Appropriate Use Criteria for Lymphoscintigraphy in Sentinel Node Mapping and Lymphedema/Lipedema

Kevin J. Donohoe[1], Brett J. Carroll[2], David K. V. Chung[3], Elizabeth H. Dibble[1,4], Emilia Diego[5], Francesco Giammarile[6], Frederick D. Grant[1], Stephen Y. Lai[7], Hannah Linden[8], Megan E. Miller[9], Neeta Pandit-Taskar[1,10], Nicholas E. Tawa Jr.[11], Sergi Vidal-Sicart[6]

[1]Society of Nuclear Medicine and Molecular Imaging, [2]Society for Vascular Medicine, [3]Australia and New Zealand Society of Nuclear Medicine, [4]American College of Radiology, [5]Society of Surgical Oncology, [6]European Association of Nuclear Medicine, [7]American Head and Neck Society, [8]American Society of Clinical Oncology, [9]American Society of Breast Surgeons, [10]American College of Nuclear Medicine, [11]American College of Surgeons
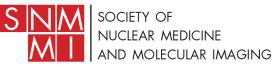
EXECUTIVE SUMMARY

Nuclear medicine is an essential tool in the delivery of high-quality medical care, going beyond simple anatomical imaging to the use of physiological processes for both imaging and therapy. Nuclear medicine techniques were applied to the lymphatic system as early as the 1950s by Sherman et al. (*1*), using [198]Au colloid (a beta emitter) as a therapeutic agent for lymph node metastasis. In the late 1960s and early 1970s, the ready availability of technetium-99m (^{99m}Tc) allowed more widespread lymphatic imaging (lymphoscintigraphy) with ^{99m}Tc colloid. In 1976, Ege (*2*) studied lymphatic flow in 848 patients, suggesting lymphoscintigraphy could demonstrate variable lymphatic drainage patterns, therefore allowing more accurate radiation therapy fields. In recent years, advances in radiopharmaceuticals and imaging technology have allowed more accurate localization of lymph nodes during lymphoscintigraphy and the development of the sentinel lymph node (SLN) concept.

One of the first mentions of SLN was made in 1960 by Gould and Philben (*3*). They described a specific location of a node that drained the parotid gland. This node, located at the junction of the anterior and posterior facial veins, was described as the node most likely to contain metastasis. It was recommended that this node be investigated first before carrying out complete node dissection (*3*). The SLN concept was further explored by Cabanas (*4*) in 1977 when lymphangiography with contrast was used to identify a specific location for lymphatic drainage from the penis. Similar to what was described by Gould and Philben, Cabanas (*4*) felt that this 1 specific lymph node (located at the superficial epigastric vein by Cabanas for penile carcinoma) could be defined as the SLN for all patients.

Individual variations demonstrated in the lymphatic channels and the location of the sentinel node since the initial investigations have confirmed that mapping of lymphatic drainage needs to be carried out for each patient undergoing SLN sampling. SLN identification can be done with optical agents, such as isosulfan or methylene blue, as well as with radiotracers and fluorescent tracers. Localization of the SLN(s) with these techniques in individual patients has allowed a more focused investigation of nodal drainage from a primary tumor site, preventing the morbidity and mortality of complete node bed dissection in patients with no clinical evidence of tumor in the regional nodal basin (*5*). One difficulty with reviewing the literature describing lymphoscintigraphy is the variety of tracers in use around the world and throughout the history of lymphoscintigraphy. Smaller particles tend to move through the lymphatics more quickly. Some tracers are more likely to stop at the first node they encounter, while others are more likely to move through the lymphatic system more readily, demonstrating channels, node beds, and central lymphatic structures. The tracer used depends on the clinical indication (e.g., sentinel node scintigraphy, lymphedema, or lymphatic vessel integrity), as well as availability and local regulations. In the United States, there are only 2 tracers generally available for clinical use: [99m]Tc sulfur colloid and ^{99m}Tc tilmanocept. In addition, injection techniques, imaging protocols, and camera technology can vary substantially, making comparisons between studies challenging. A discussion of these technical differences is beyond the scope of this document.

These appropriate use criteria (AUC) have been developed to describe the appropriate use of radiopharmaceuticals for lymphoscintigraphy in SLN mapping and lymphedema. It is hoped that through these recommendations, nuclear medicine lymphatic imaging techniques will be used to benefit patients in the most cost-effective manner.

Representatives from the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the Society for Vascular Medicine (SVM), the Australia and New Zealand Society of Nuclear Medicine (ANZSNM), the American College of Radiology (ACR), the Society of Surgical Oncology (SSO), the European Association of Nuclear Medicine (EANM), the American Head and Neck Society (AHNS), the American Society of Clinical Oncology (ASCO), the American Society of Breast Surgeons (ASBrS), the American College of Nuclear Medicine (ACNM), and the American College of Surgeons (ACS) assembled as an autonomous workgroup to develop

these AUC. This process was performed in accordance with the Protecting Access to Medicare Act of 2014 (*6*). This legislation requires that all referring physicians consult AUC by using a clinical decision support mechanism before ordering any advanced diagnostic imaging services.

Such services are defined as diagnostic magnetic resonance imaging (MRI), computed tomography (CT), and nuclear medicine procedures, including positron emission tomography (PET) and others, as specified by the Secretary of Health and Human Services in consultation with physician specialty organizations and other stakeholders (*3*).

Lymphoscintigraphy usually causes trivial radiation exposures for the patient, the surgeon, and the staff handling any specimens that may contain radioactivity. Local regulations that address the handling of radiopharmaceuticals and exposure of the public should always be followed. Radiation exposures are also trivial for pregnant patients and infants exposed to someone who has been injected with lymphoscintigraphic agents labeled with ^{99m}Tc. The amount of radiopharmaceutical transferred from the interstitium into the blood and from the blood to the milk is very low. However, when performing an SLN procedure for breast cancer, it seems prudent to recommend the interruption of direct breastfeeding for 24 hours after administration of the radiopharmaceutical. There is a potential for more fetal or infant exposure if the radioisotope dissociates from the radiopharmaceutical; however, exposures will remain very small and likely of no consequence. The rapid decay of ^{99m}Tc (6-hour half-life) also allows for rapid return of radiation exposures to background levels within a short time. More detailed information can be found in the document "Advisory Committee on Medical Uses of Isotopes (ACMUI) Sub-Committee on Nursing Mother Guidelines for the Medical Administration of Radioactive Materials" (https://www.nrc.gov/docs/ML1803/ML18033B034.pdf).

INTRODUCTION

This document describes the appropriate use of nuclear medicine for SLN and lymphedema lymphoscintigraphy. Common clinical scenarios for scintigraphy in patients are addressed, the most common clinical use of lymphoscintigraphy currently being for SLN detection of breast and cutaneous malignancies; therefore, these indications are covered in more detail in this document. However, the value of lymphoscintigraphy is recognized for SLN detection in other malignancies, as well as for mapping lymphatic flow in lymphedema. Where literature and expert opinion are available, these additional clinical indications are discussed. The reader is reminded that a patient may present with variations of the scenarios covered here, or with signs or symptoms not described, for which nuclear medicine techniques may still be indicated. This document is presented to assist health care practitioners in considering nuclear lymphoscintigraphy. However, each patient is unique; therefore, this document cannot replace clinical judgment.
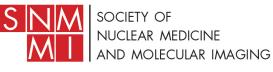
METHODOLOGY
Expert Workgroup Selection

The experts of this AUC workgroup were convened by the SNMMI to represent a multidisciplinary panel of health care providers with substantive knowledge in the use of nuclear medicine in lymphoscintigraphy. In addition to SNMMI members, representatives from the SVM, ANZSNM, ACR, SSO, EANM, AHNS, ASCO, ASBrS, and ACNM were included in the workgroup. Thirteen physician members were ultimately selected to participate and contribute to the AUC. A complete list of workgroup participants and external reviewers can be found in Appendix A.

In addition, Appendix B presents a summary of definitions of terms and acronyms, Appendix C provides the disclosures and conflicts-of-interest statement, and Appendix D describes the solicitation of public commentary.

AUC Development

The process for AUC development was modeled after the RAND/UCLA Appropriateness Method for AUC development (*7*). The process included identification of a list of relevant clinical scenarios in which lymphoscintigraphy may be used, a systematic review of evidence related to these clinical scenarios, and a systematic synthesis of available evidence, followed by grading of each of the clinical scenarios through the use of a modified Delphi process. In addition, this process strove to adhere to Institute of Medicine standards for developing trustworthy clinical guidance (*8*). The final document was drafted on the basis of group ratings and discussions.

Scope and Development of Clinical Scenarios

To begin this process, the workgroup discussed various potential clinical indications and applicable scenarios for the use of lymphoscintigraphy. For all indications, the relevant populations were patients with cancer or lymphedema. The workgroup identified 4 clinical categories (breast cancer, skin cancer, cancer of other sites, lymphedema) with a total of 32 clinical scenarios for this document. The resulting AUC are based on evidence and expert opinion regarding diagnostic accuracy and effects on clinical outcomes and clinical decision making. Other factors affecting the AUC recommendations were potential harm—including long-term harm that may be difficult to capture—costs, availability, and patient preferences.

Systematic Review

The Pacific Northwest Evidence-based Practice Center at the Oregon Health and Science University conducted a literature review, led by Roger Chou, MD, FACP, to synthesize evidence on lymphoscintigraphy. The workgroup asked 4 key questions:

1. In patients undergoing nodal staging for breast cancer, squamous cell skin cancer, basal cell skin cancer, melanoma, cervical cancer, head and neck cancer, penile cancer, or vulvar cancer, what proportion undergoing lymphoscintigraphy are identified as having a sentinel node?
2. In patients undergoing nodal staging for breast cancer, squamous cell skin cancer, basal cell skin cancer, melanoma, cervical cancer, head and neck cancer, penile cancer, or vulvar cancer, what is the accuracy of lymphoscintigraphy for staging?
3. In patients with lymphatic dysfunction, what is the accuracy of lymphoscintigraphy for identifying normal/abnormal lymphatic flow?
4. In patients with lymphatic dysfunction, what are the effects of performing lymphoscintigraphy versus no lymphoscintigraphy on management decisions?

The inclusion criteria for the search were based on population, intervention, comparators, and timing. A protocol for each systematic review defined parameters for a targeted literature search. Additional parameters included relevant study designs, literature sources, types of reports, and prespecified inclusion and exclusion criteria for the literature identified.

The Cochrane Central Register of Controlled Trials (through February 2021), Cochrane Database of Systematic Reviews, and Ovid MEDLINE (through April 5, 2021) databases were searched, along with a reference list review and studies suggested by the workgroup members.

Data Extraction

Literature results were reviewed and deemed appropriate by Pacific Northwest Evidence-based Practice Center staff. A total of 2,300 citations were reviewed, resulting in a review of 307 full-text papers. The papers represented 140 studies across the cancer types. The evidence was evaluated qualitatively by considering the small number of studies, variability in populations, radiopharmaceuticals, and reference standards, among other factors. The quality was assessed by using criteria adapted from QUADAS (Quality Assessment of Diagnostic Accuracy Studies). The strength of the evidence for each key question was assessed, using the GRADE approach, on the basis of study limitations, inconsistency, imprecision, indirectness, and reporting bias.

Rating and Scoring

In developing these criteria, the workgroup members used the following definition of appropriateness to guide their considerations and group discussions: "The concept of appropriateness, as applied to health care, balances risk and benefit of a treatment, test, or procedure in the context of available resources for an individual patient with specific characteristics." At the beginning of the process, workgroup members convened via webinars to develop the initial clinical indications. On evaluating the evidence summary of the systematic literature review, the workgroup further refined its draft clinical indications to ensure their accuracy and to facilitate consistent interpretation when scoring each indication for appropriateness. Using the evidence summary, workgroup members were first asked individually to assess the appropriateness and to provide a score for each of the identified indications. Workgroup members then convened in a group setting for several successive webinars to discuss each

indication and associated scores from the first round of individual scoring. After deliberate discussion, a consensus score was determined and then assigned to the associated appropriate use indication. For this scoring round, the expert panel was encouraged to include their clinical expertise in addition to the available evidence in determining the final scores. All members contributed to the final discussion, and no one was forced into consensus. After the rating process was completed, the final appropriate use ratings were summarized in a format similar to that outlined by the RAND/UCLA Appropriateness Method.

The workgroup scored each indication as "appropriate," "may be appropriate," or "rarely appropriate" on a scale from 1 to 9. Scores 7–9 indicate that the use of the procedure is appropriate for the specific clinical indication and is generally considered acceptable. Scores 4–6 indicate that the use of the procedure may be appropriate for the specific indication. This implies that more research is needed to classify the indication definitively. Scores 1–3 indicate that the use of the procedure is rarely appropriate for the specific indication and is generally not considered acceptable.

As stated by other societies that develop AUC, the division of these scores into 3 general levels of appropriateness is partially arbitrary, and the numeric designations should be viewed as a continuum. In addition, if there was a difference in clinical opinion for an indication such that workgroup members could not agree on a common score, that indication was given a "may be appropriate" rating to indicate a lack of agreement on appropriateness based on available literature and the members' collective clinical opinion, indicating the need for additional research.

