Evaluating the Impact of Immediate Lymphatic Reconstruction for the Surgical Prevention of Lymphedema

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Background: Breast cancer–related lymphedema affects one in five patients. Its risk is increased by axillary lymph node dissection and regional lymph node radiotherapy. The purpose of this study was to evaluate the impact of immediate lymphatic reconstruction or the lymphatic microsurgical preventative healing approach on postoperative lymphedema incidence.

Methods: The authors performed a retrospective review of all patients referred for immediate lymphatic reconstruction at the authors' institution from September of 2016 through February of 2019. Patients with preoperative measurements and a minimum of 6 months' follow-up data were identified. Medical records were reviewed for demographics, cancer treatment data, intraoperative management, and lymphedema incidence.

Results: A total of 97 women with unilateral node-positive breast cancer underwent axillary nodal surgery and attempt at immediate lymphatic reconstruction over the study period. Thirty-two patients underwent successful immediate lymphatic reconstruction with a mean patient age of 54 years and body mass index of 28 ± 6 kg/m^2. The median number of lymph nodes removed was 14 and the median follow-up time was 11.4 months (range, 6.2 to 26.9 months). Eighty-eight percent of patients underwent adjuvant radiotherapy of which 93 percent received regional lymph node radiotherapy. Mean L-Dex change was 2.9 units and mean change in volumetry by circumferential measurements and perometry was −1.7 percent and 1.3 percent, respectively. At the end of the study period, we found an overall 3.1 percent rate of lymphedema.

Conclusion: Using multiple measurement modalities and strict follow-up guidelines, the authors' findings support that immediate lymphatic reconstruction at the time of axillary surgery is a promising, safe approach for lymphedema prevention in a high-risk patient population. (*Plast. Reconstr. Surg.* 147: 373e, 2021.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, IV.

Breast cancer–related lymphedema affects approximately 20 to 45 percent of breast cancer survivors after surgical intervention.[1–7] This surgical sequela is associated with decreased patient quality-of-life measures, increased susceptibility to infection, and increased medical expenditure.[8,9] Treatment for breast cancer–related lymphedema is largely palliative in nature and focused on reducing symptoms and preventing disease progression. Conservative measures require strict patient adherence to lifelong therapies, including manual lymphatic drainage, compression bandaging/garments, pneumatic pump use, and physical therapy.[1,10,11] Despite improvements in microsurgical techniques such

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as vascularized lymph node transfer and lymphovenous bypass for the treatment of chronic lymphedema, none of these options has proven curative. As long-term overall survival increases in tandem with advancements in treatment, efforts toward minimizing or eliminating breast cancer–related lymphedema are paramount. The advent of the lymphatic microsurgical preventive healing approach has introduced the concept of surgical prevention for lymphedema.

In the seminal study by Boccardo et al., lymphedema rates were 4 percent with 4 years' follow-up in a high-risk patient cohort where the majority of patients underwent axillary lymph node dissection with regional lymph node radiotherapy.[12] This finding has been replicated at other institutions, where similar decreases in rates of lymphedema after immediate lymphatic reconstruction were found in comparable patient cohorts.[13,14] Some criticisms of these studies include variation in the criteria used to diagnose "lymphedema," heterogeneity of measurement modalities used, and varying follow-up periods.[15]

At our institution, the lymphatic microsurgical preventive healing approach is termed "immediate lymphatic reconstruction," as divided lymphatics are reconstructed at the time of tumor extirpation.[16] We use multiple lymphedema measurement modalities preoperatively and during postoperative surveillance. Moreover, we impose follow-up criteria to capture the long-term effects of this technique.

Our present study aims to introduce and review our institutional experience with immediate lymphatic reconstruction in a node-positive breast cancer patient population undergoing axillary surgery. To this end, we performed a retrospective review of a quality improvement database to identify all patients who underwent axillary surgery with immediate lymphatic reconstruction at our institution and describe our surgical outcomes.

