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Recent progress in lymphovenous anastomosis

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Abstract

Breast cancer-related lymphedema (BCRL) is a debilitating disorder affecting an estimated 1 in 5 women and men treated for breast cancer. Fortunately, super microsurgical techniques have advanced in recent years and now provide better options for the treatment of lymphedema, allowing timely surgical intervention that can delay or even prevent lymphatic degeneration. Lymphovenous anastomosis (LVA), a physiologic procedure that restores lymphatic drainage by connecting functioning lymphatic vessels with nearby veins, has been shown to be both minimally invasive and highly effective. The authors describe innovative approaches to LVA that will help optimize outcomes for patients with BCRL.

Keywords: Lymphovenous anastomosis, lymphedema, super microsurgery

INTRODUCTION

Breast cancer-related lymphedema(BCRL) is a frequent complication of axillary lymph node excision with adjuvant therapy, and affects both women and men diagnosed with breast cancer[1,2]. As secondary lymphedema is a progressive disorder that results in irreversible damage to the lymphatic vessels and surrounding tissue[3], patients should be encouraged to seek surgical advice in an early phase, particularly when refractory to initiated compression therapy[4]. While surgical treatment for lymphedema previously focused on ablative procedures, current surgical techniques for the treatment of lymphedema aim to restore the drainage of lymphatic fluid from the affected limb. Lymphovenous anastomosis (LVA) consists of an anastomosis between a lymphatic vessel and a subcutaneous vein, and because it allows the lymphatic fluid

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to drain into the systemic circulation, LVA has an immediate positive impact[5]. Furthermore, as LVA does not require harvesting of existing lymphatic tissue, the latter carrying an inherent risk of donor-site lymphedema, it is also a safe procedure[6]. Another advantage of LVA is that it requires only a small incision in the skin that can be performed under loco-regional anesthesia, resulting in a very low complication rate. Thanks to these advantages, LVA is particularly suitable as a first-line surgical option for the treatment of BCRL[7-9]. However, one must be aware that experience, together with specialized equipment, are prerequisites for a good patient outcome[10,11].

SURGICAL TECHNIQUE

The earliest series of LVAs in humans were described several decades ago[12,13], but the technique in current use was first developed by Koshima[14]. Supermicrosurgery refers to the handling of vessels with a diameter less than 1 mm, but the lymphatic vessels targeted in LVA are usually considerably smaller, between 0.20 and 0.80 mm in diameter. Several factors play a role in the outcome, including the incision location, the size and configuration of vessels, and the type of anastomosis.

An LVA skin incision is, on average, 2 cm in length and, despite directly interrupting superficial lymphatic vessels, does not provoke iatrogenic lymphedema. The location of the incision is based on the identification of lymphatics and veins during pre-operative assessment. Intra-operatively, the choice of suitable vessels can be challenging. Ideally, equally-sized vessels and/or vessels with favorable lymph-to-blood pressures should be used for the creation of the LVA. However, in case of a mismatch, several different approaches are available, ranging from venous-branch-plasty[15] and interposition[16] to funnelization[17] [Figure 1A]. The choice of a favorable recipient vein is also crucial[18]. It has been suggested that a relatively smaller subcutaneous vein should be selected for LVA when the lymphatic vessels are abnormally dilatated[5]. Particular importance should be paid to the prevention of blood reflux, for instance, by valvuloplasty[19], although[20] found no adverse effect on the outcome after blood reflux through anastomosis.

The efficacy of LVA is also determined by the quality of available lymphatics. ‘Normal’ or ‘ectatic’ lymph vessels are preferred when creating a functioning LVA[11,21], although the true histopathology of the vessel is rarely known intra-operatively. An intima-to-intima approach is essential to prevent post-operative occlusions[5]. Intraluminal insertion of a custom-made nylon stent can help to avoid picking up the back wall, as well as to prove the patency of the LVA[22] [Figure 1B].

