# Breast lymphoscintigraphy for sentinel node identification in breast cancers with clinically-negative axillary nodes

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## ABSTRACT

**Introduction: To analyse and determine the clinical value of lymphoscintigraphy for sentinel lymph node (SLN) localisation in woman undergoing surgery for breast cancer, and evaluate the predictive value of SLN versus axillary lymph node (ALN) status in these patients.**

**Methods: Preoperative breast lymphoscintigraphy was performed in 35 female patients with breast cancer and clinically-negative ALNs. The mean age was 52.8 years (age range 38 to 73 years). The lymphoscintigraphy was performed using 74 MBq of Tc-99m nanocolloid subdermal injection over the tumour. The SLN location was marked on the skin. All patients underwent standard modified radical mastectomy with axillary lymph node dissection (ALND). A comparison of SLN and ALN histopathological results was completed in order to define the means by which the SLN biopsy was able to reflect the final status of ALNs.**

**Results: In 20/35 (57.1 percent) cases, SLNs were visualised in 20-minute dynamic imaging. In 12 patients, SLNs were seen after delayed imaging and/or by repositioning the patient. Overall, the estimated SLN identification rate was 91.4 percent. Of 32 patients in whom SLNs were localised by lymphoscintigraphy, nine were positive for metastatic tumours and the rest were negative for tumour involvement. In four of these nine patients, SLN was the only node that contained metastatic tumour cells while in five patients, an additional concomitant ALN metastasis was detected. In four patients, SLN was negative on frozen section, but skip ALN metastases were noted. Of three patients in which SLNs were not localised by lymphoscintigraphy, two had positive ALNs for tumour cells and the remaining one was negative for tumour involvement.**

**Conclusion: We concluded that SLN localisation using lymphoscintigraphy is an accurate minimally-invasive procedure for staging breast cancer patients with clinically-negative ALNs, and can substantially reduce the morbidity and costs of surgical treatment by avoiding unnecessary ALND in the majority of patients.**


**Keywords: axillary lymph node, breast cancer, lymphoscintigraphy, preoperative breast lymphoscintigraphy, sentinel lymph node localisation**

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## INTRODUCTION

Axillary lymph node (ALN) status is one of the most important prognostic indicators in patients with early stage breast carcinoma[1]. Standard axillary lymph node dissection (ALND) may be associated with significant morbidity, including the need for a general anaesthesia, postoperative lymphoedema of the involved extremity[2], neuropathy of the arm[3], seroma formation, formation of a painful neuroma, or local wound problems[4]. Due to a relatively low incidence of ALN metastasis in tumours of less than 2cm, the role of ALND for these patients has been questioned. The sentinel lymph node (SLN) biopsy has been developed for the purpose of minimally invasive diagnostic procedure to provide accurate ALN status. Therefore, the standard ALND could be avoided in patients with a histopathologically-negative SLN biopsy.

The technique of SLN localisation was first described by Morton et al using blue dye[5,6], and later by van der Veen et al using lymphoscintigraphy[7]. Lymphoscintigraphy is increasingly used to identify the SLN. If the SLN is tumour-free, then the remainder of the nodes in that specific nodal bed is likely to be free of metastases. After widespread clinical use in the staging of malignant melanoma patients, the SLN biopsy has been introduced in the clinical management of clinically node-negative breast cancer. The aims of this study were to analyse and determine the clinical value of lymphoscintigraphy for SLN localisation in women undergoing surgery for breast cancer and evaluate

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**Table I. Characteristics of 35 patients (all patients had clinical N0M0).**

| Characteristics of patients | Number of patients |
|---|---|
| Age (in years)* | 52.8 (38-73) |
| Tumour location | |
| Right | 13 |
| Left | 22 |
| Histological tumour size (in mm)* | 2.54 (1-4) |
| Tumour staging | |
| T1 | 7 |
| T2 | 24 |
| T3 | 2 |
| T4 | 2 |

* Median (range)

the predictive value of SLN versus ALN status in these patients.

## METHODS

From May 2000 to May 2003, 35 patients with newly-diagnosed operable invasive breast carcinoma and clinically-negative ALNs were included in this prospective study. All patients had biopsy-proven invasive ductal breast carcinoma by prior fine needle or exisional biopsy. The patients were referred to the Division of Nuclear Medicine, Department of Radiology, Faculty of Medicine, Chiang Mai University for SLN localisation prior to surgery. The characteristics of the patients are presented in Table I.

Preoperative breast lymphoscintigraphy was performed using 74 MBq of technetium-99m nanocolloid with particle size of less than 80 nm in a volume of 0.2 to 0.5 ml injected subdermally over the tumour mass. Lymphoscintigraphy was performed one day before (21 patients) or on the same day of surgery (14 patients). In all patients, the injection sites were massaged for about one minute after the injection. The patients were placed in the supine position under the gamma camera, and the injected arm was placed over the head to optimise axillary exposure. After injection, dynamic anterior imaging was obtained at ten seconds/image for 20 minutes, using a large-field of view single-head gamma camera (Apex-SP4 Elscint) equipped with a high-resolution collimator and ten percent imaging window at a 140-KeV energy peak. Subsequently, planar anterior and lateral images were obtained at 30 minutes and one hour after the injection, with a preset count of 500K for each image in a matrix size 256 x 256. If the SLN could not be identified within one hour after the tracer injection, the delayed planar images would be recorded at two hours. The location of the SLNs was marked externally on the skin with a permanent pen.

