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RESEARCH ARTICLE

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# Axillary reverse mapping and lymphaticovenous bypass: Lymphedema prevention through enhanced lymphatic visualization and restoration of flow

Graham S. Schwarz MD, FACS[1] | Stephen R. Grobmyer MD, FACS[2] | Risal S. Djohan MD[1] | Cagri Cakmakoglu MD[1] | Steven L. Bernard MD, FACS[1] | Diane Radford MD, FACS, FRCSEd[2] | Zahraa Al-Hilli MD, FACS[2] | Rebecca Knackstedt MD, PhD[1] | Michelle Djohan MS[1] | Stephanie A. Valente DO, FACS[2]

[1]Department of Plastic Surgery, Cleveland Clinic, Cleveland, Ohio

[2]Department of General Surgery, Division of Breast Surgery, Cleveland Clinic, Cleveland, Ohio

**Correspondence**
Graham S. Schwarz, MD, FACS Department of Plastic Surgery Cleveland Clinic, A60, 9500 Euclid Avenue, Cleveland, OH 441295.
Email: schwarg@ccf.org

## Abstract

**Background:** A lymphedema (LE) prevention surgery (LPS) paradigm for patients undergoing axillary lymphadenectomy (ALND) was developed to protect against LE through enhanced lymphatic visualization during axillary reverse mapping (ARM) and refinement in decision making during lymphaticovenous bypass (LVB).

**Methods:** A retrospective analysis of a prospective database was performed evaluating patients with breast cancer who underwent ALND, ARM, and LVB from September 2016 to December 2018. Patient and tumor characteristics, oncologic and reconstructive operative details, complications and LE development were analyzed.

**Results:** LPS was completed in 58 patients with a mean age of 51.7 years. An average of 14 lymph nodes (LN) were removed during ALND. An average of 2.1 blue lymphatic channels were visualized with an average of 1.4 LVBs performed per patient. End to end anastomosis was performed in 37 patients and a multiple lymphatic intussusception technique in 21. Patency was confirmed 96.5% of patients. Adjuvant radiation was administered to 89% of patients. Two patients developed LE with a median follow-up of 11.8 months.

**Conclusion:** We report on our experience using a unique LPS technique. Refinements in ARM and a systematic approach to LVB allows for maximal preservation of lymphatic continuity, identification of transected lymphatics, and reestablishment of upper extremity lymphatic drainage pathways.

**KEYWORDS**
axillary lymph node dissection, axillary reverse mapping, ICG lymphangiography, lymphaticovenous bypass, lymphaticovenular anastomosis, lymphedema

**Abbreviations:** ALND, axillary lymphadenectomy; ARM, axillary reverse mapping; BI, bioimpedance; CA, circumferential arm; ICG, indocyanine green; ISL, International society of lymphology; L-Dex, lymphedema index; LE, lymphedema; LPS, lymphedema prevention surgery; LVB, lymphaticovenous bypass; MRM, modified radical mastectomy; SLN, sentinel lymph node; UE, upper extremity.

## 1 | INTRODUCTION

Lymphedema (LE) is a critical, underappreciated problem with long-term health, functional, aesthetic, and economic implications. Although sentinel lymph node (SLN) biopsy has reduced the incidence of lymphatic disruption and LE, many patients with breast cancer still require axillary lymph node dissection (ALND).[1] Those who undergo lymphadenectomy with radiotherapy are at a particularly increased risk.[2] The mainstay of LE treatment involves physiotherapy and strict compression regimens.[3] Time-consuming and cumbersome, controlling LE progression has a significant negative impact on patients' quality of life. A growing interest in LE prevention has motivated protective surgical strategies and recommendations.[4,5]

Axillary reverse lymphatic mapping (ARM) has shown promise in identifying upper extremity (UE) lymphatic drainage pathways coursing through the axilla. During ARM, tracer is injected into the extremity before lymphadenectomy. Employing this technique during ALND allows the surgeon to visualize and preserve lymphatic channels and lymph nodes draining the arm, thereby minimizing disruption of the lymphatic vasculature.[6-8] Although it is inevitable that some lymphatics will be divided for oncologic control, ARM allows for differentiation of UE and breast drainage pathways. Prior studies evaluating reverse mapping have demonstrated success rates in identifying UE lymphatic channels from 61%-71%.[9,10] In patients undergoing ALND, ARM has facilitated lymphatic sparing in up to 67.3% of patients.[6]

