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ORIGINAL ARTICLE – BREAST ONCOLOGY

Omission of Axillary Lymph Node Dissection is Associated with Inferior Survival in Breast Cancer Patients with Residual N1 Nodal Disease Following Neoadjuvant Chemotherapy

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ABSTRACT

Background. The appropriateness of substituting sentinel lymph node dissection (SLND) and regional nodal irradiation (RNI) for axillary lymph node dissection (ALND) in patients with residual lymph node (LN) disease following neoadjuvant chemotherapy (NAC) is unknown. We used the National Cancer Database (NCDB) to compare survival following SLND and ALND in breast cancer patients with residual LN disease.

Methods. We analyzed NCDB patients, treated between 2006 and 2014, with cT1–3, cN1, cM0 breast cancer and residual disease in 1–3 axillary LNs (ypN1) following NAC. Patients were grouped into those who received SLND (defined as removal of ≤ 4 LNs) and RNI, or ALND and RNI. Patients were matched for all patient, tumor, and treatment characteristics.

Results. We identified 1313 eligible patients in the ALND group and 304 patients in the SLND group. For the matched cohorts, SLND was associated with significantly lower survival in both univariate and doubly robust multivariable analyses (MVA) (HR 1.7, 95% CI 1.3–2.2, $P < 0.001$ for MVA), with estimated 5-year OS of 71%, compared with 77% in the ALND group ($P = 0.01$). Exploratory subgroup analyses showed that SLND was comparable with ALND in patients with luminal A or B tumors with a single metastatic LN (HR 1.03, 95% CI 0.59–1.8, $P = 0.91$).

Conclusions. Our analysis suggests that, while an ALND may not be needed for patients with limited residual nodal burden and biologically favorable tumors, SLND should not be routinely substituted for ALND in patients with ypN1 disease following NAC until its efficacy is confirmed by prospective trials.

Axillary lymph node involvement in breast cancer is a well-documented prognostic factor that predicts locoregional recurrence (LRR) and correlates strongly with overall survival (OS).[1,2] Historically, axillary lymph node dissection (ALND) has been the standard of care in the management of patients with lymph node-positive disease. ALND serves to stage the axilla and provide regional control.[3] ALND, however, significantly increases the risk of morbidity, including lymphedema and diminished range of motion, and has deleterious long-term effects on quality of life in breast cancer survivors.[4] As such, there have been increasing efforts over the last two decades to investigate the feasibility of replacing ALND with the less morbid sentinel lymph node dissection (SLND).

The role of SLND following neoadjuvant chemotherapy (NAC) in patients with LN-positive breast cancer remains controversial, and determining its utility in this subset of patients is increasingly pertinent given the sharp rise in the use of NAC over the past two decades.[5,6] Utilization of

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NAC in breast cancer nearly doubled between 2003 and 2011.[6] ACOSOG Z1071 was a phase III trial that examined the feasibility of SLND in patients with cN1 disease who received NAC. The study determined an false negative rate (FNR) of 12.6% for all comers receiving SLND, which was considered unacceptably high, as it exceeded the FNR of $\sim$ 10% established for cN0 patients.[7] However, there is increasing acceptance of omission of ALND following NAC in patients with cN1 disease who are found to have a negative SLND.[8] A secondary analysis of ACOSOG Z1071 and the recent SN FNAC trial both showed an FNR $< 10\%$ for SLND when using a combination of a radiocolloid and blue dye.[9,10] Furthermore, the FNR may be reduced below 5% with the addition of a "targeted axillary dissection" that retrieves the clinically involved LN in addition to any sentinel LNs.[11]

Whether omission of ALND is feasible in patients with cN1 disease who are found to have pathologically involved LN following NAC is yet to be determined. Residual nodal disease is a poor prognostic factor that portends a high incidence of LRR.[12,13] However, similar to patients with LN-positive breast cancer who do not receive NAC, RNI following SLND may mitigate the increased risk of LRR in patients with ypN1 disease. Several ongoing studies are testing whether the feasibility of SLND in pathologically LN-positive disease in patients who do not receive NAC can be extended to those who do. The ALLIANCE A011202 trial randomizes patients with cT1–3, cN1, cM0 breast cancer with residual axillary disease following NAC to ALND and RNI or SLND and RNI.[14] Other pertinent ongoing studies include the TAXIS and SUPREMO trials, both of which allow for SLND in certain patients with residual nodal disease.[15,16] In this analysis, we compare OS between patients treated with SLND and RNI or ALND and RNI in those who meet the eligibility criteria of the ALLIANCE A011202 trial using the National Cancer Database (NCDB).

