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The Role of Axillary Lymph Node Dissection in Breast Cancer Patients With Residual Nodal Disease After Receiving Neoadjuvant Chemotherapy

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Abstract

Background: While sentinel lymph node biopsy (SLNB) in breast cancer patients with limited axillary disease undergoing upfront surgery is well-accepted, there are insufficient data supporting its safety with residual nodal disease (RND) following neoadjuvant chemotherapy (NAC). **Objectives:** To evaluate axillary management and oncologic outcomes of patients with RND. **Design:** A retrospective review comparing patients receiving SLNB to those receiving axillary lymph node dissection (ALND). **Methods:** Patients treated for breast cancer at our institution between 2015 and 2023, who received NAC and had RND, were identified. Patient and tumor characteristics, treatments, and outcomes information were collected. The relationship between axillary management and oncologic outcomes was examined. **Results:** Of 155 patients, median age was 55 years (interquartile range [IQR] 46–64) and follow-up 56 months (IQR 34–73). Most patients were pathologic tumor stage 1–2 (105, 67.7%) and nodal stage 1 (106, 68.4%), with ductal histology (127, 81.9%). The most common receptor pattern was estrogen receptor-positive, progesterone receptor-positive, and human epidermal growth factor receptor 2-negative. A total of 107 (69.0%) underwent mastectomy, 47 (30.3%) lumpectomy, and 138 (89.0%) received adjuvant radiation. Regarding axillary management, 121 (78.1%) underwent ALND and 34 (21.9%) SLNB. Univariate analysis found no differences in overall survival (68.6% vs 70.6%; $P = 1$), any recurrence (local, axillary, or distant; 36.4% vs 35.3%; $P = 1$), or specifically axillary recurrence (9.9% vs 8.8%; $P = 1$), between ALND and SLNB groups, respectively. This was also demonstrated on multivariate analysis. Conversely, there was a significantly increased rate of lymphedema in the ALND, 57.9%, vs the SLNB group, 35.3% ($P = 0.03$). **Conclusions:** ALND was not associated with improved survival or recurrence risk compared with SLNB in patients with RND following NAC, but was found to have a higher rate of lymphedema. This study is limited due to its retrospective nature. Further data, such as from the ALLIANCE A011202 trial, will help to further clarify the optimal oncologic management for this group of patients.

Keywords

Breast cancer, neoadjuvant chemotherapy, axillary lymph node dissection, residual nodal disease, breast surgery, lymphedema, sentinel lymph node biopsy

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Introduction

The surgical management of breast cancer has significantly evolved throughout the years. This has progressed from radical mastectomy, a more extensive and morbid surgery, comprising removal of the entire breast, pectoralis muscles, and axillary nodes, to simple mastectomy, and later to the acceptance of breast conservation surgery, with studies such as NSABP-04 and NSABP-06.[1–3] Similarly, with advances in early diagnosis, systemic therapies, and radiation, there has also been a gradual de-escalation of axillary surgery.[4] As axillary lymph node dissection (ALND) has been associated with notable morbidity, including diminished arm mobility, lymphedema

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of the upper extremity, and neuropathy, clinical trials like NSABP-32 helped to demonstrate that less extensive axillary surgery, or sentinel lymph node biopsy (SLNB) alone, did not compromise oncologic outcomes if the sentinel nodes were negative.[5] Studies such as ACOSOG Z0011, then took this a step further, again indicating oncologic safety in de-escalating axillary surgery, even in the scenario of 1-2 positive sentinel nodes.[6]

However, these studies have examined the de-escalation of axillary surgery in the upfront surgery setting. With advantages from neoadjuvant chemotherapy (NAC), including the potential for breast conservation, direct evaluation of treatment response allowing for the more rapid development of new therapies, and prognostic information, pre-surgical chemotherapy has been increasingly utilized.[7] In light of this, the efficacy of SLNB following NAC for patients with initial nodal involvement was examined, as treatment changes in the axilla could alter the accuracy of SLNB. Studies such as ACOSOG Z1071 have indicated that SLNB in this setting is feasible. They found that the false negative rate (FNR) was acceptably low in patients who converted to cN0 with NAC and that ALND could be avoided when the initial, biopsy-proven, metastatic node was excised as part of the SLNB specimen, or if at least three negative sentinel nodes were found.[8,9]

