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Effectiveness of immediate preoperative injection of radiopharmaceutical and blue dye for sentinel node biopsy in patients with breast cancer

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ABSTRACT

Background: Sentinel node biopsy (SNB) in breast cancer conventionally utilises a preoperative radioisotope injection and lymphoscintigraphy, which is time consuming and painful. The aim of this study was to evaluate a potentially more efficient and practical technique of immediate preoperative injection of blue dye and radiopharmaceutical by the surgeon (without involvement of a nuclear medicine department).

Method: One hundred and sixty three clinically node negative patients with invasive breast cancer undergoing breast-conserving surgery were included. The radiopharmaceutical was delivered to the operating suite and injected by the surgeon in the subareolar region immediately after induction of anaesthesia. Sentinel node biopsy was performed in conjunction with removal of any palpable axillary lymph nodes (axillary node sampling).

Results: Sentinel nodes (SNs) were detected in 161 of 163 women. On average, 3.0 sentinel nodes were identified. Twenty nine patients had involved nodes of whom 28 had a positive sentinel node. Of the two patients with failed identification, one had involved axillary lymph nodes on sampling and the other had an involved intramammary lymph node.

Conclusion: This method produces results identical to those obtained with other techniques. This study shows that sentinel node biopsy can be performed safely without involvement of a nuclear medicine department with the added benefits of no preoperative injection and improved efficiency in the operating suite.

1. Introduction

Axillary lymph node status has been shown consistently to be the most significant prognostic factor in patients with breast cancer.[1] The method of sentinel node biopsy (SNB) is now well accepted for evaluation of axillary node status. Large validation studies including the recent ALMANAC trial have shown that SNB in patients with breast cancer is a safe, reliable technique that stages the axilla accurately.[2] Despite widespread use of SNB, many questions remain regarding the technical aspects of this procedure. Most surgeons use a combination of radioisotope and blue dye as it has been shown to provide the highest rates of sentinel node (SN) identification.[3,4]

Radioisotope is generally available only in those institutions with a nuclear medicine department, and a

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lymphoscintigram is usually carried out in conjunction with the injection of the radioisotope. The need for a lymphoscintigram poses scheduling difficulties between nuclear medicine and surgery. Some centres continue to use blue dye alone because of difficulty in accessing radiopharmaceuticals.

Controversy surrounding the optimal site of injection for radioactive colloid and blue dye continues. A central subareolar injection technique is being used increasingly based on an improved understanding of lymphatic drainage.[5,6] Although radioactive colloid travels rapidly through lymphatics, it has been the tradition to inject the radiopharmaceutical some hours prior to surgery. The ALMANAC study showed that SNB detection rate was not influenced by the interval between time of injection and time of surgery.[7]

There are obvious advantages to being able to inject the radiopharmaceutical along with the blue dye following induction of anaesthesia. Injection of the radioisotope by the surgeon after the patient is asleep decreases the number of patient appointments required (and hence improves efficiency), eliminates the need for an uncomfortable pre-anaesthetic injection and would allow the use of radioisotope in SNB to be more widely available.

Potential issues related to administering radioactivity in the operating theatre include safety to the patient and staff. Preliminary data indicate that a satisfactory rate of SN detection can be obtained with immediate preoperative injection of radiopharmaceutical.[8]

The primary aim of this study was to determine whether immediate preoperative injection of radiopharmaceutical and blue dye into the subareolar region produces a satisfactory rate of sentinel node detection and to determine whether it accurately identified those nodes involved by cancer. The secondary aim was to determine whether SNB can be carried out safely by a surgeon with a licence to administer radioisotope without direct involvement of a nuclear medicine department.

2. Materials and methods

The principal author (J.M.D.) is an Administration of Radioactive Substances Advisory Committee (ARSAC) licence holder. All procedures were either performed by or supervised by the principal author. All staff in the theatre were educated in the use of radioactive materials by one of the authors (T.K.). An initial pilot study was performed to evaluate the safety of injecting the radiopharmaceutical in the anaesthetic room. This demonstrated rapid transit of the radiopharmaceutical and identified no significant radioactive contamination of swabs, gloves or any other material following the procedure. It was thus deemed a safe technique for introduction into clinical practice.