The criteria for identifying the SLN by lymphoscintigraphy were visualisation of an afferent lymphatic vessel leading from the injection site to the lymph node and/or the first lymph node appearing in each nodal basin. All patients underwent standard modified radical mastectomy with ALND as part of their standard treatment. A skin incision was made so as to achieve first the radiolabled SLN biopsy. The SLN was harvested intraoperatively using a sodium iodide hand-held gamma-detecting probe (GDP) and excised before the standard ALND was performed. Any remaining radiolabelled lymph nodes were removed. No frozen sections were performed. All lymph nodes were analysed by serial sectioning of the whole node after formalin fixation and paraffin embedding. Every section was stained by haematoxylin and eosin, and examined carefully by a skilled histopathologist.

Each lymphoscintigram was reviewed by the nuclear medicine physician. The parameters analysed in this study were SLN visualisation rate, accuracy, skip metastases, scintigraphical findings, and histopathological results. Accuracy was calculated by the number of patients in which the histology of the SLN was reflective of that in the remainder of the nodal basin. Skip metastases were defined as a negative histopathological result of SLN, with other nodes in the basin being positive for metastatic breast cancer.

## RESULTS

Preoperative breast lymphoscintigraphy could demonstrate the SLNs in 32 patients (91.4%). In three patients (8.6%), scintigraphy revealed no definite visualisation of SLNs for up to two hours after the injection. The SLNs were visualised before 20 minutes in 20 of 35 patients (57.1%) during dynamic imaging. In an additional 12 patients, SLNs were identified after delayed imaging and/or by repositioning the patients. The overall SLN visualisation rate was 91.40%, with a rate of 57.14% at 20 minutes, 85.70% at one hour and 91.40% at two hours. The median number of visualised nodes was 1.54 (range 0-4).

The detection rate varied with the tumour size; 100% for tumours with a diameter of less than 1 cm, 94.12% with a tumour diameter of between 1 to 2 cm, 81.82% with a tumour diameter of between 2 to 3 cm and 100% with a tumour diameter of more than 3 cm. The accuracy also varied with the tumour size;

**Table II. SLN detection rate, accuracy and skip metastatic rate according to the tumour size.**

| Tumour size | Number of patients | SLN detection rate (%) | Accuracy (%) | Skip metastatic rate (%) |
|---|---|---|---|---|
| Less than 1 cm | 3 | 100 | 66.67 | 33.33 |
| 1-2 cm | 17 | 94.12 | 87.50 | 5.88 |
| 2-3 cm | 11 | 81.82 | 88.87 | 9.09 |
| More than 3 cm | 4 | 100 | 75.00 | 25 |

66.67% for tumours with a diameter of less than 1 cm, 87.50% with a tumour diameter of between 1-2 cm, 88.87% with a tumour diameter of between 2-3 cm and 75.00% with a tumour diameter of more than 3 cm (Table II). We were able to identify the SLN intraoperatively using a radioguided probe in all patients with positive lymphoscintigraphy.

A comparison of SLN and ALN histopathological results was completed in order to define the means by which the SLN biopsy was able to reflect the final status of ALNs. 55 lymph nodes were identified from breast lymphoscintigraphy and a total of 556 ALNs were removed during surgery. Of the 32 patients with positive SLN by lymphoscintigraphy, SLN metastases were found in nine (28.1%). Of these, the SLNs were the only site of metastasis in four patients, while other ALNs were also positive for metastasis in the remaining five patients. In 23 patients (71.9%), the SLNs were found to be negative for metastasis. In 19 of these patients, both SLNs and ALNs were negative, whereas four patients which were SLN-negative had other ALNs that were positive for metastasis (12.5% skip metastases).

In patients with positive SLNs for tumour metastasis, five of nine (55.6%) had concordance between SLN and ALN status, and in those with negative SLNs, 19 of 23 (82.6%) had concordance. Therefore, overall, there was concordance between SLN and ALN status in 24 of 32 cases (75.0%). Biopsy of the SLN was 84.4% accurate in predicting the absence of nodal metastases. Of three patients in whom the SLNs were unable to be localised by lymphoscintigraphy, the ALNs were found as positive for metastases in two patients, and the remaining one patient was free from tumour involvement.

