Clinical relevance of sentinel lymph nodes in the internal mammary chain in breast cancer patients

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Abstract. *Purpose:* Despite the widespread use of sentinel lymph node (SLN) biopsy in breast cancer patients, some controversy exists about the correct management of extra-axillary nodes, especially those located in the internal mammary chain. The aim of this study was to evaluate the incidence of SLNs in this region, calculate the lymphoscintigraphic and surgical detection rates and evaluate the clinical impact on staging and therapeutic decisions.
Methods: The study involved 383 consecutive women diagnosed with early breast cancer with T1 or T2 tumours. Eight patients had a bilateral tumour, which brought the total to 391 lesions. Lymphoscintigraphy was performed on the day before surgery by injection of ^{99m}Tc-labelled nanocolloid. The injection site was subdermal (68 patients), peritumoural (107 patients) or intratumoural (216 patients). During surgery a gamma probe was used to guide the surgeon and the SLNs were removed. SLNs were analysed by a conventional pathological study and processed for H&E examination and immunohistochemistry.
Results: Lymphoscintigraphy detected at least one SLN in 369 out of the 391 procedures (94.4%). SLNs were found in the axillary chain in 367 cases and in the internal mammary chain in 55. In two of these 55 cases (3.6%), the SLN was the only one detected. There was no drainage to the internal mammary chain in any case of subdermal injection but such drainage was found in 15.9% of cases with peritumoural injection and 17.6% of those with intratumoural injection. Compared with tumours located in the outer quadrants, a higher percentage of tumours located in the inner quadrants showed drainage to the internal mammary chain (p<0.001). A total of 42 SLNs in the internal mammary chain could be removed in 32 patients without appreciable morbidity. In 20 cases both axillary and internal mammary SLNs were negative, in four both were positive, and in five axillary SLNs were positive and internal mammary SLNs were negative. More interestingly, in the remaining patient with both axillary and internal mammary SLNs, the axillary SLN was negative while malignant cells were found in the internal mammary region. In the evaluation of the clinical impact of internal mammary SLN biopsy, we found that staging was modified from pN1a to pN1c in four patients and, more importantly, from pN0 to pN0(i+) in one patient. The change in stage led to a modification of the postoperative treatment plan with respect to radiotherapy and systemic therapy.
Conclusion: Evaluation of the SLNs in the internal mammary chain provides more accurate staging of breast cancer patients. If internal mammary sampling is not performed, patients can be understaged. This technique can offer a better indication of those patients who will benefit from selective treatment options like radiotherapy to this region or systemic therapy.

Keywords: Breast cancer – Sentinel node – Lymphoscintigraphy – Internal mammary chain – Gamma probe

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Introduction

The management of patients with breast cancer is becoming more non-invasive and less surgically radical. In recent years, scintigraphic sentinel lymph node (SLN) detection has helped to stage patients more accurately and also contributed to less extensive surgical interventions.

The SLN is the first node to receive lymphatic drainage from a tumour and it is considered to be the first affected by metastasis [1]. Knowing whether or not axillary nodes are involved, by performing an SLN biopsy, allows accurate breast cancer staging and is associated with a decrease in early and late postoperative morbidity. This procedure allows, with a high negative predictive value, the evaluation of the axillary status by resection of a single or a few lymph nodes. It is progressively replacing standard lymphadenectomy in the surgical treatment of breast cancer [2].

Although SLN biopsy is widely used in breast cancer patients, some controversy exists about the correct management of extra-axillary nodes, especially those located in the internal mammary chain. Obviously these nodes carry important prognostic information, since involvement of both axillary and internal mammary lymph nodes is associated with a worse prognosis [3]. SLN biopsy can also have a therapeutic impact, as the removal of the internal mammary nodes provides a greater degree of staging accuracy. Based on this fact, some groups add radiotherapy to their protocols when these SLNs are positive [4, 5]. Furthermore, in a small but not negligible percentage of patients without axillary metastases, malignant lymphatic involvement is confined to the internal mammary lymph nodes [6].

