Reduced Incidence of Breast Cancer–related Lymphedema following Mastectomy and Breast Reconstruction versus Mastectomy Alone

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Level of Evidence for Therapeutic Study: II
Abstract

**Background:** As breast cancer survivorship has increased, so has an awareness of the morbidities associated with its treatment. The incidence of breast cancer–related lymphedema (BCRL) has been reported to be 8-30% in all breast cancer survivors. To determine whether breast cancer reconstruction has an impact on the incidence of BCRL, we compared the incidences of BCRL in patients who underwent mastectomy with reconstruction versus mastectomy alone.

**Methods:** All patients who underwent mastectomy, with or without immediate breast reconstruction, between 2001 and 2006 were identified through a search of prospective institutional databases. To reduce variation due to known predictive factors, the individuals were cross-matched for age, axillary intervention, and postoperative axillary radiation. BCRL incidence was based on the presence of arm edema that lasted more than 6 months and was documented on clinical examination.

**Results:** Of the 574 cross-matched patients included in the study, 78 (6.8%) developed lymphedema: 21 in patients with reconstructed breasts and 57 in patients with unreconstructed breasts. Patients who did not undergo breast reconstruction were significantly more likely to develop BCRL (9.9% vs. 3.7%, p<0.001). Postoperative axillary radiation therapy (p<0.001), 1 or more positive lymph node (p=0.010), and body mass index greater than or equal to 25 (p=0.021) were also associated with an increased incidence of BCRL. Breast reconstructive patients developed BCRL significantly later than non-reconstructed patients (p<0.001).

**Conclusions:** Patients who undergo breast reconstruction have a lower incidence of BCRL and a delay in onset of BCRL compared to patients who undergo mastectomy alone.
Introduction

Breast cancer remains the most common cancer among women. Early detection and treatment is decreasing cancer-associated mortality but increasing post-treatment morbidity. Over 80% of newly diagnosed breast cancer patients are predicted to survive five years.[1] As breast cancer survivorship increases, clinicians are gaining awareness of the associated morbidities that impact daily life and learning to predict and prevent these morbidities, which is vital to improving the quality of life of breast cancer survivors.[2, 3] Breast cancer–related lymphedema (BCRL) is one such morbidity that affects an estimated 6-30% of survivors.[4, 5]

BCRL has been linked to body mass index (BMI), mastectomy, axillary dissection, axillary radiation, and lymph node status.[4, 6-13] Most studies have focused on patients who undergo mastectomy for primary cancer treatment.[14] The goal of recent studies has been to assess the extent of axillary damage and compare rates of lymphedema with or without radiation therapy, sentinel lymph node biopsy (SLNB), and/or axillary lymph node dissection (ALND).[11, 12, 15-17] As cancer treatments increase survival, patients are pursuing breast reconstruction and becoming more aware of their available reconstructive options. It is possible that reconstructive surgical interventions in the mastectomy or axillary field could alter the risk of developing BCRL. Studies addressing this concern have found no increased incidence of lymphedema due to reconstructive surgery, and limited retrospective data indicate that delayed autologous breast reconstruction may reduce the severity of existing lymphedema.[18, 19] However, no control groups of mastectomy-only patients were included in those studies.

The primary goal of this study was to compare the incidences of BCRL in patients who undergo mastectomy and reconstruction versus those treated with mastectomy alone and to address the question of whether immediate breast reconstruction has a beneficial effect in reducing the incidence of lymphedema. Our secondary goal was to identify the independent variables affecting the incidence and time to development of BCRL when axillary interventions
are cross-matched and controlled. To the best of our knowledge, this is the first study to do a direct cohort comparison of BCRL incidence in patients who did and did not undergo reconstruction after mastectomy.

