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Inflammatory Breast Cancer-Related Lymphedema

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Abstract

Background: Breast cancer-related lymphedema (BCRL) is a potentially debilitating outcome following breast cancer treatment. Much attention has been given to preventive and curative strategies for BCRL. Patients with inflammatory breast cancer (IBC) are at particularly increased risk, with approximately half of patients with IBC developing BCRL. We present preliminary outcome data for inflammatory breast cancer patients who undergo a multipronged preventative strategy with immediate lymphatic reconstruction at the time of axillary lymph node dissection, compressive arm sleeve wearing, and occupational therapy. We also present a literature review on IBC and BCRL. Methods: A retrospective review of patients with IBC undergoing immediate lymphatic reconstruction with lymphovenous bypass at the time of axillary lymph node dissection was performed. All patients were referred to occupational therapy for establishment of care and arm sleeve fitting and had at least 12 months of follow-up. The primary outcome of interest was the development of lymphedema. Additionally, a narrative review of the literature was performed. All English language studies pertaining to BCRL in patients with IBC were considered. Results: Eighteen patients with IBC underwent immediate lymphatic reconstruction with lymphovenous bypass between April 2022 and September 2023 by three reconstructive microsurgeons. Average follow-up time was 24.4 months (range 12.5–33.9 months). All patients underwent successful lymphovenous bypass of at least 1 channel. Of the 18 patients, 3 (16.6%) developed symptoms of lymphedema, such as heaviness of the posterior arm (2/3, 67%) or edema of the forearm (1/3, 33%). No patients developed >10% change in extremity volume. Conclusions: BCRL is a debilitating and common outcome following breast surgery in patients with IBC. Immediate reconstruction with lymphovenous bypass coupled with occupational therapy and compression sleeve management may reduce the risk for BCRL in this population.

Keywords: lymphedema; inflammatory breast cancer (IBC); immediate lymphatic reconstruction (ILR); lymphovenous bypass (LVB); LYMPHA; breast cancer-related lymphedema (BCRL); lymphatic microsurgical preventive healing approach

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1. Introduction

Inflammatory breast cancer (IBC) is a relatively rare but highly aggressive form of breast cancer that is associated with an increased risk for the development of breast cancer-related lymphedema (BCRL) [1]. As compared to 30% of all breast cancer survivors, studies have shown that lymphedema develops in upwards of 47–50.6% of patients with IBC [2–4]. Because of the profound impacts of lymphedema on patient quality of life, much attention has been given to improving lymphedema prevention and treatment [5]. Understanding

how to improve lymphedema prevention and treatment in patients with IBC is particularly warranted given their elevated risk for BCRL development.

Here, we review the literature regarding BCRL in patients with IBC. We also present preliminary data on the overall efficacy of immediate lymphatic reconstruction using lymphovenous bypass together with physical and occupational therapy and compressive sleeve therapy in reducing lymphedema in patients with inflammatory breast cancer after axillary lymph node dissection (ALND). To the best of our knowledge, no studies to date have specifically examined immediate lymphatic reconstruction in the inflammatory breast cancer patient population despite that fact this patient population is at the greatest risk for lymphedema development.

2. Results

Results are demonstrated in Table 1. Eighteen inflammatory breast cancer patients underwent immediate lymphatic reconstruction with lymphovenous bypass between April 2022 and September 2023 with three reconstructive microsurgeons. The average follow-up time was 24.4 months (range 12.5–33.9 months). All patients identified in this database underwent successful lymphovenous bypass of at least one channel. Of the 18 patients, 3 (16.6%) developed symptoms of lymphedema, including heaviness of the posterior arm (2/3, 67%) or edema of the forearm (1/3, 33%). No patients developed >10% change in extremity volume. The average age for all patients was 48.2 years (range 35–63 years). The average BMI for all patients was 29.4 (range 20.5–49.7). Of the 18 patients included in this study, 14 patients were identified as "White/Not Hispanic," 1 patient identified as "Black or African American/Not Hispanic," 1 patient identified as "Race not listed/Not Hispanic," 1 patient identified as "White/Hispanic," and 1 patient identified as "Asian, White/Not Hispanic." The average follow-up duration for all patients was 742.4 days (range 379–1030 days). The average radiation dose for all patients was 5864.0 cGy (range 5000–6040 cGy). The average number of LVB anastomoses for all patients was 1.1 (range 1–2). All patients received taxane-based chemotherapy as part of their oncologic treatment.

