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Quantifying the Impact of Axillary Surgery and Nodal Irradiation on Breast Cancer–Related Lymphedema and Local Tumor Control: Long-Term Results From a Prospective Screening Trial

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abstract

PURPOSE To independently evaluate the impact of axillary surgery type and regional lymph node radiation (RLNR) on breast cancer–related lymphedema (BCRL) rates in patients with breast cancer.

PATIENTS AND METHODS From 2005 to 2018, 1,815 patients with invasive breast cancer were enrolled in a lymphedema screening trial. Patients were divided into the following 4 groups according to axillary surgery approach: sentinel lymph node biopsy (SLNB) alone, SLNB+RLNR, axillary lymph node dissection (ALND) alone, and ALND+RLNR. A perometer was used to objectively assess limb volume. All patients received baseline preoperative and follow-up measurements after treatment. Lymphedema was defined as a $\geq$ 10% relative increase in arm volume arising $>$ 3 months postoperatively. The primary end point was the BCRL rate across the groups. Secondary end points were 5-year locoregional control and disease-free-survival.

RESULTS The cohort included 1,340 patients with SLNB alone, 121 with SLNB+RLNR, 91 with ALND alone, and 263 with ALND+RLNR. The overall median follow-up time after diagnosis was 52.7 months for the entire cohort. The 5-year cumulative incidence rates of BCRL were 30.1%, 24.9%, 10.7%, and 8.0% for ALND+RLNR, ALND alone, SLNB+RLNR, and SLNB alone, respectively. Multivariable Cox models adjusted for age, body mass index, surgery, and reconstruction type showed that the ALND-alone group had a significantly higher BCRL risk (hazard ratio [HR], 2.66; $P = .02$) compared with the SLNB+RLNR group. There was no significant difference in BCRL risk between the ALND+RLNR and ALND-alone groups (HR, 1.20; $P = .49$) and between the SLNB-alone and SLNB+RLNR groups (HR, 1.33; $P = .44$). The 5-year locoregional control rates were similar for the ALND+RLNR, ALND-alone, SLNB+RLNR, and SLNB-alone groups (2.8%, 3.8%, 0%, and 2.3%, respectively).

CONCLUSION Although RLNR adds to the risk of lymphedema, the main risk factor is the type of axillary surgery used.

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ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

An important goal of treating patients with breast cancer with positive axillary lymph nodes (LNs) is achieving optimal tumor control while minimizing adverse effects such as breast cancer–related lymphedema (BCRL). The NSABP-32, MILAN, and ALMANAC trials led to transition from routine axillary lymph node dissection (ALND) to sentinel lymph node biopsy (SLNB) for patients with a clinically negative axilla.[1-3] Furthermore, results from the ACOSOG-Z0011 and IBCSG23-01 trials demonstrated that SLNB for patients with a low volume of positive LNs (1-2 LNs) is as safe as ALND.[4,5] This evolving body of research focusing on axillary management has spared many women the negative sequelae of ALND, leading to improvement in quality of life.[6]

However, results from the European Organisation for Research and Treatment of Cancer (EORTC) 22922/10925 and MA.20 trials showed that regional lymph node radiation (RLNR) results in significant improvement in local control and distant metastasis–free survival.[7,8] This led to a nationwide increase in RLNR rates for patients with breast cancer with positive LNs, as demonstrated by a National Cancer Database study

CONTEXT

Key Objectives

The goal of this study is to prospectively quantify the impact of axillary surgery and regional lymph node radiation (RLNR) on breast cancer–related lymphedema (BCRL) and tumor control.

Knowledge Generated

The results of our study showed that although RLNR slightly increases the risk for BCRL, the main driving risk factor remains axillary dissection. The key strategy to prevent BCRL is to omit axillary lymph nodal dissection (ALND), whenever possible.

Relevance

Similar tumor control rates between SLNB+RLNR and ALND alone for patients with 1-2 positive lymph nodes and a lower BCRL rate with SLNB+RLNR support routine substitution of ALND with RLNR for these patients.

showing that RLNR rates increased from 19.1% in 2003 to 30.3% for patients with 1-3 positive LNs after mastectomy.[9] The trade-offs of RLNR are increased risks of radiation pneumonitis and BCRL.[10-12] Therefore, individualizing treatment decisions regarding axillary surgery (ALND *v* SLNB), with or without RLNR, is a crucial part of clinical decision making impacting all disciplines.

