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Report

An axilla scoring system to predict non-sentinel lymph node status in breast cancer patients with sentinel lymph node involvement

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Summary

Background. Axillary lymph node dissection (ALND) is the current standard of care for breast cancer patients with sentinel lymph node (SN) involvement. However, the SN is the only involved axillary node in a significant proportion of these patients. Here we examined factors predictive of non-SN involvement in patients with a metastatic SN, in order to develop a scoring system for predicting non-SN involvement.

Materials and Methods. This study was based on a prospective database of 337 patients who underwent SN biopsy for breast cancer, of whom 81 (24%) were SN-positive; we examined factors predictive of non SN involvement in the 71 of these 81 women who underwent complementary ALND. All clinical and histological criteria were recorded and analysed according to non-SN status, by using Chi-2 analysis, Student's *t*-test, and multivariate logistic regression.

Results. Univariate analysis showed a significant association between non-SN involvement and histological primary tumor size ($p = 0.0001$), SN macrometastasis ($p = 0.01$), the method used to detect SN metastasis (H&E versus immunohistochemistry) ($p = 0.03$), the number of positive SNs ($p = 0.049$), the proportion of involved SNs among all identified SNs ($p = 0.0001$) and lymphovascular invasion ($p = 0.006$). Histological primary tumor size ($p = 0.006$), SN macrometastasis ($p = 0.02$) and the proportion of involved SNs among all identified SNs ($p = 0.03$) remained significantly associated with non-SN status in multivariate analysis. Based on the multivariate analysis, we developed an axilla scoring system (range 0–7) to predict the likelihood of non-SN metastasis in breast cancer patients with SN involvement.

Conclusion. In patients with invasive breast cancer and a positive SN, histological primary tumor size, the size of SN metastases, and the proportion of involved SNs among all identified SNs were independently predictive of non-SN involvement.

Introduction

Axillary lymph node status is the most important prognostic factor for patients with breast cancer [1]. Axillary lymph node dissection (ALND) has traditionally been the principal method for evaluating axillary lymph node status, but is associated with significant morbidity [2]. Management of the axilla in patients with operable breast cancer has thus become one of the most controversial topics in clinical oncology, with regard to the value and optimal extent of surgical dissection. Sentinel node (SN) biopsy, introduced by Krag et al. [3] and Giuliano et al. [4] in the early 1990s, represents a new standard of care for axillary node staging in patients with early-stage, clinically node-negative breast cancer. The goals of SN biopsy are to reduce the morbidity of breast cancer surgery by avoiding unnecessary ALND in patients with negative SN. However, if a positive SN is found, it is currently recommended to continue with ALND. In 40–70% of patients the SN is the only involved axillary node [5–8], implying that these patients undergo ALND unnecessarily. Furthermore, patients with metastatic SN receive systematic therapy. It would therefore be useful to be able to identify patients with SN involvement but whose non-SN are uninvolved. We examined factors potentially predictive of axillary non SN status in patients with SN involvement.

Patients and methods

Patients

From May 2001 to May 2003, 337 consecutive patients with invasive breast cancer and clinically negative

axillary nodes underwent SN biopsy. Exclusion criteria were a breast tumor measuring more than 2 cm on physical or radiological examination, multiple primary or inflammatory tumors, pregnancy, diabetes and neo-adjuvant therapy. All the patients signed an informed consent form. All patients had cytologically or histologically proven breast cancer prior to SN biopsy, based on core needle biopsy or fine needle aspiration. The same surgeon operated on all the women.

