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REVIEW ARTICLE

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Immediate lymphatic reconstruction

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Abstract

Although surgical and medical treatment options are available for the treatment of chronic lymphedema, there is no cure. Recent advances in microsurgery have provided an opportunity to perform immediate lymphatic reconstruction after lymphadenectomy for disease prevention. In this review, we provide the historical background leading to a paradigm shift in performing this procedure. We will also discuss the current evidence for immediate lymphatic reconstruction, potential oncologic procedures amenable to this approach, and detail ongoing challenges.

KEYWORDS

LYMPHA, lymphatic reconstruction, lymphedema, microsurgery

1 | INTRODUCTION

Lymphedema (LE) is a debilitating and progressive disease associated with physical, psychological, and economic costs.[1] The disease is characterized by insufficient drainage of interstitial fluid by the lymphatic system, most commonly involving the extremities, that can initiate a pathophysiologic cascade leading to chronic inflammation and eventual deposition of fibrotic adipose tissue. LE can cause a constellation of symptoms, including pain, heaviness, impaired mobility and function, and psychosocial impairment.[2] These symptoms can also have a significant long-term impact on the patient's quality of life.[3,4] Furthermore, infection is a potentially life-threatening complication in patients with chronic LE. Current management of LE requires lifelong patient participation to manage the disease and reduce the risk of these complications. The cornerstones of treatment have included manual lymphatic drainage, compressive bandaging, physical therapy, and a meticulous skin care regimen.[5,6] However, conservative efforts are at best palliative in nature and intended to limit disease progression and provide symptomatic relief. In our current medical environment that emphasizes cost containment, patients with LE face barriers to continued care because chronic treatment is often limited by insurance coverage.[4,7] For a condition whose management is predicated on life-long treatment, these barriers to care can result in disease exacerbation, predisposition to complications, and patient dissatisfaction.

The etiology of LE can be described as primary or secondary. Primary LE occurs due to a congenital disorder of the lymphatic system, whereas secondary LE occurs after a direct insult to an otherwise normal lymphatic architecture. Filariasis is the most common global cause of secondary LE and is estimated to affect 140 to 200 million people worldwide.[1,8] In the developed world, iatrogenic causes of LE, commonly secondary to surgical and radiotherapy interventions, predominate. In the United States, breast cancer-related lymphedema (BCRL) is the most common etiology.[1] Of the 3.5 million current breast cancer survivors living in the United States, one in five will be diagnosed with LE during their lifetime.[9] Factors that increase the risk of developing BCRL include increasing number of lymph nodes excised, radiotherapy, chemotherapeutic agents, and an elevated body mass index (BMI > 30).[1,8,10,11] Research that can better explain the impact of LE in this BCRL cohort has provided insight into its associated survivorship burden.[4,12] Women with BCRL are more likely to have worse physical and mental health outcomes, including higher rates of anxiety and depression, compared with their counterparts with breast cancer without LE.[2] Additionally, BCRL patients report higher rates of impaired vocational, domestic, social, and sexual functioning.[3,13-16] Furthermore, improved early surveillance of patients at high risk of LE has demonstrated that early detection and intervention are associated with a decreased need for intensive therapy(ies) and improved long-term outcomes, including quality of life.[17-21]

For patients with chronic LE, aside from the palliative conservative measures previously described, surgical interventions can be considered. In a recent systematic review, techniques for the treatment of peripheral LE, including lymphovenous bypass and vascularized lymph node transplant, were associated with increased quality of life, discontinued use or decreased need for therapy,

and objective reductions in extremity size.[22] Despite these advancements and their associated success, none to date provide an ultimate cure.[22,23] These promising surgical interventions, however, do open up speculation as to whether any microsurgical techniques are available to provide immediate lymphatic reconstruction at the time of lymphadenectomy to prevent this disease.

A combination of a better anatomic understanding of lymphatic anatomy and an ability to real-time image individual drainage patterns has facilitated a technological jump away from pure extirpative procedures to those that can best preserve anatomy while providing optimal oncological control. The evolution of "surgical prevention" in LE can be conceptualized as an evolution of thought and experience emphasizing minimization of axillary nodal excision, improved ability to identify and preserve specific lymphatic drainage pathways, and reconstruction of critical lymphatic pathways that have been disrupted.

