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ORIGINAL ARTICLE – BREAST ONCOLOGY

Risk of Surgical Overtreatment in cN1 Breast Cancer Patients who Become ypN0 After Neoadjuvant Chemotherapy: SLNB Versus TAD

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ABSTRACT

Background. Two surgical approaches have emerged for axillary staging in cN1 breast cancer patients after neoadjuvant chemotherapy (NAC): sentinel lymph node biopsy (SLNB) and targeted axillary dissection (TAD). Direct comparisons of technical and oncological outcomes with SLNB versus TAD are lacking.

Methods. We routinely performed SLNB from 2017 to 2018 for cN1 breast cancer patients who converted to cN0 after NAC, then adopted TAD from 2019 to 2022. To minimize the false-negative rate (FNR), we required retrieval of ≥3 sentinel lymph nodes (SLN) (2017–2018) or retrieval of the clipped node (CN) and ≥2 SLN (2019−2022). In ypN0 cases meeting these criteria, axillary lymph node dissection (ALND) was omitted. We compared the rate of per-protocol required ALND due to technical failure of SLNB versus TAD and reported axillary recurrence rates.

Results. Among 191 cN1 ypN0 patients, 77 underwent SLNB and 114 underwent TAD. The overall rate of required ALND due to technical failure was 14.7% and did not differ between SLNB versus TAD (16.9% vs. 13.2%, $p = 0.38$). The most common technical failure with SLNB was retrieving <3 SLN (10.4%); for TAD, it was not retrieving the CN (7.1%). Median follow-up was 3.9 years for SLNB patients and 1.7 years for TAD patients; there were 1 (1.3%) and 0 (0.0%) axillary recurrences, respectively.

Conclusions. Sentinel lymph node biopsy and TAD for cN1 patients after NAC showed equivalent technical failure rates and low axillary recurrence rates. When applying strict criteria to minimize FNR of axillary staging surgery, approximately 15% of ypN0 patients may be overtreated with ALND.

Keywords Breast cancer · Neoadjuvant chemotherapy · Axillary surgery · Sentinel lymph node biopsy · Targeted axillary dissection · Axillary recurrence

More than 40% of clinically node-positive breast cancer patients treated with neoadjuvant chemotherapy (NAC) will have a pathologic complete response (pCR) in the axilla, presenting an opportunity to omit axillary lymph node dissection (ALND) and its associated morbidity.[1] Multiple trials have demonstrated that in cN1 breast cancer patients treated with NAC, the sentinel lymph node biopsy (SLNB) procedure has an overall false-negative rate (FNR) of 8.4–14.2%.[1–4] The use of dual tracer, retrieving ≥3 sentinel lymph nodes (SLN) and/or utilizing immunohistochemistry (IHC) for nodal evaluation, lower the FNR to a

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more acceptable range of 4.9–9.1%.[1–4] The FNR is further reduced to 2.0–3.5% with targeted axillary dissection (TAD), which involves marking (clipping) and targeting the initially biopsy-proven malignant lymph node for retrieval in combination with SLNB.[5,6]

When the above trials evaluating accuracy of axillary staging surgery were first published, there was limited oncologic outcome data for omitting ALND in the setting of negative axillary staging after NAC. As such, clinical practice guidelines cautiously endorsed this approach but encouraged use of all techniques to minimize the FNR, including removing the biopsy-proven clipped node (CN), using dual tracers, and retrieving ≥3 SLN.[7] However, there remains significant debate in the breast surgery community regarding the optimal axillary staging surgery in this population (SLNB vs. TAD), and mounting data suggest that oncologic outcomes are acceptable regardless of approach,[8–12] despite the small differences in FNR. As such, the likelihood of technical failure with each staging procedure warrants consideration, with an important goal of avoiding unnecessary ALNDs in patients who experience a nodal pCR (ypN0).

Our institution developed a standardized operating procedure for axillary staging in this population, which has evolved over time in line with clinical practice guidelines. Briefly, we initially used dual-tracer SLNB and subsequently adopted TAD in 2019. Our protocolized experience with SLNB and then TAD affords an opportunity for comparison of the two techniques within a single group of surgeons. This study evaluates the likelihood of surgical overtreatment with ALND due to technical failures of SLNB or TAD in cN1 patients who converted to cN0 status after NAC and were ypN0 on final pathology. Furthermore, we report oncologic outcomes among patients treated without ALND and compare these to a historical institutional cohort when ALND was routine regardless of nodal response.

