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ORIGINAL ARTICLE – BREAST ONCOLOGY

Oncologic Outcomes with De-Escalation of Axillary Surgery After Neoadjuvant Chemotherapy for Breast Cancer: Results from > 1500 Patients on the I-SPY2 Clinical Trial

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ABSTRACT

Introduction. The desire to reduce patient morbidity has led to de-escalation of axillary surgery after neoadjuvant chemotherapy (NAC) for breast cancer; however, the impact of such de-escalation on oncologic outcomes is unknown.

Methods. We evaluated the relationship between axillary surgery type (sentinel lymph node [SLN] only vs. axillary lymph node dissection [ALND]) and 5-year outcomes in I-SPY2 trial patients from 2011 to 2022 who completed NAC and surgery. Rates of axillary recurrence (AxR), locoregional recurrence (LRR), distant recurrence-free survival (DRFS), and event-free survival (EFS) were compared.

Results. Of 1515 patients, SLN-only was performed in 804/1014 (79.3%) ypN0 patients and 127/501 (25.3%) ypN+ patients. Median follow-up time was 3.5 years. Most patients received adjuvant radiation (73.8% of ypN0 patients and 90.8% of ypN+ patients). In ypN0 cases, there was no difference between the SLN-only and ALND groups in 5-year estimated AxR (2.0% vs. 0.8%, $p = 0.57$), LRR (4.6% vs. 4.4%, $p = 0.72$), or EFS (88.3% vs. 86.4%, $p = 0.09$). On multivariable analysis, SLN-only was associated with better DRFS (90.8% vs. 87.9%; hazard ratio [HR] 0.54, $p = 0.04$). In ypN+ cases, there was no difference between the SLN-only and ALND groups in 5-year estimated AxR (5.2% vs. 3.6%, $p = 0.81$), LRR (7.7% vs. 14%, $p = 0.13$), DRFS (70.0% vs. 66.7%, $p = 0.09$), or EFS (70.4% vs. 63.2%, $p = 0.07$).

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Conclusions. With short-term follow-up, omission of ALND in selected patients was not associated with worse AxR, LRR, DRFS, or EFS in patients with ypN0 or ypN+ disease. While prospective trial results are awaited, these data suggest that ALND may not be necessary for all patients with residual nodal disease after NAC.

Keywords Breast cancer · Neoadjuvant chemotherapy · Axillary surgery · Targeted axillary dissection · Sentinel lymph node surgery · De-escalation

In the management of breast cancer, the surgical approach to the breast and axilla has continued to evolve along with advances in pathology, imaging techniques, systemic therapy, and radiotherapy. The initial role of neoadjuvant chemotherapy (NAC) in breast cancer was to downstage tumors, making inoperable cases operable, and increasing rates of breast conservation in those who would otherwise have required mastectomy;[1,2] however, modern data have shown that assessment of tumor response to NAC is prognostic and can guide adjuvant therapy. Indeed, studies have shown that response to NAC identifies patients who will benefit from additional adjuvant therapy that can improve survival outcomes,[3,4] and thus NAC allows tailoring of systemic therapy (escalating or de-escalating) based on response. Recently, locoregional management studies have focused on how to de-escalate both breast and axillary surgery after NAC while maintaining optimal oncologic control. Such reductions in the extent of surgery can significantly reduce morbidity for patients undergoing breast cancer treatment, such as decreasing the risk of lymphedema by avoiding axillary lymph node dissection (ALND).[5]

While historically ALND was routinely performed in all patients with advanced breast cancer, the surgical approach to the axilla has evolved over the last decade. Trials have moved from establishing the safety of sentinel lymph node (SLN) surgery in clinically node-negative (cN−) patients,[6,7] to incorporating use of SLN surgery after NAC,[8,9] to avoiding axillary dissection in clinically node-positive (cN+) patients with pathologic complete nodal response after NAC,[10–12] and finally to the current interest in omitting ALND in patients with residual node-positive disease after NAC. The Alliance for Clinical Trials in Oncology A11202 clinical trial was designed to evaluate whether omission of ALND is non-inferior to ALND in patients with pathologic node-positive disease after NAC and the trial has completed accrual.[13] While follow-up data from this prospective trial are awaited, clinical practice continues to evolve.

In this study, we evaluated the relationship between type of axillary surgery and oncologic outcomes in patients treated on the I-SPY2 clinical trial, a prospective, multicenter, clinical trial in which patients with high molecular risk breast cancer by Mammaprint are randomized to novel NAC agents. This platform trial focuses on improving the rates of pathologic complete response (pCR) to NAC while minimizing treatment toxicity for patients with stage II or III breast cancer. A recent evaluation of clinical practice trends from the I-SPY2 clinical trial demonstrated a significant decrease in the use of ALND within the study population over time. This was true for patients with both cN− and cN+ disease at presentation, and, strikingly, also among those with pathologic node-positive disease after NAC.[14] In this study, we report on the oncologic outcomes of these patients.

METHODS

We retrospectively evaluated the type of axillary surgery performed and the oncologic outcomes of patients enrolled in the I-SPY2 clinical trial from January 2011 through December 2022 who were treated with NAC and completed surgery. All patients on I-SPY2 undergo imaging, including axillary ultrasound and breast magnetic resonance imaging (MRI), at diagnosis. If warranted by imaging or physical examination, ultrasound-guided needle biopsy of the most abnormal axillary lymph node and clip placement are performed prior to starting systemic therapy. Patients are considered cN+ if percutaneous lymph node biopsy prior to NAC was positive for malignancy. Patients are treated with NAC, including randomization to novel chemotherapeutic agents, followed by surgery; axillary surgery is not permitted prior to NAC. Type of breast surgery and type of axillary surgery was at the discretion of the treating surgeon and shared discussion with the patient. The I-SPY2 protocol recommended the use of SLN surgery after NAC for those with cN0 disease at presentation, while SLN or ALND were permitted after NAC for patients with cN+ disease at presentation. For patients identified to have positive node(s) at SLN surgery, the use of completion ALND was at the discretion of the surgeon.

Axillary surgery was classified as SLN surgery-only or ALND (with or without SLN surgery). Rates of axillary recurrence (AxR), locoregional recurrence (LRR), distant recurrence (DR) and event-free survival (EFS) were compared by axillary surgery type in univariate and multivariate analyses. AxR was defined as recurrent disease in the axilla. LRR included recurrence to the breast, chest wall, or any of the regional nodal basins. EFS included any recurrence or death with patients without events being censored at the date of last follow-up. Patients were followed annually for up to 10 years after enrollment in the trial. For this analysis, data through 5 years are reported due to the low number of patients with follow-up beyond 5 years.

