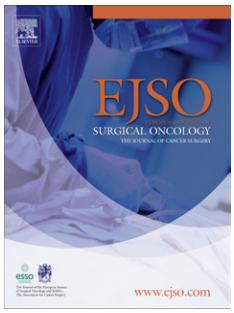
# Accuracy of sentinel lymph node biopsy after neo-adjuvant chemotherapy in patients with locally advanced breast cancer and clinically positive axillary nodes

Giuseppe Canavese, Beatrice Dozin, Carlo Vecchio, Daniela Tomei, Giuseppe Villa, Franca Carli, Lucia del Mastro, Alessia Levaggi, Carlo Rossello, Stefano Spinaci, et al.

# Accepted Manuscript




Title: Accuracy of sentinel lymph node biopsy after neo-adjuvant chemotherapy in patients with locally advanced breast cancer and clinically positive axillary nodes

Authors: Giuseppe Canavese, MD Beatrice Dozin, PhD Carlo Vecchio, MD Daniela Tomei, MD Giuseppe Villa, MD Franca Carli, MD Lucia Del Mastro, MD Alessia Levaggi, MD Carlo Rossello, MD Stefano Spinaci, MD Paolo Bruzzi, MD Alessandra Catturich, MD

PII: S0748-7983(11)00296-4

DOI: 10.1016/j.ejso.2011.05.012

Reference: YEJSO 3171

To appear in: *European Journal of Surgical Oncology*

Accepted Date: 23 May 2011

Please cite this article as: Canavese G, Dozin B, Vecchio C, Tomei D, Villa G, Carli F, Del Mastro L, Levaggi A, Rossello C, Spinaci S, Bruzzi P, Catturich A. Accuracy of sentinel lymph node biopsy after neo-adjuvant chemotherapy in patients with locally advanced breast cancer and clinically positive axillary nodes, European Journal of Surgical Oncology (2011), doi: 10.1016/j.ejso.2011.05.012

# Accuracy of sentinel lymph node biopsy after neo-adjuvant chemotherapy in patients with locally advanced breast cancer and clinically positive axillary nodes.

Giuseppe Canavese, MD[a], Beatrice Dozin, PhD[b], Carlo Vecchio, MD[a], Daniela Tomei, MD[a], Giuseppe Villa, MD[c], Franca Carli, MD[d], Lucia Del Mastro, MD[e], Alessia Levaggi, MD[e], Carlo Rossello, MD[f], Stefano Spinaci, MD[f], Paolo Bruzzi, MD[b] and Alessandra Catturich, MD[a]

[a] Surgical Senology Unit, National Cancer Research Institute Genova, Italy.

[b] Clinical Epidemiology Unit, National Cancer Research Institute, Genova, Italy.

[c] Department of Nuclear Medicine, A.O.U San Martino, Genova, Italy.

[d] Anatomy and Pathological Cytohistology Unit, National Cancer Research Institute, Genova, Italy.

[e] Medical Oncology A Unit, National Cancer Research Institute, Genova, Italy.

[f] Plastic and Reconstructive Surgery Unit, National Cancer Research Institute, Genova, Italy.

Corresponding author : Beatrice Dozin, PhD
Clinical Epidemiology Unit
National Cancer Research Institute
Largo Rosanna Bensi, 10
16132 Genova, Italy
Phone : 39-010-5737492
Fax : 39-010-354103
e-mail : beatrice.dozin@istge.it

**Abstract**

*Background:* Feasibility and accuracy of sentinel node biopsy (SLNB) after the delivery of neo-adjuvant chemotherapy (NAC) is controversial. We here report our experience in NAC-treated patients with locally advanced breast cancer and clinically positive axillary nodes, and compare it with the results from our previous randomized trial assessing SLNB in early-stage breast cancer patients.

*Patients and Methods:* Sixty-four consecutive patients with large infiltrating tumor and clinically positive axillary nodes received NAC and subsequent lymphatic mapping, SLNB and complete axillary lymph node dissection (ALND). The status of the sentinel lymph node (SLN) was compared to that of the axilla.

*Results:* At least one SLN was identified in 60 of the 64 patients (93.8%). Among those 60 patients, 37 (61.7%) had one or more positive SLN(s) and 23 (38.3%) did not. Two of the patients with negative SLN(s) presented metastases in other non-sentinel nodes. SLNB thus had a false-negative rate, a negative predictive value and an overall accuracy of 5.1%, 91.3% and 96.7%, respectively. All these values were similar to those we reported for SLNB in the settings of early-stage breast cancer.

