

Avoiding Axillary Treatment in Sentinel Lymph Node Micrometastases of Breast Cancer: A Prospective Analysis of Axillary or Distant Recurrence

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ABSTRACT

Background. The need for axillary lymph node dissection (ALND) in breast cancer patients with sentinel lymph node (SLN) micrometastases remains controversial. The aims of the study were to evaluate the locoregional failure and outcome of breast cancer patients with sentinel node micrometastases who did not undergo completion ALND.

Methods. Between November 2000 and December 2006, SLN biopsy was successfully performed in 1178 patients with invasive breast carcinoma. Only patients with macrometastasis (>2 mm) underwent ALND, while patients with negative SLN or micrometastases did not undergo further treatment of the axilla, by either surgery or radiotherapy. Regarding adjuvant therapy decision, patients with SLN-micrometastases (pN1_{mi}) were considered as node-positive patients.

Results. Of 1,178 patients, 59 (5%) had micrometastases. Of those with micrometastases, 14 (24%) underwent ALND because the intraoperative study of the SLN yielded a positive result. With a median follow-up of 60 (range, 8–94) months, none of the patients with SLN micrometastases in whom ALND was omitted developed an axillary

recurrence, while one patient in whom ALND was performed developed infraclavicular lymph node recurrence. One patient, who declined postoperative breast irradiation, developed breast recurrence and distant metastasis.

Conclusions. Breast cancer patients with SLN micrometastases in whom ALND was omitted had a very low locoregional failure rate. This study supports the theory that ALND might be avoided in these patients, providing that adjuvant systemic treatment equal to treatment provided to treat node-positive disease is administered. However, longer follow-up and results of additional prospective studies are needed.

As sentinel lymph node (SLN) biopsy (SLNB) has become a widely accepted alternative to axillary lymph node dissection (ALND) and SLNs are examined more meticulously by applying step sectioning and immunohistochemical staining, identification rates of micrometastases (>.2 mm to <2 mm) and isolated tumor cells have increased. Despite the absence of level 1 guidance, the more extended procedure when micrometastases are found in the SLN is completion of ALND because of the risk of additional non-SLN metastases. However, the prognostic significance of SLN micrometastases and its management implications, such as the need for further axillary treatment and adjuvant systemic treatment, remain a matter of debate.

In approximately 60% of patients, the positive SLN is the only site of regional metastases. In case of

micrometastases, the percentage of patients who do not have disease in other non-SLN increases from 85 to 90%.¹ Therefore, the role of ALND with its associated morbidity such as lymphedema, pain, shoulder dysfunction, and neuropathy in these patients remains controversial.

The purpose of the present study was to analyze the long-term evolution of patients with SLN micrometastases in whom no further axillary treatment was performed. We present the results of our prospective study, focusing on axillary recurrence rate and distant metastases, with 5-year follow-up.

PATIENTS AND METHODS

Between November 2000 and December 2006, SLN was successfully performed in 1,178 consecutive patients with invasive early-stage breast cancer (identification rate of 95.6%). Patients were offered SLN if they met the following criteria: (1) they had histological proven invasive breast carcinoma, (2) they were node negative after clinical exploration and ultrasound scan, and (3) tumor size was clinically <3 cm in diameter, and tumor had favorable characteristics. Written informed consent was obtained from all patients. Patients with SLN macrometastases underwent ALND, whereas patients with SLN micrometastases, isolated tumor cells, or tumor-free SLN did not undergo further axillary treatment, following our institution's protocols.

All consecutive breast cancer patients with a SLN that contained micrometastases were prospectively included in this study. Primary tumor size, histological subtype, presence of vascular invasion, Ki67, estrogen receptor, progesterone receptor, and HER2 status were determined. Data concerning adjuvant treatment were also recorded.

SLN Mapping

SLN mapping was performed by a radiolabeled colloid. A total of 55 MBq of ^{99m}Tc albumin-nanocolloid was injected peritumorally in palpable lesions, and in nonpalpable lesions, 37 MBq was injected guided by ultrasound or mammography. Lymphoscintigraphy was performed before surgery in all patients and in case of palpable lesions the day before surgery. Hot spots were marked on the skin. From December 2004, in patients in whom lymphoscintigraphy was negative, subdermal reinjection was performed above the tumor site because it has been proven that this procedure increases the SLN detection rate without increasing the false-negative rate.² Surgical dissection of the SLN was guided by a handheld gamma probe (Europrobe, Eurorad S.A., France). All nodes with a count rate of >10% of the maximal activity were excised and

labeled separately as SLNs. Dissection was continued until the background count of the axilla was <10% of the hottest SLN.

