



Immediate lymphatic reconstruction for breast cancer

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Abstract: Upper extremity lymphedema remains a significant source of morbidity in breast cancer patients despite significant improvements in breast cancer care. The risk of lymphedema is particularly elevated in patients requiring an axillary lymph node dissection and/or adjuvant radiation to treat their disease. Current treatment options for lymphedema, including conservative management or surgery, are limited and are often aimed at improving symptoms and quality of life rather than curing the disease. In this review we describe immediate lymphatic reconstruction, a novel surgical procedure that is done concurrent with axillary lymph node dissection in an effort to prevent the development of breast cancer-related lymphedema. Based on our growing knowledge of the pathophysiology of lymphedema, microsurgical techniques are used at the time of axillary lymph node dissection to perform a lymphovenous bypass between transected, leaking lymphatic channels and an adjacent, small calibre vein in the axilla. Using several objective metrics for short- and long-term surveillance, patients are monitored for the development of postoperative lymphedema. Early outcomes from using this technique have been promising, both in the literature and within our own institutions, demonstrating significant improvements in rates of postoperative lymphedema. However, future study is still required to better understand the long-term efficacy of immediate lymphatic reconstruction.

Keywords: Breast cancer; lymphedema; lymphatic reconstruction

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Background

Breast cancer remains one of the most commonly diagnosed forms of cancer in women, with 1 in 8 women developing breast cancer over the course of her lifetime (1). Since the advent of the Halsted mastectomy in 1912, treatment for breast cancer has significantly evolved (2). The use of more minimally invasive surgical techniques, combined with neoadjuvant and adjuvant therapy, has improved overall mortality, postoperative morbidity, and aesthetic outcomes (3-6). However, despite more conservative measures for the management of breast cancer-related axillary disease, including staging with sentinel lymph node biopsy, upper extremity lymphedema remains a significant complication

of breast cancer care. A 2013 systematic review still placed the overall rate of breast cancer-related lymphedema (BCRL) in breast cancer survivors at 21.4%, including those who received no surgical intervention (7). Risk factors for the development BCRL continue to be debated in the literature, but include axillary lymph node dissection (ALND), number of nodes removed, number of positive nodes, radiation, taxane-based chemotherapy, and elevated BMI (7-13).

BCRL is a chronic disease that results in asymmetric swelling of the upper extremities, with the underlying pathophysiology of the disease defining its clinical manifestations. An initial inciting insult to the lymphatic system, including surgery, trauma, radiation and/

or infection, results in increased resistance within the lymphatic channels and decreased flow, leading to the accumulation of lymph within the channels (14). The valves of the lymphatic system fail, and bidirectional flow of lymph continues to worsen, resulting in dependent edema and increased rates of extremity cellulitis, which are hallmarks of BCRL. However, the build-up of lymph also triggers a chronic inflammatory response that causes hypertrophy of lymphatic channel walls and adjacent smooth muscle cells, accumulation of fibroblasts, adipocytes, keratinocytes and mononuclear cells, and ultimately irreversible fat and collagen deposition (14). Although the severity of lymphedema is thought to be progressive in nature, early development of soft tissue edema is most likely occurring simultaneously with underlying hypertrophy and smooth muscle changes, which define the chronic nature of the disease.

Ultimately, BCRL leaves patients with both physical limitations and a visible aesthetic deformity, which can significantly impact vocation, social, and sexual interaction (15-17). Moreover, the chronicity of the disease can result in a dramatic financial burden to both the patient and the healthcare system. The mainstay of treatment for lymphedema has historically relied on conservative management including compression and decongestive therapy. However, these treatments are palliative in nature while also being cumbersome and expensive for patients, further underscoring the chronicity of the disease (16,18). Surgical management of BCRL has evolved, and currently includes debulking procedures such as liposuction, vascularized lymph node transfer, and lymphovenous bypass (16). To be considered a surgical candidate for these therapies, patients must demonstrate evidence of stability in their disease progression, which may not be attainable despite aggressive conservative management. Furthermore, although surgical treatment of lymphedema can improve quality of life and achieve objective reductions in limb volume, none of these treatments have proven to be consistently effective in all patients. Ultimately, the fact that treatment of BCRL remains limited and outcomes are inconsistent underscores the importance of any modality that may assist in preventing the development of BCRL.