METHODS

Data Source

This study is a retrospective review of patient outcomes collected from the NCDB, which is a joint program of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The NCDB collects information from hospital registry data in more than 1500 CoC-accredited facilities and tracks patients with malignant neoplastic diseases, their treatments, and outcomes. Data in the NCDB represent more than 70% of newly diagnosed cancer cases in the U.S. and more than 34 million historical records.[17]

Patient Selection

We included patients with non-metastatic cT1–T3, cN1(f) breast cancer who received NAC with residual nodal disease in 1–3 axillary LNs (ypN1), including micrometastases. We only included patients who received regional nodal irradiation (RNI). Variables from the 2014 NCDB Participant Use Data File (PUF) Dictionary were used for patient inclusion, exclusion, and matching. We used the International Classification of Diseases for Oncology, 3rd edition [ICD-O-3] topography codes C50.00–C50.09. Patients were diagnosed between 2006 and 2014. The SLND cohort was defined as patients with ≤ 4 LN removed if treated prior to 2012, or coded as having an SLND in 2012 or later, since an SLND-specific code was added in 2012. We chose ≤ 4 LN as the definition of SLND as it encompasses the maximum number of retrieved sentinel LN in $> 90\%$ of patients.[18] ALND was defined as removal of > 4 LNs. We excluded male patients and patients with mortality within 90 days of surgery, multiple cancers, > 90 days between diagnosis and start of treatment, unknown or no definitive surgical resection, unknown or positive margin status, unknown or no regional nodal evaluation, unknown chemotherapy status, unknown ypT- or ypN-stage, or unknown radiotherapy treatment status.

Covariates

All available patient, tumor, and treatment related variables were included in the univariate and propensity score analyses. Covariates with $P < 0.1$ in the univariate analysis were incorporated into multivariable Cox proportional hazards regression modeling using backward stepwise methodology. Patient related variables included race, age at diagnosis, Charlson-Deyo comorbidity index, year of diagnosis, facility type, insurance status, median income, receipt of high school degree, U.S. region, urban versus rural location, and distance from treatment facility. Tumor related variables included tumor laterality, tumor grade, lymphovascular invasion (LVI), ER/PR/HER-2 receptor status, cT-stage, and ypT-stage. Treatment related variables included type of surgery and receipt of adjuvant endocrine therapy. All patients received RNI.

Statistical Analysis

OS was defined as the time from diagnosis to death due to any cause. Baseline patient characteristics were assessed pre- and post-matching with Chi square analysis and standard mean difference (SMD), where a SMD > 0.1 was considered unbalanced.[19] Survival was estimated using the Kaplan–Meier method, with the stratified log-rank method

to assess for significance. Univariate and multivariable analysis (MVA) of patient characteristics and OS was performed using Cox proportional hazards regression modeling. A propensity score-matched analysis with inverse probability of treatment weighting (IPTW) was performed to account for indication bias. Binary logistic regression modeling was used to generate propensity scores for receipt of ALND or SLND.[20,21] Next, IPTW was calculated as 1/propensity score and 1/(1-propensity score).[22] Finally, weight-adjusted univariate Kaplan–Meier analysis was performed, and doubly robust, IPTW-adjusted Cox proportional hazards regression modeling was performed. Doubly robust MVA takes into account the covariates of interest while simultaneously incorporating their respective IPTW score.[23]

Subset analyses were evaluated for heterogeneity using a fixed effects model. Quantification of heterogeneity was assessed with the τ^2 and I^2 statistics where I^2 values of 75–100% were considered to have considerable heterogeneity. Multiple imputation by chained equations (MICE) was used to replace missing data.[24] Specifically, multiple imputations were performed for LVI and HER2 receptor status. These two variables were relatively recently added to the NCDB and, as such, approximately a third and half of patients had unknown LVI status and HER2 receptor status, respectively. A total of 50 imputations were generated and five different iterations were used; the average of the five iterations was used as the imputed value. The distribution of the incomplete and imputed data was assessed graphically and numerically to assess the quality of imputation. For all analyses, P-values < 0.05 were considered statistically significant. All statistics were completed using RStudio (v1.2.1335). R markdown is available upon request.

RESULTS

Patient and Treatment Characteristics

We identified 2,445,870 patients with breast cancer diagnosed between 2006 and 2014, of whom 1617 met our eligibility criteria: 1313 in the ALND group and 304 in the SLND group (Fig. 1). Multiple imputation by chained equations was performed for unknown LVI and HER2 receptor status. The majority of patients with residual nodal disease underwent ALND, but the proportion undergoing SLND alone nearly doubled over the study period, with a clear uptrend after 2011 (supplementary Fig. 1). Detailed baseline patient, tumor, and treatment characteristics for the unmatched and IPTW-matched cohorts are listed in Table 1. Most notably, compared with the ALND group, patients in the SLND cohort were more likely to be treated after 2011 (64% vs 48%), undergo partial mastectomy (57% vs 49%), and have residual disease in a single LN (69% vs 43%). There were no differences in any of the baseline characteristics after matching. Median number of removed LNs was 13 (IQR 9,17) and 3 (IQR 1,4) in the ALND and SLND groups, respectively.

