Review Article

Immediate lymphatic reconstruction: an overview

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Abstract: Breast cancer related lymphedema (BCRL) is estimated to affect up to 50% of patients after lymph node surgery, with risk factors including axillary lymph node dissection (ALND), radiation therapy, and higher body mass index (BMI). BCRL causes significant morbidity for patients and is currently a chronic, progressive disease with no known medical or surgical cure. Immediate lymphatic reconstruction (ILR) is a promising surgical intervention performed at the time of lymph node dissection to prevent secondary lymphedema. Using axillary reverse mapping (ARM), lymphatic channels draining the upper extremity can be identified and preserved during lymph node surgery. Lymphatic channels that are unable to be preserved are bypassed to a nearby recipient vein, physiologically restoring lymphatic drainage from the extremity into the venous system. This lymphovenous bypass (LVB), also called lymphatic microsurgical preventive healing approach (LYMPHA), is most often performed with microsurgical techniques, though other techniques such as simplified or S-LYMPHA have also been described. Therefore, ILR requires close communication and a learning curve for both the oncologic and reconstructive surgeon. Early clinical outcomes show that ILR reduces the incidence of lymphedema, though short follow up times and heterogeneity between studies make it difficult to draw conclusions. As part of a series on BCRL, the purpose of this review article is to provide an overview of ILR with a focus on the historical background, surgical considerations, current outcomes data, and future directions of ILR.

Keywords: Immediate lymphatic reconstruction (ILR); lymphatic microsurgical preventive healing approach (LYMPHA); microsurgery; upper extremity lymphedema; breast cancer

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Introduction

Breast cancer related lymphedema (BCRL) is a negative outcome after breast cancer treatment, with an estimated incidence ranging as high as 50% depending on diagnostic criteria (1). Known risk factors include axillary lymph node dissection (ALND), adjuvant regional lymph node radiation (RLNR) therapy, and higher body mass index (BMI) (1-4). As breast cancer survival rates continue to improve due to advances in treatment, there is increasing focus on addressing post-treatment quality of life, particularly BCRL.

Patients with BCRL may suffer from decreased mobility and function, recurrent infections, loss of body confidence due to disfigurement, emotional and psychological distress, and impaired quality of life (3). First line interventions including complete decongestive therapy with a certified lymphedema therapist, which includes manual lymphatic drainage, compression bandaging, exercise, and meticulous skin care. These nonsurgical options are expensive, uncomfortable, and time-consuming, with some patients reporting greater than 40 hours per week dedicated to therapy (5). In addition, these modalities require strict patient compliance to be successful. Physiologic and debulking surgeries can help alleviate lymphedema symptoms, but they cannot return the affected extremity back to its premorbid state.

Because lymphedema is a chronic, progressive disease with no known cure, there has been growing interest in prevention or risk reduction of lymphedema occurring after breast cancer treatment. Immediate lymphatic reconstruction (ILR) is a surgical intervention performed with axillary reverse mapping (ARM) at the time of ALND to reduce the risk of BCRL. Often also called lymphatic microsurgical preventive healing approach (LYMPHA), it involves using microsurgical techniques to perform a lymphovenous bypass (LVB) between lymphatic channels draining the upper extremity that were cut during the ALND and nearby recipient veins to restore physiologic lymphatic drainage. As part of a larger series on BCRL, the purpose of this article is to review the historical background, surgical considerations, current outcomes data, and future directions of ILR in this patient population.

Historical background

The history of ILR is closely related to the history of LVB and the advent of supermicrosurgery. The concept of creating LVB to treat extremity lymphedema was first described in the 1960s (6,7), with several small clinical studies reported in the 1980s as the field of microsurgery developed further (8-12). ILR was first reported by Pronin *et al.* in 1989, who described a technique of creating microsurgical LVB at the time of radical mastectomy to surgically prevent lymphedema (13). However, LVB and ILR did not gain traction until the 2000s, after the introduction of supermicrosurgery by Koshima in 1997 (14,15). Supermicrosurgery is formally defined as a technique of dissection and anastomosis of vessels <0.8 mm in diameter, and it requires highly delicate microsurgical instruments and sutures with needles <30–80 µm in size to perform (15). Since most lymphatic channels are <0.5 mm, successful LVB was not consistently possible until the development of specialized equipment and techniques for supermicrosurgery.