Tumor biology was categorized based on hormone receptor (HR) status and HER2/neu expression. HR positivity was defined by immunohistochemistry showing >1%

estrogen receptor and/or progesterone receptor positively stained cells. HER2 positivity was defined as 3+ staining on immunohistochemistry or amplification on fluorescence in situ hybridization. Approximated biologic subtypes were categorized as follows; HR+/HER2−, HR−/HER2−, and HER2+. Pathologic node-positive disease was defined as ypN1 or greater disease, including ypN1mi.

Since axillary management decisions are predominantly driven by post-treatment clinical evaluation and pathologic nodal status after chemotherapy at the time of surgery, analysis was performed separately for patients with pathologic node-negative (ypN0) disease and those with pathologic node-positive (ypN+) disease at surgery after NAC. We compared clinicopathologic characteristics in the SLN-only and ALND groups, including self-reported race, ethnicity, age, tumor stage, and tumor biologic subtype.

Statistical Analysis

Our primary outcomes were AxR, LRR, distant recurrence-free survival (DRFS), and EFS (including all recurrences and deaths) within 5 years after surgery. Kaplan–Meier survival curves were used to estimate survival probabilities over time for the entire cohort, and differences in survival between the axillary surgery groups were assessed using the log-rank test. We performed univariate and multivariate survival analyses to control for confounding factors, including patient age at screening, cN category, tumor biologic subtype, and post-NAC T category (ypT). Hazard ratios (HRs) and their associated confidence intervals (CI) are reported.

Since there was non-random assignment of surgical procedures, and thus potential selection bias, we also performed propensity score matching (PSM) to achieve balance between treatment groups. We used logistic regression to estimate the propensity score and performed nearest-neighbor matching to pair individuals with similar propensity scores based on age at screening, tumor biologic subtype, ypN category, ypT category, and year of surgery. We assessed the matching and conducted our primary endpoint analyses on both the overall study population and again in the propensity score-matched dataset.

RESULTS

Of 1515 patients, 931 underwent SLN-only surgery and 584 underwent ALND (±SLN surgery). Patient demographics and tumor features are shown in Table 1. Patients selected for SLN surgery only were more commonly White, had lower clinical T and N category at diagnosis, had lower pathologic ypT and ypN category, and had HER2+ or HR−/HER2− disease compared with those selected for ALND. Of the overall cohort, 714 (47.1%) were cN0 at diagnosis and 801 (52.9%) were cN+ at diagnosis. Among those patients with cN0 disease, 104 (14.6%) were ypN+ at surgery, whereas among those patients with cN+ disease at diagnosis, 397 (49.6%) were ypN+. Overall, 1014 patients had ypN0 disease and 501 patients had ypN+ disease. Among the 1014 patients with ypN0 disease, 804 patients (79.3%) had SLN-only surgery and 210 patients (20.7%) had ALND. In contrast, for the 501 patients with ypN+ disease, 127 patients (25.3%) had SLN-only surgery and 374 patients (74.7%) had ALND. Median follow-up time was 3.5 years (range 42 days–5 years).

Among patients with ypN0 disease at surgery, the SLN-only and ALND groups did not differ in age, ethnicity, tumor biology, or ypT category. Patients who had SLN-only were more frequently cN0 at diagnosis than patients who had ALND (70.9% vs. 18.6%, $p < 0.001$). Similarly, the SLN-only group was more often cT1/2 compared with the ALND group (79.1% vs. 65.2%, $p < 0.001$). ALND was more frequent in Black-identifying patients and less frequent in White-identifying patients (Table 2). As expected, the total number of nodes removed was higher in those undergoing ALND (mean 14.8) than in those undergoing SLN-only (mean 3.2, $p < 0.001$).

Among patients with ypN+ disease at surgery, the SLN-only and ALND groups did not differ in age, race, ethnicity, or tumor biology. Patients who had SLN-only were more often cN0 or cT1/2, and less often ypT3/4, compared with the ALND group. Among the SLN-only group, 30.7% were cN0 compared with 17.4% of the ALND group ($p = 0.001$), and 64.6% were cT1/2 compared with 54.0% of the ALND group ($p = 0.007$). At surgery, the SLN-only group was less likely to have ypT3/4 disease than the ALND group (15.0% vs. 27.5%, $p = 0.004$). As expected, the number of nodes removed was higher in patients undergoing ALND (mean 17 nodes) than in patients undergoing SLN surgery (mean 5 nodes, $p < 0.001$). Similarly, the number of positive nodes was higher among the ALND group (mean 5 positive nodes) than in the SLN-only group (mean 2 positive nodes, $p < 0.001$) [Table 2]. The number of nodes removed at SLN surgery was higher in the ypN+ group than in ypN0 patients ($p < 0.001$), and the number of nodes removed at ALND was also higher in ypN+ ($p < 0.001$).

Most patients received adjuvant radiation (78.7%), which was significantly more common in the ypN+ group compared with the ypN0 group (90.8% vs. 72.8%, $p < 0.0001$). Radiation use was lower in ypN0 patients with SLN-only compared with those with ALND (71.8% vs. 85.3%, $p < 0.001$), whereas in the ypN+ patients, use of radiation did not differ by type of axillary surgery (94.4% vs. 93.4%, $p = 0.86$).