Lymphaticovenous bypass (LVB) is a microsurgical technique that reroutes lymphatic fluid into the venous system via anastomosis of divided lymphatics with recipient veins proximal to the level of obstruction. LVB has emerged as a promising treatment to potentially reverse the progression of LE.[11-13] Early stage LE patients have experienced up to 35% limb volume reduction following LVB.[12,14] Prophylactic use of this technique at the time of lymphatic disruption during ALND has also shown encouraging results in decreasing postoperative LE.[9,10,14,15] Only limited reports of this promising approach to immediate lymphatic reconstruction are available in the literature.

Our aim was to describe a unique approach to LE preventative surgery in patients with breast cancer undergoing ALND and to report on our clinical outcomes. Lymphedema preventative surgery (LPS) combines ARM and LVB to maximally preserve lymphatic continuity and reestablish physiologic UE lymphatic drainage pathways. Our particular intraoperative paradigm focuses on enhanced lymphatic visualization and refinements in surgical technique for protection against iatrogenic LE.

## 2 | METHODS

We performed an analysis of a prospectively maintained database to evaluate patients with breast cancer who underwent ALND, ARM, and LVB at our institution from September 2016 to December 2018. Patient demographics and tumor data were recorded. Oncologic and reconstructive operative details were described and documented. Successful LVB patency was documented by blue dye and indocyanine green (ICG) lymphangiography.[16] Patient treatment details, LPS complications, and follow-up were noted. Baseline bioimpedance (BI) measurements, postoperative 3-month, 6 month, 1 year, and subsequent annual BI measurements were performed on patients. All patients were referred to a postoperative breast rehabilitation program for a range of motion exercises at 3 to 4 weeks after the surgery. Patients with subjective symptoms of LE, signs on physical examination, changes in screening circumferential arm (CA) measurements or abnormal BI measurements as defined by a LE index (L-Dex) value of 10 were subsequently re-evaluated by a certified LE therapist to confirm the diagnosis of LE.

### 2.1 | Technique

#### 2.1.1 | Axillary reverse mapping and axillary dissection

In a sterile manner, 3 cc of isosulfan blue dye was injected in an area 6 cm distal to the axilla in 4 to 6 aliquots in a linear band pattern into the subdermal plane of the ulnar volar aspect of the upper arm

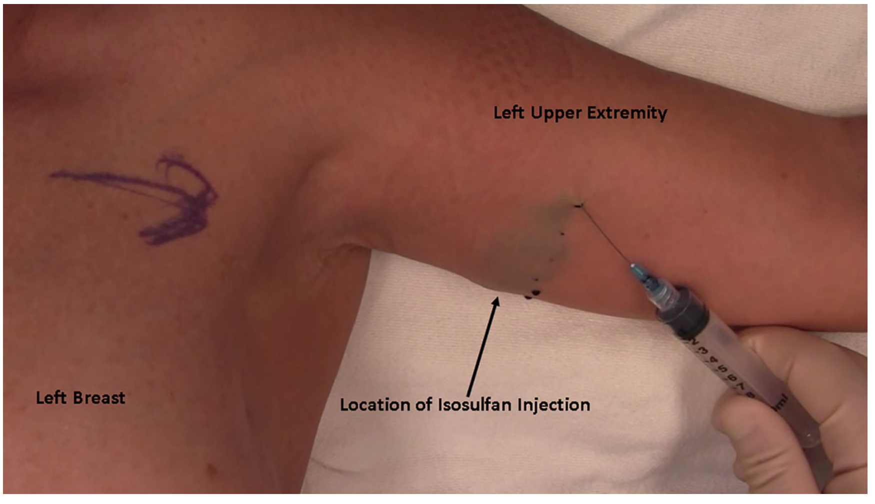


**FIGURE 1** Axillary reverse mapping injection technique, site of Injection of Blue Dye at the proximal arm to visualize lymphatic channels in the Axilla. 4 to 6 aliquots of isosulfan blue dye is injected in a linear circumferential pattern across the ulnar volar aspect of the upper arm [Color figure can be viewed at wileyonlinelibrary.com]

