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Original Paper

Tagging Sentinel Lymph Nodes: a Study of 100 Patients with Breast Cancer

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The aim of this study was to evaluate in breast cancer patients the feasibility of sentinel lymph node (SLN) identification and the sensitivity of this technique to detect node metastases. Between January and July 1997, SLNs were tracked with Evans Blue dye in 100 patients with breast cancer who then underwent complete level I/II axillary lymph node dissection (ALND). All SLNs were examined by haematoxylin–phloxin–saffron (HPS) staining and immunohistochemistry (IHC) of multiple sections. The findings for the SLNs were compared with results on ANLD. Axillary SLNs were identified in 83 patients (detection rate = 83%; 95% confidence interval (CI) 74–90%). Axillary SLNs were detected in 58/83 cases (70%) at level I only, and in 69/83 (83%) at levels including level I. Histologically positive axillary SLNs were found in 45% (37/83) of patients, including 2 patients with malignancy (micrometastases) detected by IHC only. The sensitivity of axillary SLN to detect axillary lymph nodes metastases was 37/39 = 95% (95% CI 83–99%). SLNs of the internal mammary chain (IMC) were dissected for 33 tumours of the median or inner quadrants and detected in 26/33 = 79% of cases (95% CI 61–91%). In our experience, the overall sensitivity of SLN identification as a predictor of node (axillary or IMC) metastases was 41/43 = 95% (95% CI 84–99%), confirming the usefulness of the procedure.

Key words: sentinel lymph nodes, axillary lymph node dissection, internal mammary chain, breast cancer, staging
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INTRODUCTION

Axillary lymph node dissection (ALND) is central to staging operable breast cancer, affording regional control of disease, establishing a prognosis, and identifying those patients who might benefit from adjuvant therapy and especially from intensified chemotherapy [1–4]. The practice is nevertheless considered controversial. Indeed, it has yet to be definitively established whether early breast cancer is a local disease or not [4]. Over 90% of patients with small (< 1 cm) tumours treated by breast-conserving surgery, ALND and radiotherapy have a disease-free survival of at least 10 years [5]. However, according to the National Cancer Institute's 1988 *Clinical Alert* [6] and the recent results of NSABP trials [7–9], all patients should be prescribed systemic adjuvant therapy regardless of nodal status. This obviates the need for an ALND and means that patients who, on ALND, are node-negative, would nevertheless receive such adjuvant treatment [10–12]. Furthermore, with the expansion of mass screening programmes, more and more patients are being treated for infraclinical lesions where the risk of metastatic nodal involvement is less than 20% [13–15]. In such cases, ALND becomes unacceptable because of its associated morbidity [16–18].

Clearly, therefore, there is a need to reappraise the role of systematic ALND in clinically node-negative breast cancer [19–21] and to develop a reliable and non-invasive surgical technique with minimal morbidity for tumour staging that will identify pN_1 cases requiring ALND. One such technique is intra-operative tagging of the first nodes with a high risk of metastases, the sentinel lymph nodes (SLNs), that was

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pioneered by Morton and colleagues [22] for stage I melanoma and transposed by Giuliano and colleagues to breast cancer [23]. It rests on the hypothesis that if the first node(s) tagged by dye injected around the primary tumour is (are) negative, then the risk of metastases elsewhere is close to nil. SLN identification avoids depriving a patient with positive nodes of an ALND, whilst sparing patients with negative nodes.

We report here our results on the feasibility of SLN detection and its sensitivity in forecasting node involvement in a series of 100 patients with breast cancer. We focus, in particular, on SLNs of the internal mammary chain for inner quadrant and median tumours.

PATIENTS AND METHODS

From January to July 1997, 100 patients (median age 50.5 years; range, 30–82) with breast cancer, in whom either mastectomy or lumpectomy was indicated, underwent sentinel lymph node (SLN) biopsy followed immediately by standard level I and II axillary lymph node dissection (ALND). Patients with *in situ* multicentric or multifocal cancers, or who had relapsed after previous breast conservative surgery were excluded. 16 patients with inflammatory cancers received neoadjuvant chemotherapy after axillary clearance. All operations were performed by the senior surgeon (J.-Y.B.). Invasive cancer was diagnosed either by preoperative microbiopsy, fine needle aspiration cytology, or excisional biopsy and frozen sections before SLN identification. In 33 patients with a primary tumour located in the inner or central quadrants, the internal mammary chain (IMC) was explored.