*Conclusion:* SLNB after NAC is safe and feasible in patients with locally advanced breast cancer and clinically positive nodes, and accurately predicts the status of the axilla.

**Keywords** : axillary lymph node dissection, locally advanced breast cancer, lymphatic mapping, neo-adjuvant chemotherapy, sentinel node biopsy

## Introduction

The surgical management of patients presenting early-stage breast cancer (T1-T2) and clinically negative lymph nodes (N0) has long included both primary tumor resection and level I/II axillary lymph node dissection (ALND). This last procedure has been largely substituted by the sentinel lymph node biopsy (SLNB) which is nowadays recommended by most clinical guidelines for this subgroup of patients [1]. Indeed, the well documented accuracy of SLNB in predicting the axillary status [2-6] implies that, in these patients, a negative sentinel lymph node (SLN) is considered sufficient to rule out metastases in other axillary nodes and to avoid axillary dissection. Several randomized clinical trials, including ours, have further indicated that SLNB and ALND are comparable in terms of overall survival and incidence of nodal failure [7-11].

Over the years, neo-adjuvant chemotherapy (NAC) has become the preferred treatment for patients with operable locally advanced breast cancer, in an attempt to reduce the tumor mass and to favor breast-conservative surgery over mastectomy [12-14]. In addition, NAC has been shown to down-stage the axillary status in some 30-40% of the patients treated [13, 15, 16]. Based on the SLNB validation studies mentioned above, it would be reasonably legitimate to introduce the SLNB procedure also in the context of NAC. However, one frequent adverse effect of NAC is the anatomical alteration of the lymphatic drainage, with lymphatic vessels disrupted by tumor, inflammation or fibrosis, or blocked by necrotic and/or apoptotic cells [17]: in addition, NAC could induce a non-uniform tumor regression in the axillary modes, being most effective in some nodes but not in others [17-19]. These events could prevent a proper diffusion of the scintigraphic tracer during lymphatic mapping, in the one hand, and contribute to a reduction in the rate of successful SLN identification and, more importantly, an increase in the rate of false-negative SLN [18-20]. Therefore, the demonstration of the feasibility and accuracy of SLNB after NAC is of major interest since in the future responders to NAC who would be down-staged to a negative nodal status (N0) could be spared a complete axillary dissection and the immediate sequelae of axillary surgery [7, 21].

The present study evaluates the feasibility, accuracy and negative predictive value of SLNB in patients treated with NAC prior to SLN mapping and surgery. The population here considered includes patients with locally advanced infiltrating breast cancer at presentation, that is with a tumor of at least 2cm (T>2) and clinically positive axillary nodes (≥N1). The SLNB results obtained in these patients are compared to those we previously observed at our institution in patients presenting early-stage infiltrating breast cancer and clinically negative axillary nodes [11]. The SLNB results reported by other institutions in the NAC settings are also discussed.

## Materials and methods

*Patient population*

This single-center study was conducted at the National Cancer Research Institute of Genoa, Italy. The protocol, which introduced SLNB in the surgical management of patients with locally advanced breast cancer, was approved by the Institutional Ethical Committee and conducted in accordance with International Good Clinical Practice Guidelines. Patients admitted for breast cancer surgery were first subjected to careful baseline clinical staging. Primary tumor dimension was evaluated by mammography and/or ecography, and nuclear magnetic resonance (NMR); tumor histotype was determined by core-biopsy. Axillary status was assessed by palpation and ultrasound imaging; node biopsy was not performed. Absence of distant metastases was verified by combined Positron Emission Tomography / Computerized Axial Tomography. The study included patients with large infiltrating carcinomas (>2cm in the major axis), ductal or lobular but not inflammatory, and clinically positive axilla, thus clinically staged IIB or higher. Patients with clinically negative nodes were excluded. All patients enrolled were informed on the study aims and implications, and signed a consent form.

From pre- and post-NAC clinical evaluation through surgery, each patient was followed by a single disease management team including the same radiologist, surgeon, pathologist and oncologist.

*Study design*

The study aim was to verify whether SLNB is feasible and has a relevant negative predictive value for the axillary status when it is performed after the delivery of NAC. All patients thus received neo-adjuvant chemotherapy (see below). During surgery, primary tumor was resected, and the SLN was localized and removed. Intra-operative SLN evaluation on frozen sections was not performed but deferred to definitive diagnosis on paraffin sections. All patients received concomitant level I/II/III axillary dissection. The SLN status was compared to the definitive evaluation of the axillary status.

