Immediate lymphatic reconstruction for the prevention of breast cancer-related lymphedema: an experience highlighting the importance of lymphatic anatomy

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Abstract

Immediate lymphatic reconstruction (ILR) has become increasingly utilized for the prevention of breast cancer-related lymphedema (BCRL). A growing body of evidence has demonstrated the long-term efficacy of ILR in reducing the rate of BCRL. While certain risk factors for BCRL are well-recognized, such as axillary lymph node dissection, regional lymph node radiation, and elevated body mass index, other potential risk factors such as age and taxane-based chemotherapeutics remain under discussion. Our experience with ILR has highlighted an additional potential risk factor for BCRL. Lymphatic anatomy, specifically compensatory lymphatic channels that bypass the axilla, may play a largely underrecognized role in determining which patients will develop BCRL after ILR. Foundational anatomic knowledge has primarily been based on cadaveric studies that predate the twentieth century. Modern approaches to lymphatic anatomical mapping using indocyanine green lymphography have helped to elucidate baseline lymphatic anatomy and compensatory channels, and certain variations within these channels may act as anatomic risk factors. Therefore, the purpose of this review was to highlight ways in which variations in lymphatic anatomy can inform the application and improve the accessibility of this procedure. As ILR continues to advance and evolve, anatomical mapping of the lymphatic system is valuable to both the patient and lymphatic microsurgeon and is a critical area of future study.
INTRODUCTION

A significant survivorship issue following breast cancer treatment is breast cancer-related lymphedema (BCRL). BCRL arises due to the accumulation of lymphatic fluid in the upper extremity as a result of damage to the lymphatic system during axillary lymph node dissection (ALND)\(^1\). The fluid accumulation can result in disfiguring edema, erythema, pain, tightness, heaviness, and diminished function of the affected extremity\(^2-3\). If left untreated, BCRL is typically progressive and can be complicated by life-threatening infections. In addition to distressing physical symptoms, patients may face psychosocial burdens secondary to BCRL\(^4-5\). Additionally, patients with BCRL face considerable out-of-pocket costs irrespective of treatment modality\(^7,8\).

The incidence of BCRL following axillary lymph node dissection is reported to be between 21% to 34%\(^9-14\). Variation in reported incidence may be due to the lack of standardization in methods of assessment and diagnostic criteria. Notably, the incidence of lymphedema is disproportionately higher among Black and Hispanic patient populations, highlighting a healthcare disparity among breast cancer survivors\(^15\). Breast cancer mortality rates have declined due to advancements in diagnostic modalities and clinical management\(^16\). Therefore, the rates of BCRL can be expected to increase in the coming decades and there remains an unmet need for physicians and researchers dedicated to the prevention and treatment of this disease\(^17\).

The pathophysiology of BCRL occurs through three stages: fluid accumulation, fibrosis, and fatty tissue deposition. In the initial stages, interstitial fluid stasis takes place and proliferation of inflammatory cells ensues\(^18\). This inflammatory response leads to lymphatic vessel deterioration, fibrosis, and inhibition of lymphangiogenesis\(^19-22\). Lastly, subcutaneous adipose tissue is deposited\(^23,24\). Notably, multiple genes have been implicated in the development of BCRL, including HGF and GJC2 genes\(^25-28\). This knowledge has been utilized clinically by recommending genetic testing for patients for earlier detection of lymphedema, though further research is warranted\(^29\).

As the underlying inciting event of BCRL development is the disruption of lymphatic vessels during oncologic surgery, our team has focused on the operative prevention of BCRL. The purpose of this review is to highlight ways in which variations in lymphatic anatomy can inform the application and improve the accessibility of the surgical prevention of lymphedema. In order to adequately discuss surgical prevention, it is important to first understand identifiable preoperative risk factors.

