Guidelines of care for the management of primary cutaneous melanoma

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The incidence of primary cutaneous melanoma continues to increase each year. Melanoma accounts for the majority of skin cancer—related deaths, but treatment is usually curative following early detection of disease. In this American Academy of Dermatology clinical practice guideline, updated treatment

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recommendations are provided for patients with primary cutaneous melanoma (American Joint Committee on Cancer stages 0-IIC and pathologic stage III by virtue of a positive sentinel lymph node biopsy). Biopsy techniques for a lesion that is clinically suggestive of melanoma are reviewed, as are recommendations for the histopathologic interpretation of cutaneous melanoma. The use of laboratory, molecular, and imaging tests is examined in the initial work-up of patients with newly diagnosed melanoma and for follow-up of asymptomatic patients. With regard to treatment of primary cutaneous melanoma, recommendations for surgical margins and the concepts of staged excision (including Mohs micrographic surgery) and nonsurgical treatments for melanoma in situ, lentigo maligna type (including topical imiquimod and radiation therapy), are updated. The role of sentinel lymph node biopsy as a staging technique for cutaneous melanoma is described, with recommendations for its use in clinical practice. Finally, current data regarding pregnancy and melanoma, genetic testing for familial melanoma, and management of dermatologic toxicities related to novel targeted agents and immunotherapies for patients with advanced disease are summarized. (J Am Acad Dermatol 2019;80:208-50.)

Key words: biopsy; follow-up; genetic counseling; imiquimod; melanoma; Mohs micrographic surgery; molecular techniques; pathology report; pregnancy; nonsurgical techniques; radiation therapy; sentinel lymph node biopsy; skin toxicities; surgical margins; staged excision; treatment.

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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, and the known variability and biologic behavior of the disease. This guideline reflects the best available data at the time the guideline was prepared. 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 pediatric, adolescent, and adult patients with American Joint Committee on Cancer (AJCC) clinical stages 0 to IIC primary cutaneous melanoma (CM), including melanomas arising from the nail unit, who may also have histologic evidence of regional nodal disease at presentation via sentinel lymph node biopsy (SLNB), from the perspective of the US dermatologist and other practitioners who treat melanoma. The guideline does not address primary melanoma of the mucous membranes or uveal melanoma. Topics related to melanoma prevention, screening/early detection, and diagnosis and management of atypical/dysplastic nevi and atypical Spitz tumors are beyond the scope of the guideline, as is discussion of the management of nodal, in-transit, and distant metastasis, histopathologic and immunohistochemical analysis and pathologic reporting of sentinel lymph node (SLN) specimens, and the use of available systemic adjuvant therapies or those being investigated for patients with CM who are at higher risk of metastasis (generally, AJCC stage IIB and IIC). Consultation with a physician or multidisciplinary group with specific expertise in melanoma, such as a medical oncologist, surgical oncologist, radiation oncologist, and/or dermatologist specializing in melanoma, should be considered for patients with high-risk CM.

METHOD

A multidisciplinary work group (WG) consisting of academic melanoma specialists in cutaneous, medical, and surgical oncology, dermatopathology, Mohs micrographic surgery (MMS), and cutaneous surgery, as well as representatives from private practice and a patient advocacy organization, was convened to update and expand on the previously published 2011 AAD melanoma clinical

Abbreviations used:

AAD:	American Academy of Dermatology
AJCC:	American Joint Committee on Cancer
ART:	assisted reproductive technology
BRAFI:	B-Raf proto-oncogene, serine/threonine kinase inhibitor
CPG:	clinical practice guideline
CLND:	completion lymph node dissection
CM:	cutaneous melanoma
cSCC:	cutaneous squamous cell carcinoma
CT:	computed tomography
FDA:	US Food and Drug Administration
GEP:	gene expression profiling
HRT:	hormone replacement therapy
LDH:	lactate dehydrogenase
LN:	lymph node
MAPK:	mitogen-activated protein kinase
MBAIT:	melanocytic BAP1-mutated atypical intradermal tumor
MEKI:	mitogen-activated protein kinase kinase inhibitor
MIS, LM type:	melanoma in situ, lentigo maligna type
MMS:	Mohs micrographic surgery
MPM:	multiple primary melanoma
MRI:	magnetic resonance imaging
MSLT:	Multicenter Selective Lymphadenectomy Trial
NCCN:	National Comprehensive Cancer Network
OCT:	oral contraceptive therapy
PAM:	pregnancy associated melanoma
PD-1:	programmed cell death protein 1
PD-L1:	programmed death ligand 1
PET:	positron emission tomography
RCT:	randomized controlled trial
RCM:	reflectance confocal microscopy
RT:	radiation therapy
SLN:	sentinel lymph node
SLNB:	sentinel lymph node biopsy
WE:	wide excision
WG:	work group

practice guideline (CPG).[1] The WG determined the scope of the guideline, and identified important clinical questions in the management of primary CM (Table I). WG members completed disclosures of interest that were periodically updated and reviewed for potential relevant conflicts of interests throughout guideline development. If a relevant conflict was noted, the WG member recused himself or herself from the drafting of recommendations pertinent to the topic area of the disclosed interest.

An evidence-based approach was used; available evidence published since the completion of the 2011 melanoma CPG was obtained by using a systematic search and review of published studies from the PubMed and Google Scholar databases from January

1, 2010, to April 30, 2017, for all identified clinical questions. A targeted secondary search was conducted to identify and review key published studies from May 1 to October 31, 2017, to provide the most current information. Searches were prospectively limited to clinical studies in the English language. MeSH (Medical Subject Heading) terms used in the literature search included *biopsy* (*incisional, excisional*); *comparative genomic hybridization*; *contraceptive agents*; *diagnosis, differential*; *diagnosis*; *documentation*; *epidemiology*; *fluorescence in situ hybridization*; *follow-up*; *gene expression*; *genetic counseling*; *germ cells*; *hormones*; *humans*; *imiquimod*; *lentigo*; *lentigo maligna*; *lymph nodes*; *margins of excision*; *melanoma* (*cutaneous*); *melanoma in situ*; *Mohs* (*micrographic*) *surgery*; *neoplasm metastasis*; *pathology*; *patients*; *pregnancy*; *risk*; *prognosis*; *radiotherapy*; *recurrence*; *research design*; *sentinel lymph node biopsy*; *survival*; *surveillance*; *therapeutics*; *toxicity*; and *ultrasonography*.