Sentinel lymph node identification

Our SLN detection technique was based on that first described by Giuliano and colleagues [23]. Briefly, 5 ml of Evans Blue dye (Pharmacie des Hôpitaux de Paris) was injected into the tissue surrounding the tumour. After a soft massage of the breast for 8–10 min, the tumour was excised and sent to the histopathology laboratory for frozen sections and to the biology laboratory for the assessment of prognostic factors. A 4–5 cm incision was made behind the front edge of the pectoralis major muscle to locate the stained lymphatic(s) whose path was traced to the first coloured node(s) (SLNs). At times, the SLNs were stained in their entirety but, mostly, just the efferent sinus was stained. The SLNs were excised and sent as separate specimens to the histopathology laboratory. A standard level I/II ALND (or level III in the presence of visibly suspicious nodes) was performed. The interpectoral lymph node (Rotter's node) was always explored.

For tumours located in the inner or in the central quadrants, conservative internal mammary chain (IMC) dissection could be performed easily and safely through the incision of the breast-conserving treatment without morbidity. Excision of the SLNs of the IMC was standard without section of the intercostal cartilages and was performed on spaces 1 and 2—sometimes 3—depending upon tumour location. After opening the intercostal muscles, where the coloured lymphatic proceeded to the IMC, it was very easy to identify the small blue IMC SN. Haemostasis was performed with bipolar coagulation. After IMC clearance, the major pectoral muscle was sutured over the opened intercostal spaces without drainage. If the parietal pleura was opened or removed when an invaded node was attached to it, the patient was put under positive lung pressure to avoid a pneumothorax. There was no need for a pleural drainage.

Histological examination of sentinel lymph nodes

SLNs were never examined using frozen sections. They were fixed in Bouin fluid. After 24 h, they were separated and cut into 3-mm sections, embedded in paraffin and stained with haematoxylin–phloxin–saffron (HPS). If no malignancy was noted, immunohistochemistry (IHC) was performed with cyto-keratin KL1 (dilution 1/100) (Immunotech, France) on 4-mm sections of fixed tissue using the streptavidin–biotin peroxidase complex method (Kit LSAB DAKO, Denmark) with diaminobenzidine as the chromogen with a slight counterstain. Non-sentinel nodes underwent the same HPS evaluation as SLNs but no IHC was done.

Statistics

The detection rate of SLNs was defined as the ratio of the number of patients with identified SLNs over the total number of patients. The sensitivity was calculated as the ratio of the number of patients with SLNs metastases over the number of patients with identified SLNs and lymph node metastases. Exact 95% confidence intervals (95% CI) of detection rate and sensitivity based on binomial distribution were calculated.

RESULTS

Description of patient population

The clinical characteristics of patients and tumours are given in Table 1. All 100 patients underwent an investigation for SLNs, then a complete ALND. The IMC was dissected in 33 patients. Overall, 42 patients had pathologically confirmed

Table 1. *Patient and tumour characteristics*

Characteristic		No. of patients
Clinical stage	T0	13
	T1	45
	T2	27
	T3	8
	T4	5
	Tx	2
	N0-N1a	94
	N1b	6
Tumour location		
Upper	Outer	33
	Median/central	7
	Inner	22
Central		11
Lower	Outer	21
	Median/central	3
	Inner	3
Histopathology	Ductal	85
	Lobular	9
	Miscellaneous	6
Surgical treatment	Conserving	22
	Mastectomy	62
Neoadjuvant chemotherapy		16
IMC node dissection		33
Steroid receptors	ER^+	61
	ER^-	28
	ER unknown	11
	PR^+	71
	PR^-	18
	PR unknown	11

ER, oestrogen receptor; PR, progesterone receptor.

Table 2. Patient distribution according to tumour size and axillary nodal involvement

	Entire patient population		Patients in whom SLNs were identified	
Tumour size	$n = 100$	Axillary pN_1 ($n = 42$)	$n = 83$	Axillary pN_1 ($n = 39$)
pT_1 (total)	63	16	52	15
T_{1a}	8	0	6	0
T_{1b}	21	3	17	3
T_{1c}	34	13	29	12
pT_2 (total)	21	14	16	12
$20 < \text{size} \leq 30$ mm	16	9	11	7
$30 < \text{size} \leq 50$ mm	5	5	5	5
Before neo-adjuvant chemo-therapy	16	12	15	12

pT_1, ≤ 2 cm; T_{1a}, ≤ 5 mm; T_{1b}, > 5 mm and ≤ 10 mm; T_{1c}, > 10 mm and ≤ 20 mm.

invaded axillary lymph nodes (pN_1) and, in 6 of them, metastatic spread had already been noted on clinical examination.The mean number of excised nodes (SLNs and ALND) was 14 (range 2–31) for axillary nodes and 3 (range 1–6) for IMC nodes.

Tumours were pT_1 (≤ 2 cm) in 63 patients and pT_2 (> 2 to 5 cm) in 21. There were 16 patients who received neoadjuvant therapy prior to surgery. The distribution of the patients as a function of tumour size and nodal involvement is given in Tables 2 and 3.