METHODS

This study was approved by the Dana-Farber Cancer Institute's research ethics board and a waiver of consent was obtained. Nonmetastatic noninflammatory cN1 breast cancer patients treated with NAC and surgery from January 2017 to March 2022 were identified from a prospectively maintained institutional database. During this time, we had a standardized operating procedure (SOP) for axillary staging surgery in this population (Fig. 1). For patients who became cN0 by clinical exam after NAC, we first adopted SLNB with a requirement to use dual tracer, retrieve ≥3 SLN, and use IHC for nodal pathologic evaluation. Axillary lymph node dissection was omitted for ypN0 patients if all these technical criteria were met. Nodal clipping and/or localization was not performed at our institution during this time. In 2019, we transitioned to strongly encouraging the use of TAD, involving SLNB with dual tracer and IHC, as well as marking the biopsy-proven lymph node with a high-visibility clip before NAC initiation and using radioactive seed localization to retrieve the CN. Under this SOP, ALND was omitted for ypN0 patients if the CN was confirmed to be retrieved by intraoperative specimen x-ray with the retrieval of at least two additional SLN. If radiology was unable to visualize the CN for seed localization, SLNB could be performed with specimen x-ray of the SLNs and omission of ALND if all criteria were met (including confirmation of retrieval of the CN). In both timeframes, use of intraoperative nodal evaluation with touch prep or frozen section was the standard approach to allow immediate ALND if indicated.

For this analysis, patients with attempted SLNB or TAD and ypN0 status were included. Patients with residual nodal micrometastases or isolated tumor cells were not included, because this was considered node-positive with recommendation for completion ALND during this time period. Demographics, tumor characteristics, and treatment details were abstracted from the institutional database. Medical record

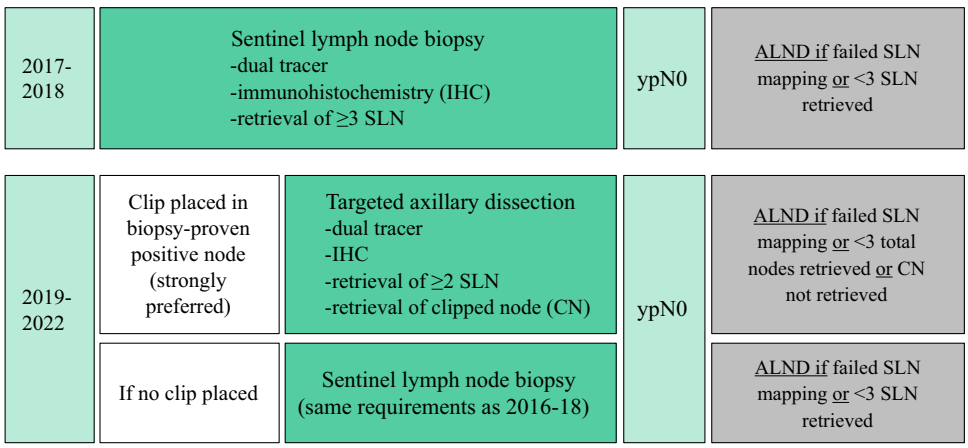

FIG. 1 Dana-Farber Cancer Institute standardized operating procedure (SOP) for axillary staging surgery in cN1 → ycN0 breast cancer patients after NAC (2017-2022) *Abbreviations*: NAC, neoadjuvant chemotherapy; ALND, axillary lymph node dissection; SLN, sentinel lymph node

review was performed to collect vital status and oncologic outcomes, including local, regional, and distant recurrences.

We reported technical outcomes of SLNB and TAD, including rates of failed mapping, <3 nodes retrieved, and CN not retrieved. The primary outcome of interest was the rate of per-protocol required ALND because of any technical failures. Technical outcomes were compared for SLNB versus TAD with chi-square tests; patients were categorized according to the planned initial axillary staging procedure. As a sensitivity analysis, we also evaluated technical outcomes when including patients who were ypNx/ypN0 by SLNB/TAD (ypNx = failed mapping) but with ypN+ disease on final ALND pathology. We used Kaplan-Meier methods to characterize recurrence-free survival (RFS).

