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Review

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Fat grafting in autologous breast reconstruction: applications, outcomes, safety, and complications

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Abstract

Autologous fat grafting is an important surgical technique in aesthetic and reconstructive procedures. Fat grafting for breast reconstruction is now an established procedure for adding volume and improving cutaneous pliability; it can be used independently to replace more invasive flap procedures or implants, or as an adjunct for smaller volume supplementation. The breadth of applications in the breast necessitates diversity in technique and approach, and while there is no universally agreed-upon protocol, basic principles have guided the evolution of some commonly adopted tenets. Broadly, fat grafting outcomes are highly favorable but dependent on patient and procedure factors, requiring learned patient selection and expertise in recipient site assessment. Common complications from fat grafting, such as fat necrosis and the development of nodules, are particularly troublesome for post-oncologic patients, requiring considerable pre-surgical consultation for patient education and managing expectations. In addition to volume and contour augmentation, fat grafting has additional beneficial effects that have recently drawn increased attention including pain reduction from implant capsular contracture or post-mastectomy pain syndrome, improved skin quality and reduced fibrosis following radiation, and possible anti-tumorigenic effects. New developments in clinical fat grafting research that are promising include the use of adipose progenitor cells admixed with lipoaspirate for improved volume retention or alternative biologics such as platelet-rich plasma. Preclinically, research towards safe and effective regenerative medicine approaches is actively underway, with the ultimate goal of achieving predictable and increased graft retention, reducing the number of

required surgical procedures and enabling on-table results to reflect procedure outcomes.

Keywords: Fat grafting, fat transfer, autologous breast reconstruction, implant reconstruction, lipo-injection, breast augmentation, graft survival, skin expansion, mastectomy, post-mastectomy pain, breast fibrosis, capsular contracture

INTRODUCTION

Reconstruction is a critical component of post-oncologic care for breast cancer survivors, and thus, reconstructive procedures connected with mastectomy are protected by United States federal law by the Women's Health and Cancer Rights Act of 1998 (WHCRA)[1]. The overall goal of breast reconstruction is to achieve a better quality of life and body image, higher self-esteem and sexuality, and overall psychological well-being[2]. Towards these goals, immediate reconstruction has been found to reduce psychiatric morbidity and body stigma in comparison to delayed reconstruction[3,4]. Methods to optimize outcomes are constantly evolving to address physical and psychological challenges associated with different types of reconstructive procedures to facilitate survivors' acceptance of oncologic care and avoid long-term negative psychological effects[5-7].

Adipose tissue (fat) is a biocompatible and readily available filler with beneficial biologic effects not observed with inert biomaterials. Indications for autologous fat grafting in the breast are rapidly expanding and currently include deformity correction after mastectomy, augmentation, lumpectomy, mastopexy, reduction mammoplasty, and implant reconstruction[8-11]. While initially used primarily as an adjunct procedure to other reconstructive approaches, including implants or muscle flaps, the fat grafting technique has evolved to inject increasingly larger volumes and is now also used for primary reconstruction[12,13]. The benefits of using fat grafting for reconstruction include reduced morbidity compared to more invasive procedures with similar outcomes[14]. In this review, current applications of fat grafting in breast reconstruction will be described with indications, outcomes, and possible complications, along with patient selection criteria, preoperative assessment, variables that affect graft survival, possible challenges, and techniques developed to overcome these challenges in comparison with conventional reconstruction methods.

FAT GRAFTING SECONDARY TO TRADITIONAL RECONSTRUCTION

Conventional methods of breast reconstruction include implants/prosthetics, autologous flaps, or hybrid flaps with an implant. The choice between reconstruction approaches is often based on several factors, including the patient's age, overall health condition, body type, lifestyle, breast size, amount of tissue available for reconstruction, patient's willingness to go through more than one surgery, and recovery time. Other medical or surgical factors used to determine the choice of reconstruction include the extent of oncologic surgery, the further need for post-mastectomy chemotherapy or irradiation, and whether reconstruction is needed for one or both breasts. Additionally, insurance coverage and financial constraints may be considered[15-20].

Implant-based reconstruction

Breast implants remain the most common approach to breast reconstruction according to the American Society of Plastic Surgeons (ASPS) report[21], likely due to the less invasive nature of the surgery and reduced recovery time compared to flap-based reconstruction. Out of the 137,808 breast reconstructions reported by ASPS in 2020, over 103,000 were implant-based, either exclusively or with a tissue expander. In implant-based reconstruction, the implant is placed subpectoral or pre-pectoral and is done either in a single

procedure or as a two-staged approach in which a tissue expander is placed immediately and then subsequently exchanged with an implant in a second procedure[22,23].

Drawbacks of implant reconstruction include the development of contracture, rippling (especially in subglandular reconstruction and thin patients) and/or undesirable physical appearances. For these reasons, surgeons have evolved implant-based surgeries to include autologous fat grafting, either in one setting or as a delayed surgical procedure, as an adjunct for improving contouring and correcting residual deformities. In the two-staged approach, delayed fat grafting is performed to reduce irregularities or implant delineations which may result from the implant folding over time[9,11,23-25]. Studies have shown high levels of patient satisfaction and low complication rates with this technique[26-28]. Fat grafting can effectively improve the overall breast contour and achieve a more natural-looking shape[29,30]. Delayed grafting is often favored as the recipient tissue bed becomes more vascularized with time and yields increased graft retention. Alternatively, pre-pectoral fat grafting may be performed before implant insertion to increase skin quality and flexibility, improve vascularization, and achieve better overall aesthetic outcomes[24,25,31,32]. Sforza and Spear (2021) proposed that the future of hybrid procedures should include creating a concept for hybrid breast augmentation surgery that provides reproducibility, predictability, and better surgical outcomes based on a safe 3D algorithm[33].

While implant reconstruction is an easier surgery in regard to the required surgical technique and patient recovery, there are some drawbacks. Challenges of implant reconstruction include a high early and long-term failure rate, especially when used following radiation therapy. As it is not always possible to address implant failure or unnatural feel with adjunct fat grafting, many patients opt for flap-based reconstruction[25]. Further, autologous reconstruction can be more cost-effective in the long term compared to implants when considering follow-up health care use required to address adverse events.

Reconstruction with autologous flaps

Flap-based reconstruction is a versatile, reliable, and autologous approach for breast reconstruction and may utilize pedicled flaps such as latissimus dorsi (LD) flap, transverse rectus abdominis (TRAM) flap, thoracodorsal artery perforator (TDAP) flap, or free flaps such as free TRAM, free muscle-sparing TRAM, the deep inferior epigastric perforator (DIEP) flap, or superficial inferior epigastric artery (SIEA) flap. Other rarely used free flaps are lumbar artery perforator (LAP) flap, Gluteal artery perforator (GAP) free flap, Upper gracilis flap (either transverse TUG, vertical VUP, or diagonal DUG), profunda artery perforator (PAP) flap, and lateral thigh perforator (LTP) flap[34]. While implant-based reconstruction requires a shorter operative time, autologous flap-based reconstruction such as latissimus dorsi (LD), transverse rectus abdominis (TRAM), and deep inferior epigastric perforator (DIEP) flaps often yield more satisfactory results for patients[35-39]. Sinna *et al.* and Bennet *et al.* reported flap-based reconstruction to provide higher satisfaction and psychological and sexual well-being than implant-based reconstruction[40,41].

Pedicled flaps are most useful in irradiated breast or secondary salvage operations in case of autologous free flap failure. Fat grafting may be used as an adjunct to flap procedures to augment the overall volume and improve contour deformities, minimizing rippling and dynamic distortion[23,40,42-44]. It is relatively common to use fat grafting for secondary procedures after free flaps including PAP and DIEP flaps. Fat grafting may be performed either in conjunction with the flap as a single procedure or as a secondary revision to avoid damaging the flaps and/or circumventing an unfavorable recipient site[45]. Fat grafting with flap reconstruction has also been noted to have beneficial biologic effects in addition to correcting contour deformities, including improvement of skin quality after mastectomy and radiotherapy[46-49].

