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Role of routine preoperative lymphoscintigraphy in sentinel node biopsy for breast cancer

Amit Goyal [a], Robert G. Newcombe [b], Robert E. Mansel [a,*], on behalf of the ALMANAC Trialists Group

[a] *Department of Surgery, University of Wales College of Medicine, Cardiff, CF14 4XN, UK*
[b] *Department of Epidemiology, Statistics and Public Health, University of Wales College of Medicine, Cardiff, UK*

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Abstract

Sentinel node biopsy (SNB) is rapidly emerging as the preferred technique for nodal staging in breast cancer. When radioactive colloid is used, a preoperative lymphoscintiscan is obtained to ease sentinel lymph node (SN) identification. This study evaluates whether preoperative lymphoscintigraphy adds diagnostic accuracy to offset the additional time and cost required. 823 breast cancer patients underwent SNB based on lymphoscintigraphy, intraoperative γ probe detection, and blue dye mapping using 99 mTc-nanocolloid and Patent Blue V injected peritumourally. The SNB was followed by standard axillary treatment at the same operation. Preoperative lymphoscintigraphy was performed around 3 h after the radioisotope injection. Preoperative lymphoscintigraphy revealed SNs in 593 (72%) of the 823 patients imaged. SN visualisation on lymphoscintigraphy was less successful in large tumours and tumours involving the upper outer quadrant of the breast ($P = 0.046$, $P < 0.001$, respectively). Lymphoscintigraphy showed internal mammary sentinel nodes in 9% (62/707) patients. The SN was identified intraoperatively in 98% (581) patients who had SN visualised on preoperative lymphoscintigraphy, with a false-negative rate of 7%. In patients who did not have SN visualised on preoperative lymphoscintigraphy, the SN was identified at operation in 90% (204) patients, with a false-negative rate of 7%. The SN identification rate was significantly higher in patients with SN visualised on preoperative lymphoscintigraphy ($P < 0.001$). SN identification rate intraoperatively using the γ probe was significantly higher in the SN visualised group compared with the SN non-visualised group (95% vs. 68%; χ^2 (1 degrees of freedom (df)) $P < 0.001$). There was no statistically significant difference in the false-negative rate and the operative time between the two groups. A mean of 2.3 (standard deviation (SD) 1.3) SNs per patient were removed in patients with SN visualised on preoperative lymphoscintigraphy compared with 1.8 (SD 1.2) in patients with no SN visualised on lymphoscintigraphy ($P < 0.001$). Although SN visualisation on preoperative lymphoscintigraphy significantly improved the intraoperative SN localisation rate, SN was successfully identified in 90% of patients with no SN visualisation on lymphoscintigraphy. Given the time and cost required to perform routine preoperative lymphoscintigraphy, these data suggest that it may not be necessary in all cases. It may be valuable for surgeons in the learning phase to shorten the learning curve and in patients who have increased risk of intraoperative failed localisation (obese or old patients). A negative preoperative lymphoscintiscan predicts the inability to localise with the hand-held γ probe. Therefore, if the SN is not visualised on lymphoscintigraphy then the addition of intraoperative blue dye is recommended to increase the likelihood of SN identification.
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1. Introduction

Sentinel lymph node biopsy (SNB) is rapidly emerging as the new 'standard of care' in breast cancer. Numerous studies have documented SNB to be highly predictive of axillary node status, with a false-negative rate of less than 5% [1–3]. Because of the multiple approaches to sentinel

Abbreviations: SN, sentinel lymph node; SNB, sentinel node biopsy.

* Corresponding author. Tel.: +44-2920-742749; fax: +44-2920-761623.
E-mail address: manselre@cf.ac.uk (R.E. Mansel).

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lymph node (SN) mapping, a number of areas of controversy have developed as the use of this procedure has evolved. One of the controversial areas is the necessity for routine preoperative lymphoscintigraphy. Efforts are now being made to standardise and optimise the technical aspects of the procedure, as well as reduce the cost and inconvenience for patients.

When radioactive colloid is used, a preoperative lymphoscintiscan is often obtained for ease of SN identification. A preoperative lymphoscintiscan for melanoma is often useful because it may identify SNs in unexpected locations or in multiple nodal basins [4–7]. Unlike melanoma, breast cancer lymphatic drainage patterns are fairly predictable, with the vast majority of lesions exhibiting primary drainage to axillary lymph nodes. Therefore, it is not clear whether preoperative lymphoscintigraphy adds diagnostic accuracy to offset the additional time and cost required.

