preoperative sepsis	6	0.1	0	0.0
Prior operation within 30 days	8	0.1	0	0.0
Overall comorbidities				
0	3,722	61.9	195	51.6
1	1,725	28.7	125	33.1
2 or more	569	9.5	58	15.3

Total comorbidities were determined by evaluating the following comorbidities: diabetes, smoking, alcohol use, dependent functional status, respiratory disease (ventilator dependence, chronic obstructive pulmonary disease, pneumonia and dyspnea), hypertension, history of transient ischemic attack and cerebrovascular accident, 30-day prior wound infection, steroid use, liver disease, heart disease (congestive heart failure, myocardial infarction, previous cardiac surgery, history of angina), recent weight loss, bleeding disorder, low albumin, low hematocrit, preoperative sepsis, prior operation within 30 days

active smoking, alcohol use, dependent functional status, respiratory disease (chronic obstructive pulmonary

Table 2: Case characteristics

	Overall		Complications	
	n	%	n	%
Overall	6,016		378	
ASA classification				
1	1,682	28.0	97	25.7
2	3,629	60.4	214	56.6
3	688	11.4	67	17.7
4	11	0.2	0	0.0
Year of procedure				
2005-2009	1,718	28.6	100	26.5
2010-2013	4,298	71.4	278	73.5
Admission status				
Inpatient	877	14.6	81	21.4
Outpatient	5,139	85.4	297	78.6
Operative time (min), median and range	148	13-739	148	30-484

Complication rates were analyzed in terms of the following case characteristics: American Society of Anesthesiologists (ASA) classification (1, 2, 3, or 4), year of procedure, inpatient versus outpatient, and operative time

Table 3: Complications

	Overall		Complications	
	n	%	n	%
Overall	6,016		378	
Surgical complication	100	1.7	100	26.5
Wound complication	275	4.6	275	72.8
Medical complication	38	0.6	38	10.1
Return to operating room	99	1.6	99	26.2
Superficial SSI	208	3.5	208	55.0
Deep SSI	29	0.5	29	7.7
Organ/space SSI	4	0.1	4	1.1
Wound dehiscence	42	0.7	42	11.1
Venous thromboembolism	8	0.1	8	2.1
Pulmonary embolism	7	0.1	7	1.9
Deep venous thrombosis	3	0.1	3	0.8
Unplanned reintubation	2	0.1	2	0.5
Urinary tract infection	8	0.1	8	2.1
Other bleeding	15	0.2	15	4.0

Surgical complications included graft failure and an unplanned return to the operating room. Wound complications included superficial surgical site infection (SSI), deep SSI, organ/space SSI and wound dehiscence. Medical complications contained National Surgical Quality Improvement Program defined endpoints including renal complication (renal failure and renal insufficiency), neurological complications (cerebrovascular accident, coma, peripheral nerve injury), cardiac complications (myocardial infarction and cardiac arrest), sepsis, death, venous thromboembolism, failure to wean, reintubation, pneumonia, bleeding, and urinary tract infection

disease and dyspnea), hypertension, wound infection with in the prior 30 days, heart disease (previous

Table 4: Comorbidities by body mass index group

	Underweight and normal		Overweight		Class I		Class II		Class III		P-value	Sub-analysis
	n	%	n	%	n	%	n	%	n	%		
Overall	951		2,011		1,708		830		516			
Race												
White	407	42.8	947	47.1	801	46.9	390	47.0	228	44.2	0.0004	abcdefghijkl
Black	55	5.8	187	9.3	275	16.1	209	25.2	192	37.2		
Hispanic	10	1.1	10	0.5	9	0.5	4	0.5	0	0.0		
Other	14	1.5	18	0.9	11	0.6	6	0.7	4	0.8		
Unknown	465	48.9	849	42.2	612	35.8	221	26.6	92	17.8		
Age, years											0.0045	bhi
< 45	503	52.9	1,005	50.0	797	46.7	432	52.0	272	52.7		
45-65	393	41.3	876	43.6	806	47.2	358	43.1	230	44.6		
> 65	55	5.8	130	6.5	105	6.1	40	4.8	14	2.7		
Diabetes											0.0004	abcdefghijkl
None	941	98.9	1,962	97.6	1,618	94.7	775	93.4	440	85.3		
Insulin dependent	2	0.2	7	0.3	12	0.7	15	1.8	16	3.1		
Non-insulin dependent	8	0.8	42	2.1	78	4.6	40	4.8	60	11.6		
Any diabetes	10	1.1	49	2.4	90	5.3	55	6.6	76	14.7	< 0.0001	abcdefghijkl
Active smoking	89	9.4	212	10.5	209	12.2	110	13.3	55	10.7	0.0474	bcf
Alcohol use	7	0.7	17	0.8	13	0.8	1	0.1	2	0.4	0.1788	
Respiratory disease	5	0.5	26	1.3	45	2.6	42	5.1	51	9.9	< 0.0001	bcdefghij
Hypertension	81	8.5	319	15.9	433	25.4	254	30.6	220	42.6	< 0.0001	abcdefghijkl
30-day prior wound infection	3	0.3	5	0.2	12	0.7	1	0.1	2	0.4	0.1641	
Heart disease	5	0.5	9	0.4	11	0.6	4	0.5	5	1.0	0.6535	
Weight loss	3	0.3	2	0.1	4	0.2	2	0.2	1	0.2	0.6470	
Bleeding disorder	6	0.6	6	0.3	9	0.5	2	0.2	5	1.0	0.2148	
Preoperative sepsis	1	0.1	0	0.0	0	0.0	4	0.5	1	0.2	NR	
Prior operation within 30 days	0	0.0	6	0.3	1	0.1	1	0.1	0	0.0	NR	
Total comorbidities											< 0.0001	abcdefghijkl
0	736	77.4	1,385	68.9	978	57.3	419	50.5	204	39.5		
1	184	19.3	517	25.7	547	32.0	295	35.5	182	35.3		
2 or more	31	3.3	109	5.4	183	10.7	116	14.0	130	25.2		

P-value subanalysis key: P-value < 0.05 in a (underweight and normal vs. overweight), b (underweight and normal vs. class I), c (underweight and normal vs. class II), d (underweight and normal vs. class III), e (overweight vs. class I), f (overweight vs. class II), g (overweight vs. class III), h (class I vs. class II), i (class I vs. class III), j (class II vs. class III). P-values are not reported (NR) for any variables with a cell size of 0

cardiac surgery and history of angina), recent weight loss, bleeding disorder, preoperative sepsis, and prior operation within 30 days.

Surgical complications included wound complications, unplanned return to the operating room and graft/flap failure. Wound complications encompassed superficial surgical site infection (SSI), deep SSI, organ/deep space SSI, and wound dehiscence. Medical complications were defined as renal (renal failure and renal insufficiency),

neurologic (stroke, coma, peripheral nerve injury), cardiac (myocardial infarction and cardiac arrest), sepsis, death, venous thromboembolism, failure to wean from ventilator, unplanned reintubation, pneumonia, bleeding, and urinary tract infection. Multivariable analysis of postoperative outcomes was performed to control for those preoperative and intraoperative variables with $n > 10$ events, and $P < 0.05$ on bivariate screen.

Obese and non-obese patients were then 1:1

Table 5: Complications and body mass index group

	Underweight and normal		Overweight		Class I		Class II		Class III		P-value	Sub-analysis
	n	%	n	%	n	%	n	%	n	%		
Overall	951		2,011		1,708		830		516			
Any complication	42	4.4	115	5.7	105	6.1	53	6.4	63	12.2	< 0.0001	dgij
Surgical complication	14	1.5	33	1.6	20	1.2	16	1.9	17	3.3	0.0214	dgi
Wound complication	27	2.8	79	3.9	81	4.7	40	4.8	48	9.3	< 0.0001	bcdgij
Medical complication	3	0.3	11	0.5	9	0.5	7	0.8	8	1.6	0.0739	
Return to operating room	14	1.5	33	1.6	19	1.1	16	1.9	17	3.3	0.0156	dgi
Superficial SSI	26	2.7	56	2.8	62	3.6	27	3.3	37	7.2	< 0.0001	dgij
Deep SSI	0	0.0	15	0.7	8	0.5	5	0.6	1	0.2	NR	
Organ/space SSI	0	0.0	0	0.0	2	0.1	2	0.2	0	0	NR	
Wound dehiscence	1	0.1	8	0.4	13	0.8	6	0.7	14	2.7	< 0.0001	bdgij
Venous thromboembolism	2	0.2	2	0.1	2	0.1	2	0.2	0	0	NR	
Unplanned reintubation	0	0.0	1	0.1	0	0	0	0	1	0.2	NR	
Urinary tract infection	0	0.0	3	0.1	1	0.1	3	0.4	1	0.2	NR	
Other bleeding	1	0.1	3	0.1	6	0.4	1	0.1	4	0.8	0.1024	
Hospital length of stay, median and range	0	0-234	0	0-31	0	0-32	1	0-6	1	0-15	< 0.0001	bcdefghij

P-value subanalysis key: P-value < 0.05 in a (underweight and normal vs. overweight), b (underweight and normal vs. class I), c (underweight and normal vs. class II), d (underweight and normal vs. class III), e (overweight vs. class I), f (overweight vs. class II), g (overweight vs. class III), h (class I vs. class II), i (class I vs. class III), j (class II vs. class III). P-values are not reported (NR) for any variables with a cell size of 0. SSI: surgical site infection

propensity score matched to control for preoperative and intraoperative variables, in order to isolate the effect of obesity on postoperative outcomes. Patient characteristics were matched if $n > 10$ (i.e., greater than 10 events) and $P < 0.05$ on bivariate screen. Based on these criteria, matched characteristics included the following: age; diabetes mellitus; active smoking; alcohol use; hypertension; respiratory disease; heart disease; history of transient ischemic attack or stroke; bleeding comorbidity; preoperative wound infection; steroid or immunosuppressant use; recent weight loss > 10% of total body weight in 6 months prior to surgery; total number of comorbidities (none, one, or two or more); American Society of Anesthesiologists (ASA) class; inpatient versus outpatient status; operative time; and total work relative value units.

Statistical analysis

Characteristics of the sample were summarized using descriptive statistics. Medians and ranges were reported for continuous variables; frequencies and percentages are reported for categorical variables. The chi square test, Fisher's exact test and the Kruskal-Wallis test were used to determine association between BMI groups and various demographic, comorbidity and outcome variables. If a statistically significant association was detected between a BMI group and a variable, a subgroup analysis was performed using the same tests to determine which of the groups were significantly different from each other. Multivariable analysis of postoperative outcomes was

performed for those preoperative and intraoperative variables with $n > 10$ events, and $P < 0.05$ on bivariate screen.

Data were then separated into two groups: patients who were obese (BMI of 30 or more) and patients who were not obese (BMI below 30). Patients were matched on a 1:1 basis using propensity scores from a logistic regression model (as described above). Outcomes were then compared between the matched cohorts using McNemar's test and the Wilcoxon signed rank test. Statistical significance is indicated by $P < 0.05$.

RESULTS

Overall

Between 2005 and 2013, the NSQIP datasets identified a total of 6,016 patients who underwent primary reduction mammoplasty with 30-day postoperative follow-up. The patients were predominantly white, comprising 46.1% of the cohort, and 15.3% were black. Fifty percent were younger than 45 years of age, 44.3% were between 45 and 65 years, and only 5.7% were older than 65 years.

From the total group of patients, 28.7% had at least one preoperative comorbidity, and 9.5% had two or more. Common comorbidities included hypertension (21.7%), active smoking (11.2%), and diabetes (4.7%) [Table 1]. Other factors to assess preoperative risk included ASA classification, with 28.0% in class 1, 60.4% in class 2, 11.4%

Table 6: Complications and obesity status - unmatched analysis

	Obese		Non-obese		P-value
	n	%	n	%	
Overall	3,054		2,962		
Any complication	221	7.2	157	5.3	0.0024
Surgical complication	53	1.7	47	1.6	0.7263
Wound complication	169	5.5	106	3.6	0.0004
Medical complication	24	0.8	14	0.5	0.1706
Return to operating room	52	1.7	47	1.6	0.8011
Superficial SSI	126	4.1	82	2.8	0.0050
Deep SSI	14	0.5	15	0.5	0.9342
Organ/space SSI	4	0.1	0	0.0	0.1251
Wound dehiscence	9	0.3	33	1.1	0.0005
Venous thromboembolism	4	0.1	4	0.1	1.0000
Unplanned reintubation	1	0.0	1	0.0	1.0000
Urinary tract infection	5	0.2	3	0.1	0.7266
Other bleeding	11	0.4	4	0.1	0.1357
Hospital length of stay, median and range	1	0-32	0	0-234	< 0.0001

The rates of overall complication ($P = 0.0024$), wound complication ($P = 0.0004$), superficial surgical site infection (SSI) ($P = 0.0050$), and wound dehiscence ($P = 0.0005$) were found to be different between obese and non-obese patients. The distribution of the total hospital length of stay was also found to differ by obesity status ($P < 0.0001$).

in class 3, and 0.2% in class 4. A majority of cases (85.4%) were outpatient, and median operative time was 148 min, with a range of 13 to 739 min [Table 2].

Overall complications within the early postoperative period were rare, at a rate of 6.3%. These were comprised mostly of wound complications (4.6% of total, 72.8% of all complications). The most common wound complication was superficial SSI, occurring in 3.5%. Surgical complications occurred in 1.7%, and medical complications occurred in only 0.6% [Table 3].

Analysis by WHO obesity classification

BMI data were then assessed according to WHO obesity classification. Overall, 3,054 of the patients (50.8%) were obese, with 1,708 (28.4%) classified as class I, 830 (13.8%) as class II, and 516 (8.6%) as class III. Analysis among the non-obese, overweight, and three classes of obesity showed statistically significant differences in demographic values and several comorbidities. Black patients comprised an increasingly large proportion with each class of obesity (5.8% underweight/normal, 9.3% overweight, 16.1% class I, 25.2% class II, and 37.2% class III) [Table 4].

Regarding comorbidities, there was a significant increase in the rate of diabetes with increased obesity class: 1.1% in the underweight/normal, 2.4% in the overweight, 5.3% in class I, 6.6% in class II, and 14.7% in class III ($P < 0.0001$). Hypertension (8.5% underweight/normal, 15.9% overweight, 25.4% class I, 30.6% class II, and 42.6%

class III) and respiratory disease (0.5% underweight/normal, 1.3% overweight, 2.6% class I, 5.1% class II, 9.9% class III) increased as well ($P < 0.0001$). As the class of obesity increased, there were greater total comorbidities (3.3% of underweight/normal patients had at least two comorbidities, compared to 25.2% of class III obese patients) ($P < 0.0001$). Smoking and alcohol use rates did not increase proportionally with increasing obesity class [Table 4].

Multivariable analysis of postoperative outcomes was performed for those preoperative and intraoperative variables with $n > 10$ events, and $P < 0.05$ on bivariate screen [Tables 5 and 6]. After controlling for preoperative and intraoperative differences by multivariable analysis, a significant increase was noted in any complication in class III obese patients (12.2%), when compared to underweight/normal (4.4%), overweight (5.7%), class I (6.1%) and class II (6.4%) patients ($P < 0.0001$). Surgical complications were significantly greater when comparing class III (3.3%) with underweight/normal (1.5%), overweight (1.6%) and class I patients (1.2%) ($P < 0.0214$). Regarding wound complications, class III patients had significantly increased rates (9.3%) compared to all other categories. However, they were also found to be greater in class I (4.7%) and class II patients (4.8%) when compared to underweight and normal weight patients (2.8%) ($P < 0.0001$). An unexpected return to the operating room occurred more frequently in class III patients (1.6%) relative to underweight/normal, overweight and class I patients ($P < 0.0156$). Superficial SSI and wound dehiscence also occurred significantly more in class III

Table 7: Using propensity scores, obese patients were matched to non-obese patients on the variables listed

	Full cohort			Matched cohort		
	% of patients		P-value	% of patients		P-value
	Non-obese n = 2,962	Obese n = 3,054		Non-obese n = 1,464	Obese n = 1,464	
Age, years			0.0399			0.1067
< 45	50.9	49.1		54.1	52.9	
45-65	42.8	45.6		41.1	43.7	
> 65	6.2	5.2		4.8	3.3	
Diabetes	2.0	7.2	< 0.0001	1.8	2.0	0.8774
Hypertension	13.5	29.7	< 0.0001	15.2	16.9	0.1344
Respiratory disease	1.0	4.5	< 0.0001	1.5	1.2	0.5708
ASA class			< 0.0001			0.3593
1 or 2	94.2	82.7		93.0	93.8	
3 or 4	5.7	17.3		7.0	6.2	
Total comorbidities			< 0.0001			0.4571
0	71.6	52.4		69.1	68.2	
1	23.7	33.5		25.1	26.8	
2 or more	4.7	14.0		5.7	50.0	
Inpatient status	11.6	17.5	< 0.0001	11.8	13.9	0.0831
Total RVU, median (range)	16.0 (16.6-54.7)	16.0 (15.6-52.0)	< 0.0001	16.0 (15.6-49.2)	16.0 (15.6-51.9)	0.7769
Operating time, min, median (range)	133 (13-739)	163 (14-636)	< 0.0001	146 (14-543)	146 (14-488)	0.3134

Prior to matching, obese patients were found to be significantly different from non-obese patients on all of the characteristics. After matching, none of these characteristics were found to differ between the two groups. ASA: American Society of Anesthesiologists; RVU: relative value units

patients (7.2% and 2.7%, respectively) compared to all other categories; wound dehiscence occurred more in class I obese patients compared to the underweight and normal ($P < 0.0001$) [Table 5].

Unmatched multivariable analysis

Again on multivariable analysis, obese patients (BMI 30 or more) were compared to the non-obese (BMI < 30) in an unmatched analysis. Rates of overall complications (7.2% vs. 5.3%, $P = 0.0024$), wound complications (5.5% vs. 3.6%, $P = 0.0004$), superficial SSI (4.1% vs. 2.8%, $P = 0.0050$), and wound dehiscence (0.3% vs. 1.1%, $P = 0.0005$) were found to be statistically different. Total hospital length of stay was found to change with obesity status ($P < 0.0001$) [Table 6].

Propensity score matched analysis

Using propensity scores, obese patients were then matched to non-obese patients according to preoperative and operative variables, totaling 1,464 patients in each group. After matching, none of these variables were found to differ between the two groups. When comparing the matched obese vs. non-obese patients, only wound complications (4.6% vs. 3.1%, $P = 0.0334$) and hospital length of stay ($P < 0.0001$) were significantly increased in the obese cohort.

DISCUSSION

Obesity continues to be an epidemic not only in North America, but globally as well. Thirty-six percent of the population is considered obese, with a greater proportion of women than men.^[19,20] Symptomatic macromastia is a common condition which afflicts many women, particularly the obese population. Although obesity has been correlated with increased complication rates,^[9-13] this population also has a propensity towards having greater medical comorbidities. With literature demonstrating improved longevity in overweight patients compared to normal weight patients,^[21] BMI and obesity must therefore be assessed independent of these confounding comorbidities.

Obesity is an often assumed risk factor for postoperative complications following breast reduction surgery. However, its effect on risk outcomes remains incompletely understood. Our study hopes to better define obesity as a preoperative risk factor for breast reduction. Multivariate analysis both before propensity score matching [Tables 5 and 6] and after matching [Tables 7 and 8] was utilized to isolate the effects of obesity alone on postoperative outcomes. Propensity score matching produces estimates that are less biased, more robust, more precise, and with greater empirical power than logistic regression when

Table 8: Complications and obesity status - matched analysis

	Obese		Non-obese		P-value
	n	%	n	%	
Overall	1,464		1,464		
Any complication	91	6.2	72	4.9	0.1456
Surgical complication	22	1.5	24	1.6	0.8828
Wound complication	68	4.6	45	3.1	0.0334
Medical complication	9	0.6	5	0.3	0.4227
Return to operating room	22	1.5	24	1.6	0.8828
Superficial SSI	55	3.8	36	2.5	0.0536
Deep SSI	8	0.5	5	0.3	0.5465
Organ/space SSI	3	0.2	0	0.0	0.2482
Wound dehiscence	4	0.3	4	0.3	1.0000
Venous thromboembolism	2	0.1	3	0.2	1.0000
Unplanned reintubation	0	0.0	0	0.0	NR
Urinary tract infection	1	0.2	2	0.1	1.0000
Other bleeding	3	0.2	0	0.0	0.2482
Hospital length of stay, median and range	0	0-32	0	0-234	< 0.0001

A total of 2,928 patients (1,464 per group) were matched using propensity scores. The unmatched patients were discarded from the analysis. McNemar's test and the Wilcoxon signed rank test were used to compare the two matched groups. The rate of wound complication ($P = 0.0334$) and the distribution of length of stay ($P < 0.0001$) was found to differ between the matched groups. SSI: surgical site infection; NR: not reported

the number of events are low and there are multiple confounders.^[22]

Many authors have tried to definitively determine the correlation between obesity and adverse events after surgery. Although many studies consistently demonstrate the deleterious effect of obesity, nearly all analyses are confounded by the effects of associated medical conditions on outcomes. One such study did not find a statistical difference in obese versus non-obese patients in relation to complication and hospital length of stay.^[23] Another did not find significant differences in complications attributable to age, BMI, size of resection, smoking status, comorbidities, or surgical technique, even in the morbidly obese.^[16] Other studies similarly found no statistically significant difference in complication rates among the obese.^[14,15,17]

However, contradictory findings exist in the literature as well, supporting obesity as a risk factor.^[6,9-13] Chun *et al.*^[13] identified a threshold of BMI 35.6 at which postoperative complications were increased two-fold, the most common complication being infection. The pioneering study using NSQIP data to analyze BMI and breast reduction complications by Nelson *et al.*^[6] included 4,545 patients between 2005 and 2011. This study used logistic regression to account for demographics and comorbidities. They found an increased rate in overall complications, wound complications in all obesity classes, and major surgical complications in class III obesity.

Multivariate analysis among the non-obese, overweight, and three classes of obesity showed statistically significant differences in demographics, comorbidities, and complication rates [Tables 4-6]. In our unmatched analysis [Table 6], overall complications, wound complications, superficial SSI, and wound dehiscence were significantly increased in the obese population compared to the non-obese cohort after multivariable analysis controlling for significantly different variables between obese and non-obese cohorts. Comorbidities may confound the isolated risk of obesity on complication rates. The distinguishing feature of our study was matching obese patients to non-obese patients with similar preoperative and operative variables, thus eliminating the confounding effect of associated comorbidities on outcomes. While multivariable analysis attempts to control for comorbidities via advanced statistical techniques, 1:1 matching is a dramatically more powerful technique that matches each study patient with a near-identical "control" patient, in spite of detractors of this technique.^[24] After analysis of matched cohorts, only wound complications were increased in the obese population [Table 8]. On further analysis, the difference was mainly attributed to a risk of increased surgical site infection in the obese cohort. Of note, length of hospital stay was found to be significantly increased in the normal-weight cohort. On close examination, this was due to a statistical aberrancy (in that the range of values for length of stay for non-obese patients was greater than for obese patients).

In previous studies, dissatisfied patients had frequently

experienced postoperative soft tissue necrosis.^[4] The pathophysiology of wound healing in obese patients is currently being studied. Obesity has been shown to inhibit bone marrow-derived vasculogenic progenitor cell mobilization, trafficking and function. This in turn impairs the normal response to tissue injury and the proliferation of blood vessels.^[25] Adipocytes in fat also produce macrophage migration inhibitory factor, a factor which decreases wound healing through impairment of macrophage polarization/activation and inhibition of adipocyte progenitor cells.^[26]

Like other NSQIP-based analyses of reduction mammoplasty, there are limitations to this study.^[6,27] Follow-up was only 30 days, a relatively short period of time. NSQIP does not include complications such as seroma, hematoma, fat necrosis, altered nipple sensation, aesthetic outcomes, or hypertrophic scarring. Setala *et al.*^[15] report complication rates amongst normal BMI, overweight, and obese, respectively, as follows: seroma, 8.6% vs. 10.0% vs. 3.0%; hematoma, 8.6% vs. 5.4% vs. 3.0%; and fat necrosis, 1.7% vs. 2.0% vs. 6.1%. These are significant complications for this operation, which vary amongst different BMI classes and may explain a lower overall complication rate in our analysis. These datasets also do not report pedicle design/skin incision or resection weights, which may also affect complication rates.^[9] Although NSQIP provides a powerful dataset, further investigation is warranted through prospective analysis, longer follow-up, and more comprehensive collection of operative and complication data.

In conclusion, the increasing number of obese patients accompanied by their desire for breast reduction surgery poses a significant challenge to surgeons. To provide optimal care and minimize surgical risk, understanding the role of obesity in postoperative outcomes is essential. This study was able to independently assess obesity as a surgical risk factor for postoperative wound complications following reduction mammoplasty using multivariate analysis and propensity score matching. Obesity alone should not be the sole determining factor of a patient's surgical candidacy, but rather as a component of a complete preoperative evaluation. We recommend thorough risk stratification and patient counseling prior to surgical intervention.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. American Society of Plastic Surgeons. 2014 Plastic Surgery Statistics Report. Available from: <http://www.plasticsurgery.org/Documents/Plast Aesthet Res || Volume 3 || July 28, 2016>
2. Corididi M, Nadeau M, Taghizadeh M, Taylor A. Analysis of satisfaction and well-being following breast reduction using a validated survey instrument: the BREAST-Q. *Plast Reconstr Surg* 2013;132:285-90.
3. Blomqvist L, Brandberg Y. Three-year follow-up on clinical symptoms and health-related quality of life after reduction mammoplasty. *Plast Reconstr Surg* 2004;114:49-54.
4. Carty MJ, Duclos A, Gu X, Elele N, Orgill D. Patient satisfaction and surgeon experience: A follow-up to the reduction mammoplasty learning curve study. *Eplasty* 2012;12:e22.
5. Davis GM, Ringle SL, Short K, Sherrick D, Bengtson BP. Reduction mammoplasty: long-term efficacy, morbidity, and patient satisfaction. *Plast Reconstr Surg* 1995;96:1106-10.
6. Nelson JA, Fischer JP, Chung CU, West A, Tuggle CT, Serletti JM, Kovach SJ. Obesity and early complications following reduction mammoplasty: an analysis of 4545 patients from the 2005-2011 NSQIP datasets. *J Plast Surg Hand Surg* 2014;48:334-9.
7. Sieffert M, Fox JP, Abbott LE, Johnson RM. Obesity is associated with increased health care charges in patients undergoing outpatient plastic surgery. *Plast Reconstr Surg* 2015;135:1396-404.
8. Nguyen JT, Wheatley MJ, Schnur PL, Nguyen TA, Winn SR. Reduction mammoplasty: a review of managed care medical policy coverage criteria. *Plast Reconstr Surg* 2008;121:1092-100.
9. Zubowski R, Zins JE, Foray-Kaplan A, Yetman RJ, Lucas AR, Papay FA, Heil D, Hutton D. Relationship of obesity and specimen weight to complications in reduction mammoplasty. *Plast Reconstr Surg* 2000;106:998-1003.
10. Blomqvist L. Reduction mammoplasty: analysis of patients' weight, resection weights, and late complications. *Scand J Plast Reconstr Surg Hand Surg* 2006;30:207-10.
11. Gamboa-Bobadilla GM, Killingsworth C. Large-volume reduction mammoplasty: the effect of body mass index on postoperative complications. *Ann Plast Surg* 2007;58:246-9.
12. Baldwin CJ, Kelly EJ, Batchelor AG. The variation in breast density and its relationship to delayed wound healing: a prospective study of 40 reduction mammoplasties. *J Plast Reconstr Aesthet Surg* 2010;63:663-5.
13. Chun YS, Schwartz MA, Gu X, Lipsitz SR, Carty MJ. Body mass index as a predictor of postoperative complications in reduction mammoplasty. *Plast Reconstr Surg* 2012;129:e228-33.
14. Wagner DS, Alfonso DR. The influence of obesity and volume of resection on success in reduction mammoplasty: an outcomes study. *Plast Reconstr Surg* 2005;115:1034-8.
15. Setala L, Papp A, Joukainen S, Martikainen R, Berg L, Mustonen P, Härmä M. Obesity and complications in breast reduction surgery: are restrictions justified? *J Plast Reconstr Aesthet Surg* 2009;62:195-9.
16. Roehl K, Craig ES, Gomez V, Phillips LG. Breast reduction: safe in the morbidly obese? *Plast Reconstr Surg* 2008;122:370-8.
17. Cunningham BL, Gear AJ, Kerrigan CL, Collins ED. Analysis of breast reduction complications derived from the BRAVO study. *Plast Reconstr Surg* 2005;115:1597-604.
18. Shiloach M, Frencher SK Jr, Steeger JE, Rowell KS, Bartzokis K, Tomeh MG, Richards KE, Ko CY, Hall BL. Toward robust information: data quality and inter-rater reliability in the American College of Surgeons National Surgical Quality Improvement Program. *J Am Coll Surg* 2010;210:6-16.
19. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA* 2014;311:806-14.
20. Wang Y, Beydoun MA. The obesity epidemic in the United States - gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis. *Epidemiol Rev* 2007;29:6-28.
21. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA* 2013;309:71-82.
22. Cepeda MS, Boston R, Farrar JT, Strom BL. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. *Am J Epidemiol* 2003;158:280-7.

23. Tadiparthi S, Liew SH. Use of patient body mass index as a rationing tool in breast reduction surgery. *Plast Reconstr Surg* 2008;122:35-6.
24. Kitsios GD, Dahabreh IJ, Callahan S, Paulus JK, Campagna AC, Dargin JM. Can we trust observational studies using propensity scores in the critical care literature? A systematic comparison with randomized clinical trials. *Crit Care Med* 2015;43:1870-9.
25. Wagner IJ, Szpalski C, Allen RJ Jr, Davidson EH, Canizares O, Saadeh PB, Warren SM. Obesity impairs wound closure through a vasculogenic mechanism. *Wound Repair Regen* 2012;20:512-22.
26. Kim BS, Pallua N, Bernhagen J, Bucala R. The macrophage migration inhibitory factor protein superfamily in obesity and wound repair. *Exp Mol Med* 2015;47:e161.
27. Fischer JP, Cleveland EC, Shang EK, Nelson JA, Serletti JM. Complications following reduction mammoplasty: a review of 3538 Cases from the 2005-2010 NSQIP data sets. *Aesthet Surg J* 2014;34:66-73.

Two-millimeter dermoscopically detected excision margins in the treatment of basal cell carcinoma: an assessment of radicality and recurrence

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Sir,

Eighty-five percent of all basal cell carcinomas (BCCs) are located in the head and neck, with a markedly increased incidence after the age of 40 years. Complete extirpation in the early phase allows to limit skin excision and facilitates reconstruction, reducing consequent scarring. In the medical literature, it is reported that appropriate excision margins should be included between 3 and 10 mm, based on location, dimensions, margins and histology.^[1] BCC margins are defined by the discontinuation of well-known dermoscopic features along the skin lesion borders, so separating cancer from healthy skin.^[2] The authors conducted a study to assess the effectiveness of preoperative dermoscopic evaluation of BCC peripheral margins, in order to achieve complete excision.

Fifty-seven patients presenting BCC in the head and neck areas were operated on, from February 2012 to June 2012, at the Department of Plastic and Reconstructive Surgery of the Campus Bio-Medico University, Rome, Italy. Morphea-type, recurrent and superficial multifocal BCC were not included in the study. In all cases, margins were identified with a polarized-light dermoscope, at 30-fold magnification (Videocap®, Video Loupe VL-7EXII). A 0.5-mm tip skin marker was used to draw incision lines, 2 mm off the dermoscopically detected borders [Figure 1]. The contact

plate was applied to the skin with little pressure, to avoid blanching of vessels. The study protocol and procedures met the ethical standards of the committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983.

Excised skin lesions varied from 4 to 15 mm in maximum diameter. The histology report showed: nodular 25 cases (43.9%), infiltrating 2 cases (3.5%), superficial 30 cases (52.6%). In all patients, tumours resulted as being totally excised after histological evaluation. Moreover, at follow-up visits, between 12 and 36 months postoperatively, no recurrence was detected. In terms of lesion dimensions, clinical and dermoscopic assessment corresponded. In 12 cases (21%), borders were apparently well-defined, but dermoscopy showed larger extension, with histologically confirmed excision margins.

Reduced excision margins allowed preservation of healthy tissue, which consented ellipse excision and direct wound closure in most cases. This reflects in better aesthetic results, particularly noteworthy in the facial area.^[3]

Less invasive reconstructive procedures, fewer secondary surgeries for reoperation imply reduced costs. Preoperative

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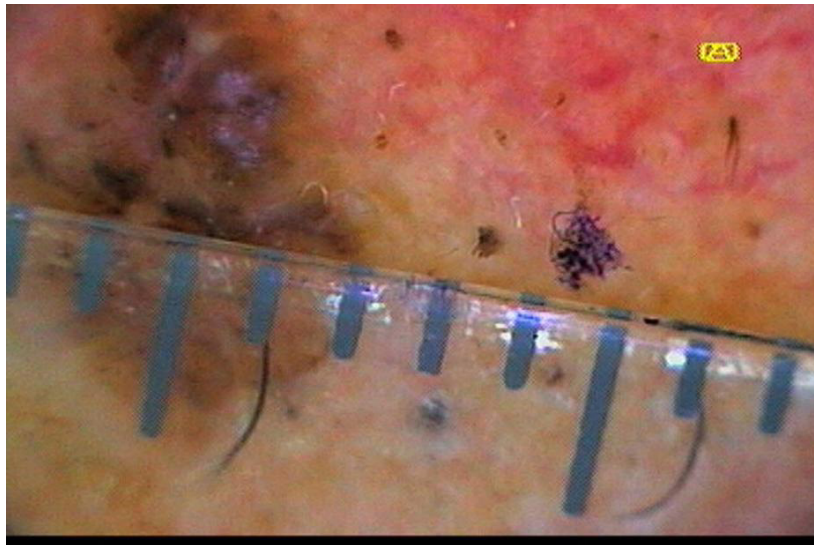


Figure 1: Two-millimeter excision margins in a case of a nodular basal cell carcinoma on the nasal dorsum

dermoscopy is quick, straightforward and less expensive than Mohs surgery.

It is evident that an adequate dermoscopic assessment can be performed in every surgical setting, with a portable device.^[4]

Our study showed that, following a 2-mm margin excision, no recurrence was observed after a 36-month follow-up period, in contradistinction to the data reported in the medical literature (3.96%).^[5]

We believe that a thorough dermoscopic detection of tumour borders contributes significantly to the identification of safe BCC excision margins.

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REFERENCES

1. Sterry W; European Dermatology Forum Guideline Committee. Guidelines: the management of basal cell carcinoma. *Eur J Dermatol* 2006;16:467-75.
2. Giacomel J, Zalaudek I. Dermoscopy of superficial basal cell carcinoma. *Dermatol Surg* 2005;31:1710-3.
3. Caresana G, Giardini R. Dermoscopy-guided surgery in basal cell carcinoma. *J Eur Acad Dermatol Venereol* 2010;24:1395-9.
4. Carducci M, Bozzetti M, Foscolo AM, Betti R. Margin detection using digital dermoscopy improves the performance of traditional surgical excision of basal cell carcinomas of the head and neck. *Dermatol Surg* 2011;37:280-5.
5. Gulleth Y, Goldberg N, Silverman RP, Gastman BR. What is the best surgical margin for a Basal cell carcinoma: a meta-analysis of the literature. *Plast Reconstr Surg* 2010;126:1222-31.

Body contouring: “less is more and don’t throw anything away”

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Year after year, body contouring (BC) request in getting higher, this is confirmed by the most respected society in the field of aesthetic plastic surgery;^[1] this is related not only by post bariatric surgery’s patients seeking, but also by patients that due to bad habits, sedentary job, *etc.* lost their ideal physical shape and look for getting better and healthy. Results achieved after surgical BC procedures can be terrific, changing patient's self esteem, however sometimes are not so good as patients can expect: why?

BC surgical procedures have more than a century of history, during this period were refined and improved, reducing surgical risk and gaining better results. An easy example of how BC procedures changed during the time can be shown by tummy tuck surgery.

Traditional abdominal plastic surgery result in a high rate of morbidity stemming from the necessity for a large undermining of the flap in which the perforating vessels are sectioned,^[2-5] consequently, the vascularity of the remaining flap is supplied only by the intercostal, subcostal, and lumbar per-forating branches, which are situated in the back and flank regions.^[6] Moreover the occurrence of ischemic processes with tissue necrosis and dehiscence of the suture has been described when ab-dominoplasty is associated with liposuction.

In 1995, Matarasso^[7] focused on the complications of combined liposuction and abdominoplasty, he considered the back and the flanks safe areas, did not regard the lateral region of the abdomen as a safe area, and

considered the central region of the abdomen prohibited for lipo-suction.

In 2001, the Brazilian plastic surgeon Saldanha *et al.*,^[8] for the first time, described the so called “li-poabdominoplasty”, a technique characterized by selective undermining between the medial borders of the rectus abdominal muscles combining abdominoplasty and liposuction.^[9,10]

The new and conservative concept is based on the preservation of the abdominal perforating vessels (subcutaneous pedicle);^[6] this technique conserves about 80% of the blood supply of the abdominal flap compared with traditional abdominoplasty, moreover, lymphatic nodes and nerves are preserved, which is an improvement on traditional abdominoplasty.^[8-11]

This is a great example how in BC surgery: “less is more”; and how the exact knowledge of the anatomy let to achieve better and safer results.

The same concept can be extended in BC performed after massive weight loss; in buttock reshaping, as a logical extension of Millard’s principle: “don’t throw anything away”; it is imperative not just excising tissue’s excess, but use it for buttock’s shape remodeling.^[12]

After massive weight loss, buttock lowers and flattens, in this clinical cases, the gluteal dermal flaps (the tissue that would be discarded in a simple dermolipsectomy) can be harvested and used to get better body proportions.^[9]

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One more big evolution in the field of BC has been also given by the structural fat graft.

Fat grafting is characterized by a simple concept, fat removal where it is in excess and re-injection of it in areas that need to be augmented: also with this technique “don’t throw anything away”!

However, fat grafting isn’t a “novel technique”; in 1912, Joseph,^[13] a German surgeon, for the first time published photographic documentation of natural appearing changes after infiltration of fat into 2 patients with facial lipoatrophy; in 1926, Miller^[14] described his experience with infiltration of fatty tissue through cannulas on 36 cases correcting cicatricial contraction on the face and neck; however, this technique never became widely used.

In the 1980s, Illouz^[15,16] described great results for iatrogenic liposuction deformities and facial lipodystrophies, although his later reports were discouraging and claimed that grafted fat had a survival similar to that of injectable collagen. Later on similar results were reported by Ersek *et al.*^[17,18] for first and then by Ellenborg,^[19] both had disappointing results that discouraged plastic surgeon on this technique, even when a few years later, both of them, changing their fat processing technique reported long term results if fat grafting. Only in the 1990s, thanks to the American plastic surgeon Coleman,^[20] who firstly described and codified the technique called “structural fat graft”, fat grafting gained popularity; although not all the surgeons use the technique described by Coleman,^[20] fat grafting is performed routinely in plastic surgery, often and often as ancillary procedure in body contouring.

Although some question the long-term survival potential of fat transfer, nowadays there are hundreds of papers outlining how great is this surgical procedure, with a resorption that tends to be uniform in the first 3 to 6 post operative months; in fact patient are told that the final results are not fully evident until that time and, if at that time they desire further augmentation, this can be repeated, since patients looking for BC procedures frequently have multiple areas of lipodystrophy that may necessitate additional procedures.^[11]

However, even fat grafting is only one of the thousands refinements that have been described in BC in last century...

This surgery is changed a lot in last years, is changing now, year after year, and will also changes a lot in the future, fundamental concepts are represented by doing

safe procedure and trying to reduce at least the use of prosthesis: “less is more” and “don’t throw anything away” seems to be paradigmatics. An appropriate preoperative plan is mandatory to get the best! However, surgeons have also to encourage patients, after BC, to have an healthy life style, get sport and follow a right dietary; only with a good surgeon and a good patient, unbelievable result can be achieved!

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REFERENCES

1. The American Society for Aesthetic Plastic Surgery. Cosmetic Surgery National Data Bank Statistics. Available from: <http://www.surgery.org/sites/default/files/Stats2015.pdf>. [Last Accessed on June 20, 2016].
2. Callia WEP. Dermolipectomia abdominal. Sao Paulo, Brazil: Carlo Erb; 1963.
3. Cardoso de Castro C, Salema R, Atias P, Aboudib JH Jr. T abdominoplasty to remove multiple scars from the abdomen. *Ann Plast Surg* 1984;12:369-73.
4. Dillerud E. Abdominoplasty combined with suction lipoplasty: a study of complication, revisions, and risk factors in 487 cases. *Ann Plast Surg* 1990;25:333-8; discussion 339-43.
5. Pitanguy I. Abdominoplasty: classification and surgical techniques. *Rev Bras Cir* 1995;85:23-44.
6. Huger WE Jr. The anatomic rationale for abdominal lipectomy. *Am Surg* 1979;45:612-7.
7. Matarasso A. Liposuction as an adjunct to full abdominoplasty. *Plast Reconstr Surg* 1995;95:829-36.
8. Saldanha OR, Pinto EB, Matos WN Jr, Lucon RL, Magalhães F, Bello EM. Lipoabdominoplasty without undermining. *Aesthet Surg J* 2001;21:518-26.
9. Saldanha OR, De Souza Pinto EB, Mattos WN Jr, Pazetti CE, Lopes Bello EM, Rojas Y, dos Santos MR, de Carvalho AC, Filho OR. Lipoabdominoplasty with selective and safe undermining. *Aesthetic Plast Surg* 2003;22:322-7.
10. Saldanha OR. Lipoabdominoplastia. 1st ed. Rio de Janeiro, Brazil: Di-Livros; 2004.
11. Saldanha OR. Lipoabdominoplasty. 1st ed. Rio de Janeiro, Brazil: Di-Livros; 2006.
12. Aly AS. Body Contouring after Massive Weight Loss. St. Louis, MO: Quality Medical Publish-ing, Inc; 2005.
13. Joseph M. Handbuch der kosmetik. Leipzig: Veit & Co.; 1912.
14. Miller C. Cannula Implants and Review of Implantation Techniques in Esthetic Surgery. Chicago: The Oak Press; 1926.
15. Illouz YG. The fat cel “graft”: a new technique to fill depression. *Plast Reconstr Surg* 1986;78:122-3.
16. Illouz YG. Present results of fat injection. *Aesthetic Plast Surg* 1988;12:175-81.
17. Ersek RA. Transplantation of purified autologous fat: a 3-year follow-up is disappointing. *Plast Reconstr Surg* 1991;87:219-27; discussion 228.
18. Ersek RA, Chang P, Salisbury MA. Lipo layering of autologous fat: an improved technique with promising results. *Plast Reconstr Surg* 1998;101:820-6.
19. Ellenborg R. Free autogenous pearl fat grafts in the face: a preliminary report of a rediscovered technique. *Ann Plast Surg* 1986;16:179-94.
20. Coleman RS. Structural fat grafting: more than a permanent filler. *Plast Reconstr Surg* 2006;118:S108-20.

Peno-scrotal soft tissue loss: a need for multidisciplinary and multimodal integration

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ABSTRACT

Aim: Scrotal soft tissue loss is a part of the challenging conditions for plastic surgeon. The non-availability of adequate nearby healthy soft tissue and its probability of frequent contamination by excretory substances make the issue of reconstruction complicated. The authors present their experience with penoscrotal soft tissue loss with hyperbaric oxygen therapy as an adjunct. **Methods:** This retrospective study was undertaken in the department of plastic surgery, over a period of 2 years. Nine patients with scrotal or penile injury and infection were enrolled in the study. Age of the patients ranged 20-60 years. Five patients had traumatic loss of scrotal skin and 4 resulted following necrotizing soft tissue infection. All patients underwent hyperbaric oxygen therapy before and following surgery. **Results:** Healing was complete in all patients with minor complications as partial skin graft loss in 2 patients. Five patients (55.5%) had sustained the soft tissue loss due to trauma. The cause of necrotizing fasciitis was found in 4 patients (44.4%). The mean length of hospital stay was 42.5 days. **Conclusion:** Management of soft tissue loss of penoscrotal region requires an organized approach and the utilization of newer modalities for early recovery of these injuries is of primary need. Operating surgeons should know the various reconstructive pathways and use of adjunct measures like hyperbaric therapy for early recovery.

Key words:

Scrotal soft tissue loss; necrotizing fasciitis; soft tissue reconstruction; hyperbaric oxygen therapy

INTRODUCTION

Scrotal soft tissue loss is one of the perplexing conditions for plastic surgeon. The non-availability of adequate nearby healthy soft tissue and its probability of recurrent faecal and urinary contamination make the issue of reconstruction complicated. All necessary effort to

decrease the time period of healing of scrotal wounds should be undertaken as the condition may increase the morbidity following these injuries. Most of these patients suffer multiple co-morbidities and are immune-compromised adding to the complication of such conditions.

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Figure 1: (a) Posttraumatic avulsion injury penoscrotal region; (b) bilateral pedicled gracilis muscle flap harvested for reconstruction of scrotal tissue; (c) split thickness skin grafting done on the muscle and penile shaft region; (d) early postoperative picture following bilateral gracilis flap cover; (e) late postoperative picture following bilateral gracilis flap cover

We present our experience with penoscrotal soft tissue loss with hyperbaric oxygen therapy as an adjunct.

METHODS

This retrospective study was undertaken in the department of plastic surgery, over a period of 2 years from January 2012 to December 2014. The records of patients who underwent scrotal reconstruction were reviewed. Nine patients with scrotal or penile injury and infection were enrolled in the study. Informed written consent was obtained from all the patients enrolled in the study. Age of the patients ranged 20-60 years. Five patients had traumatic loss of scrotal skin and 4 resulted following necrotizing soft tissue infection. No patient had injuries or infection to urethra. Patients with necrotizing soft tissue infection of the scrotum were diabetic. Rest of the patients did not have any comorbidity. All patients underwent hyperbaric oxygen therapy before and following surgery. Patient requiring intensive care unit admission was excluded from our study, as we are not equipped with hyperbaric oxygen therapy settings in

critically ill patients.

RESULTS

The mean patient age was 41.5 years. Five patients (55.5%) had sustained the soft tissue loss due to trauma. The cause of necrotizing fasciitis was found in 4 patients (44.4%). The majority of necrotizing soft tissue infection was referred to plastic surgery following initial debridement in general surgery or urology department. All of the patients underwent multiple surgical debridements when required and several reconstruction techniques were utilized as mentioned in Table 1. The median length of hospital stay was 42.5 days. Healing was complete in all patients with minor complications as partial skin graft loss in two patients, which required repeated skin grafting procedure. Patients were satisfactory in terms of aesthetic outcome and sexual life during the follow up period.

Case I

A 23-year-old patient came with avulsion injury due

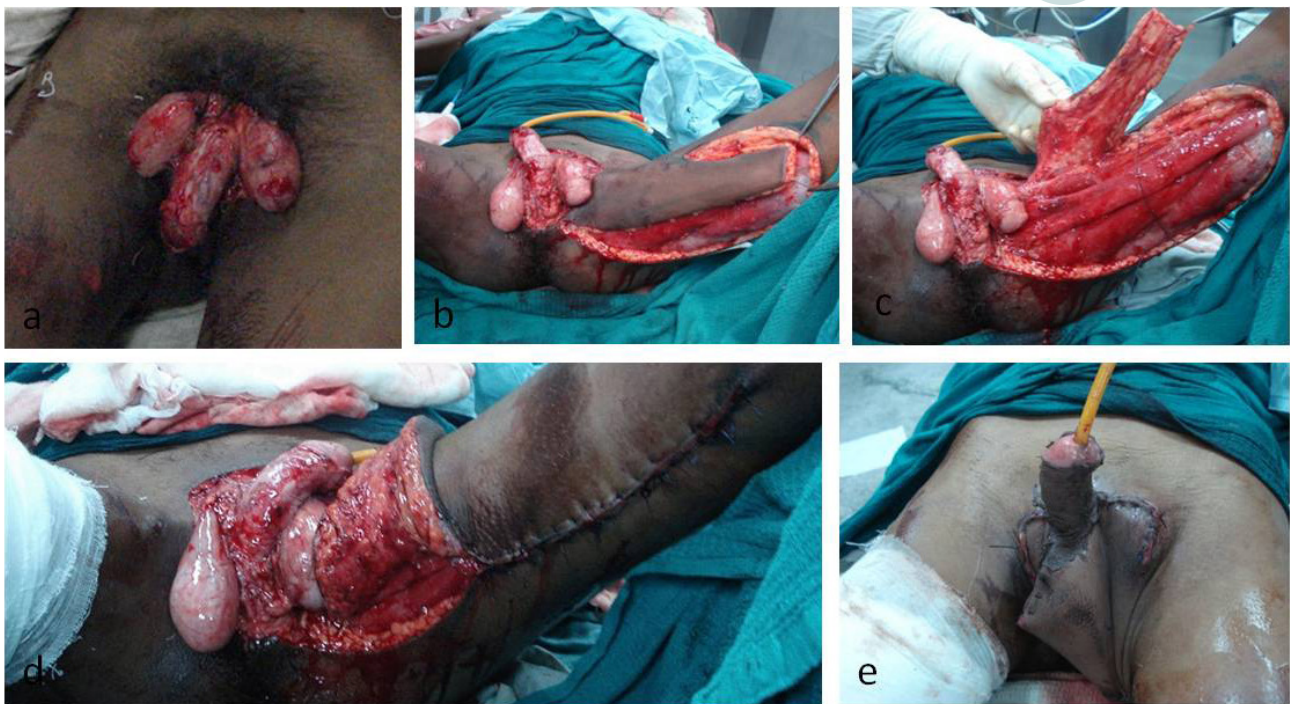


Figure 2: (a) Posttraumatic avulsion injury penoscrotal region; (b) superomedial thigh flap planned for reconstruction of scrotal tissue; (c) superomedial thigh flap harvested for reconstruction of scrotal tissue; (d) donor area closed primarily by local mobilization; (e) early postoperative picture following superomedial thigh flap cover

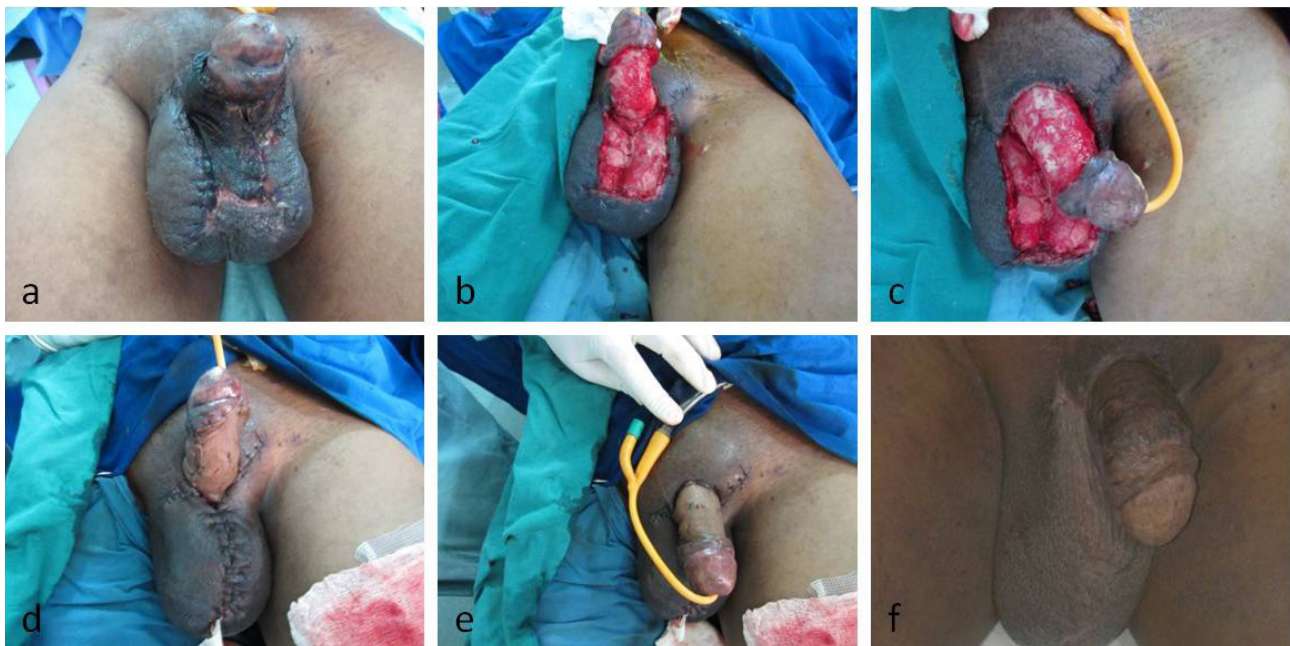


Figure 3: (a) Necrotising soft tissue infection involving the penoscrotal region; (b) post debridement soft tissue loss penoscrotal region - volar view; (c) post debridement soft tissue loss penoscrotal region - dorsal view; (d) split thickness skin grafting procedure done for the penoscrotal defect - volar view; (e) split thickness skin grafting procedure done for the penoscrotal defect - dorsal view; (f) late postoperative picture following procedure

to road traffic accident with loss of soft tissue in the peno-scrotal region [Figure 1a]. Wounds debrided and soft tissue loss was reconstructed with bilateral pedicle gracilis muscle flap cover and split thickness skin grafting [Figure 1b and c]. Six sessions of hyperbaric oxygen therapy were administered. Wounds healed well [Figure 1d and e] and the patient was discharged in

three weeks following injury.

Case 2

A 35-year-old patient has come with avulsion injury due to road traffic accident with loss of soft tissue in the peno-scrotal region [Figure 2a]. Wounds debrided and soft tissue loss was reconstructed with Superomedial

Table 1: Patients with soft tissue loss and methods of reconstruction

No.	Age/ gender	Trauma/etiology	Occupation	Co-morbidity	Site	Flap pattern	Duration of hospital stay
1	23/M	Road traffic accident	Auto mechanic	Nil	Peno-scrotal region	Bilateral gracilis flap cover + SSG	21 days
2	35/M	Road traffic accident	Agriculture	Nil	Peno-scrotal region	Superomedial thigh flap + SSG	28 days
3	55/M	Necrotizing soft tissue infection	Plumber	DM, HTN Non-smoker	Scrotal region	SSG	56 days
4	60/F	Necrotizing soft tissue infection	Retired personal	DM Non-smoker	Scrotal region	SSG	67 days
5	41/F	Road traffic accident	Auto mechanic	Nil	Scrotal region	Bilateral gracilis flap cover + ssg	25 days
6	43/M	Necrotizing soft tissue infection	Manager	DM Non-smoker	Scrotal region	SSG	65 days
7	52/M	Necrotizing soft tissue infection	Teacher	Non-smoker DM, HTN	Scrotal region	SSG	63 days
8	29/M	Road traffic accident	Agriculture	Nil	Peno-scrotal region	Bilateral gracilis flap cover	27 days
9	36/M	Road traffic accident	Taxi driver	Nil	Scrotal region	Superomedial thigh flap	31 days

DM: diabetes mellitus; HTN: hypertension; SSG: split skin graft

thigh flap [Figure 2b and c]. Donor area closed primarily [Figure 2d] and penile region covered with skin graft. Six sessions of hyperbaric oxygen therapy were administered. Wounds healed well [Figure 2e] and the patient was discharged by four weeks following injury.

Case 3

A 55-year-old patient presented with necrotizing soft tissue infection of the scrotal region [Figure 3a]. Debridement of necrotic tissue has done [Figure 3b and c]. Patient subjected to hyperbaric oxygen therapy 18 sessions. Skin grafting was done once the wound was healthy [Figure 3d-f]. Duration of stay in hospital was 56 days.

DISCUSSION

Scrotal injuries are of a highly distressing wound to the patients and serious surgical problem resulting in a high incidence of morbidity and mortality. The key in management of scrotal injury is timely planning of the type of management and execution of surgeries in appropriate time. Most of the scrotal avulsion injuries are associated with loss of penile skin. Soft tissue reconstruction when delayed may result in the onset of infection due to contamination from excretory substances. Immediate reconstruction following wound debridement reduces the morbidity resulting from scrotal injuries.

