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ORIGINAL ARTICLE

Prognostic role of micrometastases in sentinel lymph node in patients with invasive breast cancer

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ABSTRACT

Background and Purpose of the study: Axillary lymph node status at the time of diagnosis remains one of the most important prognostic factors in women with breast cancer. Sentinel lymph node biopsy (SLNB) proved to be a reliable method for the evaluation of axillary nodal status in early-stage invasive breast cancer. The prognostic value and potential therapeutic consequences of SLN micrometastases remains a matter of great debate.

Patients and Methods: From January 1998 to March 2011, 1,976 consecutive patients with non-metastatic invasive breast cancer underwent surgical treatment; 1,080 of them (54.6%) underwent SLNB. We collected data regarding demography, preoperative lymphoscintigraphy, type of surgery, histopathologic and immunohistochemical features and adjuvant treatment.

Main findings: A mean number of 2.1±1.4 (range 1–13) SLN per patient were collected, a total of 2,294 nodes. SLNs were macrometastatic in 16.7% of patients and micrometastatic in 3.3%. Among the patients with positive SLN 93.6% underwent complete ALND. The overall survival (OS) and disease-free survival (DFS) of 72 patients with micrometastases in SLN at 60 months was 100%, similar to patients with negative SLN (98.7%), quite different from the DFS of N1–N3 patients (85.8%). Statistically significant differences in OS and DFS were observed between patients with N1mi and the group with N1–N3 sentinel node ($p < 0.001$ and $p = 0.04$) and also between patients with negative SLN and those with macrometastatic SLN ($p < 0.001$ for both).

Conclusion: SLN micrometastases could represents an epiphenomenon of peritumoral lymphovascular invasion which impacts independently on the survival of patients with invasive breast cancer.

1. Introduction

Axillary lymph node status at the time of diagnosis remains one of the most important prognostic indicators for women with breast cancer. [1] The presence of lymphogenic metastases and number of lymph nodes involved significantly contribute to adjuvant systemic treatment decision; in fact they are associated with an increased probability of recurrence and mortality. [2,3]

The goal of axillary lymph node dissection is to provide accurate staging information and local control of disease. However, the procedure has many potential complications, including lymphedema, persistent seroma, shoulder disfunction and paresthesias. [4]

Nowadays, sentinel lymph node biopsy (SLNB) provides information on the axillary node status with lower morbidity than complete axillary lymph node dissection (ALND). Therefore, according to the results of several international randomized trials SLNB is considered the standard of care for patients with early breast cancer and negative axillary nodes. [5,6]

The complexity of breast tumor biology has changed cancer treatments, consequently the choice of administering systemic therapy is influenced by a variety of clinical and pathology-related factors, with lymph node tumor status influencing but not necessarily dictating the use of chemotherapy. [7] These evolving concepts have called into question the need for ALND, especially for limited sentinel lymph node involvement.

Published data suggest that the absence of metastatic tumor cells in the sentinel lymph node accurately predicts the absence of metastases in the remaining axillary nodes in 95–100% of cases. [8–10] Actually, SLNB may be more sensitive to detect metastases than axillary node dissection. [4] Compared with analysis with hematoxylin and eosin (H&E) only in axillary lymph node dissection specimens, the use of step sectioning and immunohistochemistry in the sentinel lymph node results in a more accurate histopathologic examination

and is associated with a higher detection rate of small metastases (micrometastases and isolated tumor cells). [11,12] In the 7th edition of the AJCC staging system the concept of "micrometastases" (N1mi) has been introduced in the official staging criteria: micrometastase is defined as a metastases measuring from 0.2 mm to not more than 2.0 mm. [13]

However, the prognostic significance of micrometastases in the sentinel node is currently unclear and creates a new dilemma in the clinical management of patients with breast cancer. [14] In this study we examine the overall survival and disease free survival of a large cohort of patients in order to assess the prognostic meaning of sentinel node micrometastases.

2. Patients and methods

From January 1998 to March 2011, 1,991 consecutive patients with invasive breast cancer underwent surgical treatment at the Division of General Surgery of Ospedale di Circolo, University of Insubria Varese.

