Predictive Factors of Non-sentinel Lymph Node Involvement in Patients with Invasive Breast Cancer and Sentinel Node Micrometastases

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Abstract. *Patient-related, tumor-related, and sentinel node (SN)-related factors have been identified with the aim of predicting non-SN status in patients with SN micrometastases. According to our previous experience, primary tumor size (p=0.005) and the presence of lymphovascular invasion (LVI) (p=0.000) significantly predicted non-SN status in patients with SN micrometastasis; moreover, non-SN metastases were never detected in patients with pT1a-1b, G1, and no LVI. A prospective assessment was undertaken in a validation set of 126 patients to confirm these findings. Univariate analysis indicated that primary tumor size (p=0.05), Scarff-Bloom-Richardson (SBR) grade (p=0.008), LVI (p=0.001), and the number of mitoses/mm^2 (p=0.01) were significant predictors of non-SN status. By logistic regression analysis, tumor size (p=0.03), LVI (p=0.001), grade (p=0.003) and the number of mitoses/mm^2 (p=0.01) were the only variables remaining in the model. Three subsets of patients were identified: i) 18.3% of patients (pT1, G1, and no LVI) had tumor-negative non-SN (no risk group); ii) 37.3% of patients (number of mitoses/mm^2 <10, SBR grade II-III) had a rate of tumor-positive non-SN <15% (intermediate risk); iii) 44.4% of patients had a mean rate of non-SN involvement of 46% (high risk). By these parameters, more than 50% of patients could be selectively spared unnecessary axillary lymph node dissection without staging or therapeutic benefit, especially in patients with well-differentiated pT1 tumors without LVI.*

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Sentinel lymph node (SN) biopsy has gradually replaced axillary lymph node dissection (ALND) for the pathological staging of the axilla in patients with early-stage breast cancer. This procedure avoids unnecessary ALND in SN-negative patients with similar locoregional recurrence and overall survival, coupled with an improved quality of life and fewer side-effects (1-5). Noteworthy, in 38-67% of patients with node-positive disease the only tumor-involved lymph node is the SN, hence most patients would not benefit at all from ALND. This rate is constantly increasing thanks to the widespread use of screening mammography, with earlier diagnosis of breast cancer and a risk of axillary metastases close to 10% in tumors of less than 1 cm (2, 6-9). Moreover, the selection of patients eligible for systemic adjuvant treatment is currently influenced by various patient- and tumor-related factors, such that axillary lymph node status, as well as the extent of lymph node involvement, no longer determines this decision analysis (10).

The need for therapeutic ALND is also the subject of ongoing debate, and the recommendation of ALND as standard-of-care in SN-positive patients should be re-evaluated, as suggested in recent data from the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial (11, 12). Notably, while the incidence of non-SN involvement in patients with SN macrometastases is rather high, ranging from 39-79% of cases, with a mean value of 52.3%, thus justifying ALND, the rate of non-SN involvement in patients with SN micrometastases is much lower, ranging from 0-57% (13, 14), with a pooled proportion of 20.2% in the meta-analysis by Cserni *et al.* (14). This observation suggested the identification of patient-related, tumor-related, and SN-related factors which might predict for non-SN status with the aim of detecting a subset of patients having micrometastasis only within the SN to spare them unnecessary ALND. In our previous

