

## FROM THE ACADEMY

# Guidelines of care for the management of primary cutaneous melanoma

Work Group: Christopher K. Bichakjian, MD,<sup>a</sup> Allan C. Halpern, MD (Co-chair),<sup>b</sup> Timothy M. Johnson, MD (Co-Chair),<sup>a</sup> Antoinette Foote Hood, MD,<sup>c</sup> James M. Grichnik, MD, PhD,<sup>d</sup> Susan M. Swetter, MD,<sup>e,f</sup> Hensin Tsao, MD, PhD,<sup>g</sup> Victoria Holloway Barbosa, MD,<sup>h</sup> Tsu-Yi Chuang, MD, MPH,<sup>i,j</sup> Madeleine Duvic, MD,<sup>k</sup> Vincent C. Ho, MD,<sup>l</sup> Arthur J. Sober, MD,<sup>g</sup> Karl R. Beutner, MD, PhD,<sup>m,n</sup> Reva Bhushan, PhD,<sup>o</sup> and Wendy Smith Begolka, MS<sup>o</sup>

*Ann Arbor, Michigan; New York, New York; Norfolk, Virginia; Miami, Florida; Palo Alto, Los Angeles, Palm Springs, San Francisco, and Fairfield, California; Boston, Massachusetts; Chicago and Schaumburg, Illinois; Houston, Texas; and Vancouver, British Columbia, Canada*

The incidence of primary cutaneous melanoma has been increasing dramatically for several decades. Melanoma accounts for the majority of skin cancer–related deaths, but treatment is nearly always curative with early detection of disease. In this update of the guidelines of care, we will discuss the treatment of patients with primary cutaneous melanoma. We will discuss biopsy techniques of a lesion clinically suspicious for melanoma and offer recommendations for the histopathologic interpretation of cutaneous melanoma. We will offer recommendations for the use of laboratory and imaging tests in the initial workup of patients with newly diagnosed melanoma and for follow-up of asymptomatic patients. With regard to treatment of primary cutaneous melanoma, we will provide recommendations for surgical margins and briefly discuss nonsurgical treatments. Finally, we will discuss the value and limitations of sentinel lymph node biopsy and offer recommendations for its use in patients with primary cutaneous melanoma. (J Am Acad Dermatol 10.1016/j.jaad.2011.04.031.)

**Key words:** biopsy; follow-up; melanoma; pathology report; sentinel lymph node biopsy; surgical margins.

## DISCLAIMER

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore, these guidelines should not be interpreted as setting a standard of care, or be deemed inclusive of all proper methods of care nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient,

### Abbreviations used:

AAD:	American Academy of Dermatology
AJCC:	American Joint Committee on Cancer
LND:	lymph node dissection
PET:	positron emission tomography
SLN:	sentinel lymph node
SLNB:	sentinel lymph node biopsy

and the known variability and biological behavior of the disease. This guideline reflects the best available data at the time the guideline was prepared.

From the Department of Dermatology, University of Michigan Health System and Comprehensive Cancer Center<sup>a</sup>; Department of Dermatology, Memorial Sloan-Kettering Cancer Center, New York<sup>b</sup>; Department of Dermatology, Eastern Virginia Medical School<sup>c</sup>; Department of Dermatology, University of Miami Health System, University of Miami Hospital and Clinics, Sylvester Comprehensive Cancer Center, Melanoma Program<sup>d</sup>; Department of Dermatology, Stanford University Medical Center<sup>e</sup> and Department of Veterans Affairs Palo Alto Health Care System<sup>f</sup>; Department of Dermatology, Massachusetts General Hospital and Harvard Medical School<sup>g</sup>; Department of Dermatology, Rush University Medical Center, Chicago<sup>h</sup>; University of Southern California, Los Angeles,<sup>i</sup> and Desert Oasis Healthcare, Palm Springs<sup>j</sup>; Department of Dermatology, University of Texas MD Anderson Cancer Center<sup>k</sup>; Division of Dermatology, University of British Columbia<sup>l</sup>; Department of

Dermatology, University of California, San Francisco<sup>m</sup>, and Solano Dermatology, Fairfield<sup>n</sup>; and American Academy of Dermatology, Schaumburg.<sup>o</sup>

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Reprint requests: Reva Bhushan, PhD, American Academy of Dermatology, 930 E Woodfield Rd, Schaumburg, IL 60173. E-mail: rbhushan@aad.org.

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The results of future studies may require revisions to the recommendations in this guideline to reflect new data.

## SCOPE

This guideline addresses the treatment of patients with primary cutaneous melanoma (including those in the nail unit), who may also have clinical or histologic evidence of regional disease, from the perspective of the US dermatologist. The guideline does not address primary melanoma of the mucous membranes. A discussion of adjuvant therapies for patients with high-risk melanoma (stage  $\geq$  IIB), such as interferon and radiation therapy, falls outside the scope of this guideline. Consultation with a physician or multidisciplinary group with specific expertise in melanoma, such as a medical oncologist, surgical oncologist, radiation oncologist, or dermatologist specializing in melanoma, should be considered for patients with high-risk melanoma. Finally, as an extensive discussion beyond the management of melanoma falls outside the scope of the current guidelines, the expert work group recommends that separate guidelines be developed on screening and surveillance for early detection, clinical diagnosis of primary cutaneous melanoma, and the molecular assessment of borderline/indeterminate melanocytic lesions.

