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ASCO SPECIAL ARTICLE

Sentinel Lymph Node Biopsy and Management of Regional Lymph Nodes in Melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Clinical Practice Guideline Update

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Editor's note: This American Society of Clinical Oncology Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with additional evidence tables, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/melanoma-guidelines and www.asco.org/guidelineswiki.

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ABSTRACT

Purpose
To update the American Society of Clinical Oncology (ASCO)-Society of Surgical Oncology (SSO) guideline for sentinel lymph node (SLN) biopsy in melanoma.

Methods
An ASCO-SSO panel was formed, and a systematic review of the literature was conducted regarding SLN biopsy and completion lymph node dissection (CLND) after a positive sentinel node in patients with melanoma.

Results
Nine new observational studies, two systematic reviews, and an updated randomized controlled trial of SLN biopsy, as well as two randomized controlled trials of CLND after positive SLN biopsy, were included.

Recommendations
Routine SLN biopsy is not recommended for patients with thin melanomas that are T1a (nonulcerated lesions < 0.8 mm in Breslow thickness). SLN biopsy may be considered for thin melanomas that are T1b (0.8 to 1.0 mm Breslow thickness or < 0.8 mm Breslow thickness with ulceration) after a thorough discussion with the patient of the potential benefits and risk of harms associated with the procedure. SLN biopsy is recommended for patients with intermediate-thickness melanomas (T2 or T3; Breslow thickness of > 1.0 to 4.0 mm). SLN biopsy may be recommended for patients with thick melanomas (T4; > 4.0 mm in Breslow thickness), after a discussion of the potential benefits and risks of harm. In the case of a positive SLN biopsy, CLND or careful observation are options for patients with low-risk micrometastatic disease, with due consideration of clinicopathological factors. For higher-risk patients, careful observation may be considered only after a thorough discussion with patients about the potential risks and benefits of foregoing CLND. Important qualifying statements outlining relevant clinicopathological factors and details of the reference patient populations are included within the guideline.

Additional information is available at www.asco.org/melanoma-guidelines and www.asco.org/guidelineswiki.

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ASSOCIATED CONTENT

Appendix
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Data Supplement
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INTRODUCTION

In 2017, approximately 87,100 new cases of melanoma will be diagnosed and over 9,730 deaths due to melanoma are expected in the United States.[1] Although melanoma only accounts for approximately 1% of skin cancers, it is responsible for the majority of skin cancer morbidity and mortality, and incidence has been increasing over the past 30 years.[2] The mainstay of melanoma treatment options continues to be resection (local excision of the tumor with wide margins) but strategies for management of regional and systemic disease have evolved considerably over the past two decades. Biopsy of the sentinel lymph node (SLN), the first node in a group of nodes to be affected by metastatic cancer, has become an established procedure

THE BOTTOM LINE

Sentinel Lymph Node Biopsy and Management of Regional Lymph Nodes in Melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Clinical Practice Guideline Update

Guideline Question

- What are the indications for sentinel lymph node (SLN) biopsy?
- What is the role of completion lymph node dissection (CLND)?

Target Population

Patients with newly diagnosed melanoma without clinical evidence of lymph node involvement.

Target Audience

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

Methods:

An Expert Panel was convened to update the clinical practice guideline recommendations based on a systematic review of the medical literature.

Note: Breslow thickness categories are defined according to the AJCC staging system 8th edition (Gershenwald et al, manuscript submitted for publication).

Key Recommendations

- Thin melanomas: Routine SLN biopsy is not recommended for patients with melanomas that are T1a (nonulcerated lesions < 0.8 mm in Breslow thickness). SLN biopsy may be considered for T1b patients (0.8 to 1.0 mm Breslow thickness or < 0.8 mm Breslow thickness with ulceration) after a thorough discussion with the patient of the potential benefits and risks of harm associated with the procedure (Type of recommendation: evidence based; potential benefits outweigh risks of harm; Quality of evidence: low to intermediate; Strength of recommendation: moderate).
- Intermediate-thickness melanomas: SLN biopsy is recommended for patients with melanomas that are T2 or T3 (Breslow thickness of $>$ 1.0 to 4.0 mm) (Type of recommendation: evidence based; potential benefits outweigh risks of harm; Quality of evidence: intermediate; Strength of recommendation: moderate).
- Thick melanomas: SLN biopsy may be recommended for patients with melanomas that are T4 ($>$ 4.0 mm in Breslow thickness), after a thorough discussion with the patient of the potential benefits and risks of harm associated with the procedure (Type of recommendation: evidence based; potential benefits outweigh risks of harm; Quality of evidence: low to intermediate; Strength of recommendation: moderate).
- Either CLND or careful observation may be offered to patients with low risk micrometastatic disease, with due consideration of clinicopathological factors. For higher risk patients, careful observation may be offered only after a thorough discussion with patients about the potential risks and benefits of foregoing CLND (Type of recommendation: evidence based; potential benefits outweigh risks of harm; Quality of evidence: intermediate to high; Strength of recommendation: strong).

Important qualifying statements for CLND versus careful observation:

- Key evidence for this recommendation comes from the Multicenter Selective Lymphadenectomy II (MSLT-II) and German Dermatologic Oncology Cooperative Group (DeCOG-SLT) RCTs.[26,27] In both trials, the authors reported no difference in melanoma-specific survival between the CLND and close observation groups. Incidence of lymphedema was significantly higher in the CLND group in the MSLT-II trial.[26] The percentage of patients with sentinel node metastases that were < 1.01 mm in size in these two trials was 66%.
- High-risk features of the SLN can be defined on the basis of the exclusion criteria of the MSLT-II RCT,[27] such as extracapsular spread/extension, concomitant microsatellitosis of the primary tumor, greater than three involved nodes, greater than two involved nodal basins, and immunosuppression of the patient. Lower risk may be defined as patients without the characteristics defined as high risk, but should also take into account other clinicopathological features, after thorough discussion with the patient.

(continued on following page)

THE BOTTOM LINE (CONTINUED)

- Both MSLT-II and DeCOG-SLT were conducted in patient populations in which the observation group received frequent follow-up evaluations, including the use of serial nodal ultrasound.[26,27] Consequently, results from these trials may have limited applicability in settings where patients are unable to undergo frequent follow-up evaluations, or in patients who receive treatment at institutions that are not able to perform high-quality nodal ultrasonography.

Additional Resources:

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/melanoma-guidelines and www.asco.org/guidelineswiki. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

for identifying nodal metastases. Knowledge of regional lymph node status helps to determine prognosis, facilitates strategies for regional disease control, and aids in the selection of patients who may benefit from adjuvant therapy.[3] SLN biopsy is a minimally invasive procedure that accurately detects nodal metastases in patients with clinically occult disease. In 2009, the 7th edition of the American Joint Committee on Cancer (AJCC) staging system formally recognized the prognostic value of micrometastases.[4,5] Five-year survival rates range from 70% for patients with one SLN with micrometastatic disease to 39% for patients with four or more involved nodes or with nodes that are extensively involved (Gershenwald et al, manuscript submitted for publication).

