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REVIEW ARTICLE

Primary surgical prevention of lymphedema

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Abstract

Lymphedema in the upper and lower extremities can lead to significant morbidity in patients, resulting in restricted joint movements, pain, discomfort, and reduced quality of life. While physiological lymphatic reconstructions such as lymphovenous anastomosis (LVA), lymphovenous implantation (LVI), and vascularized lymph node transfer (VLNT) have shown promise in improving patients' conditions, they only provide limited disease progression control or modest reversal. As lymphedema remains an incurable condition, the focus has shifted toward preventive measures in developed countries where most cases are iatrogenic due to cancer treatments. Breast cancer–related lymphedema (BCRL) has been a particular concern, prompting the implementation of preventive measures like axillary reverse mapping. Similarly, techniques with lymph node-preserving concepts have been used to treat lower extremity lymphedema caused by gynecological cancers. Preventive lymphedema measures can be classified into primary, secondary, and tertiary prevention. In this comprehensive review, we will explore the principles and methodologies encompassing lymphatic microsurgical preventive healing approach (LYMPHA), LVA, lymphaticolymphatic anastomosis (LLA), VLNT, and lymph-interpositional-flap transfer (LIFT). By evaluating the advantages and limitations of these techniques, we aim to equip surgeons with the necessary knowledge to effectively address patients at high risk of developing lymphedema.

Keywords: Immediate lymphatic reconstruction; Lymph vessel transfer; Lymphatic microsurgical preventing healing approach; Lymphedema prevention; Lymphovenous anastomosis

1. INTRODUCTION

Upper and lower extremity lymphedema can lead to significant morbidity in patients. They often complain of restricted joint movements, pain and discomfort, inability to don clothes and footwear, and intermittent attacks of cellulitis. Physiological lymphatic reconstructions such as lymphovenous anastomosis (LVA), lymphovenous implantations (LVI), and vascularized lymph node transfer (VLNT) have been gaining prominence in the past three decades. While these forms of lymphatic reconstruction have shown promise in improving patients' conditions, they only provide limited disease progression control or modest reversal.

The leading cause of secondary lymphedema worldwide is filariasis, caused by infection by Wuchereria bancrofti. This is vastly different in developed countries, as most cases are due to malignancy or related to surgical extirpation and adjuvant cancer therapy. As lymphedema in developed countries is mainly iatrogenic, the focus for clinicians has shifted to more preventive measures. Although the cumulative incidence of breast cancer–related lymphedema (BCRL) has been shown to be 13.5% at 2 years of follow-up, 30.5% at 5 years and 41.1% at 10 years,[1] breast surgeons have successfully reduced the incidence of lymphedema after axillary lymph node dissection and sampling through axillary reverse mapping.[2] In lower extremity lymphedema, techniques with similar lymph node-preserving concepts are utilized to treat gynecological cancers.[3]

Lymphedema prevention is an attractive proposition for surgeons and patients alike. Patients avoid the need for lifelong compression garments, and surgeons can get away with performing less invasive and extensive operations. Prevention can be broadly classified into primary, secondary, and tertiary prevention. Primary prevention focuses on avoiding the disease entirely by performing interventions before it occurs. Secondary prevention involves screening or testing the patient to identify the disease as early as possible. Tertiary prevention refers to measures to mitigate or halt the illness after a diagnosis. Preventive surgery can be performed in situ at the level of the lymph node dissection or, ex situ, distal to the level of lymph node dissection. This review article provides a comprehensive overview of the primary prevention measures for upper and lower extremity lymphedema so that surgeons can adequately equip themselves to help at-risk patients.

2. PREDICTORS OF SECONDARY LYMPHEDEMA AFTER CANCER TREATMENT

Understanding the predictors of cancer-related lymphedema is critical in applying primary prevention measures. It helps clinicians stratify patients into different risk groups to administer suitable interventions. Numerous studies have examined the risk factors associated with cancer-related lymphedema development. This is especially so for BCRL. The presence of axillary lymph node dissection coupled with adjuvant therapy are well-known risk factors. Diving deeper, a recent study by Martínez-Jaimez et al[4] involving 504 European women

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undergoing breast conservation treatment summarized it into five factors that significantly increased the risk of BCRL. These were:

1. Body mass index (BMI). An elevated BMI ≥25 g/m^2 increased the odds ratio to 1.05
2. Postoperative complications such as seroma, infection, and early edema increased the odds ratio to 1.61.
3. The number of lymph nodes extracted was an independent risk factor with an odds ratio of 1.03.
4. The level of lymph node dissection based on Berg levels was a strong predictor and had an odds ratio of 2.51.
5. Positive lymph node status had an odds ratio of 1.83.

