PERGAMON

European Journal of Cancer 37 (2001) 454–458

European Journal of Cancer

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Sentinel lymph node biopsy as an indicator for axillary dissection in early breast cancer

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Received 12 July 2000; received in revised form 26 September 2000; accepted 10 November 2000

Abstract

Sentinel node biopsy (SNB) is a new component of the surgical treatment of breast cancer that accurately predicts axillary status. Although the procedure is still mainly investigational, many patients are requesting SNB to avoid axillary dissection if the sentinel node (SN) is negative. From March 1996 to December 1999, 373 patients with breast carcinoma and clinically negative axillary nodes underwent breast surgery, mainly conservative, and SNB. If the SN was histologically uninvolved no further surgical treatment was given. All patients were informed in detail and signed a consent form. SNB involved injection of labelled albumin particles close to the primary tumour, lymphoscintigraphy and location of the sentinel node with a gamma probe during surgery. 379 SNBs were performed on 373 patients (6 were bilateral). In 94, the SN was positive and complete axillary dissection was performed. In 285 cases (280 patients) the SN was negative and no dissection was performed: these were carefully followed with quarterly clinical examination of the axilla. A total of 343 years at risk were available for evaluation from which seven cases of axillary metastases were expected. No cases of clinically evident axillary node metastasis have occurred. These findings provide further confirmation of the validity of SNB and prompt us to suggest that it should become the method of choice for axillary staging in small-sized breast cancer.

Keywords: Sentinel node; Breast cancer; Histological examination

1. Introduction

Sentinel node biopsy (SNB) is becoming an important component of the surgical treatment of breast cancer, as it accurately predicts axillary status and permits avoidance of axillary dissection in patients with negative axillary nodes [1–3].

Numerous breast cancer patients have undergone SNB in the last few years, most of whom have also received total axillary dissection as part of studies to validate the method. Randomised trials are in progress in several countries in which some patients receive SNB only — without axillary dissection — when the sentinel node (SN) is negative. In most centres, SNB has not been introduced as a routine procedure. However, since initial reports that the technique often allows avoidance of axillary dissection, increasing numbers of breast cancer patients are specifically requesting SNB, to receive no axillary dissection if the SN is negative. These patients are generally informed that the procedure is still investigational and that available data suggest it is effective.

We considered it useful to evaluate SNB outcome and risks in 373 patients who, outside of research protocols, specifically requested the procedure instead of routine axillary dissection.

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0959-8049/01/$ - see front matter
PII: S0959-8049(00)00410-X

2. Patients and methods

2.1. Patient characteristics

From March 1996 to December 1999, 373 patients with breast cancer and clinically negative axillary nodes underwent breast surgery and SNB. An additional four cases (1.1%) are not included in the present report as lymphoscintigraphy was unable to identify a sentinel node. If the SN was negative at histological examination, no further axillary treatment was given. In 6 patients, the cancer was bilateral. We therefore report on 379 breast cancers, 193 (50.9%) in the right breast and 186 (49.1%) in the left breast. In 94 cases (24.8%), an excisional biopsy had been performed previously (68 elsewhere and 26 at our centre). The division by quadrants was: 225 (59%) upper outer, 63 (17%) upper inner, 55 (15%) lower outer, 24 (6%) lower inner, and 12 (3%) central.

Before surgery, patients were informed in detail of the SNB procedure and of the fact that it is not a standard clinical treatment for breast cancer. They were also informed that randomised clinical trials on SNB were in progress. All patients signed an informed consent form.

The distribution of patients according to age, and tumour size, type, biological and histological characteristics is shown in Table 1. 40.8% of patients were aged 50 years or younger and 32.2% were over 60 years. Forty-one point two per cent of tumours were 1 cm or less, 13.5% of which had a positive SN; 58.8% were larger than 1 cm and 32.7% of these had a positive SN. There were also significant differences between the SN+ and SN− cases in terms of tumour grade and Ki-67 index. More SNs were positive when the tumour was grade 2 and 3 compared with grade 1, and when the Ki-67 was high compared with when it was low.

In 28 patients, the cancer was bilateral; in 22 of these, axillary dissection was carried out on one side and SNB on the other. In 6 patients, SNB was bilateral. 38 patients had a previous contralateral cancer and 19 others had a previous operation for cancer at another site. The majority of cancers were less than 2 cm (89.2%). The 41 cases over 2 cm were associated with a high incidence of positive SNs (20 cases, 48.8%) and of these 5 had other positive axillary (non-sentinel) nodes.