Survival Analysis

For the matched cohorts, univariate (UVA) and doubly robust multivariable (MVA) Cox regression analyses showed SLND to be associated with inferior OS compared with ALND (MVA HR 1.74, 95% CI 1.34–2.25, $P < 0.001$) (Table 2). Notable factors associated with improved survival included better performance status, later year of diagnosis, lack of LVI, grade 1 tumors, lower cT-stage, receipt of endocrine therapy, and residual disease in a single LN. Median follow-up was 44 (IQR 29, 63) and 36 (IQR 25, 54) months for the ALND and SLND groups, respectively. IPTW-adjusted Kaplan–Meier analysis showed improved survival in the ALND group ($P = 0.006$), with estimated 5-year OS of 77% vs 71% (Fig. 2). We also performed a sensitivity analysis using the same patient cohorts without imputation, considering unknown LVI and HER2 receptor status as another factor in the match. Baseline characteristics are listed in supplementary Table 1. The results similarly showed inferior survival in the SLND group (MVA HR 1.64, 95% CI 1.26–2.15, $P < 0.001$) as shown in supplementary Table 2.

Subgroup Analyses

To identify a subset of patients for whom omission of ALND may be feasible, we performed subgroup analyses based on age, cT-stage, ypT-stage, number of metastatic lymph nodes, tumor grade, and tumor molecular subtype. Subgroups were combined when feasible for groups that comprised $< 10\%$ of the total number of patients for a particular characteristic, as shown in Fig. 3. For instance, ypT0 and ypT1 patients were combined. SLND was associated with either significantly inferior OS or a trend toward inferiority in nearly all the examined subgroups (Fig. 3). ALND appeared equivalent to SLND in patients with tumors of the HER2 molecular subtype, cT1-stage, and grade 1 tumors, but the number of patients in these groups was too small to make definitive conclusions.

To see whether ALND may be omitted in patients with ypN1 disease with the most favorable characteristics, we performed an IPTW-matched comparison between ALND and SLND in patients with luminal A or B tumors and residual disease in a single LN. SLND and ALND were equivalent in this subset of patients (UVA HR 1.03, 95% CI 0.59–1.8, $P = 0.91$). IPTW-adjusted Kaplan–Meier

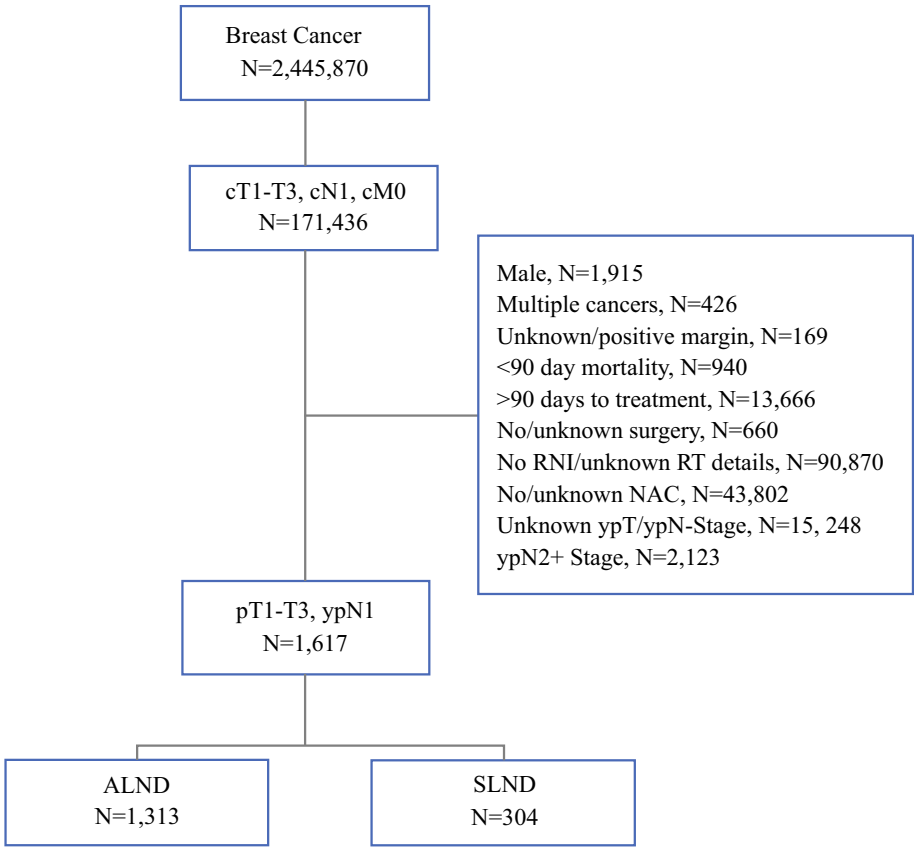

FIG. 1 CONSORT diagram. *SLND*: sentinel lymph node dissection, *ALND*: axillary lymph node dissection, *RNI*: regional nodal irradiation, *NAC*: neoadjuvant chemotherapy

analysis showed similar survival between both treatment groups ($P = 0.88$), with estimated 5-year OS of 85% and 82% for SLND and ALND, respectively (Fig. 4). Baseline characteristics of the unmatched and matched cohorts are listed in supplementary Table 3. UVA and doubly robust MVA Cox regression models for predictors of OS are summarized in supplementary Table 4.

