
Evaluation of Mammary Lymphoscintigraphy by a Single Intratumoral Injection for Sentinel Node Identification

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The aim of this study was to evaluate the findings of mammary lymphoscintigraphy by a single intratumoral injection in 150 patients with breast carcinoma: 100 patients (group A) investigated in the validation phase of the study and 50 (group B) studied after the tracer dose was optimized. **Methods:** Immediately after injection of ^{99m}Tc -nanocolloid using a 25-gauge needle and a 0.2-mL volume, simultaneous anterior and lateral images were acquired with a dual-head gamma camera during 20 min followed by sequential static anterior and prone lateral breast images after 30 min and after 2 and 4 h. ^{57}Co -assisted skin marking defined the sentinel node location for subsequent γ probe, blue dye-guided sentinel node biopsy. **Results:** In group A (mean dose, 61.6 MBq; range, 42–88 MBq) scintigraphy revealed lymph nodes in 83 patients (83%), with an increase in the rate of visualization from 72% for the first 40 patients to 90% for the last 60; patient age ($P = 0.01$) and administered tracer dose ($P = 0.04$) were found to be significant factors for visualization, with optimal results obtained from doses higher than 65 MBq. Lymph nodes were visible in 34 patients (41%) during the first 30 min after injection, whereas in 49 patients appearance occurred at 2–4 h. A total of 97 lymphatic basins were visualized (80 axillary, 3 clavicular, 14 internal mammary). In group B (mean dose, 90.8 MBq; range, 68–124 MBq), the visualization rate was 94%, with early lymph node appearance in 27 patients (57%) and a total of 53 basins (45 axillary, 8 internal mammary). In combination with intraoperative blue dye mapping and γ probing, the identification rate increased to 90% in group A and 98% in group B. Prone lateral images contributed to identification of intramammary lymph nodes in a total of 14 patients and axillary nodes close to the injection site in 8 other patients. **Conclusion:** Mammary lymphoscintigraphy by single intratumoral injection is a valid method for lymphatic mapping and identification of both axillary and nonaxillary sentinel nodes. Lymph node visualization appears to be improved with higher tracer doses. The compactness of the injection site enables high-quality additional lateral images that can depict intramammary or axillary lymph nodes adjacent to the injection site.

Key Words: lymphoscintigraphy; intratumoral injection; sentinel node; breast cancer

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Since the description of the technique (1) and its introduction for melanoma by Morton et al. (2), sentinel node biopsy has been rapidly adopted for application in breast cancer. Although some studies have prescinded from lymphoscintigraphy as a part of the sentinel node procedure (3–5), interest in this modality is increasing because it enables preoperative lymphatic mapping and indicates the site of the sentinel node, which can subsequently be found with a γ probe in the operating room (6).

Mammary lymphoscintigraphy after multiple peritumoral injections has been shown to be effective for preoperative lymphatic mapping and sentinel node localization (7–9). However, the bloom of activity from multiple injection depots may obscure the depiction of intramammary lymph nodes (7) and of axillary lymph nodes located close to the injection site and may lead to incorrect identification of the sentinel node. Furthermore, because of the different patterns of lymph drainage from the 4 quadrants of the breast (10), the use of multiple injections around tumors located between quadrants or in central areas of the breast may increase the variability of results. Finally, visualization of the lymphatic vessels, a major criterion in identifying the sentinel node, is less frequent after a peritumoral injection (8,9).

Mammary lymphoscintigraphy by a single subdermal injection has also been found to be effective for detection of axillary sentinel nodes (11), but the method appears to be less sensitive for depicting lymphatic drainage to the internal mammary chain (12). Administration of the tracer farther from the tumor also increases the chance that a lymphatic watershed is crossed and that the visualized node is not the node that drains the tumor.

Although tracer administration into the tumor has been described for sentinel node identification in tumors of the gastrointestinal tract, thyroid, and head and neck (13), its use for sentinel node visualization in breast cancer has not yet been validated. The migration of radiolabeled colloid particles from the tumor site to the lymph nodes after intratumoral administration has been documented by mammary lymphoscintigraphy used for axillary staging in breast cancer (14,15). The satisfactory imaging results of these

studies and our experience with intratumoral administration of blue dye for sentinel node identification in breast cancer (16) led us to evaluate mammary lymphoscintigraphy by a single intratumoral injection for sentinel node detection. In addition, this study was aimed at evaluating tracer dose-dependent aspects of lymph node visualization and at improving the depiction of intramammary or axillary lymph nodes located close to the injection site by obtaining sequential anterior and prone lateral (hanging breast) images.