When the previous version of this guideline was published in 2012, SLN biopsy was an established procedure for newly diagnosed patients with primary cutaneous melanoma; however, there was a need to develop and formalize guideline recommendations for its indications in specific subpopulations. Since the risk of lymph node involvement varies by thickness of melanoma, recommendations were stratified by this variable.[6,7] The joint ASCO-Society of Surgical Oncology (SSO) guideline panel concluded that the potential benefits of SLN biopsy outweighed the risk of harm for patients with intermediate-thickness melanoma. SLN biopsy was also recommended as an option for thick melanomas for staging purposes and to facilitate regional disease control. SLN biopsy was not routinely recommended for patients with thin melanomas; however, it could be considered in patients with higher risk features, which were previously defined as 0.75 to 0.99 mm Breslow thickness with ulceration and/or mitotic rate $\geq$ 1/mm^2. A completion lymph node dissection (CLND) was recommended for all patients with a positive SLN biopsy to complete staging and to achieve regional disease control.[6,7]

This guideline was prioritized for updating during a routine assessment process that is undertaken annually to ensure the currency of all ASCO guidelines. This update includes new observational studies and final results from randomized controlled clinical trials. A panel of clinical experts used this evidence to evaluate and update the recommendations contained in the 2012 guideline on SLN biopsy in melanoma. A summary of the key recommendations can be found in the Bottom Line Box.

GUIDELINE QUESTIONS

This clinical practice guideline addresses two overarching clinical questions: (1) what are the indications for SLN biopsy, and (2) what is the role of CLND?

Methods

Guideline update process. The Expert Panel (Appendix Table A1, online only) met via teleconference and/or webinar and corresponded through e-mail. Based upon the consideration of the evidence from a systematic review of the literature conducted by a trained Methodologist, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of guideline. This guideline was also reviewed and approved by the ASCO Clinical Practice Guideline Committee and by the SSO Executive Council prior to publication. All funding for the administration of the project was provided by ASCO. The recommendations were developed by an Expert Panel with multidisciplinary representation, including expertise in medical oncology, surgical oncology, nuclear medicine, pathology, and plastic and reconstructive surgery.

Articles were selected for inclusion in the systematic review based on the following criteria:

Clinical question 1.

- Patients with primary cutaneous melanoma without clinical evidence of lymph node involvement
- Subgroups of interest: Patients with melanoma of varying Breslow thickness, including thin ($\leq$ 1.0 mm), intermediate ($>$ 1.0 to 4.0 mm), and thick ($>$ 4.0 mm; Gershenwald et al, manuscript submitted for publication).
- Intervention: Wide excision and SLN biopsy
- Comparison: Wide excision and nodal observation
- Outcomes: Melanoma-specific survival, disease-free survival, recurrence, variation in rate of SLN positivity according to established risk factors (eg, ulceration, mitotic rate), morbidity
- Eligible study designs: Systematic reviews, randomized and nonrandomized studies

Clinical question 2.

- Patients with newly diagnosed primary cutaneous melanoma
- Intervention: CLND after a positive SLN biopsy
- Comparison: Observation (no CLND) after a positive SLN biopsy
- Outcomes: Survival (melanoma-specific, disease-free), regional disease control, operative morbidity
- Eligible study designs: For the previous version of this guideline, the Expert Panel stated that the results of phase III randomized controlled trials (RCTs) were awaited and would inform the recommendation related to CLND after positive SLN biopsy; therefore, the standard for clinical question 2 was limited to phase III RCTs.

PubMed was searched from September 2011 to June 16, 2017. Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, narrative reviews; (3) published in a non-English language. In addition, because sentinel node status has already been established as a prognostic indicator and has been incorporated into the AJCC staging system, studies reporting outcomes related to the prognostic significance of a positive sentinel node were excluded. Test performance characteristics of SLN biopsy, eg, false negative rates, were considered to have already been established[8]; therefore, studies reporting only these outcomes were also excluded from this guideline update. To avoid duplication, data were not extracted from studies that were included in eligible systematic reviews or meta-analyses.

The guideline recommendations are crafted, in part, using the Guidelines Into Decision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software.[9] In addition, a guideline implementability review is conducted. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation (Methodology Supplement).

Detailed information about the methods used to develop this update is available in the Methodology Supplement at www.asco.org/melanoma-guidelines, including an overview (eg, panel composition, development process and revision dates; the recommendation development process [GLIDES and BRIDGE-Wiz]; and quality assessment).

The Expert Panel and ASCO guidelines staff will work with cochairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update. The Methodology Supplement (available at www.asco.org/melanoma-guidelines) provides additional information about the signals approach.[10]

This is the most recent information as of the publication date. Visit the ASCO Guidelines Wiki at www.asco.org/guidelineswiki to submit new evidence.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by ASCO and the SSO to assist providers in clinical decision-making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO and the SSO provide this information on an "as is" basis and makes no warranty, express or implied, regarding the information. ASCO and the SSO specifically disclaim any warranties of merchantability or fitness for a particular use or purpose. ASCO and the SSO assume no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

Clinical Question 1. What Are the Indications for SLN Biopsy?

Study characteristics and quality assessment. Twelve studies of SLN biopsy compared with nodal observation met the inclusion criteria.[11-22] Six studies compared survival and/or recurrence outcomes between two groups, typically comparing SLN biopsy and wide local excision to wide local excision and nodal observation (Table 1).[11-16] An additional six studies reported rates of sentinel node positivity by Breslow thickness category (ie, thin, intermediate thickness, thick) and explored risk factors that could be used to predict sentinel node positivity (Table 2).[17-22] Median age of study participant groups ranged from 50[22] to 79 years of

age[12] and differed significantly in one study where the median ages of SLN biopsy patients versus observation group patients were 79 and 65 years of age, respectively ($P < .001$).[12] Across most studies, more than 50% of the population was male. Most studies included a mix of primary melanoma locations, including upper and lower extremities, trunk, and head and neck. One study exclusively included patients with head and neck melanoma.[15] Some studies included analyses of a specific Breslow thickness category, including:

- Thin melanoma (n = 4)[17-19,22]
- Intermediate-thickness melanoma (n = 2)[14,20]
- Thick melanoma (n = 2)[12,13]

Morton et al[11] and van der Ploeg et al[16] included results for intermediate-thickness and thick melanoma. Sperry et al[15] and Balch et al[21] included results for all thickness categories of melanoma.

