

Lymphatic Drainage of the Skin

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A successful sentinel lymph node biopsy (SLNB) in melanoma patients requires an accurate map of the pattern of lymphatic drainage from the primary site. Lymphoscintigraphy (LS) can provide such a map. LS needs an understanding of lymphatic physiology, an appropriate small-particle radiocolloid, high-resolution collimators, and imaging protocols that detect all sentinel nodes (SNs). Patterns of lymphatic drainage from the skin are not clinically predictable. Unexpected drainage has been found from the skin of the back to SNs in the triangular intermuscular space (TIS) and the paraaortic, paravertebral, and retroperitoneal areas. It can also occur from the base of the neck up to nodes in the occipital or upper cervical areas or from the scalp down to nodes at the neck base, bypassing many node groups. Upper limb drainage can be to SNs above the axilla. Interval nodes not uncommonly can be SNs, especially on the trunk. Lymphatic drainage may involve SNs in multiple nodal fields, and drainage across the midline of the body is quite common. Because micrometastatic disease can be present in any SN regardless of its location, all true SNs must be biopsied. LS is an important first step to ensure this goal is achieved.

Key Words: Lymphoscintigraphy—Lymphatic drainage—Melanoma—Sentinel node biopsy—Skin.

Accurate sentinel lymph node biopsy (SLNB) requires close cooperation between the nuclear medicine physician, surgeon, and histopathologist. Nuclear medicine's role in this technology is to provide an accurate map of the pattern of lymphatic drainage from the primary tumor site by means of lymphoscintigraphy (LS), so that the surface location of every sentinel node (SN) can be marked on the skin. The pursuit of this goal has led to the discovery of several new lymphatic drainage pathways from the skin.^{1–5} Several factors are critical for an accurate map of lymphatic drainage.

PHYSIOLOGY OF LYMPHATIC FLOW

Lymph flow is increased by heat, massage, inflammation, movement of the part, and an increase in the hy-

drostatic pressure within the lumen of the lymphatic collecting vessel. It is decreased by cold, lack of movement, and external pressure.¹ During LS the patient must be kept warm to encourage movement of the radiocolloid or blue dye, and massage can be a very useful intervention to enhance flow. Even light external pressure dramatically reduces lymph flow and should be avoided. Patients should be encouraged to ambulate between the early and delayed images to further enhance flow; the increased intraluminal hydrostatic pressure in the lymphatics of the lower limb, which accompanies standing, increases lymph flow from this area.⁶

The velocity of lymphatic flow is not uniform throughout the body and in fact varies systematically throughout the skin⁷ (Table 1). This information can be quite useful in timing blue dye injection prior to surgery and is also relevant in terms of the incidence of tracer movement to second-tier nodes beyond the SN. The faster the lymph flow, the more second tier-nodes are seen.⁸ Second-tier nodes are thus more common in the groin than elsewhere in the body.

Lymph nodes are not passive mechanical filters; radiocolloids are trapped and retained in the SN by an active physiological process. Opsonized radiocolloid is phagocytosed by the macrophages and tissue histiocytes that line the subcapsular sinus and other sinuses of the

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TABLE 1. *Lymph flow rates*

Region	Average flow (cm/min)
Head and neck	1.5
Anterior trunk	2.8
Posterior trunk	3.9
Arm and shoulder	2.0
Forearm and hand	5.5
Thigh	4.2
Leg and foot	10.2

lymph node.⁹ These processes take time and can be overwhelmed if too many radiocolloid particles reach the SN per unit time. When this happens it will be seen on dynamic imaging as the movement of tracer to second-tier nodes during the first 10 to 15 minutes postinjection when the bolus of particles reaches the SN. From this point on, there is no further migration of the radiocolloid particles; the pattern of uptake at 15 minutes is essentially the same as that at 2 hours and 24 hours. This is not a function of particle size. The assertion that big particles stay in the SN and small ones do not is incorrect. Lymph nodes are not passive mechanical filters.

There is a rough correlation between the number of lymphatic collecting vessels seen on dynamic or early imaging and the number of SNs.¹ This is not always the case, however, and a single lymphatic collecting vessel may divide to reach two or more SNs. This occurs especially in the groin for leg lesions. The reverse may also occur: two or more collecting vessels may converge to meet a single SN. This occurs most often in the axilla.