The present study was designed to ascertain the impact of preoperative lymphoscintigraphy on the SN identification rate and the false-negative rate in a large multi-institutional experience. Patients with visualised SNs on preoperative lymphoscintigraphy were compared with those with non-visualised SNs.

2. Patients and methods

The Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial [8] is a multicentre randomised trial in the United Kingdom comparing SNB with standard axillary treatment in the management of patients with early breast cancer. The trial consists of two phases. In phase 1, a validation phase, all surgeons performed SNB in 40 patients with invasive breast cancer followed by the axillary procedure, sampling or clearance, which would be the standard treatment in that centre. The second phase of the trial is the randomised phase comparing SNB with conventional axillary treatment. The data presented here are from the validation phase.

From February 1998 to December 2001, 823 patients underwent SNB followed by the axillary procedure, sampling or clearance which would be the standard treatment in that centre at the same operation. In each centre, local ethics committee approval and written consent for all patients were obtained. The study conformed to the Declaration of Helsinki. Pregnant women, patients with known multicentric tumours and those with previous surgery to the same breast or axilla were excluded. All surgeons along with their team of nuclear physicians and pathologists attended a course on SNB. The surgeons were taught the technique in their own institution by the Principal Investigator of the trial. The SNB was performed according to a standardised protocol using a combination of radiopharmaceutical and blue dye with routine preoperative lymphoscintiscans. Briefly, 2 ml of 99 mTc-radio labelled colloidal albumin (Nanocoll, Nycomed Amersham) was injected at four sites peritumourally. The dose was 40 MBq if injected the day before surgery or 20 MBq if injected on the day of surgery. After injection of radiocolloid, the area was massaged gently for approximately 5 min to improve the lymphatic drainage. Static scintigraphic images were obtained around 3 h after injection of tracer using a dual-head γ camera (Millennium VG; General Electric) with a low energy, high resolution collimator (4 min acquisition in a 256×256 matrix). Anterior and oblique views were obtained. The location of axillary and non-axillary SNs was marked on the skin. A second injection of radiocolloid was not administered if no hot node was visualised after the first injection. After induction of general anaesthesia in the operating room, 3–5 min before the incision, 2 ml of Patent Blue V dye (Laboratoire Guerbet, Aulnay-sous-Bois, France) diluted with saline to a total volume of 5 ml was injected peritumourally. Intraoperative identification of the SNs was based both on blue dye mapping and γ probe detection. A SN was defined as any blue-stained node or any node with radioactive counts more than 10 times the background count. The extra-axillary sites were not routinely removed as this is not the 'standard of care'.

All lymph nodes were bisected if less than 5 mm or sliced at 3 mm intervals if greater than 5 mm and assessed using single sections stained with haematoxylin and eosin (H&E). Intraoperative histological examination was not utilised.

3. Results

Preoperative diagnosis of cancer was documented by fine-needle aspiration or core biopsy in all 823 patients who underwent SNB. SN was visualised on preoperative lymphoscintigraphy in 72% (593/823) of the patients and non-visualised in 230 (28%) (Table 1). Lymphoscintigraphy visualised axillary hot spots in 70% (571/816) of patients. In 9% (62/707), hot spots were noted in the internal mammary chain and exclusive drainage to the internal mammary nodes was seen in 10 patients (Table 1). Patients who had SN identified on preoperative lymphoscintigraphy were compared with those who did not have any SN identified on preoperative lymphoscintigraphy. Patient characteristics of each group are given in Table 2.

Patients with visualised SNs were younger compared with those with non-visualised SNs ($P < 0.001$; Table 2). Non-obese patients (BMI < 30) were more likely to have SN visualisation on lymphoscintigraphy compared with obese patients (BMI > 30) ($P < 0.001$; Table 2).

There was a significant negative correlation between tumour size and success on lymphoscintigraphy ($P = 0.046$; Table 2). Tumours involving the upper outer quadrant of the breast had a lower chance of SN

Table 1
Results of preoperative lymphoscintigraphy

SN identified on preoperative lymphoscintigraphy	No. of patients (%)
No drainage	230/823 (28%)
Any drainage	593/823 (72%)
Axillary drainage[a]	571/816 (70%)
Internal mammary (IM) drainage[b]	62/707 (9%)
Among those with IM drainage	
Axillary + IM	48/62(77%)
IM only	10/62(16%)
Axillary drainage unknown	4/62 (6%)
Drainage to other sites noted	11/823 (1%)

SN, sentinel lymph node.
[a] Axillary drainage for seven patients was unknown.
[b] Adequate data on internal mammary drainage was available for 707 patients.

visualisation on preoperative lymphoscintigraphy $P < 0.001$; Table 2).