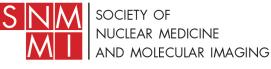**BREAST CANCER**

Introduction

In the United States, breast cancer is the most common malignancy in women and the second leading cause of cancer death in women (9). All patients with breast cancer should be assigned a clinical or, when appropriate, pathological stage, as this informs both treatment options and prognosis. Accurate nodal assessment is essential to accurate breast cancer staging and prognostication.

Background

Historically, breast cancer treatment consisted of lumpectomies and breast amputations without anesthesia. In 1882, William Halsted (10) performed the first radical mastectomy, which consisted of removal of all breast tissue, all axillary lymph nodes, and both pectoralis muscles. The surgery was disfiguring, and complications included arm weakness and lymphedema.

Since then, treatment for breast cancer has become progressively less invasive. Research over the past 40 years has shown similar survival rates in women with early-stage breast cancer treated with lumpectomy and radiation as for women treated with mastectomy (11,12). For patients requiring mastectomy, the radical mastectomy has largely been replaced with the modified radical mastectomy (13), which leaves the pectoralis muscles in place and can spare the nipple when appropriate. Lymphadenectomy, however, has remained important for staging and locoregional control. Imaging can identify potentially abnormal lymph nodes, but tissue is required for more accurate local nodal staging.

Based on early work by Morton et al. (14) in patients with melanoma, SLN biopsy (SLNB) was evaluated in patients with breast cancer and clinically node-negative disease. In theory, the SLN represents the first lymph node with direct lymphatic drainage from the primary tumor. Of the subset of patients who have non-visualization of an SLN on lymphoscintigraphy, most will have at least 1 lymph node detected intraoperatively. Multiple randomized trials have shown that SLNB can safely be performed in place of axillary lymph node dissection (ALND) for women with small tumors of <2 cm and no clinical evidence of metastatic disease, and SLNB has lower rates of lymphedema and other morbidities than ALND does (15,16). The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial (17) further showed that SNLB was sufficient for patients with only 1 or 2 positive axillary lymph nodes. The ACOSOG Z1071 (Alliance) (17), SENTINA (SENTinel NeoAdjuvant) (18), and SN FNAC (Sentinel Node biopsy after NeoAdjuvant Chemotherapy) (19) trials showed that SLNB can also be acceptable in patients with known axillary lymph node metastases who complete neoadjuvant chemotherapy with good clinical response. Further, the AMAROS trial (Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer [European Organization for Research and Treatment of Cancer 10981-22023]) showed that axillary radiation has decreased morbidity and is an acceptable alternative to ALND for patients with positive SLNs (20).

Clinical Scenarios and AUC Scores

Clinical scenarios for the use of lymphoscintigraphy in patients with breast cancer and final AUC scores are presented in Table 1.

Scenario 1: Invasive breast cancer of any histological type without evidence of axillary or distant metastases and without evidence of skin or chest wall invasion (Score: 9 – Appropriate)

Lymphoscintigraphy for SLNB is appropriate for patients with T1 and T2 (<5 cm) invasive breast cancer without evidence of axillary or distant metastases (*17*). SLNB can be omitted in patients whose axillary status will not change adjuvant treatment. Most notably, SLNB can be omitted in patients ≥70 years old with early-stage, hormone receptor-positive, HER2-negative breast cancer.

Although most clinical trials of SLNB versus ALND limit the use of SLNB to patients with small primary tumors, SLNB can be appropriate in patients with larger tumors and clinically node-negative disease. Patients with inflammatory breast cancer and patients with skin and/or chest wall involvement of tumor are not candidates for SLNB due to high false-negative rates, possibly due to altered lymphatic drainage.

Scenario 2: Invasive breast cancer of any histological type with pathological evidence of axillary metastases and no evidence of skin or local chest wall invasion or distant metastases (Score: 5 – May be Appropriate)

Patients with breast cancer who have node-positive disease prior to neoadjuvant therapy can undergo SLNB after neoadjuvant therapy if they meet all ACOSOG Z1071 criteria (*21*). The false-negative rate of SLNB is improved by placing a clip in the initially diagnosed positive node to confirm removal at the time of surgery, using a dual-tracer technique, and removing >2 SLNs (*22,23*). Patients who have axillary micrometastases identified at SLNB do not need to undergo additional ALND (*24*). There is no evidence of benefit of SLNB over ALND in patients with invasive breast cancer with evidence of axillary metastases (not micrometastases) who do not meet ACOSOG Z1071 criteria.

Scenario 3: Invasive breast cancer of any histological type with evidence of distant metastases (Score: 5 – May be Appropriate)

Because lymphoscintigraphy is used for primary staging of breast cancer without clinical evidence of metastatic disease, lymphoscintigraphy for SLNB is usually not appropriate for patients with known distant metastases. In patients with oligometastatic disease treated with curative intent, however, SLNB may be appropriate.
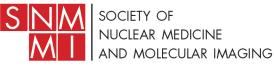
Scenario 4: Ductal carcinoma in situ (DCIS) without suspicious features and DCIS or pleomorphic lobular carcinoma in situ (LCIS) without planned mastectomy or other surgery affecting lymphatic drainage (Score: 2 – Rarely Appropriate)

DCIS by definition is not invasive cancer and therefore typically does not require axillary evaluation by SLNB. SLNB is usually not appropriate for patients who are undergoing breast-conserving surgery without planned mastectomy or large oncoplastic rearrangement or reduction (*25*).

Scenario 5: DCIS with suspicious features or DCIS or pleomorphic LCIS with planned mastectomy or other surgery affecting lymphatic drainage (Score: 8 – Appropriate)

DCIS by definition is not invasive cancer and therefore typically does not require axillary evaluation by SLNB. Patients with DCIS who are undergoing total mastectomy or large oncoplastic rearrangement or reduction, however, should undergo SLNB (*26*). Postmastectomy lymphatic drainage will be altered and subsequent SLNB may not be accurate if invasive cancer is identified on the mastectomy specimen. Similarly, patients undergoing lumpectomy for DCIS at a site that would compromise future SLN mapping (e.g., the axillary tail or central breast) may undergo SLNB at the time of lumpectomy. In addition, patients with DCIS with suspicious features such as a large or palpable area (*26,27*) can undergo SLNB at the time of lumpectomy to eliminate the need for a possible second surgery to evaluate the axilla if invasive cancer is found on surgical pathology after lumpectomy.

Scenario 6: Planned reduction mammoplasty or risk-reducing mastectomy in patients without a known breast cancer diagnosis (Score: 1 – Rarely Appropriate)

Although SLNB can be considered in patients with contralateral locally advanced breast cancer (*28*), it is usually not appropriate in patients undergoing breast surgery without a known cancer.

Scenario 7: In-breast recurrence or de novo ipsilateral breast cancer without evidence of axillary or distant metastases and without evidence of skin or chest wall invasion (Score: 9 – Appropriate)

Although SLNB appears to be accurate in patients with prior excisional biopsies, patients with more extensive prior breast or axillary surgery, including prior reduction mammoplasty, breast lumpectomy for breast cancer (especially with adjuvant radiation), and breast augmentation may have altered lymphatic flow that reduces the accuracy of SLNB. There are, however, studies showing successful second SLNB in patients with recurrent breast cancer. The Sentinel Node and Recurrent Breast Cancer studies showed that repeat SLNB had no impact on survival, although the findings warrant validation with a larger prospective study. Repeat SLNB can be considered in patients with recurrent breast cancer and prior SLNB (*29,30*), although the accuracy is unknown. Lymphoscintigraphy can be considered in order to evaluate altered lymphatic drainage in the postsurgical breast.

Scenario 8: Inflammatory breast cancer or breast cancer with evidence of skin or local chest wall invasion (Score: 1 – Rarely Appropriate)

ALND is favored over SLNB in patients with locally advanced or inflammatory breast cancer (*25*). Although SLNB can be accurate in patients with larger tumors and clinically node-negative disease, SLNB is usually not appropriate in patients with inflammatory carcinomas and tumors with skin and/or chest wall involvement due to the high false-negative rate likely related to altered lymphatic drainage (*26,31*).

Scenario 9: Phyllodes tumor (Score: 1 – Rarely Appropriate)

Phyllodes tumors rarely metastasize to axillary lymph nodes. Metastasis of a phyllodes tumor is through presumed hematogenous spread with common sites, including lungs, pleura, and bones. Therefore, SLNB is usually not appropriate for patients with phyllodes tumor, including benign, borderline, and malignant phyllodes. In most cases, wide excision should be performed without axillary staging (National Comprehensive Cancer Network [NCCN]) (*32*).

Scenario 10: Paget's disease of the breast, cancer not identified prior to surgery (Score: 6 – May be Appropriate)

If a patient has Paget's disease and plans to undergo mastectomy for treatment of Paget's disease or associated DCIS, SLNB should be performed (*33*).

If breast cancer is not identified prior to breast-conserving surgery for Paget's disease, SLNB can be omitted. If breast cancer is subsequently identified at the time of surgery, SLNB should be performed in accordance with management recommendations of the primary cancer.

If a patient has known DCIS associated with Paget's disease, but no evidence of invasive cancer and plans to undergo breast-conserving surgery, SLNB may not be necessary (*34*).

TABLE 1
Clinical Scenarios for Breast Cancer

Scenario no.	Description	Appropriateness	Score
1	Invasive breast cancer of any histological type without evidence of axillary or distant metastases and without evidence of skin or chest wall invasion	Appropriate	9
2	Invasive breast cancer of any histological type with pathological evidence of axillary metastases and no evidence of skin or local chest wall invasion or distant metastases	May be Appropriate	5

3	Invasive breast cancer of any histological type with evidence of distant metastases	May be Appropriate	5
4	Ductal carcinoma in situ (DCIS) without suspicious features and DCIS or pleomorphic lobular carcinoma in situ (LCIS) without planned mastectomy or other surgery affecting lymphatic drainage	Rarely Appropriate	2
5	DCIS with suspicious features and DCIS or pleomorphic LCIS with planned mastectomy or other surgery affecting lymphatic drainage	Appropriate	8
6	Planned reduction mammoplasty or risk-reducing mastectomy in patients without a known breast cancer diagnosis	Rarely Appropriate	1
7	In-breast recurrence or de novo ipsilateral breast cancer without evidence of axillary or distant metastases and without evidence of skin or chest wall invasion	Appropriate	9
8	Inflammatory breast cancer or breast cancer with evidence of skin or local chest wall invasion	Rarely Appropriate	1
9	Phyllodes tumor	Rarely Appropriate	1
10	Paget's disease of the breast, cancer not identified prior to surgery	May be Appropriate	6

Summary of Recommendations

The use of radiopharmaceuticals for SLN mapping in breast cancer is appropriate for patients <70 years old following the initial diagnosis of invasive breast cancer of any histological type as long as there is no physical examination or imaging evidence of axillary or distant metastasis, either in the de novo setting or in the setting of an in-breast recurrence. In patients with evidence of local or distant metastatic disease, however, the benefit of SLN mapping is less apparent.

SLNB may be appropriate in patients ≥70 years old if the results will impact adjuvant treatment. It may also be considered appropriate in patients with DCIS or pleomorphic LCIS for whom a mastectomy is planned, or in the setting of breast breast-conserving surgery where the procedure may affect future lymphatic mapping, and the suspicion for upstaging to invasive disease is present.
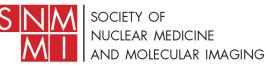
SLN mapping is rarely appropriate in patients diagnosed with an inflammatory breast cancer or breast cancer with evidence of skin or local chest wall invasion, Paget's disease of the breast without evidence of an underlying invasive cancer identified prior to surgery, or Phyllodes tumors, or in the setting of a prophylactic mastectomy or reduction mammoplasty in women without a history of breast cancer.

SKIN CANCER

Introduction

Many tumors arising in the skin have a propensity for lymphatic metastasis. For certain histological structures such as melanoma and Merkel cell carcinoma (MCC), SLNB has become the accepted standard of care for initial staging in the absence of clinically evident metastatic disease. More controversial lesions for SLNB include non-melanoma primary tumors such as squamous cell carcinoma (SCC) and malignant cutaneous adnexal tumors (MCATs) such as eccrine carcinoma, although for genital primary SCC arising in the vulva or penis, SLNB is now common practice.

When initially described by Morton et al. (14), Bagaria et al. (35), Kelley et al. (36), and Krag (37), the technique for SLNB included lymphoscintigraphy with concurrent injection of a vital dye (lymphazurin, methylene blue) for visual as well as scintigraphic identification of the node at surgery in order to increase the overall diagnostic yield of the procedure. However, use of vital dyes has become more variable over time, particularly in cosmetically more sensitive areas, although it remains

standard practice in some regions (e.g., Australia). In addition to cosmetic concerns, there is a very small risk of anaphylaxis with vital dyes.

Another technical consideration is the scintigraphic agent used for lymphatic mapping. For example, technetium99m (^{99m}Tc) sulfur colloid has a stable molecular bond to technetium and can be used at any anatomical site. However, tilmanocept, a more recently introduced agent, is composed of a dextran backbone with multiple glucose and mannose residues attached to diethylenetriamine pentaacetic acid for ^{99m}Tc labeling. Tilmanocept offers more rapid transit and better sequestration in the SLN with less diffusion to secondary nodes, and it is receptor targeted (CD206) to reticuloendothelial cells (38). However, tilmanocept dissociates more rapidly from ^{99m}Tc in vivo, leading to urinary excretion and progressive bladder radioactivity, which can make probe localization of nodal activity adjacent to the bladder difficult. Therefore, for truncal or lower extremity primary tumors with the potential to drain to the inguinal-femoral nodal basin, tilmanocept may be less desirable. For primary lesions high on the trunk, in the upper extremities, and in the head and neck, tilmanocept can be useful.