MATERIALS AND METHODS

Data were evaluated from 100 consecutive patients (age range, 29–83 y; mean age, 53.2 y) with breast cancer proven on the basis of clinical examination, mammography, or sonography as well as fine-needle aspiration cytology (group A). Only patients with an operable, palpable breast tumor were enrolled; exclusion criteria were clinical evidence of axillary lymph node metastases, previous excisional biopsy, and pregnancy. The study protocol was approved by the institutional ethical committee, and informed consent was obtained from all patients. With respect to lymph node visualization by scintigraphy, the data were compared with those of 50 consecutive patients (age range, 34–83 y; mean age, 54.1 y) investigated after the tracer dose was optimized (group B). Clinical staging data and tumor locations of both groups are summarized in Table 1.

Lymphoscintigraphy was performed the day before surgery after administration of a ^{99m}Tc -labeled nanocolloid (for group A, dose range, 42–88 MBq; mean dose, 61.6 MBq; for group B, dose range, 68–124 MBq; mean dose, 90.8 MBq) with a particle size of less than 80 nm (Amersham Cygne, Eindhoven, The Netherlands). The nanocolloid was administered through a single intratumoral slow injection (0.2 mL) using a fine needle (25 gauge). The activity remaining in the syringe was measured after injection to calculate the net administered dose. Immediately after injection, simultaneous anterior and supine lateral dynamic lymphoscintigraphy of the affected region was performed. Twenty-second images were obtained over a period of 20 min using a dual-head gamma camera with low-energy high-resolution collimators. Subsequently, 5-min anterior, supine, and prone lateral planar images were obtained after 30 min and after 2 and 4 h with simultaneous transmission scanning using a ^{57}Co flood source. The location of the sentinel node was defined using ^{57}Co markers and was marked on the skin with ink. The sentinel (first-echelon) node was identified as the

afferent lymphatic vessel leading from the injection site to the first node or, if no afferent vessels were seen, the first lymph node appearing in each basin.

Shortly before surgery, 1.0 mL patent blue dye (Blue Patenté V; Laboratoire Guerbet, Aulnay-sous-Bois, France) was injected into the tumor. Subsequently, measurements were made over the skin marks with a γ -ray detection probe (Neoprobe 1000/1500; Neoprobe Corporation, Dublin, OH) to confirm the location of the sentinel node as seen on scintigraphy and to indicate the incision site. If no sentinel nodes were seen on scintigraphy, the lower axilla was explored. Sites other than the lower axilla were explored only when scintigraphy revealed sentinel nodes in these basins. A small incision was made, the afferent blue vessel was dissected, the radioactivity of the blue node was confirmed with the probe, and the sentinel node was identified and removed. The sentinel node and, in cases for which axillary lymph node dissection followed, additional lymph nodes were separately submitted for microscopic evaluation. Microscopic evaluation included step sectioning, hematoxylin-eosin staining, and immunohistochemistry (CAM 5.2; Becton Dickinson, San Jose, CA)

RESULTS

In group A, lymph nodes were visualized by scintigraphy in 83 of the 100 patients (83%). The rate of visualization was 65% for the first 20 patients, 80% for the second 20, and an average of 90% for the last 3 subgroups of 20 patients (Fig. 1A). Using multiple linear logistic regression analysis, age ($P = 0.01$) and tracer dose ($P = 0.04$), but not patient order number, were found to be significant factors for lymph node visualization. Nonvisualization occurred almost always in older patients and with doses less than 65 MBq (Fig. 1B). For group A, the distribution of results as the study progressed showed that both factors, injected tracer dose and patient age, did not increase (Figs. 1C and D).