## DISCUSSION

Lymphoscintigraphy has been used since the 1950s to delineate the lymphatic drainage pathways. The most widely-accepted is SLN biopsy in malignant melanoma and carcinoma of the penis. In early stage breast cancer, the advantage of the preoperative breast lymphoscintigram is still debatable. SLN localisation by the lymphoscintigraphical technique has been studied with varying degrees of success. The advantage of preoperative breast lymphoscintigraphy is that it may help the surgeon to define the number and location of SLNs by showing more than one afferent lymphatic channel leading from the primary tumour site to a regional lymphatic basin. Lymphoscintigraphy is also an essential part of the radioguided SLN biopsy because images are used to direct the surgeon to the site of the node. SLN biopsy is a simple technique that identifies the first lymph node draining from a primary tumour. Numerous studies have documented that SLN to be highly predictive of axillary lymph node status, with false-negative rate of less than 5% after an initial learning curve[8-10].

The visualisation rate of the SLN was 91.4% in our study. The accuracy rate of SLN biopsies for overall axillary nodal status prediction and the skip metastases were 87.5% and 12.5%, respectively. The tumour size was not a dependent factor for increasing the number of visualised SLNs and the accuracy in this study. False-negative was defined as the ratio of the number of the patients in whom non-sentinel lymph nodes were invaded histologically, even though their SLNs were not, over the total number of patients with sentinel or non-sentinel lymph node invasion. Calculation of false-negative rate only included patients in whom SLN had been detected. We observed the false-negative SLNs in four cases, which represented 30.8% of cases with positive ALNs. These results were higher than other series with false-negative rates[8-10].

Earlier reports cite skip metastases (defined as a negative SLN, with higher nodes in the chain, being positive for tumour involvement) that occurred in 0% to 15% of the patients with metastatic breast cancer[11-15]. The risk of metastasis in non-SLN was related to the volume of the tumour in SLN. In all four patients with skip metastases in our study, lymphoscintigraphy could identify the location of the SLNs and also demonstrate increased activity in other ALNs. The number of visualised lymph nodes ranged from two to four. From a scintigraphical point of view, when more than one SLN is demonstrated on the preoperative breast lymphoscintigraphy studies, all of the non-SLNs should be removed.

We found that the negative breast lymphoscintigraphy rate was 8.6%, which was somewhat higher than the 1.5% reported by the Milan group[16], but lower than the incidence reported by others. In all three cases, the surgeon could localise and remove SLNs intraoperatively using a gamma probe. That increased the SLN detection rate to 100% in our study. Therefore, a gamma detection probe has the means to facilitate identification and dissection of the SLN. Several factors might increase the negative result of breast lymphoscintigrahy, including a large tumour size[17,18], multifocality of the tumour[19,20], and extensive lymphovascular invasion[20]. Our false-negative SLN biopsies may be attributed to some of these factors.

Gulec et al[21] found that the radioactivity levels in the SLNs were proportional to the mass of the normal reticuloendothelial (RE) tissue in the nodes. If the SLN is invaded by metastases and the normal RE cells are completely replaced by tumour cells, the SLN might become non-visualised on preoperative breast lymphoscintigraphy. The combination of preoperative breast lymphoscintigraphy and a hand-held gamma probe allows the surgeon to identify the SLN on the basis of intraoperative gamma counting. The small hand-held gamma detecting probe can locate the node and indicate exactly where the skin incision should be made.

Although we found a quite impressive sentinel node detection rate of 91.4%, the weakness in our study is evident by the 30.8% of false-negative rate, which is higher than other series. It can be explained that the high false-negative rate tends to occur at the beginning of our learning curve. The most dominant reason for unsuccessful lymphoscintigraphy and sentinel lymphadenectomy described by several investigators is the technical learning curve[8,9,22,23]. Many studies have reported that there is a correlation between the number of procedures performed and the success rate, and the learning curve is completed after performing about 60-80 procedures[9,24-27]. As with other new techniques, there is a learning curve associated with the procedure that we need to achieve. We consider that enough experience in the hands of our team and long-term follow-up are still needed to prove the safety of this technique.

A number of studies which have evaluated the use of FDG-PET axillary staging in breast cancer patients, showed a sensitivity in 57% to 100% and specificity in 66% to 100%[28-34]. Recent studies comparing preoperative FDG-PET with pathological results from SLN biopsy in patients with early stage breast cancer show sensitivity in a range of 20% to 50% with false-negative FDG-PET occurring predominantly in small-sized (10 mm or less) metastatic sentinel nodes[35-39]. These more recent studies indicate the potential limitation of the ability of PET to detect small-volume axillary disease in early-stage breast cancer. The studies suggest that PET scanning cannot replace histological staging in early stage breast cancer. Although recent data do not support the routine use of FDG-PET for axillary staging of early breast cancer, FDG-PET may be complementary to SLN mapping and other standard axillary procedures in patients with more advanced tumours and/or equivocally palpable axillary nodes.

In conclusion, SLN biopsy in early breast cancer is emerging as a highly-sensitive technique for identifying axillary metastasis in a minimally invasive manner. Our study indicates the importance of completing the proper learning phase with complete ALND prior to abandoning routine axillary dissection. The lymphatic mapping team must pass through a learning phase before using the SLN biopsy as a standard procedure in breast cancer patients.

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