Despite these considerations, the issue of selective internal mammary node dissection based on lymphatic mapping remains controversial. Until now, internal mammary chain SLNs have been evaluated only in a limited number of studies and the findings have not always agreed [3–5, 7–11]. We hypothesised that careful evaluation of internal mammary lymph nodes by SLN detection could have a clinical impact in patients with breast cancer.

Our aim was to study a large group of patients with early stage breast cancer in order to evaluate the incidence of SLNs in the internal mammary chain, to calculate the lymphoscintigraphic and surgical detection rate and to assess the clinical impact on staging and therapeutic decisions. It was hoped that the findings would help to clarify the practical implications of assessing internal mammary SLNs.

Materials and methods

Patients

The study included 383 consecutive women (mean age 58 years, range 31–84) with breast cancer, referred to the Nuclear Medicine Department for SLN detection. Patients were enrolled prospectively between June 1998 and July 2004. They had all been recently diagnosed with early breast cancer, with T1 or T2 tumours less than 3 cm in the greatest diameter according to the TNM classification. Eight patients had a bilateral tumour, making a total of 391 lesions. Of these, 162 were non-palpable. Preoperative diagnosis had been made by fine-needle aspiration or needle core biopsy and the primary tumour was still present in all cases. All patients had clinically negative axillary nodes. Location of the primary tumours, according to quadrant, is shown in Table 1. All patients underwent lymphoscintigraphy, tumourectomy and SLN detection. Informed consent to the performance of SLN biopsy was obtained in all cases.

Table 1. Number of lesions draining to the internal mammary chain depending on the injection site and the quadrant of the primary tumour

	Peritumoural	Intratumoural	Total
Upper outer quadrant	5	12	17/205 (8.3%)
Lower outer quadrant	3	7	10/53 (18.9%)
Upper inner quadrant	4	10	14/76 (18.4%)
Lower inner quadrant	5	8	13/41 (31.7%)
Central	0	1	1/16 (6.25%)
Total	17	38	55/391 (14.1%)

Lymphoscintigraphy

Lymphoscintigraphy was performed 1 day prior to surgery by injection of 111 MBq of ^{99m}Tc-labelled nanocolloid (Nanocoll, Amersham, UK). At the beginning of the study the injection site was subdermal (68 patients from June 1998 to February 1999). Later the injection site was changed to peritumoural (107 patients from March 1999 to November 2000) and then intratumoural (216 patients from December 2000 until now) in the search for internal mammary SLNs. In the case of non-palpable lesions, the peritumoural and intratumoural injections were guided by ultrasonography. Static planar images (256×256 matrix size, with each image acquisition lasting at least 180 s) were acquired at 30 min and 120 min. Anterior, lateral and anterior oblique views were obtained. In those cases without evidence of drainage, later images were performed. A single-head gamma camera (SP4-HR Elscint-GE, Haifa, Israel) fitted with a low-energy, high-resolution collimator was used. A methacrylate phantom filled with 37–55 MBq of ^{99m}Tc was also used to draw the anatomical outline. The location of the SLN was marked on the overlying skin with a water-resistant dye and the guidance of a ^{57}Co marker pen. A hot spot on lymphoscintigraphy was considered to be an SLN if (a) it was the first lymph node that lit up on lymphoscintigraphy, (b) it was the first node that depended on a lymphatic channel, (c) it was a node that appeared simultaneously in the same or different lymphatic basins or (d) the hot spot was the only one depicted. If there was any difference between the first images, taken at 30 min post injection, and the later acquisitions, the first hot spot was considered as the SLN.

Surgery

Shortly before surgery, and after the induction of anaesthesia, blue dye was injected (methylene blue, Dr. Carreras Chemistry, Barcelona) and then a gamma probe (Navigator, USSC, Norwalk, USA) was used to guide the surgeon. Firstly, the axillary region was explored to remove the SLN seen on lymphoscintigraphy. During surgery, a lymph node was considered an SLN when it coincided with the SLN depicted on lymphoscintigraphy (usually the one with maximum activity). Moreover, a lymph node was also considered an SLN when the total counts of the node were greater than 10% of the maximum activity of the SLN with the highest counts. Subsequent exploration of the internal mammary chain was carried out only if lymphoscintigraphy indicated drainage to this field. A thinner, straight probe (10-mm diameter) was used in this area in order to fit better into the reduced field of the intercostal spaces. When SLNs from the axillary chain were positive under pathological examination, axillary lymphadenectomy was performed.

