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Original article

# Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with T2 to T4, N0 and N1 breast cancer

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ABSTRACT

*Background:* Histological status of axillary lymph nodes is an important prognostic factor in patients receiving surgery for breast cancer (BC). Sentinel lymph node (SLN) biopsy (B) has rapidly replaced axillary lymph node dissection (ALND), and is now the standard of care for axillary staging in patients with clinically node-negative (N0) operable BC. The aim of this study is to compare pretreatment lymphoscintigraphy with a post primary systemic treatment (PST) scan in order to reduce the false-negative rates for SLNB.

*Methods:* In this single-institution study we considered 170 consecutive T2-4 N0-1 M0 BC patients treated with anthracycline-based PST. At the time of incisional biopsy, we performed sentinel lymphatic mapping. After PST, all patients repeated lymphoscintigraphy with the same methodology. During definitive surgery we performed further sentinel lymphatic mapping, SLNB and ALND.

*Results:* The SLN was removed in 158/170 patients giving an identification rate of 92.9% (95% confidence interval (CI) = 88.0–96.3%) and a false-negative rate of 14.0% (95% CI = 6.3–25.8%). SLNB revealed a sensitivity of 86.0% (95% CI = 74.2–93.7%), an accuracy of 94.9% (95% CI = 90.3–97.8%) and a negative predictive value of 92.7% (95% CI = 86.1–96.8%).

*Conclusion:* Identification rate, sensitivity and accuracy are in accordance with other studies on SLNB after PST, even after clinically negative node conversion following PST. This study confirms that diagnostic biopsy and neoadjuvant chemotherapy maintain breast lymphatic drainage unaltered.



## Introduction

The histological status of axillary lymph nodes is an important prognostic factor in patients receiving surgery for breast cancer (BC) and is used to guide subsequent therapy decisions in early stage disease [1,2]. Sentinel lymph node biopsy (SLNB) has replaced axillary lymph node dissection (ALND) [3,4], and is now the standard of care for axillary staging in patients with clinically node-negative (cN0) operable breast cancer [5,6].

To date, SLNB seems reproducible and accurate in patients with stage I or II BC. This technique is successful in up to 90% of women and its accuracy might exceed 95%, but the main predictor of success is the surgeon's familiarity with the technique [3,4,7,8].

Since the early 1980s, primary systemic treatment (PST) has been part of the multidisciplinary approach to locally advanced BC.

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PST is currently accepted as a therapeutic option for patients with early-stage BC. Its objectives are to increase the chance of undergoing conservative surgery and, similarly to adjuvant chemotherapy, to reduce the risk of distant recurrence [9]. PST has also been shown to eradicate FNAB-proven axillary metastases as well as primary tumors in patients with large primary and locally advanced BC [10]. As the axilla of these patients often becomes clinically and pathologically negative due to PST, in theory these patients do not require an ALND. In this setting, SLNB has been considered a sufficiently safe and accurate method for screening the axillary nodes for metastasis in women with a small breast [11,12]. The false-negative rates for SLNB range from 0% to 20% after chemotherapy in patients with cN0 disease [5,13,14]. Despite high overall identification success rates with introduction of different mapping techniques, false-negative rates remained unchanged in most recent meta-analyses [15]. Therefore surgeons considered SLN mapping in patients with BC diagnosed by incisional biopsy [16] and treated with PST, having potentially compromised lymphatic drainage. All these data highlight the need to improve the accuracy of SLNB in PST in order to help surgeons to identify patients that have been down staged by treatment to N0 and benefit from avoiding the morbidity associated with ALND.

Lymphoscintigraphy is the technical name for the various procedures used to study the lymphatic system. In the context of BC, lymphoscintigraphy is a reliable and reproducible approach for lymphatic mapping assessment from a BC to the draining SLN. The aim of this study is to compare pretreatment lymphoscintigraphy with a post PST scan in order to reduce the false-negative rates for SLNB.