While there have been several trials supporting the de-escalation of axillary surgery, or SLNB alone, for patients with initially clinically positive nodes and complete response to NAC, there is limited data to indicate that SLNB alone is adequate with residual axillary involvement as has been demonstrated in the upfront surgery setting.[10,11] Currently, the standard of care is to proceed with ALND when there is residual nodal disease (RND) in the axilla, which may in part be due to concern for refractory disease or that the potential nodal disease burden may not be effectively treated by radiation.[12,13] However, there is some evidence suggesting that RND does not require a completion ALND, that SLNB is oncologically safe, and that the use of SLNB in this scenario is increasing.[14,15] As clinical practice patterns are already trending toward increasing use of SLNB in this scenario, higher level studies, such as ALLIANCE A011202 and TAXIS, are currently underway examining this question.[16,17]

In the interim, additional studies are needed to determine the oncologic safety of de-escalating axillary surgery in the post-NAC setting when RND is present. Accordingly, the primary objective of this study was to examine axillary surgical management and subsequent oncologic outcomes of breast cancer patients who received NAC and were found to have RND. Secondary objectives included examining lymphedema rates and outcomes regarding retrieval of the biopsy-proven metastatic axillary node. We anticipated that SLNB alone, even when RND was found, would not compromise oncologic outcomes and result in a lower rate of lymphedema when compared with ALND.

Methods

Approval from the Novant Health Institutional Review Board was acquired (approval #24-2612) on April 19, 2024 for this retrospective study, utilizing de-identified information, and patient consent was not required. The reporting of this study conforms to the STROBE statement (Supplementary Document 1).[18] Patients treated for breast cancer at our institution between 2015 and 2023 were included if they received NAC followed by surgical management and were found to have residual nodal disease on final surgical pathology. Patients were excluded if they presented with distant metastatic disease, were determined to be node positive based only on an intramammary node, had only residual isolated tumor cells in the nodes, or received definitive oncologic treatment outside of our hospital system. Primary outcomes included the association between type of axillary surgery received with survival and recurrence, comprising local, axillary, and distant recurrences. Secondary outcomes included the association of axillary surgery received and lymphedema, and association of confirmed retrieval of the biopsy-proven metastatic axillary node with oncologic outcomes.

Patient and tumor characteristics were collected, including demographics, tumor histology and biomarkers, tumor size, clinical and pathological staging, and residual cancer burden (RCB). Oncologic management including receipt of and deviations from planned course of NAC, type of breast and axillary surgery received, retrieval of biopsy-proven clipped node, receipt of radiation, receipt of adjuvant systemic therapy, and outcomes data were also compiled. Axillary surgery groups were divided into ALND and SLNB groups. The ALND group included patients undergoing ALND alone and SLNB $\pm$ targeted axillary dissection (TAD) followed by ALND. The SLNB group comprised patients undergoing SLNB $\pm$ TAD. The type of axillary surgery received was determined by the procedure documented in the operative report.

Patients were considered to have completed NAC if they ultimately completed the planned course despite any delays or dose reductions and were considered not to have completed NAC if the course was discontinued early due to disease progression or intolerance. Patients were regarded to have lymphedema if this was included as a diagnosis in the electronic medical record following breast cancer treatment, was documented by physical therapy, or if there was documentation of arm swelling by a member of the breast cancer treatment team. Retrieval of the biopsy-proven metastatic axillary node was considered confirmed if the biopsy clip was verified to be excised by pathology report or specimen radiograph. Local recurrence was defined as any relapse following surgical excision involving the residual breast tissue or mastectomy flap; axillary recurrence as relapse in the ipsilateral axillary nodes; and distant recurrence as relapse in the contralateral axilla or other remote disease sites.

All analyses were conducted using R Statistical Software (version 4.3.2).[19] After excluding any necessary data points, descriptive statistics were generated for all variables. Numeric variables were summarized using the median and range. Statistical comparisons were conducted using t-tests, analysis of variance (ANOVA), or Wilcoxon tests for

continuous variables. For categorical data, chi-squared tests or Fisher's exact tests were used when appropriate. To assess the relationship between axillary surgery type and recurrence or survival while accounting for potential confounders, a matching method via the MatchIt package in R was utilized. When a confounding variable was found to be significant, cohorts were subset, and matched pairs were created to achieve balanced groups. This process was repeated for each response variable analyzed (any recurrence; distant, local, or axillary recurrence; and survival). The number of matched pairs was maximized, ensuring cohort balance while retaining the largest possible sample sizes for statistical testing.