The imaging technology used for lymphoscintigraphy can influence the success of surgical localization. Planar imaging can be complemented with single-photon emission computed tomography combined with CT (SPECT/CT) in anatomical sites where the location of the SLN may be unusually complex (39,40). For example, for a head and neck cutaneous primary lesion, the SLN may often be found within the superficial parotid gland. In the head and neck in particular, the injection site is often in close proximity to the SLN, which can make it difficult to find the node with planar imaging alone. In the case of a lower extremity or truncal lesion, drainage to external iliac or other deep pelvic locations is frequent and can be confused with a more accessible superficial inguinal focus. SPECT/CT may also be valuable in patients with elevated body mass index. The addition of SPECT/CT provides 3-dimensional information about the location of the sentinel node, including its relationship to vital structures. Another general principle is that although any radioactive node is by definition "sentinel," an anatomically deep focus such as a pelvic external iliac or thoracic internal mammary node would in most instances not be considered appropriate for surgical retrieval if the morbidity of dissection required to retrieve the target is considered unacceptable. For example, retrieval of deep pelvic nodes, if felt to be secondary echelon nodes, would not be acceptable, but if the same nodes are considered primary SLNs, retrieval should be considered. In these cases, SPECT/CT can again be helpful in identifying the location, size, and contour of the node for future anatomical imaging follow-up, if appropriate.
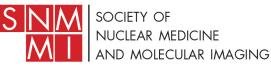
Clinical Scenarios and AUC Scores

Clinical scenarios for the use of lymphoscintigraphy in patients with skin cancer and final AUC scores are presented in Table 2.

Scenario 11: Cutaneous melanoma without clinical evidence of metastasis (Score: 9 – Appropriate)

Prior to the introduction of SLNB, lymphatic staging for melanoma in the absence of clinical or radiological evidence of metastasis consisted of elective, anatomically complete nodal basin lymphadenectomy. Patients were selected for lymphadenectomy on the basis of perceived risk for nodal metastasis (e.g., initial T-stage) and on non-validated anatomical "rules" predicting where a metastatic node should be found. Such approaches could miss the relevant basin, which could result in delayed appearance of local-regional metastasis. The work of Morton and collaborators (14) in the early 1990s demonstrated that when SLNB was followed by immediate complete lymphadenectomy of the affected basin, the incidence of a metastatic "non-sentinel" node being found when the SLN was histologically normal was only 1%–2%. In an environment with experienced surgeons and nuclear medicine clinicians, an SLN will be recovered in the vast majority of patients. The incidence of false-negative nodal staging in such an environment will be low (<5%). False-negative rates are influenced by the likelihood of true positives in a particular cohort. The negative predictive value (NPV) of SLNB was 95% or greater and the rate of false positives 11% in the large Sunbelt Melanoma Trial (41).

One issue is how a false-negative node is defined. From a practical standpoint, a false negative occurs when a delayed metastasis appears in the nodal basin where the SLN had been declared normal, or in another draining basin that had not been identified at the time of the original lymphoscintigram. A much more difficult interpretation is when a patient otherwise staged as having a favorable overall prognosis (e.g., node negative) shows a more aggressive natural history than predicted. In such an instance, it is impossible to discern whether the poor outcome resulted from a false-negative SLNB, or simply reflects the limitations of a truly negative SLN in predicting future hematogenous spread.

Several studies have shown that at initial presentation, the status of the SLN is one of the most important multivariate predictors of hematogenous metastasis and death from melanoma (42). In addition to prognosis, a positive SLNB with

progression to stage III disease allows for the selection of adjuvant therapy, which has become highly effective in lowering rates of subsequent hematogenous metastasis following the advent of immune checkpoint and protein kinase inhibitor therapies. A third, often overlooked, rationale for SLNB in melanoma is improved local-regional control and the prevention of bulky metastasis, the resection of which can be technically challenging and morbid. For example, in an elderly patient with a high-risk T4b lesion, there would be no survival advantage if an occult positive SLN were demonstrated. However, early retrieval of such a node, in this instance predicted to be metastatic in up to 60% of patients, will often avoid the need for a much larger palliative procedure in the future.
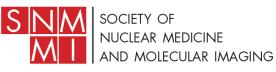
The scope of this document does not allow for discussion of completion regional lymphadenectomy following a positive SLNB, although recent and conclusive American (Multicenter Selective Lymphadenectomy Trial II [MSLT-II]) and European trials (Dermatologic Cooperative Oncology Group-Sentinel Lymph Node Trial) have shown no overall survival advantage for the procedure (*43,44*). For this reason, observation of the SN-positive nodal basin has become the standard of care within the past 3 years. A different and more controversial question is whether early identification and excision of a positive SLN alone confers any survival advantage. Intuitively, the presence of tumor in the SLN would be predicted to be immuno-stimulatory. However, several studies have suggested that microscopic tumor in the node is associated with reduced T-cell activation and immune suppression (*45–47*). In the original MSLT-I trial of Morton et al. (*48*) involving intermediate-thickness melanomas, patients were randomized to wide excision with immediate SLNB, or excision with observation only, with subsequent regional lymphadenectomy. In a controversial subset analysis, 10-year melanoma-specific survival in the setting of a positive node was much better in the early SLNB group (75%) than in those observed with delayed nodal recurrence (59%). Whether such observations suggest that early SLNB may improve immune competence, or whether early nodal resection via SLNB is directly therapeutic, remains controversial.

By convention, pursuing an SLNB is thought to be appropriate when the predicted incidence of positivity is 5% or greater. For that reason, any melanoma of 1 mm or greater thickness (T2a or greater) would be appropriate for SLNB, as the incidence of positivity at 1 mm is approximately 5% (*49*). For thinner melanomas (T1), T1b lesions are considered the threshold lesion to consider SLNB, as the positivity rate approaches 5%. By any staging criteria, any ulcerated lesion <1 mm thick is a T1b and appropriate for SLNB. Unfortunately, the definition of a non-ulcerated T1b lesion has changed with each iteration of the American Joint Committee on Cancer (AJCC) staging system and is now defined in the current 8th edition (AJCC 8) as any lesion between 0.8 and 1 mm (*50*). The prior version 7 defined a T1b as any lesion <1 mm with visible mitotic activity (*51*). In practice, some flexibility in patient selection is understandable and some non-ulcerated T1 lesions of <0.8 mm may remain appropriate for SLNB. For example, current NCCN guidelines (*49*) support SLNB for T1a lesions if there is a transected specimen, lymphovascular invasion, younger age, high mitotic rate, or a combination of such features.

Occasionally, a wide excision will be performed without concurrent SLNB, for example, when the original biopsy suggests a T1a lesion but on final pathology the true depth proves greater. Under such circumstances, a delayed SLNB is often appropriate. Compared with a small biopsy site, the larger incision of a wide local resection introduces reasons that an SLNB might be less accurate and thus less predictive: (1) The pattern of lymphatic drainage on scintigraphy may be more diffuse and less representative than if the injection site were more focal around the primary lesion, (2) a skin flap or other postoperative issues such as scarring may impede lymphatic drainage, and (3) excessive or unnecessary surgery may be performed if multiple basins are demonstrated. These issues are identical to those accompanying any false-negative SLNB. However, the predictive value of a negative SLNB was similar in the setting of a prior wide excision versus at the time of the excision, with no reported difference in local-regional relapse when upfront versus delayed patients were compared (*52*).

Scenario 12: Cutaneous melanoma following a local-regional recurrence (Score: 6 – May be Appropriate)

Locoregional metastatic melanoma, in lieu of a nodal basin recurrence, can be defined as either recurrence within the wide excision scar, or a satellite or in-transit metastasis. Whether the 2 phenomena are equivalent in risk, specifically as a harbinger of additional metastatic events, is unclear. Satellite and in-transit lesions are essentially identical biologically, thought to arise from tumor in dermal lymphatics, and in the present AJCC 8 staging system, they have equivalence for predicting future hematogenous stage IV disease as 1 or more positive SLNs (*50*). In one study, Yao et al. (*53*) showed that if lymphatic mapping is performed by using a new in-transit focus as the target, a positive SLN can be found in as many as 47% of cases. In their study, performed before current medical therapies were available, the median disease-free survival for patients with new in-transit metastases was 16 months when an SLN was positive and 36 months when the SLN was negative. Improved locoregional control when a positive node is identified may also be an argument to support this practice. In addition, if a scar recurrence is not considered a hematogenous epidermotropic metastasis, it may be reasonable to consider SLNB. However, with the advent of effective medical therapies for melanoma, most patients upstaged to stage III by virtue of a new in-transit metastasis would receive medical therapy, which in turn might suppress or eliminate any potential secondarily involved basin node, obviating

surgery. In general, SLNB in the setting of a local recurrence cannot be considered a standard procedure. A more appropriate approach in that setting is probably high-resolution cross-sectional imaging alone for restaging.

Scenario 13: Pigmented lesions of uncertain metastatic potential (Score: 6 – May be Appropriate)

Under some circumstances, a definitive diagnosis of invasive melanoma cannot be achieved. A classic example in a usually younger population is the "atypical Spitz nevus." A general adage applied to such difficult-to-classify lesions is MELTUMP, or "melanocytic lesion of uncertain metastatic potential." In such instances, if certain pathological features are present, for example, depth ≥1 mm, that is, a potential T2 melanoma, SLNB may be considered (*54*). When studied, the incidence of nodal positivity in such instances is variable, for example, low in 1 study (*55*), but as high as 29% in a series of patients who were <21 years old (*56*). On the other hand, in the latter series, there was no recurrence in any of the node-positive patients, suggesting that the presence of a metastatic node in atypical lesions may carry less prognostic significance or utility. As a group, patients with MELTUMPs have a good prognosis and the value of SLNB is not clear. However, many such patients are young and the desire to identify subjects who might benefit from effective adjuvant therapy is often particularly strong. The addition of genetic profiling assays of the primary tumor is a new adjunct to discriminate higher risk MELTUMPs, but such approaches have not yet matured (*57*).

Scenario 14: Primary melanoma of the anus or vagina without clinical evidence of metastasis (Score: 7 – Appropriate)
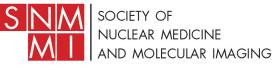
Primary melanomas arising in the anus and female genitalia may be of cutaneous or mucosal origin. True mucosal lesions are extremely rare, constituting <1% of all melanomas (*58*). As the transition from skin to the mucosal junction can sometimes be anatomically unclear, some lesions in these areas are difficult to classify. For lesions of true cutaneous origin (anal verge, labia majora), staging would follow usual AJCC 8 guidelines for cutaneous melanoma, potentially including SLNB. For vulvar melanoma, the AJCC 8 criteria have been found to be more predictive than alternative systems (*59,60*). However, no staging system has been found to be useful in predicting the behavior of true mucosal lesions, which have an unusually high potential for systemic metastasis. Anal and genital melanomas are also often detected late and at an advanced tumor stage due to misinterpretation by clinicians or patients as a benign process, such as a bleeding hemorrhoid. For that reason, when performed for an anal verge lesion, for example, SLNB will often be positive, reflecting the presenting high-risk T-stage. Interestingly, the lymphatic drainage pattern of the anus appears most prominent via the lateral buttocks versus the anterior perineal body, and it is far more common for isolated transmission to the inguinal nodal basin to occur (cephalad to the inguinal ligament) than it is to the femoral triangle. In general, such patients do poorly with an unusually short life span following diagnosis. Given the reality of high rates of nodal positivity and progression to hematogenous metastasis, perhaps the greatest rationale for SLNB in this setting is improved local-regional control of disease.

Scenario 15: Cutaneous and mucosal (penile, vulvar) squamous cell or basal carcinoma without clinical evidence of metastasis (Score: 8 – Appropriate)

Vulvar cancer is a rare neoplasm (1% of all cancers in women), and it is more frequent in older women. The most frequent histological type is SCC. Nearly 30% of patients may have subclinical lymph node involvement at staging. The lymph node status is the most powerful prognostic factor. Overall survival at 5 years drops from 90% in N0 patients to 50% in N1. The lymphatic spread of vulvar cancer is observed first in ipsilateral superficial inguinal nodes and, subsequently, in deep inguinofemoral nodes.

Because of a <1% risk for lymph node metastasis in stage IA disease, lymphadenectomy can be omitted in patients with stage IA (T1A and N0 tumors) primary disease with a clinically negative inguinal exam. Inguinofemoral lymphadenectomy is recommended for patients with stage IB/II disease due to a higher risk for metastatic disease of 8% or more. Standard treatment of vulvar SCC in those with T1–2, N0–1, and M0 tumor includes surgical excision of the tumor with unilateral or bilateral nodal dissection of the inguinofemoral nodal basins. Total lymphadenectomy is associated with postoperative sequelae, including cellulitis and lymphedema, that result in increased morbidity and lower quality of life. SLN mapping is useful in allowing sampling of nodes and planning lymphadenectomies (*61*).