Pathologic Examination

Sentinel nodes were bisected if they measured <.5 cm in their greatest dimension and were serially sectioned at 2-mm intervals along the short axis if they measured >.5 cm. Touch imprints were made of both surfaces of the lymph node sections, and they were then stained with Diff-Quick. Final pathologic evaluation was performed on formalin-fixed, paraffin-embedded tissue sections of the lymph node. Hematoxylin and eosin staining of the first, third, and fifth sections were performed, as was cytokeratin (CAM5.2) immunostaining of the second and fourth level (Fig. 1).

Micrometastases were defined as tumor involvement of >.2 mm and ≤2 mm in diameter according to the American Joint Committee on Cancer classification.³ Tumor involvement of <.2 mm was classified as isolated tumor cells and therefore considered to be negative SLN.

Primary tumor size, histological type, tumor grade, and the presence of vascular or lymphatic invasion were determined. Estrogen receptor, progesterone receptor, HER2 status, and Ki67 were also recorded.

Adjuvant Therapy and Follow-Up

Regarding adjuvant systemic therapy, patients with micrometastases were considered to be node positive. Therefore, all of them received chemotherapy, hormone therapy (tamoxifen or aromatase inhibitors), or both. Chemotherapy regimens were based on anthracyclines, and since 2004, taxanes were also included.

Patients underwent radiotherapy after breast-conserving surgery. Patients were scanned by computed tomography (scan thickness and index of 5 to 10 mm), and data for all

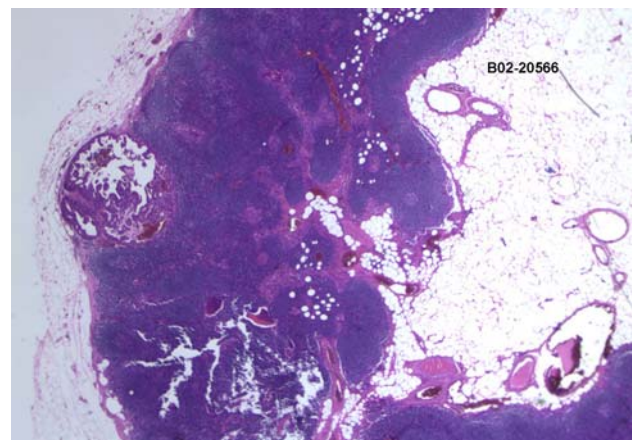


FIG. 1 Sentinel lymph node micrometastasis

patients were transferred to the 3D treatment planning system. The characteristics of the fields were defined on the treatment planning system (Cadplan; Varian). Radiotherapy consisted of 50 Gy in 5 weeks to the breast by means of a 2-Gy-per-fraction protocol. A 10- to 20-Gy boost was added to the tumor bed in high-risk patients, with electrons or brachytherapy. No radiation was provided specifically to the axilla, and there were no differences in radiotherapy patterns for the completion ALND group compared to the no-ALND group. Therefore, according to previously published data, standard tangential breast radiation fields failed to deliver an adequate therapeutic dose to the axillary level I–II lymph node region.

The follow-up procedures were clinical examination every 6 months and annual mammography. Ultrasound of the breast was performed in cases of suspicious mammographic findings.

Statistical Analyses

Summary tables of absolute and relative frequencies were used for descriptive analysis of categorical variables, with 95% confidence intervals obtained in those variables where necessary. Central value, average or median, and their rank or 95% confidence intervals were applied for continuous variables.

RESULTS

SLNB was successfully performed in 1,178 patients with invasive breast carcinoma between November 2000 and December 2006. Of these 1,178 patients, 59 (5%) had micrometastases. These patients were prospectively included in this study. The characteristics of these patients are listed in Table 1. Median age was 54 (range, 32–83) years. All patients underwent breast-conserving surgery. Tumor characteristics are summarized in Table 2. Median tumor size was 15 mm. The most common histological subtype was invasive ductal carcinoma (86.4%), and seven patients had invasive lobular carcinoma. Hormone receptors were positive in 86.3% of tumors. Lymphatic or vascular invasion was present in 15.3% of patients, and Her2/neu was overexpressed or amplified in 15.2% of cases.