In the AMAROS trial, patients with 1-2 positive LNs were randomly assigned to either SLNB+RLNR or ALND without RLNR in an intent-to-treat (ITT) noninferiority design.[13] The final report revealed that 4% of the patients had 3 positive LNs and were randomly assigned between both trial arms, whereas 1% of patients had ≥ 4 LNs and received both ALND and RLNR. After randomization, 1,425 patients with T1-2 tumors and positive SLNB were analyzed. Results showed similar locoregional control between the ALND and SLNB+RLNR groups. Furthermore, their secondary end point showed that the 5-year cumulative incidence of BCRL was significantly lower in the SLNB+RLNR arm compared with the ALND arm. These results support SLNB+RLNR as a substitution for ALND for patients with 1-2 positive LNs, particularly if an indication for nodal radiation is anticipated preoperatively.[14] A major caveat in AMAROS is the measurement of BCRL (defined as a 10% change in arm circumference), which relied upon tape measurement at 15 cm above and/or 15 cm below the medial epicondyle. This method neglects swelling elsewhere in the arm (eg, elbow or hand) and has low interrater reliability,[15,16] calling for analogous studies to be performed with more objective quantification methods such as the perometer. Moreover, AMAROS included patients who received both RLNR and ALND, limiting the ability to assess the impact of each axillary approach on BCRL.

Herein, we prospectively quantify BCRL rates among different axillary surgery types with and without RLNR, using perometer measurements. In addition, we evaluate the different locoregional control rates among axillary surgery types.

PATIENTS AND METHODS

Starting in 2005, 2,889 patients with newly diagnosed breast cancer were prospectively screened for lymphedema as part of our institutional Lymphedema Screening Program (ClinicalTrials.gov identifier: NCT01521741; institutional review board identifiers: 2008P000540 and 2005P001038). To match AMAROS eligibility criteria, we excluded patients who received neoadjuvant chemotherapy, did not receive axillary surgery, and had bilateral breast cancer. After applying those criteria, 1,815 patients were available for analysis. This cohort was categorized into the following 4 groups according to axillary surgery and RLNR treatment: SLNB alone, SLNB+RLNR, ALND alone, and ALND+RLNR.

Surgery and Radiation

Breast surgery consisted of lumpectomy or mastectomy with or without reconstruction. All types of reconstruction, including autologous flaps, tissue expanders followed by exchange to implant, and single-stage direct-to-implant reconstruction, were included.[17] Tumor and treatment characteristics were identified from surgical pathology notes and were stored in a database using REDCap 7.0.14 (Vanderbilt University, Nashville, TN). The radiation modalities included partial-breast irradiation (PBI), whole-breast/chest wall radiation, and RLNR. In the great majority of patients, the supraclavicular LNs (SCV) and level I, II, and III axillary LNs were contoured according to the Radiation Therapy Oncology Group or RADCOMP atlases.[3,18] When RLNR was used for patients with SLNB, the SCV and level I, II, and III axillary LNs received prescription dose. When RLNR was used after ALND, the SCV and only level III axillary LNs received the prescription dose. When there was extensive LN involvement, gross extracapsular extension, or perinodal fat invasion, RLNR included SCV and level I, II, and III axillary LNs.

A prescription dose of 50-50.4 Gy in 25-28 fractions, followed by boosts of 10 Gy in 5 fractions if needed, was used for patients treated with whole-breast and/or chest wall

RLNR.[19] Hypofractionation was used with whole-breast radiation only, delivering 42.4 Gy over 16 fractions and a boost of 10 Gy over 4 fractions. For patients receiving PBI, a dose of 4 Gy per fraction twice daily with 3-dimensional conformal mixed photon/electron or photon-alone techniques was delivered in a dose-escalation clinical trial (ClinicalTrials.gov identifier: NCT00694577). All patients with PBI received SLNB.