*Neo-adjuvant chemotherapy, response to treatment, surgery and adjuvant treatment*

Patients received an anthracycline/taxane-based regimen including 4 courses of FEC (5-fluorouracil 600 mg/m$^2$, epirubicin 90 mg/m$^2$ and cyclophosphamide 600 mg/m$^2$, every 21 days), followed by 12 courses of 80 mg/m$^2$ paclitaxel once a week.

Before each cycle of NAC and through the end of the treatment, sizes of the primary tumor and of any palpable axillary node as well as their respective response to therapy were assessed by physical examination and ultrasound imaging. Before surgery, a final accurate ecographic evaluation of the axilla was performed while the primary tumor was also assessed by mammography and NMR, in addition to ultrasound imaging. At variance to the primary tumor, NMR was not used for the axilla because of its limited diagnostic significance (low sensitivity) on lymph nodes.

Clinical response to NAC was defined as complete if there was no evidence of palpable tumor in the breast and in axillary nodes. A reduction in tumor size (breast primary and/or axillary nodes) by ≥50% at the time of surgery was considered a clinical partial response. An increase in tumor size of >25% (compared with baseline measurements) or the appearance of new suspicious ipsilateral axillary adenopathy was considered a disease progression. Tumors that did not meet the criteria for objective response or progression were considered as stable disease. Surgical breast resection specimens were evaluated for pathological tumor response. Patients with no residual invasive cancer were considered to have a pathological complete response.

Patients received either breast-conservative surgery or mastectomy, and concomitant ALND. No adjuvant chemotherapy was given. All patients received post-surgery radiotherapy to the ipsilateral breast (50-Gy dose over 8 weeks). Patients with a HER2-overexpressing tumor also received trastuzumab (14 courses at 6 mg/kg every 21 days).

*SLN identification and definitive post-operative evaluation on paraffin sections*

The SLN was identified by lymphoscintigraphy. The day before surgery, a subdermal injection of 0.2 mCi of $^{99m}$Technetium (Nanocol, Amersham-Sorin Biomedica, Saluggia, Italy) was performed at the tumor site. At the time of surgery, a small axillary incision was performed, and the radioactive SLN was localized with a γ-ray detecting probe. The SLN was retrieved, bisected along its major axis, fixed in formalin and embedded in paraffin. In each half, 10 sections, 4-µm thick, were cut every 50 µm (first 5) and every 150 µm (next 5). All sections, but the second and the ninth, were stained with hematoxylin-eosin. If the histological evaluation resulted negative or ambiguous, the second and the ninth sections were tested by immunohistochemistry for the presence of cytokeratins (EPOS method with cytokeratin MNF116 monoclonal antibody and horseradish peroxidase, Dako).

*Statistical considerations*

The major parameters assessed were the rate of successful identification of the sentinel lymph node (SIR) and the rate of false-negative sentinel lymph node (FNR) which corresponds to the ratio between the number of patients with negative SLN but with metastases in other axillary non-sentinel node(s), and the total number of SLN true positive patients. Other parameters estimated were the negative predictive value (NPV), sensitivity, specificity and overall accuracy of SLNB.

## Results

*Study population*

Between August 2005 and April 2009, 64 consecutive eligible patients with locally advanced breast cancer were included. Table 1 summarizes the main patient and tumor characteristics in. Clinical staging in terms of tumor size and axillary status, and overall clinical TNM before NAC are further detailed in Table 2. Most patients had a tumor larger than 5 cm (T3, n=47) and metastases in movable ipsilateral axillary nodes (N1, n=54). Two patients staged N3 had not only axillary but also supraclavicular nodes involved. No patient presented distant metastases. Overall, the clinical stage at presentation was mostly stage III A (n=50, 78.1%).

*Response to neo-adjuvant chemotherapy and pathological definitive staging*

After NAC, 44 patients presented an overall clinical down-staging with respect to the baseline estimates, the ycTNM being stage 0 (n=17), I A (n=9) or II A (n=18) (Table 2).
Noteworthy, in light of the purpose of our study, NAC down-staged the axillary status in most patients who resulted ycN0 (n=40) or ycN1 (n=24). The ycN0 group included the 2 patients clinically diagnosed N3; these patients whose supraclavicular nodes resulted fully down-staged by NAC were thus eligible for SLNB.

In order to determine the pathological response to NAC, post-surgical histological examination and staging of the resected tumor and of the axillary nodes were compared to the baseline parameters (Table 3). Out of the 64 patients, 22 (34.4%) presented a complete pathological response at the level of the axilla, and 17 (26.6%) at the site of the primary tumor where no sign of infiltrating carcinoma was detected. Among those 17 patients, 3 had some residual carcinoma in situ. Most of the remaining patients presented partial response or stable disease at either site. One case of progression was observed at the site of the primary tumor.