Articles were included in evidence tables on the basis of relevancy and the highest level of available evidence for the outlined clinical questions. These evidence tables were utilized by the WG in developing recommendations, in addition to the tables previously generated for the 2011 melanoma guideline, to provide continuity for repeated clinical questions. Other current guidelines on melanoma were also evaluated.[2-6]

The available evidence was evaluated by using a unified system called the Strength of Recommendation Taxonomy (SORT), which was 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*).[7] Evidence was graded by using a 3-point scale based on the quality of methodology (eg, randomized controlled trial [RCT], case control, prospective or retrospective cohorts, case series, etc) and the overall focus of the study (ie, diagnosis, treatment, prevention, screening, or prognosis) 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 basis of the best available evidence. The strength of recommendation was 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 situations in which documented evidence-based data were not available, or showed inconsistent or limited conclusions, expert opinion and medical consensus were utilized to generate clinical recommendations.

This guideline has been developed in accordance with the AAD/AAD Association *Administrative Regulations for Evidence-Based Clinical Practice Guidelines* (version approved in August 2012), which includes the opportunity for review and comment by the entire AAD membership and final review and approval by the AAD Board of Directors.[8] This guideline is considered current for a period of 5 years from the date of publication, unless reaffirmed, updated, or retired at or before that time.

INTRODUCTION

The AAD CPG for CM was last published in 2011.[1] This update provides current, evidence-based information on topics relevant to the diagnosis and management of CM, including (1) appropriate biopsy and pathology reporting (by the clinician and pathologist); (2) primary surgery and staging of the regional lymph nodes (LNs) with SLNB; (3) baseline and surveillance studies, and; (4) surgical and nonsurgical therapy considerations for melanoma in situ (MIS), lentigo maligna (LM) type. In recognition of advances in CM treatment, this CPG also provides expanded discussion of the use of new technologies and molecular techniques that may aid both diagnosis and prognosis; the impact of the 2017 eighth edition of the AJCC melanoma staging system on pathology reporting and SLNB consideration[9]; additional techniques for staged surgery (including MMS) for MIS, LM type; and the use of topical imiquimod cream for primary or adjuvant therapy of MIS, LM type. Lastly, this CPG provides new information and recommendations regarding radiation therapy (RT) for CM (focusing on primary treatment for MIS, LM type, and adjuvant therapy for desmoplastic melanoma), pregnancy and melanoma risk/outcome, genetic testing for germline and multi-gene mutations, and discussion of dermatologic toxicities of novel targeted therapies and immunotherapies for patients with advanced disease. The

eighth of the edition *AJCC Cancer Staging Manual* was implemented nationwide on January 1, 2018.[9] Staging changes that affect CM pathology reporting and management are discussed in the relevant sections later in this CPG. The eighth edition of the AJCC tumor (T), node (N), metastasis (M) categories and stage groupings are listed in Tables II and III.

BIOPSY

Skin biopsy remains the first step to establish a definitive diagnosis of CM, although various molecular and imaging techniques have been studied as adjuncts to histopathologic assessment of melanocytic neoplasms. Once a lesion has been identified as clinically concerning, dermoscopy can improve diagnostic accuracy and/or help direct optimal and adequate tissue sampling in the case of very large lesions or those in cosmetically or functionally sensitive areas. Newer noninvasive techniques (eg, reflectance confocal microscopy [RCM], as well as electrical impedance spectroscopy, gene expression analysis, optical coherence tomography, and others [see the section Emerging Diagnostic Technologies]) can also be considered as these become more readily available.[10-12] Prebiopsy photographs are an important aid to clinical/pathologic correlation and help to prevent wrong-site surgery if further treatment is required. Photographs may be taken by the patient and/or health care provider and should include a regional photograph that encompasses anatomic landmarks. Recommendations for diagnostic biopsy of primary CM are summarized in Table IV; the level of evidence and the strength of these recommendations are shown in Table V.[2,13-73]

Skin biopsy may be performed by removing part of the lesion, in what is termed an *incisional*, *partial*, or *incomplete* diagnostic biopsy, or it may be performed with the intent to remove the entire lesion (eg, excisional or complete).[13-30] Partial biopsy may inaccurately stage CM at the outset and could negatively affect treatment planning.[20,26,74] For a lesion clinically suggestive of CM, an excisional/complete biopsy is ideally performed to encompass the entire breadth of the lesion with clinically negative margins, and to extend to a depth sufficient to ensure that the lesion is not histologically transected at the deep margin.[1,74,75] In general, this can be achieved with a narrow peripheral margin of 1 to 3 mm around the concerning skin lesion.[1,2]

Diagnostic excisional biopsy can be accomplished in 3 ways: (1) elliptical (fusiform) excision; (2) punch excision around the clinical lesion; or (3) deep shave/saucerization to a depth below the

