

Anatomy and Physiology of Lymphatic Drainage of the Breast from the Perspective of Sentinel Node Biopsy

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The introduction of lymphatic mapping with sentinel node biopsy has evoked a renewed interest in the anatomy and physiology of the lymphatic system of the breast. In an increasing number of hospitals, lymphatic mapping with sentinel node biopsy is an essential component of staging patients with breast cancer.

Several aspects of mammary lymphatic drainage are unclear, causing important differences in the technique of sentinel node biopsy among both nuclear medicine physicians and surgeons. The choice of a certain injection type and the time of scintigraphic imaging or surgery are based on theories about the structure of the lymphatic network, about particle uptake into lymphatic channels, and about lymph flow. The purposes of this article are to review current knowledge on the anatomy and physiology of the lymphatic system of the breast, to translate this into implications for the clinical practice of lymphatic mapping, and to point out areas of controversy.

GENERAL ANATOMY AND PHYSIOLOGY OF THE LYMPHATIC SYSTEM

Lymph is absorbed from the interstitial space into blind-ending lymphatic capillaries. Lymphatic capillaries are 10 to 50 μm in diameter and consist of a single layer of endothelial cells with a discontinuous basement membrane.¹ Overlapping interendothelial junctions function as valves with openings that are 10 to 25 nm wide, permitting the entrance of small particles. Pinocytosis may be responsible for the vesicular transport of larger particles through the endothelium. Collagen filaments an-

chored to the surrounding connective tissue prevent the collapse of lymphatic capillaries.

The filling of lymphatic capillaries can be explained by the osmotic pressure gradient and by fluctuating intraluminal pressures caused by contractions and forward flow of lymph.^{1,2} Lymph formation, active contractions, and external pressures generate lymph flow. Peristalsis occurs at 10 to 15 contractions per minute by longitudinal and circular layers of smooth muscle in the media. Peristalsis is regulated by filling pressure, humoral mediators (serotonin, prostaglandins), and neural mechanisms.³ A transmural distending pressure of 2 to 4 cm H₂O is required for these contractions, which spread at a velocity of 4 to 5 mm/s. The flow is unidirectional because of the lymphatic valves. Sustained external pressure reduces the flow speed, and intermittent external pressure enhances it.

Lymphatic capillaries drain into collecting lymphatic vessels, which in turn drain into a lymph node. The afferent vessels drain into a marginal sinus and subsequently into medullary sinuses between the germinal centers. These centers contain large numbers of phagocytic cells that accumulate protein colloids, such as the radiolabeled tracers, but not vital dyes. The plexus within the lymph node drains to the efferent lymphatic vessel, which joins the artery and vein in the hilum. Direct drainage of the marginal sinus into the efferent vessel also exists.

Ludwig⁴ demonstrated two main types of relation between lymph vessels and lymph nodes. In the first type, the lymph node receives lymph from the afferent duct, filters it, and then discharges it into the efferent channel. In the other type, the lymphatic vessel runs through the lymph node or over its surface without discharging its contents into that node (Fig. 1). This means that the first lymph node to which the afferent channel runs is not always directly at risk of harboring tumor cells, which may be one of the explanations of a false-negative sentinel node. The lymph of the entire body is collected in

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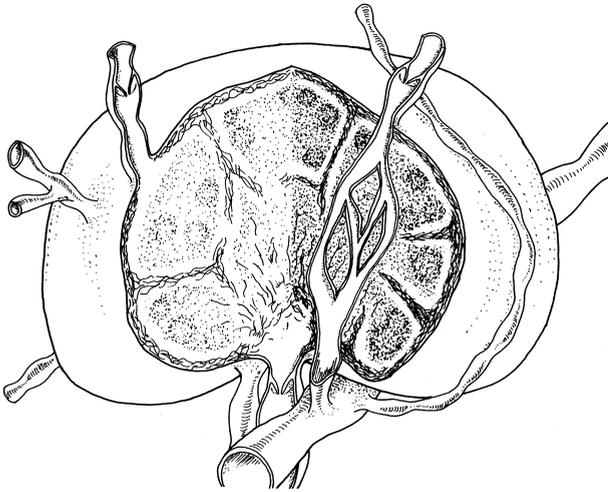


Figure 1. The different relations between lymphatic vessels and lymph nodes according to Ludwig.⁴ Afferent lymphatic ducts on the left discharge their contents into the marginal sinus. One lymphatic duct runs through the node on the right and another over its surface, bypassing the germinal centers.

several large trunks that drain into the venous circulation. The lymph flow of the entire body amounts to 2 to 4L/d at rest, but varies with a diurnal rhythm and according to physiologic needs.^{3,5}

LYMPHATICS OF THE BREAST

The anatomy of the lymphatic system of the mammary gland has been studied for several centuries. The history of the lymphatic system of the breast has been described in detail by Haagenen.⁶ At the end of the 18th century, Cruikshank⁷ and Mascagni⁸ independently described two main lymphatic drainage routes of the breast: an external system and an internal system. The external route from the nipple, the integuments, and the lactiferous tubules was shown to run to the axilla. The internal route from the dorsal part of the breast was thought to perforate the pectoral and intercostal muscles. Within the intercostal spaces, these lymphatics were seen to subsequently join the plexus coming from the liver and the diaphragm and then to run on each side of the internal mammary artery and veins.

