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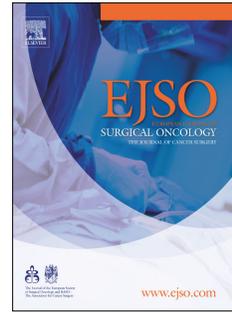
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**Sentinel Node Imaging in Breast Cancer using Superficial Injections: Technical
Details and Observations**

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Abstract:

Introduction:

Sentinel lymph node (SLN) biopsy is the evolving standard of care for the management of early breast cancer. Accurate identification of the SLN is paramount for success of this procedure. Various techniques are described for SLN identification, but the superficial injection techniques, advocated by the UK national training programme (NEW START) are validated, reproducible and rapid. Pre-operative lymphoscintigraphy provides a road map for the surgeon and requires a reporting template.

Methods:

As one of the NEW START training institutions in the UK practising this technique, we reviewed a mature series of 100 unselected, consecutive SLN lymphoscintigraphy procedures. We correlated the imaging, operative and pathology findings and have provided technical details of the technique and a template for reporting SLN lymphoscintigrams.

Results:

The SLN localisation rate was 99% with one failed imaging. Seven patients required delayed imaging. The mean activity of the radiocolloid injected was 14.4 MBq (range 8.3-23 MBq). The SLNs were visualised in the ipsilateral axilla in 98 images, intramammary in 3, and internal mammary in 1. A mean of 1.35 nodes were classified as 'True' SLNs on imaging criteria. Intra-operatively, a mean of 1.91 SLNs were excised. 32 of 116 hot and blue nodes, 7 of 15 only blue nodes, 13 of 47 only hot and 7 of 13 parasentinel nodes harboured metastases.

Conclusion:

The NEW START recommended, combined superficial injection techniques, have high localisation rates. Pre-operative sentinel node imaging is recommended and a template for reporting is provided.

Key words;

- 1) Breast cancer
- 2) Sentinel lymph node biopsy
- 3) NEW START
- 4) lymphoscintigraphy
- 5) Reporting template

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Introduction

Sentinel lymph node biopsy (SLNB) is the evolving standard of care for lymphatic staging in early breast cancer patients. The histological status of the sentinel lymph node (SLN) predicts the status of the remaining lymph nodes in that lymphatic basin, which has prognostic significance and guides regional and adjuvant systemic treatment. There is significant evidence to prove that SLNB is an accurate, minimally invasive procedure which avoids the unnecessary morbidities of an axillary lymph node dissection (ALND) in node negative breast cancer patients(1-5). The success of the UK National Health Service Breast Screening Programme has increased the detection of early node-negative breast cancers, making this procedure even more pertinent(6).

The accurate detection of the SLN is paramount for the success of this procedure. The UK National training programme for SLN biopsy in breast cancer (NEW START) was introduced for structured training in this new technique to avoid the pitfalls of low localisation and high false negative rates which could compromise patient safety. The primary aim of this programme was to achieve SLN localisation rate of at least >90% with a false negative rate of 10% or less(7).

Various injection techniques for SLN localisation have been described in the literature. These are either superficial (intra-dermal, subdermal and periareolar) or deep (intratumoural and peritumoural) injection techniques. There is, however no worldwide consensus on either the choice of the dye used, the plane or site of the injection. The NEW START programme recommends the combined technique of radiocolloid and blue dye injection injected in a superficial plane for SLN localisation. This has been well validated, is easy to teach and use, is predictable, has rapid migration, high radiocolloid nodal uptake resulting in improved image quality and high SLN identification rates with comparable false negative rates to other techniques(8).

The combined technique of radiocolloid and blue dye injection for SLN identification is widely used as it offers the highest SLN identification and lowest false negative rates(9-

11). Radiocolloid injection allows pre-operative SLN imaging which predicts the success of the procedure(12), the number of SLNs and the lymphatic basin of the SLN. It helps to differentiate between true SLN and second echelon nodes and shows SLNs in unusual locations, such as intramammary or internal mammary nodes.

