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Sentinel Lymph Node Biopsy for Melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Joint Clinical Practice Guideline

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This guideline was developed through collaboration between the American Society of Clinical Oncology and Society of Surgical Oncology and has been published jointly by invitation and consent in both *Journal of Clinical Oncology* and *Annals of Surgical Oncology*.

Editor's note: This represents a brief summary overview of the complete "Sentinel Lymph Node Biopsy for Melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Joint Clinical Practice Guideline" and provides the recommendations with brief discussions of the relevant literature for each. The complete guideline, which includes comprehensive discussions of the literature, methodologic information, and additional citations, along with an Appendix and Data Supplement, is available on the American Society of Clinical Oncology Web site (http://www.asco.org/guidelines/snbmelanoma) and Society of Surgical Oncology Web site (http://www.surgonc.org/practice--policy/practice-management/clinical-guidelines/snbmelanoma.aspx).

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ABSTRACT

Purpose
The American Society of Clinical Oncology (ASCO) and Society of Surgical Oncology (SSO) sought to provide an evidence-based guideline on the use of lymphatic mapping and sentinel lymph node (SLN) biopsy in staging patients with newly diagnosed melanoma.

Methods
A comprehensive systematic review of the literature published from January 1990 through August 2011 was completed using MEDLINE and EMBASE. Abstracts from ASCO and SSO annual meetings were included in the evidence review. An Expert Panel was convened to review the evidence and develop guideline recommendations.

Results
Seventy-three studies met full eligibility criteria. The evidence review demonstrated that SLN biopsy is an acceptable method for lymph node staging of most patients with newly diagnosed melanoma.

Recommendations
SLN biopsy is recommended for patients with intermediate-thickness melanomas (Breslow thickness, 1 to 4 mm) of any anatomic site; use of SLN biopsy in this population provides accurate staging. Although there are few studies focusing on patients with thick melanomas (T4; Breslow thickness, $>$ 4 mm), SLN biopsy may be recommended for staging purposes and to facilitate regional disease control. There is insufficient evidence to support routine SLN biopsy for patients with thin melanomas (T1; Breslow thickness, $<$ 1 mm), although it may be considered in selected patients with high-risk features when staging benefits outweigh risks of the procedure. Completion lymph node dissection (CLND) is recommended for all patients with a positive SLN biopsy and achieves good regional disease control. Whether CLND after a positive SLN biopsy improves survival is the subject of the ongoing Multicenter Selective Lymphadenectomy Trial II.

INTRODUCTION

Metastasis to regional nodes is the most important prognostic factor in patients with early-stage melanoma and has been shown to occur in approximately 20% of patients with intermediate-thickness tumors.[1,2] As such, it is critically important to identify those patients for whom the expected benefits of resecting regional lymph nodes outweigh the risks of surgical morbidity.

Sentinel lymph node (SLN) biopsy is commonly used by surgeons who treat melanoma in the United States, Canada, Australia, and Western Europe and has been endorsed by the American Joint Committee on Cancer (AJCC) as a valuable staging procedure for patients with melanoma who are at risk of clinically occult nodal metastases. This highly accurate and low-morbidity staging procedure should be used to guide treatment decisions (ie, completion lymph node dissection [CLND] and adjuvant therapy) as well as entry into clinical trials.[3]

To develop and formalize guideline recommendations for the use of SLN biopsy in oncology practice, the American Society of Clinical Oncology (ASCO) and Society of Surgical Oncology (SSO)

convened a joint Expert Panel. This guideline addresses two overarching clinical questions:

What are the indications for SLN biopsy?

What is the role of CLND?

This article represents a brief summary overview of the full guideline. Table 1 provides the recommendations. The full guideline, which includes comprehensive discussions of the literature, methodologic information, and additional citations, can be found online on the ASCO Web site (http://www.asco.org/guidelines/snbmelanoma) and SSO Web site (http://www.surgonc.org/practice--policy/practice-management/clinical-guidelines/snbmelanoma.aspx). An Appendix providing a discussion of some of the key technical considerations for SLN biopsy, a Data Supplement, and clinical tools and resources are also available on the Web sites.

METHODS

ASCO and SSO convened an Expert Panel (members listed in Appendix Table A1, online only) to develop guideline recommendations based on its assessment of evidence from a comprehensive systematic review and meta-analysis of the literature.[4]

Literature Review and Analysis

Literature search strategy. A comprehensive systematic review of the literature published between January 1990 and August 2011 was completed using MEDLINE and EMBASE. Abstracts from ASCO and SSO annual meetings were also included in the evidence review. A detailed description of the systematic review methodology has been published elsewhere.[4]

Inclusion and exclusion criteria. Studies were required to report the number of patients in whom SLN biopsy was attempted, the number who had successful identification and removal of an SLN, and continuous follow-up for the group of patients who had a negative SLN biopsy. No exclusion was made based on Breslow thickness, type of study, or whether the study was retrospective or prospective in nature. However, the population reported had to be original. When a single institution had multiple reports on its populations, the report that had the largest population, longest follow-up, and/or more appropriate outcomes was selected. Studies were excluded if they reported only patients with positive SLN biopsy, referred only to a highly specific population or location, and/or involved ≤ 50 patients.