Lymphatic drainage exclusively to the lower axilla was seen in 67 of the 83 patients (81%) with lymph node visualization. Drainage outside the lower axilla was found in 16 patients (19%). In 12 patients, lymphatic drainage to both the axilla and the internal mammary chain was seen. In 1 patient, lymph nodes both in the axillary and in the clavicular regions were visualized; in another patient, both infraclavicular and internal mammary nodes were depicted (Fig. 2). Exclusively internal mammary flow was seen in 1 patient, and only an infraclavicular sentinel node was seen in another patient.

In 32 patients (39%), only 1 node was visualized; in 51 patients (61%), 2–8 nodes were visualized. Lymphatic flow was seen in 34 patients (41%) during the first 30 min. In 24 of these 34, the flow was seen during the dynamic acquisition (0–20 min), and in 10 others, on early static images. In 21 patients, lymphatic vessels were visualized. A late appearance (2–4 h) was observed in 49 patients (59%).

Drainage to a total of 97 basins was seen: 80 axillae, 14 internal mammary chains, 3 clavicular regions. If one considers the sentinel node to be the first visualized node with or without an afferent lymphatic vessel (Figs. 3 and 4), scintigraphy was conclusive for 73 basins (75%). For 24 basins (23 axillae) in which multiple nodes appeared simul-

TABLE 1
Tumor Staging and Breast Quadrant Distribution

Group	No. of patients	T-stage (all patients clinically NO M0)	Breast quadrant
A	100 (right breast, 48; left breast, 52)	57 T1, 42 T2, 1 T3	45 upper outer 27 upper inner 9 lower outer 10 lower inner 9 central
B	50 (right breast, 22; left breast, 28)	34 T1, 16 T2	25 upper outer 10 upper inner 8 lower outer 4 lower inner 3 central

