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ORIGINAL LABORATORY INVESTIGATION

Oncologic safety of axillary lymph node dissection with immediate lymphatic reconstruction

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Abstract

Purpose Immediate lymphatic reconstruction (ILR) at the time of axillary lymph node dissection (ALND) can reduce the incidence of lymphedema in patients with breast cancer. The oncologic safety of ILR is unknown and has not been reported. The purpose of this study was to evaluate if ILR is associated with increased breast cancer recurrence rates.

Methods Patients with breast cancer who underwent ALND with ILR from September 2016 to December 2020 were identified from a prospective institutional database. Patient demographics, tumor characteristics, and operative details were recorded. Follow-up included the development of local recurrence as well as distant metastasis. Oncologic outcomes were analyzed.

Results A total of 137 patients underwent ALND with ILR. At cancer presentation, 122 patients (89%) had clinically node positive primary breast cancer, 10 patients (7.3%) had recurrent breast cancer involving the axillary lymph nodes, 3 patients (2.2%) had recurrent breast cancer involving both the breast and axillary nodes, and 2 patients (1.5%) presented with axillary disease/occult breast cancer. For surgical management, 103 patients (75.2%) underwent a mastectomy, 22 patients (16%) underwent lumpectomy and 12 patients (8.8%) had axillary surgery only. The ALND procedure, yielded a median of 15 lymph nodes pathologically identified (range 3–41).

At a median follow-up of 32.9 months (range 6–63 months), 17 patients (12.4%) developed a local (n = 1) or distant recurrence (n = 16), however, no axillary recurrences were identified.

Conclusion Immediate lymphatic reconstruction in patients with breast cancer undergoing ALND is not associated with short term axillary recurrence and appears oncologically safe.

Keywords Lymphovenous bypass · Immediate lymphatic reconstruction · Axillary lymph node dissection · LYMPHA · Lymphedema

Abbreviations

ILR Immediate lymphatic reconstruction
ALND Axillary lymph node dissection
SLNB Sentinel lymph node biopsy
LVB Lymphovenous bypass
ARM Axillary reverse mapping
LYMPHA Lymphatic microsurgical preventative healing approach
pCR Pathologic complete response
NAC Neoadjuvant chemotherapy
RCB Residual cancer burden

Introduction

Lymphedema is a potentially distressing problem for patients after surgical intervention for breast cancer. Rates of lymphedema after sentinel lymph node biopsy (SLNB) are approximately 5%, while rates after axillary lymph node dissection (ALND) are up to four times higher [1–3]. Lymphedema treatment in the past was largely palliative, with most modalities focusing on reducing progression of...
disease, preventing complications, restoring limb function, and relief of patient’s symptoms [4, 5]. Surgical treatment for lymphedema was first described in the 1960s, and now includes both ablative and physiologic operations [5]. Only recently has there been a shift from surgical treatment of lymphedema to preventative surgical procedures.

Immediate lymphatic reconstruction (ILR) for lymphedema prevention consists of both axillary reverse mapping (ARM) to identify arm lymphatics combined with ILR to re-anastomose the arm lymphatics to axillary vein branches. This can restore continuity of lymphatic flow, by diverting it to the venous system and thereby reduce the incidence of lymphedema [6]. Immediate lymphatic reconstruction in the axillary region, was first described by Boccardo et al. in 2008 with Lymphatic Microsurgical Preventative Healing Approach (LYMPHA) [7]. Their group reported an overall lymphedema rate of 4.05% following ILR, similar to what is seen after SLNB [8]. Other studies have also shown decreased rates of lymphedema when ILR was used in the prophylactic setting [9–12]. A previous study at our institution reported a lymphedema rate of 4.6% after ILR [9]. Since the introduction of the LYMPHA procedure, other similar preventative surgical procedures have been described, including lymphovenous bypass (LVB). This article will refer to these various procedures as ILR, as a recent publication describes this terminology as being a more succinct and accurate term [13].

While there are promising results with ILR for preventing lymphedema, it is unknown whether this procedure is safe from an oncologic perspective. In the past, some have raised concern about the oncologic safety of the ARM procedure [14–16]. While this exact concern has not been specifically raised for ILR, it remains an important topic to address given the novelty of the procedure. There have been a number of studies reporting on the safety of the ARM procedure [17–19], but it remains unclear if ILR has any effect on breast cancer recurrence rates. The basis for concern over the oncologic safety of the ILR procedure may stem from the fact that the preserved lymphatics are anastomosed to nearby veins, re-establishing lymphatic flow. The purpose of this study was to evaluate the oncologic safety of ILR in patients with breast cancer.