## METHOD

A work group of recognized melanoma experts was convened to determine the audience and scope of the guideline, and identify important clinical questions in the management of primary cutaneous melanoma (Table I). Work group members completed a disclosure of commercial support that was updated throughout guideline development.

An evidence-based model was used and evidence was obtained using a search of the PubMed database spanning the years 2000 through 2010 for clinical questions addressed in the previous version of this guideline published in 2001, and 1960 to 2010 for all newly identified clinical questions. Only English-language publications were reviewed. Published guidelines on melanoma were also evaluated.<sup>1-3</sup>

The available evidence was evaluated using a unified system called the Strength of Recommendation Taxonomy developed by editors of the US family medicine and primary care journals (ie, *American Family Physician*, *Family Medicine*, *Journal of Family Practice*, and *BMJ USA*). This strategy was supported by a decision of the Clinical Guidelines Task Force in 2005 with some minor modifications for a consistent approach to rating the strength of the

**Table I.** Clinical questions used to structure evidence review for management of primary cutaneous melanoma

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What is the standard grading system for melanoma?
What clinical and histologic information is useful in the pathology report?
What are standard biopsy techniques?
What are recommended surgical margins stratified by grading system?
What is the effectiveness of sentinel node biopsy?*
What diagnostic laboratory and imaging tests are useful in asymptomatic patients with primary cutaneous melanoma?
What is the effectiveness of imiquimod?*
What is the effectiveness of cryotherapy?*
What is the effectiveness of radiation?*
What is effective for follow-up of asymptomatic patients with primary cutaneous melanoma to detect metastases and/or additional primary melanomas?
How long should asymptomatic patients be followed up?
What diagnostic and imaging tests are effective in follow-up of asymptomatic patients?

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\*New clinical questions for 2010 guideline.

evidence of scientific studies.<sup>4</sup> Evidence was graded using a 3-point scale based on the quality of methodology as follows:

- I. Good-quality patient-oriented evidence (ie, evidence measuring outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life).
- II. Limited-quality patient-oriented evidence.
- III. Other evidence including consensus guidelines, opinion, case studies, or disease-oriented evidence (ie, evidence measuring intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes).

Clinical recommendations were developed on the best available evidence tabled in the guideline. These are ranked as follows:

- A. Recommendation based on consistent and good-quality patient-oriented evidence.
- B. Recommendation based on inconsistent or limited-quality patient-oriented evidence.
- C. Recommendation based on consensus, opinion, case studies, or disease-oriented evidence.

In those situations where documented evidence-based data are not available, we have used expert opinion to generate our clinical recommendations. This guideline has been developed in accordance with the American Academy of Dermatology (AAD)/AAD Association "Administrative Regulations

for Evidence-based Clinical Practice Guidelines” (version approved March 2009), which include the opportunity for review and comment by the entire AAD membership and final review and approval by the AAD Board of Directors.

## DEFINITION

Primary cutaneous melanoma is defined as any primary melanoma lesion, regardless of tumor thickness, in patients without clinical or histologic evidence of regional or distant metastatic disease (stage 0-IIIC).

## INTRODUCTION

Since the last publication of the guidelines of care for primary cutaneous melanoma by the American Academy of Dermatology in 2001, the most significant changes in the management of primary melanoma are a result of the acknowledgment of the dermal mitotic rate as an important prognostic parameter.<sup>5,6</sup> This change is reflected in the recently published seventh edition of the American Joint Committee on Cancer (AJCC) staging system for melanoma, effective January 1, 2010 (Tables II and III).<sup>7</sup> In the new staging system, mitotic rate has replaced Clark level of invasion as the second factor predicting melanoma survival in addition to tumor (Breslow) thickness for tumors less than or equal to 1 mm in thickness.

Although nonsurgical treatments of primary melanoma, in particular lentigo maligna, have been increasingly used in recent years, their efficacy has not been established. Suggestions on the use of these alternative treatments have been included in the current guidelines.

A significant amount of data has become available on the use of sentinel lymph node (SLN) biopsy (SLNB) for melanoma since the previous guidelines. Although the procedure is not performed by dermatologists in the United States, the decision by a patient with melanoma to proceed with this staging procedure is frequently based on the advice from their dermatologist. Recommendations for the use of SLNB for primary melanoma are therefore included in the current guidelines. However, with regard to treatment recommendations, the current guidelines continue to be limited to the management of primary cutaneous melanoma. For patients with regional or distant metastases, we refer physicians to clinical practice guidelines, such as those developed by the National Comprehensive Cancer Network.<sup>1</sup>

## BIOPSY

The first step for a definitive diagnosis of cancer is a biopsy that may occur by removing part of the lesion (incisional biopsy) or the entire lesion (excisional biopsy). For a lesion clinically suspicious for cutaneous melanoma, one should ideally perform a narrow excisional biopsy that encompasses the entire breadth of the lesion with clinically negative margins to a depth sufficient to ensure that the lesion is not transected.<sup>8-18</sup> It has been suggested that 1- to 3-mm margins are required to clear the subclinical component of most atypical melanocytic lesions.<sup>1,3,19</sup> This can be accomplished in a number of ways including elliptical or punch excision with sutures, or shave removal to a depth below the anticipated plane of the lesion. The latter is commonly used when the suspicion of melanoma is low, the lesion lends itself to complete removal by this technique, or in the setting of a macular lesion suspicious for lentigo maligna where a broad biopsy specimen may aid in histologic assessment.<sup>11,13</sup>