For the present study, 15 patients with distant metastases at the time of diagnosis were excluded, hence the sample consisted of 1,976 patients, whose mean age at diagnosis was 61.1±12.4 years; 1,080 of them (54.6%) underwent sentinel lymph node biopsy. The other patients did not undergo sentinel node biopsy either because they were treated before the introduction of the sentinel lymph node biopsy technique into routine clinical practice (2001) or due to evidence of metastatic axillary nodes.

We retrospectively collected data regarding demography, pre-operative lymphoscintigraphy, type of surgery, histopathologic and immunohistochemical features and adjuvant treatment.

Pathologic assessment included evaluation of the size, grade, histological type, peritumoral vascular invasion of the primary tumor and lymph node status.

Data regarding tumor expression of estrogen and progesterone receptors, Ki-67 antigen, HER-2 and p53 over-expression were also collected.

The nodal status was determined according to the 7th edition of the AJCC cancer staging manual. [13] If no regional lymph node metastasis was detected, the tumor was classified as pN0.

In case of micrometastases (larger than 0.2 mm but none larger than 2 mm in greatest dimension) the tumor was classified as pN1mi. If nodal metastases larger than 2 mm were diagnosed, the tumor was classified as pN1. [13]

2.1. Lymphatic mapping and operative technique

Sentinel node mapping was performed using a radiolabelled colloid. The day before surgery ^{99m}Tc- labelled nanocolloid (Nanocoll) was injected intradermally above the tumor site. Lymphoscintigraphy was performed preoperatively to identify lymphatic flow to axillary lymph nodes, hot spots were marked on the skin.

SLN was intraoperatively identified by use of a gamma probe (Neoprobe); all hot lymph nodes were excised and labelled separately as SLN, until all hot lymph nodes had been removed, and the background count of the axilla was < 10% of the hottest lymph node. [14] If no SLNs were found, a complete ALND was performed.

2.2. Surgical treatment

All patients received adequate local treatment (breast-conserving surgery or total mastectomy) plus SLNB or ALND.

2.3. Pathological examination of sentinel nodes

Intraoperative frozen section analysis of the axillary SLN was routinely conducted in order to perform axillary dissection during the same operative procedure in case of lymphatic metastases.

Lymph nodes > 5 mm in diameter were bisected, nodes ⩽5mm were not bisected but totally submitted for frozen section analysis; the sections were cut at 50–200 μm intervals and they were examined with H&E. In addition, the sentinel nodes were fixed in formaline and embedded in paraffin for definitive histopathologic analysis. During the definitive histopathologic analysis the sections were stained with both H&E and immunohistochemically with antibodies against keratin. [14,15]

2.4. Adjuvant therapy

When breast-conservative surgery was performed, patients received adjuvant radiotherapy with 50 Gy over 5 weeks with a boost of 10 Gy to the tumor site, marked with clips during surgery in patients without contraindications for radiotherapy.

Moreover, adjuvant therapy consisted of hormone treatment (tamoxifen or aromatase inhibitors), and/or chemotherapy according to established prognostic factors (age, comorbidities, axillary lymph node status and features of primary tumor). [16,17]

On the basis of the St. Gallen Consensus recommendations, [17,18] patients with SN micrometastases were considered SN negative and adjuvant therapy was administered only according to the characteristics of the primary tumor.

2.5. Follow up

After surgery, patients were observed every 4 months in the first 3 years, every 6 months in the next 2 years, and once a year thereafter; mammography and breast ultrasound were performed annually.

Registry offices were actively contacted for additional information, especially for the cause of death, when patients were lost to follow up.

Follow up started at the time of the operation. As per December 2011, 63 patients (3.2%) were lost to follow up; in the survival analyses these were "censored" at the time of last contact.

For all patients, the median follow-up was 53.4 months (range 1–160 months) and for the survivors the median follow-up was 55.3 months (range 1–160 months).

2.6. Statistical analysis

The primary end-points were overall and disease-free survival of our group of patients in order to calculate the survival impact of SN micrometastases.