Study design aspects related to study quality and risk of bias were assessed. Only one study included in the evidence base for Clinical Question 1 had a randomized controlled study design. The remainder of the studies were nonrandomized and mostly retrospective. Studies with a nonrandomized design have a higher risk of bias because of greater potential for confounding; therefore, these studies are usually considered low quality (ie, low certainty of evidence). However, this rating can be upgraded to moderate or high where a large effect of treatment is observed, if there is a dose response gradient, or where potential confounding would reduce the demonstrated effect.[23] The small number of studies included in this review update largely corroborate previous findings of longer disease-free interval with SLN biopsy compared with observation and lack of an overall or melanoma-specific survival (MSS) advantage.[16] The consistency of these findings provides a rationale for upgrading the quality of the observational studies included in this update; therefore, the quality may be considered low to intermediate. A Cochrane review concluded that evidence from the Multicenter Selective Lymphadenectomy I (MSLT-I) trial was of low quality because only one RCT was available that addressed SLN biopsy versus nodal observation, and because risk of bias was high or unclear for a number of items in MSLT-I, including blinding and selective outcome reporting.[24]

Outcomes: SLN biopsy versus nodal observation. As shown in Table 3, 10-year results from the MSLT-I trial showed a significant difference in DFS between the SLN biopsy and the observation groups (HR, 0.70; $P = .03$) for patients with thick melanoma (defined in MSLT-I as > 3.5 mm); however, there was no difference between these groups for MSS (HR, 1.12; $P = .56$).[11] Likewise, in the population of patients with intermediate-thickness melanoma (defined as 1.2 to 3.5 mm), significant differences were found between groups for 10-year DFS (HR, 0.76; $P = .01$) but not MSS (HR, 0.84; $P = .18$).[11] One study that used data from the SEER database found a significant difference in MSS for patients with intermediate-thickness melanoma (HR, 1.18; $P = .009$).[14]

In another SEER database study of patients with thick melanoma (using an overlapping but updated cohort), no significant differences were found between treatment group and survival in a Cox regression analysis that included advanced age, male sex, trunk location, and ulceration ($P = .20$).[12] A single institution study of patients with thick melanoma found no significant differences in DFS; however, there was a significant difference in disease-free interval favoring the SLN biopsy group over the observation group (HR, 0.59; 95% CI, 0.43 to 0.79; $P = .001$).[13] Similarly, a study of patients with intermediate-thickness melanoma found no difference in MSS, but significant differences in DFS (HR, 0.71; $P < .001$) and distant metastasis-free survival (HR, 0.81; $P = .041$) favoring SLN biopsy over observation.[16]

No significant differences were found between SLN biopsy and observation groups for any thickness of melanoma in a study that included only patients with head and neck melanoma.[15]

Study outcomes: Risk factors for sentinel node positivity. Table 4 presents data from several studies that examined risk factors associated with sentinel node positivity in thin melanoma. A systematic review of 60 studies found that after adjusting for all potential risk factors, Breslow thickness ≥ 0.75 mm (SLN positivity likelihood, 8.8%; 95% CI, 6.4% to 11.2%), Clark level ≥ IV (SLN positivity likelihood, 7.3%; 95% CI, 6.2% to 8.4%), presence of microsatellites (SLN positivity likelihood, 22.6%; 95% CI, 4.3% to 48.9%), and ≥ 1 mitoses/mm^2 (SLN positivity likelihood, 8.8%; 95% CI, 6.2% to 11.4%) were significant risk factors for sentinel node positivity.[17] Han et al, the largest study included in that systematic review, with 1,250 patients from multiple institutions, found that Breslow thickness ≥ 0.75 mm, Clark level ≥ IV, and ulceration were significantly associated with sentinel node positivity in a multivariate analysis, while there was no significant association with mitotic rate ≥ 1/mm^2.[25] Another systematic review that looked at mitotic rate in thin melanoma found that the sentinel node positivity rate for patients with 0 mitoses/ mm^2 was 0.0% and ranged up to 9.4% for patients with a rate of ≥ 1 mitoses/ mm^2.[18] A retrospective multicenter adjusted analysis of mitotic rate found that it did not predict SLN positivity in patients with thin melanoma (however, it was a predictor for patients with intermediate-thickness melanoma) and that the predictive ability of mitotic rate decreased with decreasing Breslow thickness.[19]

A study of risk factors for sentinel node positivity in patients with intermediate-thickness melanoma found that age, thickness (1.00 to 1.49 mm *v* 1.50 to 4.00 mm), tumor infiltrating lymphocytes, lymphovascular invasion, and microsatellites were significant predictors in a multivariate analysis.[20] Younger age was found to be predictive of sentinel node positivity; however, younger patients also had better rates of survival in a study of the 7th edition AJCC staging system database.[21] See Table 4 for additional factors that were tested in univariate and multivariate models.

Clinical Question 2: What Is the Role of CLND?

Study characteristics and quality assessment. Two RCTs comparing CLND to close observation met the updated literature search inclusion criteria for this question.[26,27] The first compared CLND (n = 242) to observation (n = 241) for patients with a positive SLN, mostly representative of micrometastatic disease (Table 5). The study groups were balanced in terms of patient and tumor characteristics. Over 50% of patients in both study groups had melanoma of the trunk, and the study did not include patients with head and neck melanoma. All melanomas were at least intermediate-thickness lesions. This study demonstrated adequate randomization techniques and allocation concealment, but could not blind study participants or investigators. The authors noted that selection bias was found; patients included in the study

Table 1. Characteristics of Studies Reporting Outcomes of SLNB Versus Nodal Observation

Author, Year	Type of Study (years of data collection)	Interventions Comparisons	No. of Patients	Median Age (years)	Male (%)	Median Breslow Thickness (mm)	Primary Melanoma Location (%)
Morton et al, 2014 (MSLT-I)[11]*	Phase III RCT	Intervention: Wide excision plus SLNB and immediate lymphadenectomy in the case of positive nodes Comparison: Wide excision plus nodal observation with lymphadenectomy when nodal metastases developed	Thick melanoma (> 3.5 mm): SLNB: 185 OBS: 126 Intermediate-thickness melanoma (1.2-3.5 mm): SLNB: 805 OBS: 522	SLNB: 53 OBS: 53 (P = .900)	SLNB: 58 OBS: 55 (0.2833)	SLNB: 1.8 OBS:1.9 (0.3927)	SLNB: Arm or leg: 46.5 Other: 53.5 OBS: Arm or leg: 42.6 Other: 57.4 (P = .1730)
Kachare et al, 2015[12]	SEER (2003-2010)	Intervention: Wide local excision and SLNB Comparison: Wide local excision alone (observation)	SLNB: 2,746 OBS: 1,825	SLNB: 65 OBS: 79 (P < .001)	SLNB: 65.2 OBS: 62.8 (P = .09)	Clinically node-negative thick melanoma (> 4mm; median not reported)	SLNB: Head and neck: 22.1 Extremity: 45.6 Trunk: 32.3 OBS: Head and neck: 39.3 Extremity: 37.9 Trunk: 22.8 (P < .001)
Ribero et al, 2015[13]	Retrospective single institution	Intervention: Wide local excision and SLNB Comparison: Wide local excision and observation Only patients submitted to SLNB, whose node stage was known were considered as candidates for immunotherapy, according to evidence-based recommendation.	SLNB: 178 OBS: 172	SLNB pos.: 58.8 SLNB neg.: 63 OBS: 71	SLNB: 70 OBS: 44.5	Thick melanoma: SLNB pos.: 6.7; SLNB neg.: 6.2; OBS: 7.5.	SLNB: Upper extremity: 6.7 Trunk: 40.4 Head and neck: 11.8 Lower extremities: OBS: Head and neck: 14.6 Trunk: 39.4 Upper extremities: 13.4 Lower extremities: 30.8
Kachare et al, 2014[14]	SEER (2003-2008)	Intervention: SLNB Comparison: Observation	Total: 15,274 PSM: 7,910	SLNB: 70 OBS: 71	SLNB: 61.8 OBS: 62.8	SLNB: 1.01-2.00 mm: 63.6%; 2.01-4.00 mm: 36.4%; OBS: 1.01-2.00 mm: 64.5%, 2.01-4.00 mm: 35.5%	SLNB: Extremity: 41.7 Trunk: 26.6 Head and neck: 31.7 OBS: Extremity: 43.0 Trunk: 27.4 Head and neck: 29.7
Sperry et al, 2014[15]	SEER (2004-2011)	Intervention: SLNB Comparison: Nodal observation	7,266 (2,808 in the intermediate-thickness PSM analysis)	Mean (SD) SLNB: 66.2 (14.3) OBS: 66.2 (13.8)	SLNB: 50 OBS: 50	Mean (SD) SLNB: 2.3 (2.1) OBS: 2.4 (1.8)	Head and neck: 100
van der Ploeg et al, 2014[16]	Retrospective single institution	Intervention: Wide local excision plus SLNB Comparison: Wide local excision and observation	5,840	Mean (SE) SLNB: 56.1 ± 0.3. OBS: 60.2 ± 0.3. (P < .001)	SLNB: 59.9 OBS: 57.2 (P = .041)	≥ 1 mm SLNB: 1.8 (74.6% intermediate) OBS: 1.5 (58.9% intermediate) (P < .001)	SLNB: Extremity: 45.5 Trunk: 39.1 Head and neck: 15.4 OBS: Extremity: 39.7 Trunk: 35.2 Head and neck: 25.1