THE SENTINEL NODE

A sentinel lymph node is any lymph node that receives lymph drainage directly from a tumor site.¹ An SN is not just the first node seen on dynamic imaging, because there may be multiple separate lymph channels that have different rates of lymph flow. If they drain to different nodes, these are all SNs, regardless of the time taken for the lymph containing the radiocolloid to reach them. An SN is also not necessarily the closest node to the primary site. Lymphatic vessels can bypass many nodes and even whole nodal fields before reaching the SN.

An SN on LS is identified by visualization of the lymphatic collecting vessel as it drains directly to the node. In order to achieve this there must be adequate numbers of radiocolloid particles in the lymph fluid during the early dynamic phase, and this requires the use of small-particle radiocolloids.

APPROPRIATE RADIOCOLLOID

Small-particle radiocolloids best enter the lymphatic capillaries so they can be visualized on dynamic LS. The lymphatic endothelial cells that line the walls of the initial lymphatic capillaries overlap over a significant distance, and there is a 10- to 25-nanometer gap between the cells¹⁰ through which material can enter the lumen of the lymphatic. Small-particle radiocolloids such as 99mTc antimony sulfide colloid (particle size, 5 to 15 nm),¹ nanocolloid of albumin labeled with 99mTc (particle size, 3 to 80 nm),¹¹ filtered 99mTc sulfur colloid (100 nanometer filter; particle size, 5 to 100 nm)¹² and 99mTc rhenium sulfide colloid (particle size, around 50 nm)¹³ will all pass through this gap in adequate numbers under physiological conditions.

HIGH-RESOLUTION COLLIMATORS

Regardless of the radiocolloid used, the majority of the injected dose for lymphatic mapping will remain at the site of injection. Even the best small-particle colloids such as 99mTc antimony sulfide colloid show only 5% to 8% migration to the SN; thus, 92% to 95% remains at the injection site. With 99mTc sulfur colloid, 99% remains at the injection site.¹⁴ In melanoma patients the injected activity often remains in the field of view. Since the SN contains a small amount of activity compared with the injection site, the image must be digitally enhanced so that even the faintest uptake is seen. With many collimators, this digital enhancement will cause star artifact that may obscure possible SNs. This is caused by septal penetration of the collimator. This star can bloom on the image and completely obscure true SNs in the field.

To avoid this we use a super-high-resolution microcast collimator. The amount of lead is the same in any direction, thus minimizing star artifact. The extra lead also reduces septal penetration to less than 1% at an energy of 140 KeV, the energy of the gamma ray emitted by 99mTc. If a super-high-resolution collimator is unavailable, we recommend using a medium-energy collimator. Although this will result in loss of resolution, it will prevent star artifact. An alternate approach is to attempt to shield the injected activity with use of lead sheets. This will be effective if carefully performed but is cumbersome and time-consuming and thus not a practical solution for most busy nuclear medicine departments.

IMAGING PROTOCOLS

Imaging protocols for LS should be designed to detect all SNs. In melanoma a full understanding of the unusual

patterns of lymphatic drainage that can be seen from the skin is required. In the trunk, posterior and lateral views are required for back lesion sites, and a check should be made for intra-abdominal drainage. The nape of the neck area and the head and neck region can also be challenging and usually require superior oblique or vertex views to ensure that SNs are not obscured by the injected activity, a situation which is common on straight antero-posterior views in this area.

LYMPHOSCINTIGRAPHY METHOD FOR MELANOMA

LS to locate SNs in patients with melanoma involves the intradermal injection of a radiocolloid around the melanoma site or excision biopsy site.¹ Usually, four injections of 5 to 10 MBq (0.05 to 0.1 mL/injection) are used, although this will depend on the primary melanoma size. After tracer injection, dynamic imaging is performed to follow the lymphatic collecting vessels until they reach the draining SNs. This phase of the study usually takes 10 to 20 minutes.

Delayed scans are performed 2 to 2.5 hours later, at which time all regions that could possibly drain the primary melanoma site are examined with 5- to 10-minute static images. Appropriate lateral, posterior, oblique, or vertex views are also acquired as necessary to define the exact location of all SNs. We routinely use a transmission source on all delayed images to highlight the body outline; these images are especially useful when performing a retrospective review of the scans.