In the 1830s, Sappey⁹ performed a more thorough study with mercury injection into the lymphatic channels. He concluded that most breast tissue drains centripetally into the subareolar plexus and then on to the axilla. These findings were later confirmed by Rouvière¹⁰ and Grant and associates.¹¹ Around the end of the 19th

century and the beginning of the 20th century, anatomists gained more knowledge of the mammary lymphatics by using postmortem injections of various tracer fluids. Evidence was presented that Sappey's concept⁹ was incomplete and that additional lymphatic routes exist.⁶

A Dutch physician named Camper was the first to identify lymphatic drainage to lymph nodes along the internal mammary vessels in 1770.¹² These nodes extend upward from the fifth intercostal space to the retroclavicular glands. Injection studies with vital dyes showed that the internal mammary nodes receive their lymph from deep lymphatics.^{6,13,14} These lymphatics arise from the breast lobules, leave the posterior surface of the breast, and pass through the pectoral and intercostal muscles to reach the internal mammary chain (Fig. 2). Knowledge increased in the 20th century by using new techniques such as autoradiography of surgical specimens with radioisotopes. In the 1950s, colloidal gold 198 with a particle size of about 5 nm was injected into the breast parenchyma. On the basis of this technique, Turner-Warwick¹⁴ stated that the ipsilateral axillary lymph nodes receive more than 75% of the lymph of the breast. Hultborn and colleagues,¹⁵ Vendrell-Torné and associates,¹⁶ and Turner-Warwick¹⁴ confirmed that the ipsilateral internal mammary chain undoubtedly represents another important pathway of lymph drainage from both the lateral and medial halves of the breast.

Other less common drainage routes have been described. Lymphatics sometimes pass through lymph nodes on their way to the axilla or internal mammary chain, so-called interval nodes (Fig. 2). These are the interpectoral nodes as described by Grossman¹⁷ and Roter¹⁸ or lymph nodes in the breast parenchyma (intramammary or paramammary nodes) as observed by Cruikshank⁷ and Gerota.¹⁹ Mornard²⁰ first described occasional direct drainage from the breast parenchyma to the supraclavicular nodes. Retrosternal lymphatic drainage to the contralateral internal mammary chain occurs sporadically. Subcutaneous drainage to the contralateral axilla is unlikely to occur unless the ipsilateral drainage is impaired by lymphatic obstruction caused by tumor growth, previous surgery, or irradiation.²¹ Blockage of normal lymph flow can also cause drainage in a retrograde direction to the liver through the internal mammary chain.⁶ The posterior intercostal lymph nodes have been shown to receive lymph from the breast in a small