Materials and methods

This study was approved by our institutional review board. An analysis was performed of a prospectively maintained database of patients with breast cancer who underwent ALND with ILR at our institution from September 2016 to December 2020. Patients selected for ILR included those with clinically node positive disease where an ALND was planned pre-operatively, and those who underwent a SLNB where pathologic analysis showed metastases and ALND with ILR was then performed. Patient demographics and tumor characteristics were recorded. Treatment data regarding neoadjuvant and adjuvant systemic therapy and radiation, and rates of complete pathological response (pCR) after neoadjuvant chemotherapy (NAC) were recorded. Residual cancer burden (RCB) scores were calculated for those patients treated with NAC and compared for recurrence risk.

Operative details including type of surgery for the primary tumor, number of lymph nodes pathologically identified and number of lymphatic vessels anastomosed were recorded. The standard ARM procedure at our institution included injection of ~3 mL of isosulfan blue into the subdermal plane of the upper, inner arm. The ILR at our institution was performed by mobilizing transected, blue lymphatics under microscopic visualization and anastomosing these to nearby veins with an 11-0 or 12-0 nylon suture. This is done via either an end-to-end microanastomosis for an appropriately size-matched lymphatic channel and vein, or via an intussusception technique for significant size discrepancy or multiple transected lymphatic channels adjacent to a vein [20]. Follow-up data was documented including the development of local recurrence in the breast and chest wall, regional recurrence, as well as presence of distant metastasis. Local recurrence was defined as recurrence within the breast or chest wall, regional recurrence was defined as recurrence within the axilla, and distant recurrence was defined as any recurrence outside of the breast or axilla.

At our institution, we selected patients for immediate lymphatic reconstruction in two different clinical scenarios.

1. Patients with planned ALND (e.g., inflammatory breast cancer, poor nodal response to NAC) were referred for a multidisciplinary discussion preoperatively, to include a plastic surgeon, and consented for ILR and the procedure was scheduled concomitantly with the ALND.
2. Patients with clinically node positive disease who underwent NAC were also referred for a multidisciplinary discussion preoperatively with a plastic surgeon and consented for possible ALND and ILR. Sentinel lymph node biopsy was performed with frozen section analysis of nodes intra-operatively and the ALND and ILR procedures were performed if frozen section revealed positive lymph nodes. Descriptive analysis was then performed to determine rates of local, regional and distant recurrence. Data was tabulated and presented as frequencies and percentages to summarize categorical variables. Univariate analysis was performed to compare characteristics between those who developed recurrence (n = 17) and those that did not (n = 120).
Results

Study population

Between 2016 and 2020, a total of 137 patients with breast cancer underwent ALND with ILR. Of the 137 patients, one was male and 136 were female. A total of 138 ILR procedures were performed during the four-year study period. One patient, with contralateral axillary metastases, underwent a bilateral ALND with ILR. Patient demographics and tumor characteristics are shown in Table 1.

Tumor characteristics

At cancer presentation, 122 patients (89%) had clinically node positive primary breast cancer and 3 patients (2.2%) had recurrent breast cancer involving both the breast and axillary nodes. Of those that were classified as Tx/T0, 10 patients (7.3%) had recurrent breast cancer involving the axillary lymph nodes and 2 patients (1.5%) presented with axillary disease only/occult breast cancer.

The majority (83/137, 60.6%) of patients in our cohort had hormone receptor-positive/HER2-negative tumors. Of the 101 patients with a hormone receptor-positive tumor, 92.1% (93/101) received endocrine therapy. Adjuvant radiation was administered in 92.0% (126/137) of patients. Of the 11 patients who did not receive adjuvant radiation therapy, six patients declined recommended treatment, three elected not to proceed after a discussion of the risks and benefits after having a favorable response to NAC, one patient did not receive radiation as per a multidisciplinary tumor board recommendation, and one patient was enrolled in a clinical trial and randomized to not receive radiation therapy. Chemotherapy was administered in 91.2% (125/137) of patients, with 69.3% (95/137) receiving it in the neoadjuvant setting. Neoadjuvant endocrine therapy was administered in 2.2% of patients (3/137). Nine patients did not receive any systemic therapy (6.6%). After NAC, 18.9% (18/95) had a pCR (Table 2).

