Lymphoscintigraphy and Intraoperative Lymphatic Mapping of Sentinel Lymph Nodes in Melanoma Patients

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Identification of sentinel lymph nodes (SLNs) using lymphoscintigraphy, the blue dye technique and intraoperative lymphatic mapping with a gamma-detecting probe has become the standard of care in diagnosing and treating melanoma. Numerous clinical studies have proven the reliability of predicting the histology of remaining lymph nodes in the lymphatic basin from the histologic evaluation of the SLNs. Technical and clinical factors presented in this paper have been shown to increase the accuracy of localization of SLNs. The nuclear medicine technologist shares a vital role in the radiopharmaceutical preparation and administration for preoperative lymphoscintigraphy and intraoperative lymphatic mapping in patients with melanoma.

Key Words: lymphoscintigraphy; melanoma; sentinel lymph node; gamma-detecting probe; intraoperative lymphatic mapping; oncology

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The American Cancer Society estimates 44,200 new malignant melanoma cases in 1999. The overall incidence rate, currently increasing by 4.3% each year, is increasing faster than that of any other cancer. Melanoma is now the most common disease in women between 25 and 29 y of age and is second to breast cancer in women between the ages of 30 and 34 y. The US mortality rate is projected to be 7300 deaths in 1999 (*1*,*2*).

One encouraging point is the increasing public awareness of various prevention and treatment options for melanoma. Unfortunately, the preventative measures put forth by physicians, so far, have not shown a significant impact on the alarming increase in the rate of skin cancer. This increasing rate of melanoma has led to new diagnostic and treatment options.

The standard diagnostic work-up includes a general physical examination and biopsy of suspicious areas of the skin. These procedures have proven to be good indicators of primary melanoma, but have been less accurate in showing the extent and location of possible metastatic disease. Initial staging by biopsy may be very accurate, but determining the extent of disease has been limited by current conventional diagnostic methods. Currently, most physicians use head, chest, abdomen and pelvis computed tomography (CT) for staging. The use of CT is standard, but it has limitations related to lesion size. It is agreed by most radiologists that a lymph node is abnormal if it is greater than 1.5–2.0 cm, depending on its location. Unfortunately lymph nodes may harbor metastases without being abnormally large. Lymph node size alone can result in unnecessary surgery. Previously, the surgical oncologist determined the extent of disease by extensive lymph node dissections based on predicted drainage patterns or identification of the drainage basin(s). An accurate diagnostic procedure would lead to less extensive surgery and could result in less disfigurement and less morbidity.

Sentinel lymph node (SLN) mapping has proven to be beneficial to patients with melanoma (*3–21*). To continuously produce useful images for the surgeon, we suggest that technologists develop a basic understanding of the specific physiology and behavior pattern of melanoma before establishing protocols.

ANATOMY, PHYSIOLOGY AND PATHOLOGY OF MELANOMA

The lymphatic system maintains fluid balance in the tissues. The lymphatic system, unlike the circulatory system, only carries fluid away from tissues. Therefore, foreign material entering into interstitial space first enters the lymph vessels that lead to tiny (1–25-mm) lymph nodes. These lymph nodes trap and filter the fluid before it enters the bloodstream. Situated all over the body, these lymph vessels virtually cross all tissues and organs (Fig. 1) (*22*).

Unfortunately, this is the same route melanoma uses to spread so rapidly throughout the body. The prognosis for patients with melanoma is closely related to the presence or absence of lymph node metastases. Once in the lymph nodes, melanoma can spread to secondary areas including the lungs, liver, brain and bones. It is encouraging that 82% of patients with newly diagnosed melanoma have local disease with no

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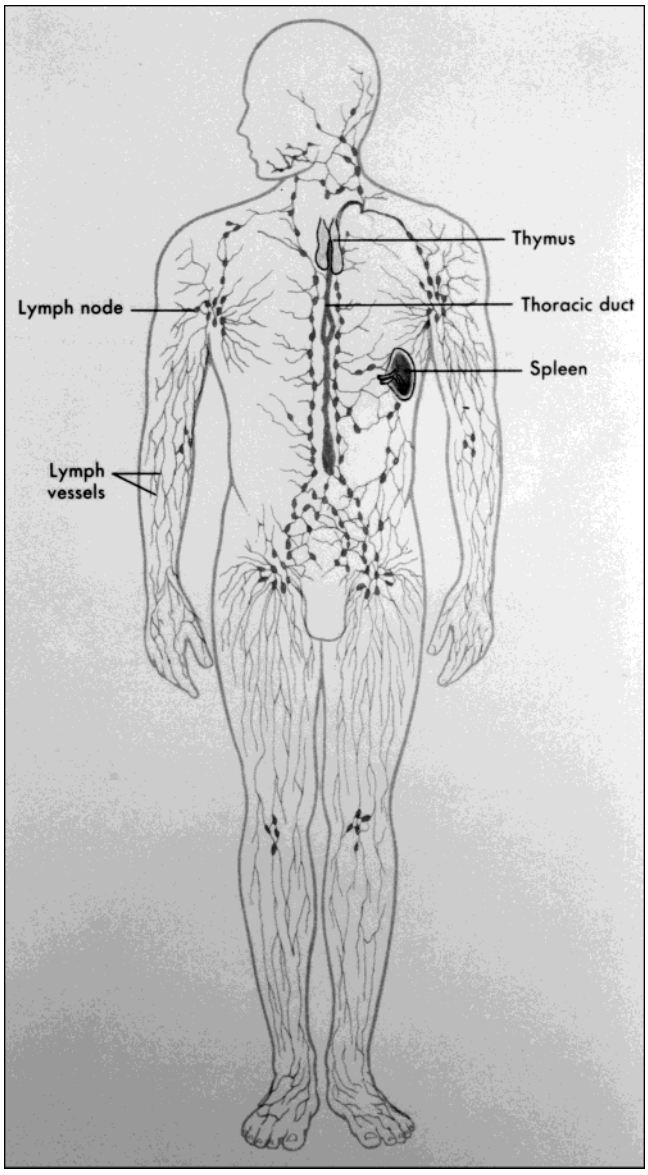

FIGURE 1. Lymphatic system shows the major lymphatic organs and vessels (reprinted by permission of The McGraw-Hill Companies, New York, NY (*22*)).

lymph node involvement (*1*). Early detection is the key to successful treatment of melanoma.