TABLE 1 Patient demographic and tumor features of the 1515 patients

	Overall [$N = 1515$]	ALND [$n = 584$]	SLN-only [$n = 931$]	p-Value
Age, years				
<50	819 (54.1)	319 (54.6)	500 (53.7)	0.727
≥50	696 (45.9)	265 (45.4)	431 (46.3)	
Race				
Asian	114 (7.5)	44 (7.5)	70 (7.5)	0.019
Black	174 (11.5)	86 (14.7)	88 (9.5)	
White	1198 (79.1)	443 (75.9)	755 (81.1)	
Other	29 (1.9)	11 (1.9)	18 (1.9)	
Ethnicity				
Hispanic or Latino	178 (11.7)	67 (11.5)	111 (11.9)	0.158
Non-Hispanic or Latino	1332 (87.9)	513 (87.8)	819 (88.0)	
Unknown	5 (0.3)	4 (0.7)	1 (0.1)	
Clinical T category at diagnosis				
cT1/T2	1057 (69.8)	339 (58.0)	718 (77.1)	< 0.001
cT3/T4	458 (30.2)	245 (42.0)	213 (22.9)	
Clinical N category at diagnosis				
cN+	801 (52.9)	480 (82.2)	321 (34.5)	< 0.001
cN0	714 (47.1)	104 (17.8)	610 (65.5)	
Pathological T category				
ypT0/Tis	604 (39.9)	155 (26.5)	449 (48.2)	< 0.001
ypT1	468 (30.9)	182 (31.2)	286 (30.7)	
ypT2	286 (18.9)	132 (22.6)	154 (16.5)	
ypT3/T4	154 (10.2)	113 (19.3)	41 (4.4)	
ypTx	3 (0.2)	2 (0.3)	1 (0.1)	
Pathological N category				
ypN0	1014 (66.9)	210 (36.0)	804 (86.4)	< 0.001
ypN1	341 (22.5)	219 (37.5)	122 (13.1)	
ypN2/pN3	160 (10.6)	155 (26.5)	5 (0.5)	
Tumor subtype				
HER2+	345 (22.8)	123 (21.1)	222 (23.8)	< 0.001
HR−/HER2−	518 (34.2)	161 (27.6)	357 (38.3)	
HR+/HER2−	652 (43.0)	300 (51.4)	352 (37.8)	
Axillary surgery				
ALND and SLN	129 (8.5)	129 (22.1)	0 (0.0)	< 0.001
ALND-only	455 (30.0)	455 (77.9)	0 (0.0)	
SLN-only	931 (61.5)	0 (0.0)	931 (100.0)	
Radiation				
Yes	1193 (79.3)	511 (88.1)	682 (73.8)	< 0.001
No	282 (18.8)	54 (9.3)	228 (24.7)	
Unknown	40 (2.6)	19 (3.3)	21 (2.3)	
Type of breast surgery				
Breast-conserving surgery	658 (43.4)	184 (31.5)	474 (50.9)	
Mastectomy	857 (56.6)	400 (68.5)	457 (49.1)	
Total number of nodes removed				
Median (IQR)	5 (2–13)	15 (11–20)	3 (2–4)	< 0.001
Total number of positive nodes				
Median (IQR)	0 (0–1)	1 (0–4)	0	< 0.001

Data are expressed as *n* (%) unless otherwise specified

ALND axillary lymph node dissection, *SLN* sentinel lymph node, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor, *IQR* interquartile range

TABLE 2 Comparison of patient and tumor characteristics between patients undergoing SLN surgery and those undergoing ALND (±SLN surgery), in patients with ypN0 or ypN+ disease

		Pathologic node-negative (ypN0) [$n = 1014$]			Pathologic node-positive (ypN+) [$n = 501$]		
		ALND [$n = 210$]	SLN-only [$n = 804$]	p-Value	ALND [$n = 374$]	SLN-only [$n = 127$]	p-Value
Age, years	<50	115 (54.8)	425 (52.9)	0.623	204 (54.5)	75 (59.1)	0.377
	≥50	95 (45.2)	379 (47.1)		170 (45.5)	52 (40.9)	
Race	Asian	15 (7.1)	56 (7.0)	0.019	29 (7.8)	14 (11.0)	0.098
	Black	37 (17.6)	80 (10.0)		49 (13.1)	8 (6.3)	
	White	155 (73.8)	651 (81.0)		288 (77.0)	104 (81.9)	
	Other	3 (1.4)	17 (2.1)		8 (2.1)	1 (0.8)	
Ethnicity	Hispanic or Latino	27 (12.9)	100 (12.4)	0.856	40 (10.8)	11 (8.7)	0.496
	Non-Hispanic or Latino	182 (87.1)	703 (87.4)		331 (89.2)	116 (91.3)	
Clinical T category at diagnosis	T1/T2	137 (65.2)	636 (79.1)	<0.001	202 (54.0)	82 (64.6)	0.038
	T3/T4	73 (34.8)	168 (20.9)		172 (46.0)	45 (35.4)	
Pathologic T category	ypTis/0/1/2	200 (95.2)	781 (97.1)	0.132	271 (72.5)	108 (85.0)	0.004
	ypT3/4	10 (4.8)	22 (2.7)		103 (27.5)	19 (15.0)	
Clinical N category at diagnosis	cN0	39 (18.6)	571 (71.0)	<0.001	65 (17.4)	39 (30.7)	0.001
	cN+	171 (81.4)	233 (29.0)		309 (82.6)	88 (69.3)	
Tumor subtype	HER2+	66 (31.4)	199 (24.8)	0.128	57 (15.2)	23 (18.1)	0.479
	HR−/HER2−	76 (36.2)	334 (41.5)		85 (22.7)	23 (18.1)	
	HR+/HER2−	68 (32.4)	271 (33.7)		232 (62.0)	81 (63.8)	
Total number of positive nodes [mean (SD)]		0.00 (0.00)	0.00 (0.00)	NA	4.57 (5.14)	1.62 (1.40)	< 0.001
Total number of nodes removed [mean (SD)]		14.80 (7.79)	3.19 (2.10)	<0.001	17.03 (8.28)	4.54 (3.67)	< 0.001
Adjuvant radiation	No	30 (14.7)	221 (28.2)	<0.001	24 (6.6)	7 (5.6)	0.679
	Yes	174 (85.3)	564 (71.8)		337 (93.4)	118 (94.4)	

Data are expressed as *n* (%) unless otherwise specified

ALND axillary lymph node dissection, *SLN* sentinel lymph node, *HER2* human epidermal growth factor receptor, *HR* hormone receptor, *SD* standard deviation, *NA* not available

Axillary Recurrence

Overall, 28 patients developed AxR, with a 5-year estimated rate of AxR of 2.4% (95% CI 1.6–3.5%). The 5-year estimated AxR rate was significantly higher in patients with ypN+ disease at surgery, at 3.9% (95% CI 2.2–6.3%), compared with those with ypN0 disease, at 1.8% (95% CI 0.95–3.0%, $p = 0.012$). We found no increased risk of AxR among SLN-only patients compared with ALND when stratifying by both cN category and ypN category (Table 3).

Among ypN0 cases, there was no difference in the 5-year estimated rate of AxR by type of axillary surgery (2.0% in the SLN-only group compared with 0.8% in ALND group, $p = 0.57$) [Fig. 1A]. On univariate analysis, the only factor associated with AxR was extent of residual disease in the breast at surgery (higher ypT category). In a multivariate Cox proportional hazards model for AxR that included patient age, cN status at diagnosis, ypT category, and tumor receptor subtype, there was no association between type of axillary surgery and AxR. In this model, ypT category remained significantly associated with AxR, with higher AxR risk seen in patients with ypT1 and ypT2 disease compared with those with ypT0/pTis disease (HR 6.4 and 7.8, respectively; $p = 0.02$ in each) [Table 4].