For comparison, we identified a historical institutional cohort of cN1 ypN0 patients treated from 2006 to 2015, a timeframe when ALND was routine after NAC for clinically node-positive patients. Patient and tumor characteristics between the two cohorts were compared with descriptive statistics. We used Cox proportional hazards analysis to compare RFS between cohorts, including a multivariable model adjusting for age, tumor size, and subtype. All statistical analyses were performed in Stata IC v16.1 (College Station, TX), and $p < 0.05$ was considered statistically significant.

RESULTS

Among 597 cN1 patients treated with NAC and surgery from 2017 to 2022, 478 (80.1%) had axillary staging surgery attempted, of whom 191 (39.9%) were ypN0 and included in this analysis. Planned axillary staging surgery was SLNB in 77 patients and TAD in 114. There were no differences in baseline characteristics between axillary surgery groups (Table 1).

Technical failures of SLNB and TAD are shown in Table 2. The rate of failed mapping was 4.2% overall and did not significantly differ by axillary surgery ($p = 0.19$). The rate of retrieving <3 nodes was higher in the SLNB versus TAD group (10.4% vs. 3.5%), but this did not reach statistical significance ($p = 0.06$). The rate of not retrieving the CN among patients with planned TAD was 7.1%. Notably, challenges related to seed localization of the CN were common, although often successful retrieval of the CN was still achieved. For example, in 14 patients, the CN could not be visualized for seed localization (12.3% of planned TAD), and in 20 patients, the seed was not found to be within the CN by the surgeon intraoperatively (20.0% of those with seed placed). The overall rate of required ALND owing to technical failures of axillary staging surgery was 14.7% (95% confidence interval (CI) 10.0–20.5%) and did not differ between SLNB versus TAD (16.9% vs. 13.2%, $p = 0.48$). In a sensitivity analysis, we included an additional 24 patients who were ypNx/ypN0 by SLNB/TAD pathology but ypN+ on ALND (Supplemental Table 1). Failed mapping rates increased in both groups in this analysis and did become significantly higher for SLNB versus TAD, demonstrating that there is high likelihood of residual disease in the setting of failed mapping (19/27; 70.4%). There was otherwise

TABLE 1 Baseline characteristics of cN1 ypN0 breast cancer patients at Dana-Farber Cancer Institute (2017–2022) by planned axillary staging surgery

	Planned SLNB (n = 77)	Planned TAD (n = 114)	*p*
Median age (IQR)	49 (40–59)	49 (38–56)	0.24
Race	7 (9.1%)	9 (7.9%)	0.11
African American	0 (0%)	5 (4.4%)	
Asian/Pacific Islander	63 (81.8%)	96 (84.2%)|	
White	7 (9.1%)	4 (3.5%)	
Unknown			
Ethnicity	5 (6.5%)	8 (7.0%)	0.47
Hispanic	71 (92.2%)	106 (93.0%)	
Non-Hispanic	1 (1.3%)	0 (0%)	
Unknown			
Mean tumor size, cm (SD)	5.5 (2.6)	4.8 (2.6)	0.09
Histology	70 (90.9%)	104 (91.2%)	0.51
Ductal	6 (7.8%)	8 (7.0%)	
Lobular/mixed	1 (1.3%)	2 (1.8%)	
Other			
Grade	20 (26.0%)	22 (19.3%)	0.30
2	57 (74.0%)	90 (79.0%)	
3	0 (0%)	2 (1.7%)	
Unknown			
Receptor status	5 (6.5%)	9 (7.9%)	0.90
HR+/HER2−	20 (26.0%)	30 (26.3%)	
HR+/HER2+	24 (31.2%)	39 (34.2%)	
HR-/HER2−	28 (36.3%)	36 (31.6%)	
HR-/HER2+			
Nodal presentation	54 (70.1%)	76 (66.6%)	0.61
Palpable	23 (29.9%)	38 (33.3%)	
Imaging-detected			

SLNB sentinel lymph node biopsy; *TAD* targeted axillary dissection; *IQR* interquartile range; *SD* standard deviation; *HR* hormone receptor; *HER2* human epidermal growth factor receptor 2

TABLE 2 Technical failures of SLNB versus TAD in cN1 ypN0 breast cancer patients at Dana-Farber Cancer Institute (2017–2022)