Clinically clear but narrow lateral margins on excisional biopsy, oriented along the longitudinal axis on extremities, will permit optimal subsequent wide local excision and, if indicated, SLNB. Incisional biopsy, with a variety of techniques noted above, of the clinically or dermatoscopically most atypical portion of the lesion, is an acceptable option in certain circumstances, such as a facial or acral location, low clinical suspicion or uncertainty of diagnosis, or a very large lesion, although the selected area may not always correlate with the deepest Breslow depth.<sup>9</sup> If an incisional biopsy specimen is inadequate to make a histologic diagnosis or to accurately microstage the lesion for treatment planning, a repeat biopsy should be performed.<sup>9</sup>

When a biopsy is performed of a suspicious nail lesion (melanonychia striata, diffuse pigmentation, or amelanotic changes, eg, ulceration), the nail matrix should be sampled. Because of the complexity of nail anatomy and the fact that melanoma arises in the nail matrix, suspicious nail lesions are best evaluated and sampled by a physician skilled in the biopsy of the nail apparatus. For suspicious subungual lesions, the nail plate should be sufficiently removed to expose the underlying lesion and an excisional or incisional biopsy should be performed based on the size of the lesion. Recommendations for the use of a biopsy for primary cutaneous melanoma are summarized in Table IV. The strength of these recommendations is shown in Table V.

**Table II.** 2010 American Joint Committee on Cancer TNM definitions

Primary tumor (T)		
TX	Primary tumor cannot be assessed (eg, curettaged or severely regressed melanoma)	
T0	No evidence of primary tumor	
Tis	Melanoma in situ	
T1	Melanomas $\leq 1.0$ mm in thickness	
T2	Melanomas 1.01-2.0 mm	
T3	Melanomas 2.01-4.0 mm	
T4	Melanomas $>4.0$ mm	
<i>Note: a and b subcategories of T are assigned based on ulceration and No. of mitoses per mm<sup>2</sup> as shown below:</i>		
T classification	Thickness, mm	Ulceration status/mitoses
T1	$\leq 1.0$	a: Without ulceration and $<1$ mitosis/mm <sup>2</sup> b: With ulceration or $\geq 1$ mitosis/mm <sup>2</sup>
T2	1.01-2.0	a: Without ulceration b: With ulceration
T3	2.01-4.0	a: Without ulceration b: With ulceration
T4	$>4.0$	a: Without ulceration b: With ulceration
Regional lymph nodes (N)		
NX	Patients in whom regional lymph nodes cannot be assessed (eg, previously removed for another reason)	
N0	No regional metastases detected	
N1-3	Regional metastases based on No. of metastatic nodes and presence or absence of intralymphatic metastases (in transit or satellite)	
<i>Note: N1-3 and a-c subcategories assigned as shown below:</i>		
N classification	No. of metastatic nodes	Nodal metastatic mass
N1	1 Node	a: Micrometastasis* b: Macrometastasis <sup>†</sup>
N2	2-3 Nodes	a: Micrometastasis* b: Macrometastasis <sup>†</sup> c: In transit met(s)/satellite(s) <i>without</i> metastatic nodes
N3	$\geq 4$ Metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) <i>with</i> metastatic node(s)	
Distant metastasis (M)		
M0	No detectable evidence of distant metastases	
M1a	Metastases to skin, subcutaneous, or distant lymph nodes	
M1b	Metastases to lung	
M1c	Metastases to all other visceral sites or distant metastases to any site combined with elevated serum LDH	
<i>Note: Serum LDH is incorporated into M category as shown below:</i>		
M classification	Site	Serum LDH
M1a	Distant skin, subcutaneous or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

LDH, Lactate dehydrogenase.

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\*Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed).

<sup>†</sup>Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

## **PATHOLOGY REPORT**

When a biopsy is performed of a lesion clinically suspicious for primary cutaneous melanoma, the expert work group recommends that the following

pertinent information is provided to the pathologist (Table VI; strength of recommendations shown in Table V). For identification purposes, the age and gender of the patient and the anatomic location of

**Table III.** 2010 American Joint Committee on Cancer anatomic stage/prognostic groups

Clinical staging*			Pathologic staging†				
<b>Stage 0</b>	Tis	N0	M0	<b>0</b>	Tis	N0	M0
<b>Stage IA</b>	T1a	N0	M0	<b>IA</b>	T1a	N0	M0
<b>Stage IB</b>	T1b	N0	M0	<b>IB</b>	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
<b>Stage IIA</b>	T2b	N0	M0	<b>IIA</b>	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
<b>Stage IIB</b>	T3b	N0	M0	<b>IIB</b>	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
<b>Stage IIC</b>	T4b	N0	M0	<b>IIC</b>	T4b	N0	M0
<b>Stage III</b>	Any T	≥ N1	M0	<b>IIIA</b>	T1-4a	N1a	M0
					T1-4a	N2a	M0
					T1-4b	N1a	M0
				<b>IIIB</b>	T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a	N2c	M0
				<b>IIIC</b>	T1-4b	N1b	M0
					T1-4b	N2b	M0
					T1-4b	N2c	M0
					Any T	N3	M0
<b>Stage IV</b>	Any T	Any N	M1	<b>IV</b>	Any T	Any N	M1

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\*Clinical staging includes microstaging of primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of primary melanoma with clinical assessment for regional and distant metastases.

