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Changes in Surgical Management of the Axilla Over 11 Years – Report on Over 1,500 breast Cancer Patients Treated with Neoadjuvant Chemotherapy on the Prospective I-SPY2 Trial

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Abstract

Background: Axillary surgery in patients treated with neoadjuvant chemotherapy (NAC) is becoming less extensive. We evaluated the evolution of axillary surgical management in patients treated with NAC on the multi-institutional I-SPY2 prospective trial.

Methods: We examined annual rates of sentinel lymph node (SLN) surgery (with resection of clipped node, if present), axillary lymph node dissection (ALND) and SLN & ALND in patients enrolled in I-SPY2 from 1/1/2011 to 12/31/2021 by clinical N status at diagnosis, and pathologic N status at surgery. Cochran-Armitage trend tests were calculated to evaluate patterns over time.

Results: Of 1,578 patients, 973 patients (61.7%) had SLN-only, 136 (8.6%) had SLN & ALND, and 469 (29.7%) had ALND-only.

In cN0 group, ALND-only decreased from 20% in 2011 to 6.25% in 2021 ($p=0.0078$) and SLN-only increased from 70.0% to 87.5% ($p=0.0020$). This was even more striking in patients with clinically node-positive (cN+) disease at diagnosis, where ALND-only decreased from 70.7% to 29.4% ($p<0.0001$) and SLN-only significantly increased from 14.6% to 56.5% ($p<0.0001$). This change was significant across subtypes (HR-/HER2-, HR+/HER2- and HER2+).

Among pathologically node-positive (pN+) patients after NAC ($n=525$) ALND-only decreased from 69.0% to 39.2% ($p<0.0001$) and SLN-only increased from 6.9% to 39.2% ($p<0.0001$).

Conclusion: Use of ALND after NAC has significantly decreased over the last decade. This is most pronounced in cN+ disease at diagnosis with an increase in the use of SLN surgery after NAC. Additionally, in pN+ disease after NAC there has been a decrease in use of completion ALND, a practice pattern change that precedes results from clinical trials.

Keywords

sentinel lymph node surgery; axillary dissection; neoadjuvant chemotherapy

Introduction

While historical management of breast cancer included resection of the breast primary along with routine axillary lymph node dissection (ALND), there has been significant evolution in the surgical management of the axilla over the last several decades with incorporation of sentinel lymph node (SLN) surgery.¹⁻⁵ Additionally, with advancements in systemic therapy, there has been an increase in the use of neoadjuvant chemotherapy (NAC) for patients with locally advanced disease and also, in early-stage disease with aggressive tumor biology.

Initially SLN surgery was adopted in patients with clinically node-negative (cN0) disease undergoing primary surgical resection;¹⁻⁵ however, additional studies demonstrated that SLN surgery was also appropriate for patients with cN0 disease who were treated with neoadjuvant chemotherapy.⁶⁻¹⁰ Furthermore, several clinical trials evaluated de-escalation of axillary surgery with use of SLN surgery after completion of NAC in patients initially diagnosed with clinically node-positive (cN+) breast cancer. At the San Antonio Breast Cancer Symposium in 2012, the results of the first two of these trials ACOSOG Z1071 (Alliance for Clinical Trials in Oncology)¹¹ and the SENTINA study¹² were presented. These and subsequent trials^{13,14} demonstrated a false negative rate (FNR) of 8.4–14.2% and SLN identification rate of 87.6–97.2% with use of SLN surgery after NAC in this setting. These trials led to the incorporation of SLN surgery after neoadjuvant chemotherapy for patients with cN+ disease at presentation to assess for residual nodal disease. This approach

allows potential for omission of ALND for those patients with clinically positive nodes that convert to pathologically node negative disease.¹⁵

The I-SPY2 trial is a prospective adaptive randomized trial in the neoadjuvant setting evaluating pathologic complete response rates to novel chemotherapeutic agents for patients with high-risk breast cancer – defined as tumor size over 2.5cm and high-risk on Mammprint. It was activated in 2010 with 20–30 sites participating across the United States. A survey of I-SPY2 surgeons in 2018 showed that for patients with node-positive disease at presentation, 48% of surgeons would manage the axilla on a case-by-case basis with SLN surgery and consider omission of ALND, while another 17% would always offer SLN surgery with possible omission of ALND.¹⁶ The axillary management protocol in I-SPY2 was clarified in 2017/8 to recommend placing a clip in the biopsy-proven positive node at diagnosis and localization of the clipped node at time of SLN surgery.

While SLN surgery after NAC with no further axillary surgery is appropriate for patients who have pN0 disease, for patients with positive sentinel node(s) after neoadjuvant chemotherapy, the standard of care remains completion ALND. However further de-escalation of axillary surgery is being evaluated in the Alliance A11202 clinical trial which is comparing completion ALND to axillary nodal radiation in the setting of node positivity after NAC.¹⁷

The goal of this study was to evaluate the evolution of axillary surgical management in both cN0 and cN+ patients with breast cancer treated with NAC on the multi-institutional I-SPY2 prospective trial.