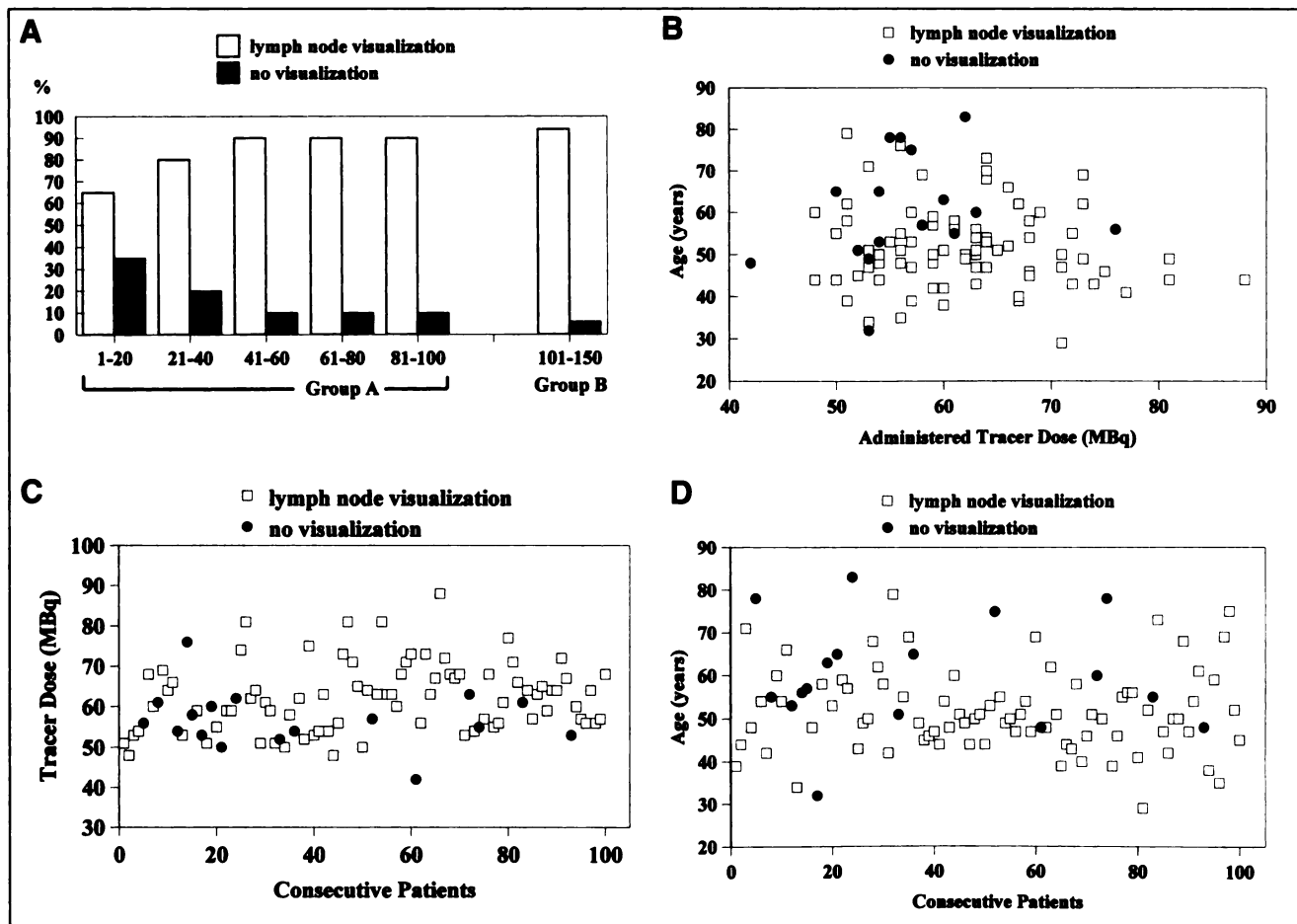


FIGURE 1. (A) Lymph node visualization analysis of first 100 consecutive patients (group A) referred for mammary lymphoscintigraphy shows stable 90% rate of visualization for last 3 subgroups of 20 patients. After tracer dose was optimized (group B), visualization rate increased to 94%. (B) Patient age and administered tracer dose analysis of group A shows that nonvisualization occurred more often in older patients and after administered doses of less than 65 MBq ^{99m}Tc -nanocolloid. (C) Distribution analysis of individual administered tracer doses in group A during progress of study. (D) Individual patient age analysis of group A during progress of study.

taneously without lymph vessel visualization, scintigraphy was considered inconclusive as to which node was sentinel (Fig. 5).

Blue dye mapping was performed as a complement to surgery. For 7 patients, the mapping identified axillary sentinel nodes that could not be identified scintigraphically. The mapping also identified axillary sentinel nodes for all

except 4 basins that had inconclusive lymphoscintigraphy findings. The total identification rate was 90%.

A total of 152 sentinel nodes (range, 1–5 nodes per patient; mean, 1.5 nodes per patient) were excised. In the axilla, an average of 1.3 sentinel nodes were removed. One or more axillary sentinel nodes contained tumor in 35 patients, 3 of whom also had a tumor-positive sentinel node

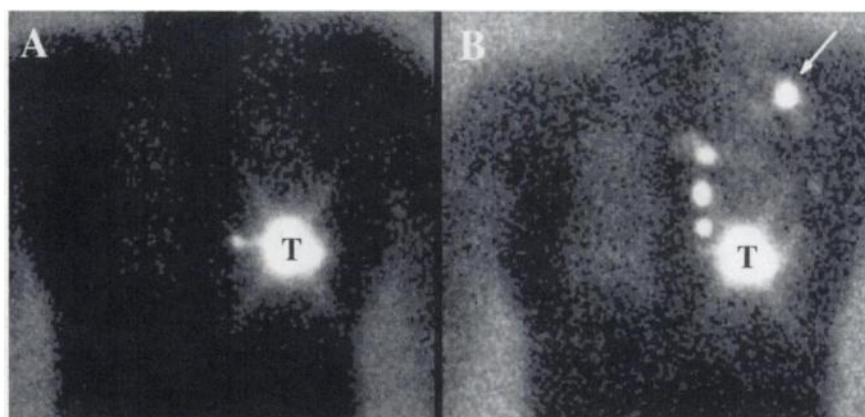


FIGURE 2. Anterior images obtained at 30 min (A) and 4 h (B) show lymphatic flow to internal mammary chain and to infraclavicular region (arrow) after administration of ^{99m}Tc -nanocolloid at tumor site (T) in lower inner quadrant of left breast.