RISK FACTORS FOR DEVELOPING BCRL

The single greatest risk factor is ALND. Patients who undergo ALND are at a substantially higher risk of developing BCRL, with a relative risk of 3.47 in comparison to those who do not require ALND for oncologic treatment\(^11,30,31\). Findings from Yusof et al. determined that ten or more excised lymph nodes was associated with a three-fold increased risk of BCRL, due to more extensive damage to the lymphatic vessels\(^32\). Furthermore, patients with a larger burden of oncologic disease within the lymph nodes may be at higher risk of BCRL development, as the invasion of cancer cells within the lymph nodes may overcrowd and disrupt normal lymphatic architecture, thereby impairing lymphatic flow\(^30,33\).
Regional lymph node radiation (RLNR) substantially increases a patient’s risk of BCRL in a delayed manner, as it can take months or years for radiation-related fibrosis to develop\textsuperscript{[34,35]}. The development of fibrosis within the lymph node can compress and distort the lymphatic tissue, resulting in increased fluid accumulation in the distal lymphatics\textsuperscript{[36,37]}. RLNR targeted at supraclavicular or axillary lymph nodes presents the greatest risk of BCRL, whereas the risk after chest wall radiotherapy appears to be lower\textsuperscript{[45]}.

Body mass index (BMI) is recognized as the primary modifiable risk factor linked to the development of BCRL\textsuperscript{[30,38-40]}. A higher BMI has been positively correlated with the development of BCRL, with obese patients having a greater risk of developing lymphedema compared to those who are overweight or within the normal range\textsuperscript{[39]}. This correlation may be explained by underlying biochemical changes to the lymphatic system in patients with higher BMI, including inflammatory processes and direct injury to lymphatic endothelial cells, which likely induce baseline lymphatic disruption\textsuperscript{[41]}.

There are other important risk factors that remain controversial. Multiple studies have reported an association between taxane-based chemotherapeutic administration and BCRL development\textsuperscript{[42-46]}, while other studies have not supported this finding\textsuperscript{[47]}. Cariati \textit{et al.} demonstrated that the use of adjuvant taxane-based chemotherapy conferred a threefold increase in the risk of BCRL development\textsuperscript{[46]}. In a large prospective study, Swaroop \textit{et al.} noted that adjuvant docetaxel increased the risk of mild swelling though taxane-based chemotherapy was not a risk factor for BCRL development\textsuperscript{[47]}. Fewer studies have focused on examining the effects of neoadjuvant taxane-based chemotherapy on the development of BCRL\textsuperscript{[44-50]}. Johnson \textit{et al.} demonstrated that patients who received neoadjuvant taxane-based chemotherapy had a reduction in lymphatic contractile function and demonstrated a possible association with the presence of peripheral neuropathy in those who received neoadjuvant taxane-based chemotherapy\textsuperscript{[48]}.

Multiple prior studies have noted an association between increasing age and BCRL\textsuperscript{[51-53]}. Shang \textit{et al.} demonstrated that aging results in loss of muscle cells, impairment of lymphatic contractile function, and increased production of inflammatory cytokines\textsuperscript{[59]}. However, other studies offer contradictory findings, with some reporting that the incidence of BCRL is higher in younger women\textsuperscript{[55-57]}.

There is uncertainty as to how factors pertaining to oncologic breast surgery, such as the extent of breast surgery and reconstruction, may modify individual risk of BCRL. A previous investigation reported that modified radical mastectomy appeared to be an independent risk factor for BCRL\textsuperscript{[58]}. Other studies have indicated that the rate of BCRL was higher in those who underwent a total mastectomy compared to those who underwent partial mastectomy\textsuperscript{[59]}. Additionally, patients undergoing multiple surgeries including both mastectomy and lumpectomy on the same breast are likely at higher risk of BCRL than those having only one procedure alone\textsuperscript{[62]}. In addition, multiple studies have examined the relationship between breast reconstruction and BCRL development. In a meta-analysis, Siotos \textit{et al.} determined that breast reconstruction was associated with a lower risk of lymphedema compared to mastectomy alone\textsuperscript{[60]}. In a matched cohort study of over 400 patients, Basta \textit{et al.} reported that immediate breast reconstruction did seem to influence the risk of BCRL development\textsuperscript{[61]}. Though the influence of breast reconstruction on the risk of BCRL development is not fully understood, breast reconstruction does not appear to adversely affect the risk of BCRL\textsuperscript{[62]}.

