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Impact of Lymphoscintigraphy on Sentinel Node Identification with Technetium-99m-Colloidal Albumin in Breast Cancer

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Identification of the sentinel node by using colloidal tracers and a gamma probe or lymphoscintigraphy could be an effective alternative for the complicated original dye-oriented approach. We studied the sentinel node detection rate using early and delayed imaging in breast cancer patients. **Methods:** Thirty-seven patients were imaged 2 hr and 18 hr after peritumoral injection of ^{99m}Tc-colloidal albumin. Preoperatively, axillary foci were located with a handheld gamma probe that was also used to isolate radiolabeled nodes from the axillary dissection specimens. The predictive value of the sentinel node for the axillary tumorstatus was evaluated with histological examination. **Results:** Two and 18 hr after injection, lymphoscintigraphy revealed one to three separate axillary lymph nodes in 33 and 34 patients, respectively. In 30 patients the axillary foci were easily localized with the gamma probe preoperatively. In all 34 patients (92%), with visualized axillary foci, at least one radioactive sample could be retrieved using the gamma probe (total 53 samples). Metastases were found in the sentinel nodes of 11 patients, in seven of 11 being the only tumor-positive lymph node in the axilla. There were no false-negative sentinel nodes. **Conclusion:** The selective targeting and prolonged intranodal retention of ^{99m}Tc-colloidal albumin allows successful sentinel node identification in most (92%) patients.

Key Words: sentinel node; technetium-99m-colloidal albumin; breast cancer; gamma probe; lymphoscintigraphy

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In breast cancer, axillary involvement is still the most important prognostic factor on which adjuvant therapy is based (*1*). Staging of the regional lymphatic basin is traditionally performed by axillary lymph node dissection (ALND). Whereas most axillary specimens do not contain metastases (*2*), ALND accounts for more morbidity and costs than the surgical treatment of the primary tumor (*3–5*).

Selective biopsy of the first tumor draining lymph node (sentinel node, SN) may be an alternative for ALND in staging breast cancer patients. The SN concept has been validated in melanoma by intraoperative lymphatic mapping, using vital dye (*6*) or radioactive tracers (*7–9*). A tumor-negative SN virtually excluded lymphatic involvement of the entire regional lymphatic basin.

The concept is now being evaluated in breast cancer. The largest study was performed by Giuliano et al. who used dye-guided lymphatic mapping for SN biopsy. They reported

that the SN predicted the axillary tumor status correctly in 96% of the successful biopsies (*10*). However, the method is tedious and, even in experienced hands, meticulous search revealed no SN in 20% of the patients. The apparent extensive learning curve seems to be another obstacle, since surgical breast cancer treatment should remain feasible in daily clinical practice and not just in specialized centers. Attempts are made to simplify SN identification using radioactive colloidal tracers.

Krag et al. described 100% accuracy in 18 patients, using ^{99m}Tc-sulfur colloid and a gamma probe (*11*). This method appears to be considerably easier than the dye approach. However, in this study no SN could be detected in 18% of the patients. It has been suggested that smaller particles like ^{99m}Tc antimony sulfide show faster passage through the lymphatics, and could reduce the number of negative procedures to about 10% (*12*). In an earlier study in melanoma patients with ^{99m}Tc-colloidal albumin we found labeling of SNs in each patient, and an attractive dwell time in the SN (*9*). Kinetic data of colloidal tracers are not available for SN localization in breast cancer. In this study, we determined the SN detection rate using the independent variable of early and delayed imaging followed by gamma probe guided search for the SN in the axillary specimen.

