A 4-Year Institutional Experience of Immediate Lymphatic Reconstruction

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Background: Up to one in three patients may go on to develop breast cancer–related lymphedema (BCRL) after treatment. Immediate lymphatic reconstruction (ILR) has been shown in early studies to reduce the risk of BCRL, but long-term outcomes are limited because of its recent introduction and institutions' differing eligibility requirements. This study evaluated the incidence of BCRL in a cohort that underwent ILR over the long term.

Methods: A retrospective review of all patients referred for ILR at the authors' institution from September of 2016 through September of 2020 was performed. Patients with preoperative measurements, a minimum of 6 months of follow-up data, and at least one completed lymphovenous bypass were identified. Medical records were reviewed for demographics, cancer treatment data, intraoperative management, and lymphedema incidence.

Results: A total of 186 patients with unilateral node-positive breast cancer underwent axillary nodal surgery and an attempt at ILR over the study period. Ninety patients underwent successful ILR and met all eligibility criteria, with a mean patient age of 54 ± 12.1 years and median body mass index of 26.6 kg/m^2 [interquartile range (IQR), 24.0 to 30.7 kg/m^2]. The median number of lymph nodes removed was 14 (IQR, eight to 19). Median follow-up was 17 months (range, 6 to 49 months). Eighty-seven percent of patients underwent adjuvant radiotherapy, and among them, 97% received regional lymph node irradiation. The overall rate of lymphedema was 9% at the end of the study period.

Conclusions: With the use of strict follow-up guidelines over the long term, the authors' findings support that ILR at the time of axillary lymph node dissection is an effective procedure that reduces the risk of BCRL in a high-risk patient population. *(Plast. Reconstr. Surg.* 152: 773e, 2023.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, IV.

The literature details an enormous burden of breast cancer–related lymphedema (BCRL) after breast cancer treatment. Specifically, a 2019 meta-analysis reported that patients who undergo axillary lymph node dissection (ALND) have an incidence of BCRL of 14.1%, and for those who undergo ALND with regional lymph node radiation (RLNR), 33.4%.[1] These data likely underreport the true burden of disease, as most of the studies included did not have a long-term surveillance program, and patients who are symptomatic are more likely to re-present to the clinic. A novel surgical technique, LYMPHA, now termed immediate lymphatic reconstruction (ILR), first described by Boccardo et al. in 2009, reduces the risk for the development of BCRL.[2] Although this

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Received for publication January 27, 2022; accepted October 6, 2022.

DOI: 10.1097/PRS.0000000000010381

Disclosure statements are at the end of this article, following the correspondence information.

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technique has gained considerable traction in the field since its description in 2009, there is a lack of objective outcomes that can be easily aggregated and that quantify technique efficacy, and there is a paucity of long-term data available.

In a previous publication by our group of early ILR outcomes, the rate of BCRL was 3.1%.[3] In a meta-analysis of the available literature on ILR outcomes, the incidence of BCRL after ILR was 2.1%. In those who underwent ILR and had adjuvant RLNR, a known risk factor for the development of this disease, this rate increased to 10.3%.[1] As more institutions offer this procedure and report on their outcomes, our understanding of its effectiveness has grown. However, a limitation of the available literature on ILR is the variable and relatively short follow-up time reported, with some studies including patient outcomes based on as little as 9 days of follow-up.[4] Long-term outcomes from ILR are described by Boccardo et al.[5] In this cohort following 71 patients, the 4-year incidence of BCRL was 4.05%. Notably, this cohort differed from that described in this study, as they had a body mass index (BMI) greater than or equal to 30 kg/m^2 or lymphoscintigraphy transport index of greater than or equal to 10, and less than half were treated with radiotherapy (47%).

In this review, we describe the outcomes of ILR in a cohort of 90 node-positive breast cancer patients with at least 6 months of follow-up over 4 years. All patients undergoing ALND at our institution are eligible to undergo ILR.

PATIENTS AND METHODS

Retrospective Review

A review of a prospectively maintained clinical and quality improvement (QI) database was performed. Consecutive patients with a diagnosis of node-positive breast cancer who underwent attempted ILR after ALND between September 1, 2016, and September 1, 2020, were identified. Patients were excluded if ILR was aborted, if there were no preoperative measurements, or if the patient had preoperative measurements consistent with an existing diagnosis of lymphedema (LE). Of the patients who met our inclusion criteria, only those with a minimum of 6 months of follow-up were included for final analysis. Patient demographics, cancer characteristics, intraoperative specifics, and surveillance measurements were extracted for analysis. This study was deemed exempt by our institutional review board (protocol 2020P000900).

Preoperative Evaluation

The standardized approach to preoperative evaluation at our institution has previously been described.[3] Briefly, all patients must have at least one preoperative volumetry measurement using either circumferential measurement or perometry and bioimpedance spectroscopy/L-Dex (Sozo, Impedimed Limited, Australia).