In 1994, Levenback et al. (*62*) reported the first study on SLNB for vulvar cancer. They used isosulfan blue as a marker for visual guidance and identified the SLN in 7 of 9 patients (7 of 12 groins) without false-negative results. Currently, SLN mapping is increasingly being used in gynecological cancers, including vulvar cancer, to prevent morbidity from en bloc inguinofemoral dissection.

Sulfur colloid labeled with ^{99m}Tc is currently the most widely used tracer in the United States, although nanocolloids are available in other countries. ^{99m}Tc-labeled colloids may be used alone or in combination with blue dye; the combined use is currently the most sensitive technique for finding the SLN in gynecological cancers.

In the last decade, guidance with a fluorescent agent such as indocyanine green (ICG) has been introduced for lymphatic mapping in gynecological cancers. This marker emits a visual signal in the near-infrared band after excitation, thereby offering real-time intraoperative guidance with higher tissue penetration than the blue dye. However, the rapid lymphatic diffusion of ICG causes visualization of more than SLNs. Additional imaging equipment is also needed in the operating room to detect fluorescent nodes (63).

Preoperative lymphoscintigraphy may be helpful for locating the SLN, particularly when SPECT/CT is used. SPECT/CT imaging is more sensitive for SLN detection than planar imaging. In addition, sites of aberrant nodal drainage can be identified with SPECT/CT.

The European Society of Gynaecological Oncology (ESGO) guidelines for SLNB in vulvar cancer mandate the use of a radioactive tracer, whereas the use of blue dye is optional (64). Moreover, lymphoscintigraphy is advised to enable the preoperative identification, location, and number of SLNs. The combined use of lymphoscintigraphy and an intraoperative gamma probe has higher sensitivity than blue dye only and an NPV ranging from 80% to 100% (65).

The safety and accuracy of SLNB was examined in an observational multicenter study (GROningen INternational Study on Sentinel lymph nodes in Vulvar cancer [GROINSS-V]), in which 377 patients with early-stage disease (T1/T2, primary lesion <4 cm, and clinically non-suspicious inguinofemoral lymph node) had a negative SLN and did not undergo lymphadenectomy. The groin recurrence rate was 2.5% for SLN-negative and 8% for SLN-positive patients at a median follow-up of 105 months. Low incidence rates of short- and long-term morbidity were reported in SLN-negative patients versus SLN-positive patients who underwent lymphadenectomy (66).

In a GOG-173 study, 452 women (with vulva-confined primary tumors of 2–6 cm, at least 1-mm invasion, and clinically node negative) underwent SNL mapping and biopsy followed by inguinofemoral lymphadenectomy. The false-negative predictive value of SLN in those with a primary lesion measuring <4 cm was only 2%, but was higher at 7.4% for lesions measuring 4–6 cm. On a patient-based analysis, the sensitivity of the SLNB procedure was 91.7% and the false-negative value was 3.7% (67).

On the basis of both GROINSS-V and GOG-173 trials, SLNB is currently the standard of care for early-stage patients with a unifocal primary tumor <4 cm in diameter with >1 mm depth of invasion, and which is clinically at the N0 stage.

Recently, a systematic review and a meta-analysis of the literature showed that pooled patient SLN detection rates were 94.4% with a sensitivity of 92% and an NPV of 97%. The per-groin detection rate was 87% when scintigraphic and optical agents were used, with a false-negative rate of 6.4%. The accepted indications for SLNB are patients with FIGO stages IB and II without any clinical evidence of lymph node involvement (68).

Finally, current NCCN recommendations suggest that the use of SLNB of the inguinofemoral lymphatic basin is an alternative standard-of-care approach to lymphadenectomy in select women with SCC of the vulva. SLNB allows decreased postoperative morbidity without compromising detection of lymph node metastases.
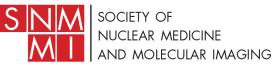
Candidates for SLNB include patients with a negative clinical examination and/or imaging and a primary unifocal vulvar tumor size of <4 cm. Important issues to keep in mind are that a side-specific complete inguinofemoral lymphadenectomy is recommended if an ipsilateral SLN is not detected. A complete inguinofemoral lymphadenectomy is the preferred approach in the presence of metastases >2 mm in diameter in the SLNs. Moreover, if the ipsilateral SLN is positive, the contralateral groin should be evaluated surgically and/or treated with external beam radiation therapy (69).

Penile cancer is a relatively rare disease in the Western world, with an incidence of approximately 1 per 100,000. Nearly all penile malignancies are SCCs. Lymph node involvement is the single most important prognostic factor for cancer-specific death and warrants a poor cancer-specific survival of 80%, 66%, or 37%, for N1, N2, or N3 disease, respectively.

The development of lymphatic metastases in penile cancer follows the route of anatomical drainage. The inguinal lymph nodes, followed by the pelvic lymph nodes, provide the regional drainage system of the penis. The superficial and deep inguinal lymph nodes are the first regional node group to be affected, which can be unilateral or bilateral. Pelvic nodal disease does not occur without ipsilateral inguinal lymph node metastasis.

The management of regional lymph nodes is decisive for patient survival. Cure can be achieved in limited lymph node disease. Treatment is dependent on the clinical inguinal lymph node status. There are 3 possible scenarios: First, the clinical lymph nodes appear normal on palpation and are not enlarged; second, the inguinal lymph nodes are palpably enlarged, either unilaterally or bilaterally; third, there may be grossly enlarged and sometimes ulcerated inguinal lymph nodes, unilaterally or bilaterally (70).

Noninvasive staging techniques lack sufficient accuracy to reliably detect small lymph node metastases; therefore, surgical staging remains the standard in clinically node-negative (cN0) patients. To this end, inguinal lymph node dissection is

still routinely performed at the time of primary tumor surgery in many countries. However, this procedure can lead to substantial morbidity and may be considered overtreatment in most patients; only 20%–25% of cN0 patients are found to have occult nodal metastasis. SLNB is therefore becoming the nodal staging procedure of choice (71).

The current European Association of Urology (EAU) guidelines recommend SLNB for cN0 patients with a T1G2 tumor. Lymphoscintigraphy is the cornerstone of the technique, as the procedure is routinely performed by using a radiocolloid (e.g., [^{99m}Tc]-Tc-nanocolloid) combined with an optical (blue) dye. This combination was shown to be superior to using either modality separately (72).

The radiocolloid is injected proximal to the tumor. For large tumors not restricted to the glans, the radiocolloid can be injected in the prepuce. Injection margins within 1 cm from the primary tumor are recommended. A reproducibility rate of 100% for penile lymphoscintigraphy has been reported with an injection distance of 5 mm. The most frequently visualized lymphatic drainage pattern is bilateral to both inguinal regions (80%). This pattern is asynchronous in two-thirds of cases, and often visualization of the contralateral lymph nodes is only obvious on late imaging. Drainage from the injection site mostly occurs through 1 or 2 visualized afferent lymphatic tracks leading to 1 or 2 SLNs in each inguinal region. In some cases, a cluster of inguinal lymph nodes is observed. One of the advantages of preoperative lymphoscintigraphy is its ability to identify SLNs outside the expected nodal basins. In penile cancer, direct drainage to prepubic nodes has been described, and lymphatic vessels have also been observed to directly lead to deep inguinal and even to iliac SLNs (73).
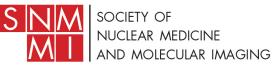
Neither the EAU or the NCCN guidelines discuss the role of SPECT/CT in sentinel node imaging (74); however, in 1 study, SPECT/CT was compared with planar scintigraphy alone for sentinel node identification in 115 patients with a T1G2 or greater primary tumor and nonpalpable nodes. SPECT/CT changed the findings on planar scintigraphy in 76% of the patients. In most of these cases, SPECT/CT reclassified nodes from inguinal to pelvic or vice versa, and an additional 21 inguinal nodes were identified (75).

In an attempt to improve the optical detection and assure intraoperative alignment with preoperatively defined radioactive nodes, a dual-labeled (hybrid) tracer consisting of the fluorescent dye ICG and ^{99m}Tc- nanocolloid was introduced (ICG-^{99m}Tc-nanocolloid). Recently, results for 400 patients demonstrated that ICG-^{99m}Tc-nanocolloid is safe and allows for accurate preoperative lymphoscintigraphy and intraoperative SLN localization, improving optical SLN detection compared with blue dye (76).

The role of SLNB for staging of SCC of cutaneous, as opposed to mucosal, origin remains unclear. Current AJCC 7 staging criteria for SCC are of unclear predictive value (51), and for that reason, alternative staging systems for SCCs have been proposed (77). Lesions of higher risk for nodal metastasis include T2 lesions (diameter >2 cm) or T1 lesions (diameter <2 cm) with 2 or more high-risk features (invasion to >2 mm or Clark IV, perineural invasion, poor differentiation), where rates of nodal positivity historically are as high as 10% for elective formal nodal basin dissections (78). Another group thought to be at higher risk for metastasis are immunosuppressed patients such as those who have undergone organ transplantation. However, in that cohort, rates of metastasis in retrospective series do not seem higher than in non-immunosuppressed patients (79). Whether SLN status and the early detection of lymphatic metastasis has any beneficial effect on survival is unclear. However, a meta-analysis that included 130 patients undergoing SLNB for high-risk SCC suggested that T2 lesions may carry a 7%–10% incidence of positive SLN, which rose to as high as 60% for more advanced lesions (80), similar to data from other series (81,82). In general, high-resolution cross-sectional imaging for staging of high-risk SCC may be of greater usefulness than SLNB. SLNB should be applied selectively and only for T2 lesions or above. If a positive node is found, the usual practice is to perform completion lymphadenectomy. However, the advantage of complete node dissection has become less clear following the introduction of immune checkpoint therapy and alternatives for local control such as radiotherapy. Regarding basal cell carcinoma, the primary morbidity for advanced disease is local invasion, usually in the setting of a neglected tumor (83,84). Lymphatic or systemic metastasis from this histological subtype is extremely rare (0.1%) (85) and there are no data to support SLNB in this setting.

Scenario 16: Merkel cell carcinoma without clinical evidence of metastasis (Score: 9 – Appropriate)

Merkel cell carcinoma (MCC) is a cutaneous tumor of neuroendocrine lineage that shares many biological characteristics with melanoma. MCC has a propensity for nodal metastasis, and lymph node status is a strong predictor of survival and distant metastasis (86). For example, of 9,387 patients with MCC from the National Cancer Database (87), a negative SLNB predicted improved 5-year overall survival (55%) compared with those with a positive node (40%). Therefore, SLNB has an important role in the management of MCC and should be performed for lesions of any T-stage. MCC is also unusually radiosensitive, which distinguishes it from melanoma, and adjuvant radiotherapy to the primary site is an important cornerstone of management to prevent local recurrence, even when an adequate surgical margin has been achieved (88,89). In the instance of nodal basin involvement, consolidating radiotherapy is probably appropriate for most patients. Therefore, early identification of an involved SLN has many implications both for instituting systemic therapy, for example, with an immune

checkpoint inhibitor, and for maximal local-regional control of the nodal basin. Up to 30% of patients with clinically negative lymph nodes will have microscopic tumor involvement on pathological examination (*90*). Although current practice by NCCN guidelines is to perform completion lymphadenectomy in the face of a positive SLNB (*91*), it is not known if this practice confers any overall survival advantage in the absence of randomized trials. It is also uncertain whether primary radiotherapy as an alternative to completion lymphadenectomy may be adequate (*92*), or if adding radiotherapy following aggressive lymphadenectomy clearly provides improved local control (*93*).

Scenario 17: Malignant adnexal cutaneous tumors (eccrine, sweat gland, SCC with eccrine de-differentiation) without clinical evidence of metastasis (Score 6 – May be Appropriate)

Malignant cutaneous adnexal tumors (MCATs) are a group of rare neoplasms characterized as primary epithelial adenocarcinomas arising in glandular structures embedded in the skin, which are uniformly cytokeratin positive. The natural history of MCATs is poorly understood. Some studies report them to be locally aggressive and to carry a significant risk for nodal involvement and distant metastasis (*94–96*). Other reports suggest a much more indolent course (*97*). The criteria for malignancy for such lesions are also complex and can often be indeterminate. There are no specific staging criteria for MCATs, as the current AJCC 7 staging system was originally developed for SCCs (*51*). Although MCATs are included in it, there has never been any validation of the predictive value for these lesions, and the role of lymphatic surgery for MCATs remains unclear. On the basis of analogy to other adenocarcinomas, it is assumed that a lymphatic route of transmission would be the preferred initial route of metastasis from MCATs. Therefore, SLNB as a staging method may have relevance. However, in a recent extensive series of MCATs staged by SLNB, no positive nodes were found in 22 patients with T1 or T2 lesions, including subtypes traditionally thought to be at unusually high risk for metastasis such as digital papillary adenocarcinoma and porocarcinoma (*98*). In most reported cases of elective nodal dissection for lymphatic metastasis in MCATs, a high-risk population of T3 or T4 tumors was likely selected, and there is no knowledge of whether identification of an involved node changes prognosis (*99–101*). For these reasons, the role of SLNB in MACT remains undefined, but most likely should be considered for high-risk T2 lesions or greater.

