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## Original Research Article

# The influence of the extended indications for sentinel node biopsy on the identification of metastasis-free and metastatic sentinel nodes

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### ABSTRACT

**Background and objective:** Rates of sentinel node (SN) identification and metastasis-positive SNs were compared between the group with highly selective indications for sentinel node biopsy (SNB) and the group with merely no contraindications for SNB (Groups A and B, respectively).

**Materials and methods:** We performed a single-center retrospective data analysis of 471 breast cancer patients treated during 2004–2010. Data on clinical and pathologic staging, frozen section results, radiological measurements and pathologic examination results were obtained from patient records. Patients were analyzed in two groups. Group A ( $n = 143$ ) had SNB performed only when the patients fulfilled to the following criteria: breast tumor no greater than 3 cm in diameter, unifocal disease, no pure ductal carcinoma in situ, no history of previous breast or lymph node surgery, and no neoadjuvant chemotherapy. Indications for SNB were extended in Group B ( $n = 328$ ) so that inflammatory breast cancer and positive lymph nodes became the only exclusion criteria.

**Results:** The rate of SN identification was 97.9% in Group A vs. 99.09% in Group B ( $P = 0.29$ ). SNs were metastasis positive and frozen sections false negative at comparable proportions in both groups.

**Conclusions:** The extension of indications for SNB did not reduce the rates of SN identification or did not create any impact on the rate of metastatic SNs.

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## 1. Introduction

Sentinel node biopsy (SNB) has become a standard method to determine the metastatic involvement of regional lymph node basin in breast cancer. At the onset of SNB adoption, the indications for the procedure were strict. The American Society of Clinical Oncology (ASCO) published the recommendations for SNB in 2005 [1] where it was stated that SNB should not be employed in case of T<sub>3</sub> or T<sub>4</sub> tumors, inflammatory breast cancer, ductal carcinoma in situ (DCIS) without mastectomy, nodes suspicious for metastasis, pregnancy, prior axillary surgery, previous nononcologic breast surgery, and after preoperative systemic therapy. The ASCO guidelines supported the use of SNB for multicentric tumors, DCIS when mastectomy or immediate reconstruction is planned, for older or obese patients, in male breast cancer, previous excisional or diagnostic biopsy, and before preoperative systemic therapy [1].

Currently, indications for SNB are widely discussed in the literature. The overall fraction of patients who cannot benefit from SNB is very small. Cheng et al. [2] have suggested that this proportion should be limited to patients with histologically confirmed positive axillary or extra-axillary lymph nodes and patients with inflammatory breast cancer. Similarly, SNB can be omitted if information on SNs does not affect treatment decisions, e.g. patients with low-grade DCIS [2] in whom resection is surely curable.

The aim of the study was to evaluate the influence of the extended indications for SNB on the rates of SN identification and metastasis-positive SNs.

## 2. Materials and methods

Data on 471 patients treated for breast cancer in 2004–2010 in a single institution (Clinic of Surgery, Hospital of Lithuanian University of Health Sciences Kauno Klinikos) were analyzed retrospectively. Patient records were reviewed to obtain information on clinical and pathologic staging, frozen section results, radiological measurements and histopathologic examination results. The patients were divided in two groups:

- The first cohort of patients ( $N = 143$ ) had SNB performed only when they fulfilled to the following criteria: breast tumor no greater than 3 cm in diameter, unifocal disease, no pure DCIS, no history of previous breast or lymph node surgery, and no neoadjuvant chemotherapy (Group A, highly selective indications).
- Indications for SNB were extended in the second cohort of patients ( $N = 328$ ) so that inflammatory breast cancer and positive lymph nodes (verified by ultrasound or biopsy) became the only exclusion criteria (Group B, extended indications).

SNs were marked with 99 m technetium-labeled colloid and identified employing the lymphoscintigraphy technique. Radioisotope injection was applied 24 h before surgery.

The study was approved by the Local Bioethics Committee (no. of approval 125/2004).

Data analysis was performed with Statistica 8.0, using the Student *t* and Pearson chi-square tests. Confidence level of  $P < 0.05$  was considered statistically significant.

## 3. Results

The groups were matched for age or clinical tumor staging. The mean age of the patients in Group A and Group B was 58.66 years (SD 11.04; range 34–83), and 57.1 years (11.6; 28–88), respectively ( $P = 0.17$ ). In Group A, 67.83% of the patients had no clinically detectable lymph nodes compared with 68.6% of the patients in Group B ( $P = 0.87$ ). No patients had distant metastases in either group.