Results

A total of 155 patients were included. The median age was 55 years (IQR 46–64), and follow-up 56 months (IQR 34–73 for living patients, IQR 3–108 when including patients who passed away during the follow-up period). Most patients were White 89 (57.4%) or Black/African American 63 (40.6%), followed by Asian 2 (1.2%), and other 1 (0.6%). Most patients were pathologic tumor stage 1–2, pathologic nodal stage 1, had ductal histology, and were estrogen receptor-positive (ER), progesterone receptor-positive (PR), and human epidermal growth factor receptor 2-negative (HER2). Most patients also completed their anticipated course of NAC and received adjuvant radiation (Table 1).

Of the 37 patients who did not complete the intended course of NAC, 7 stopped early due to disease progression, and 30 due to intolerance or medical complications. Of the 17 patients who did not receive adjuvant radiation, 12 refused, and 5 did not make it to radiation due to rapid recurrence and metastatic disease. Of the patients recommended for adjuvant endocrine therapy, 9 refused, and of the patients recommended for adjuvant chemotherapy, 9 refused. The remaining 146 (94.2%) either received the recommended adjuvant systemic therapies or it was not applicable due to rapid recurrence and metastatic disease necessitating changes to the planned treatments.

Regarding breast surgical management, 107 (69.0%) underwent mastectomy, and 47 (30.3%) lumpectomy, while one patient received axillary surgery only for clinical T0 N1 disease. For axillary surgical management, 121 (78.1%) underwent ALND, and 34 (21.9%) SLNB. The median number of nodes examined in the ANLD group was 12 (IQR 8–15) and 4 (IQR 3–5) in the SLNB group. The median number of positive nodes in the ALND group was 3 (IQR 1–5), and 1 (IQR 1–3) in the SLNB group. The biopsy-proven metastatic node, when marked by a clip, was confirmed excised in 54 (34.8%) and not confirmed removed in 37 (23.9%). The metastatic node was not marked in 64 (41.3%).

The median time to any recurrence was 8.5 months (IQR 3–24.5). Of the 56 (36.1%) patients who experienced any type of recurrence, overall, 18 (11.6%) had a local recurrence, 15 (9.7%) had an axillary recurrence, and 51 (32.9%) had a distant recurrence. Most patients experienced only a distant recurrence, 33 (21.3%), followed by all three types of recurrence, 9 (5.8%). The remaining experienced local and distant recurrence in 5 (3.2%), axillary and distant recurrence in 4 (2.6%), local recurrence only in 3 (1.9%), axillary and local recurrence in 1 (0.6%), and axillary recurrence only in 1 (0.6%).

Univariate analysis found no differences in any recurrence (local, axillary, or distant; 44/121 [36.4%] vs 12/34 [35.3%], $P=1$), axillary recurrence (12/121 [9.9%] vs 3/34 [8.8%], $P=1$), or overall survival (83/121 [68.6%] vs 24/34 [70.6%], $P=1$), between the ALND and SLNB biopsy groups, respectively. There was also no difference in breast cancer-specific survival (BCSS) between ALND (83/110 [75.5%]) and SLNB (24/33 [72.7%], $P=0.82$) or distant recurrence (39/121 [32.2%] vs 12/34 [35.3%], $P=0.84$), as shown in Figure 1. This trend was also demonstrated on multivariate analysis, when accounting for receptor status, pathologic tumor and nodal stage, histology, RCB status, retrieval of clipped node, receipt of adjuvant RT, and completion of NAC (Table 2). Conversely, there was a significantly increased rate of lymphedema in the ALND group, 57.9%, vs the SLNB group, 35.3% ($P=0.03$).

Subgroup analyses examining oncologic outcomes by the number of nodes retrieved, <10 vs >10, also revealed no significant differences in local recurrence (9/75 [12%] vs 9/80 [11.2%], $P=1$), axillary recurrence (6/75 [8%] vs 9/80 [11.2%], $P=0.59$), distant recurrence (25/75 [33.3%] vs 26/80 [32.5%], $P=1$), or overall survival (53/75 [70.7%] vs 54/80 [67.5%], $P=0.80$), respectively (Figure 2). An analysis was also performed to examine outcomes by confirmed retrieval of the clipped node compared with outcomes for those patients where the clipped node was not confirmed excised, or the metastatic axillary node was not marked. There was no significant difference between when the marked node was confirmed excised vs not confirmed/not marked for any recurrence (31.5% vs 38.6%, $P=0.48$), local recurrence (9.3% vs 12.9%, $P=0.61$), axillary recurrence (5.6% vs 11.0%, $P=0.26$), or distant recurrence (25.9% vs 36.6%, $P=0.24$). However, there was a significant difference in overall survival, 83.3% in the confirmed excised group vs 61.4% in the group where the node was not confirmed excised/not marked ($P=0.01$) and in BCSS, 84.9% vs 68.9% ($P=0.05$), respectively.