*Identification of the sentinel lymph node and evaluation of the axilla status*

A total of 106 SLNs and of 932 non-sentinel lymph nodes (NSLN) were removed from the 64 patients, which corresponds to respective means of 1.7 SLN/patient (range 1 to 4) and 14.6 /patient (median 14, range 5 to 29).

Upon intra-operative scintigraphy, no radioactive SLN was revealed in 4 (6.3%) patients (Table 4). Among them, only 1 patient resulted pN0 at axillary definitive diagnosis while the 3 others had several axillary nodes involved (rang 2 to 9). Out of the remaining 60 patients, 23 (35.9%) had a negative SLN and 37 (53.9%) had a positive one. Among those positive cases, 34 presented macrometastases (foci > 2 mm) and 3 had only micrometastases (foci > 0.2 mm but ≤ 2 mm). When comparing the SLN status with the axillary nodes status, we observed that 2 patients with a negative SLN presented macrometastases in other NSLN (1 node in 1 case and 2 nodes in the other case), thus being false negative patients. In all 3 patients who presented only micrometastases in the SLN, the other axillary nodes were free of disease. Among the 34 patients with SLN macrometastases, 26 had additional metastatic NSLN and only 8 did not. Overall, 31 of the 64 patients had axillary burden in non-sentinel nodes; by contrast, disease, when present, was confined to the only sentinel lymph node in 11 out of the 60 patients whose SLN was identified.

*Accuracy of the SLNB procedure in the present settings as compared to early- stage breast cancer.*

Table 5 summarizes the results of the SLNB procedure here performed after NAC. These results are compared with those we previously obtained in a randomized study comparing SLNB with complete ALND in patients with early-stage breast cancer at diagnosis [11].

In the present settings, 2 patients had a negative SLN but a positive axilla, which results in a false-negative rate (FNR) of 5.1% (2 of 39). In 4 patients, the SLN was not detected at intra-operative scintigraphy, thus giving a successful identification rate (SIR) of 93.8% (60 of 64). Overall, the SLNB procedure had a negative predictive value (NPV) of 91.3% (21 of 23), a sensitivity of 88.1 % (37of 42), a specificity of 100% (by definition) and an overall accuracy of 96.7%. All these values were similar to those previously reported in our study on the assessment of

SLNB in the context of early-stage breast cancer [11]. In that context, FNR, SIR, specificity, NPV and overall accuracy were 5.8%, 98.7%, 100%, 91.1% and 93.0%, respectively. Only the sensitivity was somehow lower as compared to the present value (77.1% *vs* 88.1%).

## Discussion

*SLNB validation in the context of neo-adjuvant chemo-therapy: overview*

Safety and efficacy of lymphatic mapping and SLNB to stage the axilla are supported by at least four randomized clinical trials, including ours, involving early-stage breast cancer patients treated with adjuvant therapy [10, 11, 22, 23].

With the advent of pre-operative chemotherapy as initial management of operable but large breast tumors, the question arose whether SLNB could be safely applied to this subset of patients. The two main parameters to evaluate SLNB feasibility and accuracy in the context of NAC are the rate of successful SLN identification and the rate of false negative SLN. Regarding locally advanced breast cancer patients, these two criteria have been addressed mostly by small, single-institution studies that reported quite variable values ranging from 86.5%, to 98.0% for SIR and from 0% up to 25.0% for FNR [24-27]. This variability may be due to the limited number of patients evaluated and to their heterogeneity in terms of tumor size (T1-T4) and clinical node status (N0-N2) within and between studies.

*SLNB validation in the present study*

At variance with the above mentioned studies, the present patient population was somehow more homogeneous. Patients were to have a tumor of more than 2 cm (T >2) and clinically positive axillary nodes (N ≥1). Patients with large tumor but clinically negative axillary nodes were excluded because at our institution they currently receive SLNB before NAC. Indeed, as reviewed by Chung and Giuliano [28], the timing of SLNB with respect to NAC should be evaluated according to the clinical nodal status. Based on their findings, SLNB before NAC would be recommended for patients with clinically negative nodes. By contrast, patients with clinically positive nodes should undergo fine-needle biopsy to ascertain the true nodal status. Still, the management of those patients remains controversial as, quite possibly, the practice of SLNB before