Scenario 18: Selected sarcoma subtypes (synovial, epithelioid, rhabdomyosarcoma, angiosarcoma, clear cell sarcoma) without evidence of metastasis (Score: 6 – May Be Appropriate)

Sarcoma is traditionally considered a tumor with a low proclivity for nodal involvement and a preference for hematogenous metastasis. Certain sarcoma subtypes do, however, carry a significant risk of nodal metastasis, including epithelioid sarcoma, synovial cell sarcoma, rhabdomyosarcoma, clear cell sarcoma, and many sarcomas of vascular origin (*102–105*). In some instances, nodal metastasis may occur in up to 10%–30% of cases. When present for extremity or truncal sarcoma, nodal metastasis carries a similar risk for death as hematogenous metastasis and is considered stage IV disease (*106*). If only for local control of disease, lymphadenectomy is recommended if clinical or radiological evidence of lymph node involvement is present (*103,104*). However, it is not known if early detection of occult lymphatic metastasis by SLNB, with subsequent completion lymphadenectomy, if positive, confers improved disease-free or overall survival. The available literature for SLNB in sarcoma is sparse and largely comprises case reports and small series (*107–112*). The literature therefore does not allow any conclusion about therapeutic lymphadenectomy following an SNB or if a negative SNB predicts lower rates of hematogenous metastasis. For these reasons, the role of SNB in sarcoma remains indeterminate, although selective use in the appropriate setting may be justified.

TABLE 2
Clinical Scenarios for Skin Cancer

Scenario no.	Description	Appropriateness	Score
11	Primary cutaneous melanoma without clinical evidence of metastasis	Appropriate	9
12	Cutaneous melanoma following a local-regional recurrence	May be Appropriate	6
13	Pigmented lesions of uncertain metastatic potential	May be Appropriate	6
14	Primary melanoma of the anus or vagina without clinical evidence of metastasis	Appropriate	7
15	Cutaneous and mucosal (penile, vulvar) squamous cell or basal carcinoma without clinical evidence of metastasis	Appropriate	8

16	Merkel cell carcinoma without clinical evidence of metastasis	Appropriate	9
17	Malignant adnexal cutaneous tumors (eccrine, sweat gland, SCC with eccrine de-differentiation) without clinical evidence of metastasis	May be Appropriate	6
18	Selected sarcoma subtypes (synovial, epithelioid, rhabdomyosarcoma, angiosarcoma, clear cell sarcoma) without evidence of metastasis	May be Appropriate	6

Summary of Recommendations

Sentinel node biopsy has been shown to be helpful in the management of patients with melanoma and MCC. Preliminary evidence of SLNB with other cutaneous lesions suggests there may be some utility; however, more controlled studies are needed. At present, SLNB in rare tumors may be performed when the nodal status will affect management, when the possibility of nodal metastasis is felt to be significant, and when there is no other evidence of metastatic disease. As therapy for some cutaneous malignancies improves, the need for SLNB will change, particularly when sentinel node status no longer changes management or prognosis.

CANCERS AT OTHER SITES

Introduction

Since the first decade of this millennium, the SLN concept has been expanded, thus facilitating radioguided SLNB under more complex anatomical conditions.
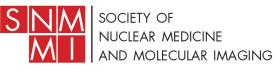
The addition of SPECT/CT has improved the accuracy of the SLN procedure to areas with particularly complex lymphatic drainage, such as the head and neck region and the pelvis. From this experience, regional sentinel node staging in oral cavity cancers and in malignancies of the female and male reproductive systems is now becoming more accurate. The SLNB technique has now also been used for thyroid and gastrointestinal (GI) tract malignancies.

Gynecological cancers: Although the indications for SLNB (and preoperative lymphatic mapping) continue to evolve, their inclusion in clinical guidelines has not been consistent. In gynecological cancers, SLNB in cervical and endometrial cancer has now been introduced in the majority of clinical guidelines (NCCN, ESGO, European SocieTy for Radiotherapy and Oncology [ESTRO]). Similar to the European recommendations that include the use of radiotracers alone or combined with vital dyes for the detection of the SLN in cancer of the vulva, the NCCN, ESGO, and ESTRO guidelines suggest that cervical and endometrial cancer lymphatic drainage can also be mapped (*113,114*). However, some societies recommend the use of fluorescent tracers as a first-choice modality, especially in endometrial cancer (*115*).

In cervical cancer, a recent meta-analysis that included 2,234 patients found lymphatic mapping to have 88% side-specific sensitivity. Side-specific detection rates were similar with technetium-based or ICG-based mapping. In endometrial cancer, retrospective comparison of SLNB to complete node dissection found fewer complications for SLNB patients, particularly in relation to lymphedema, with similar oncological outcomes (*116–118*). The use of SLNB in ovarian cancer is under investigation and no current recommendations can be given.

GI tract cancers: Increasingly, early-stage gastric cancer and colorectal cancers are detected that have a low incidence of lymph node metastasis. For this reason, there is interest in using minimally invasive approaches for staging. SLN mapping allows for more accurate staging of these cancers and the combination of radiotracer and vital dye. Intraoperative SLN mapping in patients with gastric and colorectal cancer can identify aberrant/unexpected lymphatic drainage (*119*). SLN mapping has been shown to be feasible and can be integrated with general and laparoscopic surgical approaches. The use of SPECT/CT imaging and intraoperative imaging with portable gamma cameras allows better lymph node detection than planar imaging does. Recently, near-infrared fluorescence imaging has been used with excellent acceptance (*120–125*). The role of SLNB in anal cancer is yet to be established in large studies (*126*).

The majority of the GI SLNB experience has been with gastric cancer. In Asia, where high rates of gastric cancer are noted, lymphatic mapping is incorporated into clinical practice, particularly in Japan (*127*). Although high sensitivity and specificity have been noted by some groups, high variability in detection and accuracy remains (*128*). The experience with SLNB in other GI cancers is limited to small studies. Moreover, overall clinical application of SLNB in GI cancer treatment has been more than challenging because of the complicated nature of GI lymphatic drainage and the high possibility of skip metastasis. Outside of a few specialized

centers, use of SLN mapping for colon cancer has been limited and the technique remains mostly investigational. The potential role of SLNB for gastric cancer staging is a topic that remains highly controversial. More clinical trials are needed.

Urological cancers: The application of SLN mapping and biopsy in prostate, bladder, and renal cancer remains limited and is not part of routine management. For prostate cancer, there is consensus regarding the use of SLNB among European urologists. It is generally accepted that extended pelvic lymph node dissection (ePLND) provides important information for staging and prognosis. Sentinel node dissection has shown sensitivity of 95.2% and an NPV of 98% for nodal metastases in a systematic review. However, on the basis of insufficient quality evidence, sentinel node biopsy is still considered an experimental nodal staging procedure (*129,130*).

Bladder and renal carcinomas: The SLNB approach has been reported by several investigators, but its routine use in clinical care remains investigational. For renal carcinoma, lymphatic drainage is unpredictable and metastatic disease often spreads hematogenously. The likelihood of identifying only nodal metastasis is low. Lymphatic mapping of kidney tumors, including planar lymphoscintigraphy and SPECT/CT imaging, has been described in 2 pilot studies and in a phase II study with 40 patients. The more recent study showed that 35% of lymphatic drainage is outside the suggested lymph node dissection templates, and 20% of lymph flow drains directly to the thoracic area (*131–133*). Regarding bladder cancer, a recent systematic review and meta-analysis included a total of 336 patients with muscle-invasive bladder cancer who underwent SLN mapping with different methods and tracers. The lowest SLN detection rate (21%) was found for studies that used visual guidance with the blue dye, and the pooled detection rate for all studies combined was 91% (*134*). The data across studies are variable; a prospective study noted variations in detection based on nodal sites (*135*). The SLNB procedure is therefore not yet considered part of standard management.

Thyroid cancer: Thyroid lymphatic drainage pathways are complex. Although lymphatic channels usually accompany blood vessels and nerves, the drainage is not predictable. The optimal surgical management of papillary thyroid cancer for early-stage tumors without pre- or intrasurgical evidence of lymph node metastasis (cN0) remains controversial, since approximately 40% of patients have lymph node involvement that becomes evident when a prophylactic lymphadenectomy is performed. However, prophylactic central neck dissection may cause complications such as a damaged recurrent laryngeal nerve or hypoparathyroidism. The most common site of nodal metastases is in the central neck (cervical level VI). In many patients, lymph node metastases in this area do not appear abnormal on preoperative imaging or by inspection at the time of surgery, defining a cN0 group. The value of routine prophylactic level VI (central) neck dissection for cN0 disease remains unclear.

The information from prophylactic central neck dissection must be used cautiously for staging. Since microscopic nodal positivity occurs frequently, prophylactic dissection often converts patients from clinical N0 to pathological N1a, upstaging patients from AJCC stage I to stage III. However, microscopic nodal positivity does not carry the recurrence risk of macroscopic clinically detectable disease. Thus, microscopic nodal upstaging may lead to excess radioiodine treatment (*136*).

The SLNB concept in differentiated thyroid cancer has been suggested as an alternative to elective lymph node dissection in patients with clinically node-negative disease. Large randomized prospective studies are lacking, and the significance of microscopic nodal disease detected through sentinel node mapping is not well known (*137–139*).

SLNB may, however, find a place as an adjunct to surgical treatment. Unfortunately, earlier studies reported inconsistent detection rates and diagnostic value of this technique. The role of SLNB in thyroid cancer needs to be better established before it can be recommended for integration into clinical care (*140,141*).

Clinical Scenarios and AUC Scores

Clinical scenarios for the use of lymphoscintigraphy in patients with cancers at other sites and final AUC scores are presented in Table 3.

Scenario 19: Prostate cancer (initial stage) (Score: 7 – Appropriate)

In prostate cancer, lymph node staging is important for both prognosis and therapeutic management. To date, none of the available diagnostic imaging modalities offer a reliable assessment of micrometastases in regional lymph nodes.

Surgical staging by ePLND is the current standard of care. However, SLNB is emerging as an alternative staging method, with fewer side effects and with the potential to identify relevant lymph nodes outside the standard ePLND field (*142*).

Current international guidelines recommend that a pelvic lymph node dissection (PLND) should be performed at the time of a radical prostatectomy in men with intermediate- or high-risk prostate cancer, if the estimated risk of lymph node metastases exceeds 5% in the current EAU guidelines or 2% with NCCN guideline nomograms (grade

recommendation: "B") (*143*). However, 25%–35% of patients with prostate cancer who undergo curative intent with radical prostatectomy and ePLND develop clinically significant biochemical recurrence with local and/or distant disease.

Like the indications for ePLND, SLNB can be performed in all men with intermediate- and high-risk prostate cancer if the estimated risk of lymph node metastases exceeds the percentages reported beforehand in the current guideline nomograms and if prostate-specific membrane antigen PET/CT or any other conventional imaging modality shows no evidence of lymph node metastases.

Roughly 20% of SLNs cannot be visualized by ICG alone because of limited tissue penetration of the fluorescent signal. Nodes missed by using fluorescence imaging can be localized by lymphoscintigraphy and SPECT/CT and intraoperatively with the use of a gamma detection probe (*144*).

The use of preoperative lymphoscintigraphy for SLN identification has the potential advantage of depicting the draining lymph nodes outside the field of an ePLND and of lowering the incidence of complications compared with those for ePLND. However, accurate localization of SLNs in the pelvis can be challenging, especially when SLNs are located near the injection site. Because there is a lack of reliable evidence showing an impact on outcome improvement, the role of scintigraphic SLNB in prostate cancer remains controversial.

Scenario 20: Cervical cancer (initial stage) (Score: 7 – Appropriate)

SCC is the most common cancer of the uterine cervix. The key prognostic factor for cervical cancer is the presence of pelvic lymph node metastasis. Indeed, the 5-year overall survival rate decreases from a range of 88%–95% in the absence of lymph node metastasis to a range of 51%–78% in the presence of lymph node metastasis in early-stage IB and IIA disease. In cervical cancer of stage IA1, the rate of lymphatic/vascular invasion is <1% and pelvic node metastases are detected in 0%–4.8% of patients (*145*). In stage IB disease, pelvic metastasis is seen in 0%–17% and in stage II cervical cancers approximately 20%–40% of patients will have lymph node metastasis (*146*).

Pelvic lymphadenectomy is overtreatment in early-stage cervical cancer due to the low incidence of metastatic lymph nodes. Moreover, it is associated with short- and long-term morbidities such as lymphocyst formation, nerve injury, venous thromboembolism, and lower extremity lymphedema. In an attempt to reduce these morbidities, SLNB was introduced into the management of women with early cervical cancer. In 2002, Levenback et al. (*147*) described the first study on preoperative and intraoperative SLN mapping for invasive cervical cancer. They identified 1 or more SLNs with preoperative lymphatic mapping in 33 patients and intraoperatively in all 39 patients, with 1 false-negative case.

SLNB is recommended in women with early-stage cervical cancer who have a primary tumor ≤4 cm in diameter with depth of stromal invasion >3 mm and which is clinically at the N0 stage (stage IA1 with lymphovascular invasion, stages IA2, IB1, and IIA1) (*148*). However, the best detection rates and mapping results are in tumors <2 cm in diameter.