Invasive group A streptococcus was considered to be the most frequently isolated causative bacterium in necrotizing soft tissue infection.^[1] About 20-70% of the patients may have diabetes mellitus with necrotizing infection of scrotum.^[2] Other predisposing factors include alcoholism, intravenous drug use, low socioeconomic status, immune

disorders, and cancerous conditions.^[3] Urgent debridement of necrotic tissue and the need for repeated debridements till the infective focus is removed becomes the crucial measure for early recovery. Multidisciplinary approach involving urologist, microbiologist and nutritionist should be taken into consideration. Further progression of the disease could be eliminated by prompt administration of hyperbaric oxygen therapy, which provides optimal tissue oxygenation, enhances the host's bactericidal mechanism and promotes wound healing. The vascularity to the tissue involved is disrupted due to necrotic fascia, which results in a hypoxic and oedematous environment.^[4] Hyperbaric oxygen administration increases tissue oxygen tension in necrotizing fasciitis with delivering oxygen to the critically ischaemic areas. Further, hyperoxia helps in increasing the antibiotic efficiency, improves white cell killing efficacy and reduces inflammation which aids to the outcome of reconstruction in scrotal region.^[5]

Surgical intervention remains dynamic with debridement and soft tissue reconstruction when the wounds are healthy. Plastic surgical ladder of reconstruction could be applied to reconstruct the tissue loss in terms of primary or secondary suturing, skin grafting, local advancement flaps, fasciocutaneous flaps, muscle flaps, myocutaneous flaps or perforator flaps. General condition of the patient, site, size, location of the defects and the availability of donor tissue all are considered before proceeding to reconstruction. Surgical options include gracilis muscle flap, superomedial thigh flap, anterolateral thigh (ALT) flap, pudendal thigh flap, vertical rectus abdominis myocutaneous flap or Split thickness skin grafting. The split-thickness skin graft is not functionally and aesthetically pleasing in terms of reconstruction of scrotal tissue and hence not preferred frequently unless all the measures of reconstructions were failed.

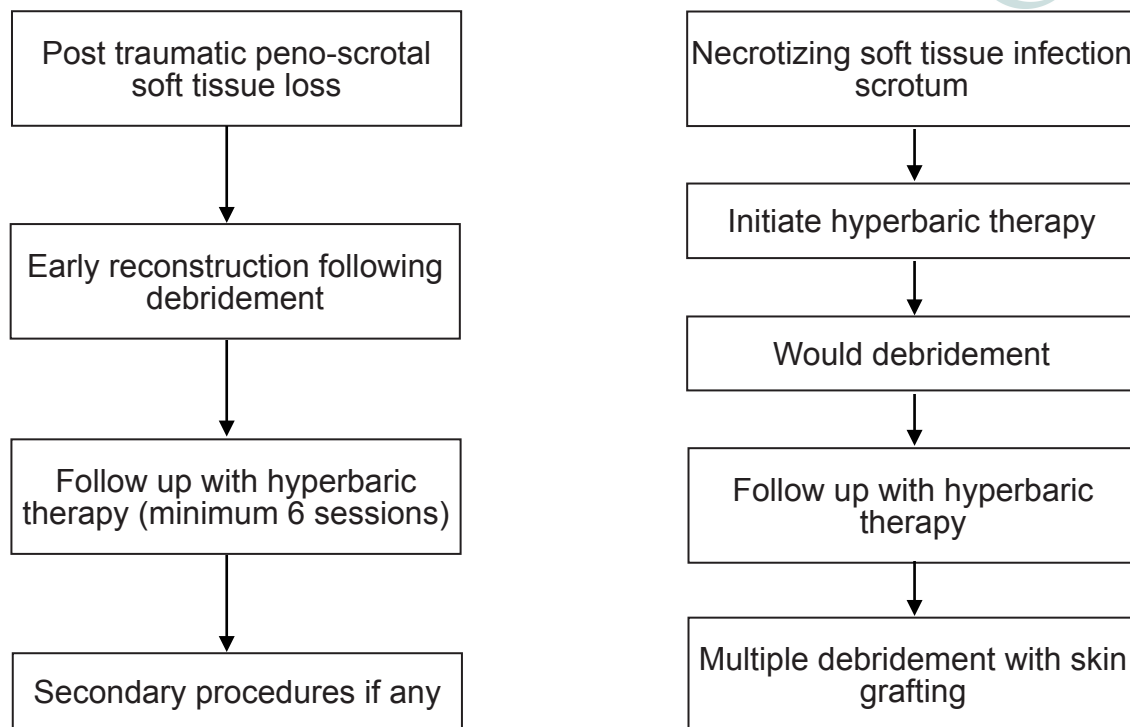


Figure 4: Algorithm devised for incorporating hyperbaric oxygen therapy into the treatment protocol of penoscrotal injuries

Pedicle gracilis muscle flap is useful in cases of unilateral or bilateral scrotal tissue loss. Gracilis muscle flap eliminates the dead space and provides appropriate padding of testicular tissue with appropriate cosmetic appearance. This well vascularized muscle flap prevents bacterial inoculums and provides optimal wound healing.^[6] Superomedial thigh flap is another alternative for soft tissue reconstruction of the scrotal region. The genital branch of genitofemoral nerve and ilioinguinal provides sensation to the flap. Flap has a sensate component compared to the gracilis flap but may be bulky and may not be aesthetically pleasing. Partial wound dehiscence, serous fluid collection at the donor site, paraesthesia over the anterior part of thigh and bulky flaps were significant to note as complications in utilizing these flaps.^[7] The pudendal thigh flap is another fasciocutaneous flap are relative simple for flap elevation with reliable. The donor site can be closed primarily and no muscle function is sacrificed. Other Flaps are ALT flap and vertical rectus abdominis muscle flap, which may require long transit of pedicle, microsurgical expertise, increased donor site morbidity, and may result in a bulky flap.

Gracilis muscle flap for scrotal reconstruction easily covers the scrotal defects with deep pockets. As the muscle flap is well vascularized, there is greater resistance to further infection, adequate bed for skin grafting, also eliminates the risk of skin loss associated with potentially non reliable skin paddle in the myocutaneous or fasciocutaneous flap. Donor site morbidity considerably less compared to the superiorly based medial thigh flap and the flap is aesthetically well appealing. Disadvantage of the flap is the need for microsurgical expertise for

flap elevation.^[8] Superiorly based medial thigh flap is early single staged sensate flap coverage. The flap has the advantage of utilizing a single lower extremity and the ipsilateral gracilis muscle flap could also be included if the defects are larger. Donor area could be closed primarily which prevents the need for skin grafts. Flap dissection is easier compared muscle flap with fewer kinks at the pedicle and dog ear formation. However, in fatty individual, it results in bulky neoscrotal bag and there will be difficulty in the transposition of the flap to the scrotal region.^[9] Skin grafting to the scrotal defect is useful in Fournier's gangrene where there is adequate granulation tissue formation filling the deep pockets in the testicular region. The technique is quite simple and easily reproducible compared to the flaps. The reconstruction also provides tension-free, cosmetically appealing scrotum with complete testicular coverage. The disadvantage of skin grafting technique is that it may require multiple stages if the wound bed is not even or healthy. Deep pockets in the testicular region following trauma are difficult to cover with skin grafting procedure.^[10]

Our preferred method of scrotal reconstruction in posttraumatic defect is gracilis muscle flap with skin grafting. Skin grafting is preferred for necrotizing fasciitis involving the scrotal and testicular region. Hyperbaric oxygen therapy as an adjunct enhances the recovery in both traumatic and infectious condition.

In our series, we utilized gracilis muscle flap in 3 patients with scrotal tissue loss and superomedial thigh flap in 2 patients. Patients with necrotizing soft tissue infection were managed with multiple debridement and skin

grafting. Negative pressure wound therapy was used in patients with necrotizing soft tissue infection to evacuate wound secretions and blood, thereby shortening the duration for split thickness skin grafting.^[11] In all the patients hyperbaric oxygen therapy was initiated as earlier as possible. Hyperbaric oxygen was delivered by means of monoplace chamber with pressure ranging from 1.8 to 2.4 ATA for 90 min in duration. Reduction of edema due to hyperbaric oxygen therapy helps in increased uptake of the skin graft and prevents venous congestion in the transferred flaps. Hyperoxia may also enhance intracellular transport of antibiotics. We did not experience the toxicity related to hyperbaric oxygen therapy. Hyperbaric oxygen therapy is used as an adjunct to prevent propagation of infection following wound debridement. The length of hospital stay of necrotizing infection could be significantly reduced if there is early detection of inflammation, early application of hyperbaric therapy and early surgical intervention.^[12] In our institution, an algorithm [Figure 4] was developed for incorporating hyperbaric oxygen therapy into the treatment protocol.

In conclusion, management of soft tissue loss of penoscrotal region requires an organized approach and the utilization of newer modalities for quick recovery of these injuries is of foremost need. Operating surgeons should know the various reconstructive pathways and use of adjunct measures like hyperbaric therapy for prompt recovery.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Hodgins N, Damkat-Thomas L, Shamsian N, Yew P, Lewis H, Khan K. Analysis of the increasing prevalence of necrotizing fasciitis referrals to a regional plastic surgery unit: a retrospective case series. *J Plast Reconstr Aesthet Surg* 2015;68:304-11.
- Morpurgo E, Galandiuk S. Fournier's gangrene. *Surg Clin North Am* 2002;82:1213-24.
- Pastore AL, Palleschi G, Ripoli A, Silvestri L, Leto A, Autieri D, Maggioni C, Moschese D, Petrozza V, Carbone A. A multistep approach to manage Fournier's gangrene in a patient with unknown type II diabetes: surgery, hyperbaric oxygen, and vacuum-assisted closure therapy: a case report. *J Med Case Rep* 2013;7:1.
- Korhonen K, Kuttala K, Niinikoski J. Tissue gas tensions in patients with necrotizing fasciitis and healthy controls during treatment with hyperbaric oxygen: a clinical study. *Eur J Surg* 2000;166:530-4.
- Flam F, Boijesen M, Lind F. Necrotizing fasciitis following transobturator tape treated by extensive surgery and hyperbaric oxygen. *Int Urogynecol J Pelvic Floor Dysfunct* 2009;20:113-5.
- Chen SY, Fu JP, Wang CH, Lee TP, Chen SG. Fournier gangrene: a review of 41 patients and strategies for reconstruction. *Ann Plast Surg* 2010;64:765-9.
- Oufkir AA, Tazi MF, El Alami MN. The superomedial thigh flap in scrotal reconstruction: technical steps to improve cosmetic results. *Indian J Urol* 2013;29:360-2.
- Katusabe LJ, Balumuka D, Hodges A. Scrotal reconstruction with a pedicled gracilis muscle flap after debridement of Fournier's gangrene: a case report. *East Afr Med J* 2013;90:375-8.
- El-Mageed MA. Evaluation of the anteromedial thigh fasciocutaneous flap for scrotal reconstruction. *J Plast Reconstr Surg* 2007;31:149-55.
- Konofaos P, Hickerson WL. A technique for improving cosmesis after primary scrotum reconstruction with skin grafts. *Ann Plast Surg* 2015;75:205-7.
- Agostini T, Mori F, Perello R, Dini M, Russo GL. Successful combined approach to a severe Fournier's gangrene. *Indian J Plast Surg* 2014;47:132-6.
- Mallikarjuna MN, Vijayakumar A, Patil VS, Shivswamy BS. Fournier's gangrene: current practices. *ISRN Surg* 2012;2012:942437.

A case of 25-year-old giant neurofibromatosis

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ABSTRACT

In this paper, the authors presented a case report of a 39-year-old man taken to the Emergency Unit with a 25-year-old giant neurofibromatosis. Moreover, the treatment applied for this case and the physiopathology of the neurofibromatosis disease are also discussed.

Key words:

Giant neurofibromatosis; physiopathology; neurofibromas

INTRODUCTION

Neurofibromatosis is a neurocutaneous condition that can involve almost any organ system. Thus, the signs and symptoms presented may vary widely. Two major subtypes exist: neurofibromatosis 1 (NF-1), which is the most common subtype, referred to as peripheral NF, and neurofibromatosis 2 (NF-2), which is referred to as central NF^[1,2]

We report a case of a giant neurofibroma kept for 25 years without treatment.

CASE REPORT

A 39-year-old male patient arrived at the Emergency Department with a history of bleeding from a moll on his back for the last 3 days. The patient also sustained episodes of nausea with no associated vomit, weakness and sleepiness.

At examination, we found a giant mass on his sacrococigeal region [Figures 1 and 2] with small areas of scarification with punctiform mild bleeding. Patient was mildly dispneic with taquicardia associated. No other symptoms were found.

According to the patient, the mass started to develop at the age of 14 years and he never felt compelled to have that examined by doctor. In fact, he regarded this as a phenomenon rendering him different from others.

Blood tests showed severe anemia (hemoglobin 6.9 g/dL). Computed tomography scan of thoracic and abdominal areas didn't reveal any tumors or abnormalities with the patient.

The patient was diagnosed with neurofibromatosis, the anemia was corrected with blood transfusion and the patient was taken to the operating room.

Through a direct ellipse incision the tumor was dissected, appearing to be limited to the epidermic region [Figure 3].

While incising its base, we were not able detect any infiltration on the subjacent subcutaneous tissues. The tumor was completely removed and the surgery was completed with a simple closure of the lateral skin flaps [Figure 4]. The tumor weight was 5,276 g [Figure 5]. The patient was

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Figure 1: Lateral aspect of the tumor



Figure 3: Dissection of the tumor showing limitation to the epidermis



Figure 2: Posterior view of the tumor demonstrating much narrower base that allowed direct excision

discharged 48 h later after an uneventful postoperative recovery. Histopathological analysis confirmed diagnosis of benign neurofibroma.

DISCUSSION

Neurofibromas are tumors composed of schwann cells, fibroblasts, mast cells, and vascular components. They can be found in nerves, independently of the location in its surface. Moreover, many authors consider neurofibromas the commonest benign tumors of the NF-1.^[3] Neurofibromas can be presented in three subtypes: cutaneous, subcutaneous,



Figure 4: Final aspect of the mass after removal with over 5 kg total weight

and plexiform. Cutaneous lesions and subcutaneous lesions are circumscribed, however none of them have compatible features with NF-1.^[4]

During physical examination, neurofibromas may present a pathognomonic buttonhole invagination when pressed with a finger. However, their morphology is not always consistent, resulting in lesions either soft or firm to the touch. Plexiform neurofibromas are noncircumscribed, thick and irregular. This specific subtype for NF-1 can be associated with aesthetic deformation by entwining important supportive structures.^[5]

One of the main physical signs encountered along with neurofibromatosis diagnosis is the presence of café au lait spots. These rather unfamiliar pigmentary patterns are brown macules irregularly shaped and evenly pigmented. Usually, when neurofibromatosis is diagnosed, subjects have 6 or more spots that are 1.5 cm or greater in diameter. However, in young children, 5 or more café au lait macules greater than 0.5 cm in diameter are indicative of neurofibromatosis and for which investigation is required. Less than 1% of healthy children have 3 or more of such spots, although 1 or 2 café au lait macules are commonly encountered in healthy individuals without disease. Due to the large volume of the mass presented in this case, it was difficult to determine if the alterations on the skin colour were café au lait spots or



Figure 5: Final aspect of the wound closed

decurrent from years of scarification under clothes.^[6]

Neurofibromatosis is a dominant autosomal neurogenetic disorder that tends to change and develop with time.^[7] Many authors demonstrated the development of this disease with increment of the nerve growth stimulation.^[8,9] NF-1 is a pathology that can be associated with different phenotypical manifestations where a group of patients often express cutaneous findings as first symptoms, whilst others might develop life-threatening or severely disfiguring complications. Moreover, amongst individuals from the same family, neurofibromatosis presents itself in different degrees of severity and incidence. The spontaneous mutation rate is 100 times greater than many other genes, and it is considered to contribute to approximately 30-50% of neurofibromatosis cases, however many different mutations in the neurofibromatosis gene have been described.^[10]

NF-1 is linked to a large gene on band 17q11.2. It encodes a protein called neurofibromin, which has a guanosine triphosphatase region that binds to Ras and positively modulates conversion of guanosine triphosphate to guanosine diphosphate. Several studies confirmed the negative regulation of Ras by this protein, allowing authors to

infer that the neurofibromin may act as a tumor suppressor.^[11]

Many individuals with this pathology are known to present below average intelligence and some types of learning disabilities, which may comprise neuromotor dysfunction, attention deficit hyperactivity disorder and deficits in visual-spatial processing.

It was also found that 25-40% of individuals with NF-1 might present learning disabilities and up to 5-10% have mental retardation.^[4]

It should also be noted that when the lesion has a benign aspect and there are no other signs of malignancy, the excisional biopsy is the treatment of choice and it is normally curative.

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Conflict of interest

There are no conflicts of interest.

REFERENCES

1. Fitzpatrick TB. Neurofibromatosis. In: Color Atlas and Synopsis of Clinical Dermatology. New York, NY: McGraw-Hill; 1997. p. 458-62.
2. Parry DM, Eldridge R, Kaiser-Kupfer MI, Bouzas EA, Pikus A, Patronas N. Neurofibromatosis 2 (NF2): clinical characteristics of 63 affected individuals and clinical evidence for heterogeneity. *Am J Med Genet* 1994;52:450-61.
3. Morse RP. Neurofibromatosis type 1. *Arch Neurol* 1999;56:364-5.
4. National Institutes of Health. Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. *Arch Neurol* 1988;45:575-8.
5. Reith JD, Goldblum JR. Multiple cutaneous plexiform schwannomas. Report of a case and review of the literature with particular reference to the association with types 1 and 2 neurofibromatosis and schwannomatosis. *Arch Pathol Lab Med* 1996;120:399-401.
6. Karnes PS. Neurofibromatosis: a common neurocutaneous disorder. *Mayo Clin Proc* 1998;73:1071-6.
7. Gutmann DH. Recent insights into neurofibromatosis type 1: clear genetic progress. *Arch Neurol* 1998;55:778-80.
8. Howell SJ, Wilton P, Lindberg A, Shalet SM. Growth hormone replacement and the risk of malignancy in children with neurofibromatosis. *J Pediatr* 1998;133:201-5.
9. Brookes JP, Breakefield XO, Martuza RL. Glial growth factor-like activity in Schwann cell tumors. *Ann Neurol* 1986;20:317-22.
10. Barker D, Wright E, Nguyen K, Cannon L, Fain P, Goldgar D, Bishop DT, Carey J, Baty B, Kivlin J, Willard H, Wayne JS, Greig G, Leinwand L, Nakamura Y, O'Connell P, Leppert M, Lalouel J-M, White R, Skolnick M. Gene for von Recklinghausen neurofibromatosis is in the pericentromeric region of chromosome 17. *Science* 1987;236:1100-2.
11. Ward K, O'Connell P, Carey JC, Leppert M, Jolley S, Plaetke R, Ogden B, White R. Diagnosis of neurofibromatosis 1 by using tightly linked, flanking DNA markers. *Am J Hum Genet* 1990;46:943-9.

Medicine and new social media: the good and the bad of taking a “selfie” for skin problems

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Sir,

According to the Oxford English Dictionary, selfie is a photograph that one has taken of oneself, typically by means of a smartphone or webcam and uploaded to a social media and shared with other people. The use of selfies has been dramatically increasing among the general population in the course of the last decade. Admittedly, most of us are used to take selfies in any kind of situation, for example to show others how we spent our spare time or simply how we enjoy meals, or to show off ourselves in dangerous or breathtaking panoramas. We love posting our pictures on the social networks to share them with family and friends.

The habit of taking selfies is so widespread to become even one of the means of communication between patients and doctors for example by mobile social media like WhatsApp. It is a raising issue for many medical specialties and overall for dermatology because of the fact that the skin is the largest, the most visible and the most accessible organ.

It is becoming more and more common that doctors are asked an opinion by patients who have sent some pictures showing unusual skin rashes, moles of dubious nature or unidentifiable lesions. All too often, making a correct and well-pondered diagnosis is an impossible achievement.

Patients may for instance also use selfies to have their moles checked. The device used to take the pictures, their brightness, contrast and sharpness can impact heavily on the quality of images. We can miss important additional information such as time of appearance, modifications over time *etc.* Furthermore, dermoscopy may be required, hence we can rarely provide a sound “safe” diagnosis.

On the other hand, encouraging patients to take a selfie to monitor existing moles or ascertain the appearance of new ones is likely to increase awareness about the need of a regular mole check and the risk of melanoma. It may provide an important benefit for subjects who are living in rural communities with limited access to medical facilities.^[1] We can recall the personal experience of seeing a patient in an outpatient skin cancer department of a county hospital who declared himself enthusiastic to have been asked to take “selfies of his moles”, saying that for once he was happy to take a “useful selfie” after taking so many pointless so far. Furthermore, selfies may represent the only way of documenting short-lived lesions, such as hives and can in certain cases be extremely helpful to put together a significant medical history.

Dermatologists and plastic surgeons could potentially encourage patients to take selfies for post interventional

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monitoring in skin surgery or cosmetic treatments (fillers, botox injections), and acne treatments in order to optimize results when adjustments may be needed in due course, or to prevent complications and increase adherence to treatment. A point that must be properly considered in acne treatment is that selfies taken by minors and sent to doctors can represent a serious legal issue.

Up to date, taking a selfie for medical purposes is currently discouraged, because of the several ethical and legal issues it can imply: the responsibility of the physician is questionable, personal images may be shared inappropriately, all sorts of data and information may remain unprotected, misdiagnoses are likely to occur.

As it was rightly put before,^[2] the use of selfies raises important questions about data ownership, privacy, and responsibility from the part of clinicians; still, an indiscriminate opposition to this use is not justified. Specific programs, smartphone application and also guidelines regarding their use are currently available to general doctors and specialists who work with teledermatology.^[3,4] Increasing evidence support the use of teledermatological techniques in clinical practice but their possible influence on doctor-patient relationship, on adherence to treatment and on effectiveness of care requires constant monitoring and assessment.^[5]

It has hence become necessary at this stage to start reflecting on the adequate use of selfies taken by patients and on how this habit of patients may be properly directed in medicine.

Doctors should think of developing adequate, simple and standardized systems accessible to patients to facilitate

teledermatological consultations, and educational interventions should be considered in the next future to this purpose. Moreover, a well-founded juridical basis for the use of “uncontrolled” selfies needs to be established, aspects of insurance coverage requires clearing, since probably soon standardized apps to optimize the quality of images and to store these images, along with the relevant clinical information, in the cloud may become available.

Overall, there is little point in negating or fighting the trend in patients’ empowerment brought in by the information technology revolution. It is better to convey the energy of these impending changes to the benefit of public health.

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REFERENCES

1. Byamba K, Syed-Abdul S, García-Romero M, Huang CW, Nergyi S, Nyamdorj A, Nguyen PA, Iqbal U, Paik K, Celi L, Nikore V, Somai M, Jian WS, Li YC. Mobile teledermatology for a prompter and more efficient dermatological care in rural Mongolia. *Br J Dermatol* 2015;173:265-7.
2. David Kerr: Rise of the medical selfie. Available from: <http://blogs.bmj.com/bmj/2014/12/22/david-kerr-rise-of-the-medical-selfie>. [Last Accessed on January 3, 2016].
3. AccessDerm teledermatology program. Available from: <https://www.aad.org/members/volunteer/accessderm-teledermatology-program>. [Last Accessed on January 10, 2016].
4. Whited JD. Teledermatology. *Med Clin North Am* 2015;99:1365-9.
5. Al Quran HA, Khader YS, Ellauzi ZM, Shdaifat A. Effect of real-time teledermatology on diagnosis, treatment and clinical improvement. *J Telemed Telecare* 2015;21:93-9.

A mammometric comparison of modified Robertson versus Wise pattern inferior pedicle reduction mammoplasty

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ABSTRACT

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Key words:

3D photography,
mammometrics,
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Aim: The advent of 3D photoimaging and mammometrics has allowed for quantitative, volumetric breast analyses. This study uses 3D photoimaging and mammometrics to compare the postoperative morphometric outcomes of the modified Robertson technique to the more traditional Wise pattern inferior pedicle technique. **Methods:** Inferior pedicle reduction mammoplasty was performed using either a Wise pattern or modified Robertson skin incision. 3D photography and analysis were done at 1-3 months and 6-12 months postoperatively. **Results:** There were 14 breasts in the modified Robertson group (ROB) and 24 breasts in the Wise pattern group (WISE). There were no significant differences in demographic data or amount of tissue resected. At 6-12 months, the modified Robertson cohort demonstrated increased superior pole fullness (62.9% ROB vs. 58.3% WISE, $P = 0.05$). The Wise cohort, however, maintained greater maximum breast projection (5.52 cm ROB vs. 6.54 cm WISE, $P = 0.01$) and increased medial pole fullness (29.6% ROB vs. 46.9% WISE, $P < 0.01$). There was no difference in tissue shifting from the superior pole to the inferior pole over time (+3.36 superior pole % ROB vs. +1.42 superior pole % WISE, $P = 0.28$). Areola surface area increased equally in both cohorts (+3.08 cm² ROB vs. +2.59 cm² WISE, $P = 0.77$); however, the final size of the areola was greater in the modified Robertson cohort (26.9 cm² ROB vs. 21.6 cm² WISE, $P < 0.01$). **Conclusion:** Using 3D mammometrics, we found increased superior pole fullness in the modified Robertson group while the Wise pattern group demonstrated greater medial pole fullness and maximum breast projection.

INTRODUCTION

Reduction mammoplasty is one of the most commonly performed operations in plastic surgery and has some of the highest patient reported levels of satisfaction.^[1-5] The

inferior pedicle Wise pattern technique is considered the “gold standard” due to its consistently reproducible results, even in large reductions;^[2,6,7] however, critics of the technique describe the final result as wide, flat, “boxy” in appearance, and lacking in superior pole



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fullness.^[9] More importantly, over time, this technique has been shown to undergo tissue redistribution from the superior to inferior pole. This phenomenon is referred to as pseudoptosis and further exacerbates the lack of superior pole fullness.^[2,9-11]

The Robertson technique was first described in 1964^[12-14] as an alternative to free nipple grafting in massive reductions. Later modifications incorporated a bell-shaped incision followed by the development of a superior apron flap to lower the position of the transverse bell-shaped scar.^[15] These modifications eliminated the vertical midline scar found in the Wise pattern, while offering greater flexibility to manipulate and shape the breast inferior pedicle. Proponents also claim that the modified Robertson technique allows for greater nipple projection, improved preservation of the inframammary crease, and less pseudoptosis.^[3,16]

While the use of linear measurements can be used as a proxy for pseudoptosis and changes over time, the advent of 3D photography and stereophotogrammetry has allowed for volumetric measurement and objective analysis of breast outcomes.^[17-19] The use of 3D mammometrics has been validated over the last decade, and has been established in the analysis of breast reductions.^[20-23]

This study uses 3D breast photography and mammometrics to compare postoperative volumetric and morphologic outcomes between modified Robertson and Wise pattern inferior pedicle breast reductions. Specifically, we aim to compare postoperative superior pole fullness, pseudoptosis, and breast projection over time. Other measurements with clinical and aesthetic relevance include sternal notch to nipple distance, nipple to inframammary fold (IMF) distance, inter-nipple distance, areola surface area, total breast volume, and medial pole fullness. This is the first quantitative analysis comparing these two different skin resection patterns for the inferior pedicle breast reduction.

METHODS

After obtaining Institutional Review Board approval, patients seeking breast reduction operations between 2012 and 2014 were invited to participate in this study. Patients were randomly assigned by the scheduling department to either surgeon A, who used a modified Robertson skin incision pattern, or surgeon B, who used a Wise pattern. Exclusion criteria included age less than 18 years or more than 65 years, the history of breast surgery, the history or presence of breast malignancy, and the significant weight change affecting breast volume during the course of the study.

Outlier patients with extreme body mass index (BMI) ($> 40 \text{ kg/m}^2$ or $< 26 \text{ kg/m}^2$), postoperative breast volume at early postoperative time point ($< 400 \text{ mL}$ or $> 1,300 \text{ mL}$), and the weight of breast tissue resected ($< 400 \text{ g}$ or $> 1,300 \text{ g}$) were also excluded.

Both surgeons marked patients in the standing position preoperatively, placing the nipple position at Pitanguy's point. In the modified Robertson cohort, the IMF incision was then determined 8 cm below the new nipple position and marked accordingly. Intraoperatively, the new IMF marking was used to elevate a superior breast apron down to the chest wall. The inferior pedicle was created with a base width of 12-16 cm, depending on the length of the nipple to IMF. Once the pedicle was defined, the intervening tissue was removed, and the apron was draped over the pedicle with transposition of the nipple. In the Wise cohort, the pedicle width was 10-12 cm, and the vertical skin incision was made 6-7 cm below the areola.

After the surgery, 3D photographs (Canfield Vectra 3D Camera) were taken during the early postoperative period (1-3 months postoperatively) and the late postoperative period (6-12 months postoperatively). Patients who did not return for both photographs were removed from the study. Complications were recorded during these follow-up visits, including painful scars, wound dehiscence, infection requiring antibiotics, and surgical revision.

Mammometric and volumetric breast analyses were completed using Geomagic software. Important landmarks were consistently marked on all images. These included sternal notch, nipple, and point of maximum breast projection. The point of maximum projection was defined as the point maximally projected on the Z-axis on a lateral, profile view of the breast. The nipple was usually also the point of maximum projection but this did not hold true in all cases. Linear measurements recorded include sternal notch to nipple surface distance, internipple vector distance, nipple to IMF surface distance, and projection of the breast from the chest wall to the nipple and point of maximum breast projection.

Surface area measurements recorded include the areola. Volumetric measurements recorded include total breast volume, percent volume in superior pole, and percent volume in medial pole. The borders of the breast were defined using the anterior axillary line as the lateral boundary, the sternal midline as the medial boundary, the IMF as the inferior boundary, and the chest wall as the dorsal boundary. Percent superior pole volume was defined as volume of the breast superior to an YZ axial plane through the point of maximum projection divided

Table 1: Demographic statistics

	ROB (range)	WISE (range)	P value
Age (years)	36.9 (30-41)	38.5 (21-65)	0.74
BMI (kg/m ²)	33.9 (31.1-37.2)	30.9 (26.4-35.7)	0.08
Total breast volume (mL)	809 (459-1,080)	729 (555-1,253)	0.26
Tissue resected (mL)	695 (406-1,000)	712 (449-1,280)	0.84

Table 2: Early postoperative period

	ROB (range)	WISE (range)	P value
SNtoNIP (cm)	23.1 (20.1-25.3)	23.7 (20.9-25.6)	0.24
NIPtoIMF (cm)	12.3 (9.3-15.3)	10.6 (8.4-12.9)	0.00*
NIPtoNIP (cm)	23.6 (15.5-27.7)	21.6 (17.0-24.6)	0.17
NipProj (cm)	5.91 (2.15-8.70)	6.97 (5.09-9.26)	0.10
MaxProj (cm)	5.55 (4.09-8.64)	6.69 (4.67-9.26)	0.01*
AreolaSA (cm ²)	23.8 (21.3-28.1)	19.0 (13.17-24.05)	0.00*
BreastSA (cm ²)	490 (388-571)	422 (355-547)	0.00*
TotVol (mL)	809 (459-1,081)	729 (555-1,253)	0.26
SupPole%	59.6 (45.7-69.4)	56.9 (44.2-66.6)	0.21
MedPole%	27.0 (20.5-50.2)	45.5 (31.2-63.1)	0.00*

*Statistically significant

by total breast volume. Percent medial pole volume was defined as volume of the breast medial to a XZ sagittal plane through the point of maximum projection divided by total breast volume.

Statistical analysis was completed using Statistical Package for the Social Sciences. Independent samples *t*-tests and chi-squared tests (Fischer's exact) were used where appropriate and a $P \leq 0.05$ was considered statistically significant. With an estimated 3% effect size in the modified Robertson group and 6% in the inferior pedicle group for tissue movement to the inferior pole, a common standard deviation of 2, a 0.5 level of significance, and a 0.8 power level, the sample size was calculated to be 7 in each cohort.

RESULTS

Twenty-two patients consented and completed the required components of the study. Two patients were excluded as outliers due to excessive BMI and excessive volumes resected, and 1 patient was excluded due to low BMI. In total, there were 14 measured breasts in the modified Robertson cohort (ROB) and 24 breasts in the Wise cohort (WISE).

No statistically significant differences were found between the 2 cohorts regarding age (36.9 years ROB vs. 38.5 years WISE, $P = 0.74$), BMI (33.9 kg/m² ROB vs. 30.9 kg/m² WISE, $P = 0.08$), total breast volume (809 mL ROB vs. 729 mL WISE, $P = 0.26$), or the weight of breast

Table 3: Late postoperative period

	ROB (range)	WISE (range)	P value
SNtoNIP (cm)	24.4 (21.4-26.4)	24.1 (21.5-26.4)	0.57
NIPtoIMF (cm)	13.2 (10.3-15.9)	10.8 (8.3-14.2)	0.00*
NIPtoNIP (cm)	24.8 (22.5-27.6)	21.3 (17.3-23.6)	0.00*
NipProj (cm)	6.59 (3.18-9.00)	6.70 (4.65-9.18)	0.83
MaxProj (cm)	5.52 (4.08-7.46)	6.54 (4.50-8.77)	0.01*
AreolaSA (cm ²)	26.9 (16.3-37.1)	21.6 (12.9-33.7)	0.02*
BreastSA (cm ²)	494 (402-593)	419 (344-559)	0.00*
TotVol (mL)	856 (486-1,183)	709 (489-1,123)	0.06
SupPole%	62.9 (51.1-73.6)	58.3 (42.3-69.9)	0.05*
MedPole%	29.6 (20.3-42.1)	46.9 (34.2-62.9)	0.00*

*Statistically significant

tissue resected (695 g ROB vs. 712 g WISE, $P = 0.84$; Table 1). Complications requiring surgical revision were minimal (Fisher's exact test: 2/14 ROB vs. 0/24 WISE, $P = 0.13$). The 2 complications were both dog-ears that developed at the late postoperative period and revised under local anesthesia. Preoperative 3D photographs were not taken or analyzed due to the limitations of the software to accurately measure massive breasts with ptosis resting on the abdominal wall.

Early postoperative period

In the early postoperative period [Table 2], sternal notch to nipple distance was not significantly different between the 2 cohorts (23.1 cm ROB vs. 23.7 cm WISE, $P = 0.24$); however, nipple to IMF was significantly greater in the modified Robertson cohort (12.3 cm ROB vs. 10.6 cm WISE, $P < 0.01$). Internipple distance was not significantly different between the 2 cohorts (23.6 cm ROB vs. 21.6 cm WISE, $P = 0.17$). Nipple projection was not significantly different between the 2 cohorts (5.91 cm ROB vs. 6.97 cm WISE, $P = 0.10$); however, maximum breast projection was greater in the Wise cohort (5.55 cm ROB vs. 6.69 cm WISE, $P = 0.01$). Areola surface area was greater in the modified Robertson cohort (23.6 cm² ROB vs. 19.0 cm² WISE, $P < 0.01$).

Total breast volume was not significantly different between the two cohorts (809 mL ROB vs. 729 mL WISE, $P = 0.26$). Percent volume in the superior pole was not different between the 2 cohorts (59.6% ROB vs. 56.9% WISE, $P = 0.21$); however, percent volume in the medial pole was greater in the WISE cohort (27.0% ROB vs. 45.5% WISE, $P < 0.01$).

Late postoperative period

In the late postoperative period [Table 3, Figure 1], sternal notch to nipple distance was not significantly different between the 2 cohorts (24.4 cm ROB vs. 24.1 cm WISE, $P = 0.57$); however, nipple to IMF remained

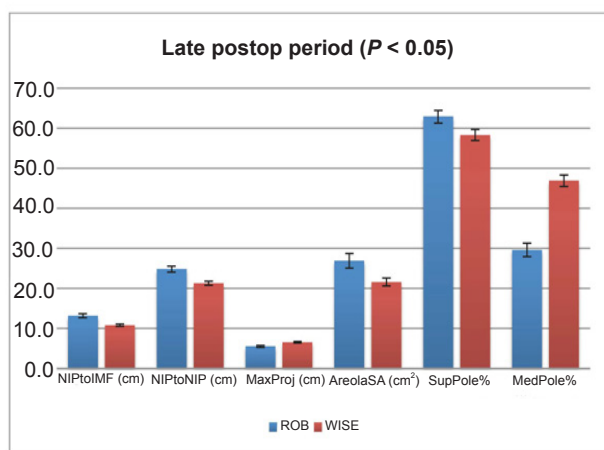


Figure 1: Late postoperative period significant findings (all $P < 0.05$). Statistically significant differences during the late postoperative period between the modified Robertson and Wise pattern cohorts. Y-axis displays units in cm, cm², and %, depending on the variable. X-axis displays the name of the variable presented with the units in parenthesis. ROB cohort is represented by blue bars and WISE cohort is represented by red bars. Error bars show standard error. Nipple to inframammary fold distance (NIPtoIMF) was greater in the ROB cohort than the WISE cohort. Internipple distance (NIPtoNIP) was greater in the ROB cohort than the WISE cohort. Maximum breast projection (MaxProj) was greater in the WISE cohort than the ROB cohort. Areola surface area (AreolaSA) was greater in the ROB cohort than the WISE cohort. % volume in the superior pole (SupPole%) was greater in the ROB cohort than the WISE cohort. % volume in the medial pole (MedPole%) was greater in the WISE cohort than the ROB cohort.

significantly greater in the modified Robertson cohort (13.2 cm ROB vs. 10.8 cm WISE, $P < 0.01$). Interestingly, internipple distance became significantly different during the late postoperative period (24.8 cm ROB vs. 21.3 cm WISE, $P < 0.01$). Nipple projection was not significantly different between the 2 cohorts (6.59 cm ROB vs. 6.70 cm WISE, $P = 0.83$); however, maximum breast projection remained greater in the Wise cohort (5.52 cm ROB vs. 6.54 cm WISE, $P = 0.01$). Areola surface area remained greater in the modified Robertson cohort (26.9 cm² ROB vs. 21.6 cm² WISE, $P < 0.01$).

Total breast volume was not significantly different between the 2 cohorts (856 mL ROB vs. 709 mL WISE, $P = 0.06$). Interestingly, the percent volume in the superior pole was greater in the Robertson cohort (62.9% ROB vs. 58.3% WISE, $P = 0.05$), while percent volume in the medial pole remained greater in the WISE cohort (29.6% ROB vs. 46.9% WISE, $P < 0.01$).

Comparing changes over time between modified Robertson vs. Wise cohorts

Analyzing the change over time (late postoperative measurement minus early postoperative measurement) between the two cohorts [Table 4, Figures 2 and 3], modified Robertson cohort patients experienced greater lengthening of both the sternal notch to nipple distance

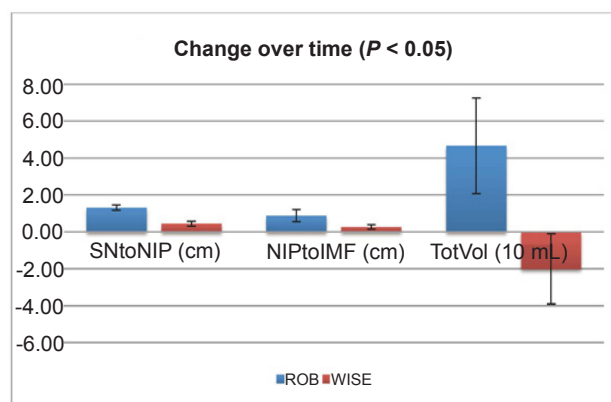


Figure 2: Change over time significant findings (all $P < 0.05$). Statistically significant differences from the early postoperative period to the late postoperative period between the modified Robertson and Wise pattern cohorts. Y-axis displays units in cm and 10 mL, depending on the variable. X-axis displays the name of the variable presented with the units in parenthesis. ROB cohort is represented by blue bars and WISE cohort is represented by red bars. Error bars show standard error. The change in sternal notch to nipple distance (SNtoNIP) was greater in the ROB cohort than the WISE cohort. The change in nipple to inframammary fold distance (NIPtoIMF) was greater in the ROB cohort than the WISE cohort. The change in total volume (TotVol) increased in the ROB cohort but decreased in the WISE cohort.

(1.31 cm ROB vs. 0.44 cm WISE, $P < 0.01$) and the nipple to IMF distance (0.88 cm ROB vs. 0.27 cm WISE, $P = 0.05$). While internipple distance increased 1.20 cm in the modified Robertson cohort and decreased 0.26 cm in the Wise cohort, this difference did not reach statistical significance ($P = 0.09$). Nipple projection increased significantly more in the modified Robertson cohort than the Wise cohort (0.69 cm ROB vs. -0.26 cm WISE, $P < 0.01$); however, there was no difference in the change in maximum breast projection between the two cohorts (-0.02 cm ROB vs. -0.15 cm WISE, $P = 0.67$). Areola size increased in both the modified Robertson and Wise cohorts, but this increase was not significantly different between the two cohorts (3.08 cm² ROB vs. 2.59 cm² WISE, $P = 0.77$).

Interestingly, total volume increased in the modified Robertson cohort but decreased in the Wise cohort; this difference was statistically significant (46.7 mL ROB vs. -20.1 mL WISE, $P = 0.04$). The change in percent superior pole volume was greater in the modified Robertson cohort (3.36%) than the Wise cohort (1.42%); however, this difference did not reach statistical significance ($P = 0.28$). The change in percent medial pole volume (2.57% ROB vs. 1.36% WISE, $P = 0.60$) was not significantly different between the two cohorts.

DISCUSSION

This study is the first to use 3D mammometrics to provide quantitative analysis comparing the modified

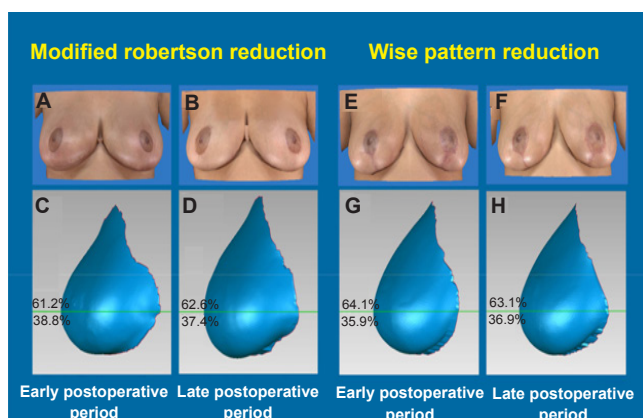


Figure 3: Example images. Patient photographs and 3D reconstruction images showing volumetric analysis. Images A-D are from the same ROB patient (age: 31 years) and images E-H are from the same WISE patient (age: 26 years). (A) AP photograph of ROB breasts at early postoperative time period; (B) AP photograph of ROB breasts at late postoperative time period; (C) 3D reconstruction lateral view of left breast of ROB patient at early postoperative period showing 61.2% superior pole volume; (D) 3D reconstruction lateral view of left breast of ROB patient at late postoperative period showing superior pole volume of 62.6%; (E) AP photograph of WISE breasts at early postoperative time period; (F) AP photograph of WISE breasts at late postoperative time period; (G) 3D reconstruction lateral view of left breast of WISE patient at early postoperative period showing 64.1% superior pole volume; (H) 3D reconstruction lateral view of left breast of WISE patient at late postoperative period with superior pole volume of 63.1%

Robertson and Wise patterns for inferior pedicle reduction mammoplasty. Movassaghi *et al.*^[15] directly compared the two skin patterns in breast reduction; however, their analysis focused on complication rates of hematoma, minor wound dehiscence, and scar hypertrophy. They found a reduced complication rate in the modified Robertson technique with decreased skin breakdown, since this skin pattern does not have an intersecting triple point. Chalekson *et al.*^[3] evaluated morphologic outcomes of modified Robertson patients; however, they compared the results to aesthetically optimal breasts, instead of other reduction patients. Their recorded outcomes included patient satisfaction, symptom reduction, scarring, nipple position, ptosis, pseudoptosis, shape, and overall appearance several years following surgery. They found excellent satisfaction among patients and no difference between their reduction patients and aesthetically ideal patients with regards to pseudoptosis.

Using 3D analysis to compare the late postoperative result of the modified Robertson to the Wise pattern breast reduction, the modified Robertson technique demonstrated greater superior pole volume by approximately 5%. This difference was both statistically and clinically significant. Previous research by Mallucci *et al.*^[24] analyzed breast photographs with 5% differences in superior to inferior pole ratio to determine ideal breast shape, finding that the 45:55 ratio was

Table 4: Change over time

	ROB (range)	WISE (range)	Pvalue
SNtoNIP (cm)	1.31 (0.60-2.31)	0.44 (-0.52-2.10)	0.00*
NIPtoIMF (cm)	0.88 (-1.25-3.26)	0.27 (-0.76-1.82)	0.05*
NIPtoNIP (cm)	1.20 (-1.21-6.98)	-0.26 (-1.66-0.87)	0.09
NipProj (cm)	0.69 (-0.80-2.00)	-0.26 (-2.15-1.81)	0.00*
MaxProj (cm)	-0.02 (-1.85-1.43)	-0.15 (-2.24-2.01)	0.67
AreolaSA (cm ²)	3.08 (-7.13-9.81)	2.59 (-3.86-10.14)	0.77
BreastSA (cm ²)	4.00 (-31.83-50.46)	-2.89 (-29.50-36.55)	0.28
TotVol (mL)	46.7 (-112.7-170.5)	-20.1 (-168.1-216.5)	0.04*
SupPole%	3.36 (-4.06-7.82)	1.42 (-11.16-22.05)	0.28
MedPole%	2.57 (-8.16-12.39)	1.36 (-17.94-17.96)	0.60

*Statistically significant

aesthetically preferred over the 50:50 ratio. It is possible that the superior breast apron of the modified Robertson technique supports the inferior pedicle and maintains superior pole volume without the presence of a vertical incision in the Wise pattern technique.

In addition, the Wise technique demonstrated greater medial pole volume by approximately 17% and greater maximum breast projection by 1 cm. The presence of a vertical scar may distribute the inferior pedicle medially and narrow the width of the breast, leading to improved breast projection. The vertical incision may also prevent lateral migration of the nipple position as demonstrated by the smaller internipple distance in the Wise pattern cohort (21.3 cm WISE vs. 24.8 cm ROB, $P < 0.01$).

The total breast volume of the modified Robertson cohort increased over time (+47 mL), whereas the Wise cohort decreased (-20 mL). It is possible that these changes reflect systemic changes in the patient with weight and/or menstrual cycle. This change in total volume is consistent with an increase in notch to nipple and nipple to IMF measurements in the modified Robertson cohort. An increase in overall volume of the breast may also explain the increase in nipple projection found in the modified Robertson cohort. In contrast, the Wise cohort had a decrease in total volume over time, which is also consistent with the decrease in nipple projection and maximum breast projection.

The modified Robertson cohort consistently demonstrated longer nipple to IMF distances compared to the Wise pattern, and this can be explained by the surgeon preference to widen the skin bridge of the breast apron below the areola to minimize ischemic complications.

The areola surface area was consistently larger in the modified Robertson cohort compared to the Wise pattern cohort at all time points. Both surgeons

reported using the same 38 mm “cookie cutter” when inseting the areola; however, the superior breast apron of the modified Robertson places greater tension and outward pull on the areola compared to the Wise pattern. Despite these absolute differences, the areola surface area in both cohorts increased equally over time. The inferior pedicle may apply pressure and weight behind the areola that results in similar expansion over time.

Although statistically significant, some of the measured differences between the two cohorts were clinically small and may seem within the margin of error for 3D analysis. This error in 3D analysis is the result of limitations of 3D photography and minor computational inaccuracies in the software. This is especially true when measuring the lower pole and determining the IMF in patients with extremely ptotic breasts. However, we firmly believe that these measurements are valid since each image was measured three times, averaged, and pooled with other images within the same cohort. User dependent differences in making measurements can also lead to inaccuracies in 3D analysis; however, all measurements were performed by the same person, who had extensive experience performing 3D analysis. This study is also adequately powered as determined by the sample size calculation and the fact that the results were statistically significant.

This report represents the outcomes of individual surgeons at one institution and considering that there are many technical variations within each technique, the results may not be generalizable to all surgeons. It is possible that the variation in surgical technique, rather than the chosen skin incision pattern, has a greater impact on volumetric distribution. Further study of other surgeons who perform these techniques could determine reproducibility of our results. Future studies could also evaluate whether further morphologic changes occur in the 6-12 month time frame. Larger sample sizes will also help to further support our findings.

In conclusion, using 3D mammometrics, our results suggest that in the late postoperative period, the modified Robertson technique provides increased superior pole fullness, whereas the Wise technique provides increased medial pole fullness and maximum breast projection. These quantitative results allow plastic surgeons to choose the technique that may be most suitable for a patient seeking reduction mammoplasty.

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Conflicts of interest

There are no conflicts of interest.

Patient consent

Obtained.

Ethics approval

Approved by the Institutional Review Board.

REFERENCES

1. American Society of Plastic Surgeons. 2013 Plastic Surgery Statistics Report. Available from: <http://www.plasticsurgery.org/Documents/news-resources/statistics/2013-statistics/plastic-surgery-statistics-full-report-2013.pdf>. [Last Accessed on 23 July 2015].
2. Spear SL. Surgery of the breast principles and art. Philadelphia, United States: Lippincott Williams & Wilkins; 2006.
3. Chalekson CP, Neumeister MW, Zook EG, Russell RC. Outcome analysis of reduction mammoplasty using the modified Robertson technique. *Plast Reconstr Surg* 2002;110:71-81.
4. Collins ED, Kerrigan CL, Kim M, Lowery JC, Striplin DT, Cunningham B, Wilkins EG. The effectiveness of surgical and nonsurgical interventions in relieving the symptoms of macromastia. *Plast Reconstr Surg* 2002;109:1556-66.
5. Strong B, Hall-Findlay EJ. How does volume of resection relate to symptom relief for reduction mammoplasty patients? *Ann Plast Surg* 2015;75:376-82.
6. Wise RJ. A preliminary report on a method of planning the mammoplasty. *Plast Reconstr Surg* 1956;17:367-75.
7. Courtiss EH, Goldwyn RM. Reduction mammoplasty by the inferior pedicle technique. An alternative to free nipple and areola grafting for severe macromastia or extreme ptosis. *Plast Reconstr Surg* 1977;59:500-7.
8. Hall-Findlay EJ. Vertical reduction mammoplasty. In: Thorne CH, editor. *Grabb and Smith's Plastic Surgery*. 7th Ed. Philadelphia, USA: Lippincott Williams & Wilkins; 2014.
9. Hudson DA, Geldenhuys S, Duminy F, Adams K. Another look at breast projection after breast reduction. *Aesthetic Plast Surg* 2008;32:928-32.
10. Shiffman MA. Mastopexy and breast reduction principles and practice. Berlin, Germany: Springer; 2009.
11. Hall-Findlay EJ. Pedicles in vertical breast reduction and mastopexy. *Clin Plast Surg* 2002;29:379-91.
12. Robertson DC. Reduction mammoplasty using a large inferior flap. Transactions of Third International Congress of Plastic Surgery. Washington DC, United States: Excerpta Medical Foundation; 1964.
13. Robertson DC. The technique of inferior flap mamma-plasty. *Plast Reconstr Surg* 1967;40:372-7.
14. Robertson DC. Follow-up clinic: the technique of inferior flap mamma-plasty. *Plast Reconstr Surg* 1973;52:438.
15. Movassaghi K, Liao EC, Ting V, Matros E, Morris DJ, Orgill DP, Pribaz JJ. Eliminating the vertical scar in breast reduction-Boston modification of the Robertson technique. *Aesthet Surg J* 2006;26:687-96.
16. Zook EG, Sommer NZ. The Modified Robertson Reduction Mammoplasty. Mastopexy and Breast Reduction: Principles and Practice. Berlin, Germany: Springer; 2009. p. 483-7.
17. Kovacs L, Eder M, Hollweck R, Zimmermann A, Settles M, Schneider A, Udolic K, Schwenzer-Zimmerer K, Papadopoulos NA, Biemer E. New aspects of breast volume measurement using 3-dimensional surface imaging. *Ann Plast Surg* 2006;57:602-10.
18. Kovacs L, Eder M, Hollweck R, Zimmermann A, Settles M, Schneider A, Endlich M, Mueller A, Schwenzer-Zimmerer K, Papadopoulos NA,

- Biemer E. Comparison between breast volume measurement using 3D surface imaging and classical techniques. *Breast* 2007;16:137-45.
19. Losken A, Seify H, Denson DD, Paredes AA, Carlson GW. Validating three-dimensional imaging of the breast. *Ann Plast Surg* 2005;54:471-8.
 20. Quan M, Fadl A, Small K, Tepper O, Kumar N, Choi M, Karp N. Defining pseudoptosis (bottoming out) 3 years after short-scar medial pedicle breast reduction. *Aesthetic Plast Surg* 2011;35:357-64.
 21. Small KH, Tepper OM, Unger JG, Kumar N, Feldman DL, Choi M, Karp NS. Re-defining pseudoptosis from a 3D perspective after short scar-medial pedicle reduction mammaplasty. *J Plast Reconstr Aesthet Surg* 2010;63:346-53.
 22. Tepper OM, Unger JG, Small KH, Feldman D, Kumar N, Choi M, Karp NS. Mammometrics: the standardization of aesthetic and reconstructive breast surgery. *Plast Reconstr Surg* 2010;125:393-400.
 23. Tepper OM, Small K, Rudolph L, Choi M, Karp N. Virtual 3-dimensional modeling as a valuable adjunct to aesthetic and reconstructive breast surgery. *Am J Surg* 2006;192:548-51.
 24. Mallucci P, Branford OA. Population analysis of the perfect breast: a morphometric analysis. *Plast Reconstr Surg* 2014;134:436-47.

Medially based de-epithelialized flap for nasal base narrowing and nostril sill augmentation in a cleft lip nasal deformity

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ABSTRACT

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Key words:

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Aim: The authors observed the nostril floor in a gross cadaver specimen histologically and innovated a medially based de-epithelialized flap for nasal base narrowing and nostril sill augmentation. **Methods:** In cadaver, fully thick section was taken from the nostril sill at the midpoint of the columella base and ala base, and stained with Masson-Trichrome. In eight patients, circumferential incision along the nostril sill and alar base freed the alar base from the upper lip. At the columellar base, fresh epithelium was shaved on the medial side of the incision line. The widened scar on the upper lip was excised. The de-epithelialized tip of the columellar base was pulled under the medial tip of the alar base flap and sutured tightly. Four anthropometric distances were measured preoperatively and postoperatively. **Results:** Histologically the nostril sill was composed of thickened dermis. Just below the dermis, the depressor septi nasi muscle ran obliquely, augmenting the nostril sill. The nostril floor width, alar distance, and alar curvature distance decreased on the cleft side after the operation. **Conclusion:** A medially based de-epithelialized flap narrows the alar base and augments the nostril sill simultaneously, since the de-epithelialized part of the excess skin augments the depressed nostril sill.



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INTRODUCTION

In patients with cleft lip nasal deformities, the upper lip scar is widened and the nasal base is wider than the unaffected side. Alar base reduction is an important technique for narrowing the frontal view of the nose.^[1]

Moreover, the nostril sill is deficient on the affected side. Excision of the scar of the upper lip and nostril sill may leave a depressed nostril.^[2] Some authors have used laterally based alar flaps,^[3] stating that they were able to reduce the risk of notching by adapting a two-layer closure of the vestibular floor.^[2]

We hypothesized that a medially based de-epithelialized flap might avoid the notching of the nostril sill, since the de-epithelialized part of the excess skin could augment

the depressed nostril sill.

We performed a histological observation of the nostril floor in a gross cadaveric specimen and created a medially based de-epithelialized flap for nasal base narrowing and nostril sill augmentation in cleft lip nasal deformities.

METHODS

Cadaveric study

On a cadaver, the nose including the upper lip was removed and fixed in 4% natural buffered formaldehyde. A fully thick section was taken from the nostril sill at the midpoint of the columellar base and the alar base. Following routine histologic procedures, the specimens were embedded in paraffin, sectioned at 10 μ m, and stained with Masson trichrome. The prepared slides were observed under a light microscope. In the perpendicular section, the nostril sill was composed of thickened dermis. Just below the dermis layer, the depressor septi nasi muscle ran obliquely and augmented the nostril sill. No alar cartilage was found [Figure 1].