NAC would lead at the time of surgery to a proportion of unnecessary axillary dissection since the down-staging effect of NAC would not have been evaluated. Nevertheless, as summarized by Sabel [29], neither approach, i.e SLNB before or after NAC, should be universally applied and the timing of SLNB in patients candidates for NAC should be discussed in a multidisciplinary setting taking into account, among others, the nodal status, systemic regimen and possible additional radiotherapy. The SIR and FNR values we here obtained were 93.8% and 5.1%, respectively. These values are quite similar to those reported by 2 other larger and/or multicentric prospective studies on operable breast cancer patients treated with NAC : results from the "National Surgical Adjuvant Breast and Bowel Project B-27" from 343 patients suitable for evaluation indicated SIR and FNR values of 84.8% and 10.7%, respectively [30]; likewise, in the French prospective study "Ganglion Sentinelle et Chimiothérapie Néoadjuvante" involving 195 patients from 12 institutions, SIR and FNR values were 90.0% and 11.5%, respectively [31]. Even though our estimates are based on a smaller number of patients, they were obtained from a somehow more homogeneous population of patients, which is feasible in a single-institution study.

The FNR here reported deserves some consideration based on the clinical response to neo-adjuvant therapy. Among the 2 false-negative patients, one had a complete clinical response at the axilla level while the other had a stable disease. The finding of false negative cases is most probably due to alterations of the lymphatic drainage that deviate the radioactive tracer towards node(s) free of disease. Several factors could alter the lymphatic drainage, e.g heavily fatty or metastatic nodes impeding normal lymph flux, tumor cells infiltrating lymphatic vessels and/or the use of NAC itself that provokes fibrosis, necrosis and granulation tissue formation, or could produce a non-homogeneous disease regression, being more effective in the SLN than in other nodes [17,18,19, 32]. In patients whose axilla remains clinically involved after NAC, it is thus advisable to perform an accurate and extensive clinical palpation of the axillary nodes during surgery in order to identify, remove and analyze any suspicious node, as recommended by International Guidelines

[1,33]. This recommendation would apply also for patients with early-stage breast cancer and clinically negative nodes.

*SLNB validation in the present study as compared with SLNB performed in early-breast cancer patients at our institution*

Another purpose of our study was to verify whether at our institution, the SLNB procedure is performed with comparable efficacy and accuracy in two different settings, i.e in the one hand, in early-stage breast cancer patients receiving adjuvant therapy [11] and, in the other hand, in locally advanced breast cancer patients receiving NAC (present data). Besides SIR and FNR, the other parameters assessed were SLNB sensitivity, specificity, negative predictive value and overall accuracy. As seen in Table 5, all values were quite similar between the two settings. Thus, although the present data derive from a limited number of patients, which we acknowledge as a possible weakness of our study, we believe that the comparative results with those obtained in our series of patients with early-breast cancer represent a valuable and reliable contribution to the validation of the SLNB procedure; indeed, in both settings of systemic therapy, the SLNB procedure was performed at the same institution by a single disease management team including the same surgeons, oncologists, radiologists, pathologists and radiotherapists. This demonstrates that the procedure is feasible, accurate and reliable in terms of negative predictive value of the axillary nodes, regardless of the clinical status of the patient and of the timing of chemotherapy delivery.

*Factors affecting SIR and FNR*

Several studies have attempted to correlate the findings of low SIR and/or high FNR values with some clinical parameters of the patients at presentation. Regarding the rate of false-negative SLN, no correlation was found with patient age, clinical nodal status, clinical tumor size or tumor location within the breast [27, 30, 31]. More contrasting results have been reported for the rate of successful SLN identification: lower SIR values have been observed in patients with N1-axillary

status versus N0-patients [31, 34] or in patients with a residual tumor > 2 cm after NAC [27]; Mamounas et al. [30], however, found no significant differences in SIR according to clinical tumor size, clinical nodal status or patient age. We here did not attempt to assess any similar correlation that, we believe, would not have been reliable due to the rather small size of the study and to the limited number of false-negative and unidentified sentinel nodes.

*Conclusions*

Intra-operative lymphatic mapping and SLNB are nowadays part of the standard management of patients with early-stage breast cancer and clinically negative axillary nodes. Based on the present results, we conclude that this procedure is feasible and is an accurate predictor of the axillary nodal status also when it is performed after NAC in patients with locally advanced breast cancer. However, before introducing SLNB as a routine procedure in the context of NAC, clinical trials will have to demonstrate that overall survival and disease-free survival do not worsen when ALND is not performed in the subset of post-NAC SLN-negative patients, thus leaving behind down-staged axillary nodes.

**Conflict of interest statement**

The authors have no conflict of interest to declare.