Table I. Clinical questions used to structure the evidence review

Biopsy	• What biopsy techniques are effective in establishing accurate histopathologic diagnosis of CM?
Pathology	• What clinical information should be provided to the pathologist to improve or facilitate diagnosis?
	• What histopathologic information should be included in the pathology report to improve or facilitate clinical treatment?
	• Is there a benefit to using new molecular techniques, including GEP, to provide more accurate prognosis beyond currently known clinicopathologic factors?
Surgery	• What are the recommended surgical margins and appropriate depth for invasive CM based on Breslow thickness?
	• What are the most appropriate clinical margins for MIS (including LM type)?
	• What is the role of staged excision or MMS for MIS, LM type?
SLNB	• What is the role of SLNB for staging, regional nodal control, and survival in patients with CM?
	• In what settings should SLNB be considered and/or recommended in patients with CM?
Alternative/adjunctive therapies for MIS (LM type)	• For patients with MIS, LM type, does the evidence support the use of topical imiquimod cream as primary therapy over surgical excision or other therapies?
	• Among patients with MIS, LM type, that has been "optimally" surgically resected, does the use of adjuvant imiquimod help to prevent local recurrence?
RT	• What is the role for RT for the primary treatment of CM (focusing on MIS, LM type)?
	• What is the role of RT as an adjuvant treatment in CM (focusing on desmoplastic CM with high-risk features)?
Work-up and follow-up	• What laboratory, molecular, and imaging tests should be performed at baseline (following CM diagnosis) and for surveillance in asymptomatic patients to detect occult metastasis?
	• What is the role of ultrasound imaging in initial evaluation and surveillance of the regional LN(s), either before or after SLNB?
	• What is the optimal frequency and duration of clinical dermatologic surveillance for detection of CM recurrence and/or additional primary CM?
Pregnancy and exogenous hormones	• Is there evidence to suggest that pregnancy increases the risk of developing CM?
	• Is there evidence to support a waiting period before a woman with a history of CM becomes pregnant?
	• Does pregnancy affect the outcome in patients for whom cutaneous vs metastatic melanoma has been diagnosed?
	• Should pregnant women be more vigilant about changes in their skin or take additional precautions, particularly in the setting of risk factors such as increased mole count, history of excessive sun exposure, and/or family history of CM?
	• Are exogenous hormones, oral contraceptives, and other contraceptive devices safe in women in whom CM has been diagnosed?
Germline mutations and multigene testing	• Is genetic testing for germline risk prediction useful and recommended for patients or families at high risk of CM development?
	• Are there selection criteria according to which individuals who have or are at risk of developing CM should be referred for multigene testing for familial CM?
Dermato-oncology considerations	• How often should patients with metastatic CM on newer systemic therapies be followed for management of cutaneous side effects?
	• What is the role of the dermatologist in the surveillance of patients with advanced/metastatic CM

CM, Cutaneous melanoma; *GEP*, gene expression profiling; *LN*, lymph node; *MIS, LM type*, melanoma in situ, lentigo maligna type; *MMS*, Mohs micrographic surgery; *RT*, radiation therapy; *SLNB*, sentinel lymph node biopsy.

anticipated plane of the lesion, usually extending to the deep reticular dermis.[1,2,28,29] Saucerization (or "scoop") biopsy is the most common diagnostic technique used by dermatologists and other practitioners because of ease of use and time efficiency[18,25,27,29,76] and should not be confused with a superficial shave biopsy, which should be used only when invasive melanoma is not suspected. Fig 1 depicts the excisional saucerization technique.

Table II. AJCC TNM definitions for invasive CM

T classification

T1 ≤1.0 mm	a. <0.8 mm without ulceration
	b. <0.8 mm with ulceration *or* 0.8-1.0 mm with or without ulceration
T2 >1.0 to 2.0 mm	a. Without ulceration
	b. With ulceration
T3 >2.0 to 4.0 mm	a. Without ulceration
	b. With ulceration
T4 >4.0 mm	a. Without ulceration
	b. With ulceration

N and M classification

N1: 1 node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	a. Clinically occult*
	b. Clinically detected[†]
	c. Intralymphatic metastases[‡] *without* regional lymph node disease
N2: 2-3 nodes or in-transit, satellite, and/or microsatellite metastases with 1 tumor-involved node	a. Clinically occult*
	b. Clinically detected (≥1)[†]
	c. Intralymphatic metastases[‡] with 1 occult or clinically detected regional LN
N3: ≥4 tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with ≥2 tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	a. ≥4 metastatic clinically occult nodes with *no* intralymphatic metastases
	b. ≥4 metastatic nodes (≥1 clinically detected), or matted nodes (any number) with *no* intralymphatic metastases
	c. ≥2 clinically occult or clinically detected nodes and/or presence of matted nodes (any number) *with* intralymphatic metastases
M1a: Distant skin, soft tissue (including muscle), and/or nonregional lymph nodes	With or without elevated LDH level
M1b: Lung metastasis with or without M1a	With or without elevated LDH level
M1c: Distant non-CNS visceral with or without M1a or M1b	With or without elevated LDH level
M1d: Distant metastasis to CNS with or without M1a, M1b, or M1c	With or without elevated LDH level

AJCC, American Joint Committee on Cancer; *CM*, cutaneous melanoma; *CNS*, central nervous system; *LDH*, lactate dehydrogenase; *LN*, lymph node; *TNM*, tumor, node, metastasis.

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*Clinically occult tumor-involved regional lymph nodes are microscopically diagnosed after sentinel lymph node biopsy.

[†]Clinically detected tumor-involved regional lymph nodes are defined as clinically evident nodal metastases confirmed by fine-needle aspiration, biopsy and/or therapeutic lymphadenectomy.

[‡]Intralymphatic metastases are defined by the presence of clinically apparent in-transit/satellite metastasis and/or histologically evident microsatellite metastases in the primary tumor specimen.

Superficial shave biopsies may underestimate Breslow thickness[23,27,30] and clinical stage and are thus generally discouraged for CM diagnosis. An exception occurs in the setting of a macular lesion suggestive of MIS, LM type, in which case a broad shave biopsy (extending into the deep papillary or superficial reticular dermis) may provide more thorough histologic assessment of potential focal microinvasion than multiple incisional/partial punch biopsies within the lesion would.[77,78] Fig 2 depicts the broad shave technique.

