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Evolution of Axillary Surgical Management of Patients with Occult Breast Cancer with Axillary Metastasis

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Abstract

Background As axillary surgery de-escalates and neoadjuvant systemic therapy (NST) improves, we sought to evaluate changes in axillary surgery and impact on overall survival (OS) in occult breast cancer with axillary metastasis.

Patients and Methods Using the National Cancer Database, we identified patients with cT0N+ breast cancer who underwent axillary surgery between 2012 and 2023. Lymph node surgery trends were assessed using Cochran–Armitage trends tests and the Kaplan–Meier method evaluated OS.

Results We identified 1817 patients with cT0N+ breast cancer (75% had surgery first and 25% received NST). NST use significantly increased over time. Patients undergoing upfront surgery primarily underwent ALND (94% ALND, 6% SLN only); however, ALND decreased from 96 to 82% (2012–2023), $p < 0.001$. Three-year OS was similar between SLN and ALND in this cohort (96% versus 93%, $p = 0.12$). In patients who received NST, ALND rate was lower and had a greater decrease from 97 to 70% (2012–2023), $p < 0.001$, especially 2017 onwards. Of ypN0 patients, 26.0% underwent SLN only with highest rates in the most recent year (2023: 44.4%), whereas 9.6% of patients with ypN+ had SLN only. OS was similar between SLN only and ALND for patients with ypN0 disease (3 year Kaplan–Meier estimates 100% versus 96%, $p = 0.77$) as well as ypN+ disease (93 versus 91%, $p = 0.43$).

Conclusions For patients with occult breast cancer with axillary metastases, the extent of axillary surgery is deescalating, with the greatest decrease in those receiving NST. Early survival data suggests a lack of survival benefit with ALND compared with SLN surgery with appropriate patient selection.

Keywords Axillary surgery · Breast cancer · Occult breast cancer · Sentinel lymph node surgery · Axillary dissection

Background

Occult breast cancer (OBC) is defined as breast cancer with no identifiable primary breast tumor. This is a rare entity and most commonly presents with axillary metastasis.[1] The American College of Radiology recommends breast magnetic resonance imaging (MRI) for further workup of metastatic cancer suspected to be of breast origin.[2] Breast MRI finds a suspect lesion in the breast in around 70% of cases.[3] Thus, the overall incidence of true OBC without any primary cancer identified in the breast remains low, around 0.1%,[4,5] making large scale randomized control trials challenging to perform.

National Comprehensive Cancer Network (NCCN) provides guidelines on occult primary lesions describing detailed workup; however, once the diagnosis of axillary-limited adenocarcinoma is made, recommendations are to follow NCCN guidelines for breast cancer.[6] NCCN breast cancer guidelines further recommend treatment on the basis of nodal status. For N1 disease, treatment includes either an axillary lymph node dissection (ALND) with mastectomy or ALND with whole breast radiation plus or minus regional nodal irradiation. For cN2 or cN3 disease, neoadjuvant systemic therapy should be considered first followed by ALND and mastectomy. Systemic therapy is otherwise recommended per treatment guidelines for stage II and III breast cancer.[7]

In primary breast cancer, major trials have led to the de-escalation of axillary dissection in both the upfront setting

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(SENOMAC, AMAROS, ACOSOG Z0011, SINODARONE) and after receipt of NST (ACOSOG Z1071, SENTINA, SN FNAC, GANEA).[8–15] With this ongoing trend of deescalating surgery as well as continuous improvements in systemic therapy, such as the introduction of pembrolizumab in triple negative breast cancer and dual agent HER2-targeted therapy in HER2+ disease, we sought to evaluate changes in national practice patterns of axillary management of patients with OBC.[16,17] We also assessed the impact of the type of axillary lymph node surgery on overall survival (OS) in the upfront surgery setting, as well as in the setting of residual nodal disease and nodal pCR after neoadjuvant systemic therapy (NST).

Patients and Methods

The National Cancer Database (NCDB) collects data from Commission on Cancer facilities all over the USA. Over 80% of newly diagnosed breast cancers in the USA are represented.[18] The 2023 de-identified NCDB Participant User File was used for this study. The institutional review board at Mayo Clinic designated this study exempt from review.