**References**

1. Lyman GH, Giuliano AE, Somerfield MR et al. American Society of Clinical Oncology Guideline Recommendations for Sentinel Lymph Node Biopsy in Early-Stage Breast Cancer. J Clin Oncol 2005; 23: 7703–20.

2. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg 1994; 220: 391–401.

3. Albertini JJ, Lyman GH, Cox C et al. Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. JAMA 1996; 276: 1818–22.

4. Krag D, Weaver D, Ashikaga T et al. The sentinel node in breast cancer - a multicenter validation study. N Engl J Med 1998; 339: 941–46.

5. Veronesi U, Paganelli G, Viale G et al. Sentinel lymph node biopsy and axillary dissection in breast cancer: results in a large series. J Natl Cancer Inst 1999; 91: 368–73.

6. Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a meta-analysis [review]. Cancer 2006; 106: 4–16.

7. Mansel RE, Fallowfield L, Kissin M et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. J Natl Cancer Inst 2006; 98: 599–609.

8. Veronesi U, Paganelli G, Viale G et al. Sentinel-lymph-node biopsy as a staging procedure in breast cancer: update of a randomised controlled study. Lancet Oncol 2006; 7: 983–90.

9. Cox C, White L, Allred N et al. Survival outcomes in node-negative breast cancer patients evaluated with complete axillary node dissection versus sentinel lymph node biopsy. Ann Surg Oncol 2006; 13: 708–11.

10. Zavagno G, De Salvo GL, Scalco G et al. A randomized clinical trial on sentinel lymph node biopsy versus axillary lymph node dissection in breast cancer: results of the Sentinella/GIVOM trial. Ann Surg 2008; 247: 207–13.

11. Canavese G, Catturich A, Vecchio C et al. Sentinel node biopsy compared with complete axillary dissection in staging early breast cancer with clinically negative lymph nodes : results of a randomized trial. Ann Oncol 2009; 20: 1001-7.

12. Bodonna G, Veronesi U, Brambilla C et al. Primary chemotherapy to avoid mastectomy in tumors with diameters of three centimeters or more. J Natl Cancer Inst 1990; 82: 1539 – 45.

13. Fisher B, Brown A, Mamounas E et al. Effect of preoperative chemotherapy on loco-regional disease in women with operable breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol 1997; 15: 2483 – 93.

14. Makris A, Powles TJ, Ashley SE et al. A reduction in the requirements for mastectomy in a randomized trial of neoadjuvant chemoendocrine therapy in primary breast cancer. Ann Oncol. 1998; 9: 1179-84.

15. Bear HD, Anderson S, Brown A et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide. Preliminary results from National Surgical Adjuvant Breast and Bowel Protocol B-27. J Clin Oncol 2003; 21: 4165-74.

16. Mamounas BP. Sentinel lymph node biopsy after neoadjuvant systemic therapy. Surg Clin North Am 2003; 83: 931-42.

17. Charfare H, Limongelli S, Purushotham AD. Neoadjuvant chemotherapy in breast cancer. Br J Surg 2005; 92: 14-23.

18. Mason KS, Anderson BO, Byrd DR et al. Increased false negative sentinel node biopsy rates after preoperative chemotherapy for invasive breast carcinoma. Cancer 2000: 89: 2187-94..

19. Pecha V, Kolarik D, Kozevnikova R et al. Sentinel lymph node biopsy in breast cancer patients treated with neoadjuvant chemotherapy. Cancer 2011; doi: 10.1002/cncr.26102. [Epub ahead of print]

20. Cohen LF, Breslin TM, Kuerer HM, Ross MI, Hunt KK, Sahin AA.. Identification and evaluation of axillary sentinel lymph nodes in patients with breast carcinoma treated with neoadjuvant chemotherapy. Am J Surg Pathol 2000; 24: 1266–72.

21. Land SR, Kopec JA, Julian TB et al. Patient-Reported Outcomes in Sentinel Node–Negative Adjuvant Breast Cancer Patients Receiving Sentinel-Node Biopsy or Axillary Dissection: National Surgical Adjuvant Breast and Bowel Project Phase III Protocol B-32. J Clin Oncol 2010; 28: 3929-36.

22. Veronesi U, Paganelli G, Viale G et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med 2003; 349: 546-53.

23. Krag DN, Anderson SJ, Julian TB et al. Technical outcomes of sentinel-lymph node resection and conventional axillary-lymph-node dissection in patients with clinically node-negativebreast cancer: results from the NSABP B-32 randomised phase III trial. Lancet Oncol 2007; 8: 881–8.