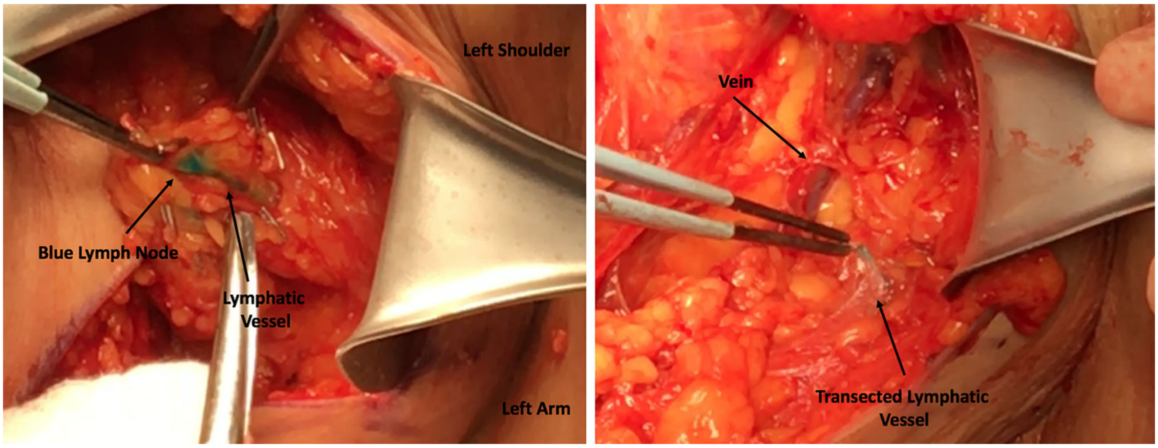


**FIGURE 2** Identification of blue stained upper extremity lymphatic vessels. A, (Left) Lymphatic vessel draining into blue axillary lymph node B, (Right) transected blue upper extremity lymphatic vessel identified for LVB [Color figure can be viewed at wileyonlinelibrary.com]

(Figure 1). The injection site was then massaged with the arm in an elevated position to allow dye transit through the axilla.

Exposure was obtained via a superior-lateral oblique extension of the mastectomy incision or through a superiorly positioned axillary counter incision. Consideration regarding optimal incision placement was given in anticipation of the need for self-retaining retraction during microsurgery.

Level 1 & 2 ALND was performed using loupe magnification and minimal cautery to avoid thermal injury. Meticulous dissection was performed to identify blue stained lymphatic channels draining laterally into the axilla from the UE. Blue lymphatic channels unassociated with at-risk axillary lymph nodes were left in-continuity and blue stained LNs outside the axillary resection borders were noted and preserved. Axillary contents were resected as indicated, and vascular clips were placed on transected blue lymphatic vessels at the lateral dissection border of the axilla. Careful dissection was used to identify and preserve the maximal length of sharply transected blue lymphatic channels as well as tributary branching veins from the lateral thoracic and throacodorsal vein systems (Figure 2).

### 2.1.2 | Lymphaticovenous bypass

After completion of ALND, the remaining lymphatic architecture was assessed, and self-retaining retraction placed. Avoidance of excessive retraction while ensuring appropriate exposure contributed to operative efficiency. Transected, blue dye-containing lymphatics were carefully mobilized under high power loupe or microscopic visualization. Target veins were identified and assessed for size match, proximity to lymphatic structures, excursion, and valvular competency. Those with extensive backflow were excluded to maximize sustained anterograde lymphatic flow. Recipient veins were mobilized to allow for adequate coaptation in a tension-free manner. Branches of the thoracodorsal vein or the distal continuation of the lateral thoracic vein were often used. Favoring vein mobilization over more extensive perilymphatic dissection resulted in less trauma and kinking of lymphatic vessels.

In the instance of precise size match and availability of a single transected lymphatic, an end-to-end microanastomotic technique was used using 11-0 or 12-0 nylon suture (Figure 3A,B). Stay sutures were placed at 180 degrees and LVB was completed circumferentially in an interrupted fashion. Gentle irrigation and stimulation of anterograde lymphatic flow via arm massage was utilized to help prevent a collapse of the thin-walled lymphatics while minimizing interference of visualization. An intravascular stent, if used, was removed before placement of the last stitch.