The aims of this paper are:

- 1) To provide detailed description of the technique of performing sentinel node biopsy using the UK national training programme (NEW START) method.
- 2) To evaluate the NEW START method for sentinel node detection in routine practice in a single experienced unit
- 3) To determine the diagnostic information provided and suggest a standard template for reporting breast lymphoscintograms (currently lacking in literature and clinical practice).

Materials & Methods

Radiocolloid Injection:

Pre-operative SLN imaging was performed on the same day or a day prior to surgery by a standard protocol injecting 0.2ml Nanocoll (GE Healthcare) labelled with 10-20MBq Technetium-99m depending on the timing of their surgery. The radiocolloid was injected superficially, either intradermally over the tumour or at the periareolar margin (in an intradermal plane) in the index quadrant (the quadrant in which the tumour lies), using a 5/8 inch 25G needle tightly applied to a 1ml syringe. Patients with multifocal and central tumours were injected at the periareolar margin in the upper outer quadrant. Patients who had undergone a previous excision biopsy had 2 injections of 10MBq in 0.2ml adjacent on either side of the centre of the scar. Patients undergoing injection and imaging on the day of surgery had the activity of the injected dose reduced to 10MBq (2 x 5MBq, if previous excision biopsy).

Prior to injection, the patient's identity was confirmed and informed consent obtained. To reduce skin contamination, the injection site was covered by an absorbent pad with an approximately 1 inch diameter centrally located circular hole, taped to the breast exposing the injection site (figure.1). Prior to injection, a 0.2ml air bubble was drawn up behind the nanocolloidal albumin to ensure the entire dose was delivered and to aid dispersion of the radiocolloid. To be confident that the colloid was injected sufficiently superficial, we aimed to be able to see the needle through the skin, and ensured that a bleb was raised within the skin during injection (figure 1). On withdrawing the needle, slight negative pressure was maintained on the syringe, and a cotton wool ball applied to the injection site. A sterile waterproof circular adhesive dressing was then applied to the injection site to contain any leakage around the injection site. The injection site was massaged for approximately 60 seconds with a further clean cotton wool ball following the injection, and imaging commenced immediately thereafter.

Gamma camera positioning and image acquisition:

The gamma camera was positioned to cover the entire axilla, shoulder, neck, sternal notch to beyond midline of the thorax and the costal margin as shown in figure 2. The patient's arm was positioned abducted 90 degrees on an arm board.

Image acquisition was started immediately and four static image acquisitions were performed in sequence: An anterior-oblique emission image, mimicking the patient's position in the operation theatre was acquired for 5 minutes at an angle of approximately 30° to the horizontal plane with the arm abducted in the operating position. This was followed immediately by a 2 minute transmission image using a Cobalt-57 flood source to outline the body contour for better orientation of the SLN. A lateral image, as shown in figure 3, was then acquired - both to reveal SLN depth and any SLN underlying the injection site, performed with the arm and hand behind the head for 5 minutes. This was immediately followed by a matching lateral transmission image for 2 minutes.

Care was taken to ensure that neither the patient nor the camera was moved between the emission and transmission acquisitions to ensure exact registration of these two images. All images were acquired using a large field of view gamma camera with low energy high resolution collimator and 256x256 pixel matrix in word mode. Energy windows of 20% with 3% offset centred on 140keV and 20% centred on 122keV were set for emission and transmission imaging respectively. Images were processed by summation of the emission and transmission images and displayed as a composite review screen, as shown in figure 4.

Patients in whom the nanocolloidal albumin failed to migrate to the sentinel node on immediate imaging underwent delayed imaging either later the same day (typically with a 2-4 hour delay) or the following morning, if feasible.