24. Patel NA, Piper G, Patel JA, Malay MB, Julian TB. Accurate axillary nodal staging can be achieved after neoadjuvant therapy for locally advanced breast cancer. Am Surg 2004; 70:696-9.

25. Shen J, Gilcrease MZ, Babiera GV et al. Feasibility and accuracy of sentinel lymph node biopsy after preoperative chemotherapy in breast cancer patients with documented axillary metastases. Cancer 2007; 109: 1255-63.

26. Newman EA, Sabel SS, Nees AV et al. Sentinel lymph node biopsy performed after neoadjuvant chemotherapy is accurate in patients with documented node-positive breast cancer at presentation. Ann Surg Oncol 2007; 14: 2946-52.

27. Ozmen V, Unal ES, Muslumanoglu ME et al. Axillary sentinel node biopsy after neoadjuvant chemotherapy. Eur J Surg Oncol 2010; 36: 23-9.

28. Chung A, Giuliano A. Axillary staging in the neoadjuvant setting. Ann Surg Oncol 2010; 17: 2401-10.

29. Sabel MS. Sentinel lymph node biopsy before or after neoadjuvant chemotherapy: pros and cons. Surg Oncol Clin N Am 2010; 19: 519-38.

30. Mamounas EP, Brown A, Anderson S et al. Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol. 2005; 23: 2694-702.

31. Classe JM, Bordes V, Campion L et al. Sentinel lymph node biopsy after neoadjuvant chemotherapy for advanced breast cancer: results of ganglion sentinelle et chimiothérapie neoadjvante, a French prospective multicentric study. J Clin Oncol 2009; 27: 726-32.

32. Krag DN, Weaver D, Ashikaga T et al. The sentinel node in breast cancer – a multicenter validation study. N Engl J med 1998; 339: 941-46.

33. Schwartz GF, Giuliano AE, Veronesi U, and the Consensus Conference Group Proceedings of the Consensus Conference on the Role of Sentinel Lymph Node Biopsy in Carcinoma of the Breast. Breast J 2002, 8: 126-38.

34. Jones JL, Zabicki K, Christian RL et al. A comparison of sentinel node biopsy before and after neoadjuvant chemotherapy : timing is important. Am J Surg 2005; 190:517-20.

**Table 1. Patient characteristics at presentation**

| Characteristics | *n* | % |
|---|---|---|
| Age | | |
| Mean 50.5 ± 10.9 | 64 | 100 |
| Median 48.0 (31.8 – 71.5) | | |
| Age category | | |
| ≤ 45y | 21 | 32.8 |
| 46 – 55y | 23 | 35.9 |
| > 55y | 20 | 31.3 |
| Tumor histology | | |
| ductal | 53 | 82.8 |
| lobular | 8 | 12.5 |
| other | 3 | 4.7 |
| Quadrant | | |
| outer | 24 | 37.5 |
| inner or center | 16 | 25.0 |
| > 1 quadrant | 24 | 37.5 |
| Grading | | |
| G1 | 11 | 17.2 |
| G2 | 39 | 60.9 |
| G3 | 14 | 21.9 |
| Hormonal status | | |
| ER+/PgR+ | 30 | 46.9 |
| ER+/PgR- | 18 | 28.1 |
| ER-/PgR- | 14 | 21.9 |
| missing | 2 | 3.1 |
| Ki67 activity | | |
| low (≤ 15%) | 24 | 37.5 |
| intermediate (16 – 30%) | 8 | 12.5 |
| high (> 30%) | 28 | 43.8 |
| missing | 4 | 6.3 |
| c-erb-2 | | |
| negative | 47 | 73.4 |
| 1+ | 2 | 3.1 |
| 2+ | 2 | 3.1 |
| 3+ | 10 | 15.6 |
| missing | 3 | 4.7 |

