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From cN+ to ycN0: Sentinel Node Biopsy as a Safe Alternative to ALND Post-Neo-Adjuvant Chemotherapy

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ABSTRACT

Sentinel lymph node biopsy (SLNB) has largely replaced axillary lymph node dissection (ALND) for breast cancer (BC) patients receiving neo-adjuvant chemotherapy (NAC). It is routinely used in individuals who present with clinically node-negative (cN0) disease, but its value in those who begin as clinically node-positive (cN+) remains unsettled. We retrospectively reviewed BC cases treated with NAC followed by SLNB to determine the relevance of this approach. Clinical features and oncologic outcomes were contrasted between patients who were cN0 or cN+ before NAC, as well as according to the type of axillary surgery performed. The study involved 291 patients: 131 were cN0 and 160 were cN+ converting to ycN0 after NAC. After a median monitor period of 43 months, axillary relapse was identified in three cN0 (2.3%) and two cN+ (1.3%) patients. No significant discrepancies were found in disease-free survival, distant disease-free survival, overall survival, or breast-cancer-specific survival between the groups or between SLNB-only and ALND procedures. When performed after NAC, SLNB appears to be a reliable option with favorable prognostic patterns and low axillary recurrence rates for both cN0 and cN+ patients.

Keyword: Sentinel lymph node biopsy, Breast cancer, Neo-adjuvant chemotherapy, Surgery

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Introduction

SLNB has become the preferred technique for axillary staging in early breast cancer (BC), replacing routine ALND in those presenting with a clinically negative axilla (cN0) [1–3]. For patients with T1–2, cN0 tumors undergoing breast-conserving surgery, ALND is often omitted even when one or two sentinel lymph nodes (SLNs) contain metastases [4, 5]. Compared with ALND, SLNB offers equivalent staging capability with minimal impact on arm function [1].

As part of treatment for more advanced local–regional BC, neo-adjuvant chemotherapy (NAC) has been explored as a strategy to reduce nodal disease and limit the need for extensive axillary surgery [6–10]. Nonetheless, the actual oncologic implications of carrying out SLNB in individuals who are either cN0 or clinically node-positive (cN+) before NAC are still debated. Pre-operative systemic treatment might modify lymphatic flow, potentially affecting SLNB accuracy [9, 11].

For patients who are cN0 at the outset, SLNB after NAC is widely used, with false-negative rates (FNRs) near 10% and generally good identification rates reported [12–16]. Modern chemotherapy regimens—anthracyclines, taxanes, and HER2-directed agents such as Trastuzumab and Pertuzumab—can clear nodal disease in roughly 50–75% of selected tumor subtypes [7, 13, 17–19].

The role of SLNB in patients initially presenting as cN+ who convert to cN0 after NAC remains uncertain. Prior studies have documented FNRs between 8.4% and 23.9% [8–10, 20–22]. To counteract this, targeted axillary dissection (TAD)—which relies on marking metastatic nodes before NAC, using dual tracers, or excising at least three SLNs—has been proposed [23–25]. However, these strategies have not been evaluated for their long-term

prognostic impact. In contrast, several investigations indicate that using SLNB alone does not appear to increase axillary recurrence or compromise oncologic results [3, 26–29].

Given these uncertainties, the purpose of this retrospective analysis was to determine how dependable and clinically meaningful SLNB is when performed after NAC by comparing patient characteristics and outcomes between those who began as cN0 or cN+ and by examining differences based on axillary surgical approach.

Materials and Methods

Study design and patient management

This retrospective study included consecutive BC patients planned for NAC and SLNB at the Breast Unit of the IRCCS Humanitas Research Hospital (Milan, Italy) from November 2008 to December 2021. All participants provided consent for both surgery and data usage. Initial assessment consisted of clinical examination and bilateral breast and axillary ultrasound (US). Although optional, most patients also underwent mammography and magnetic resonance imaging (MRI). Suspicious axillary nodes prompted fine-needle aspiration, core biopsy, and/or PET scanning.