Methods

I-SPY2 is an adaptive platform trial for patients with high-risk breast cancer (>2.5cm in size and molecularly high risk) recommended for treatment with NAC.^{18–24} Patients undergo standard imaging work-up per local institution and axillary ultrasound is recommended, along with percutaneous biopsy of any abnormal axillary lymph nodes for clinical staging. Per protocol, all patients undergo baseline dynamic contrast enhanced breast magnetic resonance imaging (MRI) at diagnosis. Patients are then randomized to neoadjuvant novel systemic therapy agents, followed by surgical resection to evaluate response to therapy. The type of breast surgery is at the discretion of the treating surgeon and patient. Axillary surgery is not permitted prior to neoadjuvant chemotherapy as the primary endpoint of the trial is pathologic complete response rate. SLN surgery is recommended after NAC for patients with cN0 disease at presentation, with ALND recommended for failed lymphatic mapping or failure to identify at least 2 SLNs. In patients with cN+ disease at presentation either SLN or ALND are allowed, and if SLN surgery is performed, resection of at least 2 nodes and resection of the clipped node is required per protocol. Resection of the lymph node with the clip is included within SLN surgery, so SLN surgery category includes SLN surgery +/- targeted axillary dissection. In the setting of pathologic positive node(s), further axillary surgery is not mandated and is at the discretion of the treating surgeon in both cN0 and cN+ groups.

We evaluated the axillary surgical management of patients enrolled across all arms of the I-SPY2 clinical trial from January 1, 2011 to December 31, 2021. Type of axillary surgery was SLN-only, SLN & ALND, or ALND-only. The post-surgery summary form collected the number of SLNs resected and the number of ALNs resected. In cases with 10 or more SLNs, or fewer than 6 ALNs, review of the pathology report was undertaken for verification of procedure performed and number of nodes resected.

Type of axillary surgery was examined across all patients over time and separately by clinical N category (cN0 vs cN+) at time of initial diagnosis and by axillary pathologic nodal status. Frequency and proportion of type of axillary operations were measured by year. The false negative rate (FNR) for SLN procedure was calculated in the subset of patients with residual disease who underwent SLN & ALND. Tumor biology was categorized as hormone receptor (HR) positive if tumor was estrogen receptor (ER) positive or progesterone receptor (PR) positive (1% positively staining cells by immunohistochemistry respectively). Approximated biologic subtypes were HR+/HER2neu negative (HR+/HER2-), HER2+ and HR-/HER2-.

Statistics

Summary statistics were performed to describe the cohort. The Cochran-Armitage trend test was used to evaluate patterns over time. T-tests, Chi-square and Fisher exact tests were used as appropriate. Mean proportion for the first 5 years and the last 6 years for each type of axillary surgery were reported and compared using two sample t-test. P value of <0.05 was considered significant. RStudio 2021.09.2 Build 382 was used for the statistical analysis.

Results

Of 1,632 patients enrolled and randomized in the I-SPY2 trial from January 1, 2011 through December 31, 2021, 1,584 patients completed NAC and had evaluable data regarding axillary surgery. Six patients (0.4%) did not have axillary surgery, largely due to patient choice. The clinical and pathologic characteristics of the 1,578 patients are shown in Table 1. Mean age was 48 years and the majority of patients had cT2 or cT3 disease at presentation with 53.6% being cN+ at diagnosis. Tumor subtypes were 43% HR+/HER2-, 34% HR-/HER2-, and 22% HER2+.

All patients

Overall, SLN-only was performed in 973 patients (61.7%), SLN & ALND in 136 patients (8.6%) and ALND-only in 469 patients (29.7%). Use of SLN-only was highest in patients that were cN0 at diagnosis (85.7%) and lower in cN1 and cN2/3 patients (43.1% and 31.2% respectively).

The type of axillary surgery significantly changed over the time period of the study with an increase in SLN-only (from 38.0% in 2011 to 69.2% in 2021, $p < 0.0001$) and concomitant decrease in ALND-only (49.3% to 19.9%, $p < 0.0001$), while SLN surgery with completion ALND did not change significantly (Figure 1A).

False Negative Rate (FNR) of SLN surgery

The rate of SLN surgery and completion ALND was around 6–12% and did not change significantly over time. A total of 136 patients underwent SLN surgery and completion ALND, of which 8 patients had a negative SLN and positive node(s) identified on ALND for an overall false negative rate (FNR) of 7.5% (8/106). The FNR was numerically lower in cN0 than cN+, however this was not statistically significant. In patients who were cN0 (n=38), there was only 1 false negative (FNR=1/31=3.2%). In patients who were cN+ (n=98), there were 7 false negative cases (FNR=7/75=9.3%, p=0.43).

cN0 patients

In cN0 disease (n=732), the axillary surgery performed in the vast majority was SLN-only (85.7%), with low rates of ALND-only (9.1%). Over the study period, use of SLN-only increased from 70.0% in 2011 to 87.5% in 2021 (p=0.0020), while use of ALND-only decreased from 20% to 6.25% (p=0.0078). There was no significant change in the use of SLN with completion ALND (Figure 1B).

