Short Communication

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^{99m}Tc-Phytate Lymphoscintigraphy for Detection of Sentinel Node: Preliminary Results of the First Year's Clinical Experience in Isfahan, Iran

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ABSTRACT

Sentinel lymph node is the first regional lymph node that drains the lymph from the primary tumor. It is potentially the first node to receive the seeding of lymph-borne metastatic cells. This study aimed to discuss lymphoscintigraphy procedural guidelines for detection of sentinel node using ^{99m}Tc-Phytate in Isfahan, Iran. Moreover, the preliminary results of the first year's clinical experience of lymphoscintigraphy in Isfahan, Iran are also presented. A total of 36 consecutive sentinel node procedures were performed following our protocol in March 2013 to March 2014. For all 36 patients, after intradermal injection of 0.5–1 mCi of ^{99m}Tc-Phytate, 5, 30 and 120 min with hands up lymphoscintigraphy was performed. All procedures were performed in a 1-day setting with ^{99m}Tc-Phytate injection in intradermal volume of about 0.1 cc. At 5, 30 and 120 min after injection, anterior and lateral images (4 min), were acquired using gamma-camera (energy 140 keV, window 15–20% and LEHR collimator). For all patients, at least one axillary sentinel lymph node was detected. For three patients, 2 SNs were seen. The images 5 min after injection showed at least one axillary sentinel node in 18 of 36 patients. However for the remaining patients, more delayed images (after 30 and 120 min) were needed. Although, no changes were seen in 120 min images compared to 30 min images. Considering the used protocol, from the evaluated data it can be concluded that lymphoscintigraphy after 30 min periareolar injection of about 0.5–1 mCi ^{99m}Tc-Phytate in an intradermal volume of about 0.1 cc yields an axillary sentinel node in all the patients. Imaging 120 min after injection is of no additional value and can be omitted.

Key words: *^{99m}Tc-Phytate, breast cancer, lymphoscintigraphy, sentinel node*

INTRODUCTION

Sentinel lymph node is the first regional lymph node that drains the lymph from the primary tumor. It is potentially the first node to receive the seeding of lymph-borne metastatic cells.[1] Lymphoscintigraphy allows the surgeon to identify easily and biopsy the sentinel lymph node.[2] This method identifies the sentinel node (SN) but cannot determine if it is involved with cancer.[3]

The presence or absence of metastasis to locoregional lymph nodes, especially axillary nodes, has major prognostic and therapeutic implications for patients with breast cancer.[4-6] There are ample evidences that, a tumor negative sentinel lymph node is a reliable predictor for the absence of tumor invasion in other lymph nodes.[4]

In this regard, one of the most often used methods in developed countries is radionuclide SN detection.[7-9] Guidelines do not provide defined protocols for image acquisition, and there is much controversy about the usefulness of dynamic imaging. The European Association of Nuclear Medicine (EANM) recommends the commencement of imaging within 15 min after injection.

Generally, it is stated that static images should be taken hours after injection (2–18 h).[7] The Society of Nuclear Medicine has no specific guidelines on SN scan procedures.

Because of the low visualization rate of SNs on dynamic imaging during the 30 min after injection, we changed our protocol.[10-12] In March 2013 we started our current protocol, in which static images are acquired 5, 30 and

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120 min after injection. Thirty-six SN procedures were performed in patients with breast cancer in Isfahan, Iran. This study aimed to discuss lymphoscintigraphy procedural guidelines for detection of SN using ^{99m}Tc-Phytate in Isfahan, Iran. Moreover, the preliminary results of the first year's clinical experience of lymphoscintigraphy in Isfahan, Iran are presented.

MATERIALS AND METHODS

General Guidelines

General guidelines are in agreement with those previously reported by EANM.[7] This section is based on our guidelines in Isfahan, Iran first reported in the literature and those approved by EANM.[8]

In this method, no special preparation for the test is needed. The patient should remove all clothing and jewels above the waist. The time of last menses and pregnancy and lactating status of the patient should be determined. A breast physical examination should be performed by the nuclear medicine physician.

A variety of colloids has been used in this technique. The radiopharmaceuticals commonly employed are ^{99m}Tc-sulphur colloid (particles' size: 15–5,000 nm), ^{99m}Tc-nanocolloid (5–100 nm), ^{99m}Tc-antimony trisulfide (3–30 nm).[13,14] In our center, 0.5–1 mCi of ^{99m}Tc-Phytate is used.

There is a general agreement that a radiocolloid with the majority of particles ranging between 100 and 200 nm in size can be considered the best compromise between fast lymphatic drainage and optimal retention in the sentinel lymph node.[13,14] If just a single node detection is needed and imaging times cannot be coordinated with the operating theater time, a large colloid with a size of 200–1000 nm is recommended.[2,15] It has been found that these larger colloids tend to "stick" in the SN and allow imaging for up to 20 h postinjection.