The surface location of all SNs is marked on the overlying skin with an "X" of indelible ink. A permanent point tattoo of carbon black can also be applied and is a useful guide for clinical or ultrasound follow-up over subsequent years. The depth of the SN from the skin mark is measured in an orthogonal view with a radioactive marker placed on the skin mark. The operating surgeon must understand completely the presentation of the patient and the scan data; very close communication with surgical colleagues is vital for the SLNB method to be accurate. A more detailed description of the technique and imaging protocol may be found elsewhere.¹⁵

LYMPHATIC DRAINAGE OF THE SKIN

When Morton and colleagues¹⁶ described successful SLNB in melanoma patients with injection of blue dye, our group began to apply the method described above to locate the SNs with LS the day before surgery. All patients with intermediate-thickness melanomas were studied, regardless of the site of the lesions on the skin.

We began to observe drainage to lymph nodes in completely unexpected places.^{1,2} Some were in new nodal fields not previously known to drain the skin. There was unambiguous drainage from very few sites on the skin; without preoperative LS, accurate SLNB was simply not possible in many patients. This variability in lymph drainage and drainage to SNs in unexpected places has also been observed by others.¹⁷⁻¹⁹

As of October 2002, we have performed lymphatic mapping in 3280 patients with cutaneous melanoma and have accumulated a large body of data relating to common and uncommon cutaneous lymphatic drainage pathways. The following is a detailed description of the patterns of lymphatic drainage we have observed.

PATTERNS OF LYMPH DRAINAGE FROM THE SKIN

Posterior Trunk

Melanoma sites on the posterior trunk included axillary drainage in 91% of our 1086 patients. Flow to the groin occurred in 11% of patients with back lesions. Drainage across the midline of the patient to contralateral SNs occurred in 35% of patients with back melanomas, and 20% showed drainage over the shoulders to SNs in the neck. Further unexpected drainage was seen, including lymphatic pathways that drain to the triangular intermuscular space (TIS) lateral to the scapula, behind the axilla,²⁰ and pathways that pass through the posterior body wall directly to SNs in the retroperitoneal and paravertebral areas.²¹

The more common of these two pathways is drainage from the skin of the back to the TIS. We have observed this drainage pathway in 11% of our patients with back melanomas (Fig. 1). Older protocols called only for

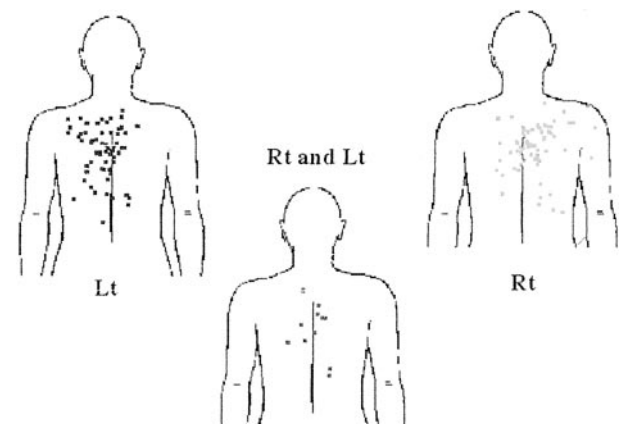


FIG. 1. The surface location of melanomas that showed lymphatic drainage to sentinel nodes in the triangular intermuscular space (TIS). Drainage can be seen to the right and/or left TIS.

anterior views of the axilla, but posterior and lateral views are required to identify SNs in this unexpected location because attenuation of photons passing through the patient's body may prevent visualization of TIS nodes in an anterior view. Drainage to an SN in the TIS often accompanies drainage to an SN in another nodal field, but we have seen eight patients with exclusive drainage to an SN in this unexpected location.

The second unexpected lymphatic drainage pathway from the skin of the back passes directly through the posterior body wall to SNs in the paravertebral, para-aortic, or retroperitoneal areas (Fig. 2). This drainage pattern is usually to intra-abdominal sites, but we have also seen paravertebral nodes in the thorax as SNs draining the skin of the back. We have observed this pathway in 3% of patients with back melanomas, making it much less common than the pathway draining to the TIS. If we consider only the posterior loin area, however, we find drainage via this pathway in 24% of patients. Again, drainage to SNs in these unexpected areas is usually accompanied by drainage to SNs in expected nodal fields (the axilla and groin), but we have encountered four patients who had exclusive drainage to SNs in these areas with no drainage to axilla or groin.²² The importance of identifying drainage to SNs in the paravertebral, para-aortic, and retroperitoneal areas is that metastatic

disease in one of these nodes represents locoregional metastasis, not systemic disease. Drainage to combinations of nodal fields is also very common and will be missed without preoperative lymphatic mapping with LS. Interval nodes, which are nodes that lie along the course of a lymphatic collecting vessel between a primary site and a draining nodal field, were seen as SNs more commonly on the back than elsewhere in our patients with melanoma.