When significant size discrepancy existed between the lymphatic and recipient vein (1:3), or if there were multiple transected lymphatics in proximity to a recipient vein, we utilized an intussusception technique. Lymphatics were cleared of perilymphatic tissue for 1 to 2 mm from the end. A 11-0 or 12-0 nylon "u-stich" was placed first from outside to inside through the recipient vein 1 to 2 mm from the cut end. The needle was then passed tangentially, in a mattress fashion though the front wall(s) of each lymphatic vessel. The needle is passed transluminally back through the vein. The suture was then tied loosely, intussuscepting the one or more lymphatic vessels into the vein. Microanastomosis was completed circumferentially with interrupted sutures incorporating the vein edge and the perilymphatic tissue (Figure 3C,D). The u-stitch was then released. Unclamping was performed, leaks were repaired, and the anastomosis checked for patency.

If the blue dye was visualized traversing the lymphaticovenous anastomosis, the coaptation was deemed patent. Because of the sometimes-thick wall of the vein, or staining of tissue, we routinely confirmed patency in all cases with ICG lymphangiography (Figure 4). This also served to identify occult leaks requiring repair at the anastomosis. A total of 0.8 cc of ICG in 4 aliquots was injected into the dorsal web spaces of the hand for both baseline lymphangiography of the UE and confirmation of patency.

When performed in tandem with implant breast reconstruction, LVB was performed after pocket construction and before implant placement. This avoided prolonged exposure of the implant device and risk of device injury during retraction.

