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Risk of lymphedema after mastectomy – potential benefit of applying ACOSOG Z0011 protocol to mastectomy patients

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Abstract

Purpose—Axillary lymph node dissection (ALND) and radiation therapy (RT) are commonly recommended for mastectomy patients with positive sentinel lymph node biopsy (SLNB). Effective alternatives to ALND that reduce lymphedema risk are needed. We evaluated rates of lymphedema in mastectomy patients who received SLNB with RT, compared to ALND with or without RT.

Methods—627 breast cancer patients who underwent 664 mastectomies between 2005–2013 were prospectively screened for lymphedema, median 22.8 months follow-up (range 3.0–86.9). Each mastectomy was categorized as: SLNB-no RT, SLNB+RT, ALND-no RT, or ALND+RT. RT included chest wall +/− nodal radiation. Perometer arm volume measurements were obtained pre- and post-operatively. Lymphedema was defined as ≥10% arm volume increase. Kaplan-Meier and Cox regression analyses were performed to determine lymphedema rates and risk factors.

Results—Of 664 mastectomies, 52% (343/664) were SLNB-no RT, 5% (34/664) SLNB+RT, 9% (58/664) ALND-no RT, and 34% (229/664) ALND+RT. The two-year cumulative lymphedema incidence was 10.0% (95% CI: 2.6–34.4%) for SLNB+RT compared with 19.3% (95% CI: 10.8–33.1%) for ALND-no RT, and 30.1% (95% CI: 23.7–37.8%) for ALND+RT. The lowest cumulative incidence was 2.19% (95% CI: 0.88%–5.40%) for SLNB-no RT. By multivariate analysis, factors significantly associated with increased lymphedema risk included RT (p=0.0017), ALND (p=0.0001), greater number of lymph nodes removed (p=0.0006), no reconstruction (p=0.0418), higher BMI (p<0.0001) and older age (p=0.0021).

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Conclusion—Avoiding completion ALND and instead receiving SLNB with RT may decrease lymphedema risk in patients requiring mastectomy. Future trials should investigate the safety of applying the ACOSOG Z0011 protocol to mastectomy patients.

Keywords

Mastectomy; Lymphedema; Quality of Life; Radiation Therapy; Sentinel Lymph Node Biopsy

INTRODUCTION

Quality of life and long-term effects of treatment have become increasingly important for breast cancer patients due to improved survival outcomes [1–3]. A potential side effect of treatment is lymphedema, a chronic condition characterized by swelling of the arm, hand, breast, or trunk, which may develop from the accumulation of lymphatic fluid in the interstitial tissues. Lymphedema is known to have detrimental effects on quality of life due to body image changes, alterations in arm function, and increased complications such as infection and cellulitis [3–6].

Axillary lymph node dissection (ALND) and radiation therapy (RT) are commonly recommended for mastectomy patients with positive sentinel lymph node biopsy (SLNB). Previous studies have consistently identified ALND as the most significant risk factor for lymphedema, with a reported incidence of >20% compared with 3.5–11% for SLNB [7–12]. In addition, studies have shown that RT – particularly regional lymph node radiation (RLNR)— may contribute to even greater lymphedema risk [13,14]. Effective alternatives to ALND that reduce the risk of lymphedema are needed.

Findings from recent studies may impact treatment of the axilla in breast cancer patients. The ACOSOG Z0011 trial demonstrated no significant difference in the rates of regional recurrence, disease free survival (DFS), or overall survival (OS) in 891 women with limited nodal involvement randomized to completion ALND or SLNB followed by radiation to the breast without RLNR [15,16]. Participants did not receive a third field for RLNR, however, it is possible that they had high tangents which can cover a significant part of the axilla [17]. The trial excluded patients requiring mastectomy and therefore applicability of these findings are limited to women undergoing breast conserving therapy (BCT).

We sought to determine the rates of lymphedema in mastectomy patients who received SLNB with RT, compared to ALND with or without RT. Arm volume measurements, patient demographics and treatment characteristics were analyzed to identify risk factors for development of lymphedema.