Evaluating this by tumor subtype, this significant increase in use of SLN-only and decrease in ALND-only was significant in HER2+ disease (p=0.0045 and p=0.0026 respectively), but there was no significant change in type of axillary surgery over time in cN0 HR-/HER2- or in cN0 HR+/HER2- disease.

Figure 2 shows the axillary management of the 732 patients with cN0 disease. Of the 665 patients who had SLN surgery (either alone or SLN & ALND), the majority had negative SLNs (592/665 – 89%). Of the 73 with positive SLN(s), only 30 patients (41%) went on to ALND and of those, there were additional positive axillary nodes identified in 10 patients (33.3%).

Rate of completion ALND in the 73 patients with positive SLN was similar in those undergoing lumpectomy (10/25, 40%) and mastectomy (20/48, 41.7%, p=0.999) and was numerically, but not significantly higher in patients age <50 (18/39, 46%) than in those age 50 (12/34, 36%, p=0.549).

cN+ patients

In cN+ disease (n=846), ALND was the most commonly performed surgery in 2011 with 70.7% of patients having ALND-only. There was a significant decrease in use of ALND-only to 29.4% in 2021 (p<0.0001), while SLN-only increased from 14.6% to 56.5% (p<0.0001) during this timeframe, with SLN-only being more common than ALND-only from 2017 onwards. (Figure 1C). Overall, 47.5% of patients went straight to ALND, 40.9% had SLN-only and 11.6% had SLN & ALND.

Add data on cN1 versus cN2 and cN3—The increase in SLN-only and decrease in ALND-only over time was significant in all subtypes (HR-/HER2-, HR+/HER2- and HER2+) in the cN+ group (p<0.0001 for decrease in ALND-only and for increase in SLN-only in each subgroup, see Figure 3).

Figure 4 shows the axillary management of the cN+ patients. ALND was the initial surgery in 47.5% of these patients (402 patients) and most of these patients had positive nodes on ALND (62.7%). For the 444 patients (52.5%) who started with SLN surgery first, the majority of these patients had negative SLNs (61.9%). Among the 169 patients with positive SLN, 68 (40.2%) underwent ALND, and additional positive nodes were identified in 41 cases (60.3%). This is significantly higher than seen in the cohort of patients with cN0 disease at presentation that had a positive SLN and went on to ALND (60.3% versus 33.3%, $p=0.025$).

The rate of completion ALND (cALND) increased with increasing number of positive SLN. Completion ALND was performed in 39% of cases with 1 positive SLN, in 38% of cases with 2 positive SLNs, 42% with 3 positive SLNs, 40% with 4 positive SLN and 60% with 5 positive SLNs and 100% with 6 positive SLNs.

The rate of cALND in the 169 patients with positive SLN was similar in lumpectomy (25/65, 38.5%) and mastectomy (43/104, 41.3%, $p=0.833$) and was also similar between patients age <50 (41/105, 42.2%) than in those age \geq 50 (27/64, 39.0%, $p=0.809$).

pN0 patients

Evaluating the type of axillary surgery performed by pathologic nodal status, most patients with pathologic negative nodes ($n=1053$) had SLN-only surgery performed with rates of SLN-only increasing from 59.5% in 2011 to 83.8% in 2021 ($p<0.0001$) and ALND-only decreasing from 35.7% to 10.5% ($p<0.0001$). (Figure 1D). This was true across all 3 tumor subtypes.

pN+ patients

Among patients with confirmed pathologic positive nodes after NAC ($n=525$), the most common procedure performed was ALND-only (54.5%) with an additional 19.6% having SLN & ALND. However, ALND-only decreased over the timeframe studied from 69.0% to 39.2% ($p<0.0001$) and SLN-only increased from 6.9% to 39.2% ($p<0.0001$) (Figure 1E). These changes were more striking in 2016–2021 compared to 2011–2015, $p=0.0067$ for ALND-only and $p=0.0073$ for SLN-only. Overall, the majority of patients (60.6%) still underwent ALND in 2021 (39.2% having ALND-only and 21.6% having SLN & ALND), however 39.2% of patients with positive node(s) at surgery had omission of ALND.