Discussion

The oncologic safety of omitting ALND in the setting of RND following NAC is a current area of interest. The de-escalation of axillary surgery can help to minimize associated morbidity such as lymphedema. While the safety of omitting ALND in the event of positive sentinel lymph nodes has been demonstrated with upfront surgery, data in the post-NAC setting is lacking. This study sought to examine the oncologic outcomes between ALND and SLNB, for patients with RND following NAC.

Our study indicated that a greater extent of axillary surgery in the post-NAC setting with RND was not associated with improved oncologic outcomes such as a lower risk of recurrence, including local, axillary, or distant

Table 1. Patient, malignancy, and non-surgical treatment characteristics in patients with residual nodal disease.

Patient characteristics (n = 155)	ALND (n = 121)	SLNB (n = 34)	*P*-value
Age, years, median (IQR)	56.0 (45.0-65.0)	55.0 (46.8-62.0)	0.80
BMI, kg/m^2, median (IQR)	29.6 (26.0-33.3)	26.7 (23.8-31.9)	0.13
ECOG PS (n, %)			
0	89 (79.5)	28 (87.5)	0.66
1	20 (17.9)	4 (12.5)	
2	3 (2.7)	0 (0.0)	
Unknown	9 (7.4)	2 (5.9)	
Malignancy characteristics (n, %)			
Clinical tumor stage			
T0	1 (0.8)	0 (0.0)	0.37
T1	18 (14.9)	7 (20.6)	
T2	51 (42.1)	17 (50.0)	
T3	34 (28.1)	9 (26.5)	
T4	17 (14.0)	1 (2.9)	
Pathological tumor stage			
T0	8 (6.6)	2 (5.9)	0.37
T1	37 (30.6)	16 (47.1)	
T2	41 (33.9)	11 (32.4)	
T3	29 (24.0)	5 (14.7)	
T4	6 (5.0)	0 (0.0)	
Clinical nodal stage			
N0	11 (9.1)	7 (20.6)	0.17
N1	86 (71.1)	23 (67.6)	
N2	14 (11.6)	1 (2.9)	
N3	10 (8.3)	3 (8.8)	
Pathological nodal stage			
N1	76 (62.8)	31[a] (91.2)	**0.004**
N2	36 (29.8)	3 (8.8)	
N3	9 (7.4)	0 (0.0)	
RCB			
1	3 (2.5)	1 (2.9)	0.54
2	26 (21.8)	10 (29.4)	
3	46 (38.7)	9 (26.5)	
Not specified	46 (38.0)	14 (41.2)	
Grade			
1	13 (10.7)	4 (11.8)	0.85
2	49 (40.5)	15 (44.1)	
3	59 (48.8)	15 (44.1)	
Tumor histology			
Ductal	96 (79.3)	31 (91.2)	0.36
Lobular	11 (9.1)	1 (2.9)	
Other	14 (11.6)	2 (5.9)	
Invasive cancer receptors			
ER+, PR+/−, HER2−	59 (48.8)	16 (47.1)	0.76
ER+, PR+/−, HER2+	13 (10.7)	6 (17.6)	
ER−, PR−, HER2+	5 (4.1)	1 (2.9)	
ER−, PR−, HER2−	44 (36.4)	11 (32.4)	
Non-surgical treatment characteristics (n, %)			
Completed course of NAC			
Yes	93 (74.4)	25 (83.3)	0.35
No	32 (25.6)	5 (16.7)	
Adjuvant radiation			
Yes	109 (90.1)	29 (85.3)	0.53
No	12 (9.9)	5 (14.7)	

ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; ECOG PS, Eastern Cooperative Oncology Group performance status; RCB, residual cancer burden; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor; NAC, neoadjuvant chemotherapy.

