

The use of blue dye alone for sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initially node-positive breast cancer

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ABSTRACT

Introduction: False-negative sentinel lymph node biopsy (SLNB) rates following neoadjuvant chemotherapy (NACT) in initially node-positive (cN1/2) breast cancer patients are high, but decrease when lymph nodes are clipped, ≥ 3 sentinel lymph nodes (SLN) are removed or dual-tracer localization (radioisotope and blue dye) is used. Radiotracer, however, is often unavailable and outcomes with blue dye alone are unknown.

Materials and methods: Initially cT1-4, cN1/2 patients treated with NACT in 2013–2023 who underwent SLNB using blue dye alone were evaluated regarding SLN identification, axillary recurrence, disease-free and overall survival rates.

Results: Of 119 patients included, 19 remained cN1/2 after NACT. SLNB was performed using blue dye alone in 100 ycN0 cases (84%), with an identification rate of 96%. The SLN was negative in 70/119 cases (i.e. 59% avoided axillary dissection). The number of SLN detected was ≥ 3 in 55/70 cases (78%) (median 3.1; 1–6). Median age was 49 years (25–84). Most were T2 (n = 40, 57.1%), N1 (n = 64, 91.4%). Predominant subtypes were ERBB2 (52.9%) and triple-negative (20%). No axillary recurrence occurred over a median 36-month period. Five-year disease-free and overall survival were, respectively, 85.9% (95%CI: 74–99.8) and 96.3% (95%CI: 89.4–100). The ERBB2 subtype (1.99, 95%CI: 1.02–3.85, p = 0.04) and N1 lymph node status (2.58, 95%CI: 1.54–9.10, p = 0.03) were associated with a greater likelihood of undergoing SLNB alone without axillary dissection.

Conclusions: SLNB with blue dye alone following NACT in initially cN1/2 patients avoided axillary dissection in almost 60% of cases, with no recurrences during the period evaluated. Longer follow-up studies are necessary.

1. Introduction

Sentinel lymph node biopsy (SLNB) is the gold standard for the evaluation of the axilla in upfront surgery for non-metastatic breast cancer, with a similar recurrence rate and lower morbidity compared to axillary dissection despite a false-negative rate of around 10% [1–3]. In patients who underwent neoadjuvant chemotherapy (NACT) and who

had initially negative axilla (cN0), the false-negative rate is similar to that found with upfront surgery [4–6]. Conversely, in patients with non-metastatic breast cancer and initially positive axilla at first presentation (cN1/2) and who achieved complete clinical and imaging response, false-negative rates have traditionally tended to be higher [5].

Recently, studies have indeed shown that the false-negative rate of SLNB following NACT is high (>10%) in cases of cN1/2 at first

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presentation. However, rates would decrease when certain strategies were used such as clipping the lymph node prior to NACT and then resecting the clipped node; identifying and removing three or more sentinel lymph nodes (SLN); and using a dual tracer of technetium-99 and blue dye to facilitate identification of the lymph nodes [7–10]. Those studies changed clinical practice, with international guidelines now recommending the use of these strategies to minimize false-negative rates. The oncological safety of these techniques has yet to be validated in randomized clinical trials, although retrospective analyses have shown a low rate of axillary recurrence [11–13]. Nevertheless, the use of clips to mark lymph nodes and indeed the availability of nuclear medicine services are limited in many countries including Brazil, with blue dye often being the only tracer available for SLNB in many centres [14]. Moreover, since data on the use of blue dye alone in SLNB following NACT in initially cN1/2 patients are sparse, and experience with a single agent for this purpose is restricted to the use of a radioactive tracer, the effectiveness and the oncological safety of performing SLNB using this method could be questioned [7,8].

The primary objective of this study was to calculate the rate of SLN identification and axillary recurrence, as well as disease-free and overall survival rates when SLNB is performed using blue dye alone in patients with non-metastatic breast cancer who were cN1/2 at first presentation and who achieved complete clinical and imaging response in the axilla following NACT. The secondary objective was to assess whether the initial clinical stage of the tumour, the initial clinical nodal stage and the subtypes as defined by immunohistochemistry are factors that influence SLNB in this scenario.