LD flaps

The LD flap is a pedicled flap and is one of the best options for immediate or delayed breast reconstruction. While the LD is relatively easy to harvest compared to other donor tissues, it is limited by a relatively small tissue volume provided by the flap. One approach to achieve larger volumes is a more aggressive extended LD flap technique which involves harvesting the subcutaneous tissue with the skin paddle, though this carries a higher risk of seroma, contour deformities, and lumbar hernia and is restricted to patients with higher BMI[50-54]. Therefore, LD flaps often require augmentation with an implant to achieve satisfactory aesthetic outcomes[55,56]. Despite its widespread use, the risk associated with implant-based reconstruction after LD flap is relatively high, including capsular contracture, implant displacement and rupture, infection, and the possibility of repeating the procedure to exchange the implant after its expected end-of lifetime[56,57].

Because of the high vascularity of LD flaps[58], they are well suited for adjunct fat grafting to improve the resulting appearance and symmetry [9,49,59,60]. Volumes reported in several studies ranged between 90.5-425 mL[51,56,61,62]. The timing of fat grafting with regard to flap procedures does not appear to affect flap survival, as Zhu *et al.* showed that all flaps survived regardless of the timing of grafting with no fat-grafting-related complications except for one patient that had undergone radiotherapy and needed additional fat grafting[51,63]. Further, Santanelli di Pompeo *et al.* demonstrated that immediate intraoperative fat grafting with LD flap surgery was successful with no effect on the outcome or complications and offered direct visualization of fat injection to avoid flap injury[58]. When used in delayed grafting, fat is grafted into all possible recipient sites, including the LD skin paddle, LD muscle caudal to skin paddle, pectoralis major muscle, serratus muscles, mastectomy skin flaps, and thoracoabdominal advancement flaps. In immediate reconstruction, fat grafting and LD flaps may be used after tumor removal with fat injected only into the LD skin paddle and the LD muscle caudal to the skin paddle or after prophylactic mastectomy with fat grafting into the previously mentioned sites as well as the pectoralis major, serratus muscles, and the non-undermined portion of the mastectomy skin flaps. Thus, adjunct fat grafting for LD flaps is a favorable alternative to implant-based reconstruction with fewer complications and is expected to minimize radiation-induced tissue damage[51]. The determination of the relative superiority of one flap over another, when considering various comparator variables, is inherently subjective in nature. The ultimate decision on flap choice can be made on a more individualized basis based on patient and surgeon preference and available tissue donor sites[51].

Transverse rectus abdominis muscle (TRAM) flaps

Originally introduced by Dr. Carl R. Hartrampf to reconstruct the breast using part of the transverse rectus abdominis muscle either pedicled or as a free flap, TRAM flaps often provide larger volume than LD. Alternatively, the DIEP flap spares the abdominal muscle and uses only the skin, fat, and blood vessels. Ideal candidates for TRAM flaps are non-smoking patients that have undergone a single or double mastectomy and have enough excess tissue to reconstruct a whole breast in addition to the general criteria of flap reconstruction including no comorbidities and good overall health condition. A limitation of TRAM flaps is the development of contour irregularities, mostly the superior portion of the breast, that can be corrected with immediate or delayed fat grafting. Because mammary vessels, the dominant vascular pedicle to TRAM flaps may incur trauma during flap harvest, it is generally advised to graft smaller volumes of fat than in double-pedicled or free TRAM flaps, which likely have enhanced flap vascularity and perhaps superior graft survival[64,65].

Challenges inherent to adjunct fat grafting use

Implant and flap-based reconstruction with fat grafting can be challenging because of the unpredictability of fat retention and the possible need for multiple sessions to achieve satisfactory results[6,11,59]. Additional challenges include volume limitations in the amount injected in a healthy chest wall or previously irradiated

breast[8]. Though fat grafting has been used for years, researchers and clinicians have yet to come together on an evidence-based, standardized protocol for its use, the steps of the procedure, or a measure of its outcome[66]. Therefore, a variety of techniques and approaches have been used for every step of the procedure, from donor and recipient site preparation, harvesting and processing to reinjection and follow-up procedures. However, most plastic surgeons follow Coleman's principles in which fat is first concentrated with centrifugation and then injected in small parcels using multiple passes[67,68].

Patient selection

Candidates for fat grafting with breast reconstruction are selected depending on the patient's acceptance of possible multiple surgeries, the availability of satisfactory donor sites, and the patient's physical and psychological health condition[48]. It is not favorable if the patient is a smoker or belongs to a high-risk group, including diabetic, obese, and of advanced age[56,69]. Throughout the preoperative assessment, gauging the patient's mindset and expectations of fat grafting is crucial to outcome success and the patient's satisfaction. Patients should be informed of the extent of the procedure and possible outcomes to prepare them psychologically for the surgical journey and avoid early disappointment if not well-informed. For example, for some patients, the first fat grafting session does not yield significant volumization and is used to prepare the skin of the recipient site by increasing pliability. Thus, graft resorption is to be expected[13]. To aid in this process, photographs of both donor and recipient sites from different angles can be used to provide a blueprint for both the surgeon and the patient to track the changes and compare the preoperative outlook with the postoperative outcome.

Safety is another important issue to discuss with the patient to eliminate any misunderstanding and explain the frequency of breast imaging needed after the surgery in case of post-cancer reconstruction and the possibility of recurrence and its relation to fat grafting[9,49,70].

TOTAL AUTOLOGOUS BREAST RECONSTRUCTION

Recently, fat grafting has been used independently for primary augmentation, total breast reconstruction, and post-implant replacement, making it an increasingly accepted alternative to the more invasive approaches, especially in small to moderate-volume breasts[47,71-73]. Despite the aforementioned fat grafting drawbacks, using autologous tissue may be preferable to prosthetics for many patients as it does not have implant-related risks and gives a more natural look and feel in comparison[13,46,47,60,74-76]. High satisfaction rates have been described by Dayal, Bhatia, and Hsu, with over 86.5% of patients reported to have either good or very good results judged by an independent panel of surgeons with a mean follow-up of 12 months[47]. Similarly, Groen *et al.* demonstrated that 92% of patients and 89% of surgeons were satisfied with the results. Finally, fat grafting for breast reconstruction has been linked to psychosocial well-being and improved sexual satisfaction[41,77,78].

Total breast reconstruction with fat grafting is recommended for women requiring small to moderate volume augmentation, such as breast-conserving mastectomy (lumpectomy) to fill contour defects[9,46,48,60]. It is also recommended to minimize significant asymmetry and to improve cleavage appearance by adjusting intermammary distance[9]. Along with its application in congenital anomalies, including tuberous breast deformity and Poland syndrome, fat grafting is used to correct breast hypoplasia and to fill the sub-clavicular and anterior axillary fold defects[48,70,79]. In patients desiring removal of their implants and in cases of implant complications, including malposition, rupture, pain, asymmetry, size change, and capsular contracture, fat grafting is an option to restore lost volume[64].

The outcome of total breast reconstruction with fat grafting can often be better than conventional methods; fat is autologous and readily available, and harvesting and injecting are easily performed[13,75]. The hospital stay in fat grafting alone without any other procedures is often short and the patient is discharged sooner. Ecchymosis and edema are expected in the breast or donor site that usually subsides within 3 weeks after surgery. The long-term result of the operation is most accurately assessed starting 3-6 months post-surgery up to a year to assess the extent of resorption[80].

Reconstruction surgical timing and irradiation considerations

Aside from primary reconstruction in aesthetic cases and congenital anomalies, there is no standard timeline for reconstructive fat grafting after primary surgical care. Traditionally, in cases of breast cancer, fat grafting is performed several months after primary reconstruction at the end of oncologic treatment[40,43,44,51]. Radiation therapy following lumpectomy is believed to adversely affect fat graft survival, making the graft more susceptible to ischemia, fibrosis, and necrosis; thus, fat grafting is delayed in these instances until the completion of oncologic treatment[81]. Alternatively, fat grafting used on irradiated expanders is believed to reduce ulceration and implant exposure[82]. When fat grafting is used after the removal of an implant, the best outcomes are achieved when grafting is performed immediately to take advantage of tissue laxity[23].