For SLN characteristics, the median number of SLN removed was 1, with a median of 1 positive SLN identified

per patient (Table 3). Multiple foci of micrometastases within a single SLN were observed in 2 patients.

ALND was performed in 14 cases because the intraoperative study of the SLN yielded a positive result. Out of these 14 patients, only in one case were additional metastases found in non-SLN, resulting in an upstaging to pN1a (the non-SLN metastases size was 4 mm).

Median follow-up was 60.4 months, ranging from 8 to 94 months. Two patients were lost to follow-up (at 46 and 8 months from surgery, respectively). None of the patients bearing micrometastases in the SLN and in whom ALND was omitted (45 patients) manifested axillary or distant recurrence, while one patient with ALND developed infraclavicular lymph node recurrence. Only one patient, who declined postoperative breast irradiation, developed recurrence in the breast followed by distant metastases and died 28 months after surgery. Therefore, the 5-year survival rate for these node-positive patients is 98% (95% confidence interval, 93.5–100).

DISCUSSION

SLNB can accurately predict node status with minimal morbidity.⁴ The exhaustive pathological evaluation of SLN by serial sectioning, immunohistochemistry, and reverse transcriptase–polymerase chain reaction resulted in an increased detection of micrometastases.⁵

One must take into consideration the fact that some aspects, such as the definition of micrometastases and isolated tumor cells, were chosen arbitrarily and that the classification of isolated tumor cells and micrometastases is not reproducible among pathologists. Moreover, there is growing evidence that the detection of isolated epithelial tumor cells in lymph nodes can be due to iatrogenic dislodgment after manipulation such as core biopsy, and this can be misinterpreted as micrometastatic disease.⁶

According to guidelines, the presence of macrometastases in the SLN is an indication for further treatment of the axilla, either by surgery or radiotherapy. However, optimal management of patients with SLN micrometastases remains unclear. On the one hand, some authors recommend ALND in all patients with micrometastases because of the likelihood of non-SLN metastasis and staging information.^{7–9} On the other hand, others think that ALND could be spared in these patients because of the low likelihood of non-SLN metastases, the lack of benefit of the ALND, and its increased morbidity.^{10–12}

Currently, this is a matter of controversy, and there is not enough evidence to guide management regarding this common clinical issue, as recently reported by Bilimoria et al. in an observational study from the National Cancer Data Base (1998–2005).¹³ The objectives of that study

TABLE 1 Patient characteristics

Characteristic	<i>n</i>	No ALND	Completion ALND
All patients	59	45	14
Age, median (range)	54 (32–83)	55 (35–83)	51 (32–67)

TABLE 2 Tumor characteristics

Classification	Total number, n (%) (n = 59)	No ALND, n (%) (n = 45)	Completion ALND, n (%) (n = 14)
Histological subtype			
Invasive ductal carcinoma	51 (86.4%)	40 (67.8%)	11 (18.6%)
Invasive lobular carcinoma	7 (11.9%)	5 (8.4%)	2 (3.3%)
Other	1 (1.7%)	0	1 (1.7%)
Size (mm)			
Median (range)	15 (7–32)	15 (7–32)	19 (12–31)
0–10	7 (11.9%)	7 (11.9%)	0
11–20	37 (62.7%)	29 (49.1%)	8 (13.5%)
21–30	12 (20.3%)	7 (11.9%)	5 (8.4%)
>30	3 (5.1%)	2 (3.3%)	1 (1.7%)
Tumor grade			
1	2 (3.3%)	2 (3.3%)	0
2	26 (44%)	23 (38.9%)	3 (5%)
3	24 (40.6%)	16 (27.1%)	8 (13.5%)
Unknown	7 (11.9%)	4 (6.7%)	3 (5%)
Lymphatic or vascular invasion			
Present	9 (15.3%)	4 (6.7%)	5 (8.4%)
Absent	50 (84.7%)	41 (69.4%)	9 (15.2%)
ER and PR			
ER positive/PR positive	45 (79.6%)	33 (73.3%)	12 (26.6%)
ER positive/PR negative	6 (10.1%)	5 (8.4%)	1 (1.7%)
ER negative/PR positive	0	0	0
ER negative/PR negative	8 (13.5%)	7 (11.9%)	1 (1.7%)
Her2/neu			
Positive	7 (11.9%)	5 (8.4%)	2 (3.3%)
Negative	39 (66.1%)	31 (52.5%)	8 (13.5%)
Unknown	13 (22%)	9 (15.2%)	4 (6.7%)
Ki67			
<20%	30 (50.8%)	27 (45.7%)	3 (5%)
≥20%	13 (22%)	9 (15.2%)	4 (6.7%)
Unknown	16 (27.1%)	9 (15.2%)	7 (11.9%)