Disease-free survival (DFS) was defined as the lenght of time from the date of surgery to any relapse; overall survival (OS) was defined as the time from surgery until the date of cancer-related death.

Survival rates for DFS and OS were estimated by the Kaplan–Meier method. The survival comparisons between the different groups were carried out by the Log-rank test.

The secondary aim of this study was to identify predictors for micrometastases in SLN. We subdivided patient and tumor-related factors. Continuous variables were expressed as mean and standard deviation (SD) or as median and range. The association between micrometastases and patients and tumor-related factors were analyzed by non-parametric test as appropriate.

Multivariate analysis was performed by stepwise backward logistic regression, including only variables with $p < 0.1$ at univariate tests.

Table 1
Patient and tumor characteristics

Characteristic	Number (%) or Mean±SD
Age	61.1±12.4
Multifocality[a]	
Yes	217 (11.1)
No	1733 (88.9)
Tumor size (cm)	1.8±1.1
Histology	
Ductal	1464 (74.1)
Lobular	213 (10.8)
Other	299 (15.1)
p T stage[a]	
Tis	30 (1.5)
T1	1318 (67.3)
T2	522 (26.7)
T3	34 (1.7)
T4	53 (2.7)
p N[a]	
N0	1308 (69.1)
Nmi	72 (3.8)
N1–3	513 (27.1)
Grading[a]	
G1	146 (8.1)
G2	1224 (67.5)
G3	443 (24.4)
Lymphovascular invasion[a]	
Yes	130 (23.7)
No	419 (76.3)
ER%[a]	69.6±36.4
PgR%[a]	44.5±37.1
c-erb-B2[a]	12.8±27.2
Ki 67[a]	24.3±16.9
p53[a]	11.9±24.4

[a] Data not available for all patients.

The level of significance was set, as usual, at $p < 0.05$ (two-tailed model for unpaired data).

All statistical tests were two sided. Statistical analyses were performed by SPSS v.13 software for Windows.

3. Results

From January 1998 to March 2011, 1,976 consecutive patients with non-metastatic invasive breast cancer underwent surgical treatment. Among them 1,080 underwent SLNB (54.6%), in 853 cases associated with breast conservative surgery, and in 227 patients with radical mastectomy. Patient and tumor characteristics are reported in Table 1.

A mean number of 2.1±1.4 (range 1–13) SLN per patient was collected for a total of 2,294 nodes. The SLNs were macrometastatic in 181 patients (16.7%) and micrometastatic in 72 patients (3.3%).

Among the 253 patients with positive SLN, 237 (93.6%) underwent complete ALND, adding to the 738 patients who underwent complete ALND ab initio. Among the patients with positive SLNs, 16 did not undergo complete ALND because of high surgical risk or patient's choice.

Up to December 2010, 46 patients died from breast cancer, and actuarial OS at 12, 36 and 60 months was 99.8%, 98.7% and 97.0% (Fig. 1).

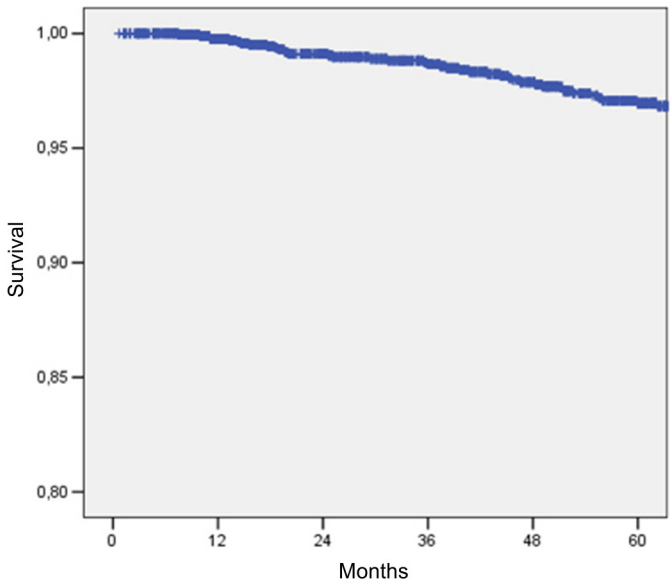

Fig. 1. Actuarial overall survival up to 60 months.