Surgical technique

A circumferential incision along the nostril sill and alar base freed the alar base from the upper lip. At the

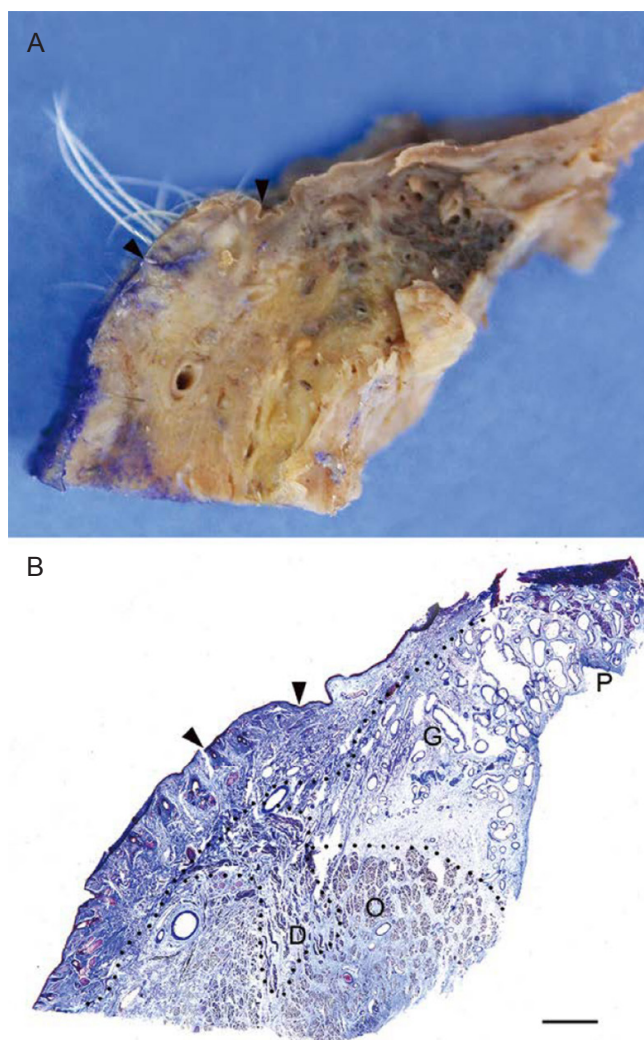


Figure 1: A perpendicular section of the nostril sill. Two arrowheads indicate the span of the nostril sill. A: Gross specimen; B: Histology with Masson trichrome stain, bar indicates 1.5 mm. Note the thick dermis and the obliquely running depressor septi nasi muscle (D) comprising the nostril sill. O: orbicularis oris muscle; P: periosteum; G: nasal glands

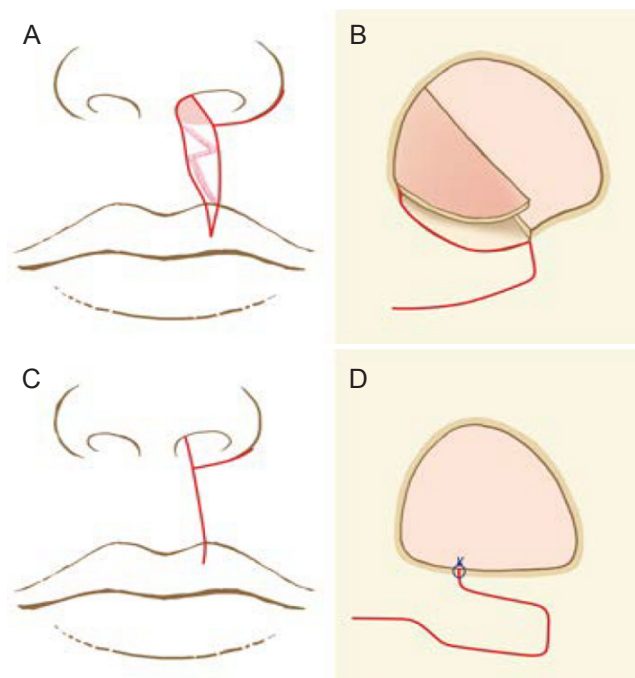


Figure 2: Surgical technique for the medially based de-epithelialized flap. (A and B): A circumferential incision along the nostril sill and alar base freed the alar base from the upper lip. At the columellar base, fresh epithelium was shaved on the medial side of the incision line. The widened scar on the upper lip was excised. (C and D): The raw (denuded and de-epithelialized) tip of the columellar base was pulled under the medial tip of the alar base flap and sutured tightly. (A and C): frontal view; (B and D): worm's eye view

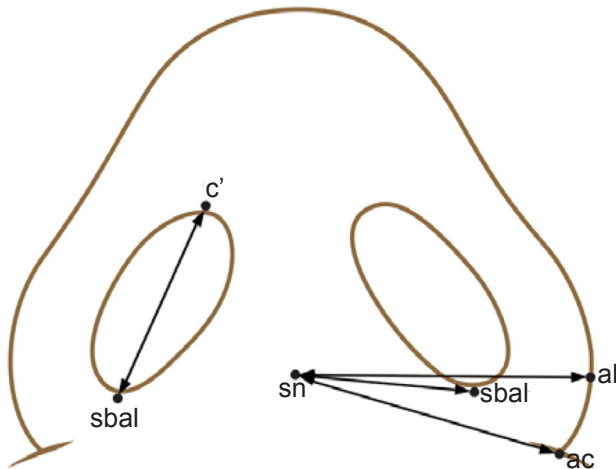


Figure 3: Four anthropometric distances were measured: nostril floor width (Sbal-Sn), alar distance (Sn-Al), alar curvature distance (Sn-Ac), and nostril length (Sbal-C'). al: alare; ac: alar curvature point; sn: subnasale; sbal: subalare; c': highest point of the columella

columellar base, fresh epithelium was shaved on the medial side of the incision line. The widened scar on the upper lip was excised. The raw (denuded and de-epithelialized) tip of the columellar base was pulled under the medial tip of the alar base flap and sutured tightly. The nasal base was then narrowed and the nostril sill was augmented [Figure 2].

Anthropometric measurements

Four anthropometric distances were measured preoperatively and postoperatively using Adobe Photoshop CS2 version 9 (Adobe Systems Inc., San Jose, CA, USA). All values were obtained in pixels. In order to avoid personal bias and random systematic error, all measurements and statistical analyses were performed by a single researcher.

Four distances were measured on the cleft side and non-cleft side preoperatively and postoperatively [Figure 3]:^[4,5] the nostril floor width (Sbal-Sn), the alar distance (Sn-Al), the alar curvature distance (Sn-Ac), and nostril length (Sbal-C'). These were transferred along the relative length to the intercanthal distance and the reduction rate (RR) was calculated [RR = (preoperative measurement - postoperative measurement)/preoperative measurement]. Statistical significance was evaluated using the independent two-sample *t*-test.

Patients

Nine patients (3 males and 6 females) were operated on using the medially based de-epithelialized flap technique. Among these 9 patients, 6 patients underwent follow-up for more than 12 months and their preoperative and postoperative worm's eye views were compared.

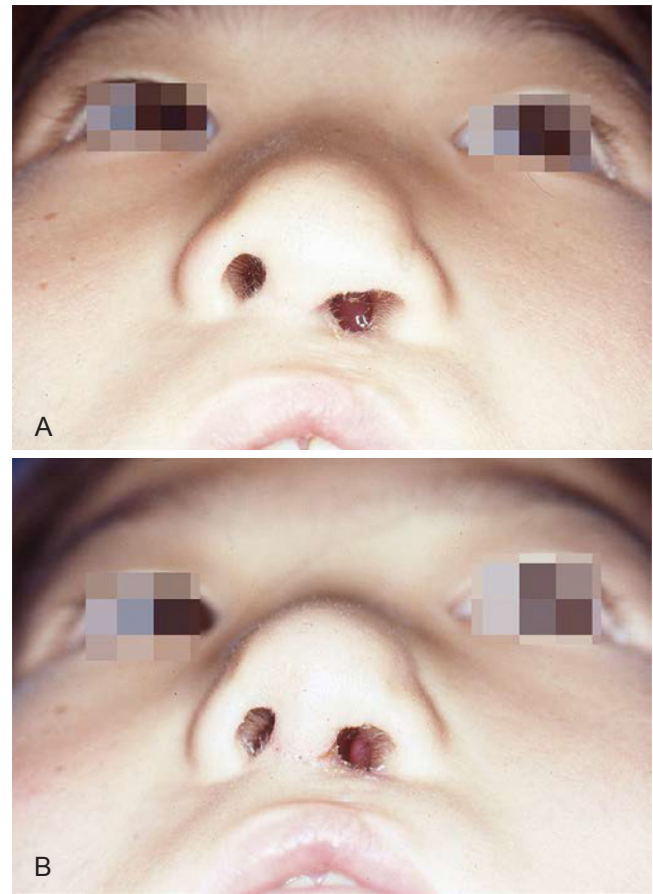


Figure 4: A 7-year-old girl with a cleft lip nasal deformity. The nostril sill was reduced using a medially based de-epithelialized flap. A: Preoperative worm's eye view; B: postoperative view

RESULTS

Anthropometric results

Although not to a statistically significant extent ($P > 0.05$, independent two samples *t*-test) the nostril floor width (Sbal-Sn), alar distance (Sn-Al), and alar curvature distance (Sn-Ac) decreased on the cleft side after the operation. The RR of the nostril floor was $7.72\% \pm 3.62\%$. The RRs of the alar distance and alar curvature distance were $7.09\% \pm 3.72\%$ and $6.46\% \pm 6.24\%$, respectively [Table 1]. On the non-cleft side, the nostril floor width (Sbal-Sn), alar distance (Sn-Al), and alar curvature distance (Sn-Ac) did not change after the operation ($P > 0.05$, independent two samples *t*-test). The RR of the nostril floor was $0.17\% \pm 7.45\%$. The RRs of the alar distance and alar curvature distance were $1.58\% \pm 6.37\%$ and $1.71\% \pm 4.42\%$, respectively [Table 1]. The nostril length (Sbal-C') increased on the non-cleft side ($6.17\% \pm 15.60\%$; $P = 0.04$, independent two samples *t*-test). The nostril length decreased on the cleft side ($2.95 \pm 30.81\%$), although this change was not statistically significant ($P > 0.05$, independent two samples *t*-test) [Tables 1 and 2].

Table 1: Comparison of the reduction rate between the non-cleft and the cleft side (independent two samples *t*-test)

Point	Definition	Reduction rate (%)		<i>P</i> -value
		Non-cleft	Cleft	
sbal-sn	Nostril floor width	0.17 ± 7.45	7.72 ± 3.62	0.19
sn-al	Ala distance	1.58 ± 6.37	7.09 ± 3.72	0.10
sn-ac	Ala curvature distance	1.71 ± 4.42	6.46 ± 6.24	0.67
sbal-c'	Nostril length	-6.17 ± 15.60	2.95 ± 30.81	0.25

Data expressed in relative length of intercanthal distance. al: alare; ac: alar curvature point; c': highest point of the columella; sn: subnasale; sbal: subalare

Table 2: Comparison of non-cleft and cleft side preoperatively and postoperatively (independent *t*-test)

Point	Definition	Non-cleft				Cleft			
		Pre		Post	<i>P</i>	Pre		Post	<i>P</i>
sbal-sn	Nostril floor width	0.24 ± 0.03	=	0.24 ± 0.04	0.47	0.29 ± 0.06	≥	0.27 ± 0.04	0.75
sn-al	Ala distance	0.51 ± 0.05	=	0.51 ± 0.07	0.22	0.61 ± 0.06	≥	0.57 ± 0.06	0.80
sn-ac	Ala curvature distance	0.50 ± 0.03	=	0.50 ± 0.04	0.35	0.62 ± 0.05	≥	0.58 ± 0.04	0.38
sbal-c'	Nostril length	0.22 ± 0.01	<	0.23 ± 0.04	0.04	0.21 ± 0.04	≥	0.20 ± 0.05	0.87
		Pre-operation				Post-operation			
		Non-cleft		Cleft	<i>P</i>	Non-cleft		Cleft	<i>P</i>
sbal-sn	Nostril floor width	0.24 ± 0.03	≤	0.29 ± 0.06	0.47	0.24 ± 0.04	≤	0.27 ± 0.04	0.91
sn-al	Ala distance	0.51 ± 0.05	≤	0.61 ± 0.06	0.39	0.51 ± 0.07	≤	0.57 ± 0.06	0.59
sn-ac	Ala curvature distance	0.50 ± 0.03	≤	0.62 ± 0.06	0.12	0.50 ± 0.04	≤	0.58 ± 0.04	0.79
sbal-c'	Nostril length	0.22 ± 0.01	≥	0.21 ± 0.04	0.10	0.23 ± 0.04	≥	0.20 ± 0.05	0.85

Data expressed in relative length of intercanthal distance. al: alare; ac: alar curvature point; c': highest point of the columella; sn: subnasale; sbal: subalare. =: same mean value; ≥ and ≤: no significant difference ($P > 0.05$); <: significant difference ($P < 0.05$)

Patient case

A 7-year-old girl had a cleft lip nasal deformity. Her nasal tip was augmented with a conchal cartilage graft and her nostril sill was reduced with a medially based de-epithelialized flap [Figure 4].

DISCUSSION

A nasal base reduction typically involves the soft tissue resection of one or more of the nasal bases (ala, sill, or columellar base).^[6] Anatomically, the labio-nostril floor angle is approximately 105° and acute. In cleft lip patients, the labio-nostril floor angle is obtuse due to the soft tissue defect of the nostril sill and the supporting bony framework.^[7]

Buried flaps have been used in the lip.^[8-11] In order to shorten the lip, Kostianovsky^[8] augmented the upper and lower lip using buried de-epithelialized local flaps. In order to improve the senile lip, Guerrissi^[9,10] de-epithelialized a strip of skin on the vermilion border and buried the remaining dermal flap in the pocket, which was performed by undermining the skin of the superior third of the upper lip.

In the above studies, the buried flaps were used to augment the upper or lower vermilion. In our study we used a de-epithelialized flap for simultaneous nasal base narrowing and nostril sill augmentation.

In order to replace deficient nostril sills, Millard^[11] denuded the epithelium of the alar base flap (D-flap) and pulled it under the lateral tip of flap C. In the present study, we used a medially based de-epithelialized flap that did not require a pull-out suture or cinching suture in the nasal septum.

In an embryological study, Green^[12] found that two relevant muscular systems exist: sphincteric fibers below the mucosal surface that are more prominent at the nasal sill, and a more superficial layer corresponding to the muscles of facial expression. He noted that the lateral external muscle fibers pass around the lower free border of the alar cartilage to insert into the sphincteric muscle.

Recently, Oh *et al.*^[13] observed that the nasalis muscle lies most superficially in the nostril sill, followed by the depressor septi nasi and the orbicularis oris underneath. In our observations, we did not find the nasalis muscle in the middle of the nostril sill. Instead, obliquely running depressor septi nasi muscle fibers comprised the nostril sill [Figure 3]. In this study, we observed a depressor septi nasi muscle that ran obliquely and comprised the nostril sill just beneath a thick layer of dermis.

The measurements we used in this patient cohort (alar distance, nostril floor width) supported the proposal that narrowing the alar base is beneficial. The RR of the nostril floor was 7.72% ± 3.62%. The RRs of the alar

distance and alar curvature distance were $7.09\% \pm 3.72\%$ and $6.46\% \pm 6.24\%$, respectively [Table 1]. Nostril length increased on the non-cleft side ($6.17\% \pm 15.60\%$; $P = 0.04$). Although it was not a statistically significant finding ($P > 0.05$), nostril length decreased on the cleft side ($2.95\% \pm 30.81\%$) [Tables 1 and 2]. This indicates that flap augmentation was beneficial.

We think that this is an advantageous technique that uses tissue that may be discarded to improve nasal symmetry. The medially based de-epithelialized flap may be a viable method for nasal base narrowing and nostril sill augmentation in cleft lip nasal deformities.

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Conflicts of interest

There are no conflicts of interest.

Patient consent

Informed consent for medical photographs was obtained.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

REFERENCES

1. Hamilton GS 3rd. Y-V alar base reduction. *Ear Nose Throat J* 2014;93:98-102.
2. Ismail AS. Nasal base narrowing: the alar flap advancement technique. *Otolaryngol Head Neck Surg* 2011;144:48-52.
3. Foda HM. Alar base reduction: the boomerang-shaped excision. *Facial Plast Surg* 2011;27:225-33.
4. Farkas LG, Kolar JC, Munro IR. Geography of the nose: a morphometric study. *Aesthetic Plast Surg* 1986;10:191-223.
5. Stewart A, Edler RJ. Efficacy and stability of the alar base cinch suture. *Br J Oral Maxillofac Surg* 2011;49:623-6.
6. Gruber RP, Freeman MB, Hsu C, Elyassnia D, Reddy V. Nasal base reduction by alar release: a laboratory evaluation. *Plast Reconstr Surg* 2009;123:709-15.
7. Uhm KI, Shin KS, Lee YH, Lew JD. Nostril sill augmentation in secondary cleft lip. *Ann Plast Surg* 1987;19:391-9.
8. Kostianovsky AS. Upper and lower lip augmentation by buried, deepithelialized local flaps: an alternative to the use of foreign material implants when shortening the lips. *Aesthetic Plast Surg* 1996;20:433-7.
9. Guerrissi JO, Sanchez LI. An approach to the senile upper lip. *Plast Reconstr Surg* 1993;92:1187-91.
10. Guerrissi JO. Surgical treatment of the senile upper lip. *Plast Reconstr Surg* 2000;106:938-40.
11. Millard DR. Cleft Craft. The Evolution of Its Surgery. In: The Unilateral Deformity (Vol 1). 1st ed. Philadelphia: Lippincott Williams & Wilkins; 1976.
12. Green MF. The embryological, developmental and functional importance in the repair of the nasal musculature to reduce the deformity of the cleft lip nose. *Scand J Plast Reconstr Surg Hand Surg* 1987;21:1-5.
13. Oh M, Lee DC, Choi TH, Kim S. Anatomic study of the nostril sill: classification and histologic findings. *Ann Plast Surg* 2010;65:56-9.

Photometric analysis of absorbable barbed suture for periareolar closure in mastopexy

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Dr. Allen D. Rosen is a distinguished spokesperson for the American Society of Plastic Surgeons. After finishing his surgical training at Columbia Presbyterian Medical Center in New York City, Dr. Rosen relocated to New Jersey where he became Founding partner and Medical director of the Plastic Surgery Group and North Fullerton Surgery Center, private group practices, in Montclair, NJ. In addition, he is an Assistant Clinical Professor in the Department of Plastic Surgery at University Hospital in Newark, NJ. He holds licenses to practice in New York, New Jersey and Florida and is widely recognized as an expert in techniques utilizing barbed suture in plastic surgery.

ABSTRACT

Article history:

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Key words:

Mastopexy,
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purse-string,
circumvertical,
permanent expanded
polytetrafluoroethylene suture,
GORE-TEX® suture,
breast lift

Aim: The primary author previously described his technique for periareolar closure in mastopexy using a pinwheel interlocking purse string with absorbable barbed suture and now reports the results of a retrospective photometric analysis comparing this technique with the same closure using Gortex® suture. This study is designed to compare the degree of areolar widening and safety profile of using absorbable barbed sutures for periareolar closure versus permanent smooth suture. **Methods:** A retrospective chart review was conducted of all patients whose periareolar closures were performed using an interlocking purse-string technique over a 10-year period. Only patients undergoing circumvertical mastopexy were included. All had photometric evaluation and follow-up performed within 6-24 months. **Results:** In total, 20 patients (40 areolas), which were closed with absorbable barbed suture, were analyzed photometrically. In this suture group, areola size increased a mean of 4.9% from baseline, and no complications (0%) were observed. This compared favorably with previously reported complication rates using permanent sutures and with a series of cases presented herein in which permanent smooth suture was used for purse string closure. The degree to which absorbable barbed suture controls areolar spread was shown to be significantly better than those where permanent smooth purse string techniques were employed. **Conclusion:** Circumvertical mastopexy closures using absorbable barbed suture was shown to be safe and effective and compared favorably to older techniques using permanent smooth suture for similar closures. This paper lends support to the safety of using absorbable barbed suture in circumareolar closures to limit areolar spread.



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INTRODUCTION

According to the American Society of Plastic Surgeons, approximately 90,000 breast lifts were performed in the United States in 2013.^[1] Mastopexy closure techniques have evolved over the past decade to help limit scarring associated with the classic inverted-T technique, replacing it with Concentric (Donut) and circumvertical techniques with or without short horizontal scars.^[2-4] Even the concept of a simple purse-string periareolar closure, first described by Benelli,^[2] evolved to the more popular interlocking (pinwheel) purse-string technique, as described by Hammond *et al.*,^[5] using permanent expanded polytetrafluoroethylene (ePTFE, GORE-TEX®, W. L. Gore, Phoenix, AZ) suture for the deep layer. Franco *et al.*^[6] reaffirmed the safety and reliability of the interlocking purse-string periareolar closure using ePTFE, by evaluating a retrospective series of 50 patients who underwent augmentation mastopexy. They found a complication rate of 6% specifically associated with infected ePTFE requiring removal of this permanent foreign body. Other complications that we encountered with ePTFE in our work prior to 2008 included wound dehiscence, knot extrusion, suture palpability, fat necrosis, and areolar widening. Non-interlocking purse-string techniques using ePTFE prior to 2008 were occasionally complicated by herniation of the areola secondary to a “cerclage” effect with spread of the areola beyond the boundaries of the initial suture placement.

In 2008, with the introduction of absorbable barbed suture (Quill™ Knotless Tissue Closure Device, Surgical Specialties Corporation®, Wyomissing, PA) we began using this new suture technology instead of ePTFE sutures for interlocking purse-string periareolar closure in our mastopexy, reduction mammoplasty, and augmentation mastopexy patient population.^[7] Demonstration of this

technique can be found at <https://www.youtube.com/watch?v=IHxKsC4S85c>. We observed a satisfactory preservation of areolar size post op and had no knot-related infections. No herniated or distorted areolas were noted and no palpability or visibility of the suture was encountered. In addition, the long-term potential nidus for infection was eliminated. Previous studies have confirmed the cost effectiveness, safety and efficacy of using barbed suture.^[8,9]

We published our work with absorbable bidirectional barbed suture for wound closure in abdominoplasty and body contouring procedures.^[10,11] Shortly after, we expanded its application to include our mastopexy closures. We undertook a formal chart review to test our hypothesis that the absorbable barbed suture, when applied using an interlocking purse-string technique, was effective in limiting the spread of the areola size post mastopexy. Swanson^[12] found photometric analysis of outcomes to be effective in assessing outcomes of breast surgery and we decided to apply similar assessment tools to our study population.

METHODS

We conducted a 10-year retrospective chart review of consecutive patients (71 patients/142 breasts) who underwent mastopexy, either alone or in conjunction with other aesthetic breast and body procedures. From 2003 to 2008, all mastopexy closures (30 patients/60 breasts) at our center were performed using permanent ePTFE sutures for the subdermal layer and smooth absorbable Monocryl suture for deep dermal and subcuticular closure. From 2008 to 2013, mastopexy closures (41 patients/82 breasts) were performed exclusively with absorbable barbed suture. We used bidirectional PDO™ (polydioxanone) for the deep layer and Monoderm™

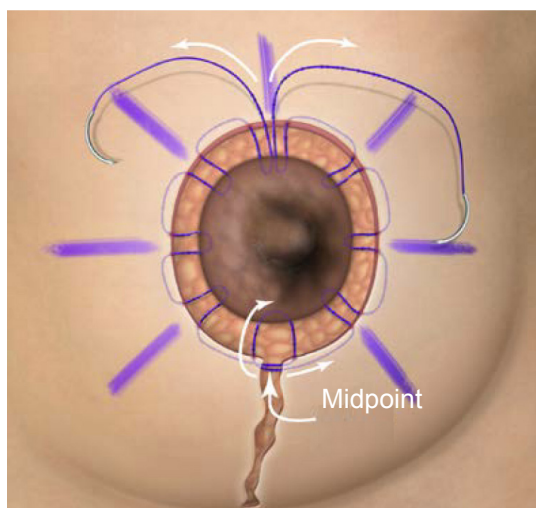


Figure 1: Interlocking purse string suture technique (deep layer with 2-0 PDO Quill)



Figure 2: The periareolar wound prior to suture deployment is marked in divided quadrants



Figure 3: Intra operative photo with interlocking purse-string barbed suture prior to cinching (outlined diagrammatically in Figure 2 above).

(PGA-PCL) for subcuticular layer. Monoderm™ retains 62% of its original tensile strength at 7 days, and 27% at 14 days, with absorption essentially complete within 90-120 days, while the longer-term PDO™ retains 50-80% of its original tensile strength at 4 weeks, with absorption essentially complete within 180 days.^[13,14]

We selected a patient population specifically to limit variables related to skin tension forces. We, therefore, excluded reduction mammoplasty and augmentation mastopexy and focused solely on patients undergoing mastopexy alone. The study population was further limited to patients with postoperative photographs between 6 months and 24 months after the mastopexy to minimize variables associated with aging.

The final analysis was performed on 20 eligible patients (40 breasts) in whom closures were performed using absorbable barbed suture exclusively. Since no previous reports of areolar spread rates have been published, for comparison purposes, we assessed 12 eligible patients (24 breasts) in whom mastopexy closures were performed with ePTFE/Monocryl. The primary author performed all surgeries using the same circumvertical technique^[4] at the same surgical center. Diagrammatic representation of interlocking purse string technique is demonstrated in [Figure 1]. Intraoperative photos are shown below depicting the periareolar wound, prior to suture deployment [Figure 2], after suture placement [Figure 3], and after final closure [Figure 4].

In the permanent suture group, a ligature was secured with a surgeons knot at the T-zone. Cinching of the suture was performed to the desired areolar size in both groups. Data were compiled for patient demographics [age, body mass index (BMI)], medical history (hypertension, smoking status, diabetes, previous breast surgery), surgical record (technique used, additional procedures)



Figure 4: The final intra operative appearance of the 2-layer absorbable barbed suture closure as described

and complications. Both pre- and postoperative photos were taken with Mirror Image Software (Canfield Scientific Corp, Fairfield, NJ). Surgical areola marker size was obtained from operative report review. Follow-up assessments were based on photos taken between 6 and 24 months postoperatively, and postoperative areola sizes were measured using free digital photo software (GNU Image Manipulation Program/www.gimp.org). Areolar width and height measurements were completed using the GIMP software.

The primary outcome was the change from baseline areolar template size used and the photometrically measured postoperative areola size. T-test statistics were used to compare within group pre-operative areola size with postoperative areola size. Analysis of variance (ANOVA) was used to compare change from baseline scores between groups, using XLSTAT software, Version 2014.5.01. This latter test was considered to be the preferred test to assess changes from baseline in studies with a non-randomized design.^[15] The incidence of complications was considered a secondary outcome.

RESULTS

The 32 patients assessed had a mean age of 41.6 years, and mean BMI of 23.5 kg/m². Patients whose mastopexy incisions were closed with absorbable barbed sutures were similar in both age and mean BMI to those closed with permanent sutures [Table 1]. The two groups were also similar in the incidence of hypertension, diabetes and in the percentage that were current smokers. Many (12/32, 37.5%) had a history of other relevant medical conditions. More subjects in the barbed suture closure group had undergone previous breast surgeries: 6/20, 30.0% vs. 2/12, 16.7% in the ePTFE group.

In 62.5% of cases (20/32), mastopexy was performed

Table 1: Baseline characteristics and medical history

Characteristic/history	Absorbable barbed suture (<i>n</i> = 20)	Permanent suture (<i>n</i> = 12)
Age, years, mean (range)	42.6 (24-66)	40.1 (20-71)
BMI, kg/m ² , mean (range)	22.9 (18.5-28.5)	24.4 (19.0-34.7)
Hypertension, <i>n</i> (%)	2 (10.0)	1 (8.3)
Current smoker, <i>n</i> (%)	4 (20.0)	3 (25.0)
Diabetes, <i>n</i> (%)	1 (5.0)	1 (8.3)
Any other relevant medical history, <i>n</i> (%) [*]	6 (30.0)	6 (50.0)
Previous breast surgery, <i>n</i> (%) [†]	6 (30.0)	2 (16.7)

^{*}Patients in the barbed suture group also had other relevant medical history that included a history of: leukopenia (1); kidney disease (1); rheumatoid arthritis (1); heavy scars (2); lupus and fibromyalgia (1); and high blood pressure, steroid use, blood clots, and Hodgkin Lymphoma (1); patients in the smooth suture group also had a history of: allergies and exercise-induced asthma (1); hypercholesterolemia, cough and asthma (1); breast cancer (1); cough and in-utero fibroids (1); medullary sponge kidney (1); and heart and gastrointestinal disease (1).[†]Patients in the barbed suture group had previously undergone bilateral mastopexy (1), breast reduction (3), lumpectomy (1) and biopsy (1); patients in the smooth suture group had previously undergone lumpectomy and axillary node dissection (1) and excision of a benign cyst

Table 2: Surgical record

Surgical record	Absorbable barbed suture (<i>n</i> = 20)	Permanent suture (<i>n</i> = 12)
Mastopexy only, <i>n</i> (%)	9 (45.0)	3 (25.0)
Mastopexy in conjunction with other aesthetic procedures, <i>n</i> (%) [*]	11 (55.0)	9 (75.0)
Abdominoplasty	6 (30.0)	5 (41.7)
Blepharoplasty	3 (15.0)	1 (8.3)
Correction of inverted nipple, bilateral	1 (5.0)	0 (0)
Hernia repair	2 (10.0)	0 (0)
Liposuction [†]	2 (20)	1 (10)
Filler to lips and/or nasolabial folds	2 (20)	0 (0)
Upper abdominal lift	0 (0)	1 (8.3)
Mastopexy technique, <i>n</i> (%)		
Circumvertical	20 (100)	12 (100)

^{*}Some patients had multiple additional procedures. [†]Patients in the barbed suture group had power-assisted lipoplasty of the hips, abdomen and thighs (1) and bilateral anterior axillary liposuction (1). The patient in the smooth suture group had liposuction of the neck

in conjunction with various other aesthetic surgical procedures [Table 2]. Of these, abdominoplasty was the most common procedure; it was performed in 30% of procedures in which the mastopexy incision was closed with absorbable barbed suture, and in 41.7% of procedures in which ePTFE sutures were used.

Follow-up photos used for the assessment of areola size were taken a mean of 11.2 months postoperatively. Mean follow-up times were similar for both cohorts: 10.7 and 12.0 months, respectively [Table 3]. Among patients in the ePTFE suture group, areola size for both breasts increased a mean of 0.49 ± 0.57 cm from a baseline mean of 3.90 ± 0.18 cm ($P = 0.011$), representing a 12.5% increase from baseline.

Using absorbable barbed suture, areola size increased a mean of 0.20 ± 0.70 cm from a baseline mean of 4.11 ± 0.24 cm ($P = 0.236$), representing a 4.9% increase from baseline. The increase in areola size was a mean of 0.29 ± 0.16 cm less for patients in the absorbable barbed suture group; however, the difference between groups in the change from baseline areola size did not reach statistical significance ($P = 0.092$, based on ANOVA).

No major or minor complications were reported for any patient who underwent mastopexy closure using the absorbable barbed suture [Table 4]. In contrast, 2 of the 24 breasts (8.3%) where ePTFE suture was used had complications. In one case, complications included wound dehiscence and infection; this patient had a history of breast cancer. In a second case, complications were limited to wound dehiscence and fat necrosis; this patient had a history of hypertension and diabetes.

DISCUSSION

We believe the unique property of the barbed suture allows redistribution of tension forces throughout the entire length of the closure, and is particularly effective for round closures under circumferential tension. Smooth sutures, whether permanent or absorbable, allow tissues to slide along the length of the suture and “bunch up” similar to the way a shower curtain slides unevenly along its rod. Furthermore, we have found that long-acting absorbable sutures provide enough strength to allow quality tension-free healing to occur without leaving permanent foreign body material beneath thin areolar

Table 3: Mastopexy closure with barbed and smooth sutures

Surgical record	Absorbable barbed suture (<i>n</i> = 20)	Permanent suture (<i>n</i> = 12)
Mastopexy only, <i>n</i> (%)	9 (45.0)	3 (25.0)
Mastopexy in conjunction with other aesthetic procedures, <i>n</i> (%) [*]	11 (55.0)	9 (75.0)
Abdominoplasty	6 (30.0)	5 (41.7)
Blepharoplasty	3 (15.0)	1 (8.3)
Correction of inverted nipple, bilateral	1 (5.0)	0 (0)
Hernia repair	2 (10.0)	0 (0)
Liposuction [†]	2 (20)	1 (10)
Filler to lips and/or nasolabial folds	2 (20)	0 (0)
Upper abdominal lift	0 (0)	1 (8.3)
Mastopexy technique, <i>n</i> (%)		
Circumvertical	20 (100)	12 (100)

^{*}*t*-test for within group pre-op areola marker size vs. post-op areola size, using Excel. [†]Analysis of variance for between groups change from baseline scores, using XLSTAT software, Version 2014.5.01

Table 4: Postoperative complications

Complication	Absorbable barbed suture (<i>n</i> = 40)	Permanent suture (<i>n</i> = 24)
Any complication, <i>n</i> (%)	0 (0)	2 (8.3)
Wound dehiscence, infection	0 (0)	1 (4.15)
Wound dehiscence, fat necrosis	0 (0)	1 (4.15)

tissues. Absorbable suture eliminates long-term suture palpability, both at the knot and the circumferential portion of the permanent suture.

We also strongly believe that the tension relieving nature of the interlocking purse-string technique is further enhanced by the tension redistribution noted with barbed sutures. The combination of the novel interlocking technique and the improved absorbable barbed suture technology acts in synergy to reduce wound tension and minimize complications.

Various complications in procedures involving periareolar closures have been reported in the literature, most typically in association with breast reduction or augmentation/mastopexy surgeries.^[16-21] Delayed wound healing, wound dehiscence, hematoma or seroma formation, wound infection, fat necrosis, stitch abscess, diminished nipple sensation and scarring have been reported but limited data are available for mastopexy alone. Franco's review^[6] using interlocking ePTFE reports similar complications. Since the wound healing problems listed in the permanent suture cohort in our review occurred in patients with systemic comorbidities, this could have played a role in the healing process. In addition, the retrospective nature of this review and the small, uneven sample size do not allow us to make statistically significant comparisons between groups, but the limited sample did show that areolar size was well preserved and no complications were seen in this particular group when closing the periareolar tissues exclusively with absorbable barbed suture.

Although complication rates for mastopexy are well

reported in our literature, the effectiveness of controlling the degree of areolar spread has not. Many authors have made references to this outcome, but the incidence rates in a population of mastopexy patients without augmentation or volume reduction have not been previously reported. For this reason, we included a small sample of our own patients to serve as a comparative cohort in assessing post op areolar widening, an important parameter to demonstrate efficacy of periareolar closure techniques.

Certainly, some limitations of this study are inherent to the nonrandomized retrospective study design. A prospective, randomized multicenter trial with a larger sample size would be necessary to validate our observational findings. In addition, since only barbed suture was used we could not assess whether smooth absorbable suture might perform as well at lower cost.

Although the mean follow-up period was similar between groups, the range was wide varying from 6 to 24 months. It would have been preferable if all follow-up photographs had been recorded within an even narrower window to better restrict changes in breast size that may otherwise been due to weight gain or loss or other variables. It is possible that direct postoperative areolar measurements with calipers would have been preferable to photometric measurements, although both methods have a degree of inherent inaccuracy. We are also aware that due to the contractile properties of the nipple areolar complex, areolar size may vary based on environmental conditions, room temperature, stress and other unforeseen stimulatory factors.

In our surgical practice, the use of absorbable barbed

suture for circumareolar closure was found to be effective in limiting post op areolar widening and was without complications. We present our data as a comparative photometric and clinical analysis for surgeons considering making the “leap of faith” and performing periareolar closure with absorbable barbed suture alone.

The tension reducing benefits of the interlocking purse-string technique combined with absorbable barbed suture technology yields predictable areolar size outcomes and minimizes suture related complications in mastopexy. As plastic surgeons continue to evolve and explore new suture technologies and techniques, this study will support the safety and efficacy of doing so exclusively with absorbable barbed suture.

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Conflicts of interest

There are no conflicts of interest.

Patient consent

Not applicable.

Ethics approval

Not applicable.

REFERENCES

1. American Society of Plastic Surgeons. 2013 Plastic Surgery Statistics Report. Available from: www.plasticsurgery.org. [Last Accessed on 24 June 2014].
2. Benelli L. A new periareolar mammoplasty: the “round block” technique. *Aesthet Plast Surg* 1990;14:93-100.
3. Lejour M. Vertical mammoplasty and liposuction of the breast. *Plast Reconstr Surg* 1994;94:100-14.
4. Hall-Findlay EJ. A simplified vertical reduction mammoplasty: shortening of the learning curve. *Plast Reconstr Surg* 1999;104:748-59.
5. Hammond DC, Khuthaila DK, Kim J. The interlocking Gore-Tex suture for control of areolar diameter and shape. *Plast Reconstr Surg* 2007;119:804-9.
6. Franco J, Kelly E, Kelly M. Periareolar augmentation mastopexy with interlocking Gore-Tex suture, retrospective review of 50 consecutive patients. *Arch Plast Surg* 2014;41:728-33.
7. Rosen AD. Periareolar closure with barbed sutures. *Aesthet Surg J* 2016;36:372-5.
8. Ruff G. Technique and uses for absorbable barbed sutures. *Aesthet Surg J* 2006;26:620-8.
9. Paul MD, Budd M. Evaluating the Quill self-retaining system. Available from: <http://www.plasticsurgerypractice.com/2009/03/evaluating-the-quill-self-retaining-system/>. [Published on 24 March 2009; Last Accessed on 08 September 2016].
10. Rosen AD. Use of absorbable running barbed suture and progressive tension technique in abdominoplasty: a novel approach. *Plast Reconstr Surg* 2010;125:1024-7.
11. Rosen A, Hartman T. Repair of the midline fascial defect in abdominoplasty with long-acting barbed and smooth absorbable sutures. *Aesthet Surg J* 2011;31:668-73.
12. Swanson E. A retrospective photometric study of 82 published reports of mastopexy and breast reduction. *Plast Reconstr Surg* 2011;128:1282-301.
13. Quill™ self-retaining system (SRS) comprised of Monoderm™ (PGA-PCL) synthetic absorbable surgical suture material. Instructions for use. Angiotech, Reading, PA.
14. Quill™ self-retaining system (SRS) comprised of dyed PDO (polydioxanone) synthetic absorbable surgical suture material. Instructions for use. Angiotech, Reading, PA.
15. Van Breukelen GJ. ANOVA versus change from baseline had more power in randomized studies and more bias in nonrandomized studies. *J Clin Epidemiol* 2006;59:920-5.
16. Shiffman MA. Mastopexy complications. In: Shiffman MA, Di Giuseppe A, editors. *Body Contouring*. Berlin: Springer; 2010. p.145-7.
17. Hidalgo DA, Spector JA. Mastopexy. *Plast Reconstr Surg* 2013;134:e642-56.
18. Stevens WG, Stoker DA, Freeman ME, Quardt SM, Hirsch EM. Mastopexy revisited: a review of 150 consecutive cases for complication and revision rates. *Aesthet Surg J* 2007;27:150-4.
19. Stevens WG, Spring M, Stoker DA, Freeman ME, Cohen R, Quardt SM, Hirsch EM. A review of 100 consecutive secondary augmentation/mastopexies. *Aesthet Surg J* 2007;27:485-92.
20. Spear SL. Augmentation/mastopexy: “surgeon, beware”. *Plast Reconstr Surg* 2006;118:S133-4.
21. Spear SL, Boehmler JH 4th, Clemens MW. Augmentation/mastopexy: a 3-year review of a single surgeon’s practice. *Plast Reconstr Surg* 2006;118:S136-47.

Case Report

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Non-odontogenic hard palate cysts with special reference to globulomaxillary cyst

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ABSTRACT

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Palatal cysts are always confusing by defining their exact nomenclature or conclusive diagnosis. One of these presentations is globulomaxillary cyst which requires to be categorized under appropriate head for the management point of view. Though this entity appears to be of odontogenic in origin but because of its anatomical relation and histo-pathological background this is placed in non odontogenic group. Though the mechanism of its formation remains the same but this cyst cannot be mixed up with nasopalatine cyst as per their location. Globulomaxillary cyst appears as inverted pear shaped radiolucency in all radiological procedures. This remains asymptomatic for a long time and rarely gets infected. We present a 29-year-old male who reported with one year history of asymptomatic right side hard palate swelling. He was subsequently diagnosed as globulomaxillary cyst with the help of radiological modalities like computerized tomography and magnetic resonance imaging. This article will highlight mainly the clinical and radiological features of these cysts with particular reference to globulomaxillary cyst which is our presenting case.



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INTRODUCTION

Cysts in the oral cavity can either be of soft tissue origin or from within the bone. Non-odontogenic hard palate cysts arise from the tissues which do not participate in tooth formation. There are many palatal cysts and their variants are encountered during the course of embryonic palate development. One of the cysts is globulomaxillary cyst and this terminology had a lot of dispute to be used. It was earlier thought to be of embryonic origin because of entrapment of the ectoderm but now this hypothesis is no longer considered. These have been considered as fissural entrapment of epithelium rather than embryonic ectoderm.^[1] There are many other cysts reported in the palate region and have been categorized as per the origin and anatomical location.

CASE REPORT

A 29-year-old male reported to otolaryngology outpatient department with the swelling in the hard palate of one year duration [Figure 1].

This was asymptomatic in the beginning but subsequently developed some roughness along with slight local tenderness. There was no history of trauma or fever. On examination there was slight protuberance over the right side of the hard palate. This was of slight dull pink in coloration. There was no ulceration seen locally over the swelling. There was no divergence of roots of central incisors. The adjoining teeth reacted normally to the electric vitalometer test and to temperature stimulation. All the biochemical parameters were within normal limits. The further detailed initial work up confirmed the swelling as that of the non odontogenic origin. The patient was referred for evaluation of the tumor. The oral occlusal film had confirmed the swelling of non odontogenic origin. The patient was subjected to plain as well as contrast enhanced computerized



Figure 1: A 29-year-old male with hard palate swelling which is slightly pink in coloration (white vertical arrow)

tomography (CT) scanning of the face and neck region. The findings revealed a radiolucent pear shaped non enhancing unilocular, inverted pear shaped cystic lesion 2.5 cm × 3.5 cm in size between the lateral incisor and canine on right side [Figure 2].

There was also thinning out of the bony outline [Figure 3].

Patient was also subjected to magnetic resonance imaging (MRI) scanning of face and neck region. The mass was of fluid density which was hypointense in T1W and hyperintense in T2W images. There were no associated findings [Figure 4].

Fine needle aspiration cytology has shown some seropurulent secretion and confirmed as non odontogenic cyst coming in the category of globulomaxillary cyst. The histo-pathological images were not available. The patient has been planned for

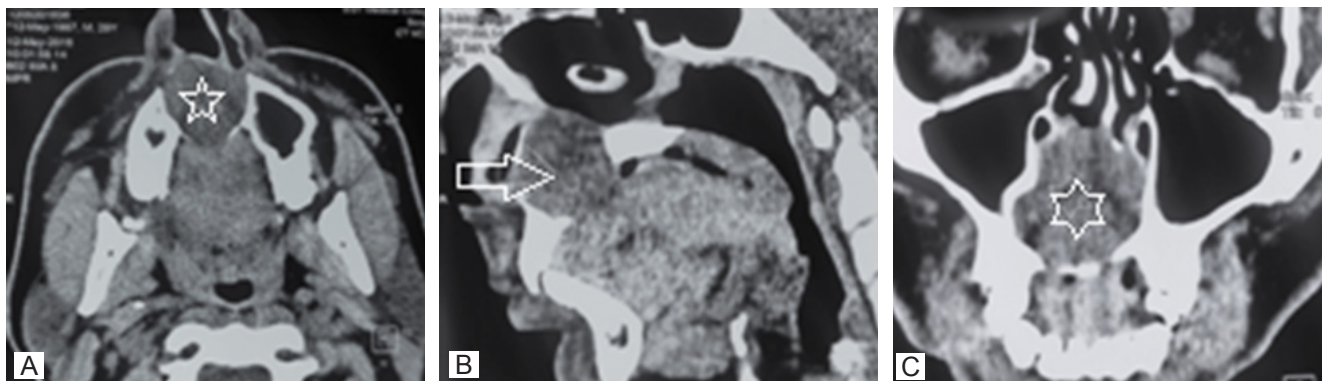


Figure 2: Contrast enhanced computerized tomography of face and neck region. (A) Axial section shows a radiolucent non enhancing lesion (white star) present on right side of the hard palate; (B) reformatted sagittal section shows the same as pear shaped lesion (horizontal white arrow) abutting the right nasal cavity; (C) reformatted coronal section shows the lesion is encroaching upon the right maxillary sinus (white star) without invading the same

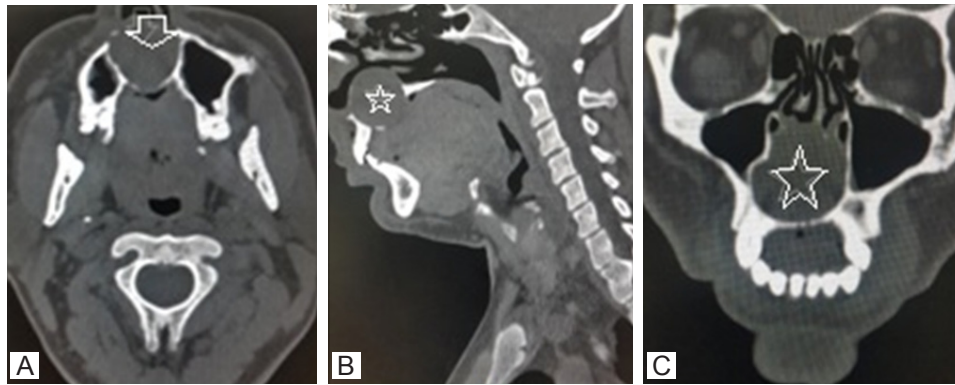


Figure 3: Non contrast computerized tomography of facial and neck region in 3D reformatted bone window. (A) Axial section shows expanded radiolucent lesion with “egg shell” appearance at the base of nasal region predominantly on right side (vertical white arrow); (B) sagittal section shows the superior extent of lesion from hard palate (white star); (C) coronal section delineate the lesion separate from the maxillary sinuses but obscuring the nasal passages predominantly on right side (white star)

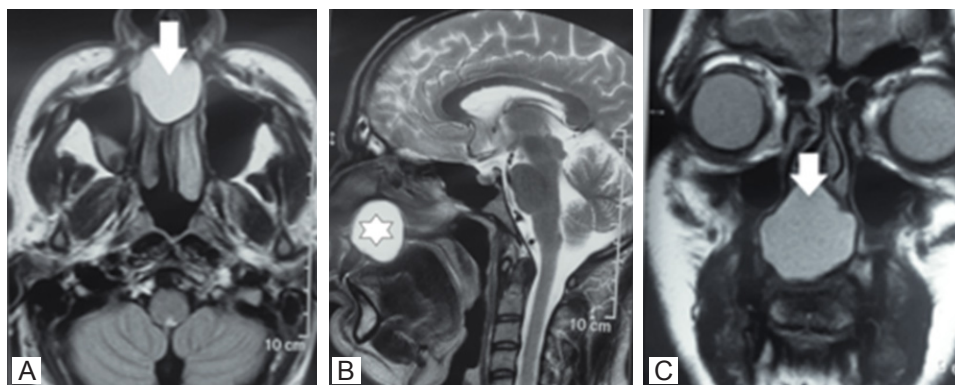


Figure 4: Plain magnetic resonance imaging face and neck region. (A) T2W image shows the well contained hyperintense cystic lesion on right side of the hard palate (vertical arrow); (B) T2W sagittal image shows hyperintense well demarcated lesion on the superior part of the hard palate (white star) on right side; (C) same lesion in T2WI coronal section with its superior extent (vertical arrow)

enucleation of the cyst as this being the most preferred method of treatment of these entities.

DISCUSSION

Hard palate forms the floor of the nostrils and roof of the oral cavity. This is thicker in front and thin in its posterior aspect. Globulomaxillary cysts are still disputable in their origin but majority of studies have shown these as not of embryonic origin.^[2]

Oral origin cysts can be placed in to two categories as follow: (1) non-odontogenic (fissural) category includes globulomaxillary, nasopalatine, median palatal and nasolabial (nasoalveolar) cysts; and (2) odontogenic category includes dentigerous cysts, primordial cysts, odontogenic keratocysts and residual cysts.

Globulomaxillary cysts fall in non-odontogenic category. These can be distinguished based on the origin of the epithelial rests. Odontogenic cysts arise from tooth developing epithelium contrary to non odontogenic which arise from the trapped epithelium because of the

fusion of upper jaw bones.^[3] Non-odontogenic cysts can further be differentiated on the basis of their anatomical location. All the cysts around incisive canal fall in this group [Figure 5].

Globulomaxillary cysts arise at the junction between maxilla and premaxilla. There are three main subtypes of non-odontogenic fissural cysts described as nasoalveolar, nasopalatine and median palatal.^[4] These are usually discovered during routine clinical or radiographic examinations. The average duration of these cysts vary from one week to two years. The occlusal images are the first to lead in radiological investigations. In plain X-ray this may present as radiolucent region. These are usually asymptomatic and also found as incidental findings in CT examinations. Their pathogenesis though controversial but non disintegrated epithelium in the fissural sites remains the most accepted hypothesis. These are usually painless and rarely get infected and that is the reason for their delayed diagnosis.^[5] These are oval or round and hypodense on CT examination and do not enhance in post contrast studies. Bone resorption is often present

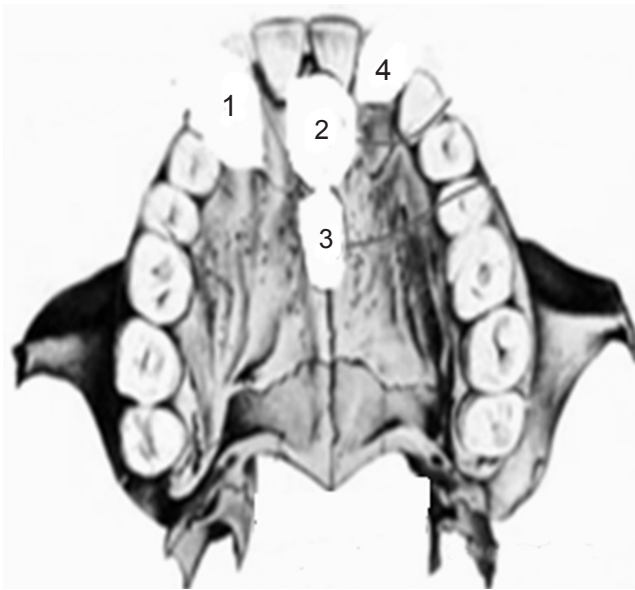


Figure 5: Diagrammatic representation of hard palatal cysts as per locations. Globulomaxillary cyst (1), nasopalatine cyst (2), median palatal cyst (3) and nasolabial cyst (4) are shown as white oval regions

because of their expansile nature but the cortical break is very rare. The classical egg shell type of margins is present as was also seen in our case. Hisatomi *et al.*^[6] has described the classical features of these cysts in MRI. MRI show intermediate signal in T1W and hyper intensity on T2W images. There is no post-gadolinium enhancement seen in T1W fat saturated sequences. Histologically these present as a cystic cavity covered by epithelium that contain stratified squamous cells with some respiratory epithelial components. The wall is composed of thick dense collagenous fibrous tissues. Median palatine cysts are easy to diagnose on CT and MRI modalities as their locations are self explanatory.^[7,8] There are cases where these entities have been managed with non-surgical endodontic treatment^[9] but the gold standard is complete surgical excision via intraoral approach.^[10] Sometimes the part of nasal mucosa has to be sacrificed as the lesion is close to the floor of the nose.^[11]

In conclusion, globulomaxillary cysts draw attention only after these are diagnosed. These cysts remain

undiagnosed for a long period because of their asymptomatic background. CT and MRI modalities have brought revolution in diagnosing these entities while performed for some other reasons. These should be classified in their proper category before treating them.

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Conflicts of interest

There are no conflicts of interest.

Patient consent

The consent of the patient was taken before subjecting the patient for investigation.

Ethics approval

The approval for publishing this case and paper had been obtained from the institute.

REFERENCES

1. Haring P, Filippi A, Bornstein MM, Altermatt HJ, Buser D, Lambrecht JT. The "globulomaxillary cyst" a specific entity or a myth? *Schweiz Monatsschr Zahnmed* 2006;116:380-97. (in French, German)
2. Dammer U, Driemel O, Mohren W, Giedl C, Reichert TE. Globulomaxillary cysts--do they really exist? *Clin Oral Invest* 2014;18:239-46.
3. Alimendinger A, Gabe M, Destian S. Median palatine cyst. *Neuroradiology* 2009;3:7-10.
4. De Cuyper K, Vanhoenacker FM, Hintjens J, Verstraete KL, Parizel PM. Nasopalatine duct cyst. *JBR-BTR* 2008;91:179.
5. Yerli H, Cabbarpur C, Aydin E. CT findings of a nasoalveolar cyst. *Br J Radiol* 2009;82:e76-8.
6. Hisatomi M, Asaumi J, Konouchi H, Shigehara H, Yanagi Y, Kishi K. MR imaging of epithelial cysts of the oral and maxillofacial region. *Eur J Radiol* 2003;48:178-82.
7. Karacal N, Ambarcoglu O, Kutlu N. Median palatine cyst: report of an unusual entity. *Plast Reconstr Surg* 2005;115:1213-4.
8. Hadi U, Younes A, Ghossein S, Tawil A. Median palatine cyst: an unusual presentation of a rare entity. *Br J Oral Maxillofac Surg* 2001;39:278-81.
9. Abdel-Aziz MM. Healing of globulomaxillary cyst after non-surgical endodontic treatment--"case report". *Egypt Dent J* 1995;41:1295-8.
10. Fonseca R, Marciani R, Turvey T, editors. *Oral and Maxillofacial Surgery*. 2nd ed. St. Louis: Elsevier; 2008. p. 418-65.
11. Hupp JR, Ellis E, Tucker MR. *Contemporary oral and maxillofacial surgery*. 5th ed. St. Louis: Mosby Elsevier; 2008. p. 450-6.

Case Report

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Total nasal septal reconstruction using costal cartilage in difficult cases of secondary septoplasty

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ABSTRACT

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Rhinoplasty and septal reconstruction often require the use of cartilage grafts. Complete nasal septal reconstruction may be required in very specific situations like difficult secondary septoplasty or severely deformed post traumatic noses. Usually in these cases the septal cartilage or bone is insufficient for septal reconstruction. The authors hereby describe a new technique of complete septal reconstruction by using the 7th rib (costal) cartilage combined with author's ingenious technique to prevent warping.



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INTRODUCTION

Rhinoplasty and septal reconstruction often require the use of cartilage grafts. Occasionally, the unsuspecting rhinoplasty surgeon may hitherto stumble upon such noses which have paucity of native cartilaginous and bony septum. In post-septoplasty severely deviated nose and severely deformed post traumatic nose, the native septal cartilage and bony septum may be thin, fragmented or inadequate. The reconstruction of a complete septum with costal cartilage may restore a strong support in such situations. Here we describe two such cases.

CASE REPORT

Case 1

A 26-year-old male had a history of injury to the nose by cricket ball 5 years ago. His nose had gradually deviated and owing to severe breathing problems, he underwent septoplasty 2 years ago. There was considerable relief in breathing after the surgery but the nose remained crooked. He presented to us with a crooked nose for aesthetic correction [Figure 1A and B].