## Patients and methods

### *Patients*

In this report we considered 170 consecutive BC patients enrolled in a randomized trial comparing anthracycline-based PST for T2-4 N0-1 M0 BC. This analysis aimed to evaluate success rate for identification and isolation of SLN in patients treated with PST, and investigate whether treatment, diagnostic biopsy and the tumor biological and clinical characteristics affect the lymphatic drainage and thereby influence SLN technique accuracy. Patients' characteristics are described in Table 1. Diagnostic and surgical approaches are fully described elsewhere [17]. An incisional biopsy (IB) was performed on each patient at baseline. Initial staging comprised clinical examination, bilateral mammography, breast ultrasound, chest X-ray, liver imaging or CT-scan and bone scintigraphy. All patients gave informed consent for diagnostic procedures and proposed treatment.

**Table 1**
Patients and tumor characteristics before PST (n = 170).

| | | |
|---|---|---|
| Age | | |
| Median | 53.2 years | |
| Range | 25.4–73.4 years | |
| | **No. of patients** | **%** |
| Menopausal status | | |
| Pre-menopausal | 74 | 43.5 |
| Post-menopausal | 96 | 56.5 |
| Clinical stage | | |
| T2 | 158 | 92.9 |
| T3 | 3 | 1.8 |
| T4 | 9 | 5.3 |
| N0 | 118 | 69.4 |
| N1 | 52 | 30.6 |
| Grade | | |
| II | 51 | 30.0 |
| III | 119 | 70.0 |
| Histotype | | |
| DIC | 131 | 77.1 |
| LIC | 14 | 8.2 |
| Mixed DIC-LIC | 6 | 3.5 |
| Other | 19 | 11.2 |
| Hormonal receptor status | | |
| ER+ | 137 | 80.6 |
| ER− | 33 | 19.4 |
| PgR+ | 95 | 55.9 |
| PgR− | 75 | 441 |
| HER-2 status | | |
| HER2+ | 24 | 141 |
| HER2− | 146 | 859 |
| Ki67 | | |
| <14% | 46 | 271 |
| ≥14% | 124 | 729 |
| Tumor subtype | | |
| Luminal A | 45 | 26.5 |
| Luminal B/HER2− | 86 | 506 |
| Luminal B/HER2+ | 9 | 53 |
| HER2+ (nonluminal) | 12 | 70 |
| Triple Negative | 18 | 10.6 |

## Methods

Before performing IB, each patient received 1 intradermal injection, under ultrasound guidance on the dermal projection of the BC, of $^{99m}$Tc-labeled nanocolloid albumin (NANOCOLL, Amersham Health), activity 10 MBq in 0.2 ml of saline. Then oblique 45° and lateral 90° chest lymphoscintigraphy images were obtained with the same gamma camera at 30′ and 120′ p.j. Skin projection of the SLN approximate location was then marked with permanent ink. PST was started within 5 days from diagnosis and SLN localization. After PST, all patients repeated lymphoscintigraphy with the same methodology and the same gamma camera. To evaluate the reproducibility of lymphoscintigraphy before and after IB and PST, we evaluated the 2 sets of lymphoscintigraphy images. We also examined whether after IB and PST the ink-marked SLN remained unchanged or were altered due to the modified lymphatic drainage.

Definitive surgery with the planned lumpectomy or mastectomy according to clinical/radiological response was performed 18–27 h after the second injection by the same 3 specialist breast surgeons (A.B.; A.S.; G.A.). Intraoperative detection of the SLN was performed with the same gamma probe (Neoprobe 2000, Ethicon Breast Care). After the SLN has been excised, a full ALND was performed if necessary.

### *Histological evaluation*

Grading was performed according to the Elston and Ellis grading system [18]. The immunohistochemical assays used in this study are fully described elsewhere [19–21]. The SLN and other surgically removed axillary lymph nodes were fixed in formalin and cut in to 0.2 cm sections. Each section was examined using standard histopathologic techniques with hematoxylin and eosin (H&E) staining. From each paraffin block of the non-malignant SLNs, 15 sections were cut at 100 μm intervals and stained for cytokeratins (CAM5.2).