Meta-analysis. A meta-analysis was the evidentiary base for the guideline recommendations. The meta-analysis was conducted based on the results of an initial systematic review of the literature and included literature published from January 1990 through December 2009. Valsecchi et al[4] provide a detailed description of the methods and findings from the meta-analysis. Primary outcomes consisted of measures of test performance, including: the proportion

THE BOTTOM LINE

Sentinel Lymph Node Biopsy for Melanoma: ASCO and SSO Joint Clinical Practice Guideline

Intervention

- Sentinel lymph node (SLN) biopsy for patients with newly diagnosed melanoma

Target Audience

- Surgical oncologists, medical oncologists, dermatologists, primary care physicians, pathologists, nuclear medicine specialists

Key Recommendations

- Intermediate-thickness melanomas: SLN biopsy is recommended for patients with cutaneous melanomas with Breslow thickness of 1 to 4 mm at any anatomic site
- Thick melanomas: SLN biopsy may be recommended for staging purposes and to facilitate regional disease control for patients with melanomas that are T4 or $>$ 4 mm in Breslow thickness
- Thin melanomas: There is insufficient evidence to support routine SLN biopsy for patients with melanomas that are T1 or $<$ 1 mm in Breslow thickness, although it may be considered in selected high-risk patients
- Completion lymph node dissection is recommended for all patients with a positive SLN biopsy

Methods

- An Expert Panel was convened to develop clinical practice guideline recommendations based on a review of evidence from a systematic review of the medical literature

Additional Information

- This Executive Summary of the full guideline includes the clinical questions, recommendations, a brief summary of the literature, and discussions.

The full guideline (which includes a comprehensive discussion of the literature, description of the methodology, and complete reference list), along with an Appendix, a Data Supplement, and clinical tools and resources, can be found on the ASCO Web site (http://www.asco.org/guidelines/snbmelanoma) and SSO Web site (http://www.surgonc.org/practice--policy/practice-management/clinical-guidelines/snbmelanoma.aspx).

Table 1. Summary of Clinical Practice Guideline Recommendations

Clinical Question	Recommendation
What are the indications for SLN biopsy?	
Intermediate-thickness melanomas	SLN biopsy is recommended for patients with intermediate-thickness cutaneous melanomas (Breslow thickness, 1 to 4 mm) of any anatomic site. Routine use of SLN biopsy in this population provides accurate staging, with high estimates for PSM and acceptable estimates for FNR, PTPN, and PVP
Thick melanomas	Although there are few studies focusing specifically on patients with thick melanomas (T4; Breslow thickness, > 4 mm), use of SLN biopsy in this population may be recommended for staging purposes and to facilitate regional disease control
Thin melanomas	There is insufficient evidence to support routine SLN biopsy for patients with thin melanomas (T1; Breslow thickness, < 1 mm), although it may be considered in selected patients with high-risk features when the benefits of pathologic staging may outweigh the potential risks of the procedure. Such risk factors may include ulceration or mitotic rate ≥ 1/mm^2, especially in the subgroup of patients with melanomas 0.75 to 0.99 mm in Breslow thickness
What is the role of CLND?	CLND is recommended for all patients with positive SLN biopsy. CLND achieves regional disease control, although whether CLND after a positive SLN biopsy improves survival is the subject of the ongoing MSLT II

Abbreviations: CLND, completion lymph node dissection; FNR, false-negative rate; MSLT II, Multicenter Selective Lymphadenectomy Trial II; PSM, proportion successfully mapped; PTPN, post-test probability negative; PVP, positive predictive value; SLN, sentinel lymph node.

successfully mapped (PSM), false-negative rate (FNR), post-test probability negative (PTPN), and predictive value positive (PVP) using same nodal basin recurrence as the outcome of interest. The PSM was defined as the ratio between the number of patients who had at least one SLN excised and the total number of patients included in the study. Specifically, for the calculation of the FNR, the following formula was used: FN/(TP + FN), where FNR = patients with regional recurrence after negative SLN biopsy/(patients with positive SLN biopsy regardless of recurrence + patients with regional recurrence after negative SLN biopsy). PTPN was calculated as the ratio of patients with negative SLN biopsy who recurred to all patients with negative SLN biopsy. This is equivalent to 1 − predictive value negative of the test. PVP was calculated as the ratio of patients with positive SLN biopsy with recurrence, divided by all patients with positive SLN biopsy. Secondary outcomes included the results of CLND and the same measurements of test performance as for primary outcomes, focusing on regional recurrences with or without distant metastases.

Study quality and limitations of the literature. There is currently only one randomized controlled trial (Multicenter Selective Lymphadenectomy Trial I [MSLT I]) that addresses whether patients with melanoma managed using SLN biopsy have better clinical outcomes than those whose disease is managed with nodal observation.[5] Hence, observational studies were included in the systematic review of the literature.

Two reviewers independently assessed the quality of the selected studies using the criteria from the Methodological Index for Non-Randomized Studies.[4,6] The methods and results of the quality assessment have been reported elsewhere.[4]

Guideline Policy

This Executive Summary for clinicians is an abridged version of the ASCO and SSO clinical practice guideline. Neither the practice guideline nor this summary is intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients and may not reflect the most recent evidence. This summary does not recommend any particular product or course of medical treatment. Use of the practice guideline and this summary is voluntary. The full practice guideline and additional information are available on the ASCO Web site (http://www.asco.org/guidelines/snbmelanoma) and SSO Web site (http://www.surgonc.org/practice--policy/practice-management/clinical-guidelines/snbmelanoma.aspx).