The SN is, generally, visualized in 2 h, and the patient should be in the operating theater within about 16–20 h after the injection of the colloid.[1,3,6,9,14] The colloid must be labeled with technetium pertechnetate using manufacturer's instructions. A labeling yield >95% must be assessed before injecting the radiopharmaceutical. General radiopharmaceutical requirements for quality control must be used.[14]

Large volumes of colloid may disrupt local lymphatics; therefore, small volumes should be injected.[3,16] A single aliquot of 5–20 MBq (depending on the elapsed time between scintigraphy and surgery) of colloid in 0.2 ml is considered sufficient. A higher activity can be used for late procedures. The syringe should also contain a similar amount of air to clear any dead space within the syringe and the needle. The syringe dead space is referred to the volume in which the fluid is remaining within the needle and between the syringe hub and the plunger. In deep lesions, a slightly larger volume (0.5 ml) may be used.[3,16]

Two types of injection are widely used for this method, namely; peritumoral and periareolar injections. A sub-dermal injection over the tumor site is sufficient for all tumors, except the deepest ones.[3,16] The site of injection can be gently massaged after the administration or if passage of activity from the injection site is delayed at any time during the study. A peritumoral injection of 0.5 ml is recommended in all deep tumors.[16,17] If the lump is not palpable, ultrasound can be used to guide the injection.

Periareolar injection can be used particularly in upper quadrant tumors to avoid possible cross-talk due to a short distance between peritumoral depot and the axillary SN.[17,18] This technique has the advantage of demanding less experience, particularly in nonpalpable lesions. At present, there is no evidence to justify intratumoral injections of colloids.

Imaging is strongly recommended before any operative procedure as there is some variability in breast lymphatic drainage into the axilla, and more than one SN can be visualized in up to 20% of patients.

The gamma-camera should be equipped with a low-energy, high-resolution collimator. The energy window should be 15% (±5%) centered over the 140 keV photopeak of ^{99m}Tc.[5,19]

The patient lies supine with hands up for imaging on the gamma-camera bed. Anterior and 45° anterior oblique imaging should be obtained. It is useful if the arm on the side of the cancer is extended laterally to 90° as this will be the position during surgery.[5,19]

Imaging should be performed within 5 min after the injection, but, if required, it can be performed 30 min or up 120 min after. Planar images are acquired for 3-5 min using a 64 × 64 matrix.[5,19]

Truncation of the high activities (injection site) will improve visualization of the SN. A logarithmic scale to enhance low-count areas instead of a linear scale is preferable for image display.[5,19]

Interpretation criteria

In this method, the first "hot spot" detected on images has to be considered as the sentinel lymph node. During the operation, the surgeon guided by the skin pen mark will locate the lymph node with the highest radioactivity. If there are two or more such lymph nodes, all should be removed. Before sending for histological examination, any

lymph node removed should be re-checked by the probe to demonstrate that they are radioactive. The decision to perform "frozen section" on the removed lymph node and subsequent axillary node clearance should follow national guidelines. The radioactivity within the node is not sufficient to preclude frozen section.[2]

Reporting

The report to the referring physician should describe: The site of image acquisition (projections of breast and axilla), radiopharmaceutical, way of administration, and the amount of activity injected. In addition, the physician should describe the location of the SN (s) on gamma-camera images and any source of error or inaccuracy of the procedure.[2,14,17]

Sources of error

As the rate of passage of the smaller colloids is variable, it is advisable that frequent or continuous measurement is performed to identify when activity has reached the SN and determine when intra-operative probing will be optimal.[19,20]

Lymphoscintigraphy Guidelines in Isfahan, Iran

Lymphoscintigraphy for detection of SN in Isfahan, Iran is included intradermal injection of 0.5–1 mCi of ^{99m}Tc-Phytate. Then, 5, 30 and 120 min lymphoscintigraphy with hands up is performed. All images in this center are acquired using gamma-camera (energy 140 keV, window 15–20% and LEHR collimator). For all patients, the scintigraphic images are retrospectively evaluated. All hot spots are noted and classified according to anatomic location and designated as SN or higher echelon node.

The evaluation is carried out by one nuclear medicine physician and one trainee in nuclear medicine, both experienced in SN procedures. Where there are different interpretations, a consensus will be found. All surgical and pathologic reports are retrospectively screened to score the number of nodes removed, the histology of the primary tumor, the presence of malignant cells in the SN, the number of axillary lymph node dissections (ALND) and to determine whether malignancy was present in the nodes after ALND.

Report of the first year's clinical experience of ^{99m}Tc-Phytate lymphoscintigraphy for detection of SN using the above-mentioned protocol is presented below.