End Points and Lymphedema Definitions

Among the 4 groups, the primary end point was BCRL. Patients newly diagnosed with breast cancer undergo a bilateral, preoperative, baseline arm volume measurement using a perometer. Postoperatively, patients are observed during their regular oncology clinics (every 6 months) as well as at regular intervals after completion of treatment. Arm volume changes from baseline are calculated for patients undergoing unilateral breast cancer surgery using the relative volume change (RVC) formula[20]:

$$\mathrm{RVC} = \frac{A_2 \times U_1}{U_2 \times A_1} - 1,$$

where A_1 and A_2 and U_1 and U_2 are the arm volumes of the affected and unaffected arms at preoperative baseline and follow-up, respectively.[20] For patients undergoing unilateral breast surgery, BCRL is defined as an RVC $\geq$ 10% occurring $>$ 3 months after surgery. The RVC equation uses contralateral arm volume as the control and takes the preoperative asymmetry between arms into account. However, this equation cannot be used for patients who underwent prophylactic contralateral surgery. Therefore, arm volume changes from baseline are calculated for patients undergoing bilateral breast surgery using the weight-adjusted change (WAC) formula[21]:

$$\mathrm{WAC} = \frac{A_2 \times W_1}{W_2 \times A_1} - 1,$$

where A_1 and A_2 are the arm volumes of the affected arm and W_1 and W_2 are body weight at preoperative baseline and follow-up, respectively.[21] For patients undergoing bilateral breast surgery, BCRL is defined as a WAC $\geq$ 10% occurring $>$ 3 months after surgery.[21]

The secondary end points were locoregional failure (LRF) and distant disease–free survival. LRF was defined as biopsy or surgery-proven recurrence within the breast, chest wall, or ipsilateral axilla. Axillary failure involved recurrence within the axilla only.

Statistical Analysis

Sample characteristics are described overall and by treatment group. All patients were free of outcomes on the day of surgery (breast and axillary surgery in same setting). A few patients were excluded from their respective group analysis because they developed BCRL, LRF, or distant metastasis before receiving RLNR. This included 22 patients (1.2%) from the entire cohort with BCRL, 1 patient with axillary failure, and 1 patient with distant metastasis. For the ALND+RLNR and SLNB+RLNR treatment groups, treatment date was defined as the later of the surgery and radiation dates. A graph of cumulative incidence stratified by treatment group was produced for each outcome.

A multivariable Cox proportional hazards regression model was performed on the BCRL outcome and treatment group, controlling for age, body mass index (BMI; a well-established BCRL risk factor[22]), and type of breast surgery. The proportional hazards assumption for the model was first inspected visually for approximately parallel Kaplan-Meier curves stratified by categorical covariates and/or by assessing statistical significance of time-dependent covariates in the model. A Bonferroni-adjusted significance threshold of $P = .025$ was used to account for the use of 2 reference groups among the 4 treatment groups. All statistical analyses were performed using SAS/STAT version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patients Demographics

From 2005 to 2018, 1,815 patients were enrolled in our prospective screening protocol. Among these patients, 1,340 received SLNB alone, 121 received SLNB+RLNR, 91 received ALND alone, and 263 received ALND+RLNR. Table 1 lists the sample characteristics overall and within each treatment group. Median age for the whole cohort was 56 years (interquartile range [IQR], 24.4-87.9 years), the overall median BMI was 26.1 kg/m^2 (IQR, 16.5-58.4 kg/m^2), and the overall median follow-up time was 52.7 months (IQR, 6-163 months). Across the 4 groups, median age and median BMI were similar. The median follow-up time was longer in patients who underwent ALND compared with those who underwent SLNB. The clinicopathologic features were distributed in a stepwise ascending pattern across the groups, where the patients who underwent ALND+RLNR had larger tumors, more advanced N staging, more aggressive tumor grade, and a higher percentage receiving adjuvant chemotherapy compared with patients in the other 3 groups. The rates of lumpectomy were higher in the SLNB-alone group (73.5%) and decreased gradually with more aggressive axillary approach (62.8% for SLNB+RLNR, 42.9% for ALND alone, and 29.3% for ALND+RLNR). Similarly, mastectomy rates increased in a stepwise manner with more aggressive axillary management. The median number of malignant LNs in patients treated with either SLNB+RLNR or ALND alone was 1. Only 1 patient had 13 positive LNs and refused radiation after ALND completion. The median number of malignant LNs was 0 in the SLNB-alone group and increased to 3 in the ALND+RLNR group.