2. Materials and Methods

This retrospective, observational cohort study was conducted with cT1-4 cN1/2 patients with non-metastatic breast cancer. All patients underwent NACT at a public healthcare facility in Brazil between 2013 and 2023. Patients with inflammatory breast cancer, those with cN0 or cN3 at first presentation, and cases for which data in the hospital records were incomplete were excluded from the study. All the patients who achieved complete clinical response following NACT (ycN0) underwent SLNB using a single tracer (blue dye) without axillary dissection if the SLN was negative (ypN0) at frozen section and confirmed at final pathology. For evaluation of the principal objective, patients who remained cN1/2 following NACT were also excluded from the analysis, as were those who underwent SLNB and in whom the SLN remained positive (ypN+) at final histopathology.

The internal review board of the Fortaleza General Hospital, an institute that provides healthcare within the public healthcare network, approved the study protocol prior to its initiation under reference CAAE 42697221.8.0000.5040.

2.1. Clinical evaluation and treatment

The patients with clinically positive axilla were diagnosed through ultrasound-guided percutaneous axillary lymph node biopsy. In cases in which there was a strong clinical suspicion in addition to abnormal axillary findings at ultrasound, diagnosis was made without biopsy. Mammography and ultrasound of the axilla were performed prior to and following NACT in all cases, while magnetic resonance imaging of the breasts could be performed or not. Neoadjuvant and adjuvant treatment of non-metastatic breast cancer (either systemic treatment or radiotherapy) was conducted according to international guidelines. None of the patients in the study used trastuzumab emtansine as adjuvant treatment, since this was not available within Brazil's public healthcare system up to the cut-off date for this study. The use of dual anti-ERBB2 therapy (receptor Erb-B2, tyrosine kinase 2 [formerly HER-2], human epidermal growth factor receptor 2) as neoadjuvant therapy is also not universally available within the public sector; however, trastuzumab can be recommended as routine. The decision regarding whether to

perform breast-conserving surgery or mastectomy was made at the discretion of the surgical team. The histological subtypes of non-metastatic breast cancer were also recorded, together with the patient's age, initial tumour stage (T1, T2, T3 or T4), initial clinical lymph node status (N1 or N2) and immunohistochemical subtypes: hormone receptor-positive/ERBB2-negative, hormone receptor positive/ERBB2-positive, hormone receptor-negative/ERBB2-positive and triple-negative (absence of hormone receptors and ERBB2).

2.2. Description of the SLNB technique

The tracer, blue dye alone (Patent Blue V sodium 2.5%), was applied by intradermal injection (1–4 points) into the breast (1–2 ml), in the periareolar region or in the upper lateral quadrant, following general anaesthesia. Massage was performed at the site of the injection for at least 1–2 min. The occurrence of side effects associated with blue dye, particularly severe allergic reactions (grade III and IV), was evaluated. A separate incision was made into the axilla to identify the SLN except in cases of simple mastectomy without reconstruction. No minimum number of SLN to be identified and resected was pre-established.

Briefly, a negative SLN at frozen section analysis, confirmed at final histopathology, was sufficient to avoid axillary dissection. The median number of SLN resected was analysed. Palpable lymph nodes other than the SLN were only resected if metastasis was suspected. Immunohistochemistry of the SLN was not routinely performed except when required to confirm indeterminate results. All patients with residual disease in the SLN underwent axillary dissection, including those whose diagnosis was made at final histopathology, irrespective of the extent of the metastasis (isolated tumour cells, micro- and macro-metastases).

2.3. Outcome evaluation

The principal oncologic outcomes evaluated were: *axillary recurrence*, defined as any recurrence in the ipsilateral axilla; *lymph node recurrence*, which includes recurrence in the axilla and supraclavicular fossa or internal breast; *ipsilateral breast recurrence*; *new primary contralateral*; *distant recurrence*; and *death*. Follow-up was measured from the time of SLNB surgery. The likelihood of undergoing SLNB alone or axillary dissection was evaluated according to *immunohistochemical subtype*, *initial tumour stage* (cT3/T4 versus cT1/2) and *axillary lymph node status* (cN2 versus cN1).

2.4. Statistical analysis

Categorical data were described as absolute and relative frequencies, while medians and interquartiles range were used to describe patients' age and the number of SLN removed. Disease-free and overall survival rates were calculated using the Kaplan-Meier method. To evaluate factors associated with undergoing SLNB alone, Poisson models with robust estimation of variance were used to calculate relative risk. Factors with p-values <0.20 in the univariate analysis were included in the multivariate analysis. Only factors with p-values <0.05 remained in the final model. Analysis was performed using the R software, version 4.2.2 [15].