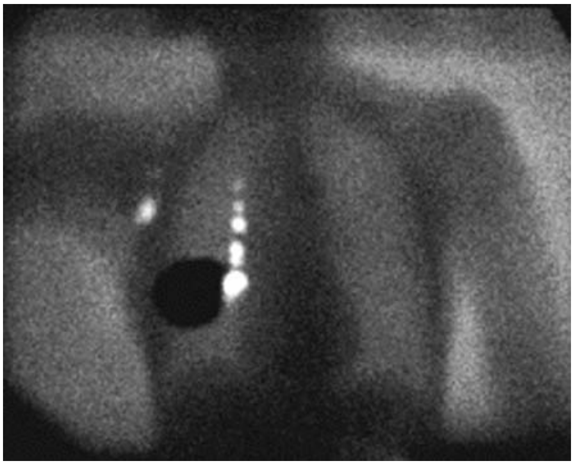

Fig. 1. Lymphoscintigraphy showing drainage to both fields: two nodes with different uptake are present in the axillary region and several nodes are visualised along the internal mammary chain

Pathology

SLNs from the axillary and internal mammary chain were subjected to intraoperative pathological examination. The intraoperative examination consisted of cytological imprints and subsequent frozen sections. All nodal structures were serially cross-sectioned at 2-mm intervals perpendicular to the longitudinal axis and stained with haematoxylin-eosin (H&E). Moreover, all SLNs were later analysed by a conventional study and processed for H&E examination and immunohistochemistry with anti-Cam 5.2 (monoclonal, 1/100, Becton-Dickinson, San José, California).

Statistical analysis

Statistical analysis was performed using the SPSS 9.0 for Windows statistical program package. The chi square test was performed to assess the significance of the difference between groups in order to evaluate: (a) differences in drainage according to the location of the primary tumour and (b) differences in drainage according to the injection site. A p value of 0.05 or less was considered significant.

Results

Lymphoscintigraphy

Lymphoscintigraphy detected at least one SLN in 369 out of the 391 procedures (94.4%) (Fig. 1). SLNs were found in the axillary chain in 367 cases (Fig. 2) and in the internal mammary chain in 55 cases. In two of these 55 cases (3.6%), this SLN was the only one detected (Fig. 3). In addition, there were eight intramammary, three supraclavicular, two infraclavicular, one laterocervical and one subscapular SLNs.

Taking into account the injection site, there was no drainage to the internal mammary chain in any case of subdermal injection (0/68). Among the 107 cases in which peritumoural injection was used, SLNs were found in the internal mammary chain in 17 (15.9%). When intratumoural injection was used, SLNs were found in the internal mammary chain in 38 of 216 cases (17.6%). The difference between peritumoural and intratumoural injection was not statistically significant.

Table 1 details the drainage to the internal mammary chain according to the injection site and the quadrant where the primary tumour was located. Tumours located in the inner quadrants more commonly showed drainage to the internal mammary chain than did those located in the outer quadrants. Of the 258 tumours located in the outer quadrants, 10.5% (n=27) drained to the internal mammary chain, whereas of the 117 tumours in the inner quadrants, 23.1% (n=27) drained to this region (p<0.001).