Similarly, among patients with ypN+ disease, there was no significant difference in 5-year estimated AxR rate by type of axillary surgery (5.2% in the SLN-only group compared with 3.6% in the ALND group, $p = 0.88$) [Fig. 1B]. On univariate analysis in patients with ypN+ disease, HR−/HER2− disease (HR 3.3, $p = 0.04$) was associated with a higher risk of AxR, while clinical N+ disease at diagnosis (HR 0.3, $p = 0.02$) was associated with a lower risk of AxR. However, on multivariate analysis including patient age, cN status at diagnosis, ypT category, tumor receptor subtype, and type of axillary surgery, none of these factors were significantly associated with AxR (Table 4).

TABLE 3 Estimated cumulative axillary recurrence at 5 years by clinical N category at diagnosis, pathological N category after chemotherapy, and type of axillary surgery performed

		ypN0		ypN+	
		cN0	cN+	cN0	cN+
Events/*N* (estimated cumulative axillary recurrence at 5 years, with 95% CI)					
Type of axillary surgery	SLN-only	11/571 (2.5%, 1.3–4.5%)	1/233 (0.4%, 0.04–2.2%)	1/39 (6.3%, 0.36–25%)	3/88 (4.0%, 1.0–10%)
	ALND	0/39 (0%, 0%)	1/171 (0.9%, 0.08–4.5%)	6/65 (12%, 4.8–23%)	5/309 (1.7%, 0.64–3.7%)
Number of nodes (positive/removed)/mean (SD)					
Type of axillary surgery	SLN-only	0(0)/3(2)	0(0)/4(2)	1(1)/3(2)	2(2)/5(4)
	ALND	0(0)/13(8)	0(0)/15(8)	3(3)/19(8)	5(5)/17(8)

CI confidence interval, *SLN* sentinel lymph node, *ALND* axillary lymph node dissection, *CI* confidence interval, *SD* standard deviation

Locoregional Recurrence

Overall, the estimated rate of LRR at 5 years was 7.1% (95% CI 5.7–8.7%) and was higher in patients with ypN+ disease compared with those with with ypN0 disease (12.0% vs. 4.6%, $p < 0.01$). The 5-year estimated rate of LRR did not vary by type of axillary surgery in either the ypN0 or ypN+ groups. When comparing the SLN-only group with the ALND group in ypN0 patients, the LRR rate was 4.6% and 4.4%, respectively ($p = 0.07$) [Fig. 1C]; in ypN+ patients, the LRR rate was 7.7% and 14.0%, respectively ($p = 0.13$) [Fig. 1D].

In patients with ypN0 disease, both univariate and multivariate analysis showed that ypT1 and ypT2 disease were associated with higher rates of LRR than ypT0/Tis disease. While the rate of LRR in ypT3/4 disease was also numerically higher, this did not reach statistical significance due to the small sample size (Table 4).

In patients with ypN+ disease, triple-negative tumor receptor subtype (HR−/HER2− disease) was associated with a higher LRR rate on both univariate and multivariate analyses (HR 4.97, $p < 0.0001$ on multivariate analysis). Additionally, the multivariate analysis showed that pathologic T3/4 disease was associated with higher LRR compared with pT0/Tis disease (HR 3.7, $p = 0.04$).

Distant Recurrence-Free Survival

The overall estimated 5-year DRFS was 82.9% (95% CI 80.7–85.2%). Patients with ypN0 disease had better DRFS at 5 years than those with ypN+ disease (90.2% vs. 68.2%, $p < 0.01$).

In the ypN0 population, 5-year DRFS was not different between patients undergoing ALND surgery (87.9%) and those undergoing SLN-only surgery (90.8%) on univariate analysis ($p = 0.09$) [Fig. 2A]. However, in a multivariate Cox proportional hazards model, SLN-only surgery was associated with improved DRFS over ALND (HR 0.539, $p = 0.04$). Additionally, patients with higher pathological T category had worse DRFS (Table 4).

In the ypN+ population, 5-year DRFS was significantly lower in patients undergoing ALND, at 66.7%, compared with 70.0% in the SLN-only group on univariate analysis (HR 0.61, $p = 0.04$) [Fig. 2B], however there was no association on multivariate analysis ($p = 0.09$). Additionally, patients with higher pathological T category and triple-negative tumor subtype had significantly worse DRFS (Table 4).

Event-Free Survival

The estimated overall 5-year EFS rate was 80.4% (95% CI 78.0–82.8%) and was worse, in patients with ypN+ disease compared with patients with ypN0 disease (65.2% vs. 88.0%, $p < 0.01$).

Among ypN0 patients, the 5-year estimated EFS did not differ between patients treated with SLN-only surgery compared with ALND (88.3% vs. 86.4%, $p = 0.09$) [Fig. 2C]. Higher ypT category and HR−/HER2− disease were associated with poorer EFS on multivariate analysis.

Among ypN+ patients, the 5-year estimated EFS was better in patients treated with SLN-only surgery compared with those treated with ALND (70.4% vs. 63.2%, $p = 0.03$) [Fig. 2D]. However, this was not significantly different on multivariate analysis ($p = 0.06$). Pathologic T3/4 disease and HR−/HER2− disease were associated with poorer EFS on both univariate and multivariate analyses.