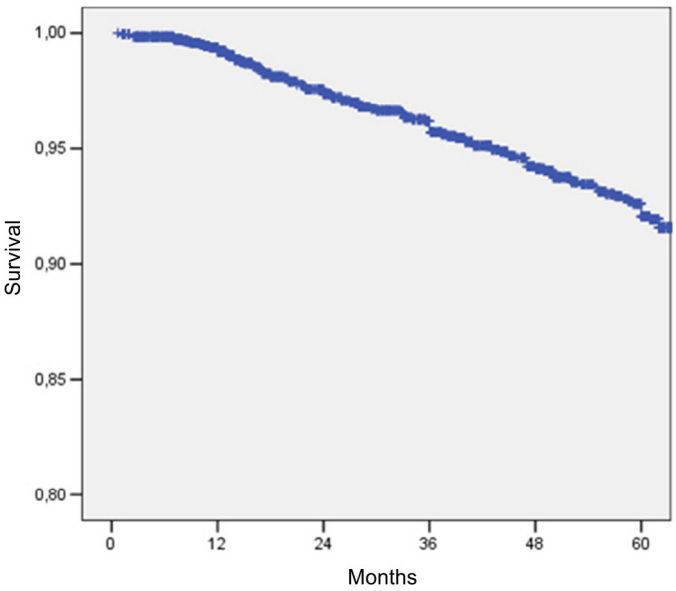

Fig. 2. Actuarial disease-free survival up to 60 months.

During follow up 133 recurrences were observed: the actuarial DFS at 12, 36 and 60 months was 99.2%, 95.7% and 92.0% (Fig. 2).

The OS of the 72 patients with micrometastases in SLN at 60 months was 100%, similar to that of patients with negative SLN (98.7%). Surprisingly, for the group of patients with micrometastases in SLN the DFS at 60 months (95.7%) was also similar to that of patients with negative SLN (94.6%), quite different from the DFS of N1–N3 patients (85.8%).

No statistically significant difference in overall survival and disease-free survival were detected between patients with negative SLN and patients with SLN micrometastases. Statistically significant differences in OS and DFS were observed between patients with N1mi and the group with N1–N3 sentinel node ($p < 0.001$ and $p = 0.04$) and also between patients with negative SLN and those with macrometastatic SLN ($p < 0.001$ for both) (Figs.3, 4).

Table 2 reports the results of univariate analysis for predictors of SLN micrometastases. The results of multivariate analysis are displayed in Table 3. The presence of peritumoral lymphovascular in-

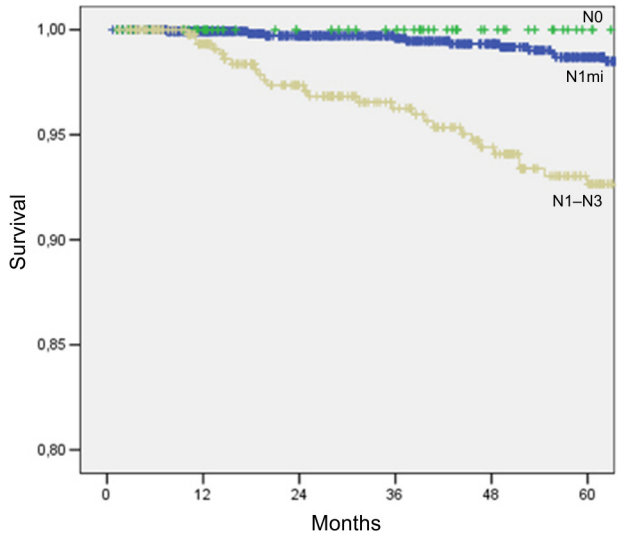

Fig. 3. Overall survival (OS) comparison between negative SLN (N0), SLN micrometastases (N1mi) and SLN macrometastases (N1–N3).