†Pathologic staging includes microstaging of primary melanoma and pathologic information about regional lymph nodes after partial or complete lymphadenectomy. Patients with pathologic stage 0 or IA are the exception; they do not require pathologic evaluation of their lymph nodes.

the lesion must be included.<sup>20-34</sup> The clinical information in the pathology report should contain the type of surgical procedure performed (ie, biopsy intent—excisional or incisional) and size of the lesion. Additional optional, but desirable, clinical information include ABCDE criteria, dermatoscopic features, a clinical photograph, and the presence or absence of macroscopic satellitosis.

The pathology of melanocytic tumors should be read by a physician experienced in the interpretation of pigmented lesions. The list of histologic features to be included in the pathology report is based on their prognostic value (Table VII; strength of recommendations shown in Table V). Definitions of histologic features are listed in Table VIII. There is strong evidence to support that 3 histologic features are the most important characteristics of the primary tumor to predict outcome.<sup>6,20-23,25,26,30-32,34-40</sup> (1) Maximum tumor (Breslow) thickness is measured from the

**Table IV.** Recommendations for biopsy

Preferred biopsy technique is narrow excisional biopsy that encompasses entire breadth of lesion with clinically negative margins to depth sufficient to ensure that lesion is not transected, which may be accomplished by elliptical or punch excision with sutures, or shave removal to depth below anticipated plane of lesion. Partial sampling (incisional biopsy) is acceptable in select clinical circumstances such as facial or acral location, low clinical suspicion or uncertainty of diagnosis, or very large lesion. Repeat biopsy is recommended if initial biopsy specimen is inadequate for diagnosis or microstaging of primary lesion.

granular layer of the overlying epidermis or base of a superficial ulceration to the deepest malignant cells invading dermis to the nearest 0.1 mm, not including deeper adventitial extension. Microsatellitosis should not be included in this measurement, but commented on separately. (2) Presence or absence of microscopic ulceration, which is defined as tumor-induced full-thickness loss of epidermis with subjacent dermal tumor and reactive dermal changes.<sup>41</sup> (3) Mitotic rate, measured as the number of dermal mitoses per mm<sup>2</sup> (with 1 mm<sup>2</sup> approximately equal to 4.5 high-power [×40] microscopic fields, starting in the field with most mitoses), was included as a prognostic value in the 2010 AJCC staging system to upstage patients with melanoma less than or equal to 1 mm in thickness from IA to IB, replacing Clark level.<sup>6</sup> Regardless of tumor thickness, a dermal mitotic rate greater than or equal to 1 mitosis/mm<sup>2</sup> is independently associated with a worse disease-specific survival. It is essential that these 3 characteristics are included in the pathology report. The anatomic (Clark) level of invasion is only included in the 2010 AJCC staging system for staging tumors less than or equal to 1 mm in thickness when mitotic rate cannot be assessed and is considered optional for tumors larger than 1 mm. An additional essential element of the pathology report is the status of the peripheral and deep margins (positive or negative) of the excision. The presence or absence of tumor at the surgical margin indicates whether the entire lesion was available for histologic evaluation and provides guidance for further management. It should be emphasized that for the management of primary cutaneous melanoma, treatment recommendations are based on the clinical measurement of surgical margins around the tumor and not on histologically measured clear peripheral margins.<sup>1</sup> The presence of microsatellites upstages the tumor to N2c (stage IIIB)

**Table V.** Strength of recommendations for management of primary cutaneous melanoma

	Strength of recommendation	Level of evidence	References
Biopsy	B	II	8-18
Pathology report:			
Clinical information	A	I-II	20-34
Tumor (Breslow) thickness	A	I-II	6,20-23,25,27-32,34,36-38,40,41,46-48
Ulceration	A	I-II	6,20,27,29,30,34,36,37,40,41
Mitotic rate	A	I-II	6,23,24,26,27,34,35,37,39,40
Level of invasion (Clark)	B	II	6,21,23-25,27,33-35,37,38,46
Microsatellitosis	B	I-II	6,27,37,42-44
Angiolymphatic invasion	B	II	27,33,37,40
Histologic subtype	B	II	23,25,28,31,37,40
Regression	B	II	21,23,35,37,48
Tumor-infiltrating lymphocytes	B	II	21,23,25,35,46,47
Staging workup	B	II-III	53-58,63,65,67,68,85
Follow-up:			
Interval	B	II	58,75,76,79
Duration	B	II	73-75,77,78
Patient skin/self-examination	B	II	83,84
Imaging and laboratory tests	B	II	58,64,66,76,86,87
Surgical management:			
In situ	C	III	No clinical trials
≤ 1.0-mm thickness	A	I	91,92,94-97
1.01- to 2-mm thickness	A	I	30,90-92,94-97,100,101
>2-mm thickness	B	I-III	30,100-102
Nonsurgical treatments:			
Imiquimod	C	III	108-112
Radiotherapy	C	III	113-116
Cryosurgery	C	III	117-121
Sentinel lymph node biopsy	B	I-III	6,123-125,130,131,133-141,143

**Table VI.** Recommended clinical information to be provided to pathologist

Essential	Strongly recommended	Optional
Age of patient	Biopsy technique (excisional or incisional)	Clinical description and level of clinical suspicion
Gender	Size of lesion	Dermatoscopic features
Anatomic location		Photograph
		Macroscopic satellitosis

melanoma according to the 2010 AJCC staging criteria and therefore must also be reported.<sup>27,37,42-44</sup>

There is evidence that several other histologic features of a primary melanoma provide prognostic value, including the presence or absence of a vertical growth phase, tumor-infiltrating lymphocytes, dermal regression, and angiolymphatic invasion.<sup>21,23,27,33,35,37,38,45-48</sup> Although not essential, the expert work group recommends that these histologic characteristics are included as optional elements of