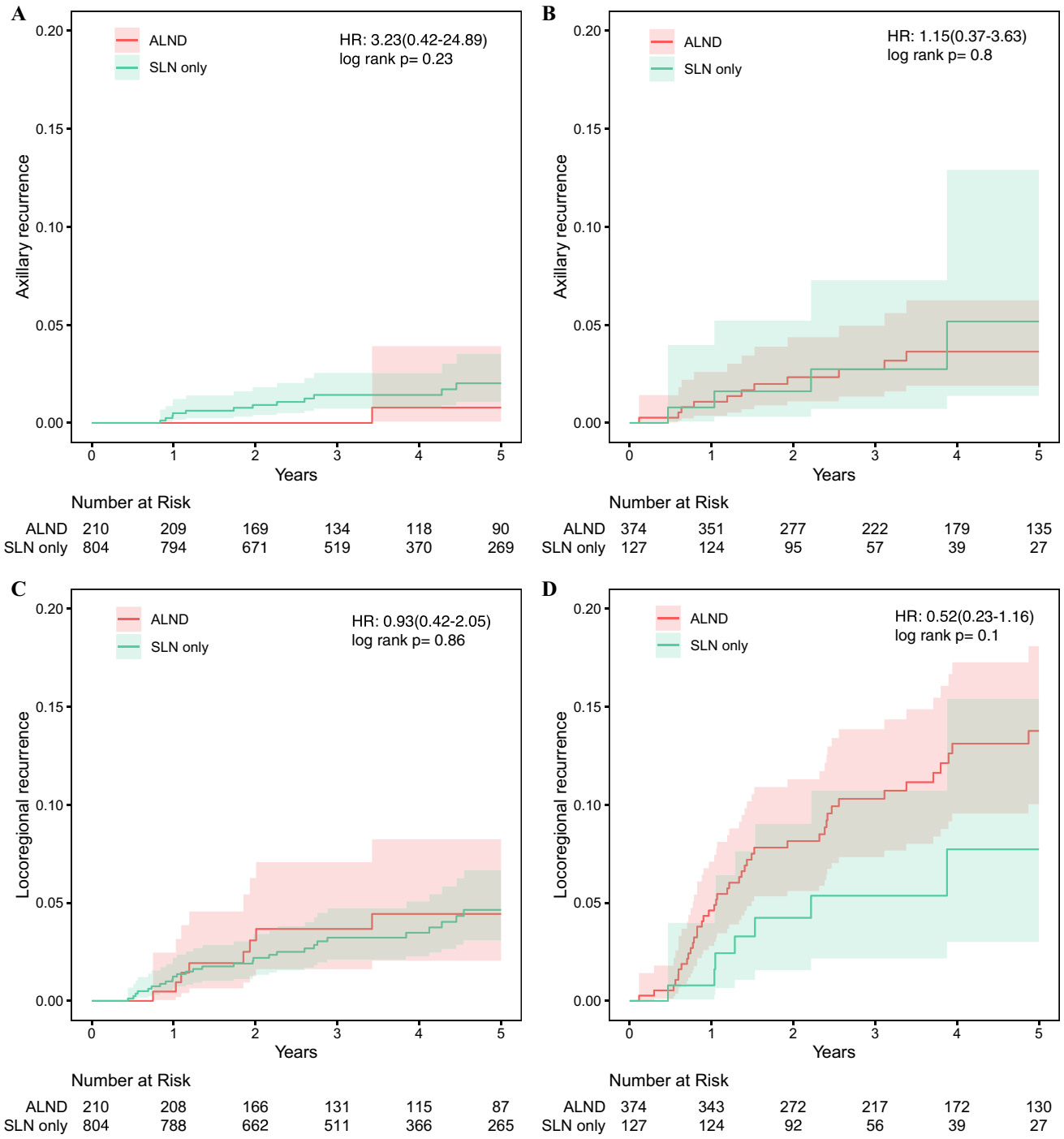

FIG. 1 Axillary recurrence outcomes by type of axillary surgery (SLN-only vs. ALND) in patients with **A** pathologic node-negative (ypN0) disease and **B** pathologic node-positive (ypN+) disease, as well as locoregional recurrence outcomes in **C** ypN0 and **D** ypN+. *SLN* sentinel lymph node, *ALND* axillary lymph node dissection, *HR* hazard ratio

Propensity Score-Matched Model

The propensity score-matched analysis included 664 patients with ypN0 disease (65.5% of the ypN0 cohort) and 500 patients with ypN+ disease (99.8% of the ypN+ cohort). In ypN0 disease, PSM multivariate analysis showed that there was no difference between the SLN-only and ALND groups in 5-year estimated AxR, LRR, DRFS, and EFS. In ypN+ patients, patients with triple-negative tumor subtype or higher ypT category had significantly higher rates of LRR

TABLE 4 Multivariate analysis of factors influencing axillary recurrence, locoregional recurrence, distant disease-free survival, and event-free survival in patients with ypN0 or ypN+ disease

		AxR		LRR		DRFS		EFS	
		Estimated rate of 5-year AxR (95% CI)	HR (multivariable)	Estimated rate of 5-year LRR (95% CI)	HR (multivariable)	Estimated 5-year DRFS (95% CI)	HR (multivariable)	Estimated 5-year EFS (95% CI)	HR (multivariable)
ypN0 [n = 1014]									
Type of axillary surgery	ALND [*n* = 210]	0.78% (0.07–3.9%)	–	4.4% (2.0%–8.2%)	–	87.9% (83.2–92.9%)	–	86.4% (81.5–91.6%)	–
	SLN-only [*n* = 804]	2.0% (1.1–3.5%)	1.881 (0.217–16.329, $p = 0.5668$)`	4.6% (3.1–6.7%)	0.846 (0.344–2.079, $p = 0.7155$)	90.8% (88.3–93.2%)	0.539 (0.302–0.961, $p = 0.0362$)	88.3% (85.6–91.1%)	0.632 (0.371–1.078, $p = 0.0923$)
ypT category	ypT0/pTx/pTis [*n* = 564]	0.39% (0.08–1.3%)	–	1.6% (0.68–3.3%)	–	95.2% (93.3–97.2%)	–	94.2% (92.0–96.5%)	–
	ypT1 [*n* = 290]	3.3% (1.4–6.6%)	6.398 (1.308–31.309, $p = 0.0220$)	8.6% (5.3–13%)	5.980 (2.493–14.345, $p = 0.0001$)	87.7% (83.3–92.4%)	2.408 (1.359–4.266, $p = 0.0026$)	84.3% (79.4–89.4%)	2.865 (1.715–4.787, $p = 0.0001$)
	ypT2 [*n* = 126]	4.6% (1.4–11%)	7.764 (1.383–43.591, $p = 0.0199$)	7.9% (3.5–15%)	5.688 (2.014–16.065, $p = 0.0010$)	76.2% (67.8–85.7%)	5.484 (2.976–10.107, $p < 0.0001$)	72.1% (63.2–82.2%)	5.548 (3.167–9.722, $p < 0.0001$)
	ypT3/4 [*n* = 32]	NA	NA	6.7% (0.38–27%)	2.770 (0.338–22.736, $p = 0.3427$)	82.5% (69.6–97.8%)	4.388 (1.643–11.716, $p = 0.0032$)	76.6% (61.3–95.8%)	4.579 (1.867–11.227, $p = 0.0009$)
Tumor subtype	HR+/HER2− [*n* = 339]	1.9% (0.60v4.7%)	–	4.6% (2.3–8.0%)	–	89.1% (85.0–93.4%)	–	86.9% (82.4–91.6%)	–
	HR−/HER2− [*n* = 410]	2.0% (0.86–3.9%)	1.835 (0.531–6.335, $p = 0.3372$)	5.2% (3.1–7.9%)	1.787 (0.838–3.809, $p = 0.1329$)	88.3% (84.8–92.0%)	1.616 (0.977–2.673, $p = 0.0616$)	86.8% (83.2–90.6%)	1.616 (1.019–2.564, $p = 0.0413$)
	HER2+ [*n* = 265]	1.2% (0.22–3.9%)	0.911 (0.165–5.045, $p = 0.9153$)	3.5% (1.5–6.9%)	1.130 (0.434–2.947, $p = 0.8019$)	94.2% (90.9–97.5%)	0.711 (0.355–1.421, $p = 0.3339$)	91.1% (87.2–95.3%)	0.935 (0.519–1.684, $p = 0.8221$)
Patient age, years	<50 [*n* = 540]	1.8% (0.76–3.6%)	–	5.7% (3.6–8.3%)	–	91.4% (88.8–94.0%)	–	88.5% (85.5–91.7%)	–
	50 [*n* = 474]	1.7% (0.68–3.6%)	0.905 (0.303–2.701, $p = 0.8574$)	3.3% (1.8–5.7%)	0.543 (0.271–1.088, $p = 0.0851$)	89.0% (85.6–92.5%)	1.107 (0.707–1.733, $p = 0.6565$)	87.4% (83.8–91.1%)	0.956 (0.638–1.433, $p = 0.8288$)
cN status at diagnosis	cN0 [*n* = 610]	2.4% (1.2–4.2%)	–	4.9% (3.2–7.2%)	–	89.6% (86.7–92.6%)	–	87.2% (84.1–90.5%)	–
	cN+ [*n* = 404]	0.69% (0.13–2.4%)	0.511 (0.103–2.526, $p = 0.4102$)	3.9% (2.1–6.8%)	1.020 (0.462–2.251, $p = 0.9618$)	91.4% (88.5–94.4%)	1.108 (0.648–1.895, $p = 0.7082$)	89.3% (85.9–92.8%)	1.098 (0.677–1.782, $p = 0.7041$)
ypN+ [n = 501]									