MATERIAL & METHODS

Study Design

Beginning in 2005, with Institutional Review Board approval, we prospectively obtained bilateral arm volume measurements on women diagnosed with breast cancer using a Perometer. The Perometer is an optoelectronic device that utilizes infrared beams to measure circumferences of the limb and calculates volume based on these measurements.

Measurements were obtained pre- and post-operatively, during treatment for breast cancer, and at follow-up oncology visits after completion of breast cancer treatment. The protocol for lymphedema screening has previously been published [18].

For this study, we utilized a weight-adjusted arm volume change equation which calculates change in arm volume compared to a pre-operative measurement and accounts for temporal changes in patient weight, which may cause arm size changes unrelated to lymphedema [19]. Weight-adjusted arm volume change (WAC) was calculated for the left and right arm independently at each post-operative assessment according to the formula, $\mathrm{WAC}=(\mathrm{A2}^{*}\mathrm{W1})/(\mathrm{W2}^{*}\mathrm{A1})-1$, where A1 is pre-operative arm volume, A2 is arm volume at a post-operative assessment, and W1 and W2 are the patient's weights at these time points [19]. Use of the WAC equation allowed for inclusion of patients who underwent bilateral mastectomy, since arm volume change could be assessed in each arm individually and did not rely on comparison of size between arms. All patients included in this analysis had a pre-operative measurement and at least one follow-up measurement occurring >3 months after surgery.

Lymphedema was defined as a measurement with ≥ 10% WAC, based on consensus in the literature [20,21]. Measurements recorded within the first 3 months after surgery were not utilized for lymphedema assessment, because patients may experience transient increases in measured arm volume during this period related to post-surgical changes [22]. Measurements obtained after a patient was diagnosed with distant metastasis or local recurrence were excluded to avoid potential confounding.

Patient Population

627 patients who underwent 664 mastectomies for a diagnosis of primary breast cancer between 9/2005 – 2/2013 at our institution were included in this analysis, with a median post-operative follow-up of 22.8 months (range 3.0– 86.9). Prophylactic mastectomies were excluded. Each breast was considered individually, and mastectomies were categorized into four treatment groups: SLNB-no RT, SLNB+RT, ALND-no RT, ALND+RT. RT included chest wall with or without regional lymph node radiation (supraclavicular and/or axillary radiation). Mastectomies were categorized into these groups to replicate the treatment assignments for patients receiving breast conservation therapy (BCT) in the ASCOGO Z11 protocol [16]. Patient demographics, surgical, radiation and medical oncology treatments for the cohort were collected via medical record review to analyze as risk factors. The variable "reconstruction" included patients who underwent immediate breast reconstruction with implant-based or autologous reconstruction at the time of mastectomy. Patients who did not undergo immediate breast reconstruction or who underwent delayed breast reconstruction were classified as "no reconstruction". At the time of this analysis, only 4 patients had undergone delayed breast reconstruction, and were classified as "no reconstruction" with measurements occurring after reconstruction excluded from the analysis.

Statistical Analysis

Univariate and multivariate Cox proportional hazard models were used to evaluate risk factors for lymphedema. Time-dependent covariates were included for use of systemic

therapies and radiation fields such that cases were included in the unexposed group prior to initiation of a given treatment and in the exposed group thereafter. Regression parameters in the Cox models were estimated using a robust sandwich covariance matrix estimate to account for the correlation induced by including data from both sides for women who had bilateral mastectomies [23]. The Kaplan-Meier method was used to estimate and plot cumulative incidence of lymphedema by treatment group (SLNB-no RT, SLNB-RT, ALND-no RT, ALND-RT).

RESULTS

Patient Population

627 patients were included in this analysis, of whom 345 underwent unilateral mastectomy for unilateral breast cancer, and 282 underwent bilateral mastectomy for unilateral (245) or bilateral (37) breast cancer (Table 1). Median age at breast cancer diagnosis was 50 years (range 22–85), and median BMI at diagnosis was 25.0 kg/m^2 (16.5–59.0). Of the total 664 mastectomies, 52% (343/664) were SLNB-no RT, 5% (34/664) SLNB+RT, 9% (58/664) ALND-no RT, and 34% (229/664) ALND+RT. In the SLNB-RT group, 38% (13/34) received RT to the chest wall only, and 62% (21/34) received radiation to the chest wall with RLNR. 15 of the 34 (44%) SLNB-RT mastectomies had a positive SLNB, and 7 of the 34 (21%) SLNB-RT mastectomy patients received neoadjuvant chemotherapy. In the ALND-RT group, 6% (14/229) received RT to the chest wall only, 92% received chest wall radiation with RLNR (211/229), and radiation fields were unknown for 2% (4/229).

