Intra-Individual Comparison of Lymphatic Drainage Patterns Using Subareolar and Peritumoral Isotope Injection for Breast Cancer

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ABSTRACT

Background. Controversy exists in the literature regarding the optimal site for lymphatic mapping in breast cancer. This study was designed to characterize lymphatic drainage patterns within the same patient after subareolar (SA) and peritumoral (PT) radiopharmaceutical injections and examine the impact of reader interpretation on reported drainage.

Methods. In this prospective trial, 27 women with breast cancer underwent sequential preoperative SA and PT injections of 0.5 to 2.7 mCi of technetium-99 m filtered sulfur colloid 3 days or more apart. Patterns of radiopharmaceutical uptake were reviewed independently by two nuclear medicine physicians. Inter-reader agreement and injection success were assessed in conjunction with observed drainage patterns.

Results. There was near perfect inter-reader agreement observed on identification of axillary LN drainage after PT injection ($P = 0.0004$) and substantial agreement with SA injection ($P = 0.0344$). SA injection was more likely to drain to only axillary LNs, whereas PT injection appeared more likely to drain to both axillary and extra-axillary LNs,

although no statistically significant differences were found. All patients with extra-axillary drainage after PT injection ($n = 6$ patients) had only axillary drainage after SA injection. Dual drainage was observed for six patients with PT injection and one patient with SA injection.

Conclusions. Our findings suggest that radiopharmaceutical injected in the SA location has a high propensity to drain to axillary LNs only. After controlling for patient factors and demonstrating inter-reader agreement, the inability to demonstrate statistically significant differences in drainage based on injection site suggests that lymphatic drainage patterns may be a function of patient and tumor-specific features.

Axillary node involvement remains a key determinant of prognosis for patients with breast cancer. Clinical trials and numerous single institution series have demonstrated that sentinel lymph node biopsy (SLNB) can determine the status of the axillary lymph nodes with 96–98% accuracy and should be offered to patients with clinically node-negative breast cancer, sparing them the associated morbidities of axillary lymph node dissection (ALND).^{1–3} The optimal technique for SLNB remains a subject of great debate, and no standard for SLN mapping exists.

Studies investigating what to inject—technetium-99 m labeled sulfur colloid, vital blue dye, or both—and where to inject it—subareolar, periareolar, intratumoral, or peritumoral locations in dermal versus subdermal planes—abound in the literature. This stems from uncertainty and/or observed variability among the lymphatic drainage patterns of the breast.^{4–6} Most contemporary studies base lymphatic drainage concepts on early cadaver and surgical specimen

Presented in part at the Society of Surgical Oncology 60th Annual Cancer Symposium, March 15–18, 2007, Washington, D.C.
Research supported by funding from NIH Avon Supplement 3 P30 CA16672-29S (to GVB).

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First Received: 1 September 2008;
Published Online: 13 August 2009

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studies conducted by Sappey, Delamere, and the schematics later published by Rouviere in 1938.⁷⁻⁹ The first published description of intraoperative visualization of the breast lymphatic system by Kinmoth in 1952 inspired further interest in image-guided visualization, establishing the framework for present-day lymphatic mapping.¹⁰

After early SLNB validation studies, peritumoral injection became the “gold standard” for performing SLNB. Continued debate over the anatomical pathway of lymph flow, even with the advent of newer techniques to image the breast lymphatics, has inspired the search for other sites of injection.¹¹ Several investigators have compared subareolar and peritumoral injection for axillary SLN identification. Klimberg et al. performed subareolar injection of technetium-99 sulfur colloid and peritumoral injection of isosulfan blue, noting that all blue nodes removed at the time of surgery were radioactive.¹² The study concluded similar accuracy for axillary SLN identification among the two methods, yet preoperative lymphoscintigraphy was not performed to evaluate drainage to extra-axillary sites. Zavagno et al. performed subdermal, peritumoral injection of 99 m-Tc colloidal albumin and concomitant subareolar injection of patent blue dye in 50 patients with breast cancer, finding a 93% intraoperative concordance between the two methods in identifying the same axillary lymph nodes.¹³ Other studies have demonstrated concordance between PT and SA injection of radiotracer, citing comparable success rates for axillary SLN identification, yet completion ALND has only rarely been performed to evaluate the false-negative rate.¹⁴⁻¹⁸