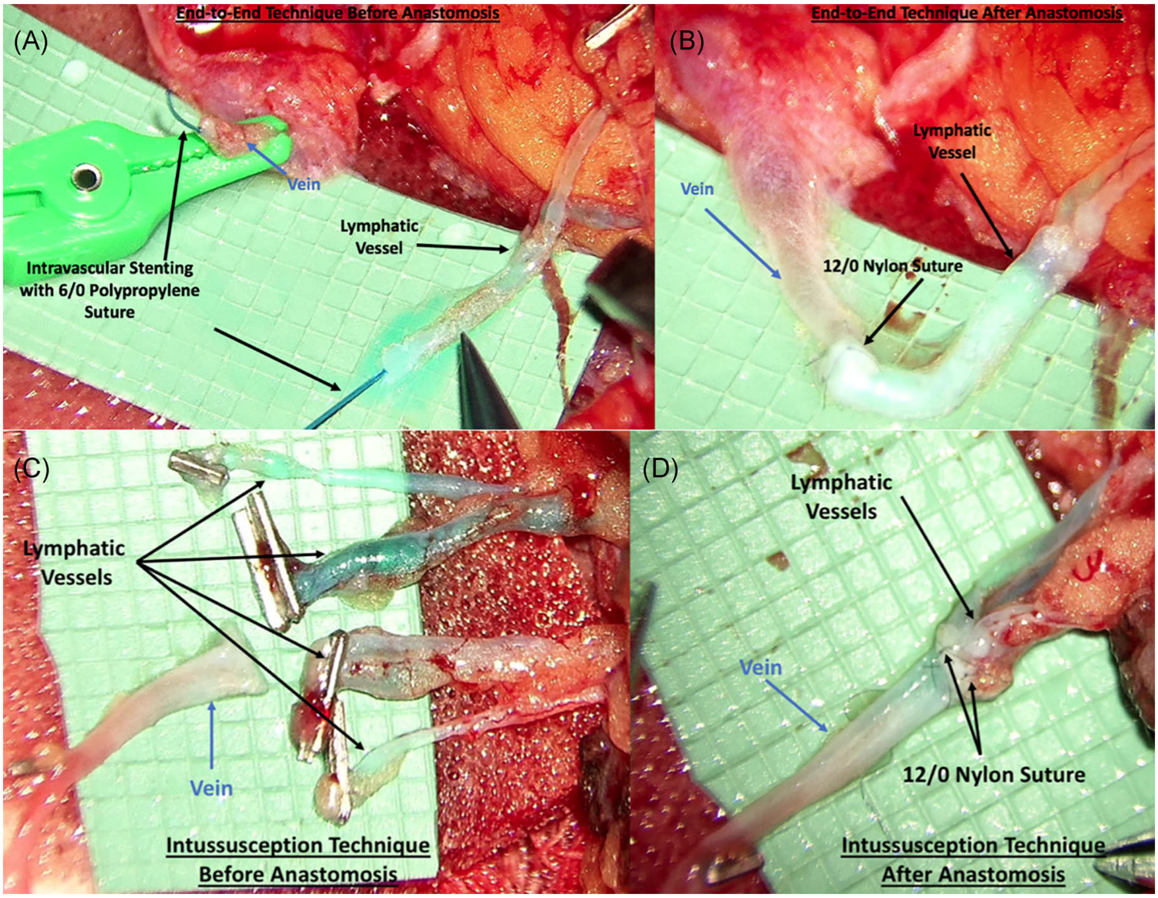


**FIGURE 3** Lymphaticovenous bypass with end to end and intussusception techniques. A, LVB with end-to-end technique before anastomosis. B, LVB with end-to-end technique after anastomosis. C, LVB with intussusception technique before anastomosis. D, LVB with intussusception technique after anastomosis [Color figure can be viewed at wileyonlinelibrary.com]

A closed suction drain was placed at the most dependent area of the axilla, and the wound was closed as desired. Immediately postoperatively the affected UE was wrapped in a lightly compressive bandage for 10 days to limit postoperative swelling. Immediate standard postoperative exercises were initiated with the abduction of the UE limited to 60 degrees for 2 weeks to discourage inadvertent tension on the anastomotic site. After this time, patients participated in graduated increases in ROM. If by 3 to 4 weeks postoperatively, our patients did not achieve full ROM at the shoulder, our physiotherapists were notified to specifically address limited mobility issues during patients' standard postoperative breast rehabilitation visits.

## 3 | RESULTS

Sixty patients were consented for planned LPS, in whom 58 procedures were completed using our intraoperative algorithm (Figure 5). Blue UE lymphatics were not identifiable in one patient who had severe axillary cancer nodal involvement, and no available

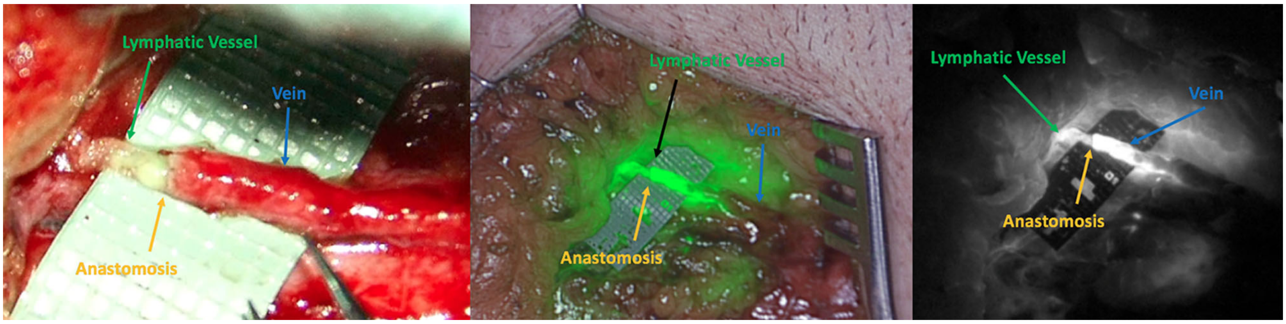


**FIGURE 4** Dual confirmation of patency with ICG lymphangiography. Confirmation of the patency of lymphaticovenous anastomosis with ICG [Color figure can be viewed at wileyonlinelibrary.com]

