Procedure Guideline for Lymphoscintigraphy and the Use of Intraoperative Gamma Probe for Sentinel Lymph Node Localization in Melanoma of Intermediate Thickness 1.0*

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I. PURPOSE

The purpose of this guideline is to assist nuclear medicine practitioners in recommending, performing, interpreting, and reporting the results of (1) lymphoscintigraphy for identifying sentinel lymph nodes for excisional biopsy in patients with melanoma and (2) the use of the intraoperative gamma probe in the operating room.

II. BACKGROUND INFORMATION AND DEFINITIONS

A. This guideline is written specifically for lymphoscintigraphy in patients with primary melanomas that originate in the skin. Staging of these tumors is based on tumor thickness (Breslow measurement) and level of skin invasion (Clark's level), both of which are determined by the pathologist from a biopsy sample. Ample data correlate patient survival with Breslow and Clark measurements.

In the past, elective lymph node dissection (ELND) of the lymphatic bed believed most likely to drain the primary tumor site (based on Sappey's classic anatomic description of cutaneous lymphatic flow) was used as part of the staging procedure for melanoma. ELND has been a controversial staging procedure for patients with intermediate (I and II)-stage melanoma, because approximately 80% have tumor-negative lymph nodes and therefore do not need ELND, a procedure associated with significant morbidity and cost. The sentinel lymph node excisional biopsy procedure, in contrast, is simpler and not associated with significant morbidity, provides accurate information about lymphatic drainage patterns, and allows the surgeon to make a smaller incision directly over the node, based on the image and probe counts.

Lymphoscintigraphy images readily demonstrate the unpredictability of lymphatic drainage patterns. Sentinel lymph node biopsy, after identification by lymphoscintigraphy and excision using the intraoperative gamma probe and/or blue dye technique, is frequently performed in patients without either clinically apparent metastases or early intermediate-stage melanoma (Clark level, <4; Breslow thickness, 0.76–4 mm) because of its significant diagnostic and prognostic information.

B. Definitions
   1. Lymphoscintigraphy: Imaging pathways of lymphatic flow and lymph nodes after injection of a radiopharmaceutical that is absorbed by the lymphatics.
   2. Sentinel lymph node: The first lymph node in a lymph node bed to receive lymphatic drainage from a tumor. Often drainage to more than 1 lymph node group and sentinel node is identified.
   3. Blue dye technique: Intraoperative injection (usually peritumoral) of isosulfan blue dye for the purpose of staining lymphatic vessels and sentinel lymph nodes so that they can be identified visually during surgery for excisional biopsy.
   4. Gamma-detecting intraoperative probe: Small, hand-held radiation-detecting device that uses auditory signals and meter readouts of counts detected. The intraoperative gamma probe can be used effectively by the surgeon and nuclear medicine physician as a guide to find the radiolabeled sentinel lymph node(s).

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III. COMMON INDICATIONS

A. Sentinel node localization and excision using radionuclide methods are performed in the care of patients with:
   1. Intermediate-stage primary melanoma (Breslow, 0.76–4 mm).
   2. No clinical evidence of nodal involvement.
   3. No clinical evidence of distant tumor spread.

B. Exclusions may include patients with:
   1. Extensive previous surgery in the region of the primary tumor site or targeted lymph node bed.
   2. Patients with known metastases.

IV. PROCEDURE

A. Patient Preparation
   There are no dietary or medication restrictions for the procedure. Patients should follow preoperative restrictions if the procedure is performed on the same day as scheduled surgery.

B. Information Pertinent to Performing the Procedure
   The patient usually has had a previous biopsy that showed cutaneous malignancy and the pathologic classification of the tumor (Breslow, thickness of the tumor, and/or Clark, skin-layer penetration of the tumor, which are prognostic). Recent extensive surgical excision of the primary lesion can be the cause of a rare unsuccessful study because of surgical disruption of lymphatic vessel integrity.