The development of ARM is also critical to the history of ILR. One of the earliest descriptions of ARM was by Thompson *et al.* in 2007, who used intradermal injections of blue dye in the upper extremity to map and preserve its lymphatic drainage (16). ARM was soon found to be technically feasible in oncologic axillary node surgery (17), and the first modern description of ILR for BCRL was published by Boccardo *et al.* in 2009 (18). Anatomic studies of the lymphatic drainage of the breast and upper extremity have revealed connections in sentinel node groups in 24% of cases (19). Therefore, from an oncologic perspective, it is often impossible to completely spare the lymphatic drainage of the upper extremity. ARM is still routinely used to help identify lymphatic channels draining the extremity that are transected during ALND as potential targets for ILR. In addition, the use of ARM alone in reducing BCRL rates is currently being studied in the Alliance A221702 trial by Klimberg (NCT03927027) (20), though the study protocol allows for lymphatic re-approximation and LYMPHA.

Surgical considerations

Pre-operative considerations

Inclusion criteria for ILR for breast cancer treatment at most institutions are patients undergoing ALND and ARM (5,21-24). At our institution, all breast cancer patients with positive axillary lymph nodes are considered candidates for ILR. General exclusion criteria include pre-existing lymphedema, prior history of breast cancer, prior history of axillary or breast surgery (including those patients who underwent radiation therapy), and active extremity malignancy.

Logistically, ILR requires close coordination between the oncologic and reconstructive surgical teams. Depending on institutional policy, the decision to proceed with ALND may depend on frozen sections from sentinel lymph node biopsy (SLNB), requiring the reconstructive surgeon to be "on standby" and available while awaiting pathology results. Alternatively, ALND may be performed in a staged manner after permanent sections from SLNB have resulted, which facilitates surgery scheduling for both teams. ILR also requires the surgical infrastructure to perform microsurgery, including an operating room microscope, specialized microsurgical instruments and sutures, and agents to visualize lymphatic channels.

Identification of lymphatic channels

Lymphatic channels draining the upper extremity can be identified intra-operatively in several ways, depending on surgeon preference, imaging and equipment availability,

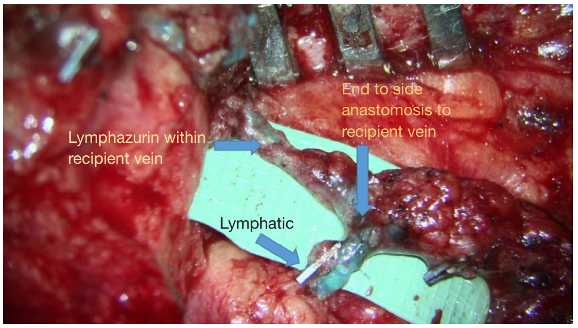

Figure 1 Immediate lymphatic reconstruction involving a lymphatic (identified with lymphazurin blue), which was anastomosed in an end-to-side matter to an identified recipient vein. Following successful anastomosis, the lymphazurin blue can be seen within the recipient vein, confirming patency.

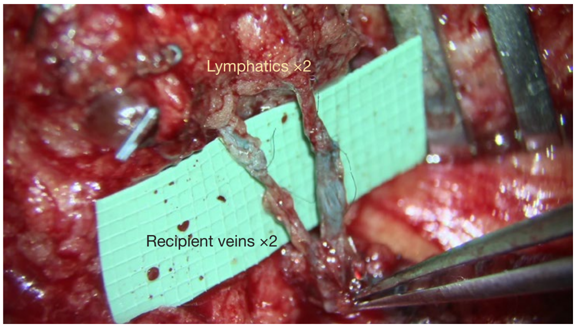

Figure 2 Two separate immediate lymphatic reconstructions performed between identified lymphatics and recipient veins, in end-to-end manner. End-to-end anastomosis was performed as the caliber of vessels was similar and there was no back flow of blood upon division of the recipient veins.

and institutional policy. Commonly used imaging agents include lymphazurin (isosulfan blue), indocyanine green (ICG), and fluorescein isothiocyanate (FITC). However, ICG and FITC require either near-infrared fluorescence imaging systems or special microscope filters, respectively. The advantage of isosulfan blue is that it does not require additional equipment for visualization. However, it has a 1–3% risk of severe allergic reaction and anaphylaxis (25). In addition, if it is injected into the breast for SLNB, it can be difficult to distinguish between lymphatic drainage from the breast versus from the extremity.