In instances in which a broad shave or saucerization biopsy is performed, hemostasis with electrocauterization or electrofulguration (hyfrecation) of the base may eradicate underlying melanoma that would otherwise be present in the wide excision (WE) specimen for microstaging. Although spot electrocautery may be necessary to control postprocedural bleeding, the use of topical hemostatic agents such as aluminum chloride or ferric subsulfate solution is preferred, with the addition of topical coagulants (absorbable gelatin

Table III. Pathologic stage groups according to the eight edition of the AJCC

Pathologic TNM stage groupings			
When T is	And N is	And M is	Pathologic stage
Tis*	N0	M0	0
T1a*	N0	M0	IA
T1b*	M0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T0†	N1b, N1c	M0	IIIB
T0†	N2b, N2c, N3b, or N3c	M0	IIIC
T1a/b-T2a	N1a or N2a	M0	IIIA
T1a/b-T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a-N2b	M0	IIIB
T1a-T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N ≧N1	M0	IIIC
T4b	N1a-N2c	M0	IIIC
T4b	N3a/b/c	M0	IIID
Any T, Tis	Any N	M1	IV

AJCC, American Joint Committee on Cancer; *TNM*, tumor, node, metastasis.

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*Melanoma in situ (Tis) and most T1 melanomas do not require sentinel lymph node biopsy to complete AJCC pathologic staging; clinical nodal status may be used to assign stage.

†T0 indicates that primary tumor cannot be assessed.

Table IV. Recommendations for diagnostic biopsy of suspected melanoma

Preferred biopsy technique is a narrow excisional/complete biopsy with 1- to 3-mm margins that encompass the entire breadth of lesion and is of sufficient depth to prevent transection at the base. This may be accomplished by fusiform/elliptical or punch excision or deep shave/saucerization removal to depth below the anticipated plane of the lesion.

Partial/incomplete sampling (incisional biopsy) is acceptable in select clinical circumstances such as facial or acral location, very large lesion, or low clinical suspicion or uncertainty of diagnosis.

Narrow-margin excisional biopsy may be performed if an initial partial biopsy is inadequate for diagnosis or microstaging, but it should not generally be performed if the initial specimen meets the criteria for consideration of sentinel lymph node biopsy.

sponge) when hemostasis cannot be achieved with topical agents alone. Hemostasis with ferric subsulfate solution results in deposition of brown ferric pigment in the dermis, which may be misinterpreted histologically in CM specimens, although an iron stain can confirm the nature of the pigment. The use of this hemostatic agent should be noted on the pathology requisition.

Large clinical lesions and/or challenging anatomic locations such as the face or acral surfaces may preclude excisional diagnostic biopsy of a suspicious lesion. In this instance, partial sampling with a punch, shave, or elliptical/fusiform incisional biopsy (or combination thereof) may be performed of the most clinically and/or dermoscopically atypical portion(s) of the lesion, although the selected area(s) may not represent the greatest Breslow thickness or most atypical pathologic regions.[24] There is no evidence that partial/incisional biopsies adversely affect patient outcome by transferring melanoma cells into cutaneous lymphatics or blood vessels.[19] Biopsy type (incisional vs excisional) does not affect rates of SLN positivity or disease recurrence, nor does it have any impact on the risk of metastasis.[17,19,26]

When a partial biopsy demonstrates melanoma that meets criteria for SLNB, there is generally no need to remove the residual lesion before definitive surgery. The additional procedure may delay definitive surgery and pathologic staging of the regional LNs, add to procedural costs and patient morbidity, and potentially affect the accuracy of SLNB in instances in which a larger elliptical/fusiform excision with redundant skin repair is performed. However, if a partial biopsy specimen is inadequate to make a histologic diagnosis or to accurately microstage the lesion for treatment planning (including WE surgical margins or SLNB), a narrow-margin excisional biopsy should be performed if possible.[20] When performed on the extremities, diagnostic elliptical/fusiform excisional biopsies should generally be oriented longitudinally (ie, axially) (Fig 3). This permits optimal subsequent WE and, if indicated, SLNB staging.

When a biopsy of a suspicious nail lesion (eg, melanonychia striata, diffuse pigmentation, or amelanotic changes) is performed, the nail matrix should be sampled. Because of the complexity of nail anatomy and fact that melanoma arises in the nail matrix, suspicious nail lesions are best evaluated and sampled by a practitioner skilled in biopsy of the nail apparatus.[79] For suspicious subungual lesions, the nail plate should be sufficiently removed to expose the underlying lesion and an excisional or incisional biopsy performed depending on size of the lesion.

Table V. Level of evidence and strength of recommendations for biopsy of suspected cutaneous melanoma, clinical information, and pathology report

Recommendation	Strength of recommendation	Level of evidence	References
Biopsy	B	II	13-30
• Excisional biopsy with 1- to 3-mm clinically negative margins			
• Partial biopsy in select circumstances			
• Follow-up excisional biopsy to partial biopsy			
Clinical information provided to the pathologist	C	III	Expert opinion
Pathology report			
Clinical information	C	III	31
Tumor (Breslow) thickness	A	I/II	9,32-42
Ulceration	A	I/II	9,32-43
Mitotic rate	A	I/II	9,32-42,44,45
Level of invasion (Clark level)	B	II	36,38,39,46
Microsatellitosis	B	II	45,49-51
Angiolymphatic invasion	B	II	45,48,52-54
Histologic subtype	B	II	36,48,54,56
Neurotropism/perineural invasion	C	III	57,58
Regression	B	I/II	42,59-63
Tumor-infiltrating lymphocytes	B	II	42,64,65
Use of ancillary molecular diagnostic techniques for equivocal melanocytic neoplasms	C	III	66-73
Against testing for oncogenic mutations in the absence of metastatic melanoma or outside of a clinical study	C	III	2
			Expert opinion