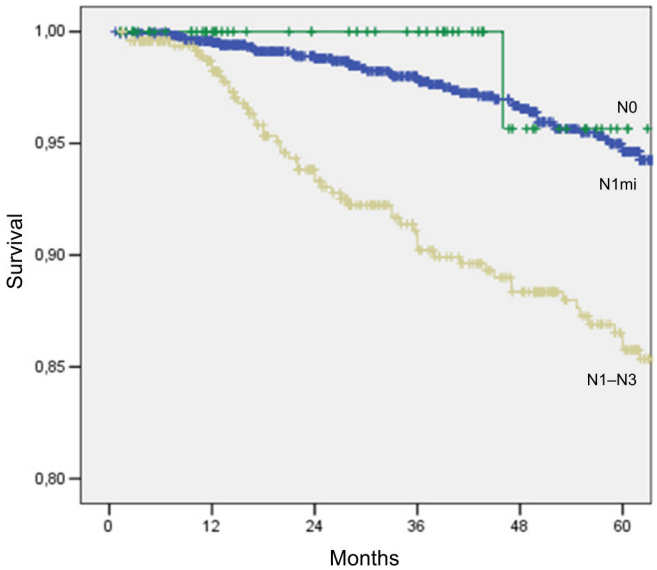

Fig. 4. Disease-free survival (DFS) comparison between negative SLN (N0), SLN micrometastases (N1mi) and SLN macrometastases (N1–N3).

vasion represents the only independent predictor of micrometastases in the SLN (Table 3).

In order to compare the prognostic role of micrometastases in SLN and the peritumoral lymphovascular invasion (LI), and to understand their cause–effect relation, we stratified the patients into 4 groups: (1) patients with SLN micrometastases and LI;, (2) patients with SLN micrometastases without LI, (3) patients without micrometastases but with LI, and (4) patients without micrometastases and without LI, and we compared OS and DFS by the Kaplan–Meier method (Figs. 5, 6). The peritumoral LI seems to have a greater prognostic role than the presence of micrometastases in SLN in our cohort of patients.

4. Discussion

Sentinel lymph node biopsy determines with high accuracy the axillary lymph nodes status and is one of the prognostic indicators that influence the choice of local and systemic therapy in breast cancer management. [9,18,19] It is currently known, however, that there

Table 2
Results of multivariate analysis of the predictors of SLN micrometastases

Characteristic	Number/total or Mean±SD		p-value
	SLN N1mi	SLN N0	
Age	60.5±11.4	60.6±12.1	0.755
Multifocality [a]			0.026
Yes	12/71	116/1294	
No	59/71	1178/1294	
Tumor size (cm)	2.0±0.9	1.6±0.9	<0.001
Histology			<0.001
Ductal	67/72	922/1306	
Lobular	4/72	137/1306	
Other	1/72	247/1306	
p T [a]			0.018
Tis	0/71	30/1306	
T1	45/71	993/1306	
T2	24/71	256/1306	
T3	2/71	15/1306	
T4	0/71	12/1306	
Grading [a]			0.043
G1	1/67	121/1212	
G2	53/67	819/1212	
G3	13/67	272/1212	
Lymphovascular invasion [a]			<0.001
Yes	14/35	44/360	
No	21/35	316/360	
ER% [a]	81.2±30.8	70.2±36.2	0.003
PgR% [a]	58.6±36.0	45.7±37.5	0.004
c-erb-B2 [a]	8.8±19.3	11.4±25.6	0.215
Ki 67 [a]	21.6±17.8	23.4±16.9	0.237
p53 [a]	12.0±22.4	11.7±24.1	0.024

[a] Data not available for all patients.