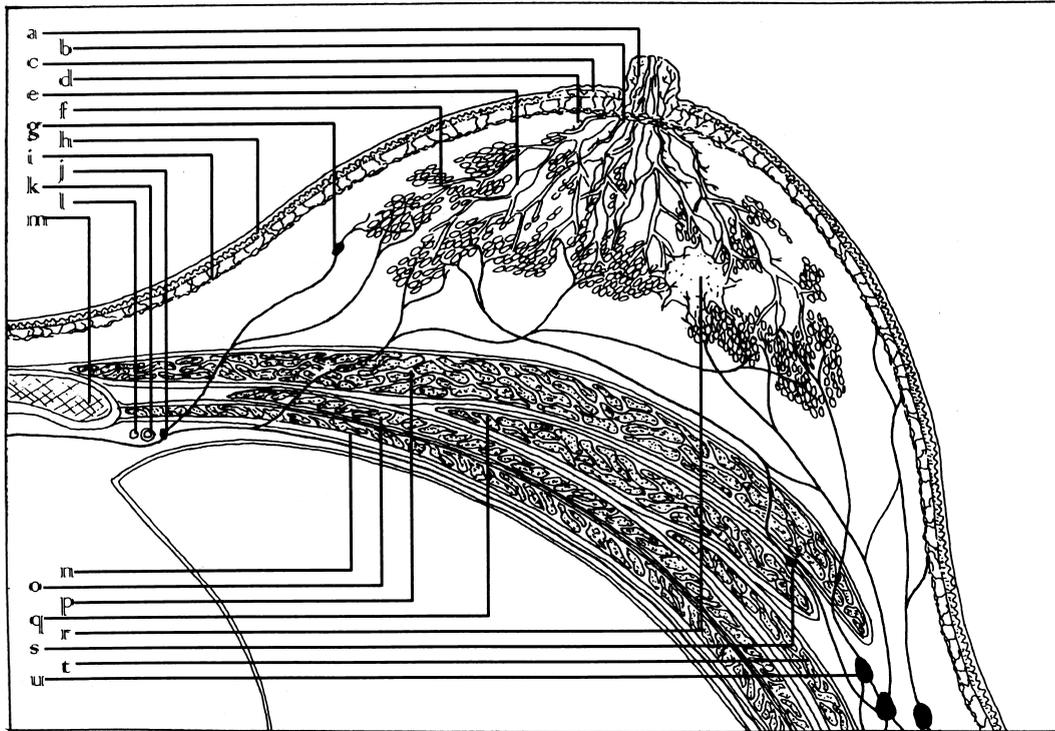


Figure 2. The arrangement of the lymphatics of the breast schematically drawn in a transverse plane. Lymphatic capillaries arise from the breast lobules, leave the posterior surface of the breast, and run to the axillary, internal mammary chain, and interpectoral lymph nodes accompanying perforating blood vessels. a, nipple lymphatics; b, subareolar lymphatic plexus; c, areolar lymphatics; d, collecting lymphatic trunks along the lactiferous ducts; e, lactiferous sinus; f, lactiferous ducts; g, intramammary lymph node; h, superficial dermal lymphatics; i, subcutaneous lymphatic plexus; j, internal mammary chain node; k, internal mammary artery; l, internal mammary vein; m, sternum; n, internal intercostal muscle; o, external intercostal muscle; p, major pectoral muscle; q, minor pectoral muscle; r, breast tumor; s, interpectoral lymph node; t, anterior serratus muscle; u, axillary lymph node.

proportion of patients.¹⁴ Caplan²² described drainage to the anterior intercostal nodes.

COURSE OF LYMPH FLOW

It is uniformly accepted that drainage from the breast can occur to lymph nodes at a number of different sites. There is also consensus that the axilla is the main basin for lymphatic drainage from the breast. No agreement exists about the course of lymph flow between the breast tissue and the nodal basins. Turner-Warwick¹⁴ suggested that the lymphatics run within the breast parenchyma and drain directly to the axilla. He stated that the importance of the subareolar plexus in the resting breast parenchyma had been overemphasized by Sappey⁹ and Rouvière¹⁰ and he indicated why earlier investigators were misled.¹⁴ Filling of the lactiferous system with tracer by random injections and observations in a lactating breast and infant cadavers had been confounding

factors. Spratt²³ stated that the lymphatics paralleling the lactiferous ducts are equivalent to the vertical lymphatics that connect the subepithelial and subdermal lymphatics. Their valve structure may be similar, and lymph flow will be from superficial to deep. In a study of mastectomy specimens, we never found lymphatic channels from the tumor pass through the subareolar plexus before heading to the axilla.²⁴ Our lymphoscintigraphy experience points in the same direction. After injection of technetium-99m (^{99m}Tc)-labeled nanocolloid into the breast carcinoma, a lymphatic channel is typically depicted running a direct course from the tumor to the axilla (Fig. 3). Rarely, a curved lymphatic channel with an indirect course is visualized, but there is certainly no constant route through the subareolar plexus (Fig. 4). Although Sappey's view⁹ of drainage of the breast parenchyma through a subareolar plexus to the axilla is supported in the current literature,^{25,26} Turner-Warwick,¹⁴