2 | HISTORICAL BACKGROUND

2.1 | Minimizing damage: from the Halsted mastectomy to the sentinel lymph node biopsy

Until the late 19th century, breast cancer carried a uniformly fatal prognosis. William S. Halsted was the first to reject this notion and attempt to achieve disease control by resecting breast tissue, pectoralis major and minor muscles, and axillary lymph nodes to prevent disease progression.[24] Although this approach did decrease mortality, surgeons have since aimed for less radical excisions while carefully monitoring disease-free survival and recurrence rates.[25] For example, studies that compared lumpectomy and mastectomy found no differences in the overall survival rates, shifting the paradigm toward less extensive surgical dissections of the breast.[26-28] Improvements in diagnostic imaging, histopathologic margin evaluation, and the advent of effective chemoradiation and hormonal therapies further decreased the need to perform massive resections.[24]

Analogous to the breast where we witnessed the transition from the Halsted mastectomy to breast-conservation surgery, similar patterns in our approach to axillary intervention begin to emerge. The sentinel lymph node (SLN) biopsy provides valuable prognostic information and has now widely supplanted the axillary lymph node dissection (ALND).[29] The SLN biopsy (SLNB) allows for nodal staging to determine prognosis while minimizing the iatrogenic lymphatic damage associated with an ALND. The adaptation of this nodal-sparing technique led to a steep decline in LE rates from 25% to 6%. Moreover, compared with ALND, SLNB confers advantages, including increased quality-of-life indices and decreased postoperative sensory loss. Multiple large trials have demonstrated the utility of minimizing axillary surgery in patients with a negative SLN.[30-33] Moreover, data from the NSABP-B32 randomized trial showed statistically equivalent overall survival rates between groups undergoing SLN resection alone in node-negative women and ALND.[34] Pushing this concept even further, the American College of Surgeons Oncology Group Z0011 trial reported no long-term differences in survival in those with stage T1 and T2 invasive breast cancer with no palpable lymphadenopathy or documented metastatic disease with up to two sentinel node metastases who underwent ALND compared with those undergoing breast-conservation treatment.[33] However, despite decreased rates of axillary dissection, LE development persisted, albeit at lower rates.[10] Explanations include the continued need for regional lymph node radiotherapy, chemotherapy, and obesity.[15,31,35] Additionally, anatomic variations in lymphatic drainage were hypothesized to predispose some individuals to an increased risk of postoperative LE.[36,37]

2.2 | Preserving lymphatic drainage pathways

Preventing significant damage to the lymphatic system is considered paramount to reduce the risk developing LE. The SLNB reduced the risk of LE across multiple studies. However, for patients undergoing SLNB alone, postoperative LE was still observed in 0% to 13% of patients.[38-42] A group of surgeons attempted to explain this clinically significant rate of LE and hypothesized that varying drainage patterns of arm lymphatics increased susceptibility to lymphatic damage during ALND or SLNB.[43] This led to the development of a novel technique, axillary reverse mapping (ARM). The mapping of the lymphatics draining through a subcutaneous injection of blue dye into the ipsilateral volar forearm would enable identification and preservation of draining arm lymphatics during axillary lymph node dissection.[41,44] The results of ARM illustrated the significant variability in the anatomic location of "low-lying" arm lymphatics that were distinct from adjacent breast lymphatics.[45] ARM provides the breast surgeon the opportunity to modify the nodal dissection to a patient's individual lymphatic anatomy to preserve the lymphatic drainage of the arm during SLNB or ALND. In a feasibility study examining ARM in a patient cohort undergoing SLNB, only 3% of the blue or arm lymph nodes contained the radioactive tracer that had been previously injected into the breast, providing evidence that lymphatics draining the tumor are often different from those draining the upper extremity.[46]

Preservation of arm lymphatics should theoretically lead to a decreased risk of upper extremity LE. A recent meta-analysis showed an incidence of LE of 4.1% in patients with ARM undergoing SLNB or ALND.[47] However, the potential to leave occult residual malignancy in the axilla is an important technological caveat. Oncologic resection should not be compromised to reduce the risk of LE. In a study investigating the utility of ARM in node-positive women, metastatic disease was found in 18% of ARM lymph nodes, suggesting that this technique is not appropriate for more advanced malignancies.[48] There is currently no evidence to support ARM for patients with high axillary tumor burden, less than 10 positive nodes, or nodes suspicious for malignancy.[44,45,49] This lack of evidence questions the feasibility of ARM in patients with advanced-stage disease.[50] The ssafety of this technique and the lack of prospective, long-term studies documenting its efficacy in reducing rates of LE require further study. However, the implications of this technique

revolutionized primary preventative surgery for LE. If visualization and recognition of divided lymphatics were achievable during nodal dissection, then established microsurgical techniques, including lymphaticovenous bypass, could potentially be performed at the time of oncologic resection to restore lymphatic flow after the removal of lymph nodes draining the arm.