Surgery

In the first 11 cases with SLNs in the internal mammary chain, these nodes were not removed as we were still in the learning curve of the SLN technique. In the remaining 44 patients, the SLNs could be removed in 32 cases (72.7%), obtaining a total of 42 SLNs. In 85% of cases, the SLN was located in the second or the third intercostal space. Blue dye was injected in 29 of these 32 patients and 35 SLNs

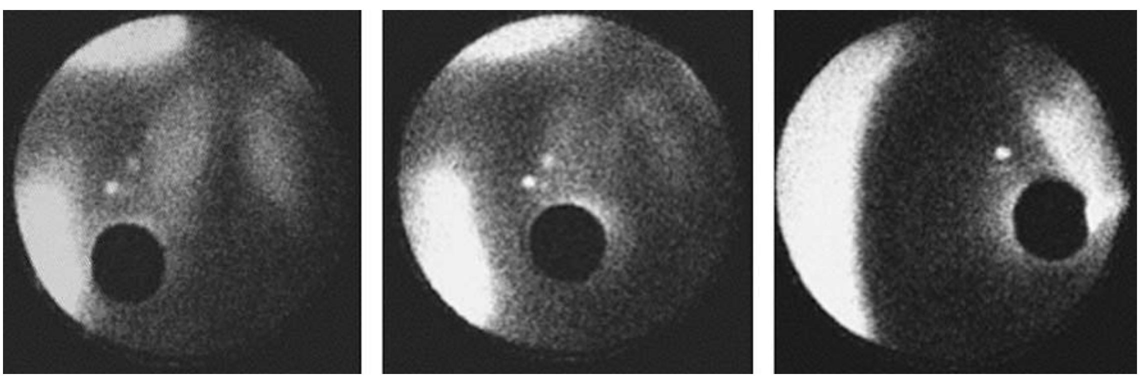

Fig. 2. Anterior, right anterior oblique and right lateral views showing uptake in two nodes in the right axillary chain

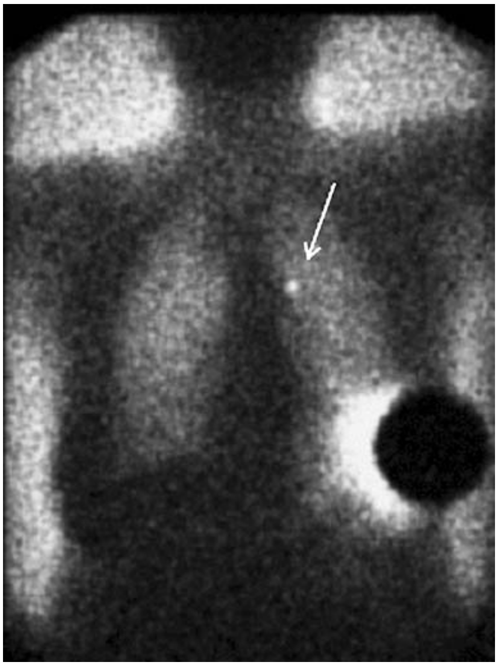

Fig. 3. One SLN in the internal mammary chain was the only site of uptake detected in a 75-year-old woman with a tumour in the upper inner quadrant of the left breast (*arrow*)

were removed, although only five were blue stained (17.2%). In one patient a minor pleural lesion was detected but no complications were observed after surgical repair. No other complications were seen in other patients.

Pathology

Among the 32 patients in whom SLNs in the internal mammary chain were removed, in 20 cases (62.5%) both axillary and internal mammary SLNs were negative, in four (12.5%) both were positive, and in five (15.6%) axillary SLNs were positive while internal mammary SLNs were negative. More interestingly, in the one remaining patient (3.1%) with both axillary and internal mammary SLNs, the axillary SLN was negative while the fat around the internal mammary SLN showed isolated malignant cells. In the two patients (6.25%) with only internal mammary SLNs, the SLNs were negative; the surgical team performed an axillary lymphadenectomy and all the nodes (seven in one patient and 14 in the other) were negative. There were no changes between the preoperative and conventional pathological tests.

Of the eight patients with bilateral breast cancer, two showed internal mammary drainage and in one of these cases, the internal mammary chain was bilaterally affected.

Discussion

The resection of axillary lymph nodes in breast cancer has been considered essential for primary surgical treatment in order to adequately stage the tumour and permit individualised planning of adjuvant therapy strategies. However, owing to the limited experience, there has to date been no clear recommendation regarding routine removal of internal mammary SLNs.