Table 1. Study characteristics of IBC patients after immediate lymphatic reconstruction.

Subject	Age (Years)	Body Mass Index	Race/Ethnicity	Follow-Up Duration (Days)	Radiation Dose (cGy)	Number of Anastomoses
Lymphedema						
6	38	40.8	White/Not Hispanic	637	Unknown	1
8	38	20.5	White/Not Hispanic	988	6040	1
12	41	21.3	White/Not Hispanic	931	Unknown	1
No Lymphedema						
1	52	21.8	White/Not Hispanic	771	6000	1
2	38	25.1	White/Not Hispanic	824	6000	1
3	44	28.5	Black or African American/Not Hispanic	615	Unknown	2
4	58	27.4	White/Not Hispanic	789	6000	1
5	62	27.3	White/Not Hispanic	664	Unknown	1
7	54	25.6	Race not listed/Not Hispanic	655	6000	1
9	43	23.6	White/Hispanic	1030	6000	1
10	56	26.9	White/Not Hispanic	752	5600	1
11	44	25.9	Asian, White/Not Hispanic	692	Unknown	1
13	35	49.7	White/Not Hispanic	569	Unknown	1
14	50	35.8	White/Not Hispanic	819	Unknown	1
15	56	33.9	White/Not Hispanic	868	6000	1
16	63	40.3	White/Not Hispanic	734	5000	1
17	43	28.9	White/Not Hispanic	379	Unknown	1
18	52	25.5	White/Not Hispanic	646	6000	1
Average	48.2 (35–63)	29.4 (20.5–49.7)	White/Not Hispanic	742.4 (379–1030)	5864.0 (5000–6040)	1.1 (1–2)

3. Methods

A retrospective review of patients with IBC undergoing immediate lymphatic reconstruction at the time of axillary lymph node dissection was performed. Inclusion criteria were: (1) diagnosis of inflammatory breast cancer, (2) immediate lymphatic reconstruction with lymphovenous bypass performed at the time of ALND, and (3) minimum of 12 months of follow-up after the procedure. All patients were referred to occupational therapy for establishment of care and arm sleeve fitting in the perioperative period. Data were obtained from chart review and included the number of LVB anastomoses performed, follow-up duration in days, chemotherapy type, total radiation dose, race/ethnicity, body mass index, age, and lymphedema diagnosis. Given the sample size, a descriptive analysis was performed.

Immediate lymphatic reconstruction procedures with lymphovenous bypass were performed by three reconstructive microsurgeons at a single institution (Division of Plastic Surgery, Brigham and Women's Hospital). A solution of ICG was injected into the first and third webspaces of the hand, volar wrist, and proximal arm in 0.1 mL aliquots to aid in visualization of the lymphatic vessels during lymphovenous bypass. Occupational therapy and compression sleeve fitting were implemented before surgery in many cases, or shortly thereafter based on insurance coverage of these services. Routine, postoperative surveillance was performed at 2 weeks, 1 month, 3 months, 6 months, 1 year, and 2 years. Arm volumes were recorded via traditional circumferential measurements and the LymphaTech system when available. A diagnosis of lymphedema was made based on the presence or symptoms of lymphedema including heaviness of the posterior arm and edema of the forearm. Patients did not need a limb volume measurement difference of >10% to receive a diagnosis of lymphedema.

A narrative review was performed in the literature to investigate the intersection of inflammatory breast cancer and lymphedema. PubMed was searched using the terms "lymphedema," "breast cancer," "inflammatory breast cancer," "breast cancer-related lymphedema," and "BCRL." All English-language studies were considered. This study was approved by the Brigham and Women's Hospital institutional review board (IRB) under protocol number 2025P003250.