A multidisciplinary panel—breast surgeons, oncologists, radiologists, radiotherapists, pathologists, and plastic surgeons—reviewed each case. NAC regimens were selected according to tumor biology and institutional protocols aligned with international recommendations. Every patient underwent mandatory clinical and imaging reassessment after NAC. Physical evaluation followed each chemotherapy cycle, and after three months, a repeat bilateral breast and axillary US was performed. Patients initially staged with PET underwent a follow-up scan using the same modality.

Only those who remained or became ycN0 at the completion of NAC proceeded to surgery, which was scheduled within 30 days after the final treatment cycle. Exclusion criteria included: patients directed to NAC followed by immediate ALND, progression during NAC according to RECIST criteria [30], any history of previous cancers, follow-up less than 12 months, or loss to follow-up.

Lymphatic mapping, sentinel lymph node biopsy, and axillary treatment

In this study, lymphatic mapping relied solely on a radioisotope-based method, and no targeted axillary dissection (TAD) techniques were incorporated. For tumors that could be palpated, 99Technetium-labeled radiocolloid was deposited around the lesion to simulate the natural intramammary drainage pattern. For lesions that were non-palpable or consisted of multiple foci, the tracer was instead injected into the sub-areolar dermal plexus. Lymphoscintigraphy was performed either the day before surgery or on the day of operation. To limit both incision length and dissection area, the approximate site of the sentinel lymph node (SLN) was marked on the skin using permanent ink. Before making the incision, the radioactive hotspot was once again localized through the skin with a gamma probe, which helped determine the most appropriate incision path. Typically, only a small cut was needed to expose the SLN.

During the operation, the gamma probe was advanced into the axillary wound to direct the surgeon toward the node until it was identified. Every patient who was ycN0 after NAC underwent SLNB, and at least one SLN was successfully located for all individuals. Once identified, the node was removed and immediately examined through intra-operative frozen section analysis. If the SLN was confirmed to be free of metastasis (ypN0), ALND was not carried out. A full ALND was reserved for cases in which the frozen section showed nodal involvement. Starting in December 2018, patients who met the eligibility criteria for the NEONOD2 study were enrolled, allowing omission of ALND in situations where only micrometastatic disease was present [31].

Statistical analysis

Patients were identified through the institutional dataset, with follow-up updated through 9 December 2022. Baseline characteristics are presented according to initial clinical nodal status (cN0 versus cN+) and summarized using medians with ranges for continuous variables and absolute numbers with percentages for categorical variables. Comparisons between cN0 and cN+ groups—including demographic details, tumor biology, and treatment features—were performed using the chi-square or Fisher's exact tests.

For recurrence and survival analyses, patients were evaluated according to both pre-NAC nodal classification (cN0 versus cN+) and the axillary surgical method used (SLNB alone versus ALND). Disease-free survival (DFS) was measured from surgery until any form of disease progression, whether loco-regional or distant. Distant disease-free survival (DDFS) was defined as the period between surgery and the detection of metastatic disease

at distant sites. Overall survival (OS) referred to the time from surgical treatment until death from any cause or most recent contact. Breast-cancer-specific survival (BCSS) was calculated by counting only deaths attributed to BC, censoring all unrelated deaths. Survival outcomes and recurrence curves were generated using the Kaplan–Meier method. All tests were two-sided, and statistical significance was defined as $p < 0.05$.

Results and Discussion

Characteristics of patients and axillary surgery

The study included 291 individuals with cT1–4 and cN0–cN+ BC who were treated with NAC followed by SLNB: 131 were initially cN0 and remained ycN0, while 160 entered treatment as cN+ and converted to ycN0. Median age was 48 years (range 28–79) in the cN0 population and 50 years (range 29–87) in the cN+ group. Among these patients, 63 cN0 (48.1%) and 81 cN+ (50.6%) were post-menopausal at the time of surgery. Tumor size before NAC had a median of 30 mm in both cohorts ($p = 0.288$). Most cases involved cT2 disease (cN0 67.9% vs. cN+ 68.8%, $p = 0.627$). There were no notable differences between the two groups in clinical variables, pathology, NAC protocol, or adjuvant treatments. However, ALND was performed more frequently among cN+ patients ($p = 0.001$).