2.3 | Reconstructing lymphatic drainage pathways

In 1969, lymphaticovenous bypass was first described as a treatment approach for chronic LE where diseased lymphatics were bypassed by performing anastomosis of healthy lymphatics to a nearby vein to facilitate normal flow.[51] As detailed above, ARM provided an individualized blueprint of the lymph nodes, and therefore the individual lymphatics, draining the arm. By performing a lymphaticovenous anastomosis immediately after ALND, afferent draining arm lymphatics could be rerouted in collateral branches of the axillary vein to restore physiologic lymphatic flow. Most importantly, this technique also eliminated the potential of leaving residual occult malignancy in the axilla. In their pilot study of 19 patients, Boccardo et al[52] rerouted afferent divided blue dyed lymphatics to branches of an axillary vein at the time of axillary nodal dissection. The authors named this technique the LE Microsurgical Preventative Healing Approach or LYMPHA. In their continued study of LYMPHA in a high-risk patient population undergoing nodal dissection, the authors reported a 4% rate of LE over a 4-year follow-up period in 74 patients.[53] The study also reported the added benefits of a decreased rate of other complications secondary to reduced regional intralymphatic pressure. These include lymphorrhea and lymphocele. Lymphoscintigraphy demonstrated the patency of the anastomosis at up to 4 years of follow-up, with concomitant increased lymphatic transport indices.

These results were replicated in the United States in two single-center studies where rates of LE were reported at 12.5% after ALND with LYMPHA.[19,54] This technique was then further modified by utilizing fluorescein isothiocyanate to identify arm lymphatics. This modification became necessary as breast surgeons often choose blue dye for the identification of breast lymphatics and SLNs, thereby complicating the reconstructive surgeon's ability to differentiate between arm and breast lymphatics (Figure 1).[55] Fluorescein isothiocyanate has the technical advantage of providing real-time visualization of lymphatics through the binoculars of a microscope. This dye can also be washed away without permanently staining tissues.

Patients with breast cancer are not the only oncologic group at risk of developing LE. Other solid tumors whose treatment can result in lymphatic disruption are also at a heightened risk.[56-63] A more extensive lymph node dissection is often needed for solid tumors without an established effective form of systemic treatment to achieve optimal oncologic control.[14] A systematic review assessed the risk of LE in gynecologic and urologic procedures and found pooled rates of 20% and 10%, respectively. Both groups underwent equal rates of inguinal node dissection. However, a higher rate of adjuvant radiotherapy in the gynecologic cancer group has been hypothesized to account for higher rates of LE. Of the gynecologic malignancies, vulvar cancer has been associated with a 30% to 39% postoperative rate of LE.[64-66] Some studies have demonstrated that the SLNB should be used in some early-stage vulvar cancers as it has been associated with decreased rates of treatment-related morbidity, including LE.[67,68] However, a high incidence of postoperative LE after dissection of the inguinofemoral lymph nodes is alarming. Clinicians posit that this may be due to the lower prevalence of available collateral lymphatic channels, an increase in individual anatomic variation, and a heightened immune response to damaged lymphatics.[14] In 2013, Morotti et al[69] described success with a pilot study using inguinofemoral reverse mapping and LYMPHA in