3. Results

Of a total of 209 patients with non-metastatic breast cancer who underwent NACT between 2013 and 2023, 119 initially cT1-4, cN1/2 patients were included in the analysis. Of these, 19 (15.9%) remained cN1/N2 after NACT and underwent axillary dissection without SLNB.

3.1. Analysis of the patients who underwent SLNB

The 100 patients who obtained clinical and imaging complete response following NACT underwent SLNB using blue dye alone. The identification rate was 96%. No case of severe allergic reaction (grade III

or IV) was recorded; however, one patient had a mild skin allergy. Thirty of these patients (30%) had a positive lymph node at final histopathology, including the four patients in whom the SLN was not identified, all of whom underwent axillary dissection. Five patients with a negative frozen section (5/26; 19%) had residual SLN disease identified in the final pathology and returned to the operating room for axillary dissection: 1 with isolated tumour cells diagnosed by immunohistochemistry, 2 with micro-metastases and 2 with macro-metastases. Regarding residual disease identified at axillary dissection after positive SLN, 14 patients (53.8%) presented with additional residual disease: 11/17 cases (64.7%) with macro-metastasis and 3/7 cases (42.8%) with micro-

metastasis. In 70 cases, the SLN was successfully identified and found to be negative at final histopathology (no axillary dissection). The rate of cT1-4, cN1/2 patients with non-metastatic breast cancer who did not require axillary dissection was estimated at 58.8% (95%CI: 49.4–67.8) (Fig. 1).

3.2. Analysis of cases of SLNB alone

The mean age of patients undergoing only SLNB, performed using blue dye alone, was 49 years (interquartiles range [IQR] 25–84). The median number of SLN identified was 3.1 (1–6), with ≥ 3 SLN being