Identification of axillary sentinel lymph nodes

Axillary SLNs were not detected in 17 patients, so the overall SLN detection rate was 83% (95% CI: 74–90%). The distribution of these 83 patients according to tumour size and nodal involvement is given in Tables 2 and 3. The number of SLNs removed from the axilla is given in Figure 1 and the level at which they were excised is shown in Table 4. Axillary SLNs were detected in 58/83 cases (70%) at level I only, and in 69/83 cases (83%) at levels including level I (Table 4). The proportion of cases with direct staining of a level II SLN without staining of a level I SLN was 12/83 (14%). There was no staining at level III. Rotter's node was the SLN for two tumours. Overall, a single SLN was excised in 17 patients (21%) and less than 4 SLNs in 57 patients (69%).

Table 3. Patient distribution according to axillary node histopathology

	Entire patient population ($n = 100$)	Patients in whom SLNs were identified ($n = 83$)
pN_0	58	44
pN_1	42	39
Micrometastases*	8	8
Macrometastases without capsule rupture†	11	11
Macrometastases with capsule invasion‡	23	20

*Two micrometastases were detected by immunohistochemistry only; †2 cases with manifest clinical invasion (N_{1b}); ‡4 cases with manifest clinical invasion (N_{1b}).

Table 4. Distribution of patients according to the axillary level of the excised sentinel lymph nodes

Level of excised SLNs	No. of patients $n = 83$
Level I	58 (70%)
Level I + II	5 (6%)
Level I + Rotter	6 (7%)
Level II only	12 (14%)
Level III	0
Rotter alone	2 (2%)

Positive axillary SLNs were identified in 37 of the 42 patients who proved to have pN_1 tumours on ALND (Table 5), of the 5 failures (2 T_1c, 2 $T_2 \leq 30$ mm, 1 T_{4d}), 3 were SLN detection failures and 2 false-negatives. The sensitivity of the technique was, therefore, $37/39 = 95\%$ (95% CI: 83–99%). In 2 patients, SLN positivity was established by immunohistochemistry only (2/8 micrometastases). 6 of the 37 SLN-positive patients had clinically N_1 tumours, with 2 cases of macrometastases without capsule rupture and 4 cases with capsule invasion. If we exclude those patients as other teams have done [24, 25] and only consider clinically node-negative patients, we were able to detect an axillary SLN in $77/94 = 82\%$ (95% CI 73–89%) of patients.

Of the 37 patients with axillary metastatic SLNs, 23 (62%) patients had only 1 SLN, 7 (19%) had 2 SLNs, 3 (8%) had 3 SLNs, 2 had 4 SLNs, and 2 had 5 SLNs i.e. only 4 (11%) patients had > 3 SLNs.

After SLN excision, complete ALND resulted in the detection of another 78 residual axillary nodes which were positive. 59 of these occurred in 10 patients who had a positive SLN, 5 were in 2 false-negative cases and 14 in 3 patients in whom no SLN was detected.

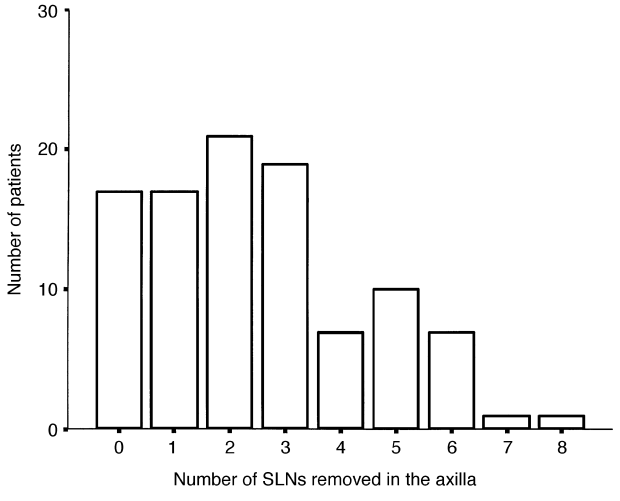

Figure 1. Distribution of patients according to the number of SLNs removed in the axilla.

Table 5. *Identification and positivity of SLNs according to nodal involvement*

	No SLN detected	Detected SLN negative	Detected SLN positive
Axillary nodes			
Positive ($n = 42$)	3	2	37
Negative ($n = 58$)	14	44	–
Total ($n = 100$)	17	46	37
Axillary and/or IMC nodes			
Positive ($n = 45$)	2	2	41
Negative ($n = 55$)	6	49	–
Total ($n = 100$)	8	51	41

Identification of internal mammary chain sentinel lymph nodes

SLNs were identified in 26 of the 33 patients in whom the IMC was dissected (detection rate: 26/33 = 79%; 95% CI 61–91%). These SLNs were located as follows: first intercostal space (3 patients), second (7 patients), first + second (5 patients), third (7 patients) and second + third (4 patients). Overall, 16 patients (62%) had SLNs located in the second intercostal space. A total of 55 IMC-SLNs were excised: 1 SLN in 8 patients, 2 SLNs in 11, 3 SLNs in 5, and 5 SLNs in 2.