Cumulative Incidence of Lymphedema

The overall two-year cumulative incidence of lymphedema was 13.8% (95% CI: 11.0–17.3%), 10.0% (95% CI: 2.6–34.4%) for SLNB+RT compared with 19.3% (95% CI: 10.8–33.1%) for ALND-no RT and 30.1% (95% CI: 23.7–37.8%) for ALND+RT (Table 2, Figure 1). The lowest cumulative incidence of lymphedema was 2.19% (95% CI: 0.88%–5.40%) for SLNB-no RT.

Univariate and Multivariate Analysis

By univariate analysis, factors significantly associated with increased risk of lymphedema included RT ($p<0.0001$), ALND ($p<0.0001$), greater number of lymph nodes removed ($p<0.0001$), no breast reconstruction ($p<0.0001$), neoadjuvant ($p<0.0001$) and adjuvant chemotherapy ($p=0.0083$), higher BMI ($p<0.0001$), and older age at breast cancer diagnosis ($p=0.0021$) (Table 3). Unilateral compared with bilateral mastectomy ($p= 0.0521$) and hormonal therapy ($p= 0.2781$) were not significant predictors of lymphedema.

By multivariate analysis, factors significantly associated with increased risk of lymphedema included RT ($p=0.0017$), ALND ($p=0.0001$), greater number of lymph nodes removed ($p= 0.0006$), no breast reconstruction ($p=0.0418$), higher BMI ($p<0.0001$), and older age at breast cancer diagnosis ($p=0.0021$) (Table 4). Multivariate analysis revealed a significant interaction between ALND and RT ($p=0.005$). Risk of lymphedema was significantly greater for SLNB-RT compared with SLNB-no RT ($p=0.0017$), but there was no significant

difference in risk for SLNB-RT compared with ALND-RT (p=0.9327) or ALND-no RT (p=0.9709).

DISCUSSION

In this series of 664 therapeutic mastectomies from breast cancer patients prospectively screened for lymphedema at our institution, the two-year cumulative incidence of lymphedema was 10% for SLNB with RT, compared with 19% for ALND without RT and 30% for ALND with RT. By multivariate analysis, RT (p=0.0017) and ALND (p=0.0001) were significant risk factors for lymphedema, however, there was no significant difference in risk for SLNB-RT compared with ALND-no RT (p=0.9709) or ALND-RT (p=0.9327). Patients who require post-mastectomy RT after ALND remain at the highest risk for lymphedema; therefore, avoiding completion ALND and instead receiving SLNB with RT may decrease the risk of lymphedema.

Axillary lymph node dissection is the most frequently cited risk factor for lymphedema, with an incidence of >20% following ALND [7,9,11,12]. Post-mastectomy RT is routinely recommended for patients with advanced primary tumors and 4 or more positive lymph nodes, and may also be recommended for patients with 1–3 positive lymph nodes [24–26]. In addition to ALND, regional lymph node radiation (RLNR) is also frequently cited as a risk factor for lymphedema [13,14]. Studies limited to mastectomy patients have shown an increased risk of lymphedema associated with post-mastectomy RT [27]. Thus patients who undergo mastectomy with ALND and RT are at a significant risk for lymphedema, and alternative treatment strategies that minimize this risk are necessary.