All patients with cT0N+ breast cancer in the NCDB between January 2012 and December 2023 who underwent any axillary lymph node surgery were identified. Estrogen receptor (ER) and progesterone receptor (PR) status were considered positive if there was ≥ 1% staining.

HER2 status was defined using the HER2 summary results from immunohistochemistry, fluorescent in situ hybridization, and chromogenic in situ hybridization. Neoadjuvant systemic therapy included chemotherapy, immunotherapy, or endocrine therapy and was defined as being received prior to first surgical procedure. Patients with negative nodes at time of upfront surgery, and those with unclear use of NST were excluded. SLN surgery versus ALND was defined using the scope of regional lymph node surgery 2012 variable and categorized into the levels of SLN surgery (code 2), ALND (codes 3,4 & 5) and any patients undergoing SLN surgery followed by ALND were categorized as ALND (codes 6 & 7). Given the rarity of use of neoadjuvant radiation therapy, adjuvant radiation therapy was defined using an overall radiation use variable which was not dependent on relation to surgery.

Statistics

Patient demographics and clinical characteristics were reported overall among those who were treated with upfront surgery and NST. Continuous variables were reported as median and interquartile range while categorical were reported as number and percentage. Cochran–Armitage trends were used to evaluate overall axillary lymph node surgery trends and among patients undergoing surgery upfront and those undergoing NST followed by surgery. Multivariable logistic regression models were used to evaluate predictors associated with omission of ALND. Patients who were missing data on the predictors included in the models were excluded from that analysis. The 3 year OS was evaluated using the Kaplan–Meier method and reported as Kaplan–Meier estimates with 95% confidence interval. Log-rank tests were used to evaluate OS comparisons. Sensitivity analysis was performed excluding patients who underwent breast conserving surgery (BCS).

SAS version 9.4 (SAS Institute Inc., Cary NC) and R version 4.2.2 (R Foundation for Statistical Computing, Vienna Austria) were utilized for analysis. p values < 0.05 were considered statistically significant.

Results

We identified 3733 patients with cT0N+ breast cancer from 2012 to 2023 in the NCDB and 1817 patients met study inclusion. The median patient age was 61.0 (IQR 53.0, 69.0) years overall and the majority were female (99.0%). The majority of patients underwent upfront surgery (75.1%; 1365/1817), while 23.8% had neoadjuvant chemotherapy (NAC), and 1.1% had neoadjuvant endocrine therapy (NET). Most patients presented with cN1 disease (71.3%). The majority of tumors were ER+/HER2− (52.2%). The most common surgical management of the ipsilateral breast was no breast surgery (45.1%), followed by mastectomy (40.6%) and breast conserving surgery (14.3%) (Table 1).

Use of NST significantly increased from 19.9% in 2012 to 42.4% in 2023 ($p < 0.001$). This increase is predominantly attributed to an increase in use of NAC as use of NET remained low and largely unchanged (Fig. 1). Overall, ALND rates decreased significantly over the time period from 95.9 in 2012 to 77.1% in 2023 ($p < 0.001$).

Patients Treated with Upfront Surgery

The majority of patients underwent upfront surgery, and the average age of these patients was 62 years (IQR 54.0, 69.0) and most commonly had cN1 disease at diagnosis (73.4%) and ER+/HER2− subtype (59.0%). Most patients (56.2%) did not undergo surgery on their breast, 32.2% underwent mastectomy, and 11.6% underwent breast conserving surgery. The majority of patients underwent an ALND (93.6%) with 6.4% of patients having SLN surgery only. Patients had primarily pN1 disease at the time of surgery (59.9%). Overall, 80.6% of patients received adjuvant radiation, with lower rates of adjuvant radiation in pN1 disease at 74.6% compared with 89.0% among pN2 and 88.4% among pN3 disease ($p < 0.001$).