ALND-only patients—In 469 patients, ALND-only was performed, without SLN surgery. The majority of these ($n=402$, 85.7%) were patients with cN+ disease at diagnosis (302 cN1, 43 cN2 and 57 cN3). Overall, the rate of pathologic nodal positivity in patients going straight to ALND was 61.0% (286/469) and did not vary significantly over time ($p=0.7895$). The rate of pathologic nodal positivity was 62.7% (252/402) in cN+ disease and was 50.7% (34/67) in cN0 disease ($p=0.086$) in patients who had ALND-only. The rate of nodal positivity was significantly higher in HR+/HER2– disease at 75.2%, compared to HR–/HER2– (48.8%, $p<0.001$) and HER2+ disease (43.8%, $p<0.001$).

Discussion

In this multicenter study of patients with high-risk breast cancer treated with neoadjuvant chemotherapy, the use of ALND significantly decreased over the last decade. This is most pronounced in patients with cN+ disease at diagnosis where there has been a significant increase in the use of SLN surgery after NAC and a decrease in proceeding directly with ALND. Additionally, in patients with a pathologically positive SLN after NAC, there has been a decrease in use of completion ALND, even though data from prospective clinical trials evaluating the oncologic outcomes of this approach have not yet been reported.

The vast majority of patients did undergo some form of axillary surgery, with omission of axillary surgery occurring in 6 patients (0.38%) and this was predominantly due to patient preference. Surgical evaluation of axillary nodes after neoadjuvant chemotherapy remains standard of care and is required on this clinical trial whose primary endpoint is pathologic complete response.

For patients with cN0 disease at presentation, the use of SLN was more frequent than for those with cN+ disease. This is because SLN surgery in patients with cN0 disease treated with NAC has been more widely accepted over a longer period of time than in patients with cN+ disease. However, there was still a significant increase in use of SLN-only and decrease in use of ALND in patients with cN0 disease over the last decade, reflecting increased comfort with use of SLN surgery after NAC in this population. Over time, the use of ALND as the initial surgery for axillary staging after NAC has significantly decreased such that this is rarely performed in the current era for cN0 disease treated with NAC.

The majority of patients (70–77%) with cN+ breast cancer at diagnosis in 2011–2012 underwent ALND-only (i.e. no SLN surgery). The ACOSOG Z1071 and SENTINA trials were presented at San Antonio Breast Cancer Symposium in December 2012 and reported in 2013 demonstrating the feasibility and accuracy of SLN surgery for patients with cN+ disease that converted to pN0 after NAC.^{11,12} The rate of ALND-only (without SLN surgery) decreased to 40–55% in 2015–2018 and continued to decrease to 28–32% in 2019–2021 demonstrating the implementation of SLN surgery for staging the axillary response to NAC in patients who originally presented with cN+ breast cancer. This decrease in ALND-only is mirrored by an increase in SLN-only with rates rising from 15% to 55–60% over the time period. Interestingly the rate of SLN surgery with completion ALND has not changed significantly and remained around 10–15%.

These findings are consistent with several single institution publications showing a significant decrease in use of ALND and increase in use of SLN surgery following NAC. At Mayo Clinic, the use of ALND (+/- SLN surgery) decreased from 100% in 2009 to 57.2% in 2015–2019.^{25 26} Memorial Sloan Kettering Cancer Center published on their series of 195 patients with node positive disease who underwent surgery and ALND alone was performed in 63 patients (32%) and the remaining 68% underwent SLN surgery.²⁷ Data from the National Cancer Database (NCDB) demonstrate that the national rates of ALND in node-positive breast cancer treated with NAC have decreased from 88.7% to 77.1% from 2013 to 2015 with this pattern seen in both community and academic institutions.²⁸

Similar trends were seen across different types of tumor biology with increase in SLN surgery and decrease in ALND seen in HR-/HER2-, HER2+ disease and in HR+/HER2- disease. This is consistent with findings from the NCDB that showed an increase in use of SLN surgery in HR-/HER2- from 20% in 2012 to 46% in 2017²⁹ and in HER2+ disease from 20% in 2012 to 50% in 2017.³⁰

The FNR of SLN surgery in cN+ patients treated with NAC has been shown to vary across clinical trials ranging from 8% to 14%.^{11 12 13,14} In our study, the majority of patients with cN+ disease who had negative SLNs did not have ALND, and our study was not designed to evaluate the false negative rate. Nevertheless, there were 98 patients who underwent SLN and completion ALND and in 7 of these, the patient was pathologically node-positive based on the ALND findings, for an overall FNR of 9.3%. Information regarding resection of the clipped node is not currently available on these cases and will be important to evaluate. It is important to note that there is surgeon selection in terms of which patients with negative SLNs undergo completion ALND and therefore this FNR is likely an over-estimate.

The majority of the data from the prospective clinical trials is in patients with cN1 disease and not in cN2/cN3 disease. ACOSOG Z1071 included 38 patients with cN2 disease of which 26 had 2 SLNs excised and there were no false negatives among these 26 women, however the primary endpoint of the trial was restricted to cN1 disease. However, despite the lack of data in patients with more advanced nodal disease at presentation, in this study we found that SLN surgery is being used in selected patients with cN2 or cN3 disease at presentation. The reasoning behind this decision is not known. One hypothesis is that while SLN surgery after NAC is not recommended for patients with bulky nodal disease at presentation, it may be reasonable to consider SLN surgery in the setting of low volume axillary disease along with internal mammary or supraclavicular disease, in which the surgical management of the axilla can be guided by burden of axillary disease at presentation.

