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# Factors Affecting Visualization Rates of Internal Mammary Sentinel Nodes During Lymphoscintigraphy

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There is great variation in the reported frequency of internal mammary (IM) sentinel node (SN) visualization. We observed a marked increase in our IM SN detection rate after 2 factors were changed simultaneously: depth of perilesional injection and dose. **Methods:** A retrospective review of 82 consecutive patients (group 1) was compared with 61 consecutive patients (group 2) after changing the depth of perilesional injections and dose. Both groups had perilesional injections of  $^{99m}\text{Tc}$ -sulfur colloid followed by intradermal injections at the areolar cutaneous junction. For group 2, activity was increased in all patients scheduled for next-day surgery. Group 2 had perilesional injections on top of, beside, and just below the estimated level of the tumor in an infiltrative manner, versus injections just on top of and beside the tumor as performed for group 1. **Results:** The rates of IM SN visualization were 4.9% (4/82) for group 1 and 23.0% (14/61) for group 2 ( $P < 0.003$ ). IM SNs were hotter in group 2 than in group 1. The total number of IM SNs detected per patient was also higher for group 2 than for group 1: 2.1 and 1.2, respectively. In group 2, patients with small breasts had an IM SN visualization rate of 46.2%; those with medium breasts, 21.1%; and those with large breasts, 0% ( $P < 0.017$ ). In group 2, primary lesions located medially had a higher rate of IM SN visualization than did lesions located laterally: 38.9% (7/18) and 16.2% (6/37), respectively ( $P = 0.066$ ). Dose was not a statistically significant factor within group 2 or group 1 when comparing IM SN visualization rate for doses above or below the mean or median. **Conclusion:** Modification of just these 2 factors resulted in a striking change in our IM SN detection rates. The injection depth was the most important factor. Breast size had a marked effect on the probability of detecting IM SNs. This suggests that the variation in detection rates reported in the literature could be at least partly dependent on variations in these factors, among others. Many surgeons do not routinely harvest IM SNs, but information about their presence can potentially alter treatment decisions.

**Key Words:** internal mammary; sentinel node; lymphoscintigraphy; breast

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**T**he importance of the detection of internal mammary (IM) sentinel nodes (SN) during lymphoscintigraphy is controversial in regard to staging and managing breast cancer. Should IM SNs be harvested at all to potentially more accurately stage the disease, or should treatment be altered if IM SNs are present but not harvested? Because the issues are not fully resolved, we have elected to retain perilesional injections as part of our hybrid combination-injection technique.

Injections into the skin above the tumor and at the areolar cutaneous junction, rarely, if ever, allow visualization of IM SNs detected with the gamma camera or handheld probe (1–4). Those wishing to visualize and harvest IM SNs need to perform intralesional or perilesional injections. However, even with perilesional injections, the reported rates of IM SN visualization vary significantly. Our experience has been an IM SN visualization rate of 3%–5% with perilesional injections. This is lower than seen by other authors, who have reported rates up to 45% or even greater (4,5). Our perilesional injections were part of an evolving hybrid combined-injection technique that sought to increase SN activity levels with additional booster dermal injections, especially useful for next-day surgery protocols (4), while attempting to avert the controversy of congruence and IM SNs by “covering all bases.” This hybrid technique included perilesional injections followed immediately by intradermal injections above the tumor or injections at the areolar cutaneous junction to augment SN activity from the original perilesional injections (4). We noted in the course of refining our perilesional-injection technique that a sudden increase in IM SN visualization rate occurred. This prompted us to search for factors that could account for the sudden increase. The only factors that changed in the newest protocol were an increased perilesional dose for next-day surgery and an alteration in the injection technique to extend the injection zone to include the tissues just beneath the tumor. Large breast size has been associated with decreased SN visualization in the axilla. A similar effect was noted for the rate of IM SN visualization in our study.