Surgical Technique

The surgical technique used to perform ILR has been described previously.[3] An updated injection protocol was used for visualization of the lymphatics that includes a solution of 0.25 cc of 2% fluorescein isothiocyanate (Alcon Laboratories, TX) mixed with albumin injected into the dermis in four locations: the first and fourth web spaces and the ulnar and radial aspects of the volar forearm 1 cm proximal to the wrist crease. One cubic centimeter of 1% isosulfan blue (Mylan Institutional, IL) is injected 4 cm proximal to the antecubital crease into the dermis overlying the cephalic vein as identified by ultrasound.

Postoperative Surveillance

Postoperative management, including incisional and drain care has been described previously.[3] Patients undergo routine postoperative surveillance with certified lymphedema therapists (CLTs) at prescribed time intervals: 4 weeks, 3 months, and every 3 months postoperatively for 2 years, then every 6 months for an additional 2 years. At each visit, LE symptoms are assessed, and repeated volumetry and bioimpedance measurements are obtained. Symptoms assessed include swelling, heaviness, tightness, achiness, numbness/tingling, pain, and fatigue. A diagnosis of LE is made with the presence of symptoms attributable to the disease as determined by a CLT and one objective measurement consistent with LE, of either (1) an increase in L-Dex of 10 from the patient's preoperative baseline, or (2) a relative volume change (RVC) of 10% or more. RVC is calculated using the following formula:

$$\mathrm{RVC} = (\mathrm{A2U1}) / (\mathrm{A1U2}) - 1,$$

where *A1* and *A2* are the baseline (preoperative) and interval volume measurements of the affected arm and *U1* and *U2* are the baseline and current measurements of the unaffected arm. RVC is rounded to the tenths place. If perometry was unavailable, circumferential measurements

were taken and the truncated cone formula was used to calculate extremity volume.[6]

Statistical Analysis

We used descriptive statistics to characterize our overall sample and, specifically, those who had adequate follow-up (≥6 months). We reported mean and SD or median and first and third quartiles (IQR) for continuous data. We summarized categorical data using counts and percentages. To compare categorical variables, we performed chi-square tests; and to compare continuous variables, we performed *t* tests for data we present as means and standard deviations and Wilcoxon rank sum tests for data we present as median (IQR). As patients do not always follow-up on the exact prespecified timeline, we binned follow-up into discrete time windows. (**See Table, Supplemental Digital Content 1**, which shows the grouping of respective postoperative days into reported follow-up time points by months, ***http://links.lww.com/PRS/G184***.) Time points and their respective windows were selected a priori and based on prior research.[3] The time windows were used to ensure all surveillance visits were captured during follow-up. At each discrete follow-up time point, we assessed whether the patient met our criteria for a diagnosis of LE. We represented these data graphically to show the follow-up and trajectory of each patient. We used R v4.1.1 (R Development Core Team, 2019) for all statistical analysis.

RESULTS

One hundred eighty-six patients were brought to the operating room between September 1, 2016, and September 1, 2020. for planned ILR following ALND. Twenty-eight patients were excluded because of an aborted procedure (15%), 19 because of missing preoperative measurements (10%), and three because of preoperative measurements consistent with LE (2%). An additional 46 patients (25%) were excluded because they had less than the requisite 6 months of follow-up data available. Ultimately, 90 patients remained in the cohort (Fig. 1). These patients were mostly female (99%), with an average age of 54 ± 12.1 years and with a median BMI of 26.6 kg/m^2 (IQR, 24.0 to 30.7 kg/m^2). They had similar demographics as compared with the entire cohort