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with the ASCO Conflict of Interest Management Procedures for Clinical Practice Guidelines (summarized at http://www.asco.org/guidelinescoi). Members of the Panel completed a disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Procedures, the majority of the members of the Panel did not disclose any such relationships.

RESULTS

There were 73 studies, including more than 25,000 patients, that met full eligibility criteria. A QUOROM diagram is available in the online Data Supplement, along with a table that summarizes the characteristics and outcomes of studies included in the systematic review and meta-analysis (refer to the ASCO Web site [http://www.asco.org/guidelines/snbmelanoma] or SSO Web site [http://www.surgonc.org/practice--policy/practice-management/clinical-guidelines/snbmelanoma.aspx]). Valsecchi et al[4] provide detailed findings from the systematic review and meta-analysis.

GUIDELINE RECOMMENDATIONS

CLINICAL QUESTION 1

What are the indications for SLN biopsy?

Recommendation

Intermediate-thickness melanomas. SLN biopsy is recommended for patients with intermediate-thickness cutaneous melanomas (Breslow thickness, 1 to 4 mm) of any anatomic site. Routine use of SLN biopsy in this population provides accurate staging, with high estimates for PSM and acceptable estimates for FNR, PTPN, and PVP.

Thick melanomas. Although there are few studies focusing specifically on patients with thick melanomas (T4; Breslow thickness, > 4 mm), use of SLN biopsy in this population may be recommended for staging purposes and to facilitate regional disease control.

Thin melanomas. There is insufficient evidence to support routine SLN biopsy for patients with thin melanomas (T1; Breslow thickness, < 1 mm), although it may be considered in selected patients with

high-risk features when the benefits of pathologic staging may outweigh the potential risks of the procedure. Such risk factors may include ulceration or mitotic rate $\geq 1/mm^2$, especially in the subgroup of patients with melanomas 0.75 to 0.99 mm in Breslow thickness.

Literature Review and Analysis

The systematic review of the literature and meta-analysis demonstrate that SLN biopsy is a feasible and accurate technique, with PSM estimates ranging from 97.3% to 98.6% in the meta-analysis.[4] Across studies, weighted summary estimates of 12.5% and 3.4% for FNR and PTPN, respectively, support the reliability of this minimally invasive staging technique.[3,4] After a positive SLN biopsy, 97.5% of patients underwent CLND, and 20.1% were found to have additional positive lymph nodes. Overall, the recurrence rate in the same nodal basin after a positive SLN biopsy was 7.5%, despite CLND in nearly all patients.[4]

More recent articles tended to report even higher PSM estimates, demonstrating improvements in technical performance with more experience. Because of the stringency of the criteria for inclusion in this systematic review of the literature, many SLN biopsy studies representing large single-institution experiences and reporting outcomes such as PSM and FNR could not be included. Cited FNRs have been as low as 0% to 2%,[7-10] although the meta-analysis found that FNR tended to be higher with longer follow-up. Overall, the SLN biopsy procedure is well tolerated and associated with low complication rates.[11]

Intermediate-thickness melanomas. Although clinical variables such as older age have been variably reported as lower risk factors,[12-14] there are no specific variables that can reliably identify patients with intermediate-thickness melanomas at low risk for metastases. The definition of intermediate-thickness melanoma varied by study. Nevertheless, it is clinically consistent with contemporary staging systems to define intermediate-thickness melanomas as those measuring 1 to 4 mm.[15]

Comorbid conditions. Clinical judgment must be used when considering SLN biopsy in patients with comorbid medical conditions. The individual risks and benefits of the procedure should be weighed against the operative and anesthetic risks as well as potential competing causes of mortality.

Complications. Complications after SLN biopsy are uncommon. The overall complication rate reported in MSLT I was 10.1% after SLN biopsy compared with 32.7% after CLND.[16] The most common complications after SLN removal documented in MSLT I included seroma (5.5%), infection (4.6%), and wound separation (1.2%). The Sunbelt Melanoma Trial (also a prospective randomized trial) similarly showed a low overall rate of complications from SLN biopsy (4.6%) compared with CLND (23.2%).[11,12] Most complications were noted to be short-term issues that resolved over time with wound care and selective use of antibiotics.