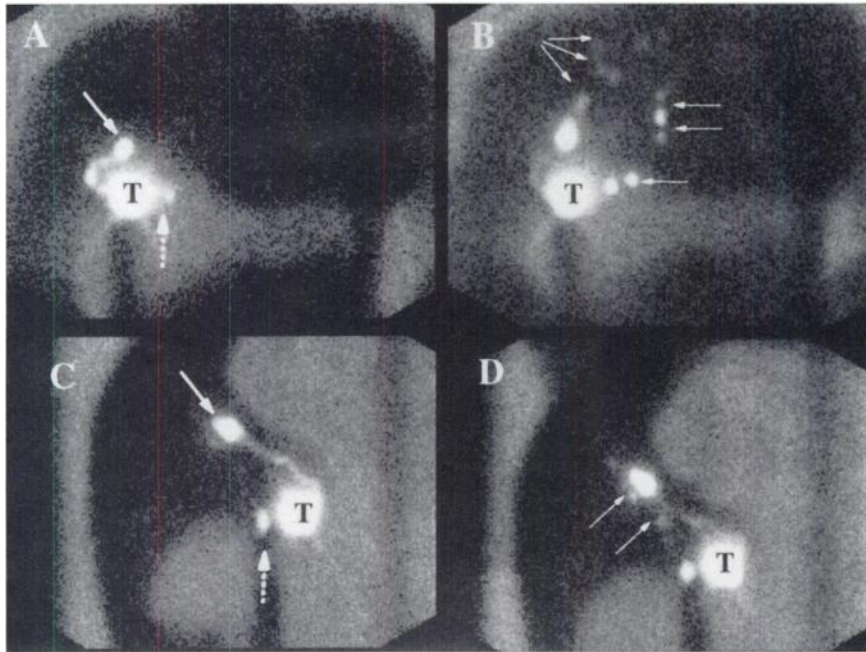


FIGURE 3. Sequential lymphoscintigraphy of patient with T1 carcinoma in lower outer quadrant of right breast. Direct drainage to right axilla (solid arrow) and to intramammary node (dotted arrow) is observed on anterior (A) and prone right lateral (C) views obtained 30 min after administration of ^{99m}Tc -nanocolloid at tumor site (T). After 2 h (B and D), substantial number of secondary (nonsentinel) nodes is observed in axilla, breast, and along internal mammary chain (arrows).

outside the axilla; 1 additional patient had a nonaxillary tumor-positive sentinel node only (in other words, the incidence of pathologic nonaxillary nodes was 4/16, or 25%). Two patients had metastases in second-echelon lymph nodes despite tumor-negative sentinel nodes (false-negative findings).

In group B, the rate of lymph node visualization was 94% (Fig. 1A). Nonvisualization occurred in 3 patients, who were 73, 83, and 58 y old; in 2 of these patients, sentinel nodes were subsequently identified by blue dye (i.e., a total identification rate of 98%). In this group, a total of 53 basins (45 axillae, 8 internal mammary chains) were depicted, and lymphoscintigraphy was considered conclusive for 42 basins (79%); additional blue dye mapping revealed sentinel nodes in all basins for which scintigraphy had been inconclusive. Early visualization occurred in 27 patients (57%), and lymph nodes were seen after 2–4 h in 20 patients. In 16 patients, lymphatic vessels were visualized. A total of 94 sentinel nodes (range, 1–4 nodes per patient; mean, 1.9 nodes per patient) were excised. In the axilla, an average of

1.8 nodes were removed. Sentinel node metastases were found in 16 patients: in the axilla of 14, in both the axilla and the internal mammary region of 1, and exclusively in the internal mammary chain of 1. Additional results from group B and a comparison of group B with group A are presented in Table 2.

Prone lateral images contributed to the identification of intramammary lymph nodes (Fig. 6) in 14 patients (7 in group A and 7 in group B), and axillary nodes close to the injection site, not seen on anterior images, contributed in 8 other patients (6 in group A and 2 in group B).

