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Single Intralesional Tracer Dose for Radio-Guided Excision of Clinically Occult Breast Cancer and Sentinel Node

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Background: The purpose of this study was to determine the feasibility of both lymphatic mapping and probe-guided primary tumor excision by use of intralesional tracer administration in clinically occult breast cancer.

Methods: Sixty patients with a clinically occult breast lesion were prospectively included. Lymphoscintigraphy was performed after intratumoral injection of ^{99m}Tc-labeled nanocolloid guided by ultrasound or stereotaxis. A catheter over a localization wire was inserted for intraoperative blue dye administration by using the same imaging techniques. After sentinel node identification, the gamma-ray detection probe was used for radio-guided wide local excision in patients who underwent breast-conserving therapy.

Results: A sentinel node was visualized on the scintigrams in 56 patients (93%) and could be identified intraoperatively in 58 patients (97%). A sentinel node contained tumor in 10 (17%) of these patients. Extra-axillary sentinel nodes were visualized in 43%, were collected in 38%, and contained metastasis in 7% of the patients. Complete excision of the primary tumor could be accomplished in 39 (87%) of 45 patients.

Conclusions: Both sentinel node biopsy and probe-guided excision of a nonpalpable breast cancer is feasible with the aid of intralesional tracer administration. Sentinel node metastasis was found in 17% of the patients. A remarkably high percentage of extra-axillary drainage (43%) was observed.

Key Words: Breast cancer—Non-palpable tumor—Sentinel node—Radio-guided surgery.

Radio-guided surgery of primary breast cancer and lymph node metastases has been described with intravenous injection of tumor-seeking agents such as somatostatin analogs.[1] The limited sensitivity of these agents prevented general acceptance of this approach. Recent developments in lymphatic mapping evoke renewed interest in radio-guided surgery. ^{99m}Tc-labeled colloid administered at the primary tumor site is taken up by the lymphatic capillaries and accumulates in the sentinel lymph node through phagocytosis. However, most of the injected dose remains at the injection site. The retention of radioactivity provides the opportunity to localize the tumor in clinically occult breast cancer, with a gamma ray detection probe obviating the need for wire localization. The purpose of this study was to determine the feasibility of identification of the sentinel node as well as excision of the tumor in nonpalpable or clinical occult breast carcinomas by using intralesional tracer administration.

MATERIALS AND METHODS

Sixty-four patients with a clinically occult breast lesion underwent sentinel node biopsy between November 1999 and February 2001. Patients with a prior excisional biopsy were not enrolled. Four patients were excluded from the analysis because of multicentricity of the tumor in three patients and preoperative chemotherapy in a patient with a simultaneous T4 contralateral breast car-

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cinoma. A preoperative diagnosis was obtained with the aid of mammography, ultrasonography, and fine-needle aspiration cytology or core biopsy. The mean age was 62 years (range, 35 to 83 years). The tumor was situated in the upper outer quadrant in 28 patients, the lower outer quadrant in 9 patients, the upper inner quadrant in 10 patients, the lower inner quadrant in 6 patients, and the central part of the breast in 7 patients. All patients had a node-negative axilla on the basis of physical examination and ultrasonography. The mean tumor diameter measured by the pathologist was 1.2 cm (range, .2 to 2.2 cm). The pathological stage was carcinoma in situ in 3 patients, T1a in 2 patients, T1b in 22 patients, T1c in 32 patients, and T2 in 1 patient. The pathologic type of invasive carcinoma was ductal in 49 women, lobular in 2, mucinous in 1, tubular in 1, and a mixed type of ductal and lobular carcinoma in 4 patients. Routine confirmatory axillary lymph node dissection was not performed. A total of 177 patients with a palpable breast cancer underwent sentinel node biopsy in the same period. These were used to compare drainage patterns.