Table 1 Patient demographics and clinical characteristics overall and among patients treated with upfront surgery or neoadjuvant systemic therapy

	Total ($N=1817$)	Upfront surgery ($N=1365$)	NST ($N=452$)
Age at diagnosis, median (IQR)	61.0 (53.0, 69.0)	62.0 (54.0, 69.0)	58.0 (49.0, 66.0)
Sex			
Male	18 (1.0%)	NR	NR
Female	1799 (99.0%)		
Clinical N category at diagnosis			
cN1	1296 (71.3%)	1002 (73.4%)	294 (65.0%)
cN2	364 (20.0%)	258 (18.9%)	106 (23.5%)
cN3	157 (8.6%)	105 (7.7%)	52 (11.5%)
Receptor subtype			
ER+/HER2+	162 (9.5%)	86 (6.7%)	76 (17.6%)
ER+/HER2−	890 (52.2%)	752 (59.0%)	138 (32.0%)
ER−/HER2+	171 (10.0%)	113 (8.9%)	58 (13.5%)
ER−/HER2−	483 (28.3%)	324 (25.4%)	159 (36.9%)
Unknown	111	90	21
Axillary surgery			
SLN	167 (9.2%)	87 (6.4%)	80 (17.7%)
ALND	1650 (90.8%)	1278 (93.6%)	372 (82.3%)
Breast surgical resection			
None	808 (45.1%)	758 (56.2%)	50 (11.3%)
BCS	256 (14.3%)	156 (11.6%)	100 (22.7%)
Mastectomy	726 (40.6%)	435 (32.2%)	291 (66.0%)
Unknown	27	16	11
Pathologic N category			
pN0	208 (14.2%)	–	208 (51.1%)
pN1	754 (51.5%)	633 (59.9%)	121 (29.7%)
pN2/3	502 (34.3%)	424 (40.1%)	78 (19.2%)
Unknown	353	308	45
Adjuvant radiation			
No radiation therapy	338 (19.6%)	251 (19.4%)	87 (20.2%)
Radiation therapy	1389 (80.4%)	1045 (80.6%)	344 (79.8%)
Unknown	90	62	23
Tumor histology			
IDC	988 (54.4%)	718 (52.6%)	270 (59.7%)
ILC	123 (6.8%)	99 (7.3%)	24 (5.3%)
Other	706 (38.9%)	548 (40.1%)	158 (35.0%)
Neoadjuvant systemic therapy			
No NST	1365 (75.1%)	NR	NR
NAC	432 (23.8%)		
NET	20 (1.1%)		

SLN sentinel lymph node, *ALND* axillary lymph node dissection, *BCS* breast conserving surgery, *NST* neoadjuvant systemic therapy, *NAC* neoadjuvant chemotherapy, *NET* neoadjuvant endocrine therapy, *N* Nodal, *ER* estrogen receptor

Over time rates of omission of ALND (i.e. SLN surgery only) increased from 4.3% in 2012 to 18.1% in 2023 ($p<0.001$) (Fig. 2). This change was most predominant in HER2+ (0.0% to 28.6%, $p=0.001$) and ER−/HER2− subtypes (7.1% to 23.5%, $p=0.001$) (Fig. 3A). Rate of use of adjuvant radiation remained relatively stable over time with rate of 78.1% in 2023. Use of adjuvant radiation among patients who underwent ALND was similar to that of those who underwent SLN only (81.1% versus 74.4%, $p=0.13$). On univariate analysis, increasing clinical N category and non-IDC tumor histology were associated with higher likelihood of undergoing ALND while patients undergoing breast-conserving surgery was significantly more likely to have omission of ALND than those not undergoing breast

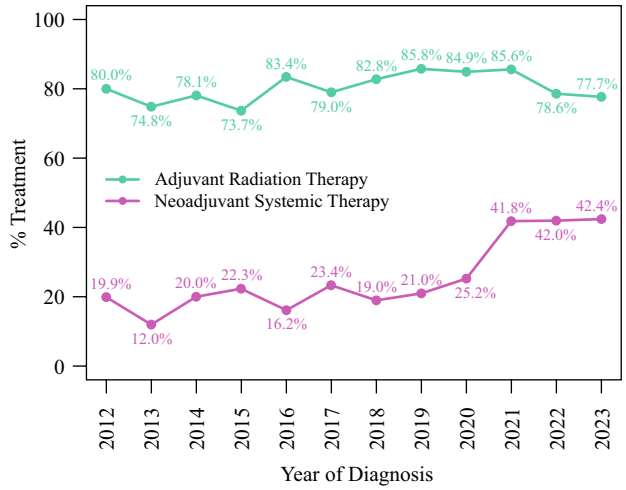

Fig. 1 Rates of neoadjuvant systemic therapy and adjuvant radiation rates over time