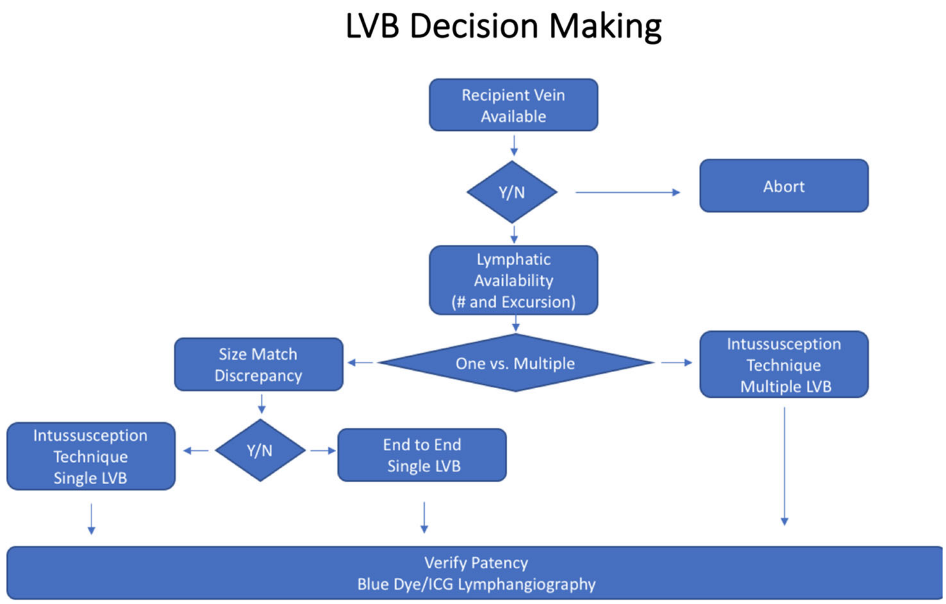


**FIGURE 5** Intraoperative microsurgical decision-making algorithm [Color figure can be viewed at wileyonlinelibrary.com]

recipient vein for LVB could be located in the other. The mean patient age was 51.7 years (range 31-78). Table 1 shows the patient, tumor characteristics, and operative details of our study population.

The placement of multiple, subdermal, medial upper arm blue dye injections as part of the ARM procedure allowed for routine visualization and preservation of a mean of 1.1 in-continuity lymphatics per patient (range 1-3) and a mean of 2.1 transected lymphatics post-ALND (Table 1).

An average of 1.4 LVBs (range 1-4) were performed per patient. End-to-end anastomoses was performed in 64% (37/58) of patients and intussusception anastomosis was performed in 36% (21/58) of patients. Intraoperative patency with ICG lymphangiography and/or blue dye was confirmed in 96.5% (56/58). Two anastomoses were felt to be insufficient because of excessive venous backflow into the lymphatics. Operative time for immediate lymphatic reconstruction after ALND ranged from 40 to 150 minutes and incorporated identification of structures, mobilization, and preparation as well as anastomotic completion.

Postoperative axillary drain duration ranged from 6 to 29 days. One infected axillary seroma occurred and was treated with aspiration and intravenous antibiotics. Comprehensive axillary and chest wall radiotherapy was performed in 52 patients. Patients received initial CA measurements and bioimpedance measurements and were subsequently followed postoperatively and at 3 to 6 month intervals.

Overall median postoperative follow-up was 11.8 months (1-29 months). Six, 12, and 24 month postoperative follow-up was performed in 43, 28, and 4 patients, respectively. Post-radiation follow-up duration was 6, 12, and 24 months in 37, 23, and 4 patients, respectively. LE occurred in 2/43 (4.6%) of patients with more than 6 months of follow-up as confirmed by differential CA measurements. One patient presented with International Society of Lymphology (ISL) stage 1 LE 2 months after completion of radiotherapy complicated by grade 3 radiation dermatitis.[17] Referral for LE physiotherapy resulted in near complete resolution. The second patient, in whom ALND was complicated by axillary surgical site infection, developed LE within 2 months of surgery and progressed to ISL stage 2 after radiation. She was treated with complex decongestive therapy.

## 4 | DISCUSSION

While trends are emerging that advocate for a reduction in axillary surgery, selected patients to continue to benefit from axillary nodal clearance.[18] Patients who require ALND are at increased risk for LE and its medical, social, and psychological implications.[19-22] Additional risk factors associated with the development of LE include the quantity of nodes removed, number of lymph nodes with cancer metastasis, axillary radiation, taxane chemotherapy, postoperative seroma, and increased BMI.[23] Although 75% of patients who develop LE do so within first 3 years, LE can manifest up to 30 years later.[24] A meta-analysis of patients who underwent ALND for breast cancer demonstrated a highly variable rate of postoperative LE from 7%-77%.[24] This variation is likely because of the ALND technical approach and manner of measuring LE.