The day before surgery, a 22-gauge needle was placed into the center of the tumor under ultrasound guidance in 56 patients (13-MHz probe, Siemens Sonoline Elegra™, Siemens Medical Systems, Erlangen, Germany) and stereotaxis (StereoGuide™, LORAD®, Trex Medical Corporation, Danbury, IA) in 4 patients. Subsequently, nanocolloid (Amersham Cygne, Eindhoven, the Netherlands) labeled with ^{99m}Tc (average net dose 122 MBq, range 100 to 159 MBq) was administered through the needle in a volume of .2 ml. After removal of the needle, the patient went to the nuclear medicine department for lymphoscintigraphy. Anterior and prone lateral images with hanging breast were obtained with a dual-head gamma camera (ADAC, Milpitas, CA) with low-energy high-resolution collimators. Static imaging was performed after 20 minutes, 2 hours, and 4 hours postinjection with simultaneous transmission scanning by use of a ^{57}Co flood source to outline the body contour. A hot spot was considered to be a sentinel node when an afferent lymphatic channel was visualized, the hot spot was the first one seen in a sequential pattern, the hot spot was the only one in a particular lymph node basin, or a combination of criteria was present. The location of the sentinel node was marked on the skin with a ^{57}Co pen.

After the last scintigraphic image, a localization procedure was performed. An 18-gauge needle with a central venous catheter (Secalon™, Ohmeda, Swindon, UK) was loaded with a X-shaped hookwire (Cook, Bjaeverskov, Denmark), as shown in Fig. 1. The needle was inserted and positioned at the primary tumor site under local anesthesia by use of ultrasound or stereotaxis. The

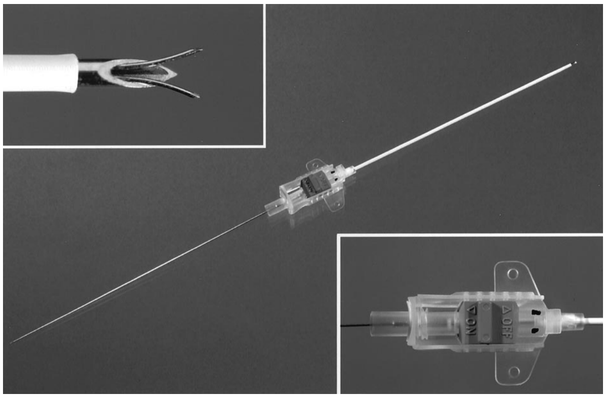

FIG. 1. An 18-gauge needle with a central venous catheter (Secalon) is loaded with a X-shaped hookwire to enable intraoperative blue dye administration into the tumor. After the wire is removed from its original localization needle, it is inserted into the 18-gauge needle in a retrograde direction with manual compression of the proximal part of the X-shaped ending *(left upper corner)*. Subsequently, a standard localization procedure is performed. The needle is retracted while leaving the catheter with the localization wire in situ. The catheter is unable to dislocate after moving the flow switch *(right lower corner)* forward.

X-shaped hookwire was pushed out and the needle was retracted while leaving the catheter with the localization wire in situ. To prevent dislocation of the catheter, the flow switch was moved forward, fixating the catheter to the wire. Mammography in a cranial-caudal and medial-lateral direction confirmed the correct position of the catheter (Fig. 2).

The next day, 1.4 ml of patent blue dye (Blue Patenté V™, Laboratoire Guerbet, Aulnay-sous-Bois, France) was administered through the catheter after the wire was cut. The injection site was massaged. The sentinel node was identified and collected after careful dissection of blue lymphatic vessels and detection of radioactivity with a gamma-ray detection probe (Neoprobe™ 2000, Johnson & Johnson Medical, Hamburg, Germany). Palpation of the biopsy wound was performed after excision

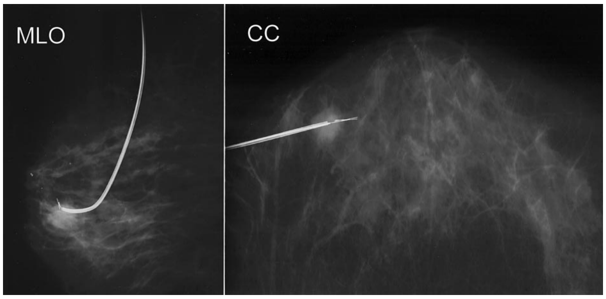

FIG. 2. Medial-lateral-oblique (MLO) and cranial-caudal (CC) mammography after ultrasound-guided localization of a tumor in the upper inner quadrant of the right breast.

of the sentinel node to identify suspicious lymph nodes without tracer uptake.