2.2. Sentinel node biopsy technique

In all 379 cases, the method used was that developed at our centre and in use since 1996. Briefly, 5–10 MBq of technetium-99-labelled human colloid particles (Albures, Sorin Biomedica, Italy) in 0.2 ml saline were injected the day before surgery in the subdermis above the tumour or peritumorally [4,5]. Anterior and anterior oblique planar scintigraphic scans of the involved breast and axilla were acquired 30 min after injection. In cases where no node, or more than two nodes, were identified, a further scan was taken 3 h later. The skin above the first node to become radioactive was marked to assist its location during surgery. A hand-held γ-detecting probe was used during surgery to confirm the location of the SN and aid its removal, via a small skin incision. The probe gives out a recognisable acoustic signal when directly over the labelled node.

The SN was usually found lying deep, along the lateral margin of the pectoralis minor; using the probe as guide approximately 10 min were required to remove it

Table 1
Distribution of patients according to age, size, histological and biological characteristics of the primary tumour

	No. of cases *n* (%)	Positive sentinel node *n* (%)	*P* value
All cases	379	94 (24.8)	
Age (years)[a]			
$>21\leqslant40$	47 (12.6)	13 (27.7)	$\chi^2=1.5$
$>40\leqslant50$	105 (28.2)	31 (29.5)	4 df
$>50\leqslant60$	101 (27.1)	21 (20.8)	$P=0.84$
$>60\leqslant70$	80 (21.4)	17 (21.2)	
$>70\leqslant90$	40 (10.7)	11 (27.5)	
Tumour size (cm)			
$\leqslant1$	156 (41.2)	21 (13.5)	$\chi^2=28.1$
$>1\leqslant1.5$	135 (35.6)	34 (25.2)	3 df
$>1.5\leqslant2.0$	47 (12.4)	19 (40.4)	$P<0.0001$
>2	41 (10.8)	20 (48.8)	
Histology			
Infiltrating ductal	91 (24.0)	26 (28.6)	$\chi^2=7.5$
Infiltrating lobular	20 (5.3)	2 (10.0)	3 df
Infiltrating ductal + DCIS	157 (4.1)	46 (29.3)	$P=0.06$
Other	113 (29.6)	20 (17.9)	
Oestrogen receptor status			
Positive	322 (85.0)	84 (26.1)	$\chi^2=1.26$
Negative	51 (13.5)	9 (17.6)	1 df
Missing	6 (1.6)	1 (16.7)	$P=0.26$
Tumour grade			
1	111 (29.3)	17 (15.3)	$\chi^2=9.0$
2	179 (47.2)	53 (29.6)	2 df
3	66 (17.4)	21 (31.8)	$P=0.01$
Missing	23 (6.1)	3 (13.0)	
Proliferation index (Ki67)			
$\leqslant20$	211 (58.3)	43 (19.5)	$\chi^2=9.2$
>20	140 (36.9)	48 (34.3)	1 df
Missing	18 (4.7)	3 (16.7)	$P=0.002$
Previous excisional biopsy	94 (24.8)	21 (22.3)	$\chi^2=0.25$
No excisional biopsy	285 (75.2)	73 (25.6)	1 df
			$P=0.002$
Outer upper quadrant	225 (59.4)	57 (25.3)	$\chi^2=0.02$
Other quadrants	154 (40.6)	37 (24.0)	1 df
			$P=0.87$

df, degrees of freedom; DCIS, ductal carcinoma *in situ*; χ^2 = Chi squared.

[a] On 373 patients.

[6,7]. Care was always taken to identify and spare vessels and nerves close to the node wherever possible.

2.3. Statistical methods

Chi-squared tests were used to test associations between SN status and tumour characteristics. The observed number of axillary occurrences during follow-up was compared with the expected number using a Poisson distribution [8]. A P value of <0.05 was considered significant.

2.4. Axillary dissection

Following histological evaluation of the SN, 93 patients underwent complete axillary dissection (performed on 94 axillas) using our standard method [9,10].

2.5. Pathology

In the initial 16 patients of the series, the SN was analysed by serial sectioning of the whole node after formalin fixation and paraffin embedding. Every tenth section was stained with haematoxylin and eosin (H&E) with the adjacent section stained with anticytokeratin antibodies. The remaining sections were stored. In the next 47 patients, the removed SN was cut longitudinally in half. One half was frozen for immediate intraoperative examination with three contiguous frozen sections stained with H&E. The remaining half node was fixed and embedded for conventional histological analysis.