In most cases, LVB has been used as a treatment option after the development of LE. A meta-analysis identified 22 studies that reported on outcomes with therapeutic LVB. Eighty-nine percent of patients reported subjective improvement, 88% experienced a quantitative improvement, and 56% of patients were able to discontinue compression therapy.[25] The success of LVB appears dependent on the stage of LE and degree of injury to lymphatic vasculature, with early treatment giving more favorable results. The ability of the surgeon to identify patent and contractile lymphatic channels decreases as LE becomes chronic.[26] In 1989, prophylactic LVB in the cubital region of the UE at the time of ALND was described.[27] We agree that a protective strategy incorporating lymphatic reconstruction has the potential to mitigate LE risk.

**TABLE 1** Patient, tumor, treatment, and operative details

| Patients | N = 58 | Percent |
|---|---|---|
| Mean age (range) | 51.7 y (31-78) | |
| Sex | 57 F, 1 M | |
| BMI kg/m2 (range) | N = 58 | |
| BMI < 25 | 25 | 43% |
| BMI 25-30 | 18 | 31% |
| BMI 30.1-35 | 7 | 12% |
| BMI > 35.1 | 8 | 14% |
| Type of cancer | N = 58 | |
| Invasive Ductal | 33 | 57% |
| Invasive Lobular | 5 | 9% |
| Mixed | 20 | 34% |
| Stage | | |
| Tx | 2 | 3% |
| T1 | 8 | 13% |
| T2 | 30 | 51% |
| T3 | 13 | 22% |
| T4 | 5 | 8% |
| N1 | 32 | 55% |
| N2 | 17 | 29% |
| N3 | 9 | 16% |
| Breast procedure | | |
| Mastectomy | 51 | 87% |
| Lumpectomy | 7 | 13% |
| Adjuvant radiation therapy | | |
| | 52 | 89% |
| Chemotherapy | | |
| Neoadjuvant | 43 | 74% |
| Adjuvant | 10 | 17% |
| None | 5 | 9% |
| Mean number of lymph nodes removed (range) | 14 (5-41) | |
| Mean number of LN with metastasis (range) | 2.6 (1-22) | |
| Mean of blue lymphatics identified (range) | 2.1 (1-5) | |
| Mean LVB time (range) | 85 min (40-150) | |
| Number of LVBs performed per patient | | |
| 1 | 40 | 68% |
| 2 | 15 | 26% |
| 3 | 2 | 4% |
| 4 | 1 | 2% |

Abbreviation: LVB, lymphaticovenous bypass.

LVB in the axilla offers a promising surgical approach for LE prevention. Performing lymphatic mapping at the time of ALND allows for the identification of lymphatic channels that drain the arm, and when used in combination with LVB, allows for a reconstruction of compromised afferent lymphatic pathways.[9,10,14] Variations of these techniques have been reported, most with promising early results.[9,15] However, studies thus far have been heterogeneous. Limitations include the inability to identify transected lymphatic afferents and low-resolution confirmation of intraoperative LVB patency.

Our approach to LE prevention in patients undergoing ALND incorporates ARM and enhanced lymphatic visualization with an algorithmic approach to LVB. Several refinements, described in this paper, have resulted in enhanced intraoperative UE lymphatic identification (98%).

Meticulous axillary dissection with loupe magnification and minimal cautery decreased lymphatic and recipient vein injury, while assuring oncologic control. Conversion from a single site deep upper brachial injection to a subdermal injection of several aliquots of dye circumferentially in the medial upper arm resulted in superior visualization and preservation of uninvolved lymphatics. This represents an improvement over the report by Feldman et al[9] where 5/35 patients were unable to undergo LVB because of the inability to identify suitable lymphatics. Our results are consistent with, and reveal a slight improvement over the lymphatic identification rate of 96% (75/78 patients) reported by Boccardo et al[28] in their 4-year follow-up report. Our method resulted in consistent identification of up to five transected lymphatic afferents in 98% (59/60) of all patients. Similarly, initial standard ARM tracer techniques popularized by Klimberg resulted in only 71.8% identification of ARM lymphatics or nodes.[6] Although others have demonstrated success in lymphatic identification with varied injection methods, our results suggest that the linear circumferential band pattern of ARM injection described in this report allows the surgeon to identify draining UE lymphatics with increased frequency. Comparative studies specifically designed to elucidate injection technique superiority are an area for future investigation.