**Methods**

Following internal institutional review board approval, two independent, secure, and prospectively maintained departmental databases were searched to identify all consecutive female breast cancer patients who underwent therapeutic mastectomy over a 6-year period from January 1, 2001 until December 31, 2006 at The University of Texas MD Anderson Cancer Center. The Department of Plastic Surgery database identified patients who underwent mastectomy and reconstruction, and the Department of Surgical Oncology database identified patients who underwent mastectomy alone. These databases were cross-referenced to remove any duplication of individuals. Patients were excluded if they had missing data for pertinent variables, lymphedema (LE) prior to mastectomy or at presentation, edema that occurred within 2 weeks of surgery and resolved within 30 days, or a history of preoperative radiation therapy (RT) or were lost to follow-up within 6 months of surgery. To reduce variation of potential factors inducing bias between the two populations from the queried databases, the two data groups or cohorts were cross-matched for age (+/- 5 years), postoperative RT, and SLND +/- ALND to obtain our study population for evaluation of BCRL incidence. Information regarding patient demographics, axillary intervention, and oncologic treatments was obtained from the prospectively maintained databases and validated by individual patient medical record review by a postdoctoral research fellow. The following patient characteristics were recorded: age, BMI, race, comorbidities, oncologic neoadjuvant and adjuvant treatments, type of axillary intervention and number of lymph nodes removed. All patients had at least 3 years of follow-up to capture the development of BCRL in the majority of the patients. BCRL was diagnosed using subjective
data that were documented in the prospective database. All cases of BCRL were reviewed and confirmed on the basis of objective data (e.g., arm circumference measurements) that were documented by designated health care providers in the medical record. Axillary interventions were classified as sentinel lymph node dissection (SLND), axillary lymph node dissection (ALND), ALND with or without SLND, or postoperative axillary RT.

Means and standard deviations were used to summarize continuous variables. Frequencies and proportions were used to present the categorical clinical characteristics. A correlated logistic regression model was used to test associations between incidence of BCRL and demographic or clinical characteristics. SAS GENMOD procedures were used to calculate the odds ratios (ORs). Time to lymphedema was defined as the time interval from mastectomy date to BCRL diagnosis date or last follow-up date, whichever occurred first. Patients who had not developed BCRL at the time of last follow-up were censored in the analyses. The incidence rates of BCRL over time were estimated by the Kaplan-Meier product-limit method. Kaplan-Meier curves were used to present BCRL incidence over time for patients in each subgroup. Univariate and multivariate Cox proportional hazard (Cox PH) regression models were used to estimate the hazard ratios (HRs) of predictors. The robust sandwich estimate method was used to analyze the clustered time-to-event data. The SAS command “proportionality test” was applied to test the proportionality assumption of Cox PH models. The significant or marginally significant factors in univariate models were the candidates to fit a multivariate model. The backward model selection method was used to construct the most parsimonious model. All tests were two-sided. A p value of <0.05 was considered significant. All analyses were performed in SAS 9.2 (SAS Institute Inc., Cary, NC) and R (The R Foundation for Statistical Computing).
Results

Over the 6-year study period 1080 patients were identified in the plastic surgery database and 1596 in the surgical oncology database. After cross-matching, 576 pairs remained. Following individual record review, two pairs were excluded because one or both patients had poorly determined BCRL status. The final data set included 574 pairs, or 1148 breasts, overall. The average follow-up was 59 ± 26.9 months.

The total number of patients was 1090, with 58 undergoing bilateral therapeutic mastectomies. The average age was 55 years (range, 25-83 years). The average BMI at surgery was 27.2 kg/m². Seven hundred and eighty-two (72%) of the 1090 patients were white and 79% were non-smokers. When patient characteristics based on reconstruction status were analyzed, some differences between the two study groups became evident (Table 1b). In 94.6% of the breasts studied, at least one type of surgical axillary intervention was performed. Of the reconstructive breasts, 280 breasts had tissue expander reconstruction, 41 had latissimus dorsi myocutaneous flaps with implants, and 253 had free autologous abdominal tissue only (Table 2). Eleven percent of the breasts were treated with post-operative RT. Both of these parameters were matched between the data sets and did not differ significantly between the reconstruction and no reconstruction groups. Positive lymph nodes were strongly associated with mastectomy-only cases (p<0.001). BCRL developed in 78 (6.8%) of the 1148 breasts: 21 (3.7%) in the reconstructed and 57 (9.9%) in the mastectomy-only group (p<0.001) (Table 2).