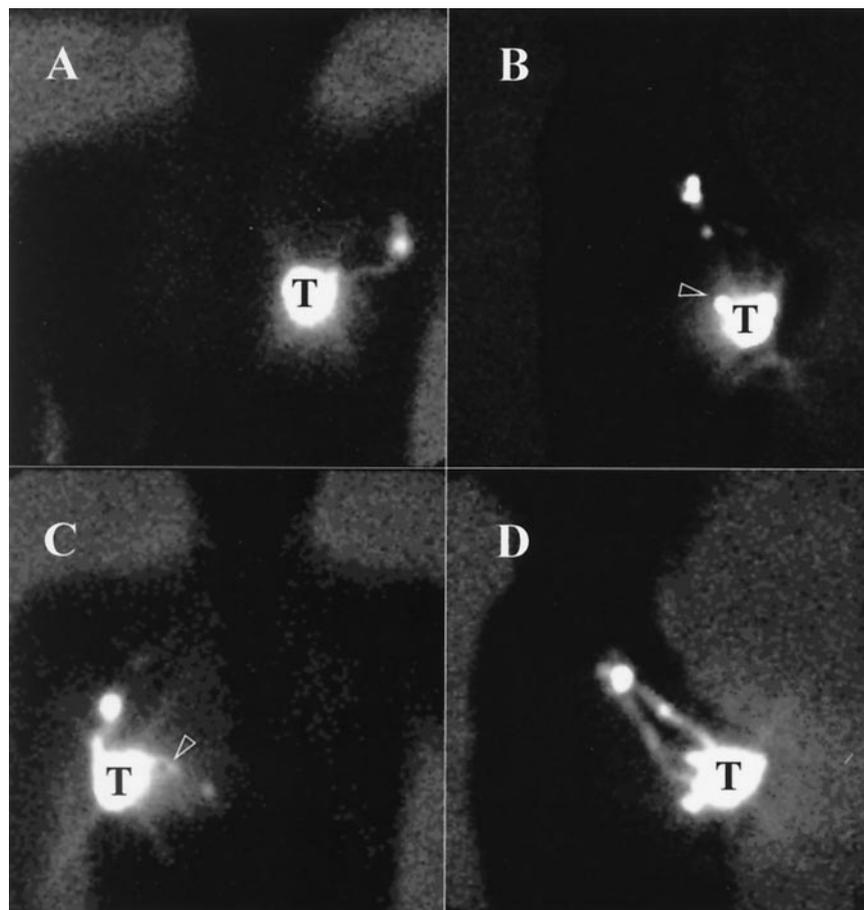


Figure 3. The lymphatic route between the tumor and the lymph node has a direct course in most patients. (A) Lymphoscintigraphy using ^{99m}Tc -nanocolloid with direct drainage from the tumor (T) in the upper medial quadrant to an axillary lymph node. (B) Three separate lymphatics to three axillary sentinel nodes, each running on a different level, are visualized in a patient with a tumor in the lower lateral quadrant. Another sentinel node is situated in the breast tissue just lateral to the tumor (arrow). (C and D) Anterior and right lateral views of three lymphatic ducts from a central tumor to an internal mammary chain node (arrow) in the fourth intercostal space and to two axillary sentinel nodes.

Spratt,²³ and we believe that direct drainage from the breast to the axilla is the rule.

CLINICAL IMPLICATIONS

Tracer uptake and lymph flow

The structure of the lymphatic system has implications for the choice of labeled colloid. Colloids with a small particle size (eg, antimony trisulfide, 3 to 12 nm) can rapidly pass the openings of the interendothelial junctions (10 to 25 nm) and often allow one to visualize the lymphatic channels leading directly to the sentinel node. A disadvantage of these small particles is that phagocytic cells in a sentinel node often cannot trap them all, so that some of the tracer moves on to lodge in secondary nodes.

Larger particles (eg, unfiltered sulfur colloid, 50 to 1,000 nm) enter the lymphatic channels more slowly through pinocytosis. The channel is visualized less often, but the tracer travels on to secondary nodes less frequently. Even larger particles do not migrate from the injection site. The optimum size is probably between 10 and 100 nm.^{27,28}

The timing of scintigraphy must be chosen carefully because lymphatic flow and absorption of tracer are highly variable. Early static images at 1 hour after injection fail to identify sentinel nodes in patients with a slow tracer uptake and flow. Late images 18 to 24 hours after injection depict all radioactive nodes, but discrimination between first- and second-tier nodes is more diffi-