### *Statistical methods*

The primary end points used for statistical analysis were the success rate for identification and removal of the SLN in patients who had attempted a SLNB (n = 170), and the false-negative rate of SLNB in patients who had at least 1 positive sentinel or non-sentinel (n = 49) at the time of definitive surgery. The identification rate was defined as the number of patients who had undergone a successful SLNB divided by the total number of patients who had

attempted a SLNB. The result of each successfully identified SLN was categorized as true-positive, true-negative or false-negative, taking the outcome of the complete ALND as reference standard. A true-negative SLNB was defined as a negative SLNB and a negative ALND; a false-negative as a negative SLNB with a positive lymph node in the ALND; and a true-positive as a positive SLNB with or without a positive ALND. Based on these definitions, we found no false-positive cases.

Calculation of SLNB accuracy parameters included false-negative rate (false negative/(false negative + true positive)), sensitivity (true positive/(true positive + false negative)), and negative predictive value (true negative/(true negative + false negative)). Accuracy was calculated as the sum of all true-positive and true-negative patients, divided by the number of patients with a successfully identified SLNB.

Comparisons of these rates were made in both analyzing simple proportions and performing logistic regression analyses with adjustment of the stratification variables (menopausal status, clinical stage, tumor subtype, grading and histotype). Comparisons of proportions were performed using Pearson's chi-square test with Yates' correction, and Fisher's exact test when necessary, whereas comparison of continuous variables was performed with Mann–Whitney U test. Relationships between variables were examined using Spearman's rank correlation. Disease-Free Survival (DFS) and Overall Survival (OS) were calculated from the date of diagnosis to first relapse, or death (irrespective of the cause). Patients who did not experience either relapse or death were censored at their last clinical visit. DFS curve was plotted with the Kaplan–Meier method and compared with the log-rank test. All tests were two-sided; $P < 0.05$ was considered statistically significant. Data were analyzed using Statistica software (StatSoft, Inc., Tulsa, OK) and SPSS software (SPSS, Chicago, IL).

## Results

### *Patient and tumor characteristics*

In this investigation we included 170 consecutive women treated in our institution with anthracycline-based neoadjuvant chemotherapy for T2-4 N0-1 M0 BC. The enrolled patients received 4 cycles of epirubicin 120 mg/m$^2$/q21. The patient and tumor characteristics are listed in Table 1. The median age at the time of diagnosis was 53.2 years (range, 25.4–73.4 years). Clinical number stage at diagnosis was IIA in 113 patients (66.5%), IIB in 46 patients (27.0%), IIIA in 2 patients (1.2%) and IIIB in 9 patients (5.3%). No clinically palpable axillary lymph node was detected in 118 patients (69.4%). A total of 52 patients (30.6%) were N1.

Molecular tumor subtypes [22] determined by analysis of hormonal receptors, HER2 status and Ki67 labeling index was: Luminal A BC in 45 cases (26.5%); Luminal B with HER2-ve in 86 cases (50.6%); Luminal B-HER2 enriched in 9 cases (5.3%); HER2+vel) in 12 cases (7.0%) and Triple Negative in 18 cases (10.6%).

### *Surgical treatment and evaluation of response to PST*

After the PST, surgery was performed as planned. We performed breast conservative surgery in 150 patients (88.2%), and radical mastectomy in 20 patients (11.8%). Surgical breast resection specimens were evaluated for pathologic tumor response. Patients who had no invasive or in situ cancer residuals in the breast and in the axilla were considered pathologic complete response (CR). The absence of metastasis in the axilla defined the pN0 [16].