The gamma probe was subsequently used for lumpectomy in the 45 patients scheduled for breast-conserving therapy. The signal processor with a digital readout was adjusted on the 10.000 count range because of the high residual radioactivity in the primary tumor. The exact location of the primary tumor was determined through the intact skin to make a proper incision. The skin overlying the lesion was dissected from the subcutaneous tissue. As the procedure progressed, the probe was inserted into the wound repeatedly at different angles to assess the position of the tumor. The resection level was guided by count readings, with the aim of obtaining a margin of approximately 1 cm around the lesion. The remaining 15 patients underwent simple mastectomy.

Sentinel nodes were submitted fresh for frozen-section investigation. The sentinel node was bisected. A frozen section was made at one level and stained with hematoxylin and eosin (H&E). The remaining lymphatic tissue was formalin fixated, paraffin embedded, and cut at six levels with intervals of 100 to 150 μm. Paraffin sections were stained with H&E and immunohistochemistry by using CAM 5.2™ (Becton Dickinson, San Jose, CA). In case other lymph nodes were removed, these were completely embedded and examined with immunohistochemistry staining at one level. The margins of the excised lump were marked with ink. The specimen was subsequently cut, formalin fixated, and paraffin embedded. Sections were stained with H&E. The resection was considered complete when a microscopically tumor-free margin of at least 1 mm was obtained.

The χ^2 test was used to compare the incidence of extra-axillary drainage between subgroups of patients. Statistical analyses were performed with Statistical Package for the Social Sciences™ software (SPSS, Inc., Chicago, IL).

RESULTS

Lymphoscintigraphy (Fig. 3) visualized at least one sentinel node in 56 (93%) of 60 patients. The mean number of sentinel nodes on the images was 2.1, with a range from 1 to 5. Second-echelon nodes or lymph nodes at higher levels were seen in 40 patients (71%), with a mean number of 2.8 (range, 1 to 8). Sentinel nodes were located in level I or II of the axilla in 49 patients (88%) and outside the axilla in 24 patients (43%). Seventeen patients (30%) had both axillary and extra-axillary drainage, and seven patients (13%) showed extra-axillary drainage alone. A sentinel node in the internal mammary chain was seen in 17 patients. Five patients had a sentinel node in the lateral breast parenchyma, three in the medial parenchyma, one between the pectoral muscles, two in the subclavicular fossa, and one in the supraclavicular fossa. The percentage of extra-axillary drainage on the lymphoscintigrams was significantly higher (χ^2, P = .006) than in patients with palpable tumors who underwent sentinel node biopsy in the same period (43% [24 of 56] and 24% [42 of 177], respectively). The percentage of inner-quadrant tumors was similar in the two groups (27% and 24%, respectively).

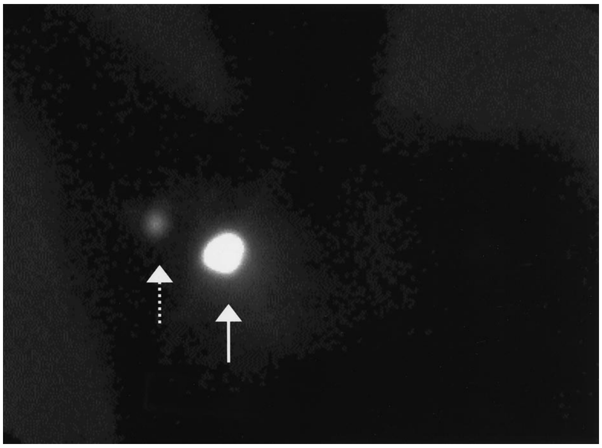

FIG. 3. Preoperative lymphoscintigraphy after intratumoral injection of ^{99m}Tc-labeled nanocolloid in a patient with clinically occult breast cancer. The transported and retained radioactivity enable radio-guided excision of the sentinel node (dotted arrow) and of the primary tumor (arrow), respectively.