From December 2005 to December 2007, 163 patients with clinically node negative invasive breast cancer undergoing breast-conserving procedures were enrolled into this prospective audit. The median age was 63 years (range 31–89 years). No patient was excluded based on the size of tumour or previous surgical intervention. All patients had an ultrasound scan of the axilla. Any sonographically suspicious lymph nodes were subjected to fine needle aspiration cytology (FNAC) or core biopsy. If malignancy was demonstrated on FNAC or core biopsy, the patient was excluded from the audit and proceeded to an axillary lymph node clearance (ALNC).

Three patients had previously undergone an axillary node sampling as part of surgery for a previous breast cancer. Four patients had a prior breast-conserving procedure and had only a sentinel node biopsy performed during this procedure. Eight patients had SNB following neoadjuvant chemotherapy and 26 had SNB following neoadjuvant endocrine therapy.

The radiopharmaceutical used in the study was Technetium-99m [^{99m}Tc] Albumin Nanocolloid Injection (Nanocoll, GE Healthcare, Amersham, United Kingdom (UK)). It was prepared in a central radiopharmacy and delivered to the hospital in a single dose syringe containing a nominal 25 MBq/0.5 ml. The activity of each syringe on entry to the hospital was confirmed in the oncology physics department. Thereafter, the syringe was stored at room temperature in a locked cupboard in the anaesthetic room of the operating theatre.

The radioisotope was injected following induction of anaesthesia while the patient was in the anaesthetic room. The syringe containing the radiopharmaceutical was connected to a one-way valve (R-Lock, Codan, Lensahn, Germany) and to a 23-gauge (blue) needle. This was inserted subcutaneously at the 6 o'clock position of the nipple areolar complex. The radiopharmaceutical was then injected and the syringe was removed and placed in a labelled incinerator bin. In the first 48 patients, 2 ml of Patent blue-V sodium 2.5% (Guerbet, Roissy, France) diluted to 5 ml with sodium chloride was then injected through the same one-way valve and needle into the subareolar region. For the remaining patients following injection of radiopharmaceutical, 1–2 ml of undiluted dye was injected, followed by 3 ml of sodium chloride. After injection of the blue dye and radiopharmaceutical, the breast was massaged for 60 s. The patient was then immediately transferred to the operating theatre.

The minimum time between the injection of isotope and the performance of the sentinel lymph node biopsy was 7 min and the mean time in the first 100 patients was 19.94 min, with a median of 19.5 min.

A Navigator probe™ was used intraoperatively to identify radioactive nodes. All blue and/or radioactive nodes (with 10 s counts greater than 10 times background) were sent for pathological analysis. Any enlarged or suspicious nodes were sent separately as sampled nodes. Extra-axillary lymph nodes were not sought.

Specimens that were not sent to pathology immediately were stored in a sealed cupboard. This precaution was taken even though the levels of radioactivity in these specimens were minimal. Nodes were processed in a standard manner with routine H&E staining. Immunohistochemistry (IHC) was not used routinely to confirm nodal involvement. If there was suspicion but no definite evidence of malignancy on H&E, IHC was used to confirm that the abnormal cells were epithelial.

3. Results

3.1. *Sentinel node detection*

In 161 of 163 women (98.8%), SNs were detected. Of the two women who did not have SNs detected, one had an involved

intramammary node adjacent to the cancer – which was blue but at some distance from the axilla – and the second had two involved axillary nodes on sampling, both nodes being replaced by cancer. Neither patient had undergone surgery previously. All the four patients who had SNB/ANS without a concurrent breast procedure had SNs identified. Fig. 1 illustrates the number of SNs detected, nodes sampled and pathology.

In the remaining 161 women, 495 SNs were detected of which 368 (74%) were radioactive and blue, 94 (19%) were radioactive only and 33 (7%) were blue only. The mean of the number of SNs was 3.2 with a median of 3.0. The numbers of SNs per patient are shown in Fig. 2. It can be seen that almost three quarters of patients had between two and four SNs. Sixty seven patients did not have any suspicious palpable lymph nodes following SNB which warranted axillary sampling. The mean number of nodes removed by subsequent axillary sampling of palpable or suspicious nodes was 1.35 with a median of 1. Overall, a mean of 4.39 nodes were removed from each patient, the median being 4.