The cervix is a midline organ with bilateral lymphatic drainage, making identification of at least 1 SLN in each side of the pelvis ideal. However, the bilateral SLN identification rate varies widely, with implications regarding the sensitivity of the technique. For midline tumors, each side can be considered as a separate unit and the sensitivity can be calculated on a per-unit (side) basis. Bilateral identification is reported to be higher in younger patients and for small tumors. As in other cancers, an important cause of unilateral SLN identification is pre-existing metastatic nodal involvement. This can lead to false-negative results if the identified SLNs are pathologically negative for metastasis (*149*).

Lymphoscintigraphy can be performed either on the day of surgery or 1 day before surgery to map the nodal drainage. Various injection techniques and radiolabeled tracers have been used for nodal mapping in cervical and endometrial cancers. External iliac and obturator nodes are most frequently seen on lymphoscintigraphy, and bilateral nodal drainage is common. Using this imaging procedure alone, the detection rate is between 80% and 93%, and combined blue dye and scintigraphy increases the detection rate to 78%–100%. False-negative rates are very low, with an overall rate of <1% and a high NPV of up to 100%. SPECT provides 3-dimensional imaging information that, when combined with CT imaging (SPECT/CT), can help to improve localization of SLNs. SPECT/CT imaging for SLN localization in endometrial and cervical cancer is superior to planar imaging and improves the sensitivity of detection (*150–152*).

In a group of 59 patients with early-stage cervical cancer, Klapdor et al. (*153*) demonstrated a detection rate of 84.3% for planar imaging and 92.2% for SPECT/CT. Accurate anatomical localization of SLNs preoperatively can also aid in probe-

directed surgery and in reducing operator-dependent variation and time involved in surgery. SPECT/CT helps achieve faster intraoperative localization and SLN removal; an average time advantage of 25 minutes in lymph node retrieval was noted with the use of SPECT/CT (*154*). A meta-analysis of data from 8 studies (*n* = 208) for SLNB in early-stage cervical cancer showed an overall SLN detection rate of 98.6% for SPECT/CT versus 85.3% for planar lymphoscintigraphy, although bilateral nodal site localization was similar (69% vs. 67%). With SPECT imaging, there was increased sensitivity of SLN detection, with a 100% detection rate with SPECT/CT compared with planar lymphoscintigraphy, hand-held probe, or blue dye alone (75%, 92.5%, and 82.5%, respectively, for endometrial cancer and 70%, 90%, and 90%, respectively, for cervical cancer), as well as compared with combined planar imaging plus probe and blue dye injection (94.2%) (*155*).

In addition, preoperative lymphoscintigraphy can identify patients with an atypical drainage pattern in early-stage cervical disease. In the prospective SENTICOL study, 57% of 139 patients with early-stage cervical disease were noted to have atypical sites of SLN localization with lymphoscintigraphy compared with 38% by intraoperative mapping. In 13 patients, only a parametrial SLN was seen with lymphoscintigraphy, whereas 3% of patients had common iliac and para-aortic SLNs shown only on lymphoscintigraphy (*156*).

Current guidelines favor a minimally invasive approach, yet the standard lymph node staging procedure is a systematic pelvic lymphadenectomy. Although SLNB before pelvic lymphadenectomy is strongly recommended, this procedure alone cannot be recommended outside prospective clinical trials.

Lymph node assessment should be performed as the first step of surgical management. Intraoperative assessment of lymph node status (frozen section) is recommended. All SLNs from both sides of the pelvis and/or any suspicious lymph nodes should be sent for frozen section. If an SLN is not detected, intraoperative assessment of the pelvic lymph nodes should be considered. If the result of intraoperative lymph node assessment is negative or it is not done, systematic pelvic lymph node dissection should be performed (*114,148,157*).

In summary, SLNB is an accurate method for the assessment of lymph node involvement in uterine cervical cancers. Selection of a population with small tumor size and lower stage will ensure the lowest false-negative rate. Lymphatic mapping can also detect SLNs outside of routine lymphadenectomy areas, providing additional histological information that can further improve staging. Lymphoscintigraphy with ^{99m}Tc-labeled agents combined with blue dye or mapping with ICG techniques enables SLN detection with high sensitivity.

Scenario 21: Endometrial cancer, low-risk patient (Score: 5 – May be Appropriate)

Endometrial cancer is the most common gynecological oncological disease, with a 5-year overall survival rate of between 74% and 91%. In 75% of cases, postmenopausal bleeding triggers early medical assessment, allowing the diagnosis to be made in early-stage disease. In patients with low-risk endometrial cancer (FIGO stage 1, endometrioid histology, grades 1 and 2 with <50% myometrial invasion), the risk of lymph-node involvement ranges between 4% and 17%. In stage I and occult stage II endometrial cancers, the incidence of lymph node metastases is approximately 10% (*158–160*).

Lymphadenectomy is an integral part of the comprehensive surgical staging of endometrial cancer. Standard lymphadenectomy of the pelvic and para-aortic nodes performed as part of the initial surgical evaluation causes lymphedema in >30% of patients (*161*).

However, in early endometrial cancer, the role of lymphadenectomy is unclear, and controversy remains regarding the indications for, the anatomical extent of, and the therapeutic value of lymphadenectomy in the management of the disease. Routinely performed extensive nodal dissection in patients who otherwise have a low likelihood of nodal metastasis suggests that a number of patients undergo dissection without clinical benefit but with a potential for increased complications and morbidity. Two prospective randomized studies showed no improvement in overall and disease-free survival by adding a pelvic lymphadenectomy in stage I disease (*162,163*). The incidence of nodal metastasis is also low in patients presenting with a low-grade endometrioid adenocarcinoma in which the overall prognosis is excellent.

For these reasons, systematic lymphadenectomy in this population is not mandatory. However, there is no clear consensus for lymphadenectomy between European and American oncological societies in current treatment guidelines for low-risk endometrial carcinomas (*164–166*).

In the past decade, SLNB has been developed and refined with the use of pathological ultrastaging (histopathological evaluation of the sentinel node in multiple sections) as part of surgical staging. Bilateral SLNs that are identified are removed (or a side-specific lymphadenectomy is performed if the SLN is not identified) and pathological ultrastaging of the sentinel nodes is conducted (*167,168*).

In low- and intermediate-risk endometrial cancer, the rationale is different to that for cervical cancer, as the need for SLNB is controversial (*167,169*). However, the SLNB approach could represent a compromise between no dissection (leaving a small proportion of node-positive patients) and full dissection. In addition, ultrastaging of the SLNs enables detection of micrometastases missed by conventional histology. The use of lymphatic mapping and SLN identification in these patients may help reduce the morbidity of surgery without compromising the identification of patients who require adjuvant treatment.

SLNB has high specificity for positive pelvic nodes. In a multicenter prospective study in which completion lymphadenectomy was performed after SLN mapping, among 385 women, 86% underwent successful mapping of at least 1 SLN, and the false-negative rate was 2.8% (*170*).

The SLNB procedure includes use of either ICG dye or a ^{99m}Tc-labeled radiotracer. The optimal site to inject radiotracer for preoperative lymphoscintigraphy in patients with endometrial cancers is not well established, and various techniques have been used that include either cervical, fundal, or hysteroscopic injections. Cervical injection for preoperative mapping has several advantages over the other methods, such as being easily accessible and less invasive and overcoming the influence of anatomical variation in the uterus that may affect detection following fundal injection and tumor infiltration (*167,171*).

The use of alternative injection sites in the endometrium or uterine fundus, which are anatomically more logical, is still a topic for investigation. Injection under hysteroscopic, ultrasound, laparoscopic, or open guidance in patients with endometrial cancer has been addressed, without evidence of distinct benefit of these more demanding and less practical modalities.

In general, planar imaging is performed. SPECT/CT is desirable because of its higher sensitivity for SLN detection and more accurate localization. SLNB in early-stage endometrial cancer shows a detection rate of between 50% and 67% for planar imaging and between 84% and 91% for SPECT/CT (*172,173*).

In addition, use of SPECT/CT lowers false-positive findings and provides superior localization of para-aortic and pelvic nodes than planar imaging does. A change in location has been reported in 37% of patients and in 22% of nodal sites compared with those with planar imaging (*151,152*).

In patients with low- to intermediate-risk endometrial carcinoma, SLNB can help detect nodes with micrometastasis, upstage patients, and change their management (*174*). In this group of patients, current NCCN guidelines state that SLNB with ultrastaging may increase the detection of lymph node metastasis with low false-negative rates. This approach can be considered for the surgical staging of apparent uterine-confined malignancy when there is no metastasis demonstrated by imaging studies. However, SLNB should be done in institutions with expertise in the procedure (*166*).

Scenario 22: Endometrial cancer, high-risk patient (Score: 6 – May be Appropriate)

Although the effect of lymphadenectomy on outcomes is unclear, it is an integral part of comprehensive staging. The advantages of comprehensive surgical staging are a better definition of prognosis and appropriate triage of patients for adjuvant therapy. Non-directed sampling of lymph nodes has a low sensitivity in endometrial cancer. It has been shown that para-aortic nodes may be positive in the absence of positive pelvic nodes, suggesting that para-aortic lymph nodes should be removed in cases where a lymphadenectomy is indicated (*175,176*).

In 1996, Burke et al. (*177*) introduced the SLNB in high-risk endometrial cancer, using isosulfan blue for visual guidance, and identified sentinel nodes in 10 of 15 patients. Historically, SLNB has been controversial in patients with high-risk histological types (e.g., serous carcinoma, clear cell carcinoma, carcinosarcoma). However, recently, SLN mapping in patients with high-risk histological findings (i.e., grade 3, serous, clear cell, carcinosarcoma) has shown promising results as a potential alternative to complete lymphadenectomy (*178–180*).

One study noted successful mapping of at least 1 SLN in 89% of the patients with a false-negative rate of 4.3% (*181*). Another study in 123 high-risk patients observed a preoperative detection rate of 70.7% with SLNB. Pelvic drainage, with or without para-aortic drainage, was observed in 96.6% of positive lymphoscintigraphy, whereas only 37% of these patients showed bilateral sentinel nodes and 41.4% of patients had para-aortic drainage (*182*).

Current NCCN guidelines accept the use of SLNB in high-risk histological findings (i.e., serous carcinoma, clear cell carcinoma, carcinosarcoma) because nodal metastasis detected with an SLN procedure is of potential value to staging (*166*).

Scenario 23: Ovarian cancer (Score: 3 – Rarely Appropriate)

Lymphoscintigraphy and SLNB are not standard procedures for staging or management of ovarian cancer. The majority of ovarian cancers present with widespread metastatic disease in the abdomen and peritoneum that requires primary surgery and debulking of tumor with further chemoradiation. Currently there is no consensus for use of SLNB in ovarian cancer, though in recent years, data have emerged for use in early ovarian cancer where disease is macroscopically limited to the ovaries at the time of initial diagnosis. About 25% of patients present with early ovarian cancer in which routine management includes surgical staging with pelvic and retroperitoneal lymphadenectomy, which can lead to significant morbidity. The role of SLNB has therefore been explored in some studies (*183,184*).

A meta-analysis of 10 studies involving 43 patients with confirmed early ovarian cancer showed an overall detection rate of 97.6% for para-aortic and/or pelvic nodes with an overall sensitivity of 66.7% and an NPV of 96.6%. The detection rate was lower for pelvic nodes (43%) than for retroperitoneal nodes (83%) (*185*).

In a multicenter prospective phase II single-arm study of 31 patients with stage I or II epithelial ovarian cancer, SLNB with ICG showed 98.5% sensitivity in detecting histologically positive lymph nodes, with a prevalence rate of 14.2% (*186*). ICG with laparoscopy has also been used for the detection of SLNs. A recent case study showed feasibility of the laparoscopic method (*187*).

Scenario 24: Vaginal SCC (Score: 6 – May be Appropriate)

There is overall no guideline recommendation for routine use of SLNB in vaginal cancers and limited data exist regarding use of SLNB in vaginal cancer. The majority of vaginal cancers involve the upper third of the vagina and are treated with radiotherapy. Surgery that includes partial vulvectomy with hysterectomy may be performed in those with small superficial lesions. Feasibility of the SLNB with lymphoscintigraphy has been shown in 11 patients in which SLNs were detected in 5 of them in the inguinal region only; 4 had pelvic SLN only, and 2 had SLNs in both groin and pelvis (*188*). The ICG technique has also been successfully used in patients with submucosal injection at the 3 and 9 o' clock positions in the vagina (*189,190*). In summary, the role of SLNB in vaginal cancer remains limited. A possible application may be in early and small vaginal cancers that are surgically managed. However, this is still under investigation and lacks supportive data for routine application in clinical management.

Scenario 25: Primary malignancy of the GI tract without clinical evidence of metastasis (Score: 5 – May be Appropriate)

An accurate evaluation of lymph node status is essential for staging GI tract malignancies. SLN mapping has become highly feasible and accurate in staging these cancers; however, much of the literature describes optical or near-infrared SLN mapping. Lymphatic mapping while performing surgery in patients with gastric and colorectal cancer can identify cases with aberrant/unexpected lymphatic drainage. This technique works well with a laparoscopic approach. The combination of radiotracer and vital dye staining optimizes SLN identification. The use of SPECT/CT imaging and intraoperative imaging with portable gamma cameras allows better lymph node detection than planar imaging does. Recently, near-infrared fluorescence imaging has been used to detect lymph nodes, with excellent acceptance (*122,124,125,191–193*). More published trials that use scintigraphic tracers are needed before a recommendation of "Appropriate" can be conferred.