Staging. Accurate identification of patients with node-negative (stage I or II) or node-positive (stage III) disease improves staging and may facilitate regional disease control and decision making for treatment with adjuvant therapy.[3,17] With substantive changes in the melanoma staging guidelines in 2002, the AJCC staging system effectively linked disease stage and prognosis.[18,19] At that time, the number of nodal metastases and whether nodal disease was occult or clinically apparent (ie, how the N category was defined with regard to burden of disease) were noted to be the most significant independent predictors of survival in patients with stage III melanomas. With later iterations of the AJCC staging system (2009), additional refinements were made in the N category based on the prognostic value of distinguishing micrometastases (as would be diagnosed after SLN biopsy) from macrometastases.[20,21] A melanoma macrometastasis is detected by clinical examination (not by size criteria) and confirmed pathologically, whereas a melanoma micrometastasis is a clinically occult nodal metastasis that is detected by a pathologist on microscopic examination of lymph nodes, with or without immunohistochemistry, and is not limited by any minimum or maximum size threshold. Recognizing the value of examining SLNs to detect low volumes of metastatic disease (aggregates of only a few cells), the current staging system[1,22] incorporates the use of immunohistochemistry and eliminates any minimum size threshold for defining nodal metastases. Molecular diagnostics, such as reverse transcriptase-polymerase chain reaction, have unproven prognostic significance, and these results are not used to define positive nodes. As a result, more refined definitions of the N category are now used for classification. Distinct differences in classifications have validated prognostic significance. For example, 5-year survival ranges from 70% for patients with one SLN positive with micrometastatic disease to 39% for patients with $>$ four involved nodes or with nodes that are extensively involved (eg, matted nodes).[1]

Thick melanomas. Although SLN biopsy has been widely accepted for the pathologic staging of patients with intermediate-thickness melanomas, somewhat more controversy exists regarding the value of this procedure for patients with thick primary tumors (T4; Breslow thickness, $>$ 4 mm). Conventional wisdom asserts that patients with thick melanomas have a high risk of systemic disease at the time of diagnosis and that no survival benefit can be derived from removal of regional lymph nodes. However, among patients without distant disease, it can be argued that those with thick melanomas have indications for SLN biopsy similar to those of patients with intermediate-thickness melanomas and derive the same benefits from SLN biopsy as a pathologic staging procedure. One of the main advantages of SLN biopsy in patients with thick melanomas is better regional disease control, which is especially important in a population with $>$ 30% chance of lymph node involvement.[20,21,23]

Evidence from multiple retrospective studies has demonstrated that SLN biopsy provides important staging and prognostic information for patients with thick melanomas. Seven of eight published studies—each evaluating SLN biopsy in $>$ 100 patients with T4 melanomas—have shown that SLN biopsy is a significant predictor of overall survival.[2,20,21,23-28] The one study that did not show a significant difference in overall survival demonstrated a significant difference in disease-free survival.[24]

Thin melanomas. A majority (70%) of melanomas diagnosed in the United States are thin melanomas (T1; Breslow thickness, $<$ 1 mm).[29] In general, the routine use of SLN biopsy in patients with thin melanomas has not been advocated, because the overall risk of nodal involvement is estimated to be only approximately 5.1%,[30] although there are reports of positive SLNs in up to 20% of patients in subsets with thin melanomas (especially those that are 0.75 to 0.99 mm in thickness with ulceration and/or mitotic rate $\geq 1/mm^2$).[22]

An individualized approach to SLN biopsy for patients with thin melanomas has been advocated in many treatment centers based on risk factors that have been shown to be associated with SLN metastasis. Use of SLN biopsy in patients with thin melanomas must consider the

low rate of positivity in the context of a known FNR. Further investigation is also needed to better identify the subgroups of patients with thin melanomas with a greater risk of nodal metastasis.

CLINICAL QUESTION 2

What is the role of CLND?

Recommendation

CLND is recommended for all patients with a positive SLN biopsy. CLND achieves regional disease control, although whether CLND after a positive SLN biopsy improves survival is the subject of the ongoing Multicenter Selective Lymphadenectomy Trial II (MSLT II).

Literature Review and Analysis

Patients with tumor-positive SLNs. Currently, CLND is the standard recommendation for patients with tumor-positive SLNs. The goals of CLND are to improve survival rates, maximize regional disease control, and minimize operative morbidity. Whether CLND improves survival is the subject of the ongoing prospective randomized MSLT II study.[31] The main objective of MSLT II is to determine if there is a therapeutic benefit to removing any non-SLNs in patients who have already had their tumor-positive SLN removed. In MSLT I, patients with demonstrated nodal metastases had a survival advantage with early intervention compared with those who had a delayed lymphadenectomy when they presented with clinically evident nodal metastases.[5] Hence, although two goals of CLND are regional disease control and cure, there is currently insufficient evidence to determine whether omission of CLND is safe.

Risk of regional nodal recurrence if CLND is not performed. In the two large prospective randomized trials (ie, the Sunbelt Melanoma Trial[12] and MSLT I[5]), the rate of positive non-SLNs among patients who underwent CLND for a tumor-positive SLN was 16%. In a retrospective multi-institutional study by Wong et al,[32] which included 134 highly selected patients with positive SLNs who did not undergo CLND, regional nodal metastasis was a component of first recurrence in 15% of these patients. Therefore, it is reasonable to conclude from these data that the risk of developing regional nodal metastasis as a first site of recurrence, if no CLND is performed, is at least 15% to 20%.[33,34]

Effect of CLND on regional disease control. In MSLT I, the rate of regional nodal recurrence after CLND was 4.2%[5]; in the Sunbelt Melanoma Trial, it was 4.9% (unpublished data). These rates are much lower than the 15% rate of regional nodal recurrence as a site of first metastasis and the 41% overall regional nodal recurrence rate when CLND was not performed, reported in the study by Wong et al.[35]

Until final results of MSLT II are available, we will not be able to determine, with higher-level evidence, the impact of CLND on regional disease control. Until that time, the best available evidence suggests that CLND is effective at achieving regional disease control in the majority of patients with positive SLNs.