According to the WHO criteria [23], a total of 154 patients achieved clinical response (objective response rate 90.6%): 59 (34.7%) clinical CR and 95 (55.9%) partial responses (PR). Only 2 patients (1.2%) progressed under treatment. The corresponding radiological response rate by ultrasound and mammography was 66.8% (8.4% CR and 58.5% PR) and 64.3% (15.9% CR and 58.4% PR), respectively. Nine patients (5.3%) achieved a pathologic CR, and 7 patients (4.1%) had residual carcinoma in situ only. Forty-nine patients (31.0%) had involved nodes at SLNB. Lymph node involvement was significantly associated with positivity at the clinical evaluation of the axilla ($P < 0.05$). Overall, 62 patients (36.5%) had involved nodes at SLNB and/or ALND. Lymph node involvement was significantly associated with baseline ER positivity rather than negativity ($P < 0.009$), and with Luminal B subtype (regardless of the HER2 status) rather than other subtypes ($P < 0.03$).

**Table 2**
Rate of identification and removal of SLN according to clinical and tumor characteristics.

| | Number of patients | SLNB done | Success rate (%) |
|---|---|---|---|
| Overall | 170 | 158 | 92.9 |
| Age | | | |
| <50 | 66 | 63 | 95.5 |
| ≥50 | 104 | 95 | 91.3 |
| Menopausal status | | | |
| Pre-menopausal | 74 | 69 | 93.2 |
| Post-menopausal | 96 | 89 | 92.7 |
| Clinical Tumor Stage | | | |
| T2 | 158 | 147 | 93.0 |
| T3 | 3 | 3 | 100 |
| T4 | 9 | 8 | 88.9 |
| Clinical nodal status | | | |
| Negative | 118 | 112 | 94.9 |
| Positive | 52 | 46 | 88.5 |
| Grade | | | |
| II | 51 | 50 | 98.0 |
| III | 119 | 108 | 90.8 |
| Histotype | | | |
| DIC | 131 | 122 | 93.1 |
| LIC | 14 | 13 | 92.9 |
| Mixed DIC-LIC | 6 | 6 | 100 |
| Other | 19 | 17 | 89.5 |
| Ki67 | | | |
| <14% | 46 | 43 | 93.5 |
| ≥14% | 124 | 115 | 92.7 |
| Tumor subtype | | | |
| Luminal A | 45 | 42 | 93.3 |
| Luminal B/HER2- | 86 | 80 | 93.0 |
| Luminal B/HER2+ | 9 | 9 | 100 |
| HER2+ (nonluminal) | 12 | 10 | 83.3 |
| Triple Negative | 18 | 17 | 94.4 |

**Table 3**
Status of SLN and Non-SLN.

| | Non-SLN (status) | | Total |
|---|---|---|---|
| | Positive | Negative | |
| SLN (status) | | | |
| Positive | 28 | 21 | 49 |
| Negative | 8 | 101 | 109 |
| **Total** | 36 | 122 | 158 |

Identification rate: 92.9% (95% CI, 88.0–96.3%); false-negative rate: 14.0% (95% CI, 6.3–25.8%); overall accuracy: 94.9% (95% CI, 90.3–97.8%); negative predictive value: 92.7% (95% CI, 86.1–96.8%); positive predictive value: 100% (by definition); sensitivity: 86.0% (95% CI, 74.2–93.7%).

### *Rate of SLN identification and removal*

Out of the 170 patients included in this study, the SLN was identified and removed in 158, with an identification rate of 92.9% (95% confidence interval (CI), 88.0–96.3%). Twelve patients declined SLNB and underwent the ALND. The SLN marked before

**Table 4**
False negative rate of SLNB according to clinical and tumor characteristics, and clinical, imaging and pathologic response.