A total of 36 consecutive SN procedures were performed following our protocol in March 2013 –2014. The study protocol was approved by the Association of Nuclear Medicine of Iran. Patients were eligible if they had no axillary lymph node problems on physical examinations and ultrasound imaging. They gave written, informed consent to the study and underwent diagnostic lymphoscintigraphy.

For all 36 patients, after periarolar intradermal injection of 0.5–1 mCi of ^{99m}Tc-Phytate, 5, 30 and 120 min lymphoscintigraphy with hands up was performed. All procedures were performed in a 1-day setting with ^{99m}Tc-Phytate injection in intradermal volume of about 0.1 cc.

At 5, 30 and 120 min after injection, anterior and lateral images (4 min), were acquired using gamma-camera.

For all 36 consecutive patients, the scintigraphic images were retrospectively evaluated according to our basic protocol.

RESULTS

For all 36 patients the scintigraphic images 5, 30 and 120 min after injection were analyzed. In 33 of 36 patients (91.6%) at least one axillary node were seen. For most of the patients (33 out of 36) one SN was seen. For 3 out of 36 patients, 2 SNs were observed. The images 5 min after injection showed at least one axillary SN in 18 of 36 patients clearly, however for the remaining patients, more delayed images (after 30 and 120 min) were needed [Figure 1].

In 15 patients in which scintigraphy revealed no clear (faint) SN 5 min after injection, 30 and 120 min SN scintigraphy was performed [Figure 2], although, no changes were seen in 120 min images compared to 30 min images. In three patients in which scintigraphy revealed no SN 5 min after injection; it was observed in 30 min images faintly. For this group of patients, no changes were seen in a routine 120 min image compared to 30 min images.

In all of the patients, the surgeon was able to follow the axillary nodes using a gamma probe. In one patient, surgeon used methylene blue for more confidence on following the axillary nodes.

Analysis for factors influencing the time point of visualization of an SN revealed that, in 15 patients (41.6%), axillary nodes were faintly visualized on a 5 min postinjection images. Among these, in 12 patients the axillary nodes were seen clearly after 30 min postinjection [Figure 3]. In three patients of this group, no significant changes were seen between 5 min and 30 min postinjection images. We performed 120 min images for these three patients and no change was seen, too [Figure 4].

In 3 out of 36 patients (8.3%), axillary nodes were not visualized on the 5 min postinjection images. However, 30 min images showed SNs faintly (not clearly) and no changes were seen on 120 min images. In 18 (50.0%) patients, the axillary nodes were seen after 5 min postinjection and images of 30 and 120 min postinjection did not give any further information.

Figure 1: Scintigraphy 5 min after injection revealed one clear sentinel node

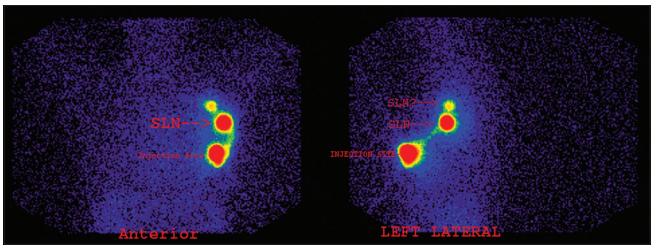

Figure 2: Scintigraphy 5 min after injection revealed both clear and indistinct sentinel nodes

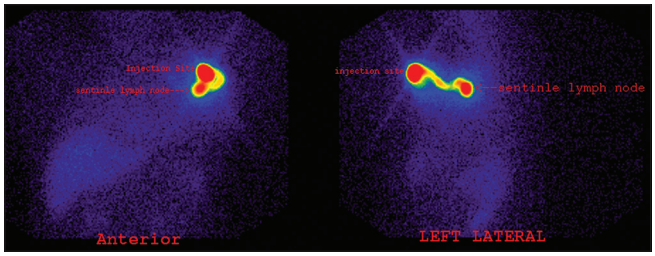

Figure 3: Scintigraphy 30 min after injection revealed a clear sentinel node

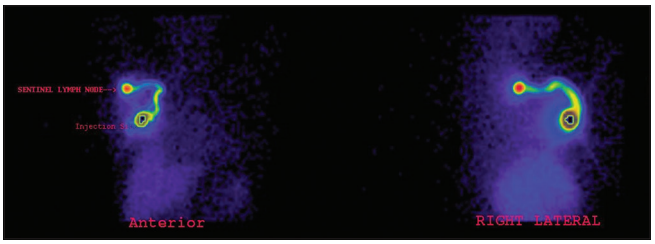

Figure 4: Scintigraphy 120 min after intradermal injection of 99mTc-Phytate

DISCUSSION

According to the definition, the SN is the first draining lymph node on the direct pathway from the primary tumor site.[19,20] This is a good argument for dynamic imaging directly after injection because it provides the possibility of detecting the "real" SN. However, this definition is not always applicable during surgery for practical considerations. Therefore, guidelines usually provide more practical definitions for pointing out the SN with the gamma probe during surgery. It should be noted that since each department has its own conditions and instruments, to produce the best outcomes, specific protocols used in individual departments may differ from each other.