Injection of these imaging agents is done intradermally in small aliquots at the upper medial arm, webspaces, and/or volar wrist to visualize lymphatic drainage from the entire limb. It is important to note that different lymphosomes, or lymphatic territories that drain to specific lymph nodes, can be distinguished by injecting different imaging agents at various locations (26). The timing of injection can either be done prior to SLNB/ALND or afterwards. For instance, some authors advocate using ICG lymphography prior to axillary surgery to see baseline lymphatic anatomy, while others perform SLNB first so that ARM does not impact the accurate identification of sentinel nodes draining the breast (26). The selection of the best lymphatic channels to bypass is unclear, but it is generally thought that larger channels with a higher amount of active lymphatic flow seen should be prioritized.

Recipient vein selection

Multiple recipient vein options exist in the axilla, including the thoracoepigastric vein, lateral thoracic vein, medial pectoral vein, circumflex scapular vein, and other smaller unnamed vein branches. The thoracodorsal vein should be avoided in case the latissimus dorsi is needed for future breast reconstruction or salvage. The recipient vein should be left as long as possible and mobilized to allow for tension-free anastomosis. In addition, it should be checked for intact valves and lack of back bleeding, as higher venous pressure will cause the bypass to clot and fail.

Anastomotic technique

Many anastomotic techniques have been described for ILR, though it remains unclear if and how specific technique affects outcomes. In their initial report of LYMPHA, Boccardo *et al.* described an intussusception technique where lymphatic channels are introduced inside a vein using a U-shaped stitch (18,21). This U stitch may be used temporarily to hold the anastomosis in place while the bypass is being buttressed by external sutures, then removed to minimize foreign material inside the vessel lumen. This technique allows for multiple lymphatic channels to be bypassed into a single draining vein in an arborized pattern. Alternative techniques include end-to-end or end-to-side anastomoses (*Figures 1,2*). The immediate patency of ILR should be confirmed by seeing the lymphatic channel agent drain into the recipient vein without leakage.

Technical tips and potential pitfalls

Successful ILR requires close coordination and special considerations for both the oncologic and reconstructive surgeon. Communication between teams is key for surgical scheduling and planning. For example, an incision designed too low in the axilla limits visualization. It is also recommended that potential recipient veins be preserved with longer lengths, and that veins and lymphatic channels be clipped not cauterized. As these structures are being dissected by the oncologic surgeon at the time of axillary surgery, some institutions have recommended that the reconstructive surgeon initially assist in identifying favorable vessels until the oncologic surgeon has gained enough experience (27). For the reconstructive surgeon, proper vein selection and microsurgical skill is key. Other centers have reported a simplified technique coined S-LYMPHA, where a "sleeve technique" is used to invaginate lymphatic channels into a recipient vein without a microscope, allowing the procedure to be performed entirely by the oncologic surgeon (28).

ILR may sometimes be unsuccessful, with feasibility rates reported in the literature ranging from 73% to 97% (22,24,29). A 2022 systematic review and meta-analysis found a combined feasibility rate of 83% across seven studies (30). Commonly reported reasons for aborting ILR included no good recipient vein with adequate length and intact proximal valve, no good lymphatic channel with active drainage, and extensive axillary disease.

Outcomes

Several centers have reported their early experiences with ILR showing a reduced rate of BCRL incidence post-operatively. One of the first groups with the longest follow up time, Boccardo et al, reported an incidence of BCRL after LYMPHA of only 4.05% (3/74) over 4 years of follow up (21). Feldman *et al.* reported an incidence rate of BCRL of 12.5% (3/24) in patients who underwent ILR compared to 50% (4/8) in patients where ILR was unable to be performed, and an institutional rate of 30.6% (52/170) in patients who underwent ALND alone (22). Similarly, Schwarz *et al.* had a BCRL incidence of 4.7% (2/43) after ILR with a median follow up time of 11.8 months (24). Johnson *et al.* reported a 3.1% (1/32) rate of BCRL and 12.5% (4/32) rate of transient lymphedema in patients who underwent ILR with >6 months of follow up (29). Lipman *et al.* reported a 5% (1/19) rate of BCRL in patients who underwent ALND and LYMPHA with an average follow up time of 9.9 months, but they noted that the one patient with mild lymphedema still had intact lymphatic drainage across the axilla as seen by ICG lymphography (31). However, two studies with longer term follow up have recently been published with mixed results. Granoff *et al.* reported their series of 90 patients who underwent ILR with a mean follow up time of 17 months (range, 6–49 months) with a 9% rate of lymphedema (32). Conversely, Levy *et al.* reported no significant differences in lymphedema incidence between 45 women who underwent LYMPHA *vs.* 45 women who did not (31.1% *vs.* 33.3%, P>0.99) with a median follow up time of greater than 4 years (33).