Table 1. Demographic information, clinicopathologic features, and treatment characteristics of breast cancer patients stratified by cN status before neoadjuvant chemotherapy.

Characteristic	cN0 (n = 131) Tot. (%)/Median (Range)	cN+ (n = 160) Tot. (%)/Median (Range)	Univariate p-Value
Patient			
Age (years)	48 (28–79)	50 (29–87)	0.144
Post-menopausal	63 (48.1%)	81 (50.6%)	0.668
Tumor			
Dimension pre-NAC (mm)	30 (12–90)	30 (7–100)	0.288
Clinical T pre-NAC			0.627
cT1b	0 (0%)	1 (0.6%)	
cT1c	23 (17.6%)	24 (15.0%)	
cT2	89 (67.9%)	110 (68.8%)	
cT3	15 (11.5%)	19 (11.9%)	
cT4	4 (3.0%)	6 (3.7%)	
cM1	0 (0%)	2 (1.3%)	0.200
Multifocality/multicentricity	30 (22.9%)	55 (34.4%)	0.469
Chemotherapy Regimen			0.094
Anthracycline only	10 (7.6%)	7 (4.4%)	
Anthracycline and taxanes	67 (51.2%)	75 (46.9%)	
Anthracycline, taxanes, and Trastuzumab	53 (40.5%)	75 (46.9%)	
Anthracycline, taxanes, and Pertuzumab	1 (0.7%)	2 (1.3%)	
CDK inhibitor	0 (0%)	1 (0.6%)	
Subtype			0.715
Luminal-like	32 (24.4%)	43 (26.9%)	
HER2+	56 (42.8%)	78 (48.8%)	
Triple negative	43 (32.8%)	39 (24.3%)	
Histotype			0.366
Ductal	127 (97.0%)	151 (94.4%)	
Lobular	2 (1.5%)	7 (4.4%)	
Mucinous	2 (1.5%)	1 (0.6%)	
Papillary	0 (0%)	1 (0.6%)	
Vascular invasion	22 (16.8%)	25 (15.6%)	0.788
Ki67	15 (2–90)	10 (1–85)	0.091
Dimension post-NAC (mm)	8 (0–70)	7 (0–60)	0.086
Pathological T post-NAC			0.051

ypT0	22 (16.8%)	38 (23.8%)	
ypTis	19 (14.5%)	20 (12.5%)	
ypTmi	2 (1.5%)	8 (5.0%)	
ypT1a	8 (6.1%)	8 (5.0%)	
ypT1b	22 (16.8%)	26 (16.3%)	
ypT1c	27 (20.6%)	39 (24.3%)	
ypT2	28 (21.5%)	20 (12.5%)	
ypT3	2 (1.5%)	1 (0.6%)	
ypT4	1 (0.7%)	0 (0%)	
Surgery			
BCS	81 (61.8%)	100 (62.5%)	0.907
Mastectomy	50 (38.2%)	60 (37.5%)	
ALND	18 (13.7%)	47 (29.4%)	0.001[a]
Post-operative treatment			
Chemotherapy	20 (15.3%)	18 (11.3%)	0.313
Radiotherapy	97 (74.1%)	133 (83.1%)	0.059
Endocrine	66 (50.4%)	86 (53.8%)	0.569
T-DM1	34 (26.0%)	42 (26.3%)	0.434

A detailed summary of demographics, tumor features, and treatments by pre-NAC nodal status appears in **Table 1**. Footnotes: cN0 = clinically node-negative; cN+ = clinically node-positive; NAC = neo-adjuvant chemotherapy; CDK = cyclin-dependent kinase; HER2 determined by immunohistochemistry or in situ hybridization under ASCO CAP guidelines; BCS = breast-conserving surgery; ALND = axillary lymph node dissection; T-DM1 = Trastuzumab emtansine; a = statistically significant.