C. Precautions
   If surgery is to be performed using the intraoperative gamma probe to assist in finding the sentinel node, the tracer must be injected approximately 0.5–3 hours before surgery. If surgery is further delayed (by 6 or more hours), another image before surgery is advisable to define further migration of tracer to additional nodes, if any.

D. Radiopharmaceuticals
   No radiopharmaceuticals have been specifically approved by the U.S. Food and Drug Administration for lymphoscintigraphy in the United States. Tc-99m sulfur colloid is used in the United States in a filtered (usually 0.22-μm filtration) or unfiltered form. Smaller particles are generally recommended as more frequent visualization of lymphatic channels is achieved with the filtered formulation.

   There is worldwide variation in radiopharmaceuticals used for lymphoscintigraphy. Tc-99m antimony trisulfide colloid (particle size, 0.015–0.3 μm) and Tc-99m nanocolloid (particle size, 0.05–0.8 μm) are used in Australia and Europe.
   1. Radiotracer injections
      a. Approximately 0.1 mL containing at least 3.7 MBq (100 μCi) Tc-99m sulfur colloid, filtered (0.22-μm millipore filter), is administered as 4–8 peritumoral intradermal injections (fewer than 4 may be performed if appropriate) within 1 cm from the melanoma or the excisional biopsy site at which the melanoma was located.
      b. Injections should surround the lesion or biopsy site to best sample lymphatic drainage in all directions. An exception may be in primary cutaneous melanoma in the head or neck, in which lymphatic drainage is often caudad. Injections inferior to those lesions may be omitted to avoid masking a sentinel node in close proximity to the primary lesion.
      c. The injection should be performed by an authorized user physician or his/her designee.
      d. The high pressure of the intradermal bleb can result in leakage of some of the radioactivity on needle removal. Care should be taken to avoid radioactive contamination, which can be confused with lymph node "uptake."
      e. Gentle finger massage should be considered at each injection site to promote uptake of the tracer into lymphatic channels and lymphatic flow.
      f. The injection site should be covered with a bandaid or cotton ball to prevent leakage of tracer through the needle puncture site.
   2. Dosimetry
      In the dosimetry tables included here, the local radiation dose has been ignored and the effective dose has been calculated assuming that 20% of the administered activity has been absorbed systemically (Kaplan, 1985). The reasons for ignoring the local radiation dose are that:
      a. Deterministic effects (e.g., local skin necrosis) are not a concern for Tc-99m–labeled radiopharmaceuticals.
      b. The estimated local radiation dose varies greatly, depending on the assumptions used (Castronovo, 1994; ICRP 60).
      c. The local radiation dose contributes little to the effective dose. A 50-rem dose averaged over 10 cm^2 skin is comparable with an effective dose of 1.7 mrem (Baum, 2001).
      d. Melanoma is very uncommon in children but lymphoscintigraphy is occasionally performed in children to determine the cause of extremity swelling.

E. Image Acquisition
   1. Acquisition parameters
      Sequential or continuous imaging begins immediately after completion of injections and continues for 30–60 minutes. Continuous imaging may include dynamic imaging at 30 seconds per frame for 2–30 minutes and/or sequential static images every 5 minutes for up to 1 hour or until the sentinel lymph node is identified. For trunk le-

TABLE 1
Radiation Dosimetry for Adults

Radiopharmaceuticals	Administered activity MBq (mCi)	Organ receiving the largest radiation dose[1] mGy/MBq (rad/mCi)	Effective dose[2] mSv/MBq (rem/mCi)
Tc-99m small or large colloids[1]	15–35 Intradermal (0.5–1.0)	0.015 Spleen (0.057)	0.0019 (0.0071)

[1]ICRP 53, pp. 180 and 182.
[2]ICRP 80. Note: Values in this table are only 20% of the values found in ICRP 80 because of the assumption that only 20% of the administered activity is absorbed systemically.

sions, images of both axillary and inguinal regions should be obtained. Lateral or oblique views are often helpful to uncover multiple nodes that overlie one another on a single projection. The patient's body contour may be defined on the image in relation to the injection site, lymph drainage, and sentinel node(s) by transmission imaging or by manual tracing with an external source. Other anatomic structures marked on the images using external sources, particularly in head and neck images, may be useful. Transmission images can be obtained using a Co-57 flood source placed so that the patient is between the camera and the source for about 10–15 seconds during dynamic and static image acquisitions.