	Planned SLNB (n = 77)	Planned TAD(n = 114)	*p*
Failed mapping	5 (6.5%)	3 (2.6%)	0.19
<3 nodes retrieved	8 (10.4%)	4 (3.5%)	0.06
CN not retrieved	--	8 (7.1%)	--
Total rate of required ALND	13 (16.9%)	15 (13.2%)	0.48

SLNB sentinel lymph node biopsy; *TAD* targeted axillary dissection; *CN* clipped node; *ALND* axillary lymph node dissection

no difference in the overall rate of other technical failures between the SLNB and TAD groups (11.8% vs. 10.3%, $p = 0.64$) and rates of overtreatment with ALND among ypN0 patients on final pathology (14.0% vs. 12.3%, $p = 0.72$), consistent with the findings of the primary analysis.

Protocol compliance was high at 91.4%. Four patients received ALND despite technically satisfactory axillary staging surgery, and 12 patients did not receive ALND despite a technical limitation of SLNB/TAD. Median follow-up was 3.9 years (interquartile range [IQR] 2.6-4.7) for the SLNB group with two isolated in-breast local recurrences, one isolated axillary recurrence, and two distant recurrences. The axillary recurrence (1/77, 1.3%) occurred in a patient with cT4aN1 hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative disease with 6 negative SLN. Median follow-up was shorter for the TAD group at 1.7 years (IQR 1.0–2.7) with no breast cancer events but one nonbreast cancer death. Overall, the 3-year RFS for the cohort was 94.9% (95% CI 88.4–97.8%).

We identified a comparison cohort of 178 cN1 ypN0 patients treated with NAC and surgery from 2006 to 2015, predating our institution's protocolized use of SLNB/TAD in this population. Patients in the historical cohort were significantly older (median age 52 vs. 49, $p = 0.01$) and had smaller tumors (mean size 3.5 vs. 4.4 cm, $p < 0.001$). The historical cohort also had higher proportions of HR+/HER2− subtype (16.3% vs. 7.3%), although this did not reach statistical significance (p for overall subtype category = 0.06). There were no significant differences in distribution of grade and histology. In the historical cohort, ALND was performed in 77.5% (vs. 10.5% in modern cohort, $p < 0.001$). Median follow-up was 6.3 years (IQR 4.5–8.7 years), and there were 23 RFS events, none of which were isolated axillary recurrences; overall 3-year RFS was 90.6%. Treatment in the modern cohort when most patients received SLNB/TAD alone was not associated with worse RFS compared with the historical cohort when most patients received ALND (hazard ratio [HR] 0.42, $p = 0.07$). Results were unchanged when adjusting for age, tumor size, and subtype (adjusted HR 0.47, $p = 0.11$). Results were also unchanged when restricting only to 309 (83.7%) patients who were in the modern cohort and treated with SLNB/TAD alone or the historical cohort and treated with ALND (HR 0.51, $p = 0.17$; adjusted HR 0.55, $p = 0.24$).

DISCUSSION

This study demonstrates that applying strict technical criteria to minimize the FNR of axillary staging surgery in cN1 patients after NAC may result in overtreatment with ALND in up to 15% of patients. This likelihood was the same whether using SLNB or TAD, with differing limitations observed between the two techniques. With SLNB, the most common source of technical failure was not retrieving at least 3 nodes (10%), whereas with TAD, nonretrieval of the CN (7%) was most prevalent. Overall, our data do not support superiority of one technique over the other from the perspective of minimizing overtreatment.

Inability to identify ≥3 nodes with SLNB has been a longstanding concern. In the ACOSOG Z1071 trial, the rate of retrieving <3 SLN was 43%.[1] In the SN-FNAC and GANEA-2 trials, the mean/median number of nodes identified was 2.7 and 2, respectively.[2,4] However, dual tracer was not mandated in any of these studies, and surgeons were naïve to the importance of identifying ≥3 nodes in this population. In real-world series adopting SLNB in the cN1 post-NAC population after the publication of ACOSOG Z1071 trial, SLN yield has been consistently higher. Among 132 cN1 patients treated at Memorial Sloan Kettering Cancer Center (MSKCC), ≥3 SLN were identified in 86%.[13] In the international, multicenter OPBC-04/EUBREAST-06/OMA observational study, among 565 with SLNB performed, the median number of SLN was 4 (IQR 3–5).[11] Collectively, our study findings along with others support that with routine dual tracer use and meticulous attention to maximizing SLN yield, ≥3 nodes can be retrieved in the large majority of patients.