Immediate lymphatic reconstruction

Introduction

Current surgical therapies for BCRL, as previously

outlined, are utilized in a delayed manner after BCRL has developed. In contrast, immediate lymphatic reconstruction (ILR) is a surgical procedure that aims to *prevent* the development of BCRL. By performing lymphovenous anastomoses at time of axillary nodal dissection, ILR aims to promote restoration of physiologic lymphatic flow and thus prevent the cascade of pathophysiologic events that result in BCRL development. ILR was initially described by Boccardo *et al.* in 2009 and at the time was termed the lymphatic microsurgical preventative healing approach or LYMPHA (19). Divided lymphatics are visualized after completion of ALND and are anastomosed to tributaries of an adjacent vein. In the authors seminal study, with 4-year of follow-up, post-operative rates of BCRL were shown to be 4% (20). Similar promising results in reduction of BCRL with ILR have been replicated by other institutions (21-23).

Anatomic considerations

The boundaries of standard level I and II ALND are defined as the axillary vein superiorly, serratus anterior medially, thoracodorsal vessels posteriorly, and latissimus muscle laterally (24). Within these boundaries, identification of both lymphatics and veins appropriate for anastomosis are critical to the success of ILR. Identification and preservation of appropriate veins occurs at the time of ALND to prevent inadvertent sacrifice of potential venous targets by the extirpative surgeon. In this way, a coordinated and collaborative approach at the time of ALND between the oncologic and reconstructive surgeons is important for successful execution of ILR.

The venous anatomy of the axilla is perhaps the most varied between patients. A commonly utilized vein for anastomosis is the accessory vein of the axilla, which arises directly from the axillary vein and generally travels 2-cm anterior and parallel to the thoracodorsal vessels through the axillary bed (25,26). Other named secondary venous options include the lateral thoracic and thoracodorsal vein, which hold an increased risk of injury to the long thoracic nerve and thoracodorsal neurovascular bundle, respectively. To minimize these risks, branches off the thoracodorsal system or venous collaterals running along the chest wall or laterally within the soft tissue may also be utilized. Anecdotally, more extensive axillary disease may increase the number of venous collaterals available for anastomosis, but may also require a more aggressive extirpative surgery that may make these collaterals unavailable. The presence or absence of valves can often be visualized during venous

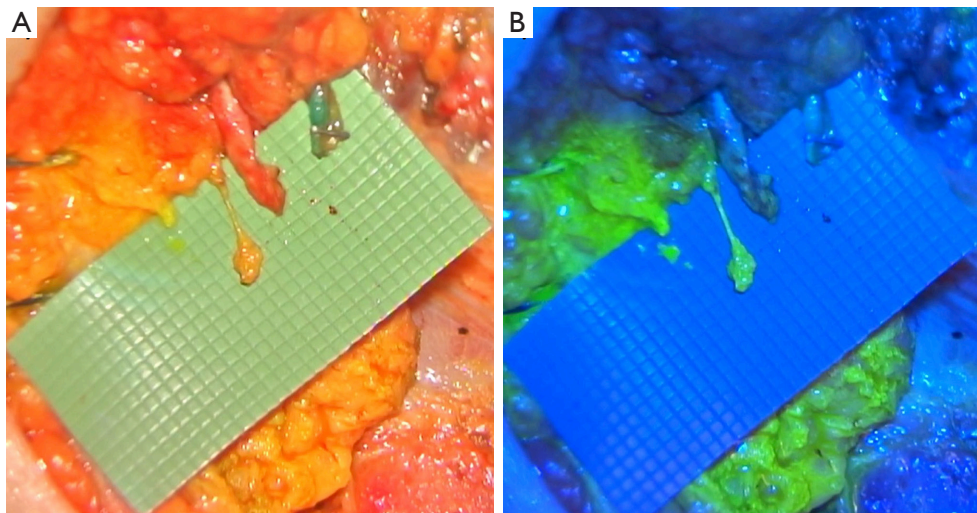


Figure 1 Demonstration of the two distinct pathways of the upper extremity. Isosulfan blue is injected prior to axillary dissection into the posterolateral pathway, demonstrating a blue-colored lymphatic. (A) Meanwhile, fluorescein isothiocyanate (FITC) dye was injected into the medial pathway, demonstrating a green-colored lymphatic under the FITC filter on the microscope (B).

dissection of the vein. Competent valves are critical to minimize back-bleeding from the vein and are ultimately thought to allow for low-pressure flow between the anastomosed lymphatic channels and veins.

