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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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Editor's note: This is 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 comprehensive discussions of the relevant literature for each. The Executive Summary of the guideline, 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.

Lymphatic mapping and sentinel lymph node (SLN) biopsy were introduced by Morton et al3 in 1992 as a minimally invasive alternative to elective lymph node dissection for the evaluation of regional lymph nodes from a primary melanoma. The procedure was initially performed by intradermal injection of a vital blue dye to the primary cutaneous melanoma site, with the subsequent addition of radiocolloid injection. By mapping the lymphatic drainage from the tumor site to a tumor-draining regional lymph node, the first draining SLNs could be harvested for a focused histologic examination. SLN biopsy, which includes a pathologic assessment and use of immunohistochemical staining,[4,5] has been shown to be accurate in the staging of regional lymph nodes in patients with melanoma.[3,6-10] The benefits of the procedure include low morbidity and accurate selection of patients without nodal metastases (node negative).

The international Multicenter Selective Lymphadenectomy Trial I (MSLT I) was initiated in 1994. The purpose was to examine the utility of SLN biopsy in the identification of patients with clinically occult nodal metastases and evaluate the effectiveness of immediate completion lymph node dissection (CLND) in patients with positive SLNs.[11] Patients were randomly assigned to wide local excision with nodal observation or wide local excision and SLN biopsy (with CLND for those with positive SLNs). The interim results of this trial were reported in 2006 and confirmed that SLN biopsy is highly accurate in patients with melanomas 1.2 to 3.5 mm in thickness.[2,12] To date, no difference in melanoma-specific survival has been demonstrated between the SLN biopsy and nodal observation groups. However, SLN biopsy followed by CLND was associated with prolonged disease-free survival[12]; a 26% reduction in the relative risk of recurrence was observed (hazard ratio [HR], 0.74; 95% CI, 0.59 to 0.93; P = .009).[12] In addition, clinically node-negative patients found to have SLN metastases who underwent CLND were noted to have significantly increased melanoma-specific 5-year survival rates compared with those undergoing delayed CLND for clinically detected nodal relapse (72.3% v 52.4%).[12]

SLN biopsy 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. The procedure currently is commonly used by surgeons who treat melanoma in the United States, Canada, Australia, and Western Europe. This highly accurate and low-morbidity staging procedure should be used to guide treatment decisions (ie, CLND and adjuvant therapy) as well as entry into clinical trials.[13]

To develop and formalize 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 representing a range of specialties. The Panel conducted a comprehensive assessment of SLN biopsy (based on test performance and impact on various outcomes) and its use in clinical practice for the staging of patients with newly diagnosed melanoma and developed recommendations for clinical practice based on its assessment of the available evidence.

This guideline provides: the Panel's recommendations; summaries of the literature review and analyses; and discussions about patient and clinician communication, disparities, and future directions (Table. Bottom Line). Although technical considerations for SLN biopsy are beyond the scope of this guideline, a discussion of some of the key technical considerations, including mapping and laboratory evaluations, is provided in an Appendix at the end of this document and available 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 Executive Summary of this guideline has been published concurrently in *Journal of Clinical Oncology (JCO)* and *Annals of Surgical Oncology (ASO)*

GUIDELINE QUESTIONS

This guideline addresses two overarching clinical questions:

What are the indications for SLN biopsy?

What is the role of CLND?

Table 1 provides a summary of the guideline recommendations. A Data Supplement, a patient guide, and other clinical tools and resources to help clinicians implement this guideline 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).

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
An Executive Summary of this complete guideline has been published concurrently in *Journal of Clinical Oncology* and the *Annals of Surgical Oncology*. 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.

CLINICAL PRACTICE GUIDELINES

Practice guidelines are systematically developed statements that assist practitioners and patients in making decisions about care. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, flexibility, clarity, multidisciplinary process, review of evidence, and documentation. Guidelines may be useful in producing better care and decreasing cost. Specifically, use of clinical guidelines may provide:

1. Improvements in outcomes
2. Improvements in medical practice
3. A means for minimizing inappropriate practice variation
4. Decision support tools for practitioners
5. Points of reference for medical orientation and education
6. Criteria for self-evaluation
7. Indicators and criteria for external quality review
8. Assistance with reimbursement and coverage decisions
9. Criteria for use in credentialing decisions
10. Identification of areas in which future research is needed

METHODS

ASCO and SSO convened a Panel consisting of expert surgeons and medical oncologists from both societies. The Panel also included experts in nuclear medicine, pathology, and patient advocacy. Panel members are listed in Appendix Table 2.