[a]One patient was at least pN1 but difficult to quantify due to matted disease.

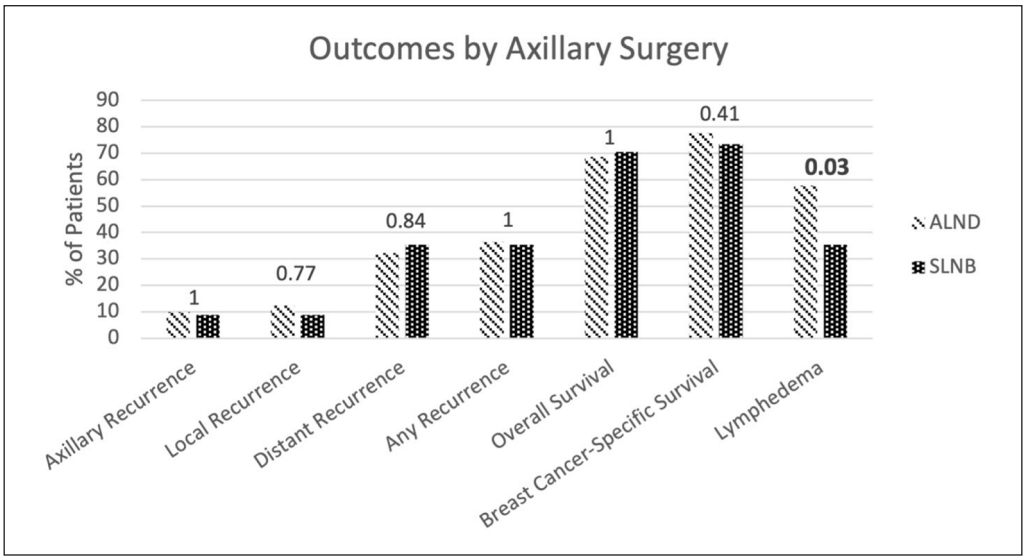

Figure 1. Percent of patients by oncologic outcome and compared by type of axillary surgery received. *P*-values from univariate analysis indicated above each comparison with bold text indicating statistically significant difference.

Table 2. Multivariate analysis accounting for confounding variables when assessing for oncologic outcomes.

	Axillary Recurrence	Local Recurrence	Distant Recurrence	Any Recurrence	Overall Survival	Breast Cancer-Specific Survival	Lymphedema
	P	*P*	*P*	*P*	*P*	*P*	*P*
Axillary surgery (ALND vs SLNB)	0.68	1.00	0.30	0.37	0.35	0.68	**0.03**
Receptor status							
ER (negative vs positive)	0.53	0.24	1.00	0.20	0.88	0.88	0.92
PR (negative vs positive)	0.75	0.38	1.00	0.20	0.95	0.95	1.00
HER2 (negative vs positive)	1.00	1.00	1.00	1.00	1.00	1.00	0.45
ypT Stage (T0-1 vs T2/3)	0.48	0.19	0.14	0.37	0.92	0.92	0.72
ypN Stage (N1 vs N2/3)	0.48	0.19	0.26	0.36	0.76	0.92	1.00
Histology (ductal vs lobular)	0.46	1.00	0.62	1.00	1.00	1.00	0.23
RCB (1–2 vs 3)	NA	NA	0.17	1.00	1.00	1.00	0.69
Retrieval of clipped node (yes vs no)	1.00	0.99	0.47	0.87	0.71	1.00	0.60
Received radiation (yes vs no)	0.06	0.40	0.76	0.10	1.00	0.59	0.07
Completed NAC (yes vs no)	0.42	0.29	1.00	0.60	1.00	1.00	0.98

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor; residual cancer burden; NAC, neoadjuvant chemotherapy.

recurrences. This trend also held true whether defining extent of axillary surgery by the number of nodes removed, >10 vs <10, or by ALND vs SLNB. This is comparable to another retrospective review from Park et al where there were also no significant differences found in recurrence rates over a median follow-up of 75.3 months, between ALND and SLNB, with regional recurrence rates of 9.3% and 8.2%, axillary recurrences rates of 4.8% and 4.7%, and distant recurrence rates of 29.1% and 18.2%, respectively. In addition, this study similarly showed that the most common pattern of failure was distant recurrence.[15] However, our study noted somewhat higher rates of distant failure, from 32.2% to 35.3%. This difference may be explained by greater disease burden in our study. Dissimilar from the study by Park et al, we did not specifically exclude patients with suspicious internal mammary or supraclavicular nodes, and our patients may reflect a group with more unfavorable prognostic factors such as higher RCB status and progression during NAC.