The patency of the LVA after anastomosis can now be easily confirmed through washout by lymphatic fluid in the vein and/or by observing indocyanine green (ICG) in the vein[23][Figure 2]. Indeed, thanks to the improvement in operative microscopes in terms of magnification and built-in infrared cameras, intra-operative visualization of lymphatic vessels is now common practice. Any leak can also be easily traced with the ICG module and should be rectified in order to prevent thrombosis. Before closing the incision, the position of the LVA and the vessels should be checked in order to optimize the long-term patency of the anastomosis: traction or aberrant position of the new construction should be avoided.

Depending on the available vessels preoperatively, a variety of anastomotic configurations can be created with the aim of increasing maximal lymphatic drainage into the venous system[23-25]. However, in the large majority of cases, an end-to-end anastomosis will be performed. Other configurations, including end-to-side, side-to-end, and side-to-side, are sometimes required, depending on the venous pressure and anatomy[26].

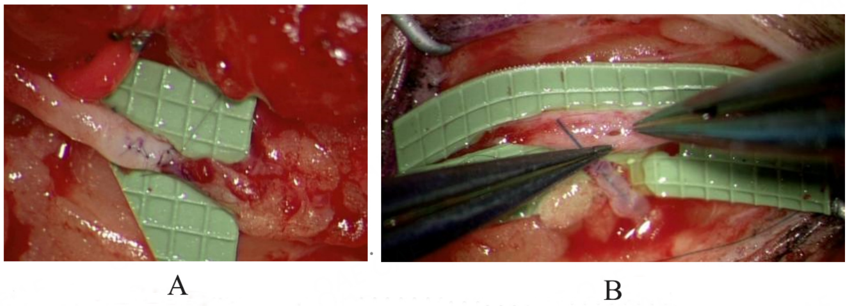

Figure 1. A: Funnelization of the vein; B: Intraluminal insertion of nylon stent in preparation for an end-to-side anastomosis.

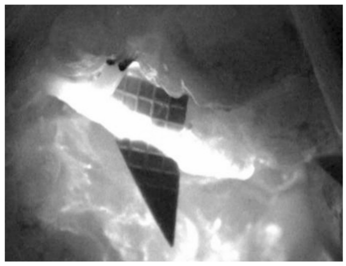

Figure 2. Peri-operative proof of patent anastomosis.

IMAGING AND EQUIPMENT

An already successful LVA procedure for lymphedema treatment can be further enhanced by the use of innovative technology and refined techniques[27]. While ICG lymphography is the gold standard for the identification of lymphatic vessels[28], deeper vessels (> 2 cm subcutaneously) cannot be visualized due to the limitations of current infrared cameras. The identification of lymphatics by ICG lymphography in patients with severe lymphedema is also limited due to the overlying dermal backflow. The implementation of super microsurgery for lymphedema treatment permitted the use of small vessels, an issue of particular importance in patients with BCRL who often present with swelling of the hand. Visualizing small lymph vessels in the distal region of the upper limb is paramount, as these vessels may allow anastomosis to low-pressure venules[14]. As LVA requires lymphatic vessels to be connected to nearby veins, the identification of suitable veins is obviously crucial.

The introduction of ultra-high-frequency ultrasound allows the detection of small-sized lymph vessels and veins in a non-invasive manner[29-31] [Figure 3]. While ultra-high frequency ultrasound has been revolutionary in the imaging of small-sized lymphatic vessels and veins, finding lymphatics with ultrasound in cases of severe lymphedema can nevertheless be challenging due to the limitations of coaptating contrast. Multispectral optoacoustic tomography (MSOT) is a 3D imaging modality based on the photoacoustic effect which allows exact spatial identification of (fluorescent) lymphatics and adjacent veins, thus overcoming these drawbacks[32] [Figure 4]. In a pilot study involving 11 patients, MSOT was found to accurately differentiate between distinct types of vessels including lymphatics, even in areas of dermal backflow, and provided images with high spatio-temporal resolution[33]. Of particular relevance to lymphatic surgery, we were able to successfully perform an LVA between an MSOT-identified lymphatic vessel and an adjacent vein[33]. In addition to identifying lymphatic vessels appropriate for LVA, photoacoustic imaging has also been used to confirm the post-operative patency of LVAs[34].