In our group of patients, 55 out of 391 tumours (14.1%) showed drainage to the internal mammary chain. This percentage is lower than the results obtained in other studies [7, 9, 10, 12], probably owing to a lower rate of deep injection in our study. When we first began performing SLN detection, we used subdermal injection but this was subsequently abandoned in favour of peritumoural and intratumoural injection as no instances of drainage to the internal mammary chain were observed following subdermal injection. If the cases with subdermal injection are excluded, the rate of internal mammary chain visualisation using deep injection (peritumoural and intratumoural) is 17% (55/323). In agreement with other authors, we also recommend deep injection when extra-axillary regions have to be evaluated [13–15]. Currently we perform a deep injection, usually intratumoural, in order to ascertain internal mammary chain drainage when it occurs. This injection technique is used because it offers the highest rate of visualisation of the internal mammary chain.

Drainage to the internal mammary chain is not exclusive to medial tumours [16], although most studies have reported that tumours located in the inner quadrants have a higher rate of such drainage than other tumours [9, 11]. In our group of patients, the highest percentage of tumours were located in the upper outer quadrant, but the location with the highest rate of drainage to the internal mammary chain (31.7%) was the lower inner quadrant; this is in agreement with the results of Estourgie et al. [9].

Removal of internal mammary nodes is not an easy task initially, and some experience is needed. Our surgeons have been able to harvest at least one SLN in 72.7% of patients, and nowadays this procedure is routinely performed in our centre. This percentage is quite similar to that reported by other groups [9, 17]. These nodes are now quite easily removed, with no increase in postoperative hospitalisation. We did not have any morbidity except in one patient (3.1%) who had a minor pleural tear that was sutured and resolved spontaneously. Blue dye can offer some help during surgery [18, 19] and we have used it in some cases without any adverse reactions. It will always be additional to lymphoscintigraphy as the percentage of SLNs stained is very low (17.2% in our patient group).

It has been demonstrated that the frequency of metastases in the internal mammary nodes is associated with patient age, the size of the primary tumour and the presence of axillary node metastases [6, 20]. We found metastases in 5 out of the 32 patients in whom SLNs in the internal mammary region were retrieved, and four of them also presented with axillary metastases.

The study of drainage to the internal mammary chain has prognostic value, because in some patients it changes the disease stage [10]. Veronesi et al. demonstrated with 30-year results that patients with isolated disease in the internal mammary field have a prognosis equivalent to that of patients with isolated axillary metastases [3]. In cases of tumour-positive internal mammary nodes, radiotherapy can be added [21] as SLN biopsy allows the selection of those patients who are most likely to benefit from additional regional therapy to these nodes with the goal of improving regional tumour control [4, 5].

In evaluating the clinical impact of internal mammary SLN biopsy in our group of patients, we would like to highlight certain findings. We tried to retrieve SLNs in the internal mammary field in 44 patients, and this was achieved in 32 cases (72.7%) without appreciable morbidity. In five of these cases (15.6%), SLNs were tumour-positive. According to the International Union Against Cancer staging classification (latest version, 6th edition), in four patients staging was altered from pN1a (metastasis in one to three axillary lymph nodes) to pN1c (metastasis in one to three axillary lymph nodes and in internal mammary nodes, with microscopic disease detected by SLN dissection). More importantly, one patient changed from pN0 (no regional lymph node metastasis histologically) to pN0(i+) (isolated tumoural cells). In this patient, radiotherapy to the internal mammary region was added to conventional treatment. Therefore, the change in stage led to a modification of the postoperative treatment plan.

The currently available evidence is insufficient to allow internal mammary SLN biopsy to become established as a standard procedure, and at present the correct management of patients with positive internal mammary nodes is controversial. We support the use of such information to guide the administration of systemic therapy or direct radiation therapy to the internal mammary chain. However, in order to establish the future importance of the technique for therapeutic purposes in patients with breast cancer, clinical trials will be needed to determine whether it improves survival rates.

Conclusion

In conclusion, evaluation of the SLNs in the internal mammary chain provides more accurate staging of breast cancer patients, because if internal mammary sampling is not performed, patients can be understaged. The technique can offer better identification of which patients may benefit from selective treatment options like systemic therapy or radiotherapy to this region.

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