Table I. *Characteristics of the patients and breast tumor description.*

Characteristic	Total patients		Non-SN Negative (n=93)		Non-SN Positive (n=33)		p-Value
	No.	%	No.	%	No.	%	
Age at diagnosis, years							
<50	35	27.8	25	71.5	10	28.5	
50-70	53	42.0	43	81.1	10	18.9	
>70	38	30.2	25	65.8	13	34.2	0.242
Tumor size, mm							
1-20	88	69.8	69	79.3	18	20.7	
> 20	38	30.2	24	58.5	15	41.5	0.05*
Histological type							
Non-lobular	106	84.1	79	74.5	27	25.5	
Lobular	20	15.9	14	70.0	6	30.0	0.673
SBR Grade							
I	26	20.6	24	92.3	2	7.7	
II	65	51.6	49	75.4	16	24.6	
III	35	27.8	20	57.1	15	42.9	0.008*
LVI							
No	65	51.6	56	86.2	9	13.8	
Yes	61	48.4	37	60.7	24	39.3	0.001*
Number of mitoses/mm^2							
1-9	65	51.6	57	87.7	8	12.3	
>10	47	37.3	28	59.6	19	40.4	0.01*
na	14	11.1					
Ki-67 proliferative index							
<10%	17	13.5	15	88.2	2	11.8	
>10%	109	86.5	78	71.6	31	28.4	0.146
c-ERBB2 expression							
Negative	86	68.3	62	72.1	24	27.9	
Positive (+)	17	13.5	15	88.2	2	11.8	
Highly positive (++/+++)	21	16.7	15	71.4	6	28.6	0.362
na	2	1.5					
Hormonal expression							
ER-positive/PgR-positive	99	78.6	74	74.4	25	25.3	
ER-negative/PgR-positive	-	-	-	-	-	-	
ER-positive/PgR-negative	14	11.1	12	85.7	2	14.3	
ER-negative/PgR-negative	13	10.3	7	53.8	6	46.2	0.153

ER, Estrogen receptor; PgR, progesterone receptor; LVI, lymphovascular invasion; SBR, Scarff-Bloom-Ricahrdson; na, not available; c-ERBB2, HER-2/neu; SN, sentinel lymph node; No, number; *statistically significant.

experience in an evaluation set of 116 patients with SN micrometastases, greater tumor size (p=0.005) and the presence of lymphovascular invasion (LVI) (p<0.001) were significantly related to the occurrence of metastasis in non-SN lymph nodes; moreover, non-SN metastases were never detected in patient with pT1a-1b, G1, and no LVI (15). We performed a prospective assessment in a validation set of 126 patients with SN micrometastases undergoing completion ALND to confirm the reliability of these findings in order to identify a subset of patients who could be safely spared ALND.

Patients and Methods

Between January 2005 and June 2012, 1,564 patients with early-stage (T1-2 N_0 M_0) breast cancer underwent SN biopsy and ALND as part of their standard treatment at the Department of Surgical Oncology of the IRRCS “Azienda Ospedaliera Universitaria San Martino-IST” of Genoa. One hundred and twenty-six patients with SN micrometastases (between 0.2 and 2 mm) that were usually detected at definitive histological examination were prospectively recruited in this study. Inclusion criteria for SN biopsy were the following: i) patients older than 18 years of age; ii) mammographic/sonographic and histological diagnosis of invasive breast cancer, and iii) clinically node-negative patients. Patients with: i) known adverse reaction to any contrast medium; ii) who were pregnant; iii) who were unable to attend regular follow-up, and iv) with life-threatening clinical conditions that might preclude a systemic adjuvant treatment were excluded. The study protocol was approved by the Ethics Committee of the IRRCS "Azienda Ospedaliera Universitaria San Martino-IST", and all patients were fully-informed before giving their written consent to the procedure.

As regards SN detection, a standard procedure was adopted, as previously described (16). An intraoperative examination of the SN was performed in each patient; at frozen section examination, the SN was bisected along its major axis, and five sections cut at 20 μm intervals were obtained from each half. Three of these sections were stained with hematoxylin-eosin (H&E); if they were negative or doubtful, the other two sections were stained with AE1/AE3 antibodies to keratin. The SN was then processed routinely for permanent sections, and at least four additional sections were examined with H&E and immunochemistry (IHC). The ALND specimens were also examined according to the standard Departmental protocol: the non-SN were identified without clearance of the fat; all lymph node material was processed, stained, and examined; two H&E-stained sections from each half lymph node were examined, and IHC was not used to evaluate these sections. Pathological staging was defined according to the International Union Against Cancer (UICC) TNM classifications of malignant tumors (17).

A specific database was developed including data concerning: i) clinical and histological data of the tumor (size, histological type, Scarff-Bloom-Richardson (SBR) grade, LVI, expression of estrogen and/or progesterone receptors, Ki-67 proliferative index, c-ERBB2, number of mitoses/mm^2); ii) histology of SNs (number of histologically positive SN, the ratio of histologically positive SN to the total number of removed SNs) and non-SN (total number, number of histologically positive non-SN, size of metastatic foci).

