

## Assessment the diagnostic accuracy of sentinel lymph nodes lymphoscintigraphy using Technetium-99m phytate in breast cancer

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Received 21 Apr 2009; Revised 25 May 2009; Accepted 31 Jun 2009

### ABSTRACT

**Background:** Technetium-99m phytate (<sup>99m</sup>Tc-ph) is a readily available radiopharmaceutical and has been suggested as a suitable agent for sentinel lymph node (SLN) detection. In this study, the diagnostic accuracy and false-negative rate of radionuclide SLN mapping using <sup>99m</sup>Tc-ph were investigated.

**Methods:** Forty three women (mean age 52.3 years, range 31-74 years), who all had been diagnosed with breast cancer were enrolled in the study. All patients had no palpable axillary lymph nodes and had not undergone exploratory tumor resection or any drug treatment, previously. <sup>99m</sup>Tc-ph was injected peri-tumorally at four sites. Following SLN scintigraphic imaging, the patients were operated. Intraoperatively SLN were detected by a scintillation probe and a blue dye technique. Modified radical mastectomies with radical axillary dissection were performed with excision of the lymph nodes, to evaluate the accuracy of the SLN technique.

**Results:** Intraoperative scinti-mapping identified SLN in 40 of the 43 patients (detection rate: 93%). Scintigraphically, none of the patients had internal mammary drainage or contralateral axillary involvement. The blue dye detection rate in 23 patients under study was 87% and all lymph nodes detected by the blue dye technique were also detected as "hot" spots in the lymphoscintigraphy. Using pathology as the gold standard, the sensitivity and negative predictive value of scintigraphic lymphatic mapping in detection of SLN by <sup>99m</sup>Tc-ph were 90% and 90.9%, respectively. The same values for blue dye lymphatic mapping were 84.6% and 77.7%, respectively.

**Conclusion:** <sup>99m</sup>Tc-ph used for SLN mapping is readily available, has low cost and gives better results than the blue dye technique. Long-term follow-up is required to assess accurately the incidence of failure in patients with negative SLN and the overall diagnostic accuracy and efficacy of the SLN mapping using <sup>99m</sup>Tc-ph as the radioactive tracer.

**Keywords:** <sup>99m</sup>Tc-phytate, Radiopharmaceutical, Lymphoscintigraphy, Breast cancer, Sentinel, Lymph node

### INTRODUCTION

Axillary lymph nodes with metastatic involvement is an important prognostic factor in breast cancer and in making decision for the mode of treatment (1,2). Axillary lymph node dissection can be avoided because of the fact that approximately 60–70% of patients with early breast cancer have no metastases to the regional lymphatic basin (3-5), as confirmed by sentinel lymph node (SLN) mapping and subsequent

biopsy (3). SLN mapping technique may suggest that axillary lymph nodes are positive or negative for breast cancer metastases in a relatively simple and a minimally invasive technique (1,3). Studies of SLN biopsy validated by a backup axillary lymph node dissection suggest that the SLN procedure has an acceptable identification and accuracy rates (1,6,7). SLN mapping with different radiopharmaceuticals often combined with the blue dye technique, has been advocated

for the staging of breast cancer, especially in cases of clinically negative axilla (1). Radionuclide SLN mapping has been widely investigated with varying accuracy rates; however, the optimal radiotracer for this procedure is still to be defined. While  $^{99m}\text{Tc}$ -ph is a readily available radiopharmaceutical; however, there has not been enough experience with this agent, especially concerning its diagnostic accuracy when combined with the blue dye technique (8-10). Although in Iran  $^{99m}\text{Tc}$ -Antimony sulfide has been one of the most frequently used radiopharmaceuticals for SLN mapping, due to easy availability, the lack of requirement to boil it at 100 °C during the preparation and low cost of  $^{99m}\text{Tc}$ -ph, the diagnostic accuracy and false-negative rate of the SLN mapping using  $^{99m}\text{Tc}$ -ph in relation to the blue dye technique was assessed (11-14).

### PATIENTS AND METHODS

Forty three consecutive women (mean age 52.3 y, range 31-74 y), who were referred to the department of surgery, Imam Khomeini Complex Hospital agreed to participate in this study. Pregnant or nursing mothers, those who had received prior breast surgery, chemotherapy or radiotherapy were excluded. All patients had breast cancer diagnosed either by fine needle aspiration biopsy or by strong clinical and mastographic evidence of malignancy.

#### *$^{99m}\text{Tc}$ -phytate scintigraphy*

A commercial phytate kit (AEOI, Tehran, Iran) was used to prepare  $^{99m}\text{Tc}$ -ph according to the manufacturer's instructions. Approximately 9.8-14.4 MBq (0.3-0.4 mCi) of  $^{99m}\text{Tc}$ -ph was injected peri-tumorally at four sites using a 25-gauge needle. The total volume injected was 1.0 ml, and the volume of each injection 0.2-0.4 ml. After injection, gentle local massage was applied for 1-2 min. A single-head gamma camera (Sopha  $\gamma$ -camera, SMV International, France) was used for imaging. Anterior, anterolateral, and lateral static images were obtained using a 140-keV peak and 20% window. Depending on the site of the primary tumor and the result of the previous images, additional views were taken. Images were acquired for 10 min using a 256  $\times$  256 matrix and evaluated qualitatively by two nuclear medicine specialists.