Early detection will demonstrate a lesion or mole on the skin that has changed in shape, size or color. The next step is biopsy of the lesion. From this biopsy, the Breslow thickness and Clark level are determined. Pathologically, there are 5 stages of melanoma that are based on the combination of the Breslow thickness and Clark level. Treatment is based on this staging (Table 1)(*1,2*). As with any disease, melanoma spread is ultimately unique to each person. Therefore treatment is individualized.

The majority of melanomas at diagnosis are Stage I or II. Previously, the treatment involved a total lymph node dissection (TLND). This consisted of removing all the lymph nodes(10–30 nodes) in the lymph node basin and usually required a 2–3-d hospital stay. Sequela included painful edema and possible infection. Lymphoscintigraphy and out-patient SLN biopsies have decreased treatment cost by 1/3 and post-operative sequela is distinctly unusual.

RADIOPHARMACEUTICALS

Several radioactive compounds have been used over the years to evaluate lymphatic drainage of melanoma and breast cancer. The physiologic mechanism used includes the deposition of the radioactive compound into tissue surrounding the primary tumor or prior surgery site. The tracer enters the lymph channels passively or may be phagocytosed by macrophages and transported in lymphatic channels (*23*).

The mechanism of uptake into the lymphatics depends primarily on the particle size and stability of the radiopharmaceutical. A uniform distribution of small particles (< 0.1 μm) is necessary for the particles to translocate from the interstitial injection site to the lymphatic channels and nodes. Large particles (0.5–2 μm) remain trapped at the injection site (*26*). Although a comprehensive discussion of the advantages/disadvantages of the various radiopharmaceuticals used for lymphoscintigraphy and lymphatic mapping is beyond the scope of this manuscript, several articles are recommended to the reader for comparison of the various radiolabeled compounds (*21,23–26*).

All patients studied at our institution received infusions of technetium ^{99m}Tc sulfur colloid, prepared according to a procedure recommended by Alazraki et al. (*21*). Briefly, ^{99m}Tc sulfur colloid was prepared using sodium pertechnetate from a radionuclide generator that had a long ingrowth time to have the most ^{99m}Tc on the column. A heating time of 3 min followed by a cooling time of 2 min before the addition of the buffer was used in an effort to obtain a higher percentage of smaller (< 0.4 μm) particles. Finally, the prepared ^{99m}Tc sulfur colloid was filtered through a 0.22-μm filter. Patient administration included 4 separate syringes each containing 0.1 mCi in a final volume of 0.1 mL of normal saline as described in the next section.

RADIOPHARMACEUTICAL ADMINISTRATION

There are no specific patient preparations for lymphoscintigraphy, however, patient preparation instructions are given for surgery. The following materials are needed for administration: 0.4 mCi of 0.22-μm-filtered sulfur colloid, 1% Lidocaine hydrochloride injection (USP), 4 insulin syringes, isopropyl alcohol swabs or betadine, absorbent pads and 4-in. × 4-in. gauze.

Each of 4 insulin syringes containing 0.02–0.05 mL filtered ^{99m}Tc sulfur colloid are combined with 0.05 mL 1.0% Lidocaine hydrochloride injection (USP) to yield a total volume of 0.10 mL We have not seen any fluctuations from the drainage patterns by adding the 1.0% Lidocaine hydrochloride injection (USP) to the filtered ^{99m}Tc sulfur colloid. Other sites have adopted a protocol to inject 1.0% Lidocaine hydrochloride injection (USP) 1 h before the ^{99m}Tc sulfur colloid injections. The Lidocaine hydrochloride decreases the irritation caused by the pH of the ^{99m}Tc sulfur colloid preparation. The insulin syringes are used because the needle is an extension of the syringe, not a separate piece as with many tuberculin syringes.

TABLE 1
Staging and Treatments of Melanoma (*1, 2*)

Stage	Clark level*	Breslow thickness†	Classical treatments‡	Current treatments§	5-y survival rates
0	In situ	—	Watch and wait	Watch and wait	—
1	Invasion in papillary dermis	<0.75 mm	Watch and wait	Sentinal lymph node biopsy	>96%
2	Adjacent to the papillary-reticular dermal interface and possible lymph node invasion	0.75–1.5 mm	Total lymph node dissection, radiation therapy	Sentinal lymph node biopsy	96%
3	Invasion to reticular dermis and lymph nodes with possible satellite lesions	1.5–4.0 mm	Total lymph node dissection, radiation therapy	Sentinal lymph node biopsy, radiation therapy, total lymph node dissection	59%
4	Invasion to subcutaneous tissues, lymph nodes, and organs with presence of satellite lesions	>4.0 mm	Chemotherapy, radiation therapy, immunotherapy	Chemotherapy, radiation therapy, immunotherapy, T-cell research, MAb research	12%

*Clark level = Reported on the surgical pathology report describing the microscopic cell analysis of tumor invasion into the dermis and surrounding tissues.

†Breslow thickness = The vertical growth of the melanoma.

‡Classical treatments = Treatments used according to initial biopsy staging, physical examination and CT scans.

§Current treatments = Accepted treatments according to initial biopsy staging, physical examination, lymphoscintigraphy and SLN biopsy results.

Using these unibody insulin syringes also decreases the chance of contamination.