Focusing on pathology findings from surgery, the majority of patients with pathologically positive node(s) at surgery had ALND – either ALND-only or SLN and completion ALND. Omission of ALND in the setting of pN+ disease was rare in 2011 at 6.9%. Interestingly, this increased over the last decade to 38–42% in 2018–2021. The Alliance A11202 clinical trial randomized patients with positive SLN to completion ALND versus axillary radiation. When this trial opened in 2014 most patients were having ALND and the motivation to enroll in this trial was to try to avoid ALND. This trial closed to accrual in 2022, however the primary endpoint of local recurrence has not yet been reported. Across the timeframe of the study, especially over the last four years, patients and surgeons have become more interested in avoiding ALND and treating residual node positive disease after NAC with radiation instead of ALND. While the current standard of care is for ALND in the setting of residual disease in the SLN, the findings in the patients treated on I-SPY2 demonstrate that the use of completion ALND in this setting is decreasing even though the results from definitive studies [the Alliance A011202 (NCT01901094) trial and the OPBC-03/TAXIS trial] have not yet reported on the oncologic safety of omission of ALND in this situation. While some of the patients in this cohort may have been enrolled in the A11202 study, the rates of ALND continued to decrease while the A11202 trial was temporarily closed and

after the A11202 trial closed to accrual, demonstrating this this pattern is not driven by patients enrolled on the clinical trial.

Add re cN2/cN3

This study has several limitations. This study describes practice patterns, but the reasons behind clinical decision making regarding the type of axillary surgery as well as decision to omit ALND is not known. Furthermore, the clinical status of the axilla by physical examination and imaging after completion of NAC is not available and this also impact decision making. There is guidance for axillary management in the I-SPY2 protocol, however, these patients are managed across 26 different sites with multiple surgeons at each site, and ultimately the protocol provides guidelines but not requirements for management. Information regarding the size of metastasis in the nodes and resection of the clipped node in the setting of cN+ disease is not available and may be factors which influence surgical decision making. Most importantly, the long-term oncologic outcome of these patients will be critical to evaluate in order to provide guidance regarding whether these changes in practice patterns are appropriate and that omission of ALND does not result in more breast cancer events, in particular regional recurrence or distant recurrence.

The use of ALND after NAC has markedly decreased among patients in the I-SPY-2 cohort and this practice pattern change is occurring before results from ALLIANCE A011202. This trend will likely reduce the side effects of surgical treatment for patients with pathologically negative lymph nodes. We await the results of randomized clinical trials to determine whether ALND can be safely omitted among patients with pathologically positive lymph nodes after NAC.

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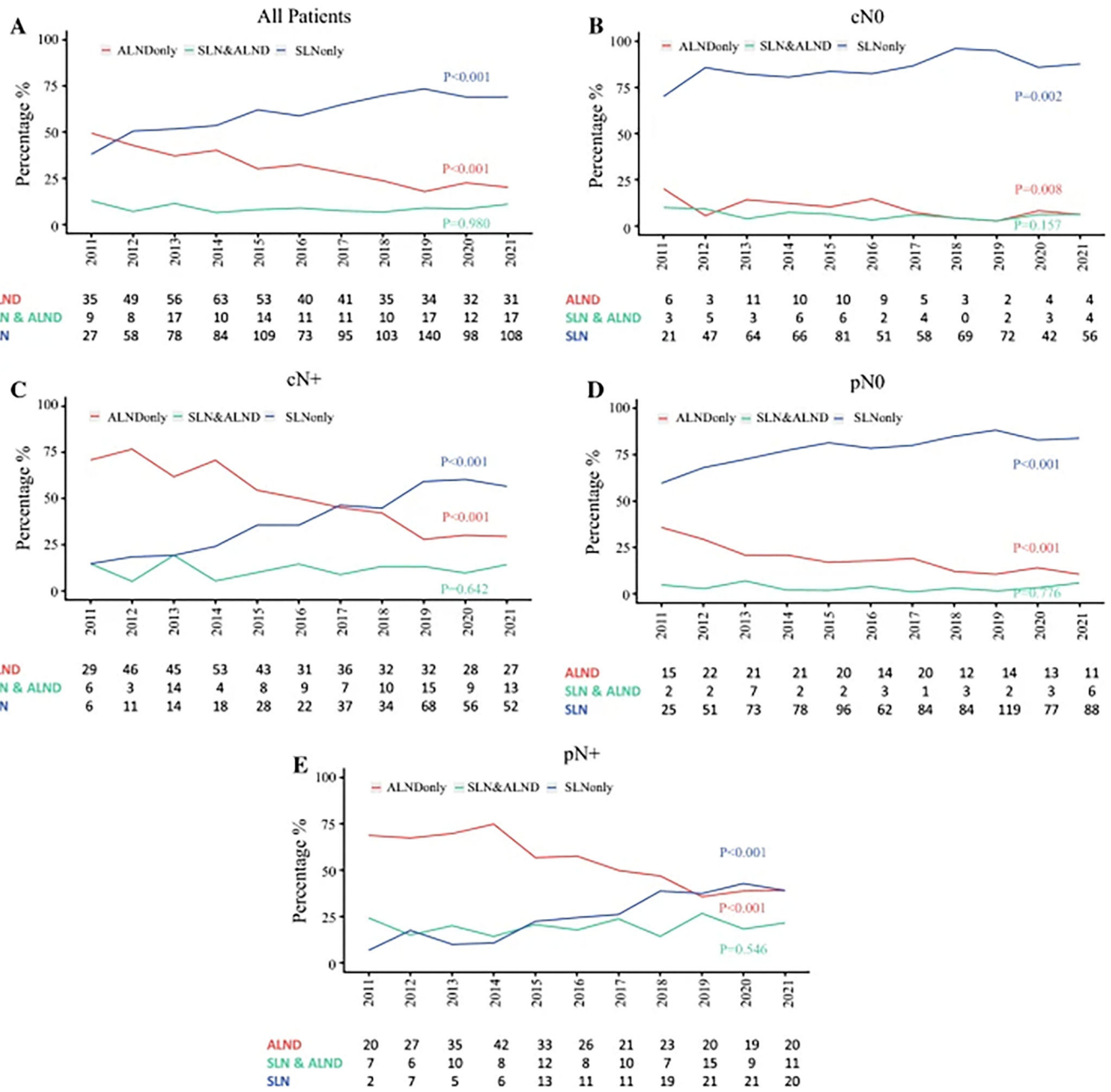


