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Axillary Sentinel Node and Tumour-related Factors Associated with Non-sentinel Node Involvement in Breast Cancer

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Background: After completion of axillary dissection, many breast cancer patients with axillary sentinel nodal involvement are found to have regional disease limited to the sentinel nodes. These patients are exposed to the morbidity of axillary clearance without any expected therapeutic benefit.
Methods: Sentinel node biopsy was performed either with Patent blue dye or with a combined dye, radiocolloid and gamma-probe-guided method involving peritumoral tracer administration. For a series of 150 consecutive patients with involved axillary sentinel nodes and axillary dissection, factors associated with non-sentinel nodal involvement were analysed in a multivariate analysis based on logistic regression with the use of fractional polynomials.
Results: The following variables were found to be potentially associated with non-sentinel node metastases: tumour size, sentinel node metastasis size, number of examined sentinel nodes, percentage of involved sentinel nodes (the latter two were found to be significant only when in combination), and extracapsular perinodal spread.
Conclusions: Isolated tumour cells and micrometastases in axillary sentinel nodes carry a low risk of non-sentinel node metastasis. The risk of metastasis to further echelon nodes is higher with macrometastases, especially if there is extracapsular growth and the proportion of involved sentinel nodes is high.

Key words: breast cancer – metastasis – multivariate analysis – non-sentinel lymph nodes – sentinel lymph nodes

INTRODUCTION

Sentinel lymph node (SN) biopsy (SNB) is a minimally invasive method for the surgical and pathological nodal staging of breast cancer. Most of the larger series reported have attained an accuracy of 98–99%, with the false-negative rate ranging between 5 and 10% (1–3). Selective axillary dissection (as a treatment option for regional disease control) based on the results of SNB is on the way to becoming the standard of care (4). While there is a general consensus regarding the omission of axillary clearance in SN-negative patients, there still remains a substantial proportion of SN-positive patients who have metastases limited to the SNs only (5,6). Accordingly, it seems that up to 50–60% of the patients with positive SNs undergo axillary dissection with a negative nodal status for these further echelon lymph nodes. Our current understanding of breast cancer suggests that these patients do not benefit from complete axillary dissection, but are exposed to its potential morbidity. Using data from patients with positive SNs, including patients with SNs harbouring micrometastases and isolated tumour cells, this study attempts to identify factors associated with the metastatic involvement of non-SNs, and which may predict their higher incidence.

SUBJECTS AND METHODS

From our patients who underwent SNB between August 1997 and August 2002, we chose all 150 consecutive SNB procedures with positive SNs in patients who underwent a routine completion axillary dissection as part of our validation study (7) or accepted axillary dissection on a selective basis after the finding of a positive SN in their axilla. [Three further patients with isolated tumour cells and one with micrometastasis (8–10) did not accept further axillary surgery after SNB.]

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The method of SNB has been previously reported (7). Briefly, it involved either the use of peritumorally injected Patent blue dye at the beginning of the series, or a combined dye, radiocolloid and gamma-probe-guided method, with both tracers preferentially administered peritumorally or intratumorally. Ultrasound or, rarely, mammography was used for guidance in cases of non-palpable tumours. Preoperative lymphoscintigraphy was usually performed the day before surgery, 2–3 h after injection of the radiolabelled colloidal albumin (Nanoalbumon, OSSKI, Budapest, Hungary, a small-particle colloid, or Senti-Scint, OSSKI, Hungary, a large-particle colloid). A few patients with negative lymphoscintigrams after peritumoral or intratumoral radiocolloid administration received a smaller dose of the radioactive tracer subareolarly.

After intraoperative assessment by imprint cytology (11,12), SNs were fixed in formalin, embedded in paraffin and subjected to enhanced histopathology, which involved step-sectioning up to the extinction of the blocks. Three different methods of step-sectioning were used throughout the study period: SNs >5 mm were bivalved so as to reveal the largest cut-surface possible and step-sectioned at 50–100 μm (Protocol A; $n = 75$ patients) (13) or at 250 μm (Protocol B; $n = 45$ patients) (14), or were sliced perpendicularly to their longest axis and step-sectioned at 250 μm (Protocol C; $n = 30$ patients) (15). Immunostaining for the demonstration of cytokeratins (and also epithelial membrane antigen at the beginning of the study) was performed on multiple levels in the event of negative HE findings. The histological sectioning level at which SNs metastases were identified was recorded.