PATIENTS AND METHODS

A retrospective review of our lymphatic surgery Research Electronic Data Capture database was performed. Institutional review board approval was obtained (protocol no. 2019P-000190). Consecutive patients with a diagnosis of node-positive unilateral breast cancer who underwent attempted immediate lymphatic reconstruction after axillary surgery from September of 2016 through February of 2019 were identified. No patients with a history of breast cancer or breast and/or axillary surgery were eligible for inclusion. Furthermore, no patients undergoing sentinel lymph node biopsy alone were eligible for immediate lymphatic reconstruction. Patient demographics, cancer characteristics, intraoperative specifics, and surveillance measurements were extracted for analysis. The study design is illustrated in Figure 1.

Preoperative Evaluation

Certified lymphedema therapists at our institution used multiple lymphedema measurement modalities to obtain comprehensive baseline data for all patients who presented for immediate lymphatic reconstruction. These measurement modalities included (1) circumferential arm measurements at 4-cm intervals that were converted to volumes using the truncated cone formula,[17] (2) perometry, and (3) bioimpedance spectroscopy (L-Dex U400; ImpediMed, Carlsbad, Calif.).

In addition, all patients were administered the 36-Item Short-Form Health Survey questionnaire at routine intervals.[18,19] We administer the 36-Item Short-Form Health Survey to all patients preoperatively. This survey provides data on physical functioning (physical component scale) and mental health, emotional, and social functioning (mental component scale). Pertinent patient data including demographics, medical history, cancer characteristics and treatment, and baseline lymphedema measurements are entered into a Research Electronic Data Capture[20] lymphedema quality improvement clinical database to facilitate surveillance.

Surgical Technique

At our institution, sentinel lymph node biopsies are performed as permanent sections and axillary lymph node dissections occur in a staged manner. A single surgeon with fellowship training in lymphatic surgery (D.S.) performed all attempted immediate lymphatic reconstructions from September of 2016 through February of 2019 at the time of nodal extirpation. The type of axillary nodal intervention performed was determined by the lymphatic surgeon intraoperatively. Following axillary surgery, the lymphatic surgeon attempted to visualize the boundaries of a level I and II dissection including the axillary vein superiorly, serratus anterior medially, thoracodorsal vessels posteriorly, and latissimus muscle laterally.[21] If all structures were visible, the procedure was termed an axillary lymph node dissection. If