Before injection a hole is cut in the middle of an absorbent pad with edges approximately 2 in. from the borders of the lesion/biopsy site. Even with experienced personnel, contamination on the surface of the adjacent skin may occur. If this does occur, the area should be decontaminated by blotting. If this is not possible, a small lead shield can be used as long as it does not cover potential lymphatic channels or SLNs.

The accuracy of the injections is critical. The 4 injections are made within the dermis. For a reference, a tuberculin skin test is injected into the dermis, which is the level directly below the epidermis. Therefore, these 4 injections should be made very superficially so that a wheal is formed on the surface of the skin. The insulin needle advances only 0.15–0.25 mm into the skin. The needle should be directed at a 10–20° angle from the horizontal plane of the melanoma. If there is a question of injection technique and the sulfur colloid is not draining, then a second dose made more superficially can be given.

Using aseptic technique, by either applying betadine or external isopropyl alcohol around the melanoma site, ensures 4 sterile injection sites. These intracutaneous injections should be made at 12-, 3-, 6- and 9-o'clock positions around the lesion/biopsy site. An exception is when the melanoma is located on the head or neck. Injection sites and lymph nodes in the head and neck can be in very close proximity. In this case the

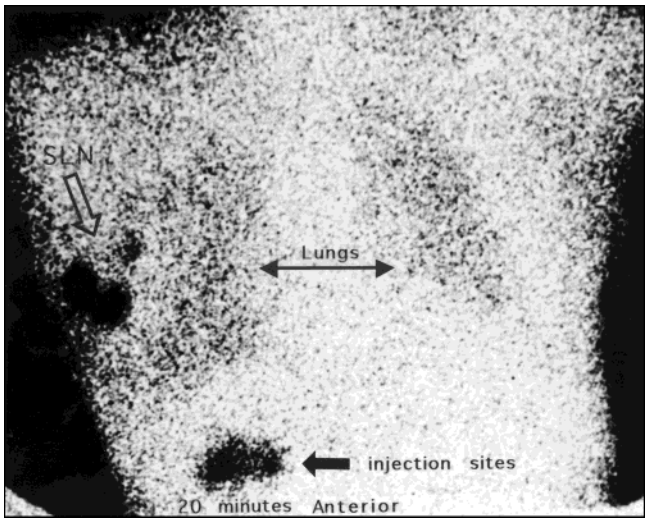

FIGURE 2. Twenty-minute anterior chest image with arms raised above the head. The ^{57}Co sheet source was left under the patient too long resulting in a burning through in the lung fields and body. This resulted in poor separation of 3 sentinel lymph nodes (open arrow).

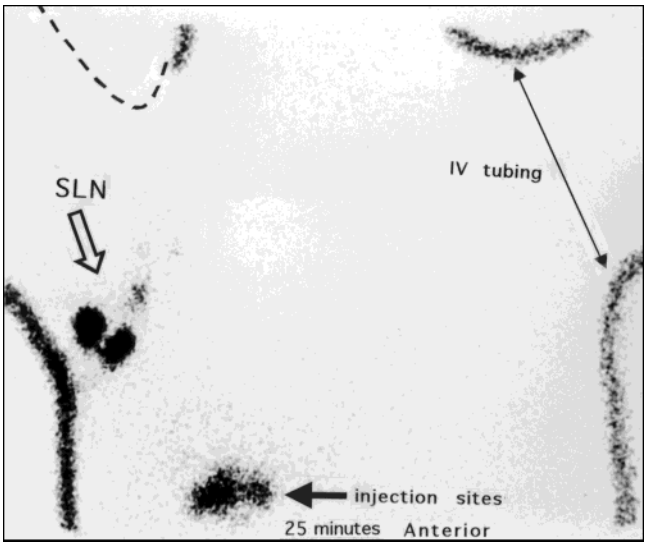

FIGURE 3. This is the same patient as in Figure 2, however, sealed intravenous tubing containing a small amount of radioactivity was used to outline the body instead of the ^{57}Co sheet source.

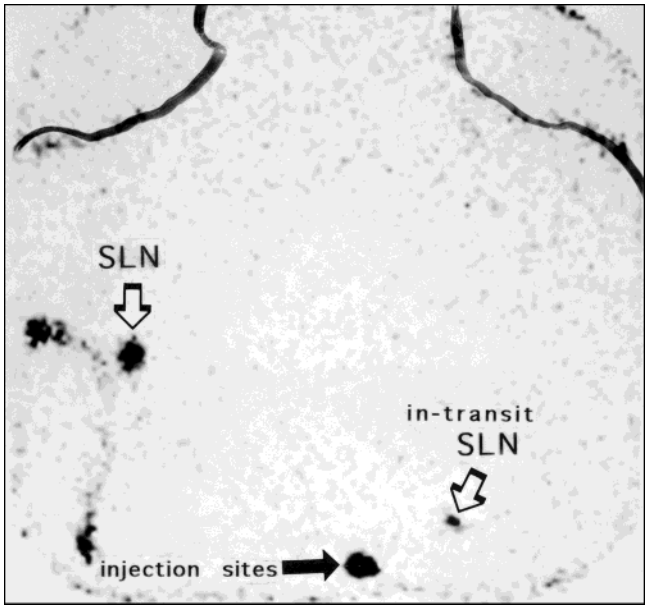

FIGURE 4. Anterior chest view reveals a right axillary sentinel lymph node and a focal area of uptake just left of the injection site. Orginally thought to be skin contamination, at surgery the gamma-detecting probe indicated the source of radioactivity was internal and not on the skin. This left medial area of uptake was determined at surgery to be an in-transit lymph node. Both the right axillary sentinel lymph node and left medial in-transit lymph node were positive for metastatic melanoma.

injections should be made superior to the melanoma site. Four injections, instead of 1, enhance flow to all possible routes for the spread of metastatic disease. After the 4 injections are made, a 4-in. × 4-in. gauze should be applied delicately. This gauze should be taped to the skin to decrease the possibility of contamination from leakage from the injection sites.