In the last 316 patients, the node was bisected along its major axis, both halves were embedded in OCT embedding medium, cut surfaces up, and immediately frozen in isopentane/liquid nitrogen. Fifteen pairs of adjacent frozen sections, 4 μm thick, were cut at 50 μm intervals in each half node (60 sections). Whenever residual tissue was left, additional pairs of sections were cut at 100 μm intervals until the node was completely sampled. One section of each pair was routinely stained with H&E. If the results were doubtful, the other section was immunostained for cytokeratins, using a rapid method with monoclonal anti-cytokeratin antibody (DAKO, Copenhagen, Denmark). This new technique of histological analysis was developed and introduced during the period of the present study, and was designed to provide a definitive histological examination intraoperatively.

2.6. Treatment of primary

Of 379 breast operations, 364 (96.0%) were conservative and 15 (4.0%) were mastectomies. In the 285 cases (75.2%) with a negative SNB, 276 quadrantectomies (96.8%) and nine mastectomies (3.2%) were performed, while in the group that underwent axillary dissection, there were 88 quadrantectomies (93.6%) and six mastectomies (6.4%).

Table 2
Adjuvant treatment in 373 breast cancer patients according to SN/axillary node status (N+ or N−)

Adjuvant therapy	N+ *n* (%)	N− *n* (%)
No therapy	4 (4.3)	50 (17.9)
Hormone therapy	27 (29.0)	174 (62.1)
Chemotherapy + hormone therapy	53 (57.0)	35 (12.5)
Chemotherapy	9 (9.7)	21 (7.5)
Total	93 (24.9)	280 (75.1)

SN, sentinel node.

2.7. Adjuvant treatments

All patients who underwent conservative surgery also received radiotherapy to the operated breast according to the conventional schedule (50 Gy + 10 Gy boost). Table 2 summarises the adjuvant systemic treatments given to the node-positive (N+) and node-negative (N−) groups.

2.8. Follow-up

The 280 SN-negative patients (285 cases) were carefully followed with quarterly physical examination of the axilla and ultrasound examination every 8 months. Patients were also instructed to self examine the axilla every month. A total of 343 person-years of risk have been accumulated. Of 280 patients with a negative SN, 2 (0.7%) have a follow-up of more than 4 years, 25 (8.9%) of 3 to 4 years, 62 (22.1%) of 2 to 3 years, and then remaining 191 (68.2%) patients have less than 2 years.

3. Results

Of the 373 patients in this series who underwent SNB, 6 had bilateral early carcinoma and the biopsy was conducted on both sides giving a total of 379 SNBs performed. In 285 cases (281 patients, 76.4%), the SN was negative on histological examination and no further axillary treatment was given. In 94 cases (93 patients, 24.9%) one or more positive SNs were found and total axillary dissection was performed. In 84 of these patients, the positive SNs were identified by intraoperative frozen section examination and axillary dissection was performed at the same time as the breast operation. In 9 patients, the positive node was found at final histological examination 3 days after SNB. The axillary dissection was therefore delayed 1 to 3 weeks. These patients were disturbed by the news of a positive axilla

Table 3
Follow-up status of present series

Number of positive SNBs 94 (93 patients)	(24.8%)
Number of negative SNBs 285 (280 patients)	(75.2%)
Number of person-years at risk at most recent follow-up	343
Number of overt axillary metastases	
Expected	7
Observed	0

(mainly for fear of chemotherapy), but none refused the second operation or questioned its necessity.

Among the 94 axillary dissections performed because the SN was positive, 147 SNs were found (average 1.56). In 58 cases, there was one SN, in 26 cases two SNs and in 10 cases more than two SNs. In 63 cases (67.0%) the SN(s) were the only positive nodes; in 16 cases (17.0%) a SN and one other node were metastatic, and in 15 (16.0%) cases a SN and two or more non-SNs were involved up to a maximum of 12. In 41/94 cases (43.6%), there was micrometastasis only (less than 2 mm in maximum diameter).

Among the 285 cases with negative SNs, a total of 475 nodes were marked as SN (average 1.67). There was no difference between the SN-positive and SN-negative cases with regard to the number of SNs found ($Chi^2 = 1.38$, 3 df, $P = 0.7$).