Safety and complications

The main drawback of the fat grafting procedure is unpredictable long-term graft survival and the lengthy process potentially requiring several surgeries with 3 months intervals in between[47]. Furthermore, as fat grafting is recommended for those with smaller breast sizes, these patients often do not have enough excess donor material for multiple harvesting requirements. In contrast, those with abundant fat reserves tend to have larger breast sizes that present difficulty in achieving symmetry[13,80]. Finally, weight fluctuation immediately prior to or during graft integration periods has been noted to adversely affects outcomes[8,80].

When large volume replacement is necessary, one session of fat grafting is typically not favorable as boluses of avascular fat lead to central necrosis, adipocyte lysis, oil cyst accumulation and calcification. Hence, multiple sessions with moderate injection volumes are needed to achieve the targeted outcome, which may dissuade patients from requiring large-volume replacement[8]. To address this issue, pre-expansion by either external or internal expanders has been suggested[12,83]. However, proposed devices, such as the Brava, are not broadly available commercially, and when available, require arduous patient compliance[84].

Fat grafting complications can be classified as occurring at the donor site, recipient site or systemically. Donor site complications are dependent on the liposuction technique and the surgeon's skill[8], and may include swelling, bruising, dimpling, hematoma, seroma, pain, infection, paresthesia, hypertrophic scarring, and contour irregularities. Injury to the underlying structures due to cannula penetration is possible but rare. Recipient site complications include infection, resorption, ecchymosis, striae, hematoma, fat necrosis, oil cyst formation, calcification, asymmetry, and failure of graft take, along with persistent pain[23,48,70]. Systemic complications are infrequent and include sepsis, septic shock, pneumothorax, fat embolism, and stroke[85].

While overall complications are relatively low, the rates are higher in patients that have had radiotherapy following modified radical mastectomy and skin-sparing mastectomy[23,86]. Smoking is another factor that could cause unexpected complications, and lastly, larger volume grafting in one session is related to a higher rate of complications[87,88].

Understanding the incidence of postoperative complications following breast augmentation with fat grafting could enhance the collaborative decision-making process between patients and healthcare providers in determining whether fat grafting is a preferential alternative to conventional breast implant-based techniques in specific cases. The majority of fat grafting reported complications include asymmetry, skin irregularities, oil cysts, calcifications, palpable cysts, fat necrosis, infection, hematoma, and seroma. The incidence of these complications varied among the studies, with oil cysts and calcifications being the most frequently observed radiologic changes. The formation of oil cysts ranged from 0-83%, with a reported incidence of 6.5% following radiologic analysis. Calcification incidence ranged from 0-80%, with a reported incidence of 4.5% following radiologic analysis. The incidence of fat necrosis varied from 0-10%, with a reported incidence of 1.2% following radiologic analysis. Palpable cysts ranged from 0-15%, with 40%-100% requiring aspiration. The incidences of infection, hematoma, and seroma were under 5%[24,89-91].

There has been an evident concern raised in the literature regarding the possibility that fat grafting could promote cancer recurrence; however, an abundance of clinical evidence has yet to demonstrate any clear statistical correlation between cancer recurrence and autologous fat grafting in the majority of patients[81,92]. Further, the mixed use of implants with fat grafting in reconstructive surgery does not appear to have any impact on cancer recurrence and may reduce implant-associated risks, including fibrosis and capsular contracture[23,93-95]. Similarly, fat grafting used with implants in patients with BRCA mutation undergoing prophylactic mastectomy or in patients who have had implants removed due to breast implant-associated anaplastic large cell lymphoma (ALCL) has not demonstrated any increased risk of tumorigenicity[96-98]. Of note, a 2013 study by Petit *et al*. showed a higher risk of a local oncologic event in intraepithelial neoplasia patients following lipofilling compared to a matched cohort (59 and 118 patients in each respective group) and thus, fat grafting may need to be avoided in patients belonging to this subgroup[99]. Moreover, there has been significant concern regarding fat necrosis and calcification in the breast and its effects on the accuracy of mammography, particularly in patients who are receiving fat grafting after breast cancer surgery. Multiple studies have addressed the detection of subsequent malignancy in the setting of fat necrosis. One such comprehensive systematic review, which incorporated a cohort of 4,601 patients who underwent breast fat grafting for the purpose of augmentation and reconstruction, was conducted to evaluate the incidence of radiographic abnormalities at 12 months post-procedure. The results of this review revealed that 13% of patients developed radiographic abnormalities, which is comparable to the rate of radiographic abnormalities observed following other procedures involving the breast. Another retrospective analysis of mammography reports of 31 patients who underwent fat grafting was conducted, which revealed the presence of microcalcifications, macrocalcifications, and cysts in postoperative mammograms; however, all lesions were classified as benign according to the Breast Imaging Reporting and Data System II. A comparative analysis of 20 pre- and post-graft mammograms was performed, and no statistically significant difference in breast tissue density or in the Breast Imaging Reporting and Data System II assessment category was observed after fat grafting. Together, these findings provide evidence that fat grafting does not impede mammographic follow-up[75,100,101].

Patient selection

Candidates must be carefully selected depending on their acceptance for multiple surgeries, availability of satisfactory and sufficient donor sites, the patient's physical and psychological health condition, and no active cancer or recurrence within 6 months of surgery[48]. Fat grafting outcomes are more favorable in a nonirradiated breast after mastectomy, and if the reconstruction involves only one breast rather than two. In instances where fat grafting is used following implant failure, replacement of the failed implant with fat grafting has been proposed as an option for those that cannot tolerate lengthy flap procedures or those who had recurrent prosthetic infections either due to being high-risk patients or comorbidities that make them unfit for anesthesia.[9,23,69].

FAT GRAFTING FOR PAIN REDUCTION

Some of the most current and emerging uses for autologous fat grafts are scar and pain treatment following mastectomy and/or radiation therapy[23,102-105]. Post-mastectomy pain syndrome (PMPS) entails more than just post-surgical pain; it is neuropathic, lasts at least 6 months, occurs at least 50% of the time and presents as dull, burning, and aching sensations involving the chest, axilla, and ipsilateral upper extremity[23,72,88,106-108]. Activities such as movement, straining, overhead activity, and cold weather can exacerbate symptoms and cause further disability, reduced quality of life, and emotional distress. Jung *et al*. classified PMPS into four categories; phantom breast pain, intercostobrachial neuralgia stemming from intercostobrachial nerve damage, neuroma pain, and other nerve injury pain from surrounding nerves' damage[60,106,107].

The current leading hypotheses on PMPS etiology include intraoperative nerve damage to any of the primary nerves affected during mastectomy or breast surgeries in general, i.e., the intercostobrachial, medial and lateral pectoral, thoracodorsal, long thoracic, and intercostal nerves[108,109], and subsequent entrapment in cicatricial fibrosis, which may incite continuous nervous excitement. Additional hypotheses include decreased circulation, scarring/fibrosis, and injury to fibroblasts after radiation[60,106,110].

Autologous fat grafting is believed to help with scar remodeling, enhance angiogenesis, reduce nerve entrapment within adhesions, and provide local analgesia by inhibiting the inflammatory response[60,105,106,110]. Several Level I/II clinical studies have shown that fat grafting significantly reduces PMPS-related pain compared to control cohorts[87,105,111-113]. Lisa *et al*. analyzed patient demographic factors affecting fat grafting clinical efficacy and found no significant association between age, BMI, the menopausal status of patients, time from oncologic surgery to autologous fat grafting and reduction of the Visual Analogue Scale (VAS) values over time[87]. Smoking and axillary dissection were the main factors significantly associated with reduced fat grafting efficacy (respectively, $P = 0227$ and $P = 0066$)[87].

There have been very few mechanistic rationales provided as to why fat grafting improves fibrosis; however, the above studies postulated regenerative factors produced by tissue after grafting. This aligns well with preclinical research showing that lipoaspirate particles continue to secrete high concentrations of growth factors such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF) and anti-inflammatory cytokines such as IL-10 in hypoxic environments that occur immediately after graft injection[114-116], which may improve the recipient tissue health. However, significantly more research is needed in this area.