MATERIALS AND METHODS

Thirty-seven consecutive patients (age 58 ± 12 yr) with breast cancer (core biopsy proven) and without clinical evidence of axillary metastases, scheduled for lumpectomy or mastectomy and ALND, were included in the study. The tumor measured <2.0 cm (T1) in 14 patients and 2.0–4.0 cm (T2) in 23, and was located in the following quadrants: upper outer (17 tumors), lower outer (4 tumors), lower inner (3 tumors), upper inner (6 tumors) and central (7 tumors). The day before surgery, 40 MBq ^{99m}Tc-colloidal albumin in 4 ml saline (particle size 3–80 nm; 77 ± 12% <30 nm) was injected in two to four depots in the axillary peritumoral hemisphere. Medial depots were not given as visualization of parasternal drainage does not have clinical consequences presently. Anterior and lateral views (300 sec) were obtained after 2 hr and 18 hr postinjection using a LFOV dual-head gamma camera. Anterior images were obtained both with and without medial shift of the breast. During lateral imaging the arm was abducted at an angle of 180° to minimize attenuation. Images were acquired in a 128 × 128 matrix (16-bit deep pixels) and stored on optical disk. Anatomical landmarks (acromion, jugular notch, xiphoid process) were indicated on the skin with indelible ink and imaged (^{57}Co-
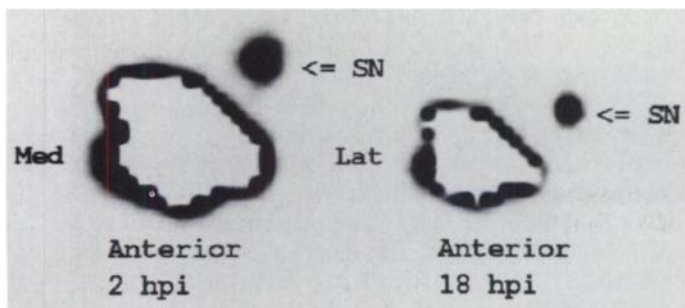
FIGURE 1. Early (2 hr postinjection) and late (18 hr postinjection) images revealing the injection site and only one sentinel node (<= SN). The tumor was situated in the upper outer quadrant of the left breast.

FIGURE 3. A right lateral image discloses the SN (=>) which cannot be seen on the anterior image. The tumor was situated in the upper outer quadrant of the right breast.

penmarker) to allow qualitative comparison between early and late imaging. Transport from the injection depots towards the SN between imaging moments was calculated using decay-corrected counts from ROIs around the injection site and SNs (anterior projection).

Preoperatively, we attempted to localize the axillary focal accumulations with a handheld collimated gamma probe. Surgery was performed 22 ± 2 hr after injection of the tracer. After surgery the operation field was checked for residual radioactivity. All radioactive lymph nodes were isolated from the surgical specimen using the gamma probe, followed by ex vivo measurement (10 sec) of their radioactivity. Parasternal lymph nodes were not removed. The number and site of scintigraphic foci were compared to the lymph nodes detected with the gamma probe.

The SNs and remaining lymph nodes from the axillary specimens were cut in slices of approximately 0.2 cm, fixed in 10% buffered formalin and embedded in paraffin according to standard procedures. Four micron-thick sections were cut and stained with hematoxylin and eosin for light microscopic evaluation.

The protocol was approved by the local ethical committee and informed consent was obtained from all patients. All results are presented as means ± s.d., unless specified otherwise.

RESULTS

No side effects of the injected tracer were observed. After 18 hr, lymphoscintigraphy showed axillary foci in 34 of 37 patients. In 79% of these (n = 27), the tracer only or preferentially accumulated in one focus (Fig. 1). In 11 patients, a faint node was visualized apart from one or two intense foci (Fig. 2). In six patients, two evident foci were found.

Drainage to the ipsilateral internal mammary chain occurred in five patients (three upper inner, two upper outer quadrant). In
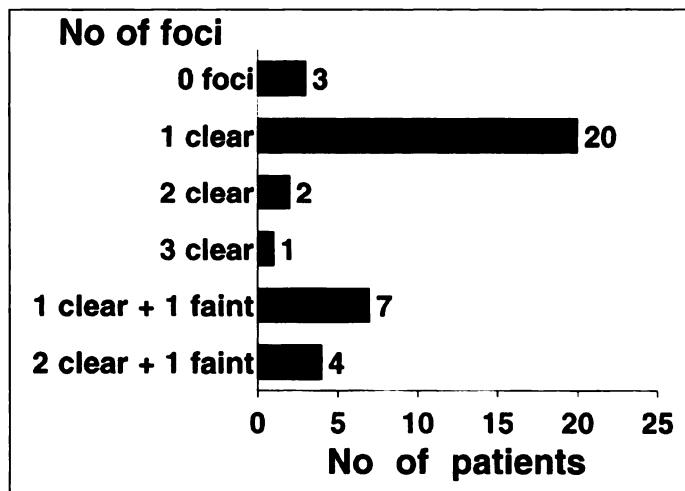