**Table VII.** Recommended histologic features of primary melanoma to be included in pathology report

Essential	Optional
Tumor (Breslow) thickness, mm	Angiolymphatic invasion
Ulceration	Histologic subtype
Dermal mitotic rate, mitoses/mm <sup>2</sup>	Neurotropism
Peripheral and deep margin status (positive or negative)	Regression
Anatomic level of invasion (Clark level)*	T-stage classification
Microsatellitosis	Tumor infiltrating lymphocytes
	Vertical growth phase

\*Essential for staging only in tumors ≤ 1 mm in thickness when mitotic rate cannot be assessed; optional for tumors > 1 mm in thickness.

the pathology report. The prognostic value of the histologic subtype of melanoma has not been established, with some notable exceptions.<sup>31</sup> The lentigo maligna pattern is associated with broader

**Table VIII.** Definitions of histologic features

Clark levels	
Level I	Tumor confined to epidermis
Level II	Tumor present in papillary dermis
Level III	Tumor fills papillary dermis
Level IV	Tumor present in reticular dermis
Level V	Tumor present in subcutis
Vertical growth phase	Presence of $\geq 1$ clusters of dermal tumor cells larger than largest epidermal tumor cluster and/or presence of any dermal mitotic activity
Tumor regression	Apparent loss of dermal tumor with associated nonlamellar fibrosis, mononuclear cell inflammation, and vascular proliferation or ectasia
Microsatellitosis	Nest(s) of tumor cells ( $>0.05$ mm in diameter) located in reticular dermis, subcutis, or vessels, separated from invasive component of tumor by $\geq 0.3$ mm of normal tissue

superficial subclinical extension, often requiring wider surgical margins to clear histologically.<sup>49,50</sup> In addition, there is some evidence to support that primary melanomas with a purely desmoplastic histologic subtype have a lower risk of nodal and distant metastases, but potentially higher risk of local recurrence.<sup>51,52</sup> The expert work group recommends that histologic subtype be included in the optional list of elements of the pathology report. Although the prognostic value of neurotropism is uncertain, its presence or absence provides valuable information that may alter future management of the primary tumor and is therefore included as an additional optional histologic characteristic to be reported.<sup>27,42-44</sup>

Finally, reporting microscopic features in a synoptic report provides a level of completeness and standardization, which is strongly encouraged by the expert work group (Table IX).

## STAGING WORKUP AND FOLLOW-UP

### Initial workup for patients with newly diagnosed cutaneous melanoma

After the diagnosis of melanoma has been histologically confirmed, a thorough history and physical examination comprise the cornerstone of the initial diagnostic workup of a patient with newly diagnosed cutaneous melanoma. For invasive disease, a

**Table IX.** Synoptic melanoma report

Diagnosis	
Tumor (Breslow) thickness	mm
Ulceration	Present or absent
Dermal mitotic rate	Mitoses per mm <sup>2</sup> or dermal tumor volume $<1$ mm <sup>2</sup>
Margins (peripheral and deep)	Positive or negative
Anatomic (Clark) level of invasion	Level II-V
Histologic subtype	Superficial spreading, nodular, lentigo maligna, acral lentiginous, desmoplastic/neurotropic, nevoid, or other
Perineural involvement	Present or absent
Regression	Present or absent
T-stage classification	T1a-T4b
Tumor infiltrating lymphocytes	Not identified, nonbrisk, or brisk
Vertical growth phase	Present or absent

detailed patient history should include a focused review of systems with particular attention to constitutional, neurologic, respiratory, hepatic, gastrointestinal, musculoskeletal, skin, and lymphatic signs or symptoms. The physical examination should include a total body skin examination and palpation of both regional and distant lymph node basins. Any abnormal finding should direct the need for further studies to detect regional and distant metastases.

In asymptomatic patients with localized cutaneous melanoma of any thickness, baseline blood tests and imaging studies are generally not recommended and should only be performed as clinically indicated for suspicious signs and symptoms. Currently available treatment for patients with asymptomatic stage IV disease is not associated with better outcomes than intervention when the patient becomes symptomatic. Furthermore, screening blood tests, including serum lactate dehydrogenase, are insensitive for the detection of metastatic disease.<sup>53</sup> The use of routine imaging studies is limited by a very low yield and the frequent occurrence of false-positive findings.<sup>54,55</sup> Ample evidence exists that a routine chest x-ray is a cost-inefficient test for the detection of metastatic disease with a consistent relatively high false-positive rate.<sup>53,56-59</sup> Although cross-sectional imaging by computed tomography is equally limited by a low detection rate of occult metastases and relatively high false-positive rate, the increased dose of ionizing radiation associated with repeated tests also needs to be considered.<sup>57,60</sup> Positron emission tomography (PET) has gained increasing popularity in recent years, particularly for detection of distant

metastatic disease. However, both PET and ultrasound have been found to have a low sensitivity for the detection of occult regional nodal metastases in comparison with SLNB.<sup>61-66</sup> The impact of false-positive findings, whether by PET, computed tomography, chest x-ray, or lactate dehydrogenase, that lead to unnecessary invasive procedures and substantial patient anxiety, should not be underestimated.