FAT GRAFTING FOR CAPSULAR CONTRACTURE

Despite advancements in biomaterial's texture and composition, implant-based breast reconstruction remains challenging due to the prevalence of postoperative complications; one of the most common is capsular contracture, especially in patients who have received radiation therapy as part of their cancer treatment[117]. The development of a thin capsule around foreign objects is a normal immune response following implant placement and typically has minimal effects on the appearance or consistency of the operated breast. However, over-activation of the immune response can cause inflammatory cell recruitment and excessive fibrosis, which results in the synthesis of a matrix around the implant. Fibroblast proliferation and organization into structured capsules in proximity to frustrated, overactive phagocytes lead to chronic inflammation and differentiation of fibroblasts into myofibroblasts, inducing contractile scar tissue. Fat grafting purportedly ameliorates capsular contracture through the same mechanism mentioned by reducing nerve entrapment and also helps to improve skin quality and sensation after contracture[49,60,105]. An early preclinical study demonstrated that autologous fat transfer reversed capsule severity following pericapsular injection by promoting neovascularization of adjacent tissue and softening of the capsule[118]. Subsequent

research has investigated the underlying mechanisms behind these benefits. A recent in vitro study utilizing adipose-derived stem cells demonstrated secretome-mediated reversal of pro-fibrotic cellular and molecular changes in dysfunctional fibroblasts, and proposed that this is the process by which autologous fat transfer softens and reduces capsular fibrosis[119]. Animal models of capsular contracture have shown that autologous fat transfer during implant placement prevents the formation of capsular contracture by reducing tissue inflammation and decreasing collagen content, density, and fiber alignment of the capsular tissue[117,118].

There is also growing clinical evidence identifying autologous fat transfer's role in reducing the risk of capsular contracture[120]. One study showed that it can be a practical treatment strategy for symptomatic capsular contracture by mitigating fibrotic damage, reducing severity, and alleviating symptoms to the extent that corrective surgery was circumvented[121]. Another showed that autologous fat transfer could prevent the recurrence of capsular contracture when serially administered in severe cases of capsular contracture following implant removal and partial capsulectomy[122].

The benefits of autologous fat transfer are even more pronounced when implant-based breast reconstruction involves patients treated with radiation therapy. It is well-documented that there is an increased risk of capsular contracture in these patients[123,124]. The benefits were documented for the first time in 2009 when a study showed that serial autologous fat transfer could improve outcomes and reduce complications of implant-based breast reconstruction for patients with irradiated breasts[125]. Subsequent studies demonstrated that autologous fat transfer before implant placement can improve healing, increase soft tissue stability, and reduce radiation-related complications[126-128]. When used to treat post-irradiation capsular contracture, autologous fat transfer was able to decrease long-term symptom rates and reduce the need for follow-up surgery[129,130]. Although beneficial in many respects, autologous fat transfer is not without limitations. In one study, it was shown to have no protective effect as a prophylactic agent when used to prevent radiation-induced capsular contracture[131]. Additional research is needed to better understand the value and restrictions of using autologous fat transfer for the prevention and treatment of capsular contracture after implant placement.

RESEARCH ON THE HORIZON

Fat grafting is generally considered a versatile and useful method for creating autologous volume despite the aforementioned challenges regarding unpredictable retention. However, past research on total breast reconstruction with fat grafting lacks a compelling argument to convince most reconstructive surgeons to perform it regularly for breast reconstruction. There exists a need for robust and convincing data to demonstrate the superiority of fat grafting in terms of patient satisfaction. In addition, more studies are needed that address retention, cryopreservation, safety, and efficacy. It is yet to be determined if this evidence alone will encourage this technique. Other factors, such as reimbursement and feasibility, do play an important role. To ease the burden incurred by multiple harvesting procedures, research is underway to evaluate cryopreserved fat for future secondary procedures or use biologic adjuncts to improve primary fat grafting retention.

To date, Level I/II evidence suggests cryopreserved lipoaspirate has fair clinical outcomes, primarily when used for small volumization in the face[132,133]. When used in larger volumes for gluteal augmentation, one case study describes outcomes in a 42-year-old male as satisfactory using abdominal adipose cryopreserved at -20 ˚C for 3 months[134]. Therefore, secondary touch-up procedures in the breast following reconstruction may be feasible. However, significantly more work in procedure standardization is required as others have noted potential clinical risks associated with oil cyst accumulation from reduced tissue viability from storage[135] and lack of validation towards sterility, potentially causing infection such as what occurred in a

22-year-old female who presented with multiple abscesses in her face requiring a year to control[136].

To avoid secondary procedures altogether, a variety of biologics have been admixed with lipoaspirate to improve overall take. To date, the most compelling outcomes have been obtained using culture-expanded adipose stem cells, whereby Kolle *et al.* obtained mean retention of 80.9% in 10 patients measured by MRI[137,138]. Other Level I/II studies have reported utilizing platelet-rich plasma[139] or stromal vascular fraction[140,141] with lipoaspirate but have been unable to achieve reliably increased retention outcomes in the breast and both increased the incidence of complications and did not decrease the frequency of multiple operations after lipo-transfer[142]. Current clinical data suggests that the addition of adipose stromal cells (e.g., not culture expanded) to a fat graft may be most effective for treating hypertrophic or retractile scars and thus most critical when transplanting into a "hostile" recipient bed such as irradiated or scarred tissue[143].

Interestingly, studies have been conducted using lipoaspirate washed with Poloxamer 188, or P188 and determined that the copolymer may reduce apoptosis, increase the mass of the fat transplant, improve cell viability and DNA content, and enhance the histological composition of the fat grafts. The investigators hypothesized that P188 copolymer stabilized adipocyte cell membranes to, preventing reabsorption and cell death[144].

CONCLUSION

The surgical approach for breast reconstruction involves many patient-specific factors including anticipated outcomes and patient preference. Fat grafting is, by now, an established part of the surgical armamentarium for improving the final appearance and feel of the breast and can be used successfully as an adjunct to traditional prosthetic/implant or flap-based approaches. With the continuous evolution of the technique, autologous fat grafting is likely to emerge as an acceptable option to provide higher patient satisfaction and improved quality of life.

DECLARATIONS

Authors' contributions

Contributed to review design: De La Cruz C, Kokai L, Shaaban B
Contributed to writing: Shaaban B, Kokai L, Guerrero D, De La Cruz C
Approved the final draft: De La Cruz C, Kokai L

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Ethical approval and consent to participate