IMMEDIATELY Lymphatic RECONSTRUCTION

Lymphovenous bypass (LVB), as described by Yukio Yamada in 1969 as a surgical treatment for chronic lymphedema, was the first successful surgical technique developed to restore lymphatic flow in an animal model\textsuperscript{[63]}. In this study, a successful anastomosis of the thoracic duct into the venous system was created,
thereby restoring a novel afferent route for lymphatic fluid. In 2009, Boccardo et al. applied this innovation for the prevention of BCRL by rerouting arm lymphatics to an axillary vein tributary at the time of ALND\textsuperscript{[64]}. This procedure, originally termed Lymphatic Microsurgical Preventative Healing Approach (LYMPHA)\textsuperscript{[64,65]}, has more recently been referred to as immediate lymphatic reconstruction\textsuperscript{[66]}. A growing body of evidence has demonstrated promising results of ILR for the prevention of BCRL, including a recent meta-analysis which reported a BCRL incidence of 5.7\% in patients who underwent ILR compared to 34\% in those who underwent ALND alone\textsuperscript{[13]}.

An overview of the steps of immediate lymphatic reconstruction is outlined in Figure 1. Immediately prior to ALND, a lymphatic-specific dye is injected intradermally for lymphatic channel identification. In order to ensure comprehensive visualization of lymphatic channels, we perform intradermal injections of 0.25cc of 2\% fluorescein isothiocyanate (FITC) mixed with albumin at the 1\textsuperscript{st} and 4\textsuperscript{th} dorsal hand web spaces and at the radial and ulnar aspects of the volar wrist crease. Additionally, 1cc of isosulfan blue is injected intradermally over the course of the cephalic vein, identified by ultrasound, in the lateral upper arm. The anatomic location of these injections can vary, with some opting for upper arm injections as originally described\textsuperscript{[67,68]}. Once the ALND is complete, the dye allows for visualization of disrupted lymphatic channels within the axilla and the channels can then be prepared for the LVB.

Various dyes have been utilized for identification of lymphatic channels, including isosulfan blue, indocyanine green (ICG), and FITC\textsuperscript{[67]}. Isosulfan blue dye was initially used for ILR, but this dye is also frequently utilized for the oncologic mapping of sentinel lymph nodes; therefore, this presented challenges in distinguishing sentinel lymph nodes from peripheral arm lymphatics. This necessitated the adoption of novel dyes for lymphatic channel identification, such as ICG, which remains a favorable option as it is not consistently used during the oncologic portion of the procedure. However, the use of ICG is limited by the inability to visualize the dye without a near-infrared camera and can compromise the surgeon’s view of the surrounding structures under the surgical microscope. Additionally, some oncologic surgeons will utilize ICG for breast sentinel lymph node biopsy, though this is institution dependent. Some groups have utilized FITC as an effective alternative, given the ability of FITC to be visualized with a fluorescence filter applied to the microscope that does not limit the visibility of surrounding anatomical structures\textsuperscript{[69]}. Therefore, both lymphatic channel visualization and microsurgical reconstruction can be carried out without interference. Notably, each of these techniques allows for visualization of superficial structures 1-2 cm below the skin and therefore, deep lymphatic channels are not currently able to be readily identified during ILR.

While each dye has distinct advantages and disadvantages, further research is necessary to develop standardized methods for lymphatic channel identification\textsuperscript{[70]}. For example, increasing dye uptake in lymphatic vessels and improved visualization of deep lymphatic channels are notable obstacles in the application of newer dyes. Conjugating a fluorophore to a larger compound, such as to dextran, albumin, or polyethylene glycol (PEG), may have potential utilization, as any particle too small (\(<\,5\,\text{nm}\)) or too large (\(>\,100\,\text{nm}\)) precludes dye uptake into the lymphatic channels\textsuperscript{[71]}. Prior investigations determined that the optimal size for lymphatic uptake is 10-100 nm; therefore, these dyes may aid in optimizing lymphatic uptake. Furthermore, near-infrared (NIR) dyes and upconverting nanoparticles (UCNPs) are other potential methods to enhance lymphatic visualization\textsuperscript{[72]}.

Following the identification of the transected lymphatic channels, a target vein for the lymphovenous bypass is identified. There are multiple recipient venous candidates in the axilla, including the accessory vein (thoracoepigastric vein), lateral thoracic vein, medial pectoral vein, circumflex scapular vein, thoracodorsal vein, or other unnamed adjacent venous tributaries [Figure 2]\textsuperscript{[67,73]}. The accessory vein, which is the most
Figure 1. Comprehensive workflow of immediate lymphatic reconstruction (ILR) following axillary lymph node dissection (ALND).