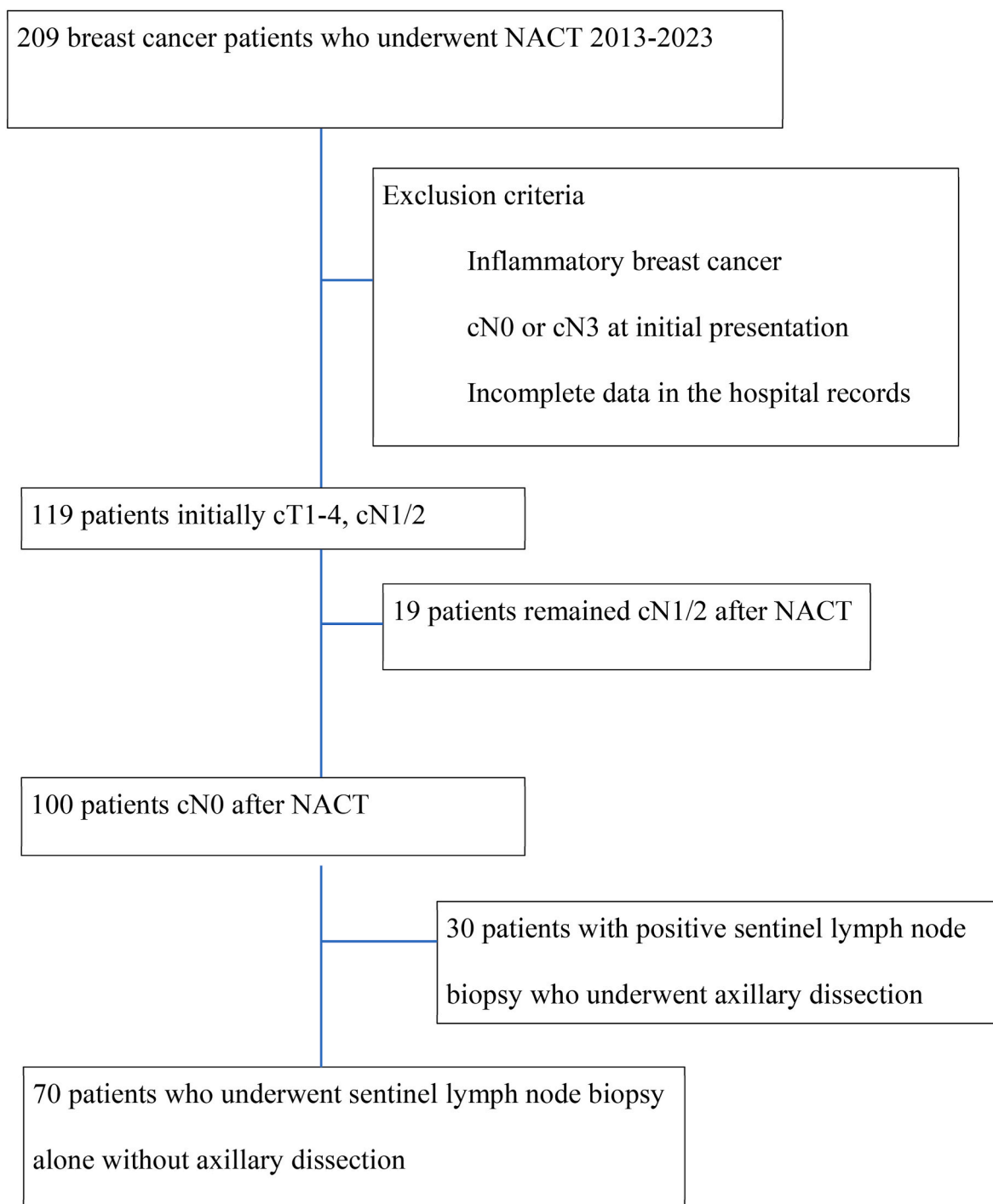


Fig. 1. Flowchart of the patients retrospectively included in the study.
cN: nodal stage; NACT: neoadjuvant chemotherapy.

identified and resected in 55 cases (78%) (Table 1). Clinical staging was T2 in most cases (n = 40, 57.1%) followed by T3 (n = 18, 25.7%), T4 (n = 6, 8.6%) and T1 (n = 6, 8.6%). The most common initial axillary lymph node status was cN1 (n = 64, 91.4%), with only 6 patients (8.6%) being cN2. Regarding immunohistochemical subtypes, 19 (27.1%) were hormone receptor-positive/ERBB2-negative, 16 (22.9%) were hormone receptor-negative/ERBB2-positive, 21 (30%) were hormone receptor-positive/ERBB2-positive and 14 (20%) were triple-negative. Breast-conserving surgery was performed in 40 cases (57%) and total mastectomy in 30 (43%) (Table 1). Fifty-five patients (79%) received regimens containing adriamycin, cyclophosphamide and paclitaxel (AC-T), while docetaxel and cyclophosphamide (TC) were used in 15 patients (21%). Anti-ERBB2 therapy was used in all cases; however, pertuzumab associated with trastuzumab was only used in 8 patients (8/37, 21.6%). Patients with hormone-positive non-metastatic breast cancer received adjuvant endocrine therapy (n = 40, 100%). Adjuvant radiotherapy was given in all cases except for one patient who underwent mastectomy (n = 69, 99%) (Table 2).

3.3. Analysis of the outcomes with SLNB alone

After a median of 36 months of follow-up, no axillary recurrence was recorded. One patient developed a new primary breast cancer in the contralateral breast. Three patients had distant disease and two died. The 5-year disease-free and overall survival rates with SLNB alone were, respectively, 85.9% (95%CI: 74–99.8) and 96.3% (95%CI: 89.4–100) (Fig. 2). In the univariate analysis, the only factors associated with undergoing SLNB alone were N1 lymph node status (RR = 2.56; 95%CI: 1.11–5.90; p < 0.001) and immunohistochemical subtype hormone receptor-negative/ERBB2-positive (76.19%; 16/21) compared to hormone receptor-positive/ERBB2-negative (Table 3).

4. Discussion

In this final cohort of 70 initially cN1/2 patients who received NACT

Table 1
Characteristics of 70 patients who underwent sentinel lymph node biopsy (SLNB) alone following SLN identification using blue dye alone.

Characteristics	Median (IQR)
Age, years	49 (25–84)
Number of sentinel nodes	3.1 (1–6)
Identification/Resection of ≥3 sentinel nodes	55 (78)
Clinical tumour stage	
T1	6 (8.6)
T2	40 (57.1)
T3	18 (25.7)
T4	6 (8.6)
Clinical node stage	
N1	64 (91.4)
N2	6 (8.6)
Histological type	
Ductal	68 (97)
Lobular	2 (3)
Immunohistochemical subtype	
Hormone receptor-positive/ERBB2-negative	19 (27.1)
Hormone receptor-positive/ERBB2-positive	21 (30)
Hormone receptor-negative/ERBB2-positive	16 (22.9)
Triple-negative	14 (20)
Type of breast surgery	
Breast-conserving surgery	40 (57)
Mastectomy	30 (43)

IQR: Interquartiles range; ERBB2: Erb-B2 receptor tyrosine kinase 2 (formerly HER2, human epidermal growth factor 2).