4. Discussion and Literature Review

This study of eighteen patients with inflammatory breast cancer undergoing lymphovenous bypass at the time of axillary lymph node dissection demonstrated an incidence of lymphedema of 16.6% at an average follow up of two years post-surgery. Prior reported incidence of lymphedema at our own institution is higher at 47% for patients with inflammatory breast cancer [3]. The systematic, multipronged approach of preventative care with lymphovenous bypass, occupational therapy, and compression sleeve wearing may reduce the risk of lymphedema in a population with exceptional lymphedema risk. Here, we further contextualize these preliminary results with a literature review of IBC and BCRL.

4.1. Inflammatory Breast Cancer

Inflammatory breast cancer (IBC) accounts for 2–4% of all breast cancer patients [6]. According to current American Joint Committee on Cancer (AJCC) guidelines, a clinical diagnosis of inflammatory breast cancer is appropriate when all of the following criteria are met: (1) rapid onset of breast erythema, edema and/or peau d'orange, and/or warm breast, with or without an underlying palpable mass, (2) duration of history no more than six months, (3) erythema occupying at least one-third of the breast, (4) pathologic confirmation of invasive carcinoma [7]. Many of the characteristic physical exam findings of inflammatory breast cancer are rarely seen in other types of breast cancer including redness,

warmth, and induration of the skin that can often resemble other inflammatory processes such as allergic reaction or mastitis. The classic description of "peau d'orange" refers to the gross appearance of the breast skin that can look like an orange peel or focal lymphedema of the breast. Histologic findings commonly show evidence of tumor cell emboli within the dermal lymphatics which may reduce the local functionality of lymphatic system resulting in accumulation of lymphatic fluid within the tissue [8]. Together, these gross and microscopic findings seem to suggest an inherent connection between inflammatory breast cancer and the lymphatic system that could contribute to the increased incidence of lymphedema in patients with inflammatory breast cancer.

4.2. Breast Cancer-Related Lymphedema and IBC

Breast cancer-related lymphedema is a chronic condition of lymphatic insufficiency characterized by upper extremity swelling that can occur in patients with breast cancer. Major risk factors for developing lymphedema include patient characteristics such as obesity and race/ethnicity [9,10]. Additionally, many of the components related to the treatment of breast cancer including axillary lymph node dissection (ALND), radiation therapy to the breast and/or axilla, and taxane-based chemotherapy further increase the risk for lymphedema development [9,10].

The presence of one or more of these risk factors can have a dramatic impact the overall risk of lymphedema for an individual patient. Patients with breast cancer subtypes that are not categorized as inflammatory who undergo breast-conserving surgery with sentinel lymph node biopsy (SLNB) have the lowest risk of 5.6% [9]. The likelihood for lymphedema development increases to approximately 20% for patients with breast cancer that require mastectomy with axillary lymph node dissection (ALND) [9,10]. By far, the group of patients that carry the greatest risk for developing upper extremity lymphedema are those who are diagnosed with inflammatory breast cancer. Recent studies have shown that lymphedema develops in upwards of 47–50.6% of patients with inflammatory breast cancer [2,3].

Some suggested explanations attempting to explain the higher incidence of lymphedema in patients with inflammatory breast cancer primarily focus on the oncologic treatment itself, which includes many of the risk factors associated with lymphedema development. Due to the aggressive nature of inflammatory breast cancer, the oncologic approach to treatment often necessitates an equally aggressive strategy. Currently, the most widely used treatment for inflammatory breast cancer is trimodal therapy which consists of a modified radical mastectomy (MRM) with axillary lymph node dissection, post-mastectomy radiation therapy, and taxane-based chemotherapy [2,11]. Patients with a non-inflammatory breast cancer subtype are frequently eligible to undergo breast-conserving surgery (i.e., lumpectomy) and may only require a select few of the components of trimodal therapy as part of their individualized oncologic treatment plan. Conversely, patients with inflammatory breast cancer typically require a modified radical mastectomy wherein significantly more skin is removed during the operation. Because lymphatic channels are present in the dermis of the skin, their removal also may contribute to the development of lymphedema.