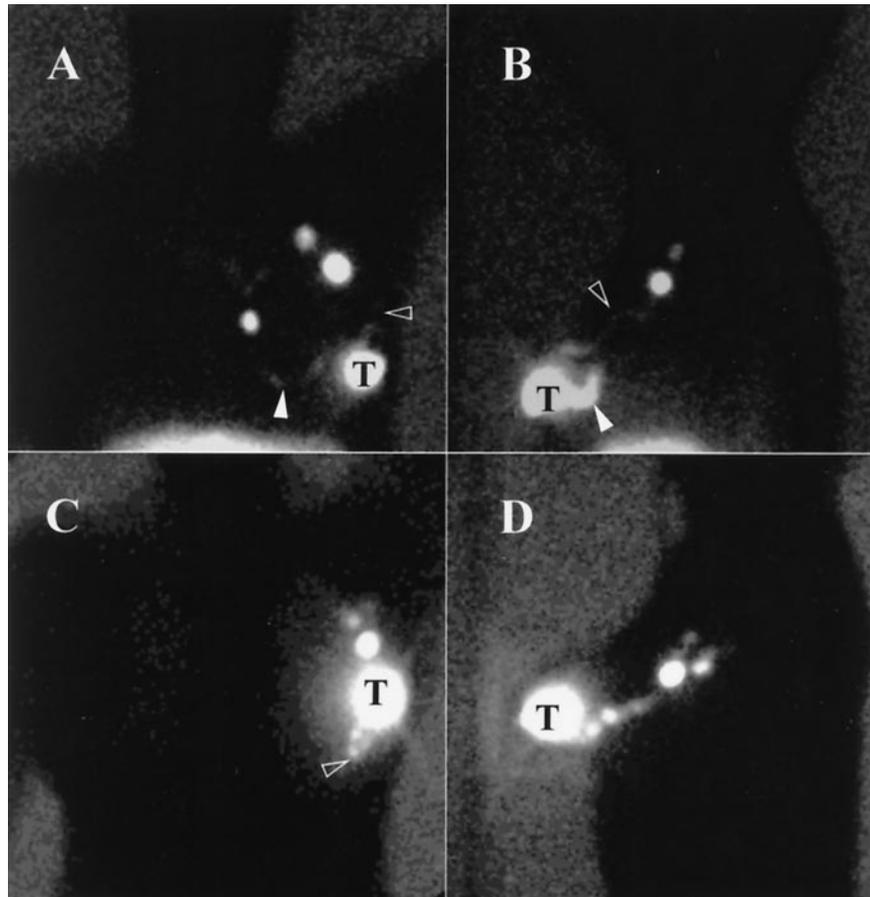


Figure 4. In some patients, an indirect drainage pattern is visualized with a highly variable course. (A and B) Anterior and left lateral views show one lymphatic vessel (open arrow) originating at the medial-anterior surface of a tumor (T) in the subareolar area and running with an S-shaped course to an axillary lymph node. Another lymphatic channel (white arrow) arises from the posterior surface of the tumor, runs to the deep part of the breast, and drains into an internal mammary chain node. (C and D) Anterior and left lateral views of a lymphatic channel running from the medial-posterior surface of a lower-lateral quadrant tumor to a sentinel node in the axilla.

cult at this time because there is not visualization of lymphatic channels. The sequential pattern of filling of the lymphatic ducts and stepwise uptake of tracer in the first- and second-echelon nodes can be visualized with multiple scintigraphic examinations between a few minutes and a few hours after injection, as used by Sandrucci and Mussa,²⁹ Veronesi and associates,³⁰ Schneebaum and colleagues,³¹ Canavese and coworkers,³² and Doting and colleagues.³³

Knowledge of the physiology makes it clear that lymph flow is guaranteed by a delicate balance between pressures inside and outside the lymphatic vessel. This has repercussions for the optimum volume of tracers. The volumes of radioisotope injection described in the

literature range from 0.2 to 16mL (Tables 1 and 2). These numbers differ by a factor of 80, and this illustrates that we do not know the optimum volume. The volumes of blue dye injection have a smaller range of 0.5 to 7.5 mL (Table 2). Investigators who use a small volume argue that they do not want to disturb the physiology of lymph flow and that they want to avoid the risk of visualizing non-sentinel nodes. A small tracer volume does not disturb the pressure equilibrium and results in 85% to 91% visualization, as shown by several investigators (Tables 1 and 2). The sentinel node was visualized in 75 of our last 76 patients (99%) with a small 0.2-mL volume of the tracer.

Investigators using the larger volumes do want to

Table 1. Sentinel Lymph Node Biopsy Techniques in Breast Cancer: Studies Using Radioactive Isotope

| First author | n | Type of colloid | Volume (mL) | Dose (mCi) | Injection site | Scintigraphy visualization (%) | Drainage IMC (%) | Identification rate (%) | False-negative rate (%) |
|--------------------------|-----|-----------------|-------------|------------|----------------|--------------------------------|------------------|-------------------------|-------------------------|
| Krag ³⁴ | 22 | SC | 0.5 | 0.4 | PT | ND | NS | 82 | 0 |
| Schmidt ³⁵ | 30 | SCf | 16.0 | 0.8 | PT | 90 | NS | 97 | 0 |
| Mertz ³⁶ | 32 | SCf | 0.4 | 0.05 | PT | 88 | NS | 97 | 10 |
| Offodile ³⁷ | 41 | DX | 0.5 | 1.0 | IT | ND | NS | 98 | 0 |
| Miner ³⁸ | 41 | SC | 4.0 | 1.0 | PT | ND | 5 | 98 | 14 |
| Mertz ³⁶ | 47 | SCf | 0.4 | 0.05 | SA | 85 | NS | 98 | 0 |
| Crossin ³⁹ | 50 | SC | 4.0 | 1.0 | PT | ND | NS | 84 | 13 |
| Rubio ⁴⁰ | 55 | SC | 4.0 | 1.0 | PT | ND | 2 | 96 | 12 |
| Snider ⁴¹ | 80 | SC | 4.0 | 1.0 | PT | ND | 1 | 88 | 7 |
| Roumen ⁴² | 83 | NC | 2.0 | 1.6 | PT | 80 | 11 | 69 | 4 |
| Sandrucchi ²⁹ | 84 | HA | 0.25 | 0.1 | SD | 90 | NS | 89 | 6 |
| Reuhl ⁴³ | 96 | NC | 0.5 | 1.5 | PT | 91 | 2 | 80 | 18 |
| Rull ⁴⁴ | 100 | LS | 2.0 | 0.3 | PT | NS | 17* | 97 | 5 |
| Borgstein ⁴⁵ | 130 | NC | 4.0 | 1.1 | PT | 89 | 16 [†] | 94 | 5 |
| Veronesi ³⁰ | 163 | HA | 0.2 | 0.2 | SD | NS | NS | 98 | 5 |
| Zurrada ⁴⁶ | 376 | HA | 0.2 | 0.2 | SD/PT | NS | 4 | 99 | 7 |
| Krag ⁴⁷ | 443 | SC | 4.0 | 1.0 | PT | ND | 4 [‡] | 93 | 11 |

*Also drainage to the intramammary nodes (4%).