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Consent for publication

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REFERENCES

1. U.S. Department of Labor. Women's health and cancer rights act of 1998. Available from: https://www.cms.gov/Regulations-and-Guidance/Health-Insurance-Reform/HealthInsReformforConsume/downloads/WHCRA_Statute.pdf [Last accessed on 29 Mar 2023].
2. Miseré RM, van Kuijk SM, Claassens EL, Heuts EM, Piatkowski AA, van der Hulst RR. Breast-related and body-related quality of life following autologous breast reconstruction is superior to implant-based breast reconstruction - a long-term follow-up study. *Breast* 2021;59:176-82. DOI PubMed PMC
3. Metcalfe KA, Semple J, Quan ML, et al. Changes in psychosocial functioning 1 year after mastectomy alone, delayed breast reconstruction, or immediate breast reconstruction. *Ann Surg Oncol* 2012;19:233-41. DOI PubMed PMC
4. Dean C, Chetty U, Forrest AP. Effects of immediate breast reconstruction on psychosocial morbidity after mastectomy. *Lancet* 1983;1:459-62. DOI PubMed
5. Holly P, Kennedy P, Taylor A, Beedie A. Immediate breast reconstruction and psychological adjustment in women who have undergone surgery for breast cancer: a preliminary study. *Psychol Health Med* 2003;8:441-52. DOI PubMed
6. Noone RB, Frazier TG, Hayward CZ, Skiles MS. Patient acceptance of immediate reconstruction following mastectomy. *Plast Reconstr Surg* 1982;69:632-40. DOI PubMed
7. Carr TL, Groot G, Cochran D, Vancoughnett M, Holtslander L. Exploring women's support needs after breast reconstruction surgery: a qualitative study. *Cancer Nurs* 2019;42:E1-9. DOI PubMed PMC
8. Sufyani MA, Al Hargan AH, Al Shammari NA, Al Sufyani MA. Autologous fat transfer for breast augmentation: a review. *Dermatol Surg* 2016;42:1235-42. DOI PubMed
9. Davis MJ, Perdanasari AT, Abu-Ghname A, et al. Application of fat grafting in cosmetic breast surgery. *Semin Plast Surg* 2020;34:24-9. DOI PubMed PMC
10. Graf RM, Closs Ono MC, Pace D, Balbinot P, Pazio ALB, de Paula DR. Breast auto-augmentation (mastopexy and lipofilling): an option for quitting breast implants. *Aesthetic Plast Surg* 2019;43:1133-41. DOI PubMed
11. Spear SL, Wilson HB, Lockwood MD. Fat injection to correct contour deformities in the reconstructed breast. *Plast Reconstr Surg* 2005;116:1300-5. DOI PubMed
12. Manconi A, De Lorenzi F, Chahuan B, et al. Total breast reconstruction with fat grafting after internal expansion and expander removal. *Ann Plast Surg* 2017;78:392-6. DOI PubMed
13. Siotos C, Aravind P, Prasath V, et al. Pure fat grafting for breast reconstruction: An alternative autologous breast reconstruction. *Breast J* 2020;26:1788-92. DOI PubMed
14. Tomouk T, Mohan AT, Azizi A, Conci E, Brickley EB, Malata CM. Donor site morbidity in DIEP free flap breast reconstructions: a comparison of unilateral, bilateral, and bipedicled surgical procedure types. *J Plast Reconstr Aesthet Surg* 2017;70:1505-13. DOI PubMed
15. Tachi M, Yamada A. Choice of flaps for breast reconstruction. *Int J Clin Oncol* 2005;10:289-97. DOI PubMed
16. Flitcroft K, Brennan M, Spillane A. Making decisions about breast reconstruction: a systematic review of patient-reported factors influencing choice. *Qual Life Res* 2017;26:2287-319. DOI PubMed
17. Hangge PT, Jogerst K, Mohsen A, et al. Making an informed choice: Which breast reconstruction type has the lowest complication rate? *Am J Surg* 2019;218:1040-5. DOI PubMed
18. Whyte S, Bray L, Chan HF, et al. Cognitive bias and therapy choice in breast reconstruction surgery decision-making. *Plast Reconstr Surg* 2022;149:629e-37e. DOI PubMed
19. Whyte S, Bray LJ, Chan HF, et al. Knowledge, consultation time, and choice in breast reconstruction. *Br J Surg* 2021;108:e168-9. DOI PubMed
20. Ananthakrishnan P, Lucas A. Options and considerations in the timing of breast reconstruction after mastectomy. *Cleve Clin J Med* 2008;75 Suppl 1:S30-3. DOI PubMed
21. Surgeons ASoP. 2020 plastic surgery statistics. In: plastic surgery statistics. American Society of Plastic Surgeons; 2020, p. 26. Available from: https://www.plasticsurgery.org/documents/News/Statistics/2020/plastic-surgery-statistics-full-report-2020.pdf [Last accessed on 29 Mar 2023].
22. Kappos EA, Schulz A, Regan MM, et al. Prepectoral versus subpectoral implant-based breast reconstruction after skin-sparing mastectomy or nipple-sparing mastectomy (OPBC-02/ PREPEC): a pragmatic, multicentre, randomised, superiority trial. *BMJ Open* 2021;11:e045239. DOI PubMed PMC
23. Turner A, Abu-Ghname A, Davis MJ, Winocour SJ, Hanson SE, Chu CK. Fat grafting in breast reconstruction. *Semin Plast Surg* 2020;34:17-23. DOI PubMed PMC
24. Blacam C, Momoh AO, Colakoglu S, Tobias AM, Lee BT. Evaluation of clinical outcomes and aesthetic results after autologous fat grafting for contour deformities of the reconstructed breast. *Plast Reconstr Surg* 2011;128:411e-8e. DOI PubMed
25. Razzouk K, Fitoussi A, Al Khori N, Pasquier J, Chouchane L, Tabrizi AR. Breast reconstruction combining lipofilling and prepectoral prosthesis after radiotherapy. *Plast Reconstr Surg Glob Open* 2020;8:e2659. DOI PubMed PMC
26. Kalaaji A, Jönsson V, Baumgartner M. Aesthetic breast augmentation using autologous fat grafting: indications, patient assessment,

and comparison between different processing methods in 204 cases. In: Amin Kalaaji, editor. Plastic and aesthetic regenerative surgery and fat grafting:Springer;2022.p.937-56. DOI

27. Pantelides NM, Srinivasan JR. Rippling following breast augmentation or reconstruction: aetiology, emerging treatment options and a novel classification of severity. *Aesthetic Plast Surg* 2018;42:980-5. DOI PubMed
28. Kanchwala SK, Glatt BS, Conant EF, Bucky LP. Autologous fat grafting to the reconstructed breast: the management of acquired contour deformities. *Plast Reconstr Surg* 2009;124:409-18. DOI PubMed
29. Turner A, Abu-Ghname A, Davis MJ, Winocour SJ, Hanson SE, Chu CK. Fat grafting in breast reconstruction. *Semin Plast Surg* 2020;34:17-23. DOI PubMed
30. Davis MJ, Perdanasari AT, Abu-Ghname A, Gonzalez SR, Chamata E, Rammos CK, Winocour SJ. Application of Fat Grafting in Cosmetic Breast Surgery. *Semin Plast Surg* ;34:24-9. DOI PubMed PMC
31. Mojallal A, Lequeux C, Shipkov C, et al. Improvement of skin quality after fat grafting: clinical observation and an animal study. *Plast Reconstr Surg* 2009;124:765-74. DOI PubMed
32. Gronovich Y, Winder G, Maisel-Lotan A, et al. Hybrid prepectoral direct-to-implant and autologous fat graft simultaneously in immediate breast reconstruction: a single surgeon's experience with 25 breasts in 15 consecutive Cases. *Plast Reconstr Surg* 2022;149:386e-91e. DOI PubMed
33. Sforza M, Spear S. Hybrid implant and grafted fat breast augmentation: designing the pathway to a future with breasts free of silicone breast implants. *Aesthet Surg J* 2021;41:NP1473-85. DOI PubMed PMC
34. Nahabedian MY. Factors to consider in breast reconstruction. *Womens Health (Lond)* 2015;11:325-42. DOI PubMed
35. Saulis AS, Mustoe TA, Fine NA. A retrospective analysis of patient satisfaction with immediate postmastectomy breast reconstruction: comparison of three common procedures. *Plast Reconstr Surg* 2007;119:1669-76. DOI PubMed
36. Eltahir Y, Krabbe-Timmerman IS, Sadok N, Werker PMN, de Bock GH. Outcome of quality of life for women undergoing autologous versus alloplastic breast reconstruction following mastectomy: a systematic review and meta-analysis. *Plast Reconstr Surg* 2020;145:1109-23. DOI PubMed
37. Siqueira HFF, Teixeira JLA, Lessa Filho RDS, et al. Patient satisfaction and quality of life in breast reconstruction: assessment of outcomes of immediate, delayed, and nonreconstruction. *BMC Res Notes* 2020;13:223. DOI PubMed PMC
38. Kolasinski J. Total breast reconstruction with fat grafting combined with internal tissue expansion. *Plast Reconstr Surg Glob Open* 2019;7:e2009. DOI PubMed PMC
39. Elliott LF, Beegle PH, Hartrampf CR. The lateral transverse thigh free flap: an alternative for autogenous-tissue breast reconstruction. *Plast Reconstr Surg* 1990;85:169-78. PubMed
40. Sinna R, Delay E, Garson S, Delaporte T, Toussoun G. Breast fat grafting (lipomodelling) after extended latissimus dorsi flap breast reconstruction: a preliminary report of 200 consecutive cases. *J Plast Reconstr Aesthet Surg* 2010;63:1769-77. DOI PubMed
41. Bennett KG, Qi J, Kim HM, et al. Association of fat grafting with patient-reported outcomes in postmastectomy breast reconstruction. *JAMA Surg* 2017;152:944-50. DOI PubMed PMC
42. Thekkinkattil DK, Salhab M, McManus PL. Feasibility of autologous fat transfer for replacement of implant volume in complicated implant-assisted latissimus dorsi flap breast reconstruction. *Ann Plast Surg* 2015;74:397-402. DOI PubMed
43. Missana MC, Laurent I, Barreau L, Balleyguier C. Autologous fat transfer in reconstructive breast surgery: indications, technique and results. *Eur J Surg Oncol* 2007;33:685-90. DOI PubMed
44. Bonomi R, Betal D, Rapisarda IF, Kalra L, Sajid MS, Johri A. Role of lipomodelling in improving aesthetic outcomes in patients undergoing immediate and delayed reconstructive breast surgery. *Eur J Surg Oncol* 2013;39:1039-45. DOI PubMed
45. Niddam J, Vidal L, Hersant B, Meningaud JP. Primary fat grafting to the pectoralis muscle during latissimus dorsi breast reconstruction. *Plast Reconstr Surg Glob Open* 2016;4:e1059. DOI PubMed PMC
46. Chan CW, McCulley SJ, Macmillan RD. Autologous fat transfer-a review of the literature with a focus on breast cancer surgery. *J Plast Reconstr Aesthet Surg* 2008;61:1438-48. DOI PubMed
47. Dayal A, Bhatia A, Hsu JT. Fat grafting in aesthetics. *Clin Dermatol* 2022;40:35-44. DOI PubMed
48. KA; ASPS Fat Graft Task Force. Current applications and safety of autologous fat grafts: a report of the ASPS fat graft task force. *Plast Reconstr Surg* 2009;124:272-80. DOI PubMed
49. Coleman SR, Saboeiro AP. Primary breast augmentation with fat grafting. *Clin Plast Surg* 2015;42:301-6, vii. DOI PubMed
50. Branford OA, Kelemen N, Hartmann CEA, Holt R, Floyd D. Subfascial harvest of the extended latissimus dorsi myocutaneous flap in breast reconstruction: a comparative analysis of two techniques. *Plast Reconstr Surg* 2013;132:737-48. DOI PubMed
51. Zhu L, Mohan AT, Vijayasekaran A, et al. Maximizing the volume of latissimus dorsi flap in autologous breast reconstruction with simultaneous multisite fat grafting. *Aesthet Surg J* 2016;36:169-78. DOI PubMed
52. Jeon BJ, Lee TS, Lim SY, et al. Risk factors for donor-site seroma formation after immediate breast reconstruction with the extended latissimus dorsi flap: a statistical analysis of 120 consecutive cases. *Ann Plast Surg* 2012;69:145-7. DOI PubMed
53. Munhoz AM, Montag E, Arruda EG, Sturtz G, Gemperli R. Management of giant inferior triangle lumbar hernia (Petit's triangle hernia): a rare complication following delayed breast reconstruction with extended latissimus dorsi myocutaneous flap. *Int J Surg Case Rep* 2014;5:319-23. DOI PubMed PMC
54. Casella D, Nanni J, Lo Torto F, et al. Extended latissimus dorsi kite flap (ELD-K Flap): revisiting an old place for a total autologous breast reconstruction in patients with medium to large breasts. *Aesthetic Plast Surg* 2021;45:390-401. DOI PubMed
55. Chang DW, Youssef A, Cha S, Reece GP. Autologous breast reconstruction with the extended latissimus dorsi flap. *Plast Reconstr*