| | Number of patients (SLNB done) | Number of patients with node + | SLNB − & ALND + | False negative rate % |
|---|---|---|---|---|
| Overall | 158 | 57 | 8 | 14.0 |
| Age | | | | |
| <50 | 63 | 19 | 2 | 10.5 |
| ≥50 | 95 | 38 | 6 | 15.8 |
| Menopausal status | | | | |
| Pre-menopausal | 69 | 34 | 5 | 14.7 |
| Post-menopausal | 89 | 23 | 3 | 13.0 |
| Clinical tumor stage | | | | |
| T2 | 147 | 51 | 8 | 15.7 |
| T3 | 3 | 2 | 0 | 0 |
| T4 | 8 | 4 | 0 | 0 |
| Clinical nodal status | | | | |
| Negative | 112 | 34 | 5 | 14.7 |
| Positive | 46 | 23 | 3 | 13.0 |
| Grade | | | | |
| II | 50 | 13 | 2 | 15.4 |
| III | 108 | 44 | 6 | 13.6 |
| Histotype | | | | |
| DIC | 122 | 48 | 6 | 12.5 |
| LIC | 13 | 5 | 0 | 0 |
| Mixed DIC-LIC | 6 | 4 | 2 | 50.0 |
| Other | 17 | 0 | 0 | 0 |
| Ki67 | | | | |
| <14% | 43 | 14 | 1 | 7.1 |
| ≥14% | 115 | 43 | 7 | 16.3 |
| Tumor subtype | | | | |
| Luminal A | 42 | 14 | 1 | 7.1 |
| Luminal B/HER2- | 80 | 35 | 6 | 17.1 |
| Luminal B/HER2+ve | 9 | 4 | 1 | 25.0 |
| HER2+ve | 10 | 3 | 0 | 0 |
| Triple Negative | 17 | 1 | 0 | 0 |
| Clinical response | | | | |
| CR | 52 | 13 | 2 | 15.4 |
| PR | 90 | 39 | 6 | 15.4 |
| SD | 14 | 4 | 0 | 100 |
| PD | 2 | 1 | 0 | 100 |
| Ultrasound response | | | | |
| CR | 14 | 3 | 1 | 33.3 |
| PR | 88 | 33 | 3 | 9.1 |
| SD | 40 | 14 | 4 | 28.6 |
| PD | 12 | 5 | 0 | 100 |
| n.e. | 4 | 2 | | |
| Mammography response | | | | |
| CR | 25 | 6 | 1 | 16.7 |
| PR | 69 | 25 | 4 | 16.0 |
| SD | 39 | 13 | 2 | 15.4 |
| PD | 14 | 7 | 1 | 14.3 |
| n.e. | 11 | 6 | | |
| Pathologic response | | | | |
| pCR | 7 | 0 | 0 | 0.0 |
| pIS | 7 | 0 | 0 | 0.0 |
| pINV | 144 | 57 | 8 | 14.0 |

starting PST was the same when removed at the end of treatment in 157 patients, without evidence of impaired lymphatic drainage (reproducibility of 99.4% in lymphoscintigraphic results). In only 1 case (0.6%), lymphoscintigraphy identified a different SLN.

Out of the 158 patients who received SLNB, the number of SLNs removed ranged from 1 to 5; in 119 patients (75.3%) only 1 node was removed, in 35 patients (22.2%) 2 nodes, in 1 patient (0.6%) 3 nodes, in 2 patients (1.3%) 4 nodes, and in 1 patient (0.6%) 5 nodes.

There were no significant differences in the identification rate according to menopausal status, clinical tumor stage, clinical nodal status, tumor grade, tumor histotype, Ki-67 index and tumor subtype. The rate of identification and removal of SLN was higher in patients aged <50 (95.5%) vs ≥50 (91.3%), with clinical node negative (94.9%) vs positive (88.5%), and with lower grade G2 (98.0%) vs G3 (90.8%) (Table 2).

There were no significant differences in the identification rate according to clinical and pathologic breast tumor response to PST. The rate of identification and removal of SLN was higher in patients with clinical CR and PR (92.2%) than in patients with stable disease (SD) and progressive disease (PD), and in patients with invasive cancer at definitive surgery (93.5%) than in patients with pathologic CR (77.8%).