Surgical procedure

For surgical management of the breast, 103 patients (75.2%) underwent a mastectomy, 22 patients (16.1%) underwent lumpectomy and 12 patients (8.8%) had axillary surgery only (2 unknown breast primary, 10 isolated axillary recurrence). Seventy-three patients (53.3%) underwent reconstruction (either delayed or immediate) with tissue expander placement, direct to implant or autologous reconstruction. The ALND procedure yielded a median of 15 lymph nodes pathologically identified (range 3–41), with an average of

Table 1 Clinical and tumor characteristics of patients undergoing axillary lymph node dissection (ALND) and immediate lymphatic reconstruction (ILR) at our institution between 2016 and 2020

| Characteristic                              | Number of patients (%) |
|--------------------------------------------|------------------------|
| Average age (range)                        | 52 (29–78)             |
| Gender                                     |                        |
| Female                                     | 136 (99.3%)            |
| Male                                       | 1 (0.7%)               |
| Race                                       |                        |
| White                                      | 124 (90.5%)            |
| Black or African American                  | 7 (5.1%)               |
| Asian                                      | 3 (2.2%)               |
| Multiracial                                | 3 (2.2%)               |
| Clinical tumor size category               |                        |
| Tx/T0                                      | 12 (8.8%)              |
| T1                                         | 29 (21.2%)             |
| T2                                         | 56 (40.9%)             |
| T3                                         | 27 (19.7%)             |
| T4                                         | 13 (9.5%)              |
| Clinical nodal category                    |                        |
| N0                                         | 3 (2.2%)               |
| N1                                         | 93 (67.9%)             |
| N2                                         | 30 (21.9%)             |
| N3                                         | 11 (8.0%)              |
| Pathologic tumor size category             |                        |
| Nx                                         | 12 (8.8%)              |
| T0                                         | 22 (16.1%)             |
| Tis                                        | 7 (5.1%)               |
| T1                                         | 54 (39.4%)             |
| T2                                         | 33 (24.1%)             |
| T3                                         | 8 (5.8%)               |
| T4                                         | 1 (0.7%)               |
| Pathologic nodal category                  |                        |
| N0                                         | 37 (27.0%)             |
| N1                                         | 62 (45.2%)             |
| N2                                         | 27 (19.7%)             |
| N3                                         | 11 (8.0%)              |
| Histology                                  |                        |
| Ductal                                     | 108 (78.8%)            |
| Lobular                                    | 17 (12.4%)             |
| Mixed                                      | 11 (8.0%)              |
| Other                                      | 1 (0.7%)               |
| Hormone receptor status                    |                        |
| Triple negative                            | 19 (13.9%)             |
| ER/PR−HER2+                                | 16 (11.7%)             |
| ER/PR+HER2+                                | 19 (13.9%)             |
| ER/PR+HER2−                                | 83 (60.6%)             |
| Systemic therapy                           |                        |
| Neoadjuvant chemotherapy                   | 95 (69.3%)             |
| Adjuvant chemotherapy                      | 30 (21.9%)             |
3.5 positive (range 0–22). The number of lymphatic anastomoses performed were 1 in 48.6% (67/137), 2 in 31.2% (43/137), 3 in 12.3% (17/137), 4 in 7.2% (10/137) and 5 in 0.7% (1/137).

Follow-up

At a median follow-up of 32.9 months (range 6–63 months) no axillary recurrences were identified in the cohort (Fig. 1). The development of any recurrence (local, regional, or distant) was logged over time (Fig. 2). One patient developed a local recurrence in the breast and axillary skin. This patient had declined all systemic therapy and adjuvant radiation recommendations. Sixteen patients developed distant metastases. Of these, 56.3% (n = 9) were hormone receptor positive and HER2-negative, 25% (n = 4) were HER2-positive and 18.8% (n = 3) were triple negative. Univariate analysis between the group of patients that developed a recurrence and those that did not, revealed no significant difference between the two groups. Of the 17 patients in the cohort who developed a recurrence, the median RCB score was III, with a median RCB score of II in the 120 patients who did not develop a recurrence (p = 0.677).