Univariate logistic regression modeling elucidated that patients who underwent reconstruction had a lower BCRL risk than patients who underwent mastectomy alone (OR=0.34, 95% CI=0.20-0.57, p<0.001, Table 3a). Overweight or obese patients (BMI >25) had a higher risk of developing BCRL (OR=2.23, 95% CI=1.29-3.83, p=0.004). To avoid having BMI confound the effect of breast reconstruction on risk of BCRL, we performed a subgroup analysis. In patients with BMI < 25, the rates of BCRL in patients undergoing reconstruction vs.
mastectomy only were 2.3% and 6.6%, respectively (p=0.02). Among patients with BMI > 25, the rates were 4.9 and 11.5%, respectively (p=0.002). Therefore, the patients who underwent reconstruction had a lower BCRL risk compared with patients who had mastectomy alone, regardless of whether the patient was normal weight, overweight, or obese. Patients treated with pre-operative chemotherapy had a greater than two-fold higher incidence of BCRL compared with patients who did not undergo pre-operative chemotherapy (OR=2.65, 95% CI=1.63-4.30, p<0.001, Table 3a). ALND (with or without SLND) increased the risk of BCRL 4-fold compared with SLND only (OR=4.06, 95% CI=2.46-6.70, p<0.001, Table 3a). Patients who underwent post-operative RT had a much higher incidence of BCRL (OR=5.83, 95% CI=3.49-9.72, p<0.001, Table 3a). Patients with 1 or more positive lymph nodes had a more than 3-times higher incidence of BCRL compared to other patients (OR=3.63, 95% CI=2.29-5.76, p<0.001, Table 3a). Race, smoking, coronary artery disease, diabetes mellitus, and hypertension were not significant predictive factors for BCRL. BCRL incidence among patients undergoing different types of reconstruction (tissue expander/implant, latissimus dorsi and implant and free autologous abdominal tissue only) was similar and ranged from 3.6% to 4.9%. Due to the small group sample sizes, subgroup analysis did not reach significance. On the basis of these results, although BCRL was less likely in patients who underwent reconstruction versus mastectomy alone, the reconstruction type had no influence on BCRL incidence. Subgroup analysis by reconstruction type was not included in the multivariate analysis because of its strong correlation to reconstructive status.

Multivariate logistic regression showed that reconstruction status, post-operative radiation therapy, BMI, and positive lymph nodes were all significant independent variables for the development of BCRL (Table 3b). After adjusting for factors significantly predictive of breast reconstruction, including BMI, breast reconstruction was associated with a statistically significant lower incidence of BCRL development (adjusted OR=0.37). Axillary intervention
(SLND vs ALND+/−SLND) was a candidate for assessment in the multivariate model but was not significant as an independent variable for the development of BCRL after stronger factors were included.

A univariate CoxPH regression model of time to BCRL development showed that patients who underwent breast reconstruction developed BCRL significantly more slowly than mastectomy-alone patients (HR=0.39, 95% CI=0.23-0.65, p<0.001, Table 4a). Overweight or obese patients developed BCRL earlier than underweight or normal weight patients (HR=2.15, 95% CI=1.27-3.64, p=0.004, Table 4a). Patients treated with neoadjuvant chemotherapy or post-operative radiation and those with at least 1 positive lymph node all had an increased incidence of early BCRL development (p<0.001). Compared to patients who underwent SLND only, the patients who underwent ALND (+/− SLND) developed BCRL four times earlier (HR=3.88, 95% CI=2.42-6.22, p<0.001, Table 4a). Breast reconstruction subgroups were not independently associated with differences in time to BCRL development.