Furthermore, the dosage of radiation is often greater for patients with inflammatory breast cancer than other types of breast cancer which can promote increased fibrosis and destruction of the dermal lymphatics. IBC patients often undergo a neoadjuvant chemotherapy including a taxane-based chemotherapy agent, known to increase the risk of lymphedema. Given these observations, the degree of mastectomy skin removal and trimodal therapy likely contribute to the increased risk of lymphedema seen in these patients due to the increased exposure to individual risk factors [2].

4.3. BCRL Prevention and Treatment

Due to the recalcitrant nature of lymphedema to treatment, the primary focus is on prevention. The most widely used method for prevention and treatment of breast cancer-related lymphedema is complex decongestive therapy (CDT) which uses a combination of manual lymphatic drainage, compression sleeves, exercise, and skin care to improve lymphatic drainage of the affected extremity. While CDT can reduce symptoms in many patients, it requires long-term adherence that patients may find burdensome and is most effective during early-stage disease [12]. Accordingly, a recent systematic review of quality-of-life outcomes by Fish et al. found that CDT was associated with mixed patient-reported outcomes [13].

Recently, preventative surgical strategies such as immediate lymphatic reconstruction with lymphovenous bypass (i.e., ILR, LVB, LYMPHA) have become increasingly popular as a preventative option to help reduce the risk of lymphedema in high-risk patient populations, such as those with inflammatory breast cancer. In high-risk groups, immediate lymphatic reconstruction is performed at the time of axillary lymph node dissection. Lymphovenous bypass involves performing a series of lymphovenous anastomoses on freshly transected lymphatic vessels to redirect the flow of lymphatic fluid back into the venous system. Preliminary results from a randomized controlled trial from Memorial Sloan Kettering that included a total of 174 patients found that patients who underwent immediate lymphatic reconstruction had an incidence of lymphedema of just 9.5% compared to 32% in the control group after 12 to 24 months of follow-up [14]. To the best of our knowledge, our preliminary data is among the first to report on lymphovenous bypass in the IBC patient population.

There are several notable challenges to prophylactic microsurgical lymphedema treatment in patients undergoing surgery for breast cancer, particularly those with IBC. First, lymphovenous bypass requires microsurgeons with specialized training which may not be available at all centers. In fact, the majority of breast surgeons (85%) report not using immediate lymphatic reconstruction in their routine practice [15]. Another contributing factor to the lack of prophylactic microsurgical lymphedema treatment is the increased cost of care; however, due largely to the debilitating costs of lymphedema, in silico studies have reassuringly shown ILR to be cost-effective [16]. Moreover, referral patterns between breast surgeons and the plastic surgeons who commonly due microsurgical lymphedema procedures may not be well-established. While patients with IBC almost always undergo ALND, patients with IBC do not commonly receive immediate breast reconstruction as compared to patients without IBC. As such, future efforts to augment microsurgical lymphedema procedures must take into account the nuances for referral patterns between patient populations.

4.4. Limitations

There were several limitations to the present study. First, our sample size of 18 patients does not allow for robust comparative statistics. As such, future studies will be needed with larger sample sizes to determine the benefit of lymphovenous bypass at that time of ALND in patients with IBC. Despite the study being conducted at a major cancer center, given the more rare presentation of IBC, this will require time to allow for sufficient patient accrual. Second, the average follow-up time in our study was 24.4 months with a minimum follow-up time of 12 months. The greatest risk for developing BCRL is within the first two years of surgery, but longer term follow-up may allow for capturing more delayed onset lymphedema [17]. Third, all patients received multimodal therapy for lymphedema prevention and our study did not control for all known risk factors for lymphedema development, so outcomes may be confounded by unmeasured variables.

5. Conclusions

Patients with IBC undergoing a targeted approach of lymphedema prevention with immediate lymphatic reconstruction using lymphovenous bypass, compressive arm sleeve wearing, and occupational therapy demonstrated reduced incidence of lymphedema. Future longer term studies with more robust sample sizes will be needed to confirm the benefit of treatment in the IBC patient population.

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