Surg 2002;110:751-9; discussion 760. DOI PubMed

56. Economides JM, Song DH. Latissimus dorsi and immediate fat transfer (LIFT) for complete autologous breast reconstruction. *Plast Reconstr Surg Glob Open* 2018;6:e1656. DOI PubMed PMC
57. Papa G, Frasca A, Renzi N, et al. Protocol for prevention and monitoring of surgical site infections in implant-based breast reconstruction: preliminary results. *Medicina (Kaunas)* 2021;57:151. DOI PubMed PMC
58. di Pompeo F, Laporta R, Sorotos M, Pagnoni M, Falesiedi F, Longo B. Latissimus dorsi flap for total autologous immediate breast reconstruction without implants. *Plast Reconstr Surg* 2014;134:871e-9e. DOI PubMed
59. Maione L, Caviggioli F, Vinci V, et al. Fat graft in composite breast augmentation with round implants: a new concept for breast reshaping. *Aesthetic Plast Surg* 2018;42:1465-71. DOI PubMed
60. Winkler NS, Tran A, Kwok AC, Freer PE, Fajardo LL. Autologous fat grafting to the breast: an educational review. *J Breast Imaging* 2022;4:209-21. DOI
61. Escandón JM, Ali-Khan S, Christiano JG, et al. Simultaneous fat grafting during tissue expander-to-implant exchange: a propensity score-matched analysis. *Aesthetic Plast Surg* 2022;Epub ahead of print. DOI PubMed
62. Mushin OP, Myers PL, Langstein HN. Indications and controversies for complete and implant-enhanced latissimus dorsi breast reconstructions. *Clin Plast Surg* 2018;45:75-81. DOI PubMed
63. Couto-González I, Vila I, Brea-García B, et al. Safety of large-volume immediate fat grafting for latissimus dorsi-only breast reconstruction: results and related complications in 95 consecutive cases. *Aesthetic Plast Surg* 2021;45:64-75. DOI PubMed
64. Delay E, Guerid S. The role of fat grafting in breast reconstruction. *Clin Plast Surg* 2015;42:315-23, vii. DOI PubMed
65. Fayanju OM, Garvey PB, Karuturi MS, Hunt KK, Bedrosian I. Surgical procedures for advanced local and regional malignancies of the breast. In: Kirby I. Bland, dward M. Copeland, editors. The Breast: Elsevier;2018.p.778-801. e4. DOI
66. Lin JY, Wang C, Pu LL. Can we standardize the techniques for fat grafting? *Clin Plast Surg* 2015;42:199-208. DOI PubMed
67. Coleman SR. Long-term survival of fat transplants: controlled demonstrations. *Aesthetic Plast Surg* 1995;19:421-5. DOI PubMed
68. Coleman SR. Structural fat grafting. *Aesthet Surg J* 1998;18:386, 388. DOI PubMed
69. Lesniak DM, Sarfati I, Meredith I, et al. Fat grafting before delayed prophylactic mastectomy and immediate implant reconstruction for patients at high risk of complications. *Plast Reconstr Surg* 2022;149:52-6. DOI PubMed
70. Simonacci F, Bertozzi N, Grieco MP, Grignaffini E, Raposio E. Procedure, applications, and outcomes of autologous fat grafting. *Ann Med Surg (Lond)* 2017;20:49-60. DOI PubMed PMC
71. Khouri RK, Rigotti G, Cardoso E, Khouri RK Jr, Biggs TM. Megavolume autologous fat transfer: part I. Theory and principles. *Plast Reconstr Surg* 2014;133:550-7. DOI PubMed
72. Khouri RK, Rigotti G, Khouri RK, Rotemberg SC, Cardoso E, Biggs TM. Total breast reconstruction with autologous fat transfer: review of a seven-year multicenter experience. *Plast Reconstr Surg* 2014;134:84-5. DOI
73. Abboud MH, Dibo SA, Abboud NM. Power-assisted liposuction and lipofilling: techniques and experience in large-volume fat grafting. *Aesthet Surg J* 2020;40:180-90. DOI PubMed
74. Pagliara D, Vitagliano S, Mangialardi ML, et al. The role of fat grafting on contracted breast implant capsules: a retrospective comparative histological and immunohistochemical study. *J Plast Reconstr Aesthet Surg* 2022;75:1083-93. DOI PubMed
75. Coleman SR, Saboeiro AP. Fat grafting to the breast revisited: safety and efficacy. *Plast Reconstr Surg* 2007;119:775-85; discussion 786. DOI PubMed
76. Saint-Cyr M, Rojas K, Colohan S, Brown S. The role of fat grafting in reconstructive and cosmetic breast surgery: a review of the literature. *J Reconstr Microsurg* 2012;28:99-110. DOI PubMed
77. Brown AWW, Kabir M, Sherman KA, Meybodi F, French JR, Elder EB. Patient reported outcomes of autologous fat grafting after breast cancer surgery. *Breast* 2017;35:14-20. DOI PubMed
78. Qureshi AA, Odom EB, Parikh RP, Myckatyn TM, Tenenbaum MM. Patient-reported outcomes of aesthetics and satisfaction in immediate breast reconstruction after nipple-sparing mastectomy with implants and fat grafting. *Aesthet Surg J* 2017;37:999-1008. DOI PubMed
79. Bayram Y, Sezgic M, Karakol P, Bozkurt M, Filinte GT. The use of autologous fat grafts in breast surgery: a literature review. *Arch Plast Surg* 2019;46:498-510. DOI PubMed PMC
80. Delay E, Meruta AC, Guerid S. Indications and controversies in total breast reconstruction with lipomodeling. *Clin Plast Surg* 2018;45:111-7. DOI PubMed
81. Hanson SE, Kapur SK, Hwang RF, Dryden MS. Autologous fat grafting in breast reconstruction: implications for follow-up and surveillance. *Gland Surg* 2021;10:487-93. DOI PubMed PMC
82. Ribuffo D, Atzeni M, Guerra M, et al. Treatment of irradiated expanders: protective lipofilling allows immediate prosthetic breast reconstruction in the setting of postoperative radiotherapy. *Aesthetic Plast Surg* 2013;37:1146-52. DOI PubMed
83. Uda H, Sugawara Y, Sarukawa S, Sunaga A. Brava and autologous fat grafting for breast reconstruction after cancer surgery. *Plast Reconstr Surg* 2014;133:203-13. DOI PubMed
84. Khouri R, Del Vecchio D. Breast reconstruction and augmentation using pre-expansion and autologous fat transplantation. *Clin Plast Surg* 2009;36:269-80, viii. DOI PubMed
85. Ross RJ, Shayan R, Mutimer KL, Ashton MW. Autologous fat grafting: current state of the art and critical review. *Ann Plast Surg* 2014;73:352-7. DOI PubMed
86. Dewael S, Vandevoort M, Fabré G, Nanhekhan L. Immediate versus delayed autologous breast reconstruction: a retrospective