Statistical methods. Comparisons of clinical characteristics between non-SN-negative and -positive cases were performed using the Chi-square test, or Fisher's exact test when appropriate. Logistic regression analysis was used to model positivity of non-SN with independent prognostic factors. All reported *p*-values are two-sided. A *p*-value <0.05 was considered statistically significant. A classification tree model for non-SN positivity was developed by recursive partitioning analysis. Final nodes were grouped according to proportions on non-SN positivity. Analyses were performed using R version 2.13 and r-part package version 4.1-1 (http://www.r-project.org).

Results

Patients characteristics and histopathological features are reported in Table I. Overall, 126 patients were included in the present analysis; the mean patient age was 63 years (range=37-85, SD=12.5 years). The mean size of the primary tumor was 14 mm (range=4-29, SD=6.5 mm). The mean number of SN examined per patient was 1.8 (range=1-4, SD=0.8), and the mean number of non-SN was 14 (range=12-18, SD=4.5). Thirty-three (26.2%) out of 126 patients had tumor-positive non-SN, with 16 and 17 patients having micro- and macrometastases, respectively (Table II).

Table II. *Characteristics of the SN and non-SN.*

	No.	%
Number of positive SNs		
1	115	91.3
>1	11	8.7
Proportion of positive SN/total SNs		
1	69	54.8
>0.5 and <1	34	27.0
<0.5	23	18.3
Number of non-SNs		
Mean	14	
Range	12-18	
Non-SN status		
Negative	93	73.8
Micrometastases	16	12.7
Macrometastases	17	13.5

Univariate test of association between clinicopathological characteristics and non-SN involvement indicated that greater tumor size (p=0.05), high SBR grade (p=0.008), the presence of LVI (p=0.001), and the number of mitoses/mm^2 (p=0.01) were significantly related to the occurrence of metastasis in non-SN lymph nodes (Table I). By logistic regression, tumor size (p=0.03), LVI (p=0.001), grade (p=0.003) and the number of mitoses/mm^2 (p=0.01) were the only variables remaining in the model.

By recursive partitioning analysis, three subsets of patients were identified: i) a no-risk group including 23 (18.3%) out of 126 patients with pT1, G1, and no LVI who had tumor-negative non-SN; ii) an intermediate-risk group of 47 (37.3%) out of 126 patients with a rate of tumor-positive non-SN ≤15% who were characterized from the histopathologic standpoint by a <10 number of mitoses/mm^2, SBR grade II-III, and iii) a high-risk group of 56 (44.4%) out of 126 patients with a mean rate of non-SN involvement of 46%.

Discussion

The role of ALND as a staging procedure has been definitively overcome by SN biopsy due to the well-accepted surgical accuracy of this procedure, with a false-negative rate lower than 5%, as well as its higher pathological accuracy for the detection of occult lymph node metastases in the SN, thanks to the focused analysis of one or a few lymph nodes and the application of more accurate histopathological evaluations, such as serial sectioning and IHC analysis (18, 19).

The therapeutic benefit of ALND is much more controversial. On the one hand, the results of the NSABP-04 study excluded any survival benefit due to ALND because, according to Fisher *et al.*, breast cancer is a systemic disease from its onset so that any treatment aimed at removing nodal

Table III. *Rate of non-SN involvement by different tumor-related factors.*

Size, mm	LVI	SBR Grade	Number mitoses/mm^2	Rate of non-SN involvement	
				No.	%
<20	No	I	Any	0/23	0
<10	No	I	1-9	0/18	0
<10	No	I	>10	0/3	0
11-20	No	I	Any	0/2	0
Any	No	II-III	1-9	3/21	14
Any	Yes	II-III	1-9	4/26	15
Any	No	II-III	>10	6/16	37
Any	Yes	II-III	>10	20/40	50

metastases is unlikely to affect survival (20, 21). On the other hand, a meta-analysis of six clinical trials suggested an average survival benefit of 5.4% from ALND; another meta-analysis of 78 clinical trials indicated that improved locoregional control in patients with early-stage breast cancer translated into a benefit on survival at 15-year follow-up observation (22, 23). Recent results of the ACOSOG Z0011 trial would suggest avoiding ALND in patients with T1-T2 breast cancer and H&E SN metastasis who are treated with breast-conserving surgery, whole-breast irradiation, and adjuvant systemic therapy (12). However, the 5-year axillary nodal recurrence was higher in patients who had SN-biopsy alone as compared to patients who underwent completion ALND (1.3 *vs.* 0.6%); moreover, there were some limitations in this study regarding both the completeness of accrual, the adherence to the scheduled surgical treatment, and the more favorable prognosis of the no-ALND group (24).