The median interval between injection of ^{99m}Tc-labeled nanocolloid and surgery was 24 hours (range, 20 to 29 hours). The mean time between incision and identification of the sentinel node was 19 minutes (range, 4 to 80 minutes). At least one sentinel node was collected during surgery in 58 of 60 patients (97% identification), with a mean number of 2.2 per patient (range, 1 to 6). The sentinel nodes were intraoperatively identified only in the axilla in 36 patients (62%), only outside the axilla in 5 patients (9%), and in both locations in 17 patients (29%). All axillary hot spots on the scintigraphy were identified, and the use of patent blue dye resulted in identification of an axillary sentinel node in four additional patients. Five (5%) of 91 axillary sentinel nodes were found only by their discoloration and 34 (37%) only by their radioactivity. Exploration of the intercostal spaces was successful in 15 of 17 patients with an internal mammary node on the scintigram. In the remaining two patients, only one of two visualized internal mammary sentinel nodes could be collected. The other extra-axillary sentinel nodes were identified in 8 (67%) of 12 patients. Thirty-two of 37 extra-axillary sentinel nodes (86%) were only radioactive, and the other 5 nodes were both blue and radioactive. Initial excision of the primary tumor to reduce the scattered background radioactivity was necessary for sentinel node identification in 8 patients (14%).

Sentinel nodes were free of tumor in 48 patients (83%). Two of these patients preferred confirmatory axillary clearance, which was concordant with the sentinel node status. Ten patients had a tumor-positive sentinel node. Sentinel node metastasis was found in the axilla in seven patients. Three patients had a tumor-positive internal mammary sentinel node, and two of them had no axillary involvement. One patient had a metastasis in a medial intramammary sentinel node. All tumor-positive axillary sentinel nodes were both blue and radioactive. The involved extra-axillary sentinel nodes were both blue and radioactive in two patients and only radioactive in the other two women. Metastasis in the axillary sentinel node was found by frozen-section investigation in four women (7%). Four of seven axillary sentinel node metastases were micrometastases smaller than 2 mm.

Treatment changed according to the extra-axillary sentinel node status in four patients. All four patients underwent radiotherapy of the internal mammary chain, and two of these patients received adjuvant systemic treatment that would not otherwise have been given. In the four patients in whom scintigraphy showed no sentinel nodes, the axilla was explored. In two, a blue sentinel node was identified. In one of the other two patients, a visible nonsentinel lymph node was excised that turned out to contain metastasis. The latter two patients underwent radiotherapy of the axilla.

Wide local excision was complete in 39 (87%) of 45 patients who were conservatively treated. The mean weight of the specimen was 63 g (range, 22 to 168 g). The mean minimum margin was 4 mm, ranging from 0 to 10 mm. Three patients with an incomplete excision underwent mastectomy. In two of these patients, residual carcinoma in situ was found, with microinvasion in one. No local or regional recurrence was seen, but follow-up was short (median 8 months, range 1 to 14 months).

DISCUSSION

Patients with nonpalpable breast lesions are frequently seen in this era of screening programs. Segmental excision and sentinel node biopsy are particularly attractive in this group of patients because of the small tumor size and the low risk of axillary metastases. In this study, 75% of the patients underwent breast-conserving therapy, and axillary treatment was avoided in 82% of the patients.

The use of a gamma-ray detection probe in breast surgery has been described after intravenous injection of tumor-seeking agents such as somatostatin analogs or monoclonal antibodies.[1,2] The purpose of these studies was to detect axillary lymph node metastases and foci of invasive carcinoma in resection margins on the basis of a specific tumor-binding capacity of the compound. With intratumoral injection of ^{99m}Tc-labeled colloid, detection of radioactivity at the site of the primary tumor and the first draining lymph nodes is based on the physiological behavior of the tracer and not on a specific tumor binding (Fig. 3).

Injection of tracers at the primary tumor site requires visualization of the carcinoma in the absence of a palpable mass. This study describes the use of ultrasound and stereotaxis for injection of radioisotope into the tumor. The blue dye was administered through an intratumorally positioned catheter by use of the same imaging techniques. Ultrasound capability in the operating room further facilitates the technique and allows the blue dye to be injected with ultrasound guidance. This obviates the need for a cannula in the breast.

Albertini et al.[3] injected the radiocolloid through a localization needle and left the needle in place for subsequent blue dye injection in the operating room. This method seems to be less comfortable for the patient and has a risk of dislocation. Another approach is to inject the tracers around the localizing wire in occult carcinomas.[4] This is not a very precise method, because depth and direction of the needle have to be estimated. Miner et al.[5] attempted to solve this problem and described injection of radiocolloid at four sites around the tumor with a certain angle and depth, previously defined by ultrasonography. Superficial injections would be easier in nonpalpable breast cancer but have some disadvantages. Intradermal or subcutaneous injection in the areolar region or in the skin overlying the tumor seems to cause a regional mismatch, because sentinel nodes outside the axilla are rarely visualized.[6–8] The reliability of such techniques for axillary staging has to be investigated further.