Proponents for the use of peritumoral injection as the site for SLNB contend that alternative sites of injection do not necessarily drain to extra-axillary nodes. Extra-axillary nodal drainage, which includes drainage to supraclavicular, infraclavicular, and internal mammary nodal basins, is observed on lymphoscintigraphy in >20% of patients and has become a topic of increasing interest due to its potential treatment implications.^{19,20} Extra-axillary lymph node status plays a role in determining prognosis and treatment, and surgeons at some centers are applying SLNB concepts to extra-axillary sites. Knowledge of extra-axillary disease equips the radiation and medical oncologists with more information upon which to base treatment decisions, as it may greatly impact radiation field planning and, in some instances, the use of chemotherapy. Much as SA and PT radiopharmaceutical injection have been used to characterize axillary drainage patterns on lymphoscintigraphy, the best site of injection to assess extra-axillary drainage also remains to be determined.

To further investigate differences in breast lymphatic drainage and mapping based on site of injection, we initiated a prospective study comparing both SA and PT

injection of technetium-99 m filtered sulfur colloid in patients with breast cancer. Because there is a paucity of data on variability of reader interpretation of lymphoscintigraphy, we sought to evaluate this end point as well.

PATIENTS AND METHODS

Approval for the study was granted by the Institutional Review Board for this single-institution, prospective trial and funding was provided in part by NIH Avon Supplement 3 P30 CA16672-29S. From April 2002 to June 2006, data were collected on women undergoing surgery for biopsy-proven, unifocal breast cancer presenting for surgery to The University of Texas M.D. Anderson Cancer Center. Written, informed consent was obtained from each patient. Inclusion criteria were the presence of biopsy-proven breast cancer and the need for surgical assessment of axillary lymph nodes for staging and prognostic purposes. Exclusion criteria included the presence of multifocal or multicentric breast neoplasms, pregnancy, male gender, and patients who did not undergo preoperative lymphoscintigraphy with both SA and PT radiopharmaceutical injection.

Radiopharmaceutical Injection and Preoperative Lymphoscintigraphy

Lymphoscintigraphy was performed preoperatively, with timing of subsequent injections ranging from 2 weeks preoperatively to the morning of surgery. Each patient underwent radiopharmaceutical injection in both SA (immediately underneath the nipple-areolar complex) and PT (into the breast parenchyma around the tumor) breast locations during separate sessions before operative intervention. Sequential injections were performed at least 3 days apart to allow for isotope washout between sequential lymphoscintigrams.²¹ For nonpalpable neoplasms and in cases where neoadjuvant chemotherapy had been received with significant treatment response, filtered technetium-99 m sulfur colloid was injected peritumorally into the primary tumor bed identified by a radio-opaque marker using ultrasonography or mammography to aid with localization.

Patients underwent injection of 0.5 mCi (if performed on the day of surgery) or 2.5 mCi (if performed 1 day before surgery) of filtered technetium-99 m sulfur colloid. Anterior, posterior, and lateral emission and transmission images were obtained at 30 minutes and sequentially up to 4 hours after injection using an e-Cam dual detector Gamma camera (Siemens, Hoffman Estates, IL). Focal areas of increased tracer uptake were documented, specifically the nodal basins involved and the number of nodes observed in each respective basin.

Lymphoscintigram Interpretation

Two participating nuclear medicine physicians specializing in breast imaging at our institution (IG and EK) performed preoperative lymphoscintigrams on patients after separate, sequential peritumoral, and subareolar injections of filtered technetium-99 m sulfur colloid. Postinjection lymphoscintigrams were reviewed independently by each nuclear medicine physician after both SA and PT injections, with each blinded to his/her own reading of observed drainage patterns for the other injection site as well as the other physician's readings. Upon review of each lymphoscintigram, each nuclear medicine physician was asked to record drainage to the high or low axillary nodal basin, superior, mid or inferior internal mammary basins, and/or the supraclavicular nodal basins. Their responses were recorded on a standardized scoring sheet and used to analyze inter-rater variation in interpretation. Patients who failed to demonstrate nodal drainage on lymphoscintigraphy after 4 hours were recorded as having no drainage for that site of injection.

SLN Identification and Use of Blue Dye

In cases in which the preoperative high-dose radiopharmaceutical injection had preceded the surgery by more than 24 hours, an additional 0.5 mCi of radiopharmaceutical was injected in a subareolar location on the day of surgery to facilitate intraoperative identification. In addition, 5 ml of 1% isosulfan blue (Lymphazurin, US Surgical, Norwalk, CT) was injected into the breast parenchyma around the known tumor before incision to facilitate intraoperative sentinel lymph node identification. The SLN was identified transcutaneously by use of a hand-held gamma probe. All lymph nodes with a radioactivity count higher than 10% above the highest ex vivo count of the sentinel lymph node and all blue lymph nodes with surrounding blue lymphatic channels were removed and labeled as SLNs.