ER estrogen receptor, PR progesterone receptor

were to examine how often women with node-positive breast cancer undergo SLN alone without a completion ALND and to determine differences in recurrence and survival for SLN alone versus SLN with completion ALND. In that study, it was shown that the proportion of patients who did not undergo completion ALND for macroscopic disease declined (24.2–16%; $P < .001$); however, the proportion of patients who underwent SLN alone for microscopic metastases increased dramatically (24.7–45.3%; $P < .001$).

Results from randomized trials would be ideal, but most of them closed early because of poor enrollment. Therefore, observational studies like this are nowadays the best available evidence for this common and controversial clinical issue.

The present prospective study provides evidence that locoregional recurrence or distant disease in breast cancer

patients with SLN micrometastases in whom ALND was omitted is very low, and thus it supports the theory that further axillary treatment may be avoided in these patients, providing that adjuvant systemic treatment is administered. Although longer follow-up is needed, most axillary recurrences occur within 24–36 months of surgery, and the median follow-up of this study is 60 months.¹⁴

As has been reported in many studies, the risk of further non-SLN involvement increases with the primary tumor size, the size of the SLN metastases, and the number of positive SLN. In case of micrometastases, it has been shown that 85–90% of patients do not have disease in other non-SLNs.^{7,9,15} Whether or not a risk of 15% of having metastases left in the axilla is acceptable is controversial. As reported by Cserni et al., if the false-negative rate of SLNB reported in multicenter trials of 5–12% is acceptable, then the 15% chance of leaving some tumor in the

TABLE 3 Sentinel lymph node (SLN) characteristics

Characteristic	Value
No. SLNs removed	
Median (range)	1 (1–4)
1	32 (54.2%)
2	16 (27.1%)
3	9 (15.3%)
4	2 (3.4%)
Positive SLNs identified per patient	
1	57 (96.6%)
2	2 (3.3%)
3	0
4	0
Patients with multiple foci of micrometastases within a single SLN	2 (3.3%)

Values are *n* (%) unless otherwise indicated

axilla might also be acceptable; only a small proportion of patients with expected non-SLN metastases will develop axillary recurrence or distant metastases if the axilla is left untreated.¹ The axillary recurrence rate after ALND ranges from 0 to 2%, and after a negative SLNB with no subsequent ALND, it ranges between 0 to 1.2%, with a median time to recurrence of 19 months.^{12,14,16} Recent retrospective studies as well as prospective analyses suggest that patients with SLN micrometastases without further ALND will not experience a higher incidence of regional recurrences, and therefore, it might be acceptable to avoid ALND when one positive SLN containing micrometastases is identified.^{10,11} In the study of Bilimoria et al., which had a median follow-up of 63 months, there were no marked differences in axillary recurrence or survival for SLN alone versus SLN with completion ALND in patients with microscopic nodal metastases.¹³ In addition, breast irradiation and adjuvant systemic treatment can eradicate expected non-SLN micrometastases and reduce the risk of axillary or distant recurrence.¹⁷ These adjuvant treatments can diminish the added benefit of ALND.

However, there is also considerable debate regarding the clinical relevance of SLN micrometastases. Previous studies reported that the prognosis of patients with SLN micrometastases was similar to that of node-negative patients.^{18,19} Other recent studies have found that SLN micrometastases greatly affect clinical outcome, with a reduced 5-year rate of disease-free survival among women with favorable early-stage breast cancer.^{20,21} However, disease-free survival was improved in patients who received systemic adjuvant therapy.²² This finding supports the use of systemic adjuvant treatment in patients with SLN micrometastases. Moreover, because third-generation

chemotherapy regimens are used, as we have used at our facility since 2004, the effect of systemic adjuvant treatment should be increased.

On the basis of a median follow-up of 60 months—one of the longest so far in the literature—our study provides evidence that breast cancer patients with SLN micrometastases in whom ALND was omitted manifest very low locoregional or distant recurrence. Therefore, this study supports the theory that further axillary treatment may be avoided in these patients if adjuvant systemic treatment is provided. However, longer follow-up is needed for mature prognostic information, and results of additional prospective studies are needed.

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