Literature Review and Analysis

Literature search strategy.

A comprehensive systematic review of the literature was completed, and a detailed description of the systematic review methodology, including the quality appraisal of the evidence and quality control measures, has been published elsewhere.[14] In summary, the systematic review included literature published from January 1990 through December 2009. MEDLINE and EMBASE were searched using the search terms "melanoma" and "sentinel lymph node." An updated literature search was conducted to review articles published since the initial search to ensure that none of the guideline recommendations would need to be changed after consideration of any new evidence. This second updated review included a search for publications from December 2009 through August 2011. The searches were supplemented with the references of the selected articles, abstracts presented at ASCO and SSO annual meetings in the last 5 years, and references provided by Guideline Panel members.

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 tumor-positive SLN biopsy, referred only to a highly specific population or location, and/or involved < 50 patients.

Two reviewers independently assessed the quality of the selected studies using the criteria from the Methodological Index for Non-Randomized Studies.[15] No article was excluded based on the quality assessment, but a sensitivity analysis was performed to estimate the effects of quality on the estimates. The methods and results of the quality assessment have been reported elsewhere.[14]

Meta-analysis.

A meta-analysis was conducted based on the results of the initial systematic review of the literature (ie, including literature published from January 1990 through December 2009). Valsecchi et al[14] provide a detailed description of the methods and findings. Primary outcomes consisted of measures of test performance, including: the proportion 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 experienced recurrence 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.

Limitations of the literature.

There is currently only one randomized controlled trial (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.[12] Hence, observational studies were included in the systematic review of the literature. Because there was significant variability and complexity across the many uncontrolled clinical trials, the systematic review included cohort studies of patients with melanoma who underwent SLN biopsy with or without CLND and who were observed for evidence of same nodal basin, regional, or distant recurrence.

Readers should be cautious when considering aggregate data, because there was significant variability across the studies identified in the systematic review, including surgical, pathologic, and nuclear medicine techniques, which have evolved substantially over time.

Guideline Development Process

The entire Panel met in February 2010 to review the evidence and draft the guideline recommendations. Additional work on the guideline was completed through a steering group and by e-mail. All members of the Panel participated in the preparation of the draft guideline document. Feedback from external reviewers was solicited, and the guideline was submitted to *JCO* and *ASO* for peer review. Before publication, the guideline was reviewed and approved by the ASCO Clinical Practice Guidelines Committee and SSO Executive Council and reviewed by the SSO Melanoma Disease Site Work Group.

Guideline Policy

The practice guideline is not 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 guideline does not recommend any particular product or course of medical treatment. Use of the practice guideline is voluntary. Additional information is available at http://www.asco.org/guidelines/snbmelanoma.

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.

Revision Dates

At annual intervals, the Panel Co-Chairs and two Panel members designated by the Co-Chairs will determine the need for revisions to the guideline based on an examination of current literature. If necessary, the entire Panel or an Update Committee will be reconvened to discuss potential changes. When appropriate, the Panel will recommend a revised guideline for review and approval by the ASCO Clinical Practice Guidelines Committee and SSO Melanoma Disease Site Work Group.

RESULTS

The search strategy retrieved 1,887 references (see the QUOROM diagram in Fig 1 in the online Data Supplement 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]. The abstracts were reviewed, and after applying the inclusion and exclusion criteria, 246 articles were selected for full-text evaluation. The systematic literature review that was conducted and initially reviewed by the Panel included 71 articles published from January 1990 through December 2009.[14] Subsequent to the initial review, two studies were identified in an updated literature search that were reviewed separately.[16,17] The Panel concluded that these two additional reports did not alter any of the observations or conclusions of the original systematic review of the literature or any of the guideline recommendations. Abstracts from the last five annual ASCO and SSO meetings were also reviewed, and national experts in the field were consulted, but no additional relevant studies were identified.