For these reasons, the debate as to the role of therapeutic ALND is far from solved. In recent years, an alternative approach has been to develop mathematical models based on tumor-related characteristics (tumor type, size, LVI, histological grading, hormonal receptor status) and SN-related characteristics (method of metastasis detection in the SN, size of metastatic foci, extracapsular spread, number and proportion of positive SN) that could predict for non-SN status in order to avoid an unnecessary ALND in patients with the lowest risk of non-SN involvement (25). However, these nomograms lack sufficient accuracy and have limited clinical practicality. As a matter of fact, no available models could identify a consistent subset of SN-positive patients who had no additional lymph node involvement at ALND completion; moreover, a preliminary validation of each of these predictive models is always required due to different clinical practices among institutions, and different patients' characteristics (25, 26).

A meta-analysis identified a limited number of parameters that were found to negatively-affect non-SN status: SN metastasis size >2 mm, presence of extracapsular extension, tumor size >2 cm, >1 positive SN, and LVI of the primary tumor (27). Notably, although the incidence of non-SN involvement is much higher in patients with SN macrometastases than with SN micrometastases (mean value: 52.3 *vs.* 20.2%), these micrometastates also have a definite prognostic relevance because the 5-year disease-free survival is significantly worse (p<0.001), as compared to patients without any nodal involvement; moreover, the use of adjuvant systemic therapy significantly improves (p<0.001) the 5-year disease-free survival of patients with nodal micrometastases (13, 14, 28). For these reasons, patients with SN micrometastases cannot be regarded *per se* as being a low-risk group not deserving axillary clearance.

In our previous experience in 116 patients with SN micrometastases, greater tumor size (p=0.005) and presence of lymphovascular invasion (LVI) (p<0.001) were significantly related to occurrence of metastasis in non-SN lymph nodes; moreover, non-SN metastases were never detected in 15 patients with pT1a-1b, G1, and no LVI (15). Although this subset of patients was rather limited in size (12.9%) as compared to the whole group, this information was particularly attractive because ALND completion could have been safely omitted in such patients, without finding any additional non-SN metastasis. Hence, we prospectively evaluated these parameters in a validation set of 126 patients with SN micrometastases to confirm their predictive value, in order to ascertain the possibility of selecting patients at low risk of non-SN involvement based on the histopathological characteristics of the primary tumor and SN.

First of all, our present findings confirmed that greater tumor size, high histological grade, LVI, and the number of mitoses were significantly related to the detection of non-SN metastases. Secondly, 21 (16.6%) out of 126 patients with pT1a-1b, G1, and no LVI had no nodal metastases at completion ALND, thus confirming our previous observation

(15). This no-risk group could also be extended to include patients with well-differentiated pT1 tumors without LVI, representing 18.3% of the whole study group, and they could be safely spared unnecessary ALND. The intermediate-risk group had a <15% rate of non-SN involvement and comprised 37.3% of the study population; in this subset, a case-by-case decision might be considered regarding completion ALND in order to define its cost/benefit ratio, due to the low risk of axillary relapse related to residual nodal disease in patients who would systematically undergo adjuvant chemo-hormonal treatment. The high-risk group included almost half of the study population with a mean rate of non-SN involvement too high (46%) to avoid completion ALND.

Overall, these findings suggest that more than 50% of patients with SN micrometastases could be spared unnecessary ALND of no staging/therapeutic benefit, especially in patients with well-differentiated pT1 tumors without LVI.

Conflicts of Interest

All the Authors disclose they have no financial and personal relationships with other people or organizations that could inappropriately influence their work.

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