Abbreviations: MSLT-I, Multicenter Selective Lymphadenectomy I; neg., negative; OBS, observation; pos., positive; PSM, propensity score matching; RCT, randomized controlled trial; SD, standard deviation; SLNB, sentinel lymph node biopsy.
*In Morton et al, thick melanomas were defined as > 3.50 mm.

Table 2. Characteristics of Studies of Risk Factors for Sentinel Node Positivity

Study (year)	Type of Study	Data Source	No. of Patients	Median Age (years)	Male (%)	Breslow Thickness (mm)	Primary Melanoma Location (%)
Cordeiro et al, 2016[17]	Systematic review	60 included studies	Median number of patients per study: 75	Not reported	Not reported	≤1 mm	Not stated
Kirkland and Zitelli, 2014[18]	Systematic review	7 studies included in analysis of SLN positivity rate stratified by MR	Patients in 7 studies of SLN positivity rate stratified by MR: 1,354	Not reported	Not reported	≤ 1 mm	Not stated
McClain et al, 2012[22]	Prospective	Single-institution clinical database (1995-2006)	Patients with regressed melanoma without other indications for SLNB: Group 1/SLNB: 35 Group 2/no SLNB: 31 Group 3: metastatic disease concurrent with regressed thin melanoma: 9	Group 1: 53 Group 2: 54 Group 3: 50 (P = .78)	Group 1: 71 Group 2: 52 Group 3: 89 (P = .07)	< 1 mm	Group 1: Trunk: 54 Extremities: 40 Head and neck: 6 Group 2: Trunk: 48 Extremities: 48 Head and neck: 3 Group 3: Trunk: 44 Extremities: 22 Head and neck: 33
Wat et al, 2016[19]	Retrospective cohort	Provincial surgical oncology database (Alberta, Canada) and centralized pathology database (Jan 2007-Dec 2013)	Patients between Jan 2007 and Dec 2013: 1,224	15-39 years of age: 12.7% 40-79 years of age: 81.5% 80-95 years of age: 5.8%	54.8	Thin melanoma with positive SLNB; median: 0.92 mm	Head and neck: 16.4 Upper extremity: 22.0 Trunk: 37.5 Lower extremity: 24.2
Bartlett et al, 2016[20]	Retrospective cohort	Institutional database (1995-2011)	Patients undergoing SLNB for intermediate-thickness melanoma (> 1 mm to 4 mm): 952	55	58	1.01-1.49: 36% 1.50-4.00: 64%	Not reported
Balch et al, 2014[21]	Retrospective cohort	AJCC melanoma staging database	Patients presenting without clinical evidence of regional lymph node or distant metastases and staged with SLNB: 7,756	≤ 39: 20.7% 40-59: 44.9% ≥ 60: 34.4%	58.3	≤1.0: 15.6% 1.01-2.0: 45.1% 2.01-4.0: 26.9% ≥4.0: 12.4%	Head and neck: 12.8 Upper extremity:21.8 Trunk: 39.8 Lower extremity: 25.6

Abbreviations: AJCC, American Joint Committee on Cancer; MR, mitotic rate; SLNB, sentinel lymph node biopsy.

Table 3. Survival and Recurrence Outcomes for Studies of SLNB Versus Nodal Observation

Study, Year	Breslow Thickness	No. in SLNB Group	No. in Observation Group	Follow-Up	MSS	DFS
Morton et al, 2014 (MSLT-I)[11]	Thick melanoma (> 3.5 mm)	185	126	10 years	10- year MSS: Biopsy: 58.9 ± 4.0% OBS: 64.4 ± 4.6% (HR, 1.12; *P* = .56) OS: not reported	10-year DFS*: SLNB: 50.7 ± 4.0% OBS: 40.5 ± 4.7% **(HR, 0.70; *P* = .03)** 10-year nodal metastases rate (± SE): SLNB: 42.0 ± 3.8 OBS: 41.4 ± 4.9
	Intermediate-thickness melanoma (1.2-3.5 mm):	805	522	10 years	10-year MSS: Biopsy: 81.4 ± 1.5% OBS: 78.3 ± 2.0% (HR, 0.84; *P* = .18) OS: not reported	10-year DFS: SLNB: 71.3 ± 1.8% OBS: 64.7 ± 2.3% **(HR, 0.76; *P* = .01)** 10-year nodal metastases rate (± SE): SLNB: 21.9 ± 1.54 OBS: 19.5 ± 1.91
Kachare et al, 2015[12]	Thick (clinically node-negative melanoma > 4 mm in depth)	2,746	1,825	Recurrence assessed 2 years after surgery (median follow-up SLNB group: 26 months, range 0-95 months; OBS group: 19 months, range 0-95 months)	Cox regression analysis with advanced age, male sex, trunk location and ulceration, 5-year DSS: SLNB *v* OBS: HR, 1.09, (95% CI, 0.95 to 1.25; *P* = .20)	Recurrence data not available in the SEER registry
Ribero et al, 2015[13]	Thick (> 4 mm; median: 7.00; SD: ± 3.42)	57	75	Median: 30.6 months (range: 2.5-193.9 months)	DSS (SLNB *v* OBS): Cox proportional hazards model: SLNB *v* OBS: HR, 0.77 (95% CI, 0.53 to 1.12; *P* = .176)	DFI: SLNB *v* OBS: **HR, 0.59 (95% CI, 0.43 to 0.79; *P* = .001)**
Kachare et al, 2014[14]	Intermediate (1-4 mm)	PSM analysis: 3,955	PSM analysis: 3,955	Diagnosis 2003-2008, followed up through 2010	Matched cohort multivariate MSS: **HR, 1.18 (1.04 to 1.34; *P* = .009)**	Recurrence data not available in the SEER registry
Sperry et al, 2014[15]	Thin (> 0.75-1.00 mm) Intermediate (> 1.00-4.00 mm) Thick (> 4.00 mm)	PSM analysis: 2,808 Thin: 552 Intermediate: 1,404 Thick: 354	PSM analysis: 2,808 Thin: 552 Intermediate: 1,404 Thick: 354	Not reported	DSS (SLNB *v* OBS): Cox proportional hazards model: Thin: HR, 1.53 (95% CI, 0.75 to 3.13; *P* = .24) Intermediate: HR, 0.87 (95% CI, 0.66 to 1.14; *P* = .31) Thick: HR, 0.80 (95% CI, 0.56 to 1.15; *P* = .23)	Recurrence data not available in the SEER registry
van der Ploeg et al, 2014[16]	Intermediate or thick (≥ 1 mm)	2,909	2,931	Median (IQR): SLNB: 40 months (18-81) OBS: 44 (20-76)	Multivariate analysis: MSS (SLNB *v* OBS): SLNB *v* OBS: HR, 0.96 (95% CI, 0.82 to 1.14)	Multivariate analysis: DFS: SLNB *v* OBS: **HR, 0.71 (95% CI, 0.63 to 0.81; *P* < .001)** DMFS for T2 and T3 groups: SLNB *v* OBS: **HR, 0.81 (95% CI, 0.67 to 0.99; *P* = .041)**