Table 1 (continued)

| Characteristic               | Number of patients (%) |
|------------------------------|------------------------|
| Neoadjuvant endocrine therapy| 3 (2.2%)               |
| None                         | 9 (6.6%)               |
| Radiation                    |                        |
| Adjuvant                     | 126 (92.0%)            |
| None                         | 11 (8.0%)              |
| Surgical procedure           |                        |
| Mastectomy                   | 103 (75.2%)            |
| Lumpectomy                   | 22 (16.0%)             |
| ALND only                    | 12 (8.8%)              |

Table 2 Hormone receptor status and residual cancer burden (RCB) scores those patients who received neoadjuvant chemotherapy (NAC)

| Hormone receptor status | Number of patients (%) | Residual cancer burden (RCB) scores | Number of patients (%) |
|-------------------------|------------------------|--------------------------------------|------------------------|
|                         | N=95                   |                                      | N=95                   |
| Triple negative         | 18 (18.9%)             | 0                                    | 4 (22.2%)              |
|                         |                        | 1                                    | 4 (22.2%)              |
|                         |                        | 2                                    | 7 (38.9%)              |
|                         |                        | 3                                    | 3 (16.7%)              |
|                         |                        | n/a                                  | 0 (0%)                 |
| ER/PR− HER2+            | 15 (15.8%)             | 0                                    | 9 (60.0%)              |
|                         |                        | 1                                    | 0 (0%)                 |
|                         |                        | 2                                    | 1 (6.7%)               |
|                         |                        | 3                                    | 2 (13.3%)              |
|                         |                        | n/a                                  | 3 (20.0%)              |
| ER/PR+ HER2+            | 17 (17.9%)             | 0                                    | 4 (23.5%)              |
|                         |                        | 1                                    | 3 (17.6%)              |
|                         |                        | 2                                    | 5 (29.4%)              |
|                         |                        | 3                                    | 3 (17.6%)              |
|                         |                        | n/a                                  | 2 (11.8%)              |
| ER/PR+ HER2−            | 45 (47.4%)             | 0                                    | 1 (2.2%)               |
|                         |                        | 1                                    | 5 (11.1%)              |
|                         |                        | 2                                    | 10 (22.2%)             |
|                         |                        | 3                                    | 27 (60%)               |
|                         |                        | n/a                                  | 2 (4.4%)               |
**Fig. 1** Follow-up time (in months) since axillary lymph node dissection (ALND) and immediate lymphatic reconstruction (ILR) was performed.

**Fig. 2** Development of all recurrences (local, regional and distant) over time.
Discussion

Numerous studies have reported on the success of lymphedema prevention surgery with ILR, however, the oncologic safety of these procedures has not been previously reported [7–12]. This study is the first to evaluate the oncologic safety of ALND with ILR in patients with breast cancer. No axillary recurrences were reported at short-term follow-up, one patient developed a local recurrence in the breast and axillary skin, and the rate of distant metastasis in the cohort was 11.7%. There was no significant correlation noted between RCB score or receptor status and risk of breast cancer recurrence at short-term follow up in this cohort.

Oncologic outcomes in patients undergoing ARM, without concomitant ILR, have been previously reported, with conflicting results [14, 18, 21, 22]. In a study by Ochoa et al. of 360 patients with clinical N1–N3 disease who underwent SLNB and/or ALND, blue lymphatics were preserved in 79.2% of patients in which they were identified, and this group developed one axillary recurrence at 17 months follow-up [18]. This study demonstrated that nodes with blue dye alone are rarely positive, and concluded that preserving ARM nodes is oncologically safe [18]. Bonetti et al. similarly reported that in a group of 131 patients with clinically negative axillae, all resected nodes that were either blue only (representing drainage of the arm), or blue and hot (representing common drainage of both the arm and breast), were negative for metastases [21]. However, not all of the existing literature has deemed ARM to be oncologically safe in patients with known node-positive disease, as many of the early studies included patients with clinically node-negative axillae [14, 21, 23]. Nos et al. for example, reported that in a cohort of 23 node-positive patients with breast cancer, 14% had metastases to the blue ARM nodes [22], questioning the safety of leaving these nodes in situ. Bedrosian et al. also questioned the oncologic safety of preserving ARM nodes in patients with documented axillary metastases as they found in their population of 30 patients who received NAC or endocrine therapy, the ARM node was found to contain metastases in close to 1 in 5 patients [14]. While ARM alone was not performed in our study, we sought to confirm the safety of ILR due to preservation of lymphatics and veins not traditionally preserved in a standard ALND in an axilla with nodal disease. Our study population consisted of a majority of patients who were clinically node positive. The three patients who were not clinically node positive, were found to have a positive node after SLNB, which prompted planned completion ALND and ILR. It is standard practice at our institution to remove all level 1 and 2 lymph nodes in an ALND, including any blue ARM nodes in the axillary field, as we are then able to perform ILR using the divided lymphatics from these ARM nodes. Regardless of extent of disease burden in the axilla when ILR was performed, no axillary recurrences were identified at short-term follow-up.