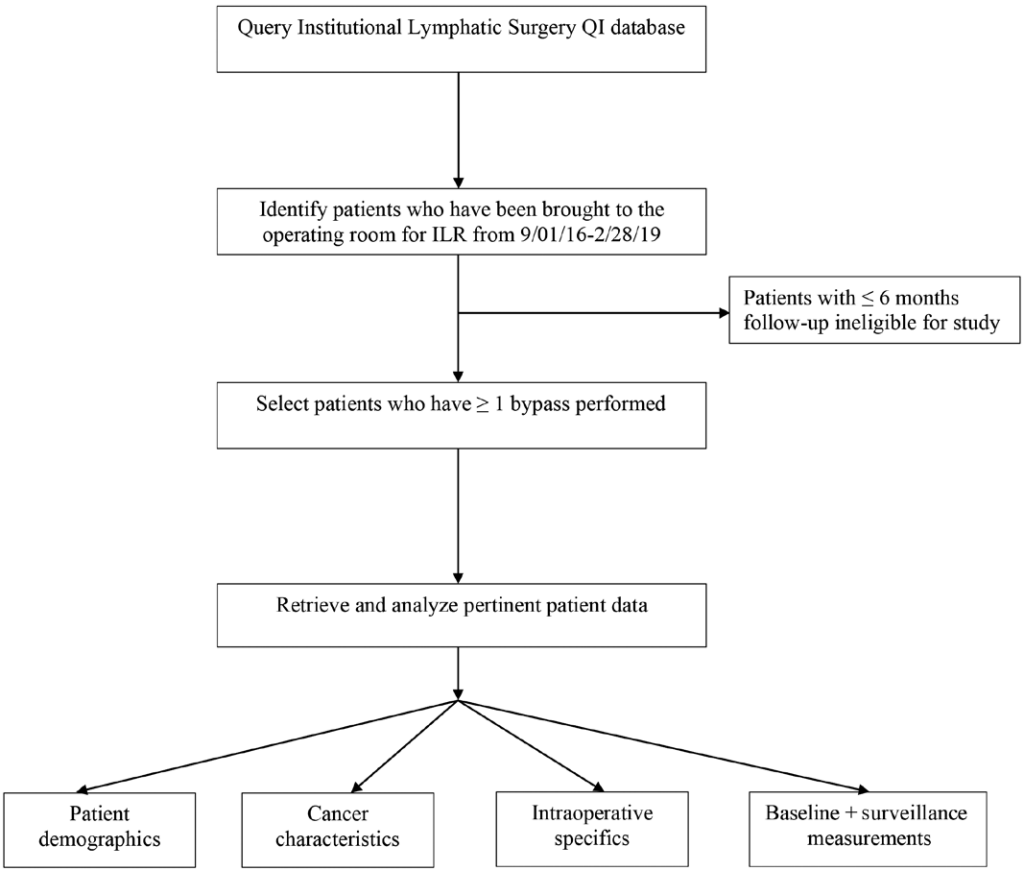

Fig. 1. Study design. *QI*, quality improvement; *ILR*, immediate lymphatic reconstruction.

any of these structures was not visible, the procedure was termed an axillary sampling procedure.

Immediately before the initiation of the axillary intervention by the breast surgical oncology service, 0.25 cc of fluorescein isothiocyanate mixed with albumin was injected into the upper medial operative extremity as described previously.[22] Following completion of the axillary lymph node dissection, using the same exposure provided by the breast surgeon, the axillary bed was evaluated, and any major venous branches draining into the axillary vein were identified. Tributaries of the axillary vein were then evaluated for adequate length and the presence of a proximal intact valve. In cases of inadequate vein length or significant venous back-bleeding, the lymphatic reconstruction was aborted.

Using a Mitaka MM51 microscope equipped with a 560-nm filter (Mitaka Kohki Co., Ltd., Mitaka, Tokyo), divided lymphatic channels were visualized and their location mapped from the axillary vein. Each lymphatic channel was isolated and measured using high magnification and fluorescent technology for visualization. The distal ends of lymphatic channels were cut to confirm active lymphatic flow using filter technology. Afferent lymphatic vessels not suitable for anastomosis were clipped. A U stitch was then passed through the prepared tributary vein and lymphatic channels to facilitate parachuting the lymphatic channels into the vein using the technique described by Boccardo and Campisi.[23] The lymphatic reconstruction was then secured using 9-0 nylon sutures (Ethicon, Inc., Somerville, N.J.), which were passed full thickness through the tributary vein into the perilymphatic tissues in a simple, interrupted manner. The initial U stitch was then cut to allow lymphatic flow into the vein. Confirmation of lymphatic flow and anastomotic patency was visualized using the Mitaka MM51 microscope, as documented in a previous study.[22] A fat graft was then harvested from the axilla that was then wrapped around the anastomotic site to secure it. [**See Video (online)**, which demonstrates the surgical technique used in immediate lymphatic reconstruction of the left axillary nodal bed.] The axillary incision was closed in standard fashion and a no. 15 Blake drain was placed exiting the dependent portion of the axillary bed away from the anastomotic site.