4. Results of sentinel lymph node biopsy (SNB)

The SN was identified intraoperatively in 581 of 590 patients (98%) who had SN visualised on preoperative lymphoscintigraphy, with a false-negative rate of 7% (13/192) (Table 3). In the 227 patients who did not have SN visualised on preoperative lymphoscintigraphy, the SN was identified in 204 (90%), with a false-negative rate of 7%. The SN identification rate was significantly higher in patients with SN visualised on preoperative lymphoscintigraphy ($P < 0.001$). The advantage was also maintained when the analysis was restricted to obese women (body mass index > 30).

The method used for intraoperative SN identification was similar between groups. In the visualised SN group, the SN was detected intraoperatively using the blue dye alone in 4% (23/573) patients, hand-held γ probe alone in 13% (73/573) patients and a combination of blue dye and γ probe in 83% (474/573) patients. In the non-visualised SN group, the SN was detected intraoperatively using the blue dye alone in 30% (61/204) patients, hand-held γ probe alone in 4% (9/204) patients and a combination of blue dye and γ probe in 64% (131/204) patients. In 3 patients from each group the node was removed because it was palpable, hard and suspicious. SN identification rate intraoperatively using the γ probe (alone or in combination with blue dye) was significantly higher in the SN visualised group compared with the SN non-visualised group (95% vs. 68%; χ^2 (1 df) $P < 0.001$).

There was no statistically significant difference in the false-negative rate and the operative time between the two groups. A mean of 2.3 (SD 1.3) SNs per patient were removed in patients with SN visualised on the preoperative lymphoscintiscan compared with 1.8 (SD 1.2) in patients with no SN visualised on the lymphoscintiscan ($P < 0.001$).

Table 2
Clinicopathological characteristics of patients undergoing sentinel lymph node biopsy (SNB)

Characteristic	SN identified on lymphoscintiscan ($n = 593$)	SN not identified on lymphoscintiscan ($n = 230$)	P value
Age (years), mean (SD)	56 (11)	61 (11)	<0.001[a]
BMI (kg/m^2), mean(SD)	26 (5)	28 (5)	<0.001[a]
Tumour size, *n* (%)			
Up to 20 mm	333 (68)	117 (59)	0.046[b]
20–50 mm	152 (31)	78 (40)	
>50 mm	7 (1)	2 (1)	
Tumour location, *n* (%)			
Upper outer quadrant	180 (40)	96 (52)	<0.001[cd]
Upper inner quadrant	63 (14)	32 (17)	
Lower outer quadrant	49 (11)	12 (7)	
Lower inner quadrant	36 (8)	7 (4)	
Central	8 (2)	5 (3)	
Mixed including UOQ	73 (16)	27 (15)	
Mixed excluding UOQ	36 (8)	4 (2)	
Axillary nodal metastases, *n* (%)			
Present	194 (33)	86 (38)	0.15[c]
Absent	396 (67)	139 (62)	
Type of surgery, *n* (%)			
Wide local excision	418 (75)	146 (67)	
Mastectomy	138 (25)	71 (33)	

BMI, body mass index; UOQ, upper outer quadrant; df, degree of freedom; SD, standard deviation.
Some data are missing in some of the categories.
[a] *t*-test.
[b] Mann–Whitney.
[c] χ^2 (1 df).
[d] UOQ involved v. uninvolved.

Table 3
Results of sentinel lymph node biopsy (SNB)

Outcome	SN identified on lymphoscintiscan	SN not identified on lymphoscintiscan	*P* value
Successful localisation of SN at operation			
All patients	581/590 (98%)	204/227 (90%)	<0.001[a]
BMI > 30	58/63 (92%)	37/46 (80%)	
False-negative rate[b]	13/192 (7%)	6/83 (7%)	0.89[a]
Operative time (min), mean (SD)	18.6 (10.8)	17.3 (10.8)	0.17[c]
No. of SNs removed, mean (SD)	2.3 (1.3)	1.8 (1.2)	<0.001[d]

[a] χ^2 (1 df).
[b] Analysis restricted to patients with positive axilla.
[c] *t*-test.
[d] Mann–Whitney.