The EANM guideline proposes that the surgeon must locate the lymph node with the highest activity guided by the skin mark based on the scintigraphic images and the gamma probe. When there are two or more of such lymph nodes, all should be removed.[13,18]

The Dutch guideline states that, after excision of the most active lymph node, the wound should be measured for high residual activity. If this activity exceeds 10% of the total activity in the removed lymph node, the surgeon must search for other active nodes and these must be removed as well.[7,15] Both of those recommendations do not take into account the anatomic basis of the SN principle. Due to this discrepancy between theoretical and practical definitions, a less active node, first draining on the pathway from the tumor, may be left *in situ*, thereby strongly reducing the added value of dynamic imaging directly after injection.

The EANM guidelines give no strong recommendations for the site of injection, and the volumes suggested differ depending on the site of injection. There are three major differences in our protocol compared with the EANM guidelines: We administered a radioactive dose of 0.5–1 mCi and in all the patients, after intradermal injection of ^{99m}Tc-Phytate, 5, 30 and 120 min lymphoscintigraphy with hands up was performed.

De Cicco *et al*. optimized the lymphoscintigraphy technique in association with a gamma ray detecting probe for identifying and removing the SN in breast cancer patients.[15] In their work, 250 patients with operable breast tumor underwent lymphoscintigraphy before surgery.[15] They found that, lymphoscintigraphy successfully revealed lymphatic drainage in 245 of 250 patients (98%).[15] In accordance to our work, De Cicco *et al*. stated that the axillary SN was identified in more than 96% of the patients.[15] Pijpers *et al*. studied the SN detection rate using early and delayed imaging in breast cancer patients.[16] They found that, 2 and 18 h after injection, lymphoscintigraphy revealed one to three separate axillary lymph nodes in 33 and 34 patients, respectively.[16] While using our current protocol, we investigated that the images 5 min after injection showed at least one axillary SN in 18 of 36 patients. Pelosi *et al*. designed a study to validate periareolar injection technique and compared it with the subdermal/peritumoral (SD/PT) injection technique.[17] In accord to our results, they suggested using the periareolar injection technique in clinical practice. They also underlined some of its reported advantages in comparison with the SD/PT technique.[17]

There is no assumption that a relatively high activity would have an effect on the time point of SN visualization. It has been suggested that administration of a larger quantity of nanocolloid would result in higher extractions from

the injected site and higher accumulations in the lymph nodes.[9,14,16,17] The use of periareolar administration techniques possibly has an effect on the time point of visualization. As shown in our analysis, there are visualizations of SN 30 min after injection in the group with periareolar intradermal injection.

In some centers, the most active node and the node closest to the tumor in the axillary region and the parasternal region are classified as SNs.[7,15] When lymph vessels are visible, the first node in the chain and the most active node are called SNs. Probably, few SNs are missed using this more conservative method, giving a better locoregional staging. In contrast, this probably results in more harvested nodes in our center, normally one to three axillary SNs and if present, one or two SNs in the parasternal chain.

Considering optimal patient care, one could propose scanning every patient 30 min after injection, allowing the patient to be operated upon faster. In our experience operating schedules allow the patient to be operated upon earlier in the day, except for the first patient of the day to undergo surgery. However, in certain circumstances it may be helpful to speed up the procedures at the nuclear medicine department, considering the chance of visualization in 5 min.

Although we performed a retrospective analysis of our SN procedures and no large prospective trial, our data clearly show that acquisition at 5 min after injection has a high visualization rate of axillary SNs (50.0%). Therefore, we suggest that the acquisition be commenced 5 min after injection. This diminishes pressure of the camera schedules, especially as the number of patients needing SN mapping is still increasing.

In the case of nonvisualization of an axillary SN on the images 5 min after injection, scanning at a longer time interval after injection may be an option. However, 3 out of the 36 patients who showed no axillary lymph nodes 5 min after injection were scanned at intervals longer than 30 min, and all SNs were detected.

CONCLUSION

From the evaluated data it can be concluded that scintigraphic imaging 30 min after periareolar injection of about 0.5–1 mCi ^{99m}Tc-Phytate in an intradermal volume of about 0.1 cc yields an axillary SN in all of the cases. Imaging 120 min after injection is of no additional value and can be omitted. In the case of nonvisualization of an axillary SN on the 5 min image after injection, scanning after 30 min is recommended. Intradermal periareolar injection for fast visualization of sentinel lymph nodes and reducing the time of patient presence in nuclear medicine center is suggested.

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