Postoperative Surveillance

On discharge, patients are advised to follow routine incisional care. When drain outputs are less than 20 cc/day for 2 consecutive days, the drain is removed, and this is usually accomplished by 14 days postoperatively. Our surveillance protocol for immediate lymphatic reconstruction patients included postoperative visits at 4 weeks, 3 months, and then every 3 months postoperatively for 2 years. During each surveillance visit, certified lymphedema therapists assessed and documented any signs or symptoms consistent with lymphedema (e.g., heaviness, swelling, numbness). All objective measurements from the preoperative evaluation were repeated at each surveillance visit. Studies have shown the success and cost-effectiveness of postoperative surveillance programs in patients at high risk for the development of breast cancer–related lymphedema.[24–26] We monitor patients closely using three measurement modalities (i.e., perometry, bioimpedance spectroscopy, and volumetry by circumferential measurements). If the patient did not develop any signs or symptoms consistent with lymphedema or objective findings (any positive quantitative change by volumetry, L-Dex, or circumferential measurements) consistent with lymphedema during this time frame, patients were then surveilled every 6 months for the subsequent 2 years. In total, patients are actively surveilled for 4 years. The need for additional surveillance is determined on a case-by-case basis. Bioimpedance spectroscopy is a sensitive modality championed for postoperative patient surveillance, as it can noninvasively detect changes in lymph fluid by assessing the "impedance," or opposition to current traveling through the body.[27]

All surveillance data were entered into a lymphatic surgery database by trained staff. The 36-Item Short-Form Health Survey questionnaires were sent to patients by automated e-mails from the database at 3, 6, and 12 months, and then annually following immediate lymphatic reconstruction. All results from completed online surveys were automatically populated within the Research Electronic Data Capture[20] database.

Lymphedema is defined at our institution as having both (1) any positive quantitative measurement meeting criteria for lymphedema and the (2) presence of symptoms (i.e., tightness, heaviness, swelling) consistent with lymphedema as determined by a certified lymphedema therapist. Objective measurements consistent with a lymphedema diagnosis included a 10-point increase in bioimpedance (L-Dex) value from baseline; a 10 percent volume increase in the dominant, affected extremity; or a 7 percent increase in the nondominant affected extremity using volumetry. If the patient met these criteria while undergoing adjuvant treatment, with the exclusion of hormone therapy and immunotherapy, or within 6 months of their last oncologic treatment, lymphedema was classified as transient (i.e., "transient lymphedema"). A diagnosis of lymphedema was given if the patient met the above-specified criteria 6 months after their last oncologic treatment (surgery, adjuvant radiation therapy, or chemotherapy). Regional lymph node radiation was defined at our institution as targeted treatment to the internal mammary, supraclavicular, and/or axillary regions.[28,29]

Statistical Analysis

Descriptive statistics of the data were performed. Continuous data were represented using mean and standard deviation or median and range or first and third quartiles. Frequencies and percentages were used to summarize categorical variables. We used t tests for continuous variables and chi-square tests for categorical variables to compare demographics between the cohort who underwent successful immediate lymphatic reconstruction with 6-month minimum follow-up (n = 32) and all other patients who underwent attempted immediate lymphatic reconstruction (n = 65). R 3.5.3 (R Development Core Team, 2019) was used for statistical analyses.

RESULTS

Ninety-seven women with unilateral node-positive breast cancer underwent attempted immediate lymphatic reconstruction at our institution during the study period. Forty-one patients had a minimum 6-month follow-up. Nine of these cases (22 percent) were excluded, as immediate lymphatic reconstruction was aborted intraoperatively. Inadequate recipient vein (e.g., lack of vein availability or back-bleeding) occurred in five of the aborted cases; lack of identifiable divided lymphatic channel occurred in four cases. A total of 18 patients had preoperative baseline measurements but did not present for 6-month follow-up and were thus ineligible for study inclusion at the time of analysis. Thirty patients underwent successful immediate lymphatic reconstruction with a mean patient age of 54 years and body mass index of 28 ± 6 kg/m^2. Patients in this cohort had similar demographics when compared to the entire patient population (Table 1).