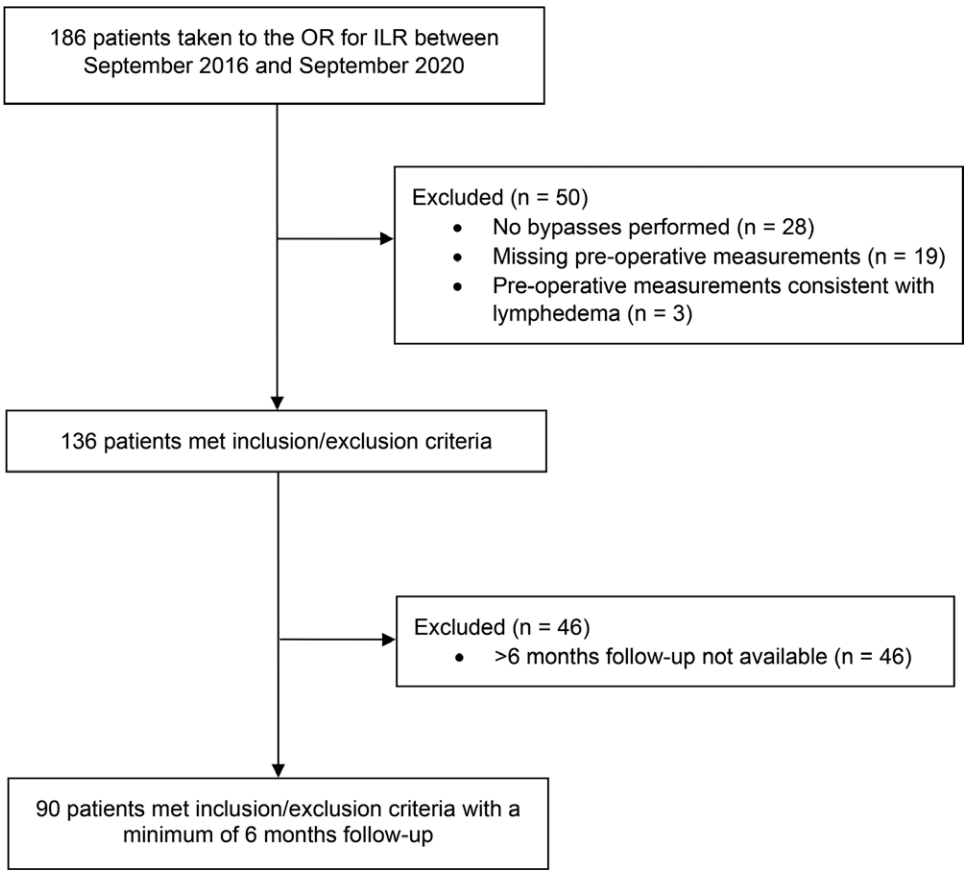

Fig. 1. Flowchart of patient inclusion/exclusion criteria.

Table 1. Patient and Disease Characteristics

Characteristic	All Patients Eligible for Follow-Up (%)	All Patients without ≥6 Mo Follow-Up (%)	All Patients with ≥6 Mo Follow-Up (%)	*P*[a]
No.	136	46	90	
Baseline characteristics				
Mean age ± SD, yr	54.9 ± 12.1	56.8 ± 11.1	53.9 ± 12.5	0.18
Female sex	134 (98.5)	45 (97.8)	89 (98.9)	0.99
Race				0.42
White	98 (72.1)	33 (71.7)	65 (72.2)	
Black or African American	19 (14.0)	6 (13.0)	13 (14.4)	
Asian	10 (7.4)	2 (4.3)	8 (8.9)	
Other	9 (6.6)	5 (10.9)	4 (4.4)	
Ethnicity, non-Hispanic	130 (95.6)	45 (97.8)	85 (94.4)	0.64
BMI, kg/m^2				0.48
Median	26.6	26.8	26.6	
IQR	24.0–30.7	23.9–32.2	24.0–29.9	
Cancer treatment characteristics				
Tumor grade				0.82
I	15 (11.0)	6 (13.0)	9 (10.0)	
II	63 (46.3)	20 (43.5)	43 (47.8)	
III	57 (41.9)	20 (43.5)	37 (41.1)	
Unknown	1 (0.7)	0 (0)	1 (1.1)	
Neoadjuvant chemotherapy	95 (69.9)	35 (76.1)	60 (66.7)	0.35
Taxane-based	89	32	57	0.49
Adjuvant radiotherapy	115 (84.6)	37 (80.4)	78 (86.7)	0.41
RLNR with or without chest wall, breast, or intrabeam	109	33	76	
Adjuvant chemotherapy	46 (33.8)	10 (21.7)	36 (40.0)	0.02
Taxane-based	31	6	11	0.088

[a]*P* value comparing patients without ≥6 months of follow-up and patients with ≥6 months of follow-up.

of patients taken to the operating room for ILR and those who met inclusion criteria but did not meet the minimum follow-up criteria (Table 1).

Of the 90 patients who met all eligibility criteria, 67% underwent neoadjuvant chemotherapy, 87% underwent adjuvant radiotherapy (which almost universally included regional lymph node irradiation), and 40% underwent adjuvant chemotherapy (Table 1).

Intraoperatively, the median number of nodes removed during axillary surgery was 14 (IQR, eight to 19), whereas the median number positive was one (IQR, zero to three) (Table 2). A median of one lymphovenous bypass was completed (range, one to three).

Postoperatively, the median follow-up time after surgery was 17 months (range, 6 to 49 months). Perometry was used to calculate RVC in 80% of follow-up visits, whereas the rest were calculated using circumferential measurements. Six patients (7%) met criteria for LE, and subsequently were found not to meet criteria for LE at future surveillance visits. (**See Figure, Supplemental Digital Content 2**, which shows patient lymphedema outcomes by month of follow-up, ***http://links.lww.com/PRS/G185***.) All these patients were stable and out of compression therapy for at least 6 months by the end of the study period. Eight patients (9%) met criteria for LE and continued to meet criteria for LE as of the end of the study. Of the patient visits at which the patient met objective measurements consistent with LE, 64% were because of RVC greater than 10%, 75% because of an increase in L-Dex of at least 10 from baseline, and 35% because of both.