Anterior Trunk

Lymph from the skin of the anterior trunk generally drains to expected nodal fields, and there tends to be less passage of lymph vessels across the midline than on the posterior trunk. In our 244 patients with anterior trunk melanoma, 83% had drainage to the axilla and 19% had drainage to the groin. Contralateral drainage was less common than on the back, occurring in 20% of patients. Drainage to interval nodes is also less common than on the back.

We did detect one new unexpected drainage pathway, from the periumbilical skin to a node in the subcutaneous fat over the costal margin.²³ The lymphatic pathway then passes medially and through the chest wall to internal mammary nodes on the same side as the costal margin node. The pathway always meets a costal margin node first, however, and thus the SN in these patients is the costal margin node, with the internal mammary node receiving drainage as a second-tier node. In fact, we have seen an internal mammary node as an SN for the skin of the anterior trunk in only two patients who had undergone previous surgery.

Head and Neck

Drainage to multiple SNs in the head and neck is common^{1,24} and the nodes are often small. The draining SNs often lie very near or sometimes immediately beneath the melanoma site. Detection of such nodes on LS is thus extremely difficult and sometimes impossible. However, if care is taken and such limitations are understood, accurate lymphatic mapping and SLNB can be achieved in the head and neck.

Lymphatic drainage from the skin of our 578 patients with head and neck melanoma is shown in Figure 3. As we have found elsewhere, clinical prediction of lymphatic drainage in the head and neck is unreliable, and 33% of patients drain to node sites discordant with clinical prediction.²⁴ This is often to postauricular nodes from the skin of the face and anterior scalp. Such nodes are not usually excised during elective neck dissections for melanoma. Drainage across the midline was seen in 10% of patients with head and neck melanomas (Fig. 4).

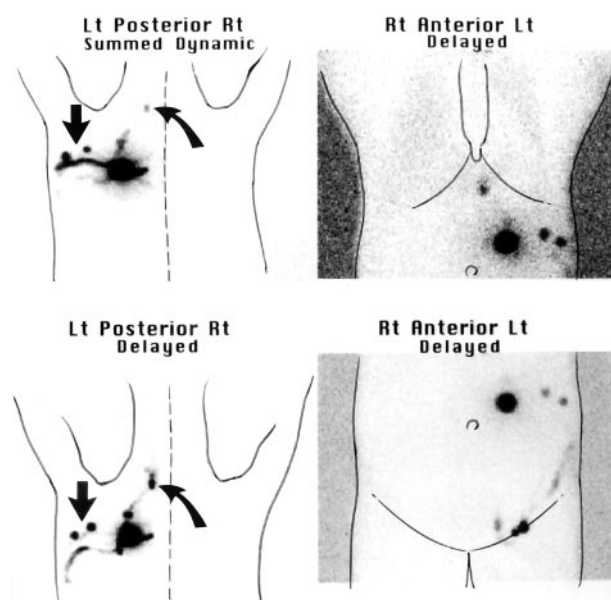


FIG. 2. Dynamic (top left) and delayed lymphoscintigraphy (top right, bottom left and right) in a patient with a melanoma excision biopsy site on the mid-posterior left-loin area. Lymphatic drainage is seen directly through the posterior body wall to sentinel nodes in the left retroperitoneal (arrows) and paravertebral regions (curved arrows) as well as to two sentinel nodes in the left groin. A faint second-tier node is also seen in the left groin.

Lymphatic Drainage of the Head and Neck
578 Patients

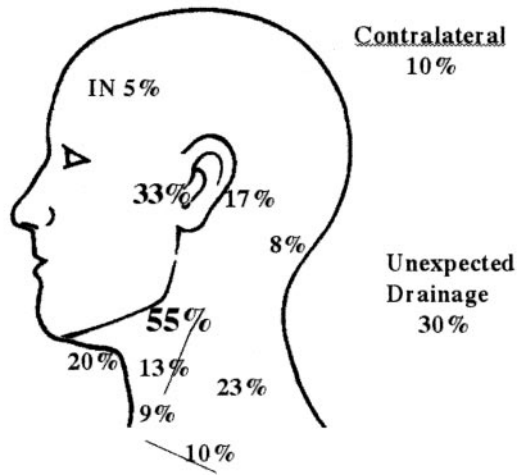


FIG. 3. Percentage of patients with head and neck melanomas showing lymphatic drainage to sentinel nodes in each neck node field (IN, interval node).