Muslumanoglu et al likewise demonstrated acceptable outcomes for patients with minimal residual nodal disease (1–3 positive nodes) undergoing only SLNB in this setting. Recurrence rates were low, with only 8 of 139 (5.6%) patients experiencing any recurrence. Specifically, no axillary recurrences were seen with a median follow-up period of 44 months.[20] This differs from our study in that our overall recurrence rate was 36.1%, but with similar recurrence rates in both the ALND and SLNB groups. And again, our study included patients with more significant clinical and residual nodal disease, without specifically excluding patients with suspicious internal mammary or

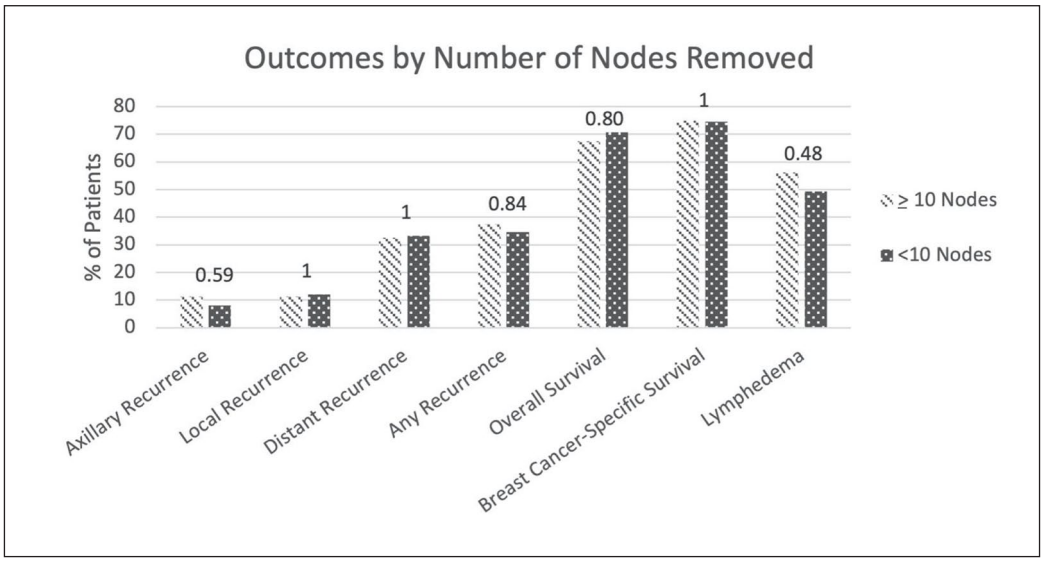

Figure 2. Percent of patients by oncologic outcome when compared by number of axillary nodes retrieved. *P*-values from univariate analysis indicated above each comparison.

supraclavicular nodes, and nearly a third of our patients had four or more metastatic axillary nodes. We also had longer follow-up, with a median of 56 months. More importantly, we found no difference in oncologic outcomes, including recurrences between the SLNB and ALND groups, despite an overall greater burden of disease.

Another retrospective study utilizing data from the NSABP-40 and NSABP-41 trials also examined this question and similarly showed that more extensive axillary surgery (ALND) did not improve oncologic outcomes vs less axillary surgery (SLNB). With a median follow-up of 4.5–5.1 years, disease-free survival at 5 years between the two trials was 50%–71% in the SLNB group and 55%–68% in the SLNB + ALND/ALND group. Analyses examining loco-regional recurrence, distant recurrence, and overall survival demonstrated no association with adverse oncologic outcomes such as increased risk for recurrence or worse survival between the SLNB and SLNB + ALND/ALND groups.[21] This is concordant with our finding that more extensive axillary surgery was not associated with worse oncologic outcomes, having similar rates of recurrence and overall survival.