Table 2. Intraoperative Characteristics in the Follow-Up Cohort

Characteristic	Value
No.	90
No. of positive nodes removed	
Median	1
IQR	0–3
No. of total nodes removed	
Median	14
IQR	8–19
No. of divided lymphatics visualized	
Median	3
IQR	2–3.8
No. of bypasses performed	
Median	1
IQR	1–2

DISCUSSION

In this study, we describe our ILR experience including nearly 200 patients over 4 years. Fourteen patients (16%) met criteria for LE at a minimum of one time point during the study period, and six of these patients did not meet criteria at the end of the study period. Ultimately, eight patients (9%) met criteria for LE as of the end of the study period.

Our long-term data continue to support the role of ILR for breast cancer patients requiring ALND with or without adjuvant RLNR. In the initial publication of Boccardo et al. of a 4-year experience with 74 patients who underwent successful ILR, eight patients demonstrated LE at one time point within the study period (11%), but five patients' LE resolved, and only three patients were ultimately diagnosed with LE (4%).[5] Although our rates of LE are higher than those reported by Boccardo et al., we do note that almost all patients in our cohort received RLNR, which may help explain our slightly elevated rate, as this is the second highest risk factor for BCRL development after ALND.

Strengths of this study include the presence of a rigorous, standardized preoperative and postoperative surveillance program. A comprehensive surveillance program allows for an accurate estimate of the incidence of LE after ILR, as patients are prospectively evaluated preoperatively and postoperatively versus a standard clinic model, where patients would likely only return to the clinic if they were to become symptomatic. The importance of surveillance programs monitoring for recurrence in the breast cancer field has previously been established, and it is an important aspect of posttreatment care guidelines.[7] We recognize that our surveillance program allows us to identify cases of LE before the patient may be aware they meet disease criteria. This is especially evident in the six patients who were found to meet criteria for LE, which later resolved, as it is highly unlikely that patients would have self-identified these cases to a threshold where they would have sought out medical care in the absence of the surveillance program. Our surveillance protocol allows us to identify cases of LE early, so our patients with LE tend to have milder cases than those who present to our clinic with chronic LE who were not prospectively followed. Therefore, we are sometimes recognizing and treating very early LE before the patient themself would recognize the presence of the disease in the absence of a targeted evaluation, which inherently means that we expect to see a higher incidence of LE based on these data. Moreover, we recognize that our reported rate of LE after 4 years is representative of ILR in the setting of a surveillance program and not of ILR alone.

This study also speaks to the importance of objectivity in the diagnosis and evaluation of LE. Although the fields of lymphatic surgery and lymphatic medicine continue to grow, the definitions that different institutions use to diagnose and evaluate the progression of this disease follow suit. Our institution is no exception. Since our last publication, we have refined our definition of LE. Specifically, we have discontinued using the term *transient lymphedema* for LE diagnosed within 6 months of the last cancer treatment, as we have since recognized that LE can develop and resolve even outside of the 6-month range, which is commensurate with many studies that estimate that the first sign of LE can occur even years after surgery.[8] Of the total of 14 patients who developed LE at some point during the postoperative surveillance, six were identified more than 6 months postoperatively. One patient first developed LE at 27 months postoperatively, and this subsequently resolved. This observation highlights that the pathophysiology of BCRL development and persistence remains poorly understood. Further study regarding specific risk factors and anatomy of these patients should continue to remain an important topic for continued study.

This study is limited by the fact that certain patients are placed into compression garments by our CLTs without the patient meeting criteria for LE based on subclinical subjective or objective findings. For example, our CLTs will place a patient with an L-DEX change between 7 and 10 from baseline into compression garments even without symptoms. Moreover, a comprehensive review of our experience has revealed that certain patients feel reassured by a compression garment and wear it without any clinical evidence of lymphedema. These cases cannot be excluded from our surveillance program, but their use of compression outside of LE complicates our assessment for LE. Finally, although some cases of LE can develop outside the time frame of our standard surveillance protocol, the literature shows a hazard rate of only less than 1% after 4 years.[9]

CONCLUSIONS

In this study, we describe one institution's experience with ILR involving 200 patients over 4 years as part of a multidisciplinary lymphatic

center with a strict surveillance program. The postoperative rate of LE found in this high-risk cohort was 9%. This study supports offering ILR to all patients undergoing ALND to reduce the risk of BCRL.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

ACKNOWLEDGMENT

Research reported in this publication was supported in part by the Jobst Lymphatic Research Grant awarded by the Boston Lymphatic Symposium, Inc. (to M.G.).

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