Table 4 (continued)

		AxR		LRR		DRFS		EFS	
		Estimated rate of 5-year AxR (95% CI)	HR (multivariable)	Estimated rate of 5-year LRR (95% CI)	HR (multivariable)	Estimated 5-year DRFS (95% CI)	HR (multivariable)	Estimated 5-year EFS (95% CI)	HR (multivariable)
Type of axillary surgery	ALND [$n = 374$]	3.6% (1.9–6.3%)	–	14% (10–18%)	–	66.7% (61.6–72.4%)	–	63.2% (57.9–69.1%)	–
	SLN-only [$n = 127$]	5.2% (1.4–13%)	1.096 (0.340–3.533, $p = 0.8774$)	7.7% (3.0–15%)	0.538 (0.240–1.205, $p = 0.1320$)	70.0% (58.8–83.4%)	0.657 (0.405–1.064, $p = 0.0875$)	70.4% (59.6–83.1%)	0.649 (0.410–1.029, $p = 0.0662$)
ypT category	ypT0/pTx/pTis [$n = 40$]	2.5% (0.19–11%)	–	11% (2.4–26%)	–	86.7% (75.3–99.8%)	–	76.9% (63.1–93.8%)	–
	ypT1 [$n = 178$]	3.4% (1.0–8.1%)	1.287 (0.141–11.779, $p = 0.8230$)	13% (8.1–20%)	2.113 (0.623–7.171, $p = 0.2300$)	69.8% (62.1–78.5%)	3.349 (1.195–9.389, $p = 0.0215$)	68.0% (60.2–76.7%)	2.066 (0.928–4.601, $p = 0.0757$)
	ypT2 [$n = 160$]	2.5% (0.64–6.6%)	1.151 (0.115–11.535, $p = 0.9051$)	5.9% (2.3–12%)	0.825 (0.204–3.337, $p = 0.7876$)	71.3% (62.7–80.9%)	3.231 (1.133–9.214, $p = 0.0283$)	69.3% (60.7–79.0%)	1.964 (0.864–4.461, $p = 0.1071$)
	ypT3/4 [$n = 122$]	7.4% (3.1–14%)	3.491 (0.418–29.176, $p = 0.2484$)	20% (13–28%)	3.670 (1.085–12.416, $p = 0.0365$)	54.4% (45.3–65.2%)	7.106 (2.552–19.788, $p = 0.0002$)	51.7% (42.7–62.7%)	4.277 (1.933–9.466, $p = 0.0003$)
Tumor subtype	HR+/HER2− [$n = 313$]	2.7% (1.1–5.7%)	–	6.8% (3.9%–11%)	–	73.4% (67.5–79.8%)	–	71.4% (65.4–77.8%)	–
	HR−/HER2− [$n = 108$]	6.5% (2.6–13%)	2.692 (0.841–8.617, $p = 0.0954$)	28% (19%–38%)	4.969 (2.630–9.389, $p < 0.0001$)	48.3% (38.7–60.1%)	2.941 (1.997–4.331, $p < 0.0001$)	43.9% (34.5–55.8%)	2.943 (2.033–4.260, $p < 0.0001$)
	HER2+ [$n = 80$]	4.7% (1.2–12%)	1.633 (0.404–6.606, $p = 0.4915$)	12% (5.0–22%)	1.550 (0.636–3.780, $p = 0.3348$)	74.2% (63.8–86.4%)	0.972 (0.559–1.689, $p = 0.9195$)	70.5% (59.6–83.5%)	0.984 (0.584–1.659, $p = 0.9515$)
Patient age, years	<50 [$n = 279$]	2.9% (1.3–5.6%)	–	10% (6.5–15%)	–	68.5% (62.3–75.3%)	–	66.3% (60.0–73.3%)	–
	≥50 [$n = 222$]	5.0% (2.3–9.3%)	1.333 (0.479–3.706, $p = 0.5819$)	15% (9.6–21%)	1.216 (0.692–2.136, $p = 0.4968$)	68.2% (61.4–75.8%)	0.912 (0.640–1.298, $p = 0.6077$)	64.3% (57.3–72.2%)	0.953 (0.681–1.333, $p = 0.7785$)
cN status at diagnosis	cN0 [$n = 104$]	9.7% (4.1–18%)	–	19% (11–29%)	–	67.3% (57.7–78.5%)	–	61.8% (51.8–73.7%)	–
	cN+ [$n = 397$]	2.2% (1.0–4.1%)	0.371 (0.131–1.049, $p = 0.0615$)	10% (7.3–14%)	0.834 (0.443–1.570, $p = 0.5738$)	68.6% (63.4–74.3%)	1.034 (0.675–1.584, $p = 0.8771$)	66.4% (61.1–72.2%)	0.998 (0.668–1.492, $p = 0.9927$)