TABLE 1. Patient Demographic and Clinical Characteristics

Characteristic	No. of Patients (%)[a]				
	SLNB Alone (n = 1,340)	SLNB+RLNR (n = 121)	ALND Alone (n = 91)	ALND+RLNR (n = 263)	Overall (n = 1,815)
Median age, years (interquartile range)	57.5 (27.7-87.9)	53.1 (24.4-79.5)	51.8 (36.4-77.6)	50.3 (24.8-82.2)	56.0 (24.4-87.9)
Median BMI, kg/m^2 (interquartile range)	26.1 (16.6-55.3)	25.6 (18.4-58.4)	25.6 (18.0-50.4)	26.4 (16.5-46.1)	26.1 (16.5-58.4)
Median follow-up time, months (interquartile range)	49.5 (6.0-163.4)	49.8 (7.8-155.8)	96.9 (6.2-161.5)	68.5 (6.7-161.9)	52.7 (6.0-163.4)
Surgery					
Lumpectomy	985 (73.5)	76 (62.8)	39 (42.9)	77 (29.3)	1,177 (64.8)
Mastectomy without reconstruction	63 (4.7)	4 (3.3)	15 (16.5)	51 (19.4)	133 (7.3)
Mastectomy with reconstruction	292 (21.8)	41 (33.9)	37 (40.7)	135 (51.3)	505 (27.8)
T stage					
Tx	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
T0/Tis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
T1	1,119 (83.8)	71 (58.7)	65 (71.4)	88 (33.5)	1,343 (74.2)
T2	202 (15.1)	37 (30.6)	25 (27.5)	126 (47.9)	390 (21.5)
T3	14 (1.0)	12 (9.9)	1 (1.1)	44 (16.7)	71 (3.9)
T4	0 (0.0)	1 (0.8)	0 (0.0)	4 (1.5)	5 (0.3)
N stage					
N0/N0+	1,286 (96.0)	40 (33.1)	17 (18.7)	7 (2.7)	1,350 (74.4)
N1	54 (4.0)	78 (64.5)	72 (79.1)	138 (52.5)	342 (18.8)
N2	0 (0.0)	3 (2.5)	1 (1.1)	80 (30.4)	84 (4.6)
N3	0 (0.0)	0 (0.0)	1 (1.1)	38 (14.4)	39 (2.1)
Median No. of sampled LNs (interquartile range)	2.0 (1.0-18.0)	2.0 (0.1-16.0)	15.0 (3.0-35.0)	18.0 (6.0-43.0)	2.0 (0.1-43.0)
Median No. of malignant LNs (interquartile range)	0.0 (0.0-3.0)	1.0 (0.0-4.0)	1.0 (0.0-13.0)	3.0 (0.0-39.0)	0.0 (0.0-39.0)
LVI					
Negative	1,155 (86.2)	46 (38.0)	63 (69.2)	104 (39.5)	1,368 (75.4)
Positive	185 (13.8)	75 (62.0)	28 (30.8)	159 (60.5)	447 (24.6)
HER2 by immunohistochemistry					
Negative	887 (66.2)	72 (59.5)	60 (65.9)	157 (59.7)	1,176 (64.8)
Borderline	313 (23.4)	36 (29.8)	19 (20.9)	85 (32.3)	453 (25.0)
Positive	114 (8.5)	13 (10.7)	11 (12.1)	19 (7.2)	157 (8.7)
Not done	26 (1.9)	0 (0.0)	1 (1.1)	2 (0.8)	29 (1.6)
HER2 by FISH					
Negative	1,036 (77.3)	91 (75.2)	61 (67.0)	208 (79.1)	1,396 (76.9)
Positive	140 (10.4)	18 (14.9)	15 (16.5)	30 (11.4)	203 (11.2)
Not done	164 (12.2)	12 (9.9)	15 (16.5)	25 (9.5)	216 (11.9)
Estrogen receptor status					
Positive	1,176 (87.8)	110 (90.9)	78 (85.7)	229 (87.1)	1,593 (87.8)
Negative	150 (11.2)	10 (8.3)	13 (14.3)	31 (11.8)	204 (11.2)
Not assessed	14 (1.0)	1 (0.8)	0 (0.0)	3 (1.1)	18 (1.0)
Progesterone receptor status					
Positive	1,101 (82.2)	106 (87.6)	74 (81.3)	207 (78.7)	1,488 (82.0)