Non-SNs were subjected to standard HE assessment, which generally meant a single HE stained slide with 2–4 consecutive sections from all non-SNs with some larger non-SNs having several levels investigated because of slicing of the lymph nodes before processing. No step sectioning was used for non-SNs. For the purposes of this study, any finding of metastatic tumour cells or tissue was considered a positive finding. However, similarly to the tumour sizes, these findings were divided into subgroups according to the tumour–node–metastasis (TNM) categories (8–10).

One case with a final pathology diagnosis of ductal carcinoma *in situ* (DCIS) was found to have a positive SN. For practical purposes, this patient was considered in the analysis to have a microinvasive carcinoma 1 mm in size. All but three tumours could be graded; these three exceptions were microinvasive carcinomas, and the grade of the associated DCIS was assigned to them, on the basis that the grades of a DCIS and the associated invasive carcinoma are often the same (16,17). The size of isolated tumour cells consisting of only one or a few cells and measuring <0.1 mm was rounded to 0.1 mm. For multiple involved SNs, or multiple separate metastases within the same SN, only the size of the largest metastasis was considered.

The probability of a positive non-SN was modelled using logistic regression (18). The following variables were considered for inclusion in the models: age, tumour size, maximum size of the SN metastasis, number of SNs recovered, number of positive SNs, percentage of involved SNs (number of positive SNs divided by the number of SNs ×100), extracapsular spread of the SN metastasis, detection of the SN metastasis by HE or immunohistochemistry, involvement of one or more than one SN, pN category of the SN metastasis, pT category of the tumour, histological grade of the tumour, presence of lymphovascular invasion and histopathological protocol used. The first six variables were treated as continuous, and the others as binary or categorical variables. The histological sectioning level where the metastasis was first detected in SNs was also analysed because of its interest for pathologists, but was not included in the logistic regression model, because it was felt that having three types of histological protocol would have biased the analysis simply because the first level did not always mean the same thing. It can be thought of as a parameter reflecting the size of nodal metastasis.

The effects of the continuous variables were modelled by using linear combinations of two power terms (fractional polynomials of order 2) (19). To find the best-fitting model, the backward elimination algorithm implemented in the routine 'mfracpol' (option 'sequential') of the STATA statistical package (Stata Corporation, College Station, TX) (20) was used. A significance level of 0.05 was used both to retain variables in a model and to select the form of the fractional polynomials.

The goodness-of-fit of the models was evaluated using the Hosmer–Lemeshow test (18). The significance of terms in the final model was assessed using the likelihood ratio test (18). In all tests, a two-sided level of significance of 0.05 was applied.

RESULTS

The mean (±SD) age of the analysed patients was 57.2 (±11.9) years. The mean (±SD) and median numbers of SNs were 1.6 (±0.9) and 1, respectively, whereas the mean (±SD) and median numbers of non-SNs were 14.4 (±6.3) and 13, respectively. At least one non-SN was found to be positive in 60 cases (40%).

The clinicopathological parameters of the patients with positive and negative non-SNs analysed in this study are compared in Table 1.

The cumulative percentage of non-SN metastases according to the histological protocol and to the sectioning level where SN metastases were first identified is depicted in Fig. 1.

The logistic regression involving the backward elimination algorithm resulted in a model that included linear effects of the tumour size, the maximum SN metastasis size, the percentage of positive SNs and the presence of extracapsular spread (as binary covariate). In the exploratory analysis, it was found that the percentage of positive SNs was strongly negatively correlated (Pearson's correlation coefficient $\rho = -0.76$) with the overall number of examined SNs. Thus, the number of examined SNs may become non-significant in a model not

Table 1. Distribution of clinicopathological variables in patients with positive SNs