Impact of CLND on overall survival. MSLT I showed no benefit of CLND with regard to overall survival, likely because only a minority of patients (16%) had tumor-positive SLNs, and the majority of the patients in the study would not have been helped by removal of regional lymph nodes.[5] However, the 5-year survival rate for patients with tumor-positive SLNs who underwent CLND was 72.3% compared with 52.4% for patients who did not undergo SLN biopsy and developed palpable nodal disease (hazard ratio, 0.51; 95% CI, 0.32 to 0.81; $P = .004$). CLND should be performed until there is convincing evidence that it does not improve regional disease control or survival.

Risk of morbidity. CLND is associated with risks of long-term morbidity, especially lymphedema. However, morbidity with CLND may be considerably worse when it is delayed until there is clinically evident disease. The observed increases in morbidity for patients who have undergone therapeutic lymphadenectomy for palpable disease and the increased morbidity associated with radiation therapy support the continued use of CLND for patients with a positive SLN biopsy rather than delayed CLND for palpable disease.

PATIENT AND CLINICIAN COMMUNICATION

Discussion with a patient about SLN biopsy for melanoma should be part of a comprehensive treatment planning process. Patient counseling regarding individual risks and benefits of SLN biopsy is essential to ensure that patients are making informed decisions. The Panel encourages health care providers to have an open dialogue with their patients to help them make informed decisions. An open dialogue should include consideration of scientific evidence, weighing individual risks with potential harms and benefits, and consideration of patient values and preferences.

HEALTH DISPARITIES

This guideline represents expert recommendations on the best practices in disease management, aimed at providing the highest level of cancer care for all patients diagnosed with cutaneous melanoma. However, racial, ethnic, and socioeconomic disparities in the quality of health care provided are realities that exist and persist in the United States. Members of racial and ethnic minorities, in general, tend to be diagnosed with cancer at more advanced stages and have worse outcomes.[36] This is because of complex and diverse reasons, which include but are not limited to: financial and insurance status, access to medical attention, language-related barriers, education, culture, and religious beliefs. These disparities seem to be constants in most cancers, and melanoma is not an exception. Moreover, disparities in the use of SLN biopsy have been noted,[37] despite the fact that cutaneous melanoma is largely (> 90%) diagnosed in white non-Hispanic populations, with middle to high levels of income.

Awareness of disparities in quality of care and access to care should be considered in the context of these clinical practice guideline recommendations. Health care providers should strive to deliver the highest level of care to all patients.

FUTURE DIRECTIONS

There is a need for future clinical trials to address many unresolved research questions related to the use of SLN biopsy in patients with melanoma. These include: determining precise criteria for selecting which patients should undergo SLN biopsy, determining whether early identification of metastases in the SLN truly improves survival or merely represents lead-time bias, identifying which criteria for individualized risks best inform appropriate risk stratification for patients at high risk for relapse and those for whom CLND and/or adjuvant

therapy are suitable, and establishing the role of prognostic markers from the primary melanoma and SLN to help assign appropriate risk stratification. Results from MSLT II, in which patients were randomly assigned to CLND or observation, will help determine whether there is any benefit to CLND after a positive sentinel node in patients with melanoma.

Answers to questions like these will assist clinicians and patients with making decisions and ultimately help to identify patients who may avoid expensive and intrusive procedures in staging and follow-up.

ADDITIONAL RESOURCES

The full guideline (which includes a comprehensive discussion of the literature, description of the methodology, and complete reference list), along with an Appendix, a Data Supplement, and clinical tools and resources, can be found on the ASCO Web site (http://www.asco.org/guidelines/snbmelanoma) and SSO Web site (http://www.surgonc.org/practice--policy/practice-management/clinical-guidelines/snbmelanoma.aspx). Patient information is also available at http://www.asco.org/guidelines/snbmelanoma and http://www.cancer.net.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Administrative support: Patricia Hurley
Manuscript writing: All authors
Final approval of manuscript: All authors

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Appendix

Technical Considerations for Sentinel Lymph Node Biopsy

The success of a sentinel lymph node (SLN) biopsy is dependent on an interdisciplinary relationship between nuclear medicine, surgery, and pathology. Lymphoscintigraphy after injection of the radiocolloid agent is important not only for the identification of the SLN within the draining basin but also for the identification of potentially involved nodal basins. A number of vital blue dyes have been used for lymphatic mapping in conjunction with a radiocolloid agent. Identification of micrometastases is dependent on a thorough pathologic assessment, including serial sections and immunohistochemistry.

Preoperative lymphoscintigraphy. Preoperative lymphoscintigraphy is typically performed in the nuclear medicine department preoperatively to allow for surgical planning. Lymphatic drainage from the site of a primary melanoma can be variable, especially in the head and neck or truncal regions. Drainage to multiple nodal basins may be identified, and lymphoscintigraphy should be used to guide the appropriate biopsy of all involved nodal basins and to guide the intraoperative identification of interval (in-transit) nodes, which can be the only site of nodal metastases.