In the operating room, a surgical gamma probe (SGP) (Neoprobe, Model 1000 Instrument Columbus, Ohio, USA) was used for detecting on of SLN. The overlying skin was marked with a suitable pen. The lymphoscintigraphic images

were used for comparison. All operations were performed by the same surgeon. One to 5 mL of blue dye (Lymphazurin Blue, 1% vital dye in an aqueous solution, Iran) was injected peritumorally just before surgery in 23 of the 43 patients and lymphatic channels were investigated visually. Intraoperative localization of SLN was performed with the SGP. The 140-keV photopeak of  $^{99m}\text{Tc}$  was captured with a 20% window and the probe sensitivity was 800 counts/sec/ $\mu\text{Ci}$  of  $^{99m}\text{Tc}$ , at the surface of the lymph node. The SGP was covered with a sterile endoscopic probe cover. The breast mass and the axillary, supraclavicular, infraclavicular, parasternal, rectus muscle sheath and internal mammary regions were detected with the SGP before incision. The sites of greatest radioactivity were marked on the skin. "Hot" spot was defined as a focus of increased activity. The node with the highest count and/or blue dye uptake and closest to the tumor was identified as the sentinel lymph node.

#### *Gold standard*

Following SLN excision, radical axillary dissection and a modified radical mastectomy were performed on all patients to evaluate the accuracy of the SNB technique. After the surgery, histopathologic examination was performed based on standard haematoxylin-eosin (HE) microscopic examination of formalin-fixed axillary node tissue specimens, including SNs.

#### *Statistical analyses*

Using pathology as the gold standard, the results of scintigraphic and blue dye lymphatic mapping were compared for detection rate, sensitivity, negative predictive values and false negative rate. All statistical analyses were performed running SPSS statistical package (Release 11.5.0, SPSS, Chicago, IL, USA) using a personal computer. A *P* value of less than 0.05 was considered significant.

The study was approved by the committee on ethics at the Tehran University of Medical Sciences. All patients gave their informed consent to participate in this study.

### RESULTS

Of patients under this study 12 had stage I, 11 had stage IIa, 17 had stage IIb, and 3 had stage IIIa tumors. Twenty-seven of tumors (62.8%) were located in the upper-lateral quadrant, 4 (9.3%) in the inferolateral quadrant, 2 (4.7%) in the upper-medial quadrant, and 10 (23.3%) in the areola area. All patients had no palpable axillary lymph

nodes and received no previous exploratory tumor resection or therapy.

Scintigraphic lymphatic mapping was successful in identifying a SLN in 40 of the 43 patients (detection rate: 93%). None of patients had internal mammary drainage. All sentinel lymph nodes were found in the ipsilateral axillary region. In 33 patients only one SLN was identified, while in the remaining 7 patients 2 SLN were detected. The blue dye detection rate was 20 of 23 (87%). All these sites were detected as "hot" spots by SGP or the scintigraphic images and were identified as SLN. Of these 20 patients, one SLN was identified in 17, and two SLN in three patients. Finally in 3 patients neither scintigraphic nor blue dye mapping techniques detected any SLN. However, all these three patients had previous history of excisional biopsy. These were patients who were only patients who had undergone excisional biopsy. The tumor was excised completely without further search for axillary lymph nodes.

Using pathology as the gold standard, the results of scintigraphic SLN mapping were analyzed: In 18 of the 40 patients with successful scintigraphic SLN mapping, metastases were revealed (true positive). In this group, nine patients had only one metastatic SLN and nine had also metastases in the axillary lymph nodes. In the remaining 22 of the 40 patients with successful scintigraphic SLN mapping, the SLN was free of metastatic lesions. In 20 of these patients the lymph nodes of the axillary region were also free of metastases (true negative), while in 2 metastatic lesions were found in the axillary lymph nodes (false negative rate: 9.1%). Finally, the sensitivity and negative predictive values of scintigraphic lymphatic mapping in detection of SLN were 90% and 90.9%, respectively.

Using pathology as the gold standard, the results of blue dye lymphatic mapping were also analyzed: In 11 out of 20 patients with successful blue dye lymphatic mapping, the SLN showed metastatic involvement (true positive). In this group, in eight patients the SLN was the only metastatic lymph node, while in the remaining 3 patients, other axillary metastatic lymph nodes were also found. In 9 patients with successful blue dye lymphatic mapping, and free of SLN metastases, seven had no axillary lymph node metastases (true negative), while two had metastatic axillary lymph nodes (false negative rate: 22.2%). Finally, the sensitivity and negative predictive values of blue dye lymphatic mapping in the detection of sentinel lymph node were 84.6% and 77.7%, respectively.