Blue dye injection:

In the operating theatre, 2 ml of Patent Blue V dye (Laboratories Guerbet, France) was injected in a slightly deeper, subareolar plane in all patients to minimise tattooing of skin. The injection was performed after the patient was anaesthetised and the area massaged to aid faster migration of the dye. Prior to the blue dye injection, the anaesthetist was warned that it might interfere with the pulse oximeter and rarely cause anaphylaxis(13).

Intra-operative SLN detection and probe-guided SLN biopsy:

The SLNB was performed by an experienced surgeon using a gamma probe to localise the radioactive and blue SLN, guided by the image data and blue coloured lymphatic tracts leading to the SLN. All blue and radioactive nodes, nodes with blue lymphatic tracts leading to them, any lymph node with 5-10 times the background activity or 10% of the lymph node with the highest radioactivity and pathologically palpable lymph nodes were excised. The number of nodes excised, their radioactivity (as determined by a 10 second ex-vivo count of the excised node using the gamma probe held in contact with the node) and the fact the nodes were blue or not were recorded.

SLN histo-pathological examination:

All excised SLNs were serially sectioned at ≤ 2 mm slices and examined at a minimum of 3 levels. Routine Haematoxylin & Eosin (H&E) staining was carried out on all nodes and nodes without any evidence of metastases underwent further staining with immunohistochemical (IHC) staining for cytokeratin antibodies.

Image analysis:

To provide guidelines for our practice and to outline a standard reporting template, 2 observers blinded to the intra-operative and histopathological findings reviewed the composite image (as in figure 4) of a mature series of 100 consecutive procedures.

For image analysis, any lymph node with high radioactive tracer uptake was termed “hot” and any hot node with a direct radioactive lymphatic tract arising from the injection site was defined as a SLN on imaging criteria. If no lymphatic tracts were identified, all hot nodes were defined as SLNs. Nodes with secondary lymphatic tracts arising from these SLNs were called second echelon nodes.

The following information was recorded from the images:

1. The number of “hot” nodes, the presence of lymphatic tracts and the lymphatic basin.
2. An opinion as to whether a hot node represented a sentinel node on imaging criteria.
3. The presence of second echelon nodes.
4. The presence of any imaging artefacts e.g. skin contamination, free pertechnetate or nanocolloid uptake by the reticuloendothelial system.

The number of nodes biopsied intra-operatively was recorded and categorised as ‘hot and blue’, ‘hot but not blue’, ‘blue but not hot’, ‘non-blue and non-hot’. In all cases, pre-operative imaging, intra-operative findings and final histopathology were recorded and compared.

Results

One hundred (100) unselected, consecutive SLN lymphoscintigram images from 98 patients (2 bilateral breast cancers) with a mean age of 55.1 (range 26 – 83) were reviewed. The patients had T1 or T2 tumours as determined by preoperative clinical and imaging modalities.

Primary tumour characteristics

The predominant location of the tumour was in the upper outer quadrant. The majority of the lesions were palpable (85) and unifocal with 53 left sided tumours. Four tumours were diagnosed as multifocal preoperatively and 5 patients had undergone a previous excision biopsy.

Injection technique

Sixty SLN localisation procedures were performed by periareolar injections and 40 by intradermal injections over the tumour site. The mean activity injected was 14.4MBq (range 8.3 – 23 MBq). Sixty six patients underwent injection and imaging on the day prior to surgery. A single adverse reaction to injection of technetium labelled Nanocoll was noted. This patient developed an urticarial rash extending from the injection site to the axilla which started 30 minutes after injection and responded promptly to a topical steroid cream(14).

Imaging

All patients had four standard images acquired: Anterior-oblique - emission and transmission images and lateral - emission and transmission images. Using the superficial injection technique outlined, hot nodes were visualised on immediate imaging in 93 SLN localisation procedures. Seven patients required delayed imaging, of which 6 had hot nodes visible and 1 patient had no uptake on delayed imaging (failed imaging, though a

weakly radioactive and blue stained axillary node was found intraoperatively with the gamma probe, but no tumour was identified on final histology). In this group, the age ranged from 45-83 with a mean age of 59.6. The localisation rate on imaging was therefore 99%.