Scenario 26: Oral cavity (Score: 9 – Appropriate)

Head and neck SCC is a promising area for SLNB. When applied in oral cavity, oropharyngeal, and supraglottic SCC, it can reveal occult metastasis in 15%–60% of cases. In early-stage cavity cancer (T1-2N0), 20%-30% of patients may harbor cervical metastasis despite negative clinical and radiographic evaluation. Several studies have validated the procedure, with overall good results (*194–196*).

Preoperative evaluation of patients with newly diagnosed head and neck SCC includes physical examination, ultrasound assessment, and other radiology-based imaging procedures (CT, MRI, PET/CT). However, all these modalities have suboptimal

sensitivity for the detection of microscopic lymph node involvement. Elective lymph node dissection has the potential for significant morbidity and this may be reduced by adopting SLNB for stage N0 patients. The assessment of lymphatic drainage in this area presents some drawbacks due to the complex anatomy and unpredictable lymphatic drainage.

Aberrant lymphatic drainage can be found in a significant subset of patients with clinically node-negative or node-positive necks, with a definite impact on treatment planning. Patients with oral SCCs should undergo SLNB if they present at stage T1 or T2 and as clinically negative by neck palpation, CT, MR imaging, or PET/CT. Mapping is performed with preoperative lymphoscintigraphy and an intraoperative gamma probe. Lymphoscintigraphy is a cornerstone of the procedure and is similar to sentinel node imaging for breast cancer and melanoma, including SPECT/CT and planar imaging. Lymph nodes may be adequately localized with planar imaging alone; however, given the anatomical complexity of the head and neck and the proximity of some primary lesions to SLNs and other important structures, SPECT/CT should be used when available. ^{99m}Tc-tilmanocept has been approved for SLNB in the management of oral SCCs (197). Experience with labeled colloids has been satisfactory, and several are routinely used.

SLNs are generally identified as soon as 15–60 minutes after radiotracer injection as 1 or more foci of tracer uptake and may be in 1 or multiple locations in the neck, ipsilateral and/or contralateral to the primary tumor (198,199).

Scenario 27: Oropharyngeal cancer (Score: 6 – May be Appropriate)

Human papillomavirus-associated SCC is rapidly increasing in incidence in the oropharynx (200). The majority of patients with oropharyngeal cancer (OPC) present with cervical metastases, which may often be unilateral (201,202). There is a risk for lateralized OPC to harbor occult contralateral nodal disease, ranging from 7% to 40% depending on primary tumor stage, that may not be detected radiographically (203–205). In addition to a curative ipsilateral neck dose, conventional radiotherapy has included a lower elective treatment dose to the contralateral neck even for lateralized primary disease. Unfortunately, patients with OPC have among the highest rates of severe treatment-related symptoms of any cancer (206–208). A lymphatic mapping-guided approach for management of the contralateral neck in patients with lateralized oropharyngeal disease may reduce the overall treatment volume receiving radiation therapy. Lymphatic mapping alone may identify at-risk nodal basins and specific lymphatic drainage pathways for each patient and tumor. In a prospective, non-randomized phase 2 clinical trial (SUSPECT trial), De Veij Mestdagh et al. (208) demonstrated a SPECT-CT guided approach to determine treatment of the contralateral neck with radiotherapy in 50 patients with lateralized head and neck cancers. Prospective randomized validation studies for lymphatic mapping-guided radiation therapy in OPC are in development.

TABLE 3
Clinical Scenarios for Cancers at Other Sites

Scenario no.	Description	Appropriateness	Score
19	Prostate cancer (initial stage)	Appropriate	7
20	Cervical cancer (initial stage)	Appropriate	7
21	Endometrial cancer, low-risk patient	May be Appropriate	5
22	Endometrial cancer, high-risk patient	May be Appropriate	6
23	Ovarian cancer	Rarely Appropriate	3
24	Vaginal squamous cell cancer	May be Appropriate	6
25	Primary malignancy of the GI tract without clinical evidence of metastasis	May be Appropriate	5
26	Oral cavity	Appropriate	9
27	Oropharyngeal cancer	May be Appropriate	6

Summary of Recommendations

The success of sentinel node localization in melanoma and breast cancer has led to the application of sentinel node scintigraphy to several other sites, as discussed above. Other than for cervical cancer and oral cavity cancers, the effectiveness of SLNB by using radiotracers in these other malignancies is still under investigation.

LYMPHEDEMA

Introduction

Lymphedema is the abnormal accumulation of lymphatic fluid caused by impaired lymphatic function. The cause of lymphatic fluid accumulation may be separated into 2 general groupings based on the underlying pathology. Primary lymphedema accounts for the minority of cases, affecting an estimated 1 in 100,000 children, and is caused by an inherent anatomical or functional abnormality (*209*). Secondary lymphedema accounts for the majority of lymphedema and most commonly results from disruption of an otherwise normally functioning lymphatic system. It may have a variety of causes, such as the sequelae of a surgical procedure or infection. Lymphedema can also develop in adulthood without clear lymphatic insult. Given the broad differential of edema and varied clinical presentations, an objective evaluation with imaging of the lymphatic system is important for the appropriate diagnosis and subsequent management. Invasive lymphangiography was the initial test of choice for the diagnosis of lymphedema; however, with the development of nuclear imaging, lymphoscintigraphy has become the preferred imaging modality (*210*).

Lymphoscintigraphy of the extremities is usually performed with injection of a radiotracer into the hand or foot followed by imaging of tracer migration for several hours. Lymphoscintigraphy offers assessment of global lymphatic function of a limb with limited anatomical detail compared with invasive lymphangiography or magnetic resonance lymphangiography. Abnormal findings include delayed transit of the tracer, decreased uptake in the regional lymph nodes, or accumulation of the tracer within the cutaneous lymphatics (dermal backflow) (*211*). Various staging systems for assessment of the severity of lymphatic dysfunction are described in the literature, but no standard staging criteria currently exists.

As there is no true gold standard imaging modality for the diagnosis of lymphedema, there are limited data demonstrating the accuracy of diagnosing lymphedema with nuclear lymphoscintigraphy compared with alternative imaging modalities. In addition, published studies vary by protocol, and new imaging protocols are regularly developed. Prior reports have demonstrated a sensitivity of 96% with a specificity of 100% for lymphoscintigraphy (*212*). ICG lymphangiography may offer improved sensitivity over nuclear lymphoscintigraphy, but experienced centers remain limited at this time and the specificity may be as low as 55% (*213,214*). Magnetic resonance lymphangiography offers assessment of the lymphatic anatomy but has only 68% sensitivity for detection of lymphedema (*215*).

The required equipment for lymphoscintigraphy is generally available at most centers. Limitations include lack of standardization of injection technique, radiotracer used, and imaging protocols. In addition, anatomical resolution of the images acquired offers little information for detailed lymphatic anatomical assessment. SPECT/CT combines scintigraphic imaging and anatomical imaging (CT), improving localization of tracer uptake. Often the physiological information provided by scintigraphic imaging and anatomical imaging studies such as CT, MRI, and lymphangiography are needed for the diagnosis and management of patients with lymphedema. There may also be a role for nuclear lymphoscintigraphy following lymphatic surgery, though the clinical utility of routine postsurgical lymphoscintigraphy remains to be determined.
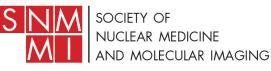
Clinical Scenarios and AUC Scores

Clinical scenarios for the use of lymphoscintigraphy in lymphedema and lipedema and final AUC scores are presented in Table 4.

Scenario 28: Clinical suspicion for primary lymphedema of the extremities (Score: 8 – Appropriate)

Primary lymphedema is the most common cause of lymphedema in children (see Pediatric Considerations section below) but it can also present in adulthood (also known as lymphedema tarda). Although physical exam features are often present to assist in differentiating lymphedema from alternative etiologies of limb edema, objective evaluation of lymphatic function is important when primary lymphedema is suspected. Lymphoscintigraphy is the recommended modality to evaluate lymphatic function in patients with suspected primary lymphedema grade 1, level of evidence B (*216,217*). In a specialized lymphatic referral center, 25% of patients referred for lymphedema were ultimately given an alternative diagnosis (*218*). It is essential to differentiate primary lymphedema from alternative causes of edema (e.g., venous compression) given the implications in management and the long-term prognosis.

Scenario 29: Clinical suspicion for secondary lymphedema of the extremities (Score: 7 – Appropriate)

A secondary lymphatic insult is the underlying mechanism for the overwhelming majority of adults presenting with lymphedema. The most common lymphatic insult in the developed world is secondary to cancer treatment (e.g., lymphadenectomy and/or radiation). Breast cancer-related lymphedema is the most frequently encountered, with rates of lymphedema following ALND and radiation reported to be 33.4% (*219*); however, lymphedema can occur with a variety of other malignancies, as well as at varying incidence (*220*). Lymphedema can present 5 or more years after the initial lymphatic insult (*221*). In patients with a clear clinical history and exam consistent with lymphedema, confirming the diagnosis with imaging is not always necessary. However, patients with concomitant malignancy or a history of malignancy are also at risk for veno-occlusive disease; thus, when the diagnosis of secondary lymphedema is not clear on history and exam, lymphoscintigraphy is an appropriate test to evaluate lymphatic function. In a retrospective review of a single referral center, over half of the patients referred with lower extremity lymphedema were ultimately diagnosed with multifactorial edema (*222*). Lymphoscintigraphy can be considered in order to evaluate the concomitant lymphatic dysfunction in such patients. In addition, objective evaluation of lymphatic function is often appropriate in patients who are being considered for surgical therapy of lymphedema (*223*).

Scenario 30: Clinical suspicion for breast lymphedema (*Score: 4 – May be Appropriate*)

Most patients with lymphedema following breast cancer treatment develop edema in the ipsilateral upper extremity; however, in some patients, edema can develop in the breast itself (*224,225*). Given the location of the edema, there are no clearly defined protocols to evaluate lymphatic function with lymphoscintigraphy. Lymphoscintigraphy of the ipsilateral upper extremity can be performed to evaluate function in that region, but often breast lymphedema is a clinical diagnosis (*226*).

Scenario 31: Lipedema of the extremities (Score: 6 – May be Appropriate)

Lipedema is an abnormality of the fibrotic loose connective tissue and adipose tissue, primarily of the lower extremities, marked by excessive accumulation of adipose tissue. Lipedema can often be differentiated from lymphedema with a thorough clinical exam; however, concomitant lymphatic dysfunction can be seen in some patients with lipedema, particularly in a more advanced stage (*222,227*). Evaluation of nuclear lymphoscintigraphy in patients with lipedema demonstrated alterations in 47%; all lymphoscintigraphic abnormalities were low or low-moderate in severity (*228*). A recent standard-of-care article recommended nuclear scintigraphy in patients with lipedema if it would change clinical management (*229*).

Scenario 32: Limb edema of unclear etiology (Score: 8 – Appropriate)

The foundation of the evaluation of limb edema is the history and physical exam. However, in patients with clinically undifferentiated edema, objective evaluation of lymphatic function can be helpful to differentiate lymphatic dysfunction from other causes of limb swelling. Given the potential implications for change in management and prognosis with a definitive diagnosis of lymphedema, nuclear lymphoscintigraphy is an appropriate test to consider in patients with limb edema of unclear etiology, particularly given the reported high specificity and sensitivity (*212*).
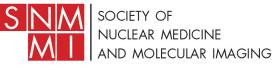
TABLE 4
Clinical Scenarios for Lymphedema and Lipedema

Scenario no.	Description	Appropriateness	Score
28	Clinical suspicion for primary lymphedema of the extremities	Appropriate	8
29	Clinical suspicion for secondary lymphedema of the extremities	Appropriate	7
30	Clinical suspicion for breast lymphedema	May be Appropriate	4
31	Lipedema of the extremities	May be Appropriate	6
32	Limb edema of unclear etiology	Appropriate	8

Summary of Recommendations

Lymphoscintigraphy is an appropriate test for the evaluation of patients suspected to have primary lymphedema or limb edema of unclear etiology. Lymphoscintigraphy can also be appropriate for patients with suspicion for secondary lymphedema, particularly if the clinical history or exam is not definitive for lymphedema. Lymphoscintigraphy can be helpful to

confirm lymphatic dysfunction prior to lymphatic surgery. Lymphoscintigraphy may be appropriate in select patients with lipedema or breast lymphedema, although the value of lymphoscintigraphy in these populations is not widely published.

PEDIATRIC CONSIDERATIONS

The pediatric indications for lymphoscintigraphy and SLNB are similar to those in adults, albeit reflecting the differing incidences and causes of lymphatic diseases in children. Although it is uncommon for studies of the clinical utility of lymphoscintigraphy to focus solely on children, many published studies include children in the study population. Lymphoscintigraphy has been reported to have a role in guiding the treatment of some pediatric cancers and in the evaluation of lymphedema in children.

Breast cancer: Although exceedingly rare in children, secretory or invasive ductal carcinoma has been reported in patients under the age of 21 years. In a single-institution retrospective study of SLNB for solid tumors of childhood (*230*), SLNB was performed in 5 individuals with juvenile breast cancer. SLNs were identified in all 5, and disease involvement was identified in 2 of 5 cases. The other 3 children received no local therapy to the lymph node basins and had clinical recurrence of disease during long-term clinical follow-up.