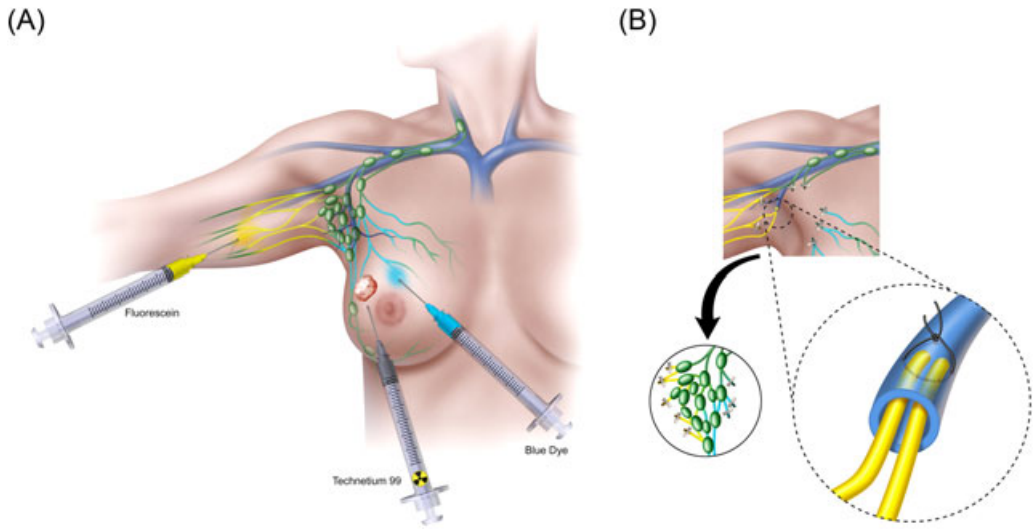

FIGURE 1 Modified LYMPHA technique schematic. A, Both blue and nuclear dyes are reserved for breast sentinel lymph node identification. Fluorescein isothiocyanate (FITC) is injected into the proximal upper inner arm. B, After completion of the axillary dissection and removal of levels 1 and 2 lymph nodes, arm lymphatic channels, now "glowing" from the FITC injection, are identified and rerouted into an axillary vein tributary. Pending copyright clearance. From figure 2 of Spiguel et al[55] [Color figure can be viewed at wileyonlinelibrary.com]

patients with vulvar cancer (stages Ib to IIIC) undergoing inguinal lymphadenectomy. In these LYMPHA cases, divided lymphatics were anastomosed to collateral vessels of the femoral vein. The authors reported that, despite a small sample size, the rate of LE in this cohort was 8.3% (1 of 12). This study group had a high-risk factor profile, including adjuvant radiotherapy, advanced-stage disease, and a mean of approximately 10 lymph nodes removed per procedure.[70-72] Primary lymphaticovenular anastomosis was also shown to decrease the rates of LE in patients undergoing total hystero-oopherectomy with inguinal and paraaortic node dissection.[73] The surgeons could complete anastomoses without the use of any mapping technique. There was no reported development of chronic LE during follow-up.

There is a pressing need for more studies to evaluate the prevention of lower extremity edema after gynecologic tumor and nodal excision. There is evidence supporting the therapeutic benefit of less radical nodal dissections in some gynecologic studies; however, widespread acceptance of less invasive staging and treatment strategies has still not been achieved.[74] Investigators are using a similar paradigm based on an improved understanding of lymphatic anatomy, a standardized oncologic technique, and immediate microsurgical reconstruction as it applies to the pelvic and lower extremity for oncologic surgeries to reduce the incidence of LE in this high-risk patient population. Additional prospective studies with a longer follow-up duration in a larger population are needed to demonstrate the ultimate efficacy of this technique.

Although rerouting of lymph from divided lymphatics into the venous circulation in breast and gynecologic malignancies significantly reduced the rate of subsequent LE development, it did not completely eliminate the disease altogether, thus providing a platform for further research into this approach.

3 | DEVELOPMENT OF AN ANIMAL MODEL

Multiple animal studies have been performed to evaluate the etiology and pathophysiology of LE, including evaluation of response to various therapeutic interventions.[75-81] These studies also include genetic models and the assessment of response to pharmacotherapies. A pilot animal model to evaluate LYMPHA, or immediate lymphatic reconstruction, was recently developed and real-time lymphatic clearance was quantified using novel fluorophores (Figure 2).[82] This study reported a 68% reduction in lymphatic clearance from a swine hind limb after lymphadenectomy. After lymphadenectomy with immediate lymphatic reconstruction, there was only a 21% decrease in lymphatic clearance from the hind limb. Improved optical imaging techniques in these animal studies allowed for real-time visualization of the lymphatics and the patency of anastomoses. Despite the limitations inherent to a nonsurvival animal study, this study led to the successful development of the first animal model for LYMPHA. In the future, survival animal studies are needed to evaluate the effects of adjunct treatments, including regional radiation, chemotherapy, hormonal therapy, and time, on the efficacy of this technique.