The patients were assessed postoperatively by clinical examination, photography, nasoendoscopy. The dorsal symmetry was confirmed postoperatively by “text neck photographic view”.^[1] The first patient has been following up regularly since 18 months [Figure 1C and D]. Clinically the nose and septum is straight and airway is patent as confirmed by nasoendoscopy [Figure 2].

Case 2

A 35-year-old female presented with severely deformed and scarred nose and breathing difficulty. Owing to a road accident one year ago, she had an adherent scar running from right nostril till junction of cartilaginous and bony dorsum, resulting in partition of right nostril. There was disjunction of cartilaginous dorsum and detachment

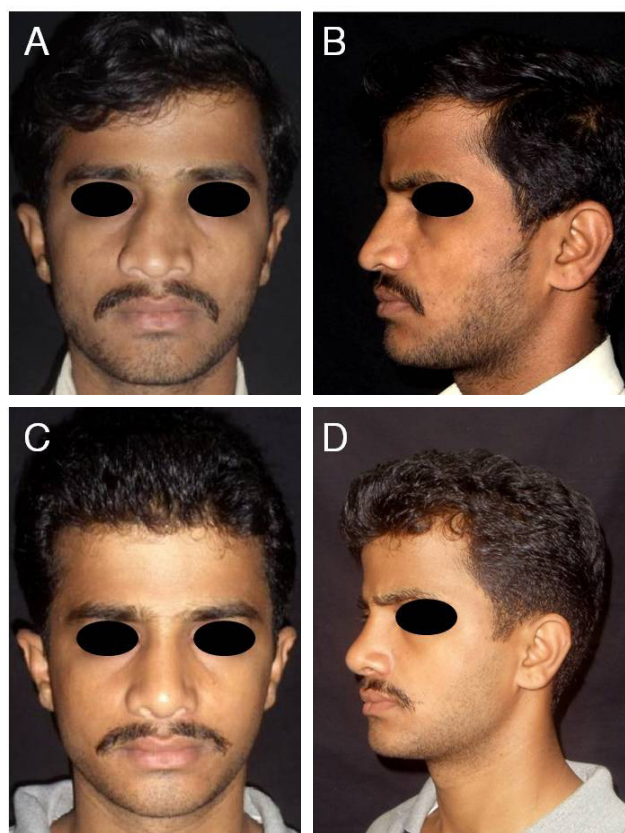


Figure 1: Patient 1. A: Preoperative photograph, frontal view; B: preoperative photograph, lateral view; C: the 1-year postoperative photograph, frontal view; D: the 1-year postoperative photograph, lateral view

of left medial canthus which was displaced in an oblique position. Also, there was shortage of skin between right ala and nasal tip [Figure 3A and B].

The patient was operated in two stages. Initially she underwent left medial canthopexy, release of synechia of right nostril, adhesiolysis, scar revision, and insertion of a costal cartilage strut to the nasal dorsum, through the existing scar. The scar revision and insertion of a

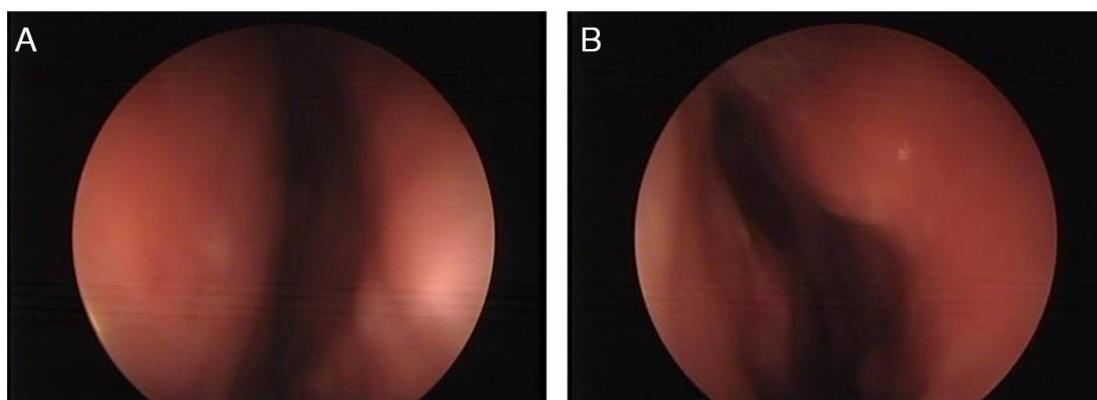


Figure 2: Patient 1. Postoperative naso-endoscopic view on right (A) and left (B) side showing patent airway

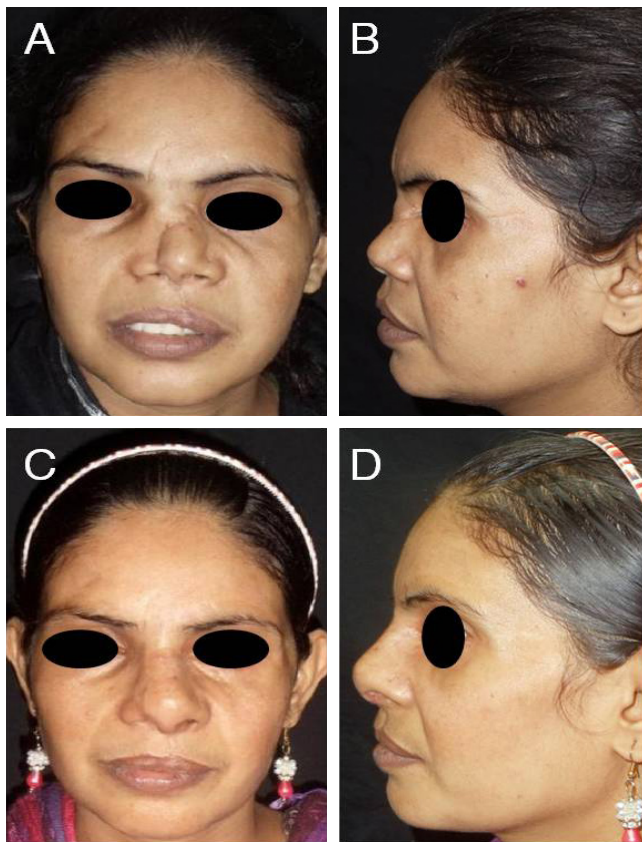


Figure 3: Patient 2. A: Preoperative photograph, frontal view; B: preoperative photograph, lateral view; C: the 3-month postoperative photograph, frontal view; D: the 3-month postoperative photograph, lateral view

strut not only improved the scar and stretched the skin envelope, but also prevented further adhesions and improved her breathing up to some extent. The final surgery was done one year later for reconstruction of the nasal septum.

The patient had clinically straight nose and patent airway on 3-month follow-up after which she was lost to follow-up [Figure 3C and D].

Surgical technique

Being broad and flat usually, the 7th costal cartilage was used for both the patients [Figure 4A]. Careful and indulgent carving of cartilage was required to get 2 equal and thin plates. Any uneven surface or discrepancy in thickness of the 2 plates was further carved either with the help of a knife or a burr. Since these plates have a tendency to warp, a straight plate was formed using authors' Counterbalancing technique^[2] in which concave surfaces of both the plates are sutured together to get a strong and an absolutely straight plate [Figure 4B and C].

The authors first used 4-0 polyglactin as, due to its better knotting property and strength, it takes all the stress in conforming the 2 concave plates. This allowed the use of a thinner non absorbable sutures (5-0 polypropylene), which usually break if used alone. Authors avoid using 4-0 polypropylene alone as it is too thick and the knots usually get exposed through the septal muco-perichondrial flaps. The length of the plate was dictated by the dimensions of the native septum as measured from the distal end of the nasal bones to the anterior nasal spine. The thickness (width) of the neo-septum was around 3 mm in both cases.

The neo-septum was kept 5-7 mm longer on its proximal end which was fed into the groove created in the middle of nasal bone for adequate support. Bilateral spreader grafts were sutured to the neo-septum, which was fixed in place, proximally to nasal bones and distally to the anterior nasal spine, by drilling 2 holes on each side [Figure 5]. The fixation was done with 4-0 polypropylene sutures. The neo-septum rests comfortably on the vomer bone. The rest of the steps were same as in any extracorporeal septorhinoplasty case.

DISCUSSION

Septal reconstruction is a frequently required difficult



Figure 4: A: the 7th costal cartilage graft; B: warping after carving of cartilage pieces; C: prepared neoseptum using counterbalancing technique to control warping



Figure 5: Placement of neoseptum

step in post septoplasty or post traumatic rhinoplasty cases. King *et al.*^[3] first described extracorporeal septoplasty in 1952 which generally produces good results. In this procedure, popularized by Gubisch in the early 1980s, the cartilaginous and bony septum were removed intact, redundant cartilage and fracture lines were excised, and the remaining pieces were sutured together.^[4,5] The main indication for extracorporeal septoplasty is severely deviated crooked septum causing both functional as well as cosmetic deformity. In majority of cases, the deformed native septum provides enough cartilage or bony plate by which a strong neo-septum can be rebuilt. L-strut [Figure 6A] or neo-septum can be made by either septal cartilage or the bony plate, or a combination thereof.^[6]

An easier option to rebuild a neo-septum is polydioxanone sulfate (PDS) plate, on which small fragments can be sutured to act as a scaffold.^[7-9] In case of paucity of septal cartilage, conchal cartilage can also be used. In the first case, due to previous septoplasty, enough cartilage and bone could not be found to reconstruct a neo-septum. The second case was severe post traumatic nasal deformity. Here too, only fragments of cartilage and bony plate could be found, which could not be used to build a neo-septum.

Although PDS plate could have been used for the reconstruction but in the first case, the authors were caught unawares and had to resort to the technique being described. The success of first case encouraged the use of the technique in second case. The replacement of full cartilaginous plate which is resting over vomer bone or in the vomerine groove akin to the native septum, and fixed properly to the anterior

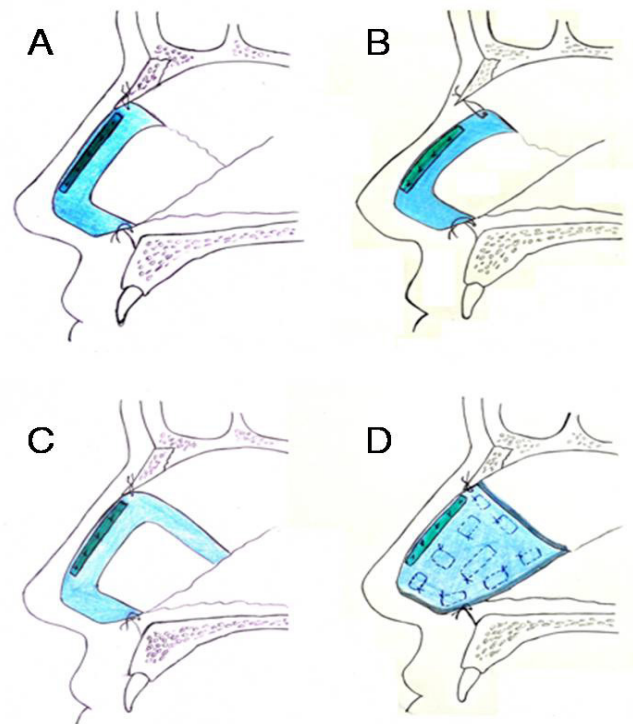


Figure 6: Schematic diagram of the technique. A: Reconstructed nasal septum with L-strut; B: collapse at the keystone area which may occur in L-strut due to inadequate suture fixation or failure of suture; C: C-shaped septal strut with two vertical limbs on both ends provides better stability; D: total septal plate replacement with costal cartilage graft. Multiple box sutures are used to hold the cartilage grafts together and prevent warping

nasal spine (ANS) caudally and nasal bone proximally, leaves no space for postoperative saddling, which is common with L-strut due to loosening or breaking of suture [Figure 6B]. Authors strongly advocate the replacement of either complete septal plate [Figure 6D] or a C-shaped septal strut [Figure 6C] with two vertical limbs on both ends (unlike L-strut which has only one vertical limb supported on ANS while the stability of cephalic end is largely dependent on suture fixation, which is not always reliable).

Replacing the complete septum is advantageous because it prevents primary sinking and collapse at the keystone area which may occur in L-strut due to inadequate suture fixation or failure of suture, secondary sinking of septum or shortening of nose due to development of fibrosis in empty space and vibration of empty mucoperichondrial flaps.^[9] It also provides a solid support to the nose, and if required later, makes the subsequent surgical dissection easier (since it is easy to separate mucoperichondrial flaps from cartilage than from each other).

This procedure is simple, easy to understand and reproducible. Though this is a very small series, authors

feel that this new technique of formation of complete neo-septum with costal cartilage is very helpful when used with specific indications and provides an additional tool to the rhinoplasty surgeon to be used in cases of difficult secondary septoplasty.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

Patient consent

Obtained.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

REFERENCES

1. Agrawal KS, Singla S, Shrotriya R. "Text-Neck View": a new photographic tool for assessment of nasal dorsum in crooked noses. *Plast Reconstr Surg* 2016;138:165e-7e.
2. Agrawal KS, Bachhav M, Shrotriya R. Namaste (counterbalancing) technique: overcoming warping in costal cartilage. *Indian J Plast Surg* 2015;48:123-8.
3. King ED, Ashley FL. The correction of the internally and externally deviated nose. *Plast Reconstr Surg* 1952;10:116-20.
4. Gubisch W. The extracorporeal septum plasty: a technique to correct difficult nasal deformities. *Plast Reconstr Surg* 1995;95:672-82.
5. Gubisch W, Constantinescu MA. Refinements in extracorporeal septoplasty. *Plast Reconstr Surg* 1999;104:1131-42.
6. Gubisch W. Extracorporeal septoplasty for the markedly deviated septum. *Arch Facial Plast Surg* 2005;7:218-26.
7. Gerlinger I, Kárász T, Somogyvári K, Szanyi I, Ráth G, Móricz P, Boenisch M. Extracorporeal septal reconstruction with polydioxanone foil. *Clin Otolaryngol* 2007;32:465-70.
8. James SE, Kelly MH. Cartilage recycling in rhinoplasty: polydioxanone foil as an absorbable biomechanical scaffold. *Plast Reconstr Surg* 2008;122:254-60.
9. Boenisch M, Tamás H, Nolst Trenité GJ. Morphological and histological findings after typical surgical manipulations on growing septal cartilage in rabbits. *Facial Plast Surg* 2007;23:231-7.

Comment on “Breast cancer-related lymphedema: quality of life after lymph node transfer”

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As plastic surgeons, improvements in quality of life are often the goal of our labor. As the vascularized lymph node transfer (VLNT) procedure continues to evolve to become the surgical solution for lymphedema, proving the efficacy not only as a technique, but equally as important, its impact on quality of life is pivotal. De Brucker *et al.*^[1] elegantly demonstrates quality improvements during a 29-month postoperative duration through a validated survey (Upper Limb Lymphedema-27 Questionnaire).

Although I largely agree with the results and the study design, I speculate recall bias may be high. In this study, patients received 2 Upper Limb Lymphedema-27 Questionnaires postoperatively. Though the surveys were identical, one was to be completed based on the patients' pre-operative status (a duration of up to 5 years previously). In addition, 22 patients of the 25 patients underwent simultaneous procedures (DIEP & lymph node transfer), combining the risk, morbidity and ultimately the patient's experience of 2 separate procedures. This may have implications in recall bias because of the resultant limitation when comparing seemingly identical procedures. Though it is certainly reasonable to perform lymph node transfer

simultaneously as part of breast reconstruction, when attempting to study the experiential effect of lymph node transfer *in situ*, it's difficult to delineate.

In my experience, breast reconstruction is an integral component of patients' wellbeing. With the prevalence of breast cancer-related lymphedema up to 49%,^[2] it is critical we seek a surgical solution. As the field of lymph node transfer continues to mature your study is the first to demonstrate an improvement in quality of life via a validated survey and furthermore sets the foundation that VLNT improves wellbeing and functionality in this patient population.

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None.

Conflicts of interest

There are no conflicts of interest.

Patient consent

Not involved.

Ethics approval

Not involved.



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REFERENCES

1. De Brucker B, Zeltzer A, Seidenstuecker K, Hendrickx B, Adriaenssens N, Hamdi M. Breast cancer-related lymphedema: quality of life after lymph node transfer. *Plast Reconstr Surg* 2016;137:1673-80.
2. Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, Intra M, Veronesi P, Robertson C, Maisonneuve P, Renne G, De Cicco C, De Lucia F, Gennari R. A randomized comparison of sentinel node biopsy with routine axillary dissection in breast cancer. *N Engl J Med* 2003;349:546-53.

Proliferation and adipogenic differentiation of human adipose-derived stem cells isolated from middle-aged patients with prominent orbital fat in the lower eyelids

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proliferation rate,
adipogenic differentiation

Aim: To evaluate the age-related effects on the adipogenic differentiation and proliferation potentials of human orbital adipose-derived stem cells (OASCs). **Methods:** Orbital adipose samples were harvested from the central fat compartment in the lower eyelids of 10 young and middle-aged patients during routine blepharoplasty surgery. After assessment of the morphological changes of adipocytes with aging, OASCs were isolated from the fat samples and expanded *in vitro*. Differences in the stem cell colony number (fibroblast colony-forming unit), growth rate and phenotype characterization (flow cytometry analysis) were evaluated. The ability of OASCs to differentiate into adipocytes was determined by oil red O staining and the mRNA expression level of peroxisome proliferator-activated receptor γ . **Results:** Fat cell size showed a decreasing trend with advancing age. Although no difference was found in the expression of cell surface markers, the colony number and proliferative rate of OASCs from middle-aged donors were significantly lower than those from the young donors. The adipogenic differentiation capacity of middle-aged OASCs was also reduced. These differences were statistically significant ($P < 0.001$). **Conclusion:** The data showed that the progenitor cell number, proliferation capacity and adipogenic potential of OASCs decreased with aging, suggesting that using OASCs from elderly patients for therapeutic purposes might be restricted.

INTRODUCTION

Adipose-derived stem cells (ASCs) are a population of postnatal progenitor cells which exist abundantly in adipose tissue. These cells can expand rapidly in

vitro, possess multi-lineage differentiation potential and remain stable over long-term culture.^[1] Compared to the adult stem cells derived from other tissue sources, such as bone marrow, muscle and synovium, advantages of utilizing ASCs include the large



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quantities of fat tissue, minimal patient discomfort, little donor-site morbidity and ease of cell isolation.^[2] Thus, there has been growing interest in applying ASCs as a potential cell source in the field of tissue engineering and regenerative medicine during the past decade.

The human body can be segmented into various depots of fatty tissue based on anatomic region.^[3] These depots vary in the amount of adipose tissue and may produce ASCs with different biological characteristics. The orbital cavity contains a highly specialized adipose depot which differs from the subcutaneous fat (SF) developmentally and functionally.^[4] The existence of human orbital adipose-derived stem cells (OASCs) also has been confirmed, which can differentiate into the corneal epithelial lineage, smooth muscle lineage and neuronal lineage under specific inductive conditions, showing great therapeutic potential in treating orbital and ocular diseases.^[4-7]

The location of orbital fat (OF) may change dramatically from young to old age, especially in the lower eyelids. Normally the OF is located behind the septum and in front of the aponeurosis, occupying most of the orbital cavity. By middle or early old age, it often migrates forward to the preseptal region, resulting in a baggy appearance of the eyes. An interesting question therefore arises from this phenomenon: will aging influence the functional characteristics of OASCs? Identifying this issue is of significance when autologous OASC-based therapies are designed for elderly patients. To date, however, little literature has investigated the relationship between age and the biological properties of OASCs.

In this study, the authors tested whether the proliferative and differentiation potentials of human OASCs are affected by donor age. First, the OF samples were harvested from young (with normal OF) and middle-aged patients (with protruded OF) during routine blepharoplasty. Histological evaluation was performed to observe the morphological changes of fat cells in relation to age. Next, OASCs were isolated from OF samples and expanded *in vitro*. The cell yield, surface marker expression and growth kinetics were assessed. Finally OASCs were cultured under adipogenic condition to compare their differentiation potential into adipocytes.

METHODS

Harvest of orbital fat samples

Adipose tissue samples were surgically harvested during lower lid blepharoplasty from the central compartments of the OF in 20 healthy female patients who had previously given informed consent. Patients

with obesity (body mass index > 25 kg/m²), orbital disease or endocrine disease were excluded from this study. The donors were divided into two age groups: group A (26.33 ± 6.48 years old, *n* = 10) and group B (56.44 ± 5.83 years old, *n* = 10). Patients in group A had no baggy eye appearance while those in group B had dermatochalasis with typical OF protrusion in the lower eyelids. Fat samples were preserved on ice under aseptic condition, transported to the laboratory immediately after surgery, and processed within 6 h.

Evaluation of adipocyte morphology

After weight measurement, four specimens in each group were fixed in 10% formalin overnight, embedded in paraffin, sectioned in 5-μm thickness and processed for routine hematoxylin and eosin (HE) staining. Images were taken in triplicate for each specimen using an optical microscope (IX70, Olympus, Tokyo, Japan). The photographs were processed with the green channel to enhance edge prominence using the Image-Pro Plus software (v6.0, Media Cybernetics, Silver Spring, MD, USA). Three main descriptive parameters were measured for evaluation of adipocyte morphology as follows: cell diameter (length of the longest line joining two points and passing through the centroid), perimeter and area.^[8] Approximately 300 adipocytes were measured for each histological image.

Isolation and expansion of OASCs

OASCs were isolated and expanded using methods previously reported with minor modification.^[4] Briefly, after washing in phosphate buffer solution (PBS, pH 7.4, Sigma, Shanghai, China) extensively, 6 OF samples from each group were minced with sterile scissors and digested with 0.1% type I collagenase solution (Worthington Biochemical Corp, Lakewood, NJ, USA) at 37 °C for 60 min with constant agitation. The upper layer of adipocytes was removed by aspiration and the remaining cells were filtered through a 100-μm and then a 40-μm nylon strainer (BD Bioscience, Franklin Lakes, NJ, USA). Filtered cells were centrifuged for 5 min at 400 *g*, and resuspended in 3 mL of growth medium [GM, containing low-glucose Dulbecco's modified Eagle's medium (LG-DMEM, Gibco, Grand Island, NY, USA) and 10% fetal bovine serum (HyClone, Logan, UT, USA) plus 1% antibiotic/antimycotic]. The viability of cells was assessed using the trypan blue exclusion method and the single-cell suspension was plated onto 35-mm culture dishes (Falcon, B&D Bioscience, San Jose, CA, USA) at a density of 50,000 cells/cm². The medium was replaced 48 h after cell plating to remove the non-adherent red blood cells and changed twice a week thereafter.

Cell colony forming and growth kinetics

The total number of fibroblastic colony-forming units

(CFU-F, a cluster of at least 20 adherent, fibroblast-like cells) was counted on the 7th day in primary culture. Upon reaching approximately 80-90% confluence, the cells were detached with 0.05% trypsin/0.5 mmol/L EDTA (Sigma), seeded into 6-well culture plates (Falcon) at a density of 5,000 cells/cm², and subcultured as first-passaged cells (P1). OASCs were passaged similarly for a total of 9 passages, and the proliferative potential was determined by calculating the cumulative population doublings using the following formula: $[\log_{10}(\text{NH}) - \log_{10}(\text{NI})]/\log_{10}(2)$, where NI is the inoculum cell number and NH is the cell harvest number. Once the cells were unable to reach confluence or a doubling time of over 100 h was obtained in two consecutive passages before achieving the 9th passage, the culture was considered to have failed at that passage.^[9]

Flow cytometry of OASCs

The phenotypic characterization of OASCs was performed using a FACScan cytometer (Coulter Epics Altra, Becton Dickinson, San Jose, CA, USA). Briefly, cells of passage 2 (P2) were trypsinized and resuspended in the flow cytometry buffer (PBS containing 0.1% FBS and 0.02% sodium azide). After blocked with human immunoglobulin, cell aliquots (1×10^5) were incubated with the following fluorescein isothiocyanate (FITC)-conjugated or phycoerythrin (PE)-conjugated monoclonal antibodies: CD14-FITC, CD19-FITC, CD34-FITC, CD45-PE, CD73-PE, CD90-FITC and CD105-FITC. Labeled cells were analyzed by flow cytometry and non-specific IgG stained cells were used as isotype controls (all antibodies from Santa Cruz Biotechnology, Dallas, TX, USA).

Adipogenic differentiation of OASCs

When OASCs of passage 3 from both young and middle-aged groups reached near-confluence, adipogenic differentiation was induced by replacing GM with the adipogenic medium (AM, consisting of GM plus 0.5 mmol/L isobutyl-methylxanthine, 10 mmol/L insulin, and 200 mmol/L indomethacin, all from Sigma). AM was changed twice a week and the intracellular lipid accumulation was assessed by oil red O staining (Sigma) after 14-day differentiation. For quantification measurement, the number of oil red O-positive-staining cells was displayed as the percentage of the total cells counted within the image. Cells cultured in GM for 2 weeks served as controls.

The mRNA level of adipogenesis-related gene, peroxisome proliferator-activated receptor γ (PPAR γ) was quantified by real-time PCR assay. Briefly, after a 2-week adipogenic-induction, total RNA was extracted from OASCs using the RNeasy Mini Kit (Qiagen, Valencia, CA, USA). RNA samples were reverse-

transcribed to cDNA using Oligo dT primers and the final cDNA was subjected to real time PCR (7300 Real-Time PCR System, Applied Biosystems, Foster City, CA, USA). Fold changes in gene expression level were calculated by the $2^{-\Delta\Delta C_t}$ method and the results were normalized to the expression of an internal control, β -actin. The PCR primer sequences were listed as followed, with primer specificity confirmed on the NCBI Primer-BLAST website:

Human PPAR γ F: 5'TCCTCGGAAATGGGACCCTC3',
R: 5'ATCCACGGAGCTGATCCCAA3'.
Human β -actin F: 5'CTGGAACGGTGAAGGTGACA3',
R: 5'AAGGGACTTCCTGTAACAATGCA3'.

Statistical analysis

All data collected were presented as mean \pm standard deviation. One-way analysis of variance and the Student-Newman-Keuls test were used to determine possible significant differences ($P < 0.05$) between groups.

RESULTS

Morphological observation

Grossly observed, the central fat taken from the lower lids in group A had fewer blood vessels and more fibrous tissue than that in group B. The average mass of OF samples was (0.412 ± 0.189) g and (0.451 ± 0.211) g for the young and middle-aged groups, respectively. No significant difference was observed regarding the tissue mass between groups ($P > 0.05$). Histologically, it was found that the septal membranes separating the adipose lobules were denser in the younger group, and that the adipocytes within fatty lobules were of similar sizes and arranged tightly. In the middle-aged group, the fat cells were arranged loosely and were of not uniform size [Figure 1]. Compared to group A, the mean diameter, perimeter and area of OF adipocytes in group B showed significantly decreasing trends ($P > 0.05$, data not shown).

Cell yield and growth kinetics

The yield of viable cells isolated from OF was $(0.75 \pm 0.17) \times 10^6$ cells/g in group A and $(0.68 \pm 0.13) \times 10^6$ cells/g in group B, with no significant difference between the two groups ($P > 0.05$). In Group A, the cell colonies were detected as early as 48 h after primary seeding and these cells proliferated rapidly. In contrast, colonies usually formed after 72 h or more in group B. When the CFU-F numbers were determined on the 7th day in culture, more and bigger colonies were observed in group A than in group B (19.45 ± 2.52 vs. 8.42 ± 1.37 , $P < 0.001$) [Figure 2]. Passaged cells from both groups exhibited similar homogeneous fibroblast-like morphology, but the doubling time in

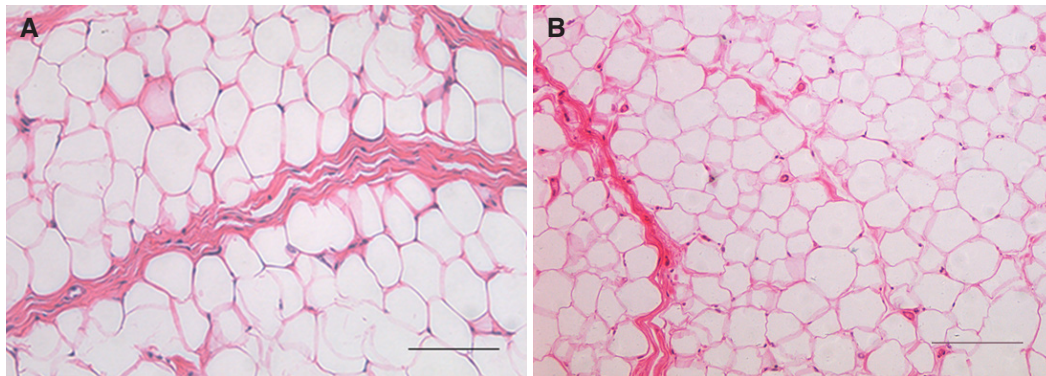


Figure 1: Representative HE staining images of the orbital fat samples from young donors (A) and middle-aged donors (B). The adipocytes were smaller and fibrous structure appeared looser in (B) than those in (A) (scale bar: 100 μ m)

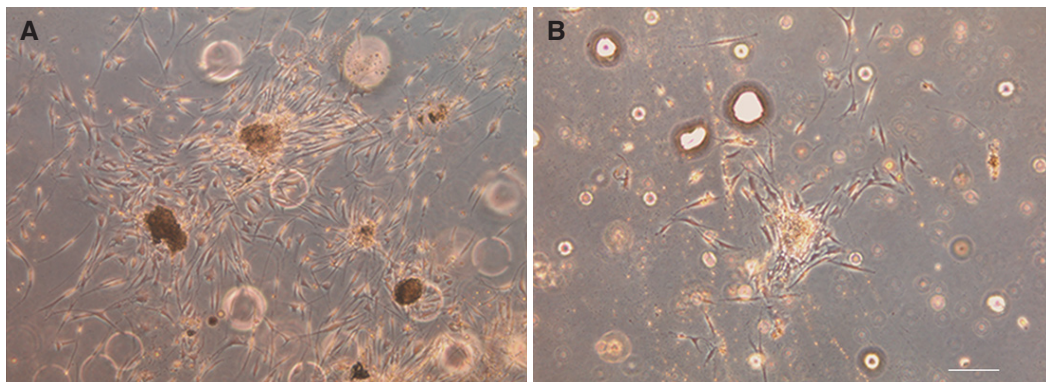


Figure 2: The colony formation of orbital adipose-derived stem cells was determined at day 7 in the primary culture. Compared to middle-aged donors (B), both the colony number and the cell number within each colony were greater in young donors (A) (scale bar: 100 μ m)

group B was significantly longer than that of group A ($P < 0.05$, data not shown). Four of 6 cell lines in group B ceased to proliferate at the 6th passage, and only two reached the 7th passage. In contrast, in group A, 5 cell lines from the 6 donors reached the 9th passage and 1 failed at the 7th passage. Thus the cell population doublings (CPDs) were compared in pairs from P1 to P5. On average OASCs in group A attained 13.41 CPDs. In contrast, only 8.7 doublings were achieved in group B ($P < 0.001$).

Flow cytometry analysis

The cell surface marker expression of OASCs from older and younger donors was compared using flow cytometry analysis. Our results showed that cells in both groups were negative for CD14, CD19, CD34 and CD45, and positive for CD73, CD90 and CD105 (typical markers for adult mesenchymal stem cells, MSCs). No significant difference existed between the two groups ($P > 0.05$).

Adipogenic differentiation potential

Adipogenic differentiation of OASCs was confirmed by oil red O staining after a 14-day induction period. Compared to the non-induced cells, which exhibited

long spindle-like morphology and failed to accumulate any lipid, differentiating OASCs assumed an expanded morphology consistent with adipocytes and contained red staining lipid droplets within the cytoplasm [Figure 3]. Quantitatively, the percentage of oil red O-positive staining cells in group A was obviously higher than that in group B ($P < 0.001$) [Figure 4A]. Consistent with the staining findings, the real-time PCR results revealed a significantly lower expression level of PPAR γ mRNA in the middle-aged group than in the younger group ($P < 0.001$) [Figure 4B].

DISCUSSION

The multi-lineage differentiation capacity of OASCs has shown great therapeutic potential in the fields of ophthalmology and regenerative medicine.^[4-7] Although the literature indicates that aging has less effect on the self-renewal and differentiation potential of ASCs isolated from SF tissue,^[10-12] whether this fact holds true in OASCs derived from elderly humans remains unknown. In this study, the authors make the first report on the age-related effects on the biological properties of human OASCs, demonstrating that the adipogenic differentiation and proliferative capabilities of OASCs decrease with advancing age.

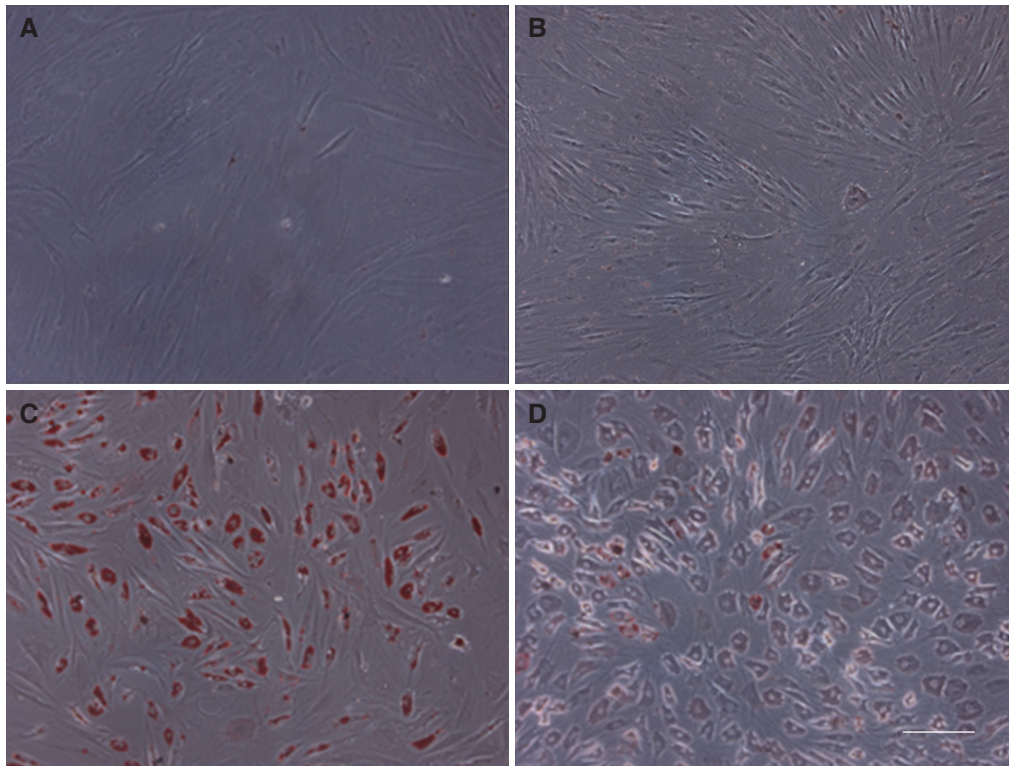


Figure 3: Adipogenic differentiation was assessed by oil red O staining after culturing orbital adipose-derived stem cells in adipogenic media for 14 days. (A, C): young group; (B, D): middle-aged group; (A, B): non-induced; (C, D): induced. More positive staining cells were observed in (A, C) than those in (B, D), and almost no staining was seen in (A, B) (scale bar: 100 μ m)

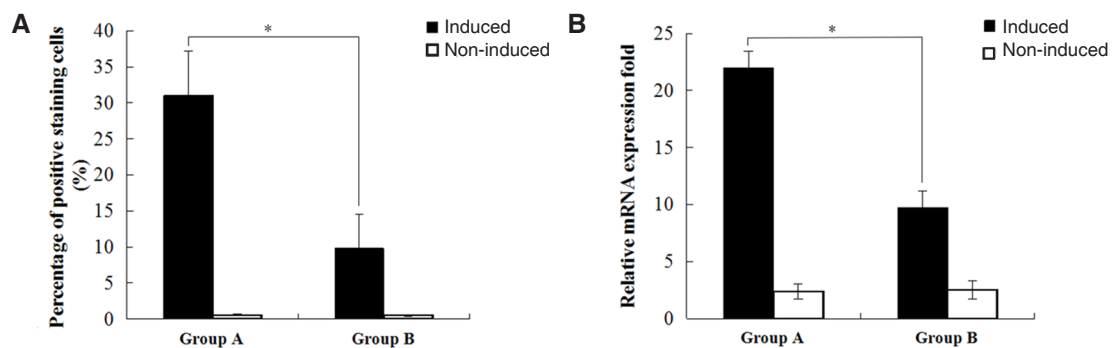


Figure 4: Quantitative analysis confirmed the adipogenic differentiation of orbital adipose-derived stem cells in contrast with the non-induced cells. Compared to the young age group, both the percentage of oil red O staining-positive cells (A) and the expression level of peroxisome proliferator-activated receptor γ mRNA (B) were significantly reduced in the middle-aged group (* $P < 0.001$)

OF is derived from both mesodermal and ectodermal cells.^[13] The central fat pads of both upper and lower lids are mesodermally derived, while the medial fat in the upper and lower eyelids develops from the neural crest cells.^[4,5] Therefore, to achieve consistency between groups, all samples used in this study were taken from the central fat compartments of the lower eyelids.

At the histological level, the fibrous septum surrounding the fat lobules was thin and sparse in the middle-aged group, and the loosely arranged adipocytes appeared smaller than those in the younger age group. Changes

of septal structure correlated with age were predicted, and were attributable to OF herniation, resulting in a baggy-eye appearance. Irregular and decreased fat cell size at middle age may indicate the reduced capacity to accumulate lipid and reserve energy.^[14]

Next, OASCs were isolated and expanded in vitro. The cell phenotype was characterized by flow cytometry, and the effects of age on the number of OASCs', their proliferation, and differentiation were investigated. OASCs from both groups expressed a similar CD marker profile, which was consistent with that reported for ASCs from SF depots. Although the viable cells

freshly isolated from OF were comparable between two groups, the progenitor cell numbers declined in the older group. Because some cell lines ceased to grow at passage 6, the cell growth kinetics were compared from passages 1 to 5. It was found that the proliferation rate of young OASCs was significantly greater than that of the middle-aged cells. Young OASCs could generally achieve more than 12 population doublings while 10 CPDs were the maximum that cells from middle-aged donors could achieve. Moreover, an age-related decrease in the adipogenic-differentiation potential of OASCs was observed. Not only the percentage of oil red O staining-positive cells but also the mRNA expression of PPAR γ , a key transcription factor regulating adipogenic differentiation and maintaining fat cell phenotype, declined with age.

In general, our data showed that aging had a great influence on the proliferation and differentiation potentials of OASCs. The OASCs' number, adipogenic differentiation and proliferative potentials began to decrease at middle or early old age, which may render their use in autologous cell therapy unsuitable in elderly patients. Whether other lineage differentiation capabilities of OASCs are correlated with age remains to be investigated in further studies. On the other side, our previous studies proved that ASCs isolated from SF depots possess low immunogenicity and can maintain their biological functions after cryopreservation.^[15,16] If these properties prove true in OASCs, allogenic or cryopreserved autologous OASCs may serve as alternatives for future clinical applications in elderly patients.

Financial support and sponsorship

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Conflicts of interest

There are no conflicts of interest.

Patient consent

All patients had previously given informed consent.

Ethics approval

The protocol for this study was approved by the Research Ethics Committee of Tongji University School of Medicine (No. 2015-0083) and conformed to the principles outlined in the Declaration of Helsinki.

REFERENCES

- De Francesco F, Ricci G, D'Andrea F, Nicoletti GF, Ferraro GA. Human adipose stem cells: from bench to bedside. *Tissue Eng Part B Rev* 2015;21:572-84.
- Oedayrjasingh-Varma MJ, van Ham SM, Knippenberg M, Helder MN, Klein-Nulend J, Schouten TE, Ritt MJ, van Milligen FJ. Adipose tissue-derived mesenchymal stem cell yield and growth characteristics are affected by the tissue-harvesting procedure. *Cytotherapy* 2006;8:166-77.
- Schipper BM, Marra KG, Zhang W, Donnenberg AD, Rubin JP. Regional anatomic and age effects on cell function of human adipose-derived stem cells. *Ann Plast Surg* 2008;60:538-44.
- Korn BS, Kikkawa DO, Hicok KC. Identification and characterization of adult stem cells from human orbital adipose tissue. *Ophthal Plast Reconstr Surg* 2009;25:27-32.
- Chen SY, Mahabole M, Horesh E, Wester S, Goldberg JL, Tseng SC. Isolation and characterization of mesenchymal progenitor cells from human orbital adipose tissue. *Invest Ophthalmol Vis Sci* 2014;55:4842-52.
- Ho JH, Ma WH, Tseng TC, Chen YF, Chen MH, Lee OK. Isolation and characterization of multi-potent stem cells from human orbital fat tissues. *Tissue Eng Part A* 2011;17:255-66.
- Lin KJ, Loi MX, Lien GS, Cheng CF, Pao HY, Chang YC, Ji AT, Ho JH. Topical administration of orbital fat-derived stem cells promotes corneal tissue regeneration. *Stem Cell Res Ther* 2013;4:72.
- Bujalska IJ, Durrani OM, Abbott J, Onyimba CU, Khosla P, Moosavi AH, Reuser TT, Stewart PM, Tomlinson JW, Walker EA, Rauz S. Characterisation of 11 β -hydroxysteroid dehydrogenase 1 in human orbital adipose tissue: a comparison with subcutaneous and omental fat. *J Endocrinology* 2007;192:279-88.
- Lin TM, Tsai JL, Lin SD, Lai CS, Chang CC. Accelerated growth and prolonged lifespan of adipose tissue-derived human mesenchymal stem cells in a medium using reduced calcium and antioxidants. *Stem Cells Dev* 2005;14:92-102.
- Mendes SC, Tibbe JM, Veenhof M, Bakker K, Both S, Platenburg PP, Oner FC, de Bruijn JD, van Blitterswijk CA. Bone tissue-engineered implants using human bone marrow stromal cells: effect of culture conditions and donor age. *Tissue Eng* 2002;8:911-20.
- Chen HT, Lee MJ, Chen CH, Chuang SC, Chang LF, Ho ML, Hung SH, Fu YC, Wang YH, Wang HI, Wang GJ, Kang L, Chang JK. Proliferation and differentiation potential of human adipose-derived mesenchymal stem cells isolated from elderly patients with osteoporotic fractures. *J Cell Mol Med* 2012;16:582-93.
- Zhu M, Kohan E, Bradley J, Hedrick M, Benhaim P, Zuk P. The effect of age on osteogenic, adipogenic and proliferative potential of female adipose-derived stem cells. *J Tissue Eng Regen Med* 2009;3:290-301.
- Billon N, Monteiro MC, Dani C. Developmental origin of adipocytes: new insights into a pending question. *Biol Cell* 2008;100:563-75.
- Kirkland JL, Dobson DE. Preadipocyte function and aging: links between age-related changes in cell dynamics and altered fat tissue function. *J Am Geriatr Soc* 1997;45:959-67.
- Liu G, Zhou H, Li Y, Li G, Cui L, Liu W, Cao Y. Evaluation of the viability and osteogenic differentiation of cryopreserved human adipose-derived stem cells. *Cryobiology* 2008;57:18-24.
- Liu G, Zhang Y, Liu B, Sun J, Li W, Cui L. Bone regeneration in a canine cranial model using allogeneic adipose derived stem cells and coral scaffold. *Biomaterials* 2013;34:2655-64.

Topical rapamycin for angiofibromas in patients with tuberous sclerosis: how does it work in clinical practice?

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ABSTRACT

Article history:

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Key words:

Tuberous sclerosis,
topical rapamycin,
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clinical practice

Aim: Topical rapamycin for angiofibromas has been reported to be a new promising treatment. This study aims to report the outcome in clinical practice. **Methods:** A retrospective clinical follow-up on twenty-three patients who had been prescribed an oral solution of 0.1% rapamycin, to be applied on facial lesions once a day. **Results:** Seventeen of 23 patients continued the treatment. Papules and nodules were improved in 8 patients (47%) and erythema in 12 (70%). Side effects, such as stinging and redness were reported in 35% of patients. Blood samples were taken from 5 patients and no rapamycin could be detected. All patients who paused the treatment relapsed. **Conclusion:** Topical rapamycin has a positive effect on angiofibromas with improvement in both erythema and papules even if only applied every second to third day, but continuous treatment is needed.

INTRODUCTION

Tuberous sclerosis complex (TSC) is a dominant autosomal disorder that affects multiple organ systems. The prevalence of the disease is estimated to 1 in 6,000 live births.^[1] Spontaneous or inherited mutations in the tumor-suppressor genes TSC1 (9q34) or TSC2 (16p13) are found in 85% result in activation of the mammalian target of rapamycin complex 1 (mTORC1) leading to uncontrolled formation of

hamartomas in the brain, retina, skin, heart, kidneys, and lungs.

These patients should be evaluated by a dermatologist for facial angiofibromas, fibrous cephalic plaques, hypomelanotic macules, ungual fibromas and shagreen patches.^[2]

Facial angiofibroma is found in 80-90% of cases and consist of vascular and fibrotic tissue, leading



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to reddish or skin-coloured papules in the centro-facial area.^[3] Patients with these lesions may suffer negative emotional impact and stigmatization. In addition, the angiofibromas can easily bleed after minor trauma. In 2008, Hofbauer *et al.*^[4] treated a patient with oral rapamycin, an mTOR inhibitor, to suppress graft rejection in one patient with tuberous sclerosis who had received a kidney transplant because of renal angiomyolipomas. They could report a marked improvement of facial angiofibromas.^[4] In 2010, Haemel *et al.*^[5] succeeded in preparing a topical ointment which had effect on facial angiofibromas. In 2011, Mutizwa *et al.*^[6] reported that an oral solution with rapamycin could be used on the skin with good result. Since then, there are several case reports^[7-10] and studies^[11-14] reporting improvement after topical rapamycin applied once or twice daily.^[15-18]

The aim of this retrospective observational study was to describe the outcome in clinical practice treating angiofibromas in TSC with topical rapamycin.

METHODS

Patients and methods

All patients, who had been treated with topical rapamycin between January 2012 through December 2014 at the Dermatology Departments Karolinska University Hospital Stockholm and Örebro University Hospital, were followed up in this retrospective observational evaluation. There were in total 23 patients. Fifteen of the 23 patients had previously been treated with CO₂ laser. Sixteen of 23 patients had tuberous-sclerosis-associated neuropsychiatric disorders (TAND) and 18 had severe epilepsy. All 23 patients had been prescribed an oral solution of 0.1% rapamycin, but told to apply it on all facial lesions once a day. In case of skin irritation the patients had been instructed to refrain from treatment for a couple of days and use a weak topical glucocorticoid cream, and then resume the rapamycin treatment when the skin irritation had subsided. In the beginning of the treatment we instructed the patients/parents to discontinue during the summer, because of uncertainty regarding interaction with sunlight. The summer pause was from mid-June to mid-August 2012. The patients were initially instructed to give blood samples for measurement of serum rapamycin after four weeks of treatment. Treatment photos were taken. Follow-up was done through visits in person or through e-mailed photos, as some patients lived far from the clinics. All evaluations were done by the authors. The authors looked at several photos prior to the evaluation in order to reach consensus about the grading, as there was no standardized grading system at the time for the evaluation. Erythema was

graded as no erythema, slight, medium, or severe erythema. Angiofibromas were described as papules (< 5 mm) or nodules (≥ 5 mm). Both effects on papules, nodules and erythema and side effects were evaluated. The results were compared with the pre-treatment photos and graded on the scale: no improvement, improvement or excellent.

Ethical considerations

This retrospective study is a clinical follow-up of the patients treated with topical rapamycin according to clinical praxis. In Sweden, a formal approval from an Ethics Committee is not needed for a clinical follow-up. This was also discussed with our Ethical Committee. All patients and/or parents got orally and written information about the treatment and potentially side effects and gave their informed consent.

RESULTS

Clinical results

Twenty-three patients (10 males) were included in the retrospective observational evaluation. The mean age was 19 years (range 2-52 years) [Table 1]. The duration of treatment was from 3 weeks to 33 months. Six patients discontinued the treatment. Of these, 2 were lost to follow-up; 2 were put on oral everolimus treatment because of internal hamartomas; and 2 discontinued the treatment after 3 weeks because of intractable side effects, such as skin pain, severe dryness, itching, burning sensations, erythema and swelling [Table 1].

Seventeen patients continued the treatment [Figure 1].

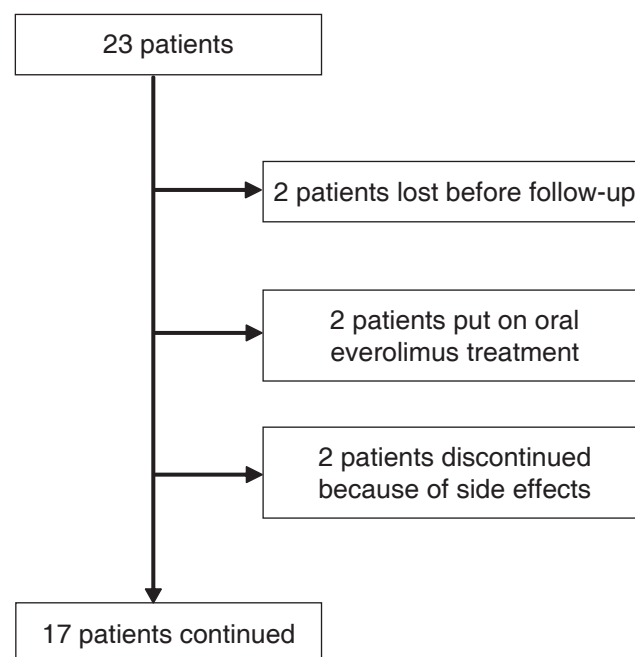


Figure 1: Flow diagram of patient population

Table 1: Patients and results

No.	Gender	Age, year	Skin lesions (pre)	Erythema (pre)	CO ₂ laser (pre)	Duration of treatment	Skin lesions post treatment	Erythema post treatment	Side effects	Sirolimus conc
1	M	15	Papules and nodules	Medium	No	6 months	Not improved	Not improved	None	Not done
2	F	4	Papules	Medium	Yes	14 months	Improved	Excellent	None	Not done
3	M	10	Papules	Slight	No	6 + 3 months*	Improved	Improved	Dryness	Not detected
4	F	2	Papules	Medium	No	7 months	Excellent	Excellent	None	Not done
5	F	13	Papules and nodules	Medium	Yes	10 months	Not improved	Improved	Dryness	Not detected
6	M	12	Papules and nodules	Medium	No	8 + 12 months*	Not improved	Improved	Dryness	Not detected
7	M	30	Papules	Slight	Yes	1.5 + 1 month*	Not improved	Not improved	Dryness	Not done
8	F	43	Papules	Medium	Yes	9 + 16 months*	Excellent	Excellent	None	Not detected
9	F	9	Papules	Medium	No	Drop out	-	-	-	Not done
10	M	2	Fibrous cephalic Plaque	Medium	No	9 + 4 months*	Not improved	Not improved	None	Not detected
11	M	7	Papules	Medium	No	Drop-out	-	-	-	Not done
12	M	19	Papules	Medium	Yes	19 + 7 months*	Improved	Improved	None	Not done
13	F	19	Papules	Medium	Yes	11 + 7 months*	Improved	Improved	None	Not done
14	M	18	Papules	Medium	Yes	5 + 14 months*	Improved	Improved	None	Not done
15	M	21	Papules	Medium	Yes	3 months	Not improved	Not improved	None	Not done
16	F	26	Papules	Medium	No	33 months	Improved	Improved	None	Not done
17	F	29	Papules	Slight	Yes	5 months	†	†	†	Not applicable
18	F	33	Papules	Medium	Yes	3 months	†	†	†	Not applicable
19	F	52	Papules	Slight	Yes	3 weeks	Discontinued		Dryness, itching and swollen	Not done
20	F	9	Papules	Medium	Yes	6 + 5 months*	Improved	Improved	Itching	Not done
21	F	10	Papules	Medium	Yes	5 + 6	Not improved	Improved	Stinging	Not done
22	F	16	Papules	Medium	Yes	3 weeks	Discontinued		Pain, erythema	Not done
23	M	32	Papules	Severe	Yes	1.5 months	Not improved	Excellent	None	Not done

*Paused the treatment during summer months; †Received oral rapamycin for internal hamartomas

All patients except three were evaluated during visits where the skin status was compared with the pre-treatment photos. Three patients lived far away and were evaluated through photos sent by e-mail. Five patients had blood samples taken for rapamycin measurement but none had detectable rapamycin levels.

Papules were improved in 9 patients (53%), of whom 2 had results classed as excellent [Figures 2 and 3]. The median treatment time for the patients who responded (improved or excellent results) was 16 months (7-33 months). The patients who did not respond (not improved results) had a median treatment time of 10 months (1.5-13 months). The 3 patients with both papules and nodules did not improve. The patient with a fibrous cephalic plaque did not respond to treatment. The median age of the patients whose skin lesions were improved was 13 years (2-43 years). The median age of the patients whose skin lesions were not improved was 14 years (2-32 years).

The erythema was improved in 12 of 17 patients (70%) [Figure 4], of whom 4 had excellent results [Table 1]. The median age of the patients whose erythema responded (improved and excellent) was 12.5 years (2-43 years) and median treatment time was 12.5 months (1.5-33 months). The median age for the patients whose erythema did not respond was 18 years (2-30 years) and median treatment time was 4.5 months (2.5-13 months). During the summer pause, lesions and erythema recurred.

Initially, rapamycin was prescribed on a daily basis. Six of 17 patients (35%) had mild side effects, such as dryness, itching and stinging, but could continue the treatment when using the solution every second to third day. In practice, the treatment was performed every second to third day. The reasons for this were both side effects and compliance problems. Eleven of these 17 patients had CO₂ laser treatment 3-5 months [Figures 3, 5, 6 and 7] before rapamycin treatment.

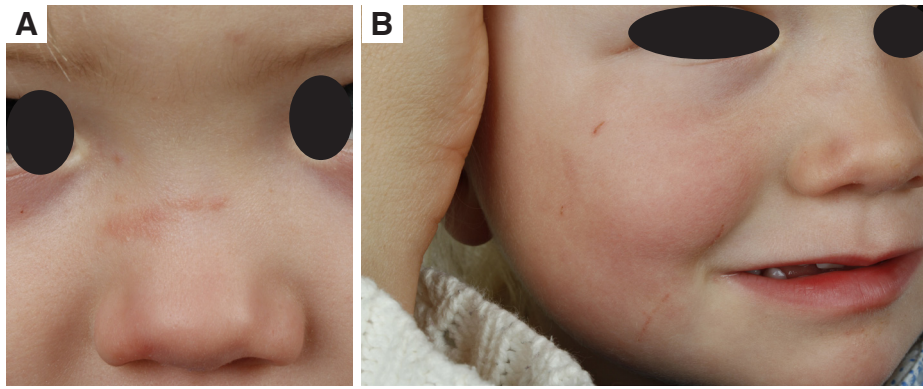


Figure 2: Patient 4. (A) before treatment; (B) after 7 months



Figure 3: Patient 8. (A) 3 months after CO₂ laser and before rapamycin; (B) 3 months after CO₂ laser and before rapamycin close-up; (C) after 6 weeks on rapamycin; (D) after 9 months with topical rapamycin; (E) after 9 months on topical rapamycin close-up; (F) after 2 years

We could not see any difference in improvement in patients who had received CO₂ laser treatment compared with patients who had not.