In patients with micrometastatic nodal disease detected by SLNB, the yield of screening computed tomography or PET scans remains low, ranging from 0.5% to 3.7%, with the majority of true positive findings detected in patients with thick, ulcerated primary melanomas or large tumor burden in the SLN(s).<sup>55,67-69</sup> The detection rate of occult distant metastases is somewhat higher in patients presenting with clinically detectable nodal disease.<sup>70-72</sup> The detection of widespread metastatic disease may alter patient treatment and obviate the need for extensive surgery. After diagnosis, consultation with a medical oncologist or other melanoma specialist should be considered for patients at higher risk of disease relapse based on disease stage, tumor thickness, ulceration, SLN status, or a combination of these.

#### Follow-up of asymptomatic patients with cutaneous melanoma

The primary goal for follow-up of patients with a history of cutaneous melanoma is early detection of surgically resectable recurrent disease and additional primary melanoma.<sup>73-79</sup> It is generally accepted that early detection of asymptomatic distant metastatic disease does not affect overall survival.<sup>80-82</sup> No strong evidence exists to support a specific follow-up interval for patients with melanoma at any stage. The expert work group recommends at least annual follow-up, ranging from every 3 to 12 months based on the risk for recurrence and new primary melanoma. Additional factors that may influence the follow-up interval include disease stage, a history of multiple primary melanomas, the presence of clinically atypical nevi, a family history of melanoma, patient anxiety, and the patient's awareness and ability to detect early signs and symptoms of disease. All patients with a history of cutaneous melanoma should be educated about monthly self-examinations of their skin.<sup>83,84</sup> If appropriate, patients can be instructed in monthly self-examination for the detection of regional lymph node enlargement.

Clinical examination remains the most important means of detecting local, regional, or distant disease. A comprehensive history and physical examination with emphasis on the skin and lymph nodes form the

#### Table X. Recommendations for staging workup and follow-up

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Baseline laboratory tests and imaging studies are generally not recommended in asymptomatic patients with newly diagnosed primary melanoma of any thickness. No clear data regarding follow-up interval exist, but at least annual history and physical examination with attention to skin and lymph nodes is recommended. Regular clinical follow-up and interval patient self-examination of skin and regional lymph nodes are most important means of detecting recurrent disease or new primary melanoma; findings from history and physical examination should direct need for further studies to detect local, regional, and distant metastasis. Surveillance laboratory tests and imaging studies in asymptomatic patients with melanoma have low yield for detection of metastatic disease and are associated with relatively high false-positive rates.

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most important components of follow-up for patients with melanoma after surgical resection. A low threshold should exist for sign- or symptom-directed workup to detect metastatic disease. However, routine surveillance laboratory tests or imaging studies are generally not useful and not recommended in asymptomatic patients.<sup>85-87</sup> Serum lactate dehydrogenase is almost never the sole indicator of metastatic disease, but is a highly significant predictor of survival in patients with stage IV disease.<sup>88,89</sup> Although surveillance imaging studies can be considered in patients at higher risk for recurrence (stage IIB and above), the yield remains low in asymptomatic patients with a relatively high false-positivity rate and is not recommended beyond 5 years. Recommendations for staging workup and follow-up for primary cutaneous melanoma are summarized in Table X and the strength of recommendations is shown in Table V.

#### SURGICAL MANAGEMENT

The primary treatment modality for cutaneous melanoma is surgical excision. After the diagnosis of melanoma has been histologically confirmed and the primary lesion has been adequately microstaged, a wider and frequently deeper excision is needed to ensure complete removal. It is recognized that melanoma cells may extend subclinically several millimeters to several centimeters beyond the clinically visible lesion. Recommended surgical margins are based partly on prospective randomized controlled trials and partly on consensus opinion when no prospective data exist.<sup>1</sup> The primary goal of surgical excision of melanoma of any thickness is to achieve histologically negative margins and prevent local



**Table XI.** Surgical margin recommendations for primary cutaneous melanoma

Tumor thickness	Clinically measured surgical margin*
In situ	0.5-1.0 cm
≤ 1.0 mm	1 cm
1.01-2.0 mm	1-2 cm
>2.0 mm	2 cm

\*Wider margins may be necessary for lentigo maligna subtype.

recurrence because of persistent disease. It is essential to recognize that surgical margin recommendations are based on studies in which margins were clinically measured around the primary tumor and may not correlate with histologically measured tumor-free margins. Nonsurgical treatment modalities are discussed under adjunctive therapies.

Specific surgical margin recommendations for primary invasive melanoma are based on 3 concepts (Table XI): (1) wide excision is associated with a reduced risk of local recurrence; (2) there is no convincing evidence in thin melanomas to confirm an improvement in survival or local recurrence rate with excision margins exceeding 1 cm; and (3) no convincing evidence exists for primary melanoma of any thickness, that excision with greater than 2-cm margins offers any benefit in terms of overall survival or local recurrence.<sup>90</sup> The expert work group therefore recommends that surgical margins for invasive melanoma should be at least 1 cm and no more than 2 cm clinically measured around the primary tumor. Although very limited data exist on excision of primary invasive melanoma less than or equal to 1.0 mm in thickness, wide excision with 1 cm margin is recommended.<sup>91-93</sup> Based on available evidence and consensus opinion, the expert work group recommends that primary melanomas 1.01 to 2.0 mm in thickness are widely excised with 1- to 2-cm margins. However, clear evidence is not available and final surgical margins may vary based on tumor location and functional or cosmetic considerations.<sup>90,94-97</sup> In melanomas thicker than 2.0 mm, one study found that narrow excision with 1-cm margin was associated with a somewhat higher combined local, regional, and nodal recurrence rate than wider excision with 3-cm margin.<sup>98</sup> There was, however, no significant difference in true local recurrence rate, melanoma-specific, or overall survival. Several other studies have found slightly higher local recurrence rates for melanomas thicker than 1 mm treated with narrow excision with a 1-cm margin versus a wider excision with a 3-cm margin.<sup>91,94</sup> For thick primary melanomas, most studies have failed to show a benefit with surgical margins