Lymphatic drainage within the upper arm can be divided into two distinct ‘lymphosomes’, medial and posterolateral, as demonstrated by Suami *et al.* (27). The medial pathway is the main lymphatic drainage pathway, running along the volar aspect of forearm up to the medial upper arm and terminating in the axilla. The posterolateral pathway, or Mascagni-Sappey (M-S) pathway, was first described by Mascagni in 1787 and then Sappey in 1875. The M-S pathway runs alongside the cephalic vein with variable drainage to the supraclavicular/infraclavicular nodes and/or axillary basin (28,29). Ultimately, the medial pathway is thought to be the predominant drainage pathway of the upper extremity, although draining lymphatics from either pathway are thought to be suitable for ILR lymphovenous anastomosis (30) (*Figure 1*).

Patient selection

Boccardo *et al.* proposed that appropriate indications for LYMPHA or ILR technique included: BMI ≥ 30 kg/m² (at highest risk) and a transit index on lymphoscintigraphy of ≥ 10 (20). They contend that patients who did not meet these criteria should not be considered as surgical candidates. At our institutions, all patients undergoing ALND are

considered for ILR. While ALND alone elevates the risk of BCRL development, these patients also frequently undergo neoadjuvant chemotherapy and adjuvant treatment including regional lymph node radiation (RLNR), further increasing their BCRL risk profile. Moreover, anecdotally, we have noted that a significant percentage of patients presenting to our Lymphatic Center for BCRL treatment have BMIs less than 30. Therefore, elevated patient BMI is not used as an indication for ILR at our institutions as statistical support for its use is lacking. Furthermore, this can prevent a specific subset of breast cancer patients from undergoing ILR despite still being susceptible to BCRL.

Surgical technique

Immediately prior to the beginning of ALND, the upper extremity is injected with dye to allow for identification of draining lymphatics from the upper extremity into the axilla following ALND. In the case of a modified radical mastectomy, timing of dye injection and ILR must be considered in the context of concurrent mastectomy and possible breast reconstruction. In the case of planned breast reconstruction, a sequence of mastectomy, dye injection, ALND followed by ILR, then breast reconstruction tends to be most favorable in our experience. Although the original description of ILR utilized isosulfan blue dye for lymphatic identification, we have found fluorescein isothiocyanate (FITC) dye to be a useful alternative, particularly if the

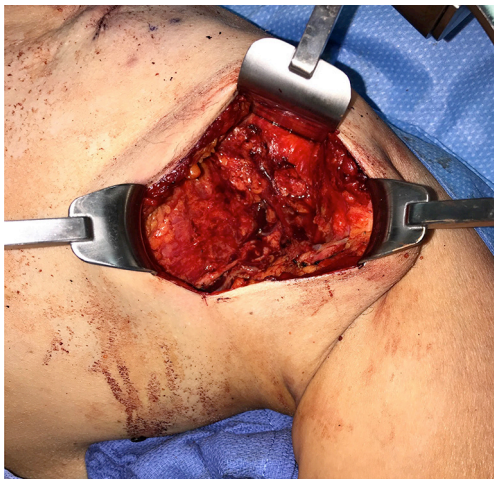


Figure 2 Triangulation of the axillary incision to achieve appropriate exposure of the axilla using a pediatric Bookwalter retractor system prior to immediate axillary lymphatic reconstruction.

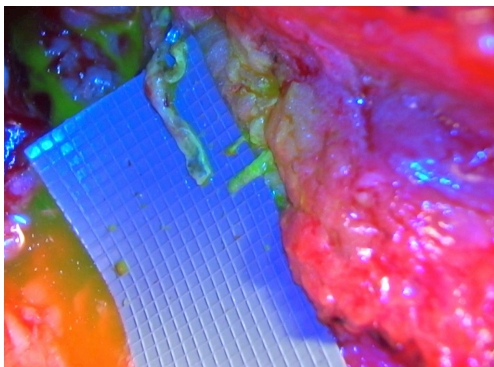


Figure 3 Identification of transected lymphatic channels and an appropriate venous target for lympho-venous anastomosis. Two identified lymphatics are anastomosed to a single adjacent vein.

oncologic surgeon is utilizing blue dye as part of the SLNB (26). A 2% solution of FITC and albumin, allowing for prolonged retention within the lymphatics, is injected intradermally into two sites on the volar wrist and in muscular fascia of upper medial arm.