NOTE. Bolded text indicates a significant result.

Abbreviations: DFI, disease-free interval; DFS, disease-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; HR, hazard ratio; IQR, interquartile range; MSLT-I, Multicenter Selective Lymphadenectomy I; MSS, melanoma-specific survival; OBS, observation; OS, overall survival; PSM, propensity score matching; SLNB, sentinel lymph node biopsy.

*In the MSLT-I trial, DFS is defined as the time to recurrence within the primary tumor region.

Table 4. Outcomes of Studies of Risk Factors for Sentinel Node Positivity in Patients With Melanoma

Study, Year	Sentinel Lymph Node Positivity Rate, % (95% CI)	Factors Included in Adjusted Model	Significant Predictor of SN Positivity on Unadjusted Analysis	Significant Predictor of SN Positivity on Adjusted Analysis	Recurrence Rate (%)
Cordeiro et al, 2016[17]	Overall: 4.5 (3.8 to 5.2) Thickness ≥ 0.75 mm: 8.8 (6.4 to 11.2) Clark level IV/V: 7.3 (6.2 to 8.4) ≥ 1 mitoses/mm$^{2:}$ 8.8 (6.2 to 11.4)	Thickness ≥ 0.75 mm, Clark level IV/V, ulceration, mitoses ≥ 1 per mm^2 *v* absent, mitoses ≥ 1 per mm^2 *v* mitoses < 1 per mm^2, regression, microsatellites, LVI, and absence of TILs	Thickness ≥ 0.75 mm, Clark level IV/V, ≥ 1 mitoses/mm^2, ulceration, and microsatellites	Thickness ≥ 0.75 mm, Clark level IV/V, and ≥ 1 mitoses/mm^2	Not reported
Kirkland and Zitelli, 2014[18]	Range across 5 studies: 0 mitoses/ mm^2 = 0.0 ≥ 1 mitoses/mm^2 = 9.4 (2 studies with small sample sizes excluded)	Not applicable	Significance testing not conducted (main outcome was sentinel node positivity rate stratified by mitotic rate)	Not applicable	Not reported
Wat et al, 2016[19]	Overall: 25.4 Thin: 8.8 Thin with mitoses ≥ 1 per mm^2: 9.8	Age, sex, Breslow depth, ulceration, location, and mitotic rate	Mitotic rate found not to be significantly associated with SLN positivity for thin melanomas.	Finding: the effect of mitotic rate on the likelihood of SLN positivity decreases with decreasing Breslow depth.	Not reported
McClain et al, 2012[22]	Not reported	Not applicable	Not applicable	Regression *not recommended* as an indicator for SLNB in T1a melanoma	Recurrence after SLNB: Local recurrence: 3.0 Regional LN: 0 Distant skin, nodes or viscera: 3.0 Recurrence after no SLNB: Local recurrence: 0 Regional LN: 7.1 Distant skin, nodes or viscera: 3.6
Bartlett et al, 2016[20]	Overall: 16.5 1.01-1.49 mm: 7.3 1.50-4.00 mm: 21.7 Thickness < 1.5 mm and absent mitoses: 7.6	Age, sex, Clark level, thickness, mitosis, TIL, regression, ulceration, LVI, and satellites	Thickness (1.00-1.49 mm *v* 1.50-4.00 mm), mitosis, TIL, ulceration, LVI, and satellites	Age, thickness (1.00-1.49 mm *v* 1.50-4.00 mm), TIL, LVI, and satellites	Developed a nodal recurrence following a falsely negative SLNB: 3
Balch et al, 2014[21]	Overall: 19.4	No adjusted analysis	Younger patient age, tumor thickness, lymphovascular invasion, trunk or lower extremity location, Clark level of invasion, and tumor ulceration	Not applicable	Not reported

Abbreviations: LN, lymph node; LVI, lymphovascular invasion; SLNB, sentinel lymph node biopsy; TIL, tumor infiltrating lymphocyte.

Table 5. Characteristics and Quality Assessment for Studies of CLND Versus Monitoring After Positive SLNB

Author, Year	Type of Study (years of data collection)	Interventions Comparisons	No. of Patients	Median Age (years)	Male (%)	Median Breslow Thickness (mm)	Primary Melanoma Location (%)
Leiter et al, 2016 (DeCOG-SLT)[26]	Multicenter phase III RCT (Jan 2006 to Dec 1, 2014; closed early due to difficulties enrolling and low event rate)	CLND *v* OBS in SLNB positive patients (majority with micrometastasis)	483	CLND: 57 (range: 47.0-67.8) OBS: 56 (range: 45.0-66.0)	CLND: 59 OBS: 41	CLND: 2.4 (1.6-4.0) OBS: 2.4 (1.5-3.85)	CLND: Trunk: 53 Upper extremity: 15 Lower extremity: 32 OBS: Trunk: 51 Upper extremity: 13 Lower extremity: 36
Faries et al, 2017 (MSLT-II)[27]	Multicenter phase III RCT (Dec 2004 to March 2014)	CLND *v* OBS with frequent nodal ultrasonography and dissection in patients with clinically detected nodal recurrence	ITT analysis: 1,934 Per-protocol analysis: 1,755*	Per protocol: CLND: 53.7 (range: 18-76) OBS: 54.9 (range: 19-76)	Per protocol: CLND: 58.0 OBS: 59.0	Per protocol: CLND: 2.10 (range: 0.23-28.0) OBS: 2.10 (range: 0.35-30.0)	Per protocol: CLND: Trunk: 46.6 Arm or leg: 39.7 Head or neck: 13.7 OBS: Trunk: 45.2 Arm or leg: 41.0 Head or neck: 13.7

Abbreviations: CLND, completion lymph node dissection; DeCOG-SLT, German Dermatologic Oncology Cooperative Group; IQR, interquartile range; ITT, intention to treat; MSLT-II, Multicenter Selective Lymphadenectomy II; OBS, observation; RCT, randomized controlled trial; SLNB, sentinel lymph node biopsy.
*The per-protocol analysis includes randomly assigned patients who received their originally assigned treatment.