SLNs were visualised in the ipsilateral axilla in 98 images. In addition 3 patients had intramammary nodes visualised. One patient had uptake only within the internal mammary chain, but not in the axilla. This patient was found to have gross axillary metastatic involvement at surgery, clinically palpable prior to surgery.

A mean of 2.2 hot nodes (including SLNs and second echelon nodes with a range of 0-6) were visualised per patient. Of these a mean of 1.35 nodes (range 0-2) were classified as true SLNs on imaging criteria. At least 1 true SLN was observed in each of the 99 images. The associated lymphatic tracts were useful to differentiate true SLNs from second echelon nodes. Eighty five lymph nodes in 54 patients were categorised as second echelon nodes based on the imaging criteria for second echelon nodes. No difference in the imaging was found between the patients injected intradermally overlying the tumour and those injected at the periareolar margin.

Observed artefacts

A limited number of imaging artefacts were noted, but these were minor in extent and did not affect SLN identification in this series. The artefacts were minor skin contamination (9 cases), free pertechnetate, seen as uptake within the thyroid, gastric mucosa and salivary glands was seen in 4 patients. Two patients had uptake within the liver.

Intraoperative and histo-pathological findings of the SLNs

A total of 191 lymph nodes (mean of 1.91) were excised as per the intra-operative criteria for SLN excision as outlined earlier and labelled as SLNs for histo-pathological

assessment. Table 1 shows the breakdown of the blue staining and radioactivity of these nodes.

Of the 191 biopsied nodes, 116 were hot and blue with 32 containing metastases. Fifteen biopsied nodes were blue but not hot, of which 7 were metastatic. Forty seven nodes were hot but not blue and 13 harboured metastases. Thirteen nodes which were neither hot nor blue were biopsied intra-operatively in this series as they were considered clinically suspicious by the operating surgeon. These were labelled as 'parasentinel' nodes for histo-pathological examination. Seven of these 13 nodes were metastatic.

In this series, there were 39 patients with node positive disease in whom the majority were staged by the presence of an involved hot and blue node. The 'only hot' and 'only blue' nodes were the only involved nodes in 7 and 2 patients respectively. All 13 parasentinel nodes had associated blue and/or hot nodes and in 3 of these 7 node positive patients, the parasentinel node was the only node containing metastases.

On an individual patient basis, 12 patients had less radioactive nodes biopsied than were seen and classified as true SLNs on imaging criteria. Of these 12 patients, 8 patients had grossly involved axillary lymph nodes and had immediate axillary lymph node dissection (ALND), 2 patients had small metastases on histopathology and proceeded to have a delayed ALND. Two patients did not have any metastases and are being followed up.

Discussion:

The success of the SLN injection technique is measured by the identification rate and false negative rate. The superficial intradermal and subareolar techniques, recommended by the UK NEW START training programme are validated and have reported identification rates of 97-100%(15;16). This is similar to the 99% identification rate reported in this series. The main advantage of this technique is that the migration is rapid requiring smaller volumes of injection and lower radioactivity. They can be administered without imaging guidance, even in impalpable tumours.

The value of pre-operative imaging is that it predicts the success of the SLNB procedure. It enables the surgeon to predict the number of the hot nodes that should be biopsied, thus avoiding understaging. It enables differentiation of true SLNs from second echelon nodes facilitating a less extensive procedure.

Second echelon nodes are nodes lying further upstream to the true SLN without direct lymphatic drainage from the primary tumour. They are seen when the tracer dye is not effectively trapped by the true SLN resulting in spillover to these second echelon nodes.