Performance metrics related to successfully localizing and retrieving biopsy-proven CNs have also been variable. Single-institution series have found success rates ranging from 71 to 100% (93% in this study).[5,14–17] In a meta-analysis of 17 studies, the success rate among 1,430 attempts was 90.0% (95% CI 85.2–95.1%).[18] In the OPBC-04/EUBREAST-06/OMA study, among 220 with attempted TAD, the CN was successfully retrieved in 94%.[11] Most had either radioactive seed (40%) or wire (46%) localization. In the German multicenter observational SenTa study in which only wire localization was used, the CN was successfully retrieved in 78%.[19] Similar to our findings, a notable challenge in the SenTa study was the inability to visualize the CN on preoperative ultrasound in 16% of patients. Overall, the ability to retrieve the CN with TAD appears variable across institutions, likely owing to varying expertise among radiologists and surgeons and perhaps based on available localization methods, with wire localization potentially associated with poorer feasibility. Individual institutions should evaluate their own technical outcomes, as based on the available literature, in some centers technical failures with TAD may surpass those of SLNB.

Beyond our technical outcome findings, our study further contributes to the mounting body of literature confirming the oncologic safety of omitting ALND in the setting of ypN0 status determined by either SLNB or TAD. We observed only a single axillary recurrence (0.5%) among patients with ALND omitted, and RFS was equivalent to a historical cohort during which time ALND was routine. Other studies

reporting oncologic outcomes in cN1 ypN0 breast cancer populations treated with NAC and omission of ALND have been consistently reassuring, regardless of the specific axillary staging surgery used. Barrio et al. at MSKCC evaluated 234 patients undergoing dual-tracer SLNB (with minimum 3 SLN).[8] At median follow-up of 40 months, there was 1 axillary node recurrence in a patient who did not receive nodal radiation, and 5-year overall survival was excellent at 94.2%. Kahler-Ribeiro-Fontana et al. at the European Institute of Oncology reported longer-term outcomes (median 9.2 years of follow-up)[9] where among 123 patients with cN1-2 ypN0 status treated with SLNB alone, there were only 2 axillary recurrences (1.6%). Notably, dual tracer was not utilized and 74% of patients had <3 SLN removed, and nodal radiation was uncommon. To our knowledge, beyond our study, the only other to have directly compared outcomes for patients treated with SLNB versus TAD is the OPBC-04/EUBREAST-06/OMA study.[11] The 2-year cumulative incidence of axillary recurrence was 0.9% for SLNB versus 0% for TAD ($p = 0.19$), and in the overall cohort, 90% were free of invasive recurrence at 5 years.

Our study has some limitations. Given the single-institution setting, technical outcomes may not be generalizable to all centers. Median follow-up was short with longer-term outcome monitoring needed, although most axillary recurrences occur early. Comparisons to the historical institutional cohort were limited by changes in systemic therapy over time. For example, the historical cohort predates the KATHERINE,[20] CREATE-X,[21] and KEYNOTE-522 trials,[22] among others, whose paradigms have improved breast cancer outcomes in the modern era.

CONCLUSIONS

Based on collective data from our study and the broader literature, we believe that either SLNB or TAD are acceptable axillary staging procedures after NAC for cN1 patients. The choice of technique should be based on local expertise, resources, and preferences of the treating multidisciplinary team. Given the additional logistical complexities of TAD related to biopsy clip and localizer placement, and in the absence of superior oncologic outcomes or lesser risk of overtreatment, we have returned to the use of dual-tracer SLNB alone at our institution. Furthermore, our data highlight that strict criteria to minimize the FNR of axillary staging surgery after NAC, as currently recommended by National Comprehensive Cancer Network® (NCCN®) guidelines, may lead to overtreatment of the axilla in a substantial minority of patients. With emerging data suggesting that small differences in FNR do not translate to differences in oncologic outcomes, we advocate that NCCN guidelines should be revised to support a more flexible approach to axillary staging surgery in this population.

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DATA AVAILABILITY The data that support the findings of this study are from an institutional database and thus are not openly available. Deidentified data may be made available from the corresponding author upon reasonable request and with permission from the Dana-Farber Cancer Institute research ethics board.

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