Since the number of LNs removed during SLND correlates with better axillary staging, we repeated the UVA and MVA analyses for patients with at least 3 LNs removed, as 50% of the SLND cohort had 2 or fewer LNs removed. Baseline characteristics are in supplementary Table 5. SLND was associated with inferior survival (MVA HR 1.87, 95% CI 1.37–2.55, $P < 0.001$) (supplementary Table 6). IPTW-adjusted Kaplan–Meier analysis similarly showed significantly lower survival in the SLND group with ≥ 3 LNs removed (supplementary Fig. 2).

Validation Cohort

To validate our approach to defining SLND and ALND and matching methodology, we repeated the analysis for patients who met the eligibility criteria of ACOSOCG Z0011, a phase III trial that reported equivalent outcomes for SLND and ALND in patients with a clinically negative axilla, cT1–2 tumors, and 1 to 2 pathologically involved LNs following partial mastectomy.[25] Patients did not receive NAC. We identified 25,236 patients who met the trial's eligibility criteria: 11,830 in the ALND group, and 13,406 in the SLND group. Baseline characteristics for the unmatched and IPTW-matched cohorts are shown in supplementary Table 7. UVA and doubly robust MVA Cox regression models for predictors of OS are summarized in supplementary Table 8. ALND and SLND were found to be equivalent (UVA HR 0.98, 95% CI 0.90–1.08, $P = 0.71$). IPTW-adjusted Kaplan–Meier analysis showed similar survival between both treatment groups ($P = 0.70$), with estimated 5-year OS of 92% and 93% in the SLND and ALND groups, respectively (Fig. 5).

DISCUSSION

The surgical management of the axilla in patients with breast cancer is an evolving paradigm that has seen a shift toward less extensive dissection over the past two decades. This change in clinical practice aims to reduce the morbidity associated with ALND. In the AMAROS trial, the rates of clinical lymphedema were 11% and 23% in patients treated with SLND and ALND, respectively.[18] Similarly, the rates of arm lymphedema were significantly lower in the SLND group in ACOSOG Z0011 (2% vs 13%).[26] As alluded to earlier, several ongoing trials are

TABLE 1 Baseline characteristics for the unmatched and IPTW-matched cohorts

Characteristic	Unmatched			IPTW-matched		
	ALND (N = 1313)	SLND (N = 304)	P	ALND (N = 1313)	SLND (N = 303)	P
Age						
≤50	628 (48%)	147 (48%)	0.919	627 (48%)	143 (47%)	0.903
>50	685 (52%)	157 (52%)		687 (52%)	160 (53%)	
Charlson–Deyo score						
0	1173 (89%)	275 (90%)	0.636	1177 (90%)	274 (91%)	0.690
1	140 (11%)	29 (10%)		136 (10%)	29 (9%)	
Race						
White	978 (74%)	229 (75%)	0.884	981 (75%)	221 (73%)	0.627
Black	261 (20%)	60 (20%)		261 (20%)	68 (23%)	
Other	74 (6%)	15 (5%)		72 (5%)	14 (5%)	
Year of diagnosis						
2006–2011	685 (52%)	109 (36%)	< 0.001	644 (49%)	147 (48%)	0.894
2012–2014	628 (48%)	195 (64%)		670 (51%)	156 (52%)	
Lymphovascular invasion						
Not present	756 (58%)	198 (65%)	0.019	774 (59%)	190 (63%)	0.308
Present	557 (42%)	106 (35%)		539 (41%)	113 (37%)	
Tumor grade						
Grade 1	61 (5%)	14 (5%)	0.214	60 (5%)	14 (5%)	0.796
Grade 2	412 (31%)	109 (36%)		421 (32%)	87 (29%)	
Grade 3	744 (57%)	153 (50%)		730 (56%)	75 (58%)	
Unknown	96 (7%)	28 (9%)		102 (8%)	27 (9%)	
Receptor status						
HR +/HER2 −	626 (48%)	154 (51%)	0.666	634 (48%)	149 (49%)	0.895
HR +/HER2 +	126 (10%)	31 (10%)		127 (10%)	29 (9%)	
HR −/HER2 +	70 (5%)	17 (6%)		70 (5%)	13 (4%)	
HR −/HER2 −	491 (37%)	102 (34%)		482 (37%)	113 (37%)	
cT-stage						
T1	200 (15%)	44 (14%)	0.897	198 (15%)	45 (15%)	0.872
T2	714 (54%)	164 (54%)		714 (54%)	170 (56%)	
T3	399 (30%)	96 (32%)		401 (31%)	87 (29%)	
No. of metastatic LN						
1	571 (43%)	210 (69%)	< 0.001	635 (48%)	149 (49%)	0.979
2	425 (32%)	66 (22%)		398 (30%)	90 (30%)	
3	317 (24%)	28 (9%)		280 (21%)	64 (21%)	
ypT-stage						
pT1	595 (45%)	132 (43%)	0.874	590 (45%)	136 (45%)	0.993
pT2	464 (35%)	111 (37%)		467 (36%)	107 (35%)	
pT3	127 (10%)	28 (9%)		126 (10%)	28 (9%)	
pT0	127 (10%)	33 (11%)		131 (10%)	32 (11%)	
Endocrine therapy						
No	620 (47%)	135 (44%)	0.398	614 (47%)	142 (47%)	0.971
Yes	661 (50%)	158 (52%)		665 (51%)	154 (51%)	
Unknown	32 (2%)	11 (4%)		34 (3%)	7 (2%)	