4 | ADJUNCT APPROACHES

Animal models have also led to a better understanding of the pathophysiological mechanisms for LE and have led to the discovery of several targets for pharmacologic intervention.[83] These studies have identified targets for the treatment of chronic LE, including transforming growth factor-β1, interleukin-6, leukotriene B4, and vascular endothelial growth factor C (VEGF-C).[84-90] Although genetic mutations associated with primary LE were identified, increased attention has been padi to potential genetic contributions to secondary LE. Studies have identified potential mutations in genes involved in the hepatocyte growth factor/mesenchymal-epithelial transition signaling pathway, mutations in connexin 47, and single-nucleotide polymorphisms in vascular endothelial growth factor receptor 2 (VEGFR2), VEGFR3, and ROR orphan receptor C (RORC) that may predispose patients to LE.[91-94] These findings challenge the notion that secondary LE is a complication caused solely by injury to the lymphatics and suggests that causation may be polyfactorial. Development of agents that target these identified mutations have significant promise for the prevention of LE in this patient cohort.

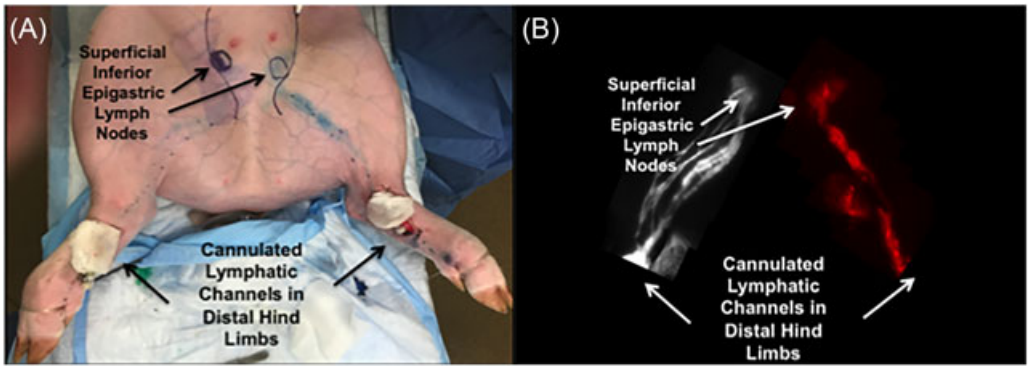

FIGURE 2 Swine model for LYMPHA. A, Lymphatic channels cannulated in the distal hind limbs bilaterally. B, FLARE video capture immediately after a bilateral distal hind limb injection of fluorophores. Stitching was done with Image J (NIH Image, WI). Right, ICG-HSA (white signal) at 250-ms exposure time; Left, EB-HSA (red signal) at 200-ms exposure time. Pending copyright clearance. From figure 2 of Tran et al[82] [Color figure can be viewed at wileyonlinelibrary.com]

5 | INTEGRATING LYMPHATIC RECONSTRUCTION INTO OUR HEALTHCARE MODEL IN THE UNITED STATES

As the clinical and research aspects of immediate lymphatic reconstruction continue to advance, surgeons must be cognizant of how to integrate this approach into practice. Specifically, our healthcare system has a historical tradition of allocating its increasingly limited funds toward treatment instead of prevention. In fact, preventative health services constitute a mere 3% of the total healthcare expenditure.[95] Our Italian colleagues developed a technique, LYMPHA, that has the potential to revolutionize treatment and prevent a surgical complication associated with high healthcare expenditure. A study by Shih et al[13] analyzed patient costs of LE during a 2-year time period. They found that increased costs for BCRL were largely driven by increased utilization of outpatient and/or inpatient medical care, diagnostic imaging testing, and mental health-related visits. The lifelong treatment costs associated with LE therapy were not captured in this cost analysis and suggests that the reported cost may represent a gross underestimation of lifelong healthcare expenditures associated with their disease management. Additionally, this study was only limited to breast cancer-related LE, precluding any discussion of disease-related costs associated with other oncologic treatments that have a high risk of postoperative LE.

Breast reconstruction is one of the most commonly performed plastic surgery procedures. In fact, the 1998 Women's Health and Cancer Rights Act (WHCRA) provides all insured women the ability to have breast reconstruction after mastectomy.[96] Ostensibly, it also provides coverage for treatment due to mastectomy-related complications, including LE. Incredibly, how we document our procedures can significantly impact whether or not they are reimbursed. While the "Lymphedema Microsurgical Preventative Healing Approach" is the original name given to this technique, the term "preventative" can often result in denial of charges. Perhaps a more effective method to obtain insurance coverage for microsurgical reconstruction at the time of ALND, and arguably a more accurate term, is to consider this approach as an "immediate lymphatic reconstruction." Similarly, the surgical management of chronic LE may be more accurately described as "delayed lymphatic reconstruction." A more precise labeling of these life-changing procedures better parallels the obligate verbiage recognized by the WHRCA and may result in improved recognition of this reconstruction.