Figure 2. Potential recipient vein options in the axilla for immediate lymphatic reconstruction (reused with permission, Coriddi et al., 2020, Plastic and Reconstructive Surgery Global Open[67]).

popular for ILR, is found coursing through the level 1 axillary lymph nodes, originating perpendicular from the axillary vein, 2 cm anterior to the thoracodorsal vessels. Due to its proximity to arm lymphatic channels, it has become an ideal candidate for the procedure[67]. Unfortunately, this proximity to the axillary lymph nodes also places this vein at risk for transection and removal during axillary lymph node excision. In this case, any of the previously mentioned veins can be used as an alternative[74,75].

The recipient vein requires adequate length, which we have found to be ideally ≥ 5cm, as it must be long enough to reach the arm lymphatic vessels while avoiding undue tension on the anastomosis. The presence of at least one venous valve is vital for preventing venous back-bleeding through the site of the anastomosis. Significant back-bleeding can overwhelm the lymphatic system, given the pressure differential across the anastomosis, thereby preventing afferent lymphatic flow. Furthermore, the size of the recipient vein is a critical consideration as the lymphatic channels are significantly smaller than that of their venous counterparts. To help alleviate this size discrepancy, multiple lymphatic channels can be intussuscepted into the vein, or if the lymphatic vessels are large enough, an end-to-end anastomosis can be performed with a small vein[67,76]. Utilization of venous branches of the recipient vein has also become an effective method to optimize the size-matching of the lymphatic channel to the recipient vein[67]. Moreover, each branch point is likely to contain a valve, thereby further preventing the backflow of venous blood[77]. Of note, unlike lymphovenous bypasses for chronic lymphedema performed in the distal extremity where preoperative ultrasound can assist in identifying reflux-free veins[74,75], this is not possible pre-operatively in preventative cases as the veins are deeper and their availability and physiology may be altered following
lymphadenectomy. Even with careful consideration and selection of the recipient vein, venous back-bleeding and inadequate recipient vein length are two technical challenges that impede the success of ILR and lead to aborting procedures intraoperatively. Recently, our team has instituted routine use of a lower extremity vein graft to overcome these venous-related complications[78]. In this technique, a 5 cm target vein is identified by ultrasound as a superficial secondary or tertiary branch of the greater saphenous vein in the medial lower leg, caudal to the medial epicondyle of the knee. This segment is ideally selected to ensure the presence of at least two branches or one venous valve, which can be visualized on ultrasonography. The vein is then harvested and anastomosed to the axillary vein tributary, maintaining the orientation of the vein graft in order to preserve the proper directionality of the venous valve. Since utilizing a lower extremity vein graft during ILR, our intraoperative aborted case rate was reduced from 14% to 0%, thereby suggesting the promising effects and potential utility of this innovation to mitigate venous-related complications[78]. Furthermore, the harvest of the lower extremity vein graft was performed synchronously with the ALND and therefore did not increase the intraoperative time of the overall operation[78].

Of note, additional preventative surgical approaches to reducing the risk of lymphedema have been proposed, including peripheral supermicrosurgical anastomoses and prophylactic lymph node transplantations and lymphatic flaps[79-83]. Prophylactic peripheral lymphovenous bypasses offer an interesting approach which would essentially eliminate the effect of adjuvant radiotherapy which is usually targeted to the nodal region. The challenge of this prophylactic approach is identifying anatomically which lymphatic channels should be bypassed. Prophylactic lymph node transplantations and lymphatic flaps offer a promising approach. However, the surgeon must carefully balance the morbidity of the donor site with the relative risk reduction of lymphedema development[83,84].