greater than 2 cm.<sup>99-102</sup> It is therefore recommended that primary melanomas greater than 2.0 mm in thickness are widely excised with 2-cm margins. Although the recommended depth of a therapeutic excision for invasive primary cutaneous melanoma has always been to the level of muscle fascia, no unequivocal evidence exists to support that this is necessary in every circumstance such as anatomic locations with an increased adipose layer. The expert work group recommends that, whenever possible, excision is performed to the level of muscle fascia, or at least deep adipose tissue depending on the location of the tumor.

No prospectively controlled data on excision margins for melanoma in situ are available. Based on consensus opinion, wide excision with 0.5- to 1.0-cm margin has been recommended.<sup>1</sup> However, because of the characteristic, potentially extensive, subclinical extension of melanoma in situ, lentigo maligna type, alternative surgical approaches may be considered. Particularly for larger lesions on the head and neck, greater than 0.5-cm margins may be necessary to achieve negative margins.<sup>49,50,103</sup> Examination with a Wood lamp may be helpful in the presurgical assessment of subclinical extension. Contralateral sampling by punch biopsy may help distinguish true atypical junctional melanocytic hyperplasia from background actinic damage. Careful histologic evaluation of surgical margins is strongly recommended. Various techniques to achieve complete histologic margin control have been described including, but not limited to permanent section total peripheral margin control and Mohs micrographic surgery.<sup>49,50,104-106</sup> No prospective randomized data are available to make specific recommendations. However, referral for more exhaustive histologic margin assessment may be considered when extensive subclinical extension is suspected. For both in situ and invasive melanoma, permanent paraffin sections rather than frozen sections are considered the gold standard for histologic evaluation of surgical margins of melanocytic lesions.<sup>107</sup> Recommendations for surgical management are summarized in Table XII and the strength of recommendations is shown in Table V.

## NONSURGICAL TREATMENTS FOR LENTIGO MALIGNA

For all stages of primary cutaneous melanoma, from in situ disease to a deeply invasive tumor, surgical excision remains the standard of care. However, for the treatment of lentigo maligna alternative therapies may be considered when surgery is not a reasonable option because of patient comorbidities or preferences. The limitations of all

**Table XII.** Recommendations for surgical management

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Treatment of choice for primary cutaneous melanoma of any thickness is surgical excision with histologically negative margins.

Surgical margins for invasive melanoma should be at least 1 cm and no more than 2 cm clinically measured around primary tumor; clinically measured surgical margins do not need to correlate with histologically negative margins.

For melanoma in situ, wide excision with 0.5- to 1.0-cm margins is recommended; lentigo maligna histologic subtype may require >0.5-cm margins to achieve histologically negative margins, because of characteristically broad subclinical extension.

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nonsurgical treatment modalities must clearly be discussed with patients when considering any alternative therapies, including the risk of missing and undertreating invasive melanoma by not microstaging the primary lesion; higher local recurrence rates because of a lack of margin control; and the absence of long-term, randomized, controlled comparative studies.

The off-label use of topical imiquimod has been proposed as an alternative treatment to surgery, and an adjunctive modality after surgical excision.<sup>108-112</sup> Studies are limited by highly variable treatment regimens and lack of long-term follow-up with an average of approximately 18 months. Histologic verification after treatment has shown persistent disease in approximately 25% of treated patients and progression to invasive melanoma has been noted. As an adjunctive modality after surgical excision, the efficacy of topical imiquimod has not been established. High cost of treatment, an appropriate low threshold for subsequent biopsy to exclude residual or recurrent disease, and the risk of a severe inflammatory reaction should be taken into account when considering imiquimod.

Primary radiation therapy for lentigo maligna, with or without prior excision of a nodular component of lentigo maligna melanoma, may be considered when complete surgical excision is not a realistic option.<sup>113-116</sup> Reported clinical recurrence rates after radiation therapy range from 0% to 14%. Histologic confirmation of tumor clearance after radiation therapy has not been well documented. Cryosurgery for lentigo maligna has not been adequately studied, but also represents an alternative option. A clinical clearance rate of 60% or higher after cryotherapy has been documented, but data are insufficient to determine a histologic clearance rate.<sup>117-121</sup>

**Table XIII.** Recommendations for nonsurgical treatments

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Nonsurgical therapy for primary cutaneous melanoma should only be considered under select clinical circumstances, when surgical excision is not feasible. Alternatives to surgery include topical imiquimod, radiation therapy, cryosurgery, and observation. Efficacy of nonsurgical therapies for lentigo maligna has not been fully established.

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When surgery for lentigo maligna is not possible, observation may also be acceptable. Although it is reasonable to assume that therapy aimed at decreasing tumor burden may improve outcome, none of the above-mentioned alternative treatment modalities have been shown to be superior to observation. Recommendations for nonsurgical treatments are summarized in Table XIII and the strength of recommendations is shown in Table V.