AxR axillary recurrence, *LRR* locoregional recurrence, *DRFS* distant recurrence-free survival, *EFS* event-free survival, *CI* confidence interval, *HR* hazard ratio, *ALND* axillary lymph node dissection, *SLN* sentinel lymph node, *HR* hormone receptor, *HER2* human epidermal growth factor receptor, *NA* not available

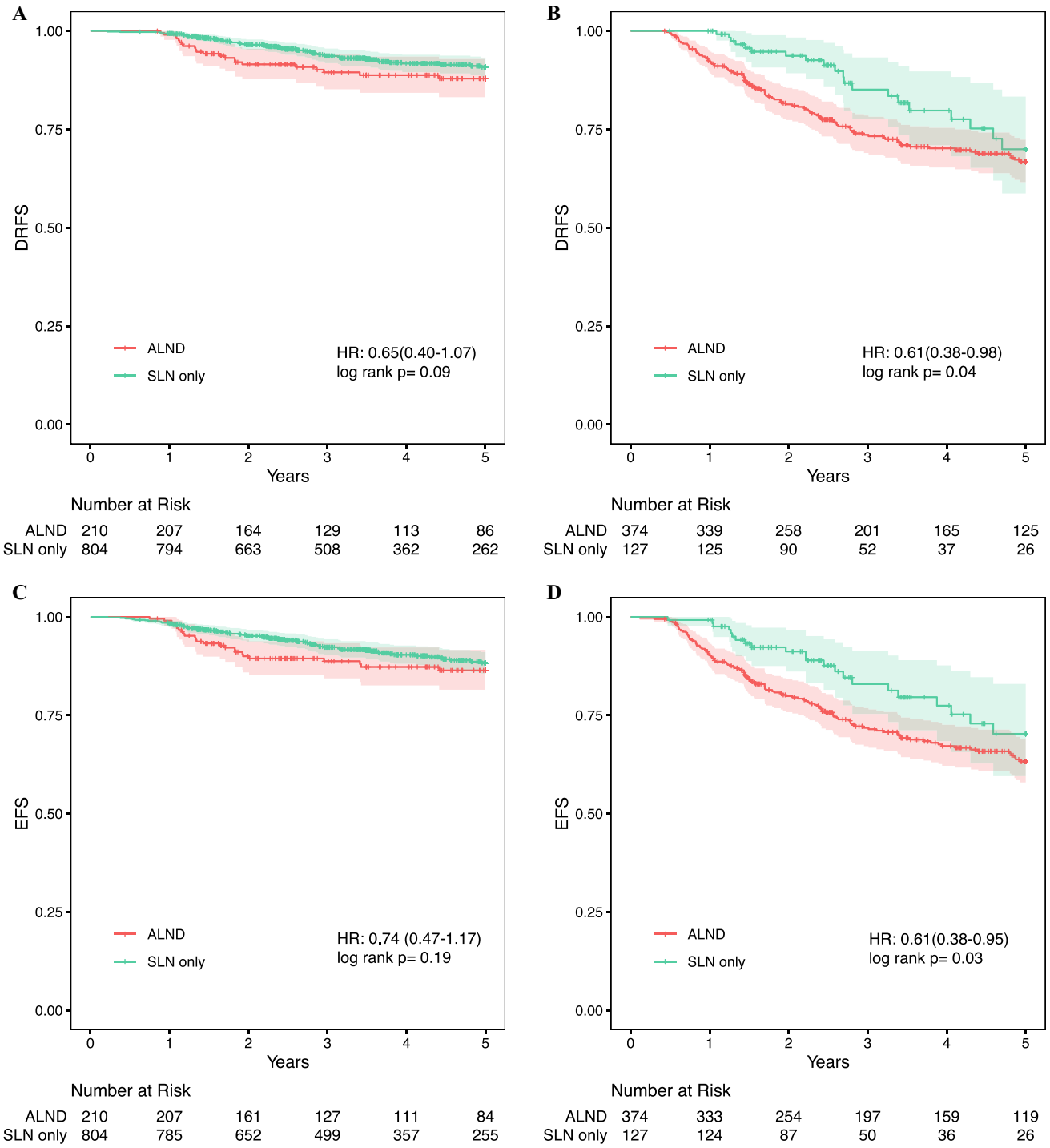

FIG. 2 Kaplan–Meier curves showing DRFS by type of axillary surgery (SLN-only vs. ALND) in patients with **A** pathologic node-negative (ypN0) disease and **B** pathologic node-positive (ypN+) disease, as well as EFS in **C** ypN0 and **D** ypN+. *SLN* sentinel lymph node, *ALND* axillary lymph node dissection, *HR* hazard ratio, *DRFS* distant recurrence-free survival, *EFS* event-free survival

and worse DRFS and EFS ($p < 0.01$); however, there was no difference by type of axillary surgery.

DISCUSSION

In this study population of patients with molecularly high-risk breast cancer who received NAC on the I-SPY2 clinical trial, with short-term follow-up we found no

difference in AxR, LRR, or EFS in those who underwent SLN-only surgery versus ALND in both ypN0 and ypN+ disease. DRFS was also not inferior with selected omission of ALND. While data from prospective trials regarding optimal oncologic management of patients with ypN+ disease are awaited to guide practice guidelines, our findings suggest that some patients with residual nodal disease after NAC may not require ALND.

Over the last 2 decades, studies evaluating the de-escalation of axillary surgery have led to a gradual stepwise decrease in the indications for ALND.[15–22] Although NSABP B-04[23] showed no association between omission of ALND and overall survival over 40 years ago, the high AxR rate of 19% in this early trial resulted in persistent concerns about the oncologic safety of omitting ALND. Hence, ALND long remained the standard of care for node-positive patients. This approach changed considerably with publication of the Z0011[24,25] and AMAROS[26] trials. In these landmark studies, omission of ALND for cN0 but pN+ patients with low burden of axillary disease who underwent upfront surgery with breast-conserving surgery did not result in an increased risk of AxR. Consequently, the omission of ALND in cN0 patients who are found to have one to two positive nodes at upfront surgery is the current standard of care. However, data are not available in the setting of NAC.