Table 4b shows the multivariate Cox PH regression model of time to development of BCRL. Post-operative RT (p<0.001), positive lymph nodes (p=0.026), and higher BMI (p=0.040) were all significant independent variables associated with earlier development of BCRL. Pre-operative chemotherapy and axillary intervention were not significantly associated with increased time to BCRL after multivariate analysis. Breast reconstruction was significantly associated with delayed development of BCRL after adjusting for other significant predictors (adjusted HR=0.44, 95% CI=0.267-0.67, p=0.002). Figure 1 shows the incidence of BCRL by breast reconstruction status over time.
Discussion

Increased breast cancer survivorship directly translates into increased longevity and the subsequently higher impact of cancer-related morbidity. BCRL is a debilitating disease that leads to pain, recurrent infections, disability, and an overall reduced quality of life. [20-22] Many breast cancer patients choose to undergo delayed or immediate breast reconstruction to improve their body image and/or the fit of clothing. Recent studies have started to show that there is little or no increased risk of BCRL with subsequent reconstruction.[18, 19] This is the first study to do a direct cohort comparison between patients who underwent mastectomy plus reconstruction versus mastectomy alone. We found that reconstruction was associated with a lower rate of BCRL (9.9% vs. 3.7%) and a delayed onset when compared to mastectomy alone. Our study points to the possibility that reconstruction may have some type of protective effect with respect to the development of BCRL.

Among the possible reasons why reconstruction may be beneficial is that transferred vascularized tissue can bridge damaged lymphatics, as well as reduce scarring following lymph node dissection. [18, 23-27] In addition, vascularized tissue has the potential to restore lymphatic flow by promoting angiogenesis and lymphatic regeneration. [28, 29] Evidence of lymphatic regeneration and spontaneous re-anastomosis with recipient vessels has been demonstrated, and these events are linked to patterns of vascular endothelial growth factor expression and macrophage infiltration.[30] In addition, there is evidence to demonstrate that the process of tissue expansion and capsule formation, which induces tissue ischemia, results in increased expression of VEGF.[31] As a result of this increased VEGF expression, tissue angiogenesis, and potentially lymphangiogenesis, may reduce the incidence of lymphedema even in patients who undergo reconstruction with tissue expanders followed by implants because of the process of continued ischemia and capsular formation.[32] Recent advances in the transfer of lymph nodes as vascularized tissue flaps or in combination with a microvascular breast
reconstruction are showing promise and may offer more insight into the molecular mechanisms of lymphangiogenesis and its role in preventing BCRL.[33-36]

Recently, lymphedema research exploring the unique biology of the lymph system has pointed towards variability in function or underlying genetics as a causative factor in the development of BCRL.[37-42] Some women who develop BCRL may have lymphatic abnormalities, such as a weaker lymphatic pump or increased lymph flow (or afterload), that predispose them to the development of BCRL.[40] It is also interesting to note that in our study, cross-matched patients undergoing mastectomy without reconstruction had significantly higher rates of diabetes mellitus, hypertension, and smoking. These patients were also more likely to be overweight or obese. Could these morbidities lead to changes in lymphatic flow and predispose women who are diagnosed with breast cancer to develop lymphedema? Alternatively, these factors may result in self-selection or physician bias in the process to determine whether patients undergo reconstructive surgery.[43]