Surgery

Surgical procedures included segmental mastectomy with SLNB and total mastectomy with SLNB. Patients underwent level I and II ALND after SLNB if no sentinel lymph node was identified intraoperatively, the patient had received neoadjuvant chemotherapy for documented node-positive disease before initiation of chemotherapy, or if at least one sentinel lymph node demonstrated tumor metastasis (pN1 or pN1mi) on intraoperative evaluation. Extra-axillary SLNB was not performed.

Pathologic Evaluation

Axillary SLNs were analyzed intraoperatively by touch prep and were subjected to permanent histopathologic analysis. Sentinel lymph nodes were serially sectioned at 2- to 3-mm intervals along the short axis of the node, embedded in paraffin blocks, and then blocks were serially sectioned at 5 μ m. Hematoxylin and eosin (H&E) staining was performed on sections; nodes that were negative on H&E were subsequently evaluated with immunohistochemical staining for cytokeratin.²² All lymph nodes from the axillary lymph node dissection were evaluated by routine hematoxylin and eosin staining after sectioning. Staging was assigned in accordance with the AJCC Cancer Staging Manual, 6th edition.²³

Statistical Analysis

Simple descriptive statistics were provided for the study population. Inter-reader agreement on the success of each injection was assessed using the simple kappa coefficient (with exact *P* value and 95% confidence interval), which measures agreement beyond that expected by chance. Differences in injection success for peritumoral and subareolar injections were assessed using the McNemar test. The null hypothesis was that the proportion of successful peritumoral injections was equal to the proportion of successful subareolar injections. *P* < 0.05 was considered statistically significant. All analyses were conducted using SAS for Windows (release 9.1, SAS Institute, Cary, NC) and performed by The Department of Biostatistics and Applied Mathematics at our institution.

RESULTS

The study population consisted of 27 women who had stage 0 to IIIC breast cancer. The mean age of our cohort was 57.4 (standard deviation = 14.0; range, 25–87) years. Mean patient body mass index was 26.9 (range, 18.7–38.1) kg/m². Other demographic, treatment, and pathological characteristics are outlined in Table 1.

Lymphoscintigrams after PT injections were read by both nuclear medicine physicians for 20 patients and after SA injection for 23 patients. The physicians showed a high degree of inter-reader reliability for PT injection (kappa = 0.8750; *P* = 0.0004) and a moderate degree of inter-reader reliability for SA injection (kappa = 0.4524; *P* = 0.1700). No pattern was seen among cases in which their readings disagreed. The patterns of lymphatic drainage based on injection site and recorded by the two nuclear medicine physicians are listed in Table 2.

To designate a single success rating for each injection method in identifying any sentinel node by

TABLE 1 Baseline characteristics of patient cohort ($n = 27$)

Characteristic	
Age (yr)	
Mean	57.4
Range	25–87
Body mass index (kg/m^2)	
Mean	26.9
Range	19–38
Menopausal status	
No. of patients (%)	
Pre	4 (15)
Peri	2 (7)
Post	21 (78)
Pathological stage	
0	1 (3.7)
I	16 (59)
IIA	4 (15)
IIB	1 (3.7)
IIIA	1 (3.7)
IIIB	1 (3.7)
IIIC	3 (11)
Final pathology	
IDC	20 (74)
Other	7 (26)
ER status	
Positive	18 (67)
Negative	8 (30)
Equivocal	1 (3)
PR status	
Positive	15 (56)
Negative	11 (41)
Equivocal	1 (3)
HER-2/neu status	
Positive	8 (30)
Negative	15 (56)
Neoadjuvant chemotherapy	7 (26)
Tumor location	
UOQ + UC	13 (48)
UIQ	8 (30)
LOQ + LC	5 (19)
LIQ	1
Operation performed	
Segmental mastectomy with SLNB	12 (44)
Total mastectomy with SLNB	15 (56)
Completion ALND	13 (48)

IDC invasive ductal carcinoma; *UOQ* upper outer quadrant; *UIQ* upper inner quadrant; *LOQ* lower outer quadrant; *LIQ* lower inner quadrant; *UC* upper central; *LC* lower central; *SLNB* sentinel lymph node biopsy; *ALND* axillary lymph node dissection