Table 2
Treatment characteristics of 70 patients who underwent sentinel lymph node biopsy (SLNB) alone following SLN identification using blue dye alone.

Treatment Characteristics	N (%)
Anti-ERBB2 therapy (n = 37)	
Trastuzumab	37 (100)
Trastuzumab + Pertuzumab	8 (22)
Neoadjuvant chemotherapy (n = 70)	
Adriamycin, cyclophosphamide and paclitaxel (AC-T)	55 (79)
Docetaxel and cyclophosphamide (TC)	15 (21)
Adjuvant endocrine therapy (n = 40)	40 (100)
Radiotherapy (n = 70)	69 (99)

ERBB2 - Erb-B2 receptor tyrosine kinase 2 (formerly HER2, human epidermal growth factor 2).

and were surgically treated with SLNB using blue dye alone without the use of lymph node markers such as clips or activated charcoal, no axillary recurrence was recorded after 36 months of follow-up. With a median number of SLN of three, together with no recurrences, these results corroborate data obtained with the standard dual tracer lymph node marking. In the present study, axillary dissection was avoided in 58% of patients who were initially cN1/2 prior to NACT. To the best of our knowledge, this is the first study to evaluate SLNB after NACT using blue dye alone in initially positive axillae.

Historically used in cases of locally advanced breast cancer, the more recent use of NACT in non-metastatic operable breast cancer had a positive effect on the rate of breast conservation and became an important strategy for cases with adverse tumour characteristics, particularly following the advent of new drugs that increased the rate of pathological complete response (pCR) in the breast and axilla, also enabling the axilla to be preserved through the use of SLNB in patients with initially node-positive axilla. The Z1071, SENTINA and SN-FNAC studies found overall false-negative rates of 12.6%, 14.2% and 13.3%, respectively, higher than those found with upfront surgery. Nevertheless, analysis of subgroups in those studies showed that clipping abnormal lymph nodes prior to NACT, identifying and resecting three or more SLN, using immunohistochemistry to assess the SLN and using a dual tracer of blue dye and radioisotope reduced the false-negative rate to ≤10% [7–9,15]. Those studies did not evaluate the oncological outcomes of the technique; however, minimizing false-negative rates using these strategies has been widely recommended with the aim of safely avoiding axillary dissection [16]. Nonetheless, many institutions around the world, particularly in low- and middle-income countries, may not have access to lymph node clipping, and services of nuclear medicine may even be unavailable, as is the case in Brazil, leaving the inexpensive and widely available blue dye as the only option of tracer for SLNB. This may limit the possibility of avoiding axillary dissection in patients who respond to treatment [14]. However, data on the use of blue dye in this setting are limited. Information on single tracers following NACT is practically restricted to the use of radiotracer. In the Z1071 study, only 25 cN1 patients (3.8%) used blue dye alone compared to 109 cases (16.7%) of radioisotope alone and 517 cases (79.4%) in which the dual-tracer method was used. In the SENTINA study, in the arm in which SLNB was performed following NACT in previously node-positive axillae, only 7 patients (1%) used blue dye alone compared to 388 (66%) who used radiocolloid alone and 164 (28%) using the dual-tracer technique [7,8,17,18]. The present analysis showed that SLNB using blue dye alone following NACT in cN1/2 patients with complete response is not only viable but also results in excellent locoregional control, avoiding axillary dissection in almost 60% of patients.