Table 1. Patient Demographics

	Patients Who Underwent Attempted ILR (%)	Patient Who Underwent Successful ILR wtih 6-Mo Minimum Follow-Up (%)	*p*
No.	97	32	
Mean age at surgery ± SD, yr	54.0 ± 13	54.1 ± 12	0.94
Mean BMI at surgery ± SD, kg/m^2	27.5 ± 6	27.7 ± 6	0.81
Female sex	97 (100)	32 (100)	
Race			0.26
White	58 (59)	23 (72)	
Black	20 (21)	7 (22)	
Asian	7 (8)	1 (3)	
Other/unknown	12 (13)	1 (3.1)	
Ethnicity, non-Hispanic	95 (98)	32 (100)	0.99

ILR, immediate lymphatic reconstruction; BMI, body mass index.

Of the 32 patients who met study eligibility criteria, 88 percent of women in this cohort underwent adjuvant radiotherapy of whom 93 percent received regional lymph node irradiation. Furthermore, 59 percent of women had adjuvant chemotherapy, with the majority (74 percent) undergoing a taxane-based regimen (Table 2).

Intraoperatively, the median number of positive lymph nodes for both the axillary sampling and axillary lymph node dissection groups was one, with the total lymph nodes removed during these interventions being 10 and 13, respectively. All immediate lymphatic reconstructions were performed by a single lymphatic surgeon (D.S.) at our institution. Three breast surgeons performed 88 percent of all nodal dissections. A median of three divided lymphatic channels were visualized in each case (range, one to six). Of these, a median of one lymphatic channel was bypassed (range, one to three). The median distance of the bypassed channel to the distal aspect of the visualized axillary vein was 3.00 cm (range, 0.25 to 5.5 cm). The median bypass time after completion of axillary intervention was 85 minutes (range, 54 to 205 minutes). Table 3 reports the intraoperative data by axillary sampling versus axillary lymph node dissection cases. The median patient follow-up time was 11.4 months (range, 6.2 to 26.9 months). There was no statistical difference between the mean number of bypasses performed in the group of patients who underwent axillary sampling (n = 1.57) compared to those who underwent an axillary lymph node dissection (n = 1.48) (p = 0.79). A summary of surveillance measurements is provided in Table 4. No intraoperative or postoperative complications were observed in this cohort.

Four patients developed transient lymphedema during postoperative surveillance (Fig. 2 and Table 4). All four patients underwent axillary lymph node dissection and not an axillary sampling. Three patients had disease resolution

Table 2. Patient Cancer Treatment Characteristics*

Characteristic	No. (%)
Tumor grade	
I	0 (0)
II	16 (50)
III	16 (50)
Neoadjuvant chemotherapy	15 (47)
Taxane-based	13 (87)
Adjuvant radiotherapy	28 (88)
Chest wall, breast, or intrabeam	2 (7)
RLNR with or without chest wall, breast, or intrabeam	26 (93)
Adjuvant chemotherapy	19 (59)
Taxane-based	14 (74)

RLNR, regional lymph node radiotherapy.
*n = 32.

Table 3. Intraoperative Specifics*

Characteristic	Value (%)
Axillary sampling	7 (22)
No. of positive nodes removed	
Median	1
IQR	0–2.5
No. of nodes removed	
Median	10
IQR	7–12
No. of divided lymphatics visualized	
Median	3
IQR	1–3
No. of bypasses performed	
Median	1
IQR	1–3
Axillary lymph node dissection	25 (78)
No. of positive nodes removed	
Median	1
IQR	1–3
No. of nodes removed	
Median	13
IQR	10–17
No. of divided lymphatics visualized	
Median	3
IQR	2–3
No. of bypasses performed	
Median	1
IQR	1–2

IQR, interquartile range.
*n = 32.