TABLE 2 Observed lymphatic drainage pattern by site of injection (SA vs. PT) and interpreting nuclear medicine physician (A or B)

Observed drainage pattern (No. of patients)	Site of radiopharmaceutical injection			
	SA		PT	
	Interpreting physician			
	A	B	A	B
Axilla only	23	20	14	10
Concomitant SCL	0	1	4	4
IM only	1*	0	0	0
No drainage	3	2	5	6

SA subareolar radiopharmaceutical injection; *PT* peritumoral radiopharmaceutical injection; *Ax* axillary; *SCL* supraclavicular; *IM* internal mammary

* Denotes same patient

lymphoscintigraphy, we designated the agreed upon result by both nuclear medicine physicians as a success. Using this method, 74% ($n = 17$) of the PT injections identified drainage, whereas 85% ($n = 23$) of SA injections identified drainage. Both PT and SA injections were judged to be successful for 73% of the cases ($n = 16$) and both unsuccessful in one case (5%). The difference in the judged success of the two procedures to identify any lymphatic drainage was not statistically significant ($P = 0.1797$).

There were no statistically significant differences by injection location for the absence or presence of lymph node drainage in the low axillary, high axillary, supraclavicular, superior internal mammary, inferior internal mammary, or internal mammary sites. For physician B, there was a trend ($P = 0.0588$) for SA injections to identify high axillary lymph nodes when the PT injection did not (32%, $n = 6$), but this trend was not seen for physician A's readings. For the five cases in which PT injection was judged unsuccessful (no identifiable drainage to regional lymph nodes), 60% ($n = 3$) of patients had received neoadjuvant chemotherapy for clinical stage II ($n = 1$) and III ($n = 2$) disease. Tumor sizes on final pathologic analyses were as follows: 0.1–1.0 cm ($n = 1$), 1.1–2.0 cm ($n = 1$), 2.1–3.0 cm ($n = 2$), and 4.1–5.0 cm ($n = 1$). Four (80%) of the PT group who failed to show drainage on lymphoscintigraphy had upper outer quadrant tumors (UOQ) tumors, whereas the remaining patient had an upper inner quadrant (UIQ) tumor. There was no statistically significant association between failure to drain by either injection method or any clinicopathological variable, such as patient age, body mass index, menopausal status, pathological stage, final tumor pathology, receptor status, or tumor location (all $P > 0.05$).

FIG. 1 Lymphoscintigrams after SA (a) and PT (b) injection of radiopharmaceutical in the same patient. After SA injection, drainage was observed to axillary lymph nodes only, whereas after PT injection, drainage was observed to the left axillary and internal mammary nodal basins

Whereas the SA injection appeared slightly more likely to identify only axillary lymph node drainage, the PT injection appeared more likely to identify extra-axillary nodes. However, there were no statistically significant differences in SA and PT injections for identification of axillary sentinel lymph nodes or extra-axillary SLNs. Drainage to extra-axillary sites was identified after PT injection but not SA injection for five patients by physician A and three patients by physician B but not by SA injection for one patient by both physicians A and B. Figure 1 displays representative images of one patient's lymphoscintigrams after SA and PT radiopharmaceutical injection, respectively, and one nuclear medicine physician's recorded responses.

The nuclear medicine physicians disagreed on drainage site for six cases. The tumor size was ≤ 2 cm for three patients and ≥ 2.1 cm for three patients. The clinical stage was I for two patients, II for three patients, and III for one patient. Two patients had received neoadjuvant chemotherapy, whereas four patients had not. Drainage patterns based on injection site for each of the physician's readings are summarized in Table 3.

The number of axillary lymph nodes observed on lymphoscintigraphy after radiopharmaceutical injection in the SA location was analyzed in conjunction to the number removed at time of sentinel lymph node biopsy. An additional radiopharmaceutical injection in the subareolar location was used to identify the SLN, with or without concomitant use of blue dye, at the time of surgery. We compared the number of SLNs read by physician A after SA injection to the number removed intraoperatively during SLNB, because physician A read more cases compared with physician B. Physician A recorded drainage in 23 of the 27 cases after SA injection. Of those 23 cases with drainage identified on lymphoscintigraphy after SA

TABLE 3 Drainage based on injection site and two nuclear medicine physicians' readings

Physician reading	Site of isotope injection	Axillary drainage	Extra-axillary drainage	No drainage
A (<i>n</i> = 23 patients)	SA	20 (87)	1 (4.3)	3 (8.7)
	PT	13 (56.5)	5 (22)	5 (21)
B (<i>n</i> = 20 patients)	SA	17 (85)	1 (5.0)	2 (10)
	PT	10 (50)	4 (20)	6 (30)

Extra-axillary includes IM + SCL nodal basins

Data are number of patients with percentages in parentheses

SA subareolar; PT peritumoral

injection, 1 case (4%) resulted in an inability to find a SLN at time of operation, resulting in an overall intraoperative SLN identification rate of 96%. In all 22 cases in which a SLN was identified intraoperatively, this node was identified by radiopharmaceutical injection regardless of whether blue dye was used. Eighty-six percent (19/22) of the cases had the same number of SLNs or more found intraoperatively compared with the number observed on lymphoscintigraphy.