2. Skin marking
   Skin is marked over the imaged sentinel node(s) in frontal and lateral views, and/or in the patient's position as it would be on the operating room table. Skin marking can be performed using the probe in nuclear medicine, if available, or using a radioactive marker source. For trunk lesions, images must include both axillary and both inguinal regions. Some unusual locations for sentinel nodes include periscapular, costal, and umbilical regions. The lateral view is essential, especially for distinguishing periscapular from axillary nodes. For head and neck lesions, images should include the entire head and neck in anterior, posterior and/or oblique projections (whichever places the primary tumor and sentinel node(s) closest to the camera face), and the lateral view. Sentinel lymph nodes and lymph drainage are particularly variable and unpredictable in the head and neck. In addition to nuclear medicine personnel, the surgeon should understand imaging techniques and projections.
3. In-transit nodes
   For extremity lesions, the knee or elbow regions should be included in the field of view on dynamic and static images to detect "in-transit" (also called "intercalated") lymph nodes, which are sentinel lymph nodes.

F. Intervention
   Use of the gamma probe in the operating room: Using the images and skin markings as guides, the probe (placed centrally over the regions of highest counts) can be used to select the optimum location for incision. The probe is placed in a sterile sleeve or glove for intraoperative use in the surgical field. The surgeon uses the probe to guide dissection to the hot node(s) and places the probe in the surgical bed after node excision to confirm removal of the hot node(s). In working with the probe, it is important to direct the probe away from activity at the injection sites. Counts are recorded per unit time with the probe in

TABLE 2
Radiation Dosimetry in Children (5 Year Old)

Radiopharmaceuticals	Administered activity mBq (mCi)	Organ receiving the largest radiation dose[1] mGy/MBq (rad/mCi)	Effective dose[2] mSv/MBq (rem/mCi)
Tc-99m small or large colloids[1]	15–35 Intradermal (0.5–1.0)	0.050 Spleen (0.185)	0.0036 (0.013)

[1]ICRP 53, pp. 180 and 182.
[2]ICRP 80. Note: Values in this table are only 20% of the values found in ICRP 80 because of the assumption that only 20% of the administered activity is absorbed systemically.

the operative field, over the node before excision (in vivo) and after excision (ex vivo). A background tissue count is also recorded with the probe pointing away from the injection site, nodal activity, or other physiologic accumulations (i.e., bladder, liver).

G. Processing

To optimize visualization of draining lymph nodes, lowering the upper threshold of the computer display or utilizing other contrast enhancement methods can enhance the low count areas of the image.

H. Interpretation Criteria

1. Image criteria
   a. Dynamic images aid in identifying the sentinel lymph node as the first to receive drainage from the tumor site. The sentinel lymph node is not necessarily the hottest node, although that is often the case.
   b. Separate lymphatic channels that drain to discrete, different lymph nodes identify each of those as distinct sentinel lymph nodes, even though they may be located in the same anatomic region. When drainage to more than 1 anatomic region is seen (e.g., axilla and inguinal), each of those regions must have at least 1 sentinel lymph node.
2. Intraoperative probe criteria
   a. A sentinel lymph node usually has at least 10 times the background counts, taken at a location remote from the injection site.
   b. Various probe criteria have been employed for identification of the sentinel node (e.g., counts per second recorded for the presumed sentinel node have been compared with nonsentinel nodes in vivo, ex vivo, or with background counts in vivo).