[†]Also drainage to the supraclavicular nodes (2%).

[‡]Also drainage to the interpectoral (0.7%), intramammary (0.2%), and supraclavicular sentinel nodes (0.2%).

DX, dextran; HA, human albumin colloid; IMC, internal mammary chain; IT, intratumoral; LS, lymphoscint; NC, nanocolloid; ND, not done; NS, not stated; PT, peritumoral; SA, subareolar; SC, sulfur colloid; SCf, filtered sulfur colloid; SD, subdermal.

change the physiology; they intend to increase the lymph flow and increase the chance of visualizing a lymph node. Krag and associates⁶⁰ reported a higher identification rate when the volume was increased from less than 3 mL to more than 8 mL, but this study was not performed in a randomized fashion, and results are likely to improve with increasing experience no matter what technique is used. Schmidt and colleagues³⁵ identified the sentinel node in 90% of patients with the combination of a high volume (16.0 mL) of filtered sulfur colloid and massaging of the injection site (Table 2). From a physiologic point of view, high volumes may result in sustained external pressure exceeding the transmural distending pressure required for uptake of the tracer and lymph flow. On the other hand, the anchoring filaments pulling on the duct cells as a result of interstitial fluid expansion may widen the clefts between ductal cells, facilitating the entry of particles.⁶⁰ A disadvantage of a large volume is an increased diffusion zone at the injection site, which hampers scintigraphy and probe detection of nodes nearby.⁶¹ Although tracer volume is a subject of controversy, detection rates seem good with both smaller and larger volumes of tracer fluid.⁶²

The amount of radioactivity that accumulates in a

lymph node depends not only on particle size and possibly the injected volume, but also on a number of other tracer variables such as radioactivity dose, the number of particles, and their surface characteristics and stability. Other factors can influence the pattern and speed of lymph drainage. Valdés Olmos and coauthors⁶³ found that the age of the patient was a significant factor for sentinel node identification. Humoral mediators and neural mechanisms play a role, but these factors are beyond our control. Anesthetic drugs may hamper the uptake of blue dye. Halothane has been shown to decrease the lymph flow rate by 25% to 59%.¹ Hydration of the patient may be a factor. Patients typically come to the operating room in a poorly hydrated state. It is conceivable that administration of ample fluids before the tracer is injected increases the likelihood of finding a sentinel node. Gentle massaging of the injection site is an important maneuver because intermittent external pressure stimulates lymph flow.⁶⁴

Injection site

As mentioned previously, different routes of tracer administration are being used in the sentinel node procedure for breast cancer. The injection can be periareolar,

Table 2. Sentinel Lymph Node Biopsy Techniques in Breast Cancer: Studies Using Radioactive Isotope and Blue Dye