(continued on following page)

TABLE 1. Patient Demographic and Clinical Characteristics (continued)

Characteristic	No. of Patients (%)[a]				
	SLNB Alone (n = 1,340)	SLNB+RLNR (n = 121)	ALND Alone (n = 91)	ALND+RLNR (n = 263)	Overall (n = 1,815)
Negative	223 (16.6)	14 (11.6)	17 (18.7)	52 (19.8)	306 (16.9)
Not assessed	16 (1.2)	1 (0.8)	0 (0.0)	4 (1.5)	21 (1.2)
Grade					
1	263 (19.6)	6 (5.0)	17 (18.7)	11 (4.2)	297 (16.4)
2	701 (52.3)	69 (57.0)	36 (39.6)	135 (51.3)	941 (51.8)
3	353 (26.3)	46 (38.0)	37 (40.7)	115 (43.7)	551 (30.4)
Not assessed	23 (1.7)	0 (0.0)	1 (1.1)	2 (0.8)	26 (1.4)
Adjuvant chemotherapy					
Yes	362 (27.0)	85 (70.2)	63 (69.2)	242 (92.0)	752 (41.4)
No	978 (73.0)	36 (29.8)	28 (30.8)	21 (8.0)	1,063 (58.6)
Patients undergoing prophylactic mastectomy for nondiseased breast	139 (10.3)	21 (17.3)	12 (13.1)	58 (22)	230 (12.6)

Abbreviations: ALND, axillary lymph node dissection; BMI, body mass index; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; LNs, lymph nodes; LVI, lymphovascular invasion; RLNR, regional lymph node radiation; SLNB, sentinel lymph node biopsy.

[a]Values are numbers and percentages, unless otherwise noted.

Lymphedema Outcomes

Among the entire cohort, 171 (9.5%) of 1,815 patients developed BCRL. The crude lymphedema rates were highest in the ALND+RLNR group (66 [26.9%] of 263 patients), followed by the ALND-alone group (20 [22%] of 91 patients). The SLNB+RLNR and SLNB-alone groups had lower crude rates of BCRL (8 [6.8%] of 121 patients and 77 [5.7%] of 1,340 patients, respectively).

Taking into account the different follow-up times between the 4 study groups, we calculated the cumulative incidence rates for BCRL. The 5-year rate was the highest among patients receiving ALND+RLNR (30.1%), followed by those receiving ALND alone (24.9%). Again, the SLNB+RLNR and SLNB-alone groups had lower 5-year rates (10.7% and 8.0%, respectively; Fig 1). The multivariable analysis (Table 2) controlling for age, BMI, and type of surgery showed no significant difference between the SLNB+RLNR and SLNB-alone groups (hazard ratio [HR], 1.33; 95% CI, 0.6 to 2.8; $P = 0.4$) and no significant difference between the ALND+RLNR and ALND-alone groups (HR, 1.20; 95% CI, 0.7 to 2.0; $P = .5$). However, those receiving ALND alone had a significantly higher expected hazard of BCRL compared with those receiving SLNB+RLNR (HR, 2.66; 95% CI, 1.2 to 6.1; $P = .02$).

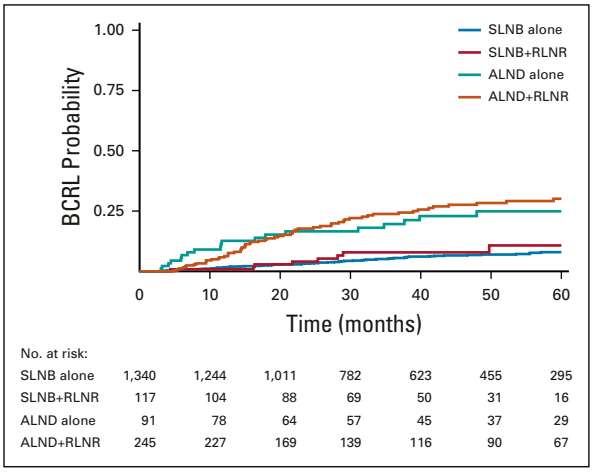

FIG 1. Cumulative incidence of lymphedema outcomes stratified by study groups. ALND, axillary lymph node dissection; BCRL, breast cancer–related lymphedema; RLNR, regional lymph node radiation; SLNB, sentinel lymph node biopsy.