**Table 2. Patient clinical and pathological staging**

| | *n* | % | *n* | % | *n* | % |
|---|---|---|---|---|---|---|
| ***Tumor size*** | **T** | | **ycT** | | **pT** [#] | |
| T0 | - | | 18 | 28.1 | 14 | 21.9 |
| Tis | - | | - | | 3 | 4.7 |
| T1a | - | | 2 | 3.1 | 3 | 4.7 |
| T1b | - | | 2 | 3.1 | - | |
| T1c | - | | 11 | 17.2 | 17 | 26.6 |
| T2 | 15 | 23.4 | 20 | 31.3 | 14 | 21.9 |
| T3 | 47 | 73.4 | 10 | 15.6 | 11 | 17.2 |
| T4b | 2 | 3.1 | 1 | 1.6 | 2 | 3.1 |
| ***Axilla status*** | **N**[§] | | **ycN** | | **pN** [¶] | |
| N0 | - | | 40 | 62.5 | 22 | 34.4 |
| N1 | 54 | 84.4 | 24 | 37.5 | 23 | 35.9 |
| N2 | 8 | 12.5 | - | | 11 | 17.2 |
| N3 | 2 | 3.1 | - | | 8 | 12.5 |
| ***Overall TNM*** | **cTNM**[*] | | **ycTNM**[*] | | **pTNM**[*] | |
| 0 | - | | 17 | 26.6 | 14 | 21.9 |
| I A | - | | 9 | 14.1 | 6 | 9.4 |
| I B | - | | - | | 2 | 3.1 |
| II A | - | | 18 | 28.1 | 12 | 18.8 |
| II B | 10 | 15.6 | 11 | 17.2 | 5 | 7.8 |
| III A | 50 | 78.1 | 8 | 12.5 | 15 | 23.4 |
| III B | 2 | 3.1 | 1 | 1.6 | 2 | 3.1 |
| III C | 2 | 3.1 | - | | 8 | 12.5 |

[#] pT categories correspond to T categories.

[§] The 2 patients clinically staged N3 had evidence of metastases both in supraclavicular and axillary lymph nodes. These 2 patients resulting ycN0 after NAC thus remained eligible for SLNB.

[¶] pN categories are pN0, pN1 (including pN1mi (n=3) and pN1a(n=20)), pN2a and pN3a.

[*] cTNM, clinical at presentation; ycTNM, clinical after NAC; pTNM, pathological at definitive diagnosis.

**Table 3. Pathological response to neo-adjuvant chemotherapy at tumor and axilla sites**

| | | Response at tumor site | | | | Total |
|---|---|---|---|---|---|---|
| | | *Complete* | *Partial* | *Stable* | *Progression* | ***n*** **(%)** |
| **Response at axilla level** | *Complete* | 14 | 8 | - | - | 22[#] (34.4) |
| | *Partial* | 1 | 5 | 4 | 1 | 11 (17.2) |
| | *Stable* | 2 | 18 | 11 | - | 31 (48.4) |
| **Total** ***n*** **(%)** | | 17 (26.6) | 31 (48.4) | 15 (23.4) | 1 (1.6) | 64 (100) |

[#] At final diagnosis, 22 patients were pN0. These patients who were clinically N1-N2 had a complete pathological response to NAC; at histological examination, the nodes presented not only fibrosis but also tumor cell shadows and areas of cellular necrosis, possibly corresponding to post-NAC residue from previous metastatic tissue. Node reactive alterations such as follicular hyperplasia and sinus histiocytosis can also be observed although they are not necessarily a direct consequence of NAC.

**Table 4. Status of sentinel and axillary lymph nodes**

| **Results of evaluation at definitive diagnosis** | **Sentinel nodes** | | **Non-sentinel nodes** | | |
|---|---|---|---|---|---|
| | *n* | % | *metastasis* | *n* | % |
| Not visualized [§] | 4 | 6.3 | no | 1 | 25.0 |
| | | | macrometastasis | 3 | 75.0 |
| Micrometastasis | 3 | 4.7 | no | 3 | 100 |
| Macrometastasis | 34 | 53.1 | no | 8 | 23.5 |
| | | | macrometastasis | 26 | 76.5 |
| Negative | 23 | 35.9 | no | 21 | 91.3 |
| | | | macrometastasis | 2[¶] | 8.7 |

[§] In 4 patients, the SLN was not identified and was thus not staged

[¶] False negative patients = patients with SLN negative at definitive evaluation on paraffin sections, but with metastasis in other axillary nodes.

**Table 5. Accuracy of SLNB procedure in the settings of locally advanced breast cancer as compared to early-stage breast cancer.**

| Test | FNR[¶] | SIR[§] | Sensitivity | Specificity | NPV[#] | Accuracy |
|---|---|---|---|---|---|---|
| Locally advanced | 5.1% | 93.8% | 88.1% | 100% | 91.3% | 96.7% |
| Early stage[*] | 5.8% | 98.7% | 77.1% | 100% | 91.1% | 93.0% |

[¶] FNR : false negative rate

[§] SIR : successful identification rate

[#] NPV : negative predictive value

[*]The values indicated for SLNB in the context of early-stage breast cancer derive from our previous randomized clinical trial comparing SLNB with conventional axillary dissection (reference 11).