The IMC-SLNs were positive in 8 of the 26 patients (15/55 IMC-SLN were positive). They all stained positive with HPS and were distributed as follows: 1 positive IMC-SLN in 5 patients, and 2, 3 and 5 IMC-SLNs in 1 patient in each instance. Of the 8 IMC-SLN positive cases, 3 had no metastatic spread to axillary nodes.

Overview of axillary and IMC sentinel node identification

SLNs were identified in the IMC of 9 patients in whom no axillary SLN had been found (9/17). Thus, in only 8 of the 100 patients (8%), was no SLN found (Table 5). The overall sensitivity of the technique (axillary and IMC-SLNs) was therefore 41/43 = 95% (95% CI 84–99%) (Table 5).

DISCUSSION

These results on axillary SLN detection compare favourably with those in the literature [23–26].

The overall sensitivity of our method (which used Evans Blue dye) for axillary nodal status was 95% (37/39) and 94% (31/33) on exclusion of the 6 patients with clinically N_1 tumours. In comparison, Giuliano and colleagues in their study using Isosulfan Blue dye identified axillary SLNs in 93.5% of patients and Veronesi and colleagues, using a radioisotope, in 98% (160/163). The slight discrepancy between their results and ours could be explained by at least two factors. First, as noted by Morton and colleagues [22] and Giuliano and colleagues [23, 24], there is an initial phase requiring about 20–30 patients in which the surgeon has to build up experience in searching for stained SLNs. This learning phase is doubtless shorter with the radioisotope method [26–28]. Second, instead of Isosulfan Blue, we used Evans Blue dye which has disadvantages. It seeps slowly into the lymphatics (approximately 15 min), diffuses poorly in fatty breasts, and stains the breast for many weeks. For these reasons, we now use Patent Blue which reaches the lymphatics and SLNs faster (5 min) and does not colour the breast long. There is, however, a minor risk of allergy with this dye.

Unlike most studies, we explored the SLNs of the internal mammary chain for inner and median tumours. We detected a SLN in 79% (26/33) of the IMC dissections; 8/26 (30.8%) of these IMC-SLNs were metastatic and, in all cases, the SLNs predicted nodal status. Disease had spread to 11.5% (3/26) of IMC-SLNs in the absence of any axillary invasion. IMC dissection is a rational procedure with no sequelae that provides a more precise staging and prognosis than any new biological breast tumour markers do [29–32].

In conclusion, SLN detection, whether using a dye or radioisotope, is a high-performance method for identifying node-negative cancers during surgery. It is particularly suited to T_0 and T_1 tumours where the risk of disease spread to axillary nodes is less than 70% [33–36]. However, until proven otherwise, these lesions still call for ALND in order to afford local control, establish a prognosis, define a cytotoxic therapy, and improve survival [11, 12, 37–40]. The technique of SLN biopsy is also suited to defining axillary LN status of node-negative cancers that are > 3 cm in size or inflammatory before their downstaging by neoadjuvant chemotherapy [26]. Those eligible for IMC-SLN are tumours located in the central or inner quadrants with the same indication and phylosophy as for axillary lymph node dissection but with less morbidity than axillary clearance. After conservative surgery, if there is no axillary and IMC invasion, irradiation is performed only on the mammary gland avoiding the morbidity of IMC irradiation. Moreover, applying the technique to IMC-SLNs for inner and median tumours is especially useful as the procedure is simple and non-mutilating and the results can modify the TNM classification of the tumour (pN_3) and the prognosis [29, 30].

Whether it is best to use a dye or radioisotope is still a moot point. In the hands of trained surgeons, the dye method gives comparable results to the isotopic method [25, 26, 41–43]. The latter has been shown to provide 100% accurate axillary LN staging with less than three excised SLNs [26] but has two disadvantages: (1) the need for a nuclear medicine department in the establishment; (2) a high cost (preoperative mammary and axillary computed tomography (CT) scans, purchase of probes and gamma counter). These are major drawbacks since breast cancer is a widespread public health problem compared, for instance, to malignant melanoma.

In order to validate both methods (use of dye and isotope) and compare their relative sensitivities, we are developing a research programme that combines both of these approaches without the use of a preoperative scintigraphy on the lines of recently published research [43–45].

Until further validation is obtained, completion of levels I and II ALND must continue to be part of the local treatment of operable breast cancer.

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