A major criticism of lymphedema incidence studies is the criteria used in the diagnosis and description of lymphedema. Currently, there is no gold standard measure or defining criteria for lymphedema assessment in the clinical setting.[44] Objective measurements are non-standardized and can vary widely.[45] Imaging techniques may provide valuable information but are limited to a select population and not used routinely for diagnosis.[45, 46] In the current study, all diagnoses of BCRL recorded in the prospective database were based on clinical suspicion and confirmed with circumferential arm measurements by trained physical and occupational therapists at an institutional lymphedema treatment referral clinic. According to the American Cancer Society Lymphedema Workshop, most cases of lymphedema are diagnosed on the basis of clinical criteria as carried out in this study.[47] Based on a cohort study of patients followed up over a 20-year time period, approximately three fourths of patients will develop BCRL in the first 3 years after mastectomy, with the remaining patients developing BCRL at a
rate of almost 1% per year.[48] Therefore, despite our almost 5-year follow-up, a few patients not captured in our analysis may still develop BCRL due to infections, trauma, or weight gain.

Many factors have been blamed for increasing the risk of BCRL.[13] The literature irrefutably supports that axillary clearance and/or axillary radiation increases BCRL incidence.[6, 49-53] In our study, we controlled for these known factors by exact cross-matching of our two patient populations. Patient age was matched within a range of +/- 5 years, which is the most common method of cross-matching for continuous variables. Advanced age has been suggested to be a significant factor in the development of lymphedema.[9, 54, 55] One variable not controlled for in our comparison was weight, or BMI. Although higher BMI is known to increase the risk of developing BCRL [7, 9, 15, 48, 56], a methodological decision was made to only cross-match for three variables in order to maintain adequate numbers for analysis. On multivariate analysis, our study showed BMI as a significant independent variable in the overall development and time of onset of lymphedema. By adjusting the BMI in the multivariate model, we eliminated the potential for BMI to confound our analysis and demonstrated that breast reconstruction patients, regardless of BMI, had a lower rate of lymphedema. In addition, breast reconstruction was found to be significantly associated with delayed development of lymphedema, after adjusting for other significant predictors on multivariate analysis. Additional long-term studies and prospective studies to evaluate BCRL incidence in patients undergoing reconstruction are necessary, as are improved objective measurements of BCRL, to further demonstrate the potential benefit of breast reconstruction in BCRL prevention.

Conclusion

Patients who undergo breast reconstruction have a lower incidence and later onset of BCRL compared to patients who undergo mastectomy alone when cross-matched for age, axillary RT, and surgical axillary interventions.
Acknowledgements

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References


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Figure Legend:

Figure 1 - Kaplan Meier Curves of Time to Lymphedema development based on Breast Reconstruction status.
Table 1a. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=1090 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at surgery</td>
<td>Mean (STD)</td>
</tr>
<tr>
<td>BMI at surgery</td>
<td>Mean (STD)</td>
</tr>
<tr>
<td>&lt;25 kg/m²</td>
<td></td>
</tr>
<tr>
<td>&gt;=25 kg/m²</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td></td>
</tr>
<tr>
<td>Active/prior</td>
<td></td>
</tr>
<tr>
<td>Pre-op chemotherapy</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
</tr>
<tr>
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<td></td>
</tr>
</tbody>
</table>