	Patients with positive non-SNs	Patients with negative non-SNs	All patients
Mean age (years)	56.8	57.4	57.2
Tumour size (TNM)			
pT1mic	0	3	3
pT1b	2	5	7
pT1c	14	36	50
pT2	40	46	86
pT3	4	0	4
Mean tumour size (±SD) (cm)	2.8	2.2	2.4
Tumour histological grade			
Grade I	22	23	45
Grade II	20	45	65
Grade III	18	22	40
Lymphovascular invasion in the primary tumour	16	18	34
Number of SNs assessed			
1	43	47	90
2	14	22	36
3	3	18	21
4	0	2	2
6	0	1	1
Mean	1.3	1.8	1.6
Number of SNs involved			
1	49	73	122
>1	11	17	28
Mean	1.2	1.2	1.2
Mean proportion of involved SNs	0.80	0.94	0.86
SN metastasis size (TNM)			
pN0(i+)	0	10	10
pN1mi	8	24	32
pN1a	52	56	108
Mean metastasis size (±SD) (mm)	9.3	4.4	6.4
Extracapsular growth of SN metastasis	33	19	52
Detection mode of SN metastasis			
HE	59	83	142
IHC	1	7	8
Detection in the 1st/1st two/1st five sectioning levels			
Protocol A	28/29/30	28/31/33	56/60/63
Protocol B	13/15/16	16/18/24	29/33/40
Protocol C	9/9/10	16/18/18	25/27/28
All patients	50/53/56	60/67/75	110/120/131

SN, sentinel node; TNM, tumor–node–metastasis; SD, standard deviation; HE, hematoxylin and eosin; IHC, immunohistochemistry.

because it has no effect, but because the percentage of positive SNs is already included in the model and, due to the correlation, accounts for part of the effect of the number of SNs. It was therefore decided to add to the final model a linear effect of the overall number of examined SNs as a covariate. As a result, the model outlined in Table 2 was obtained. The fit of the model to the data was satisfactory ($P = 0.973$, Hosmer–Lemeshow test). It is noteworthy that, although the effects of

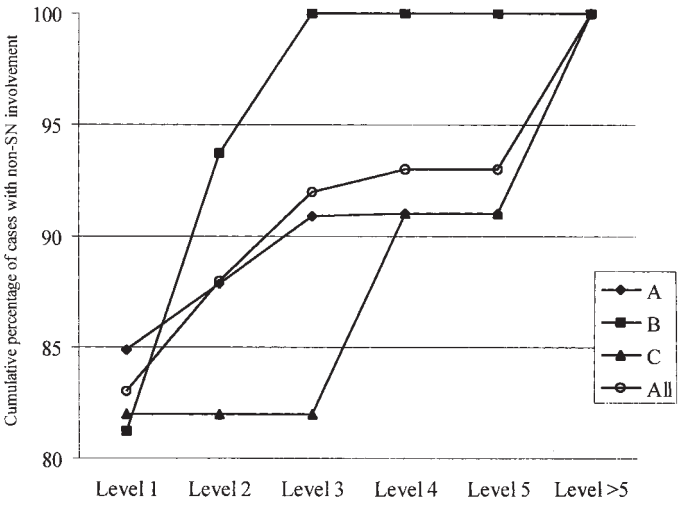

Figure 1. Cumulative percentage of patients with non-SLN metastases associated with SLN metastases first identified at the first to fifth level and beyond (the figure is based on 60 cases with metastases to both SNs and non-SNs). (A, B and C refer to different protocols, whereas All does not account for differences in slicing and sectioning method; in this last setting level 1 identification can be equated with a basic or standard nodal assessment, and the final point of axis x as a more detailed histopathological analysis, without specific details on the analysis).

Table 2. Factors associated with non-SN involvement as determined by multivariate analysis

	Odds ratio (SE)	*P*	95% CI
Tumour size (cm)	1.62 (0.35)	0.02	1.06–2.47
SN metastasis maximum size (mm)	1.13 (0.05)	0.005	1.03–1.24
Number of examined SNs	0.57 (0.22)	0.127*	0.26–1.22
Percentage of positive SNs	1.004 (0.014)	0.755*	0.977–1.033
Extracapsular spread	2.92 (1.29)	0.015	1.23–6.95

CI, confidence interval; SE, standard error; SN, sentinel node.

the number of examined SNs and the percentage of positive SNs are not significant when considered separately ($P = 0.148$ and 0.755, respectively), their joint effect is significant ($P = 0.023$ for the likelihood ratio test). This is a consequence of the strong correlation between these two variables.