POSITIONING AND IMAGING PARAMETERS

Good images can be obtained using a large-field-of-view (LFOV) camera. Using a LFOV allows more lymphatic channels and beds to be imaged simultaneously. This is critical since the drainage occurs within seconds. Our studies use a dual-head camera with ultra-high resolution, low-energy collimators set at a 15% window for ^{99m}Tc and a 5% window for ^{57}Co. The ultra-high resolution low-energy collimator can detect 2.0-mm nodes, therefore small lymph nodes (2–10 mm) can be differentiated.

Counts from the injection sites as well as the suspected lymph node basin(s) may be better localized by using a photon-emitting source to outline the body. One method is to use a ^{57}Co sheet source to produce transmission images. The ^{57}Co sheet source is placed directly under the imaging table so that a body silhouette is produced. Since these energy peaks (^{99m}Tc = 140 keV and ^{57}Co = 122 keV) are so close, using a 15% window for ^{99m}Tc and a 5% window for ^{57}Co is advised. Care should be taken when using a ^{57}Co sheet source. If the camera being used is only peaked on ^{99m}Tc, the higher activity of the ^{57}Co sheet source may result in artifact showing the emissions passing through the body (Fig. 2).

Another method to outline the body involves the use of intravenous tubing containing 40–60 μCi ^{99m}Tc. This tubing is taped around the outside of the patient's body to outline it, as shown in Figure 3. The body outline also may be demarcated using a point source and drawing the body outline.

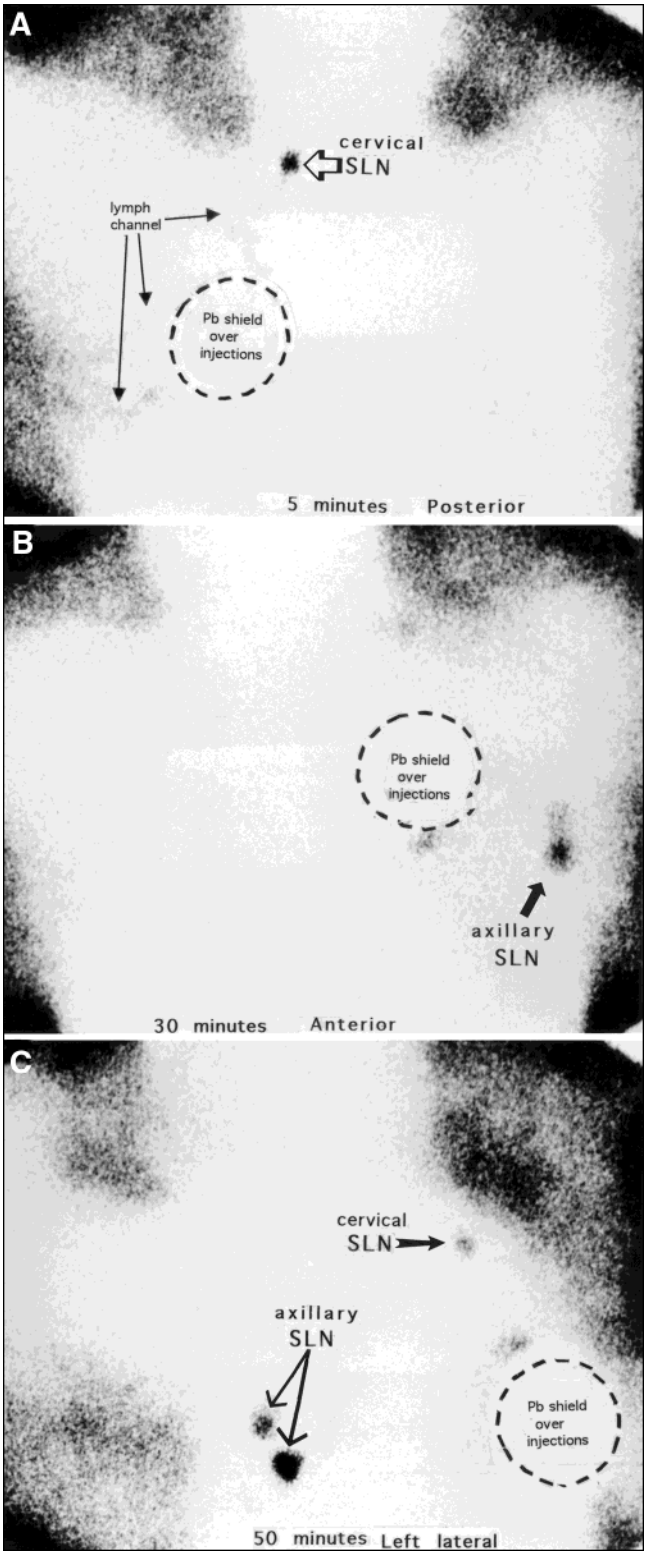

FIGURE 5. (A) Initial posterior dynamic frame image reveals the cephal drainage from the injection site to a posterior cervical sentinel lymph node. Subsequent static (B) anterior and (C) lateral views show axillary drainage.

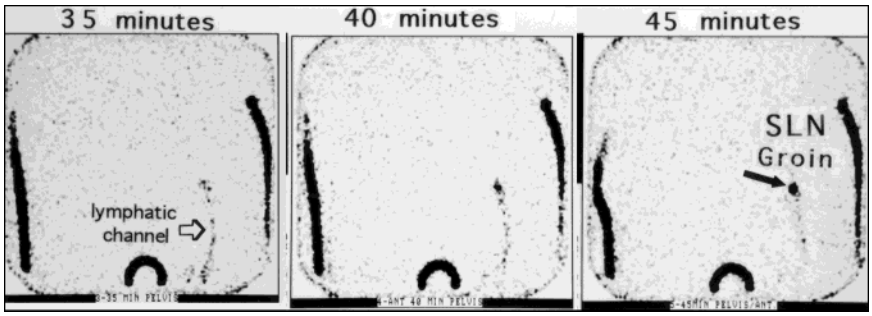

FIGURE 6. Forty minutes postinjection sequential anterior planar images reveal a left groin sentinel lymph node.