The present results corroborate those of previous real-world evidence studies on dual tracers. In a retrospective analysis of 288 cases of stage II and III breast cancer that underwent NACT at the Memorial Sloan Kettering Cancer Center, 70% of the patients were eligible for dual-tracer SLNB and in 48% of cases axillary dissection was avoided, with 110 patients (86%) having ≥3 sentinel lymph nodes identified and

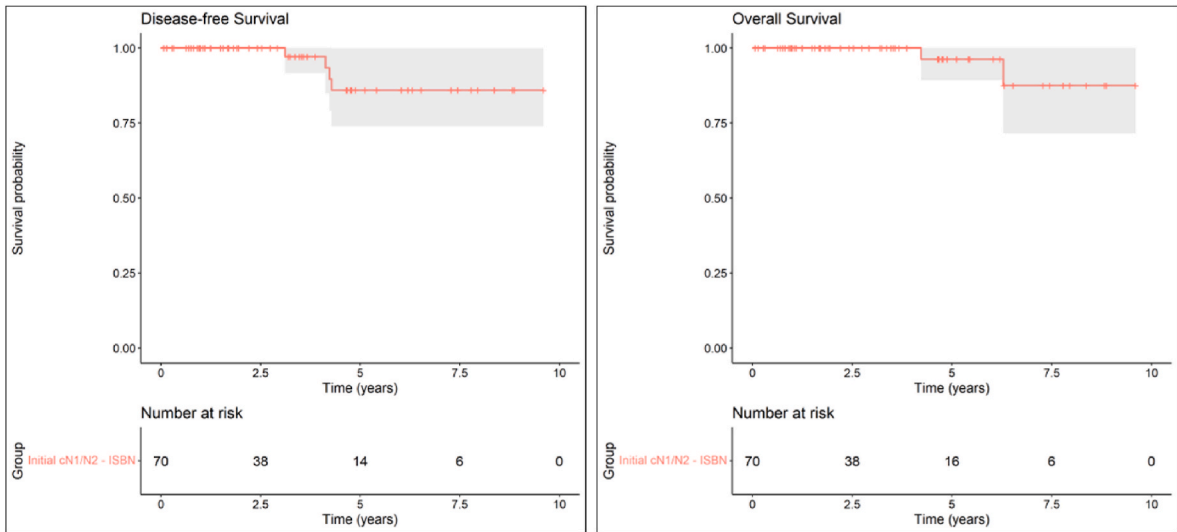


Fig. 2. Kaplan-Meier curves for disease-free and overall survival with sentinel lymph node biopsy alone without axillary dissection.

Table 3
Factors associated with the patients who underwent sentinel lymph node biopsy (SLNB) alone without axillary dissection following sentinel lymph node identification using blue dye alone (total N = 119).

Factors	SLNB N = 70/ 119 (%)	Univariate		Multivariate	
		RR (95%CI)	p-value	AOR (95%CI)	p-value
<i>Tumour stage</i>					
T1 or T2	46/76 (60.53)	1.08 (0.66–1.78)	0.75		
T3 or T4	24/43 (55.81)	1.00			
<i>Nodal stage</i>					
N1	64/96 (66.67)	2.56 (1.11–5.90)		2.58 (1.54–9.10)	0.03
N2	6/23 (26.09)	1.00	<0.001	1.00	
<i>Immunohistochemical subtype</i>					
HER2	16/21 (76.19)	1.88 (0.97–6.66)	0.06	1.99 (1.02–3.87)	0.04
Luminal	21/30 (70.00)	1.73 (0.93–3.22)		1.68 (0.90–3.12)	
HER2	14/21 (66.67)	1.65 (0.83–3.29)	0.15	1.52 (0.76–3.04)	0.23
Triple-negative	19/47 (40.43)	1.00		1.00	

RR: risk ratio; AOR: adjusted odds ratio.

resected [19]. The present study identified ≥ 3 sentinel lymph nodes in 78% of cases. Conversely, the Z1071 and SENTINA studies found ≥ 3 sentinel lymph nodes in only 57% and 34% of cases, respectively [7,8].

In fact, reducing the false-negative rate to mirror the rates found with upfront surgery has been a strategy used to compensate for the lack of randomized data on oncological outcomes. A US retrospective study, in which this strategy was applied to 234 patients who were cT1–T3, cN1 at first presentation and who had ≥ 3 sentinel lymph nodes identified at dual-tracer SLNB without axillary dissection, reported a very low rate of axillary recurrence after a mean follow-up time of 40 months, with only one patient having axillary recurrence [12]. Nevertheless, minimizing the false-negative rate may not be so important here. A retrospective Italian study with a mean follow-up time of 9.2 years analysed 123 cT1–3, cN1/2 patients who did not undergo lymph node clipping prior to NACT. The objective was not to resect at least 3 SLN (indeed < 3 were resected in 77% of cases) and radiotracer alone was used. Results showed a very low rate of axillary recurrence (1.8%) following SLNB

without axillary dissection [11]. These results corroborate the findings of the present study in which there were no cases of axillary recurrence over a mean follow-up time of 36 months.