were younger and had a lower number of metastases ≥ 5 mm than patients who were excluded from the study. This trial closed early due to slow accrual and a lower than anticipated event rate, which resulted in it being underpowered to detect some differences in end points.[26]

The Multicenter Selective Lymphadenectomy II (MSLT-II) phase III RCT compared CLND (n = 824) to observation with frequent nodal ultrasonography for patients with a positive SLN (n = 931). The study groups were balanced in terms of patient and tumor characteristics. Results were reported for the per-protocol as well as intention-to-treat patient populations. In the per-protocol analysis, 45.9% of patients had melanoma of the trunk, 40.4% had melanoma of the extremities, and 13.7% had melanoma of the head and neck. The authors note that the trial included a small number of patients with a higher volume sentinel-node tumor burden, which limits the statistical confidence for estimates within this subpopulation of patients.[27]

Study quality, assessed across outcomes for the two included RCTs for this clinical question, was considered intermediate to high, due to no major quality issues with study design or risk of bias and the consistency of results across both studies. However, in both studies, approximately two thirds of patients had micrometastases of ≤ 1 mm in their SLNs.[26,27]

Study outcomes: CLND versus observation. The primary outcome for the German Dermatologic Oncology Cooperative Group (DeCOG-SLT) trial was distant metastases-free survival, which was not significantly different between CLND and observation groups (HR, 1.19; 90% CI, 0.83 to 1.69; $P = .43$). Overall survival (HR, 1.02; 90% CI, 0.68 to 1.52; $P = .95$) and recurrence-free survival (HR, 0.959; 90% CI, 0.70 to 1.31; $P = .83$) also did not differ between groups. Adverse events occurred in 24% of 240 patients, including ≥ grade 3 adverse events in 14% of patients. Grade 3 and 4 events included lymphedema (n = 20), lymph fistula (n = 3), seroma (n = 3), infection (n = 3), and delayed wound healing (n = 5).

The primary outcome of the larger (1,934 patients) MSLT-II trial was MSS. With a median follow-up of 43 months, no significant differences were found for MSS (HR, 1.08; 95% CI, 0.88 to 1.34; $P = .42$) or secondary outcome distant metastasis-free survival (HR [adjusted], 1.10; 95% CI, 0.92 to 1.31; $P = .31$). The rate of DFS at 3 years was 68% (± 1.7%) for CLND versus 63% (± 1.7%) in the observation group (log-rank $P = .05$). The authors attributed the difference in DFS to differences in rates of disease control in the regional nodes. In addition, lymphedema was reported by 24.1% of patients in the CLND group and 6.3% of patients in the observation group (Table 6).

RECOMMENDATIONS

Clinical Question 1: What Are the Indications for SLN Biopsy?

Recommendation 1.1. **Thin melanomas.** Routine SLN biopsy is not recommended for patients with melanomas that are T1a (nonulcerated lesions < 0.8 mm in Breslow thickness). SLN biopsy may be considered for T1b patients (0.8 to 1.0 mm Breslow thickness or < 0.8 mm Breslow thickness with ulceration) after a thorough discussion with the patient of the potential benefits and risk of harms associated with the procedure (Type of recommendation: evidence based; potential benefits outweigh risk of harms; Quality of evidence: low to intermediate; Strength of recommendation: moderate).

Literature review update and analysis. Several new studies examined risk factors associated with SLN positivity in patients with thin melanoma. Cordeiro et al published a systematic review of 60 studies and 10,928 patients with thin melanoma that examined risk factors associated with sentinel node positivity, including thickness, Clark level IV/V, ulceration, mitotic rate, regression, microsatellites, lymphovascular invasion, and tumor infiltrating lymphocytes. After adjusting for all potential risk factors, Breslow thickness, Clark level, presence of microsatellites, and ≥ 1 mitoses/mm^2 were significant risk factors for sentinel

Table 6. Outcomes for Studies of CLND Versus Monitoring After a Positive Sentinel Lymph Node

Study, Year	Melanoma Thickness	No. in CLND Group	No. in Observation Group	Follow-Up (months)	Survival/Recurrence	AEs (%)
Leiter et al, 2016 (DeCOG-SLT)[26]	≥ 1 mm	242	241	Median (IQR): CLND: 33.0 (17.0-50.0) OBS:35.5 (22.7-57.0)	OBS *v* CLND: Overall survival: HR, 1.02 (90% CI, 0.68 to 1.52, *P* = .95) Recurrence-free survival: HR, 0.959 (90% CI, 0.70 to 1.31, *P* = .83) Distant metastasis-free survival: HR, 1.19 (90% CI, 0.83 to 1.69, *P* = .43)	CLND: Any AE: 24 Grade 3: 6 Grade 4: 8
Faries et al, 2017 (MSLT-II)[27]	0.34-30.0 mm	824	931	Median: 43	OBS *v* CLND: Melanoma-specific survival: HR, 1.08 (95% CI, 0.88 to 1.34, *P* = .42) Distant metastasis-free survival: Adjusted HR, 1.10 (95% CI, 0.92 to 1.31, *P* = .31) Disease-free survival*: CLND: 68 ± 1.7% *v* OBS: 63 ± 1.7%, log-rank *P* = .05	CLND: Lymphedema: 24.1 Obs: Lymphedema: 6.3

Abbreviations: AEs, adverse events; CLND, completion lymph node dissection; DeCOG-SLT, German Dermatologic Oncology Cooperative Group; IQR, interquartile range; MSLT-II, Multicenter Selective Lymphadenectomy II; Obs, observation.
*In the MSLT-II trial, disease-free survival is defined as the time to any recurrence.[9]

node positivity.[17] A study of 1,250 patients from multiple institutions found that Breslow thickness ≥ 0.75 mm, Clark level ≥ IV, and ulceration were significantly associated with sentinel node positivity in a multivariate analysis, while there was no significant association with mitotic rate ≥ 1/mm^2.[25] Mixed results for mitotic rate were found across other studies[18,19] and, in fact, the mitotic rate has recently been removed from consideration in the 8th edition of the AJCC staging system because it did not contribute to prognostication for thinner lesions (Gershenwald et al, manuscript submitted for publication). A study of data from the AJCC staging system database found an inverse relationship between age and rate of sentinel node positivity; patients under 20 years of age experienced a 25.8% rate of sentinel node metastases, while those ≥ 80 years of age had a sentinel node metastases rate of 15.5% ($P < .001$). Despite the higher rate of nodal positivity, patients in the youngest age group had more favorable survival outcomes.[21]