DISCUSSION

We found that preoperative lymphoscintigraphy by a single intratumoral tracer injection using a small volume is valid for identifying the sentinel node in the axilla. The technique is also useful for depicting other nonaxillary drainage routes so that the sentinel node can be localized during surgery with the guidance of a γ probe or blue dye. For the first 100 patients, the rate of lymph node visualiza-

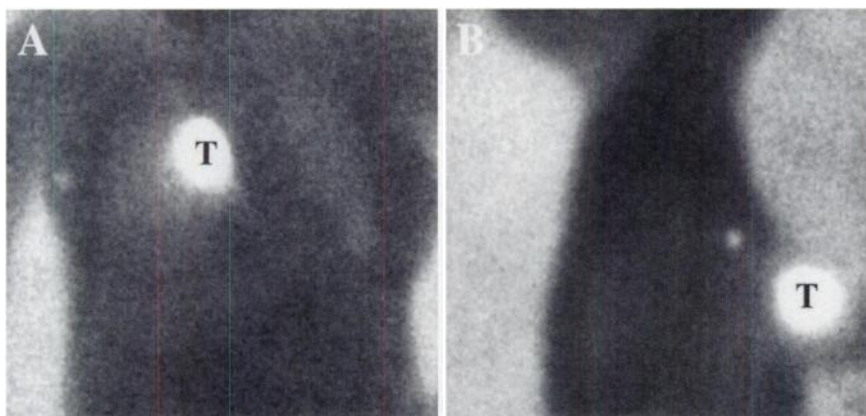


FIGURE 4. Anterior (A) and prone right lateral (B) images show single lymph node in right axilla 4 h after administration of ^{99m}Tc -nanocolloid into tumor (T) in upper inner quadrant of right breast.

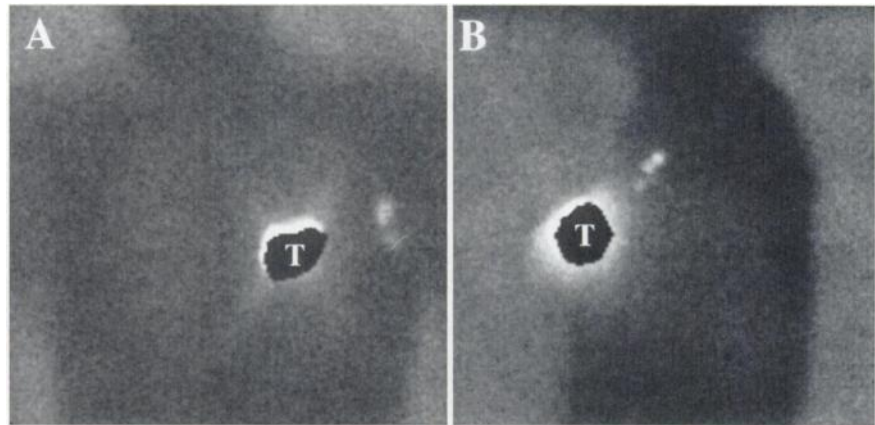


FIGURE 5. Anterior (A) and left lateral (B) images show 3 lymph nodes in left axilla 4 h after intratumoral administration of ^{99m}Tc -nanocolloid (T) in upper inner quadrant of left breast. Additional intraoperative blue dye administration allowed identification of 2 sentinel nodes with separate afferent lymphatic vessels and 1 secondary lymph node in area indicated by lymphoscintigraphy.

tion increased from 65% to 90% during the study. For the last 60 patients, the rate remained stable. This effect appeared to be influenced by the dose of the injected tracer and the age of the patient but not by the patient number order (as would be expected in a learning curve), leading to the conclusion that, for optimal results using a fixed administered volume, it is important that the specific activity be sufficient for an injection of at least 65 MBq. The improvement in lymph node visualization was illustrated by the patients in group B, for whom the identification rate was 94% without, and 98% with, blue dye mapping.

Our visualization rate appears similar to that (75%–98%) of other investigators for lymphoscintigraphy by peritumoral administration (7–9,17–21). However, the compact injection site that the single injection produced, and the prone lateral images that were acquired, better revealed the space between the injection site and the thoracic wall, enabling identification of intramammary or axillary lymph nodes close to the injection site in 16% of patients with lymph node visualization. In patients receiving a higher tracer dose, intramammary lymph nodes were observed twice as frequently as in patients receiving a low dose. Furthermore, the early visualization of lymph nodes for 47% of our patients was helpful because it depicted afferent lymph vessels or the first-appearing lymph node. Sequential

images are necessary to identify sentinel nodes. The concordance between 2- and 4-h images was high when only axillary drainage was observed. However, because uptake increases between 2 and 4 h, lymph nodes often become better delineated after 4 h. In 2 patients with axillary and nonaxillary drainage, nonaxillary lymph nodes were visualized only after 4 h. This asynchronous pattern was also observed in 2 patients with early drainage to the internal mammary chain and delayed visualization of axillary lymph nodes.