The percentage of visualized extra-axillary sentinel nodes in this study (43%) was rather high and differed significantly from the visualization rate in palpable tumors. Anatomical studies dealing with the arrangement of the breast lymphatics show that lymph flow to internal mammary nodes and interpectoral nodes is supplied by retromammarian lymphatics.[9,10] These lymphatics arise from the breast lobules, run on the surface of the pectoral fascia, and accompany penetrating blood vessels on their way through the pectoral and intercostal muscles to reach the lymph node. The finding that only deep tracer injection will visualize extra-axillary sentinel nodes supports the observation that deep lymphatics from the dorsal part of the breast drain to these nodes. Our hypothesis is that deeper-located tumors are less accessible to palpation. So the location of the tumor within the breast may be the explanation of the difference in drainage to nonaxillary sentinel nodes between palpable and nonpalpable lesions. This finding and the fact that approximately one third of the lymph node metastases in this study were found outside the axilla stresses the importance of deep tracer administration close to or into the tumor in nonpalpable breast carcinomas. The pursuit of extra-axillary sentinel nodes seems to have implications for subsequent treatment.[11]

Axillary lymph node involvement in clinically occult breast cancer ranges from 10% to 27% in studies with complete axillary lymph node dissection.[12–16] In a study of sentinel node biopsy in nonpalpable breast cancer by Schijven et al.,[17] the percentage of lymph node metastases was 16%. Of 59 patients in this study (one patient underwent radiotherapy of the axilla), 7 patients had a tumor-positive axillary sentinel node and another patient had a tumor-positive nonsentinel node in the axilla. The percentage of axillary involvement of 14% (8 of 59) is comparable with percentages described in literature. The use of intraoperative frozen-section investigation to detect axillary involvement in clinically occult carcinomas can be criticized, because it led to immediate completion lymph node dissection in only 7% of the patients.

We use a small-volume (.2 ml) injection of ^{99m}Tc-labeled nanocolloid into the tumor for lymphatic mapping, and this limits the diffusion of the tracer into the surrounding tissue. Ultrasound and stereotaxis enable deposition of the tracer exactly into the tumor. This approach allows radio-guided excision of the tumor. Recently, probe-guided excision of nonpalpable lesions after intratumoral injection of a ^{99m}Tc-labeled colloid has been reported.[18] Gray et al.[19] described placement of titanium seed containing ^{125}I at the site of the primary tumor for radio-guided lumpectomy. In combination with injection of ^{99m}Tc-labeled sulfur colloid, they were able to perform simultaneous sentinel node biopsy and probe-guided tumor excision.

The standard procedure for wide local excision of a nonpalpable tumor at our institution is the wire localization technique. In this study, both a localization wire and a gamma-ray detection probe were used because the fixation of the catheter for patent blue dye administration required a localization wire. By using the probe to assess the position of the tumor, the site of incision could often be chosen more precisely than with the localization wire. Several authors reported a high failure rate with therapeutic wire-directed excisions, ranging from 40% to 55%.[20] The accuracy of preoperative needle localization has been shown to be a significant factor for success.[20] But even when the wire is close to or within the lesion, it is difficult to envisage the precise three-dimensional situation with two-dimensional images of a compressed breast. This study shows that tumor excision with clear margins could be accomplished in 87% of the patients by using both the gamma ray detection probe and the localization wire. When the patent blue could be injected in the operation room with use of ultrasound, we would no longer need the localization wire and could rely on the gamma probe for wide local excision of the primary tumor. This approach seems attractive and should be compared with wire-directed tumor excision in a randomized fashion.

CONCLUSIONS

The technique of lymphatic mapping with sentinel node biopsy by using intralesional tracer administration is feasible in nonpalpable breast cancer. Furthermore, retention of the radioactive tracer marks the primary lesion and allows for probe-guided tumor excision. The sentinel node could be identified in 97% and complete tumor excision was accomplished in 87% of patients with use of this combined approach. We recommend parenchymal tracer injection in nonpalpable breast cancer because it seems that extra-axillary lymphatic drainage plays an important role in these frequently deep-seated lesions.

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