These findings also support the idea that breast cancer tumor biology and behavior is more significant in predicting oncologic outcomes rather than the extensiveness of surgery. It is well-known that breast cancer is a heterogeneous disease and treatments are tailored based on tumor factors such as molecular subtype, histology, and grade. Advances in systemic therapies such as chemotherapy and hormonal therapy have been attributed to improved breast cancer survival, with a 5 year relative survival rate of nearly 90%.[22] It has also been shown, for example, that HER2 + and triple negative breast cancers have the highest rates of recurrence within the first 5 years compared with hormone sensitive tumors, and that these subtypes have a propensity for different metastatic patterns, even without considering the impact from surgery.[23–25] Meanwhile, landmark studies such as NSABP-04, in which patients did not receive systemic therapy, found no significant difference in local-regional recurrence ($P = 0.67$) or overall survival ($P = 0.49$) in patients who were clinically node positive and underwent either radical mastectomy or total mastectomy with adjuvant radiation.[3] More contemporary studies have also indicated that the extensiveness of surgery does not necessarily equate to better outcomes, such as breast conservation having better overall survival compared with mastectomy (hazard ratio 1.34), even when accounting for nodal status.[26]

Another interesting concept that may be a factor in breast cancer outcomes and played a role in our findings is the extensiveness of surgery impacting the cancer microenvironment. For instance, in the previously mentioned study, breast conservation had on average a 34% greater overall survival and 38% greater BCSS than mastectomy even when adjusting for prognostic variables. Beyond attributing this to improved systemic therapies, a proposed mechanism for this relates to the extent of surgical trauma affecting the immune system.[26] Following surgical insult, the body's mechanisms that promote wound healing, such as an increase in cytokines stimulating angiogenesis, can also influence tumor growth and could activate dormant metastases. And consequently, while the surgical excision of breast cancer is beneficial, there could also be adverse immunologic effects spurring cancer progression.[27–29]

From this theory, treatment considerations for modulating inflammation in the perioperative period also arose, such as a study from Forget et al which demonstrated improved recurrence-free survival with intraoperative ketorolac use. In this retrospective study, 327 women underwent mastectomy with axillary dissection. The rate of cancer recurrence was 17% in patients who did not receive ketorolac, compared with 6% in those who received ketorolac ($P = 0.019$), with a median follow-up of 27.3 months.[30] More recently, Badwe et al also suggested

this mechanism as a factor in their findings, suggesting that modulating the body's response to surgical trauma may help prevent disseminating tumor cells and prevent the stimulation of tumor growth. In this multicenter, randomized control trial of 1,583 patients, which also included patients with cN1 disease undergoing either lumpectomy or mastectomy, they examined the effects of peritumoral lidocaine injection on oncologic outcomes. They found a 4% improvement in disease-free survival ($P=0.017$) and overall survival ($P=0.019$) in patients who received peritumoral lidocaine injections.[31] Similarly, this mechanism may relate to our findings. While there is concern that less extensive axillary surgery leads to leaving more nodal disease behind and may negatively impact oncologic outcomes, we did not find this to be the case.[32] Instead, we found equivalent oncologic outcomes regardless of the extent of axillary surgery. This could relate to provoking a lesser immune response and diminished stimulation of protumorigenic pathways with less extensive axillary surgery, despite potentially leaving behind additional nodal disease when compared with more extensive axillary surgery.

While we did not find a significant difference in oncologic outcomes based on the axillary surgery received, there was a significant association between the extent of axillary surgery and lymphedema. In our cohort, 57.9% of patients in the ALND group vs 35.3% in the SLNB group ($P=0.03$) experienced lymphedema. The association between more aggressive axillary surgery and lymphedema has been well established. For example, the AMAROS trial, which examined the de-escalation of axillary surgery with positive nodes in specifically the upfront surgery setting, demonstrated signs of lymphedema in 23% of ALND patients at 5 years vs only 11% in the SLNB with radiation group ($P<0.001$).[33] A meta-analysis examining the incidence of breast cancer–related lymphedema showed rates approaching 30% in patients undergoing ALND.[34] Additional studies have also demonstrated even higher rates of lymphedema in patients who received NAC followed by ALND compared with those who had upfront ALND, in those who received longer courses of NAC, and those who had a higher BMI, with rates of lymphedema up to 58.4%, which is in alignment with our findings.[35,36] This trend toward higher rates of lymphedema in patients receiving NAC has also been demonstrated in the setting of SLNB. In a 2024 study by Byeon et al,[37] there was a significantly increased risk of lymphedema in this group of patients (OR 5.34). While this does demonstrate the overall increased risk of lymphedema in the NAC setting, the rate is still significantly higher in patients undergoing ALND than in those undergoing SLNB. This helps to highlight the importance of balancing the extensiveness of axillary surgery with oncologic safety and quality of life in this group of patients.