The site of tracer administration is the subject of much discussion. We choose our intralesional injection site after careful consideration of accuracy and safety. Lymphatic drainage from the skin and the subareolar plexus is richer than drainage from the tumor, and administration of a tracer at these sites is supposed to enhance the identification rate of a sentinel node. However, injection of the tracer farther from the tumor increases the risk that a lymphatic watershed is crossed and that the visualized node is not the node that drains the tumor. Depositing the tracer around the tumor is, in theory, virtually as accurate as injecting the tracer into the lesion but has several drawbacks. For instance, distribution of the tracer all around the tumor is more difficult. In addition, the needle tip may wind up underneath the fascia in a deep-lying tumor because the resistance of the tumor is not

TABLE 2
Results for Group A (Validation Phase) and Group B (Optimized Tracer Dose)

Group	No. of patients	Mean age (y)	Mean ^{99m}Tc -nanocolloid dose (MBq)	Visualization by lymphoscintigraphy			Identification rate*	Patients with tumor-positive sentinel node	
				Rate	Axillary	Nonaxillary		Axillary	Nonaxillary
A	100	53.2 (range, 29–83)	61.6 (range, 42–88)	83% (83/100)	96% (80/83)	19% (16/83)	90% (90/100)	40% (35/87†)	25% (4/16)
B	50	54.1 (range, 34–83)	90.8 (range, 68–124)	94% (47/50)	96% (45/47)	17% (8/47)	98% (49/50)	32% (15/47†)	25% (2/8)
Both	150			87% (130/150)	96% (125/130)	18% (24/130)	93% (139/150)	37% (50/134†)	25% (6/24)

*Scintigraphy + blue dye + γ probe.

†Total number of patients with sentinel nodes identified by combined techniques (scintigraphy + blue dye + γ probe).

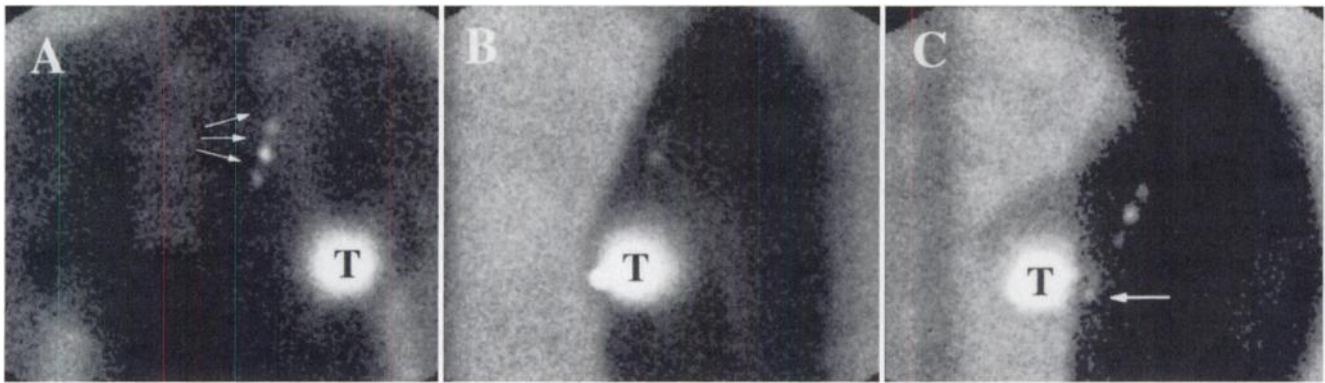


FIGURE 6. (A) Anterior lymphoscintigraphy shows 3 lymph nodes of left internal mammary chain (arrows) 4 h after intratumoral administration of ^{99m}Tc -nanocolloid at tumor site (T) in lower inner quadrant of left breast. Note difference between supine (B) and prone (C) lateral views, leading to visualization of intramammary lymph node just behind injection site on C (arrow).