LYMPHATIC ANATOMY

Despite continued evidence demonstrating the effectiveness of ILR for the prevention of BCRL, there are several barriers that may hinder the progress and advancement of this approach within the field of lymphatic surgery. Firstly, ILR remains a technically demanding procedure that is not frequently covered by health insurance[85]. Additionally, there are a limited number of lymphatic centers and surgeons formally trained in lymphatic microsurgery, and therefore patients are often required to travel long distances to undergo ILR[86]. While the incidence of BCRL after ALND and RLND approaches 25-30%, around 70% of patients do not ever develop lymphedema. Although the occurrence of BCRL may be moderate, counseling all patients regarding the risk of lymphedema after oncologic surgery is necessary for proper patient management. In addition, discussing the benefits of ILR and obtaining thorough informed consent enhances patient autonomy and understanding of medical information[87]. Importantly, identifying the individuals with the highest risk for BCRL development will allow us to overcome resource constraints and deliver this procedure to those who need it the most.

We believe that a better understanding of individual variations in lymphatic anatomy will help identify those patients in greatest need for ILR. To date, there is no modern comprehensive compendium or map of normal lymphatic anatomy and most of our current foundational knowledge has been obtained from cadaveric dissections that predate the twentieth century[88]. However, more recent efforts have been made to further the anatomic knowledge of the lymphatic system. In 2016, Suami et al. described the lymphosome concept [Figure 3], which is defined as predictable areas of the body in which the lymphatics will reliably drain to a designated group of lymph nodes[89,90]. This concept has advanced our understanding of lymphatic anatomy and allowed for more accurate predictions regarding the location of major lymphatic channels. A detailed appreciation of lymphatic anatomy based on the lymphosome concept may help guide lymphatic surgeons in selecting which lymphatic channels to bypass when multiple transected channels are identified.
intraoperatively and knowledge of lymphatic anatomy in relation to venous vasculature may facilitate lymphovenous bypass\(^9\).

Based on delineated lymphosomes, in our experience with ILR, we have noted that different regions of the upper extremity drain to distinct areas of the axilla. We previously investigated lymphosomes of the upper extremity using two distinct dyes, FITC and isosulfan blue, in order to differentiate medial and lateral upper arm lymphosomes\(^9\). In this study, we demonstrated that the lateral upper arm drained via a lymphatic channel that did not course through the axilla in the vast majority of patients\(^9\). This pathway was distinct from those of the medial upper arm, which reliably were identified as draining to the axilla. Given its extra-axillary drainage, the lateral upper arm channel had previously been described as one of the few compensatory routes of lymphatic drainage following ALND, which was further supported by our study\(^9\). The lateral upper arm channel, along with other compensatory drainage routes that bypass the axilla, are postulated to be protective against BCRL and may help to explain why only a percentage of patients undergoing the same oncologic treatments ultimately go on to develop BCRL. This finding has focused our group on lymphatic anatomy as we believe characterization of baseline anatomy and compensatory channels will help to predict which patients will develop BCRL after ALND.

A surgical prevention program cannot exist without a comprehensive surveillance protocol involving a multidisciplinary preoperative assessment. As part of our program’s preoperative assessment, we routinely perform ICG lymphography prior to ALND and ILR in order to visualize and map baseline superficial lymphatic anatomy. Over time, our group became increasingly focused on the visualization of compensatory lymphatic channels on ICG and this informed our ICG injection sites such that we implemented targeted ICG injection sites to capture these channels\(^9\). Early in our ICG experience, we performed two anterior ICG injections in the wrist crease and two posterior injections at the first and fourth webspace of the hand. However, we later refined our injection technique to include an additional injection
over the cephalic vein, which allowed us to reliably visualize the lateral upper arm channel\textsuperscript{[94]}. Additionally, we have more recently added a peri-olecranon injection to visualize another compensatory channel: the tricipital or Caplan’s pathway\textsuperscript{[95-99]}.