Clinical interpretation. The overall rate of sentinel node metastases in thin melanoma is estimated to be approximately 5.2%[25]; however, for patients with lesions > 0.8 mm in thickness, the incidence is approximately 8%.[17] Given this overall low rate of expected nodal metastases, SLN biopsy was not recommended for routine use in the thin melanoma population in the previous version of the guideline.[6] This guideline update identified limited new data. A large study confirmed Breslow thickness ≥ 0.75 mm, Clark level ≥ IV, and ≥ 1 mitoses/mm^2 as variables that are associated with higher rates of SLN positivity.[17] An additional larger study identified ulceration as an additional potential factor associated with higher risk.[25] Based on the 8th edition of the AJCC staging system, individuals with melanoma 0.8 to 1.0 mm in thickness or melanoma < 0.8 mm in thickness with ulceration were identified as higher risk lesions and designated as T1b. It is notable that the AJCC staging system has identified an improved prognosis for patients with thin melanomas > 0.8 mm in thickness who undergo SLN biopsy and are negative when compared with those who do not undergo SLN evaluation. Therefore, an individualized approach to SLN biopsy in these patients is recommended with consideration for all clinicopathological risk factors. Patients should be counseled regarding their individual risk of nodal metastases and their estimated personal risk of the procedure. Recommendations for use of SLN biopsy in patients with thin melanoma are modified from the previous version of this guideline based on these data and in keeping with modifications to the AJCC staging system. The routine use of SLN biopsy is not recommended in patients with thin melanoma, defined as T1a or lesions < 0.8 mm in thickness without ulceration. Considering all patient and disease characteristics, SLN biopsy may be offered for those with T1b lesions (0.8 mm to 1.0 mm thickness, regardless of ulceration status or ulcerated melanoma < 0.8 mm) as they may be expected to have a slightly higher rate of SLN metastases.

Recommendation 1.2. Intermediate-thickness melanomas: SLN biopsy is recommended for patients with melanomas that are T2 or T3 (Breslow thickness of > 1.0 to 4.0 mm; Type of recommendation: evidence based; potential benefits outweigh risks of harm; Quality of evidence: intermediate; Strength of recommendation: moderate).

Literature review update and analysis. This update identified five new studies reporting survival outcomes in patients with intermediate-thickness melanoma.[11,14-16,20] In a 10-year follow-up of patients in MSLT-I, DFS was significantly better in the SLN biopsy group, compared with nodal observation; however, there was no significant difference in MSS.[11] In patients with nodal metastases, overall survival was improved when diagnosed via sentinel node biopsy in contrast to when identified via clinical or radiographic evaluation.[11] A SEER database study also found a significant difference in 5-year MSS with SLN biopsy versus observation.[14] An additional SEER database study in patients with head and neck melanoma found no significant differences in disease-specific survival between these groups.[15] A study of risk factors for sentinel node positivity within this group found younger patient age (< 60 years), melanoma thickness (1.50 to 4.00 mm *v* 1.00 to 1.49 mm), lack of tumor infiltrating lymphocytes, lymphovascular invasion, and microsatellitosis to be significant predictors of SLN positivity.[20]

Clinical interpretation. The previous version of this guideline recommended SLN biopsy in patients with intermediate-thickness melanoma as a potential way to improve regional disease control

and to aid in decision making regarding adjuvant therapy.[6] The recommendation for staging with SLN biopsy in the intermediate-thickness (T2 and T3; > 1.0 to 4.0 mm thickness) population is reaffirmed in this update, based on the established prognostic significance of SLN status,[28] and the previously reported low rate (approximately 4.6%) and short-term nature of complications associated with SLN biopsy. In MSLT-I, the most common complications after SLN biopsy resolved over time and included seroma (5.5%), infection (4.6%) and wound separation (1.2%).[6] A more recent meta-analysis reported an overall complication rate of 4.6%.[29] Based on these data, the potential benefits of SLN biopsy, compared with nodal observation until lymph nodes are clinically detectable, are considered to be greater than the potential harms in this population, which has an expected nodal metastases rate of approximately 16% to 20%.[14,30]

Recommendation 1.3. **Thick melanomas**. SLN biopsy may be recommended for patients with melanomas that are T4 (> 4.0 mm in Breslow thickness), after a thorough discussion with the patient of the potential benefits and risks of harm associated with the procedure (Type of recommendation: Evidence based; potential benefits outweigh risks of harm; Quality of evidence: low to intermediate; Strength of recommendation: moderate).

Literature review update and analysis. In a 10-year follow-up of patients with thick melanoma in MSLT-I, DFS was significantly improved in the SLN biopsy group, compared with nodal observation; however, there was no difference in 10-year MSS.[11] A SEER database study did not find a significant difference in adjusted 5-year disease-specific survival with SLN biopsy versus observation.[12] An additional SEER database study in patients with head and neck melanoma also found no significant differences between these groups.[15] Likewise, a retrospective single-institution study found no difference between the SLN biopsy and observation groups in the hazard ratio for DSS, although the disease-free interval was significantly improved for the patients in this study who underwent SLN biopsy.[13]

Clinical interpretation. The previous version of this guideline noted that there are few studies of SLN biopsy in this specific population. SLN biopsy in patients with thick melanoma is somewhat controversial because it can be argued that due to a high risk of systemic disease, there is no survival benefit associated with removal of regional lymph nodes. However, SLN biopsy can be a valuable pathologic staging procedure in patients without distant disease and improves regional disease control.[31] This may be overestimated in this population where the incidence of nodal metastases is higher than in patients with intermediate-thickness melanoma. Thus, the previous ASCO guideline stated that SLN biopsy may be recommended in patients with thick melanoma for the purposes of staging and potentially for regional disease control.[6] As the limited number of studies included in this update largely corroborate the findings of the original systematic review, the update panel affirms this recommendation. Also, a positive SLN biopsy in a thick, high-risk melanoma offers the opportunity for consideration of adjuvant treatment.

Clinical Question 2: What Is the Role of CLND?

Recommendation 2.1. CLND or careful observation are options for patients with low-risk micrometastatic disease, with due consideration of clinicopathological factors. For higher risk patients, careful observation may be considered only after a thorough discussion with patients about the potential risks and benefits of foregoing CLND (Type of recommendation: evidence based; potential benefits outweigh risks of harm; Quality of evidence: intermediate to high; Strength of recommendation: strong).

Important qualifying statements.

- Key evidence for this recommendation comes from the MSLT-II and DeCOG-SLT RCTs.[26,27] In both trials, the authors reported no difference in MSS between the CLND and close observation groups. Incidence of lymphedema was significantly higher in the CLND group in the MSLT-II trial.[26] The percentage of patients with sentinel node metastases that were < 1.01 mm in size in these two trials was 66%.
- High-risk features of the SLN can be defined on the basis of the exclusion criteria of the MSLT-II RCT,[27] such as extracapsular spread/extension, concomitant microsatellitosis of the primary tumor, more than three involved nodes, more than two involved nodal basins, and immunosuppression of the patient. Lower risk may be defined as patients without the characteristics defined as high risk, but should also take into account other clinicopathological features, after thorough discussion with the patient.
- Both MSLT-II and DeCOG-SLT were conducted in patient populations in which the observation group received frequent follow-up evaluations, including the use of serial nodal ultrasound.[26,27] Consequently, results from these trials may have limited applicability in settings where patients are unable to undergo frequent follow-up evaluations or in patients who receive treatment at institutions that are not able to perform high-quality nodal ultrasonography.