Table 4. Patient Surveillance and Outcomes*

	Value (%)
Follow-up from time of ILR, mo	
Median	11.4
Range	6.2–26.9
Mean unit change of L-Dex from baseline ± SD	2.9 ± 8.4
Absolute change in circumferential measurements from baseline ± SD, %	–1.7 ± 7.1
Absolute change in perometry values from baseline ± SD, %	1.3 ± 6.7
No. of patients diagnosed with transient lymphedema	4 (12.5)
No. of patients whose transient lymphedema resolved	3 (9.4)
No. of patients with ongoing transient lymphedema	1 (3.1)

ILR, immediate lymphatic reconstruction.
*$n = 32$.

within 6 months and were not using any compression or therapy at the time of analysis. In one patient, symptoms occurred at the first follow-up visit and resolved at the 6-month visit. In the other two patients, lymphedema symptoms began at months 3 and 6, respectively, and resolved at the 9-month follow-up visit. One patient developed transient lymphedema at 3 months and has had persistent signs and symptoms at her 6-, 9-, and 12-month visits. She was still undergoing oncologic treatment at the time of analysis. This patient is currently in compression and has an elevated risk-factor profile, including axillary lymph node dissection, adjuvant regional lymph node radiation therapy including targeted treatment to the axilla, elevated body mass index (38.4 kg/m^2), and neoadjuvant taxane-based chemotherapy. In this cohort of patients who presented with transient lymphedema, L-Dex was the most sensitive measurement modality and was the first presenting abnormal quantitative measurement for all four patients. Furthermore, in patients where immediate lymphatic reconstruction was aborted, transient lymphedema developed in three of the nine patients, for a 33 percent overall rate. In these patients, lymphedema resolved in two patients and persisted in one patient, for a transient lymphedema rate of 22 percent on conclusion of the study period.

DISCUSSION

Our study found that immediate lymphatic reconstruction was effective in a high-risk patient cohort with an overall lymphedema rate of 3.1