Following completion of ALND, ideal exposure of the axillary basin can be achieved using a self-retaining retractor system. We utilize a pediatric Bookwalter retractor set (Codman Inc., Raynham, MA, USA), which functions well for both an axillary or mastectomy incision. Initial exposure is achieved through triangulation of the wound bed, including retraction of the pectoralis muscle medially (*Figure 2*). To

achieve appropriate magnification of venous and lymphatic targets, we use a Mitaka MM51 microscope (Mitaka Kohki Co, Ltd., Tokyo, Japan). The microscope is equipped with a 560-nm filter, which illuminates FITC-injected lymphatic channels arising from the arm. Respective size of leaking lymphatic channels and their relative position with respect to potential vein targets are noted. The choice of venous target is dependent on both its location relative to the desired channels to be bypassed, as well as presence of back-bleeding following division of the vein. Ideally, there is no back-bleeding from the vein, although minimal venous back-bleeding is accepted as the patient is under positive pressure ventilation and, presumably, the direction of flow will reverse after extubation. The decision of whether or not to bypass to a back-bleeding vein is ultimately at the discretion of the surgeon.

Adjustments of the microscope, patient positioning, and axillary retraction are often required prior to proceeding with lymphovenous anastomosis. In general, the anastomosis can often be ergonomically challenging, and can be aided with the use of a microscope foot pedal and long microsurgical instruments. Our anastomotic technique mirrors the original description of the procedure and, specifically, utilizes 9-0 Nylon suture (Ethicon Inc., Somerville, NJ, USA) to intussuscept lymphatic channels into a target vein (*Figure 3*). Full thickness ‘back-wall’ interrupted sutures are placed between the posterior aspect of the vein and perilymphatic tissue, allowing for approximation of the lymphatics to the vein lumen while also buttressing the ultimate anastomosis. A temporary ‘U’ stitch is then placed through the anterior wall of the vein, through and through one or more lymphatic channels, and then back out the vein, allowing the lymphatic channels to be ‘parachuted’ into the vein (2). The anastomosis is then completed with additional sutures securing the anterior vein wall to the perilymphatic tissue. The ‘U’ stitch is then cut and removed and lymphatic flow visualization through the anastomotic site can be confirmed by visualization of FITC under the microscope (*Figure 4*). Of note, if the initial U-stitch only captures the adventitia of the lymphatic channel thereby not occluding flow, the surgeon may opt to keep the U-stitch in place. Additional soft tissue can then be approximated around the anastomosis to further buttress the repair. Lymphatic channels that are not bypassed are micro-clipped. Between 1–3 lymphatic channels are generally bypassed in any given patient (20). A #15 Blake drain is placed exiting the dependent portion of the axillary bed and the axillary or mastectomy incision is closed in a

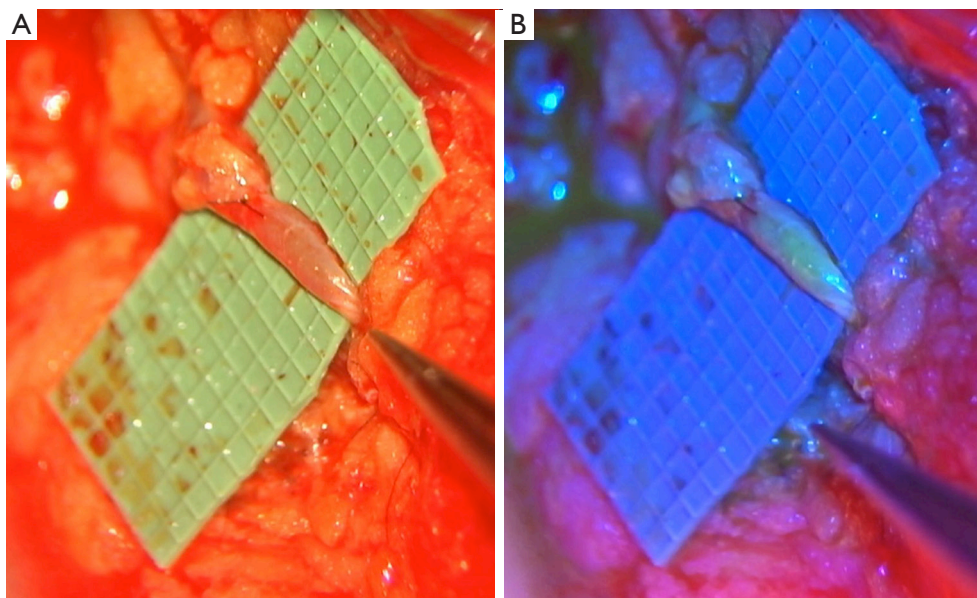


Figure 4 Completed lympho-venous anastomosis as part of immediate lymphatic reconstruction. Anastomosis is visualized both without (A) and with (B) the fluorescein isothiocyanate (FITC) filter on the microscope. Note the appearance of FITC within the vein lumen following completion of the anastomosis.

standard manner.