Superficial, partial shave biopsy leads to incomplete sampling of a larger, thicker melanoma

Sauceriziation or "scoop" technique removes the entire lesion and allows complete sampling of deep margins
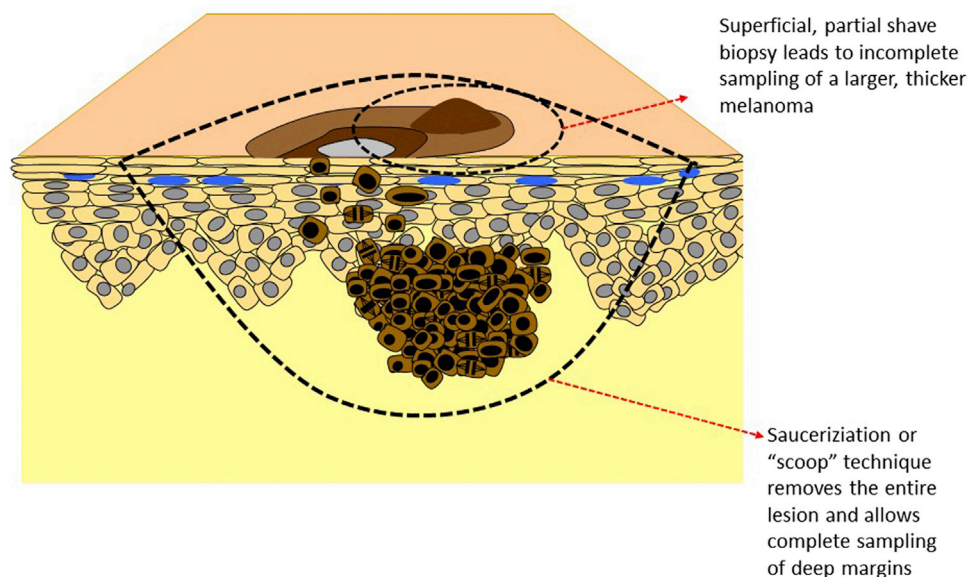
Fig 1. Diagnostic excisional biopsy with deep shave/saucerization technique.

PATHOLOGY REPORT

When a biopsy of a lesion clinically suggestive of primary CM is performed, the WG recommends that pertinent information be provided to the pathologist and likewise to the clinician performing the biopsy once the diagnosis of melanoma is histologically confirmed, with notation of essential, strongly recommended, and optional items as indicated in Tables VI and VII. The level of evidence and strength of recommendations are shown in Table V.
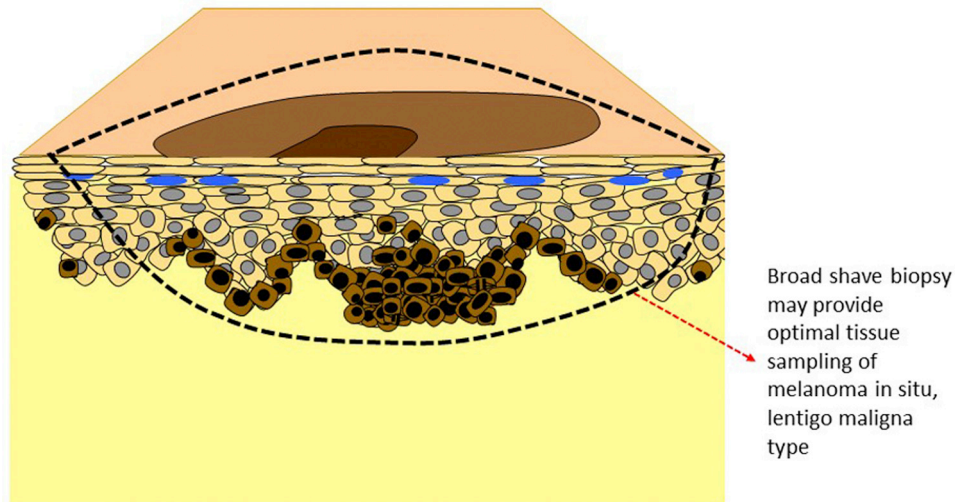
Fig 2. Diagnostic broad shave biopsy for suspected melanoma in situ, lentigo maligna type.
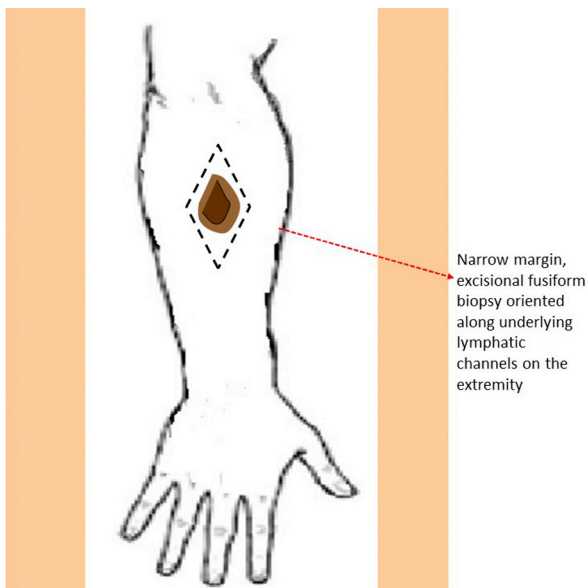
Fig 3. Longitudinal/axial orientation of diagnostic elliptical/fusiform excisional biopsy on the extremity.