5. Discussion

SNB is rapidly emerging as a minimally invasive alternative to axillary lymph node dissection for nodal staging in breast cancer. Despite the widespread use of SNB in the surgical management of breast cancer patients, several areas remain controversial. These include both technical issues, such as the necessity of preoperative lymphoscintigraphy, preferred location of injection and the best agent for mapping, as well as pure management uncertainties, such as the need to remove extra-axillary SNs or the clinical relevance of SN micrometastasis detected by immunohistochemical staining with cytokeratin.

Lymphoscintigraphy has been an important diagnostic tool for lymphatic mapping in melanoma [9,10]. This allows for identification of all lymphatic drainage basins at risk and for identification of SNs in unexpected locations. The question is whether lymphoscintigraphy contributes to lymphatic mapping in breast cancer and whether it is necessary at all since most surgeons are concerned with mapping only to the axilla. It is clear that mapping of nodes at extra-axillary sites would not be possible without lymphoscintigraphy, but these nodes do not in general affect treatment.

Hot nodes were observed in 72% of patients on lymphoscintigraphy in the present study using the peritumoural injection technique (Table 1). The success rate of lymphoscintigrapy may be improved by using the dermal or subareolar technique. The dermal technique results in significantly higher counts in the SN and compares favourably with the peritumoural injection for concordance and false-negatives [11]. The subareolar technique offers many of the advantages of the dermal injection: it is easy, it avoids the need for image-guided injection and it increases the distance of the tumour to the SN, thus eliminating shine through from upper outer quadrant lesions. The transit time is also quicker than the peritumoural technique [12]. In spite of the many advantages of the dermal or subareolar technique, some institutions continue to utilise an intraparenchymal injection, because this is the only technique that will identify internal mammary lymph nodes.

Variable success rates of lymphoscintigraphy have been reported by other investigators including 36% by Liberman and colleagues [13], 40% by Hill and colleagues [14], 75% by O'Hea and colleagues [15], and 98.7% by Veronesi and colleagues [16]. This may be the result of different imaging agents, radioisotope injection methods, dose of the radioisotope, patient positioning for γ camera imaging and time from injection to imaging.

Tumour size was a significant negative predictor of SN visualisation on lymphoscintigraphy ($P = 0.046$; Table 2). The incidence of nodal involvement increases with invasive tumour size. Extensive tumour infiltration of the primary draining node and the lymphatics in large tumours can thus decrease the migration of radiocolloid into the SN adversely affecting lymphoscintigraphy success.

Most patients (67%) in whom no node was visualised had primary tumours involving the upper outer quadrant of the breast ($P < 0.001$; Table 2). The 'shine through' of the radioactivity from the injection site may have obscured the axillary SN. Older women (>50 years) were more likely to have failure of SN visualisation on preoperative lymphoscintigraphy ($P < 0.001$; Table 2). There is a decrease in tissue turgor in older women, with a resultant decrease in the hydrostatic intralymphatic pressure that drives the mapping agent into the node. Even if the agent is delivered successfully to the node, it may not be concentrated because of the limited sinusoidal space that remains in a fat-replaced node, another feature found more commonly in older patients [17].

Obese women (BMI > 30) were more likely to have a failure of SN visualisation ($P < 0.001$; Table 2). The lymph nodes in obese patients may have undergone fatty degeneration reducing their capacity to concentrate the tracer.

Arguments have been made in favour of lymphoscintigraphy as a 'road map' for surgeons. Our results indicate that SN visualisation on preoperative lymphoscintigraphy significantly improves the intraoperative

SN identification rate ($P < 0.001$; Table 3). If a SN takes up enough radiocolloid to image with a camera, it should be easily detected with the intraoperative probe. The advantage was maintained when the analyses were restricted to obese women (BMI > 30) (Table 3). Similar findings were reported by Birdwell and colleagues [17].