These findings were similar to an earlier study by Armer et al.[5] Their analysis was performed on patients who underwent axillary lymph node dissection and neoadjuvant chemotherapy. It was found that the length of neoadjuvant chemotherapy of more than 144 days increased the risk of BCRL significantly. In addition, they qualified that patients with ≥30 lymph nodes removed were associated with the highest risk of BCRL. Kunitake et al[6] studied cancer-related lower extremity lymphedema after gynecological cancer treatment and demonstrated similar risk factors to BCRL. Although many studies have corroborated the above findings, a valid risk prediction model for clinical practice is still elusive, as currently published models demonstrate high levels of bias due to poor methodology.[7]

3. IMMEDIATE LYMPHATIC RECONSTRUCTION

There has been much advancement in the field of lymphatic reconstruction since the first mention of LVA by Jacobsen in 1962.[8] Advances in surgical instruments, optics, and lymphatic imaging propelled surgical techniques to take on the evolved form of today. The two standard techniques used in immediate lymphatic reconstruction (ILR) are LVI and intima-to-intima style supermicrosurgical LVA.

3.1. Lymphatic microsurgical preventive healing approach in ILR

LVI in ILR was popularized by Boccardo and Campisi in 2009, and they coined the term LYMPHA which stands for Lymphatic Microsurgical Preventive Healing Approach.[9] They used the LVI technique to telescope severed afferent lymphatics into axillary vein branches. Blue dye was injected into the medial arm lymphosome to visualize these severed lymphatics in the axillary dissection operating field. Two to four implantations were done per LYMPHA procedure, and patients were then followed-up for 1 year to evaluate outcomes. None of the patients experienced secondary clinical lymphedema, and there was a notable improvement in the lymphatic transport index, as shown on lymphoscintigraphy. The group released data from a 4-year follow-up in 2014.[10] Of the 74 patients who underwent LYMPHA, 71 (95.9%) showed no indications of secondary lymphedema, and their volumetric measurements were consistent with the preoperative condition. Only three (4.1%) patients were identified to have developed secondary lymphedema. Notably, although 95.9% did not show signs of lymphedema, 14 (18.9%) patients experienced cellulitis, which may indicate lymphatic dysfunction. Five of the eight patients who received radiotherapy had temporary edema, while the remaining three experienced permanent edema. The published incidence of lymphedema in LYMPHA patients was 4.05%. Many studies have since been published with similar risk reduction profiles. However, the most recent study by Levy et al[11] failed to show statistically significant benefits for the LYMPHA group. In this retrospective study, the LYMPHA group had a 31.1% incidence of lymphedema, while the non-LYMPHA group had 33.3%.

A simplified version of the LYMPHA technique known as the S-LYMPHA was devised by Ozmen et al.[12] The group suggested that some centers may have limited microsurgical techniques and microscope availability. Using the S-LYMPHA technique, ILR can be completed quickly without these resources and skills, making preventive surgery more accessible to patients. This technique involved invaginating the severed afferent lymphatics into cut ends of neighboring veins using a sleeve technique and 7-0 non-absorbable sutures. There are concerns about whether these invaginating U-shaped stitches placed without a microscope would occlude the lymphatics. Even if the lymphatics were not occluded, lymph could still flow back out of the open vein predisposing the patient to lymphorrhea and lymphoceles. Despite these concerns, Ozmen et al[12] published long-term data of 194 patients undergoing axillary lymph node dissection and SLYMPHA.[13] Lymphedema was monitored using bioimpedance spectroscopy; the average follow-up was about 4 years. They showed a significantly lower rate of lymphedema in the SLYMPHA group (16% vs 32%).

3.2. Supermicrosurgical LVA in ILR

Fewer studies combined supermicrosurgical LVA and LVI techniques into ILR.[14–17] However, combining both bypass methods based on the availability and size of lymphatics and venules also produced a low lymphedema incidence. The major limitation of these studies was the lack of a control group for comparison, thereby introducing a significant amount of bias.

Supermicrosurgical LVA is technically more demanding as it involves precise intima-to-intima coaptation using fine 11-0 and 12-0 sutures. This demands a higher learning curve; hence most of the literature on ILR solely involves LVI. Despite the lack of robust long-term data directly comparing the success rates of LVA using lymphaticovenular anastomosis (LVI) vs supermicrosurgical LVA in humans, some insights have been obtained from animal studies. Ishiura et al[18] conducted a study on 12 Wistar rats divided into two groups: one underwent LVI, and the other underwent supermicrosurgical LVA. The anastomosis patency was assessed during the operation using a patent blue dye and indocyanine green lymphography 1 week later. The results showed that the postoperative patency rate in the supermicrosurgical LVA group was significantly higher than in the LVI group. Specifically, 100% of the supermicrosurgical LVA cases (six of six) remained patent, while only 33.3 percent of the LVI cases (two of six) maintained patency ($p = 0.014$).