Local Tumor Control

The 5-year cumulative incidence rates of LRF were 2.8%, 3.8%, and 2.3% in the ALND+RLNR, ALND-alone, and

TABLE 2. Multivariable BCRL Cox Proportional Hazards Regression Model Results

Treatment Group Comparison	Hazard Ratio[a]	95% CI	P
ALND alone *v* SLNB+RLNR	2.66	1.16 to 6.06	.020[b]
ALND+RLNR *v* ALND alone	1.20	0.72 to 1.99	.486
SLNB+RLNR *v* SLNB alone	1.33	0.64 to 2.78	.441

Abbreviations: ALND, axillary lymph node dissection; BCRL, breast cancer–related lymphedema; RLNR, regional lymph node radiation; SLNB, sentinel lymph node biopsy.

[a]Hazard ratio adjusted for age, body mass index, and breast surgery type.

[b]*P* value is less than the Bonferroni-adjusted significance threshold of $P = .025$.

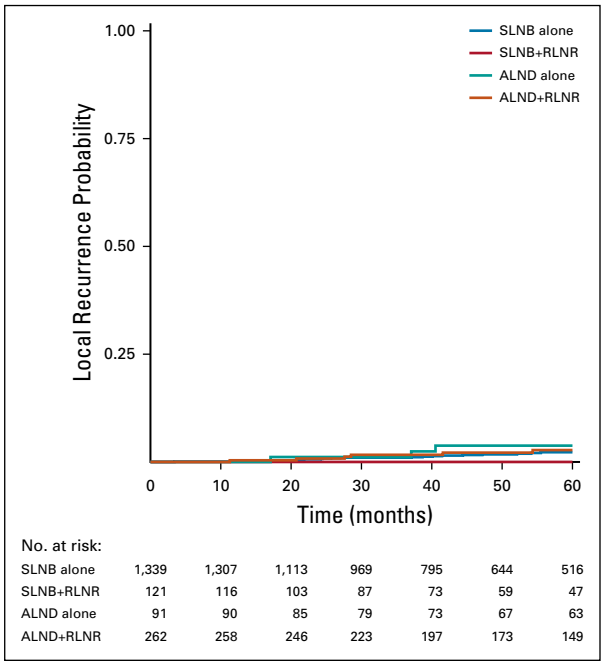

FIG 2. Cumulative incidence of local recurrence outcomes stratified by study groups. ALND, axillary lymph node dissection; RLNR, regional lymph node radiation; SLNB, sentinel lymph node biopsy.

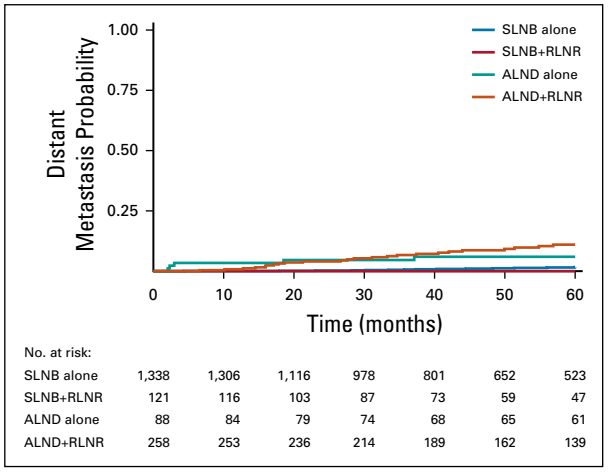

FIG 3. Cumulative incidence of distant metastasis outcomes stratified by study groups. ALND, axillary lymph node dissection; RLNR, regional lymph node radiation; SLNB, sentinel lymph node biopsy.