In our patient cohort, five patients demonstrated internal mammary nodal drainage on lymphoscintigraphy. Only one patient's treatment plan was altered with the addition of adjuvant radiotherapy to the IM chain based on findings from lymphoscintigraphy. This patient had stage IIB (T2N1) disease with one of nine axillary SLNs positive on pathological analysis. Three patients with IM nodal drainage had T1-2N0 disease by final pathology and did not receive radiotherapy; the remaining patient had T4bN1 disease and underwent treatment of the IM chain with a separate electron field as planned preoperatively based on stage.

DISCUSSION

Multiple studies have demonstrated a high concordance rate of identifying the sentinel lymph nodes after PT and SA injections.^{16,24–31} Many surgeons now use subareolar injection as their preferred approach. However, concern arises from the observation that extra-axillary drainage sites are almost never seen after SA injection, which has been noted by an equally large number of studies.^{20,32}

Possible reasons that SA injection fails to demonstrate extra-axillary drainage can be explained by theories surrounding the functional anatomy of the breast and concepts of lymphatic flow. The subareolar lymphatic plexus consists of a network of lymphatic channels that originate in the nipple-areolar complex and communicate with deep and superficial intramammary lymphatics, which then terminate in regional lymph nodes. It has been demonstrated that all lymphatic channels of the breast parenchyma and skin communicate in the subareolar lymphatic plexus.^{4,5} SA injection thus preferentially drains to this more superficial system and ultimately to the axillary nodal basin, whereas PT injection targets the deeper intramammary system and leads to drainage to regional (internal mammary and supraclavicular) lymph nodes. A recent cadaveric study by Suami et al. employed microsurgical techniques to inject breast lymphatics with lead oxide and performed subsequent radiography to demonstrate two key findings: 1) perforating lymphatic vessels in proximity to the internal mammary vessels drain into ipsilateral IM nodes; and 2) in most breast specimens, more than one sentinel lymph node drained the breast.¹¹ These observations led the authors to suggest that PT injection may be more accurate for detection of sentinel nodes draining the site of the cancer. However, one must not discount patient anatomy and tumor-specific factors.

Studies have attempted to explore patient-related and technical factors that may contribute to increased extra-axillary node visualization. Krynyckyi et al. noted that deeper injection of radiopharmaceutical (intra-/peri-lesional compared with dermal injection), smaller breast size, medial and inferior tumor location, younger patient age, lower body mass index, and nonpalpable primary lesions demonstrate increased IM nodal drainage on lymphoscintigraphy.³³ Variations in reported detection rates could be at least partly dependent on these factors. Although some of these factors might be attributed to proximity effect to the chest wall and/or the internal mammary chain, others rely on patient and tumor characteristics. Whereas the latter factors cannot be modified, the site of injection may be adjusted to demonstrate extra-axillary drainage in patients for whom this information may alter their staging and treatment.

The role for harvesting extra-axillary SLNs is a subject of debate. Complete IM node dissection was once deemed

an aggressive treatment and was not thought to significantly alter prognosis. With recent studies citing the low morbidity associated with extra-axillary, specifically internal mammary, sentinel lymph node biopsy, the question of whether extra-axillary SLNB should be performed has been raised by many authors.^{34–36} Veronesi and others have shown that IM lymph node involvement confers a poorer prognosis and shorter survival.³⁷ The 2006 revisions to the American Joint Committee on Cancer staging manual reflect the importance of IM nodes in breast cancer staging. Knowledge of extra-axillary drainage and metastasis does influence decisions regarding subsequent adjuvant systemic and radiation treatment for our patients.^{31,35,38} Internal mammary SLN biopsy is advocated as a guide for radiotherapy planning for patients with observed IM nodal drainage.³⁷ If the clinician seeks to treat extra-axillary sites of drainage, peritumoral injection may add additional information beyond what is gained from subareolar injection alone, allowing adjustment of the radiation field to include those internal mammary lymph nodes visualized on lymphoscintigraphy. Based on the data presented here, many of the surgical oncologists at our institution continue to perform PT injections and now harvest extra-axillary SLNs.