Tumor size was smaller in Group A in comparison to Group B based on mammography (16.8 mm vs. 20.25 mm;  $P = 0.005$ ) and ultrasound (12.98 mm vs. 16 mm;  $P = 0.048$ ). Pathologic tumor size was 14.42 mm (SD 6.13; 1–37) and 15.86 (8.34; 1–60) in Group A and Group B, respectively ( $P = 0.08$ ).

Among the patients of Group B, 1 patient was male, 4 patients with locally advanced tumor (T<sub>3–4</sub>), and 2 patients after previous breast surgery. There were also 4 patients after neoadjuvant chemotherapy in Group B: 2 were downstaged after neoadjuvant treatment (one case T<sub>4</sub> → T<sub>2</sub>, another T<sub>2</sub> → T<sub>1</sub>). No such cases were included in Group A.

Carcinoma in situ (pT<sub>is</sub>) was found in 4.31% of the cases in Group B; invasive tumors less than 2 cm in size (pT<sub>1</sub>) occurred in 83.69% cases in Group A vs. 73.23% cases in Group B. Tumors measuring 2 to 5 cm in size (pT<sub>2</sub>) were diagnosed in 16.31% of the cases in Group A vs. 21.85% of the cases in Group B; gross tumors exceeding 5 cm (pT<sub>3–4</sub>) were observed in 2 patients (0.62%) in Group B ( $P = 0.02$ ).

The two groups were comparable by most tumor pathologic characteristics (Table 1). The patients did not differ by the histological type of carcinoma, lymph vessel invasion, and vascular invasion. However, the prevalence of better differentiated tumors (G<sub>1</sub> and G<sub>2</sub>) was significantly greater in Group A than Group B ( $P = 0.007$ ).

The density of progesterone receptors and the degree of expression of Her2/neu gene was similar in both groups, but the density of estrogen receptors differed between the groups. ER-negative tumor accounted for 50.37% of all cases in Group A and only 27.8% of cases in Group B ( $P < 0.00001$ ).

The rate of SN identification was 97.9% in Group A compared to 99.09% in Group B ( $P = 0.29$ ) (Table 2). The mean number of harvested SNs was greater in Group A than Group B (2.21 vs. 1.95,  $P = 0.02$ ).

The rates of metastatic SNs and accuracy of frozen section did not differ. SNs were found to be metastasis-free in 76.43% and 76.31% of the cases in Groups A and B, respectively. Occurrence of macrometastases in SNs was observed in 20.71% of the cases in Group A and in 21.85% of the cases in Group B. Occurrence of micrometastases was observed in 2.14% and 1.54% of the cases in Groups A and B, respectively. There was one case in both groups (0.71% in Group A and 0.31% in Group B, respectively), when SNs were macroscopically metastatic and frozen sections were omitted ( $P = 0.89$ ).

Intraoperative diagnoses from frozen sections were correct in 94.2% of the cases in Group A and in 92.88% of the cases in Group B; intraoperative false negative results were obtained in

**Table 1 – Pathologic tumor characteristics of Groups A and B.**

Variable	Total	Group A	Group B	P
<b>Histological type</b>				
Ductal	375 (81.34)	113 (81.88)	262 (81.11)	0.92
Lobular	49 (10.63)	15 (10.87)	34 (10.53)	
Other	37 (8.03)	10 (7.25)	27 (8.36)	
<b>Lymph vessels invasion</b>				
L <sub>0</sub>	213 (49.31)	71 (55.47)	142 (46.71)	0.1
L <sub>1</sub>	219 (50.69)	57 (44.53)	162 (53.29)	
<b>Vascular invasion</b>				
V <sub>0</sub>	313 (73.3)	91 (71.65)	222 (74)	0.62
V <sub>1</sub>	114 (26.7)	36 (28.35)	78 (26)	
<b>Grading</b>				
G <sub>1</sub>	67 (15.47)	27 (21.09)	40 (13.11)	0.007
G <sub>2</sub>	252 (58.2)	79 (61.72)	173 (56.72)	
G <sub>3</sub>	114 (26.33)	22 (17.19)	92 (30.16)	
<b>Estrogen receptors</b>				
Negative	141 (33.65)	56 (51.38)	85 (27.42)	0.00001
Positive	278 (66.35)	53 (48.62)	225 (72.58)	
<b>Progesterone receptors</b>				
Negative	210 (50.12)	51 (46.79)	159 (51.29)	0.42
Positive	209 (49.88)	58 (53.21)	151 (48.71)	
<b>Her2/neu</b>				
Not expressed	365 (89.68)	90 (87.38)	275 (90.46)	0.37
Expressed	42 (10.32)	13 (12.62)	29 (9.54)	

8 cases (5.8%) in Group A and 22 cases (6.81%) in Group B. There was one case of false positive diagnosis in Group B (0.31%) ( $P = 0.74$ ).