Postoperative care and complications

The surgically placed drain is left in place until the output is less than 20cc for two consecutive days. Drains usually meet criteria and are removed by post-operative day 14. We do not prophylactically place patients in a compression garment postoperatively. In general, there is a low complication rate associated with ILR, with no complications reported in a meta-analysis by Jorgensen *et al.* (25). If a venous target is chosen with mild back-bleeding, a theoretical risk of hematoma does exist, however this has not been evident in our experience thus far. There is also the potential for hypersensitivity reactions to the injected dyes, including FITC and isosulfan blue. This risk can be mitigated by pre-emptively administering a combination of hydrocortisone, Benadryl, and Pepcid as has been previously described (31).

Outcomes

Initial work by Boccardo *et al.* has reported a rate of BCRL of 4% at 4-year follow-up in a high-risk breast cancer population that underwent ALND and RLNR with ILR (20). Since their seminal study, additional institutions have replicated these results. A 2019 meta-analysis of the

current ILR literature demonstrated rates of BCRL in patients undergoing ALND alone to be 15.6%, which increased to 26.5% with the additional of RLNR (21). When ILR was performed in these two groups, the rates of BCRL decreased to 4.6% and 10.6%, respectively. Our institutional data has mirrored these promising outcomes, although longer follow-up is required to better understand the sustainability of our results. We also to date have not experienced any significant post-operative complications associated directly with ILR.

Recent literature has also demonstrated that ILR can be cost-effective (32). Cost-efficacy was evaluated and compared amongst two main groups: (I) patients undergoing ALND alone versus ALND and ILR and (II) ALND with RLNR versus ALND with RLNR with ILR. Utilizing a previously published cost of one year of life living with BCRL (33), and the estimated cost ILR based on its associated current procedural terminology (CPT) code, an incremental cost-utility ratio (ICUR) was calculated for each patient group. For the ALND versus ALND with ILR group, the ICUR was \$1,587.73/QALY, which decreased further to \$699.48/QALY for the ALND with RLNR versus ALND with RLNR with ILR group (32). These relatively low ICURs demonstrate the substantial clinical benefit of ILR relative to its additional cost. This cost-efficacy was confirmed with even extremely conservative estimates of

post-operative BCRL incidence.

Surveillance and future directions

Given the progressive nature in which BCRL develops, understanding the long-term efficacy of ILR requires robust patient surveillance. At our institutions, certified lymphedema therapists obtain baseline data for patients prior to undergoing ILR, including both quantitative and qualitative measurements. These same measurements are then repeated at set intervals following completion of ILR to monitor for early signs of BCRL development. Quantitative measurement modalities include circumferential arm measurements at set intervals, which can then be converted to volumes using the truncated cone formula (34). Additional modalities include perometry and bioimpedance spectroscopy, which can further quantify limb volume and the extent of fluid within the limb, respectively. Qualitative measures include quality of life survey instruments such as the SF-36, LYMQOL, and DASH. All patient measurements are entered into a clinical quality database to facilitate patient surveillance. Patients are followed every 3 months for the first 2 years post-operatively, and then every 6 months the third and fourth year assuming all subjective evaluations and objective data demonstrate no evidence of lymphedema.

Despite the aforementioned standardized metrics used for assessment of BCRL following ILR at our institutions, there remains heterogeneity in the modalities used to assess BCRL. This limits the ability for comparison of results across different study groups, and thus prevents us from having a true understanding of the impact of ILR. As the implementation of ILR grows across institutions nationally and internationally, standardizing both the surgical approach and the quantitative and qualitative measures used for monitoring patients will be critical to understanding the efficacy of ILR in preventing BCRL. This efficacy data will also be important for obtaining consistent coverage of ILR by insurance payors in the United States, who often still consider the procedure experimental. As we continue to strive for more preventative and cost-effective modalities of health care, ILR may emerge as the primary approach for patients at risk for BCRL.

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