Although the study did demonstrate the superiority of supermicrosurgical LVA vs LVI, performing it as an “all seasons” technique for ILR might not be feasible. There might be a paucity of afferent lymphatics with suitable diameters, so surgeons might have to group a few smaller lymphatics to implant into a venule. Another reason would be that the available venules in the axilla may be much larger than the lymphatics. This size mismatch may ultimately affect the integrity of intima-to-intima coaptation; hence, LVI may be a more suitable option. These are the scenarios in which the clinical studies mentioned earlier performed LVI over LVA.

3.3. Lymphaticolymphatic anastomosis

Lymphaticolymphatic anastomosis (LLA) is another method of bypassing points of obstruction in the lymphatic system. LLA was first attempted in animal models by Shafiroff et al in the late 1970s and was meant to examine the main drawback of LVA[19]; it was noted on histology that little healing occurred between the lymphatic vessel intima and the venous endothelium, with a high incidence of lymphatic wall necrosis. This was different in LLAs, where the authors noted reendothelialization within 2 weeks, with good development of microvilli and restoration of cellular tight junctions. There was also no evidence of subintimal hyperplasia, a cause of stenosis. Hence, LLA is theoretically the most physiological lymphatic reconstruction, with the lowest risk of thrombosis since venous reflux is impossible. By anastomosing superficial lymphatics directly to the deep lymphatic system, superficial lymph can bypass the obstruction and shunt directly into patent deep lymphatic channels. LLAs have been used to treat lymphedema, lymphoceles, and lymphorrhea,[19–21] but reports of using this technique in the primary prevention of lymphedema have yet to be made.

3.4. Making sense of the ILR literature

Numerous studies published regarding ILR have been the subject of systematic reviews and meta-analyses. This was an attempt to provide a more evidence-based perspective on this concept.[22–27] While most of the studies demonstrated a low incidence of lymphedema in their LYMPHA/ILR patients, these studies also faced issues such as high clinical bias, insufficient sample sizes, lacking a consistent control group, and using nonstandardized outcome measures. Control groups in all the studies did not receive decongestive therapy, a conservative management option that is considered the mainstay treatment option. A valid comparison with clinical relevance would be to compare ILR with complete decongestive therapy. Many studies also evaluated lymphedema outcomes using less sensitive methods such as circumferential measurement. Moreover, a significant portion of these studies had a follow-up duration of less than 2 years, limiting the data's usefulness. To adequately identify patients experiencing cancer-related lymphedema, it is recommended to consider a minimum follow-up period of 3 years after commencing oncologic treatment. Regarding patency assessment, only Boccardo et al's[10] group conducted a direct postoperative evaluation using lymphoscintigraphy.

Although there is great heterogeneity (technique of anastomosis, lymphedema diagnosis, staging, level of lymphadenectomy, and cancer type) and high clinical bias among many of the studies, pooled data suggest that there may be reduced risk of cancer-related upper and lower extremity lymphedema when ILR is performed compared to a control group where no intervention is done. The cost-effectiveness of ILR was examined by Johnson et al,[28] and the group confirmed that the additional cost from the prophylaxis could be justified from a cost-utility perspective since ILR is a low-morbidity procedure with negligible complication rates.

Much of the data suggest that ILR confers some degree of risk reduction in cancer-related lymphedema compared to patients without intervention. However, the low quality of the studies and other weaknesses mentioned earlier make it challenging to derive firm conclusions.

Well-designed double-arm blinded studies comparing ILR and complete decongestive therapy are required to formulate evidence-based recommendations for the primary prevention of lymphedema. Another important consideration is when to apply ILR to our patients. A recent paper reported that the pooled incidence of lymphedema after axillary lymph node dissection was 14.1% and 33.4% when radiation therapy was added.[27] If ILR was applied to all patients within these groups, we might be performing surgery on more than two-thirds of patients who will not develop lymphedema. The way to reduce instances of excess surgery is to formulate a good risk prediction model, which is still elusive at this moment.

It is also important to note that LVA is technically more challenging in primary preventive cases as there is no lymph vessel expansion when the lymphatic pressure is normal. Even with the appropriate supermicrosurgical training, a surgeon has a considerable risk of creating an LVA that may not function. With this in mind, when we perform very distal bypasses (eg, hand) where the lymph vessels are even smaller in diameter, we may inadvertently create new obstructions "downstream" that can exacerbate lymphatic function. This is in comparison to in-situ axillary ILR/LYMPHA, where a failed anastomosis does not make any new obstructions since it is already at the level of lymphatic disruption (axillary lymph node dissection).