Imaging must begin immediately after the last injection of ^{99m}Tc sulfur colloid is made. A flow study is necessary to show the immediate drainage channels. The dynamic study should be acquired according to the location of the melanoma site. If a dual-headed camera is not available, an anterior or posterior flow study should be considered.

The majority of the lymph node beds within the body are anterior. Most lymphatic drainage flows anteriorly and locally, but in some cases, as seen in Figures 4 and 5, in-transit and posterior SLNs are visualized. It is customary to image with the camera facing the melanoma site to capture any unusual drainage patterns. In some cases, the location of a suspected basin is uncertain. In such cases, the FOV should be moved intermittently from one basin to the other in question until the SLNs appear. A 128 × 128 acquisition matrix was used for the dynamic imaging. When necessary, the images were folded down to a 64 × 64 matrix display to increase the counting statistics, although resolution is compromised. The initial acquisition times/frame evaluated were between 10–30 s/frame and, based on our findings, a rate of 15 s/frame for a total of 80 frames was adopted. After visualizing the SLNs, sequential planar images were acquired to identify other drainage basins and their sentinel node(s), which also were marked with indelible ink on the skin.

These planar images should be taken for a minimum of 1 h since some SLNs may not be visualized until late in the study. The patient shown in Figure 6 was instructed to exercise his legs, by walking the hallways for 15 min, to allow contractions of the muscles to initiate faster lymph flow. Even regional movement of the affected limb has caused a stagnate injection site to begin to flow. This was an unusual case. In the majority

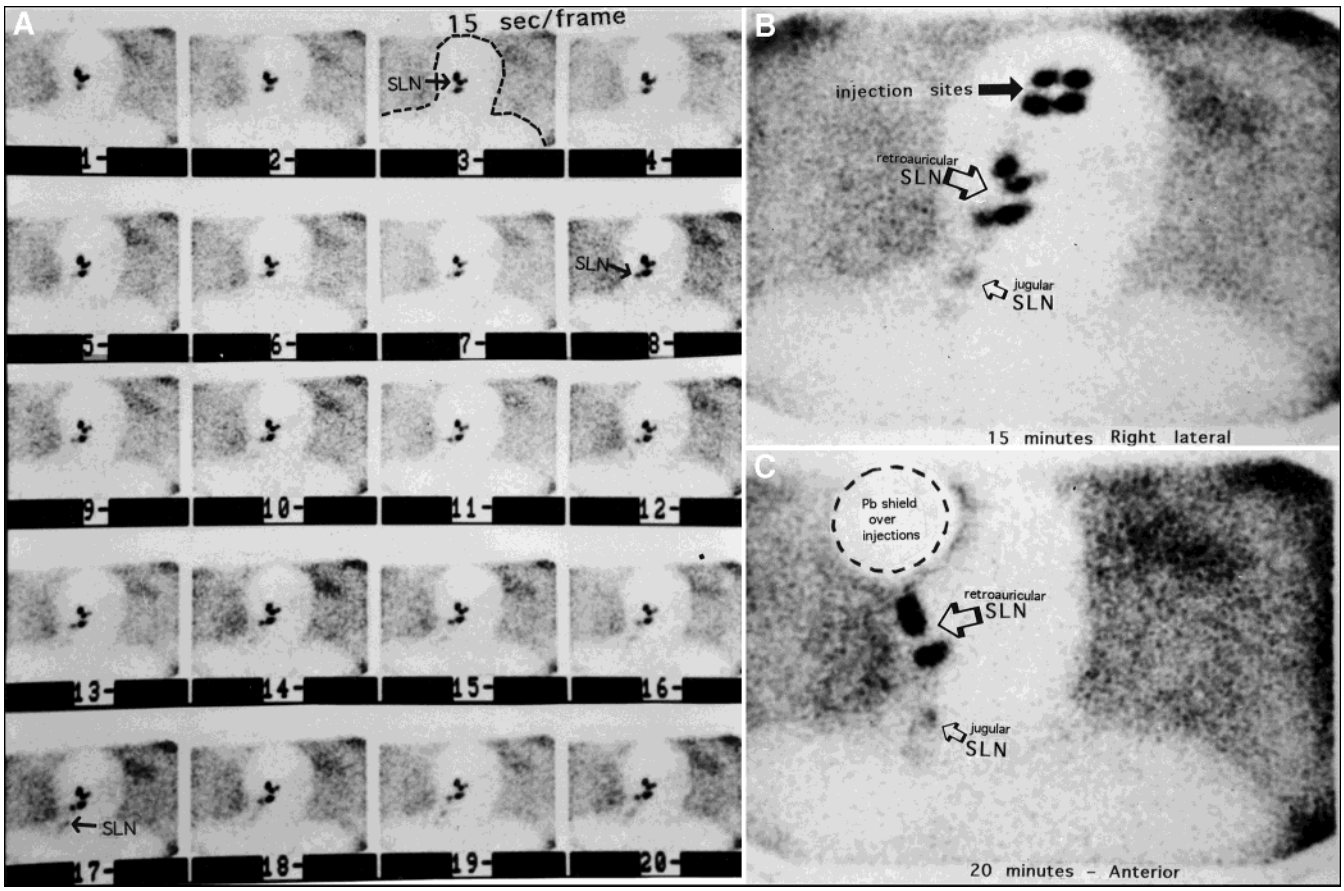

FIGURE 7. Patient with right parietal scalp melanoma. (A) Initial dynamic study shows a cervical chain starting at the retroauricular region (Frame 3) down to the jugular region (Frame 17). (B) Lateral static and (C) anterior views show these sentinel lymph nodes.