Across both nodal groups, the median SLN count removed per patient was 1. No patient with a negative frozen-section SLN result was later found positive on permanent pathology. Post-NAC SLN positivity was more frequent in the cN+ cohort (14.5% in cN0 vs. 36.3% in cN+, $p < 0.001$). NAC allowed avoidance of ALND in 113 cN+ individuals (70.6%). A nodal pathologic complete response (ypN0) was achieved in 102 cN+ patients (63.8%). Of the 13 cN+ patients who were classified as ypNi+/mi following NAC, 9 were included in the NEONOD2 study [31] and were treated with SLNB alone.

Among patients who required ALND, the median number of axillary nodes removed was 12 (range 3–28) for cN0 and 13 (range 5–27) for cN+. Importantly, 12 cN+ patients (7.5%) had more than three additional metastatic nodes on final histological review.

Table 2. Axillary nodal data according to initial nodal status are summarized

Characteristic	cN0 (n = 131) Tot. (%)/Median (Range)	cN+ (n = 160) Tot. (%)/Median (Range)	Univariate p-Value
Intra-operative SLN status			
Number of SLNs	1 (1–5)	1 (1–6)	0.004[a]
Number of patients with positive SLNs	19 (14.5%)	58 (36.3%)	<0.001[a]
Pathological N post-NAC			<0.001[a]
ypN0	112 (85.5%)	102 (63.8%)	
ypNi+	0 (0%)	1 (0.6%)	
ypNmi	5 (3.8%)	12 (7.5%)	
ypN1a	11 (8.4%)	29 (18.1%)	
ypN2a	1 (0.8%)	13 (8.1%)	
ypN3a	2 (1.5%)	3 (1.9%)	
Non-SLN status at pathological evaluation			
Number of evaluated non-SLNs	12 (3–28)	13 (5–27)	0.903
Number of positive non-SLNs	0 (0–13)	1 (0–26)	0.516
Number of patients with 1 positive non-SLN	3 (2.3%)	7 (4.4%)	0.140
Number of patients with 2 positive non-SLNs	1 (0.8%)	6 (3.7%)	-

Number of patients with 3 positive non-SLNs	0 (0%)	3 (1.9%)	-
Number of patients with >3 positive non-SLNs	3 (2.3%)	12 (7.5%)	-

Footnotes: cN0 = clinically node-negative; cN+ = clinically node-positive; SLN = sentinel lymph node; NAC = neo-adjuvant chemotherapy; a = statistically significant.

Oncological outcomes

Across a median follow-up of 43 months (range 12–169), five axillary events were documented: three in the cN0 group (2.3%) and two among cN+ patients (1.3%).

Within the cN0 subgroup, one individual developed an axillary failure that coincided with a same-side breast recurrence 10 months after the initial operation; management consisted of mastectomy combined with ALND. The remaining two cN0 patients experienced axillary relapse without disease elsewhere and were both treated with ALND.

Among the cN+ patients, one recurrence appeared at the surgical scar after mastectomy together with nodal disease and required ALND plus removal of the involved skin 15 months post-operatively. The other cN+ patient presented with a solitary axillary recurrence 58 months after surgery and underwent ALND. All five individuals who relapsed were alive with no detectable cancer at their latest clinical assessment.

Across the entire cohort, 22 of 291 patients (7.6%) had died by the last follow-up: 14 of 131 cN0 patients (10.7%) and 8 of 160 cN+ patients (5.0%). Outcomes were examined by pretreatment nodal category (cN0 vs. cN+) and by surgical strategy (SLNB alone vs. ALND).