SN biopsy technique

Four peritumoral injections of 0.2 ml (30 MBq each) of unfiltered technetium sulfur colloid (Nano cis, CIS Bio International, Saclay, France) were administered the day before surgery. Scintigraphic images, including the breast and axilla, were obtained using a triple-head hybrid gamma camera with coincidence detection (Irix, Marconi Corporation, Cleveland Heights, OH, USA) 1 h after the injections and then every 30 min until the SN was visualized. Five-minute static anterior and lateral projections were acquired with a low-energy/high-resolution collimator and a matrix size of 512×512 pixels. If the SN was not visualized on the day of the injection, a final image was acquired the next day, two hours before surgery. Under general anesthesia, the patients received a subdermal injection of 2 ml of patent blue (Bleu Patenté V, Guerbet laboratory, Issy les Moulineaux, France) above the tumor, followed by breast massage lasting 3 min. Breast surgery (mastectomy or lumpectomy) was performed 15 min after the injection, and was followed by SN detection with a handheld gamma probe (Gammed 2, Eurorad, Strasbourg, France). The SN was removed through an incision (as used for radical nodal dissection) just below the axillary hairline, where the gamma probe showed the greatest nodal radioactivity. The SN was located by following a blue lymphatic channel to a lymph node and/or by using the gamma probe to detect radioactive nodes. The SNs were removed, and the wound was then re-examined to ensure that all radiolabeled SNs had been identified and removed. The first 73 patients (corresponding to the learning phase) systematically underwent ALND after SN biopsy, whether the latter was positive or negative, in order to calculate the false-negative rate. In the subsequent 264 patients, ALND was only performed (during the same procedure) if the SN was positive by imprint cytology (IC) or if the primary tumor measured more than 20 mm intraoperatively. A second operation was performed if either hematoxylin and eosin (H&E) staining or immunohistochemistry (IHC) revealed tumor cells in the SN. ALND was also performed if the SN could not be located.

Histopathologic evaluation

Excised SNs were sent fresh to the pathology laboratory for IC. The SNs were bisected and a touch preparation was made with a glass slide, on both sides of the cut. One imprint from each pair was air-dried and stained with Diff-Quick. The results were reported to the operating room as positive (metastatic) or negative. After imprinting, the SNs were immediately placed in ethanol and stained with H&E. Each half-SN was sliced at 3-mm intervals. Each 3-mm section was analysed by four additional levels of 150 μm and four parallel sections; one was used for H&E staining and H&E-negative sections were examined by IHC with an anti-cytokeratin antibody cocktail (Cytokeratin AE1–AE3, Dako Corporation, Glostrup, Denmark). Non sentinel nodes (non-SNs) obtained during axillary dissection were totally submitted and blocked individually following 3 mm distances and H&E staining. The size of nodal metastases was estimated with an eyepiece micrometer. Micrometastases were defined as a single focus of metastatic disease per node, measuring no more than 2 mm. The presence of single non- cohesive tumor cells was recorded. SNs were recorded as positive when they contained macrometastases, micrometastases or isolated tumor cells.

Analysis

Clinical data collected for each patient included age, the pathological size of the invasive carcinoma (in mm), tumor type, nuclear grade, lymphovascular invasion, estrogen/progesterone recep tor status, number of positive SNs and type of SN metastasis (macrometastasis, micrometastasis or isolated tumor cell). Each factor was first tested individually for a significant association with non-SN status. Continuous variables were analysed in a univariate logistic regression model. Dichotomous variables were analysed using the Pearson chi-square test or Fisher's exact test. Significant factors were then included in a multivariate logistic regression model. Logistic regression analyses were performed using the TYPE TEST version Y. Univariate and multivariate analyses were performed using StatView® Software version 5.0 (SAS Institute Inc., Cary, North Carolina, USA). A p value less than 0.05 was considered significant.

An axilla scoring system was then developed from the data for patients with metastatic SN who underwent ALND. Multivariate logistic regression was used to analyse the association of each variable with the likelihood of non-SN involvement, and the axilla scoring system was based on all the variables.

Results

Three hundred thirty-seven patients, including one man, were enrolled in this study. Mean age was 57 years (range, 29–85 years). Mean histological invasive tumor size was 14.4 mm (range, 1–116 mm). Other descriptive characteristics of the study population are listed in Table 1. Breast-conserving surgery was performed in 300 cases (89%). Lymphatic mapping was based on both patent