The meta-analysis was conducted before the updated search and included only the initial 71 eligible studies. Table DS1 in the online Data Supplement summarizes the characteristics and outcomes of studies included in the systematic review and meta-analysis. A more detailed report of the methods and results of the meta-analysis can be found in a previous publication.[14] The 71 studies included 25,240 patients in whom SLN biopsy was attempted and 24,863 in whom one or more SLNs was identified. Approximately 15% of the

patients had more than one basin mapped. The primary tumor was localized to the extremities, trunk, or head/neck region in 50%, 39%, and 11% of patients, respectively. The duration of follow-up ranged from 7 to 72 months, with a mean of 32.9 months (median, 32.8 months).

The PSM was positively correlated with more recent studies, female sex, older age, proportion with primary ulcerated tumors, and better study quality scores. The FNR for nodal recurrence averaged 12.5% and increased with length of follow-up and study quality, but it decreased with greater rates of successful SLN identification. Approximately 20% of patients with nodal metastases on SLN biopsy had additional involved lymph nodes identified after CLND. It is worth noting that the overall results from prospectively performed studies were not statistically significantly different from those reported in retrospective studies.

The risk of recurrence within the same nodal basin in patients with a negative SLN biopsy ranged from 0% to 10.4%, averaging 3.4% across studies, and was positively associated with length of follow-up, younger age, female sex, greater mean Breslow thickness, and greater proportion with ulcerated tumors, but it was inversely related to successful SLN identification.[14]

The rates of distant and all recurrences were estimated in 55 and 58 studies, respectively. The rates of distant and all recurrences averaged 17.4% and 29.9%, respectively. In both cases, the recurrence rate was significantly greater in studies that were larger and had longer mean follow-up and higher average study quality score. Likewise, the probability of distant or any recurrence in patients with a negative SLN biopsy averaged 4.4% or 10.5%, respectively, and was significantly greater in studies with longer mean follow-up and higher average quality score.[14]

In patients with a positive SLN biopsy, the probability of additional nodal involvement on CLND averaged 20.1%. The average risk of recurrence in the same nodal basin in patients with a tumor-positive SLN biopsy followed by CLND was 7.5%. The probability of distant or any recurrence, inclusive of CLND in patients with a tumor-positive SLN biopsy, averaged 21% or 36%, respectively.[14]

GUIDELINE RECOMMENDATIONS

Table 1 provides a summary of the guideline recommendations. A table of the characteristics and outcomes of the studies included in the literature review and analysis is available in the online Data Supplement. This resource can be found at http://www.asco.org/guidelines/snbmelanoma and http://www.surgonc.org/practice--policy/practice-management/clinical-guidelines/snbmelanoma.aspx. A discussion of some of the key technical considerations for conducting SLN biopsy is available in the Appendix.

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.[14] 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.[13,14] 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.[14]

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%,[6,8,10,18] 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.[19]

Intermediate-thickness melanomas.

Many investigators have identified subgroups of patients with intermediate-thickness melanomas with a higher risk of nodal metastases. Although clinical variables such as older age have been variably reported as lower risk factors,[20-22] 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. Specifically, MSLT I[11,12] (the landmark prospective randomized trial) defined intermediate thickness as melanomas that were 1.2 to 3.5 mm in thickness. Nevertheless, it is clinically consistent with contemporary staging systems to define intermediate-thickness melanomas as those measuring 1 to 4 mm.[23]

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 (n= 937) compared with 32.7% after CLND (n= 234).[24] 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%).[19,20] 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.[13,25] With substantive changes in the melanoma staging guidelines in 2002, the AJCC staging system effectively linked disease stage and prognosis.[26,27] 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.[1,28] 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[1,28] 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.[29-31] Although based on limited data, the FNR is similar for SLN biopsy in patients with intermediate-thickness

melanomas. It is important to note, however, that the risk of nodal recurrence after a negative SLN biopsy increases with greater Breslow thickness because of the higher risk of disease with increasing thickness.