Our findings differ from those of McMasters and colleagues [18] and Burak and colleagues [19] who did not find any significant difference in the SN identification rate of patients undergoing preoperative lymphoscintigraphy when compared with patients in whom lymphoscintigraphy was not performed. The analyses in these studies differ from those done in the present study as all patients in our study underwent preoperative lymphoscintigraphy. We evaluated the role of preoperative lymphoscintigrapy by comparing the patients with visualised SNs with those with non-visualised SNs on lymphoscintigraphy. Both studies had a lower overall SN identification rate (approximately 90%) compared with our study (94%). The higher intraoperative SN localisation rate observed in our study may be because all participating surgeons attended a standardised training programme. Moreover, the SN biopsy was performed according to a standardised protocol. In the series reported by McMasters and colleagues, the SNB was performed using radioactive colloid alone, blue dye alone or both radioactive colloid and blue dye. Not surprisingly, the sensitivity of lymphoscintigraphy for the detection of axillary SNs was low (56%) reflecting the variable quality of the technique in their study. This should be taken into account when comparing the results of the present study with other reports in the literature.

The SN identification rate intraoperatively using the γ probe was significantly higher in the SN visualised group compared with the SN non-visualised group (95% vs. 68%; χ^2 (1df) $P < 0.001$). Similar to other studies [16,20], our results show that a negative preoperative lymphoscintiscan predicts the inability to radiolocalise with the hand-held γ probe. The relative contribution of the blue dye to SN identification was significantly more in the SN non-visualisation group. SN was identified using the blue dye alone in 30% of patients in the SN non-visualisation group compared with 4% of patients in the SN visualisation group (χ^2 (1df) $P < 0.001$). Therefore, if the SN is not visualised on preoperative lymphoscintigraphy, then the addition of intraoperative blue dye is recommended to increase the likelihood of SN identification.

Preoperative lymphoscintigraphy provides information on the number and location of hot nodes in a patient. Not surprisingly, the number of SNs removed was significantly more in the SN visualisation group compared with the non-visualisation group (Table 3). SN visualisation on preoperative lymphoscintigraphy was not associated with a decrease in the operative time probably because of the higher number of SNs removed in this group. There was no difference in the false-negative rate between the two groups.

Some have suggested that preoperative lymphoscintigraphy may be valuable for detecting drainage to internal mammary nodes [21–23]. Even when the lymphoscintiscan suggested drainage to internal mammary nodes, we found concomitant axillary drainage in 77% of patients (Table 1). The significance of internal mammary nodal involvement is controversial [24]. Most surgeons do not intend to perform internal mammary lymph node biopsies, even if drainage to this site is demonstrated on the study. Determination of internal mammary nodal involvement may alter adjuvant therapy. However, this represents only a small number of patients as few patients have an internal mammary SN containing metastatic cancer when the axillary SN is negative. Moreover, many patients currently receive adjuvant therapy based upon tumour size, even if node-negative.

One should remember that the results presented in our study are from the validation phase of the ALMANAC trial and reflect the early experience of each of the surgeons. The SN identification rate would improve once the surgeons are past their learning curve. Although imaging SN with scintigraphy effectively assures successful SN identification, negative imaging should not be the sole indicator of mapping failure or success. SNs are still identified in most of image-negative patients (90%). Given the logistics and cost required to perform preoperative lymphoscintigraphy its routine use does not appear to be justified. It may be valuable for surgeons in the learning phase to decrease the learning curve and in patients who have an increased risk of intraoperative failed localisation (obese or old patients) [2,3,25]. A negative preoperative lymphoscintiscan predicts the inability to localise with the hand-held γ probe. Therefore, if the SN is not visualised on lymphoscintigraphy then the addition of intraoperative blue dye is recommended to increase the likelihood of SN identification.

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ALMANAC Writing Committee: Mr. U. Chetty, Professor P. Ell, Professor L. Fallowfield, Mr. M. Kissin, Professor R. Mansel, Dr. R. Newcombe and Mr. M. Sibbering.

ALMANAC Trialists Group: Professor R. Mansel (Principal Investigator), Mr. T. I. Abdullah, Miss E. Anderson, Mr. L. Barr, Professor N. Bundred, Mr. M. Chare, Mr. U. Chetty, Mr. S. Courtney, Mr. D. Crawford, Mr. R. Cummins, Mr. C. Davies, Mr. M. Dixon,

Mr. D. England, Mr. J. Geraghty, Mr. H. Holliday, Mr. K. Horgan, Mr. M. Kissin, Mr. M. Lansdown, Mr. T. Mahapatra, Mr. J. McCarthy, Mr.I. Monypenny, Professor M. Perry, Professor J. Robertson, Mr. R. Sainsbury, Mr. M. Sibbering, Mr. D. Sinnett, Miss H. Sweetland, Mr. D. Webster, Mr. J. Winstanley, Mr. C. Yiangou.

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