TABLE 1 continued

Characteristic	Unmatched			IPTW-matched		
	ALND (N = 1313)	SLND (N = 304)	P	ALND (N = 1313)	SLND (N = 303)	P
Surgery type						
Mastectomy	665 (51%)	130 (43%)	0.016	646 (49%)	149 (49%)	0.999
Partial mastectomy	648 (49%)	174 (57%)		667 (51%)	154 (51%)	

Additional matched characteristics not shown in the Table include insurance status, facility type, laterality, and education and income levels

Multiple imputation by chained equations was performed for unknown LVI and HER2 receptor status

ALND axillary lymph node dissection, *SLND* sentinel lymph node dissection, *IPTW* inverse probability of treatment weighting

testing the feasibility of omitting ALND in patients with residual nodal disease following NAC, but the safety of SLND alone in these patients is currently unknown. Nonetheless, the desire to reduce morbidity appears to have led to extrapolation of the data supporting the use of SLND in LN-positive patients who do not receive NAC. Our analysis shows that slightly over a quarter of patients with ypN1 breast cancer did not undergo an ALND in NCDB-affiliated institutions in 2014. There was a clear uptrend in SLND in ypN1 patients after 2011, the year the results of ACOSOG Z0011 were published. Our study, however, should caution against this shift in clinical practice as it shows omission of ALND in ypN1 patients is associated with inferior OS even in those who receive RNI. It behooves clinicians to await the results of the ALLIANCE A011202 trial.

We found only one prior analysis that compared ALND with SLND in patients with a positive SLND following NAC. A recent retrospective study looked at 161 such patients and found equivalent 3-year locroregional control (LRC) and OS between the two treatment groups.[27] However, the study had a median follow-up of 29 months, so it is possible the outcomes will change with longer follow-up. Furthermore, compared with the ALND patients, the SLND cohort had a significantly higher proportion of patients with isolated tumor cells (15% vs 1%) and micro-metastases (38% vs 7%), with a smaller proportion of macro-metastases (47% vs 92%) in the retrieved nodes. These factors favor the SLND group and may explain the discrepancy between the reported outcomes of the study and our findings. The authors looked specifically at patients with macro-metastases and found no statistically significant difference in LRR between SLND and ALND, albeit the number of patients was small, and there was a trend favoring the latter.

Our findings are supported by a combined analysis of the NAC arms of the NSABP-B18 and NSABP-B27 trials. The analysis found residual nodal disease to be the strongest negative prognosticator, and depending on age and initial tumor size, the 10-year risk of LRR ranged from 15 to 22% in clinically and pathologically node-positive patients.[13] Notably, patients in these trials did not receive RNI or post-mastectomy radiotherapy, which may have impacted the risk of LRR. A more recent study looked at 1600 patients with cytologically confirmed axillary metastases who received NAC.[28] The 10-year OS and recurrence-free survival (RFS) in patients with an axillary complete pathologic response (pCR) were 84% and 79% compared with 57% and 50% in patients with residual axillary disease, respectively. The majority of patients with residual nodal disease received adjuvant radiotherapy, but it was not specified whether patients received RNI. These data support the notion that removal of drug-resistant cancer cells with an ALND may provide a therapeutic benefit even in patients who receive RNI. It is important to note that the data presented here do not argue for a lack of benefit for RNI following NAC. Rather, the findings highlight the importance of comprehensive therapy in patients with residual axillary disease, including ALND, RNI, and additional systemic therapy when appropriate.

Our subgroup analyses identified a subset of patients with residual axillary disease for whom omission of an ALND may not compromise survival. SLND appeared equivalent to ALND in patients with luminal A or B tumors and only one metastatic LN. This finding is not surprising since hormone-positive tumors can be controlled with long-term use of endocrine therapy. Additionally, there is a strong correlation between residual cancer burden and long-term outcomes. In a recent patient-level meta-analysis of 4077 patients, the residual cancer burden (RCB) index was highly predictive of long-term prognosis across all breast cancer sub-types.[29] For instance, in patients with hormone-positive, HER2-negative breast cancer, the 10-year event-free survival (EFS) rates were 84%, 88%, and 52% in those with a pCR, minimal residual burden, and extensive residual burden, respectively. Based on our analysis and these data, SLND may be sufficient in patients with very limited residual axillary burden.