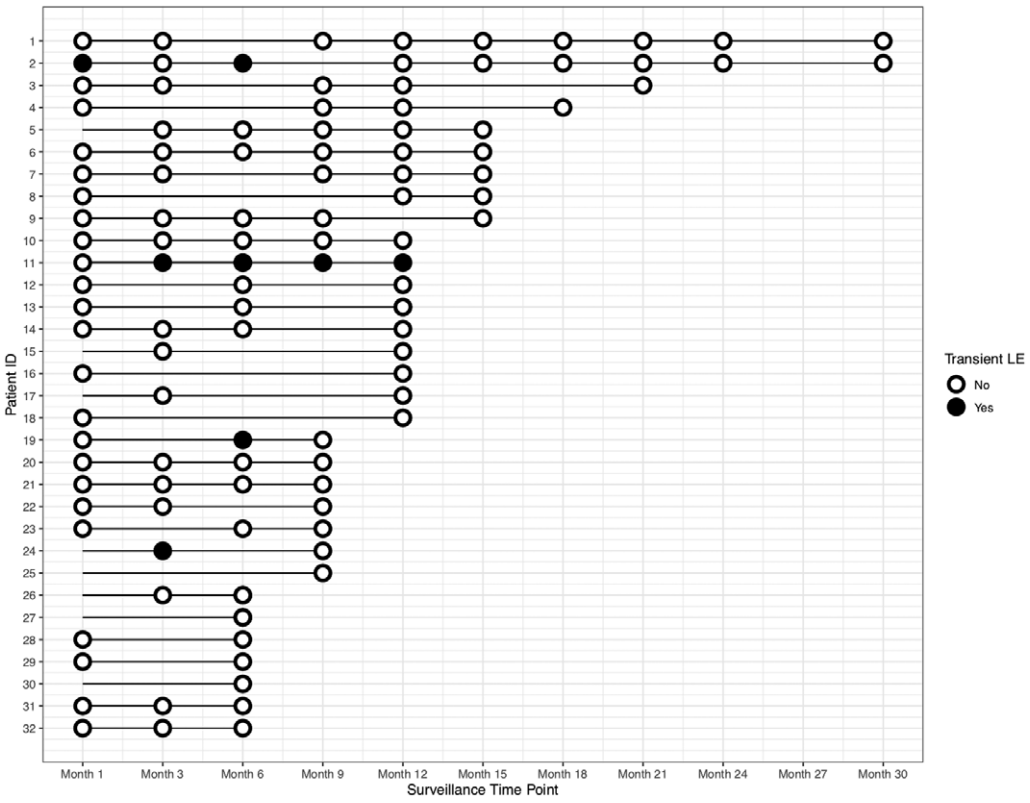

Fig. 2. Graphic of patients and follow-up during the study period. Four patients developed transient lymphedema during the study period, which resolved in three patients.

percent. Moreover, we found that quantitative measurements and symptoms consistent with transient lymphedema resolved within 6 months of initial onset in three of four patients (75 percent). In these patients, L-Dex was the first measurement to indicate lymphedema. Throughout the entire study period, immediate lymphatic reconstruction was attempted in 97 cases. Of those, 41 had a minimum of 6-month follow-up, and immediate lymphatic reconstruction was successful in 32 (78 percent) and aborted in nine. The rate of lymphedema in the aborted cohort was 22 percent. In the aborted cases, venous issues were the most common reasons for terminating the reconstruction. Finally, all four patients who developed transient lymphedema underwent axillary lymph node dissection and not axillary sampling.

Our most notable finding was the low rate of postoperative lymphedema in a patient population with multiple independent risk factors for its development. Our group's 2019 meta-analysis including over 3000 patients reported a 15.5 percent pooled incidence of lymphedema after axillary lymph node dissection.[7] This value increased to 26.5 percent with the addition of regional lymph node irradiation. In the same meta-analysis, the addition of a lymphatic microsurgical preventive healing approach or immediate lymphatic reconstruction decreased these rates to 4.6 percent and 10.6 percent, respectively. Furthermore, the seminal study by Boccardo et al. reported a lymphedema rate of 4.05 percent with 4-year follow-up.[12] These data align with our current institutional lymphedema rate of 3.1 percent. Most patients in our cohort were high risk, undergoing axillary lymph node dissection and adjuvant regional lymph node radiotherapy. Most patients also underwent chemotherapy in either the neoadjuvant (47 percent) or adjuvant setting (59 percent), with the majority undergoing taxane-based regimens. Although controversial, this risk factor has been independently associated with development of lymphedema in some studies.[30–32] The success of immediate lymphatic reconstruction in this high-risk population is promising and points to the need to determine appropriate patient selection criteria to broaden its application.

The rate of transient lymphedema observed in this cohort was 12.5 percent. This overall statistic is consistent with that reported by Boccardo et al., who found a 10.8 percent rate of transient lymphedema.[12] The majority of postoperative transient lymphedema diagnoses resolved completely within 3 to 6 months of onset. Transient lymphedema has been defined differently across studies. Increases in arm girth after surgery have resolved spontaneously in 33 to 51 percent of patients, particularly in those undergoing adjuvant treatment. In fact, Kilbreath et al. suggest that swelling observed in the first postoperative year not be defined as lymphedema unless it persists for at least 6 months.[33] This finding is the reason that we excluded all patients who did not have at least 6-month follow-up from analysis.

We recommend that patients undergoing similar regimens be closely surveilled for 4 years and that patients with transient lymphedema be defined as those that developed quantitative signs and symptoms within 6 months of their last oncologic treatment (i.e., surgery, radiation, or chemotherapy). Our prospective surveillance regimen for this high-risk patient cohort allows for the early detection of at-risk patients to facilitate early intervention.[24,34] For example, patients at our center who develop signs/symptoms and measurements consistent with lymphedema initiate a more intense regimen under certified lymphedema therapists that includes compression bandaging and heightened surveillance. In the future, standardizing the definition of transient lymphedema will not only facilitate the development of a shared, uniform vocabulary among lymphedema providers, but will also allow for better aggregation of data sets to identify particular risk factors associated with persistent lymphedema.