I. Reporting

Because surgery usually will be performed before a typed report is available, it is important that the results of this study be communicated to the surgeon expeditiously. A brief written report with annotated images should be sent to the operating room with the patient, or verbal communication with the surgeon and annotated images may be sent with the patient to the operating room. If nuclear medicine physicians or technologists go to the operating room, they should be capable of verbally explaining the imaging results and skin markings.

The final report should contain the following information in addition to routinely reported items, such as the radiopharmaceutical, dose administered, method of injection, and the imaging protocol:

- Location(s) of sentinel lymph node(s), including intransit nodes, if present;
- Presence of lymph channels, if visualized on images;
- Number of secondary lymph nodes visualized on images; and
- Probe recorded counts (per second) of sentinel node(s) in vivo, ex vivo, and in the surgical bed after node excision.

J. Quality Assurance

When external markers are used to assist in skin marking of sentinel nodes, care should be taken to avoid skin contamination. Appropriate calibration of the probe must be performed according to manufacturer instructions.

K. Sources of Error

- Skin contamination.
- Operative positioning different from positioning when overlying skin is marked.
- Failure to begin imaging immediately after injection.
- Failure to use image enhancement techniques, if warranted to visualize low count areas.
- Failure to communicate results expeditiously to the surgeon.
- Mistaking a sentinel node for a secondary node because it has fewer counts than another visualized lymph node.

V. RADIATION SAFETY CONSIDERATIONS

Radiation safety issues arise for operating room personnel, pathology personnel, and nuclear medicine personnel. Nurses, physicians, and technologists involved with patients who undergo lymphoscintigraphy and intraoperative probe sentinel node localization studies are instructed to wear radiation badges according to each institution's policy. Actual exposures from the activity levels used for these procedures are sufficiently low that badging is not essential for individuals who are not involved in other radiation procedures. The decision to badge personnel whose only radiation involvement is with sentinel node studies lies with the local institution. The following information is useful in making this determination.

A. The administered radioactivity is $<$18.5 MBq (500 μCi), of which approximately 1%, 185 kBq (5 μCi), might migrate to a sentinel lymph node.

B. The radiation dose to the hands of the surgeon has been estimated to be 5–94 μSv (0.5–9.0 mrem) per patient. Relative to the radiation doses humans receive in 1 year from cosmic and natural background sources (about 3 mSv [300 mrem] effective whole-body dose), a surgeon could perform roughly 30–60 melanoma sentinel node surgeries in a year and not receive as much finger radiation exposure as that received by the whole body from the natural environmental.

C. Radiation doses to pathology personnel who handle the radioactive sentinel node and primary tumor specimen (including the injection site) for a limited period would be no greater than that received by the surgeon.

Therefore, the histologic specimen can be processed without delay, and patient care is not compromised.

D. Radioactive waste from the operating room (sponges, etc.) and pathology should be collected according to institutional radiation safety procedures. This waste will also be a biohazard and should be handled accordingly.

VI. ISSUES REQUIRING FURTHER CLARIFICATION

A. Optimal radiopharmaceutical.
B. Importance and reproducibility of identifying the first lymph node to appear on imaging.
C. Outcomes for patients using strategies based on sentinel node studies.