Most of the patients in the present study had tumours with adverse biological features (ERBB2-positive or triple-negative), hence with a greater likelihood of pCR in the breast and axilla. A recent systematic review and meta-analysis of 33 studies involving over 57,000 patients with initially positive axilla evaluated the rate of pCR in the axilla in the different breast cancer subtypes following NACT. Results showed that pCR was lowest in the case of hormone receptor-positive/ERBB2-negative tumours (luminal A 13% and luminal B 35%) compared to 60% in hormone receptor-negative/ERBB2-positive tumours, 48% in triple-negative tumours and 45% in hormone receptor-positive/ERBB2-positive tumours [20]. Comparatively, in the present study the lowest rate for SLNB resection without axillary dissection was for the hormone receptor-positive/ERBB2-negative tumours, while the greatest benefit of SLNB alone was in cases of hormone receptor-negative/ERBB2-positive, triple-negative and hormone receptor-positive/ERBB2-positive tumours. In this study, most of the patients did not receive combination therapy with anti-ERBB2 antibodies, which is known to be associated with a higher rate of pCR in the breast and axilla, nor did they receive pembrolizumab, which would also affect the pCR in triple-negative tumours [21–23]. Another on-going debate following the advent of new drugs refers to the selection of patients for additional adjuvant therapies in cases in which pCR is not achieved, particularly those involving tumours with adverse biological features [24–26]. In this case, the false-negative rate of SLNB could hypothetically have a negative effect on this decision [27]. In this institute, only capecitabine is currently available; therefore, this potential effect would be restricted to triple-negative disease. Conversely, even in cases for which these new drugs are available, identifying residual disease in the axilla should not, in our view, affect this decision, since it is unusual to have pCR in the breast together with residual axillary disease. A retrospective analysis of 7457 triple-negative and ERBB2-positive cT1–2, cN1 patients treated with NACT, conducted using the US National Cancer Database, showed that of those who achieved pCR in the breast, only 12.4% and 14.1% had residual disease in the axilla with ERBB2-positive and triple-negative tumours, respectively [28].

There is an interconnected discussion on the need to perform dissection in cases with positive SLNB following NACT. In recent years, the tendency has been to omit axillary dissection in these cases based on the hypothesis that radiotherapy could replace surgery, particularly in situations with limited residual disease in the lymph node [29,30]. Recent studies, however, have shown a high burden of residual disease

even in cases of micro-metastasis (>60%) [31]. In the present study, residual disease was identified in 42.8% of these cases. Routine practice here is to continue to perform axillary dissection while we await the results of the Alliance A11202 trial [15]. On the other hand, with these results, together with data from the NSABP B-51/RTOG 1304 study, the debate on the false-negative rate could be less critical.

The present study involves certain limitations, notably the retrospective nature of the analysis, the fact that the study refers to a single institute, and the relatively short follow-up period. Nevertheless, to the best of our knowledge, this is the first study on the use of blue dye alone for SLNB in initially cN1/2 patients who obtained axillary response following NACT without axillary dissection. Data are provided on the initial relevant oncological outcomes, particularly lymph node recurrence, and the findings are compatible with previous real-world evidence studies on dual-tracer SLNB. Moreover, it is unlikely that a longer follow-up period would have any great effect on nodal recurrence in view of the outcomes described and since most of the population (73%) had tumours with adverse biological features. Although these data cannot be generalized, they suggest that this technique is a feasible option for performing SLNB in patients who respond to NACT at sites with limited resources, minimizing the effects of unnecessary axillary dissection while awaiting the results of randomized clinical trials.

5. Conclusion

Performing SLNB using blue dye alone following NACT in patients with initial cN1/2 who achieved complete clinical and imaging response proved feasible according to this analysis, with no axillary recurrence. It would therefore appear to represent a suitable option in institutes with limited access to resources. Results from studies with longer follow-up times, particularly randomized clinical trials, are required to validate these findings.

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CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

IQR	Interquartiles range
NACT	Neoadjuvant chemotherapy
pCR	Pathological complete response
SLN	Sentinel lymph node
SLNB	Sentinel lymph node biopsy

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