Galimberti et al. performed a pilot study to assess the feasibility of IM node biopsy, noting that deeper injection of radiotracer facilitated IM node visualization. The study observed a positive IM node in 8.8% of the patients in which SLN biopsy was performed, causing a shift in cancer stage from N0/N1 to N3.³⁵ This information altered adjuvant treatment plans with regard to systemic therapy and radiotherapy to the internal mammary chain. Likewise, a 2007 study by Madsen et al. that analyzed the frequency of lymphatic drainage to the IM chain and rate of IM SLN metastasis found that 24% of IM nodes visualized on lymphoscintigraphy contained metastasis when biopsied.³⁸ This finding led to an adjustment in the radiation field and addition of systemic adjuvant therapy in 20% and 7% of that patient cohort, respectively. Later studies served to support this finding. Radiotherapy to the IM chain has been shown to improve long-term survival by decreasing the risk of development of distant and/or a secondary breast cancer in patients with documented axillary metastases.³⁹ The additional information provided in visualizing and performing biopsy of IM nodes may have significant clinical implications for prognosis and survival. However, it is still relatively controversial whether addressing these extra-axillary sites of drainage translates into improved patient outcomes.

Our study is unique in that it is one of very few studies that compares drainage patterns on lymphoscintigraphy after both PT and SA injection techniques in the same patient. Differences in patient factors, such as breast size

and BMI, are controlled for, as are variations in lymphoscintigram interpretation. Our observation that there is a propensity for PT injection to identify concomitant extra-axillary nodal drainage is supported by numerous reports in the literature.^{11,15,17,24,27,29,31,40–43} However, the fact that there seems to be no statistical significance in lymphatic drainage patterns based on injection site after controlling for patient and tumor-specific factors and lymphoscintigram interpretation underscores the impact of patient factors and tumor biology on drainage pattern. Our discordant results challenge contemporary studies and further studies are needed to clarify this.

Only one other study to date has compared drainage patterns in the same patient after both SA and PT injection.¹⁷ Although they demonstrated concordance among the injection methods, they also observed that PT injection identified concomitant parasternal drainage in 14% of patients that was not detected by SA injection. In attempt to expand on this finding, one objective of our study was to analyze the impact, if any, of interobserver agreement on lymphoscintigram interpretation. Our review of the literature yielded no existent studies that have examined reader variation with regard to lymphoscintigraphy. Studies using computer-aided detection systems have shown a significant degree of both intra- and inter-reader variability in disease detection by computed tomography, and it is in that sense that variability in interpretation has been chiefly analyzed.²⁶ Lessons learned from breast density estimation in digital and screen film mammography suggest that optimization of a protocol, regardless of the chosen technique, is mandatory to establish uniform measuring guidelines and criteria.²⁵ Variability in radiotracer injection techniques and sites translates into variability among image interpretations.

Lymphoscintigrams in our study were reviewed by two nuclear medicine physicians, both of which specialize in breast lymphoscintigram interpretation and perform numerous readings on a day-to-day basis. This allowed us to make two key observations. First, we found that in 86% of our cases, we had the same number of SLNs or more found intraoperatively compared with the number seen on lymphoscintigraphy. Review of the literature supports the finding that visualization of axillary lymph nodes on lymphoscintigraphy is associated with a higher rate of SLN identification at operation.^{20,28,30,32} This leads us to conclude that if drainage is seen on LSG, it is likely that a SLN can be found intraoperatively by radiopharmaceutical injection. Second, our observation that SA injection has a propensity to identify axillary sentinel lymph nodes only, whereas PT injection has a propensity to also identify extra-axillary nodes, can be seen as a validation of the injection site rather than merely observer interpretation. The fact that our findings were not statistically significant

suggests the need for further intra-individual comparison studies to validate the impact of tumor biology and other patient-specific factors.

CONCLUSIONS

Our findings suggest that patients for whom sentinel lymph node biopsy of extra-axillary sites is contemplated, peritumoral injection may be the preferable approach for lymphatic mapping. However, more studies are needed to clarify further the impact of tumor biology and patient-specific factors on the lymphatic drainage patterns of the breast.

ACKNOWLEDGMENT Research supported by funding from NIH Avon Supplement 3 P30 CA16672-29S (to G.V. Babiera).

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