DISCUSSION

This is a retrospective observational study reflecting our experience in clinical practice using topical rapamycin. The solution was not applied daily because of side effects but also because of compliance problems, but we still had good clinical effect. This

is important knowledge for clinicians, parents and patients. We used an oral solution with rapamycin because it was impossible at that time to get an *ex tempore* ointment prepared in a Swedish pharmacy. We had an overall improvement of 70% which is a lower figure than what has been reported in the literature, where the majority reported improvement, which might be because of less application in our group of patients.^[5,7,11,12,14,18] The patients, with lowest response in our clinical setting, were the patients with papules and nodules. Park *et al.*^[15] found that papules

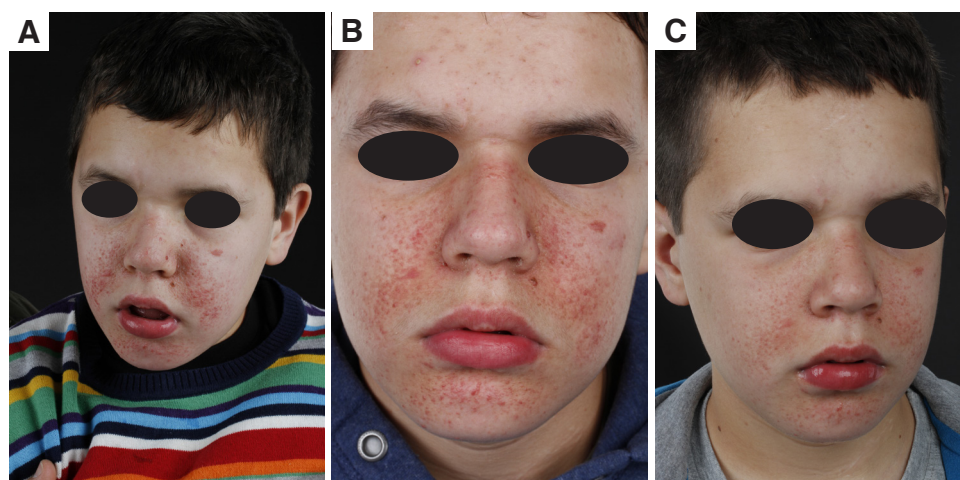


Figure 4: Patient 6. (A) before treatment; (B) after pause with rapamycin; (C) after 5 months



Figure 5: Patient 12. (A) before CO₂ laser and rapamycin; (B) before CO₂ laser and rapamycin close-up on the nose; (C) a couple of days after CO₂ laser; (D) 3 months after CO₂ laser and before rapamycin; (E) 3 months after CO₂ laser close-up; (F) 3 months after CO₂ laser close-up on the nose; (G) after CO₂ laser and 9 months on rapamycin; (H) after CO₂ laser and 9 months on rapamycin close-up nose

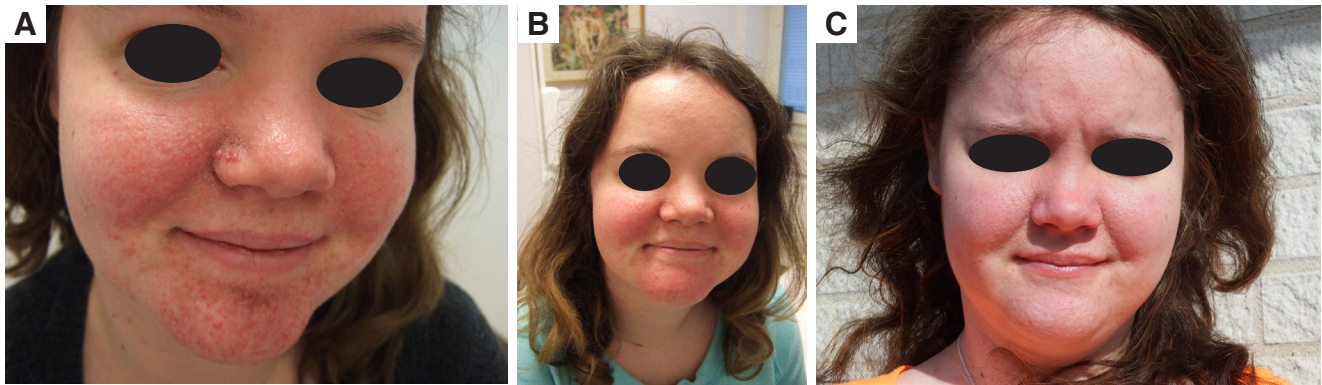


Figure 6: Patient 13. (A) before CO₂ laser and rapamycin; (B) after CO₂ laser and before rapamycin; (C) after CO₂ laser and rapamycin

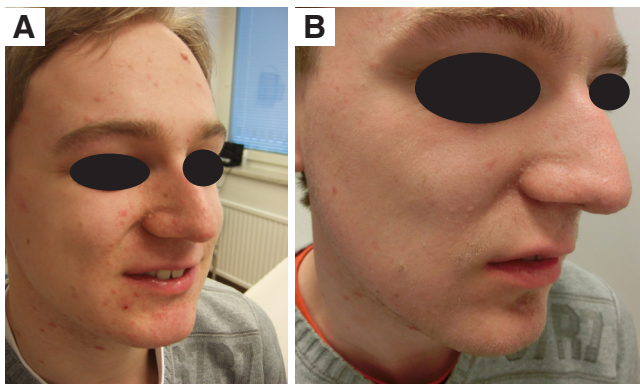


Figure 7: Patient 14. (A) after the last session of CO₂ laser and before rapamycin; (B) after CO₂ laser and rapamycin

larger than 4 mm did not respond to topical rapamycin. In our observation, all patients who paused treatment during summer relapsed, which shows that mTOR inhibition needs to be continuous. There were also tendencies for younger patients to respond better, which reflect the importance of early treatment. This is in accordance with a study by Tanaka *et al.*^[14] who also reported greater effects in patients younger than ten years. Five studies reported mild side effects, such as stinging and skin irritation.^[6,12,14,16,18] In our study, 8 of 23 patients had side effects, and 2 discontinued treatment because of pain and swelling. Six of the patients who got side effects could continue the treatment with no side effects if they used the solution every second to third day. We used an oral solution not designed for topical treatment, as has been reported in a previous study.^[6] This solution contains ethanol and propylenglycol, which might explain some of the side effects. On the other hand, the solution is without oily element and is therefore more suited for teenagers who besides angiofibromas could have facial acne. The *ex tempore* ointment that has been available lately contains petrolatum but could be a good alternative for toddlers. We could not detect rapamycin in the blood of our first 5 patients. This is in accordance to other studies in the field.^[5,6,8,10-13,17,19] So

one could conclude that blood test is not needed in patients treated with topical rapamycin.

There was a tendency that longer treatment with topical rapamycin gave better effect. However, nodules responded less to topical treatment and cephalic plaque did not respond at all.

We were initially uncertain of the interaction between rapamycin and ultraviolet radiation, so the patients were in the beginning instructed to avoid sun-light. Claims of such interactions have however been refuted, as subsequent randomized controlled studies have shown a reduced risk of malignancies and non-melanoma skin cancer in transplant recipients receiving oral rapamycin.^[20]

This is a retrospective observational study. There was no set schedule for the visits, as some of the patients lived far from the clinics and had other severe medical problems. Many of our patients had the diagnosis of TAND and could not participate in a standardized examination, however it was possible to get photos of all the patients.

Follow-up was done mainly through visits in person, but in 3 cases through the use of photos. The grading of treatment outcome did not employ the Facial Angiofibroma Severity Index. That scale has just recently been validated and published.^[21] So we graded the skin lesions in papules, nodules and erythema and discussed the photos with each other in order to reach consensus about our grading system. We used an oral rapamycin solution, which might have given more side effects. Patients who had not received CO₂ laser treatment did respond as good as patients who had not received CO₂ laser treatment. One explanation to that is probably that patients with papules bigger than 4 mm, that is known to respond less to topical rapamycin, had received CO₂ laser on these papules.^[15]

In conclusion, topical rapamycin is a valuable tool in the treatment of angiofibromas even when treatment was performed every second to third day. Erythema and papules seem to respond in most cases, but nodules respond less well to topical rapamycin. The treatment must be continuous. Rapamycin was not detected in the blood in our patients, which is in line with other studies. Topical Rapamycin could also be a valuable complement after CO₂ laser in order to maintain the improvement after the laser surgery.

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None.

Conflicts of interest

There are no conflicts of interest.

Patient consent

All patients and/or parents gave their informed consent.

Ethics approval

This kind of clinical follow-up doesn't need formal ethics approval in Sweden.

REFERENCES

- Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. *Ann N Y Acad Sci* 1991;615:125-7.
- Krueger DA, Northrup H. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol* 2013;49:255-65.
- Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. *Lancet* 2008;372:657-68.
- Hofbauer GF, Marcollo-Pini A, Corsenca A, Kistler AD, French LE, Wüthrich RP, Serra AL. The mTOR inhibitor rapamycin significantly improves facial angiofibroma lesions in a patient with tuberous sclerosis. *Br J Dermatol* 2008;159:473-5.
- Haemel AK, O'Brian AL, Teng JM. Topical rapamycin: a novel approach to facial angiofibromas in tuberous sclerosis. *Arch Dermatol* 2010;146:715-8.
- Mutizwa MM, Berk DR, Anadkat MJ. Treatment of facial angiofibromas with topical application of oral rapamycin solution (1mg/mL(-1)) in two patients with tuberous sclerosis. *Br J Dermatol* 2011;165:922-3.
- DeKlotz CM, Ogram AE, Singh S, Dronavalli S, MacGregor JL. Dramatic improvement of facial angiofibromas in tuberous sclerosis with topical rapamycin: optimizing a treatment protocol. *Arch Dermatol* 2011;147:1116-7.
- Truchuelo T, Diaz-Ley B, Rios L, Alcantara J, Jaen P. Facial angiofibromas treated with topical rapamycin: an excellent choice with fast response. *Dermatol Online J* 2012;18:15.
- Kaufman McNamara E, Curtis AR, Fleischer AB Jr. Successful treatment of angiofibromata of tuberous sclerosis complex with rapamycin. *J Dermatolog Treat* 2012;23:46-8.
- Knopfel N, Martin-Santiago A, Bauza A, Hervas JA. Topical 0.2% rapamycin to treat facial angiofibromas and hypomelanotic macules in tuberous sclerosis. *Actas Dermosifiliogr* 2014;105:802-3.
- Wataya-Kaneda M, Tanaka M, Nakamura A, Matsumoto S, Katayama I. A topical combination of rapamycin and tacrolimus for the treatment of angiofibroma due to tuberous sclerosis complex (TSC): a pilot study of nine Japanese patients with TSC of different disease severity. *Br J Dermatol* 2011;165:912-6.
- Foster RS, Bint LJ, Halbert AR. Topical 0.1% rapamycin for angiofibromas in paediatric patients with tuberous sclerosis: a pilot study of four patients. *Australas J Dermatol* 2012;53:52-6.
- Salido R, Garnacho-Saucedo G, Cuevas-Asencio I, Ruano J, Galán-Gutierrez M, Vélez A, Moreno-Giménez JC. Sustained clinical effectiveness and favorable safety profile of topical sirolimus for tuberous sclerosis - associated facial angiofibroma. *J Eur Acad Dermatol Venereol* 2012;26:1315-8.
- Tanaka M, Wataya-Kaneda M, Nakamura A, Matsumoto S, Katayama I. First left-right comparative study of topical rapamycin vs. vehicle for facial angiofibromas in patients with tuberous sclerosis complex. *Br J Dermatol* 2013;169:1314-8.
- Park J, Yun SK, Cho YS, Song KH, Kim HU. Treatment of angiofibromas in tuberous sclerosis complex: the effect of topical rapamycin and concomitant laser therapy. *Dermatology* 2014;228:37-41.
- Tu J, Foster RS, Bint LJ, Halbert AR. Topical rapamycin for angiofibromas in paediatric patients with tuberous sclerosis: follow up of a pilot study and promising future directions. *Australas J Dermatol* 2014;55:63-9.
- Koenig MK, Hebert AA, Roberson J, Samuels J, Slopis J, Woerner A, Northrup H. Topical rapamycin therapy to alleviate the cutaneous manifestations of tuberous sclerosis complex: a double-blind, randomized, controlled trial to evaluate the safety and efficacy of topically applied rapamycin. *Drug R D* 2012;12:121-6.
- Vasani RJ. Facial angiofibromas of tuberous sclerosis treated with topical sirolimus in an Indian patient. *Indian J Dermatol* 2015;60:165-9.
- Pynn EV, Collins J, Hunasehally PR, Hughes J. Successful topical rapamycin treatment for facial angiofibromata in two children. *Pediatr Dermatol* 2015;32:e120-3.
- Knoll GA, Kokolo MB, Mallick R, Beck A, Buenaventura CD, Ducharme R, Barsoum R, Bernasconi C, Blydt-Hansen TD, Ekberg H, Felipe CR, Firth J, Gallon L, Gelens M, Glotz D, Gossman J, Guba M, Morsy AA, Salgo R, Scheuermann EH, Tedesco-Silva H, Vitko S, Watson C, Fergusson DA. Effect of sirolimus on malignancy and survival after kidney transplantation: systematic review and meta-analysis of individual patient data. *BMJ* 2014;349:g6679.
- Salido-Vallejo R, Ruano J, Garnacho-Saucedo G, Godoy-Gijón E, Llorca D, Gómez-Fernández C, Moreno-Giménez JC. Facial Angiofibroma Severity Index (FASI): reliability assessment of a new tool developed to measure severity and responsiveness to therapy in tuberous sclerosis-associated facial angiofibroma. *Clin Exp Dermatol* 2014;39:888-93.

Case Report

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Morel-Lavallee lesion - radiological spectrum

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ABSTRACT

Morel-Lavallee lesion (MLL) entity represents as a haemolymph mass as a result of closed degloving injury following focal trauma. The swelling can be mistaken as a tumor or simple hematoma formation, and it can be of concern as it gradually increases in size. It is important to diagnose the entity promptly as proper management can avoid skin necrosis and further complications. We present a 20-year-old female nursing student who fell down from a scooter and developed painful massive right thigh swelling over a 3-week course following trauma. She underwent plain radiography which was unremarkable. Ultrasound and magnetic resonance imaging revealed the diagnosis of MLL and she was treated accordingly.

INTRODUCTION

Morel-Lavallee lesion (MLL) occurs when there is a collection of haemolymph due to the separation of skin and subcutaneous tissue from the underlying fascia. This usually happens after blunt trauma and patients present with progressive swelling and pain. The potential space formed by this separation of tissues is occupied by the oozing serous fluids like blood and lymph. This collection sometimes becomes encapsulated and does not resolve. Victor-Auguste-Francois Morel-Lavallée,^[1] a French surgeon described this entity first time in 1848.

CASE REPORT

A 20-year-old female reported to the orthopedic surgery department three weeks after falling from her scooter, with slightly painful swelling over the lateral aspect of the right thigh. The painful swelling increased progressively from small to massive size. On examination the site of the swelling was on the lateral aspect of the upper half of the right thigh. The swelling was soft and fluctuating, measuring approximately 15 cm × 12 cm dimensions. Mild skin discoloration was present without open wounds [Figure 1].



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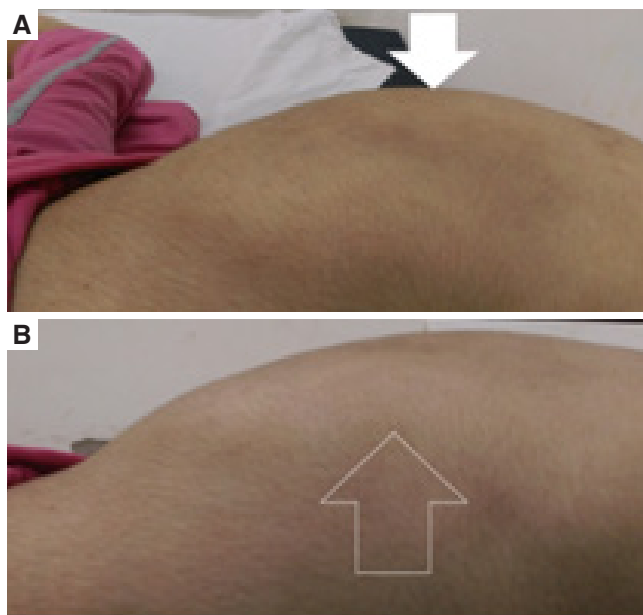


Figure 1: Photograph of the right leg with focal swelling. (A) fronto-lateral position of the thigh shows swelling on upper lateral part with slight discoloration (white solid arrow); (B) magnified view of the same swelling shows normal overlying skin surface (hollow white arrow)

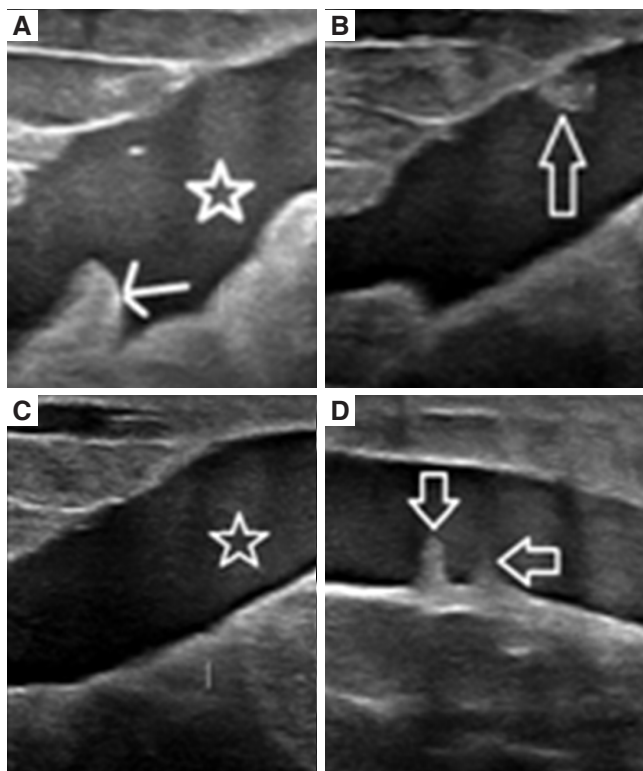


Figure 2: Greyscale images of the swelling with high frequency linear probe. (A) anechoic fluid in encapsulated space (white star) with echogenic fat lobule hanging against the margin (white arrow); (B) another similar image with fat lobule on the anterior aspect (upward arrow); (C) anechoic pure fluid in the space (white star); (D) two echogenic fat lobules (white arrows) hanging in the fluid

Plain X-ray of the right thigh and upper hip did not show any bony injury. Ultrasound (US) examination

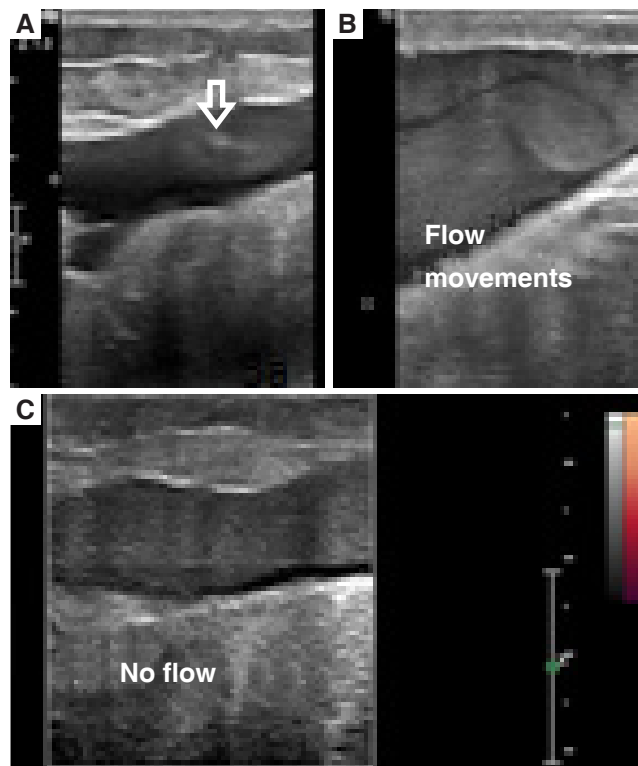


Figure 3: Ultrasound images showing the movement of the fluid. (A) few uniform soft echoes within the fluid (white arrow) because of haemolymph; (B) flow moments in the fluid because of different density of blood and lymph; (C) no color flow seen in and around the cystic fluid in color flow imaging

was done with the high frequency linear probe for this swelling and showed predominantly anechoic collection seen under the skin soft tissue extending up to deep fascia without traversing it. A few echogenic foci were present within and at the periphery of the collection [Figure 2].

The movement of the fluid was seen while scanning after changing the position of the affected limb. There was no vascularity seen within the collection or from the edges of the swelling [Figure 3].

She underwent magnetic resonance imaging (MRI) and revealed the fluid collection underneath the skin but not extending into the deep fascia. The collection was hypointense on T1W and hyperintense on T2W sequences. T1W with fat suppression sequences showed suppression of the fatty lobules seen from the margins and inside the collection [Figure 4].

There was evidence of “fluid-fluid” levels seen within the swelling [Figure 5].

The patient was treated initially managed conservatively with no relief, and subsequently underwent surgical drainage with an uneventful recovery. The patient will

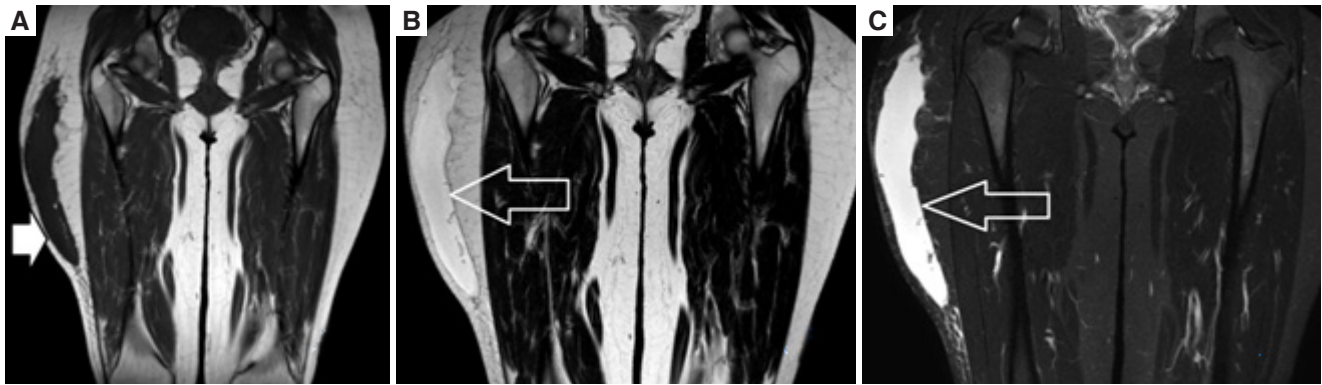


Figure 4: Magnetic resonance images. (A) T1W image shows hypointense collection under the skin but overlying the fascia (white arrow); (B) T2W image shows the collection as hyperintense with well defined margins (hollow white arrow); (C) STIR images reveal the collection as hyperintense with suppression of surrounding fat (hollow white arrow)

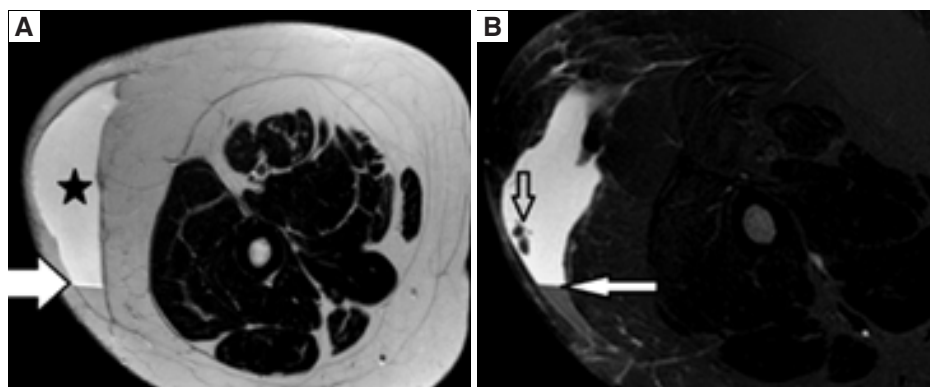


Figure 5: Magnetic resonance axial sections. (A) T2W image shows the “fluid-fluid level” (white solid arrow) within the collection (black star); (B) T2W fat suppressed image also shows the fat suppression of the fat lobule in the lumen (hollow black arrow). There is also the fluid-fluid level seen in the background of hyper intensity of the fluid and hypointensity of the old blood (white solid arrow)

be called for follow up to rule out any reaccumulation of the fluid.

DISCUSSION

MLL is a common condition and has got other names like post-traumatic soft tissue cyst or pseudolipoma. Post traumatic swelling of soft tissues is not uncommon and this can be misleading when degloving injury is present. The underlying mechanism is very simple as the small vessels and lymphatics are torn due to disruption of the skin layer from the underlying fascia by the direct and tangential forces. The fluid accumulates in this potential space and presents as swelling on the affected region.^[2] The most common place is on the lateral aspect of the greater trochanter but can happen anywhere on the thigh. These swellings can either subside because of absorption of fluid or become encapsulated. These can also become infected and there is a potential for overlying skin necrosis.^[3] The collected fluid is usually serosanguinous in nature. The septation and fat globules can also be seen in some swellings as it was in our case. These lesions may be associated with fractures, and

may form a capsule with unchanged size. Swellings of longer duration can be mistaken for soft tissue tumors and therefore have to be differentiated from sarcoma, haemangioma and fat necrosis. US imaging is characteristic of MLL as anechoic lesions with or without fat globules within it.^[4] Color flow imaging does not show any vascularity or feeding vessels. Non-contrast computed tomography of the thigh shows fluid-fluid level because of the different density of the blood and other fluid. MRI is the modality of choice for delineation of the lesions. This can differentiate the fluid contents and underlying fascia. The fat globules seen in the lesion can easily be confirmed by fat suppression sequences.^[5,6] The differential diagnosis of these lesions is haemangioma, fat necrosis, sarcoma or simple subcutaneous hematoma formation. The management is dependent on the size, location and the duration of the lesion.^[7] Conservative management is advocated for smaller lesions without presence of septations and infection.^[8] Lesions with capsule and septations require surgical drainage. Post surgical graduated compression by stocking prevent the reaccumulation of the collection by agglutinating the skin to underlying fascia.^[9]

In conclusion, the diagnosis of MLL is of great importance as the management depends upon the nature and size of collection. Radiological assessment like US and MRI play a major role in the diagnosis and treatment of the lesion. As recurrence is very common, graduated compression stocking should be worn until follow-up. Careful management will avoid skin necrosis and other associated complications.

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Conflicts of interest

There are no conflicts of interest.

Patient consent

The proper consent of the patient was taken for carrying out all the tests and management.

Ethics approval

The approval for publishing this case had been taken

from the institute board of SGT Medical College.

REFERENCES

1. Morel-Lavallee VAF. Decollements traumatiques de la peau et des couches sous-jacentes. *Arch Gen Med* 1863;1:20-38,172-200,300-332. (in French)
2. Parra JA, Fernandez MA, Encinas B, Rico M. Morel-Lavallée effusions in the thigh. *Skeletal Radiol* 1997;26:239-41.
3. Li H, Zhang F, Lei G. Morel-Lavallee lesion. *Chin Med J (Engl)* 2014;127:1351-6.
4. Goodman BS, Smith MT, Mallempati S, Nuthakki P. A comparison of ultrasound and magnetic resonance imaging findings of a Morel-Lavallee lesion of the knee. *PM R* 2013;5:70-3.
5. Mallado JM, Bencardino JT. Morel-Lavallée lesion: review with emphasis on MR imaging. *Magn Reson Imaging Clin N Am* 2005;13:775-82.
6. Gilbert BC, Bui-Mansfield LT, Dejong S. MRI of a Morel-Lavallée lesion. *AJR Am J Roentgenol* 2004;182:1347-8.
7. Hak DJ, Olson SA, Matta JM. Diagnosis and management of closed internal degloving injuries associated with pelvic and acetabular fractures: the Morel-Lavallée lesion. *J Trauma* 1997;42:1046-51.
8. Hudson DA, Knottenbelt JD, Krige JE. Closed degloving injuries: results following conservative surgery. *Plast Reconstr Surg* 1992;89:853-5.
9. Harma A, Inan M, Ertem K. The Morel-Lavallée lesion: a conservative approach to closed degloving injuries. *Acta Orthop Traumatol Turc* 2004;38:270-3.

The temporal endoscopic midface lift - centropfacial rejuvenation without facial scars

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ABSTRACT

Aim: The author describes a new endoscopic midface lifting technique using solely temporal access and evaluates its advantages and perspectives. **Methods:** This is a single-surgeon case study. Through a short temporal incision, dissection is performed along a single plane connecting the superficial surfaces of both the facial and temporal superficial musculoaponeurotic system (SMAS) layers. Subsequent midface dissection divides the malar fat pad into the deeper and superficial parts. A new concept of a combination high malar SMAS lift and internal skin flap anchorage that provides long-term stability is described. **Results:** The temporal endoscopic midface (TEM) lift technique resulted in good objective results with high patient satisfaction. The temporal access allowed proper vertical vector correction of the sagging centro-facial structures. The resulting scar was inconspicuous and hidden in the hair bearing skin, and its length was measured between 5-6 cm. A conversion to the conventional long facial scar approach was completely avoided. **Conclusion:** The TEM lift is a new and effective procedure for facial rejuvenation, especially the midface and cheek. The results illustrate the importance of internal anchorage of both the midface SMAS and skin flap. These are the keys to long-lasting and pleasing results. The procedure is best suited for younger men and women with little or no neck skin laxity.

INTRODUCTION

The midface is of central importance in facial aging as this is the first site where its signs manifest themselves. These signs comprise volume loss, deflation, malar prominence flattening, baggy eyes and development of nasolabial and nasojugal folds due to ptosis and laxity. The midface lift reverses the ptosis by reposition of the sagging tissues and has even been dubbed the the facelift of the 21st century

by Botti and Ceravolo^[1] due to its effectiveness. The midface lift has been performed using the trans-blepharoplasty,^[1,2] trans-oral,^[3] trans-temporal^[4-8] or brow-lift^[9] approach. The trans-blepharoplasty approach has all the associated disadvantages of lower lid surgery including a canthopexy requirement and risks of asymmetry, scleral show, lagophthalmus and ectropion development. With the trans-temporal subperiosteal midface lift, dissection is extensive, technically demanding, has greater risks and a



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longer recovery. The dissection plane has to be developed under the superficial temporal fascia and then transitioned to the subperiosteal plane over the zygoma. The surfaces of the zygoma and malar bone then need to be connected through subperiosteal dissection. Subsequent anchorage of the malar tissues are achieved only by suspension of the malar fat pad,^[8] and its longevity is questionable. Other alternative procedures such as the minimal access cranial suspension (MACS) lift with a third suture^[10] cause a visible facial scar of 14-16 cm in length.

METHODS

The temporal endoscopic midface (TEM) lift is a new minimal-access facelift that uses exclusively temporal access incisions thereby sparing any scars on the face itself. This utilizes endoscopic dissection and a suturing technique that was developed by the author.^[11] An incision measuring 5-6 cm is made and hidden in the hair-bearing part of the temple. Common pitfalls such as damaging the hair roots or making the flap excessively thin must be avoided at this stage. The dissection plane is developed over the superficial surface of the common facial and temporal superficial musculoaponeurotic system (SMAS). It is important to completely avoid violating the integrity of the SMAS by either inadvertent incisions or diathermy.

An alternative initial approach through the same incision is a dual plane dissection [Figure 1]. In this approach, the plane between the superficial and deep layers of the temporal fascia is first developed and dissected towards the non-hair bearing skin of the face. When or before the junction of the hairline is reached, an incision is made on the deep surface of the

superficial layer of the temporal fascia. The dissecting plane is then transitioned onto the superficial surface of the superficial layer of the temporal fascia.

The subsequent surgical steps are common to both approaches. As dissection proceeds over the zygoma, the temporal branch of the facial nerve remains protected, it is deep to the superficial layer of the temporal fascia. Both the mid-facial (malar) SMAS and the lateral facial SMAS can be easily reached this way.

Pertinent anatomy

The temporal and facial portions of the SMAS fuse over the malar bone. The facial SMAS continues in the temple as the superficial temporal fascia^[1] and the frontal branch of the facial nerve lies deep to it. Limiting dissection to the plane above this fascia without violating it will ensure avoidance of nerve injury.^[1] The facial SMAS continues in the midface as the malar SMAS and is incorporated by the thick malar fat pad.

The anatomy of the facial fat compartments and that of the malar fat pad was best described by Botti and Ceravolo^[1] through cadaveric studies. The malar fat pad was found to be divided into two parts, a superficial part and a deeper part.

The author's clinical experience is consistent with these findings. The midface can be well visualised through a medial extended facelift [Figure 2] and the parts of the malar fat pad can be easily distinguished. The superficial part originates from the skin and can be conceptualised as a condensation of the malar thickening of skin fat with the strong Camper's fascia. Under this, the deep part of the malar fat pad is found

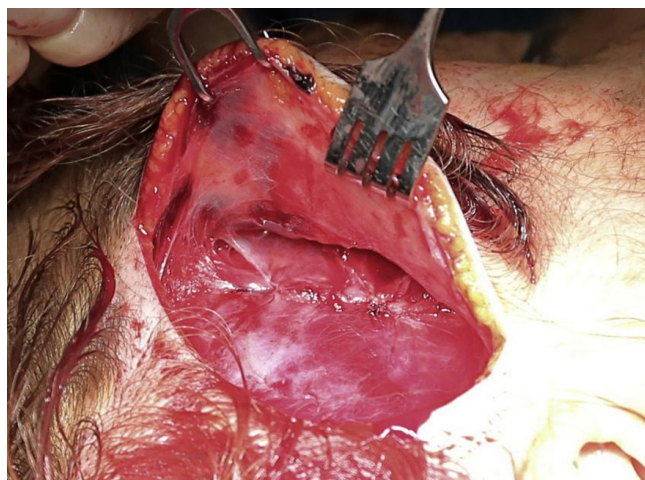


Figure 1: Dual plane temporal dissection. The superficial plane above the superficial fascia is exposed after dissecting the deep plane first. The superficial fascia is fixed by sutures onto the deeper one in order to facilitate the dissection

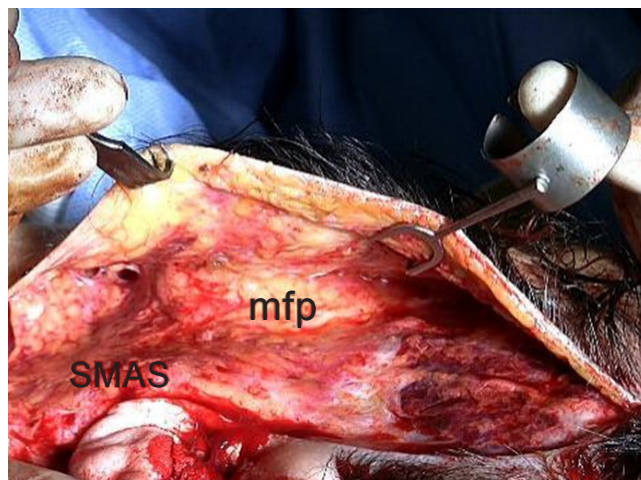


Figure 2: Demonstration of the midface with the malar fat pad (malar SMAS) during an extended temporal-cervical-facial open facelift. SMAS: superficial musculoaponeurotic system; mfp: malar fat pad

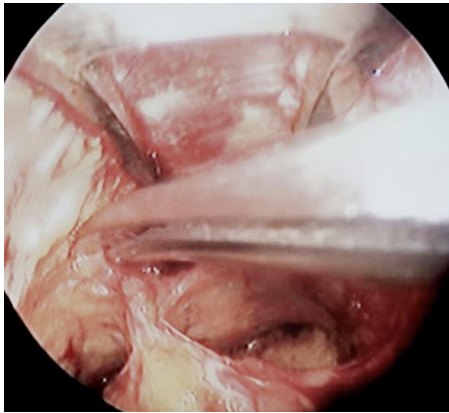


Figure 3: Mobilising of the midface by endoscopic dissection of the retaining ligaments

enmeshed and reinforced by the fibres of the SMAS. Both the superficial and deep parts of the fat pad hold sutures well as the intertwined Camper's fascia and SMAS fibres respectively, lend them strength. This unique anatomical construct of the reinforced malar fat pad serves as an effective pole for which lifting and anchoring threads can be secured to with effectiveness and longevity.

The key elements of the method are the endoscopic dissection in the superficial plane, the high malar SMAS anchor, the direct internal flap anchor and the author's suture technique in the tunnel and keyhole access.

Endoscopic dissection

Once the plane of dissection has progressed beyond the zygoma, a rigid 4 mm diameter operative endoscope with a 30-degree angle is used to visualise this area for dissection. The endoscopic dissector is introduced over the endoscope through the temporal incision. A distal spoon-shaped shield is also used to maintain proper visualization of the optical cavity.

A hollow space is created using the endoscopic dissector to progressively elevate the skin. The internal facial structures are visible throughout the dissection. The endpoint for a good working cavity is reached after release of the fasciocutaneous ligaments, especially the zygomatic and the parotido-masseteric ligaments. Attention must be paid to avoid incorrectly identifying ligaments that are branches of the facial nerves [Figure 3].

SMAS excision is not mandatory as good results can already be achieved in conventional facelifts without it. The most challenging element of the procedure is maintaining dissection in the correct plane. Adherence to this avoids any damage to the facial nerve.

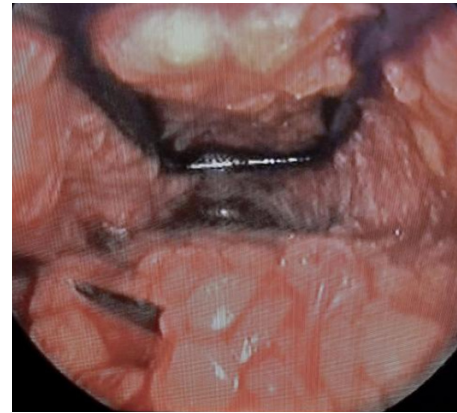


Figure 4: Superficial musculoaponeurosis system suture and imbrication under endoscopic control with the authors' technique

The results are achieved primarily through the correct repositioning of the midface, the appropriate redraping and vector rotation and anchorage of skin flap, all of which are then well supported by SMAS imbrication.

Usage of an endoscope is mandatory. The author advocates video recording of the procedure potentially for accurate documentation in case review is necessary in future. Precise haemostasis is better with endoscopic visualization.

The SMAS must be imbricated to provide stability similar to that of an open procedure [Figure 4]. This is challenging due to the long distance between the incision and imbrication sites. Furthermore, the poor ergonomics of the instrumentation requiring a key-hole like grip makes suturing more difficult.

High malar SMAS anchorage

The author advocates that the malar fat pad be viewed not as a fat pad, which implies a flimsy structure, but instead as malar SMAS that has implies a stronger structure. The justification for this nomenclature change is due to the reinforced and sturdy nature of both parts of this fat pad described above. Furthermore, usage of the new term this way is key to understanding the role of the malar SMAS for midface repositioning, special threads, special needles and anchoring points. The malar SMAS can be directly repositioned and anchored high on the zygomatic bone, approximately 2 cm below the horizontal level of the corner of the eye in the middle third of the zygomatic bone to effect the midface lift. This is what the author terms high malar SMAS anchorage and is the cornerstone-working step of the TEM.

The author uses permanent sutures for this purpose and specifically obtains informed patient consent for this purpose. Braided, non-resorbable silicone-coated



Figure 5: Endoscopic suture technique of the author

polyester threads (Astralén-R Assut Europe, Italy) are used with good results and no reactions. The thread strength for the malar SMAS should be at least USP 0-0 or USP 1-0 to avoid soft tissue cut-through after anchoring or imbrication. The anchoring suture is placed into the stable fascia or periosteum of the zygomatic bone at the high level described above. In selected cases, additional subperiosteal mobilization of the midface through the trans-oral approach is an option to achieve tension-free midface repositioning and anchorage.

The author's method of midface fixation

It is difficult to work with thick sutures and large needles of 24 mm or 36 mm length through an endoscopic tunnel. The author devised a solution to this with a technique as follows: The first stitch is placed through the skin, from the outside into the inside of the endoscopic cavity [Figure 5]. This stitch also catches the SMAS under endoscopic visualization and control. The suturing continues within the endoscopic cavity, the patency of which is maintained with the endoscopic dissector. The suture thread is then completely pulled into the endoscopic cavity and knotted instrumentally.

Direct internal flap anchorage

The redraping and stable attachment of the skin flap onto the temple is very important for lift stability and longevity. It is insufficient to rely on SMAS imbrications and the high malar SMAS lift for this. Internal flap fixation is a necessary adjunct to impart this stable attachment and has the added benefit of relieving skin tension at the wound edges [Figure 6]. This is done by repositioning, rotating and internally anchoring the skin flap.

It will be taken out by placing USP 2-0 or USP 3-0 polyglactin sutures onto the internal surface of the skin flap in two points as follows: The first skin anchoring

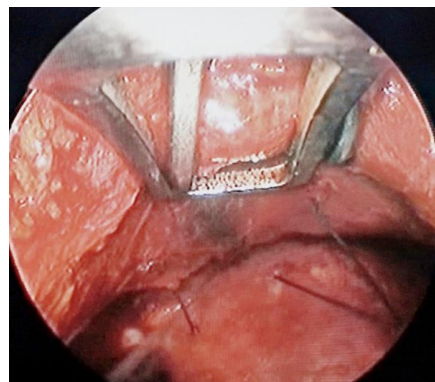


Figure 6: Internal anchoring suture of the skin flap into the inside of the flap

point is about 1 cm below the horizontal level of the corner of the eye which is anchored onto in the middle third of the zygomatic bone. The second internal skin anchorage connect the skin with the the lateral third of the zygoma or the temporal fascia at the projection of the hairline [Figure 6]. Both of the internal skin flap sutures involve the Caper's fascia of the skin but none of them should cause a visible skin dimple after knotting them. However small dimples can be good managed by subcision and/or fat or PRP filling, which are proposed for volume reconstruction and deflation correction in the postoperative period in any case of facial aging.

As a result, the skin obtains the necessary redraping with long-term internal fixation and skin tension at the temporal wound is alleviated. The skin-to-malar, zygomatic or temporal fascial anchors located 4-5 cm caudal to the wound edge, have instead taken up this tension. These internal skin flap anchors shorten the distance between the sagging and fixation points.

By a conventional facelift, the skin is pulled at the level of the wound edges, far from the sagging skin parts in the midface, which should be elevated. A conventional facelift is therefore not effective for the redraping, reposition and fixation of the midface skin. This disadvantage of the average facelift technique is compensated by internal skin fixation of the TEM lift. A further advantage of the internal skin anchorage is to prevent pulling of the hair bearing skin, to prevent excising too much from it and to prevent sliding back the hairline too much. The goal of any facelift is to elevate the sagging soft tissues. If only skin sutures alone are used to hold the sagging tissues, the skin will stretch out over a short time, resulting in loss of lifting efficiency and longevity. Resorbable threads with strength of USP 3-0 are used for this purpose and should not cause flap ischemia. If the anchoring sutures are well laid out, the yield of the skin surplus is approximately 1-2 cm in the temporal wound [Figure 7].



Figure 7: The skin adapts itself without tension after removal of the excess skin



Figure 8: Demonstrating the efficiency of temporal endoscopic midface by an intraoperative shot after completing of the left side. Fully reposition and anchoring of flat malar tissues and the sagging jowls on the left side. Note that the operation takes place under full local anesthesia, an anaesthesiologist is not present during our facelift. The patient can feel and can also give a response in cases, if the operator works nearby to the nerves. The patient can help the surgeon to prevent nerve injuries

After excising the excess skin, the skin adapts itself well and can be closed tension-free with USP 5-0 interrupted sutures.

Anaesthesia for TEM lift

Facial procedures are performed in the authors practice with a combination of sedation and local anaesthesia [Figure 8]. Approximately 100-200 mL of Klein's tumescence solution is used for local anaesthesia. The solution is made up with the following components: 500 mL 0.9% NaCl, 50 mL of 2% Lidocaine, 1 mL of 1 mg/mL epinephrine 4 from Adrenalin®. A dose of 5 mg Midazolam is given as pre-medication. Patients also receive 3-5 mg of Piritramide intravenously before the local anaesthesia infiltration

is administered. We have not observed any pain or other complications during the last 15 years using this simple and effective method, which can be applied to more extensive open face and midface lifts.

Bandaging

We apply elastic bandaging to the head for the first two postoperative days. Then we use kinesio tapes for the stabilization of the operation results during the first week, similar to that used by athletes for sport injuries. These tapes promote healing by preserving the lift as well as improving the dynamic lymphatic drainage. This thereby contributes to a quicker reduction in swelling. Conventional dressings may be omitted after the second day.

RESULTS

The lifting effect of the temporal endoscopic midface lift extends from the eyebrows to the midface, and affects also the jawline and neck [Figures 9-13]. The operation is relatively quick and takes two and a half to three hours in the hands of an experienced endoscopic surgeon. The postoperative results appear very natural and do not suffer from an "operated" look. The author attributes this to lifting using the correct vector against the force of gravity. The healing period takes approximately 14 days, and largely dependent on the variable resolution of oedema and swollen eyes. We stress that overcorrection is very important, which requires a calculated distortion. This distortion that is similar in appearance to "almond eyes" or "cat eyes" may persist for two to four weeks prior to resolution.

There are no facelift stigmas or conspicuous scars on the face. The only scar is located within the temporal



Figure 9: Before (A) and 6 months after temporal endoscopic midface (B). More pleasant looking after endoscopic midface reposition by diminishing the suborbicular hollowing



Figure 10: Before (A) and after (B) temporal endoscopic midface. Note also the juvenile V-form of the jaws 6 months after the scar free face lifting. Note the psychological status of the patient and her evident feeling of happiness



Figure 11: Before (A) and after (B) temporal endoscopic midface. A 48-year-old patient, note the improved contours of the malar and peri orbicular regions and of the jawline resulting much more pleasing face



Figure 12: Before (A) and after (B) temporal endoscopic midface. Visible rejuvenation and improving also of the psychological state of the 48-year-old patient



Figure 13: Before (A) and 6 months after (B) the procedure by a 55-year-old patient. Note the improving of the suborbicular region by temporal endoscopic midface. No blepharoplasty was performed



Figure 14: Before (A) and 3 months after (B) temporal endoscopic midface (TEM) lift by a 30-year-old patient. Note the tired look before and the pleasant refreshing effect after TEM lift with improved brow position, with correction of the suborbicular hollowing. Improving of the nasolabial folds and the centrofacial depletion by correct reposition of the mid-facial structures

hairline. It is therefore barely visible and can be well covered by the adjacent hair. Broad scarring with scar alopecia can be avoided with proper dissection and suture techniques. Due to the lack of facial scars, TEM is the method of choice for scarless facial rejuvenation. TEM is appropriate when no large jowls or skin excesses in the neck are present and is suited especially for young women and men who frequently lack such excesses [Figures 13-15].

DISCUSSION

Aging process is a combination of ptosis, deflation and wrinkling. A facelift corrects the ptosis of the lateral facial parts and of the jaws and neck, but not really works against centrofacial aging. As it described before the mid facial structures are not sufficient repositioned by a conventional facelift - they are too far from the large lateral access and the scar means a



Figure 15: Before (A) and 6 months after (B and C) temporal endoscopic midface. Note the freshness of the whole face, the diminishing of the nasolabial folds, more malar fullness, pleasant periorbital of the 55-year-old patient. A proper repositioned midface with more malar fullness, diminishing of jowling and of the nasojugal folds 6 months after temporal endoscopic midface by a middle aged woman with happiness and satisfaction

stigma forever. By the MACS lift^[10] the lateral face and the jawline can be well corrected, however on the cost of a pretrichal and praeauricular scar. The so-called “third suture” of the midface^[10] is also an additive element by the necessity of midface restoration even by young individuals. There are many subperiosteal ways of accesses to the midface to reposition and restore it efficient. All of them lack to generate a unity of the SMAS and also of the skin layer lifting each of them in one block, in one common layer.

In case of a temporal subperiosteal lifting, the fully reposition is partly blocked by the anatomical adherence of the SMAS and the facial nerve onto the zygomatic bone. The anchorage means only a suspensions lift, which does not allow the sunken part to merge with the part where the sunken part is anchored. It is then only the question of believing or not believing, whether any part of the body can be held on a cord or “cable” with longevity.

The most effectively vertical midface reposition with direct anchorage is practiced by Botti and Ceravolo,^[1] which was also adopted by the author. However, a transblepharoplasty vertical, subperiosteal midface lift supposes an extended lower lid correction with canthopexy, though has many risks of a lower lid correction such as ectropion, scleral show, conjunctivitis, chemosis, lagophthalmos, asymmetry, negative tilt, rounding of the eyes. The procedure needs drilling for bony tunnels, then also skin excision periorbital or temporal, that means three procedures in the same time: extended lower lid correction plus midface subperiosteal lift plus temporal lift. If a consent is correctly made, then such a multiplex combinative procedure will be mostly refused by a young patient and also very rarely can be indicated, than real ptosis

and sagging are not common by young patients. Rather a centropacial depletion is the case by such individuals, which is best treated by sharp needle intradermal fat or nano fat or micro fat injections in the hands of Verpaele *et al.*^[10] and by the author.

The rejuvenation effect of the TEM lift is directed on the centro- and mid- facial sagging tissues and therefore addresses the roots of deflation and flattening of the midface by young patients. The reposition of the malar fat pad in combination with tightening both of the SMAS and of the skin make a natural volume restoration malar and submalar [Figure 8] and affect also the jawline [Figures 9-12]. The jaws get the natural and youthful V- form instead of quadratic form of jawling after the TEM Lift.

So the TEM incorporates the advantages as follows: rejuvenation in the problematic centropacial region, volume restoration by reposition, affect also the lateral jawline and thus without any facial stigma.

Candidates of the TEM lift are prevented from possible complications of a lower lid operation and needs for the centropacial reposition only one procedure and not three as like by transblepharoplasty subperiosteal midface lift. For young patients without severe sagging and deflation of the midface and/or without severe jawling and neck problem this scar saving procedure seems to be the best choice of by centropacial rejuvenation by a restorative way.

An additive volume restoration should be however an adjunctive part of any rejuvenation of the face, than both the ptosis and the volume loss should be corrected in all parts of the face according to our conviction.

Older patients with significant skin excess of the jaw and neck are better suited for conventional lower facelift surgeries, intermediate cases can get a restricted pretrichial neck lift added to the scar sparing TEM lift by the author.

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None.

Conflicts of interest

There are no conflicts of interest.

Patient consent

All operations and photographs were performed after the patients' written consent.

Ethics approval

Ethics approval was given by all demonstrated patients for the presentation.

REFERENCES

1. Botti G, Ceravolo MP. Midface and Neck Aesthetic Plastic Surgery. Volume 1: Midface. 1st ed. Florence: Springer; 2012. p. 560.
2. LaFerriere KA, Kilpatrick JK. Transblepharoplasty: subperiosteal approach to rejuvenation of the aging midface. *Facial Plast Surg* 2003;19:157-70.
3. Mofid MM. A novel technique for repositioning lower eyelid fat via the trans-oral approach in association with midface lift. *Aesthetic Plast Surg* 2011;35:563-8.
4. Quatela VC, Antunes MB. Trans-temporal midface lifting to blend the lower eyelid-cheek junction. *Clin Plast Surg* 2015;42:103-14.
5. Ramirez OM. Three-dimensional endoscopic midface enhancement: a personal quest for the ideal cheek rejuvenation. *Plast Reconstr Surg* 2002;109:329-40; discussion 341-9.
6. Ransom ER, Stong BC, Jacono AA. Persistent improvement in lower eyelid-cheek contour after a trans-temporal midface lift. *Aesth Plast Surg* 2012;36:1277-82.
7. de la Fuente A, Hönig JF. Video-assisted endoscopic trans-temporal multilayer upper midface lift (MUM-Lift). *J Craniofac Surg* 2005;16:267-76.
8. Viksraitis S, Astrauskas T, Karbonskiene A, Budnikas G. Endoscopic aesthetic facial surgery: technique and results. *Medicina (Kaunas)* 2004;40:149-55. (in English, Lithuanian)
9. Williams EF 3rd, Vargas H, Dahiya R, Hove CR, Rodgers BJ, Lam SM. Midfacial rejuvenation via a minimal-incision brow-lift approach: critical evaluation of a 5-year experience. *Arch Facial Plast Surg* 2003;5:470-8.
10. Verpaele A, Tonnard P, Gaia S, Guerao FP, Pirayesh A. The third suture in MACS-lifting: making midface-lifting simple and safe. *J Plast Reconstr Aesthet Surg* 2007;60:1287-95.
11. Haffner T. Das temporal-endoskopische Mittelgesichtsift Gesichtslifting ohne Gesichtsnarben. *J f Ästhet Chirurgie* 2014;7:98-105. (in German)

Case Report

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Epidermoid and dermoid cysts of the head and neck region

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ABSTRACT

Epidermoid cysts, dermoid cysts and teratoid cysts are cystic malformations lined with squamous epithelium. They present as soft nodular lesions with a sessile base. Their prevalence is 7% in head and neck patients and 1.6% within the oral cavity. The authors present a case series of 21 patients with dermoid and epidermoid cysts who underwent surgical removal. One year of follow-up was carried out without evidence of recurrence. The removal of these cysts is of great concern as it can cause serious social stigma, aesthetic and functional impairment, dysphagia and dysphonia.

INTRODUCTION

Epidermoid, dermoid and teratoid cysts are cystic malformations lined with squamous epithelium and are classified based on whether they are lined with simple squamous epithelium (epidermoid), or skin adnexa are found in the cystic wall (dermoid), or other tissues, such as a muscle, cartilage and bone are present (teratoid).^[1] Epidermoid cysts are rare benign lesions usually located in the oral cavity. They present as soft nodular lesions with sessile base. They are frequently found in ovaries and testicles, and less frequently in the head and neck (7% of cases), or within the oral cavity (1.6%).^[1-3] The floor of the mouth is the most commonly affected area, however these cysts can be found in

the tongue, lips and buccal mucosa.^[4,5] Dermoid and epidermoid cysts of the orbit are described as both superficial and deep formations with most frequently slow intermittent growth. Other than aesthetic effects, during their growth, dermoid and epidermoid cysts can cause disturbances in the eye motility, and in rare cases, also optical nerve compression syndrome.^[6,7]

Epidermoid cysts occur more frequently in patients between 15 and 35 years but can be seen in all age groups. These are slow growing asymptomatic masses but once they increase in size, they can cause dysphagia, dysphonia and dyspnea.^[1] Prior case reports report patients that presented with pain, speech disorder, or respiratory distress due to epidermoid



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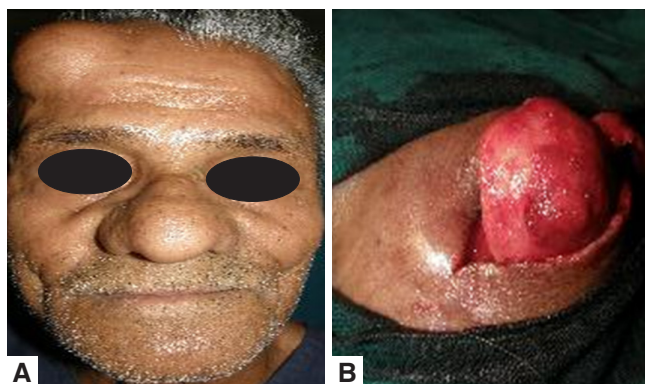


Figure 1: Preoperative (A) and intra-operative (B) view of a dermoid cyst of scalp



Figure 2: Preoperative (A) and intra-operative (B) view of a dermoid cyst of occiput

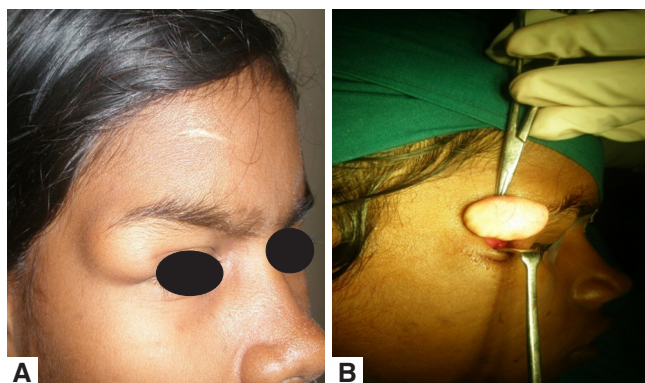


Figure 3: Preoperative (A) and intra-operative (B) view of a dermoid cyst of lateral orbital margin

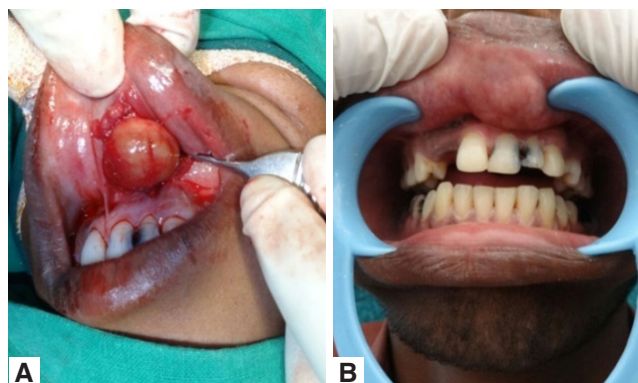


Figure 4: Preoperative (A) and intra-operative (B) view of an epidermoid cyst of the upper lip

cyst in the oral cavity, lower lip, or upper lip.^[7] Giant epidermoid cysts are rare and they present in the scalp.