3.2. *Sensitivity of sentinel node biopsy*

Twenty nine patients had histological evidence of axillary node involvement. Twenty eight of these 29 patients (96.5%) had positive SNs – an overall positive SN rate of 17.4%. In 23 patients the involved node was the hottest or bluest node, but in 5 (17.9%) the involved sentinel node was not the hottest or bluest node. Five of the 28 patients with involved nodes had received neoadjuvant hormone treatment (letrozole) and three had extranodal extension within the SNs. The remaining patient with axillary node involvement had no SN detected but had replacement metastases in two palpable nodes in the axillary node sample. In each of the affected nodes, there was extensive involvement with extranodal extension.

Overall, 45 of 716 nodes removed (6.3%) were involved and this included 40 of 495 (8.1%) SNs and 5 of 221 (2.3%) sampled nodes. Three of the 28 patients (10.7%) with involved SNs had sampled nodes removed that were also involved.

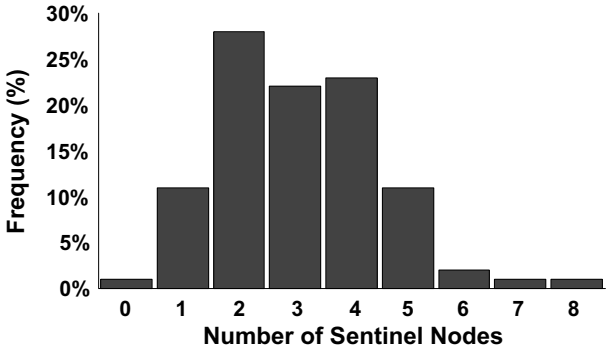

Fig. 2 – Distribution of numbers of sentinel nodes per patient.

4. Discussion

SNB has proven to be a method of accurately staging the axilla in breast cancer patients while minimising the morbidity and pain associated with ALNC. However, preoperative injection of radioisotope for lymphoscintigraphy causes discomfort and anxiety that is not well documented.[8]

This study confirms preliminary findings by other authors that immediate preoperative injection of radioactive albumin is effective in identifying sentinel nodes.[6,8] Zogakis et al. demonstrated a 99.2% SN identification rate using a similar technique of immediate subareolar radioisotope and blue dye injection.[6] The average number of sentinel nodes (3) in this study was identical to that in the large NSABP study (2.9),[9] and was somewhat higher than the number in ALMANAC.[7] The rates of SNs that were radioactive, blue or without any uptake are also consistent with other studies.[10] The radioisotope counts were also similar to those seen in the Edinburgh Unit during the ALMANAC study. This study has also con-

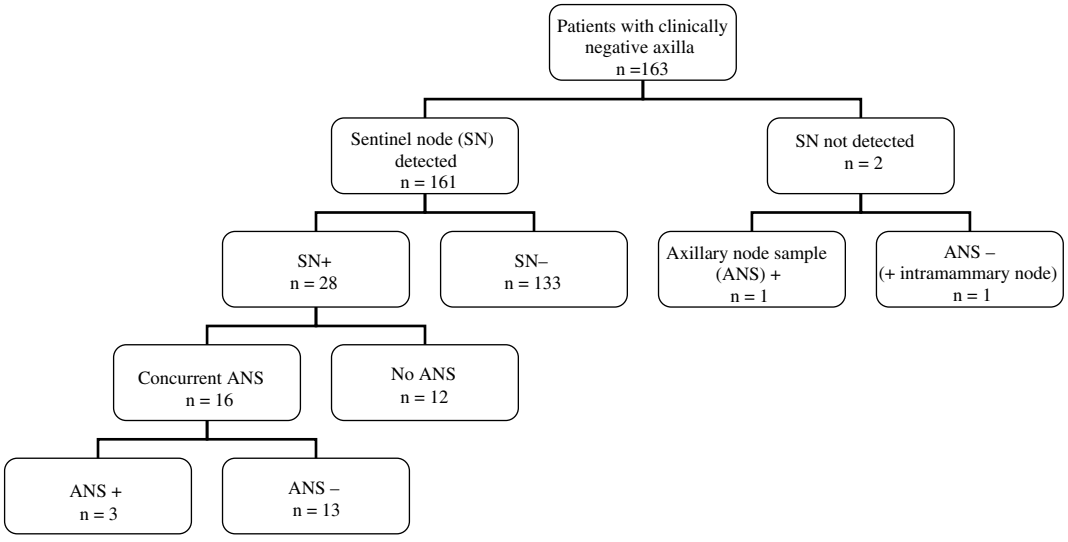

Fig. 1 – Flow chart summarising sentinel node detection and pathology results.