We found bioimpedance spectroscopy to be the most reliable assessment modality that detected changes in postoperative limb girth consistent with lymphedema. In fact, in all patients who developed transient lymphedema, L-Dex was the first measurement modality to demonstrate lymphedema. The concomitant presence of symptoms, most frequently heaviness, was reported by these patients. Bioimpedance spectroscopy has an increased sensitivity to detect subtle changes in extracellular fluid volume and has been championed for its utility in lymphedema surveillance programs.[25,35] Furthermore, this modality is operator-independent and more readably understandable, as set points are clear and findings do not necessitate interpretation of nondominant and dominant hands.[36] Other modalities including serial circumferential measurements would be more susceptible to interrater measurement variations. Nonetheless, we continue to use circumferential measurements and perometry for assessment to best capture any change in volume in the affected extremity that would be concerning for lymphedema development.

Interestingly, one commonality among patients who developed transient lymphedema is that they all underwent axillary lymph node dissection. No patients who underwent axillary sampling developed signs or symptoms consistent with lymphedema. The one anatomical area where residual nodal tissue was most often noted, thereby qualifying the case as axillary sampling, was along the axillary vein. Interestingly, although our prior report and other existing articles focus on the number of nodes removed during axillary intervention,[37–40] perhaps the extent of dissection is more clinically relevant. We do believe that, moving forward, researchers adapt a uniform definition for axillary lymph node dissection to best evaluate and distinguish outcomes (lymphedema) for this cohort compared to those who did not undergo full dissection. In breast cancer surgery, an optimal number of lymph nodes removed (i.e., >10) during axillary lymph node dissection has traditionally been proposed as a quality metric to confirm accurate staging.[41–44] However, it may be more important to consider the extent of axillary lymph node dissection as paramount.

Immediate lymphatic reconstruction was unable to be performed in nine of 41 patients (22 percent) who underwent immediate lymphatic reconstruction with at least 6-month follow-up. This was primarily secondary to venous issues, including inadequate vein length. Because immediate lymphatic reconstruction was first performed at our institution in 2016, we have noticed a decrease in rates of aborted procedures when a collaborative operative approach is used. Specifically, when able, both the breast and lymphatic surgeon are present for the axillary dissection. This provides the opportunity to facilitate dialogue between surgeons regarding preservation of appropriate and suitable veins.

There are noteworthy limitations to our study. Although our study has unique strengths, including multiple measurement modalities and a rigorous follow-up criterion for study inclusion, our study was not designed as a prospective randomized trial. Moreover, our lymphatic surgery database does not capture patients who exclusively underwent axillary lymph node dissection. Thus, we do not have a formal control group for comparison. We do acknowledge that our study was limited by the number of patients included in analysis. We restricted our eligibility criteria to include those who had sufficient follow-up and serial measurements for evaluation. Furthermore, our median follow-up time was 11.4 months. There were patients included in this cohort who met minimum follow-up criteria but did not present for surveillance measurements. Although we can contend that, in our experience, patients are less likely to present if asymptomatic, we are unable to comment on the entire cohort of patients, who theoretically met eligibility criteria. In light of this, we have modified our surveillance protocol to include direct outreach to patients to encourage adherence to appointments.

CONCLUSIONS

Data from our experience support that immediate lymphatic reconstruction demonstrates significant promise in reducing rates of postoperative lymphedema in a high-risk patient cohort with a minimum 6-month follow-up. We used multiple measurement modalities to evaluate patients at prescribed time intervals and found L-Dex to be the most sensitive. Our study fills a gap in the literature by our rigid inclusion criteria, use of multiple measurement modalities, and mode of data entry and analysis where the operating surgeon was blinded. We look forward to continuing our studies in a larger, more diverse patient cohort.

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