We further analyzed the cases with false negative frozen sections. Micrometastases (<2 mm) in SNs were found in 7 cases (5.07%) in Group A, and 17 false negative cases (5.28%) in Group B ( $P = 0.77$ ).

In 110 cases, SNB was positive; therefore, completion axillary lymph node dissection (ALND) was performed, removing at least 10 axillary nodes. Comparing definitive pathologic staging, no difference was found between Groups A and B. More than half (66.2%) of cases in Group A and 68.81% of cases in Group B had negative intraoperative frozen sections; therefore, no ALND was performed, and pN<sub>0</sub> was established as their pathologic stage (unless metastasis was found in the

definitive pathologic report). Micrometastases were identified in 7.04% and 7.03% of the cases; macrometastases, in 26.76% and 24.16% in Groups A and B, respectively ( $P = 0.83$ ) (Table 3). A total amount of positive lymph nodes removed during ALND was 3.5 in Group A vs. 2.89 in Group B ( $P = 0.36$ ).

#### 4. Discussion

There was no difference in SN identification rates, metastatic SN rates and SNB accuracy between the groups. Therefore, we can conclude that the extended indications for SNB did not render inferior results as compared to highly selective indications in our study. However, a wide diversity of opinions about the role of SNB in special circumstances can be found in literature.

##### 4.1. Locally advanced breast cancer and neoadjuvant chemotherapy

According to ASCO guideline recommendations [1], published in 2005, SNB is not recommended for locally advanced breast cancer, i.e. T<sub>3</sub> and T<sub>4</sub>, but with insufficient level of evidence. Currently many authors employ SNB in the management of breast cancer larger than 5 cm in diameter, but with certain limitations. The majority of these patients receive neoadjuvant chemotherapy (NAC) as initial treatment, and, in such patients, it is critical to accurately delineate the initial extent of disease because the initial clinical stage affects subsequent local-regional treatment decisions [3]. The crucial question is the timing of SNB related to NAC. At many centers, SNB is performed before the initiation of NAC [1,3-5]. A hypothesis substantiating this approach maintains that all involved axillary lymph nodes may not respond to chemotherapy in an identical manner [6]. Thus, an axillary lymph node with a metastatic deposit at the time of the original breast cancer diagnosis may be treated with chemotherapy and rendered pathologically free of disease. If that same axillary lymph node was designated as SN, SNB would show no evidence of tumor. However that SN may not be representative of the entire axillary region because higher echelon axillary lymph nodes may not have responded to NAC as well as the SN and still contain metastatic deposits. Another explanation exists that

**Table 2 – Sentinel node identification rates and metastatic sentinel node rates in Groups A and B.**

Variable	Total	Group A	Group B	P
SN identification rate	465 (98.73)	140 (97.9)	325 (99.09)	0.29
Number of harvested SNs, mean (SD) [range]	2.03 (1.08) [1-7]	2.21 (1.18) [1-7]	1.95 (1.02) [1-7]	0.02
<b>Frozen section answer</b>				
SN metastases-free	355 (75.37)	107 (76.43)	248 (76.31)	0.89
Macromts in SN	100 (21.23)	29 (20.71)	71 (21.85)	
Micromts in SN	8 (1.7)	3 (2.14)	5 (1.54)	
Macroscopic mts <sup>a</sup>	2 (0.42)	1 (0.71)	1 (0.31)	
<b>Frozen section accuracy</b>				
Correct	430 (91.3)	130 (94.2)	300 (92.88)	0.74
False negative	30 (6.37)	8 (5.8)	22 (6.81)	
False positive	1 (0.21)	0 (0)	1 (0.30)	

Values are number (percentage) unless otherwise indicated.

<sup>a</sup> Macroscopically obvious metastatic SN, therefore frozen section not performed.

**Table 3 – Definitive pathologic staging.**

pN value	Total	Group A	Group B	P
pN <sub>0</sub>	319 (67.73)	94 (66.2)	225 (68.81)	0.83
pN <sub>mic</sub>	33 (7.01)	10 (7.04)	23 (7.03)	
pN <sub>mac</sub>	117 (24.84)	38 (26.76)	79 (24.16)	

Values are number (percentage).

chemotherapy induces fibrosis of lymphatics while eradicating the tumor, thus impeding the flow of mapping agents to the SNs and rendering SNs no longer representative of the entire nodal basin [7].