Clinical information provided to the pathologist

On the pathology requisition, it is essential that the clinician provide the following data to the pathologist: patient identification, age, and sex and precise anatomic location (eg, forearm, hand) of the biopsy site, including laterality, to reduce chances of subsequent wrong-site surgery.[31] It is strongly recommended that the clinician include his or her clinical impression and differential diagnosis, size of the lesion, and intent of the biopsy (ie, excisional vs partial, noting the type of diagnostic biopsy performed [elliptical/fusiform, deep shave/

saucerization, broad shave, or punch]). Macroscopic satellites around the clinical lesion should be noted by the clinician, as they upstage CM to stage III at the outset and can be associated with microscopic satellites in the primary tumor.[9] It may be very useful for the pathologist to review clinical photographs, if possible. Optional but helpful items to be reported include the level of suspicion for CM, clinical description and history of the lesion beyond size (including whether there has been a change in the lesion or previous biopsy), and dermoscopic features (with or without an accompanying photograph), as these features may add specificity to the diagnosis of CM.

Pathology information provided to the clinician

The pathology of melanocytic tumors should be read by a physician experienced in the interpretation of pigmented lesions.[80] The list of histologic features to be included in the CM pathology report is based on their prognostic value, and standardized synoptic reporting has been recommended by the AJCC,[9] College of American Pathologists,[81] and various international pathology associations.[74] Recommendations for histologic factors to be included in the pathology report are shown in Table VII; the level of evidence and the strength of recommendations are listed in Table V.

There is strong evidence that at least 3 histologic features of the primary tumor are dominant predictors of outcome: Breslow thickness, ulceration, and dermal mitotic rate.[9,32-40] Mitotic rate is no longer included in the eighth edition of the AJCC CM

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

Essential	Strongly recommended	Optional
Age of patient	Biopsy intent (excisional/complete vs partial/incomplete) and technique (elliptical, punch shave/saucerization)	Clinical description/level of suspicion for melanoma/prior change or biopsy (if applicable)
Sex	Size of lesion	Dermoscopic features (with or without photograph)
Anatomic location (including laterality)	Clinical impression/differential diagnosis Macroscopic satellites Clinical photograph (if possible)	

Table VII. Recommended histologic features of primary cutaneous melanoma for inclusion in the pathology report

Essential	Optional
Size of specimen	Gross description of lesion
Tumor thickness (Breslow), nearest 0.1 mm	Angiolymphatic invasion/lymphovascular invasion
Ulceration	Histologic subtype
Dermal mitotic rate; "hotspot" method; No. of mitoses/mm^2	Neurotropism/perineural invasion
Peripheral and deep margin status (negative/positive [broad vs focal transection at deep margin])	Regression
Microsatellitosis	Tumor category for staging
	Tumor-infiltrating lymphocytes
	Anatomic level of invasion (Clark level)
	Vertical growth phase

staging system as a dichotomous variable ($<1/mm^2$ vs $\geq 1/mm^2$) for T1 primary CM because stratifying T1 tumors using a cut point of 0.8 mm was more prognostic than using mitotic rate, as in the seventh edition.[9] Therefore, T1a CM is now defined as not ulcerated and less than 0.8 mm, whereas T1b CM is defined as 0.8 to 1.0 mm regardless of ulceration status, or ulcerated CM less than 0.8 mm.[9] The WG considers it essential for maintenance of an adequate tumor registry that these 3 primary tumor characteristics be included in the pathology report.

Maximum tumor (Breslow) thickness is measured from the top of the 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 follicular/adventitial extension. The eighth edition of the *AJCC Cancer Staging Manual* has modified the reporting of thickness to the nearest 0.1 mm rather than to the nearest 0.01 mm (eg, a thickness of 0.75 to 0.84 mm would be rounded to 0.8 mm).[9] Microsatellitosis should not be included in this primary tumor measurement but commented on separately, as noted later in this guideline.

Primary tumor histologic ulceration is associated with worse prognosis for both CM and nodal disease (stage III) and should be reported as present or absent. Microscopic ulceration is defined as tumor-induced full-thickness loss of epidermis with subjacent dermal tumor and reactive dermal changes.[9,35,43] Histologic changes resulting from prior diagnostic biopsy or trauma should not be confused with ulceration in the WE specimen.

Mitotic rate, measured as the number of dermal mitoses per mm^2 via the "hot spot" technique (with 1 mm^2 approximately equal to 3-4 high-power [×40] microscopic fields, calibrated for the individual microscope type and starting in the field with most mitoses), was included as a staging attribute in the seventh edition of the AJCC CM staging system to upstage patients with CM 1 mm or less in thickness from T1a to T1b, replacing Clark level.[32,39] In the eighth edition the AJCC CM staging system, primary tumor mitotic rate as a dichotomous variable was removed as a staging criterion for T1 CM. However, mitotic rate remains an important prognostic factor that should be reported (as a whole number per mm^2) for all patients with T1 to T4 primary CM

because it is associated with survival across all thickness categories.[9,44]

An additional essential element of the pathology report is the status of the peripheral and deep margins (positive or negative) of the specimen. 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. The pathology report should ideally note whether in situ or invasive melanoma is present at the deep and/or peripheral margins and whether broad versus focal transection of the invasive component is present at the deep margin. For example, a focally transected CM at the deep margin is unlikely to result in a thicker melanoma on WE, or ultimately affect AJCC stage defined by T category. Although broad transection of both peripheral and deep margins by invasive CM is likely in partial biopsies of large clinical lesions, notation of the extent and location of the histologic transection may assist in treatment planning.

Although the College of American Pathologists and various international pathology groups[74,81] have recommended reporting measurement (in mm) of distance between the tumor and peripheral and deep margins on both biopsy and WE specimens, this practice is generally discouraged by the WG. It should be emphasized that for primary CM, treatment recommendations are based on the clinical measurement of surgical margins around the tumor and not on histologically measured peripheral or deep margins.[1,2] Routine reporting of histologic margin status (in mm) may result in unnecessary additional WE if the clinician is unaware of this. However, when a clear margin is narrow, it may be appropriate to alert the clinician and provide a measured margin width, recognizing that this is a practice that should be individualized between the dermatologist and pathologist.