## MATERIALS AND METHODS

A retrospective review of 82 group 1 patients with successful visualization of axillary SNs was performed and compared with 61 consecutive group 2 patients using the new injection protocol. As long as the location of the primary lesions could be reasonably determined, lymphoscintigraphy was performed for both groups. The methods used to guide injections included palpation, lumpectomy or biopsy sites, wire localization, or ultrasound.

### Group 1

Group 1 patients were injected with  $^{99m}\text{Tc}$ -sulfur colloid (SC) using a high-specific-activity preparation (6). The injection set consisted of 1–3 perilesional injections of filtered SC, generally at a depth of just on top of the tumor and its surrounding tissues, in a total volume of 3 mL. The mean dose was 5.37 MBq (145  $\mu\text{Ci}$ ). All doses were corrected for residual activity. This was followed immediately by a set of 1–2 intradermal injections of filtered SC above the lesion in a total volume of 0.8 mL. Early imaging was performed, and an additional injection was performed consisting of a single dose of filtered SC at the areolar cutaneous junction, in a volume of 0.8–1.0 mL. The total combined mean dose for injections into the skin above the tumor and at the areolar cutaneous junction was 10.1 MBq (274  $\mu\text{Ci}$ ). We previously reported the areolar-cutaneous-junction injection technique (which we gave the name *LymphoBoost*) as a highly efficient method to augment SN activity from perilesional injections for same- and next-day surgery (4). Dynamic imaging was performed throughout the study for both groups for most perilesional injections and all subsequent areolar-cutaneous-junction injections, which were performed within 20–120 min after the initial perilesional injections. Anterior and lateral/oblique images were obtained at the very end of the study. The patient's body was outlined using a  $^{57}\text{Co}$  sheet source. The patient was marked with indelible ink indicating the location of the SN or SNs using the anterior and lateral/oblique projections. Scatter-reducing gamma camera energy window settings, camera-based triangulation methods, breast displacement maneuvers, and other techniques to optimize the study were used for both groups (4). Regions of interest were drawn around the IM SNs for both groups, and counts obtained over 60 s were noted. A topical anesthetic was applied to the skin before the start of the study for pain control in both groups (EMLA cream: lidocaine 2.5% and

prilocaine 2.5%; Astra Pharmaceuticals, L.P.). For additional pain control, lidocaine was also added to the syringes (0.1 mL of 2% solution) that were used for dermal and LymphoBoost injections, and mild massaging of the breast was performed on both groups for all injection sets. All injections were carefully performed to avoid erroneously labeling contamination as an IM SN.

### Group 2

For group 2 as a whole, activity in the perilesional  $^{99m}\text{Tc}$ -SC injections was increased to a mean of 14.5 MBq (392  $\mu\text{Ci}$ ). The increase was greater in those patients scheduled for next-day surgery protocols, to offset decay. In addition, the perilesional-injection technique was altered to additionally include injecting just beneath the estimated level of the tumor in a more infiltrative manner, as well as just above the surface of the tumor and beside the tumor as performed on group 1. The intradermal injections above the tumor were consolidated into an injection at only the areolar cutaneous junction, with a mean dose of 9.9 MBq (267.8  $\mu\text{Ci}$ ). This decision was based on the observation from the previous group 1 patients that injections at the areolar cutaneous junction produced the desired effect of SN augmentation much more efficiently than intradermal injections above the tumor (4). Other parameters were the same for both groups, including use of anesthesia, mild massage after injections, the injected volume, and the preparation and filtration of the  $^{99m}\text{Tc}$ -SC. Data on breast size and the location of the primary lesion were obtained for group 2 patients from the clinical lymphoscintigraphy data sheet filled out by the referring clinicians and updated by the nuclear medicine physicians performing the injections. Data on breast size were not available for group 1 patients. These data were correlated with the frequency of IM SN visualization.

