Comparison of intraparenchymal and intradermal injection for identification of the sentinel node in patients with breast cancer

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Background: Sentinel lymph node (SLN) mapping with radioisotope and blue dye has been advocated for the staging of clinically negative axillae in patients with breast cancer. The optimal radiotracer injection technique is still being defined. This study compares the results of intraparenchymal and intradermal injection of technetium 99m (Tc 99m) sulfur colloid to establish an optimal method for SLN localization.

Methods: Consecutive patients (n = 435) with clinically T0-2N0 breast cancer had SLN biopsy performed by a single surgeon. All patients but one received injections of both blue dye and Tc 99m sulfur colloid; one patient had injection of blue dye only and was excluded from analysis. Blue dye injections were intraparenchymal in all patients. The results of intraparenchymal (n = 107) and intradermal (n = 327) injections of radioisotope were compared for the following endpoints: 1) successful SLN identification, 2) false-negative rate, and 3) ratio of SLN/axillary background isotope counts.

Results: Intradermal radioisotope injection was as effective as intraparenchymal radioisotope injection, identifying the SLN in 99.4% and 92.5% of cases, respectively. False-negative rates for both radioisotope injection techniques were <5%. Ratios of SLN/axillary background isotope counts were higher with intradermal than with intraparenchymal injection (193/1 vs 41/1). Patient follow-up has revealed no axillary recurrence of tumor.

Conclusions: Intradermal radioisotope injection for SLN identification appears to be a highly accurate technique with acceptable false-negative and SLN identification rates. Compared with intraparenchymal isotope injection, the intradermal technique is associated with higher levels of isotope uptake by the SLN, facilitating SLN identification.

Axillary nodal status remains an important prognostic factor in treatment of breast cancer. Sentinel lymph node (SLN) biopsy is a minimally invasive technique for evaluating the status of axillary lymph nodes in patients with operable breast cancer and clinically negative axillae. Studies of SLN biopsy validated by a backup axillary lymph node dissection (ALND) suggest that the procedure has an acceptable SLN identification rate and accuracy rate (1, 2).

Various techniques of SLN identification have been investigated, including injection of radioisotope, blue dye, or a combination of the two via intraparenchymal, intradermal, and subareolar injection sites. Intraparenchymal injection was the first technique described and is the most widely accepted (3, 4). Recent data suggest that the intradermal technique is highly accurate and may increase the SLN identification rate (2, 5, 6). Linehan et al demonstrated a high degree of concordance between intraparenchymal blue dye and intradermal radioisotope injection regardless of the site of radioisotope injection (5), suggesting that an intradermal radioisotope injection results in accurate SLN localization. Moreover, SLN localization was successful in 97% of cases with intradermal radioisotope injection and in 78% of those with intraparenchymal injection, a statistically significant difference (5). The present study compares intraparenchymal vs intradermal injection of radioisotope for identification of SLN in patients with breast cancer. We assessed the accuracy and false-negative rates for both injection sites when they are used in combination with intraparenchymal blue dye injection.

PATIENTS AND METHODS

Patients

In a prospective study conducted from May 1997 through December 2001, 435 consecutive SLN biopsies were completed in 425 patients with T0-2N0 breast cancer by a single surgeon (SMK) at Baylor University Medical Center. All patients had biopsy-proven ductal carcinoma in situ (DCIS) or invasive breast carcinoma with clinically node-negative axillae. SLN biopsy was done in patients with DCIS who underwent planned mastectomy for multifocal disease or patient preference. SLN biopsy was not done in patients undergoing lumpectomy for DCIS.

Methods

Both isosulfan blue dye (Lymphazurin; Zenith Parenterals, Rosemont, Ill) and unfiltered technetium 99m (Tc 99m) sulfur colloid were injected in all but one patient; that patient had injection of blue dye only. One hundred seven patients received intraparenchymal injection of radioisotope for SLN localization prior to July 1999, using 1.0 mCi Tc 99m sulfur colloid in an 8-mL volume. Radioisotope was injected in 2 to 4 injection sites around the periphery of the biopsy cavity or tumor site from 1 to 19 hours before surgery start time. Of the 107 patients, 39 (36.5%) were injected the evening before surgery. Beginning in July 1999, patients undergoing planned completion ALND were

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Table 1. Patient and tumor characteristics in breast cancer patients receiving intraparenchymal vs intradermal injection of radioisotope