## DISCUSSION

SLN mapping reduces surgical morbidity and allows the use of more accurate tumor staging techniques. However, radionuclide SLN mapping is preferentially performed using small colloids (1, 2), which are not readily available (8). In such settings,  $^{99m}\text{Tc-ph}$ , which is much cheaper and easily available and demonstrates similar biodistribution, has been suggested by some investigators (8).

Our results are relatively comparable with those of previous studies: In a similar study by Tavares et al (8) on 62 patients using  $^{99m}\text{Tc-ph}$  (8), in 98% of the patients at least one SLN were identified, which were positive for metastases in 41% of the cases. The method's negative predictive value was 91%. The authors finally concluded that scintigraphic and intraoperative sentinel node identification can be satisfactorily performed using  $^{99m}\text{Tc-ph}$  (8). In an overview, Noguchi (9) also mentioned that as neither  $^{99m}\text{Tc-sulfur}$  colloid nor  $^{99m}\text{Tc-colloidal}$  albumin are commercially available in Japan,  $^{99m}\text{Tc-stannous}$  phytate or  $^{99m}\text{Tc-rhenium}$  colloid appear to be ideal tracers to identify SLNs (9).

In a study carried out by Koizumi et al (10), the efficacy of  $^{99m}\text{Tc-ph}$  and of  $^{99m}\text{Tc-rhenium}$  colloid for radioguided SLN detection in breast cancer patients was compared. It was found that concordance of scintigraphically detected and surgically removed nodes was superior for the  $^{99m}\text{Tc-ph}$  than that with  $^{99m}\text{Tc-rhenium}$  colloid, with a statistically significant difference. The sensitivity and negative predictive value were also superior with  $^{99m}\text{Tc-ph}$ . However, visualization of internal mammary nodes was superior with  $^{99m}\text{Tc-rhenium}$  colloid. The authors concluded that in patients with breast cancer,  $^{99m}\text{Tc-phytate}$  is a better choice for detection of axillary SNB than  $^{99m}\text{Tc-rhenium}$  colloid. However,  $^{99m}\text{Tc-rhenium}$  colloid is a better choice for the detection of internal mammary nodes (10). There was no case of internal mammary SLN detection in patients of this study.

The results of this study and others (8, 10) using  $^{99m}\text{Tc-ph}$  show that the accuracy and efficacy of SLN mapping by  $^{99m}\text{Tc-ph}$  are comparable to those previously described using other radiopharmaceuticals (15). Therefore, it can be concluded that scintigraphic and intraoperative sentinel node identification can be satisfactorily performed using  $^{99m}\text{Tc-ph}$ . Takei et al (16) demonstrated that  $^{99m}\text{Tc-ph}$  is even better than  $^{99m}\text{Tc-human}$  serum albumin ( HAS ) as a radioactive tracer for SLN biopsy in breast cancer. In their study, the identification rate of SLN was significantly higher in the phytate-group compared to the HSA-group. Most importantly,

the highest radioactivity of SLN per case was more than five times higher in the phytate-group than in the HSA-group, and this difference was statistically significant. The authors concluded that because the specific accumulation of phytate in SLNs was greater than HSA, it might result in a higher SLN identification rate (16).

Based on the results of the present study, scintigraphic SLN mapping is superior to blue dye mapping. As intraoperatively blue dye technique is a routine device for SLN mapping to use, our finding is in concordance with previous reports and it can improve intra-surgical identification of the SLN (17, 18). Hence it can be recommended that scintigraphic SLN mapping should be added to the diagnostic procedure of all patients who undergo blue dye SLN mapping. Also in this study, there were no side-effects related to the  $^{99m}\text{Tc-ph}$ . The same finding has been reported previously by Tavares et al (8).

As mentioned earlier, in the present study scintigraphic technique showed two false negative cases. Previous investigations suggest following possible explanations for such a finding: 1) large-volume lymph node metastases, which block and prevent radiotracer entrance into the SLN; and 2) incomplete assessment of pathology specimens by the pathologist (19), which none of these considerations can explain two false negative cases of the present study. Hence, further evaluation on these issues is warranted. Although intradermal injection is the most frequent route of injection in SLN studies, in this study peritumoral injection method was used. The selection

of this approach was based on the fact that the accuracy of the intradermal route for lymphoscintigraphy and intraoperative gamma-probe-directed lymphatic mapping is debated and some experts in this field have abandoned the intradermal route because they have not observed internal mammary node drainage from the breast skin (20).

#### Limitations

Presence of few patients in stage IIIa in the study group and performing the blue dye technique on only 23 patients were the main limitations of this study. Finally, it should be emphasized that long-term follow-ups are required to assess accurately the incidence of axillary failure in patients with negative SLN or the diagnostic accuracy and efficacy of SLN mapping using  $^{99m}\text{Tc-ph}$  as radioactive tracer.

#### CONCLUSION

$^{99m}\text{Tc-ph}$  used for SLN mapping is readily available, has low cost and has no radiopharmaceutical side-effects and can be successfully used in diagnostic nuclear medicine, especially in developing countries.

#### ACKNOWLEDGEMENTS

This research has been supported by Tehran University of Medical Sciences, Tehran, Iran. The authors would like to thank the staff and technologists of our institute for their fruitful help and technical assistance.

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