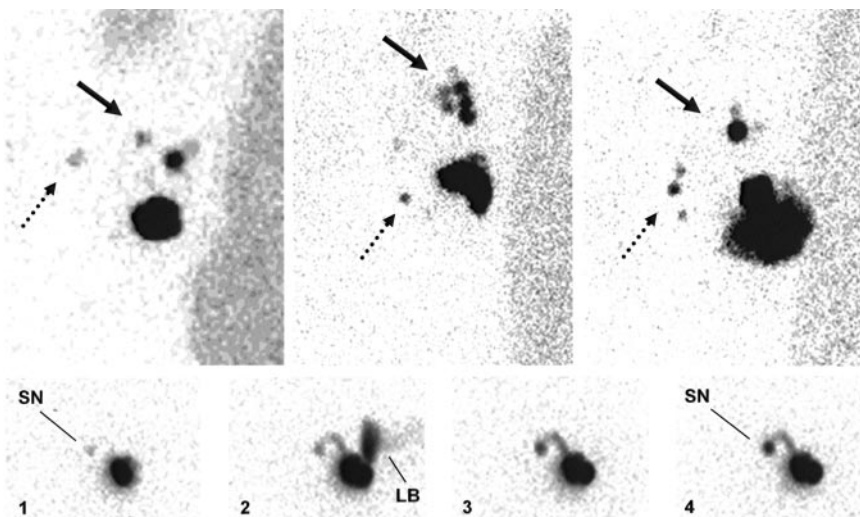
### Statistical Analysis

For comparison of the frequency of IM SN visualization between groups and in relation to dose, primary lesion location, and breast size, the  $\chi^2$  or Fisher exact test was used for statistical analysis.

## RESULTS

Examples of patients with IM SNs are presented in Figure 1. It shows the wide variation that can be present in IM SN

**FIGURE 1.** (Top) Anterior end of study views in 3 different patients: IM SNs (dashed arrows) and axillary SNs (solid arrows). (Bottom) 8-min sequence of lateral views. First frame shows SN from perilesional injection. Second frame shows injection (activity in syringe) at areolar cutaneous junction. Rapid rise in SN activity levels in subsequent frames is noted. Inverted J pattern is seen from upward tenting of lymphatic channels due to raised arm position (fourth frame). LB = LymphoBoost.



**TABLE 1**  
Results for Group 1 and Group 2

Group	No. of patients	IM-positive patients	Total IM SNs	Mean counts per node*
Group 1	82	4 (4.9%)	5 (1.2 IM/patient)	16.6
Group 2	61	14 (23.0%) <sup>†</sup>	30 (2.1 IM/patient)	26.4

\*Corrected for perilesional dose.  
<sup>†</sup> $P = 0.0013$  ( $\chi^2$ );  $P = 0.0030$  (Yates-corrected  $\chi^2$ ).

intensity, position, and number, as well as the dramatic effect of areolar-cutaneous-junction injections on SN counts originally derived from perilesional injections.