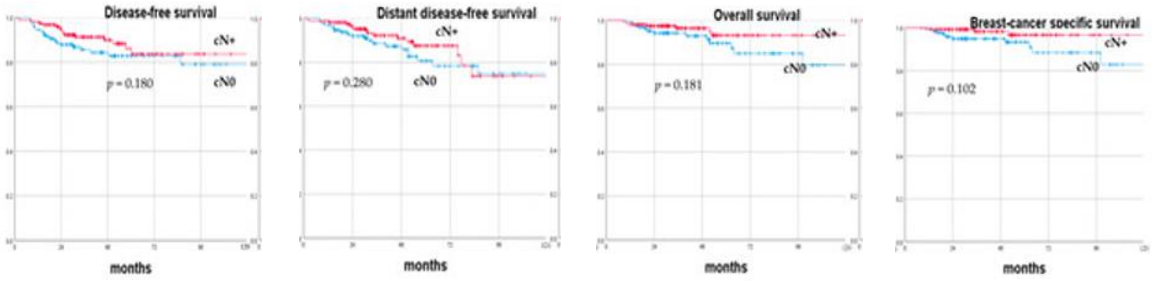
Survival according to baseline nodal status

- DFS: cN0 = 94.6%, 85.6%, 82.8% at 1, 3, 5 years;
  cN+ = 97.5%, 91.3%, 83.6%.
- DDFS: cN0 = 96.9%, 88.5%, 80.6%;
  cN+ = 98.8%, 92.2%, 87.5%.
- OS: cN0 = 99.2%, 94.2%, 89.6%;
  cN+ = 98.1%, 96.4%, 93.2%.
- BCSS: cN0 = 100%, 94.9%, 93.3%;
  cN+ = 99.4%, 98.3%, 96.7%.

Survival according to axillary procedure

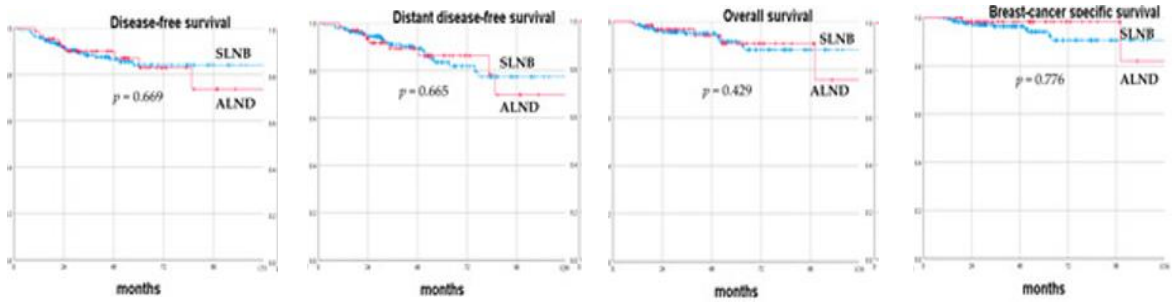
- DFS: SLNB-only = 96.0%, 88.4%, 84.0%;
  ALND = 96.9%, 90.0%, 82.8%.
- DDFS: SLNB-only = 97.8%, 90.9%, 83.5%;
  ALND = 96.9%, 89.3%, 86.3%.
- OS: SLNB-only = 98.7%, 95.0%, 91.7%;
  ALND = 98.5%, 96.8%, 90.9%.
- BCSS: SLNB-only = 99.6%, 96.4%, 94.1%;
  ALND = 100%, 98.3%, 98.3%.

There were no statistically meaningful differences between pretreatment cN0 and cN+ groups ($p = 0.180, 0.280, 0.181, 0.102$) nor between SLNB-only and ALND ($p = 0.669, 0.665, 0.429, 0.776$). Kaplan–Meier depictions of recurrence and survival are shown in **Figures 1 and 2**.



a) b) c) d)

Figure 1. DFS, DDFS, OS, and BCSS curves by initial nodal status (cN0 vs. cN+).



a) b) c) d)

Figure 2. DFS, DDFS, OS, and BCSS curves by axillary procedure (SLNB-only vs. ALND).

Discussion

The present analysis adds further support to findings from other investigations indicating that, when used in the context of NAC, SLNB is associated with low axillary relapse rates in both cN0 and cN+ breast cancer patients. The recurrence frequencies observed here fall within previously published retrospective estimates (0% to 2.3%) [26–29].