firmed that subareolar injection is effective and produces a high rate of sentinel node detection.[5] The two patients who did not have sentinel nodes detected in this study had involved nodes: the first in the lower axilla and the other an involved intramammary node. It is appreciated that blocked lymphatic drainage is a barrier to sentinel node detection. This is why we and others,[11] continue to advocate removal of residual palpable suspicious axillary nodes following completion of the sentinel node biopsy procedure. This sampling removed a median of only one node per patient. Although there were small numbers of involved sampled nodes, it did pick up one patient whose axilla was negative on SNB but had involved sampled nodes. For the extra morbidity of removing one extra node, the addition of sampling palpable suspicious nodes is considered worthwhile.

While it was not possible to ascertain the true false negative rate of this study as SNB was not carried out concurrently with ALNC, the positive SN rate of 17.4% is equivalent to other centres that perform axillary ultrasound prior to SNB.[12] This rate is obviously lower than centres that perform SNB without using ultrasound to stratify patients' risk.[2]

This study has also confirmed the importance of using both radiopharmaceutical and blue dye. Had the radiopharmaceutical not been used, 19% of the sentinel nodes that were removed would not have been detected. This suggests that the use of blue dye alone is a suboptimal technique for identifying sentinel nodes. However, not all hospitals have a nuclear medicine department. The unique aspect of this study was the lack of involvement of a nuclear medicine department. The radiopharmaceutical was supplied directly to the operating theatre in single dose syringes. This method of supply offers several advantages in that it minimises (1) the handling of radioactive material in the operating theatre, (2) the exposure of the theatre staff to radiation, (3) the potential for radioactive contamination and (4) the disposal of radioactive waste. On receipt, the activity of each syringe was checked by an oncology scientist. This confirmation of a radiopharmaceutical's activity before administration is essential. The equipment necessary to perform the measurement includes a radionuclide calibrator or other radiation monitor that is calibrated for the measurement of ^{99m}Tc. Having confirmed that the activity was within the prescribed range, the radioisotope was stored in a locked cupboard in the anaesthetic room. By using a unique single dose syringe together with a check of activity on entry into the hospital, there is little if any chance of overdosing the patient. The potential disadvantage of introducing radiopharmaceuticals into an area in the hospital where they are not routinely administered has been addressed by the adherence to stringent but simple protocols and by the involvement of theatre staff in the development of these protocols. Education of all staff involved played an important part in the success of this study. This model of radiopharmaceutical delivery, activity check and staff education is one that should work in any hospital.

A possible difficulty with this method is the lack of a lymphoscintigram to guide exploration for SNs. Lymphoscintigraphy is not always required to identify SNs.[13] Many surgeons rely on the gamma probe and sighting of blue dye for axillary SNs. For extra-axillary SNs, it is still possible to identify these nodes using the gamma probe alone. Many surgeons view SN biopsy as a less morbid replacement and better targeted procedure than axillary sampling or lower axillary dissection, and as the implications of internal mammary SN biopsy are still uncertain, many do not routinely biopsy them.[14,15]

One of the problems with SN localisation as it is currently performed in other centres is the need for patients to come to the hospital a number of hours before surgery or even the day prior to have the radiopharmaceutical injected. This is not only painful for the patient but is also time consuming. Furthermore, it limits the procedure to centres which have or are nearby a nuclear medicine department.

This study confirms the previous studies that injection of radiopharmaceutical once the patient is anaesthetised is an effective method of performing SN localisation.[8] This technique saves the patient the discomfort of a preoperative injection and streamlines scheduling in the operating suite. If further studies confirm these advantages, then it is likely that immediate preoperative injection of radiopharmaceutical and blue dye for SN localisation will become the standard of care. Furthermore and importantly, by having a surgeon with a licence to use radioactivity, this technique allows radioisotope-guided SNB to be offered to patients in all hospitals undertaking breast cancer surgery regardless of their association with a nuclear medicine facility.

Conflict of interest statement

None declared.

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