Table 1. Patient and tumor characteristics

Characteristics	Number of patients (%)
All cases	337
Mean age, years (range)	57 (29–85)
Postmenopausal	236 (70)
Mean body mass index, kg/m^2 (range)	24.7 (16.7–44.4)
Breast tumor site	
Upper outer	207 (61.4)
Lower outer	30 (8.9)
Upper inner	47 (13.9)
Lower inner	27 (8)
Subareolar	26 (7.8)
Palpable mass	177 (82.2)
Mean invasive tumor size, mm (range)	14.4 (1–116)
Breast surgery	
Lumpectomy	300 (89)
Mastectomy	37 (11)
Tumor classification	
pT1is	12 (3.6)
pT1a	37 (11)
pT1b	79 (23.4)
pT1c	166 (49.3)
pT2	40 (11.9)
pT3	3 (0.8)
Histology	
Invasive ductal carcinoma (including DCISM)	252 (74.7)
Ductal carcinoma *in situ*	16 (4.7)
Invasive lobular carcinoma	39 (11.6)
Invasive tubular carcinoma	18 (5.4)
Others	12 (3.6)
Lymphovascular invasion	
No	277 (86)
Yes	45 (14)
Estrogen/Progesterone receptor status	
Positive	293 (93.3)
Negative	21 (6.7)
HER-2-neu receptor	
Positive	8 (2.6)
Negative	305 (97.4)
Tumor grade	
1	165 (52.7)
2	110 (35.2)
3	38 (12.1)
Ki 67	
Low	262 (84.2)
High	49 (15.8)
Number of nodes	
Mean number of SNs (range)	2.03 (1–6)
Mean number of non-SNs (range)	9 (3–21)

SN: Sentinel lymph node; DCISM: Ductal carcinoma *in situ* with microinvasion; Tumor grade 1: Well differentiated; Grade 2: Moderately differentiated; Grade 3: Poorly differentiated.

blue and radioactive colloid in all cases. At least one SN was identified in 326 patients (97%). Sentinel node biopsy took a mean of 10 min (range, 5–30 min). The mean number of SNs identified was 2.03 (range, 1–6). Of the 337 patients, 81 patients (24%) had at least one metastatic SN, comprising macrometastases in 39 patients, micrometastases in 12 patients (by H&E), and micrometastases in 18 patients and isolated tumor cells in 12 patients (by immunohistochemistry). Of the 81 patients with metastatic SN, 71 patients underwent ALND. Of the remaining 10 patients with metastatic SN, four refused ALND, three patients with single malignant cells in the SN had contralateral ALND because of bilateral breast cancer, and three patients had a distant metastasis. The SN was the only involved node (73.2%) in 52 of the 71 patients with positive SN who underwent ALND. Table 2 shows the relationships between clinicopathologic variables and non-SN positivity. Univariate analysis showed a significant association between non-SN involvement and histological primary tumor size ($p = 0.0001$), SN macrometastasis ($p = 0.02$), the method used to detect SN metastasis (H&E versus immunohistochemistry) ($p = 0.03$), the number of positive SNs ($p = 0.049$), the proportion of involved SNs among all removed SNs ($p = 0.0001$) and lymphovascular invasion ($p = 0.006$). Logistic regression identified histological primary tumor size ($p = 0.006$), SN macrometastasis ($p = 0.02$) and the ratio of the number of metastatic SNs to the total number of SNs removed ($p = 0.03$) as being significantly associated with a higher likelihood of non-SN involvement. Based on these results of multivariate analysis, an axilla scoring system (range 0–7) was developed to predict the likelihood of non-SN metastasis in patients with positive SN biopsy. The axilla scoring system consisted of three variables, namely the number of positive SNs divided by the total number of SNs removed, the presence of macrometastasis in the SN; and histological primary tumor size (Table 3). For an individual patient, each variable was assigned a point value. An involved SN/total SN ratio of 1 was scored two points, a ratio between 0.5 and 1 was scored one point, and a ratio below 0.5 was scored zero points. Macrometastasis in the SN was scored two points, and its absence was scored zero points. Tumor size scored zero points if ≤ 10 mm; 1.5 points if between 11 and 20 mm; and three points if >20 mm.

Patients with scores of 3.5 (constituting the median score) or less had a 97.3% chance of having negative non-SNs (odds ratio, 42.75; 95% confidence interval, 20.5–90.0), suggesting that a complementary ALND could reasonably be avoided. The chances of having negative non-SN were 94.7% in patients with a score of 4 or less.

Discussion

In recent years, ALND has been considered as a staging procedure offering prognostic information but contributing little to the chances of breast cancer cure [9].