The model presented in Table 2 suggests that the odds of positive non-SNs increase by 62% with each extra centimetre of tumour size, by 13% with each extra millimetre of maximum SN metastasis size, and by 192% if extracapsular spread is present. The odds decrease by 43% with every examined SN, but the decrease is counterbalanced by a 0.4% increase for each percentage point of positive SNs. The 0.4% increase in the odds of non-SN involvement for each percentage point of positive SNs may seem small. Nevertheless, it implies, for instance, a 22% increase in the odds when the percentage of positive SNs increases by 50% (e.g. when both of two examined SNs are found positive instead of only one).

In principle, one could consider replacing the percentage of positive SNs in the model presented in Table 2 by their number. However, in that case the model would assume the same effect of the number of positive SNs for any number of examined SNs. Accordingly, it would imply the same increase in the odds of non-SN involvement if one positive node is found out of two, or out of six examined SNs. From this point of view, the model in Table 2 seems somewhat more plausible: it suggests a higher increase of the odds of non-SN involvement if there is one additional positive node out of three SNs examined, as compared with the case when there is one additional positive node out of six SNs.

DISCUSSION

SNB is a minimally invasive staging procedure that represents a reasonable alternative to axillary dissection in SN-negative, and therefore presumably node-negative, breast cancer patients. The demonstration of SN metastases usually invokes a complete axillary dissection, because this procedure allows nodal substaging, by specifying the number of lymph nodes involved and results in the best rates of regional disease control. Irradiation of the axilla is a reasonable alternative to complete axillary dissection for regional control of the disease (21).

Many series before the SN era and practically all studies on SNs and subsequent axillary dissection suggest that regional metastases are limited to the SNs in a significant percentage of the patients. Our current understanding of breast cancer suggests that further axillary treatment following SNB is of no therapeutic benefit for these patients. Identification of these patients on the basis of the data available after removal of the primary tumour and its SNs may have important implications in the care of SN-positive patients.

More than 80% of the non-SN involvement was associated with SN involvement detected at the first sectioning level (Fig. 1). The remaining 15–20% of non-SN involvement was associated with SN detection at other sectioning levels. Figure 1 suggests that there were some differences according to the histopathological sectioning protocol, but the sectioning protocol was not retained as a significant covariate in the regression analysis.

In the multivariate analysis we found that, among the considered clinical factors, the following may be associated with non-SN involvement: the tumour size, the maximum SN metastasis size, the number of examined SNs, the percentage of involved SNs, and the presence of extracapsular spread. Some caution is required, however. For instance, the selection of the best-fitting model was based on a stepwise procedure, which involves multiple testings. Consequently, the set of covariates included in the model might be specific to the analysed dataset (a false-positive finding). Moreover, the fact that the procedure suggested the use of only linear effects of continuous covariates might be due to the limited number of data available. Therefore, as with any modelling and experimental results, a replication of the analysis on an

independent dataset is advisable to confirm the conclusions presented below.

Our results suggest that one of the important predictors of non-SN involvement is the size of the SN metastasis. We reviewed the relevant literature, and found that this was in accordance with the results obtained in larger studies by other investigators (22–30). Similarly to earlier observations documenting a high percentage of SN-positive patients with regional disease limited to the SNs, this finding is a further argument for the sequential lymphogenic spread of breast carcinoma.

In an earlier study, we analysed the distribution of metastases in SNs, and found that the location of the SN metastasis was an important predictor of non-SN metastasis in one of the models. It was concluded that patients with pT1 tumours (<1.8 cm) metastatic only to the sinus of a single SN had a low probability of non-SN metastasis (31). In the present study, we utilised a larger dataset and a different approach. We omitted the location of the metastases as a factor. Instead, we adhered to the accepted categories of the newly revised TNM system, because we believe that the isolated tumour cell category, termed submicrometastasis by the 2001 consensus conference (32), adequately describes a subset of 'metastases' limited to the sinuses. This category includes tumour cells or small clusters of tumour cells situated in the sinuses measuring up to 0.2 mm and showing no evidence of tissue reaction. Although the maximum size of this category is arbitrary, it is easily reproducible and should be considered standard until there is support for the opposite situation. We found no metastases in non-SNs associated with isolated tumour cells in the SNs. However, on the basis of the published studies, it is suggested that there may be up to 9–12% non-SN involvement with isolated tumour cells in the SNs if it is accepted that most of the positive SN cases identified by IHC only belong in the category of isolated tumour cells (12,33).