The 280 SN-negative patients (285 cases) were carefully followed with quarterly physical examination of the axilla and ultrasound examination every 8 months. A total of 343 person-years of risk have been accumulated. One patient developed a local breast recurrence, and is alive without evidence of disease or distant metastases. One other patient developed distant metastasis (bone) and is alive with disease. All other patients are alive and well. No patients have developed axillary metastases (Table 3).

In our previous series of 376 SNB patients [6] we had a false negate rate of 6.7% (false negative rate = No. with false negative SN/total number with axillary metastases). If we assume a similar rate in the present series we would expect 6.75 cases with positive axillary nodes to have been discovered if complete axillary dissection has been performed on all 285 SN-negative patients. The number 6.75 is x in the expression: $x/(x+94) = 6.7/100$, where 94 is the number of cases in the series with a positive SN).

4. Discussion

The SN concept has been with us for long time [11]; it was first scientifically validated in melanoma by intraoperative lymph node mapping after injection of blue dye [1]. Subsequently, Giuliano and colleagues [2] reported that the SN correctly predicted axillary status in 109 of 114 (95.6%) breast cancer cases, with false-negative SNs in 5 (4.4%) (i.e. no cancer identified in the SN, but at least one other axillary node had metastases) [12]. In the multicentric trial published by Krag [3], the accuracy of SNB with respect to axillary status as a whole was 97%, the specificity of the method was 100%, sensitivity 89%, and negative predictive value 96%. The authors concluded that these figures validated the method, but pointed out that the success rate varied with the experience of the surgeon and characteristics of the patients. Our study on 376 patients [6], which is one of the largest single-centre studies published to date, found an accuracy of 97.8%, specificity of 100%, sensitivity of 93.3%, and negative predictive value of 94.1. Other studies have confirmed the accuracy of the SN relative to other dissected nodes as around 98% (95–100%) with a false-negative rate ranging from 1 to 11% (Table 4).

Table 4
Summary of results of previously published studies on sentinel node biopsy in breast cancer. False-negative rates are calculated on patients with metastatic axilla

Author [Ref]	No. of patients	Technique	SNs identified (%)	False-negative (%)
Borgstein [15]	130	R	94	5
Cox [16]	466	B, R	94	1
Giuliano [2]	174	B	66	11
Guenther (1997)	145	B	71	10
Krag [3]	443	R	93	11
Veronesi [6]	376	R	99	6

B, blue dye technique; R, radioactive tracer technique.

Our data show that the risk of developing axillary metastases correlates directly to the size of the primary carcinoma ($P = 0.0001$), the proliferation index ($P < 0.002$) and the tumour grade ($P = 0.01$), while no other variable (age, histology, oestrogen-receptor status) is related to this risk (Table 1).

Although the follow-up of the 280 patients in the present series is not long, no patient has developed axillary metastases during the 343 patient-years of careful observation. We expect that 6 to 7 of these patients may present axillary metastases in the future. In view of the intensive follow-up schedule, we expect that metastatic axillary nodes will be recognised at an early stage and successfully removed. There is also a possibility that metastases will never appear, since conservation of axillary lymphatic tissue in these women might be beneficial and perhaps improve the prognosis.

The data of the present series suggest that SNB should become a standard method of staging in patients with small-sized breast cancer and clinically uninvolved axilla, and that routine axillary dissection should be abandoned. In patients whose biopsied SN is negative and who therefore receive no further axillary treatment, the risk of understaging is small and largely compensated for by our more accurate histological examination

of the SN [12]: the large number of SN sections examined by our method results in the discovery of micrometastases which would not be recognised by a routine pathological examination [13]. Note that the standard method of breast cancer staging — pathological examination of all or most axillary lymph nodes — is largely incomplete as it ignores the internal mammary nodes, whose involvement considerably lowers survival [14]. Furthermore, the prognostic assessment of breast cancer increasingly relies on the outcome of a series of biological and molecular tests on the primary tumour, whose number and predictive power is expanding rapidly.

To conclude, our experience with 373 early breast cancer patients who specifically requested SNB, indicates that in small-sized breast cancer with clinically negative axillary nodes SNB should be the procedure of choice for staging axillary nodes.

Acknowledgements

This study was financially supported by the Italian Association for Cancer Research. The authors thank Don Ward for help with the English.

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