	Total	Intraparenchymal injection group	Intradermal injection group
Procedures	434	107	327
Mean age, in years (range)	58.8 (28–92)	58.4 (28–92)	58.9 (29–92)
Tumor location			
UOQ	219 (50%)	62 (58%)	157 (48%)
LOQ	78 (18%)	9 (8%)	69 (21%)
UIQ	53 (12%)	10 (9%)	43 (13%)
LIQ	78 (18%)	24 (22%)	54 (17%)
Central	6 (1%)	2 (2%)	4 (1%)
Tumor histology			
Invasive ductal	330 (76%)	93 (87%)	237 (72%)
Invasive lobular	50 (12%)	7 (7%)	43 (13%)
DCIS	44 (10%)	3 (3%)	41 (13%)
Other	10 (2%)	4 (4%)	6 (2%)
Average tumor size, in cm (range)	1.57 (0.1–6.5)	1.35 (0.1–3.7)	1.65 (0.1–6.5)
Stage			
T0 (in situ)	44 (10%)	3 (3%)	41 (13%)
T1a	48 (11%)	12 (11%)	36 (11%)
T1b	97 (22%)	33 (31%)	64 (20%)
T1c	146 (34%)	42 (39%)	104 (32%)
T2	92 (21%)	17 (16%)	75 (23%)
T3	7 (2%)	0	7 (2%)

UOQ indicates upper outer quadrant; LOQ, lower outer quadrant; UIQ, upper inner quadrant; LIQ, lower inner quadrant; DCIS, ductal carcinoma in situ.

Table 2. Average 10-second counts on hottest sentinel lymph nodes in breast cancer patients receiving intraparenchymal vs intradermal injection of radioisotope

	Total	Intraparenchymal injection group	Intradermal injection group
Procedures	434	107	327
Counts			
All	9236	1736 (max 17,253)	11,396 (max 242,015)
Surgical biopsy	8002	1389	10,290
Core-needle biopsy	11,153	2540	12,940
Ratio: SLN/background	—	41/1	193/1

injected via the intradermal technique, which involved injection with 0.5 mCi Tc 99m sulfur colloid in a 0.5-mL volume. Generally, 2 injection sites were used, medial and lateral to the incision or tumor site. In some cases, a single injection site was used. The radioisotope was injected intradermally, raising a skin wheal, or subdermally, without skin wheal.

Patients were taken to the operating room after injection of the radioisotope in the nuclear medicine department. Isosulfan blue dye (2–3 mL) was injected intraparenchymally 10 to 30 minutes before surgical incision without massaging the breast. External scanning was done with the gamma probe (C-Trak; Care-Wise Medical, Morgan, Calif) over the supraclavicular, internal mammary, and axillary regions before the incision was made. SLN were identified prior to lumpectomy or mastectomy by placing an incision over the external hot spot in the axilla, or lower hair-bearing area of the axilla if no hot spot was detected for lumpectomy patients. In mastectomy patients, either a separate incision was made for the SLN biopsy similar to that for lumpectomy patients or the procedure was carried out through the standard mastectomy incision. The SLN was identified both by use of the gamma probe and by visual appearance of the blue dye in the afferent lymphatic vessels or nodes.

The 10-second count for the SLN was determined ex vivo using an intraoperative gamma detection probe. Successful SLN identification was defined as either successful blue dye localization or successful radioisotope localization with postexcision axillary bed counts <20% of the SLN count. Successful blue dye localization was defined as identification of a lymph node with visible blue staining or a directly contiguous blue-stained afferent lymphatic. Patients underwent completion ALND initially in verifying the intradermal injection technique, if the SLN proved positive, if the SLN could not be found, or if intraoperative palpation of the axilla revealed clinically suspicious nonsentinel lymph nodes. In patients not undergoing completion ALND, nodes immediately adjacent to the SLN were removed along with the SLN. When no additional nodes were located immediately adjacent to the SLN, no additional dissection was done.

Intraoperative pathologic analysis of the SLN involved gross examination in all cases. Initially, frozen section examination was done on all SLN. Because of concern that this could interfere with detection of very small metastases to the node, frozen section was limited later in the study to nodes that were grossly suspicious. Postoperatively, all SLN were sectioned serially and stained with hematoxylin-eosin and immunohistochemical stains for cytokeratins (AE1:AE3) if the hematoxylin-eosin stain was negative. At least 3 sections of each SLN were examined with each stain. Nonsentinel nodes from the completion ALND specimens were examined routinely with a single hematoxylin-eosin–stained section per node.

The identification rate was defined as the proportion of procedures in which an SLN was identified. The false-negative rate was defined as the proportion of node-positive cases in which the SLN was negative.