Studies by Borgstein et al(17) have confirmed the hypothesis that the lymphatics of the overlying skin drain to the same axillary sentinel node as the underlying breast tissue. The discrepancy in the uptake of the blue dye and the radioisotope observed in our study can be explained due to the difference in the particle size and the depth of the injection. As a combination of radioisotope and blue dye is used, the dye with smaller particle size has increased tendency to spill over and a slightly deeper injection results in slower migration with nodes being biopsied as either 'blue only' or 'hot only' nodes.

In this series, 191 lymph nodes were biopsied as potential SLNs. This is less than the total number of hot nodes (220 nodes) seen on imaging, but higher than the total number of nodes classified as SLNs (135 nodes) on imaging criteria. Despite the pre-operative lymphoscintigram image, the surgeons erred on the side of caution and biopsied more

nodes than those classified as true SLNs on imaging. Different criteria are used intra-operatively for defining a node as a SLN such as the presence of a blue tract leading to a node and these account for some of the differences.

Seven of the 13 parasentinel lymph nodes harboured metastases. This supports our routine practice to remove any pathologically palpable nodes as part of the SLNB procedure to avoid the well recognised pitfall of heavily involved nodes causing diversion of both radiocolloid and blue dye(18;19). Twenty SLNs (7 – only blue and 13 – only hot) contained metastases reflecting the fact that using blue dye or radiocolloid alone for identification increases the false negative rate of the procedure².

The main drawback of the superficial injection technique is that it rarely demonstrates SLN location in the internal mammary chain. Hence if an internal mammary drainage is suspected, a deeper injection (peri or intra tumoural) technique may have to be considered.

Some authors have argued that pre-operative imaging, when a highly predictable method is used is an unnecessary, expensive optional step(20;21). We strongly recommend pre-operative imaging as it provides a “road map” for the surgeon to proceed confidently in looking for the SLN under guidance of the gamma probe. Prior information about the number and location of the SLN reduces biopsy time and helps in planning the surgery when SLNs in unusual locations are identified. Pre-operative axillary ultrasound with fine needle or core biopsy of suspicious nodes can detect as many as 50-70% of metastatic nodes, thus obviating the need for SLNB, and is thus recommended(22;23).

Following our experience in pre-operative SLN imaging with the superficial injection technique, we recommend the following template for Nuclear medicine specialists to report SLN imaging in breast cancer for better and easier interpretation by the operating surgeon.

1. Side of injection.
2. Anatomical site and plane of injection.

3. Number of injections.
4. Radiolabelled colloid used, with any relevant factor regarding its preparation.
5. Activity and volume of each injection.
6. Injection technique.
7. Details of the images acquired and timing post injection.
8. Lymphatic basin(s) revealed by imaging.
9. Number of hot nodes seen.
10. Number of lymphatic tracts seen.
11. Number of “hot”spots that fit the criterion of a sentinel node to be called as ‘True SLN’.
12. Number of “hot”spots that fit the criterion of a second echelon node to be called as ‘second echelon’ nodes
13. Any imaging artefacts eg. skin contamination, free pertechnetate or intravascular colloidal uptake.

Conclusion:

SLN biopsy is replacing routine ALND for lymphatic staging in early breast cancer patients. It is emerging as the current standard of care, avoiding the morbidities of ALND in node negative patients. Although, different SLN identification techniques described in literature can be reliably used, we recommend the combined use of both radiolabelled colloid and blue dye injected in a superficial plane as suggested by the UK NEW START National training programme.

SLN imaging prior to surgery is advantageous and logistically feasible. A uniform template providing guidance for reporting the breast lymphoscintigrams would be beneficial and is proposed for routine use.

Conflict of interest:

There is no conflict of interest to be disclosed.

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[Figure 1]

Figure 1: Superficial injection of Nanocoll administered in the periareolar region of the index quadrant.

[Figure 2]

Figure 2: Position of the gamma camera & the patient for the anterior-oblique emission image acquisition. The image on the right shows the area to be covered.