With the above discussion points in mind, our group's recommendation is such:

1. ILR can be performed with an appropriate risk stratification model that can identify patients with a high probability of developing secondary lymphedema, eg, mastectomy patients with high BMI, confirmed postoperative radiotherapy, and axillary lymph node dissection to be done without reverse mapping.
2. Axillary in-situ bypasses should be performed when ILR is attempted.
3. When the clinical and logistical setup is not possible, secondary prevention in the form of early detection and treatment is also a viable option.
4. Secondary prevention surgery can be done more distally, ex situ from the axilla, to avoid a fibrotic operating field.
5. ICG lymphography screening is recommended for secondary prevention due to its high sensitivity.[29]

4. OTHER TECHNIQUES

4.1. Vascularized lymph node transfer

In VLNT, physiologically normal lymph nodes and their vascular pedicles are harvested and implanted into lymphedematous portions of the limb, followed by microsurgical vascular anastomosis. These transplanted lymph nodes directly drain the limb via a "pump" mechanism and act as the epicenter for lymphangiogenesis.[30] Unlike LVA or LVI, there is no immediate shunting effect; surgeons can expect to see improvement only after several months post-surgery.

Compared with the LYMPHA concept, VLNT is a more invasive procedure requiring more operative time and a higher risk of complications. As such, VLNT is a less attractive primary preventive measure. This is reflected in the literature, as no published data describes using VLNT for this purpose.

4.2. Lymph-interpositional-flap transfer

Koshima et al[31] were the first to introduce the concept of lymph vessel transfer (LVT). Their objective was to replace severely diseased lymphatic vessels with healthy ones from a lymphoadiposal flap, effectively bypassing the obstructed segment affected by sclerosis. This flap was harvested from the first dorsal webspace of the foot. Chen et al expanded on this idea by employing the SCIP flap for LVT.[32] They argued that the SCIP flap was a superior choice as a lymphoadiposal flap due to its higher density of lymphatic vessels, better donor site cosmesis, and well-studied anatomy. Both studies reported positive outcomes, including limb volume reduction and symptom relief.

To further enhance LVT, the principles of lymph axiality were integrated with the concept of the lymphoadiposal flap. The notion of lymph axiality originated from direct observations of restored lymphatic flow in cases of replantation and free tissue transfer.[33] The key factors for successful lymph flow restoration involved closely aligning the proximal and distal lymphatic stumps between the flap and the recipient site, and orienting the lymphatic axes in their natural flow direction during the flap inset. These practices were the most significant predictors of lymph flow restoration.

The lymph-interpositional-flap transfer (LIFT) technique was developed to combine these principles and achieve simultaneous soft tissue and lymphatic vessel reconstruction without supermicrosurgery lymphatic anastomosis.[34] This makes LIFT a shorter and technically less demanding operation. It can effectively reduce the risk of secondary lymphedema in the recipient site limb or treat established lymphedema by draining the dermal backflow regions. Postoperative ICG lymphography demonstrated successful lymph flow restoration and fluorescence signal within the LIFT flap.

A LIFT can also be used as a primary preventive measure against lymphedema. The typical clinical scenarios are:

1. The vertical lymphatic channels in Holm's zone II of the Deep inferior epigastric perforator free flap bridge the axilla's lymphatic gap while simultaneously reconstructing the breast mound.
2. Anterolateral thigh flaps have lymphatic channels that run in a superior-oblique direction from lateral to medial. These free flaps bridge lymphatic gaps secondary to trauma, burns, and malignancy.
3. The superficial circumflex iliac artery perforator flap has lymphatic channels running in an inferior-oblique direction from lateral to medial, usually along the long axis of the flap. This flap has been used to bridge lymphatic gaps and reconstruct soft tissue defects secondary to trauma, burns, vascular malformations, and malignancies.

Although existing studies have shown that LVT provides symptomatic relief of existing lymphedema in the first six postoperative months and has a preventative effect on post-traumatic lymphedema, these studies are low-powered and may potentially be affected by significant bias.[32,35] Proper trials should be instituted so that accurate deductions of its effectiveness can be made. For now, it is prudent to consider lymphatic axiality and lymphatic stump approximation during soft tissue reconstruction, as this process does not require much additional time and effort to accomplish.

In conclusion, considering the safety, effectiveness, and practicality of LVA/LVI, initial findings lean toward incorporating ILR for the primary prevention of cancer-related lymphedema. However, the formulation of robust recommendations supporting this intervention is impeded by the presence of low-quality studies with significant heterogeneity, a high risk of bias within the studies, short follow-up periods, and variations in diagnostic methods. Conducting high-quality studies is essential to establish evidence-based guidelines for the primary prevention of lymphedema. Nevertheless, ILR can still be integrated into clinical practice by carefully assessing patients' risks and applying this preventive approach only to those most likely to develop lymphedema. In cases where risk stratification is not feasible, surgeons should consider screening for lymphedema and implementing secondary prevention strategies to minimize the impact of lymphedema on patients. Additionally, other reconstructive techniques like LIFT should be included in the armamentarium of reconstructive surgeons, as they can be utilized for both primary and secondary prevention scenarios.

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