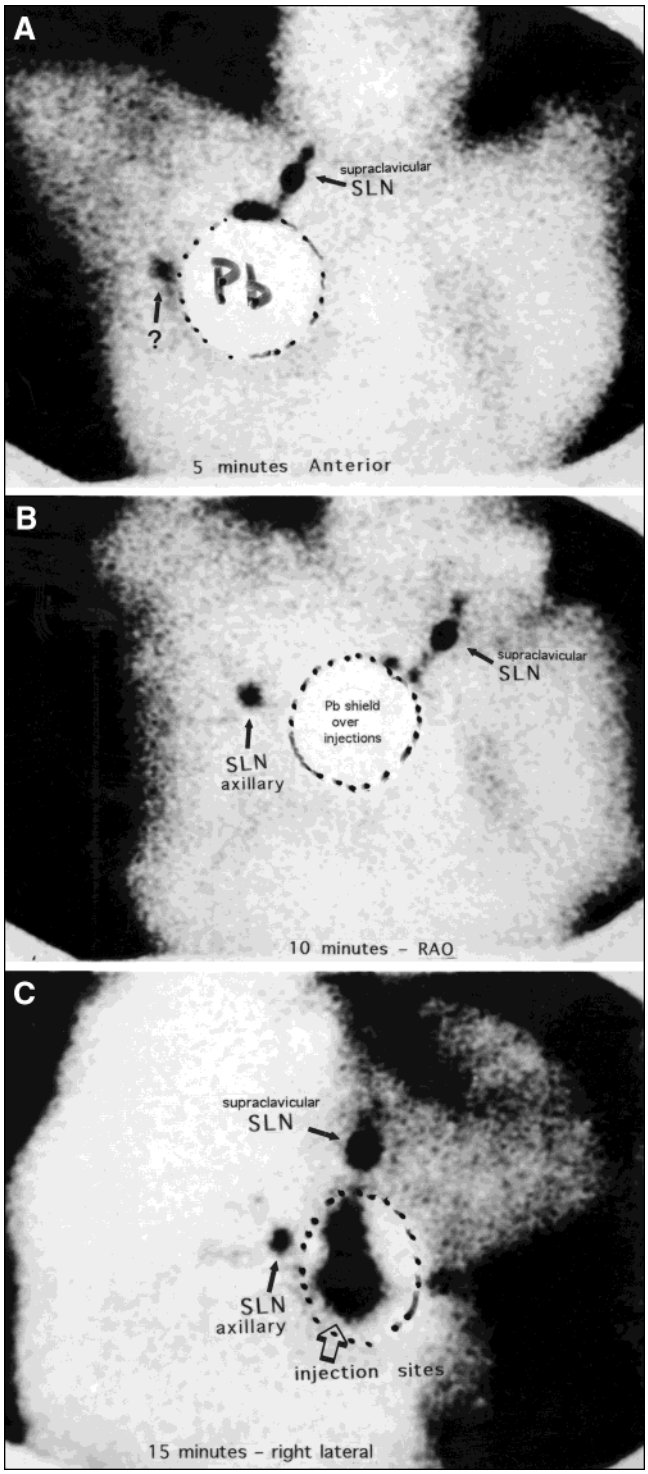

FIGURE 8. Patient with a primary melanoma site on the right upper chest that is proximal to the adjacent lymph node bed. (A) Initial anterior image shows a supraclavicular sentinel lymph node, however, the axillary bed slightly overlapped the site of injection. (B) Right anterior oblique and (C) right lateral views afforded better separation of a right axillary sentinel lymph node from the injection site.

of our imaging (98%), lymphatic flow was visualized within 10 min. The sequential planar imaging acquisitions tested ranged from 3–6 min/image with 5 min/image providing adequate counting statistics for each view. A 256 × 256 matrix with 1.0 magnification is used for the planar imaging.

Cover the injection sites with a lead shield ≧ 0.5 mm thick when acquiring images. This lead shield should remain over the injection sites for the majority of the imaging. The shield is removed during the last 5 s of each static image. This is done so that the SLNs can be separated easily from the injection sites. In addition, oblique and lateral views should be taken for better localization and separation of the SLNs, as shown in Figure 7. The correct positioning of suspected lymphatic drainage beds can be seen in Figures 8–11.

After the appearance of the SLNs on the lymphoscintigraphy study, the SLNs are pinpointed externally using an indelible ink marker and a small-volume (≦ 0.05 mL) point source containing from 40–60 μCi ^{99m}Tc. A drop of ^{99m}Tc in a needle cap or on the end of a cotton-tipped swab can be used. Once the position of the point source is over the SLNs, a mark is made on the surface of the skin using the indelible marker.

SURGERY

After lymphoscintigraphy, the patient is taken to surgery where the surgeon injects isosulfan blue (Lymphazurin™ 1%;