felt after insertion of the needle. In theory, the danger of needle tract metastasis also exists after peritumoral tracer administration because the needle may pass through 1 or more tumor protrusions. Peritumoral injection spreads the tracer over a fairly wide region, which may hamper visualization of a sentinel node close to the primary tumor. Another practical drawback is that excision of the tumor will not remove all of the injection site, as is desired when probe detection of a small amount of radioactive sentinel node is prevented by the overwhelming scattered radiation surrounding the breast cancer. By contrast, a practical advantage of intratumoral tracer administration, in comparison with multiple peritumoral injections, is that the resistance of the tumor is felt after insertion of the needle, leading to more accurate and compact deposition of the tracer.

The average case of breast cancer is present for perhaps 10 y before detection. Tumors are known to shed malignant cells into the blood stream continuously. On the basis of knowledge about breast cancer biology, it is difficult to perceive that administration of tracer into the tumor would increase the number of cells shed into the blood, and no evidence in the literature suggests that this approach is not safe. The safety of inserting a needle into a neoplasm has never, to our knowledge, been questioned by pathologists (fine-needle aspiration), surgeons (large-bore-needle biopsy), or radiologists (stereotactic core-needle biopsy).

Some have suggested that any attempt to administer a tracer directly into a tumor will lead to leakage of the tracer from the tumor into the peritumoral tissue at the injection site (22). The visualization of intramammary lymph nodes and drainage to the internal mammary chain observed in this study appear, at least partially, to contradict this assumption. The lymphatic system of the mammary gland is postulated to contain cutaneous and parenchymal lymphatics (23). A multidirectional model has been described for lymphatic drainage of the breast, including pathways to the axillary, internal mammary, and, rarely, posterior intercostal lymph nodes (24). Our findings suggest that migration of colloid particles from the tumor site after intratumoral injection may follow a multidirectional pattern both to the periphery of the

skin and to the parenchymal compartment, which can drain to the internal mammary chain or to the axillary lymph groups. This observation agrees with previous experience in which we have observed homogeneous distribution within the tumor after blue dye administration (16). A 16%–35% visualization of internal mammary lymph nodes reported for peritumoral administration (9,25) and the visualization rate found in this study are in contrast with the low incidence of internal mammary chain visualization (2%) described after subdermal injection. That technique appears to reveal only the axillary lymph nodes, via the superficial lymphatics (12).

In spite of the high rate of lymph node visualization found in this study, in approximately a quarter of patients with visualized lymph nodes, lymphoscintigraphy cannot identify with certainty which node is sentinel. In these patients, additional intraoperative lymphatic mapping with blue dye is recommended. By this combined approach, we could conclusively identify the sentinel node not only in most patients with inconclusive lymphoscintigraphy but also in a significant number with nonvisualization on lymphoscintigraphy.

The application of interpretation criteria for lymphoscintigraphy strictly in accordance with the sentinel node concept is of vital importance because it determines the strategies to be followed in intraoperative sentinel node localization. In patients with conclusive lymphoscintigraphy, the use of the γ probe may be sufficient provided that the sentinel node has been correctly marked on the skin during the scintigraphic procedure. Nevertheless, in our experience the use of blue dye may occasionally reveal an additional sentinel node. In patients with inconclusive scintigraphy, the use of a γ probe may support intraoperative detection of radioactive lymph nodes but not identification of the sentinel node, because the probe cannot visualize the lymphatic channels that determine the order in which nodes receive drainage. Blue dye mapping in these cases is indispensable for visualizing afferent lymphatic vessels, enabling adequate identification.

CONCLUSION

Mammary lymphoscintigraphy by a single intratumoral injection is a valid method for lymphatic mapping and visualization of both axillary and nonaxillary sentinel nodes. Combined use with intraoperative blue dye mapping and γ probing enables sentinel node identification in virtually all patients. Visualization appears to depend on patient age and tracer dose, with improved depiction at doses higher than 65 MBq ^{99m}Tc -nanocolloid. The compactness of the injection site allows additional prone lateral breast images for depicting intramammary or axillary lymph nodes close to the injection site.

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