Skin cancers: The incidence of skin cancers, including cutaneous melanoma and clear cell carcinoma, is increasing in children. As in adults, lymphoscintigraphy with SLNB can be useful for assessing the extent of disease without the limited accuracy and morbidity of complete nodal basin lymphadenectomy. Typically, the criteria for appropriateness of SLNB in adults can be applied to children.
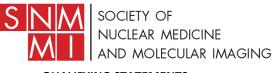
A single-institution retrospective review of lymphoscintigraphy included 33 pediatric patients with melanotic cutaneous cancers (26 melanoma, 7 others) who underwent lymphoscintigraphy with SLNB. Disease involvement of lymph nodes was found in 13 (*231*). None of the patients without evidence of disease in SLNs had disease recurrence, with a median clinical follow-up of 21.5 months.

Spitz nevi commonly present in pediatric populations and can be very challenging to distinguish pathologically from melanomas. These lesions have been classified as "melanocytic tumors of uncertain malignant potential" (MELTUMP) (see scenario 13 above) or atypical spitzoid tumors, and biologically may exhibit a more favorable clinical course. For these lesions, the relative prognostic value of SLNB is less clear, but may be appropriate, as discussed in scenario 13 above.

Pediatric sarcoma: Although sarcomas are less common in children than in adults, they are among the more common solid cancers of childhood. In children, rhabdomyosarcomas are the most common sarcomas. Among the non-rhabdomyosarcoma soft tissue tumors, one of the more common histological types is synovial cell sarcoma. A single-institution retrospective review (*228*) evaluated 30 pediatric patients (age range 2–21 years) with pediatric sarcomas who underwent 31 SLNBs over a 10-year period. SLNs were identified preoperatively in 30 of 31 cases and intraoperatively in 1 case. In a prospective comparison of SLNB and ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-PET/CT in 28 pediatric and young adult patients with sarcomas, including 8 rhabdomyosarcomas and 6 synovial sarcomas (*232*), SLNB was shown to be more accurate than FDG-PET/CT for identifying disease involvement of lymph nodes. SLNB correctly identified nodal involvement in 7 (25%) patients, which led to adjustments in planned therapy in 6 of the 7 patients. This included 3 patients without apparent metastatic disease on FDG-PET/CT or other imaging studies, including CT and MRI. By comparison, FDG-PET/CT demonstrated FDG-avid lymph nodes in 14 of 28 patients, although only 4 of those patients were proven to have disease involvement in resected lymph nodes.

Lymphedema: Children with lymphedema are more likely to have primary lymphedema than secondary lymphedema (*233*). Because of the low incidence of disease in children, large clinical trials of lymphoscintigraphy have not been performed in children. As is the case for adults, lymphoscintigraphy has been reported to be useful for the diagnosis and characterization of lymphedema in pediatric patients. In a single-institution observational study of children with swollen lower extremities (*234*), lymphoscintigraphy distinguished patients with lymphedema (73%) from those with other causes of extremity swelling. However, lymphoscintigraphy findings do not appear to correlate with the clinical severity of disease (*235*).

Lymphoscintigraphy also has reported utility for evaluating abnormal lymphatic drainage in children with secondary lymphedema. For example, lymphoscintigraphy has been shown to have utility in the diagnosis and evaluation of lymphedema or lymphatic leak after surgery for congenital heart disease, as well as in guiding management (*236*).

QUALIFYING STATEMENTS

Study/Evidence Limitations

Although a large body of literature focuses on lymphoscintigraphy for sentinel node localization, particularly in breast cancer and cutaneous melanoma, the workgroup found the body of medical literature regarding the use of lymphoscintigraphy to be limited when rigorous inclusion criteria were applied to the systematic literature review. Many articles did not use adequate patient follow-up to assess accuracy, resulting in limited sensitivity and specificity information. Information was also scarce on the role of lymphoscintigraphy in patients with breast cancer with multifocal disease at initial staging and in patients with prior breast or axillary surgery. In addition, no adequate studies were found to compare the various tracers and injection techniques for accuracy. Although many studies have evaluated sentinel node staging for patients with melanoma, there are fewer publications for other tumors such as SCC and other skin neoplasms.

The decrease in morbidity of sentinel node biopsy compared with that for complete node-bed dissection has encouraged the use of sentinel node scintigraphy for primary tumors other than breast cancer and melanoma. Although the value of sentinel node biopsy with other tumors is less well documented, particularly with regard to outcomes, such data will be difficult to collect because sentinel node biopsy is not as closely linked to outcomes as surgical practice and therapeutic interventions are, which may be affected by sentinel node scintigraphy to different degrees, depending on local practices. Future investigations should therefore be directed toward investigating the accuracy of sentinel node scintigraphy for correctly localizing micrometastatic disease. In addition, more data are needed regarding the addition of SPECT/CT to sentinel node scintigraphy and for patients with lymphedema.

Implementation of this AUC Guidance

To develop broad-based multidisciplinary clinical guidance documents, SNMMI has been working with several other medical specialty societies. It is hoped that this collaboration will foster the acceptance and adoption of this guidance by other specialties. SNMMI has developed a multipronged approach to disseminate AUC for lymphoscintigraphy to all relevant stakeholders, including referring physicians, nuclear medicine physicians, and patients. The dissemination and implementation tactics will include a mix of outreach and educational activities targeted to each of these audiences. SNMMI will create case studies for its members, as well as for referring physicians, and make them available via online modules and webinars. These cases will cover the appropriate clinical scenarios for the use of lymphoscintigraphy. Related resources such as the systematic review supporting the development of these AUC, a list of upcoming education events on the AUC, factsheets, and other didactic materials will be made available on the SNMMI website. Live sessions will be held at the SNMMI annual and midwinter meetings, as well as at other relevant professional society meetings of referring physicians to highlight the importance and application of these AUC. SNMMI also aims to create a mobile application for these AUC for both Apple and Android platforms.
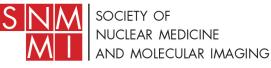
ACKNOWLEDGMENTS (Staff)

The workgroup acknowledges staff support from the Pacific Northwest Evidence-Based Practice Center of Oregon Health and Science University (Roger Chou, MD, FACP – Principal Investigator; Rebecca Jungbauer, DrPH – Research Associate; Tamara P. Cheney, MD – Research Associate; Chandler Weeks, BS – Research Assistant; Miranda Pappas, MA – Research Associate and Project Manager; Tracy Dana, MLS – Research Librarian; Elaine Graham, MLS – EPC Operations Manager provided project oversight).

APPENDIX A: WORKGROUP MEMBERS AND EXTERNAL REVIEWERS (Staff)
Workgroup

The members of the workgroup are Kevin J. Donohoe, MD (chair), Beth Israel Deaconess Medical Center, Boston, MA (SNMMI); Brett J. Carroll, MD, Beth Israel Deaconess Medical Center, Boston, MA (SVM); David K. V. Chung, MD, University of Sydney, Australia (ANZSNM); Elizabeth H. Dibble, MD, Alpert Medical School of Brown University, Rhode Island Hospital, Providence, RI (ACR, SNMMI); Emilia Diego, MD, University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, PA (SSO); Francesco Giammarile, MD, PhD, International Atomic Energy Agency, Vienna, Austria, and Centre Leon Berard Lyon, France (EANM); Frederick D. Grant, MD, Children's Hospital of Philadelphia, Philadelphia, PA (SNMMI); Stephen Y. Lai, MD, PhD,

The University of Texas MD Anderson Cancer Center, Houston, TX (AHNS); Hannah Linden, MD, University of Washington, Seattle, WA (ASCO); Megan E. Miller, MD, FACS, Case Western Reserve University School of Medicine, Cleveland, OH (ASBrS); Neeta Pandit-Taskar, MD, Memorial Sloan Kettering Cancer Center, New York, NY (ACNM, SNMMI); Nicholas E. Tawa Jr., MD, PhD, Beth Israel Deaconess Medical Center, Boston, MA (ACS); and Sergi Vidal-Sicart, MD, Hospital Clinic Barcelona, Barcelona, Spain (EANM).

External Reviewers (Staff)

The external (peer) reviewers are Bennett Greenspan, MD, FACNM, FACR, FSNMMI, Medical College of Georgia, Augusta, GA; Munir Ghesani, MD, Mount Sinai, New York, NY; and Patrick Colletti, MD, FACNM, FSNMMI, Keck School of Medicine, Los Angeles, CA.

SNMMI (Staff)

The supporting staff from SNMMI are Bonnie Clarke, Senior Director, Evidence & Quality and Research & Development, and Douglas Burrichter, Program Manager, Quality & Evidence.

APPENDIX B: DEFINITIONS OF TERMS AND ACRONYMS

ACNM: American College of Nuclear Medicine

ACOSOG: American College of Surgeons Oncology Group

ACR: American College of Radiology

ACS: American College of Surgeons

AHNS: American Head and Neck Society

AJCC: American Joint Committee on Cancer

ALND: axillary lymph node dissection

ANZSNM: Australia and New Zealand Society of Nuclear Medicine

ASBrS: American Society of Breast Surgeons

ASCO: American Society of Clinical Oncology

AUC: appropriate use criteria

Clinical decision support - software used to maintain a collection of appropriate use criteria for reference

COI: conflict of interest

CT: computed tomography

DCIS: ductal carcinoma in situ

EANM: European Association of Nuclear Medicine

EAU: European Association of Urology

ePLND: extended pelvic lymph node dissection

ESGO: European Society of Gynaecological Oncology

ESTRO: European SocieTy for Radiotherapy and Oncology

^{18}F-FDG: ^{18}F-fluorodeoxyglucose

GI: gastrointestinal

GROINSSV: GROningen INternational Study on Sentinel lymph nodes in Vulvar cancer

ICG: indocyanine green

LCIS: lobular carcinoma in situ

MCAT: malignant cutaneous adnexal tumor

MCC: Merkel cell carcinoma

MELTUMP: melanocytic lesion of uncertain metastatic potential

Micrometastasis: metastatic disease ≤2 mm in size

MRI: magnetic resonance imaging

MSLT-I: Multicenter Selective Lymphadenectomy Trial I

MSLT-II: Multicenter Selective Lymphadenectomy Trial II

NCCN: National Comprehensive Cancer Network

NPV: negative predictive value

OPC: oropharyngeal cancer

PET: positron emission tomography

PLND: pelvic lymph node dissection

QUADAS: Quality Assessment of Diagnostic Accuracy Studies

Radiopharmaceutical: Radioisotope/pharmaceutical combination. The isotope is commonly used to allow imaging of the normal movement of the pharmaceutical through biological systems.

SCC: squamous cell carcinoma

Scintigraphy: imaging of nuclear tracers with a gamma camera

SLN: sentinel lymph node

SLNB: sentinel lymph node biopsy

SNMMI: Society of Nuclear Medicine and Molecular Imaging

SPECT: single-photon emission computed tomography

SPECT/CT: single-photon emission computed tomography combined with computed tomography

SSO: Society of Surgical Oncology

SVM: Society for Vascular Medicine

[99m]Tc: Technetium 99m is the radiotracer most commonly used for lymphoscintigraphy.

APPENDIX C: DISCLOSURES AND CONFLICTS OF INTEREST (COIs) (Staff)

SNMMI rigorously attempted to avoid any actual, perceived, or potential COIs that might have arisen as a result of an outside relationship or personal interest on the part of the workgroup members or external reviewers. Workgroup members were required to provide disclosure statements of all relationships that might be perceived as real or potential COIs. These statements were reviewed and discussed by the workgroup chair and SNMMI staff and were updated and reviewed by an objective third party at the beginning of every workgroup meeting or teleconference. The disclosures of the workgroup members can be found in Table 5. A COI was defined as a relationship with industry—including consulting, speaking, research, and nonresearch activities—that exceeds $5,000 in funding over the previous or upcoming 12-month period. In addition, if an external reviewer was either the principal investigator of a study or another key member of the study personnel, that person's participation in the review was considered likely to present a COI. All reviewers were asked about any potential COI. A COI was also considered likely if an external reviewer or workgroup member was either the principal investigator or a key member of a study directly related to the content of these AUC. All external reviewers were asked about any potential COI.

TABLE 5
Relationships with Industry and Other Entities

Workgroup member	Reported relationships
Kevin Donohoe	• None
Brett Carroll	• Bristol Myers Squibb, Research Grant, Thrombosis
David Chung	• None
Elizabeth Dibble	• None
Emilia Diego	• None
Francesco Giammarile	• None
Frederick Grant	• None
Giorgos Karakousis	• None
Stephen Lai	• Cardinal Health, Medical Affairs Consultant, Sentinel Node Mapping

Hannah Linden	•	None
Megan Miller	•	None
Neeta Pandit-Taskar	•	None
Nicholas Tawa	•	None
Sergi Vidal-Sicart	•	None

APPENDIX D: PUBLIC COMMENTARY (Staff)

The workgroup solicited information from all communities through the SNMMI website and through direct solicitation of SNMMI members. The comments and input helped to shape the development of these AUC on the use of nuclear medicine in lymphoscintigraphy.

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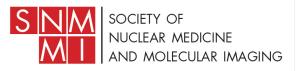
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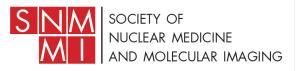
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