TABLE 2 Univariate and doubly robust multivariable analysis of predictors of OS

Characteristic	IPTW-matched UVA			IPTW-matched MVA		
	HR	95% CI	*P*	HR	95% CI	*P*
Age						
≤50	–	–		–	–	
>50	0.997	0.81, 1.23	0.981	0.937	0.75, 1.17	0.563
Charlson–Deyo score						
0	–	–		–	–	
1	1.582	1.17, 2.15	0.003	1.604	1.17, 2.20	0.003
Race						
White	–	–		–	–	
Black	1.706	1.34, 2.17	< 0.001	1.341	1.04, 1.73	0.024
Other	0.751	0.41, 1.37	0.349	0.784	0.43, 1.44	0.431
Year of diagnosis						
2006–2011	–	–		–	–	
2012–2014	0.693	0.54, 0.90	0.005	0.714	0.55, 0.93	0.012
Lymphovascular invasion						
Not present	–	–		–	–	
Present	1.343	1.09, 1.66	0.007	1.358	1.09, 1.69	0.007
Tumor grade						
Grade 1	–	–		–	–	
Grade 2	1.751	0.85, 3.60	0.127	1.707	0.82, 3.53	0.15
Grade 3	3.249	1.62, 6.51	0.001	2.179	1.06, 4.47	0.033
Unknown	1.799	0.79, 4.08	0.161	1.459	0.63, 3.38	0.378
Receptor status						
HR +/HER2 −	–	–		–	–	
HR +/HER2 +	1.273	0.87, 1.87	0.217	1.091	0.73, 1.63	0.669
HR −/HER2 +	1.818	1.11, 2.97	0.017	0.802	0.45, 1.44	0.462
HR −/HER2 −	2.24	1.77, 2.84	< 0.001	0.906	0.61, 1.34	0.623
cT-stage						
T1	–	–		–	–	
T2	1.438	1.01, 2.05	0.046	1.235	0.85, 1.79	0.265
T3	1.822	1.26, 2.63	0.001	1.656	1.12, 2.46	0.012
ypT-stage						
pT1	–	–		–	–	
pT2	1.276	1.00, 1.63	0.05	1.139	0.88, 1.47	0.321
pT3	1.692	1.21, 2.37	0.002	1.391	0.96, 2.01	0.079
pT0	1.397	0.96, 2.04	0.083	1.208	0.82, 1.78	0.338
Endocrine therapy						
No	–	–		–	–	
Yes	0.392	0.31, 0.49	< 0.001	0.375	0.25, 0.56	< 0.001
Unknown	0.853	0.46, 1.60	0.619	0.785	0.41, 1.51	0.47
Surgery type						
Mastectomy	–	–		–	–	
Partial mastectomy	0.858	0.69, 1.06	0.159	0.872	0.70, 1.09	0.228
No. of metastatic LN						
1	–	–		–	–	
2	1.228	0.96, 1.58	0.106	1.29	1.00, 1.66	0.049
3	1.446	1.11, 1.89	0.007	1.618	1.23, 2.13	0.001
LN surgery						
ALND	–	–		–	–	

TABLE 2 continued

Characteristic	IPTW-matched UVA			IPTW-matched MVA		
	HR	95% CI	*P*	HR	95% CI	*P*
SLND	1.563	1.21, 2.01	0.001	1.74	1.34, 2.25	< 0.001

UVA included all available patient, tumor, and treatment related characteristics, but only relevant variables are shown. MVA included all variables with $P < 0.1$ on UVA and selected well-established prognosticators

Multiple imputation by chained equations was performed for unknown LVI and HER2 receptor status