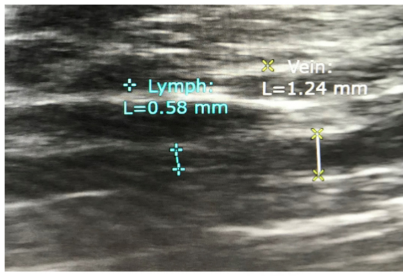

Figure 3. Visualization of lymphatic vessel and vein following ultra-high frequency ultrasound.

Figure 4. Visualization of lymphatic vessel (yellow) and vein (blue) in real-time following Multispectral optoacoustic tomography (MSOT).

The widespread application of super microsurgery, with its inherent focus on small-diameter vessels (0.1-0.3 mm), has also increased the demand for suitably-sized instruments [Figure 5] and needles[11] [Figure 6]. As all needles unavoidably cause tissue damage, with the extent directly related to needle size, fine needles are required for small and thin-walled lymphatics. For larger vessels, various 50 micron needles (suture size 11.0) are available and adequate. We recently reported on the use of a new 30 micron needle (suture size 12.0) in 20 LVAs in 10 patients with lymphedema of the limb[35]. Lymphatic vessels and veins had diameters of 0.2 to 0.4 mm and 0.3 to 0.8 mm, respectively. In total, 18 end-to-end and 2 end-to-side anastomoses were successfully performed.

Today, remarkable technological developments are underway, such as dedicated robots that have been successfully used for supermicrosurgical treatment of BCRL[36,37]. Furthermore, microscope-integrated laser tomography, which allows high-resolution assessment of the condition of the lymphatic lumen, is showing consideable promise[38].

UPPER EXTREMITY LYMPHEDEMA AND LYMPHORRHEA

Substantial evidence from a multitude of studies and reviews performed worldwide supports the efficacy of LVA for lymphedema of lower and upper extremities[39-42]. While immediate benefits include volume reduction of the affected limb, longer-term advantages include a decreased need for conservative therapy and compression garments, as well as a reduced frequency of infection[39,43,44].

LVA is typically used in the early stages of BCRL when a functional lymphatic system can still be identified. Early-stage lymphedema refers to excess volume caused by the accumulation of interstitial fluid. More advanced lymphedema is characterized by increased tissue fibrosis, hypertrophy of adipose tissue, and

Figure 5. Dedicated instrument: forceps.

Figure 6. Needles ranging from 50 microns.

sclerosis of the lymphatic vessels, which are irreversible. While LVA is efficient in early-stage lymphedema, even late-stage lymphedema, typically treated by debulking procedures[45] or combined techniques[46], is increasingly being treated using LVA[47,48]. Alternatively, lymphatic vessel transplantation can reconstruct interrupted lymphatic pathways after axillary lymph node resection in patients with breast cancer[49].

In addition to arm lymphedema, breast lymphedema (BLE) is also a major sequela of breast cancer treatments[50]. Although an estimated one-third of all breast cancer patients develop BLE after breast-conserving surgery with axillary lymph node intervention, its management remains poorly described. LVA is reportedly effective for extremity lymphedema and also has proven efficacy in BLE[51,52]. While compression therapy is a cornerstone of the treatment of extremity lymphedema, in BLE, the complexity of breast shape causes significant difficulties. Given that patients with BLE mostly complain of (lymphatic) congestion, a newly created lymph-to-venous bypass will give immediate relief. As men may also develop BLE following breast cancer treatment, LVA can also be successfully performed in this group[53].

Axillary lymph node dissection in breast cancer treatment may also result in lymphorrhea. While lymphatic discharge generally ceases spontaneously, intractable leakage may result in a lymphocele or fistula and discomfort for the patient. Sclerotherapy or macroscopic ligation of the injured lymphatic vessels carries a risk of subsequent aggravating (clinical) lymphedema. Therefore, the anastomosis of a damaged lymph vessel to a nearby intact lymph vessel or vein is a physiological approach to restoring lymphatic drainage[54]. We have previously described the successful treatment of axillary lymphorrhea in a series of patients treated by LVA for intractable lymphorrhea[55].