6 | ONGOING CONTROVERSIES

An ongoing debate in the treatment of LE is the continued search to obtain a better scheme for patient selection criteria. Elevated BMI has been described as an important risk factor for postoperative LE.[97-100] In their most recent study, Boccardo et al[53] provide a procedural algorithm that supports LYMPHA in women with a BMI > 30 who have a transit index, TI > 10. However, in this study, the mean patient BMI was 24. Statistical support for the sole use of this technique in patients with elevated BMI is lacking. Obesity has been proposed to contribute toward and/or predispose to LE after surgery by impairing fluid transport and decreasing the pump frequency of lymphatic vessels.[89] Application of a BMI cutoff without sufficient evidence could have the pernicious potential of preventing a subset of women from accessing a reconstructive procedure of the lymphatic system.

Quantification of measurement continues to be a challenge in the field of LE. Until standardized measurement techniques are adopted and implemented, comparison of outcomes across studies will remain a challenge. One review highlights the different measurement tools used across a large sample of studies and their likely contribution to the inadequate estimation of disease prevalence.[64] Additionally, routine collection of subjective outcomes through validated questionnaires is needed to gain insight into the entire patient disease experience.[4]

The patency of lymphaticovenous bypass in chronic LE has been determined. However, the patency of anastomoses after additional systemic cancer treatment, including chemoradiation, remains unknown. Only one study by Boccardo et al[53] determined patency through lymphoscintigraphy up to 4 years after anastomosis. Further research to determine how the cumulative exposure to these agents could also influence the variable time of onset of LE after oncologic treatment is needed.

7 | THE FUTURE

Lymphaticovenous anastomosis is currently the best operative technique available in the microsurgeon's armamentarium for immediate lymphatic reconstruction. Studies evaluating LYMPHA after treatment of breast cancer and gynecologic malignancies are promising. Additional research is needed to determine its efficacy in different patient populations with varying risk factor profiles and postoperative treatment regimens. The lack of uniform measurement techniques challenges our ability to draw comparisons across studies as we assess the results of lymphatic reconstruction.[4,5,14] To bridge this gap, the application of standardized objective outcome measurements is needed. Moreover, our changing healthcare environment has witnessed a shift toward the importance of patient-reported outcomes (PRO) to identify treatment modalities that are not only clinically efficacious but also improve overall patient disease experience. Incorporation of PROs provides another dimension to assessment by collecting standardized data on functional status, perceived satisfaction with treatment experience, and quality-of-life measures. Improved collection of PROs through validated instruments will also create an improved framework to guide decision-making for patients who are most likely to benefit from LYMPHA.[4,70] In a system forced to better understand the cost-effectiveness of treatments, more accurate evaluation would enable better allocation of healthcare dollars for the treatment of this difficult problem. Cost–benefit analyses for this procedure have not yet been

published. If better quality research confirms the success of this technique, it would be critical to perform immediate lymphatic reconstruction. This is necessary due to both the widespread incidence of LE after upper and lower oncologic surgeries and its devastating lifelong impact on a patient's quality of life.[3,12,70,74] Our resources would be better utilized by delivery of immediate lymphatic reconstruction rather than relying solely on early post-operative surveillance and palliative-type lifelong care.

8 | CONCLUSION

Despite tremendous advancements in lymphatic surgery, including immediate lymphatic reconstruction, LE continues to be associated with significant morbidity for many patients, including those under treatment for various malignancies. This study has highlighted the evolution of a promising approach that provides immediate lymphatic restoration at the time of nodal dissection. This technique represents further development and refinement of surgical knowledge through better quality research, improved anatomical understanding of the lymphatic system, and better imaging techniques that have enabled the application of microsurgical techniques to achieve long-term bypass patency. There remains a need to carefully evaluate this technique and its application in different patient cohorts with varying risk factor profiles, including obesity, potential genetic predispositions, chemoradiation, and endocrine therapies. Additionally, an improved understanding of the effect of immediate lymphatic reconstruction on patient quality-of-life measures and cost-effectiveness is needed.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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