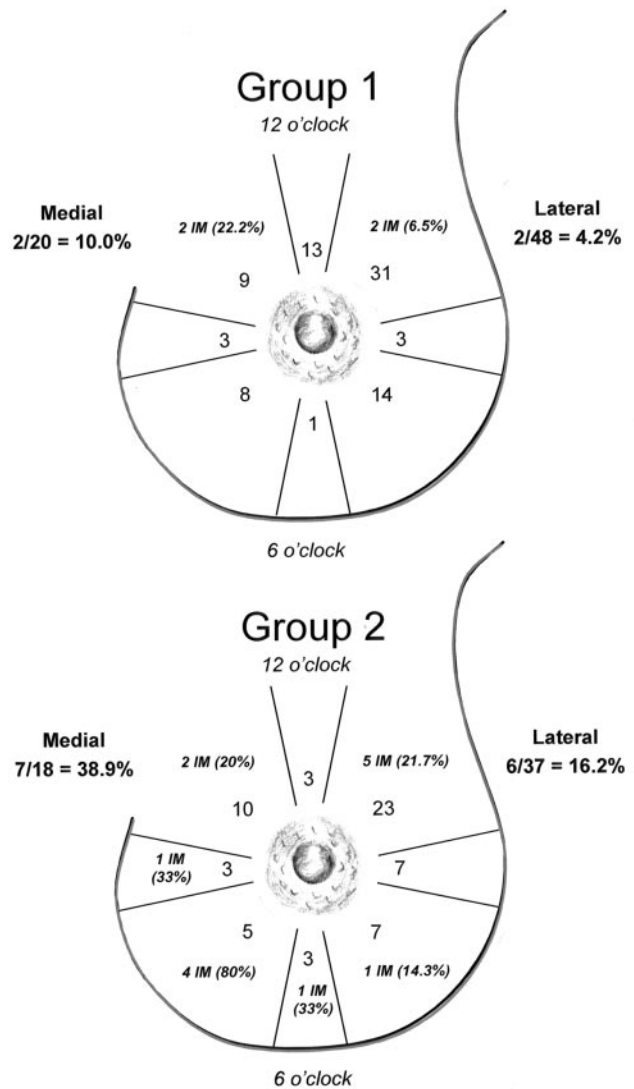
In group 1, the IM SN was visualized in 4 of 82 patients (4.9%). In 1 patient, 2 IM SNs were noted. In group 2, the IM SN was visualized in 14 of 61 patients (23.0%). Of those 14, 5 had 1 IM SN detected, 3 had 2 IM SNs detected, 5 had 3 IM SNs detected, and 1 had 4 IM SNs detected. When the groups as a whole were compared, the difference in IM SN visualization rate between groups was significant (Table 1). The mean relative count per IM SN corrected for perilesional dose for both groups is depicted in Table 1. It is higher for group 2 patients as a whole: 16.6 for group 1 versus 26.4 for group 2. More IM SNs were seen per patient in the second group: 1.2 for group 1 versus 2.1 for group 2.

Breast size versus the number of IM SN-positive patients for a specific size is depicted in Table 2. In group 2, a clear trend is noted, with IM SNs much more likely to be visualized in women with smaller breasts: 46.2% (6/13) for small breasts, 21.1% (8/38) for medium breasts, and 0% for large breasts (0/10) ( $P < 0.017$ ). The location of primary lesions in the breasts for both groups and the number of IM SNs associated with the location of the primary lesion are depicted in Figure 2. In group 1, there was a 10% rate of IM SN visualization when the primary lesion was clearly medial (2/20) and 4.2% when clearly lateral (2/48) ( $P = NS$ ). In group 2, the rate of IM SN visualization was 38.9% (7/18) for clearly medial lesions and 16.2% (6/37) for clearly lateral lesions ( $P = 0.066$ , Fisher exact test). The few lesions at the 12- and 6-o'clock positions were not included in the analysis ( $n = 14$  for group 1 and  $n = 6$  for

**TABLE 2**  
Breast Size and IM SN rate for Group 2

Parameter	Group 2 breast size		
	Small	Medium	Large
No. of patients	13	38	10
No. of IM SNs+	6	8	0
% IM SNs+	46.2	21.1	0

$P < 0.009$   $\chi^2$  trend;  $P = 0.017$  Fisher exact test (small vs. large).



**FIGURE 2.** Numeric values immediately surrounding nipple indicate location of primary lesions in breast for both groups. Bold text indicates number of IM SN-positive patients for any particular breast location. Text outside breast indicates rate of IM SN visualization for clearly medial or lateral primary lesions, excluding 12- and 6-o'clock positions.

group 2), as the position to place them into was easily influenced by minor breast displacement or position differences. Group 2 also showed differences in the frequency of IM SN visualization depending on whether the primary lesion was clearly in the lower or upper portion of the breast—6 of 15 (40.0%) versus 7 of 36 (19.4%) for inferior and superior lesions, respectively (excluding 3- and 9-o'clock lesions,  $n = 10$ )—but these differences did not reach statistical significance. In group 2 patients with clearly medial or lateral lesions, the frequency of IM SN visualization was 50% and 44% in the small breast and 42% and 10% in the medium breast for medial and lateral lesions, respectively ( $P = NS$ ).