FIGURE 2. Distribution of axillary foci in all 37 patients 18 hr after injection.

three of 37 patients (two upper inner quadrant, one upper outer quadrant) no axillary nodes were visualized. In one of these three patients (upper inner quadrant) only the parasternal chain was seen. Overprojection of injection depots and lymph node activity in the lower axilla could be circumvented by anterior imaging with the breast moved medially, and lateral imaging. In nine patients (six with outer quadrant tumors) the lateral was superior to the anterior projection (Fig. 3).

Comparison of scintigraphies of 2 hr and 18 hr postinjection, revealed that the site and number of foci were unchanged (Fig. 1) in all but one patient in whom the first nodal uptake appeared not until 18 hr postinjection. In two patients, no nodal targeting was seen, even after 18 hr. Lymph channels from the injection site towards the axilla were seen in three patients at 2 hr after injection. The contours of the injection depots remained unchanged between early and late imaging; in other words, no marked diffusion of injected tracer occurred in breast tissue. Washout from the injection sites between 2 hr and 18 hr postinjection amounted to 21% (range 8% to 36%, median 21%), whereas activity in the SN showed a mean increase of 126% (range −16 to +567%, median 57%).

Preoperatively, the gamma probe localized labeled lymph nodes in 30 of 34 patients with scintigraphically (18 hr postinjection) detectable axillary foci. The failures occurred in nodes with low radioactivity content (ex vivo 45, 12–114 counts/10 sec [median, range] compared with 221, 12–3440 in the others).

In the ALND specimens all scintigraphically visualized axillary foci could be retrieved. No additional lymph nodes were retrieved with the gamma probe. Two patients refused to have an ALND but gave permission to biopsy the single radiolabeled node, which contained no metastasis. We could, therefore, compare the histological status of the SNs and ALNDs in 32 patients. Fifty-three radioactive samples (size 1 ± 0.5 cm) contained 69 lymph nodes on histological examination. Eleven samples contained more than one lymph node (range 2–6 adherent nodes). The axillary specimens contained 13 ± 5 lymph nodes. The SN revealed micrometastases in 11 patients. In seven of 11, the radiolabeled lymph node was the only one containing tumor. In the remaining four patients, one to three additional metastatic lymph nodes were found. False-negative SNs were not encountered. In the 14 cases with multiple labeled nodes, the 11 faint nodes never contained tumor deposits.

DISCUSSION

Locoregional staging of breast cancer currently involves ALND, since no imaging technique reliably excludes axillary

involvement, and no characteristic of the primary tumor has a better prognostic value. However, for every 100 ALNDs in T1/T2 tumors, the lymph nodes do not contain tumor in approximately 70. Nonetheless, more than 50 of these node negative patients will have postoperative, ALND-related complaints (3,4). This issue may become even more pressing as mass screening results in a shift towards smaller tumors at presentation, with less likelihood of lymphatic involvement (2–4). In fact, in very small tumors, routine ALND has become controversial (2,5).

The present evidence (10,11) lends strong support to the validity of the SN principle in breast cancer, but there is a need for more data. Like Krag et al. (8), we found a perfect correlation between the SN and the axillary tumor status. These initial studies suggest that SN localization using radioactive colloid tracers performs better and is easier to master than the dye-oriented technique. Before such a procedure can be implemented in clinical practice, several issues need to be clarified: how to reduce the reported 20% unsuccessful biopsy procedures (10,11); which tracers are retained in SNs long enough to prevent sampling of nonsentinel nodes; which technique is most effective to harvest the SN.