BMI (Body Mass Index); CAD (Coronary Artery Disease)
Table 1b. Patient Characteristic by Reconstruction Status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mastectomy Alone</th>
<th>With Reconstruction</th>
<th>p-value</th>
</tr>
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<tbody>
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<td><strong>Age at surgery</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=55 yrs</td>
<td>259 (44.97%)</td>
<td>317 (55.03%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;55 yrs</td>
<td>290 (56.42%)</td>
<td>224 (43.58%)</td>
<td></td>
</tr>
<tr>
<td><strong>BMI at surgery</strong></td>
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<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean (STD)</td>
<td>28.6 (7.29)</td>
<td>25.7 (5.76)</td>
<td></td>
</tr>
<tr>
<td>&lt;25 kg/m²</td>
<td>178 (41.88%)</td>
<td>247 (58.12%)</td>
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</tr>
<tr>
<td>&gt;=25 kg/m²</td>
<td>371 (55.79%)</td>
<td>294 (44.21%)</td>
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<tr>
<td>White</td>
<td>366 (46.80%)</td>
<td>416 (53.20%)</td>
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<tr>
<td>Hispanic</td>
<td>33 (34.02%)</td>
<td>64 (65.98%)</td>
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<tr>
<td>Black</td>
<td>127 (77.44%)</td>
<td>37 (22.56%)</td>
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<td>23 (50%)</td>
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<td>1 (100%)</td>
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</tr>
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<td><strong>CAD</strong></td>
<td></td>
<td></td>
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<tr>
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<td>521 (50.05%)</td>
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<tr>
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<td>29 (59.18%)</td>
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<td>515 (51.55%)</td>
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<td>Yes</td>
<td>65 (71.43%)</td>
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<td>428 (54.73%)</td>
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<td>195 (63.31%)</td>
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<td>70 (31.25%)</td>
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<td>125 (55.80%)</td>
<td>99 (44.20%)</td>
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BMI (Body Mass Index), CAD (Coronary Artery Disease)
### Table 2. Surgical Characteristics of Study Breasts and by Reconstruction Status

<table>
<thead>
<tr>
<th>Characteristics</th>
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<th>Mastectomy Alone</th>
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<td>1070 (93.21%)</td>
<td>517 (48.32%)</td>
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<td>78 (6.79%)</td>
<td>57 (73.08%)</td>
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<td><strong>Axillary Intervention</strong></td>
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<td>31 (50%)</td>
<td>31 (50%)</td>
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<td>SLND</td>
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<td>443 (50%)</td>
<td>443 (50%)</td>
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<td>100 (50%)</td>
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<td>1022 (89.02%)</td>
<td>511 (50%)</td>
<td>511 (50%)</td>
<td>(Matched)</td>
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<td>Yes</td>
<td>126 (10.98%)</td>
<td>63 (50%)</td>
<td>63 (50%)</td>
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</tr>
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<td><strong>Positive lymph nodes</strong></td>
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<td></td>
<td></td>
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<td>0</td>
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<td>410 (45.86%)</td>
<td>484 (54.14%)</td>