Table 3
Results of regression model for multivariate analysis

Characteristic	Odds ratio	95% CI	P-value
Lymphovascular invasion			
Yes	5.212	2.130–12.758	<0.001
No	1		

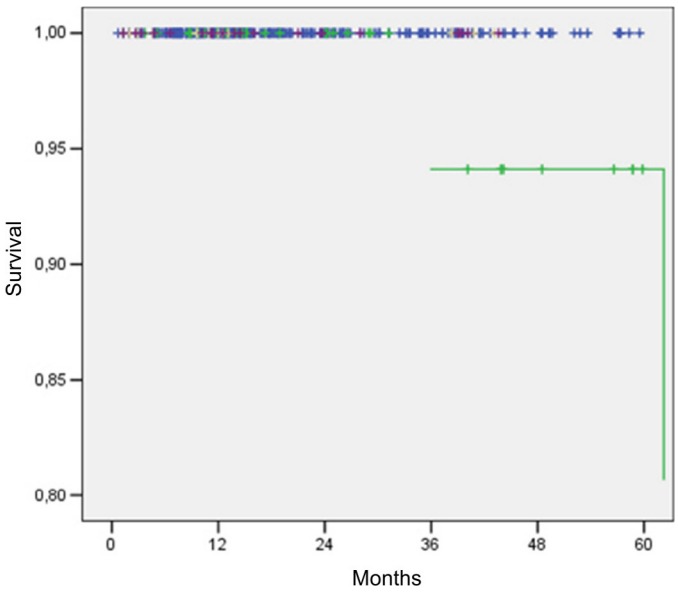

Fig. 5. Overall survival (OS) comparison between four groups of patients: (1) green line: patients with SLN micrometastases and LI; (2) yellow: patients with SLN micrometastases without LI; (3) blue: patients without micrometastases but with LI, and (4) purple: patients without micrometastases and without LI.

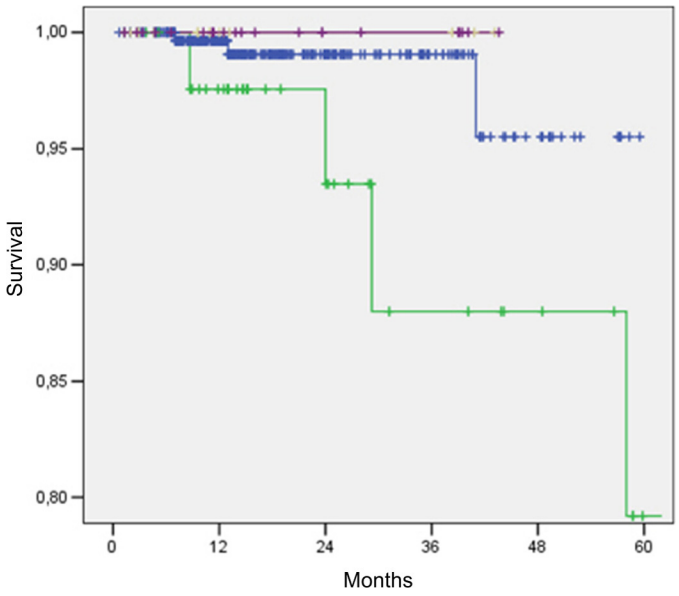

Fig. 6. Disease-free survival (DFS) comparison between four groups of patients: (1) green line: patients with SLN micrometastases and LI; (2) yellow: patients with SLN micrometastases without LI; (3) blue: patients without micrometastases but with LI, and (4) purple: patients without micrometastases and without LI.

are other factors which influence the choice of administering adjuvant therapies.

Since the introduction of the SLNB procedure into clinical practice, axillary lymph node micrometastases are more likely to be detected. [18,20–25] This is because the pathologist can focus on a few lymph nodes, which can be analyzed more thoroughly by step sectioning and immunohistochemistry. [22] Conversely, the systematic use of step sectioning and immunohistochemistry is not feasible in the assessment of all nodes in ALND specimens because of time and financial constraints. [12] However, the detection rate of micrometastases varies among different histopathological techniques and protocols.

In our cohort of patients who underwent SLNB, 3.3% were classified as N1mi with micrometastases only in the SLN. In the literature the rate of micrometastase identification in the SLN ranges between 2.3% and 27% [26]; this large range stems from the different modalities of SLN pathological examination, for which there is not yet an international standardized procedure. Additionally, we retrieved few micrometastases probably because we considered as cases only those patients who had isolated micrometastases without any other lymph nodes involved.