Table 2. Univariate analysis of clinicopathologic features of 71 patients with metastatic SNs, with or without non-SNs metastasis

	Tumor-free non-SN (%)	Metastasis in non-SN (%)	*p* value
Study population	52	19	
Age (years)			0.37
≤50	16 (30.8)	8 (42.1)	
> 50	36 (69.2)	11 (51.9)	
Mean body mass index (kg/m^2)	23.4	26.3	0.11
Palpable mass			0.27
No	24 (46.2)	6 (31.6)	
Yes	28 (53.8)	13 (68.4)	
Histological tumor size (mm)			0.0001
≤10	11 (21.2)	0	
11–20	35 (67.3)	7 (36.8)	> 20
6 (11.5)	12 (63.2)		1
25 (48.1)	6 (31.6)		2 and 3
27 (51.9)	13 (68.4)		
Estrogen/Progesterone receptor			0.6
Positive	48 (92.3)	17 (89.5)	
Negative	3 (7.7)	2 (10.5)	
Lymphovascular invasion			0.006
Yes	12 (15.4)	11 (57.9)	
No	40 (84.6)	8 (42.1)	
Ki67			0.21
Low	44 (84.6)	14 (73.7)	
High	7 (15.4)	5 (26.3)	
Macrometastasis in the SN			0.013
No	31 (59.6)	5 (26.3)	
Yes	21 (40.4)	14 (73.7)	
Histological method of detection of SN metastasis			0.03
H&E	30 (57.7)	16 (84.2)	
IHC	22 (42.3)	3 (15.8)	
Number of positive SNs			0.049
1	44 (84.6)	12 (63.2)	
≥2	8 (15.4)	7 (36.8)	
Ratio of number of metastatic SN on total number of SN			0.0001
Equal to 1	9 (17.3)	13 (68.4)	
Between 0.5 and 1	26 (50)	5 (26.3)	
< 0.5	17 (32.7)	1 (5.3)	

SN: Sentinel lymph node; H&E: Hematoxylin and Eosin; IHC: Immunohistochemistry.

Table 3. Axilla scoring system to predict the likelihood of non-SN metastases in patients with positive SN ($n = 71$)

Variable	Point value	Multivariate analysis (*p*)
Macrometastasis in the SN		$p = 0.02$
No	0	
Yes	2	
Histological tumor size (mm)		$p = 0.006$
≤10	0	
11–20	1.5	
> 20	3	
Proportion of involved SNs among all removed SNs		$p = 0.03$
< 0.5	0	
Between 0.5 and 1	1	
1	2	

SN: Sentinel lymph node.

Sentinel lymph node biopsy has emerged as an accurate method of determining axillary node status. It also provides prognostic information, but has lower morbidity than conventional ALND. However, complete ALND is still recommended for patients with metastatic SN, in order to refine the prognosis, to maintain local control of the axilla, and for a potential therapeutic benefit. However, a number of studies have shown that the only metastatic site in 40–70% of patients with metastatic breast cancer is the SN [5–8]. This has prompted studies of predictive factors for non-SN involvement in women with SN metastasis, with a view to avoiding ALND in some patients.

The size of SN metastasis is considered the best predictor of non-SN status, as confirmed by our multivariate analysis ($p = 0.01$). Only 14% of women with SN micrometastases (≤2 mm) had non-SN metastases, compared with 40% of women with macroscopic SN metastasis (> 2 mm) (Table 4).

Multivariate analysis also showed that primary tumor size also significantly influenced the risk of non-SN involvement: the risk was 0% in patients with pT1a,b tumors, 17% in those with pT1c tumors, and 67% in those with tumors measuring more than 20 mm. In the series of 157 cases published by Chu et al. [10], the rate of non-SN involvement increased from 13 to 38% from stage T1b to stage T2 tumors.

The proportion of involved SNs among all removed SNs was the third predictor of non-SN status in multivariate analysis ($p = 0.03$). Only one previous study of predictive factors examined this parameter [11]. Van Zee et al. [11], in a study of 702 patients with a tumor-involved SN, found that the number of negative SNs was significantly associated with non-SN status ($p < 0.001$).

Lymphovascular invasion is a factor of poor prognosis and correlates with nodal stage. In our study it was significantly associated with an increased risk of non-SN involvement in patients with positive SN metastasis, but only in univariate analysis ($p = 0.006$). Lymphovascular invasion has rarely been found to be an independent risk factor for non-SN involvement (Table 4).