Epidermoid cysts are relatively less common in the head and neck region, hence are likely to be misdiagnosed. The aim of this case series is to highlight the presentation of epidermoid and dermoid cysts as a differential diagnosis for head and neck masses, showing various clinical and radiological presentations as well as the surgical outcomes after their removal.

CASE REPORT

This study included all the patients of dermoid and epidermoid cysts who visited D. Y. Patil Dental College and Hospital, Pune between January 2010 to January 2015. Twenty-one patients (12 females and 9 males) were diagnosed clinically with dermoid/epidermoid cyst and confirmed by fine-needle aspiration cytology. Giant cysts were present on the anterior scalp in 5 patients [Figure 1], on the posterior scalp in the occipital region in 3 patients [Figure 2], on the frontal bone in 3 patients, on the lateral orbital margins in 9 patients [Figure 3], and 1 patient had a dermoid cyst intraorally in the upper lip [Figure 4]. The age of the patients ranged

16-78 years. The size ranged from 1.5 cm × 2 cm to 12 cm × 7 cm [Table 1]. Infected cysts were managed with preoperative antibiotics. All cysts were unilocular. No evidence of malignancy was present. None had recurrence after a minimum 1-year follow-up.

DISCUSSION

Dermoid cysts have been classified as true dermoid cysts, epidermoid cysts and teratoid cysts.^[1-3,6] Several theories have been proposed to explain the development of dermoid cysts: they may result from entrapment of ectodermal tissue of the first and second brachial arches during fetal development; they could represent a variant form of the thyroglossal duct cyst; finally, previous surgical or accidental events could lead to traumatic implantation of epithelial cells into deeper tissues.^[1,4] In our case series, we had the presentation of a patient with dermoid cyst in the upper lip region. There are paediatric cases in the literature with epidermal cyst lesions in the sublingual region, gingiva, palate, and uvula. Many of them had history of trauma or surgical intervention.^[8] An epidermoid cyst is benign and rarely occurs in the oral cavity. When lesions occur in the floor of the mouth, one must think of other diagnoses including ranula, lymphatic malformation

Table 1: Characteristics of patients and the cysts

No. of patients	Age (years)	Gender	Site	Size (cm × cm)	Surgery	Follow-up (months)
1	21	Male	Intraoral (upper lip)	2 × 2	Excision	13
2	35	Male	Anterior scalp	1.5 × 2	Excision	12
3	23	Female	Anterior scalp	3.2 × 2	Excision	18
4	35	Female	Posterior scalp	12 × 7	Excision	17
5	57	Male	Posterior scalp	5.5 × 4	Excision	14
6	17	Female	Lat orbital margin	2.5 × 2	Excision	36
7	16	Female	Lat orbital margin	2 × 1.5	Excision	25
8	22	Female	Lat orbital margin	2.2 × 2	Excision	22
9	25	Female	Lat orbital margin	2.4 × 2.2	Excision	30
10	24	Male	Lat orbital margin	2.5 × 2.5	Excision	16
11	32	Female	Lat orbital margin	3 × 2.8	Excision	14
12	36	Male	Anterior scalp	3.2 × 2.8	Excision	19
13	23	Female	Lat orbital margin	2.2 × 2	Excision	18
14	78	Male	Frontal bone	8 × 5	Excision	20
15	62	Female	Frontal bone	3.8 × 3.5	Excision	13
16	48	Female	Frontal bone	3.2 × 3	Excision	15
17	42	Male	Anterior scalp	4 × 5	Excision	12
18	40	Male	Posterior scalp	5.5 × 4	Excision	14
19	37	Male	Anterior scalp	3.5 × 3	Excision	14
20	32	Female	Lat orbital margin	2.5 × 2	Excision	12
21	22	Female	Lat orbital margin	2.6 × 2.2	Excision	18

and heterotypic gastrointestinal cyst. When lesions occur in the tongue, a differential diagnosis of tumor of granular cells, schwannoma, lipoma and neurofibroma, should be considered. When lesions occur in the orbital region, the differential diagnosis of orbital cysts are lipodermoid teratoma, plexiform neurofibroma, encephalocele, orbital cellulitis, and orbital pseudotumor deep dermoid.^[9,10] Thus besides clinical examination, other complementary tests are necessary to achieve a diagnosis and eliminate other diseases.^[2] Giant epidermoid cysts are common in females and are usually found on the scalp, in people working outdoors and who have had significant sunlight exposure. On the scalp, it occurs in an area located in a line drawn along the hairline passing through the upper border of the ear lobule and joining these two lines at the occipital area.^[11] This is a retention type of cyst and is usually unilocular and contains keratin. Size varies from a few millimetres to a few centimetres but when the size exceeds 5 cm, it is referred to as a giant sebaceous cyst.^[11,12] In our case series, giant cysts on the anterior scalp were present in 5 patients and posterior scalp in 3 patients.

Imaging has an important role in confirming the diagnosis and classifying cysts according to their relation to muscle. Ultrasound is the initial imaging modality. Epidermoid cysts are seen as well-defined cysts with multiple well-defined dependent echogenic nodules within the cyst. Computed tomography scan shows a unilocular cyst with homogenous, hypo-attenuating (0-18 HU) fluid material that contains multiple hypo-attenuating fat density nodules giving a “sack of marbles” appearance; this is a feature virtually pathognomonic for a dermoid

cyst. Magnetic resonance imaging (MRI) shows fluid signal due to high protein content, and the areas of fat component will show low signal on fat suppressed images. MRI facilitates visualization of the exact location and extent of cystic lesions in the floor of the mouth and is useful for determining their relationship to the surrounding muscles.^[3]

Pathological features of epidermoid cysts are oily or cheesy, tan, yellow, white material and the cyst wall is a fibrous capsule usually 2-6 mm in thickness.^[3] Total excision is the main treatment for intraoral epidermal cystic lesions since needle aspiration or fenestration might lead to infection, pain, and complaints after treatment. Marsupialisation is another alternative for management of large cysts.^[3] Lesions above the mylohyoid muscles are operated on intraorally, whereas those below the muscle are removed via an incision in the neck,^[1,13] however, if there is a very large sublingual cyst above the mylohyoid muscle, an extraoral approach may be preferred. An intraoral approach avoids a conspicuous scar, and the recovery time is shorter.

In a study of 103 patients with diagnosis of epidermoid and dermoid cyst of the head and neck, 46.6% of these were orbital, 23.3% buccal and submental, 12.3% nasal, 10.7% cervical and 2.9% labial. Various publications also report epidermoid cysts of the oral cavity in the soft palate, the uvula and the sublingual area. However, epidermoid cysts in tonsils are rarely reported.^[14] Our case series did not find any epidermoid or dermoid cyst in the tonsillar area.

The epidermoid cyst rarely discloses malignancy, but isolated cases of premalignant and malignant conditions (Bowen's disease, Paget's disease, and squamous cell carcinoma) have been found in their walls. Ozan *et al.*^[15] and López-Ríos *et al.*^[16] described a patient with basal cell carcinoma arising in the wall of an epidermoid cyst. Kronish and Dortzbach^[17] presented a case report stating that basal cell carcinoma originated from an epidermoid cyst in which they found nests of basal cell carcinoma connected with the epidermoid cyst. A deep dermoid cyst in the upper eyelid is not generally detected until they increase in size. Precise diagnosis and surgical removal is important because cyst growth can cause proptosis, diplopia and can restrict eye movement.^[18,19] Complications of epidermoid cysts of the floor of the mouth include disfigurement, difficulty in swallowing and airway compromise. In addition, it can become infected.^[3] In our case series, the most common location of epidermoid cysts was in the lateral orbital region.

In recent literature, we could find no reports related to orbicularis oris muscle fusion defects secondary to epidermoid cysts.^[8] Considering the fact that these kinds of cysts mostly affect children, special caution and care should be applied regarding the precise diagnosis of the type of tumour and its accurate localization. Our case series found only one adult patient with a dermoid cyst located in the orbicularis oris region. The cyst should be completely removed, with minimal trauma and a satisfactory aesthetic effect.^[8,17,18]

Dermoid cysts may increase in size, leak and cause inflammation, and thus, it is recommended that even asymptomatic cysts should be removed.^[19] The reason for early excision is to prevent incidence of secondary infection. The recurrence rate after excision of an infected cyst is 20% of all cases reported.^[20]

While dealing with scalp lesions, as well as other cutaneous lesions of the head and neck region, differential diagnosis of keratinous cysts should be kept in mind as these cysts carry certain complications such as cystic rupture, abscess, secondary, and infections, during their treatment. These cysts carry relatively higher risk of recurrence compared to lipomas and certain other benign lesions that mimic these cysts. Therefore, these cysts require thorough histopathological examination and close follow-up due to their potential for malignant transformation.^[21] Early diagnosis and removal of dermoid and epidermoid cysts are of great concern as it can cause serious social stigma, aesthetic and functional impairment, dysphagia and dysphonia.

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Conflicts of interest

There are no conflicts of interest.

Patient consent

All involved patients gave their consent forms.

Ethics approval

This study was approved by the Ethical Review Committee of D. Y. Patil Dental College and Hospital.

REFERENCES

1. Jham BC, Duraes GV, Jham AC, Santos CR. Epidermoid cyst of the floor of the mouth: a case report. *J Can Dent Assoc* 2007;73:525-8.
2. Pereira CM, Gasparetto PF, de Lucena Botelho T. Atypical appearance of epidermoid cyst in tongue's ventral surface. *RSBO* 2011;8:240-2.
3. Mirza S, Fadl S, Napaki S, Abualruz A. Case report of complicated epidermoid cyst of the floor of the mouth: Radiology-histopathology correlation. *Qatar Med J* 2014;2014:12-6.
4. Elias LSA, Oton-Leite AF, Silva CM, Ribeiro-Rotta RF, Batista AC, de Mendonça EF. Epidermoid cyst: highlights on diagnosis and magnetic resonance imaging features. *Rev odonto cienc* 2010;25:204-7.
5. Sahoo NK, Choudhary AK. Dermoid cyst of floor of mouth: a case report. *Natl J Med Dent Res* 2012;1:24-30.
6. Fuchshuber S, Grevers G, Issing WJ. Dermoid cyst of the floor of the mouth—a case report. *Eur Arch Otorhinolaryngol* 2002;259:60-2.
7. Veselinović D, Krsić D, Stefanović I, Veselinović A, Radovanović Z, Kostić A, Cvetanović M. Orbital dermoid and epidermoid cysts: case study. *Srp Arh Celok Lek* 2010;138:755-9.
8. Dogan F, Bucak IH. Congenital epidermoid cyst results in muscle fusion defect in the upper lip. *Case Rep Otolaryngol* 2014;2014:540910.
9. De Ponte FS, Brunelli A, Marchetti E, Bottini DJ. Sublingual epidermoid cyst. *J Craniofac Surg* 2002;13:308-10.
10. Gandhi N, Syed NA, Alen R. Dermoid cyst. Available from: <http://www.EyeRounds.org/cases/115-dermoid-cyst.htm>. [Posted July 26, 2010; Last accessed October 25, 2016].
11. Wani I, Jawaid H, Mir SR, Wani AM, Shah PS, Peerzada AH, Malik S, Teli B, Dar GM. Giant epidermoid cysts. *OA Case Rep* 2013;2:65.
12. Venus MR, Eltigani EA, Fagan JM. Just another sebaceous cyst? *Ann R Coll Surg Engl* 2007;89:1-3.
13. Louis PJ, Hudson C, Reddi S. Lesion of floor of the mouth. *J Oral Maxillofac Surg* 2002;60:804-7.
14. Erol K, Erkan KM, Tolga D, Bengu C. Epidermoid cyst localized in the palatine tonsil. *J Oral Maxillofac Pathol* 2013;17:148.
15. Ozan F, Polat HB, Ay S, Goze F. Epidermoid cyst of the buccal mucosa: a case report. *J Contemp Dent Pract* 2007;8:90-6.
16. López-Ríos F, Rodríguez-Peralto JL, Castaño E, Benito A. Squamous cell carcinoma arising in a cutaneous epidermal cyst: case report and literature review. *Am J Dermatopathol* 1999;21:174-7.
17. Kronish JW, Dortzbach RK. Upper eyelid crease surgical approach to dermoid and epidermoid cyst in children. *Arch Ophthalmol* 1988;106:1625-7.
18. Avakoff JC. Microincision for removing sebaceous cysts. *Plast Reconstr Surg* 1989;84:173-4.
19. Han HH, Ju RK, Seo BF, Moon SH, Oh DY, Ahn ST, Rhie JW. Dermoid cyst excision under müller muscle in a patient with blepharoptosis. *Arch Plast Surg* 2014;41:607-9.
20. Dabholkar JP, Patole AD, Sheth AS, Saaj R. Congenital cystic lesions in head and neck. *Indian J Otolaryngol Head Neck Surg* 2003;55:128-30.
21. Sabhalok S, Kalele K, Phirange A, Kheur S. Congenital giant keratinous cyst mimicking lipoma: case report and review. *Indian J Dermatol* 2015;60:637.

Development and assessment of a cutaneous tissue stretch device as a novel scar therapy

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ABSTRACT

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Mechanotransduction,
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Aim: Scar prevention and reduction is an area of therapeutic opportunity and unmet medical need. With no current effective scar therapy, patients are often disappointed in their appearance post surgery and re-present to surgeons, only to be turned away. The purpose of this study was to develop and test a device that produces intermittent parallel stretch on new scars and to analyze its potential to reduce scarring. **Methods:** Mice were randomized into 5 scar stretch treatment groups: 1 control, 1 sham, and 3 stretch models (0.5×, 1×, or 2× device strength) and treated for 10 days. Scars were scored using the Vancouver Scar Scale. Scar tissue samples were compared by histology and transforming growth factor beta 1 (TGF-β1) expression between control and treatment groups. **Results:** Scar scores of 0.5× and 1× groups were significantly lower than the control group ($P < 0.05$). Scar scores from the 1× treatment group were also significantly lower than the 0.5× group ($P < 0.05$). Sham, control scar and 2× groups showed more collagen deposition and a thicker dermal scar than the 0.5× and 1× groups. Unstretched scars had fewer fibroblasts with more collagen deposition than the 0.5× and 2× groups. TGF-β1 levels were significantly lower in the 0.5× (342.1 ± 9.2) and 1× (254.1 ± 3.1) groups than in the control group ($P < 0.05$). TGF-β1 levels in the 1× treatment group were also significantly lower than the 0.5× treatment group ($P < 0.05$). **Conclusion:** Intermittent cutaneous tissue stretch parallel to scars during the proliferative phase of wound healing decreases fibrosis on a macroscopic, microscopic and biochemical level.

INTRODUCTION

Scar formation can be a debilitating consequence of surgery, burns, trauma, or disease. Scarring can result

in loss of function, restriction of movement, adverse psychological effects due to appearance and reduced quality of life.^[1-5] Patients across wide demographic groups, gender, age, ethnicity, and geographic region



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have similar concerns about scarring and value even small improvements in scarring.^[6-11] Changes in texture, coloration and elevation of scar are of equal concern to patients with minor and severe scars.^[5,12] In addition to scars on the face, patients are often dissatisfied with scars from donor graft sites used for breast reconstruction, heart surgery, and elective procedures such as abdominoplasty.^[13,14]

Scar prevention and reduction is an area of therapeutic opportunity and unmet medical need. There is no single therapy that is accepted as the standard of care for treatment of scars.^[15-17] Many patients seek surgery for scar revision but surgeons often turn away patients, as they believe that improved results cannot be obtained with current techniques and therapies.^[12] In the US alone, 45 million patients undergo procedures yearly that would benefit from scar reduction therapy.^[18]

Current scar therapies lack a clear mechanism of action and have unpredictable efficacy. Non-surgical therapies include topical creams and preparations, wound dressings, laser treatments, and skin substitutes. Additional therapies such as massage and mechanical manipulation have also been often recommended to patients for treatment of scars with variable results.^[19-21]

To better understand then mechanism behind scar formation, the role of mechanical force in scar formation has been explored extensively.^[22-25] Studies have shown that tension resisting wound closure can worsen scar formation.^[25] However, recent data suggests that the timing, duration, and direction of force on a scar plays an important factor in scar formation, and properly aligned and timed mechanical forces could potentially decrease scar formation.^[26-29] A previous study by Alenghat and Ingber^[30] showed that mechanotransduction directly affects a variety of cellular processes involved in scar formation. Although direct manipulation of these cellular processes is still being investigated, there has been an assortment of models examining the effects of direct skin manipulation on scar formation. A randomized-control trial (RCT) showed that using tape after surgery helped prevent hypertrophic scar formation in 70 patients.^[31] Another study showed using a mouse model that when an incision is under mechanical stress, inflammatory cells become activated and apoptosis of the healing cells increases.^[32] Additionally, a review on all currently hypothesized physical treatment modalities for scar prevention and found that the success of compression therapy, silicone therapy, adhesive tape, and occlusive dressing therapy, relies on mechanotransduction mechanisms.^[24] Furthermore, recent studies evaluating tension on wounds in a pig model formed the foundation for the Embrace device, which functions to reduce scar

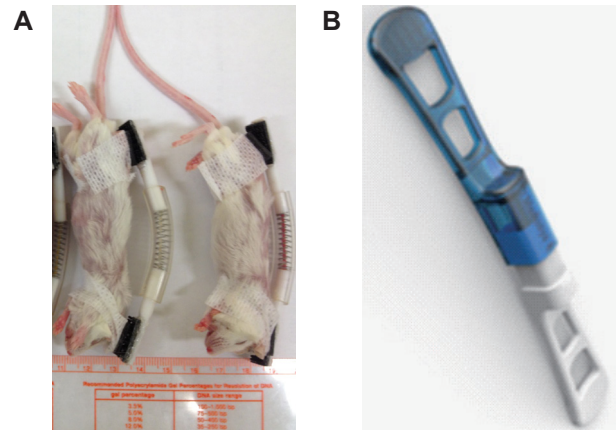


Figure 1: (A) Application of stretch device *in vivo*. Stretch treatments lasted 20 min once a day for 10 days. Mice were anesthetized under isoflurane for each stretch treatment; (B) the actual design of the stretch device

formation by applying mechanical stress to oppose wound edges.^[33,34]

Langevin *et al.*^[26-28,35] and Bouffard *et al.*^[29] have published a series of studies that demonstrate the decreased collagen and transforming growth factor beta 1 (TGF- β 1) expression, major contributors to scar formation, after longitudinal stretch parallel to a wound. Based on these data, the present study aims to develop a longitudinal stretch device that might enhance aesthetic outcome of scarring through modulation of the cellular processes involved in scar formation.

METHODS

Device development and standardization

AutoCAD was used to design a scar stretch device that could easily attach and detach from skin. The components of the device include a skin adhesive mechanism and an extension force mechanism, allowing for reliable attachment and detachment of the device [Figure 1]. The device prototypes were constructed using inert materials purchased from Small Parts Inc. (www.smallpartsinc.com): steel spring (Stainless Steel 316 Compression Spring), polyvinyl tubing (White Translucent Miniature PTFE Tubing), Teflon rods (PTFE Round Rod), and an adhesive. Three different spring strengths for the scar stretch devices were created and labeled as 0.5 \times , 1 \times and 2 \times to investigate a dose response (1 \times = 0.96 Newton, as per manufacturer specifications). The devices were standardized to ensure similar extension force using a small force gauge (Jonard Industries, Tuckahoe, NY).

Animal model

The experimental protocol was approved by the McGill University Animal Care Committee and Institutional

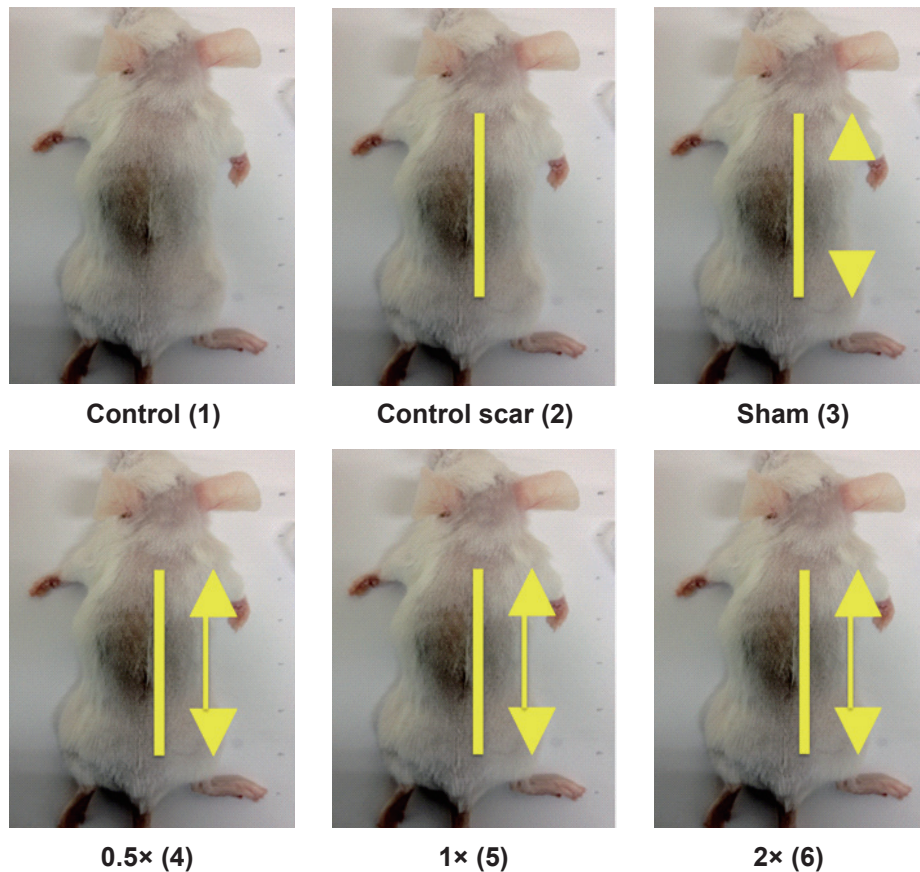


Figure 2: Representative mice from 5 stretch strength groups, with the incision and stretch guidelines. Control mouse and each stretch strength group are shown

Review Board. All mice were female, Balb/C weighing 19-21 g. Thirty mice were divided equally into 5 groups (control scar, sham, 0.5 \times , 1 \times , 2 \times), with 1 mouse not making it into the control group [Figure 2]. After anesthesia was induced with isoflurane, mice were shaved and a 3-cm incision was made with a scalpel in the middle of the back at the level of the scapula as per the procedure described by Bouffard *et al.*^[29] Incisions were closed primarily with Steri-stripsTM and were carefully observed to maintain close primary approximation. Steri-strips remained in place for five days until the device adhesive was applied. Mice were observed daily to confirm continuous primary closure of the wounds.

In vivo tissue stretch method

On day 5 post-incision in all mice, 2 U-lock mechanisms were adhered cranial and caudal to the incision, without coming into contact with the wound. The device was aligned in parallel over the scar by attaching the ends of the device to the U-lock mechanism for a 20-min stretch period. Following the 20-min stretch period, the device was removed while the U-lock mechanism remained adhered on the dorsum of the mice. All mice underwent stretching of the trunk for 20 min once per day for 10 days, and mice in groups 2, 3, 4, 5 underwent stretch

treatment with device under isoflurane anesthesia. Five days after the last stretch treatment, at 20 days post-incision, all mice were euthanized. The wounds were harvested and bisected with one piece fixed in formalin for histology and the other snap frozen in liquid nitrogen for biochemical analysis.

Morphologic scar assessment

Photos of scars 15 days after beginning tissue stretch (20 days post incision) were qualitatively analyzed by two blinded reviewers using the Vancouver Scar Scale.

Histologic analysis

Following formalin fixation, tissues were embedded in paraffin and sectioned at 7 μ m. Samples were mounted and stained with Masson-Trichrome to demonstrate collagen and examined using light microscopy. Two independent blinded histology trained observers evaluated stained sections qualitatively.

Cutaneous TGF- β 1 assay

Skin samples were harvested as above. Samples were then homogenized and immediately assayed for TGF- β 1 protein using a human TGF- β 1 ELISA assay as per manufacturer protocol to adjust for standard

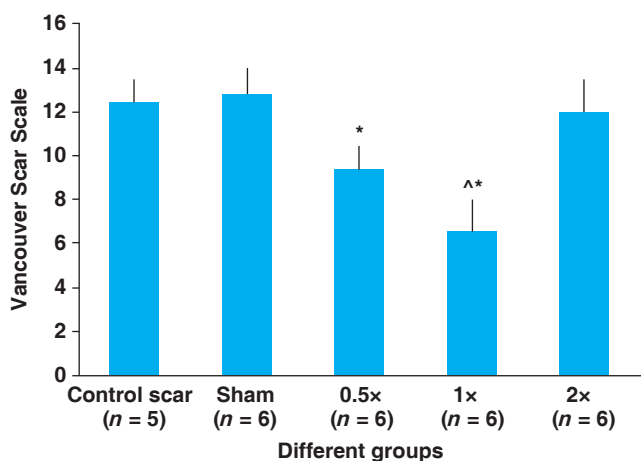


Figure 3: Morphological comparison of scars using Vancouver Scar Scale. *Significant difference from control scar group ($P < 0.05$); ^Significant difference from 0.5x stretch group ($P < 0.05$). Standard deviation is represented by error bars

level of the sample (R&D Systems, Minneapolis, MN), including sample acidification with 1N hydrochloric acid for activation of latent TGF- β 1.

Statistical analysis

Analysis of variance (ANOVA) with Bonferroni correction for multiple variables was performed to test for differences of TGF- β 1 level and Vancouver Scar Scale scores between treatment groups. ANOVA was used to analyze the effects of stretch on TGF- β 1 concentrations after 5 days of the 10 consecutive days of stretch therapy. For these analyses, TGF- β 1 data were log transformed prior to analysis in order to satisfy the normality and homogeneity of variance assumptions associated with the ANOVA. Statistical analyses were performed using SAS statistical software (PROC MIXED). P values < 0.05 were considered statistically significant.

RESULTS

Development of a scar stretch device

A total of 29 devices were created and grouped into

4 different stretch strength categories. The force produced by each device, except the sham, was measured. The strength categories were: (1) a sham device, which consisted of the device without any spring mechanism that produced no extension force; (2) a 0.5x device which exerted a mean force of 265.6 ± 1.5 g; (3) a 1x device which exerted a mean force of 532.4 ± 1.8 g; and (4) a 2x device which exerted a mean force of $1,068.4 \pm 3.4$ g.

Morphologic scar assessment

Photos of scars 15 days after beginning tissue stretch (20 days post incision) were qualitatively analyzed using the Vancouver Scar Scale [Figures 3 and 4]. Control scars averaged 12.4 ± 1.0 , sham scars 12.8 ± 1.16 , 0.5x stretch treatment group 9.4 ± 1.0 , 1x stretch treatment group 6.6 ± 1.5 , 2x stretch treatment group 12 ± 1.4 . Scar scores from the 0.5x and 1x stretch groups were significantly lower when compared to the control scar group ($P < 0.05$). Scar scores from the 1x treatment group were also significantly lower when compared to the 0.5x group ($P < 0.05$). On examination 20 days post incision (5 days after last stretch treatment) scars remained most visible in the sham, control, and 2x treatment groups [Figure 4].

Qualitative histologic analysis

Sham, control and 2x treatment groups showed greater collagen deposition and a thicker dermal scar than the 0.5x and 1x treatment groups [Figure 5]. The dermis in unstretched scars (sham and control treatment groups) had fewer fibroblasts and more collagen between cells than the 0.5x and 2x treatment groups, where fibroblasts were closely spaced [Figure 5].

Cutaneous TGF- β 1 assay

TGF- β 1 protein levels in cutaneous scars 20 days after incision were significantly higher in the control (471.9 ± 13.8 pg/mL), sham (383.3 ± 49.2 pg/mL) and 2x stretch (401.3 ± 41.1 pg/mL) treatment groups. As shown in Figure 6, TGF- β 1 levels were

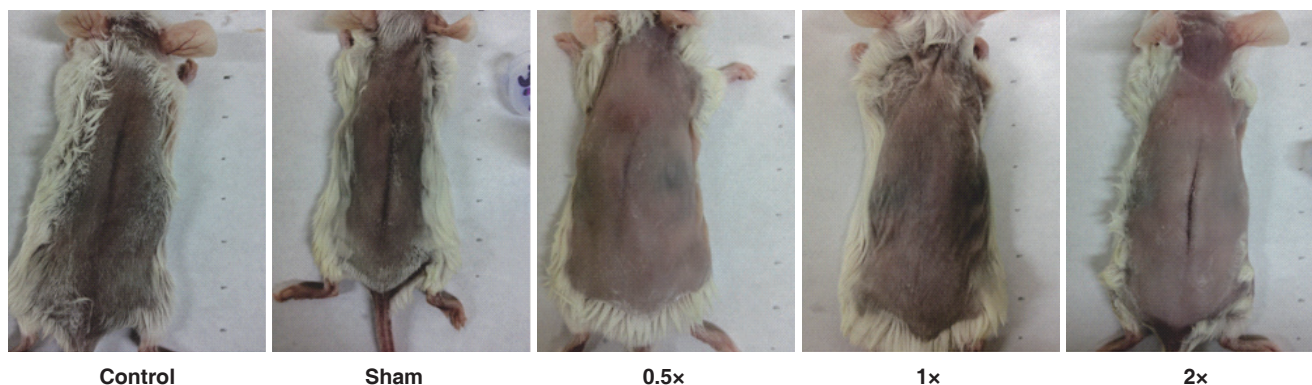


Figure 4: Representative mice from 5 groups 20 days after incision, 5 days after last stretch treatment. Control mouse without scar is not shown

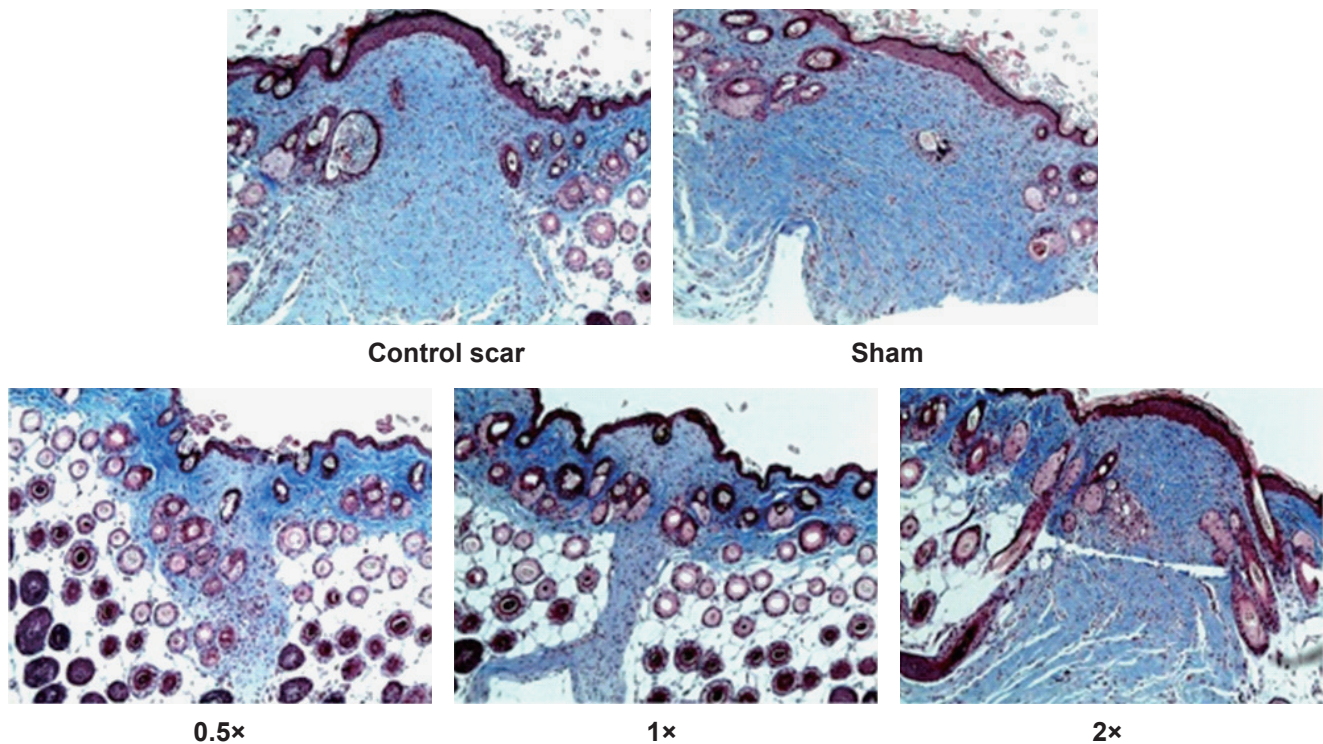


Figure 5: Mouse *in vivo* stretch model. Effect of stretch on cutaneous scar formation. Masson Trichrome (stains collagen blue) of paraffin embedded histological sections cut perpendicular to the skin at 10x magnification

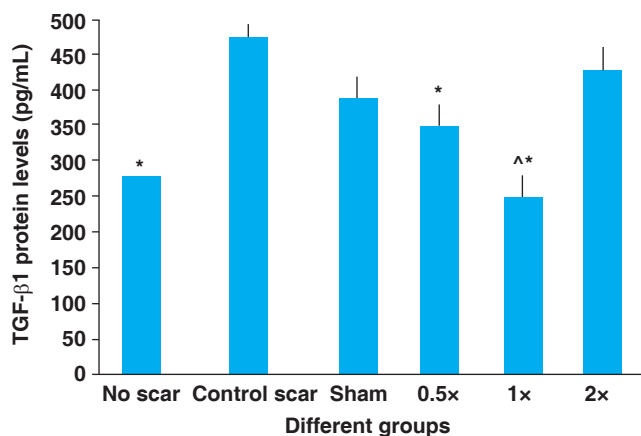


Figure 6: Levels of transforming growth factor beta 1 (TGF-β1) protein in cutaneous scar at day 20 for non-stretched and stretched tissue samples. *Significant difference from control scar group ($P < 0.05$); ^Significant difference from 0.5x stretch group ($P < 0.05$). Standard deviation is represented by error bars

significantly lower in the stretch treatment groups 0.5x (342.1 ± 9.2 pg/mL) and 1x (254.1 ± 3.1 pg/mL) when compared to the control scar group ($P < 0.05$). Furthermore, TGF-β1 levels in the 1x treatment group were significantly lower than the 0.5x treatment group ($P < 0.05$) [Figure 6].

DISCUSSION

Results of the present study demonstrate that linear stretch parallel to incisional wounds reduces scarring.

Using a newly developed cutaneous stretch device, animals treated with the device demonstrated less scarring from a morphologic, histologic, and molecular perspective. Benefits included improved scar appearance, decreased collagen deposition in the dermis and decreased TGF-β1 production.

This study demonstrates that application of linear cutaneous stretch parallel to incisional wounds reduces scarring on both macroscopic and microscopic levels. Critics of other scar reducing device papers found that only examining the aesthetic outcome of the scar is not sufficient in determining the success of the device.^[34,35] The Vancouver scar scale is comprised of four variables, which are extremely recognizable to the patient: vascularity, height/thickness, pliability, and pigmentation.^[36] This scale was selected due its relative common use in scar research, user objectivity, ease of use, and assessment of variables important to patients. The correlation of the reduction in scarring grossly and histologically supports the utility of linear cutaneous stretch in treatment of scars.

Although the exact mechanism behind the improvement in scars with linear scar stretch is unknown, one explanation is that linear stretch may decrease scar formation by minimizing perpendicular tension across the wound and thus promoting approximation of wound edges. The stretch force and overall stretch

time (total of 20 min per day) used in our study are both less when compared to other studies where skin was stretched continuously for long periods of time under higher tension.^[22-24,37] In these studies prolonged tissue stretch under high tension caused release of inflammatory mediators that promoted scar formation.^[24,38] Although such previous studies have demonstrated tissue stretch can induce scar formation, the discussion on timing, force and duration of stretch required to induce a scar remains unclear.^[22-24,38] The results from the 2× stretch group in the present study provides some support for the detrimental effects of high-tension tissue stretch, where scars in this group were comparable to controls (non-stretched scars). In addition to worse appearing scars, the 2× group also had more collagen deposition in the dermis, and higher levels of TGF-β1. Compared to the favorable scar results in the 0.5× and 1× groups, the latter data suggests that there is a threshold of tension, above which tissue stretch promotes scar formation and below which tissue stretch may decrease scar formation.

Substantial evidence describes the role of mechanotransduction in scar formation. Our study builds on preliminary findings that controlling tension in a proliferating scar modulates production of extracellular matrix proteins. Langevin *et al.*^[26-28,35] described several cellular and extracellular matrix changes that take place once skin is stretched that promote decreased scar formation. Tissue stretch causes fibroblast cell spreading, cytoskeletal and nuclear remodeling, decreased type 1 collagen production and decreased production of TGF-β1. A recent paper by Suarez *et al.*^[37] describes the role of tension in keloid pathology, specifically tension dependent proteins: Hsp27, α2β1-Integrin, and PAI-2. Furthermore, the clinical correlation of reduced fibrosis associated with intermittent parallel longitudinal tension and significant improvements in scar appearance using parallel scar massage offers further support for the clinical utility of the device presented herein. This suggests that tissue stretch induces mechanical signals that may regulate gene expression and overall function of fibroblasts.

It is important to note that this study is not without limitations. A murine model was used as a preliminary means to evaluate the efficacy of this novel device in modulating scar formation during the proliferative phase of wound healing. The cost and previous use of a murine model to study wound healing made mice a logical first choice of animal model for this investigation. Mouse skin is significantly different from human skin in elasticity and healing potential, limiting the direct translation of these findings to

humans. This study evaluated end-points correlating to the early remodeling phase of wound healing, offering assessment of fibrosis but not long-term scar remodeling. Despite these differences, there still remain substantial similarities between the underlying wound healing physiology, providing promise for the utility of this device. However, future experiments are still planned to measure the effects of the device long term on scarring. These studies, also proposed in mice, will also allow for more extensive biochemical assessment of the device by measuring parameters associated with mechanotransduction, including focal adhesion kinase levels to better describe the underlying mechanism of the observed reduction in fibrosis. Additionally, further quantitative analysis of the number of fibroblasts in numerous sections, thickness of the scars and the epidermal thickness would have added to the analysis of scar reduction.

To further elaborate the elegant mechanisms at work in the modulation of scar formation the authors plan to evaluate the device in a skin scarring animal model more indicative of human scar biology, such as the red Duroc pig.^[33] While this study provides substantial promise for the device presented here, subsequent studies will establish more precisely the optimal vector, force, and duration of tissue stretch needed to effectively and consistently reduce scar formation. Optimizing such parameters may permit the development of a novel scar treatment device that could be used to treat a wide variety of scars.

Scar formation has detrimental effects on social, psychological, and physical function.^[1-5] Current scar therapies are poorly understood and insufficient to insure optimal scar formation. In one promising study, Lim *et al.*^[39] showed in a randomized clinical trial that their Embrace device, which differs significantly from the device used in this study, managed to achieve statistically significant results. The Embrace device reduces perpendicular tension by direct opposition rather than by application of parallel stretch described in this study. The device presented herein, applied only intermittently rather than continuously as is the Embrace device, appears to function similarly in that it ultimately opposes the wound edges. The present device is only in its infancy, and further investigations of the optimal time interval of use, vector of stretch, and magnitude of stretch provide hope for an effective treatment strategy for the reduction of scar formation.

In conclusion, in this study we designed and manufactured a device that may provide parallel tissue stretch to a wound in order to improve scar formation. Our results show that the 1× strength device is overall superior

to other strengths and that tissue stretch is beneficial to scar formation in the molecular, histological and macroscopic levels. This device is a promising treatment to improve scar formation. It is safe and easy to use in clinical practice.

Financial support and sponsorship

Funding for the materials used in the animal study was provided by Menodys Inc.

Conflicts of interest

Jonathan Kanevsky, Mirko Gilardino, Satya Prakash are the inventors listed on the patent publication for the device and method used in this study (Patent: WO 2013071439 A1). Funding for the materials used in the animal study was provided by Menodys Inc., who is licensing the patent for the device used in this study from McGill University. Joshua Vorstenbosch, Julian Diaz-Abele, Markus Prinz, Youssef Tahiri and Tyler Safran have no actual or potential conflicts of interest.

Patient consent

There is no patient involved.

Ethics approval

The experimental study was approved by the McGill University Animal Care Committee and Institutional Review Board.

REFERENCES

- Lawrence JW, Fauerbach JA, Heinberg L, Doctor M. Visible vs. hidden scars and their relation to body esteem. *J Burn Care Rehabil* 2004;25:25-32.
- Bayat A, McGrouther DA. Clinical management of skin scarring. *Skinmed* 2005;4:165-73.
- Newell R. Psychological difficulties amongst plastic surgery ex-patients following surgery to the face: a survey. *Br J Plast Surg* 2000;53:386-92.
- Valente SM. Visual disfigurement and depression. *Plast Surg Nurs* 2009;29:10-6.
- Rumsey N, Clarke A, White P. Exploring the psychosocial concerns of outpatients with disfiguring conditions. *J Wound Care* 2003;12:247-52.
- McGrouther DA. Facial disfigurement. *BMJ* 1997;314:991.
- Bragg TW, Jose RM, Srivastava S. Patient satisfaction following abdominoplasty: an NHS experience. *J Plast Reconstr Aesthet Surg* 2007;60:75-8.
- Abu-Nab Z, Grunfeld EA. Satisfaction with outcome and attitudes towards scarring among women undergoing breast reconstructive surgery. *Patient Educ Couns* 2007;66:243-9.
- Tebble NJ, Thomas DW, Price P. Anxiety and self-consciousness in patients with minor facial lacerations. *J Adv Nurs* 2004;47:417-26.
- Levine E, Degutis L, Pruzinsky T, Shin J, Persing JA. Quality of life and facial trauma: psychological and body image effects. *Ann Plast Surg* 2005;54:502-10.
- Robert R, Meyer W, Bishop S, Rosenberg L, Murphy L, Blakeney P. Disfiguring burn scars and adolescent self-esteem. *Burns* 1999;25:581-5.
- Occleston NL, O'Kane S, Goldspink N, Ferguson MW. New therapeutics for the prevention and reduction of scarring. *Drug Discov Today* 2008;13:973-81.
- Stewart KJ, Stewart DA, Coghlan B, Harrison DH, Jones BM, Waterhouse N. Complications of 278 consecutive abdominoplasties. *J Plast Reconstr Aesthet Surg* 2006;59:1152-5.
- Crossland DS, Jackson SP, Lyall R, Hamilton JR, Hasan A, Burn J, O'Sullivan JJ. Patient attitudes to sternotomy and thoracotomy scars. *Thorac Cardiovasc Surg* 2005;53:93-5.
- Franz MG, Steed DL, Robson MC. Optimizing healing of the acute wound by minimizing complications. *Curr Probl Surg* 2007;44:691-763.
- Batra RS. Surgical techniques for scar revision. *Skin Therapy Lett* 2005;10:4-7.
- Meier K, Nanney LB. Emerging new drugs for scar reduction. *Expert Opin Emerg Drugs* 2006;11:39-47.
- Sen CK, Gordillo GM, Roy S, Kirsner R, Lambert L, Hunt TK, Gottrup F, Gurtner GC, Longaker MT. Human skin wounds: a major and snowballing threat to public health and the economy. *Wound Repair Regen* 2009;17:763-71.
- Field T, Peck M, Scd, Hernandez-Reif M, Krugman S, Burman I, Ozment-Schenck L. Postburn itching, pain, and psychological symptoms are reduced with massage therapy. *J Burn Care Rehabil* 2000;21:189-93.
- Field T, Peck M, Krugman S, Tuchel T, Schanberg S, Kuhn C, Burman I. Burn injuries benefit from massage therapy. *J Burn Care Rehabil* 1998;19:241-4.
- Foo CW, Tristani-Firouzi P. Topical modalities for treatment and prevention of postsurgical hypertrophic scars. *Facial Plast Surg Clin North Am* 2011;19:551-7.
- Huang C, Akaishi S, Ogawa R. Mechanosignaling pathways in cutaneous scarring. *Arch Dermatol Res* 2012;304:589-97.
- Ogawa R, Okai K, Tokumura F, Mori K, Ohmori Y, Huang C, Hyakusoku H, Akaishi S. The relationship between skin stretching/contraction and pathologic scarring: the important role of mechanical forces in keloid generation. *Wound Repair Regen* 2012;20:149-57.
- Yagmur C, Akaishi S, Ogawa R, Guneren E. Mechanical receptor-related mechanisms in scar management: a review and hypothesis. *Plast Reconstr Surg* 2010;126:426-34.
- Wong VW, Rustad KC, Akaishi S, Sorkin M, Glotzbach JP, Januszyn M, Nelson ER, Levi K, Paterno J, Vial IN, Kuang AA, Longaker MT, Gurtner GC. Focal adhesion kinase links mechanical force to skin fibrosis via inflammatory signaling. *Nat Med* 2012;18:148-52.
- Langevin HM, Bouffard NA, Badger GJ, Iatridis JC, Howe AK. Dynamic fibroblast cytoskeletal response to subcutaneous tissue stretch ex vivo and in vivo. *Am J Physiol Cell Physiol* 2005;288:C747-56.
- Langevin HM, Storch KN, Cipolla MJ, White SL, Buttolph TR, Taatjes DJ. Fibroblast spreading induced by connective tissue stretch involves intracellular redistribution of alpha- and beta-actin. *Histochem Cell Biol* 2006;125:487-95.
- Langevin HM, Bouffard NA, Badger GJ, Churchill DL, Howe AK. Subcutaneous tissue fibroblast cytoskeletal remodeling induced by acupuncture: evidence for a mechanotransduction-based mechanism. *J Cell Physiol* 2006;207:767-74.
- Bouffard NA, Cutroneo KR, Badger GJ, White SL, Buttolph TR, Ehrlich HP, Stevens-Tuttle D, Langevin HM. Tissue stretch decreases soluble TGF-beta1 and type-I procollagen in mouse subcutaneous connective tissue: evidence from ex vivo and in vivo models. *J Cell Physiol* 2008;214:389-95.
- Alenghat FJ, Ingber DE. Mechanotransduction: all signals point to cytoskeleton, matrix, and integrins. *Sci STKE* 2002;2002:pe6.

31. Von Offenberg Sweeney N, Cummins PM, Cotter EJ, Fitzpatrick PA, Birney YA, Redmond EM, Cahill PA. Cyclic strain- mediated regulation of vascular endothelial cell migration and tube formation. *Biochem Biophys Res Commun* 2005;329:573-82.
32. Aarabi S, Bhatt KA, Shi Y, Paterno J, Chang EI, Loh SA, Holmes JW, Longaker MT, Yee H, Gurtner GC. Mechanical load initiates hypertrophic scar formation through decreased cellular apoptosis. *FASEB J* 2007;21:3250-61.
33. Gurtner GC, Dauskardt RH, Wong VW, Bhatt KA, Wu K, Vial IN, Padois K, Korman JM, Longaker MT. Improving cutaneous scar formation by controlling the mechanical environment: large animal and phase I studies. *Ann Surg* 2011;254:217-25.
34. Gurtner GC, Longaker MT. Reply: tension shielding with the embrace device: does it really improve scars? *Plast Reconstr Surg* 2014;134:e664-6.
35. Langevin HM, Storch KN, Snapp RR, Bouffard NA, Badger GJ, Howe AK, Taatjes DJ. Tissue stretch induces nuclear remodeling in connective tissue fibroblasts. *Histochem Cell Biol* 2010;133:405-15.
36. Baryza MJ, Baryza GA. The Vancouver Scar Scale: an administration tool and its interrater reliability. *J Burn Care Rehabil* 1995;16:535-8.
37. Suarez E, Syed F, Alonso-Rasgado T, Mandal P, Bayat A. Up-regulation of tension-related proteins in keloids: knockdown of Hsp27, alpha2beta1- integrin, and PAI-2 shows convincing reduction of extracellular matrix production. *Plast Reconstr Surg* 2013;131:e158-73.
38. Chin MS, Lancerotto L, Helm DL, Dastouri P, Prsa MJ, Ottensmeyer M, Akaishi S, Orgill DP, Ogawa R. Analysis of neuropeptides in stretched skin. *Plast Reconstr Surg* 2009;124:102-13.
39. Lim AF, Weintraub J, Kaplan EN, Januszky M, Cowley C, McLaughlin P, Beasley B, Gurtner GC, Longaker MT. The embrace device significantly decreases scarring following scar revision surgery in a randomized controlled trial. *Plast Reconstr Surg* 2014;133:398-405.

The extended running W-plasty: an additional tool for simultaneous reduction of the hypertrophied labia minora and redundant clitoral hood

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ABSTRACT

Aim: The extended running W-plasty technique using the W-plasty principle is a modification of the conventional technique. The use of this technique was utilized for simultaneous reduction of the protuberant labia minora and the redundant clitoris. **Methods:** Twenty-three patients presented to the plastic surgery clinic between 2008 and 2015 with the complaints of protuberant and enlarged labia minora in conjunction with a hypertrophied clitoral hood. The extended running W-plasty was performed in all patients. Surgery was performed under general anesthesia as an outpatient procedure with a range of operative time from 30-45 min. The Likert scale was used to evaluate outcomes. **Results:** Patients maintained labial length with decreased scarring. Small hematomas occurred in 2 patients and were treated conservatively. One case of wound dehiscence occurred and was also treated conservatively. Patients returned to normal activity 5-7 days postoperatively. The cosmetic outcome of all patients was very satisfactory. **Conclusion:** The running W-plasty technique is ideal for closure of secondary defects following excision of both the redundant labia minora and clitoral hood, while maintaining length and providing tensionless scars. The technique conserves the original tissues while avoiding over- or under- resection of the labia.

INTRODUCTION

Repeated tearing and stretching caused by childbirth, aging, and sexual intercourse, in addition to congenital defects such as vaginal atresia and Müllerian agenesis, and gender switching play a role in the request to

change the size of the labia minora.^[1] Congenital hypertrophy of the labia minora has also been reported.^[2] Maas and Hage^[3] reported the use of a W-shaped resection of the protuberant labia minora in 13 patients. Later, Solanki *et al.*^[4] applied the same technique to 12 patients. Both groups of authors noted that the running



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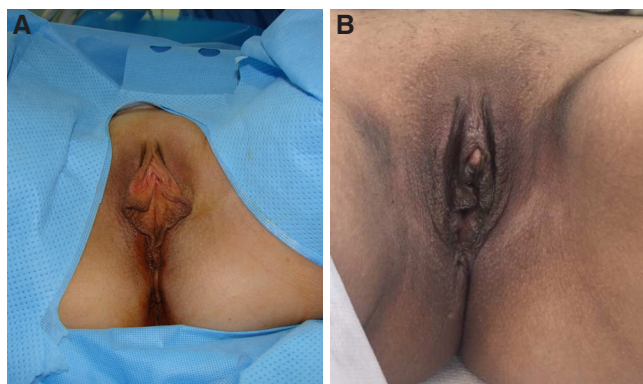


Figure 1: (A) A 34-year-old female with bilateral hypertrophy of the labia minora and a redundant clitoral hood; (B) A 27-year-old female with bilateral incomplete hypertrophy of the labia minora and a redundant clitoral hood

W-shaped resection technique avoids many potential problems which can occur with other techniques. Capraro^[5] introduced the edge resection technique in which the labia is resected at its free edges. Hamori^[6] preserved the natural rugosity by performing the central wedge technique. De-epithelialization is another tool which has been used to reduce the size of the labia, and can be performed with either a scalpel^[7] or the CO₂ laser.^[8] Gonzalez *et al.*^[9] reported the use of the custom flask labiaplasty technique in 50 patients, which permits precise reduction of the labia minora. Ostrzenski^[10] described a fenestration labiaplasty technique in which the inferior flap is transposed to reduce the height and width of the labia.

The primary goal of the extended running W-plasty technique, described in this study, is to achieve an acceptable protrusion of both the labia minora and the clitoral hood beyond the labia majora. The design reported in this study is a modification of the conventional W-plasty reported in the literature which is used for reduction only of the hypertrophied labia minora.

METHODS

Six patients with unilateral hypertrophy and 17 patients with bilateral hypertrophy of the labia minora presented for evaluation [Figure 1].

Within this group, 8 patients complained of irritation and chronic infection while the remaining 15 patients were concerned with the noticeable protrusion of the enlarged labia minora and its associated psychological and emotional distress.

Patients were admitted to the same day surgery unit after a complete examination. General endotracheal anesthesia was used in all patients. The procedure commenced with marking the running W-plasty on both sides of labia minora with an extension through the clitoral hood [Figure 2]. Excision of the pre-determined amount of tissue was performed [Figure 3], followed by meticulous hemostasis and closure of the interdigitating small triangular flaps with absorbable 4-0 monofilament [Figures 4 and 5].

A compression dressing was applied for several hours and removed prior to discharge. At the postoperative visits, an outcome evaluation questionnaire based on a 5-point Likert scale was administered. The questionnaire evaluated the level of improvement in physical exercise, improvement in sexual intercourse, improvement in appearance and shape of the labia minora and clitoral hood, elimination of fungal infection, ability of patients to wear fitted undergarments, and improvement in sense of well-being.

A 5-point Likert scale was designed with options of 1 (very dissatisfied), 2 (dissatisfied), 3 (moderately satisfied), 4 (satisfied), and 5 (highly or very satisfied).

The preoperative and postoperative photos were analyzed based on the extent of external genitalia exposure and analysis was performed by an independent



Figure 2: (A) A 34-year-old female, marked for an extended running W-plasty; (B and C) A 27-year-old female, marked with an extended running W-plasty on both sides of the labia minora

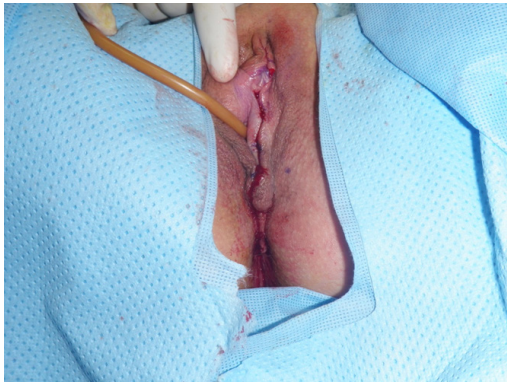


Figure 3: A 34-year-old female, appearance of the labia minora after reduction. Note the interdigitating triangles. The excision extended to involve the clitoral hood



Figure 4: Tissue excised from both labia minora (the 34-year-old female)

plastic surgeon.

RESULTS

Because the W-plasty technique conserves tissue, over-resection was avoided, and the shape and size of the labia minora were acceptable in all patients. In addition, the vertical length of the labia was preserved. All patients were noted to have symmetry with a and natural color and contour of their labia minora [Figure 6].

Small hematomas occurred in one patient and were treated conservatively. Wound dehiscence (1-2 cm in length) developed in one patient and was also treated conservatively [Table 1].