| First author | n | Type of colloid | Volume of isotope | | Injection site of isotope | Scintigraphy visualization (%) | Drainage IMC (%) | Dye | Volume of dye (mL) | Injection site of dye | Identification rate (%) | False-negative rate (%) |
|---------------------------|-----|--------------------|-------------------|-------|---------------------------|--------------------------------|------------------|-----|--------------------|-----------------------|-------------------------|-------------------------|
| | | | (mL) | (mCi) | | | | | | | | |
| Schneebaum ³¹ | 30 | RC | NS | 1.6 | NS | 93 | NS | PB | 2.0 | NS | 93 | 22 |
| Borgstein ²⁵ | 33 | NC | NS | 1.1 | PT | NS | NS | PB | 0.5 | ID | 100 | 0 |
| Lieberman ⁴⁸ | 33 | SC | 4.0 | 0.3 | PT/ID | 36 | 3 | IS | 4.0 | PT | 91 | 0 |
| Barnwell ⁴⁹ | 42 | SC ^f | 1.0+3.0* | 1.0 | PT | ND | 0 | IS | 3.0+1.0 | PT | 90 | 0 |
| Imoto ⁵⁰ | 58 | HA/TC | 2.5 | 1.1 | SD | 65 | 7 | IC | 5.0 | SD | 93 | 8–12 |
| O'Hea ⁵¹ | 59 | SC | 4.0 | 0.3 | PT | 75 | 11 [†] | IS | 4.0 | PT | 93 | 13 |
| Chatterjee ⁵² | 60 | NC | NS | 0.4 | PT | ND | 2 | PB | 1.0 | PT | 97 | 5 |
| Albertini ⁵³ | 62 | SC ^f | NS | 0.4 | PT | ND | 0 | IS | NS | PT | 92 | 0 |
| van der Ent ⁵⁴ | 70 | NC | 4.0 | 10.0 | PT | 97 | 34 | PB | 0.5–2.0 | PT/ID | 100 | 4 |
| Jaderborg ⁵⁵ | 79 | SC | 2.0–6.0 | 0.3 | PT | NS | NS | IS | 2.0–5.0 | PT | 81 | 5 |
| Canavese ³² | 99 | MS/HA | 0.1–0.3 | 0.3 | PT/SD | NS | NS | PB | 1.0–2.0 | PT/SD | 96 | 15 |
| Bedrosian ⁵⁶ | 104 | SC ^f | 6.0 | 1.0 | PT | NS | >1 | IS | 4.0 | PT | 99 | 3 |
| Hill ⁵⁷ | 104 | SC/SC ^f | NS | 0.3 | PT | 40 | 17 [‡] | IS | 4.0 | PT | 93 | 11 |
| Dotting ³³ | 136 | NC | 0.2 | 1.4 | IT | 87 | 15 [§] | PB | 1.0 | IT | 93 | 5 |
| Bass ⁵⁸ | 186 | SC ^f | 0.2 | 0.5 | PT | ND | NS | IS | 5.0 | PT | 93 | 11 |
| Cox ⁵⁹ | 466 | SC ^f | 6.0 | 0.5 | PT | NS | NS | IS | 2.5–7.5 | PT | 94 | 1 |

*Colloid and dye together.

[†]Also drainage to the supraclavicular sentinel nodes (2%).

[‡]Also visualization of supraclavicular sentinel node (2%).

[§]Also intramammary (3%) and interpectoral (2%) sentinel nodes.

HA, human albumin colloid; IC, indigo carmine; ID, intradermal; IMC internal mammary chain; IS, isosulfan blue; IT, intratumoral; MS, microcolloid sulfide; NC, nanocolloid; ND, not done; NS, not stated; PB, patent blue; PT, peritumoral; RC, rhenium colloid; SC, sulfur colloid; SC^f, filtered sulfur colloid; SD, subdermal; TC, tin colloid.

subareolar, intradermal, or subcutaneous over the primary tumor site; peritumoral; or intratumoral (Tables 1 and 2). The first four injection types are based on the hypothesis that the breast and the overlying skin share the same lymphatic drainage because the mammary gland is embryologically derived from the ectoderm. This was suggested in a study that demonstrated a 100% concordance between intradermal patent blue dye injection and peritumoral radioactive tracer injection.²⁵

Anatomic studies have shown that the density of lymphatics is greater in the skin than in breast parenchyma. This means that tracers are cleared more rapidly from the skin than from parenchyma. Lymphatic channels are visualized almost without exception after an intradermal injection, but this happens in only 40% of our patients after intraparenchymal administration. Visible lymphatic channels allow one to better distinguish first-echelon nodes from higher-echelon nodes, and this is a definite advantage of the intradermal injection technique. Another advantage is that one can choose the injection site anywhere in the skin of the breast, so that interference of scattered radiation with imaging or probe detection is kept to a minimum and lymphatic mapping in nonpalpable lesions is made easier. On the other

hand, it may be presumptuous to rely on the connections between collecting lymphatic vessels from the skin and those originating at the tumor site and to assume that there is no lymphatic watershed in between.

An increasingly popular technique is subdermal or subcutaneous injection over the primary tumor. This approach does not provide certainty that the identified lymph node is indeed the node that receives drainage from the primary tumor, and this approach is also hampered by the absence of a dense lymphatic network like the one that is present in the skin. Despite these theoretical shortcomings, this technique has provided good identification results of lymphatic mapping.^{29,30,32,46,50,65} Subareolar injection, based on Sappey's concept,⁹ has also shown good results.^{36,66}

Canavese and associates⁶⁷ compared subdermal injection of radioisotope over the tumor with subdermal or intraparenchymal injection away from the primary tumor. Because of a high percentage of mismatches, they concluded that there is not a sentinel node in the axillary basin that indiscriminately drains the entire breast. Other authors, such as Borgstein and associates,^{25,26} Roumen and associates,⁶⁸ Mertz and colleagues,³⁶ Klimberg and coworkers,⁶⁶ and Linehan and associates,⁶⁹