A four-point intradermal injection of 0.05 to 1 mCi of technetium 99–labeled sulfur colloid (^{99m}Tc–sulfur colloid) at the primary melanoma site is administered at the time of preoperative lymphoscintigraphy. Real-time images are then obtained to visualize the nodal basins. Most centers perform the lymphoscintigram on the day of surgery. There is enough sufficient residual radioactivity to detect an SLN several hours later because of the 6-hour half-life of ^{99m}Tc–sulfur colloid.

When the primary tumor is close to the nodal basin (especially in the neck), it may be difficult to determine the discrete drainage pattern. In these cases, additional anatomic views can assist in separating the radioactivity in the nodal basin from that of the primary tumor injection.

Radio colloid agents. There is variation in the radiocolloids used across institutions. ^{99m}Tc–sulfur colloid is used in the United States; ^{99m}Tc-nanocolloid and ^{99m}Tc–antimony trisulphide colloidal preparations are used in many centers outside the United States. In general, the smaller the particle size, the faster it will travel and the greater the number of nodes demonstrated. It is for this reason that many institutions in the United States filter the colloidal preparation before dispensing through a 0.22-micron filter to ensure a more consistent particle size in the injectate. Intradermal injection is preferred by most centers, because this most closely mimics the potential passage of malignant cells. Insufficient tissue tension after injection (as may be seen with a subcutaneous injection) will lead to a delay in drainage. To avoid compressing the dermal lymphatics, it is important that injected volumes are kept quite small, with volumes of approximately 0.1 mL preferred. Of note, tilmanocept (Lymphoseek; Navidea Biopharmaceuticals, Dublin, OH) is a lymphatic mapping agent that is under development and has been tested in phases II (Leong SP, Kim J, Ross M, et al: Ann Surg Oncol 18:961-969, 2011) and III trials (Cope FO, Sondak VK, Wallace AM: J Clin Oncol 29:532s, 2011 [suppl; abstr LBA8526]).

Radiation safety aspects. Both gamma cameras and gamma probes are exquisitely sensitive, such that very small amounts of radioactivity are needed to perform the procedure successfully. Doses administered range from 0.05 to 1 mCi. These doses are approximately 1/20 of the dose given for a typical ^{99m}Tc-MDP bone scan. It has been estimated that the dose to a surgeon's finger from a single SLN surgery is 1/30 of the yearly whole-body absorbed dose from background radiation (Alazraki N, Glass EC, Castronovo F, et al: J Nucl Med 43:1414-1418, 2002).

Imaging. Almost all centers perform gamma camera imaging before surgery in patients with melanoma after injection of radiocolloids to define involved nodal basins. This is particularly the case in distal upper and lower limb melanomas in which an epitrochlear or popliteal node may be involved, truncal melanomas in which contralateral rather than ipsilateral nodal basins are found to be involved, and head and neck melanomas in which pre-auricular, intraparotid, or suboccipital nodes may be involved before nodes in the cervical chain or supraclavicular fossa are involved.

Many centers perform dynamic imaging to determine nodes that receive direct lymphatic drainage. If dynamic imaging is not performed, there is a risk that an end-on lymphatic channel may be misidentified as a node on a single planar image. There are a variety of approaches to assist in the localization of nodes, including the use of cobalt-57 flood sources to outline the body's anatomy, external outlining of the body's surface using a hot source that is traced over the body's surface, and use of hybrid low-dose single-photon emission computed tomography (SPECT-CT) imaging (Even-Sapir E, Lerman H, Lievshitz G, et al: J Nucl Med 44:1413-1420, 2003). Many centers perform skin marking to identify nodes involved. If this is done, it should be performed in the expected operative position.

Head and neck melanomas should be evaluated with a SPECT-CT device whenever possible, because the combination of the anatomy demonstrated by the CT and SPECT images of the colloid allows very precise localization of the nodes demonstrated as well as the identification of nodes immediately adjacent to the injection site. These images can assist in the planning of the surgical incision/approach and have been shown to alter the surgical approach in between 20% to 50% of patients compared with planar imaging (Bilde A, Von Buchwald C, Mortensen J, et al: Acta Otolaryngol 126:1096-1103, 2006; Vermeeren L, Valdés Olmos RA, Klop WM, et al: Head Neck 33:1-6, 2011). As with any presurgical planning, good communication between the surgeon and imaging team is essential.

Technical Details of SLN Biopsy

Intraoperative lymphatic mapping and SLN biopsy are routinely performed with both preoperative ^{99m}Tc–sulfur colloid injection, which can be detected with a handheld gamma probe and vital blue dye. In the operating room, 1 to 2 mL of vital blue dye is injected intradermally at the primary tumor site. Successful delivery of the dye intradermally is important, because a subcutaneous injection into the fat may not enable adequate uptake of the radioactive tracer or dye by the cutaneous lymphatic channels. The injection of blue dye is routinely performed before sterile preparation of the patient operative sites to allow 5 to 10 minutes for the dye to reach the lymph node basin.