Results from recent studies may impact surgical and radiation approaches for treatment of the axilla in breast cancer patients. The ACOSOG Z0011 trial demonstrated no significant difference in the rates of regional recurrence, disease free survival (DFS), or overall survival (OS) in 891 women with limited nodal involvement randomized to completion ALND or SLNB followed by radiation to the breast without RLNR [15,16]. The trial was limited to women undergoing BCT, and lymphedema rates have not yet been reported. Based on these findings, BCT patients with limited nodal disease may receive SLNB with RT and avoid completion ALND. This will likely decrease the risk of lymphedema in these patients given the significantly lower incidence of lymphedema associated with SLNB compared with ALND (<11% versus >20%, respectively) [9,11,12].

We hypothesized that application of the ACOSOG Z0011 treatment protocol for patients requiring mastectomy could similarly reduce the risk of lymphedema. We evaluated the risk of lymphedema in mastectomy patients following SLNB with RT, combining patients who received radiation to the chest wall only with those who also received RLNR to increase sample size. We found that patients who underwent SLNB with RT had a lower incidence of lymphedema (10%) compared to patients who received completion ALND with (30%) or without RT (19%). However, due to small sample size and correspondingly large confidence intervals, we were unable to show a statistically significant reduction in lymphedema risk for the SLNB-RT group.

Preliminary findings of the AMAROS phase III trial comparing axillary radiation to ALND for a positive SLNB in lumpectomy or mastectomy patients demonstrated no significant differences between treatment arms with regard to OS or DFS [28], with a 5-year axillary recurrence rate of 0.54% (4/744) after ALND versus 1.03% (7/681) after axillary radiation. Lymphedema was assessed in this study post-operatively and at 1 and 5 years post-treatment, and was based on subjective clinical assessment by the study investigator. Objective lymphedema measurements were not utilized. At 1 year post-treatment, rates of lymphedema were 15% for patients receiving SLNB with axillary radiation, compared with 25% for ALND without axillary radiation ($p<0.001$ vs SLNB +axillary radiation) and 59% for ALND with axillary radiation ($p<0.001$ vs SLNB +axillary radiation) [29]. Lymphedema rates were similar at 5 years post-treatment. We noted a similar trend in our series, in which ALND- RT was associated with a 30% rate of lymphedema, compared with 19% for ALND-no RT and 10% for SLNB-RT. It should be noted that in contrast with the AMAROS trial, our study was restricted to mastectomy patients and utilized prospectively collected objective measurements for lymphedema occurring at approximately 6-month intervals throughout oncology follow-up. Preliminary findings from the AMAROS trial and results from our hypothesis-generating study support possible alternative strategies for treatment of the axilla in mastectomy patients, which may reduce lymphedema risk without compromising local control.

In our series, multivariate analysis indicated a number of independent risk factors for lymphedema in addition to ALND and RT. After controlling for type of axillary surgery, greater number of lymph nodes removed was associated with an increased risk of lymphedema, which has been demonstrated in prior studies [7,14,30]. Increased BMI and age at breast cancer diagnosis were also associated with increased risk of lymphedema in our series, and have been previously identified as independent risk factors for lymphedema [7,9,10,14,31–33]. Interestingly, we found that patients who did not undergo immediate breast reconstruction were at a significantly increased risk for lymphedema by multivariate analysis. While two previous studies have indicated similar findings, further research is warranted regarding a potential mechanism by which immediate breast reconstruction could reduce lymphedema risk [34,35].

Our study has a number of limitations, including the non- randomized selection of patients for SLNB-RT versus ALND with or without RT. The number of patients who received SLNB-RT in this series was small (n=34), and as a result we were unable to demonstrate a statistically significant reduction in risk of lymphedema for this group. In addition, we could not precisely replicate the treatment groups utilized in the ACOSOG Z0011 protocol for the mastectomy patients included in this series. In our cohort, fewer than half (44%) of mastectomy patients who received SLNB-RT had a positive SLNB. Another potential limitation is our combining of patients who received radiation to the chest wall only with those who also received RLNR to increase sample size. Due to the median 2-year follow-up for patients in our cohort and non-random assignment of axillary treatment, we did not evaluate local recurrence rates. Owing to these limitations, further research is warranted utilizing a cohort of mastectomy patients randomized to SLNB-RT compared with ALND +/− RT to evaluate differences in lymphedema rates and axillary recurrence among these groups.