VII. CONCISE BIBLIOGRAPHY

A. Alazraki N, Eshima PD, Eshima LA, et al. Lymphoscintigraphy, the sentinel node concept, and the intraoperative gamma probe in melanoma, breast cancer, and other potential cancers. *Semin Nucl Med* 1997;27:55–67.
B. Baum JW. Analysis of potential radiobiological effects related to a unified skin dose limit. *Health Phys* 2001;80:537–543.
C. Bennett LR, Lago G. Cutaneous lymphoscintigraphy in malignant melanoma. *Semin Nucl Med* 1983;13: 61–69.
D. Bongers V, Borel Rinkes IH, Barneveld PC, et al. Towards quality assurance of the sentinel node procedure in malignant melanoma patients: a single institution evaluation and a European survey. *Eur J Nucl Med* 1999;26:84–90.
E. Castronovo FP, McKusick AK, Strauss HW. Dosimetric consequences of radiopharmaceutical infiltrations. *Invest Radiol* 1994;29:59–64.
F. Glass EC, Essner R, Morton DL. Kinetics of three lymphoscintigraphic agents in patients with cutaneous melanoma. *J Nucl Med* 1998;39:1185–1190.
G. Hillier DA, Royal HD. Intraoperative gamma radiation detection and radiation safety. In: Whitman ED, Reintgen D, eds. *Radioguided Surgery*. Austin, TX: Landes Bioscience; 1998:23–38.
H. International Commission on Radiological Protection. *Radiation Dose to Patients from Radiopharmaceuticals.* ICRP Publication 53. New York, NY: Pergamon Press; 1987.
I. International Commission on Radiological Protection. *Recommendations of the International Commission on Radiological Protection.* ICRP Publication 60. Washington, DC. 1991;21:1–3.
J. International Commission on Radiological Protection. *Radiation Dose to Patients from Radiopharmaceuticals.* ICRP Publication 80. New York, NY: Pergamon Press; 1999.
K. Kaplan WD, Piez CW, Gelman RS, et al. Clinical comparison of two radiocolloids for internal mammary lymphoscintigraphy. *J Nucl Med* 1985;26:1382–1385.
L. Logic JR, Balch CM. Defining lymphatic drainage patterns with cutaneous lymphoscintigraphy in melanoma patients. In: *Human Melanoma: Surgical Treatment, Pathology and Progress.* Philadelphia, PA: J.B. Lippincott Co.; 1984.
M. Miner TJ, Shriver CD, Flicek PR, et al. Guidelines for the safe use of radioactive materials during localization and resection of the sentinel lymph node. *Ann Surg Oncol* 1999;6:75–82.
N. Mudun A, Murray DR, Herda SC, et al. Early stage melanoma: lymphoscintigraphy, reproducibility of sentinel node detection, and effectiveness of the intraoperative gamma probe. *Radiology* 1996;199:171–175,
O. Murray DR, Carlson GW, Greenlee R, et al. Surgical management of malignant melanoma using dynamic lymphoscintigraphy and gamma probe-guided sentinel lymph node biopsy: the Emory experience. *Am Surg* 2000;66:763–767.
P. Statius Muller MG, van Leeuwen PA, Borgstein PJ, et al. The sentinel node procedure in cutaneous melanoma: an overview of 6 years' experience. *Eur J Nucl Med* 1999;26:S20–S25.
Q. Uren RF, Howman-Giles RB, Shaw HM, et al. Lymphoscintigraphy in high-risk melanoma of the trunk: predicting draining node groups, defining lymphatic channels and locating the sentinel node. *J Nucl Med* 1993;34:1435–1440.
R. Waddington WA, Keshtgar MR, Taylor I, et al. Radiation safety of the sentinel lymph node technique in breast cancer. *Eur J Nucl Med* 2000;27:377–391.

VIII. DISCLAIMER

The Society of Nuclear Medicine has written and approved guidelines to promote the cost-effective use of high-quality nuclear medicine procedures. These generic recommendations cannot be applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures or exclusive of other procedures reasonably directed to obtaining the same results. The spectrum of patients seen in a specialized practice setting may be quite different than the spectrum of patients seen in a more general practice setting. The appropriateness of a procedure will depend in part on the prevalence of disease in the patient population. In addition, the resources available to care for patients may vary greatly from one medical facility to another. For these reasons, guidelines cannot be rigidly applied.

Advances in medicine occur at a rapid rate. The date of a guideline should always be considered in determining its current applicability.