Fig. 1. Rate of type of axillary surgery per year from 2011–2021: **A** in all patients ($n = 1578$), **B** in clinically node-negative (cN0) patients at diagnosis ($n = 732$), **C** in clinically node-positive (cN+) patients at diagnosis ($n = 846$), **D** in pathologically node-negative (pN0) patients at surgery ($n = 1053$) and **E** in pathologically node-positive (pN+) patients at surgery ($n = 525$). Number of patients with each procedure each year indicated below the x -axis

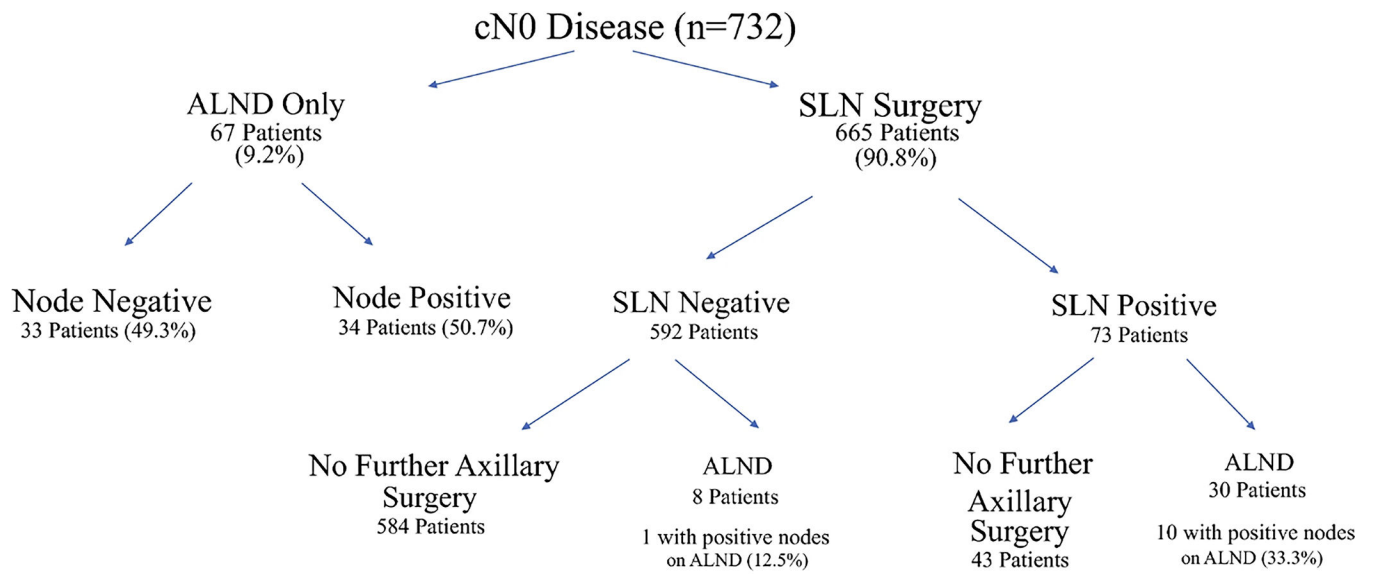


Fig. 2. Axillary management of patients with clinically node-negative (cN0) disease at diagnosis