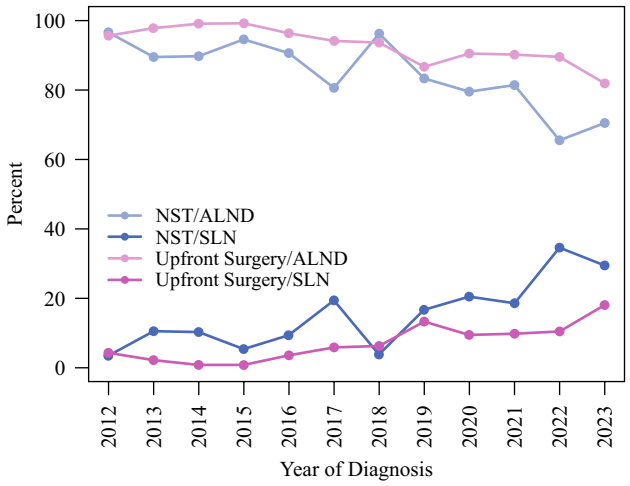

Fig. 2 Rates of ALND and of SLN surgery over time in those treated with neoadjuvant systemic therapy and those with upfront surgery

surgery (Table 2). On multivariable analysis including age at diagnosis, clinical N category, biologic subtype, tumor histology, breast surgical procedure, and facility type, the most significant predictor of omission of ALND was clinical N category with lower likelihood to omit ALND in patients with higher clinical N categories.

The 3 year OS was similar between SLN only and ALND in the upfront surgery setting (95.8% [90.0, 100.0] versus 92.9% [91.2, 94.6], $p=0.12$). Patients who underwent a SLN only procedure with pN1 disease had similar 3 year survival to those who underwent an ALND (97.6% [92.7, 100.0] versus 95.7% [94.0, 97.4], $p=0.32$). Among pN2/pN3 disease 3 year OS for SLN only was 80.0% [49.0, 100.0] and for ALND was 89.0% [85.9, 92.2], $p>0.99$) (Fig. 4A). When stratified by radiation versus no radiation, type of axillary surgery did not affect OS rates (3-year OS with RT: SLN 100.0% [63.1, 100.0] versus ALND 93.2% [91.4, 95.1], $p=0.08$; 3 year OS without RT: SLN 83.1% [63.2, 100.0] versus ALND 91.2% [87.0, 95.6], $p=0.73$.

Patients Treated with Neoadjuvant Systemic Therapy Followed by Surgery

Of the patients treated with neoadjuvant systemic therapy followed by surgery, the median age was 58.0 years (IQR 49.0, 66.0) with primarily cN1 disease at diagnosis (65.0%). The most frequent receptor subtype was triple negative disease (36.9%). The majority of patients (66.0%) underwent mastectomy followed by breast conserving surgery (22.7%) and no breast surgery (11.3%). Overall rate of ALND was 82.3%. The most common pathologic nodal stage after NST was nodal pathologic complete response (ypN0) in 51.1%. The majority of patients (79.8%) received adjuvant radiation.

Over time, ALND rates decreased from 96.6% in 2012 to 70.5% in 2023 ($p<0.001$) with the most substantial decrease occurring from 2017 onwards (Fig. 2). The largest change in ALND rates occurred in the HER2+ subtype (100% to 64%, $p=0.002$) followed by TNBC subtype (87.5% to 66.7%, $p=0.001$) (Fig. 3B). Adjuvant radiation use remained high with a nonsignificant decline from 81.5% in 2012 to 77.2% in 2023 ($p=0.93$). Adjuvant radiation use among patients who underwent ALND was similar to that of those undergoing SLN only (81.5% versus 72.2%, $p=0.06$).

Omission of ALND was higher in patients with complete nodal response (ypN0 disease) where 26.0% had SLN surgery only and 74.0% underwent ALND compared with patients with ypN+ where 9.6% had SLN surgery only and 90.4% had ALND. The highest rates of SLN only among patients with ypN0(sn) disease were seen in the most recent year with 44.4% undergoing SLN only in 2023 which is a substantial increase from 0% in 2012 and 23.5% in 2017. On univariate analysis, increasing clinical N category at diagnosis was associated with lower likelihood to omit ALND. Additionally, ALND was more likely to be omitted in patients treated with BCS (Table 3). On multivariable analysis, both predictors remained associated with the axillary surgical procedure performed.