ALND axillary lymph node dissection, *SLND* sentinel lymph node dissection

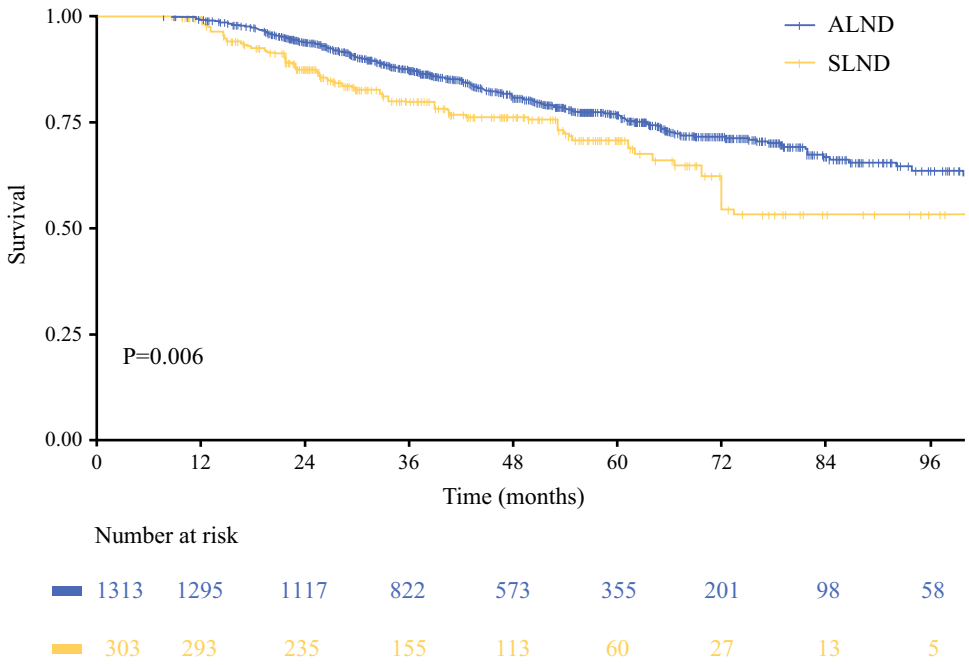

FIG. 2 Kaplan–Meier survival curve for the matched SLND and ALND cohorts

This investigation suggests the need for surgical clearance beyond SLND for patients with ypN1 nodal disease. We were only able to compare ALND with SLND using the NCDB. However, a relatively new intermediary between these two surgical procedures is a targeted axillary dissection (TAD), which retrieves the biopsy-confirmed LN, in which a clip is placed prior to initiation of NAC. In a prospective study of breast cancer patients with a clinically involved axilla, the clipped LN was not retrieved as a sentinel LN in 23% of patients, including 4.5% which had a negative SLND, but residual disease in the clipped LN.[11] As such, a combination of SLND and TAD not only provides nodal assessment of the pathological response to NAC, but may also offer the therapeutic benefit of clearance of LNs at highest risk of harboring residual disease. Additionally, TAD, inasmuch as it is an intermediate step between SLND and ALND, may have reduced morbidity compared with the latter.

Limitations

This study has several limitations. An SLND-specific code was only added during the last 3 years of the study period, and we defined SLND as removal of 4 or fewer LNs for the years preceding adoption of this code. We validated our methodology by performing an analysis on patients who matched the eligibility criteria of ACOSOG Z0011 and were able to recapitulate the trial's survival outcomes. Nonetheless, it is possible some of the patients included in the SLND group were patients who had an inadequate ALND. The NCDB also lacks detail regarding the utilization of a radioactive colloid and methylene blue dye for SLND. These techniques improve the quality of SLND and potentially increase the number of retrieved LNs, which can impact outcomes. Also, the timing of LN biopsy is not captured and, as such, it is possible that some patients were mistakenly assumed to have residual nodal disease. Another important limitation is the lack of data regarding clinical response to chemotherapy, which typically

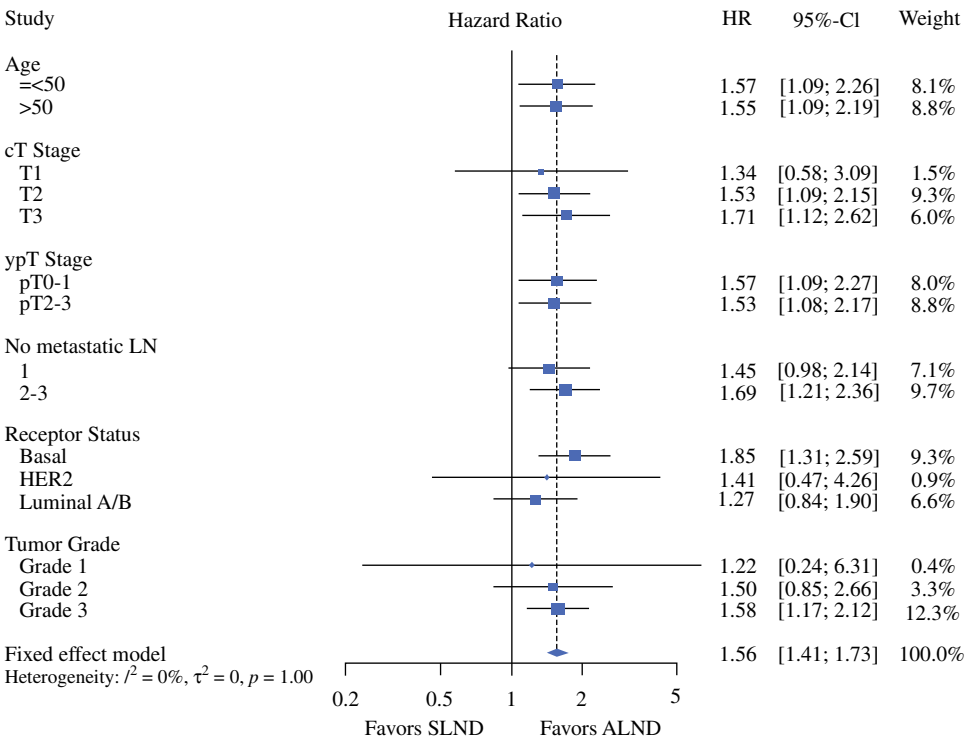

FIG. 3 Subgroup analyses. Forest plot showing association between SLND and OS. HR < 1 favors SLND and HR > 1 favors ALND. *Weight* represents contribution of each subset of patients. *Horizontal lines* show the corresponding 95% confidence interval (CI)