tried to determine the reliability of injection sites away from the primary tumor for axillary staging. Often-used criteria for judging such comparative studies are identification rates and concordance with a "gold standard" (peritumoral injection). These are questionable criteria. The identification rate is multifactorially defined, as already mentioned. Concordance when radioisotope and blue dye are injected at different sites does not necessarily signify that the hypothesis is correct. Such a result also depends on the different physiologic behaviors of the two tracers or a difference in injection techniques by the nuclear medicine physician and surgeon. Many sentinel nodes are either blue or radioactive, even when both tracers are administered at the same site.^{33,59} Variation in lymphatic flow can explain discordance after repeated radioisotope injection, as shown by reproducibility studies in melanoma.⁷⁰ Even the identification of the only tumor-positive node with intradermal injection, as described in a few patients by Borgstein and associates,²⁶ Linehan and associates,⁶⁹ Roumen and colleagues,⁶⁸ and Bourgeois and coworkers,⁷¹ is not decisive evidence of the accuracy of the technique. Hill and associates⁵⁷ noted that a positive sentinel node was only blue or radioactive with peritumoral injection of both blue dye and radioisotope. The main point is that the sensitivity has not been firmly established in all of these studies. Confirmatory axillary dissection was not performed in all patients, and non-sentinel node evaluation was insufficient by modern standards, lacking step-sectioning and immunohistochemistry staining.

The implication of the injection site for identification of sentinel nodes outside the axilla seems to be clearer. Drainage to the internal mammary nodes is rarely seen after intradermal or subdermal injection of radioisotope in breast cancer patients.^{50,66-68,72} Studies from the European Institute of Oncology in Milan nicely illustrated the difference in visualization of sentinel nodes outside the axilla after subdermal and peritumoral injection. Veronesi and colleagues³⁰ and Zurrida and associates⁴⁶ from that institution found drainage to the internal mammary nodes after replacing routine subdermal injection by peritumoral injection for deep tumors. Apparently, intradermal or subcutaneous injections visualize the superficial lymphatic system running toward the axilla but not the deep lymphatics that run to the internal mammary, interpectoral, or intramammary nodes. Internal mammary sentinel node identification after peritumoral or intratumoral injection occurs in up to 35%

of patients.^{33,45,51,54,57,73} Interpectoral and supraclavicular sentinel nodes are seen less frequently (in about 2%), but only after intraparenchymal tracer administration.^{45,47,51,57,73,74} Intramammary nodes were seen in 21 of 305 patients (7%) according to our own experience with intralesional tracer administration, and in 4% by Rull and colleagues⁴⁴ with peritumoral injection. Sentinel nodes in all of these locations can be harvested and may contain relevant staging information.^{74,75}

SUMMARY AND CONCLUSIONS

Knowledge of the anatomy and physiology of the lymphatic system is helpful when considering a particular sentinel node biopsy technique. The delicate balance between internal and external pressures in a lymphatic channel can be influenced by the injection volume and by massage in a negative or positive way. The narrow openings in the interendothelial junctions determine the speed of clearance of particles with a certain size, and this has implications for the timing of lymphoscintigraphy and surgery. Tracer uptake and lymph flow are highly variable and depend on a number of factors, some of which are beyond our control.

The lymphatic anatomy is not completely understood despite numerous studies since the end of the 18th century. Several topics have been elucidated in more recent studies and through experience with sentinel node biopsy. First, although axillary drainage is the principal lymphatic path of the breast, any drainage pattern from any quadrant of the breast can occur. Second, most lymph from the breast flows to the nodal basins with a direct course, not passing through the subareolar plexus. Another relevant point is that gentle massage encourages lymph flow and facilitates sentinel node detection.

What problems do we still face in clinical practice? The optimum size and number of labeled colloid particles remain to be established. The optimum volume of the tracer also remains to be determined. But the main controversy concerns the injection site. Although the intradermal injection technique has attractive practical features, there is currently insufficient certainty that drainage of tracer injected anywhere in or underneath the skin of the breast reflects drainage from the cancer. Connections between collecting lymphatic vessels from the tumor site and the collecting vessels from the skin and subdermal lymphatics can explain the concordance between intraparenchymal and superficial injections in most patients.

To determine the technique that yields the best sentinel node identification rate with the lowest possible false-negative rate would require a large randomized trial with all patients undergoing a complete lymph node dissection and evaluation of all other axillary lymph nodes with serial sections and immunohistochemistry. Current knowledge about sensitivity is based on examination of the other axillary nodes with hematoxylin and eosin staining and not with immunohistochemistry, with the exception of two studies.^{33,76} In addition, a complete level I to III dissection may not have been done in all patients, and it is not certain that pathologists removed and examined all the nodes from the specimens. The proposed study seems impossible now that routine axillary node dissection has been abandoned by the larger centers around the world.

Choosing the most attractive approach requires determining the aim of lymphatic mapping. A superficial injection technique may be adequate when the purpose is to spare patients without lymph node metastases in the axilla an unnecessary axillary node dissection. An intraparenchymal injection technique should be used when the additional purpose is to determine the stage as accurately as possible and to identify sentinel nodes elsewhere.

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