OS was similar between patients who underwent SLN only compared with those who underwent ALND with ypN0 disease (3-year Kaplan–Meier estimates 100% [84.6, 100.0] versus 96.1% [92.5, 99.5], $p=0.77$). Survival in ypN+ disease was lower than in ypN0 disease (96.9% [94.0, 99.6] pN0 versus 91.4% [87.0, 95.8] pN+ $p=0.001$); however, there was no difference in survival by type of axillary surgery performed in patients with ypN+ disease (92.9% [79.9, 100.0] versus 91.2% [86.6, 95.9], $p=0.43$) (Fig. 4B). When stratified by receipt of radiation versus no radiation, type of axillary surgery again did not affect OS rates (3 year OS with

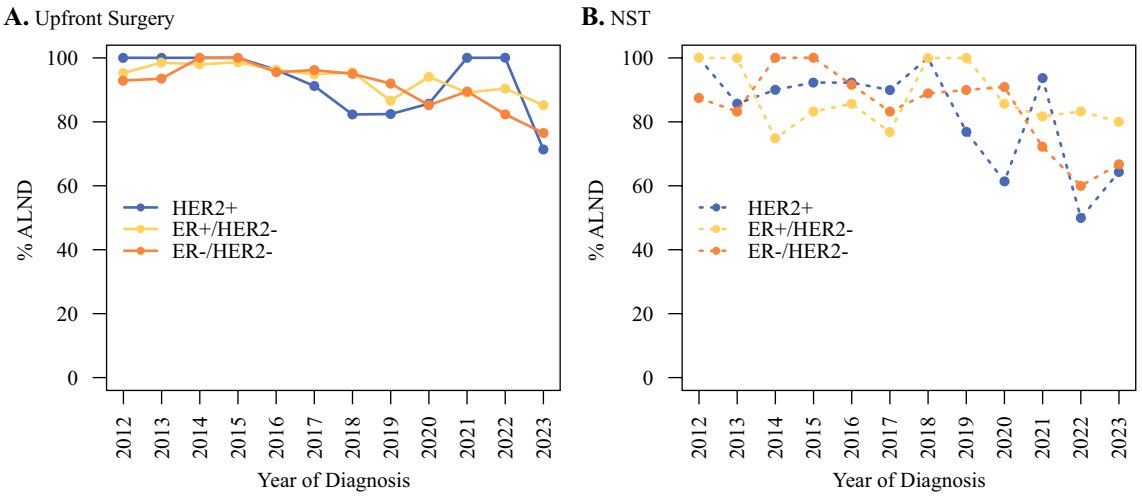

Fig. 3 ALND rates by receptor subtype in patients with occult breast cancer treated with upfront surgery **A** and neoadjuvant systemic therapy **B**

Table 2 Univariate and multivariable logistic regression models predicting omission of ALND in patients who underwent upfront surgery

		Univariate		Multivariable	
Variable	Level	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Age at diagnosis	Per 10 years	0.87 (0.72, 1.05)	0.14	0.95 (0.77, 1.17)	0.61
Clinical N Category at diagnosis	cN1	1.0 reference		1.0 reference	
	cN2	0.33 (0.15, 0.72)	0.005	0.39 (0.17, 0.85)	0.019
	cN3	0.11 (0.02, 0.82)	0.031	0.13 (0.02, 0.97)	0.046
Receptor Subtype	ER+/HER2+	0.98 (0.39, 2.49)	0.97	Not included in MVA	
	ER+/HER2−	0.87 (0.52, 1.46)	0.60		
	ER−/HER2+	0.86 (0.36, 2.07)	0.74		
	ER−/HER2−	1.0 reference			
Histology	IDC	1.0 reference		1.0 reference	
	ILC	0.75 (0.31, 1.78)	0.51	0.82 (0.34, 1.98)	0.65
	Other	0.53 (0.33, 0.87)	0.012	0.57 (0.34, 0.96)	
Breast surgical procedure	None	1.0 reference		1.0 reference	
	BCS	2.09 (1.15, 3.77)	0.015	1.62 (0.87, 2.99)	0.13
	Mastectomy	1.17 (0.72, 1.92)	0.53	0.87 (0.51, 1.49)	0.61
Academic/research facility	No	1.0 reference		1.0 reference	
	Yes	0.71 (0.43, 1.18)	0.19	0.67 (0.40, 1.12)	0.12
Grade (Among patients who underwent breast resection)	I	1.0 reference		Not included in MVA	
	II	0.50 (0.15, 1.71)	0.27		
	III	0.58 (0.18, 1.90)	0.37		