SLNB after NAC is widely accepted for individuals who initially show no clinical nodal involvement, as reported false-negative rates are comparable to those seen in patients undergoing surgery without prior systemic treatment [12–16]. In contrast, multiple studies have shown that patients who start as cN+ but convert to cN0 can experience false-negative rates above 10% [8, 9, 21, 22].

The ACOSOG Z1071 trial [8] involved 756 patients across 136 centers, of whom 649 underwent both SLNB and ALND following NAC; the reported FNR was 12.6%. The multicenter SENTINA study [9], enrolling 1737 patients from 103 institutions, reported even higher inaccuracy in those who became ycN0 (arm C): 24.3% when only one sentinel node was removed and 18.5% when two were retrieved.

A meta-analysis by van Nijnatten *et al*. [21] (eight studies) calculated a pooled FNR of 15.1%, with markedly poorer accuracy when only one SLN was taken (23.9%) compared to removal of two or more (10.4%; p = 0.026). Another synthesis by Simons *et al*. [22], covering 20 studies and 2217 patients, reported an overall FNR of 17%. These consistently elevated FNRs explain why SLNB alone has traditionally not been advised as a replacement for ALND in formerly cN+ patients.

One approach highlighted in the St. Gallen 2021 Consensus [32] to address the elevated FNR in cN+ patients who become cN0 after NAC involves retrieving more than three SLNs. Likewise, the 2022 NCCN guidelines [33] recommend TAD as another means of lowering the FNR, typically by placing a clip in the initially involved node or by employing a dual-tracer technique. The scientific basis for insisting on the localization and removal of the clipped node, however, remains relatively weak, relying mainly on retrospective datasets, particularly in situations where lymphatic mapping was suboptimal [23, 34]. Furthermore, the clipped node is not retrieved in up to 30% of procedures [35, 36], prompting reconsideration of whether a full ALND is justified in such circumstances.

From our perspective, attempts to decrease the FNR have not been shown to influence prognosis, since none of the cited investigations evaluated long-term oncological endpoints. In contrast, the present study specifically examined these outcomes and supports the conclusion that SLNB-based lymphatic mapping is suitable for both cN0 and cN+ patients who proceed to NAC. A similar position was previously demonstrated by Kahler-Ribeiro-

Fontana *et al*. [26], who evaluated consecutive cT1–3, cN0 or cN+ cases treated at the European Institute of Oncology and rendered cN0 following NAC before undergoing SLNB. With a median follow-up of 9.2 years, the rates of axillary relapse were 1.8% among those initially cN+ and 1.5% among those initially cN0, while 5- and 10-year OS for the entire cohort reached 91.3% and 81.0%, respectively.

In another retrospective series, Barrio *et al*. [27] assessed 610 consecutively treated cT1–3, cN+ patients who achieved cN0 after NAC and underwent SLNB with dual-tracer mapping. At a median follow-up of 40 months, only a single nodal recurrence was observed, occurring simultaneously with a local recurrence in a patient who declined radiotherapy. Reported 5-year DDFS and OS were 92.7% and 94.2%, respectively.

This study has several constraints. It reflects the experience of a single institution, is retrospective, and represents data captured at a specific time frame. The median follow-up was relatively short, and no power calculation was carried out to determine whether the sample size was sufficient for detecting meaningful differences.

Conclusion

Overall, the clinical practice within our unit is shifting toward less extensive axillary surgery even when NAC is part of treatment. The current findings confirm that SLNB combined with lymphatic mapping continues to offer reliable staging and useful prognostic information. In patients presenting as cN0 or cN+ who become or remain ycN0 after NAC, SLNB alone produced favorable prognostic outcomes and low rates of axillary recurrence. Although oncological results were not compromised by omitting ALND, additional research is warranted to determine how further reductions of FNR might influence long-term prognosis.

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Ethics Statement: None

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