In the eighth edition of the AJCC staging system, the presence of in-transit, satellite, and/or microsatellite metastases is categorized as N1c (pathologic stage IIIB with a T1a/b to T3a primary tumor and pathologic stage IIIC with a T3b or T4a/b primary tumor) in the absence of involved regional LN(s), and N2c or N3c on the basis of the presence of 1 (N2c) or 2 or more (N3c) concomitantly involved regional LN(s). Depending on the specific T- and N-category criteria, such patients would be staged as either stage IIIC or IIID (Table II).[9] Therefore, the presence or absence of microscopic satellites must be reported for accurate staging. The seventh edition of the AJCC melanoma staging system previously defined microsatellites as the presence of tumor nests larger than 0.05 mm in diameter located in the dermis or subcutis below or surrounding the main invasive tumor and separated by at least 0.3 mm of normal tissue.[32] The eighth edition of the AJCC melanoma staging system has broadened this definition to include any discontinuous microscopic deposit adjacent or deep to a primary melanoma, regardless of size or distance from the main tumor.[9] Microsatellite disease is frequently associated with other adverse pathologic features.[47]

The anatomic (Clark) level of invasion was a reportable feature in the 2009 AJCC staging system, but only for tumors less than or equal to 1 mm in thickness when mitotic rate could not be assessed, and it is now considered optional for all stages. Nevertheless, several studies have demonstrated relevance of Clark level in management decisions, especially when mitotic rate information is not available.[38,41,46] Therefore, assessment of Clark level may be included in the pathology report as an optional and potentially helpful feature.

There is evidence that additional histologic features of a primary CM provide prognostic value, including the extent of tumor-infiltrating lymphocytes[42,64,65] and the presence or absence of a vertical growth phase,[82] dermal regression,[42,59] and angiolymphatic invasion (also termed *lymphovascular invasion*).[52,53] Focal or partial histologic regression is commonly observed in T1 CM, previously raising concern that true Breslow thickness may be underestimated.[83] However, most contemporary data support the idea that primary tumor histologic regression is not an adverse prognostic factor for nodal metastasis or survival[60,61] and rather, is associated with a lower likelihood of SLNB positivity[62] and improved survival,[63] with the possible exception of extensive or complete regression.[84] Although not essential, it is recommended that these histologic characteristics be included as *optional* elements of the pathology report, as their inclusion may help to guide clinical management. Although the prognostic value of neurotropism (also termed *perineural invasion*) is uncertain, its presence or absence provides information that may alter management of the primary tumor, particularly for the desmoplastic subtype,[85] and is also therefore recommended as an optional histologic characteristic to be reported.

The prognostic value of the histologic subtype of CM has not been established, with some notable exceptions. For instance, 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.[55] Similarly, the LM

Table VIII. Recommendations for diagnostic, prognostic, and therapeutic molecular testing

Ancillary diagnostic molecular techniques (eg, CGH, FISH, GEP) may be used for equivocal melanocytic neoplasms.

Routine molecular testing, including GEP, for prognostication is discouraged until better use criteria are defined. The application of molecular information for clinical management (eg, sentinel lymph node eligibility, follow-up, and/or therapeutic choice) is not recommended outside of a clinical study or trial.

Testing of the primary CM for oncogenic mutations (eg, *BRAF*, *NRAS*) is not recommended in the absence of metastatic disease.

BRAF, B-Raf proto-oncogene, serine/threonine kinase gene; *CGH*, comparative genomic hybridization; *CM*, cutaneous melanoma; *FISH*, fluorescence in situ hybridization; *GEP*, gene expression profiling; *NRAS*, NRAS proto-oncogene, GTPase gene.

pattern, which is commonly observed on the head and neck, may be associated with subclinical peripheral and periadnexal extension beyond the visible margins,[86,87] which may require wider surgical margins to clear histologically.[88] Moreover, histopathologic subtypes are also associated with different profiles of driver mutations. Thus, histologic subtype is recommended as an optional element of the pathology report.

Immunohistochemistry is of greatest importance in confirming the melanocytic origin of tumors that lack compelling morphologic indicators, such as pigmentation, nesting, and pagetoid scatter. Antibodies of use for this purpose include Sox10 and S100, which are sensitive but less specific, and Melan-A/MART1, HMB45 and tyrosinase, which are more specific for melanocytic differentiation.[89] Testing of primary CM for oncogenic ("driver") mutations such as B-Raf proto-oncogene, serine/threonine kinase gene (*BRAF*), whether by immunohistochemistry or genomic techniques, is generally not recommended by the WG in the absence of metastatic disease and/or clinical trial consideration.[2] Other ancillary tests that can be of value in selected cases include HMB45 immunohistochemical staining (in which case diminution of staining can be a reassuring feature),[90] expression of Ki-67 proliferation marker, and staining for p16.[91] If present, the latter marker excludes homozygous chromosome 9p21 loss, which has been associated with aggressive behavior in some tumors, including spitzoid lesions.[92] However, absence of p16 staining is not diagnostic of CM, or reliably predictive of outcome. Telomerase reverse transcriptase gene (*TERT)* promoter mutations[93] and protein expression[94] are under investigation for diagnostic and prognostic value, especially in spitzoid lesions.