BCS breast conserving surgery, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *N* nodal, *ER* estrogen receptor

RT: SLN 97.2% [91.4, 100.0] versus ALND 92.9% [89.7, 96.2], $p=0.28$; 3 year OS without RT: SLN 100.0% [66.4, 100.0] versus ALND 94.2% [87.4, 100.0], $p=0.69$.

Subset Analysis Excluding Patients Treated with BCS

After excluding patients undergoing BCS, 1561 patients were included with a median age of 61 (53, 68). Use of ALND significantly decreased from 96.8% in 2012 to 80.8% in 2023 which is similar to what was reported in the full cohort. Among those treated with upfront surgery, the majority of patients underwent ALND (94.2%) and a decrease was seen from 97.1% to 82.3%, $p<0.001$. On multivariable analysis, increasing clinical N category remained the most significant predictor of lower likelihood

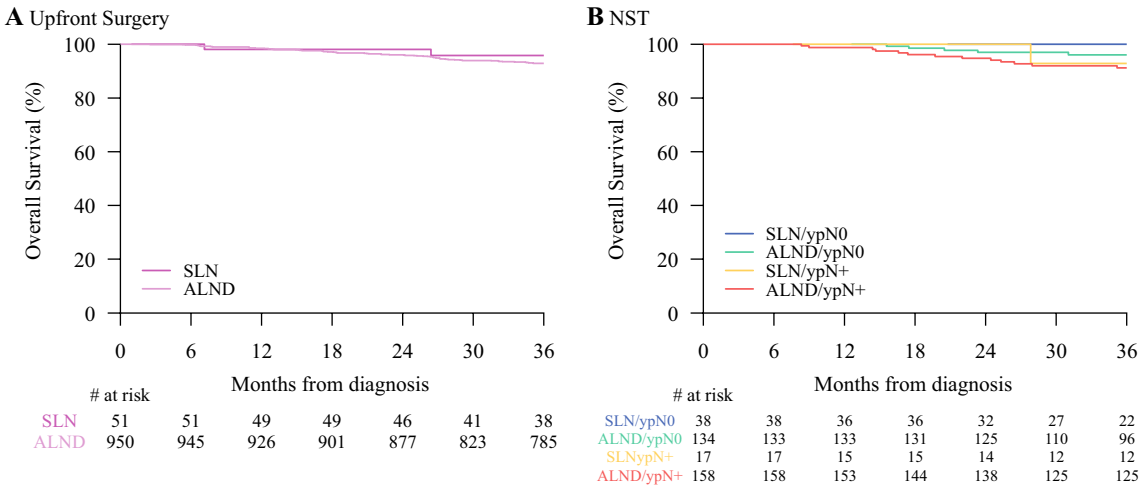

Fig. 4 Overall Survival by nodal surgery and ypN category in patients with occult breast cancer treated with upfront surgery **A** and neoadjuvant systemic therapy **B**

Table 3 Univariate and multivariable logistic regression models predicting omission of ALND in patients treated with NST

		Univariate		Multivariable	
Variable	Level	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Age at diagnosis	Per 10 years	0.96 (0.78, 1.18)	0.70	0.93 (0.70, 1.24)	0.63
Clinical N category	cN1	1.0 reference		1.0 reference	
	cN2	0.23 (0.10, 0.51)	< 0.001	0.22 (0.09, 0.52)	0.001
	cN3	0.20 (0.06, 0.65)	0.008	0.22 (0.06, 0.73)	0.013
Receptor subtype	ER+/HER2+	1.24 (0.63, 2.42)	0.53	Not included in MVA	
	ER+/HER2−	0.73 (0.39, 1.35)	0.32		
	ER−/HER2+	0.90 (0.41, 1.97)	0.78		
	ER−/HER2−	1.0 reference			
Histology	IDC	1.0 reference		1.0 reference	
	ILC	0.55 (0.16, 1.90)	0.34	0.53 (0.15, 1.92)	0.33
	Other	0.59 (0.34, 1.01)	0.055	0.70 (0.38, 1.28)	0.25
Breast surgical procedure	None	1.0 reference		1.0 reference	
	BCS	4.47 (1.47, 13.58)	0.008	4.20 (1.34, 13.17)	0.014
	Mastectomy	2.22 (0.76, 6.45)	0.15	1.88 (0.62, 5.67)	0.26
Academic/research facility	No	1.0 reference		1.0 reference	
	Yes	0.94 (0.55, 1.62)	0.82	0.81 (0.45, 1.46)	0.48
Grade (Among patients who underwent breast resection)	I	1.0 reference		Not included in MVA	
	II	1.85 (0.34, 9.96)	0.47		
	III	1.33 (0.27, 6.46)	0.72		