DISCUSSION

Lymphedema surgery has evolved rapidly in the last decades, largely thanks to the introduction of super microsurgery and the application of ICG imaging. LVA is a physiological approach to lymphedema and is now well established as an effective and minimally-invasive surgical treatment for lymphedema without risk for complications[8,9]. LVA is safe and has an immediate post-operative therapeutic effect compared to other techniques including vascularized lymph node/vessel transfer. Consequently, LVA can now be considered the first-line surgical treatment for lymphedema, including BCRL. However, several remaining challenges need to be recognized.

Supermicrosurgery is technically difficult and a steep learning curve is inevitable. While major challenges such as vessel number and/or size mismatch or difficult vessel position may be encountered preoperatively, technological advances in equipment including microscopes and robotics allow LVAs to be performed with greater confidence.

How many anastomoses should be performed in order to obtain maximal lymphatic drainage is still a matter of debate[39,56]. And which factor is most important for success, the quantity or the quality (of vessels), also remains to be unequivocally established. On average, at least 3 LVAs are performed per patient, but factors including lymphedema stage and surgeon skill should also be taken into account[57]. Everyday practice, though, is determined by the number of vessels available for anastomoses and/or the reimbursement rules imposed by authorities or insurance companies. The exact location of a skin incision is also crucial for a good clinical result: the incision site is selected primarily on the basis of the ICG pattern, but for technical reasons, lymphatics and veins should preferably be in close proximity. Therefore, it is of the utmost importance that the surgeon has access to several (innovative) technologies/devices that facilitate the identification of vessels. This will be particularly beneficial in the case of patients with dermal backflow patterns and in patients with lymphedema of the hand, which is often an indication of degenerated lymphatic status. In addition to the indisputable role of near-infrared cameras, nowadays, ultrasound is also a prerequisite for good pre-operative assessment. More specifically, ultra-high frequency ultrasound can accurately detect (histologically confirmed) functional lymphatic vessels, even in advanced cases[58]. Lymphoscintigraphy is a reliable tool in the visualization of lymphatic function but well-known disadvantages, such as the two-dimensional view and the lack of projection onto anatomical landmarks, can be overcome with the use of lympho-SPECT/CT, which provides integrated information on lymphatic pathways[59]. However, as with magnetic resonance imaging, these technologies do not provide real-time information, which makes them less suitable for pre-operative planning.

Another concern is the long-term patency of an anastomosis. Efforts to prove patency should be made during the intervention. Furthermore, post-operative patency can be confirmed by means of ICG lymphography, lymphoscintigraphy, lympho SPECT/CT, or photoacoustic lymphangiography[59]. According to one report, over 70% of patients had at least one patent anastomosis 12 months after intervention[60]. Notwithstanding the data on functioning LVAs, there is still no consensus in the literature as to which tool should be used to assess the post-operative clinical effect of LVAs. It should be stressed that many variables need to be taken into account when assessing the overall outcome after LVA, among which are the number of patent anastomoses, lymphedema staging, patient characteristics, the surgeon’s experience, and accessible equipment.

LVA is now an established treatment option for lymphedema in various parts of the body, but is also being increasingly used to treat a broad range of lymphatic diseases varying from lymphorrhea, a complication of lymph node excision, to generalized lymphatic anomalies mostly encountered in pediatric patients[61]. However, the question of whether prophylactic LVA after lymphadenectomy actually avoids the morbidity associated with lymphedema needs to be proven in high-quality studies with a long follow-up period[62-64]. New technologies that focus on lymphangiogenesis also appear promising and may contribute to the treatment of lymphedema in the near future[65,66].

CONCLUSION

Thanks to major innovations and refinements in existing technologies and techniques, the outcome of LVA has improved considerably in recent years. LVA is now an effective and safe procedure and thus has the potential to become the first-line surgical treatment for lymphedema, greatly benefiting patients experiencing BCRL.

DECLARATIONS

Authors' contributions

Made substantial contributions to the paper: Giacalone G, Belva F

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

All patients gave consent for participation and publication.

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