SLNB-alone groups, respectively (Fig 2). No patients in the SLNB+RLNR group developed any locoregional recurrence. In addition, the crude rates of true axillary recurrence were lower across the groups, where 0.8% (2 of 263 patients), 1% (1 of 91 patients), and 0.5% (7 of 1,340 patients) of patients suffered from axillary recurrence in the ALND+ RLNR, ALND-alone, and SLNB-alone groups, respectively. As a result of the low number of events and the lack of events in the SLNB+RLNR group, we could not perform a multivariable analysis controlling for different clinicopathologic risk factors distributed across the groups.

Distant Disease–Free Survival

The 5-year cumulative incidence rate of distant metastasis was highest in the ALND+RLNR group (11%), reflecting more aggressive tumor pathology in that group. The patients managed with ALND only had a 6% cumulative incidence rate of distant metastasis, whereas the rate was 1.7% in those managed with SLNB only (Fig 3). Again, no patient in the SLNB+RLNR group had any distant metastasis, hindering a multivariable analysis between the groups.

DISCUSSION

ALND and RLNR are strong risk factors for BCRL development.[12] Therefore, achieving acceptable local tumor control, especially for patients with positive LNs, without increasing BCRL risk remains a challenge. As previously mentioned, several trials (IBCSG23-01 and ACOSOG-Z0011) led to a shift from ALND to SLNB for patients with either few positive LNs or micrometastatic LNs, resulting in lower rates of BCRL.[4,23] The AMAROS trial[13] demonstrated that for patients with 1-2 positive LNs, ALND without RLNR or SLNB followed by RLNR can provide similar tumor control rates (5-year overall survival, 93.3% and 92.5%, respectively; $P = .34$). In addition, BCRL incidence at 5 years in the SLNB+RLNR group was 6% compared with 13% for ALND alone. These results imply that the risk of developing BCRL depends more on the extent of axillary surgery than on radiation.

However, most literature shows higher rates (> 20% risk) of lymphedema with ALND,[12,24,25] which questions the methodology used to measure BCRL in the AMAROS study. Although the trial included baseline preoperative tape measurements of the arms, these were taken 15 cm above and below the medial epicondyle, using only an absolute approach with questionable reliability and failure to account for swelling elsewhere along the affected arm. It is preferable that if a tape measure is used, circumferences be taken longitudinally along the arm and converted to relative volumetric measurements. Using change in circumference results in a liberal definition of lymphedema and low accuracy in diagnosis.[26] In addition, allowing combined ALND and RLNR in both groups if > 4 positive LNs are present in an ITT analysis led to biased BCRL rates because ITT analyses estimate the effect of treatment assignment rather than treatment effect.[27] Other trials, such as the IBCSG23-01, reported physician assessment for BCRL with no usage of objective arm measurement, leading to subjectivity in BCRL diagnosis. Furthermore, the MA.20 and EORTC 22922 trials reported that BCRL rates (based on subjective clinical assessment in MA.20) increased with RLNR, from 4.5% to 8.4% and from 10.5% to 12%, respectively. However, these trials did not stratify by

axillary surgery type, where only 3.7% and 7.1% of the MA.20 and EORTC 22922 cohorts included SLNB without ALND completion, respectively. Moreover, the EORTC was not clear on its BCRL assessment methodology.

Our prospective screening methods attempted to overcome these pitfalls in lymphedema assessment. Obtaining preoperative baseline measures is imperative to avoiding high misdiagnosis rates.[28] In addition, using the RVC or WAC formula introduces a control when assessing affected arm volume changes relative to either the contralateral arm (RVC) or body weight (WAC), which are both known to fluctuate throughout and beyond treatment.[20,21,29]