BCS breast conserving surgery, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma

of omission of ALND (Supplementary Table 1). Among those who underwent NST the proportion undergoing ALND was 85.2% with a decrease from 95.8% to 78.3%, $p < 0.001$. On multivariable analysis, similar to the upfront surgery group, higher clinical N category was the most significant predictor of ALND omission (Supplemental Table 2).

Discussion

In this contemporary review of axillary nodal staging in over 1800 patients with OBC with axillary metastasis, we demonstrated de-escalation of axillary surgery occurring both in patients treated with upfront surgery and those treated with NST, with increase in use of NST for OBC

and axillary surgical de-escalation being more prominent in those treated with NST. While patients selected for omission of ALND had lower risk disease (predominantly lower cN category at diagnosis), the OS of patients selected for treatment with SLN surgery alone was not different to those who underwent ALND.

OBC presents a challenge to study due to its rare incidence. In clinically node negative breast cancer, large randomized clinical trials such as Z0011, SENOMAC, SINODAR-ONE, and AMAROS have shown no difference in outcomes between SLN surgery alone and ALND, thus leading to the de-escalation of axillary surgery in patients with low volume nodal disease in the upfront surgery setting.[8–11] However, these trials were limited to cN0 disease at presentation and thus none of these trials included patients with OBC.

Prior retrospective studies have assessed national patterns of axillary surgery in the upfront surgery setting for patients with OBC. Cohen et al. utilized the NCDB from 2004 to 2014 and noted 69% of patients underwent upfront surgery with 14% undergoing SLN surgery alone.[19] While our data demonstrates a lower SLN surgery alone rate of 6% overall; the rates of SLN surgery alone have continued to increase to around 18% in 2023. There are coding differences between the studies as they defined SLN surgery as removal of 4 or less lymph nodes whereas the NCDB introduced a new axillary surgery variable in 2012 designating type of axillary surgery as SLN surgery or ALND, which was used in our study. LaBella et al. assessed the NCDB for patients with OBC over a more recent time period of 2012–2021 and utilized similar SLN surgery codes to our study. They noted an overall increase in SLN surgery alone from 5 to 16%. Our study shows the continued increase in use of SLN surgery alone to 22.9% in 2023.[20]

Of note, 80% of patients in our cohort underwent adjuvant radiation while 66% did not receive radiation therapy in Cohen's cohort. This difference may also be secondary to how receipt of radiation was defined. As use of neoadjuvant radiation for breast cancer is rare, we used a nontiming-based variable for radiation which reflects rates of adjuvant radiation that align clinically. Since in recent years adjuvant radiation is generally recommended in most node positive disease, especially when treated with upfront surgery, the contemporary cohort in our study is more in keeping with current management of OBC.

Cohen et al. also assessed OS and noted that patients who underwent ALND had a higher OS compared with those treated with SLN surgery alone.[19] This is in contrast to the majority of the literature which has never shown a survival advantage from ALND. They do note that there was no difference in survival between the two types of axillary surgery when patients treated with upfront surgery underwent radiation.