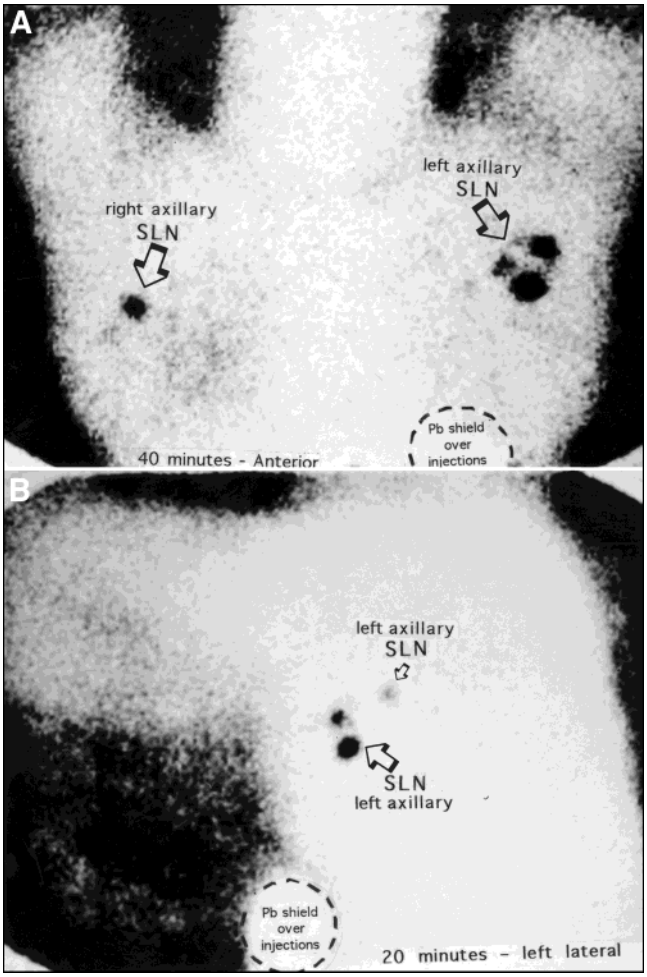

FIGURE 9. This figure illustrates the need to (A) image the thorax with the arms raised above the head or (B) 90° perpendicular to the body so that no body tissue overlaps a sentinel lymph node. (B) A left lateral view separates and provides an indication of depth of the left axillary sentinel lymph nodes.

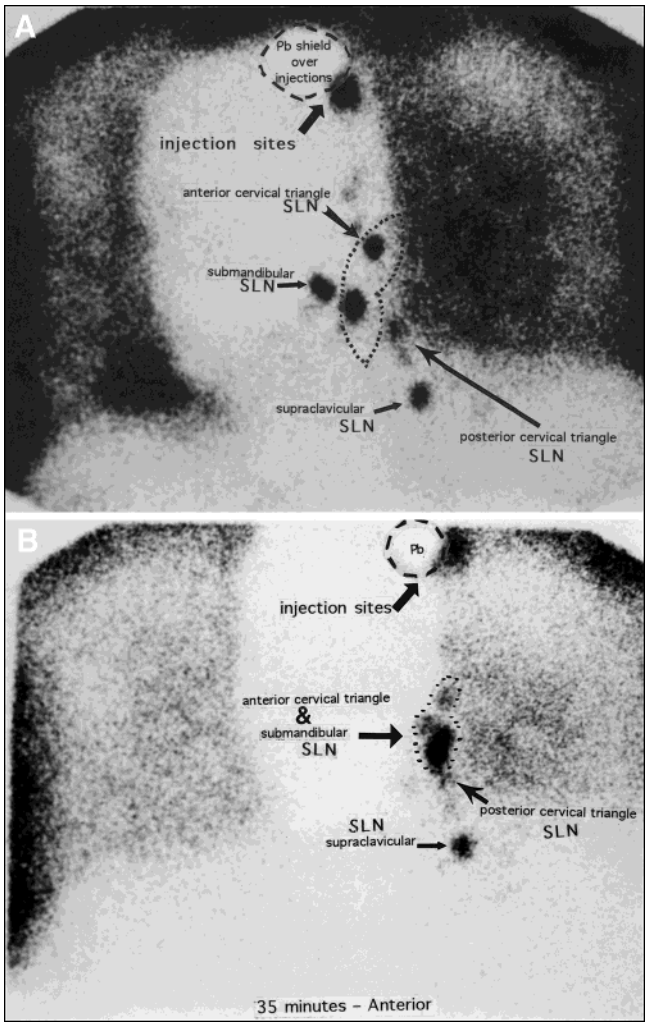

FIGURE 10. Patient with a left parietal scalp melanoma. (A) Left lateral image of the head and neck shows good separation of lymph nodes in the neck and supraclavicular area. (B) The anterior view of the head shows no drainage to the patient's right side.

United States Surgical Corp., Norwalk, CT) using the same method as the ^{99m}Tc-filtered sulfur colloid administration. Unfortunately, it was soon found that the blue dye technique was not reliable when compared with histology results. The SLNs did not contain the blue dye in 57% of our studies. Of these SLNs 5% were positive for metastatic melanoma. With these results, the notion to eliminate the blue dye injection was entertained. However, the blue dye provides an excellent visual in vivo map of the lymph vessels and the gamma-detecting probe is used for the incisional location and the location of the SLNs.

The gamma-detecting probe is either sterile or is covered with a sterile sheath. The surgical oncologist begins to guide the probe over the area in which the SLNs are suspected. The ''X'' mark made in nuclear medicine may be off by several centimeters, but it gives an initial starting point for the incision.

The probe remains in a continuous counting mode, displaying an increase in photon emissions as the SLNs are approached. Examples of these counts are shown in Table 2. A 2-, 5- or 10-s continual count then can be taken to obtain a single counting statistic. The surgeon quickly targets the SLNs through a combination of increasing counts and squelching from the probe. The surgeon also will continuously check for lymph pathways made from the blue dye.