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<td>1,2,3</td>
<td>178 (15.51%)</td>
<td>114 (64.04%)</td>
<td>64 (35.96%)</td>
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<tr>
<td>4 or more</td>
<td>76 (6.62%)</td>
<td>50 (65.79%)</td>
<td>26 (34.21%)</td>
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</tr>
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<td><strong>Reconstruction type</strong></td>
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<td>Implant only</td>
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<td>LDM</td>
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<tr>
<td>TRAM and related</td>
<td>253 (40.08%)</td>
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SLND (Sentinel Lymph Node Dissection), ALND (Axillary Lymph Node Dissection)
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<th>p-value</th>
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</tr>
<tr>
<td>Mastectomy alone</td>
<td>517 (90.07%)</td>
<td>57 (9.93%)</td>
<td>Referent</td>
<td></td>
</tr>
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<td>With Reconstruction</td>
<td>553 (96.34%)</td>
<td>21 (3.66%)</td>
<td>0.34 (0.20 - 0.57)</td>
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<td>44 (7.32%)</td>
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<td>431 (95.99%)</td>
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<tr>
<td>&gt;=25</td>
<td>639 (91.42%)</td>
<td>60 (8.58%)</td>
<td>2.23 (1.29 - 3.83)</td>
<td>0.004</td>
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<tr>
<td>Race</td>
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<td></td>
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</tr>
<tr>
<td>Other</td>
<td>289 (91.46%)</td>
<td>27 (8.54%)</td>
<td>Referent</td>
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<td>843 (92.84%)</td>
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<td>Referent</td>
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<td>Active/prior</td>
<td>227 (94.58%)</td>
<td>13 (5.42%)</td>
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<td>71 (6.48%)</td>
<td>Referent</td>
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<td>45 (86.54%)</td>
<td>7 (13.46%)</td>
<td>2.26 (0.98 - 5.18)</td>
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<td>Diabetes mellitus</td>
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<td>69 (6.55%)</td>
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<td>9 (9.57%)</td>
<td>1.50 (0.72 - 3.11)</td>
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<td>776 (94.17%)</td>
<td>48 (5.83%)</td>
<td>Referent</td>
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</tr>
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<td>48 (5.24%)</td>
<td>Referent</td>
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<td>30 (12.99%)</td>
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<td>Axillary intervention</td>
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<tr>
<td>SLND</td>
<td>847 (95.60%)</td>
<td>39 (4.40%)</td>
<td>Referent</td>
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<td>ALND+/−SLND</td>
<td>168 (84%)</td>
<td>32 (16%)</td>
<td>4.06 (2.46 - 6.70)</td>
<td>&lt;0.001</td>
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<tr>
<td>Post-op radiation</td>
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<tr>
<td>No</td>
<td>973 (95.21%)</td>
<td>49 (4.79%)</td>
<td>Referent</td>
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<td>Yes</td>
<td>97 (76.98%)</td>
<td>29 (23.02%)</td>
<td>5.83 (3.49 - 9.72)</td>
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<td>Positive lymph nodes</td>
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<td>0</td>
<td>854 (95.53%)</td>
<td>40 (4.47%)</td>
<td>Referent</td>
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</tr>
<tr>
<td>At least 1</td>
<td>216 (85.04%)</td>
<td>38 (14.96%)</td>
<td>3.63 (2.29 - 5.76)</td>
<td>&lt;0.001</td>
</tr>
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</table>