Early outcomes with S-LYMPHA have also been promising. Ozmen *et al.* reported that S-LYMPHA patients had a significantly lower rate of BCRL of 3% (2/74) compared to 19% (58/306) in patients who underwent ALND without S-LYMPHA over a mean follow up time of 15 months (28). This technique has the potential to increase the feasibility and accessibility of performing ILR at the time of ALND, using a simplified method done entirely by the oncologic surgeon without the need for microsurgical training or specialized equipment. However, these early promising results have yet to be replicated in other centers, and longer term studies are needed.

Several systematic reviews have concluded that ILR results in a reduction in the incidence of BCRL (30,34-37), including a 2021 meta-analysis reporting grade 1B evidence but with low quality data (35).

The first published systematic review and meta-analysis on ILR was by Jørgensen *et al.*, who found that ILR done either in the axilla or groin had a significant reduction in lymphedema incidence with a relative risk of 0.33 (34). Johnson *et al.* performed a systematic review and meta-analysis on BCRL incidence and found a pooled cumulative incidence of 14.1% in patients undergoing ALND compared to 2.1% in patients undergoing ALND and LYMPHA (P=0.029) (36). Pooled cumulative BCRL incidence increased to 33.4% in patients undergoing ALND and RLNR compared to 10.3% in patients undergoing ALND, RLNR, and LYMPHA (P=0.004) (36). However, only 3 of the 19 articles reviewed were on LYMPHA. Two recent meta-analyses published in 2022 also lend support to ILR reducing the risk of lymphedema. Looking at BCRL specifically, Hill *et al.* found that 6.7% (6/90) of patients who underwent ILR at the time of ALND developed BCRL compared to 34% (17/50) of the control group patients, with a risk ratio of 0.22 [95% confidence interval (CI): 0.09–0.52] and number needed to treat of 4 (30). However, the authors noted that all studies included in their review had a high risk of bias. Similarly, Chun *et al.* looked at ILR performed during axillary or groin node dissection and found an overall lymphedema incidence of 2.7% for upper extremity and 3.6% for lower extremity, though the authors noted that these findings were limited by lack of control groups and short follow up times (37).

Limitations

Many of the currently published studies are single center retrospective reviews with significant limitations, including small number of patients, non-randomized and non-blinded study design, and short follow up time. In addition, the lack of uniform ILR techniques, lymphedema diagnostic criteria (for example, transient *vs.* persistent lymphedema), and quantitative measurements make it challenging to directly compare studies. In particular, nearly all of these studies have follow up times of <24 months, which likely underestimates actual lymphedema rates. BCRL has been shown to have a variable time course, with one study showing that BCRL risk peaked at 6–12 months after ALND alone, 18–24 months after ALND and RLNR, and 36–48 months after SLNB and RLNR (4). Longer follow up is also needed to help distinguish between transient and persistent lymphedema. Though the risk factors and development of transient lymphedema are not fully understood, some studies find that 23.1% of patients experience mild waxing and waning lymphedema symptoms in the first 3 years after ALND (38). In addition, none of these studies include patient reported outcomes or outcomes regarding quality of life.

Current literature also lacks data on long term patency rates of the bypasses created in ILR. Some authors use imaging such as ICG lymphography post-operatively to show that lymphatic drainage still crosses the axilla. However, this likely shows overall lymphatic drainage patterns rather than specific anastomoses created during ILR. Data from the LVB literature estimates that long term patency rates are at least 56.5% (39).

Higher quality studies with longer follow up are needed to provide better quality evidence that ILR is effective at significantly reducing the risk of BCRL. Fortunately, there are several randomized controlled trials currently underway, including ones at the Mayo Clinic (NCT03428581), MD Anderson Cancer Center (NCT03941756), Memorial Sloan Kettering Cancer Center (NCT04241341), and Pusan National University Hospital (NCT04328610).

Future directions

While the aforementioned studies demonstrate promising results that ILR done at the time of ALND reduces the risk of BCRL, several topics require further study.