**TABLE 3**  
Intergroup Stratification by Dose

Group	Dose < median	Dose > median	<i>P</i>	Dose < mean	Dose > mean	<i>P</i>
Group 1	1/41	3/41	NS	1/45	3/37	NS
Group 2*	7/30	6/30	NS	7/29	7/32	NS

\*One patient at median value.

NS = not statistically significant by Fisher exact test.

Table 3 shows the rate of IM SN visualization for perilesional doses above and below the mean and median for both groups. Though there were 3 times as many IM SNs seen with doses above the mean and median in group 1, the differences in the rate of IM SN visualization did not reach statistical significance in either group.

## DISCUSSION

During the middle of the last century and beyond, IM SN dissection was routinely performed as part of extended radical mastectomy. During the 1980s, IM SN dissection had fallen from favor and was viewed as having low diagnostic value or limited therapeutic benefit (7). Both IM SN irradiation and dissection were increasingly viewed as providing no effective increase in survival based on analysis of patient outcome studies, though the current role of radiation is more favorably regarded (7). A poorer prognosis in patients with both IM SN and axillary disease continues to be suggested.

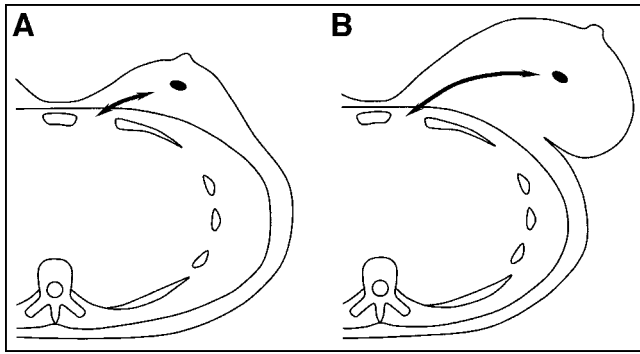
The debate on IM SNs has been intensified again with the advent of lymphoscintigraphy and SN harvesting. Reasonable arguments can be presented that the only way to be truly "accurate" in staging the disease is to include harvesting of IM SNs when they are detected during lymphoscintigraphy or with the probe. Information from this increased accuracy in staging could in theory be used to further divide patients into those with positive IM SNs and a negative axilla, who might benefit from chemotherapy or parasternal irradiation, and those with a negative axilla and parasternal regions, for whom a decision to refrain from chemotherapy or irradiation therapy might be made (8). A review several years ago of national practice patterns suggested that most surgeons in the United States did not view the effort and morbidity associated with IM SN harvesting as worthwhile; 72% of surgeons in that survey did not routinely remove IM SNs showing drainage (9). Nevertheless, the issue is extremely controversial on many fronts, with proponents on both sides of the fence (8,10–14). Indeed, there have been several reports of IM SNs occasionally containing tumor in the absence of axillary disease (15,16). In a 1,273-patient study using "traditional" perilesional-injection techniques, in only 2.4% of patients was the IM SN detected with the probe, but of these, 10% had IM SN disease exclusively, with no axillary involvement (13). This would suggest that exclusive IM SN disease (negative axilla) is rare when considering

all SN biopsy patients overall (0.24%). Yet, when considering the subgroup of patients in whom IM SNs are found, the frequency of exclusive IM SN disease is much higher (10%) and could change the patient's stage if or when these IM SNs are harvested.