Based on the results of the Likert scale and the evaluation questionnaire [Table 2] provided during the follow-up period, the aesthetic outcomes were very satisfactory in all patients. Patients experienced improvement in their daily activities, including sexual intercourse and physical exercise. Hygiene became easier, and patients stated that they did not need to apply antifungals or local steroids after surgery. All patients were able to wear bathing suits without embarrassment. No patients experienced scar

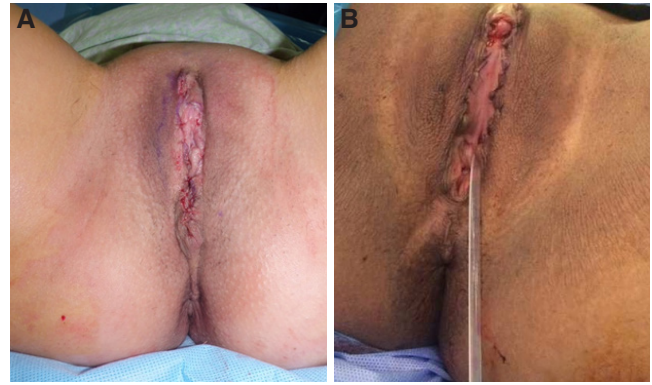


Figure 5: Immediate postoperative view of the 34-year-old female (A) and the 27-year-old female (B). The procedure is completed by suturing the interdigitating small flaps



Figure 6: One-year postoperative result of the 34-year-old female

numbness, sensitivity, or scar pain during intercourse.

DISCUSSION

The use of the extended running W-plasty technique is required for the simultaneous reduction of hypertrophied labia minora and prominent clitoral hood. The central wedge resection removes a full-thickness wedge of skin from the thickest portion of the labia minora.^[11] Giraldo *et al.*^[12] add a 90-degree Z-plasty to the central wedge procedure; this modification produces a refined surgical scar that is less tethered and has less tension. The W-plasty previously described by Maas and Hage^[3] and Solanki *et al.*^[4] is limited as it does not simultaneously address the redundant hood of the clitoris.

The technique described in the current report addresses both the hypertrophied labia and clitoral hood with an appropriate skin resection. The extended W-plasty has the same principles of the conventional W-plasty in that the angles of the "W" vary between 50 and 55 degrees, but are further extended to involve another aesthetic unit which includes the defect resulting from the reduction of the enlarged clitoris. The technique divides the scar into small triangles to break up the scar contracture and providing a more

Table 1: Patient profile

No.	Age (years)	Clinical findings	Procedure	Complications	Follow-up (months)	Outcome
1	27	Unilateral hypertrophied labia minora and hypertrophied clitoral hood	Extended W-plasty	None	30	Very satisfied
2	30	Bilateral hypertrophied labia minora and hypertrophied clitoral hood	Bilateral extended W-plasty	None	29	Very satisfied
3	35	Bilateral hypertrophied labia minora and hypertrophied clitoral hood	Bilateral extended W-plasty	Small hematoma	22	Very satisfied
4	38	Unilateral hypertrophied labia minora and hypertrophied clitoral hood	Extended W-plasty	None	13	Very satisfied
5	41	Bilateral hypertrophied labia minora and hypertrophied clitoral hood	Bilateral extended W-plasty	Wound dehiscence of 1-2 cm	31	Very satisfied
6	22	Bilateral hypertrophied labia minora and hypertrophied clitoral hood	Bilateral extended W-plasty	None	14	Very satisfied
7	29	Unilateral hypertrophied labia minora and hypertrophied clitoral hood	Extended W-plasty	None	36	Very satisfied
8	40	Bilateral hypertrophied labia minora and hypertrophied clitoral hood	Bilateral extended W-plasty	None	13	Very satisfied
9	36	Unilateral hypertrophied labia minora and hypertrophied clitoral hood	Extended W-plasty	None	12	Very satisfied
10	30	Bilateral hypertrophied labia minora and hypertrophied clitoral hood	Bilateral extended W-plasty	None	15	Very satisfied
11	33	Bilateral hypertrophied labia minora and hypertrophied clitoral hood	Bilateral extended W-plasty	None	12	Very satisfied
12	22	Bilateral hypertrophied labia minora and hypertrophied clitoral hood	Bilateral extended W-plasty	None	12	Very satisfied
13	29	Unilateral hypertrophied labia minora and hypertrophied clitoral hood	Extended W-plasty	None	27	Very satisfied
14	25	Bilateral hypertrophied labia minora and hypertrophied clitoral hood	Bilateral extended W-plasty	None	12	Very satisfied
15	26	Bilateral hypertrophied labia minora and hypertrophied clitoral hood	Bilateral extended W-plasty	Small hematoma	29	Very satisfied
16	30	Bilateral hypertrophied labia minora and hypertrophied clitoral hood	Bilateral extended W-plasty	None	22	Very satisfied
17	29	Bilateral hypertrophied labia minora and hypertrophied clitoral hood	Bilateral extended W-plasty	None	12	Very satisfied
18	33	Bilateral hypertrophied labia minora and hypertrophied clitoral hood	Bilateral extended W-plasty	None	14	Very satisfied
19	44	Unilateral hypertrophied labia minora and clitoral hood	Extended W-plasty	None	33	Very satisfied
20	48	Bilateral hypertrophied labia minora and hypertrophied clitoral hood	Bilateral extended W-plasty	None	31	Very satisfied
21	40	Bilateral hypertrophied labia minora and hypertrophied clitoral hood	Bilateral extended W-plasty	None	12	Very satisfied
22	30	Bilateral hypertrophied labia minora and hypertrophied clitoral hood	Bilateral extended W-plasty	None	21	Very satisfied
23	29	Unilateral hypertrophied labia minora and hypertrophied clitoral hood	Extended W-plasty	None	12	Very satisfied

Small hematoma is defined as less than 2 cm. LM: labia minora; CH: clitoral hood

level surface to the scar.

In the current study, the most common reason for seeking reduction of the labia minora (13 out of 20 patients) was dissatisfaction with the appearance of the labial and clitoral hood. Hong *et al.*^[13] reported the use of both the central wedge resection and asymmetric Z-plasty techniques in order to avoid the linear scar. De-epithelialization of the skin^[14] of the central region of the medial and lateral aspects of each labia minora reduces the excess vertical tissue, while preserving natural rugosity and the sensory and

erectile abilities of the labia. One disadvantage of de-epithelialization is that the width of the individual labia can increase if a large area of labial tissue is de-epithelialized. Although de-epithelialization by laser treatment has been reported,^[15] it presents the potential for the occurrence of epidermal inclusion cysts. Closure of the opposing W-shaped incisions results in a tensionless zigzag suture line running obliquely across the edge of the labium.

In this study, the running W-shaped resection technique avoids many potential problems which

Table 2: Summary of 5-point Likert scale

Questionnaire	Very satisfied	Satisfied	Unsatisfied	Very unsatisfied	Not sure
Improvement of hygiene	All patients	—	—	—	—
Improvement of sexual intercourse	All patients	—	—	—	—
Painful scar	All patients	—	—	—	—
Improvement in appearance and shape	All patients	—	—	—	—
Elimination of fungal infection	All patients	—	—	—	—
Improvement of physical exercise	All patients	—	—	—	—
Improvement in sense of well-being	All patients	—	—	—	—
Ability of patients to wear a fitted size	All patients	—	—	—	—

can occur with other techniques, including wound contracture and dehiscence. The extended running W-plasty technique is ideal for closure of the secondary defect created following excision of both the redundant labia minora and the redundant clitoral hood because it maintains the vertical length and provides tensionless scars. The reduced labia minora remains sensate and painless. This technique avoids the over- or underresection of the labia, and all patients in our series were relieved of the functional problems related to an enlarged labia minora and clitoris.

In conclusion, the extended running W-plasty technique is a viable alternative to the conventional W-plasty, central wedge resection, edge resection, de-epithelialization excision, laser de-epithelialization, and other techniques. It is a modification of the W-plasty design reported in literature, and can be used to simultaneously reduce both the hypertrophied labia minora and the redundant clitoral hood.

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None.

Conflicts of interest

There are no conflicts of interest.

Patient consent

All patients gave informed consent.

Ethics approval

The study followed the ethical rules of Alkhor Hospital and was approved.

REFERENCES

1. Kato K, Kondo A, Gotoh M, Tanaka J, Saitoh M, Namiki Y. Hypertrophy of labia minora in myelodysplastic women. Labioplasty to ease clean intermittent catheterization. *Urology* 1988;31:294-9.
2. Radman HM. Hypertrophy of the labia minora. *Obstet Gynecol* 1976;48:S78-9.
3. Maas SM, Hage JJ. Functional and aesthetic labia minora reduction. *Plast Reconstr Surg* 2000;105:1453-6.
4. Solanki NS, Tejero-Trujague R, Stevens-King A, Malata CM. Aesthetic and functional reduction of the labia minora using the Maas and Hage technique. *J Plast Reconstr Aesthet Surg* 2010;63:1181-5.
5. Capraro VJ. Congenital anomalies. *Clin Obstet Gynecol* 1971;14:988-1012.
6. Hamori CA. Aesthetic labia minora and clitoral hood reduction using extended central wedge resection. *Plast Reconstr Surg* 2009;124:337; author reply 337-8.
7. Choi HY, Kim KT. A new method for aesthetic reduction to the labia minora (the deepithelialized reduction labioplasty). *Plast Reconstr Surg* 2000;105:419-22; discussion 423-4.
8. Pardo J, Solà V, Ricci P, Guilloff E. Laser labioplasty of labia minora. *Int J Gynaecol Obstet* 2006;93:38-43.
9. Gonzalez F, Dass D, Almeida B. Custom flask labioplasty. *Ann Plast Surg* 2015;75:266-71.
10. Ostrzenski A. Fenestration labioreduction of the labium minus: a new surgical intervention concept. *ISRN Obstet Gynecol* 2014;2014:671068.
11. Alter GJ. Aesthetic labia minora and clitoral hood reduction using extended central wedge resection. *Plast Reconstr Surg* 2008;122:1780-9.
12. Giraldo F, Gonzalez C, de Haro F. Central wedge nymphetomy with a 90-degree Z-plasty for aesthetic reduction of the labia minora. *Plast Reconstr Surg* 2004;113:1820-5; discussion 1826-7.
13. Hong ZJ, Wang J, Yuan SM, Wang Y, Hu XB, Jiang HQ. Central wedge resection and asymmetric Z-plasty for minor labia reduction. *Zhonghua Zheng Xing Wai Ke Za Zhi* 2009;25:268-70. (in Chinese)
14. Cao YJ, Li FY, Li SK, Zhou CD, Hu JT, Ding J, Xie LH, Li Q. A modified method of labia minora reduction: the deepithelialised reduction of the central and posterior labia minora. *J Plast Reconstr Aesthet Surg* 2012;65:1096-102.
15. Oranges CM, Sisti A, Sisti G. Labia minora reduction techniques: a comprehensive literature review. *Aesthet Surg J* 2015;35:419-31.

Full retroauricular skin and fascia expansion in microtia reconstruction: a single center experience of 166 cases

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Microtia,
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ABSTRACT

Aim: Ear reconstruction is a challenge for plastic and reconstructive surgeons. The ear requires sufficient skin coverage and a three-dimensional (3D) cartilage framework. In this paper, the authors present their 10-year experience in microtia reconstruction using tissue expansion and an autogenous rib cartilage framework. **Methods:** Ear reconstruction was performed in 3 operative stages. During the first procedure, a 50-80 mL kidney or cylinder-shaped expander was implanted deep to the subcutaneous fascia of the retroauricular mastoid region. Over a period of 3-5 months, the expander was filled to a final volume of 80-110 mL. In the next operation, the retroauricular fascia was eliminated or reserved following expander removal, and the autogenous costal cartilage framework was placed below the expanded skin flap. At the third and final stage, the earlobe transposition, tragus construction and conchal deepening were performed. **Results:** A total of 165 patients (166 ears) were reconstructed using tissue expansion and an autogenous rib cartilage framework. Complications included hematomas in 3 cases, expander exposure in 8 cases, cartilage exposure in 6 cases, infection and cartilage resorption in 2 cases, exposure of steel wire in 4 cases, and aseptic seroma in 2 cases. Follow-up ranging from 3 months to 5 years showed that 159 patients were satisfied with the reconstructed ear including size, location, projection, convolution, skin-colour matching, symmetry with opposite ear. **Conclusion:** Expansion of the retroauricular skin and fascia can provide sufficient non-hair-bearing skin and tissue for coverage of a three-dimensional costal cartilage framework. Avoidance and prompt treatment of complications are advised in order to obtain a satisfactory reconstruction of the ear.

INTRODUCTION

Ear reconstruction with autogenous rib cartilage for congenital microtia is a challenge for plastic and reconstructive surgeons. In addition to the surgeon's

skills, successful ear reconstruction is dependent upon a framework for the ear material and the overlying skin coverage. Autogenous costal cartilage has been widely used as a source of the ear framework.^[1-4] However, great success was not achieved until 2006



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when a large series of ear reconstructions with tissue expansion were reported.^[5,6] At present, retroauricular skin tissue expansion is one of the most popular techniques for ear reconstruction. In this study, tissue expansion and autogenous costal cartilage were used for reconstruction of 165 patients with 166 cases of microtia. The majority of the reconstructed ears obtained a good contour with a low incidence of complications. In this paper, the authors report their experience with microtia reconstruction by use of full-thickness skin and fascia expansion and a three-dimensional costal cartilage framework.

METHODS

From August 2005 to August 2015, 165 patients with 166 cases of congenital microtia were reconstructed using fully expanded retroauricular skin and fascia flaps combined with an autogenous costal cartilage framework at the Department of Plastic Surgery of the Second Affiliated Hospital of Kunming Medical University. Among these patients, 112 (67.9%) were males and 53 (32.1%) were females. Patient age ranged from 7 to 52 years (average 15.8 years). Of all patients, 110 cases (66.7%) of microtia involved the right ear, 54 cases (32.7%) involved the left ear, and 1 case was bilateral [Table 1].

Table 1: Basic information of 165 patients (166 ears)

Characteristics	n (%)
Gender	
Male	112 (67.9)
Female	53 (32.1)
Side	
Right	110 (66.7)
Left	54 (33.3)
Bilateral	2 (0.60)
Associated deformities	
Hemifacial microsomia	5 (3.6)
Facial nerve weakness	1 (0.6)
Opposite ear deformity	2 (1.2)
Fistula	4 (2.4)
Accessory ear	3 (1.8)

For the patient with left-side microtia [Figure 1A], during the first procedure, a 4-cm length incision parallel to the hairline was made on the scalp and a subfascial fascia pocket was dissected. After meticulous haemostasis was obtained, a 50-80 mL (corresponding to the size of the opposite auricle) kidney-shaped or cylinder-shaped tissue expander was implanted under the fascia pocket, with the valve of the expander placed in the subcutaneous tissue of the scalp or left externally. A negative-pressure drain was placed inside the pocket prior to closure of the incision. The suction drain and the suture were removed 6 days and 10 days postoperatively, respectively. Tissue expansion was performed twice

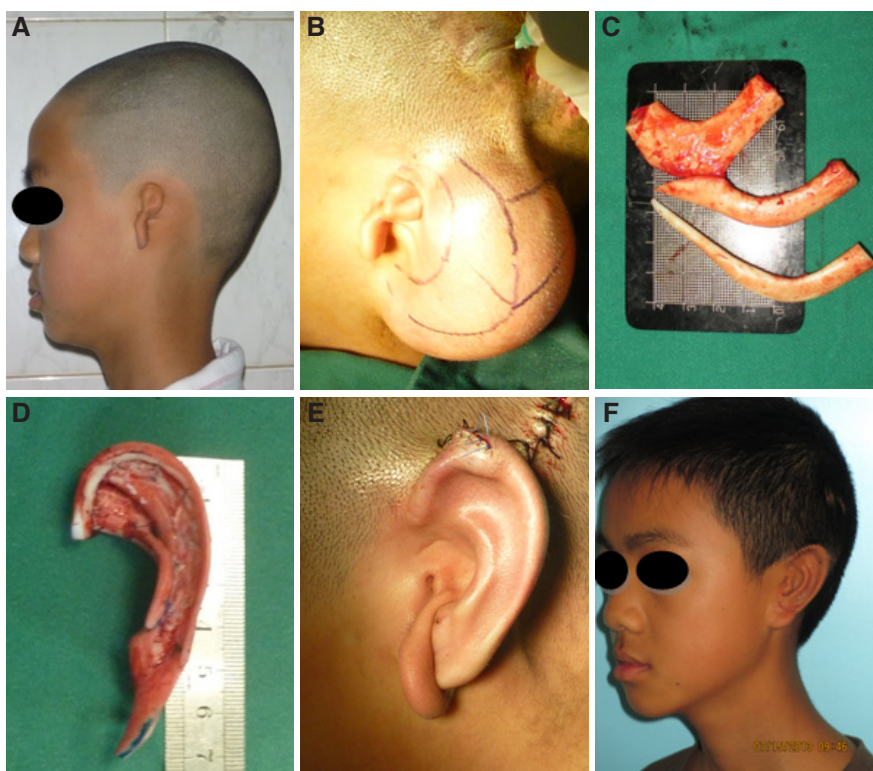


Figure 1: (A) The appearance of the left microtia; (B) the appearance of the fully expanded tissue expander in the left retroauricular region; (C) the harvested costal cartilages; (D) three-dimensional (3D) costal cartilage framework; (E) the appearance of the reconstructed ear immediately following application of the negative-pressure drain; (F) the malpositioned earlobe was transferred and connected to reconstructed ear

a week beginning 7 days after surgery and continuing until the targeted volumes were achieved [Figure 1B]. The second stage was performed following the completion of expansion. Preoperative computer tomography (CT) of the rib cartilage to be used for reconstruction was performed to assess for the degree of calcification and to measure rib cartilage parameters (length, width, and thickness). At the final surgery, the fascia was separated from the skin flap following removal of the expander, and the remnant ear cartilage was carefully dissected and preserved. Based upon the preoperative CT of the costal cartilage, normal costal cartilage from the seventh to ninth contralateral ribs were harvested by another surgical team [Figure 1C]. The harvested costal cartilages were then carved to include the structure of the ear, including the scapha, helix and triangular fossa [Figure 1D]. The redundant cartilage pieces were assembled to form a crescent-shaped pad and were inserted beneath the carved costal cartilage in order to enhance projection. The cartilage complex was assembled with 5-0 stainless steel wire and placed into the expanded pocket. The size, location and angle of the cartilage framework were adjusted until the reconstructed ear was consistent with the opposite ear. The drainage tube was inserted between the flaps and the cartilage framework. Finally, the shape of the reconstructed ear appeared after the drainage worked [Figure 1E]. The reconstructed ear was not covered dressing and a pressure dressing was applied to the retroauricular region. The dressing was removed on the first postoperative day to prevent infection. In order to maintain effective suction, the drain was evacuated every 2 h during the initial 24 h postoperative. The drain and sutures were removed at 6 and 10 days following surgery, respectively. Three to five months later, the malpositioned earlobe was transferred and connected to the reconstructed ear, the redundant cartilage and earlobe soft tissue were excised, and excess subcutaneous tissue was removed in order to deepen the conchal bowl [Figure 1F].

RESULTS

A total of 166 ear reconstructions were performed in 165 patients with microtia. There were three cases of hematoma, but expansion was successfully accomplished following evacuation. Exposure of the tissue expander occurred in 8 cases, which were performed ear reconstruction ahead of time using expanded skin and temporoparietal fascial flap with skin grafts. After the second stage, exposure of the cxf occurred in 6 patients, and was repaired by use of a local skin flap or temporoparietal fascia flap and skin graft. Infection occurred in 2 patients and was treated with systemic antibiotics. For these two patients on

Table 2: Complications in 165 cases

Complications	n (%)
Expander hematoma	3 (1.8)
Expander exposure	8 (4.8)
Exposure of cartilage	6 (4.3)
Infection and cartilage resorption	2 (1.5)
Fracture of upper pole of ear framework	4 (2.4)
Extrusion of steel wire	4 (1.80)
Sterile seroma	2 (1.5)
Pneumothorax	1 (0.61)
Subluxation of cervical vertebra	1 (0.61)
Hypertrophic scar	5 (3)

the third surgery of earlobe transposition, skin graft was performed ahead of time, which resulted in poor reconstructed ear because of partial absorption of cartilage. Sterile seromas occurred in 2 cases 2 weeks postoperatively. No seroma accrued again after negative press suction. Fracture of upper pole of the ear framework occurred in 4 cases, creating a less satisfactory auricular contour. Extrusion of the steel wire occurred in 4 cases. Other complications included 1 case of pneumothorax, 1 case of cervical vertebral subluxation, and 5 cases of hypertrophic scars at the chest harvest site. All complications were successfully treated [Table 2]. The postoperative satisfaction rate was 96.4% (159/165).

DISCUSSION

Since Hata *et al.*^[7] initially used a tissue expander for correction of congenital microtia. Since then, ear reconstruction using an expanded retroauricular skin flap and autogenous costal cartilage has been widely used.^[8-10] Skin expansion provides non-hairbearing, thin and well-vascularized skin. However, a 3D framework and skin grafts are often required as well.^[8,9] Liu *et al.*^[5] and Zhang *et al.*^[6] have reported the use of 2 expanders for ear reconstruction without skin grafting. However, this method increases the complexity of the operation and increases the risks of complications associated with expansion, including hematoma, exposure, and an obvious post-auricular scar. Chen *et al.*^[11] reported implanting a 50-mL kidney-shaped expander in the retroauricular mastoid region and infusing saline solution to a final volume of 100-120 mL. In this fashion, sufficient retroauricular non-hair-bearing skin was obtained for coverage of the auricular cartilage framework without the use of skin grafts or a retroauricular fascial flap. This method of over-expansion nonetheless risks complications including exposure, skin necrosis, and possible elongation of expansion time, or even failure of expansion.

In order to reduce the complications mentioned above, we implanted a 50-80 mL expander beneath the retroauricular fascia to reduce the risk of exposure, and infused saline solution for a total volume of 80-110 mL

to fully expand the fascia and skin. The region of non-hairbearing skin in the mastoid is relatively small, and therefore an 80 mL expander was selected. At the second stage operation, the integrated fascial flap was dissected and covered to the cartilage framework, only imperfect fascia was removed. The thickness of the expanded skin flap was approximately 1.5 mm through treated, it can wrap erect 3D framework and reproduce reconstructed auricle substructure.

Harvesting ipsilateral rib cartilage has been recommended by Nagata^[4] and Firmin.^[12] Dashan *et al.*^[13] routinely harvested rib cartilage from the right side in order to protect the left chest wall and the heart. In the current study, contralateral costal cartilage was routinely harvested to take advantage of the natural bend and tortuosity of the contralateral costal cartilage. After nearly 3 years of observation, there were no side effects to donor site. In this study, a two-dimensional X-ray template combined with a 3D plaster model was used to fabricate a cartilage framework similar to that of the opposite normal auricle. Jiang *et al.*^[14] have reported the use of four different methods to sculpt the cartilaginous framework. In our patients, we used 3-4 layers of costal cartilage to fabricate the framework, which is similar to Jiang's technique.^[14] In adult patients, the seventh rib cartilage was divided into two parts, with the external portion used for the helix and superior crus, and the internal portion used for the main body of the framework, the other cartilage were used for base to increase protrusion.

Stabilization plays an important role in construction of the cartilage framework. Therefore, each part of the framework, and in particular the helix, must have sufficient thickness. The 5-0 stainless steel wire was used to suture and fix all parts of the cartilage framework.

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Conflicts of interest

There are no conflicts of interest.

Patient consent

The patient gave full written consent to the use of images for publication.

Ethics approval

We declare that our research was carried out in a high ethical standard, and the research protocol was approved by our local Ethical Committee.

REFERENCES

1. Tanzer RC. Total reconstruction of the auricle: a 10-year report. *Plast Reconstr Surg* 1967;40:547-50.
2. Brent B. Ear reconstruction with an expansile framework of autogenous rib cartilage. *Plast Reconstr Surg* 1974;53:619-28.
3. Brent B. Technical advances in ear reconstruction with autogenous rib cartilage grafts: personal experience with 1200 cases. *Plast Reconstr Surg* 1999;104:319-34.
4. Nagata S. A new method of total reconstruction of the auricle for microtia. *Plast Reconstr Surg* 1993;92:187-201.
5. Liu J, Sun J, Li X. Total auricular reconstruction without skin grafting. *J Plast Reconstr Aesthet Surg* 2011;64:1312-7.
6. Zhang GL, Zhang JM, Liang WQ, Chen YH, Ji CY. Implant double tissue expanders superposingly in mastoid region for total ear reconstruction without skin grafts. *Int J Pediatr Otorhinolaryngol* 2012;76:1515-9.
7. Hata Y, Hosokawa K, Yano K, Matsuka K, Ito O. Correction of congenital microtia using the tissue expander. *Plast Reconstr Surg* 1989;84:741-51; discussion 752-3.
8. Jiang H, Pan B, Lin L, Cai Z, Zhuang H. Ten-year experience in microtia reconstruction using tissue expander and autogenous cartilage. *Int J Pediatr Otorhinolaryngol* 2008;72:1251-9.
9. Park C. Subfascial expansion and expanded two-flap method for microtia reconstruction. *Plast Reconstr Surg* 2000;106:1473-87.
10. Zhang Q, Quan Y, Su Y, Shi L, Xie Y, Liu X. Expanded retroauricular skin and fascial flap in congenital microtia reconstruction. *Ann Plast Surg* 2010;64:428-34.
11. Chen Z, Zhang W, Huang J, Ren J, Zhu Y. Exceedingly expanded retroauricular flaps for microtia reconstruction. *J Plast Reconstr Aesthet Surg* 2011;64:1448-53.
12. Firmin F. State-of-the-art autogenous ear reconstruction in cases of microtia. *Adv Otorhinolaryngol* 2010;68:25-52.
13. Dashan Y, Haiyue J, Qinghua Y, Bo P, Lin L, Tailing W, Yanmei W, Xiao Q, Hongxing Z. Technical innovations in ear reconstruction using a skin expander with autogenous cartilage grafts. *J Plast Reconstr Aesthet Surg* 2008;61 Suppl 1:S59-69.
14. Jiang H, Pan B, Lin L, Zhao Y, Guo D, Zhuang H. Fabrication of three-dimensional cartilaginous framework in auricular reconstruction. *J Plast Reconstr Aesthet Surg* 2008;61 Suppl 1:S77-85.

Non-invasive focused ultrasound for abdominal circumference reduction: does it really work?

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ABSTRACT

Aim: Non-invasive body contouring is a promising modality. However, due to a lack of good evidence-based data, the mechanism by which contouring occurs remains unclear. The purpose of this study was to evaluate the effect of treatment with the Contour I™ ultrasound system (Ultrashape®, Syneron®, Israel) on abdominal circumference and to compare 2 power levels for efficacy and safety. **Methods:** A prospective, self-controlled double-blind design was used. Thirty-six women, aged 30-45 years, were randomized to receive treatment with the Contour I at high or low acoustic outputs in 3 successive sessions, 1 month apart. Safety was evaluated by adverse events, local skin reaction, and pain. Efficacy was evaluated by the change in abdominal circumference relative to baseline and to the untreated thigh area (internal control). Patients were followed for 28 days after the last treatment session. **Results:** At 1 month after the first session, the mean reductions in abdominal circumference measured 1.65 cm ($P < 0.001$) and 0.87 cm ($P < 0.019$) in the high and low-power groups, respectively. At 1 month after the last session, the cumulative reductions in circumference were 2.56 cm ($P < 0.001$) and 1.49 cm ($P < 0.012$), respectively. There was no change in the internal-control circumference throughout treatment. There were no treatment-induced severe adverse events. **Conclusion:** Multiple successive treatments of the abdominal area with the Contour I lead to a significant progressive reduction in circumference. The magnitude of the reduction is directly correlated to the acoustic power output which suggests that the technology itself is the main cause for the contouring effect.

INTRODUCTION

Body contouring is one of the most popular procedures in aesthetic medicine. There is a growing demand for

non-invasive alternatives to traditional liposuction given the risk of complications^[1-5] and prolonged downtime.^[6] Multiple modalities have been developed including the use of laser and radio-frequency assisted liposuction,



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but these modalities are minimally invasive, painful, and with unproven efficacy. There is still a demand for a true noninvasive modality. Ultrasound has served as a therapeutic tool for more than 50 years.^[7,8] High-power, high-intensity ultrasound is used for ablation and lithotripsy, and low-power ultrasound is used for sonophoresis, sonoporation, gene therapy, and bone healing.^[9] The underlying mechanism of action is thermal or mechanical.

The Contour I™ (Ultrashape®, Syneron®, Yokneam, Israel) is an FDA-approved, non-invasive, focused ultrasound device designed for body contouring. It selectively and mechanically disrupts adipocytes in the subcutaneous fat layer by a process of cavitation without damaging neighboring blood vessels, nerves, or muscles. It is based on a unique design of energy spreading that is focused 1.5 cm beneath the skin for selective targeting of the fat layer without affecting the dermis or deep structures. Its safety and efficacy have been evaluated in several pre-clinical and clinical studies.^[10-14] Treatment requires no anesthesia and may be performed in a non-surgical setting.

Although its efficacy has been shown in numerous studies, as with other modalities, the main factors contributing to the body contouring effect are not clear and can be attributed to other aspects such as skin tightening, inflammatory response and lifestyle change during the treatment period.

The aim of the present study was to evaluate the cumulative effect of successive treatments with the Contour I™ device system on abdominal circumference and to compare two acoustic power levels for efficacy and safety.

METHODS

Setting

A prospective self-controlled, double-blinded trial was performed. The study was approved by the Helsinki Committee of Rabin Medical Center and Sackler Faculty of Medicine, Tel Aviv University, and was conducted in accordance with the Declaration of Helsinki and the International Conference of Harmonization/Good Clinical Practice (ICH-GCP) guidelines. Informed consent for participation in the study was obtained from participants.

Patients

The study cohort consisted of healthy Caucasian women who sought to reduce their abdominal circumference for aesthetic reasons. Inclusion criteria were age 18-50 years, body mass index ≤ 26 kg/m²

and abdominal subcutaneous adipose tissue thickness ≥ 1.5 cm, assessed by manual pinch test. The 1.5 cm criteria was instituted for procedural efficacy and safety according to the Contour I™ mechanical specifications (i.e. the focus of the ultrasonic energy). Exclusion criteria included the presence of any systemic chronic disease, blood coagulopathy or excessive bleeding, history of skin disease in the treatment area, known tendency to form keloids, poor wound healing, skin lesions in the treatment area other than simple nevi, depressed scar in the treatment area, abdominal wall diastasis or hernia on physical examination, and abnormalities in kidney or liver function, lipid profile, or blood count in the last 3 months. Women who were pregnant or lactating at baseline or during the study period and women who had given birth within the last 12 months were also excluded.

Procedure

Treatments were administered to the anterior abdominal area with the Contour I™ system, aided by computerized video tracking [Figure 1]. The targeted area was the lower abdomen, which was marked prior to the procedure. The procedure was performed with the patient in a flat supine position. The treated area is captured by the video system and is automatically divided into points of treatment that are followed by the trained operator of the device.^[10] Subjects were randomized to receive high acoustic power output (Isppa = 440 W/cm²) or low acoustic power (Isppa = 370 W/cm²). These parameters were chosen as both extremes of the device's power output. The focal depth for the selected output was 1.5 cm; the exclusion criteria of abdominal subcutaneous adipose tissue thickness ≥ 1.5 cm was set for this reason. All subjects underwent 3 treatment sessions, 1 month apart, performed by a trained physician. All patients were divided arbitrarily between the high and the low acoustic power groups. Subjects and physician were blinded to the group allocations, as the device was preset before treatment (by a technician), according to the allocation of the subject, and the settings were

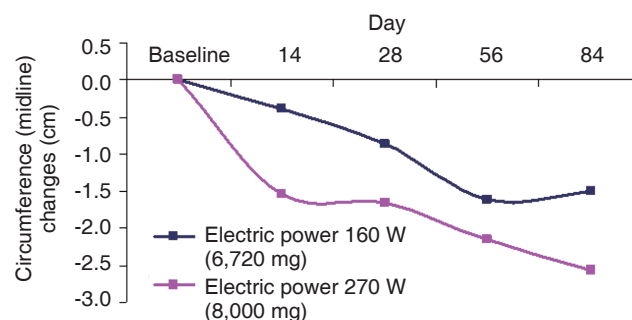


Figure 1: Circumference changes from baseline by day and study group in treatment area

not shown on the device's control panel.

Abdominal circumference measurement

At baseline (prior to treatment, day 1), each subject's abdominal circumference was measured independently by 3 trained operators who were blinded to the group allocation. All used the same standardized calibrated tape according to the same standardized and validated technique, ensuring that subject positioning, posture, and breathing were consistent for all measurements. All measurements were performed in the same anatomical spots, while standing in a standardized position. On days 14 (2 weeks after the first treatment), 28 (4 weeks after the first treatment), 56 (4 weeks after the second treatment), and 84 (4 weeks after the third treatment), measurements were repeated in the same manner, at the same height (per individual), in duplicate. The circumference of the untreated thigh area was also measured at all visits to serve as a control measurement.

Adverse events and patient satisfaction

At each follow-up visit, subjects were examined for adverse events related to the treatment, and local skin reaction. Adverse events were recorded as Medical Dictionary for Regulatory Activities (MedDRA) codes. In addition, the subjects were asked to complete a satisfaction questionnaire, as follows:

- (1) Has there been a visible change in your body contour since the beginning of the study? (yes, favorable change/no change/yes, unfavorable change)
- (2) Have other people commented on a change in your bodily appearance? (yes, favorably/no comments/yes, unfavorably)
- (3) Would you recommend this procedure to your friends? (yes/no)
- (4) Is the Contour I™ system preferable to liposuction? (yes/no)
- (5) How would you grade pain from the treatment on a scale of 1-10?

Statistical analysis

Data were analyzed with SAS software, version 9.1 (SAS Institute, Cary, NC). Paired *t*-test and nonparametric signed-rank test were used to analyze differences in circumference within each study group by time. Student *t*-test and Wilcoxon rank test were used to analyze differences in the reduction in circumference at each time point between the study groups. Mantel-Haenszel chi-square test or linear regression was used to examine *P* values or trends during the study and follow-up periods. All tests applied were two-tailed. *P* values of 5% or less were considered statistically significant.

Table 1: Subject demographic characteristics

Characteristics	High power (Isppa 440 W/cm ²)	Low power (Isppa 370 W/cm ²)	<i>P</i> value
Subjects number	19	17	
Age, years	38.02 ± 1.10	34.21 ± 1.44	0.0407
Weight, kg	61.38 ± 1.64	63.65 ± 1.19	0.2804
BMI, kg/m ²	22.89 ± 0.50	23.57 ± 0.35	0.2786
Height, cm	164.26 ± 1.43	164.12 ± 1.22	0.9396
Fat thickness, mm	25.87 ± 1.70	27.15 ± 1.98	0.6247

Data shown as mean ± SE. BMI: body mass index

RESULTS

Subject disposition and baseline demographic characteristics

All 36 subjects completed the study protocol with 19 in the high-power group and 17 in the low-power group. There were no between-group differences in mean weight, height, body mass index, or abdominal fat thickness [Table 1]. Ages ranged from 30 to 45 years. Mean age was significantly lower in the low-power than the high-power group (34 vs. 38 years, *P* = 0.04), but this 4-year difference had no clinical relevance with respect to abdominal circumference reduction.

Objective efficacy endpoints

Both study groups showed a statistically significant reduction in circumference of the treated area compared to baseline at all time points, with the exception of the low-power group on day 14 (*P* = 0.113), and a cumulative reduction over time [Table 2 and Figure 1]. On day 28 (4 weeks after the first treatment), the mean reduction in abdominal circumference was 1.65 cm in the high-power group (*P* < 0.001) and 0.87 cm in the low-power group (*P* = 0.019). On day 56 (1 month after the third treatment session), the mean reductions in the respective groups were 2.14 cm (*P* = 0.002) and 1.62 cm (*P* < 0.001), and on day 84, 2.56 cm (*P* < 0.001) and 1.49 cm (*P* = 0.012) [Table 2 and Figure 1]. The subjects' weight remained generally constant during the entire period of the study; the overall change in weight did not exceed 1.6% of baseline, with no between-group difference [Table 2].

The high-power group showed a greater and a more consistent reduction in abdominal circumference than the low-power group, but the difference did not reach statistical significance.

Analysis of the control (thigh) areas yielded an increase in circumference in both groups at all study time points [Table 3 and Figure 2], with the exception of the low-power group on day 14 (no change). There was no statistically significant difference in mean internal-control circumference between the groups (data not shown). However, a statistically significant difference

Table 2: Circumference changes from baseline by day and study group in treatment area

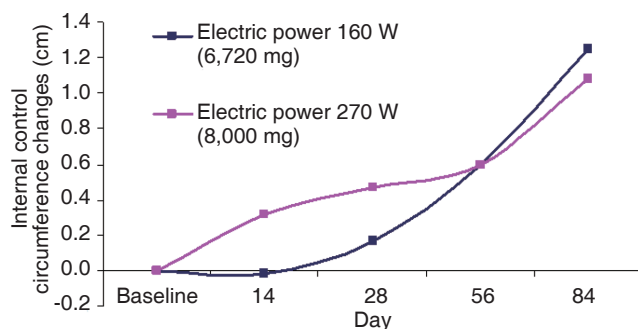
Change from baseline	High power (Isppa 440 W/cm ²)				Low power (Isppa 370 W/cm ²)				Weight differences between groups
	Number	Mean (cm)	SE	P value	Number	Mean (cm)	SE	P value	P value
Day 14	19	-1.54	0.57	0.016	17	-0.39	0.24	0.113	0.8741
Day 28	19	-1.65	0.42	< 0.001	17	-0.87	0.33	0.019	0.9317
Day 56	19	-2.14	0.60	0.002	17	-1.62	0.36	< 0.001	0.9981
Day 84	19	-2.56	0.63	< 0.001	17	-1.49	0.52	0.012	0.9896

Table 3: Circumference changes from baseline by day and study group in control area (untreated thighs)

Change from baseline	High power (Isppa 440 W/cm ²)				Low power (Isppa 370 W/cm ²)			
	Number	Mean (cm)	SE	P value	Number	Mean (cm)	SE	P value
Day 14	19	0.32	0.31	0.316	17	-0.02	0.24	0.933
Day 28	19	0.47	0.37	0.214	17	0.17	0.24	0.484
Day 56	19	0.60	0.26	0.033	17	0.60	0.42	0.176
Day 84	19	1.08	0.32	0.003	17	1.25	0.48	0.019

Table 4: Results of subject satisfaction feedback questionnaire

Questions in questionnaire	Day 28		Day 56		Day 84	
	High power	Low power	High power	Low power	High power	Low power
Subjects reported favorable change in body contour since beginning of study	27.8%	41.2%	61.1%	64.7%	68.4%	58.8%
Subjects reported receiving comments from other people regarding their appearance	27.8%	41.2%	72.2%	70.6%	57.9%	70.6%
Subjects reported to recommend this procedure to their friends	77.8%	76.5%	72.2%	76.5%	68.4%	70.6%
Subjects reported to prefer the Contour I™ treatments over a short-term body contouring procedure	66.7%	70.6%	66.7%	64.7%	89.5%	70.6%

**Figure 2: Circumference changes from baseline by day and study group in control area (untreated thighs)**

was observed in the relative change between the treated and untreated areas at all time points, with the exception of the low-power group on day 14.

Representative photographs of abdominal circumference before and after treatment are shown [Figure 3].

Subject satisfaction

Most subjects felt no pain or only minimal pain during all treatments, 92 of 108 documented encounters (85.1%). The high-power group reported a slightly greater pain sensation when compared to the low-power group: rates of no pain or minimal pain reported by the high-power group were 79.0% after the first

treatment, 84.2% after the second treatment, and 84.2% after the third; corresponding values in the low-power group were 94.1%, 82.3%, and 88.2%. “Unbearable” pain sensation was uncommon across all treatments and modalities. “Unbearable” pain sensation at all 3 sessions was reported by one subject in the low-power group, at the first session by 2 subjects in the high-power group, and at the second and third sessions by one subject in the high-power group. All reports were obtained after the treatments were done, and no treatment had to be stopped secondary to pain. Nevertheless, all subjects who reported “unbearable” pain completed all treatments and follow-up procedures as scheduled.

Evaluation of the feedback questionnaire revealed that on day 28, in response to the item on visible change in appearance, a favorable change was reported by 27.8% of the high-power group and 41.2% of the low-power group [Table 4]. On day 56, these rates rose to 61.1% and 64.7%, respectively. On day 84, 1 month following third treatment, 68.4% of the high-power group reported a positive visible change compared to 58.8% of the low-power group [Table 4]. At the same time point, 57.9% of the high-power group reported positive comments from others, and 68.4% claimed they would recommend the procedure to their friends;

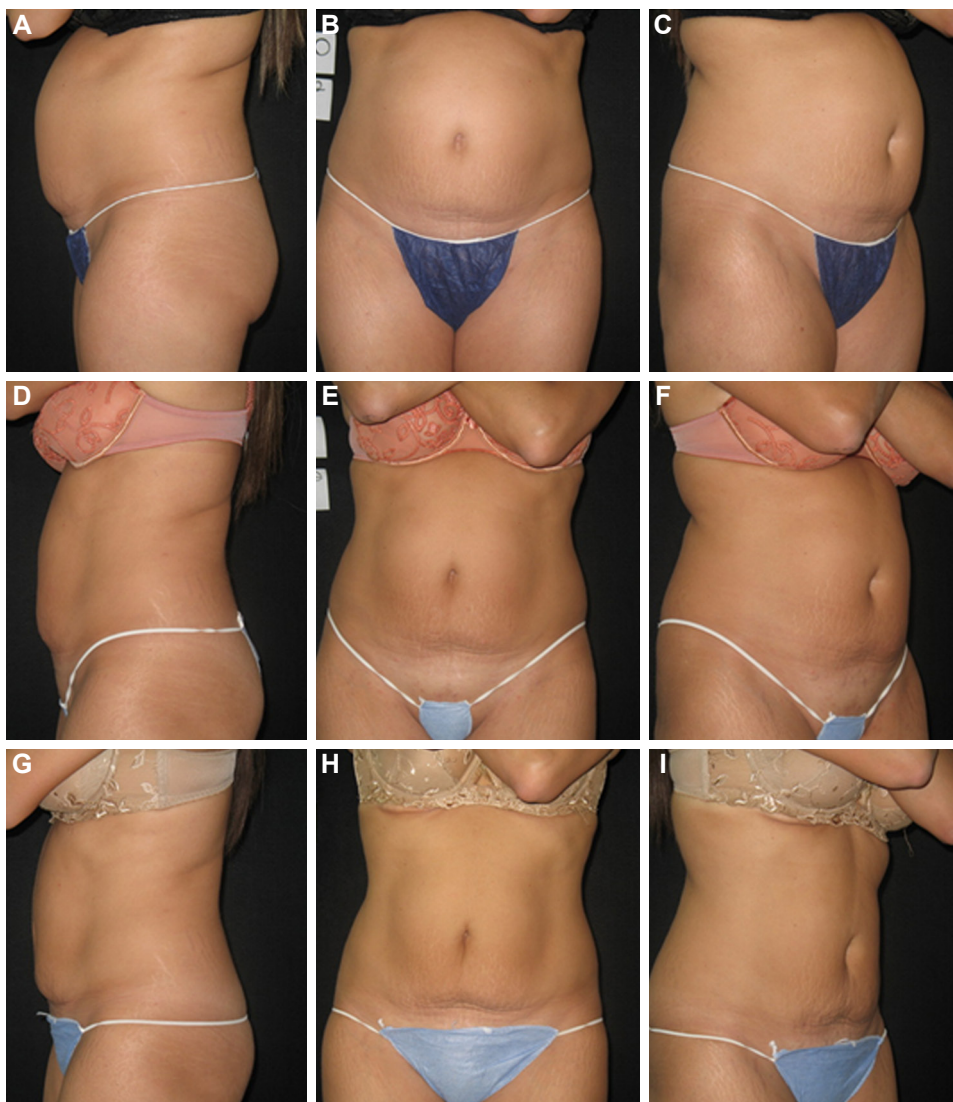


Figure 3: Representative photographs before (A-C) and after (D-I) treatments with the Contour I™ at high power ($I_{\text{sppa}} = 440 \text{ W/cm}^2$) in a single subject. Abdominal circumference decreased by 3.1 cm from baseline at 1 month after first treatment (D-F) and an additional 3.3 cm after 2 additional treatments (G-I) (total reduction, 6.4 cm). The reduction from baseline in the untreated control (thigh) area was 0.4 cm at completion of treatment

the corresponding rates in the low-power group were both 70.6% [Table 4]. More subjects in the high-power group preferred the Contour I™ over liposuction (89.5% vs. 70.6%) [Table 4].

Safety endpoints

Adverse events included erythema, petechial rash, folliculitis, and hyperesthesia. Six subjects (16.7%) reported mild to moderate adverse events, 3 in each group. There was no relationship between the occurrence of adverse events and the acoustic power of the ultrasound. The rate of adverse events per treatment sessions was 5.5%. All adverse events resolved spontaneously by the end of the study, with no need for medical intervention. In no case were the adverse events a reason for terminating a treatment.

DISCUSSION

In the search for the gold standard of non-invasive technology for body contouring, ultrasound energy is a promising tool. The present study evaluated the cumulative effect of successive treatments with the Contour I™ ultrasound system on abdominal circumference, with comparison of two acoustic output levels: 440 W/cm^2 (high power) and 370 W/cm^2 (low power). Prior studies have shown that the ultrasonic energy delivered by the Contour I™ system disrupts cells in the histological level and causes a transient increase in blood lipids.

This study had a few limitations that should be noted. Although statistically significant, the number of participating patients is not very large, and subject

variability, in terms of skin quality and elasticity, can have an effect. In addition, circumference measurement is a rather crude measurement. None of the patients underwent prior liposuction, and therefore no comparison can be made with invasive body contouring of any kind. Another important factor is that patient's lifestyle effect was not a part of this study; the only control was weight and thigh circumference. No strict protocol for diet and physical activity was taken into consideration. A final item for consideration is that study-related patient satisfaction in aesthetic procedures may not be comparable to real-life data from patients who have actually paid for the procedure.

The findings indicate that both power levels, with 3 treatment sessions, led to a statistically significant reduction in circumference of the treated area relative to baseline. Reductions were noted after each treatment session and overall, after all sessions were completed. The high-power setting was more effective than the low-power setting in reducing the circumference of the treated area after the 1st session and after the 3rd session.

As mentioned, both study groups showed a statistically significant reduction in circumference of the treated area compared to baseline at all time points, with the exception of the low-power group on day 14 ($P = 0.113$). Our assumption is that this data results from tissue edema.

The decision to use circumference measurement only, and not imaging studies, was based on two reasons. First, subjects normally measure their circumference by wearing trousers or skirts, and the aim of the treatment is to produce erect posture contouring. Secondly, the supine posture in magnetic resonance imaging or ultrasound scan does not correlate exactly with circumference measurement in the erect position since fat distributes differently in the supine position. Later studies done by Ultrashape® have failed to show a significant correlation between these two measurements.

To isolate the net effect of the device on the specific area treated and to eliminate the possibility of bias in the interpretation of the results, the circumference of the untreated thighs from each subject was used as an internal control. The results showed that the reduction in circumference of the treated area relative to the untreated area (true net effect) was statistically significant at all-time points. This finding was supported by the cumulative effect of the multiple treatments on the reduction in circumference of the treated area as well as the correlation between

the power output and the magnitude of the effect. An interesting finding was a minimal increase of thigh circumference in some groups. It is unclear if beginning a process of body contouring encourages patients to change their life-style to achieve better overall results, or if it permits them to continue their current habits while relying on technology to correct excessive food intake and a lack of physical activity. The low number of adverse events in our cohort is consistent with the high safety profile of the device reported in extensive pre-clinical^[10] and clinical studies.^[11-14]

Subjective feelings of the patients play a critical role in the outcome of aesthetic procedures, aside from objective evidence of the safety and effectiveness. Therefore, subjects completed a questionnaire evaluating their satisfaction with the results as well as the perception of others. Less than half the subjects in both groups noted a favorable visible change following the first treatment. However, on later follow-up visits, those rates nearly doubled.

In summary, multiple treatments over time with the Contour I™ device lead to a cumulative reduction in abdominal circumference. The effect is greater when high acoustic power is used. Patient satisfaction was found to be related to the measured circumference reduction. The findings support the use of the noninvasive Contour I™ as a safe, painless non-invasive means for body contouring with proven efficacy in circumference reduction, correlated to the power of ultrasonic energy delivered. Due to the limitation of the study, more studies, comparing different modalities in non-invasive body contouring, are needed. Objective non-positional related measurements in form of accurate three-dimensional photography with volume calculation may be of future assistance.

Financial support and sponsorship

The study was supported by Ultrashape®, Syneron®. The study sponsors participated in study design and analysis of data.

Conflicts of interest

There are no conflicts of interest.

Patient consent

Informed consent was obtained from participants.

Ethics approval

The study was approved by the Helsinki Committee of Rabin Medical Center and Sackler Faculty of Medicine, Tel Aviv University.

REFERENCES

1. Kelley DE. Thermodynamics, liposuction, and metabolism. *N Engl J Med* 2004;350:2542-4.
2. Kenkel JM, Lipschitz AH, Shepherd G, Armstrong VW, Streit F, Oellerich M, Luby M, Rohrich RJ, Brown SA. Pharmacokinetics and safety of lidocaine and monoethylglycinexylidide in liposuction: a microdialysis study. *Plast Reconstr Surg* 2004;114:516-24; discussion 525-6.
3. Lipschitz AH, Kenkel JM, Luby M, Sorokin E, Rohrich RJ, Brown SA. Electrolyte and plasma enzyme analyses during large-volume liposuction. *Plast Reconstr Surg* 2004;114:766-75; discussion 776-7.
4. Rohrich RJ, Leedy JE, Swamy R, Brown SA, Coleman J. Fluid resuscitation in liposuction: a retrospective review of 89 consecutive subjects. *Plast Reconstr Surg* 2006;117:431-5.
5. Trott SA, Beran SJ, Rohrich RJ, Kenkel JM, Adams WP Jr, Klein KW. Safety considerations and fluid resuscitation in liposuction: an analysis of 53 consecutive subjects. *Plast Reconstr Surg* 1998;102:2220-9.
6. Co AC, Abad-Casintahan MF, Espinoza-Thaebtharm A. Submental fat reduction by mesotherapy using phosphatidylcholine alone vs phosphatidylcholine and organic silicium: a pilot study. *J Cosmet Dermatol* 2007;6:250-7.
7. Fry WJ, Mosberg WH Jr, Barnard JW, Fry FJ. Production of focal destructive lesions in the central nervous system with ultrasound. *J Neurosurg* 1954;11:471-8.
8. Illouz YG. Body contouring by lipolysis: a 5-year experience with over 3000 cases. *Plast Reconstr Surg* 1983;72:591-7.
9. Illouz YG. Illouz's technique of body contouring by lipolysis. *Clin Plast Surg* 1984;11:409-17.
10. Brown SA, Greenbaum L, Shtukmaster S, Zadok Y, Ben-Ezra S, Kushkuley L. Characterization of nonthermal focused ultrasound for noninvasive selective fat cell disruption (lysis): technical and preclinical assessment. *Plast Reconstr Surg* 2009;124:92-101.
11. Ascher B. Safety and efficacy of UltraShape Contour I treatments to improve the appearance of body contours: multiple treatments in shorter intervals. *Aesthet Surg J* 2010;30:217-24.
12. Coleman KM, Coleman WP 3rd, Benchetrit A. Non-invasive, external ultrasonic lipolysis. *Semin Cutan Med Surg* 2009;28:263-7.
13. Moreno-Moraga J, Valero-Altés T, Riquelme AM, Isarria-Marcosy MI, de la Torre JR. Body contouring by non-invasive transdermal focused ultrasound. *Lasers Surg Med* 2007;39:315-23.
14. Teitelbaum SA, Burns JL, Kubota J, Matsuda H, Otto MJ, Shirakabe Y, Suzuki Y, Brown SA. Non invasive body contouring by focused ultrasound: safety and efficacy of the Contour I device in a multicenter, controlled, clinical study. *Plast Reconstr Surg* 2007;120:779-89.

Clinical pathway for an efficient wound care center

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Dr. Chang-Cheng Chang is a well-known microvascular reconstructive and aesthetic plastic surgeon. He is the founder of both Wound Care Center and Aesthetic Medical Center in Chang Gung Memorial Hospital, Chia Yi, in 2010. Dr. Chang had focused his studies on wound care and aesthetic laser medicine, and had published several papers which has proven to help increase treatment outcome in the past five years. He also works closely with the Wound Care Center team which further comprises of plastic surgeons, cardiovascular and metabolic physicians, rehabilitation specialists, social workers, nursing specialists and coordinators. Until present, he has published 22 peer-review scientific articles and authored one book chapter. Dr. Chang has also given numerous lectures at various international societies and centers and received national honorable awards. He is now serving as the head in Aesthetic Medical Center, China Medical University Hospital, Taichung, Taipei, China.

INTRODUCTION

Chronic wound significantly influence patients' quality of life, but wound care procedures can vary between hospitals. Wound management difficulties can be attributed to lack of standardized protocol, well-integrated multidisciplinary team, and specific wound care unit. An establishment of wound care center can help to solve above difficulties with providing wound management service.

The efficient 3-step wound management pathway has the advantage that all involved specialists from

different departments in the hospital can keep tracing the patients' condition in the same pre-existing unit of the healthcare system. In addition to improving the quality of wound care, the establishment of a wound care center will not only improve patients' pain and activities of daily life, but also achieve biopsychosocial healthcare, an approach believed to have positive effects on reducing costs and relieving the burden on the healthcare system.

WOUND MANAGEMENT DIFFICULTIES

The goals of wound management service are to treat



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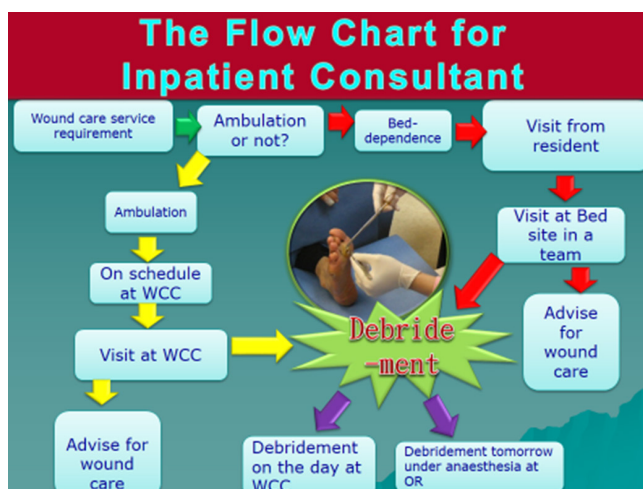


Figure 1: The conceptual framework for wound management service contains three steps, including patient entry/on-site debridement, wound re-evaluation, and individual wound bed preparation. If the ambulation is possible, we will visit the patient at WCC and do the wound management service including debridement or wound care advice. If not, we will go to bed side for visit. OR: operating room; WCC: wound care center

chronic wounds through the stages of healing, reduce infections or complications, and prevent future chronic wounds as well as restore the functional activities of daily life. Although the benefits of wound care service and multidisciplinary teams care have been well discussed,^[1-3] there is a practicing gap about the establishment of an efficient referral system. Patients are often confused regarding whom to see for wound care, and simply receive wound treatment by the individual specialists they visit, in which the specialists may not actively track wounds unless they are consulted again. And healthcare providers (plastic specialists, dermal specialists, general practitioners, nurses) also found it difficult to manage wound care across disparate levels of departments. Furthermore, a lack of organization and specific space may postpone the accurate screening and debridement on-site and on-time. Therefore, the establishment of clinical pathway for wound management service/pathway is crucial.