*Accuracy of SLN status in predicting the status of the axilla*

Out of the 158 patients receiving SLNB, the histological evaluation status revealed that in 28 patients either the SLN or ALN were positive, while in 101 cases they were both negative; in 21 out of 158 patients the SLN was positive whereas the axilla was negative. In 8 patients the SLN was negative while the ALN was positive

(Table 3). According to these results, SLNB predicted the axillary status in 150 patients (overall accuracy, 94.9%; 95% CI, 90.3–97.8%), in particular in 101 out of 109 patients with node negative (negative predictive value, 92.7%; 95% CI, 86.1–96.8%). Sensitivity was 86.0% (95% CI, 74.2–93.7%).

*False-negative rate of SLNB*

The false-negative rate was 14.0% (95% CI, 6.3–25.8%). In 6 out of 8 cases, only 1 SLN was resected.

After ALND, 4 out of 8 patients had 1 axillary node with metastasis, 2 patients had 2 positive nodes and 2 patients had 3 positive nodes. False-negative rate of SLNB was higher in patients with mixed ductal infiltrating and lobular infiltrating carcinoma (DIC-LIC) histotype (50.0%) compared to (the) other histotypes (11.3%) ($P$ for trend <0.01). There were neither significant differences in false-negative rate according to other clinical and tumor characteristics, nor clinical and pathologic breast tumor response to PST (Table 4).

Considering only the patients with N0 tumor before PST, the false-negative rate decreased to 12.8% (95% CI, 2.3–20.2%).

*Nodal status and patient outcome*

After a median follow-up of 7.4 years (range 2.2–10.5 years), 23 patients (13.5%) relapsed and 21 (12.4%) died. Positivity at the clinical evaluation of the axilla before PST correlated on univariate analysis with a decrease in OS ($P = 0.044$). In multivariate analysis, the node positivity at SLNB impacted negatively on DFS ($P < 0.03$) and OS ($P < 0.01$). Patients with false-negative SLN seem to have a shorter DFS ($P$ for trend $= 0.080$) but unvaried OS, compared with patients with positive SLN (Fig. 1). Surgical-proven metastatic involvement of the axilla (at SLNB and/or ALND) confirms the negative impact on DFS ($P < 0.0001$) and OS ($P = 0.00001$). Again, metastatic involvement of 3 or more lymph nodes correlated with a decrease in both DFS ($P < 0.03$) and OS ($P < 0.003$), compared to the cases with a smaller number of pathologic nodes.

## Discussion

The presence of axillary lymph node metastases, as one of the strongest predictors of survival, is necessary for accurate staging and the selection of local and systemic adjuvant therapies [24,25]. The status of axillary lymph nodes can be confirmed by complete ALND, but is likely to cause morbidities in almost 20% of patients [26]. Due to this, SLNB is now a standard technique that has replaced ALND for axillary staging in early BC. The SLN identification rate of 97.2%, accuracy rate of 97.1%, and false-negative rate of 9.8% were reported in a large multi-institutional randomized study [27] in clinically node-negative patients. The results of the ACOSOG Z0010 and Z0011 trials indicated that the use of SLNB for staging axillary lymph nodes exhibited a similar relapse rate compared to ALND [28,29]. If the SLN is tumor-free after SLNB, the probability of cancer-cell presence in the remaining axillary nodes is assumed to be less than 10%. In this case completion of ALND can be omitted [5]. Thus, the SLN biopsy approach could be considered today as an adequate surgical replacement for axillary dissection for staging procedures in clinically node-negative breast carcinomas [14]. The National Cancer Institute conference reported that SLNB could be performed after PST in patients with clinically negative nodes at initial diagnosis [30].

In recent years, PST has become the most common choice for the treatment of locally advanced BC [31,32]. However, the role of SLNB in patients receiving PST-based remains controversial, especially with regards to clinically node-positive BC. A recent meta-analysis showed that SLNB was also feasible after PST in node-positive BC patients, although the false-negative rate was high and requires addressing [33]. However, the meta-analysis to evaluate the feasibility of SLNB after primary chemotherapy suggested that SLNB is a reliable tool for planning treatment after preoperative chemotherapy [15]. Mamounas et al. [34] stated that after PST SLNB seems to have a similar performance outcome to SLNB before systemic therapy [35]. However, it is still unclear whether the oncological treatment administered through the PST approach affects the status of axillary lymph nodes in term of lymphatic drainage or SLN detection before and after treatment.