[Figure 3]

Figure 3: Position of the gamma camera & the patient for lateral imaging acquisition.

[Figure 4]

Figure 4: Images on the left show the emission images of the antero-oblique (top) and the lateral (bottom) views. Images on the right show the summed emission and transmission image of those 2 acquisitions.

Table 1

Table 1: Breakdown of intra-operative blue staining and radioactivity of nodes

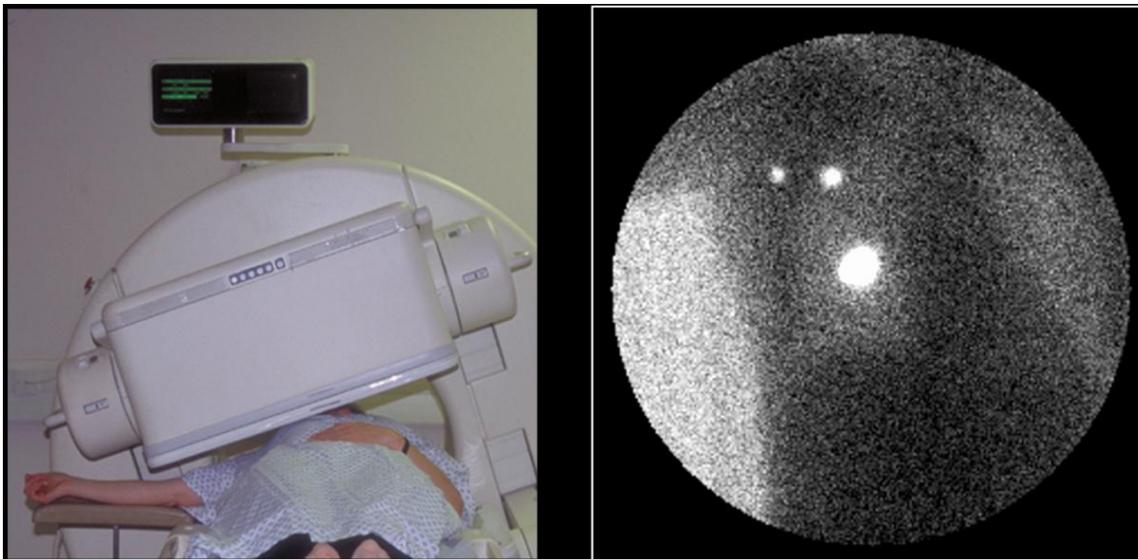
Table 1: Breakdown of intra-operative blue staining and radioactivity of nodes

	Hot	Not hot	TOTAL
Blue	116	15	131
Not blue	47	13	60
<i>TOTAL</i>	<i>163</i>	<i>28</i>	<i>191</i>

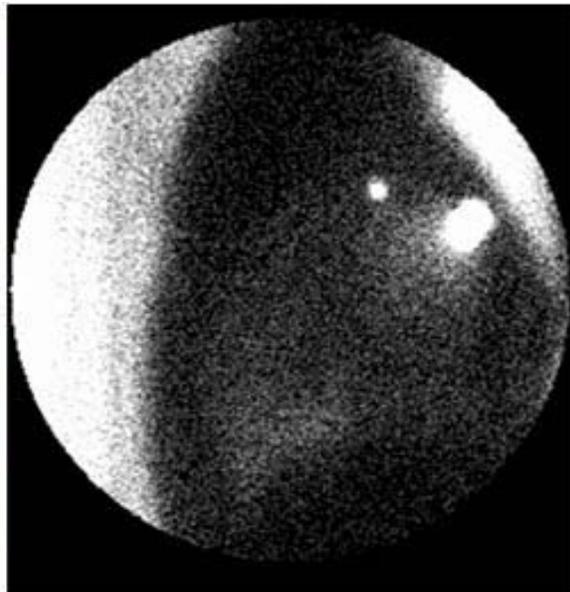
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