Such a contralateral node occasionally can be the only site of micrometastatic disease. Lymph drainage also may occur from the base of the neck upward to nodes in the upper cervical or occipital area. Again, we have seen this pattern in patients whose only positive node was an occipital node, even though other SNs were present in the axilla, upper cervical area, and lateral neck base. Drainage is also seen regularly from the upper scalp

directly down to nodes at the base of the neck or in the supraclavicular region. Lymphatic vessels reaching these nodes are thus bypassing all the nodes in the upper and mid cervical areas as well as the preauricular (parotid), occipital, and postauricular nodes. This reinforces the concept that the SN is not simply the closest node to the primary melanoma site

Upper Limb

Lymph drainage from the skin of the upper limb is to the axilla, as expected, in almost all patients. Drainage to SNs in the epitrochlear region was seen in 20% of patients with melanomas located on the forearm and hand. We also have detected direct drainage to SNs above the axilla in the supraclavicular region, interpectoral region, lateral neck base, and TIS in 6% of our 608 patients with upper limb melanomas. These patients usually also had an SN in the axilla, and the lymph drainage to these unexpected sites occurred via a separate, discrete lymph vessel. Relying exclusively on gamma probe-guided removal of axillary SNs in these patients would have missed the other SNs. Accurate lymphatic mapping with LS is thus imperative.

An interval node is regularly seen lying medially in the arm about halfway between the shoulder and elbow. We have seen one patient who had drainage exclusively to this interval node in the mid inner arm, so that it was the only SN.

Lower Limb

In our 764 patients with lower limb melanomas, the skin drained to the ipsilateral groin or popliteal fossa unless there had been prior surgery to the groin nodes. In this circumstance drainage to the contralateral groin may occur, and we have found micrometastases in such contralateral groin SNs.²⁵

Lymph drainage from the foot and leg to the popliteal lymph nodes was observed in 38 of 518 patients (7%) with melanomas in these areas (Fig. 5). The melanoma sites draining to the popliteal nodes are quite variable; it is not just the skin of the lateral heel that drains here, as was previously thought.

Interval Nodes

Interval nodes can be SNs, and we have seen 10 patients in whom they were the only SNs. When present they must be detected and removed if an SLNB procedure is to be accurate. Interval SNs contain micrometastases with the same incidence as SNs found in the standard nodal fields.²⁶ We found interval nodes in 7% of patients overall; they are more common on the trunk (12% posterior trunk and 8% anterior trunk) than in the

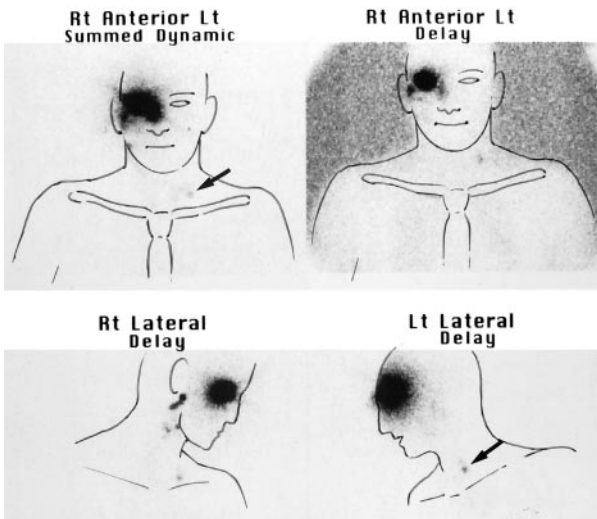


FIG. 4. Dynamic (top left) and delayed lymphoscintigraphy (top right, bottom left and right) in a patient with melanoma on the right upper eyelid. Lymphatic drainage occurs to sentinel nodes in the right parotid region, right submandibular region, and left supraclavicular region (arrow).