Our ability to complete successful LVB was not limited by lymphatic identification, rather it was impacted by the availability of recipient veins with the appropriate size, arc of rotation, and valvular competence. Of 60 patients with planned LPS, three (5%) were unable to attain successful LVB for these reasons. Continuous improvement in our modified ALND/ARM technique has allowed for more consistent identification and preservation of potential target veins and their tributaries.

We have adapted an intraoperative paradigm that accounts for post-ALND lymphatic and venous anatomy. Considering the number and mobility of transected lymphatic vessels and venous-lymphatic size match, we modify our anastomotic technique to maximally restore UE physiologic drainage. Furthermore, patency is confirmed using both ICG lymphangiography and blue dye allowing the surgeon to reliably demonstrate flow through each anastomotic variation irrespective of vessel wall thickness or admixture of lymphatic fluid and venous blood. In contradistinction to other reports, we are seldom able to perform a lymphaticolymphatic reanastomosis which provides physiologic anterograde flow following ALND. [6] The ability to select and mobilize appropriate afferent and efferent lymphatics for coaptation is limited by a sizable gap, and reliable patency of the

LVB(s) necessitates a microsurgical technique. Although others have described variations which avoid microsurgical techniques, true lymphatic reconstruction is not documented.[6,15] Reestablishment of lymphatic continuity through apposition of lymphatic channels, and not anastomosis, relies on lymphangiogenesis and is extrapolated from small animal models of lymphatic regeneration which are not immediately translatable to humans.[29,30]

Although our primary objective was to optimize the visualization and preservation of lymphatic flow at the time of ALND, limitations exist. Short-term follow up of less than 2 years and the low sample size is not sufficient to clearly demonstrate a durable protective effect against LE. Based on this data set, we are yet not able to specifically evaluate the superiority of varied LVB anastomotic techniques on the preservation of long-term lymphatic function. Multiple risk factors in addition to ALND are known to contribute to LE development, and indeed, the 2 patients who developed LE in this cohort exhibited certain risks including radiotherapy, chemotherapy, axillary seroma, and high BMI. Because the incidence of LE was so low, meaningful association with these factors could not be made at this time. Long-term follow-up and analysis including a control group without lymphatic reconstruction also will help identify which factors are the strongest contributors to the development of LE in the setting of LVB. Long term patency of LVB in the axilla is difficult to assess with current imaging modalities due to poor resolution and depth of penetration. Therefore, clinical markers of LE must serve as the primary indicators of lymphatic dysfunction and disease progression. Radiotherapy is commonly administered in this subset of patients and may injure carefully preserved lymphatics and lymphaticovenous anastomoses.[31,32] In this study, 4.6% of patients with a minimum 6-month follow-up developed LE, both of whom received radiotherapy. Comparative studies are ongoing to identify the degree to which radiation impacts the development of LE following LPS. Reports have shown a lower risk of LE in patients who have undergone SLN biopsy with radiation compared to those treated with ALND and radiation.[32] We postulate that maximally preserving and restoring lymphatic continuity when ALND is performed will create a LE development risk similar to patients who receive SLN biopsy. Long term prospective studies are needed and are underway.

## 5 | CONCLUSIONS

We have developed a unique preventative strategy to protect against breast cancer-related LE. Using this intraoperative LPS paradigm, consistent superior visualization of lymphatic structures is achieved allowing maximal preservation of lymphatic continuity during ALND. Our algorithmic approach to LVB accounts for post-ALND lymphatic and venous anatomy and optimizes restoration of physiologic UE lymphatic flow. Well-conducted, prospective studies are needed to assess the long-term efficacy of this approach for LE prevention, its effect on oncologic outcomes and its impact on patient-reported quality-of-life.

## DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## MEETING PRESENTATION

This study was presented in the American College of Surgeons Clinical Congress 2018. October 21 to 25, 2018, Boston, MA.

## ORCID

*Cagri Cakmakoglu* http://orcid.org/0000-0001-6254-8811

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