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.[2,29-36] The one study that did not show a significant difference in overall survival demonstrated a significant difference in disease-free survival.[32] Tumor-positive SLNs are found in 30% to 49% of patients with thick melanomas.[29-31] Therefore, if used for staging purposes, sufficient evidence exists to support the hypothesis that SLN biopsy provides useful prognostic information for patients with thick melanomas.

Thin melanomas.

A majority (70%) of melanomas diagnosed in the United States are thin melanomas (T1; Breslow thickness, < 1 mm).[37] 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%,[38] 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 $\geq 1/mm^2$).[28]

However, although the overall prognosis for patients with thin melanomas is excellent, with 10-year overall survival rates of 92%,[27] the impact of SLN biopsy in this group of patients remains unclear.[39,40] 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.

Primary tumor ulceration and mitotic rate were adopted as part of the seventh edition of the AJCC staging system as significant predictors of recurrence,[27,38,41] SLN positivity,[1,21,42-47] and decreased survival[1,43-47] in patients with thin lesions. A number of other clinicopathologic factors have also been suggested for consideration, although the evidence base is incomplete: possibility of underestimated tumor thickness (eg, incomplete microstaging and positive deep margins so that actual thickness is unknown), extensive regression, vertical growth phase, vascular invasion, satellitosis, and patient age < 40 years.[38,39,48-51]

Use of SLN biopsy in patients with thin melanomas must consider the low rate of positivity in the context of a known FNR. In addition, few studies to date have reported the impact of a positive SLN on recurrence and survival in patients with thin melanomas.[38] Further investigation is also needed to better identify the subgroups of patients with thin melanomas with a greater risk of nodal metastasis. It is advocated that the potential risks and benefits of SLN biopsy be discussed with patients with thin melanomas who have adverse prognostic factors (eg, ulceration and mitotic rate in those with lesions 0.75 to 0.99 mm in thickness).

Special Considerations

Head/neck location.

The often ambiguous lymphatic drainage patterns of the head and neck regions pose anatomic and technical challenges to SLN biopsy. Multiple draining basins are common, as is shine through of the radioactive isotope, described as difficulty in distinguishing potential SLNs from the nearby primary site. Several series[52-55] have suggested lower SLN biopsy positivity rates and higher recurrence rates with SLN biopsy for head and neck melanomas, although more recent large single-institution studies have demonstrated PSM of 95% to 99.7% and low FNR.[56,57] It is likely that increased use of improved lymphoscintigraphy techniques (eg, single-photon emission computed tomography) and increased experience with these operations have improved results. It seems that head and neck SLN biopsy is feasible and reliable when performed by experienced groups.

Melanoma in pregnancy.

Pregnancy increases melanocytic activity, which is associated with hyperpigmentation. However, there is no known association between pregnancy and the risk of developing melanoma. In addition, pregnant women who present with a new diagnosis of melanoma do not seem to have a worse prognosis.[58,59] The treatment of primary melanoma in women who are pregnant does not differ, and SLN biopsy should be considered based on the characteristics of the primary tumor. If SLN biopsy is performed, use of radioactive tracer for lymphoscintigraphy seems safe, although attendant risks of exposure to a low amount of radioactivity should be discussed.[60-63] Risks from blue dye injection are unknown, so it is not recommended for SLN biopsy in patients who are pregnant because of the possibility of anaphylactic shock.[60,63]

Specific histologic subtypes.

Desmoplastic melanomas, which represent a small proportion of all cutaneous melanomas, typically occur in an older age group and more commonly present with relatively thicker tumors in the head and neck regions.[64] Desmoplastic tumors, characterized by dermal spindle cells in a fibrous stroma, are

often amelanotic. When compared with other melanomas of similar thickness, overall survival does not seem to be different, but there is a well-described increased risk of local recurrence.[65] Several studies have found that SLN biopsy is less likely to be positive in desmoplastic melanomas, especially in the pure subtype. General conclusions from these studies suggest that the risk of positive nodes is still high enough to warrant SLN biopsy for patients with desmoplastic melanomas using selection criteria applied to other patients with melanoma.[66-68]

Spitzoid melanomas in the pediatric population.
Differentiating between Spitz nevi and Spitzoid melanomas can be challenging, but it is critical to distinguish benign from malignant lesions. Interestingly, despite presentation with more advanced disease, survival rates are similar or better in children compared with the adult population, even though rates of positive nodes range from 25% to > 60%.[69-73] The use of SLN biopsy for malignant lesions in children has typically mirrored that in adults, although experience with SLN biopsy in the pediatric population is limited.