The prognostic significance and therapeutic implications of SLN micrometastases remain a matter of great debate. In our study micrometastases in the SLN are not associated with worse prognosis than that for N0 patients. Indeed, the OS and DFS differ with statistical significance from those of the N+ (N1–N3) group (Figs.3, 4).

During the ALND era, various retrospective studies reported a significant disease-free and overall survival disadvantage for breast cancer patients with micrometastases; however, others failed to find any association. [15,27,28]

The American Society of Clinical Oncology (ASCO) has published a study regarding the different therapeutical approaches adopted by ASCO members (surgeons, oncologists, radiotherapists) in case of micrometastatic sentinel lymph nodes. [29] Adjuvant chemotherapy is considered by most of the ASCO members as a treatment that cannot be renounced in N1mi patients without unanimous consensus about treatment modality. Only 23% of the specialists consulted perform and recommend ADLN in N1mi patients; more often (73%) they recommend ALND based on other prognostic tumor-related factors such as tumor size, histological grade and peritumoral LI. [29,30]

On the contrary, in recent studies the presence of micrometastatic SLN is correlated with a prognosis lower than that for N0 patients. [28,31–33] Particularly Chen S et al. attribute to patients with micrometastases in the SLN a prognosis intermediate between those for N0 and N+ (N1–N3). [33,34]

Our data support the consideration by Langer et al. who consider the axillary recurrence risk in N1mi patients so slight as to consider ADLN to be overtreatment. [15] The absence of a statistically significant difference between the prognoses for N0 and N1mi patients in our study could justify the possibility to avoid complete ALND and, additionally, to prevent a systemic adjuvant overtreatment in patients with micrometastases in the SLN.

Our results indicate that the micrometastases in the SLN do not significantly affect the prognosis. In accordance with our results, the IBCSG 23-01 phase 3 randomized controlled trial confirms that axillary dissection could be avoided in patients with limited sentinel lymph node disease. [35] Trial IBCSG 23-01 was a two-group, multicenter, randomized phase 3 trial comparing no axillary dissection with axillary dissection in patients with breast cancer and micrometastases in sentinel lymph node. In this study about half of patients have no other axillary involvement and axillary dissection can be considered an overtreatment for them.

Our achievements are consistent also with those of the ACOSOG Z0011 trial, a phase 3 non-inferiority trial enrolling patients with limited sentinel lymph node disease randomized to undergo ALND or no further axillary treatment. [7] The American College of Surgeons Oncology Group (ACOSOG) tested the hypothesis that complete axillary lymph node dissection may not be necessary for women with sentinel lymph node metastases and early breast cancer. ALND did not significantly influence overall or disease-free survival of patients with clinical T1–2 breast cancer and a positive SLN, treated with lumpectomy, radiotherapy and adjuvant systemic therapy. [7]

The paper by Wasif et al. [29] supported our findings and opens a new scenario for changing clinical practice in the management of axilla in early breast cancer patients. The use of axillary radiation including level I and II axilla as an alternative to treat SLNB micrometastases instead of ALND was an option often selected.

In fact, several studies have reported on the use of radiotherapy instead of ALND for SLNB-positive nodes, although the data are difficult to interpret because of the use of systemic therapy and breast tangential radiation. [36]

Findings from the AMAROS study which compared ALND and axillary radiotherapy in patients with metastatic SLN demonstrated that axillary dissection had no influence on the choice of adjuvant systemic treatment. [37,38] Accordingly, the information offered by axillary dissection is no longer useful.

In our study we have identified no prognostic difference between the N1mi and N0 groups, so we analyzed the patient- and tumor-related factors associated with micrometastatic SLN.

Peritumoral LI emerged as the only independent predictive factor for the presence of micrometastases in SLN and it affected patient survival independently of micrometastases.

Even though our study is limited by its retrospective design and some chronological bias for the long observational time interval, we can conclude that SLN micrometastases could represent an epiphenomenon of peritumoral LI which, if at all, impacts independently on the survival of patients with invasive breast cancer.

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Disclosure statement

The authors have no conflicts of interest to declare.

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