Dividing the patients according to their axillary management allowed us to quantify the impact of each surgical, radiation, or combined intervention on BCRL. The 5-year cumulative incidence rates (accounting for different follow-up periods among the groups) for SLNB, SLNB+RLNR, ALND, and ALND+RLNR were 8.0%, 10.7%, 24.9%, and 30.1%, respectively. Acknowledging the lack of randomization between the groups, our multivariable analysis aimed to account for different risk factors such as BMI,[22] age, and different breast surgery types distributed among the 4 groups. The multiple-comparison approach with adjusted level of significance after multivariable analysis allowed us to avoid α-type error in comparing each group to the remaining 3 groups. Interestingly, for patients who underwent SLNB, adding RLNR did not significantly increase BCRL risk (HR, 1.33; 95% CI, 0.6 to 2.7; $P = 0.4$). In addition, in patients who underwent ALND, adding RLNR did not significantly increase BCRL risk (HR, 1.2; 95% CI, 0.7 to 1.9; $P = .4$). However, completion of ALND without RLNR significantly increased BCRL risk compared with the SLNB+RLNR group (HR, 2.66; 95% CI, 1.16 to 6.06; $P = .02$).

Despite the fact that patients who received ALND+RLNR had a higher BCRL risk compared with those who received ALND alone (30% *v* 25%, respectively), this difference was not significant on multivariable analysis. This is possibly a result of the low number of patients in the ALND group compared with ALND+RLNR group. Nevertheless, these results reflect that the main risk factor for BCRL is the extent of the axillary surgery rather than added RLNR (Data Supplement), which corroborates the previous AMAROS and IBCSG23-01 results. Furthermore, our study design allowed us to assess the different BCRL rates across the SLNB-alone and ALND+RLNR groups, which are commonly not included in major prospective trials.

As expected, there was no difference between the 4 groups in terms of 5-year LRF (ALND+RLNR, 2.8%; ALND alone, 3.8%; SLNB alone, 2.3%; and no events in patients treated with SLNB+RLNR). The axillary recurrence rate was $<$ 1% across these groups. We also investigated the distant disease–free survival in the 4 groups. Again, there were no events in the group treated with SLNB+RLNR, whereas the highest rate of distant metastasis at 5 years (11%) occurred in patients treated with ALND+RLNR. Patients who received ALND alone had a 6% risk of distant metastasis at 5 years compared with a 1.7% risk for those who received SLNB alone. Of note, these findings infer the association between aggressive tumor characteristics and aggressive axillary approach with ALND and radiation. The majority of patients treated with either SLNB+RLNR or ALND alone in our study, as well as in the previously mentioned trials, had 1-2 positive LNs. This raises the question of what upper limit of positive LNs is necessary to proceed with ALND completion, rather than SLNB+RLNR, to spare LN-positive patients the increased risk of BCRL after ALND. In fact, Alliance A11202 (ClinicalTrials.gov identifier: NCT01901094) might add more evidence regarding the benefit of de-escalating axillary surgery for patients with positive LNs at presentation receiving neoadjuvant chemotherapy, which was not evaluated in AMAROS or in our study.

Of note, different RLNR volume coverage from MA.20 and EORTC 22922 has invigorated research regarding RLNR techniques to mitigate BCRL risks. In prospectively screened perometer-measured patients with preoperative baselines, Chandra et al[30] demonstrated that the extent of the supraclavicular field lateral border (relative to the humeral head), dose per fraction, energy used, and tangent types were not correlated with BCRL. In contrast, Gross et al[31] found that the extent of the lateral border of the nodal field encompassing more than one third of the humoral head yielded higher BCRL rates compared with those who had less than one third of the humoral head treated. However, the major limitation of this study was the lack of preoperative baseline arm measurements and BCRL quantification using tape measurements. Using this same methodology for quantifying BCRL, in another report, Gross et al[32] found that a minimum dose to the axillary-lateral thoracic vessel juncture of $<$ 38.6 Gy significantly reduced the risk of BCRL without compromising the median lymph nodes volume receiving 45 Gy accross different axillary nodal levels. However, those results are yet to be validated in a prospectively screened cohort with preoperative baselines.

We conclude that although RLNR increases the risk of BCRL, the main contribution to this risk is the extent of axillary surgery. Therefore, omission of axillary dissection, if possible, should be the key prevention strategy. Similar tumor control rates with SLNB+RLNR and ALND alone for patients with 1-2 positive LNs support routine substitution of ALND with RLNR for these patients.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Quantifying the Impact of Axillary Surgery and Nodal Irradiation on Breast Cancer–Related Lymphedema and Local Tumor Control: Long-Term Results From a Prospective Screening Trial

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