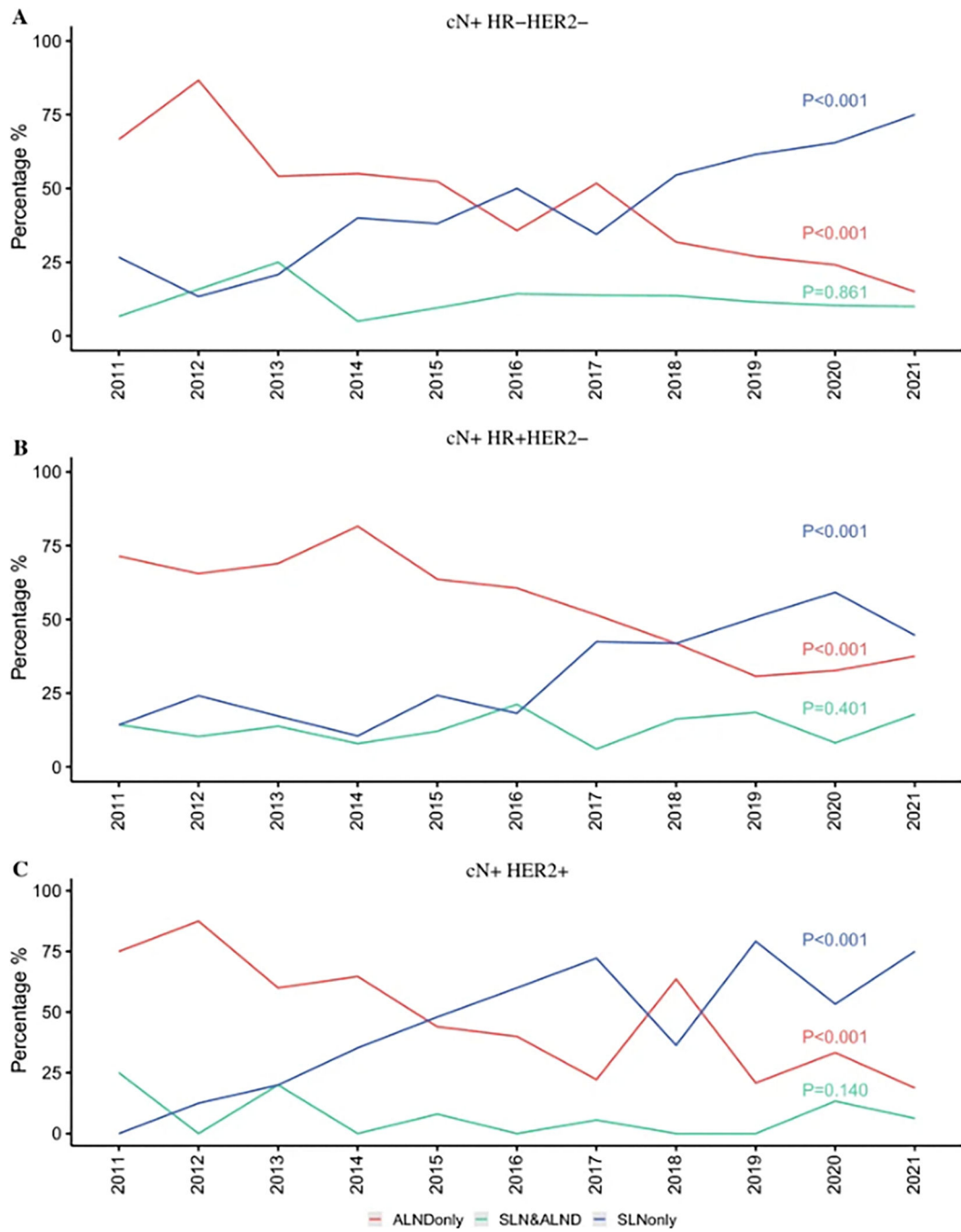


Fig. 3. Rate of type of axillary surgery per year from 2011–2021 in clinically node-positive (cN+) patients at diagnosis by tumor subtype: HR-/HER2- **A**; HR+/HER2- **B**; C HER2+ disease