Tracer kinetics may have major impact on the feasibility of SN biopsy. With small particle colloids, such as ^{99m}Tc-antimony sulfide, 3–12 nm, the risk of sampling nonsentinel nodes increases over time (12). Contrariwise, with large particles, such as ^{99m}Tc-sulfur colloid with μm range, transport may be inadequate, perhaps explaining the 20% failure rate to detect a SN (11). Using ^{99m}Tc-colloidal albumin (<30 nm) we found a highly predictable nodal targeting and retention in 95% of the patients (92% axillary), with a prolonged intranodal retention without relevant spill. Like others (11,12), our data suggest tracer transport to be slower than in melanoma; where the SN is visualized within 20 min after injection in 95% of the patients, and 100% after 2 hr (9). The present protocol was designed using data from a pilot study in which ^{99m}Tc-colloidal albumin was injected subcutaneously around the areola of the breast. In that study, 2 hr after injection no nodal targeting was seen in 16% of patients. Whether the observed difference relates to lymphatic anatomy (11,12) and/or to physiological parameters (lower interstitial driving pressure) is unclear. Under the prevailing conditions, the tracer does not appear to diffuse widely within the breast tissue, so that the observed drainage seems to be representative.

Dynamic lymphoscintigraphy may differentiate (9) between spill from the sentinel towards nonsentinel nodes and multiple SNs due to anastomosing lymph vessels. The latter situation has been demonstrated by Giuliano et al. in breast cancer (10). However, our pilot study indicated that ^{99m}Tc-colloidal albumin labeled only one to two nodes per axilla in most breast cancer patients, and at a much slower rate than with melanoma (no labeling in 16% at 2 hr postinjection compared with <5% after 20 min postinjection). In the actual study, we decided to avoid unpredictably prolonged dynamic scanning in many patients at the cost of sampling some nonsentinel nodes. So far, our results suggest that faint nodes in the presence of hot nodes represent spill of tracer from the SN, since the faint nodes never contained tumor unless the primary hottest node did. Since the activity and retrieval site of every node is documented in this study, it can be established which sampled node corresponds to which scintigraphic focus. Retrospective analysis of this ongoing investigation, in which the entire axillary content is still removed, will then reveal whether it is safe practice to leave such faint foci in situ.

In our experience, lymphoscintigraphy mainly serves to predict in which patients the SN procedure will fail (no labeled nodes). With dyes, this will not be evident until the intraoperative search has failed. In our patients, the 5-min static lymphoscintigraphy identified another 10% that might have been regarded as negative using a probe survey alone (11). The low nodal counting rate and a less aggressive search in unanesthetized patients may have contributed to the four preoperative gamma probe failures. The yield of the probe might benefit from the use of an uncollimated probe and/or a focused search using the scintigraphic data: in the surgical specimens, all labeled nodes were identified in our patients.

Biopsy of SNs using skin markings obtained with lymphoscintigraphy in combination with dye would be an inexpensive alternative for the gamma probe technique (12). However, reproducible repositioning is difficult, and one still would have to face a 20% failure rate of the dye technique. Apart from facilitating the search for radiolabeled lymph nodes, the use of the gamma probe guarantees that the intended node has been retrieved. In the actual biopsy situation, the additional use of dyes may be helpful to find small labeled lymph nodes embedded in the fatty tissues of the axilla, as was our experience in melanoma patients (9).

We conclude that selective targeting and prolonged nodal retention of ^{99m}Tc-colloidal albumin are attractive features for SN identification, and allow flexible timing of surgery. Scintigraphy effectively selects candidates for the SN procedure. We expect that the gamma probe will facilitate the biopsy considerably. Validation of the radioactive tracer approach awaits larger studies, in which the feasibility of the actual biopsy should also be addressed. The SN concept may be a breakthrough in surgical oncology, substituting extensive, often futile, operations with considerable morbidity by histological examination of a single lymph node. Instead of imaging tumor deposits and struggling with specificity and detection limits, nuclear medicine procedures then contribute to patient care by enabling the surgeon to stage the axilla with a minimally invasive procedure, and showing the radiotherapist whether treatment planning should be adjusted to an individual patients lymphatic drainage pattern. The main impact of SN procedures will be to reduce the number of tumor negative ALNDs. However, in patients with tumor-positive SNs therapeutic strategies may have to be redefined, especially if only micrometastases are present.

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