Literature review update and analysis. The two RCTs that were included in the updated evidence base did not find significant differences between CLND and observation groups for their primary outcomes, which were distant metastases-free survival (HR, 1.19; 90% CI, 0.83 to 1.69; $P = .43$)[26] and MSS (HR, 1.08; 95% CI, 0.88 to 1.34; $P = .42$) in the DeCOG trial,[26] and MSS in the MSLT-II trial (HR, 1.08; 95% CI, 0.88 to 1.34; $P = .42$).[27] Adverse events such as lymphedema were more common in the CLND group than in the observation group in MSLT-II (24.1% *v* 6.3%).[27]

Clinical interpretation. The findings of DeCOG, published in 2016, suggested that CLND may not be necessary for all patients with a positive SLN, and close observation under a defined protocol is an alternative management strategy with no differences in metastases-free survival and MSS.[26] The larger MSLT-II trial, published in 2017, independently corroborated this conclusion. Both study protocols included frequent follow-up evaluations and interval nodal ultrasonography as important components of close observation.[27] Adherence to these components of the close observation strategy are critical to its success as an option.

There were relatively small numbers of patients with higher SLN burden in both trials and results may not be generalizable to patients with more than low-risk micrometastatic disease in the nodal basin, although in the third of the patient subpopulation that had an SLN burden > 1 mm, statistical analysis did not demonstrate any improvement in this subgroup in survival in either trial. Evidence to guide decision making in patients with a higher burden of nodal disease is limited because of variation in defining micrometastatic disease (eg, < 1 mm or < 2 mm) and because of

a predominance of lower volume nodal tumor burden in the trial populations. In patients with a low tumor burden in a positive SLN, SLN biopsy has diagnostic as well as therapeutic effects, and in that context, all existing nodal disease could have been removed with the SLN biopsy, precluding any additional benefit to CLND. High-risk clinicopathological factors must be considered in the decision making between CLND and close observation for patients who have a positive SLN biopsy. Risks and benefits of CLND versus close observation should be discussed with patients, weighing morbidity and potential risk of complications with the advantages of improved regional DFS and more accurate prognostic assessment of the nodal basin, including status of the nonsentinel nodes. In those undergoing close observation, CLND can be considered if recurrence is noted in the regional nodal basin, if there is no evidence of distant metastases. Data from MSLT-I demonstrated a higher risk of lymphedema with CLND when disease is detected clinically during follow-up; however, patients were not closely followed with nodal ultrasound in that study.

DISCUSSION

SLN biopsy has been found to be useful for intermediate-thickness melanoma, based on results from a meta-analysis that showed low false-negative rates and high rates of sentinel node detection.[8] Given the expected rate of nodal metastases and low rate of complications with the procedure, the Expert Panel concluded that the potential benefits of SLN biopsy outweighed the risk of harms for patients with intermediate-thickness melanoma and that the procedure should be recommended to provide accurate staging and to decrease rates of recurrence in regional nodes. New longer-term data from MSLT-I of SLN biopsy versus nodal observation are included in this guideline update. Key findings for the intermediate-thickness melanoma subgroup include no significant difference in MSS, but a benefit in terms of rate of recurrence within the primary tumor region for SLN biopsy versus observation. The prognostic significance of SLN biopsy has been established and incorporated into the AJCC staging system. This guideline update continues to recommend the SLN biopsy as a staging procedure that can help identify patients with intermediate-thickness melanoma who may benefit from adjuvant therapy.[32]

SLN biopsy has historically been more controversial within the population of patients with thick melanoma because these patients are more likely to develop systemic disease and thus not benefit from removal of regional lymph nodes. The updated MSLT-I results also demonstrated a 10-year advantage for recurrence rates in the thick-melanoma population. In this update, the ASCO-SSO panel reaffirms its recommendation that SLN biopsy be considered within this subgroup for staging purposes as well as the possible therapeutic effect of removing an involved node. These findings are also consistent with other retrospective studies that have shown a DFS benefit with SLN biopsy, but no overall survival advantage.[13,16]

In the previous ASCO guideline, SLN biopsy was not routinely recommended for patients with thin melanoma because of the low prevalence of nodal metastases within this group. In this guideline update (and in keeping with changes in the AJCC staging system), SLN biopsy may be considered in those with T1b lesions (0.8 mm to 1.0 mm thickness regardless of ulceration status or ulcerated melanoma < 0.8 mm) as they may be expected to have a higher rate of SLN metastases and may derive a benefit from more accurate staging.

Where there is a positive sentinel node, considerations around CLND are survival rates, regional disease control, and operative morbidity.[6] The risk of recurrence where there is a positive sentinel node and CLND is not performed is approximately 26% at 5 years.[33] The previous version of this guideline noted that we were awaiting the results of the MSLT-II trial comparing CLND to observation after a positive SLN biopsy. Initial published results of the tudy show no improvement in MSS with immediate CLND. Subgroup analysis did not indicate a group that was more likely to derive benefit. DFS was improved, though this was based on improved regional DFS, as there was no improvement in distant metastasis-free survival. There was a significant increase in lymphedema in the CLND arm relative to the observation arm. The pathologic status of non-SLNs had significant and independent prognostic value, which some may find useful in deciding whether to begin adjuvant therapy. In both the MSLT-II and DeCOG studies, the protocols included frequent follow-up evaluations and interval nodal ultrasonography as important components of close observation. Patients should have a thorough discussion of the risks and benefits of each approach when deciding which option to pursue. It is also important to note that the option of careful observation does not apply to patients who have an excision of a bulky node for diagnostic or therapeutic intent, and these data should not be extrapolated to this patient population.

Consideration of options following a positive SLN biopsy must be tempered by implications for enrollment into future clinical trials evaluating adjuvant systemic therapies. CLND is currently part of inclusion criteria for most major phase II/III trials at present, though it is anticipated that many protocols could be amended without jeopardizing the integrity of the primary survival end points to allow the alternative of close observation in the setting of new guideline recommendations.

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial/ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[34-37] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which

the patient may have two or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCC, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCC and highlights the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

Practice guidelines should provide information on how to apply the recommendations for patients with MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their health care costs through deductibles and coinsurance.[38] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments or regimens.[39,40]

Discussion of cost can be an important part of shared decision making.[41] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[41]

Patient out-of-pocket costs may vary depending on insurance coverage. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[41]

As part of the guideline development process, ASCO may opt to search the literature for published cost-effectiveness analyses that might inform the relative value of available treatment options. Excluded from consideration are cost-effective analyses that lack contemporary cost data and agents that are not currently available in either the United States or Canada, and/or are industry sponsored. The Expert Panel for this guideline is not aware of any existing cost effectiveness analyses related to the clinical questions on this topic.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*.

Related ASCO Guidelines

- Screening, Assessment, and Care of Anxiety and Depressive Symptoms in Adults With Cancer[42] (http://ascopubs.org/doi/10.1200/jco.2013.52.4611)
- Integration of Palliative Care Into Standard Oncology Practice[43] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Physician Communication[44] (http://ascopubs.org/doi/full/10.1200/JCO.2017.75.2311)

ADDITIONAL RESOURCES

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about quality of evidence and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/melanoma-guidelines and www.asco.org/guidelineswiki. Patient information is available at www.cancer.net. Visit www.asco.org/guidelineswiki to provide comments on the guideline or to submit new evidence.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Table A1. Sentinel Lymph Node Biopsy and Management of Regional Lymph Nodes in Melanoma Guideline Expert Panel Membership

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