Patient selection criteria

The ideal candidate for ILR is still unclear. Presumably, patients with risk factors associated with the development of BCRL such as ALND, adjuvant RLNR, and higher BMI >30 kg/m^2 would stand to benefit more. These patients have generally been selected as ILR candidates in published and ongoing studies. Other risk factors that have been implicated but not proven are number of lymph nodes removed, as well as presence and type of chemotherapy. Identification of other risk factors for developing BCRL can help expand or refine patient selection criteria.

Changes in management of axillary metastatic disease may also affect the future of ILR. Over the history of breast cancer treatment, surgical treatment of axillary disease has evolved to become less invasive and morbid. ALND, which was once universally accepted as the standard of care for axillary metastasis, is now being performed more selectively due to studies like ACOSOG Z0011 and ACOSOG Z1071 (40,41). Current trials comparing ALND and axillary radiotherapy alone after a positive sentinel node demonstrate comparable control of axillary disease in patients with T1–T2 primary breast cancer and no palpable lymphadenopathy, with significantly less morbidity in the axillary radiotherapy group (42). The indications for ILR will likely evolve alongside the field of breast cancer therapy.

Variations in surgical technique

There is great variability in ILR surgical technique, such as lymphatic channel and recipient vein selection, number of bypasses created, type of anastomosis, and even surgeon training in the case of S-LYMPHA. These differences make it difficult to compare studies, as they have an unknown effect on outcomes. Again drawing from the LVB literature, there are mixed findings on if the number of bypasses performed results in better lymphatic drainage and therefore improved outcomes. Earlier LVB studies reported better outcomes with higher number of anastomoses (14). However, later studies have shown similar efficacy of LVB regardless of number of anastomoses, including a review of 18 articles by Onoda *et al.* on LVB for upper and lower extremity lymphedema which concluded that the number of anastomoses did not correlate with effectiveness of LVB (43). However, these findings may be confounded by lymphedema stage, lymphedema etiology, and surgeon experience, and they may also not be applicable to ILR.

Anastomotic configuration may also affect long term patency and lymphatic drainage. Some authors believe the intussusception technique is superior because it results in a lymphatic system that is more physiologically similar to normal, and because it is technically easier as it allows for greater flexibility with size mismatch and length (44). However, this technique may increase the risk of anastomotic kinking or twisting, leading to occlusion.

Adjunct therapies

Lymphedema not only results from the mechanical buildup of lymphatic fluid in soft tissues from diseased or obstructed lymphatic channels, but it also depends on inflammatory pathways that lead to tissue fibrosis. In mouse models, the pathophysiology of lymphedema in involves the activation and proliferation of CD4 T helper 2 (Th2) cells, which promote the production of profibrotic cytokines and growth factors such as transforming growth factor-beta 1 (TGF-β1), interleukin-4 (IL-4), and interleukin-13 (IL-13). Inhibition of these pathways prevents the development of fibrosis, and the severity of lymphedema is positively correlated with the degree of CD4 inflammation (45-47). These findings suggest that these growth factors are potential pharmacologic targets that can be used in conjunction with ILR or other surgeries to prevent BCRL.

Cost analysis and insurance coverage

ILR is currently still considered to be experimental treatment in the United States. Many centers do not offer ILR due to lack of surgeon experience or institutional infrastructure, but questions regarding cost effectiveness and insurance coverage patterns may also prevent more widespread adoption. An interesting 2021 cost utility analysis showed that the addition of LYMPHA to ALND was cost effective with an incremental cost utility ratio (ICUR) of $1587.73 per quality-adjusted life-year (QALY), and that the addition of LYMPHA to ALND and RLNR was also cost effective with an ICUR of $699.84 per QALY (48). LYMPHA was no longer cost effective when BCRL rates were <2.5% after ALND alone and <10.7% after ALND and RLNR (48). As more rigorous studies with longer term follow up demonstrate ILR's effectiveness in reducing the risk of BCRL, insurance coverage will likely become more uniform.

Conclusions

ILR to physiologically restore lymphatic drainage at the time of ALND is a relatively new surgical intervention in preventing BCRL. Early clinical outcomes are promising, though short follow up times and heterogeneity between studies make it difficult to draw conclusions. Future directions including more rigorous clinical studies including patient reported outcomes, more uniform surgical techniques and post-operative measurements, refinements in patient selection criteria, investigation in adjunct non-surgical treatments for lymphedema prevention, and expansion in insurance coverage will help lead to more widespread acceptance and adoption of ILR.

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