Though we have observed significant variation in baseline lymphatic anatomy between individuals, we have noticed distinct trends in both the main channels and compensatory lymphatic channels [Figure 4]. In 102 preoperative ICG lymphographies performed, we observed that the main pathways arising from the hand and forearm (posterior radial, posterior ulnar, anterior radial, and anterior ulnar) often demonstrate a functional connection to one of two channels in the upper arm: the medial and lateral upper arm channels\textsuperscript{[100]}. We also noticed variations in the connectivity of the lateral upper arm channel to the forearm channels, specifically long and short bundle phenotypes [Figure 5]\textsuperscript{[93]}. The long bundle lateral upper arm channel is defined as having a functional connection with a forearm channel, most commonly, the posterior radial channel. In the short bundle phenotype, the lateral upper arm channel lacks a functional connection to the forearm channels and is only visualized following the targeted injection over the cephalic vein. Upon postoperative surveillance of 60 patients who underwent ALND, the short bundle lateral upper arm pathway appeared to act as an anatomic risk factor for BCRL\textsuperscript{[101]}. We hypothesize that these findings were due to the short bundle phenotype resulting in a watershed region of lymphatic drainage between the forearm and upper arm. We have also observed analogous anatomic phenotypes in the tricipital pathway [Figure 6]. We believe that future investigations focusing on the anatomical variability of this and other compensatory channels such as the tricipital pathway, will help patients at the greatest risk for BCRL development\textsuperscript{[99]}.

**FUTURE DIRECTIONS**

This knowledge can be applied clinically at various levels of care in both the preoperative and postoperative settings. For the lymphatic surgeon, this information may inform which patients would benefit most from the ILR procedure. Ideally, every patient undergoing ALND would have access to ILR for the prevention of lymphedema despite their anatomical phenotype, as the morbidity of the procedure is quite low. However, the relative inaccessibility to lymphatic surgery and inconsistent healthcare coverage for ILR hinders patients’ ability to access and undergo ILR. Preoperative mapping of lymphatic anatomy using ICG lymphography can be accomplished in an outpatient clinical setting and does not require a lymphatic surgeon. Therefore, this is a feasible way to identify patients at the greatest risk for lymphedema development and for whom ILR would be most beneficial.

Moreover, a better understanding of lymphatic anatomy may inform which lymphatic channels should be prioritized for bypass or identified with an additional dye, the channels in closer proximity to the axillary vein. This knowledge would be important not only to the lymphatic surgeon, but also to members of the tumor board. For example, oncologists may choose to consider anatomical risk when determining a patient’s neoadjuvant chemotherapy regimen and avoid taxane-based regimens altogether when possible. Postoperatively, patients with high-risk anatomy can follow a more rigorous lymphedema surveillance protocol or wear compression garments prophylactically\textsuperscript{[102]}. Additionally, understanding compensatory lymphatic channels can help guide both physical therapists and patients in performing manual lymphatic drainage\textsuperscript{[103]}. Finally, anatomical knowledge can possibly inform radiotherapy planning and field design in efforts to protect collateral drainage pathways from radiation exposure\textsuperscript{[104]}. Finally, non-surgical methods for the prevention of lymphedema continue to be investigated. The use of pharmaceuticals that promote lymphangiogenesis has been developed as potential treatment for lymphedema\textsuperscript{[105]}. These drugs could potentially be applied to lymphedema prevention by enabling collateral
growth of lymphatic vessels, thereby allowing for continued lymphatic flow after ALND. Further investigation into methods of pharmacological treatment and prevention for lymphedema via
lymphangiogenic cytokine delivery, anti-inflammatory agents, as well as anti-fibrotic agents could aid in the non-surgical prevention and treatment of BCRL.

CONCLUSION

The development of breast cancer-related lymphedema following breast cancer treatment is multifactorial and surgical prevention with ILR can reduce the rate of BCRL development. Although our understanding of risk factors has evolved, currently established risk factors do not fully account for the variation in BCRL development at the individual level. A deeper appreciation of lymphatic anatomy will help to further our understanding of the pathologic changes that occur in BCRL and will help to explain why only a subset of patients develop BCRL after oncologic treatment and ILR. Therefore, there is high utility and value in anatomical mapping of the lymphatic system for both the patient and surgeon.

DECLARATION

Authors’ Contributions
Made substantial contributions to the completion or design of the work: Friedman R, Kinney JR, Bahadur A, Singhal D

Performed data acquisition, analysis, and interpretation of data for the work: Friedman R, Kinney JR, Bahadur A, Singhal D.

Helped with drafting or revision of the manuscript for important intellectual content: Friedman R, Kinney JR, Bahadur A, Singhal D.
Provided final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Friedman R, Kinney JR, Bahadur A, Singhal D.

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Conflict of Interest
None.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Consent was obtained for the acquisition of intraoperative patient photographs for research purposes.

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