matched cohort study of irradiated patients. *J Plast Reconstr Aesthet Surg* 2019;72:1769-75. DOI PubMed

87. Lisa AVE, Murolo M, Maione L, et al. Autologous fat grafting efficacy in treating PostMastectomy pain syndrome: A prospective multicenter trial of two Senonetwork Italia breast centers. *Breast J* 2020;26:1652-8. DOI PubMed
88. Ercan A, Baghaki S, Suleymanov S, Aydın O, Konukoglu D, Cetinkale O. Effects of Cigarette Smoke on Fat Graft Survival in an Experimental Rat Model. *Aesthetic Plast Surg* 2019;43:815-25. DOI PubMed
89. Gornitsky J, Viezel-Mathieu A, Alnaif N, Azzi AJ, Gilardino MS. A systematic review of the effectiveness and complications of fat grafting in the facial region. *JPRAS Open* 2019;19:87-97. DOI PubMed PMC
90. Ørholt M, Larsen A, Hemmingsen MN, et al. Complications after breast augmentation with fat grafting: a systematic review. *Plast Reconstr Surg* 2020;145:530e-7e. DOI PubMed
91. Laloze J, Varin A, Gilhodes J, et al. Cell-assisted lipotransfer: friend or foe in fat grafting? *J Tissue Eng Regen Med* 2018;12:e1237-50. DOI PubMed
92. Vyas KS, DeCoster RC, Burns JC, et al. Autologous fat grafting does not increase risk of oncologic recurrence in the reconstructed breast. *Ann Plast Surg* 2020;84:S405-10. DOI PubMed
93. Wu ZY, Han J, Kim HJ, et al. Breast cancer outcomes following immediate breast reconstruction with implants versus autologous flaps: a propensity score-matched study. *Breast Cancer Res Treat* 2022;191:365-73. DOI PubMed
94. Eriksen C, Frisell J, Wickman M, Lidbrink E, Krawiec K, Sandelin K. Immediate reconstruction with implants in women with invasive breast cancer does not affect oncological safety in a matched cohort study. *Breast Cancer Res Treat* 2011;127:439-46. DOI PubMed
95. Nava MB, Catanuto G, Rocco N. Hybrid breast reconstruction. *Minerva Chir* 2018;73:329-33. DOI PubMed
96. Senkus E, Kyriakides S, Ohno S, et al; ESMO Guidelines Committee. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015;26 Suppl 5:v8-30. DOI PubMed
97. Alhamad S, Guerid S, El Fakir EH, Biron P, Tourasse C, Delay E. Breast implant-associated anaplastic large cell lymphoma. Case report of an undiagnosed form, management and reconstruction (ALCL). *Ann Chir Plast Esthet* ;61:223-30. DOI PubMed
98. Lamaris GA, Butler CE, Deva AK, et al. Breast reconstruction following breast implant-associated anaplastic large cell lymphoma. *Plast Reconstr Surg* 2019;143:51S-8S. DOI PubMed
99. Petit JY, Gentilini O, Rotmensz N, et al. Oncological results of immediate breast reconstruction: long term follow-up of a large series at a single institution. *Breast Cancer Res Treat* 2008;112:545-9. DOI PubMed
100. Claro F Jr, Figueiredo JC, Zampar AG, Pinto-Neto AM. Applicability and safety of autologous fat for reconstruction of the breast. *Br J Surg* 2012;99:768-80. DOI PubMed
101. Veber M, Tourasse C, Toussoun G, Moutran M, Mojallal A, Delay E. Radiographic findings after breast augmentation by autologous fat transfer. *Plast Reconstr Surg* 2011;127:1289-99. DOI PubMed
102. Groen JW, Negenborn VL, Twisk DJWR, et al. Autologous fat grafting in onco-plastic breast reconstruction: a systematic review on oncological and radiological safety, complications, volume retention and patient/surgeon satisfaction. *J Plast Reconstr Aesthet Surg* 2016;69:742-64. DOI PubMed
103. Turnhout AA, Fuchs S, Lisabeth-Broné K, Vriens-Nieuwenhuis EJC, van der Sluis WB. Surgical outcome and cosmetic results of autologous fat grafting after breast conserving surgery and radiotherapy for breast cancer: a retrospective cohort study of 222 fat grafting sessions in 109 patients. *Aesthetic Plast Surg* 2017;41:1334-41. DOI PubMed
104. Caviggioli F, Maione L, Klinger F, Lisa A, Klinger M. Autologous fat grafting reduces pain in irradiated breast: a review of our experience. *Stem Cells Int* 2016;2016:2527349. DOI PubMed PMC
105. Juhl AA, Karlsson P, Damsgaard TE. Fat grafting for alleviating persistent pain after breast cancer treatment: A randomized controlled trial. *J Plast Reconstr Aesthet Surg* 2016;69:1192-202. DOI PubMed
106. Jung BF, Ahrendt GM, Oaklander AL, Dworkin RH. Neuropathic pain following breast cancer surgery: proposed classification and research update. *Pain* 2003;104:1-13. DOI PubMed
107. Waltho D, Rockwell G. Post-breast surgery pain syndrome: establishing a consensus for the definition of post-mastectomy pain syndrome to provide a standardized clinical and research approach - a review of the literature and discussion. *Can J Surg* 2016;59:342-50. DOI PubMed PMC
108. Chappell AG, Bai J, Yuksel S, Ellis MF. Post-mastectomy pain syndrome: defining perioperative etiologies to guide new methods of prevention for plastic surgeons. *World J Plast Surg* 2020;9:247-53. DOI PubMed PMC
109. Larsson IM, Ahm Sørensen J, Bille C. The post-mastectomy pain syndrome-a systematic review of the treatment modalities. *Breast J* 2017;23:338-43. DOI PubMed
110. Krastev TK, Schop SJ, Hommes J, Piatkowski A, van der Hulst RRWJ. Autologous fat transfer to treat fibrosis and scar-related conditions: a systematic review and meta-analysis. *J Plast Reconstr Aesthet Surg* 2020;73:2033-48. DOI PubMed
111. Caviggioli F, Maione L, Forcellini D, Klinger F, Klinger M. Autologous fat graft in postmastectomy pain syndrome. *Plast Reconstr Surg* 2011;128:349-52. DOI PubMed
112. Maione L, Vinci V, Caviggioli F, et al. Autologous fat graft in postmastectomy pain syndrome following breast conservative surgery and radiotherapy. *Aesthetic Plast Surg* 2014;38:528-32. DOI PubMed
113. Sollie M, Toyserkani N, Bille C, Thomsen JB, Sørensen JA. Reply: autologous fat grafting as treatment of postmastectomy pain syndrome: a randomized controlled trial. *Plast Reconstr Surg* 2023;151:521e-2e. DOI PubMed
114. Wang S, Gusenoff JA, Rubin JP, Kokai L. Molecular mechanisms of adipose tissue survival during severe hypoxia: implications for

autologous fat graft performance. *Plast Reconstr Surg Glob Open* 2019;7:e2275. DOI PubMed PMC