The commercially available vital blue dyes in the United States include isosulphan blue (Lymphazurin; Tyco Healthcare Group, Norwalk, CT) and methylene blue dye. Both blue dyes are effective for lymphatic mapping but have unique side effect profiles (Liu Y, Truini C, Ariyan S: Ann Surg Oncol 15:2412-2417, 2008; Blessing WD, Stolier AJ, Teng SC, et al: Am J Surg 184:341-345, 2002; Simmons R, Thevarajah S, Brennan MB, et al: Ann Surg Oncol 10:242-247, 2003). Allergic reactions, including anaphylactic reactions, have been reported with the use of isosulphan blue. In a review of 1,835 patients injected with isosulphan blue dye for a variety of surgical procedures, 1.5% of patients had an adverse reaction (Daley MD, Norman PH, Leak JA, et al: J Clin Anesth 16:332-341, 2004). The majority of these patients experienced minor events (eg, skin wheals, itching, and localized edema), but 0.75% suffered a major anaphylactic reaction (hypotension) while under anesthesia. No deaths have been reported from any of these reactions.

Methylene blue has been associated with tissue necrosis and should be used with care at surgical sites where the majority of the blue dye will not be surgically resected (eg, face, periorbital, wrists, or ankles). Some have diluted the blue dye to decrease risk of tissue necrosis. Small amounts of residual blue dye may persist after wide local excision (WLE) of the primary site, rarely resulting in a permanent tattoo even if the dye is unable to be totally resected. In addition, because of systemic accumulation, the blue dye will be seen in urine, stool, and lactating breasts for the first 24 to 36 hours after injection.

The handheld gamma probe is used to identify areas of focal radiotracer uptake in the nodal basins identified on preoperative lymphoscintigraphy. A small incision is made in the nodal basin, taking into consideration the incision necessary if completion lymph node dissection is subsequently required. Surgeons trace the blue lymphatic channels or follow the path of radioactivity into the SLN. Electrocautery is used to dissect away the surrounding fatty tissue. Blue lymphatic channels and vascular structures are ligated, and care is taken to not disrupt or cauterize the capsule of the SLN.

After each SLN is removed, it is checked ex vivo to document the radioactive counts per second, and the nodal basin is rescanned with the gamma probe. In general, any lymph nodes that are blue, any lymph nodes with radioactive counts $\geq$ 10% of the ex vivo count of the most radioactive SLN, and any palpably suspicious nodes are removed (McMasters KM, Reintgen DS, Ross MI, et al: Ann Surg Oncol 8:192-197, 2001). There is an average of one to three SLNs per nodal basin. If there is concern of background radiation or shine through from the primary melanoma site, WLE can be performed beforehand to decrease radiotracer activity at this site.

Concomitant WLE and sentinel lymphadenectomy are preferred. However, in patients who have undergone previous WLE, the procedure is still technically feasible (Ariyan S, Ali-Salaam P, Cheng DW, et al: Ann Surg Oncol 14:2377-2383, 2007; Evans HL, Krag DN, Teates CD, et al: Ann Surg Oncol 10:416-425, 2003; Kelemen PR, Essner R, Foshag LJ, et al: J Am Coll Surg 189:247-252, 1999; Leong WL, Ghazarian DM, McCready DR: J Surg Oncol 82:143-146, 2003; McCready DR, Ghazarian DM, Hershkop MS, et al: Can J Surg 44:432-434, 2001). In a study of 104 patients at the University of Texas MD Anderson Cancer Center (Houston, TX) who underwent sentinel lymphadenectomy after previous WLE, the SLN positivity rate was similar to that of more than 1,000 patients who had concomitant WLE and SLN removal during the same time period (Gannon CJ, Rousseau DL Jr, Ross MI, et al: Cancer 107:2647-2652, 2006). However, because extensive resection can alter lymphatic draining and may not accurately reflect the pathologic status of the draining lymph node basin, removal of the SLN at the time of primary WLE is preferred whenever possible.

Laboratory Evaluation of SLNs

Most specimens include one to three nodes considered sentinel on the basis of their blue coloration and selective radioactivity. SLN biopsy provides a limited specimen that is susceptible to a more detailed examination than is practicable for lymphadenectomy specimens that contain multiple lymph nodes.

Maximum length, width, and thickness of SLNs are measured in millimeters. SLNs are bisected through their longest meridian to detect melanoma cells that have been delivered to the subcapsular sinus from afferent lymphatics (Cochran AJ, Wen DR, Morton DL: Am J Surg Pathol 12:612-618, 1988). The cut surfaces of both halves of the SLN are closely examined for blue dye, metastatic melanoma, and foci of melanin. Imprints for cytology, if indicated, can be made at this stage. The SLN halves, or slices 2 mm thick taken parallel to the meridian in larger SLNs, should be placed (cut face down) in cassettes and fixed in formalin for 12 to 24 hours.

Nuclear medicine physicians and surgeons are best able to determine if a node is truly sentinel. Occasional technical problems lead to misidentification of a node as sentinel: blue dye is seldom seen when specimens arrive in the laboratory, the radioactive isotope decays rapidly from the peak emission values seen in the operating room, and few laboratories have equipment or expertise to measure tissue radioactivity.