On the other hand, NAC is used to downstage tumor size to convert inoperable locally advanced breast cancer to surgical candidates and to allow for breast conservation surgery. It also causes regression of axillary lymph nodes, with some studies reporting up to 40% demonstrating complete pathologic response in the axilla [8]. SNB performed after NAC may potentially identify this group of patients and reduce their surgical morbidity if they then avoid the standard ALND [7].

SNB performed after NAC has a success rate ranging from 85% to 94.3% and false negative rates (FNR) ranging from 5.6% to 14% [4,7,9,10]. These values are comparable to those accepted for use of SNB in early stage breast cancer where identification rates of 88%–97% and FNR of 5%–12% are reported [11,12].

The largest cohort to date, the NSAPB B-27 multicentre randomized trial (N = 428), evaluating the sequencing of chemotherapy, reported an identification rate and FNR of 85% and 11%, respectively [13].

They concluded that these rates are comparable to those obtained from multicenter studies evaluating SN biopsy following breast cancer diagnosis and suggest that this procedure is feasible following NAC, which is consistent with the results of a meta-analysis by Xing et al. [14].

Advantage of SNB after NAC is that it only requires one operation. One of the disadvantages is the unknown effect of no ALND in patients whose nodes were downstaged by NAC. There are no published randomized studies on this subject [4].

#### 4.2. Inflammatory breast cancer

Inflammatory breast cancer is a contraindication for SNB which all authors agree upon [1,15,16]. There are insufficient data on women with inflammatory breast cancer to recommend the use of SNB in this situation. Because the subdermal lymphatics are partially obstructed, contain tumor emboli, and are functionally abnormal, the FNR of SNB for this population may be unacceptably high [17]. A small study of 20 consecutive patients with clinically negative nodes after NAC for inflammatory breast cancer provided an identification rate of 80% and FNR of 18% which were treated as unacceptably high [18].

#### 4.3. Multiple synchronous breast cancer

Multiple synchronous breast cancer can be divided to multifocal breast cancer (two or more malignant lesions in

a single quadrant) or multicentric breast cancer (two or more lesions involving at least two quadrants). In practice the two categories are often difficult to distinguish; their definitions vary in literature therefore many authors class them together as “multiple” breast cancer cases [19,20]. Multicentricity used to be a contraindication for SNB in the past. However subdermal, intradermal and subareolar routes of injection are associated with greater success and a comparable FNR to that associated with the regular peritumoral route. If indeed the same SN is “sentinel” for the entire breast, then this SN or SNs can be identified in cases of multicentric breast cancer by subareolar or intradermal injection [21,22]. ASCO supports the use of SNB in multicentric tumors [1]. Among the studies analyzing multifocal tumors, 2 of the 6 case series had FNR over 21% [19,20]. These results pose doubt over the applicability of SNB for multiple breast cancer cases [19].

#### 4.4. Ductal carcinoma in situ

A significant number of patients who are initially diagnosed with pure DCIS will harbor missed or occult invasive disease at their definitive surgery. To provide more accurate staging information and to avoid a second operation, some investigators believe that SN mapping should be performed in DCIS patients. SNB revealed metastatic disease to the regional lymph nodes in up to 13% of 195 DCIS patients in one study. In addition, 10% of 224 DCIS patients were upstaged to infiltrating ductal carcinoma at their definitive therapy [6]. There is concordance in literature that a selective approach to SNB in DCIS is the most appropriate, based on the presence of a palpable tumor; when a mastectomy is indicated or immediate reconstruction is planned [1,15].

#### 4.5. Male breast cancer

Large studies establishing the sensitivity and specificity of SNB in male breast cancer have not been performed. However, several case series have been published that have established the feasibility of SNLB in the male patient with breast cancer. The success rates of SNB in male breast cancer are comparable to those in female breast cancer [23,24]. There is a lack of the data on FNR in male breast cancer [24–26]. However follow up information is given by some authors. All patients from three studies were free of any local or regional recurrence at the end of their follow up [27–29]. Recent reviews of male breast cancer encourage the application of SNB in this group of patients [1,23,24,30].

## 5. Conclusions

The extension of indications for SNB did not reduce the rates of SN identification or did not have any impact on the rate of metastatic SNs.

## Conflict of interest

The authors state no conflict of interest.

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