OR (Odds Ratio), BMI (Body Mass Index), CAD (Coronary Artery Disease), SLND (Sentinel Lymph Node Dissection), ALND (Axillary Lymph Node Dissection)
Table 3b. Multivariate Logistic Regression Model of Incidence of Lymphedema

<table>
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<tr>
<th>Variables</th>
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<th>p-value</th>
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<td><strong>Reconstruction status</strong></td>
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<tr>
<td>Mastectomy alone</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>With Reconstruction</td>
<td>0.37 (0.02 – 0.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Post-op radiation</strong></td>
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<tr>
<td>No</td>
<td>Referent</td>
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</tr>
<tr>
<td>Yes</td>
<td>4.74 (2.70-8.31)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Positive lymph nodes</strong></td>
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<tr>
<td>0</td>
<td>Referent</td>
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<tr>
<td>At least 1</td>
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<td><strong>BMI</strong></td>
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<td>&gt;=25</td>
<td>1.95 (1.11-3.44)</td>
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OR (Odds Ratio), BMI (Body Mass Index)
<table>
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<th>Lymphedema</th>
<th>HR (95% CI)</th>
<th>p-value</th>
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<tr>
<td>Mastectomy alone</td>
<td>517 (90.07%)</td>
<td>57 (9.93%)</td>
<td>Referent</td>
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</tr>
<tr>
<td>With Reconstruction</td>
<td>553 (96.34%)</td>
<td>21 (3.66%)</td>
<td>0.39 (0.23 - 0.65)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Age</strong></td>
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<tr>
<td>&lt;=55 yrs</td>
<td>557 (44.97%)</td>
<td>44 (7.32%)</td>
<td>Referent</td>
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</tr>
<tr>
<td>&gt;55 yrs</td>
<td>513 (93.78%)</td>
<td>34 (6.22%)</td>
<td>0.86 (0.55-1.35)</td>
<td>0.508</td>
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<tr>
<td><strong>BMI</strong></td>
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</tr>
<tr>
<td>&lt;25</td>
<td>431 (95.99%)</td>
<td>18 (4.01%)</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>&gt;=25</td>
<td>639 (91.42%)</td>
<td>60 (8.58%)</td>
<td>2.15 (1.27 - 3.64)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>289 (91.46%)</td>
<td>27 (8.54%)</td>
<td>Referent</td>
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</tr>
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<td>White</td>
<td>779 (93.86%)</td>
<td>51 (6.14%)</td>
<td>0.70 (0.43 - 1.11)</td>
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<td><strong>Smoking</strong></td>
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<tr>
<td>Never</td>
<td>843 (92.84%)</td>
<td>65 (7.16%)</td>
<td>Referent</td>
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<td>Active/prior</td>
<td>227 (94.58%)</td>
<td>13 (5.42%)</td>
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<td><strong>CAD</strong></td>
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<td>71 (6.48%)</td>
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<td>45 (86.54%)</td>
<td>7 (13.46%)</td>
<td>2.14 (0.98 - 4.68)</td>
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<td><strong>Diabetes mellitus</strong></td>
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<tr>
<td>No</td>
<td>985 (93.45%)</td>
<td>69 (6.55%)</td>
<td>Referent</td>
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</tr>
<tr>
<td>Yes</td>
<td>85 (90.43%)</td>
<td>9 (9.57%)</td>
<td>1.53 (0.76 - 3.05)</td>
<td>0.231</td>
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<tr>
<td><strong>Hypertension</strong></td>
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<tr>
<td>No</td>
<td>776 (94.17%)</td>
<td>48 (5.83%)</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>294 (90.74%)</td>
<td>30 (9.26%)</td>
<td>1.57 (0.99 - 2.50)</td>
<td>0.055</td>
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<td><strong>Pre-op chemotherapy</strong></td>
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<tr>
<td>No</td>
<td>868 (94.76%)</td>
<td>48 (5.24%)</td>
<td>Referent</td>
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</tr>
<tr>
<td>Yes</td>
<td>201 (87.01%)</td>
<td>30 (12.99%)</td>
<td>2.73 (1.71 - 4.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Axillary intervention</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>SLND</td>
<td>847 (95.60%)</td>
<td>39 (4.40%)</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>ALND+/-SLND</td>
<td>168 (84%)</td>
<td>32 (16%)</td>
<td>3.88 (2.42 - 6.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Post-op radiation</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>973 (95.21%)</td>
<td>49 (4.79%)</td>
<td>Referent</td>
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</tr>
<tr>
<td>Yes</td>
<td>97 (76.98%)</td>
<td>29 (23.02%)</td>
<td>5.69 (3.56 - 9.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Positive lymph nodes</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>854 (95.53%)</td>
<td>40 (4.47%)</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>At least 1</td>
<td>216 (85.04%)</td>
<td>38 (14.96%)</td>
<td>3.39 (2.18 - 5.26)</td>
<td>&lt;0.001</td>
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</tbody>
</table>

HR (Hazard Ratio), BMI (Body Mass Index), CAD (Coronary Artery Disease), SLND (Sentinel Lymph Node Dissection), ALND (Axillary Lymph Node Dissection)
Table 4b. Multivariate CoxPH Regression Model of Time to Development of Lymphedema

<table>
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<th>Variables</th>
<th>HR (95% CI)</th>
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<td><strong>Reconstruction status</strong></td>
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<tr>
<td>Mastectomy alone</td>
<td>Referent</td>
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<td>With Reconstruction</td>
<td>0.44 (0.26 – 6.87)</td>
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<td><strong>Post-op radiation</strong></td>
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<td>Referent</td>
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<td><strong>Positive lymph nodes</strong></td>
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<td>1.75 (1.02-2.98)</td>
<td>0.040</td>
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HR (Hazard Ratio), BMI (Body Mass Index)
Figure 1

Kaplan Meier Curves of Time to Lymphedema Development

Proportion of patients w/o lymphedema

P<0.001

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* Based on the Kaplan-Meier method, the cumulative BCRL rate can increase significantly due to one patient developing BCRL if a very small number of patients stayed in the study at that time point.

** The x-axis presents the time of follow up.