The increase in use of NST in patients with OBC seen in this study are in keeping with the increase in use of NST for invasive breast cancer due to data demonstrating improved survival with adjuvant therapy in patients identified to have residual disease after NST.[21] Significant advances have been made in systemic therapies, resulting in improvements in NST response rates such as addition of pertuzumab to trastuzumab and chemotherapy in the neoadjuvant setting for HER2+ disease[17] and use of pembrolizumab along with chemotherapy in the neoadjuvant setting in patients with node-positive TNBC.[16]

With the significant advances in systemic therapy, randomized controlled trials have shown that SLN surgery is feasible and reliable in patients with node positive disease at diagnosis that convert to node negative disease with NAC.[12–14] These studies led to the omission of ALND in patients with ypN0(sn) disease. ACOSOG Z1071 and SN FNAC included patients with T0 disease (OBC); however, these formed a very small percentage of the overall cohorts (T0/Tis: 1% Z1071, T0: 3% SN FNAC).[12,14]

Several more recent retrospective series have indicated that de-escalation of axillary surgery may be safe in appropriately selected patients in the setting of ypN0(i+), ypNmi, and possibly ypN+;[22–26] however, most of these studies did not include OBC in their cohorts. Importantly, results from prospective randomized trials are still pending and are necessary to guide practice changes. Additionally, one large retrospective study demonstrated higher axillary recurrence rates with omission of ALND in patients with TNBC, raising concern regarding oncologic safety of omission of ALND with chemotherapy resistant residual nodal disease.[23] Despite this, surgeons and patients are beginning to omit ALND in the setting of residual nodal disease in patients with a known breast primary and our data demonstrates that this is also occurring in OBC.[27–30]

Our study shows an increase in the use of NST over time in OBC similar to LaBella et al.[20] The largest decreases in ALND occurred appropriately in patients with nodal pCR and in patients with HER2+ and TNBC subtype. This is likely a result of improved systemic therapies and highest nodal pCR rates are seen in HER2+ and TNBC.[31,32] This aligns with other studies demonstrating increasing trends in the de-escalation of axillary surgery even in the setting of residual nodal disease.[27,28] We saw no differences in survival based on ALND in the setting of ypN0 as well as ypN+, though patients with ypN+ disease had significantly lower survival overall than those with ypN0. This suggests that the axillary surgery itself plays a less significant role in survival compared with tumor biology, especially as these are tumors resistant to neoadjuvant systemic therapy.

It is important to note that while we saw no difference in OS with omission of ALND, patients who were selected for SLN surgery only had lower clinical N category disease

and potentially other lower risk features that cannot be completely controlled for in this retrospective analysis. Thus, our findings support that with clinical judgement and appropriate patient selection, omission of ALND may be appropriate in patients with OBC with low volume nodal disease at time of surgery. Importantly for most patients with breast cancer, features of the primary tumor (such as tumor size, tumor grade, lymphovascular invasion, proliferation rate (if available) are taken into consideration along with nodal category and tumor subtype when making clinical decisions such as omission of axillary surgery. For patients with OBC with axillary metastasis, less information is available to guide these nuanced decisions.

Our study has several limitations to consider. As with any retrospective study, selection bias is an intrinsic risk. For example, the type of axillary surgery and the decision of undergoing upfront surgery versus NST is ultimately at the treatment team's discretion and all factors influencing this cannot be controlled for. Assessing the impact of NST, specifically pembrolizumab, on patients with TNBC is limited due to short follow up times. Additionally, as OBC is a rare diagnosis, statistical analysis on more granular details such as impact of lymph node surgery on N2 or N3 disease was limited due to small patient numbers. Many patients underwent breast conserving surgery; however, it is unclear why and what was resected and the pathologic findings. To further address this, we performed a sensitivity analysis with this subgroup excluded and found similar results. While in OBC, breast MRI is recommended and frequently identifies a primary site in the breast, the use of breast MRI in this cohort is not known. NCDB has inherent limitations including lack of breast cancer specific outcomes, possible coding errors, and its representation of a particular population, specifically patients from Commission on Cancer-accredited hospitals.

Conclusions

Our study highlights the trend for de-escalating axillary surgery that is occurring in breast cancer is also occurring in OBC with axillary metastasis. This decrease in axillary dissections occurs in the upfront surgery setting and at a larger scale in the setting of the latest neoadjuvant systemic therapies. Based on preliminary short-term data, there is no difference in OS among patients selected for SLN surgery alone versus ALND in the upfront surgery setting, in patients with nodal pCR as well as those with residual nodal disease. However, further research is needed with longer term follow-up to confirm the safety of omitting ALND, particularly in the setting of residual nodal disease after receiving neoadjuvant systemic therapy.

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