WOUND MANAGEMENT PATHWAY

The wound management pathway consists of three steps. The first step is patient entry and onsite immediate wound debridement, which indicates the patient referral process where wound center clients were referred from outpatient clinics and inward consultants. The wound care service is initiated once the physician from any other departments considered wound care service necessary. The patient is scheduled for a visit to the wound care center by the coordinator, and the appointed doctor can meet the patient and family on the arranged day to discuss the wound condition with them. Before the wound management pathway was

established, wound inpatients were referred to different specialized departments such as dermatology, surgery, and internal medicine, where wound management care was limited to that department's particular function. And the wound consultant by plastic surgeon usually took a few days even in urgent cases. In wound management pathway, without an uncertain waiting period, senior consultants can approach patients in person with professional wound assessments and perform immediate debridement on-site as needed [Figure 1]. The therapeutic process lags and can be delayed because the chronic wound may need a series of debridement and regular follow-up. The coordinator (nursing staff) also assisted the consultant in scheduling follow-up appointments at the center as clinically needed. The wound care center provides not only one-time wound care, but also a complete program of care including further education and prevention for patients and families.

After being referred and completing the first visit and debridement, the patients proceeded to step two, wound re-evaluation, including neurologic evaluation, vascular evaluation (e.g. Ankle-Brachial Index), and the TIME concept (Tissue, Infection/Inflammation, Moisture imbalance and Edge of wound).^[4] Wound size is measured by the longest length and width of the wound. All individual patient wound profiles are organized into our data bank, which can be analyzed for wound care efficacy and follow-up.

The third step includes setting up the individual wound care plan based on the results of wound re-evaluation in step two. Emphasis is placed on the importance of wound bed preparation (using TIME), early referral between members of the multidisciplinary team, such as vascular team, hyperbaric oxygenation therapy, further education and prevention. Offloading must therefore be addressed in a timely manner.

THE EFFICIENT REFERRAL SYSTEM FOR WOUND CARE CENTER

Multiple studies have supported the efficacy of protocol-based treatment for pressure ulcers, venous stasis ulcers, and diabetic foot ulcers.^[5-7] Edwards *et al.*^[8] confirmed that the implementation of evidence-based protocols for wound assessment and treatment was significantly related to improve healing outcomes. The principle of wound care protocol is easy to comprehend, but the execution of the clinical efficient wound management service is complicated and needs a standardized and well-integrated multidisciplinary team with specific capacity. The main reason for difficulty in wound care is the poor referral system, which may be attributed to

Table 1: Comparison between wound management service and conventional system

	Conventional system	Three-step wound management service
Specific wound care space	-	+++
On-time visit and on-site debridement	-	+++
Integrated multidisciplinary team	+	+++
Feasibility for regular follow-up	+	+++

The three-step wound management service has the advantage of specific wound care unit space, scheduled visit and on-site debridement, integration of multidisciplinary team, and regular following-up

the inability of the physician to identify and diagnose the wound, patient refusal to see the doctor, patient refusal to be referred to a wound care center, and the absence of a highly efficient wound care center. The lack of education and routine training for professional wound care and the huge variety of wound care products, procedures, and treatments pose a potential problem for the implementation of wound care as well.

The major and significant improvement by wound care center mainly relies on the referral system for patients, which decreases the possibility of avoiding delay of early debridement. Comparing to conventional wound care system, the three-step wound management service has the advantage of specific wound care unit space, scheduled visit and on-site debridement, integration of multidisciplinary team, and regular following-up [Table 1]. When wound care center had not been established yet, the assessor for wound consultation was usually the training physician, rather than consultants (surgeon), as they were already busy with other daily practice activities. Hospitalized patients may wait until the night for a visit as they waited until the assessor finished the daily routines. Instead of visiting the patient personally, the senior consultant sometimes assessed the wounds from only photos taken by the training physician. Then, the senior consultant still needed to arrange the next scheduled operation room for wound management (debridement, amputation or flap); this process usually took a few days even in urgent cases. Scheduling was based around the surgeon's activities rather than the patients' requirement. The delay of debridement could have caused processing or even deterioration of the wound. With the integration of the efficient standardized multidisciplinary teams in a specific wound care center, patients can schedule appointments instead of waiting indefinitely for care. Staff can approach patients in person, administer an adequate wound assessment, and perform on-time debridement. Further wound condition follow-up, education, and prevention are also

continually provided.

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Conflicts of interest

There are no conflicts of interest.

Patient consent

No patient involved.

Ethics approval

This kind of paper doesn't need ethical approval.

REFERENCES

1. Doan-Johnson S. The growing influence of wound care teams. *Adv Wound Care* 1998;11:54.
2. Steed DL, Edington H, Moosa HH, Webster MW. Organization and development of a university multidisciplinary wound care clinic. *Surgery* 1993;114:775-8; discussion 778-9.
3. Jaramillo O, Elizondo J, Jones P, Cordero J, Wang J. Practical guidelines for developing a hospital-based wound and ostomy clinic. *Wounds* 1997;9:94-102.
4. Chin GA, Schultz G, Stacey M. Principles of wound bed preparation and their application to the treatment of chronic wounds. *Wound Practice Res* 2004;11:171-4.
5. Kjaer ML, Sorensen LT, Karlsmark T, Mainz J, Gottrup F. Evaluation of the quality of venous leg ulcer care given in a multidisciplinary specialist centre. *J Wound Care* 2005;14:145-50.
6. Hsu CR, Chang CC, Chen YT, Lin WN, Chen MY. Organization of wound healing services: the impact on lowering the diabetes foot amputation rate in a ten-year review and the importance of early debridement. *Diabetes Res Clin Prac* 2015;109:77-84.
7. Chen YT, Chang CC, Shen JH, Lin WN, Chen MY. Demonstrating a conceptual framework to provide efficient wound management service for a wound care center in a tertiary hospital. *Medicine (Baltimore)* 2015;94:e1962.
8. Edwards H, Finlayson K, Courtney M, Graves N, Gibb M, Parker C. Health service pathways for patients with chronic leg ulcers: identifying effective pathways for facilitation of evidence based wound care. *BMC Health Serv Res* 2013;13:86.

Preliminary evidence using negative pressure wound therapy to achieve limb salvage for the ischemic diabetic foot

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Dr. Chang-Cheng Chang is a well-known microvascular reconstructive and aesthetic plastic surgeon. He is the founder of both Wound Care Center and Aesthetic Medical Center in Chang Gung Memorial Hospital, Chia Yi, in 2010. Dr. Chang had focused his studies on wound care and aesthetic laser medicine, and had published several papers which has proven to help increase treatment outcome in the past five years. He also works closely with the Wound Care Center team which further comprises of plastic surgeons, cardiovascular and metabolic physicians, rehabilitation specialists, social workers, nursing specialists and coordinators. Until present, he has published 22 peer-review scientific articles and authored one book chapter. Dr. Chang has also given numerous lectures at various international societies and centers and received national honorable awards. He is now serving as the head in Aesthetic Medical Center, China Medical University Hospital, Taichung, Taipei, China.

ABSTRACT

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Key words:

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Aim: Negative pressure wound therapy (NPWT) in diabetic foot ulcers (DFU) has been discussed in several studies, but without a focus on peripheral arterial disease (PAD), which is a common comorbidity. This study aims to investigate the feasibility of NPWT in the treatment of DFU with PAD in regards to limb salvage and the clinical course. **Methods:** The authors retrospectively collected patients with DFU and PAD diagnosed with either Doppler ultrasound or angiography as the PAD study group. Patients with DFU but no PAD were enrolled as the non-PAD comparison group. NPWT was applied to both PAD and non-PAD subjects. **Results:** There were 10 patients in the PAD group and 3 patients in the non-PAD group. In the PAD



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peripheral arterial disease,
limb salvage

group, there was a 70% limb salvage rate with 14.70 (\pm 10.33) treatment days. The non-PAD comparison group had a higher limb salvage rate (100% vs. 70%, respectively), but a longer treatment time (30.00 vs. 14.70 days, $P < 0.05$, respectively) when compared to the PAD group. The 3 patients in the PAD group who failed limb salvage all had issues related to uncontrolled infection. **Conclusion:** NPWT is a feasible adjuvant therapy for DFU in patients with PAD, with a 70% limb salvage rate. Prolonged treatment time was due to the initial severity of the subjects with multiple comorbidities. The main reason for limb loss was intractable infection.

INTRODUCTION

Negative pressure wound therapy (NPWT) has gained significant interest in the treatment of complex wounds and decreasing wound healing time.^[1-5] Previous studies have suggested that NPWT maximizes blood flow and promotes granulation tissue formation^[6] at an intermittent setting of -125 mmHg.^[7] Other research has also claimed benefits such as oedema reduction,^[8,9] an enhanced wound healing microenvironment, improved immunologic response,^[10,11] bacterial clearance,^[8] and higher flap survival rate.^[8,12] NPWT was originally developed as a treatment for decubitus ulcers and wounds with vascular dysfunction,^[13] but its application has now been diversified to acute complex wounds.^[14] However, there are still few articles that discuss the application of NPWT for the treatment of diabetic foot ulcers (DFU) and its potential for limb salvage.

There is a 10-25% risk in diabetics of developing a foot ulcer,^[15] and foot ulcers make up 84% of all non-traumatic amputations.^[15] Furthermore, patients with diabetic foot amputation have a five year mortality rate as high as 55%.^[16,17] In addition, 39% of diabetic patients present with peripheral arterial occlusive disease,^[18] and 46% of these patients will sustain a limb amputation.^[19] Of the few studies on the benefits of NPWT in the diabetic foot over the last ten years,^[1,20] the focus on the use of NPWT to achieve limb salvage in patients with DFU and peripheral arterial disease (PAD) is even rarer. Armstrong *et al.*^[1] in 2005 suggested an increase in the rate of wound healing and granulation tissue formation in patients with DFU and partial amputation, and Nather *et al.*^[20] in 2010 suggested the use of NPWT in preparation for split-skin graft. However, neither study addressed the presence of PAD. Thus, this study aims to investigate the feasibility of the use of NPWT in the treatment of the diabetic foot ulcer in patient with PAD in regards to limb salvage and clinical course.

METHODS

A retrospective study of patients with DFU was collected following approval by the Institutional Review Board of Chang Gung Memorial Hospital (number 101-3407B). Case inclusion criteria included

age above 18 years and the presence of type 2 diabetes mellitus. PAD was diagnosed with either Doppler ultrasound or angiography in the PAD study group. Patients with DFU but not PAD as documented by Duplex sonography or angiography were enrolled as a comparison non-PAD group ($n = 3$). Exclusion criteria included superficial wound (e.g. Wagner Grade I), burn wounds, malignant disease, collagen vascular disease, and venous insufficiency.

Patient information collected included gender, age, comorbidities, whether or not percutaneous transluminal angiography (PTA) had been performed, admission duration, diabetes diagnosis year (DDY), wound location, wound size, wound culture, University of Texas grading, Wagner grading, DFU score (DFUS), number of NPWT applications, application duration, and if the affected limb(s) had been amputated after at least 6-months of follow up. Wound size was recorded as width \times length (cm \times cm). DFU score assessment was followed by the guidelines established by Beckert *et al.*^[21] of examining for a palpable pedal pulse, probing to bone, ulcer location, and presence of multiple ulcerations. Patients were negatively selected in that only subjects who were unlikely to benefit from standard moist wound therapy, as determined by depth of the wound, were enrolled in this study. Comorbidities that were recorded include the presence of end-stage renal disease, coronary artery disease, hypertension, and cerebrovascular accidents. Treatment days were determined by the days with NPWT application. Limb salvage was determined by successful wound closure or limb preservation throughout the study for a minimum of 6 months follow-up.

Procedure

Initial treatment for the diabetic foot in both PAD and non-PAD subjects involved surgical debridement of infected and non-viable tissue around the wound until healthy tissue was exposed. Wound width and length were measured with a ruler and photos were taken with a digital camera after debridement and throughout the treatment [Figure 1]. NPWT was performed with devices from different companies (Kinetic Concepts Inc., San Antonio, Texas, or RENASYSSTM, or Smith and Nephew, Hull, UK). Application of NPWT devices began with modification of the sterile polyurethane

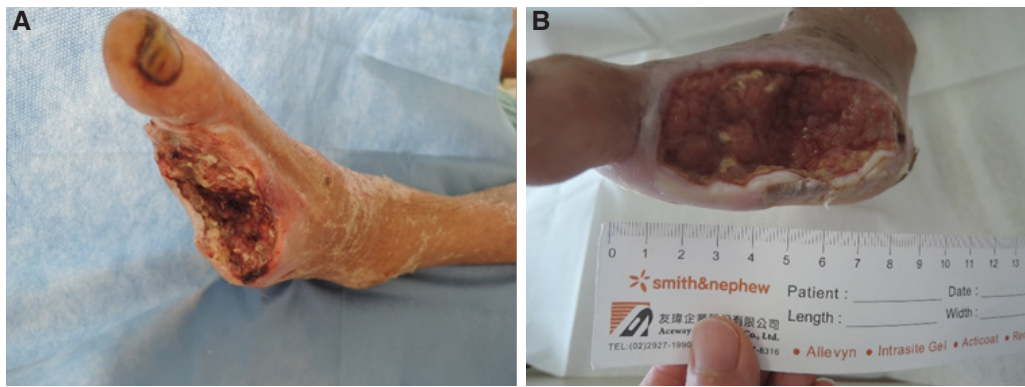


Figure 1: Healing progress of a patient with a dorsal foot ulcer after 9 treatment days of NPWT. A: patient's wound from a diabetic foot ulcer after debridement and partial foot amputation before NPWT; B: increasing granulation observable after NPWT. NPWT: negative pressure wound therapy

sponge dressing to fit the ulcer. The procedure for NPWT device installation followed the manufacture's manual, with pressure which was maintained between -100 and -125 mmHg with the intermittent mode setting.

Sponge dressing were changed every 72 h to allow wound cleansing with sterile saline. Infection control was maintained by the application of antibiotics and debridement if necessary. Wound size was also measured and photographed [Figure 1]. The NPWT device was terminated if any adverse effects, such as ongoing infection or intolerable pain, were observed. NPWT was completed once the wound had closed and patient was discharged.

Statistical analysis

The Mann-Whitney *U* test was performed for continuous variables using SPSS Statistics (version 19). A *P* value < 0.05 was considered to be statistically significant. The power of the study was determined to be 77.6%.

RESULTS

Between October 2010 and June 2015, a total of 13 patients' data were collected. Ten patients with PAD were enrolled in the study group, and 3 patients without PAD were enrolled as a comparison group. The subjects' basic information, wound character, grading, NPWT application, and outcome are presented [Table 1].

Subjects in the PAD study group were between the ages of 36-73 years old, with a mean age of 58.40 (± 10.18) years. Hospital admission duration ranged from 27-103 days, with a mean of 64.44 (± 22.10) days [Table 2]. Many subjects in the study group had additional comorbidities, including end-stage renal disease ($n = 5$), coronary arterial disease ($n = 3$), hypertension ($n = 7$), and a history of cerebrovascular accidents ($n = 2$). Eight of the 10 PAD subjects underwent successful PTA. DDY across subjects

ranged from 8-23 years, with a mean of 14.20 (± 5.67) years [Table 2]. The most common location of the wound was on the dorsal foot ($n = 6$), followed by the plantar surface ($n = 3$). The diabetic foot wound size averaged 71.83 (± 93.44) cm² and ranged 2.25-300 cm² [Table 2]. The DFUS ranged from 1-4, with a mean of 2.60 (± 0.67) [Table 2]. There was only 1 subject with grade D2 and 9 subjects with grade D3 in the University of Texas grading system. There was 1 subject with grade II, 5 subjects with grade III, and 4 subjects with grade IV in Wagner's DM foot grading [Table 2]. The number of NPWT treatments ranged from 1-13, with a mean of 4.90 (± 3.44) treatments. Treatment days ranged from 3-39 days with a mean of 14.70 (± 10.33) days. The limb salvage rate was 70% in the study group. There were three complications, all of which were due to uncontrolled infections, resulting in 1 mortality, 1 amputation, and 1 transferral to another center.

Three non-PAD subjects had grade III (1 subject) and grade IV (2 subjects) scores by Wagner's grading scale. When comparing the PAD and non-PAD subjects, their age, DDY, and hospital admission rates were similar (58.4 vs. 58.3 years old; 14.2 vs. 15.3 years; 64.44 vs. 60 days). The wound area was larger and DFUS were higher in PAD subjects than in non-PAD subjects (71.83 vs. 50.83 cm²; 2.6 vs. 2). However, the number of NPWT application was significantly lower in PAD subjects than in non-PAD subjects ($P < 0.05$). The number of treatment days were correspondingly significantly fewer in PAD subjects ($P < 0.05$) [Table 2]. All 3 complications were in the PAD study group. The non-PAD comparison group had a 100% limb salvage rate. Two non-PAD subjects continued NPWT after the study due to failure of wound closure, but their status had improved at 6-month follow-up. No known adverse events related to NPWT were observed in both groups. In the PAD group, there were no significant differences in clinical

Table 1: Patient characteristics of PAD group (No. 1-10) and non-PAD comparison group (No. 11-13)

No. of subject	Age (years)	Gender	Admission length (days)	Comorbidities	DDY	Wound size (cm ³ /cm ²)	Wound location	No. of VAC application	Treatment time	Follow up (days)	DFUS	Result
1	36	Male	64	PAD, osteomyelitis	9	12 × 4 × 1	Left dorsal foot	3	9	57	1	Spontaneous closure
2	40	Male	63	PAD, osteomyelitis, ESRD, HTN	9	7 × 3	Right plantar	5	15	114	3	Spontaneous closure
3	64	Male	56	PAD, osteomyelitis, HTN, CVA	15	15 × 7	Left dorsal foot	5	15	50	3	Spontaneous closure
4	65	Male	46	PAD	23	11 × 4 × 3	Left dorsal foot	6	18	85	2	Spontaneous closure
5	70	Male	45	PAD, osteomyelitis, ESRD, HTN, CAD	8	4 × 7 × 0.5	Left dorsal foot	3	9	122	2	Spontaneous closure
6	50	Male	69	PAD	20	20 × 15 × 1	Multiple	6	18	108	4	Closure with skin graft
7	61	Male	27	PAD, osteomyelitis, HTN	10	1.5 × 1.5	Left plantar	1	3	211	2	Improved*
8	65	Male	39	PAD, osteomyelitis, ESRD, CAD, HTN	10	17 × 7	Left plantar	2	6	39	3	Extended infection
9	73	Male	68	PAD, osteomyelitis, ESRD, CAD, HTN	18	6 × 3	Right toe	5	15	121	3	Amputation
10	60	Male	103	PAD, osteomyelitis, ESRD, HTN, CVA	20	11 × 3 × 2	Right heel	13	39	20	3	Expired due to sepsis
11	69	Male	86	Osteomyelitis, ESRD, HTN, CVA	15	5 × 4	Left heel	7	21	86	2	Spontaneous closure
12	51	Male	94	Osteomyelitis, HTN	11	11 × 7.5	Left dorsal foot	12	36	384	2	Improved
13	55	Male	60	Osteomyelitis, HTN	20	10 × 5	Right dorsal foot	11	33	388	2	Improved
58.38 ± 11.42		63.08 ± 21.78		14.46 ± 5.25		6.08 ± 3.80		18.23 ± 11.39		137.31 ± 120.38		

*Improved is defined as limb salvage within half a year, but has not achieved wound closure. DDY: diabetes diagnosis year; DFUS: diabetic foot ulcer score; PAD: peripheral arterial disease; ESRD: end stage renal disease; HTN: hypertension; CVA: cerebrovascular accident; CAD: coronary arterial disease; OSSA: oxacillin-sensitive staphylococcus aureus; MRSA: methicillin-resistant staphylococcus aureus

Table 2: Subjects with PAD compare with non-PAD in wound characteristic and NPWT application

Variable	PAD (n = 10)	Non-PAD (n = 3)	P
Age (years)	58.40 ± 10.18	58.33 ± 9.45	
DDY	14.20 ± 5.67	15.33 ± 4.51	
Wound area (cm ²)	71.83 ± 93.44	50.83 ± 31.26	
Texas grading	1 D2, 9 D3	1 B2, 2 B3	
DFUS	2.60 ± 0.67	2.00 ± 0.00	
No. of NPWT application	4.90 ± 3.44	10.00 ± 2.65	< 0.05
NPWT treatment (days)	14.70 ± 10.33	30.00 ± 7.94	< 0.05
Hospital admission (days)	64.44 ± 22.10	60.00 ± 17.78	
Limb salvage (%)	70%*	100%	

*3 infection complications resulting in 1 mortality, 1 amputation, and 1 transfer. Data shown as mean ± SD. DDY: diabetes diagnosis year; DFUS: diabetic foot ulcer score; PAD: peripheral arterial disease; NPWT: negative pressure wound therapy

features between patients who had limb salvage and those who did not [Table 3].

DISCUSSION

PAD is a known risk factor for diabetic foot amputation,^[22] with a 29% amputation rate and 55% 5-year mortality associated with ischemic DFU.^[17] Our studies have also shown that many diabetic patients present with PAD in combination with other comorbidities, including hypertension (70%) and end stage renal disease (50%). Patients with DFU and PAD usually had poor infection control, hence the majority of cases presented with deep infections with

Table 3: Subjects with limb salvaged versus limb loss

Variable	Limb salvaged (n = 7)	Limb loss (n = 3)
Age (years)	55.14 ± 13.25	66.00 ± 6.56
DDY	13.43 ± 6.02	16.00 ± 5.29
Wound area (cm ²)	78.32 ± 102.92	56.67 ± 54.50
Texas grading	1 D2, 6 D3	3 D3
DFUS	2.43 ± 0.98	3.00 ± 0.00
Number of NPWT application	4.14 ± 1.86	6.67 ± 5.69
NPWT treatment (days)	12.43 ± 5.59	20.00 ± 17.06
Hospital admission (days)	52.86 ± 14.58	70.00 ± 32.05

Data shown as mean ± SD. DDY: diabetes diagnosis year; DFUS: diabetic foot ulcer score; NPWT: negative pressure wound therapy

osteomyelitis. Repeated and frequent debridement for infection control created a vicious cycle for these patients, as frequent debridement often led to inevitable limb amputation if there was no strategy for reconstruction due to poor circulation. In this situation, it is reasonable to apply NPWT as an adjuvant therapy to achieve limb salvage. Although there have been few studies on the benefits of NPWT in the treatment of diabetic foot ulcers in the last 10 years,^[1,20] this is the first study to focus on limb salvage following NPWT in patients with diabetic foot ulcers and PAD. The current study shows a 70% limb salvage rate in a group of patients with higher wound severity.

Previous studies have demonstrated that NPWT may facilitate wound healing through extracellular, cellular and complex effects via increased blood

flow, reduced edema, promoted granulation tissue formation, decreased number of microorganisms, and fewer endotoxins.^[6-10] NPWT increases blood flow through increased blood volume, velocity and vascular diameter,^[6] which may help to restore arterial insufficiency in patients with PAD. Further actions on angiogenesis and endothelial proliferation^[6] may result in shortening of wound healing time in subjects with DFU and PAD. Although the gold standard treatments for PAD are angioplasty and surgery to fully restore blood flow, NPWT may also play a role in the wound healing process in patients with DFU and PAD by helping to achieve limb salvage. The length of treatment was not solely determined by the severity of vasculopathy. Both infection and associated comorbidities could prolong the hospitalization as observed in non-PAD subjects in the current study.

Other studies regarding limb salvage treatment for DFU regard use of free flap surgery. Although free flaps have the advantage of covering a larger wound area as compared to NPWT, there are still some drawbacks. Aside from donor side morbidity and prolonged operation time, these patients usually present with other comorbidities and a lack of recipient vessels. Also, the free flap may not always completely fill the wound, leaving a dead space and undermining, which can in turn lead to recurrence or wound dehiscence. Kallio *et al.*^[23] reported in their 2015 study that free flaps required a treatment time of 9 to 20 months, in correlation to the degree of PAD. They also identified a limb amputation rate of 30% for a correctable ischemic artery, and 50% for an uncorrectable ischemic artery in DFU patients with PAD, suggesting that flap use is less desirable in patients with severe PAD. The limb salvage rate for DFU with the use of NPWT ranges from 97-100% in previous studies.^[1,20] On the other hand, the free flap salvage rate range is 76-91%.^[23-25] Further comparative case control studies between NPWT and free flaps would be useful in highlighting the advantages of each.

NPWT also had some limitations. Coverage of wounds with the NPWT sponge makes wound observation and infection detection difficult. Although Banwell *et al.*^[10] suggested that NPWT may provide better bacterial clearance, Mouës *et al.*^[26] and Weed *et al.*^[27] have shown a constant bacterial concentration. In the current study, there were 3 complications consisting of 1 mortality due to sepsis and 2 uncontrolled infections with 1 resulting in limb amputation. Because all 3 failed cases had previously undergone PTA, the lack of circulation was unlikely to have been the only determining factor for limb salvage. Hence, this study

stresses the importance of infection control as a determining factor for the success of NPWT.

In addition to observational studies, long-term data from three non-PAD subjects allows comparison between subjects with and without PAD. The limb salvage rate was as expected lower in PAD than non-PAD subjects. However, in the current study, the mean number of NPWT treatment days was 14.7 in the PAD group, as compared to 30 days in the non-PAD group, which may be related to the lower number of NPWT applications in the PAD group than in the non-PAD group. The prolonged treatment days in the non-PAD subjects may be attributed to their stagnant improvement. Since there are additional determinants, it cannot be concluded that PAD is the sole cause for this unexpected result. These determinants include other comorbidities such as end stage renal disease, hypertension, stroke, and osteomyelitis, all of which were present in one of the non-PAD subjects. The number of lengthened treatment days may have been due to severe osteomyelitis, since most enrolled non-PAD subjects typically had an infection of which the severity rendered standardized moist wound therapy ineffective.

As this study is preliminary with a limited number of subjects in the non-PAD group, further studies with more subjects and higher power are urgently needed to determine significance. Future studies may also include qualitative data including HbA1c, kidney function, hepatic function, hemoglobin, C-reactive protein, and current medications.

In conclusion, patients with DFU and PAD possess many additional comorbidities which limit their options for reconstruction following repeated debridement. NPWT remains an effective method of treatment for DFU with PAD with a high percentage of limb salvage. The limb salvage rate was not as high as in prior studies of NPWT as their subjects were not exclusively patients with DFU and PAD. The main reason for limb loss was intractable infection.

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None.

Conflicts of interest

There are no conflicts of interest.

Patient consent

All patients gave informed consent prior to treatment.

Ethics approval

The study was approved by the Institutional Review

Board of Chang Gung Memorial Hospital (number 101-3407B).

REFERENCES

1. Armstrong DG, Lavery LA; Diabetic Foot Study Consortium. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. *Lancet* 2005;366:1704-10.
2. Eginton MT, Brown KR, Seabrook GR, Towne JB, Cambria RA. A prospective randomized evaluation of negative-pressure wound dressings for diabetic foot wounds. *Ann Vasc Surg* 2003;17:645-9.
3. Lavery LA, Boulton AJ, Niezgoda JA, Sheehan P. A comparison of diabetic foot ulcer outcomes using negative pressure wound therapy versus historical standard of care. *Int Wound J* 2007;4:103-13.
4. Zgonis T, Roukis TS. A systematic approach to diabetic foot infections. *Adv Ther* 2005;22:244-62.
5. Kloth LC. 5 questions-and answers-about negative pressure wound therapy. *Adv Skin Wound Care* 2002;15:226-9.
6. Schintler M. Negative pressure therapy: theory and practice. *Diabetes Metab Res Rev* 2012;28 Suppl 1:72-7.
7. Morykwas MJ, Faler BJ, Pearce DJ, Argenta LC. Effects of varying levels of subatmospheric pressure on the rate of granulation tissue formation in experimental wounds in swine. *Ann Plast Surg* 2001;47:547-51.
8. Morykwas MJ, Argenta LC, Shelton-Brown EI, McGuirt W. Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation. *Ann Plast Surg* 1997;38:553-62.
9. Morykwas MJ, Simpson J, Pungert K, Argenta A, Kremers L, Argenta J. Vacuum-assisted closure: state of basic research and physiologic foundation. *Plast Reconstr Surg* 2006;117:S121-6.
10. Banwell PE, Musgrave M. Topical negative pressure therapy: mechanisms and indications. *Int Wound J* 2004;1:95-106.
11. Hunter JE, Teot L, Horch R, Banwell PE. Evidence-based medicine: vacuum-assisted closure in wound care management. *Int Wound J* 2007;4:256-69.
12. Webster J, Scuffham P, Stankiewicz M, Chaboyer WP. Negative pressure wound therapy for skin grafts and surgical wounds healing by primary intention. *Cochrane Database Syst Rev* 2014;(10):CD009261.
13. Wongworawat MD, Schnall SB, Holtom PD, Moon C, Schiller F. Negative pressure dressing as an alternative technique for the treatment of infected wounds. *Clin Orthop Relat Res* 2003;(414):45-8.
14. Hunter S, Langemo D, Hanson D, Anderson J, Thomson P. The use of negative pressure wound therapy. *Adv Skin Wound Care* 2007;20:90-5.
15. Brem H, Sheehan P, Rosenberg HJ, Schneider JS, Boulton AJ. Evidence-based protocol for diabetic foot ulcers. *Plast Reconstr Surg* 2006;117:S193-209; discussion S210-1.
16. Herman W. The evidence base for diabetes care. 2nd ed. Chichester, West Sussex, UK: Wiley-Blackwell; 2010. p. 403-17.
17. Moulik P, Mtonga R, Gill G. Amputation and mortality in new-onset diabetic foot ulcers stratified by etiology. *Diabetic Care* 2003;26:491-4.
18. Mwebaze RM, Kibirige D. Peripheral arterial disease among adult diabetic patients attending a large outpatient diabetic clinic at a national referral hospital in Uganda: a descriptive cross sectional study. *PLoS One* 2014;9:e10521.
19. Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation. Basis for prevention. *Diabetes Care* 1990;13:513-21.
20. Nather A, Chionh SB, Han AY, Chan PP, Nambiar A. Effectiveness of vacuum-assisted closure (VAC) therapy in the healing of chronic diabetic foot ulcers. *Ann Acad Med Singapore* 2010;39:353-8.
21. Beckert S, Witte M, Wicke C, Konigsrainer A, Coerper S. A new wound-based severity score for diabetic foot ulcers: a prospective analysis of 1,000 patients. *Diabetic Care* 2006;29:988-92.
22. Pemayun TG, Naibaho RM, Novitasari D, Amin N, Minuljo TT. Risk factors for lower extremity amputation in patients with diabetic foot ulcers: a hospital based case-control study. *Diabet Foot Ankle* 2015;6:29629.
23. Kallio M, Vikatmaa P, Kantonen I, Lepantalo M, Venermo M, Tukiainen E. Strategies for free flap transfer and revascularization with long-term outcome in the treatment of large diabetic foot lesions. *Eur J Vasc Endovasc Surg* 2015;50:223-30.
24. Oh TS, Lee HS, Hong JP. Diabetic foot reconstruction using free flaps increases 5-year-survival rate. *J Plast Reconstr Aesthet Surg* 2013;66:243-50.
25. Schirmer S, Ritter RG, Fansa H. Vascular surgery, microsurgery and supramicrosurgery for treatment of chronic diabetic foot ulcers to prevent amputations. *PLoS One* 2013;8:e74704.
26. Mouës CM, Vos MC, van den Bemd GJ, Stijnen T, Hovius SE. Bacterial load in relation to vacuum-assisted closure wound therapy: a prospective randomized trial. *Wound Repair Reg* 2004;12:11-7.
27. Weed T, Ratliff C, Drake DB. Quantifying bacterial bioburden during negative pressure wound therapy: does the wound VAC enhance bacterial clearance? *Ann Plast Surg* 2004;52:276-9; discussion 279-80.

Original Article

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Improvements in the cervical angle and anthropometric distances using elasticum suspension

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Dr. Seong Kee Kim is a board certified plastic surgeon in South Korea. He is an owner of Kim Seong Kee Plastic Surgery Clinic, and has been practicing in it for 30 years. In addition, currently, he is a Clinical Professor in the Department of Plastic Surgery at Yonsei University and Inha University. He is widely recognized in South Korea as an expert in less invasive face lift technique.

ABSTRACT

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Aim: This study aims to characterize the effects of elastic facelifts using the elasticum suspension technique on the cervical angle and anthropometric distances. **Methods:** Forty-six patients underwent surgery. Two 4-5 mm incisions a few centimetres apart were made at sideburn. Through blunt dissection, the deep temporal fascia was approached. An elastic thread (Elasticum®) was anchored to this fascia. A 1.0 cm incision was made just in front of the earlobe. The elastic thread was anchored to the tympanoparotid fascia. Jano needle was passed under the skin surface, as determined by the depth mark of the needle along the cervicomandibular angle, and the elastic threads were looped around the contralateral tympanoparotid fascia. Standard lateral photographs were taken and evaluated. **Results:** The elasticum suspension significantly decreased the cervical angle ($P < 0.001$, $-5.5 \pm 9.8\%$). This procedure significantly decreased the distance from the gonion-gnathion to the labiale inferioris (Gn-Li) ($P < 0.001$, $-18.4 \pm 25.5\%$). The ratio of the distance from Gn to the cervical point (Gn-C) to Gn-Li increased significantly ($P < 0.001$, $62.8 \pm 85.8\%$) and the ratio of the distance from C to the visible thyroid cartilage (C-T) to Gn-C decreased significantly ($P = 0.007$, $-7.1 \pm 45.2\%$). **Conclusion:** Elasticum suspension may be a satisfactory minimally invasive method for facelifts, brow lifts, and neck lifts.



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INTRODUCTION

Most patients who desire to undergo facial rejuvenation want their skin in the mandible and zygomatic regions to be pulled cranially without a visible scar from the facelift.^[1] In order to fulfil these goals, the S-lift followed by minimal access cranial suspension (MACS) lift has been developed and put into practice.^[1-3] The MACS lift requires a smaller incision, less dissection, and less operating time than classical facelift operations. Although it has the advantage of a shorter recovery time, it nonetheless requires at least 2 or 3 weeks before patients can return to social activities. Recently, the elastic facelift technique has been introduced. Using a straight needle and elastic thread fixed at the midpoint of the needle, lower face lifts and neck lifts have been performed.^[4,5] The aim of this study is to characterize the effects of the elastic facelift procedure using elasticum suspension on the cervical angle and anthropometric distances.

METHODS

Patients

A total of 46 patients (4 males, 42 females) were operated on between July 2013 and May 2015. Their mean age was 53.9 ± 10.9 years (range 33-79 years). Most of the patients were in their 40s (12), 50s (15), and 60s (11) [Table 1].

Operative technique

Preoperatively, a marking pen was used to indicate the points where the elastic thread was to be passed and turned toward the entry site of the thread; these points were located about 3.0 cm and 1.5 cm from the preauricular fold, on and superior to a line running from below the earlobe to the lower part of the alar nasi. For the neck lift, 2 lines were marked from the earlobe junction. The 1st line was to a point near the angle of the mandible, and the 2nd line inferior to the 1st for making a loop [Figure 1].

In order to perform an elastic facelift without skin excision, two 4-5 mm incisions a few centimetres apart were made in the sideburn area. Through blunt dissection, the deep temporal fascia was approached. An elastic thread (Elasticum® EP3,5 USP 0 Jano needle® 115 mm, Korpo SRL, Genova, Italy) was anchored to this fascia. In order to perform an elastic neck lift without skin excision, a 1.0 cm incision was made just in front of the earlobe. The elastic thread was anchored to the tympanoparotid fascia (Lore's fascia).^[6]

The Jano needle was passed 5 mm under the skin surface, as determined by the depth mark of the

Table 1: Age distribution of patients

Age (years)	Number
30-39	4
40-49	12
50-59	15
60-69	11
70-79	4
Total (53.9 ± 10.9)	46

needle along the cervicomandibular angle, and the elastic threads were looped around the contralateral Lore's fascia, but were not tied. The same needle was passed along a 1.0 cm parallel line below the cervicomandibular angle. Returning to the initial Lore fascia, the elastic thread was tied under maximum tension. During passage of the Jano needle, slight up-and-down movements of the needle tip allowed the operator to ensure that the pathway of the needle was not too superficial.

In both elastic facelifts and elastic neck lifts, the excess skin could be excised in order to prevent tissue from getting jammed. Just after anchoring, patients were checked for skin dimples, and when present, filler or fat injections were performed [Figure 2].

Lateral photographs

Lateral photographs were taken in the standard manner preoperatively, 2 weeks and 6 months postoperatively.

The patients sat 90 cm from the lens (EFS18-55 mm, Canon EOS600D, Canon, Tokyo, Japan). Flashes (FOMEX D400, Fomex, Seoul, Korea) on both sides were synchronized (Shutter speed: 1/100 s, ISO: 200).

Anthropometric measurements

The preoperative and postoperative profile views were

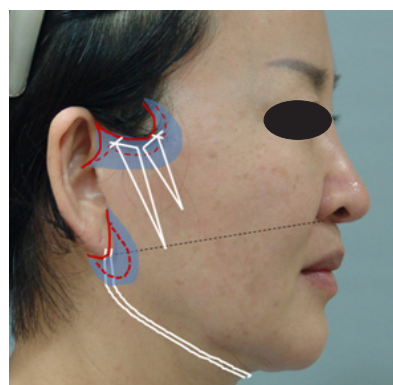


Figure 1: Preoperative design. Red solid lines: skin incision; red dotted lines: extent of skin excision; blue area: extent of dissection; white lines: passages and knots of Elasticum®. Note the lowermost point of elasticum suspension should be superior to the line from below the earlobe to the lower part of the alar nasi to avoid the parotid duct injury

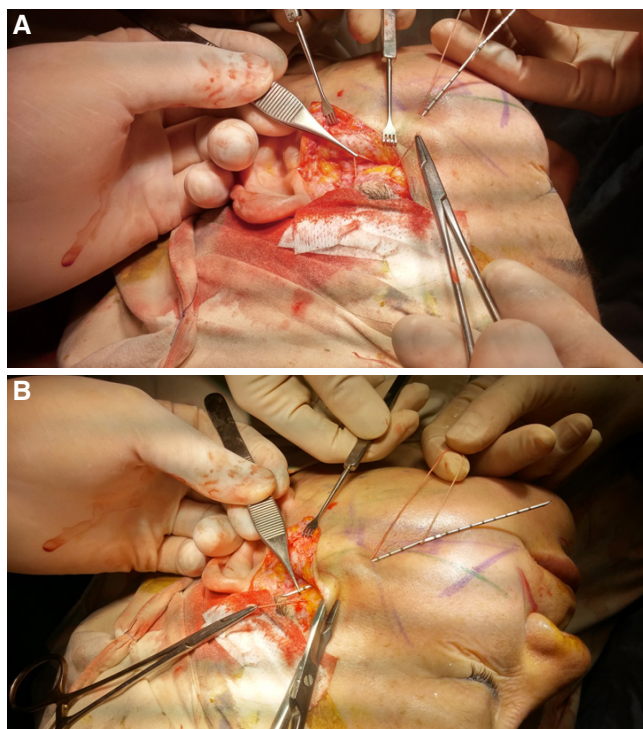


Figure 2: Operative technique. (A) After anchoring to the deep temporal fascia, two-tipped atraumatic needle (Jano needle) travels through the deep subcutaneous tissue. The needle must not be extracted completely. Once it has been pulled halfway out, the thread is pulled through. Depth marks on the shaft of the needle indicate how much of the tip remains in the tissue (about 1 cm or 1/2 cm from the surface of the skin). (B) The posterior tip of needle now become anterior and travels back toward the temporal region through the deep subcutaneous tissue until it reaches the point where the thread enters the deep temporal fascia. The elastic thread is then knotted under traction

evaluated by identifying the glabella (G), pogonion (Pg), menton (M), gonion-gnathion (Gn), cervical point (C) and visible thyroid cartilage (T) [Figure 3].^[7]

The following three anthropometric tangents were drawn: (1) glabella to pogonion (G to Pg); (2) menton to cervical point (M to C); (3) cervical point to visible thyroid cartilage (C to T).

Two angles were measured: (1) mental angle (MA): an angle formed by a line connecting G and Pg and a line from M to C (tangent to the submentum). The Gn point was identified at the intersection of the G-Pg line and the M-C line; (2) cervical angle (CA): an angle formed by a line from M to C and a line from C to T. Since neck flexion might influence the cervical angle, measured cervical angle (mCA) was converted to corrected cervical angle (cCA) by fixing the submental-sternocleidomastoid angle (SSA) at 90°. Thereafter, cCA could be calculated as mCA plus 90° minus SSA ($cCA = mCA + 90^\circ - SSA$) [Figure 4].

Three distances were measured in relation to ear

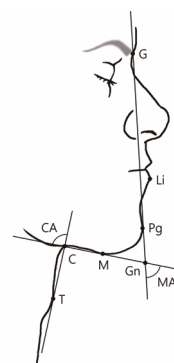


Figure 3: Measured distances and angles. Distance from the Gonion-gnathion (Gn) to cervical point (C) (Gn-C), from Gn to labiale inferioris (Li) (Gn-Li), from C to the visible thyroid cartilage (T) (C-T). Mental angle (MA): an angle formed by a line connecting glabella (G) and pogonion (Pg) and a line from the menton (M) to C. Cervical angle (CA): an angle formed by a line from the M to C and a line from C to T

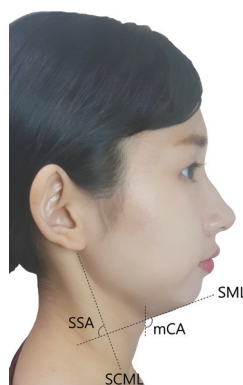


Figure 4: Calculating cCA. $cCA = mCA + 90^\circ - SSA$. mCA: measured cervical angle; SSA: submental-sternocleidomastoid angle; SML: submental line; SCML: sternocleidomastoid line (anterior border of SCM)

Table 2: Operated patients according to the skin excision

Operation type	Region	Number
SE	Face	22
	Neck	9
	Face and neck	3
	Subtotal	34
SO	Face	7
	Neck	2
	Face and neck	3
	Subtotal	12
Total		46

SE: suspension and excision; SO: suspension only

length: (1) distance from gonion-gnathion to cervical point (Gn-C); (2) distance from gonion-gnathion to the labiale inferioris (Li) (Gn-Li); (3) distance from cervical point to visible thyroid cartilage (C-T).

Two ratios were calculated: Gn-C/Gn-Li ratio and C-T/Gn-C ratio.

RESULTS

Among the 46 patients who were operated on, 34 patients [the suspension and excision (SE) group] underwent elasticum suspension with skin excision (face, 22; neck, 9; face and neck, 3). However, 12 patients underwent elasticum suspension without skin excision [suspension-only (SO) group: face, 7; neck, 9; face and neck, 3] [Table 2].

Table 3: Comparison of preoperation and postoperation measurements (mean \pm SD)

		Preoperation	Postoperation	Delta (%)	P-value
Angle (°)	Mental angle	97.2 \pm 9.4	96.9 \pm 9.1	0.1 \pm 9.0	0.831
	Cervical angle	135.1 \pm 15.6	126.9 \pm 14.6	-5.5 \pm 9.8	< 0.001
	Gn-C	56.8 \pm 17.4	62.1 \pm 15.3	19.2 \pm 47.1	0.125
Distance	Gn-Li	52.5 \pm 25.6	38.2 \pm 9.5	-18.4 \pm 25.5	< 0.001
	C-T	36.3 \pm 15.0	33.0 \pm 11.4	0.2 \pm 41.0	0.243
Ratio	Gn-C/Gn-Li	1.2 \pm 0.5	1.6 \pm 0.2	62.8 \pm 85.8	< 0.001
	C-T/Gn-C	0.7 \pm 0.3	0.5 \pm 0.2	-7.1 \pm 45.1	0.007

Delta = (preoperation value - postoperation value)/pre-operation value. Gn: gonion-gnathion; C: cervical point; Li: labialeinferioris; T: thyroid cartilage

Table 4: Angle changes and distance changes in SE group and SO group (mean \pm SD)

		SE	SO	P-value
Δ Angle	Mental angle	0.1 \pm 9.8	0.2 \pm 6.8	0.283
	Cervical angle	-5.9 \pm 10.0	-4.6 \pm 9.5	0.701
	Gn-C	9.2 \pm 43.0	47.8 \pm 48.2	0.386
Δ Distance	Gn-Li	-8.4 \pm 20.4	-46.8 \pm 15.1	0.296
	C-T	4.8 \pm 45.2	-12.6 \pm 22.0	0.027
Δ Ratio	Gn-C/Gn-Li	21.7 \pm 41.6	179.4 \pm 69.7	0.037
	C-T/Gn-C	3.6 \pm 47.4	-37.4 \pm 15.2	0.008

SE: suspension and excision; SO: suspension only; Gn: gonion-gnathion; C: cervical point; Li: labialeinferioris; T: visible thyroid cartilage; Δ Angle: angle change ratio; Δ Distance, distance change ratio; Δ Ratio: ratio change rate

The MA did not change significantly after the operation (97.2 \pm 9.4° preoperatively vs. 96.9 \pm 9.1° postoperatively; P = 0.831, paired t -test). The angle change ratio (ACR) was 0.1 \pm 9.0%. The ACR of the MA did not differ significantly between the SE group (0.1 \pm 9.8%) and the SO group (0.2 \pm 6.8%) (P = 0.283, paired t -test) [Tables 3 and 4].

The CA significantly decreased (P < 0.001, paired t -test) after the operation (135.1 \pm 15.6° preoperatively vs. 126.9 \pm 14.6° postoperatively). The ACR of the CA was -5.5 \pm 9.8%. The ACR of the CA likewise did not differ significantly (P = 0.707, paired t -test) between the SE group (-5.9 \pm 10.0%) and the SO group (-4.6 \pm 9.5%) [Tables 3 and 4].

The Gn-C distance did not differ significantly after the operation (56.8 \pm 17.4% preoperatively vs. 62.1 \pm 15.3% postoperatively; P = 0.125, paired t -test). The distance change ratio (DCR) was 19.2 \pm 47.1%. The DCR of Gn-C did not differ significantly (P = 0.083, paired t -test) between the SE group (9.2 \pm 43.0%) and the SO group (47.8 \pm 48.2%) [Tables 3 and 4].

The Gn-Li distance decreased significantly (52.5 \pm 25.6% preoperatively vs. 38.2 \pm 9.5% postoperatively; P < 0.001, paired t -test). The DCR was -18.4 \pm 25.5%, and the DCR of the Gn-Li distance did not differ significantly (P = 0.296, paired t -test) between the SE group (-8.4 \pm 20.4%) and the SO group (-46.8 \pm 15.1%) [Tables 3 and 4].

The C-T distance did not differ significantly (36.3 \pm 15.0% preoperatively vs. 33.0 \pm 11.4% postoperatively; P = 0.243, paired t -test), and the DCR was 0.2 \pm 41.0%. The DCR of the C-T distance was significantly greater (P = 0.027, paired t -test) in the SE group (4.8 \pm 45.2%) than in the SO group (-12.6 \pm 22.0%) [Tables 3 and 4].

The Gn-C/Gn-Li ratio was significantly greater (P < 0.001, paired t -test) after the operation (1.6 \pm 0.2%) than before the operation (1.2 \pm 0.5%), and the ratio change rate (RCR) was 62.8 \pm 85.8%. The RCR of the Gn-C/Gn-Li ratio was significantly greater (P = 0.037, paired t -test) in the SO group (179.4 \pm 69.7%) than the SE group (21.7 \pm 41.6%) [Tables 3 and 4].

The C-T/Gn-C ratio was significantly lower (P = 0.007, paired t -test) postoperatively (0.5 \pm 0.2%) than preoperatively (0.7 \pm 0.3%), and the RCR was -7.1 \pm 45.1%. The RCR of the C-T/Gn-C ratio was significantly higher in the SE group (3.6 \pm 47.4%) than in the SO group (-37.4 \pm 15.2%) [Tables 3 and 4].

Two complications were observed. In one patient, paralysis of the frontal branch of the facial nerve was noticed. The thread was removed on postoperative day (POD) 2, and the palsy exhibited recovery on POD 7. In the other case, a sialocele occurred due to Stenson's duct folding caused by making the knot under too much tension. The thread was loosened on POD 3, and the swelling had subsided on POD 7.



Figure 5: Preoperative (A) and postoperative 3 years (B) photographs of a 64-year-old woman who had elastic face lift and neck lift with skin excision



Figure 6: Preoperative (A) and postoperative 2 years (B) photographs of a 52-year-old woman who had elastic face lift and neck lift with skin excision

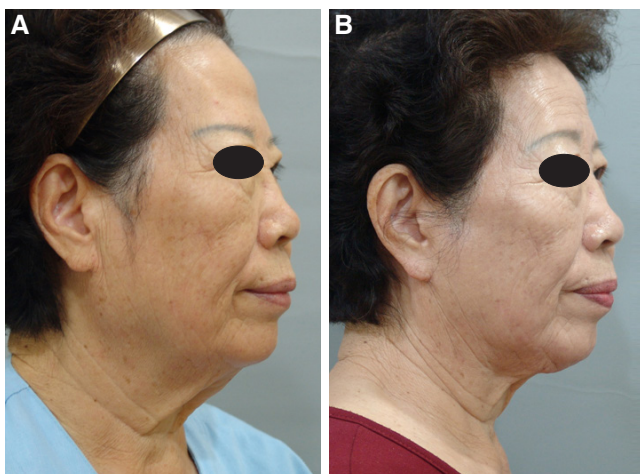


Figure 7: Preoperative (A) and postoperative 3 years (B) photographs of an 80-year-old woman who had elastic neck lift with skin excision

Case 1

A 64-year-old woman had elastic face lift and neck lift with skin excision. At 3 years postoperatively, mental angle (from 89.3° to 83.5°), and cervical angle (from 114.4° to 112.3°) decreased. The Gn-C (from 55.5% to 69.8% of ear length), Gn-Li (from 55.9% to 59.3% of ear length), and C-T (from 42.3% to 45.9% of ear length) increased [Figure 5].

Case 2

A 52-year-old woman had elastic face lift and neck lift with skin excision. At 2 years postoperatively, mental angle (from 107.3° to 77.6°) and cervical angle (from 154.1° to 99.0°) decreased. The Gn-C (from 31.2% to 64.0% of ear length), Gn-Li (from 46.3% to 66.4% of ear length), and C-T (from 29.9% to 33.4% of ear length) increased [Figure 6].

Case 3

A 80-year-old woman had elastic neck lift with skin excision. At 3 years postoperatively, mental angle (from 86.3° to 73.7°), and cervical angle (from 144.7° to 123.7°) decreased. The Gn-C (from 29.2% to 48.3% of ear length), Gn-Li (from 51.6% to 63.8% of ear length) increased. The C-T decreased (from 37.9% to 27.1% of ear length) [Figure 7].

DISCUSSION

Recently, Kang *et al.*^[8,9] performed an elastic lift using Elasticum® (Korpo SRL) and a two-tipped long needle (Jano needle). He evaluated its efficacy by rating skin laxity (6 grades of sagging and laxity) using a skin scanner. For the facelifts, the preoperative and 3-month postoperative median skin laxity scores were 5 (3-6) and 3 (2-4) respectively. For the neck lifts, the median skin laxity grade score was 5 (4-5) preoperatively and 3 at 3 months postoperatively.

Also, Stringer *et al.*^[10] assessed the surface anatomy of 98 parotid ducts using ultrasonography. In most individuals, the duct is better represented as lying within 1.5 cm of the middle half of a line between the lower border of the tragus and the angle of the mouth. Thereafter, we designed the lowermost point of elasticum suspension superior to the line from below the earlobe to the lower part of the alar nasi to avoid the parotid duct injury.

We tried to standardize the pre and postoperative pictures, however, neck flexion cannot be same. Since neck flexion might influence the cervical angle, mCA was converted to cCA by fixing the SSA at 90° as Ellanbogen and Karlen suggested.^[7] Thereafter, cCA

can be calculated as mCA plus 90° minus SSA (cCA = mCA + 90° - SSA) [Figure 4].

In our preoperative and postoperative measurements, elasticum suspension significantly decreased the CA ($P < 0.001$, $-5.5 \pm 9.8\%$). This procedure significantly decreased the Gn-Li distance ($P < 0.001$, $-18.4 \pm 25.5\%$). The Gn-C/Gn-Li ratio increased significantly ($P < 0.001$, $62.8 \pm 85.8\%$), while the C-T/Gn-C ratio decreased significantly ($P = 0.007$, $-7.1 \pm 45.2\%$) [Table 3].

In the 46 patients that were operated on, suspension was performed with skin excision in 34 patients who had skin redundancies, whereas 12 patients underwent suspension without skin excision. The purpose of skin excision was not to pull the skin, but to prevent tissue from getting jammed. Minor jammed soft tissues were found to have subsided spontaneously within a few weeks.

For three parameters (CA, Gn-C, and Gn-Li), no significant differences were found between the SE group and SO group. Regarding the Gn-C/Gn-Li ratio, the RCR was significantly higher in the SO group ($179.4 \pm 69.7\%$) than the SE group ($21.7 \pm 41.6\%$). For the C-T/Gn-C ratio, the RCR was significantly higher in the SE group ($3.6 \pm 47.4\%$) than the SO group ($-37.4 \pm 15.2\%$) [Table 4].

The advantages of the elasticum suspension are as follows. First, Elasticum® does not cut into the tissues. It is composed of a silicone core and surrounding braided polyester, and the braided polyester effectively acts as a nidus for collagen and elastin to develop, similarly to a neoligament.^[11] Second, it has the same consistency as the subcutaneous tissue, and is not palpable after placement. Third, the depth of the thread can be referenced by the depth mark on the Jano needle.

Based on our results, it appears that the elasticum suspension technique may be a satisfactory minimally invasive method for neck lifts. Elasticum suspension can be performed together with submental and superficial jowl liposuction. If necessary, a perioral fat graft could be performed. This technique could be also applied to the lifting the upper lip or breast, as well as scar revisions.

Acknowledgments

We thank Miss Seong Kyung Yoo, BS, for her help in measurement and being object of Figure 4.

Financial support and sponsorship

This study was supported by Inha University (INHA-Research Grant).

Conflicts of interest

There are no conflicts of interest.

Patient consent

Informed consent was obtained from patients.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

REFERENCES

1. Tonnard P, Verpaele A, Monstrey S, Van Landuyt K, Blondeel P, Hamdi M, Matton G. Minimal access cranial suspension lift: a modified S-lift. *Plast Reconstr Surg* 2002;109:2074-86.
2. Saylan Z. Liposhifting instead of lipofilling: treatment of postlipoplasty irregularities. *Aesthet Surg J* 2001;21:137-41.
3. Fulton JE, Saylan Z, Helton P, Rahimi AD, Golshani M. The S-lift facelift featuring the U-suture and O-suture combined with skin resurfacing. *Dermatol Surg* 2001;27:18-22.
4. Capurro S, Rava C, Berlanda M. Elastic MACS and neck lift in men. *CRPUB Med Video J* [Internet]. 2010. Available from: http://www.crpublish.org/index.php?option=com_k2&view=item&id=52:10-elastic-macs-and-neck-lift-in-men&Itemid=114. [Last accessed on 2016 Oct 17]
5. Capurro S. Elastic neck lift in elderly patient. *CRPUB Med Video J* [Internet]. 2009. Available from: http://www.crpublish.org/index.php?option=com_k2&view=item&id=51:09-elastic-neck-lift-in-elderly-patients&Itemid=114. [Last accessed on 2016 Oct 17]
6. Hwang K, Nam YS, Kim DJ, Han SH. Anatomy of tympanoparotid fascia relating to neck lift. *J Craniofac Surg* 2008;19:648-51.
7. Ellenbogen R, Karlin JV. Visual criteria for success in restoring the youthful neck. *Plast Reconstr Surg* 1980;6:26-37.
8. Kang MS, Shin JS, Nam SM, Park ES. Evaluation of elastic lift for facial rejuvenation. *Arch Aesthetic Plast Surg* 2016;22:20-7.
9. Kang MS, Kim SH, Nam SM, Park ES. Evaluation of elastic lift for neck rejuvenation. *Arch Aesthetic Plast Surg* 2016;22:68-73.
10. Stringer MD, Mirjalili SA, Meredith SJ, Muirhead JC. Redefining the surface anatomy of the parotid duct: an in vivo ultrasound study. *Plast Reconstr Surg* 2012;130:1032-7.
11. Huggins RJ, Freeman ME, Kerr JB, Mendelson BC. Histologic and ultrastructural evaluation of sutures used for surgical fixation of the SMAS. *Aesthetic Plast Surg* 2007;31:719-24.

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