For patients presenting with cN+ disease who are treated with NAC, trials have shown the accuracy of SLN surgery for detecting residual nodal disease, particularly with the use of techniques such as dual tracer and excision of the index biopsy-positive node.[10,12] These trials have allowed for omission of ALND in those patients proven to have eradication of nodal disease on SLN surgery after NAC. However, for those with residual nodal disease after NAC, no prospective studies to date have demonstrated the safety of omission of ALND. As such, one of the last remaining indications for ALND is for those patients with positive SLN(s) after completion of NAC.

There is great interest in further reducing the indications for ALND since this procedure is associated with complications such as lymphedema, numbness, axillary web syndrome, and decreased upper-extremity range of motion,[27] while omission of ALND results in reduced morbidity and improved quality of life.[15–20,25,27–29] Indeed, omission of ALND in ypN+ patients after NAC has increased despite the absence of prospective, randomized data in this patient population.[14,30,31] We previously reported the changes in axillary surgical management over the last 11 years in the I-SPY2 clinical trial, showing an increase in the omission of ALND for those with both cN0 and cN+ disease at presentation, and even in patients with ypN+ disease at surgery.[14]

While extrapolation of the results of the Z0011[24,25] and AMAROS[26] trials to the NAC setting appears to be occurring, recognition of the considerable differences in patient populations is critical. For example, both Z0011 and AMAROS enrolled cN0 patients with T1-2 tumors and largely favorable tumor biology, as reflected by the high rates of HR+HER2− disease being treated with upfront surgery. In contrast, patients selected to undergo NAC have a higher burden of disease and more aggressive tumor biology, as reflected in the I-SPY2 trial population. Furthermore, nodal disease after NAC is chemotherapy-resistant disease and reflects poorer prognosis than in the upfront surgery setting. These differences likely explain the higher rates of axillary and local recurrence seen in our study population. The 10-year AxR rate in Z0011 was 1.5% for SLN-only and 0.5% for ALND.[26] In our study, the estimated 5-year rates of AxR in patients after NAC were 1.8% for those ypN0 disease and 3.9% for ypN+ disease. While higher than seen in the Z0011 and AMAROS populations, these recurrence rates did not differ by type of axillary surgery, suggesting that ALND does not directly impact these rates. However, because type of axillary surgery was not randomized in the I-SPY2 trial and is impacted by patient selection that cannot be completely controlled for on analysis, it is possible that those patients selected to have ALND would have had higher recurrence rates if they had undergone SLN-only.

While our results suggest the oncologic safety of omission of ALND for some ypN+ patients, it is also important to note that most patients in this study received radiotherapy. A limitation of this analysis is the lack of availability of specific radiation field data. We previously reported that in the subset of I-SPY2 patients with a positive SLN who underwent completion ALND, the rate of additional positive nodes was 33.3% in cN0 patients and 60.3% in cN+ patients.[14] These rates are consistent with prior published literature. The rate of additional positive nodes in cases with macrometastatic disease was 60.1% in ACOSOG Z1071,[10] 62% in a single-institutional report,[32] and 56% in the SN FNAC trial.[12] This high rate of additional positive nodes underscores the need for longer-term oncologic outcomes of larger cohorts with omission of ALND.

To safely consider omission of ALND in practice, further investigation into predictive factors to best select candidates for axillary surgical de-escalation are needed. In our study, we saw that ypN+ patients who had SLN-only surgery were significantly more likely to have smaller tumors at presentation and at surgical resection (lower cT and ypT categories) and were more likely to have been cN0 at diagnosis. This suggests that surgeons selected patients for omission of ALND based on clinical features that were indicative of lower overall disease burden. Additionally, lower ypT category suggests better response to NAC, which is also associated with reduced risk of recurrence. For molecularly high-risk patients such as those in the I-SPY2 trial, lack of response to systemic therapy portends a higher risk of distant recurrence, which is unlikely to be modified by more

extensive surgical resection. This may be reflected in the higher rates of distant rather than local failure in this study, especially in patients with ypN+ disease regardless of axillary surgery type. This further underscores that breast cancer biology, rather than the extent of surgery, is a major risk determinant of both systemic and LRR.[33,34]

Patients with cN+ disease had more nodes removed both at SLN surgery and at ALND than patients with cN0 disease at presentation. This reflects surgeons considering the likelihood of nodal positivity while performing axillary surgery and is in keeping with prior studies that have shown more nodes are removed when there is a higher risk of nodal disease—such as larger tumor size in the breast.[35,36] Surgeon knowledge of the patient's entire case influences surgical approach as well as surgical decision making and provides a complexity to patient care that is hard to control for in any study.

Although this study has many strengths, it is not without important limitations. First, the retrospective nature and non-randomized surgical treatment led to selection bias in the application of SLN-only versus ALND. We attempted to account for this in the propensity score-matched model, but, as mentioned above, cannot include unmeasured confounders. Additionally, although molecularly high-risk tumors tend to recur early, our follow-up time of 3.5 years remains short and re-evaluation with longer-term outcomes will be needed. Furthermore, follow-up is shorter for the SLN-only group than for the ALND group, as the practice shift to SLN-only has occurred in more recent years. Finally, the study may be underpowered to detect small differences in AxR rates. Accordingly, until reporting of prospective randomized trials, ALND remains the standard of care for ypN+ patients after NAC. The strengths of our study include the multicenter nature on a prospective trial, standardized imaging including breast MRI for all patients, and centrally trained pathology evaluations. Further work to identify factors that may have contributed to surgical decision making, such as post-treatment physical examination and imaging, would be valuable.

Multidisciplinary team discussion is critically important for many breast cancer cases, and in cases where omission of ALND is being considered, discussion with both medical oncology and radiation oncology regarding the impact of ALND or omission of ALND on adjuvant systemic therapy and/or radiation therapy recommendations is crucial and should be discussed across the team, and also with the patient, to guide shared decision making.

While the definitive answer to the question regarding omission of ALND and treatment with definitive radiation for patients with residual nodal disease after NAC is being evaluated in the Alliance for Clinical Trials in Oncology A11202 trial in the US[13] and in the TAXIS study in Europe[37], the results of these studies are awaiting follow-up of patients for subsequent events. In the meantime, data such as these retrospective results from the I-SPY2 trial may help guide discussions and management decisions. For patients who request to avoid ALND, the early data from this cohort of carefully selected patients undergoing SLN-only surgery are encouraging, demonstrating that short-term oncologic control is not inferior with the omission of ALND. These findings should be validated in other studies, and further work should focus on refining predictors that allow us to further tailor surgical treatment for all breast cancer patients.

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