In recent publications from Europe, an IM SN visualization rate of 65.6% for inner-quadrant lesions and 10% for outer-quadrant lesions was noted using deeper perilesional (subtumoral) injections of nanocolloid below the tumor. These rates were in contrast to a 2.1% and 1% IM SN visualization rate for superficial injections in patients with inner- and outer-quadrant lesions, respectively (17,18). In this same study, 2% of patients with inner-quadrant lesions had a significant change in stage based on the results of IM SN harvesting; that is, in 3.4% of patients whose IM SN nodes were harvested (65.6% of all patients), the IM SNs were the only nodes with disease. An additional 3% of patients with inner-quadrant lesions were restaged upward; that is, in 5.1% of patients whose IM SNs were harvested, disease was detected in the IM SN basin as well as in the axilla (17,18). It also was suggested that when the primary lesion is in the inner quadrants, resection of the IM SNs can be attempted through the same single incision used to remove the primary tumor, with little additional morbidity.

Our results with <sup>99m</sup>Tc-SC appear to demonstrate a similar effect. The depth of perilesional injections and, to a lesser extent, the location of the primary lesion play a role in the rate of IM SN visualization, with a statistically significant difference in IM SN visualization rate demonstrated between groups as a whole: 4.9% for group 1 versus 23% for group 2 ( $P < 0.003$ ). Injection below the lesion is as valid as beside and above the lesion, as drainage can occur anywhere along the sphere surface of the tumor.

Differences within groups based on doses above and below the mean or median values were not statistically significant (Table 3). The effect of breast size on IM SN visualization rate was significant, with almost half the patients with small breasts demonstrating IM SNs whereas no IM SNs were detected in large-breasted women, a striking difference. The smaller the breast size, the higher the chances that IM SNs would be detected (Table 2). This could be explained by distance effects in large breasts (Fig. 3). A lesion in the center of a large breast (and the injected perilesional dose) would be much farther from the chest wall and the deeper lymphatic channels that course to the



**FIGURE 3.** (A) Close proximity (short arrow) of average lesion (black oval) in small breast to IM chain of nodes. (B) Markedly increased distance (long arrow) between average lesion in large breast and IM chain of nodes.

parasternal IM SNs, whereas a lesion in the center of a small breast would be much closer to the chest wall (Fig. 3), that is, an injection site proximity effect.

The location of the primary lesion has been suggested by some to influence IM SN detection, and such an influence could also be explained by a proximity effect. As noted in Figure 2, medial group 2 primary lesions had a higher rate of IM SN visualization ( $P < 0.066$ ). Other investigators have also noted higher rates of IM SN detection when the primary lesion was medially located (13), whereas still others have noted no effect (19).

The effect of breast size on IM SN visualization rate has not been widely described and could represent an important factor for tumor spread in patients with small breasts with primary tumors located anywhere in the breast, that is, regardless of medial or lateral location of the primary tumor. No differences in the high IM SN visualization rate were noted for medial or lateral primary tumors in small breasts in our data; however, this could be secondary to the small number of patients involved.

Though differences within groups based on dose did not reach statistical significance, one could theorize that a higher dose would tend to make more tracer available to the IM SNs by a mass activity effect. This type of effect has been suggested for perilesional injections in respect to axillary SNs (20–22). For similar reasons, a possible threshold effect could explain the low IM SN visualization rate in the group 1 patients when perilesional doses less than the mean were used; at these doses, the noise level of the system could have been a factor (2.2% below the mean, 8.1% above the mean,  $P = \text{NS}$ ) (Table 3).

Factors that have influenced delineation of axillary SNs other than injection location (perilesional vs. surface injections) have included increasing age (20,21,23,24) and large breast size (20,25). Both factors have been associated with decreased visualization of the SN. In addition, excisional biopsy has been associated with reduced rates of SN visualization (20,26), but this effect has not been consistently reported. Lesions in the upper lateral regions of the breast have also been associated with decreased detection of the

axillary SN, possibly from diffusion zone masking of the injection site (27). Massage (28) and a larger dose (20–22) both have been associated with improved detection of the axillary SN. Filtration, injection volume, and fatty breasts (postmenopausal), among others factors, have influenced axillary SN detection, but the exact effects and benefits are controversial (29–33). Most authors agree that smaller particles tend to delineate a greater number of nodes “downstream” from the SN along the lymphatic channels, that is, echelon nodes, as activity passes through the SN to the next node (30).