Besides the SN metastasis size, most of the studies dealing with factors associated with non-SN involvement indicate that another factor associated with non-SN metastasis is the tumour size (24–29,34). Our analysis also suggests that this variable can be associated with non-SN involvement. However, we are aware of three studies in which the tumour size was not found to be a significant predictor of non-SN metastases (22,23,30). In one of these, in which a detailed histopathology was conducted for both SNs and non-SNs, the rate of SN metastasis-associated non-SN involvement was practically the same (nearly 50%) for all tumour size categories (22). Clearly, the role of tumour size in non-SN involvement demands further investigation. The discrepant results on the role of tumour size may be due to the assessment of this variable as a categorical value instead of a value on a continous scale.

The model in Table 2 suggests a large increase in the odds of non-SN involvement associated with extracapsular spread. Extracapsular spread was rarely assessed in the series analysed to date, and it was found to be associated with non-SN involvement in four out of five studies in which it was considered (23,27,29,31), although one of these studies looked specifically at extranodal tumour involvement of the hilar pole (26).

Of the studies assessing the risks of non-SN involvement associated with SN metastasis, we have identified only three which included the number of SNs in the model (25,34,35), and a significant association was found by univariate analysis of one of these (25). The number of positive SNs was included in the models in seven studies (23,25–27,29,34,36); it was found to be significant on univariate analysis in four of these, and in one series (with no assessable data on SN metastasis size) it was also found to be significant on multivariate analysis. Our analysis indicates that the odds of non-SN involvement decrease with increase in the number of examined SNs and increase with increase in the percentage of positive SNs. (It is worth noting that the number of SNs and the percentage of positive SNs were found to be significant in the mode only when they were considered jointly.) Since the percentage of positive SNs can be considered a measure of the extent of 'a metastatic spread' that has already taken place, increasing the odds relative to an increase in the percentage appears plausible. A similar effect of the percentage of involved nodes on survival was also seen in a recent analysis of the Surveillance, Epidemiology and End Results database (37).

To our knowledge, this study is the first to include isolated tumour cells as a separate category in the analysis of factors associated with non-SN involvement and demonstrating a low associated risk of further echelon node metastases. This is in keeping with other studies. We believe that at least some non-SN metastases found in association with minimal SN involvement (isolated tumour cells or micrometastases) represent a pattern of lymphodynamics where a massive metastasis obstructs lymphatic channels and diverts the lymph flow from the normal. This phenomenon is one of the suggested mechanisms for false-negative SNBs. Massive non-SN metastasis was seen in five of our eight cases with both SN micrometastasis and non-SN involvement, and this fact alone is enough to question the relevance of omitting axillary dissection after the finding of a micrometastasis in an SN. Although massively involved lymph nodes may not always be palpable before surgery (a clinically negative nodal status is required for eligibility for SNB), intraoperative physical examination of the axilla may reveal them, and therefore the practice of intraoperative axillary palpation is recommended, as suggested by the Amsterdam Group (38). In the event of a negative peroperative clinical nodal status and isolated tumour cells or even micrometastases in the SNs, axillary nodal clearance may not be necessary, even in those institutions where clearance and not sampling is the standard of care.

Finally, it should be mentioned that the results described here could have been slightly different if the non-SNs had been subjected to the same type of pathology protocol as that for the SNs, but for practical reasons this was not done.

In summary, our results suggest that non-SN metastases may be associated with the tumour size, the SN metastasis size, the number of examined SNs, the percentage of involved SNs and the extracapsular spread of the SN metastasis. These results

require validation on independent samples of larger size and, if validated in that way (or even by means of clinical trials), could offer a guide for estimation of the risks of non-SN involvement.

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