### SLNB

Lymphatic mapping by lymphoscintigraphy and intraoperative injection of radioisotope and/or blue dye is used to identify the lymph node immediately downstream from the primary tumor.<sup>122-125</sup> Histologic examination of the first (sentinel) lymph node(s) identified with this technique has been demonstrated to identify the presence or absence of metastatic cells in the entire lymph node basin with a high degree of accuracy.<sup>126</sup> This procedure is considered the most sensitive and specific staging test for the detection of micrometastatic melanoma in regional lymph nodes.<sup>127-129</sup> This procedure is not without controversy, but is widely accepted as a component of the treatment of a subset of patients with melanoma, and is incorporated in AJCC staging. The available evidence supports SLN status as the most important prognostic factor for disease-specific survival of patients with melanoma greater than 1 mm in thickness.<sup>126,130,131</sup> Whether early detection of occult nodal disease provides greater regional control has not been definitively shown, but available evidence suggests a lower rate of postoperative complications in patients who underwent completion lymph node dissection (LND) for micrometastatic disease detected by SLNB, compared with those who underwent therapeutic LND for clinically palpable disease.<sup>132</sup> The current data from the prospective, randomized Multicenter Selective Lymphadenectomy Trial-I comparing SLNB with observation, showed no significant difference in overall survival.<sup>133</sup> Subgroup analysis of all patients with nodal metastases revealed higher 5-year

**Table XIV.** Recommendations for sentinel lymph node biopsy

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Status of SLN is most important prognostic indicator for disease-specific survival in patients with primary cutaneous melanoma; impact of SLNB on overall survival remains unclear.

SLNB is not recommended for patients with melanoma in situ or T1a melanoma.

SLNB should be considered in patients with melanoma >1 mm in tumor thickness.

In patients with T1b melanoma, 0.76-1.00 mm in tumor thickness, SLNB should be discussed; in T1b melanoma, with tumor thickness  $\leq 0.75$  mm, SLNB should generally not be considered, unless other adverse parameters in addition to ulceration or increased mitotic rate are present, such as angiolymphatic invasion, positive deep margin, or young age.

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SLN, Sentinel lymph node; SLNB, sentinel lymph node biopsy.

survival in patients who underwent completion LND for a positive SLNB, compared with those who underwent delayed therapeutic LND once palpable nodal disease developed. Whether completion LND is necessary for all patients with a positive SLNB is currently being investigated in Multicenter Selective Lymphadenectomy Trial-II.<sup>134-136</sup>

The overall rate of SLN positivity among patients with intermediate depth melanoma is approximately 15% to 20%, which decreases significantly when tumor thickness is less than 1 mm.<sup>137-141</sup> Because of a significant risk of regional micrometastatic disease with a tumor thickness greater than 1 mm, SLNB should be considered. For lesions less than 1 mm, various negative prognostic attributes have been used to identify a subset of patients whose risk of micrometastasis justifies SLNB. More caution is appropriate when considering this technique for these patients at lower risk.

Patients with T1a melanoma, or T1b melanoma less than or equal to 0.5 mm in tumor thickness, have a very low risk of nodal micrometastasis and approximately equal 5-year survival around 97%.<sup>6</sup> A noteworthy category is composed of patients with T1b melanoma greater than or equal to 0.76 mm in tumor thickness, in whom the risk of occult nodal disease increases to approximately 10%.<sup>6</sup> Data from the 2010 AJCC staging system demonstrate that SLN positivity correlates with mitotic rate as a continuous variable, and an increasing mitotic rate should therefore be viewed with greater concern for nodal metastasis. Hence, a melanoma 0.5 to 0.75 mm in thickness with 2 or more mitoses/mm<sup>2</sup>, particularly in the presence of additional adverse parameters, may have a risk of nodal micrometastasis that could

justify SLNB. Conversely, a melanoma 0.76 to 1.00 mm in tumor thickness with a mitotic rate of exactly 1 mitosis/mm<sup>2</sup> still has a relatively low risk of nodal metastasis. In patients with stage I or II melanoma, additional adverse factors outside the AJCC staging system with prognostic significance with regard to SLN positivity include angiolymphatic invasion, positive deep margin, and younger age.<sup>45</sup> Contrary to previously held beliefs that overall survival in patients with melanoma greater than or equal to 4 mm in tumor thickness (T4) is determined by high rates of distant metastasis irrespective of nodal status, SLNB remains a strong independent predictor of outcome in these patients.<sup>130,131,142,143</sup>

It is advisable to discuss with all patients given the diagnosis of primary cutaneous invasive melanoma whether SLNB is indicated. If a patient is a candidate for the procedure, the value, cost, complications, and limitations should be discussed in detail. When appropriate, the patient should be referred to a team of physicians with experience in the surgical, radiologic, and pathological aspects of SLNB. The decision not to proceed with SLNB may be based on significant comorbidities, patient preference, or other factors. Recommendations for the use of SLNB are summarized in Table XIV and the strength of recommendations is shown in Table V.

**GAPS IN RESEARCH**

In review of the currently available highest level evidence, the expert work group acknowledges that although much is known about the management of primary cutaneous melanoma, much has yet to be learned. Significant gaps in research were identified, including but not limited to the standardization of the interpretation of mitotic rate; placebo-controlled trials for the treatment of lentigo maligna; the use and value of dermatoscopy and other imaging modalities; the clinical and prognostic significance of the use of biomarkers and mutational analysis; and the use of SLNB. Because of these and other gaps in knowledge, the recommendations provided by the expert work group are occasionally based on consensus expert opinion, rather than high-level evidence as indicated in Table V. Management of primary cutaneous melanoma should therefore always be tailored to meet individual patients' needs.

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