The SLN specimens are excised, counted and sent to pathology. Next the surgeon begins the wide excision by removing the primary melanoma along with the surrounding tissue margin. At this point a background SLN bed count should be recorded. The surgeon may await the immediate frozen section results to see if the specimens are positive for melanoma. If the histology shows melanoma, surgery is completed with a total lymph node dissection (TLND). However, the current trend seems to favor performing the SLN biopsy alone and waiting for a final, permanent histology section result before scheduling a TLND. If the melanoma has not spread (the

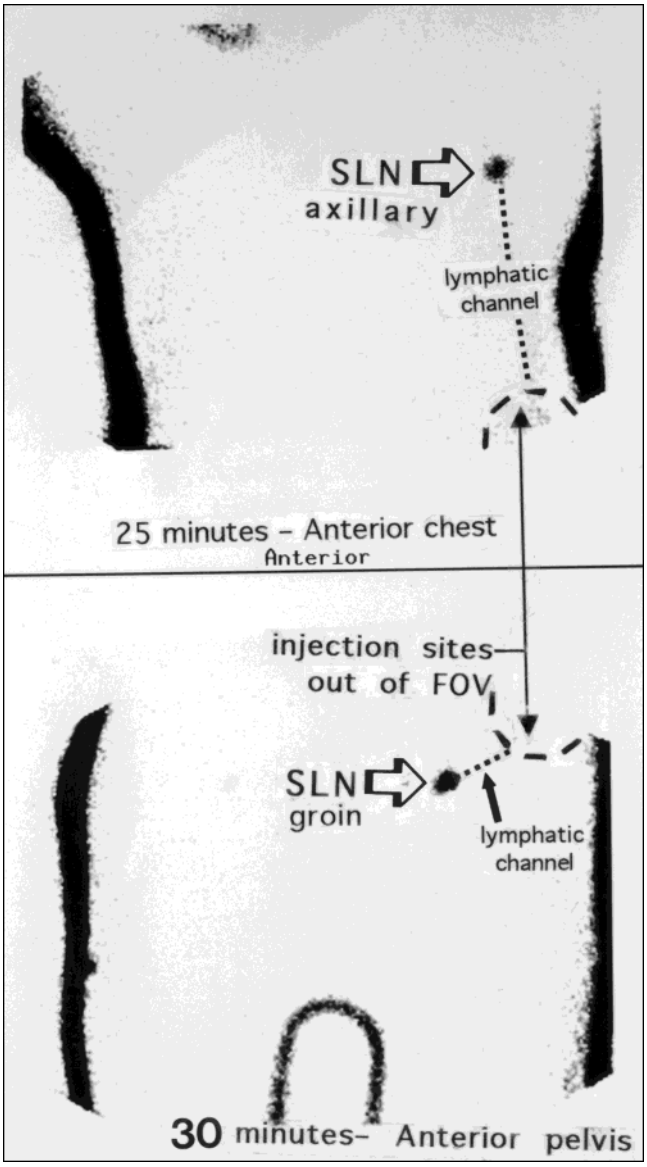

FIGURE 11. Patient with a melanoma on the left lower back within the area of Sappey's line. Lymphatic channels lead upward to a sentinel lymph node in the left axilla and downward to a sentinel lymph node in the left groin.

TABLE 2
Counts Obtained With the Gamma-Detecting Probe in 200 Sentinel Lymph Node Melanoma Biopsy Cases

Time*	Location	Preincisional	Incisional	Excisional	Average cps‡	Body BKG ratio§
<1 min	Body background	11–566 cps†	—	—	169 cps	—
<1 min	Injection sites	16,579–30,888 cps	—	—	26,102 cps	154.4:1
<1–4 min	"X" mark(s) from nuclear medicine	257–7692 cps	—	—	1704 cps	6.4:1
<1–6 min	Suspected SLN(s)	361–13,993 cps	—	—	2211 cps	13.1:1
4–68 min	Suspected SLN(s)	—	1188–19,906 cps	—	4974 cps	29.4:1
2–12 min	SLN(s)	—	—	1628–25,110 cps	8312 cps	49.2:1
<1–11 min	SLN basin before wide excision	—	98–5450 cps	—	591	3.5:1
<1–7 min	SLN(s) basin after wide excision	—	38–1519 cps	—	220	1.3:1

*Time = The minimum and maximum amount of time it would take the gamma-detecting probe to pinpoint the designated location.
†cps = An average number of counts per second of the radioactive source; this table shows the minimum, maximum and average cps.
‡Average cps = The overall total average of a specific location in cps.
§Body background ratio = A quantitative ratio comparing counting statistics from body background to a specified location.

SLN is negative for melanoma), the patient is spared the morbidity associated with TLND.

SUMMARY

Lymphoscintigraphy has proven to be extremely valuable when coupled with intraoperative lymphatic mapping. There are important considerations in deciding to exclude lymphoscintigraphy in this setting. Lymphoscintigraphy routinely shows the expected drainage route to SLN beds, but it also has shown many unsuspected drainage patterns as well. Using only the intraoperative gamma-detecting probe and the blue dye method limits the surgeons' evaluation of the lymphatic drainage. In-transit and unexpected drainage patterns most likely will be ignored without the use of lymphoscintigraphy. The blue dye method provides an excellent visual map of the lymph vessels, but has not been shown to be as reliable as the nuclear medicine method. For these reasons, we will continue to use lymphoscintigraphy, blue dye injections and the gamma-detecting probe for SLN biopsies.

The combined results generated with lymphoscintigraphy, the blue dye and the intraoperative gamma-detecting probe, have proven to be reliable and have changed the standard of care for patients diagnosed with melanoma. To change the standard of care for a particular diagnosis involves proving reliable medical benefits. These benefits include: reduced cost of care; reduced mortality; reduced morbidity; and increased value of life. These benefits are encouraging, but the SLN mapping results must continue to show a correlation with histological results.

Lymphoscintigraphy studies are now being evaluated closely at our institution. We are continuously comparing the onset of SLN visualization times to histology results, the quantity of blue dye uptake to histology results, the long-term follow-up of negative biopsies, and application in other histologically proven tumor types.

CONCLUSION

Lymphoscintigraphy was introduced more than 45 y ago. Technologists must be aware of the specific indication for SLN mapping (*27*). Lymphoscintigraphy is a nuclear medicine diagnostic study and the results directly affect the surgical treatment of melanoma patients. Using experience and good communication, the nuclear medicine and surgical oncology personnel can provide an excellent evaluation of possible lymphatic spread of melanoma.

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