115. Yang X, Egro FM, Jones T, et al. Comparison of adipose particle size on autologous fat graft retention in a rodent model. *Plast Aesthet Res* 2020;7:8. DOI
116. Ma J, Yan X, Lin Y, Tan Q. Hepatocyte growth factor secreted from human adipose-derived stem cells inhibits fibrosis in hypertrophic scar fibroblasts. *Curr Mol Med* 2020;20:558-71. DOI PubMed
117. Aladari N, Palaghia MM, Trofin A, et al. Reducing capsular contracture formation in breast augmentation with silicone implants: experimental study on rats. *Applied Sciences* 2022;12:4056. DOI
118. Komorowska-Timek E, Jaźwiec A, Adams NS, Fahrenkopf MP, Davis AT. Peri-prosthetic fat grafting decreases collagen content, density, and fiber alignment of implant capsules. *Plast Reconstr Surg Glob Open* 2021;9:e3687. DOI PubMed PMC
119. Shukla L, Luwor R, Ritchie ME, et al. Therapeutic reversal of radiotherapy injury to pro-fibrotic dysfunctional fibroblasts in vitro using adipose-derived stem cells. *Plast Reconstr Surg Glob Open* 2020;8:e2706. DOI PubMed PMC
120. Cogliandro A, Barone M, Tenna S, Morelli Coppola M, Persichetti P. The role of lipofilling after breast reconstruction: evaluation of outcomes and patient satisfaction with BREAST-Q. *Aesthetic Plast Surg* 2017;41:1325-31. DOI PubMed
121. Papadopoulos S, Vidovic G, Neid M, Abdallah A. Using fat grafting to treat breast implant capsular contracture. *Plast Reconstr Surg Glob Open* 2018;6:e1969. DOI PubMed PMC
122. Jeong TK, Han JW, Min KH. Treatment of capsular contracture after breast augmentation with serial fat grafting and implantation. *Arch Aesthetic Plast Surg* 2018;24:68-71. DOI
123. Magill LJ, Robertson FP, Jell G, Mosahebi A, Keshtgar M. Determining the outcomes of post-mastectomy radiation therapy delivered to the definitive implant in patients undergoing one- and two-stage implant-based breast reconstruction: a systematic review and meta-analysis. *J Plast Reconstr Aesthet Surg* 2017;70:1329-35. DOI PubMed
124. Olinger TA, Berlin NL, Qi J, et al. Outcomes of immediate implant-based mastectomy reconstruction in women with previous breast radiotherapy. *Plast Reconstr Surg* 2020;145:1029e-36e. DOI PubMed
125. Panettiere P, Marchetti L, Accorsi D. The serial free fat transfer in irradiated prosthetic breast reconstructions. *Aesthetic Plast Surg* 2009;33:695-700. DOI PubMed
126. Serra-Renom JM, Muñoz-Olmo JL, Serra-Mestre JM. Fat grafting in postmastectomy breast reconstruction with expanders and prostheses in patients who have received radiotherapy: formation of new subcutaneous tissue. *Plast Reconstr Surg* 2010;125:12-8. DOI PubMed
127. Salgarello M, Visconti G, Barone-Adesi L. Fat grafting and breast reconstruction with implant: another option for irradiated breast cancer patients. *Plast Reconstr Surg* 2012;129:317-29. DOI PubMed
128. Komorowska-Timek E, Turfe Z, Davis AT. Outcomes of prosthetic reconstruction of irradiated and nonirradiated breasts with fat grafting. *Plast Reconstr Surg* 2017;139:1e-9e. DOI PubMed
129. Haran O, Bracha G, Tiosano A, et al. Postirradiation capsular contracture in implant-based breast reconstruction: management and outcome. *Plast Reconstr Surg* 2021;147:11-9. DOI PubMed
130. Calabrese S, Zingaretti N, De Francesco F, et al. Long-term impact of lipofilling in hybrid breast reconstruction: retrospective analysis of two cohorts. *Eur J Plast Surg* 2020;43:257-68. DOI
131. Martin S, Cai L, Beniwal A, Tevlin R, Lee G, Nazerali RS. Autologous fat grafting and the occurrence of radiation-induced capsular contracture. *Ann Plast Surg* 2021;86:S414-7. DOI PubMed
132. Ma H, Fang Y, Lin C, Perng C, Tsai C, Hsiao F. Facial recontouring with autologous cryopreserved fat graft. *Formos J Surg* 2018;51:58-62. DOI
133. Erol OO, Agaoglu G. Facial rejuvenation with staged injections of cryopreserved fat and tissue cocktail: clinical outcomes in the past 10 years. *Aesthet Surg J* 2013;33:639-53. DOI PubMed
134. Moscatiello F, Aznar-Benitah S, Grella R, Jover JH. Gluteal augmentation with cryopreserved fat. *Aesthet Surg J* 2010;30:211-6. DOI PubMed
135. Mashiko T, Wu SH, Kanayama K, et al. Biological properties and therapeutic value of cryopreserved fat tissue. *Plast Reconstr Surg* 2018;141:104-15. DOI PubMed
136. Kim SK, Kim HJ, Hwang K. Mixed infection of an atypical Mycobacterium and Aspergillus following a cryopreserved fat graft to a face. *J Craniofac Surg* 2013;24:1676-8. DOI PubMed
137. Kølle SF, Fischer-Nielsen A, Mathiasen AB, et al. Enrichment of autologous fat grafts with ex-vivo expanded adipose tissue-derived stem cells for graft survival: a randomised placebo-controlled trial. *Lancet* 2013;382:1113-20. DOI PubMed
138. Kølle ST, Duscher D, Taudorf M, et al. Ex vivo-expanded autologous adipose tissue-derived stromal cells ensure enhanced fat graft retention in breast augmentation: a randomized controlled clinical trial. *Stem Cells Transl Med* 2020;9:1277-86. DOI PubMed PMC
139. Gentile P, Di Pasquali C, Bocchini I, et al. Breast reconstruction with autologous fat graft mixed with platelet-rich plasma. *Surg Innov* 2013;20:370-6. DOI PubMed
140. Kamakura T, Ito K. Autologous cell-enriched fat grafting for breast augmentation. *Aesthetic Plast Surg* 2011;35:1022-30. DOI PubMed
141. Tissiani LA, Alonso N. A prospective and controlled clinical trial on stromal vascular fraction enriched fat grafts in secondary breast reconstruction. *Stem Cells Int* 2016;2016:2636454. DOI PubMed PMC
142. Chen A, Zhang L, Chen P, Zhang C, Tang S, Chen X. Comparison of the efficacy and safety of cell-assisted lipotransfer and platelet-rich plasma assisted lipotransfer: what should we expect from a systematic review with meta-analysis? *Cell Transplant*

2021;30:963689721989607. DOI PubMed PMC

143. Pérez-Cano R, Vranckx JJ, Lasso JM, et al. Prospective trial of adipose-derived regenerative cell (ADRC)-enriched fat grafting for partial mastectomy defects: the RESTORE-2 trial. *Eur J Surg Oncol* 2012;38:382-9. DOI PubMed

144. Moloughney JG, Weisleder N. Poloxamer 188 (p188) as a membrane resealing reagent in biomedical applications. *Recent Pat Biotechnol* 2012;6:200-11. DOI PubMed PMC