Intraoperative assessment of SLNs. SLNs are best evaluated by examining thin sections cut from well-fixed paraffin-embedded tissues (Morton DL, Wen DR, Foshag LJ, et al: J Clin Oncol 11:1751-1756, 1993; Stojadinovic A, Allen PJ, Clary BM, et al: Ann Surg 235:92-98, 2002; Scolyer RA, Thompson JF, McCarthy SW, et al: J Am Coll Surg 201:821-823, 2005; author reply 823-824). Frozen section analysis of SLNs is not performed for melanoma because of the difficulty in reliably diagnosing microscopic metastases using immediate intraoperative pathology evaluation, and because full-face sections often require disposal of many incomplete sections with potential loss of most or all diagnostic nodal tissue. Identification of single melanoma cells, small clusters of melanoma cells, or small melanoma cells that resemble nevus cells is more difficult in frozen sections.

Evaluation of multiple levels of the SLN. Multiple sections are cut and stained with hematoxylin and eosin (HE) for immunohistochemistry. The number of sections to be stained and the optimal distance between them remain subject to debate. Early studies suggested that early melanoma metastases are found in a band of tissue adjacent to the longest nodal meridian (Cochran AJ, Wen DR, Morton DL: Am J Surg Pathol 12:612-618, 1988). On the basis of these early studies, examination of 10 full-face serial sections from both faces of the node has been recommended.

If tumor cells are not detected in the initial sections, additional sections may be evaluated in patients considered at high risk of nodal metastases. This approach detects melanoma in 16% to 20% of SLN biopsy specimens, which is close to the incidence of metastatic nodal disease in patients with melanoma after wide excision of a primary melanoma (Morton DL, Thompson JF, Cochran AJ, et al: N Engl J Med 355:1307-1317, 2006). The European Organisation for Research and Treatment of Cancer now requires examination of six pairs of sections cut at 50-μm intervals then stained with HE and S-100 for patients with melanoma entering clinical trials (Cook MG, Green MA, Anderson B, et al: J Pathol 200:314-319, 2003).

SLN tissue for research. Accurate identification of SLN melanoma metastases is essential for optimum patient management, but it may be difficult in the presence of limited and highly localized metastases. Underdetection of SLN metastases may have potential consequences for patients. Pathologists should be cautious in providing tissue for research until the SLN has been adequately sampled and the SLN tumor status established. There is, however, a legitimate need to determine whether techniques such as real-time polymerase chain reaction truly detect small amounts of clinically relevant tumor not readily identifiable by standard histopathology.

Additional research is needed regarding the molecular and cellular events that determine SLN susceptibility to metastases to be able to reverse that susceptibility. Interleaved tissue sections—one section for histology and the next for research—provide precise histologic control for biologic investigations. Research that uses formalin-fixed paraffin-embedded tissue is readily accommodated; providing unfixed tissue is more challenging. Pathologists and investigators need to understand diagnostic tissue requirements and the regulatory limitations that govern distribution of human tissues.

Immunohistochemistry. Experienced pathologists may overlook single melanoma cells or small melanoma cell clusters in up to 12% of SLNs based on HE examination alone. Antibodies to S-100 detect nuclear and cytoplasmic epitopes in nearly all melanomas. Although staining is relatively nonspecific, with experience, melanoma cells can be distinguished with considerable consistency.

MART-I, HMB-45, and anti-tyrosinase are antibodies that detect cytoplasmic epitopes expressed by melanocyte-derived cells, including melanoma cells. These epitopes are more specific than S-100 for melanocytic lineage, but they are not expressed by up to 25% of melanomas, particularly metastatic melanomas (Ohsie SJ, Sarantopoulos GP, Cochran AJ, et al: J Cutan Pathol 35:433-444, 2008). Combinations of antibodies (antibody cocktails) seem no more sensitive than S-100 and do not permit separation of melanoma cells and nevocytes on the basis of their immunophenotype. Red-colored chromogens facilitate separation of melanin-containing macrophages and melanoma cells.

It is practical to assess the immunohistochemically stained sections first, because the immunomarkers highlight small numbers of melanoma cells that are less easily seen in HE preparations. An initial low-power scan to exclude large metastases is followed by a careful examination for single tumor cells and small cell clusters within the subcapsular sinus (the common site of early metastases), the internal sinuses, and finally the parenchyma. A tumor in afferent lymphatics has the same clinical significance as an intranodal tumor. Thus, it is important to carefully examine any lymphatics that are present. Extracapsular extension by a tumor should be recorded, as should size of

the largest metastatic focus and location of the metastatic tumor (Frishberg DP, Balch C, Balzer BL, et al: Arch Pathol Lab Med 133:1560-1567, 2009).

It is important to distinguish nodal nevocytes from metastatic melanoma cells. This requires detailed cytologic evaluation as well as assessment of immunophenotype and location of cells within the nodal architecture. Melanoma cells can be distinguished on the basis of their large size, high nuclear to cytoplasmic ratio, prominent nucleoli, and atypical mitoses, whereas nodal nevocytes are generally smaller, with limited cytoplasm, and seldom show mitoses. Although both cell types may contain finely dispersed small granules of melanin, the quantity of melanin in melanoma cells usually exceeds that in nevocytes. Melanoma cells are generally positive for S-100, MART-1/Melan-A, and HMB-45, and their nuclei are reactive with Ki67/MIB1. In contrast, although nevocytes may be positive for S-100 and MART-1/Melan-A, they generally stain weakly or are negative for Ki67/MIB1 and HMB-45 (Lohmann CM, Iversen K, Jungbluth AA, et al: Am J Surg Pathol 26:1351-1357, 2002).

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