When one combines the results from this article and others, some of the factors that influence IM SN visualization include medially located primary lesions (13,17,18), injection depth (17,18), breast size, and possibly dose and massage. Leppanen et al. noted that the IM SN was more likely to be visualized in patients who were younger, had a lower body mass index, had primary lesions in lower breast segments, and had a nonpalpable tumor (27). Dermal injections do not delineate the IM SNs to any extent, as has been widely reported by multiple authors (30). In a recent study from Japan by Shimazu et al., there was a higher chance that axillary and IM SNs were going to be involved with tumor when the primary lesion was deep in the breast (34). In addition, it was reported that even areolar injections are capable of delineating IM SNs in those rare instances in which the axillary SNs are extensively replaced (blocked) by tumor (34).

The terms *peritumoral* and *perilesional* are themselves ambiguous. Do injections labeled as such include only laterally placed deposits, or does the tissue space anywhere near the surface sphere of the tumor (including above and beneath) also qualify? The exact technical details of peritumoral injections are sufficiently vague in most reports that variations in methodology could partly account for the variations in IM SN detection rates in the literature. It is easily conceivable that some of the injections could have a significant “subtumoral” component. When lesions are very small, volumes of injection very large, and the exact position of the tumor and needle tip unclear, depositing activity beneath the tumor is certainly possible even if not originally planned.

Could exclusively subtumoral injections replace perilesional injections? Using only subtumoral injections of radiocolloid, only 50% of axillary SNs would have been detected by probe alone, as referenced to the use of intradermal blue dye concurrently (34). This same patient group during lymphoscintigraphy had a 38% IM SN and 70% axillary SN visualization rate. Among patients with visualized IM SNs, only 20% of those with inner-quadrant lesions had axillary SNs visualized along with IM SNs. All patients with SNs visualized both in the IM SN and axillary SN basins had outer-quadrant tumors (34). This is in contrast to the 85% of axillary SNs detected by probe from perilesional injections of radiocolloid in another group in the same study, though perilesional injections of dye were used as a

reference. Nevertheless, the suggestion is that exclusively subtumoral injections (especially in patients with inner-quadrant lesions) could underestimate SNs in the axilla if performed alone. Because metastases can conceivably spread from anywhere along the surface of the tumor, a multidepth perilesional injection (including an injection below the level of the tumor) could provide better overall coverage for SN delineation in the axilla SN and IM SN basins, as would hybrid combination-injection techniques of concurrently administered radiocolloid at subtumoral and intradermal sites.

Radiocolloid administrations at dual injection sites were performed by Roumen et al. but not sequentially on the same day (1). Most other investigators have compared dual-injection techniques using a combination of radiocolloid and dye. Initially, we used a combination of simultaneous perilesional and intradermal radiocolloid injections over the lesion (35). Eventually, we replaced the intradermal injection with an injection at the areolar cutaneous junction while retaining concurrent perilesional injections (4). This hybrid combination-injection technique proved to be an even better method of delivering the radiotracer to the SN, with more of the injected dose reaching the SN, and was especially useful for patients undergoing next-day surgery (Fig. 1). We continue to use perilesional injections to retain the ability to visualize the IM SNs and to increase the probability that the correct nodes are assigned SN status.

## CONCLUSION

The debate over IM SNs as regards both delineation and the eventual disposition of the nodes during surgery is controversial. Until a greater consensus is achieved, measures to delineate them should not be abandoned. Our data suggest that injection depth and breast size are important factors, among others, in determining IM SN visualization and can be explained by a simple proximity effect. Centers wishing to delineate IM SNs should examine their perilesional-injection protocols for adequate injection depth. Injections that extend deeper, to below the lesion, are physically closer to the deeper lymphatic channels that drain into the parasternal nodes and more likely to be taken up by these lymphatics. Realization of the major effect of these factors on IM SN visualization allows more control over the process and could explain some of the difference noted in the literature regarding this issue.

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