Conversely, when defining extent of axillary surgery by the number of nodes retrieved, >10 compared with <10, no significant differences in lymphedema rates were found, 56.2% and 49.3%, respectively ($P=0.48$). Studies have been conflicting on whether the number of nodes removed increases lymphedema rates. For instance, studies in women undergoing SLNB alone found no differences in lymphedema rates based on the number of nodes retrieved, even when >10 nodes were removed.[38,39] On the other hand, studies have also suggested that a greater number of removed nodes increases lymphedema risk, including a study demonstrating an increased risk when >5 nodes are removed, and another finding an increase in risk of 4.1% for each node removed.[40,41] And still others have found that the differences in lymphedema rates between SLNB and ALND go beyond just the number of nodes removed, proposing that factors such as aggressiveness of the intended axillary surgery disrupting lymphatics is likely a more significant contributor.[42,43]

It has been an area of debate on whether to clip and retrieve a metastatic axillary node. On one side of the argument, studies demonstrating the safety of SLNB in the NAC setting indicated the FNR was improved with retrieval of the clipped node, wherein FNR was used as a surrogate for oncologic safety and accuracy of node sampling.[8] On the other side, some studies have showed that the status of the clipped lymph node usually did not impact adjuvant treatment recommendations but did tend to alter the extent of axillary surgery, and that when the clipped node contained metastatic disease other sentinel nodes were likely to be positive.[44–46] Interestingly, we found that when examining oncologic outcomes by whether the clipped, involved, axillary lymph node was confirmed excised, overall survival and BCSS were statistically better in the group where the clipped node was confirmed to be excised. This may suggest that clipping the involved node and confirming its excision could improve survival. One explanation could relate to differences in recurrence patterns. While outcomes remained similar overall in terms of recurrence, axillary and distant recurrences trended lower when the clipped node was excised. Although not significant in our study, the rate of axillary and distant recurrence when the clipped node was confirmed removed were lower, at 5.6% and 25.9%, than when the node was not clipped or confirmed excised, at 11.9% and 36.6%, respectively. Additional differences between the groups, such as changes in adjuvant recommendations based on the status of the clipped node, access to care, or delays in starting adjuvant therapies, could also play a role.

Overall, we found that regardless of the type of axillary surgery received, ALND or SLNB, or the extent of axillary surgery as defined by the number of nodes removed, >10 or <10, that a more extensive axillary surgery was not associated with improved oncologic outcomes. However, ALND was found to be associated with a significantly increased risk of lymphedema compared with SLNB. These results suggest that RND following NAC may not necessitate an ALND, and that SLNB alone could be an oncologically acceptable alternative, offering comparable oncologic outcomes while reducing morbidity, including the risk of lymphedema. In addition, further data, such as from the ALLIANCE A011202 and TAXIS trials, will help to further clarify the optimal oncologic management for this group of patients.

Limitations

Limitations of this study include its retrospective nature and smaller sample size at a single institution, despite congruent findings with the literature. Further higher-level data, such as from the ALLIANCE A011202 and TAXIS trials, will help to further clarify the optimal oncologic management for this group of patients.

Conclusions

SLNB was not associated with worse survival or recurrence risk compared with ALND in patients with RND following NAC. However, ALND was found to have a significantly higher rate of lymphedema. This suggests that a positive SLNB may not necessitate a completion ALND in patients treated with NAC and that SLNB alone with RND may be oncologically safe and carry less morbidity.

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Ethical Considerations

This study received ethical approval from the Novant Health Institutional Review Board (approval #24-2612) on April 19, 2024.

Consent to Participate

This is an IRB-approved retrospective study, all patient information was de-identified and patient consent was not required. Patient data will not be shared with third parties.

Author Contributions

Kristina Shaffer: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Writing—original draft; Writing—review & editing.
Lilian Harris: Data curation; Project administration; Writing—review & editing.
Lori Gentile: Conceptualization; Data curation; Writing—review & editing.
Amelia Merrill: Data curation; Writing—review & editing.
Lori Kellam: Data curation; Writing—review & editing.
Michelle Fillion: Data curation; Writing—review & editing.
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Data Availability Statement

The datasets used and/or analyzed during this study are not publicly available but are available from the corresponding author on reasonable request.

Supplemental material

Supplemental material for this article is available online.

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