Repeat SLN biopsy.
The use of SLN biopsy has been described for patients with recurrent primary lesions, and the procedure may be considered if it was not performed with the index diagnosis. However, in patients who had a prior SLN biopsy or CLND, there are insufficient data to determine whether an SLN biopsy is accurate and whether the information is prognostic and/or improves outcomes. SLN biopsy after other types of recurrence (eg, in-transit disease) is similarly not supported.[74]

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.[75] 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.[12] 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[20] and MSLT I[12]), the rate of positive non-SLNs among patients who underwent CLND for a tumor-positive SLN was 16%. It should be noted that non-SLN metastases detected at CLND were diagnosed by routine histopathology, not serial sectionings or immunohistochemical stains; the implication is that such metastases detected using this assessment may have a greater likelihood of being more clinically meaningful than small nests of isolated tumor cells. In a retrospective multi-institutional study by Wong et al,[76] 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%.[77,78]

Effect of CLND on regional disease control.
In MSLT I, the rate of regional nodal recurrence after CLND was 4.2%[12]; 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.[39] In retrospective studies of therapeutic lymphadenectomy for clinically detectable (palpable) metastases, the rates of regional nodal recurrence ranged from 14% to 52% overall and from 31% to 63% in high-risk groups with extracapsular extension, multiple positive nodes, nodal metastasis ≥ 3 cm in size, or nodes within the cervical nodal basin.[77,78] On the basis of the comparisons of data from prospective and retrospective studies, it seems that CLND for patients with tumor-positive SLNs is an excellent strategy for achieving regional nodal disease control when compared with CLND for clinically detectable metastases. Advanced regional nodal disease can cause pain and suffering, and CLND may preempt those symptoms.

Until the 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 patients in the study would not have been helped by removal of regional lymph nodes.[12] 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 (HR, 0.51; 95% CI, 0.32 to 0.81; P = .004). In the Sunbelt Melanoma Trial, the 5-year overall survival rate for patients with tumor-positive SLNs who underwent CLND was 67% (unpublished data). 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. In a study comparing patients who underwent inguinal lymph node dissection for tumor-positive SLNs compared with palpable nodal metastases, Sabel et al[79] demonstrated that wound complications (28% v 14%; *P* = .02) and lymphedema (41% v 24%; *P* = .025) were significantly greater after CLND among patients with palpable nodal disease compared with those with a positive SLN. 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. Analysis of MSLT I also found that the number of positive nodes and lymphedema risk were greater for patients who underwent lymphadenectomy for clinically evident nodal disease compared with those who underwent CLND for positive SLNs.[80]

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.

A useful way to approach this planning is through the ASCO template for a treatment plan (http://www.asco.org/ASCOv2/Practice+%26+Guidelines/Quality+Care/Quality+Measurement+%26+Improvement/Chemotherapy+Treatment+Plan+and+Summary/Cancer+Treatment+Plan+and+Summary+Resources). In nearly all patient cases of melanoma considered for potential SLN biopsy, some highly valuable clinical and pathologic information will already be available. These data will help focus both clinicians and patients on a key question with regard to SLN biopsy: What additional information necessary to guide a choice of treatment will SLN biopsy likely provide? This structured discussion, which seeks information gaps in the overall plan, will help patients understand whether SLN biopsy contributes useful information in their particular cases.

Once the patient and clinician have discussed potential benefits and agree that there may be value in SLN biopsy, the discussion should explore the risks associated with the procedure itself. There may be cases in which SLN biopsy has a small potential to provide clinically useful information, but the primary melanoma site or other risk factors would counterbalance the benefit, leading the patient to decline the procedure.

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.[81] 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,[82] despite the fact that cutaneous melanoma is largely (> 90%) diagnosed in white non-Hispanic populations, with middle to high levels of income.