Approximately one-third of our patients with a positive SN had non-SN metastasis, further suggesting that

Table 4. Studies of predictive factors for non-SNs metastases in patients with breast cancer and SN involvement (based on multivariate analysis)

Author	Number of patients with positive SN	Mean tumor size (mm)	Positive non-SN (%)	Tumor size	LVI	E/P status	ECE	Number of positive SN	Histological method of SN met (H&E versus IHC)	Size of SN met	Ratio Number Positive SN/Total SN
Chu [10]	157	20	34	0.014	NS	NS	–	NS	NS	< 0.0001	–
Reynolds [14]	60	–	47	0.0004	NS	0.03	–	–	–	0.02	–
Turner [15]	194	20	45	0.03	0.03	NS	0.0001	NS	–	0.01	–
Viale [16]	109	15	22	NS	NS	NS	–	–	–	0.02	–
Weiser [17]	206	15	32	0.007	NS	–	–	–	–	0.0002	–
Wong [18]	389	–	37	< 0.001	–	–	–	< 0.001	–	–	–
Sachdev [7]	55	13	60	0.0001	0.001	–	NS	–	–	0.02	–
Van Zee [12]	702	–	–	0.001	0.003	NS	–	< 0.001	0.0001	–	< 0.001[a]
Nos [19]	263	15	24	0.017	NS	NS	NS	NS	NS	< 0.001	–
Van Iterson [20]	135	20	34	0.035	–	–	–	0.018	–	0.006	–
Saidi [12]	34	22	32	0.04	0.03	NS	0.001	–	NS	NS	–
Fournier [21]	42	21	36	NS	NS	NS	–	–	–	0.039	–
Fleming [22]	54	26	48	NS	NS	–	0.016	–	–	0.024	–
Stitzenberg [8]	74	19	46	NS	–	–	0.011	NS	–	NS	–
Travagli [13]	50	13	30	NS	0.027	NS	–	NS	–	NS	–
Present study	71	14	27	0.006	NS	NS	–	NS	NS	0.02	0.03

SN: Sentinel lymph node; LVI: Lymphovascular invasion; NS: Not significant; E/P: Estrogen/Progesterone; met: Metastasis; H&E: Hematoxylin and Eosin: IHC: Immunohistochemistry; ECE: Extracapsular extension.

[a]Corresponds to the number of negative SNs.

the majority of patients with positive SN do not benefit from ALND. Based on the results of multivariate analysis, we developed an axilla scoring system to predict the likelihood of non-SN involvement in patients with positive SN biopsy. The three independent predictors included in the scoring system were the number of positive SN divided by the total number of SN removed; the presence of macrometastasis in the SN; and primary tumor size. Applied to our population, the score identified a subpopulation of patients with an extremely low risk of non-SN involvement, in whom full ALND could, in principle, be avoided. Patients with a score of 3.5 or less had a 97.3% chance of being free of non-SN involvement (odds ratio, 42.75; 95% confidence interval, 20.5–90.0). Two other authors have reported scores for predicting non-SN involvement after positive SN biopsy. Van Zee et al. developed a simple nomogram [11], incorporating nuclear grade, lymphovascular invasion, multifocality, estrogen receptor status, number of negative SNs, number of positive SNs, pathological size, and the method of detection of SN metastases.

The weakness of this nomogram is that it does not take into account the degree of nodal metastases. Except for three studies [8, 12, 13], it is generally considered that the size of SN metastasis is a significant predictor of non-SN status. Saidi et al. [12] also developed a score based on data for 34 patients with positive SN biopsy findings. The score (range 0–5) included tumor size, the presence of a palpable mass, angiolymphatic invasion and extracapsular extension. Patients with a score of 2 or less had only a 5.8% risk of having non-SN metastasis.

Before results of prospective randomised trials are available to determine whether completion ALND after positive SN biopsy has any significant on the clinical outcome of patients, this model could be used and have potential clinical implications identifying a subgroup of patients for whom ALND should be avoided. However, this model should be applied prospectively to a large number of patients with positive SN who underwent additional ALND to verify its validity before we recommend to abandon ALND in patients with positive SN and axilla score ≤ 3.5.

The main limitation of our score is that is does not take into account extracapsular extension of SN metastasis, which is a powerful predictor of non-SN metastasis [8]. This is because we believe all patients with extracapsular extension of SN metastasis should undergo completion ALND, and such patients were not therefore included in the study population.

Conclusion

This study shows that, in patients with invasive breast cancer and a positive SN, the histological primary tumor size, the size of metastasis within the affected SN, and the ratio between number of metastatic SNs and total number of SNs independently influence the risk of non-SN involvement. Our axilla scoring system, based on these three variables, should be helpful to determine whether completion ALND can be avoided in selected patients with metastatic SN, and now needs to be tested prospectively in a large number of patients with positive SN, all of whom undergo full ALND.

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