The current study also has many strengths, including use of a large cohort of patients prospectively screened for lymphedema with the Perometer, a device with demonstrated validity and high accuracy for lymphedema assessment [36,37]. To our knowledge, this cohort of 627 patients (corresponding to 664 mastectomies) represents the largest cohort of mastectomy patients prospectively screened for lymphedema in the literature. Patients in our series underwent pre-operative and regular post-operative measurements, and lymphedema was quantified using a validated weight-adjusted volume change (WAC) equation, which incorporates fluctuations in patient weight to account for arm size changes unrelated to lymphedema. The importance of obtaining pre-operative assessments to account for asymmetry between arms and adjustment for factors unrelated to lymphedema has been previously demonstrated [18,19,38,39].

In conclusion, findings from our hypothesis-generating study suggest that application of the ACOSOG Z0011 treatment protocol may reduce the risk of lymphedema for mastectomy patients. Preliminary findings from the AMAROS Phase III trial suggest that ALND or axillary radiation after a positive SLNB provide comparable regional control for lumpectomy and mastectomy patients. Future studies assessing the safety of applying the ACOSOG Z0011 protocol in mastectomy patients is warranted.

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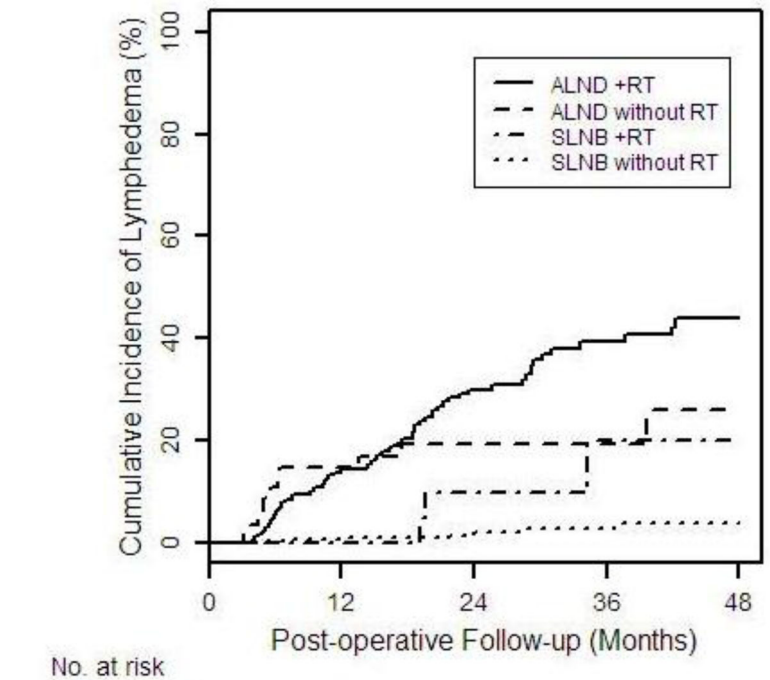

No. at risk

ALND +RT:	229	156	81	45	24
ALND w/out RT:	58	39	24	14	6
SLNB +RT:	34	26	15	6	4
SLNB w/out RT:	343	262	153	94	42

Figure 1.

Cumulative incidence of lymphedema after mastectomy (≥10% WAC)according to treatment group

Table 1

Clinical and pathologic characteristics of patient cohort

	Median (Range)	n = 664 (100%)
Patient Characteristics		
Age at diagnosis, years	50 (22–85)	-
BMI at diagnosis, kg/m^2	25.0 (16.5–59.0)	-
Breast Surgery		
Unilateral Mastectomy	-	345 (52%)
Bilateral Mastectomy	-	319 (48%)
Breast Reconstruction		
Yes	-	467 (70%)
No	-	197 (30%)
Axillary Surgery		
SLNB	-	337 (57%)
ALND	-	287 (43%)
# LN's removed	4 (0–43)	-
Pathologic Characteristics		
Invasive Carcinoma	-	594 (89%)
Ductal Carcinoma in Situ (DCIS)	-	70 (11%)
Invasive tumor size, cm	1.8 (0.01–12.5)	-
# Positive LN's	0 (0–39)	-
Radiation Therapy*		
Yes	-	401 (60%)
No	-	263 (40%)
Neoadjuvant Chemotherapy		
Yes	-	102 (15%)
No	-	562 (85%)
Adjuvant Chemotherapy		
Yes	-	350 (53%)
No	-	314 (47%)
Hormonal Therapy		
Yes	-	481 (72%)
No	-	183 (28%)