Race has been identified as a poor prognostic factor per se,[83] especially in African Americans,[84,85] and was found to be an independent risk factor for overall survival and melanoma-specific mortality when compared with white non-Hispanics (HR, 1.60; 95% CI, 1.17 to 2.18 and HR, 2.00; 95% CI, 1.30 to 3.06, respectively).[86] Relative to the practice of SLN biopsy, a recent study using data from the National Cancer Data Base[87] found that patients who were nonwhite and had stage IB/II disease had significantly fewer chances to receive SLN biopsy (odds ratio [OR], 0.66; 95% CI, 0.52 to 0.83). Similar conclusions were obtained for patients who were uninsured, were Medicare or Medicaid recipients, and/or received treatment in non-National Comprehensive Cancer Network or non-National Cancer Institute-designed centers, indicating the same trend is relevant for the lowest socioeconomic strata. Another study, using data from the Surveillance, Epidemiology, and End Results database, also found a significantly higher probability of inadequate surgical management, specifically absence of SLN biopsy for stage IB/II disease, among patients who were nonwhite and non-African American (OR, 1.8; 95% CI, 1.34 to 2.42 and OR, 1.55; 95% CI, 1.08 to 2.22 for stages IB and II disease, respectively).[88] Geographic differences[87-89] within and beyond the United States[90] have also been observed, but no consistent patterns have been recognized.

Awareness of these 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

High-resolution ultrasound and positron emission tomography (PET) have been investigated as noninvasive alternatives to SLN biopsy.[91,92] However, the reported sensitivity of high-resolution targeted ultrasound for positive SLNs was only 24%.[91] A recent systematic review of the literature, comparing SLN biopsy with PET imaging, reported that PET imaging was inferior to SLN biopsy in accurately identifying occult lymph node metastasis.[92] Although both of these staging modalities may be of value in preoperative assessment and postoperative monitoring for patients considered high risk, they are not appropriate substitutes for SLN biopsy.

There have been few effective systemic treatment options for metastatic (stage IV) melanoma, but recent reports have demonstrated improved survival with the use of ipilimumab, an anti-CTLA-4 antibody,[93,94] and vemurafenib, an inhibitor of mutated *BRAF*.[95] Neither ipilimumab nor vemurafenib is currently used in the adjuvant setting, but ipilimumab is the focus of ongoing adjuvant trials for a subset of patients with lymph node involvement (eg, http://clinicaltrials.gov/ct/show/NCT01274338 and http://clinicaltrials.gov/ct2/show/NCT00636168). It is important for clinicians to keep in mind the importance of accurate staging with SLN biopsy to identify patients with stage III melanoma who may be eligible for clinical studies evaluating these agents.

Although current recommendations include CLND after a positive SLN biopsy, this represents an evolving clinical practice. The majority of patients undergoing CLND will not have any additional disease in the CLND specimen.[96,97] Furthermore, some studies[76,77] have demonstrated that recurrence rates in regional nodal basins were similar, regardless of whether CLND was performed, in patients with positive sentinel nodes. In fact, a national study suggested that only approximately half of patients with positive sentinel nodes underwent CLND, although reasons for not undergoing the procedure were unclear.[98] In 2004, accrual began for MSLT II, in which patients were randomly assigned to CLND or observation. The primary outcome measure of the study is melanoma-specific survival. Results from MSLT II will help determine whether there is any benefit to CLND after a positive sentinel node in patients with melanoma.

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. Refinement of the semiquantitative SLN tumor burden principle is also needed.[23] In particular, because the N1a classification is diverse (comprising one immunohistochemically detected cell or large, visually evident pathologic metastases that are clinically occult for a variety of reasons), there may be identifiable subgroups of patients who are N1a positive with 5-year survival considerably better than 78%.

Answers to questions like these will assist clinicians and patients in making decisions and ultimately help to identify patients who may avoid expensive and intrusive procedures in staging and follow-up. The development of prediction-based models may also be helpful for individualized decision making.

ADDITIONAL RESOURCES

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://20273www.cancer.net.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AFFILIATIONS

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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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