Axillary recurrence has been shown to occur in as many as 5–15% of patients with breast cancer after ALND, with more recent studies showing this to be closer to 2% patients [24, 25]. Most of these recurrences occur within 24–48 months from the index surgical procedure [26–28]. The most important factors predicting axillary recurrence include ER-negative tumor status, large tumor size, high histologic grade and younger patient age [25]. While we found no isolated axillary recurrences in our cohort, this does fit with recent literature showing a very low rate of axillary recurrence overall after ALND [24, 25]. This low rate of recurrence after ALND is likely influenced by the receipt of adjuvant systemic therapy as well as radiation therapy, which the majority of our cohort received. Risk of recurrence at follow-up is also influenced by tumor biology, with triple negative and HER2-positive recurrences occurring much earlier than hormone receptor positive recurrences [29]. The majority of patients in our cohort were hormone receptor positive, and may develop a recurrence later in life that has not been captured in our average follow-up period of 32.9 months. However, in those who developed a recurrence, triple-negative tumors and HER-2 positive tumors constituted 41.2% and the median RCB score was III. These two factors contribute to early recurrence risk, and in our cohort presented itself as distant recurrence in the majority of patients.

One potential concern with ILR may be potential risk for increased rates of metastatic spread, given the re-anastomosing of lymphatics to nearby veins. The rate of distant metastasis in our study population was 11.7%, which is consistent with rates of metastases in recent literature (10–41%) [30]. Rates of distant metastases very greatly based on tumor size and nodal status [30]. A study by Colleoni et al. addressed the patterns of recurrence in patients with breast cancer after long-term follow-up [31]. They found that at a median follow-up of 24.2 years, 40.7% patients developed a distant recurrence, with higher rates in later years found in the ER-positive cohort [31]. Colzani et al. evaluated the time-dependent development of distant metastasis in 9514 women with breast cancer, and found that 10.4% developed distant metastasis after a mean follow-up of 5.7 years [32]. Rates of distant metastasis were found to be influenced by age, lymph node status, estrogen receptor status, tumor size and receipt of systemic therapy [32]. The majority of patients in our cohort were lymph node-positive undergoing primary surgery or had residual disease in the axilla after treatment with NAC, which is consistent with an elevated risk of distant recurrence.
One of the main limitations of our study is a short follow-up time, with further studies needed to determine if these results remain true after a longer period of follow-up. Despite this, this is the first known study to address the oncologic safety of ILR. Additionally, while our reported rate of distant recurrence is consistent with the reported literature, our cohort includes patients with likely more aggressive disease features. Longer follow-up and comparison with a matched cohort comparing recurrence rates over a longer time period can help address this. Furthermore, this study focuses specifically on the oncologic outcomes after ALND and ILR and does not report specifically on rates of lymphedema. Previous studies at our institution have addressed this where the rates of lymphedema after ALND and ILR at our institution have ranged from 4.6 to 5.7% at short-term follow-up, with current studies ongoing to address rates after a longer follow-up period [9, 20].

**Conclusion**

After a review of all immediate ILR procedures performed following ALND in patients with breast cancer at our institution during a 5-year period, no axillary recurrences were found in short-term follow-up and the rate of distant recurrence was 11.7%. Immediate lymphatic reconstruction in patients with breast cancer undergoing ALND is not associated with short-term axillary recurrence and appears oncologically safe.

**Author contributions** All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by HG, AE, SV, CC and ZAH. The first draft of the manuscript was written by HG and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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**Data availability** The datasets generated during and/or analyzed during the current study are not publicly available due to the personal health information contained within. The data are available from the corresponding author upon request.

**Declarations**

**Conflict of interest** Author Stephanie Valente, DO is a speaker/consultant/advisory board member for Impedimed, Pacira, AxxoGen, Merit. The remaining authors have no conflicts of interest. The corresponding author has signed the disclosure form and attached it with the manuscript stating there is no conflict of interest. Separate conflict of interest forms from remaining authors can be uploaded if needed.

**Ethical approval** This study received IRB approval.

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