Abbreviations: BMI = Body Mass Index, ALND = Axillary lymph node dissection, SLNB = Sentinel lymph node biopsy, LN = lymph node

* Radiation therapy included patients treated with chest wall alone and chest wall with regional lymph node radiation

Table 2

2-year cumulative incidence of lymphedema after mastectomy (≥10% WAC) overall and by treatment group

	N	2-year cumulative incidence	95% Confidence Interval	
Entire cohort	664	13.82%	11.01%	17.27%
SLNB-no RT	343	2.19%	0.88%	5.40 %
SLNB-RT	34	10.00%	2.60%	34.40%
ALND-no RT	58	19.27%	10.79%	33.05%
ALND-RT	229	30.08%	23.66%	37.77%

Abbreviations: SLNB = sentinel lymph node biopsy, ALND = axillary lymph node dissection, RT = radiation therapy

Table 3

Univariate analysis of risk factors for lymphedema after mastectomy (≥10% WAC)

	Hazard Ratio	95% Confidence Interval		P Value
Patient Characteristics				
Age at diagnosis, years	1.030	1.011	1.050	0.0021
BMI at diagnosis, kg/m^2	1.086	1.055	1.117	<0.0001
Surgical Characteristics				
Bilateral vs. unilateral mastectomy	0.654	0.427	1.004	0.0521
Breast reconstruction	0.283	0.186	0.430	<0.0001
ALND vs. SLNB	11.819	6.178	22.612	<0.0001
# LN's removed	1.094	1.079	1.110	<0.0001
Pathologic Characteristics				
Invasive Tumor Size, cm	1.225	1.115	1.346	<0.0001
# Positive LN's	1.091	1.066	1.116	<0.0001
Systemic/Radiation Therapy				
Neoadjuvant Chemotherapy	2.669	1.697	4.197	<0.0001
Adjuvant Chemotherapy	1.810	1.165	2.812	0.0083
Hormonal Therapy	1.317	0.801	2.165	0.2781
Radiation Therapy	4.440	2.976	6.625	<0.0001

Abbreviations: BMI = Body Mass Index, SLNB = Sentinel lymph node biopsy, ALND = Axillary lymph node dissection, LN = lymph node

* Age, BMI, invasive tumor size, # LN's removed and # positive LN's analyzed as continuous variables such that the hazard ratios reflect the change in lymphedema risk associated with a 1-unit increase in the variable

* Radiation Therapy includes radiation to the breast/chest wall +/− regional lymph node radiation (RLNR)

Table 4

Multivariable analysis of risk factors for lymphedema after mastectomy (≥10% WAC)

	Hazard Ratio	95% Confidence Interval		P Value
BMI at diagnosis, kg/m^2	1.071	1.037	1.106	<0.0001
Age at diagnosis, years	1.032	1.012	1.053	0.0021
Immediate breast reconstruction	0.623	0.395	0.983	0.0418
# LN's Removed	1.046	1.020	1.073	0.0006
ALND vs. SLNB	-	-	-	0.0001
Radiation Therapy	-	-	-	0.0017
Interaction, ALND*RT	-	-	-	0.0050
SLNB-RT vs. SLNB-no RT	6.4902	2.0183	20.8698	0.0017
ALND-no RT vs. SLNB-RT	0.9803	0.3367	2.8541	0.9709
ALND-RT vs. SLNB-RT	1.0468	0.3623	3.0245	0.9327
ALND-RT vs. ALND-no RT	1.0678	0.6662	1.7114	0.7853

Abbreviations: BMI = Body Mass Index, ALND = Axillary lymph node dissection, LN = lymph node

Note: HR's for ALND vs. SLNB and Radiation Therapy are blank due to the inclusion of the interaction term (ALND*RT)