RESULTS

The intraparenchymal injection group comprised 107 patients and the intradermal injection group, 327 patients. Patient and tumor characteristics were similar for both groups *(Table 1)*. The mean 10-second counts for the SLN were 1736 and 11,396, respectively, for intraparenchymal and intradermal injections *(Table 2)*. The ratio of SLN/axillary background counts were 41/1 and 193/1 for the intraparenchymal and intradermal groups, respectively. An average of 1.5 and 1.6 SLN were identified per patient who underwent intraparenchymal or intradermal injection, respectively. The time from radioisotope injection to surgery varied from 45 minutes to 19 hours (*Table 3)*. This variation,

Table 3. Procedures and results in breast cancer patients receiving intraparenchymal vs intradermal injection of radioisotope

	Total	Intraparenchymal injection group	Intradermal injection group
Procedures	434	107	327
Previous biopsy			
Surgical	264 (61%)	75 (70%)	189 (58%)
Core needle	170 (39%)	32 (30%)	138 (42%)
Treatment			
Lumpectomy	230 (53%)	80 (75%)	150 (46%)
Mastectomy	204 (47%)	27 (25%)	177 (54%)
Positive SLN	109 (25%)	24 (22%)	85 (26%)
Average no. of SLN	1.56	1.50	1.57
Completion ALND	144	46	98

SLN indicates sentinel lymph node; ALND, axillary lymph node dissection.

however, did not translate into substantial variation in the average number of SLN identified.

The breast cancer was treated with lumpectomy in 231 patients (53%) and mastectomy in 204 patients (47%). Prior to SLN biopsy, a core-needle biopsy had been done in 170 (39%) and excision biopsy in 265 (61%) patients, with mean 10-second counts on the SLN of 11,153 and 8002, respectively.

Several factors have been identified as possibly hindering successful identification of the SLN, including obesity and the presence of a large parenchymal defect from open biopsy. In this series, 112 patients were obese, defined as a body mass index >30 kg/m^2; 23 received intraparenchymal injection and 89 intradermal injection of radioisotope. The mean 10-second counts on the SLN were 662 and 9477, respectively. This suggests that intradermal injection may prove helpful in this patient population in eliminating some cases of nonmigration of radioisotope.

In only 2 patients in the intradermal injection group could an SLN not be identified, making the identification rate >99%. One of these was a patient who underwent biopsy at an outside institution and had a large 8-cm defect in the breast, undermining the areola. The other patient had erratic readings with the gamma probe, thought to be due to equipment malfunction. An SLN could not be identified in 8 patients in the intraparenchymal injection group, making the identification rate for this injection technique 93%.

The accuracy and sensitivity of intradermal injection for identification of the SLN were evaluated in the 98 patients in that group who underwent completion ALND. An average of 13.5 (range 4–34) nonsentinel lymph nodes were removed and examined pathologically. Fifty-five of these 98 patients (56%) had a positive SLN. The SLN was the only positive node in 55% (30/55). One patient had a false-negative SLN, making the false-negative rate in the intradermal injection group 2% (1/56). The positive node was adjacent to the SLN in a patient with invasive lobular carcinoma and was associated with a 2.5-mm metastasis. No additional nodes were positive on completion ALND. There were no false-negatives in the intraparenchymal group.

DISCUSSION

SLN biopsy for breast cancer staging purposes has allowed many patients with lymph node–negative cancer to forego completion ALND. Research continues to define the optimal technique for accurate identification of the SLN and has encompassed intraparenchymal, intradermal, and subareolar injection sites, as well as use of both radioisotope and blue dye. The combination of blue dye and radioisotope is generally accepted as preferable to either alone and was used in this study.

Intradermal injection of radioisotope for SLN identification is a highly accurate technique with acceptable false-negative and identification rates (2, 4–6). In the present study, the average 10-second count was over 5-fold higher with intradermal than with intraparenchymal injection, facilitating identification of the SLN. This is similar to results at Memorial Sloan-Kettering Cancer Center reported by Martin et al (2). Improved SLN identification with the intradermal technique may be particularly important in obese patients or patients with fatty-replaced nodules, as obesity has been identified as a possible contributor to nonmigration of radioisotope and blue dye and the subsequent inability to identify the SLN.

Although intraparenchymal injection is the most widely accepted method of administering radioisotope, the present study suggests that the intradermal technique may increase SLN identification. Significant "shine effect" from the intraparenchymal injection site can prevent SLN identification, especially in upper, outer quadrant lesions that may overlie the draining SLN. Also, intradermal injection is simpler and possibly less painful for the patient. Although not the focus of this report, the suggestion that surgeons doing infrequent SLN biopsies may have a shorter learning curve with intradermal injection is plausible.

Therefore, the present study supports use of intradermal over intraparenchymal injection of radioisotope in SLN biopsy due to its ease of use, greater SLN identification rate, and acceptable false-negative rate. The greater ease of SLN localization with intradermal radioisotope injection may be due to the rich lymphatic network of the skin overlying the breast as well as the reduction in shine effect. Intradermal injection simplifies and optimizes SLN identification because it is easier to perform and more effective than intraparenchymal injection.

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