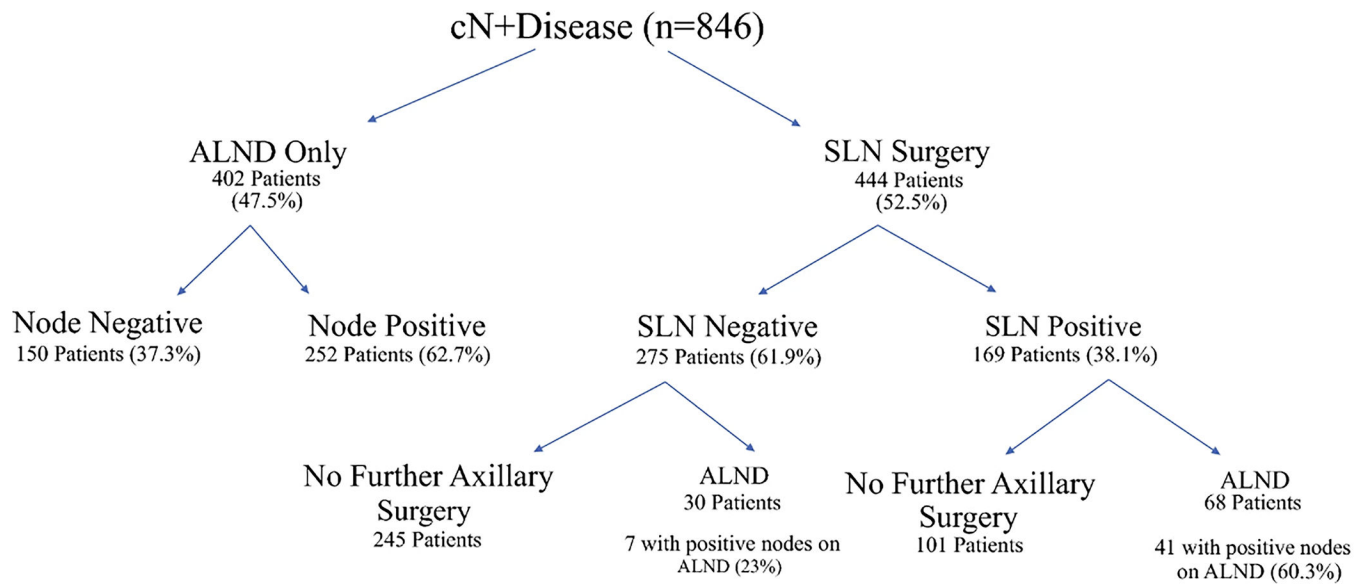


Fig. 4. Axillary management of patients with clinically node-positive (cN+) disease at diagnosis

Table 1

Clinical and pathologic characteristics of the cohort overall and by clinical N status at diagnosis

Baseline characteristics		Clinically node-negative (cN0) (n=732)	Clinically node-positive (cN+) (n=846)	Total cohort (n=1578)
Age at screening [yrs]	Mean (SD)	48.4 (11.1)	48.2 (11.3)	48.3 (11.2)
Race	Asian	61 (8.3)	56 (6.6)	117 (7.4)
	Black	72 (9.8)	107 (12.6)	179 (11.3)
	Other	15 (2.0)	18 (2.1)	33 (2.1)
	White	584 (79.8)	665 (78.6)	1249 (79.2)
Ethnicity	Hispanic or latino	82 (11.2)	101 (11.9)	183 (11.6)
	Not hispanic or latino	647 (88.4)	741 (87.6)	1388 (88.0)
	Unknown	3 (0.4)	4 (0.5)	7 (0.4)
Clinical T category	T1	33 (4.5)	10 (1.2)	43 (2.7)
	T2	557 (76.1)	498 (58.9)	1055 (66.9)
	T3	132 (18.0)	292 (34.5)	424 (26.9)
	T4	10 (1.4)	46 (5.4)	56 (3.5)
Clinical N category	N0	732 (100.0)		732 (46.4)
	N1		686 (81.1)	686 (43.5)
	N2		68 (8.0)	68 (4.3)
	N3		92 (10.9)	92 (5.8)
Tumor receptor subtype	HR+Her2-	257 (35.1)	422 (49.9)	679 (43.0)
	HR-Her2-	309 (42.2)	235 (27.8)	544 (34.5)
	Her2+	166 (22.7)	189 (22.3)	355 (22.5)
Type of breast surgery	BCS	364 (49.7)	316 (37.4)	680 (43.1)
	Mastectomy	368 (50.3)	530 (62.6)	898 (56.9)
Pathologic T category	T0	256 (35.0)	250 (29.6)	506 (32.1)
	T1	234 (32.0)	254 (30.0)	488 (30.9)
	T2	137 (18.7)	162 (19.1)	299 (18.9)
	T3	42 (5.7)	98 (11.6)	140 (8.9)
	T4	5 (0.7)	16 (1.9)	21 (1.3)
	Tis	58 (7.9)	63 (7.4)	121 (7.7)
	TX		3 (0.4)	3 (0.2)
Pathologic N category	N0	626 (85.5)	427 (50.5)	1053 (66.7)
	N1	89 (12.2)	269 (31.8)	358 (22.7)
	N2	10 (1.4)	102 (12.1)	112 (7.1)
	N3	7 (1.0)	48 (5.7)	55 (3.5)