In our study, SLNB revealed a sensitivity of 86.0%, an accuracy of 94.9% and a negative predictive value of 92.7% and an overall false-negative rate was 14.0%. In cN0 before starting treatment, the false-negative rate decreased to 12.8% and although these data are little higher than reported in the expert panel's recommendation [14,27], they are reasonable values to use in conventional clinical practice considering the ALND-related postoperative complication rates [26,36].

We admit that this study has several limitations. For example, the number of enrolled patients was small and the outcome was largely affected by a single event; only one mapping technique was used, even for those patients that failed to show any uptake in the axilla through the lymphoscintigraphy [37]. Other factors possibly related to SLNB failure were not considered in the analysis, such as the Body Mass Index and the presence of the axillary arch [38]. Moreover the false-negative SLNB results were associated with a mixed ductal-lobular but not poorly differentiated BC histologic type [39]. The results of this study have nonetheless clinical significance and provide important insight into the validation of SLNB following PST. Despite the potential residual axillary disease after SLNB, our study confirms that the SLNB without ALND gives excellent regional control and may be implemented as a reasonable management for selected patients with early-stage breast cancer treated with breast-conserving therapy and adjuvant systemic therapy as previously suggested [29,40]. In clinical practice, it is important to consider that resection of at least 2 or 3 SLNs and adoption of dual tracers or dual techniques of detection could be useful to identify suitable subgroups of BC where SLNB is a sufficient treatment approach. When SLNB is performed where lymph node involvement is initially found, a larger number of sentinel nodes should be resected to decrease the false-negative rate, especially in women with cN1 breast cancer [41]. Our study also confirmed that the successful SLN-mapping in patients who had

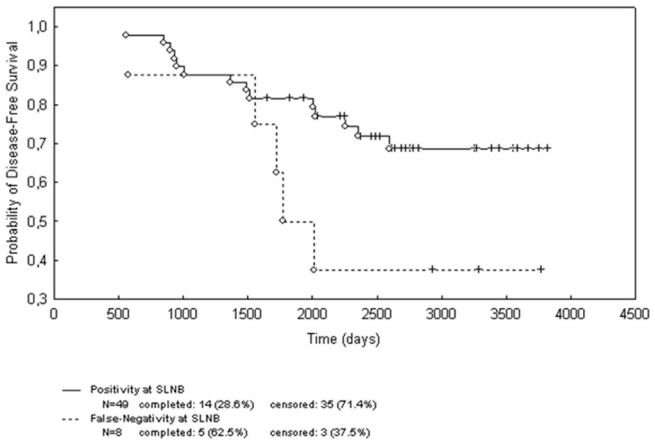


**Fig. 1.** Kaplan–Meier estimates for disease-free survival in patients with false-negative vs positive sentinel lymph node before primary systemic treatment (univariate analysis).

undergone PST was highly accurate in agreement with Koslow et al. [42]. We showed that patients with false-negative SLNB seem to have a worse DFS ($P$ for trend = 0.080) but no different OS compared to patients with positive SLNB as reported elsewhere [43,44]. This means that SLNB only can safely replace ALND as the procedure of choice for axillary staging in breast cancer patients with a clinically negative axilla. The use of combined techniques for detection of the status of SLN, such as the combination fluorescence and blue dye-based tracer technique or with the Tc99 radiotracer or superparamagnetic iron oxide [45,46], may reduce false-negative rate to improve the patient outcome in terms of quality of life [26].

In conclusion the results of this study supported the use of SLNB is feasible for patients who undergo primary treatment in BC, in particular breast lymphatic drainage remains unaltered and the use of a pretreatment lymphoscintigraphy compared with a PST scan may be helpful in reducing false-negative rate.

## Conflict of interest statement

The authors have no conflict of interest to be declared.

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