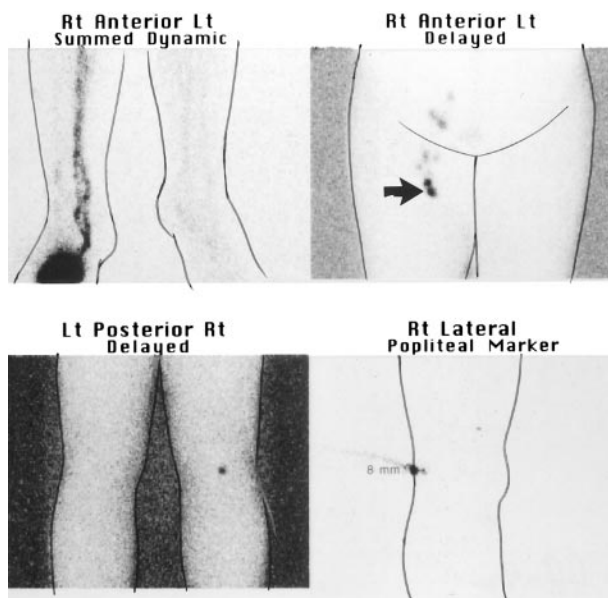


FIG. 5. Dynamic (top left) and delayed lymphoscintigraphy (top right, bottom left and right) in a patient with a melanoma excision biopsy site on the dorsum of the right foot. Two bright and one faint lymphatic collecting vessels pass up the leg on the dynamic image; these drain to a single sentinel node in the right popliteal fossa and two sentinel nodes in the right groin (arrow). Some second-tier nodes are seen above the sentinel nodes in the groin; they are seen more commonly here because lymph flow is more rapid in the leg than elsewhere. An orthogonal view is always performed to measure the depth of the sentinel node from the skin (bottom right).

head and neck (5%) or upper limb (4%), but they are rare in the lower limb (0.5%) (Fig. 6). In a large multicenter study, McMasters and colleagues³ found that in melanoma patients interval nodes were positive for metastases with the same frequency as SNs in standard nodal fields. In their 13 patients with a positive interval node, it was the only positive SN in 11 patients (85%).

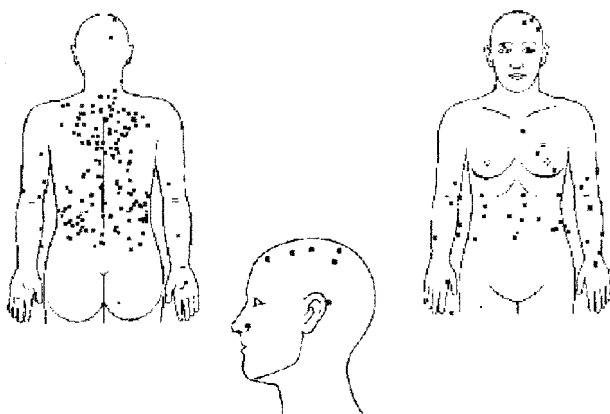


FIG. 6. The location of melanomas that showed lymphatic drainage to an interval node as a sentinel node.

Interval nodes remain “hot” on delayed scans because they retain the radiocolloid, although much of the radiocolloid reaching an interval node passes on to second-tier nodes. They thus seem to be more “porous” to radiocolloids than SNs in standard node fields.

Lymphatic Lakes

Unlike interval nodes, lymphatic lakes do not need to be examined during SLNB. They are focal dilatations of lymphatic collecting vessels. They are seen during LS as a focal area of increased tracer retention along the course of a lymphatic collecting vessel during the dynamic early postinjection phase of the study. The activity rapidly passes onward in the lymph vessel, however, so that they are not visible on delayed scans performed 2 hours later. These should not be mistaken for interval nodes, which retain tracer and are therefore hot on delayed scans.

CONCLUSION

Lymphatic drainage of the skin is highly variable from patient to patient, even when the same region of the body is being examined. Several recent studies have confirmed that the path taken by the lymphatic collecting vessels is unpredictable, as is the ultimate location of the draining SNs.¹⁻⁵

Preoperative LS with small-particle radiocolloids allows visualization of lymphatic vessels that drain directly to the SNs. Careful imaging technique will thus allow all true SNs to be identified in each patient, even if these nodes lie outside standard node fields or are interval nodes lying between the primary site and a node field. This important contribution to the management of melanoma will lead to more accurate nodal staging.

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