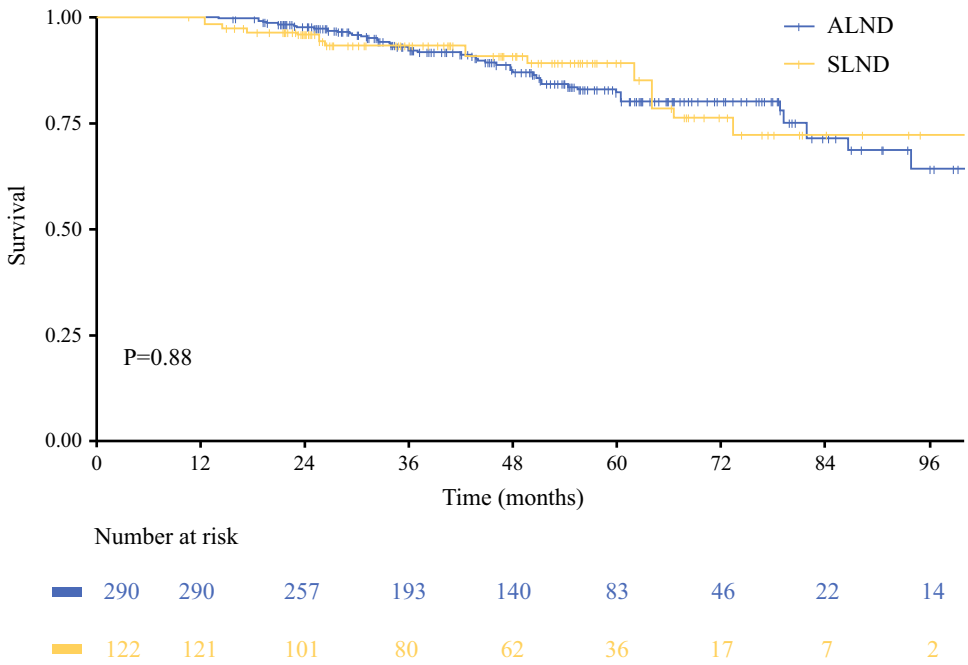

FIG. 4 Kaplan-Meier survival curve for the matched SLND and ALND cohorts for patients with luminal A or B tumors and a single metastatic lymph node

influences a clinician's decision of whether to pursue SLND or ALND. Additionally, the NCDB reports the use of RNI, but does not specify the nodal regions covered, so an imbalance between the nodal basins irradiated in each of the study groups is possible Finally, this analysis is a retrospective study with potential selection biases. We attempted to minimize the impact of these potential biases by matching for all available patient, tumor, and treatment related variables, and using doubly robust multivariable analyses, but imbalances between the treatment groups in factors not captured by the NCDB remain possible. Most notably, the NCDB does not record compliance with endocrine therapy, use of HER2-directed therapy, or the chemotherapy agents used for treatment, so it is not

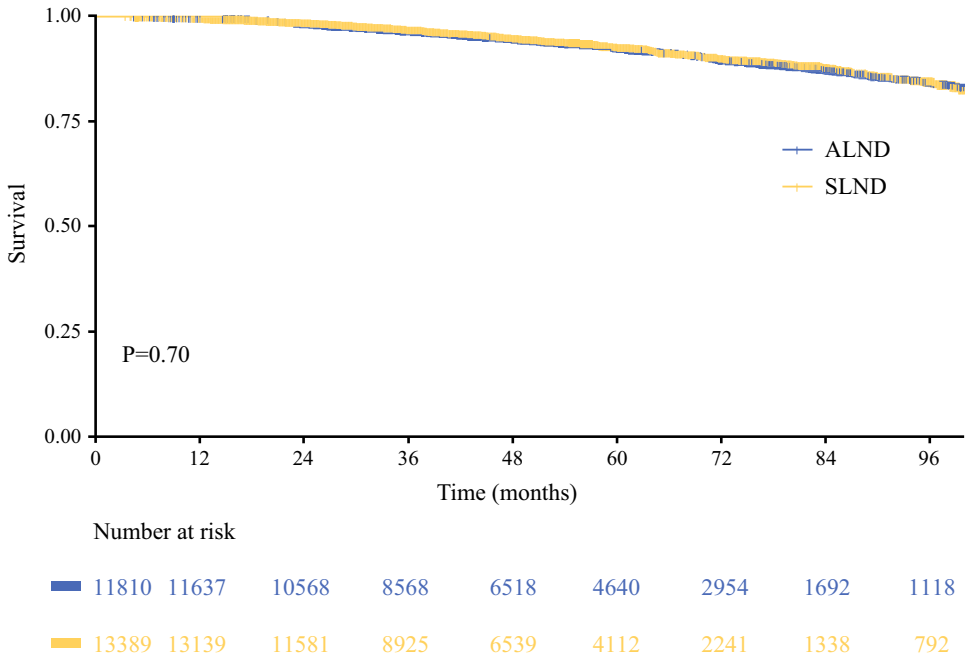

FIG. 5 Kaplan-Meier survival curve for the matched SLND and ALND cohorts for patients who met the eligibility criteria of ACOSOG Z0011

possible account for possible differences between the study groups in these factors.

CONCLUSIONS

Our analysis suggests that SLND alone, even when combined with RNI, may be associated with inferior survival in patients with residual N1 nodal disease following NAC. While exploratory subgroup analyses suggest that SLND might be appropriate in patients with minimal residual disease and favorable tumor biology, ALND should not be routinely omitted in this patient population until its efficacy is confirmed by prospective trials.

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