Diagnostic molecular techniques are still largely investigative and may be appropriate as ancillary tests in equivocal melanocytic neoplasms, but they are not recommended for routine diagnostic use in CM.[66,67] These include comparative genomic hybridization,[68] fluorescence in situ hybridization,[66,69-71] gene expression profiling (GEP),[72,73]

Table IX. Surgical margin recommendations for primary cutaneous melanoma

Tumor thickness	Surgical margin*
In situ	0.5-1 cm[†]
≤1.0 mm	1 cm
>1.0 to 2.0 mm	1-2 cm
>2.0 mm	2 cm

*Recommended surgical excision margins are clinically measured from the edge of the lesion or prior biopsy at the time of surgery; they are not histologic margins as measured by the pathologist. Margins may be modified for functional considerations or anatomic location.
[†]Margins larger than 0.5 cm may be necessary for melanoma in situ, lentigo maligna type.

and (potentially) next-generation sequencing.[95] These tests may help to differentiate benign nevi from CM, including atypical Spitz tumors. In the opinion of the WG, there is also insufficient evidence of benefit to recommend routine use of currently available prognostic molecular tests, including GEP, to provide more accurate prognosis beyond currently known clinicopathologic factors (see Table VIII for recommendations and Table V for level of evidence).[67,96,97]

Finally, CM is a cancer reportable to central registries, by both the diagnosing clinician and the pathologist. Significant rates of under-reporting occur despite the nationwide reporting mandate, which is required by law in all 50 states.[98-100] Regional and state cancer registries have mechanisms in place to aid practitioners in accurate reporting of CM.[98,101]

SURGICAL MANAGEMENT
Surgical margins and depth of excision

Surgery remains the primary treatment modality for CM, with the goals of both durable local control and cure in patients without occult regional nodal or distant metastasis.[102] Following initial biopsy, wider and deeper excision is performed to ensure complete removal of the lesion, confirm histologically clear margins, and reduce the risk of local

Table X. Recommendations for surgical management of primary cutaneous melanoma

Surgical excision with histologically negative margins is the recommended and first-line treatment for primary CM of any thickness, as well as for melanoma in situ. Surgical margins should be based on tumor thickness.

Surgical margins for invasive CM should be ≥1 cm and ≤2 cm measured clinically around the primary tumor, although margins may be narrower to accommodate function and/or anatomic location. Depth of excision is recommended to (but not including) the fascia.

For melanoma in situ, wide excision with 0.5- to 1.0-cm margins is recommended; MIS, LM type, may require >0.5-cm margins to achieve histologically negative margins because of subclinical extension.

Sentinel lymph node biopsy, when indicated, should be performed before wide excision of the primary tumor, and in the same operative setting, whenever possible.

Mohs micrographic surgery* or staged excision with paraffin-embedded permanent sections may be utilized for MIS, LM type, on the face, ears, or scalp for tissue-sparing excision and exhaustive histologic assessment of peripheral margins.

For MIS, LM type, permanent section analysis of the central MMS debulking specimen is recommended to identify and appropriately stage potential invasive CM. If invasive CM is identified on a MMS section intraoperatively, the tissue should be submitted for formal pathology review.

Sub−1-cm margins (by either WE or MMS) for primary invasive melanomas at anatomically constrained sites (eg, head and neck, acral sites) are generally not recommended until further studies are available.

CM, Cutaneous melanoma; *MIS, LM*, melanoma in situ, lentigo maligna; *MMS*, Mohs micrographic surgery; *WE*, wide excision.
*The American Academy of Dermatology is in the process of updating the Mohs Appropriate Use Criteria.

recurrence. The latter includes both true local recurrence, defined by the presence of in situ and/or radial growth phase (ie, persistent disease), and local, satellite recurrence or metastasis (ie, intralymphatic deep dermal or subcutaneous fat recurrence without an in situ or radial growth phase) within or adjacent to the scar. Recommended surgical margins for invasive CM are based on high-level, prospective RCTs (which have generally excluded head and neck and acral sites)[103-110]; however, prospective RCTs, including direct comparison of various surgical techniques, have not been conducted for MIS.[111] Surgical margins for MIS, LM type (and to a certain extent, acral lentiginous MIS), are complicated by potential for subclinical extension of CM cells, which may require different surgical approaches. Recommendations for surgical treatment of CM, including recommended surgical margins, are listed in Tables IX and X. The level of evidence and strength of recommendations are shown in Table XI.*

As noted previously, WE margin recommendations are based on studies in which the margins were clinically measured around the primary tumor at the time of surgery and not histologically measured by the pathologist. Such surgical margins do not typically correlate with histologically tumor-free margins as a result of ex vivo tumor shrinkage and formalin fixation of the WE specimen. Clinicians should not attempt to achieve a histologic margin equal to the clinical surgical margin. However, for management purposes, clinicians should record the peripheral surgical margins taken for both the

fusiform excisional biopsy and the subsequent WE. If histologically clear, the excisional biopsy margin may be added to the WE surgical margin for definitive surgical treatment.

Specific surgical margin recommendations for invasive CM are based on the following concepts: (1) WE is associated with a reduced risk of local recurrence; (2) for CM less than or equal to 2.0 mm in thickness, there is not strong evidence that surgical margins larger than 1 cm favorably affect survival or local recurrence; and (3) current data do not support that idea that surgical margins wider than 2 cm affect overall survival. The WG recommends that surgical margins for invasive primary CM be at least 1 cm and no greater than 2 cm, depending on tumor thickness.[1,2] It is important to note that most prospective RCTs have mainly included truncal and extremity CM and excluded CM on the head and neck or acral sites, where narrower margins may be necessary to preserve function and/or cosmesis.

Despite limited evidence regarding excision of CM less than or equal to 1.0 mm in thickness, WE with a surgical margin of 1 cm is recommended for T1 (≤1 mm) CM[103,111] and may be acceptable for T2 CM (>1.0 mm to 2.0 mm),[104] although 2-cm margins are also deemed appropriate for T2 lesions on the basis of prospective, randomized trials.[105-107] On the basis of the available evidence and consensus opinion, the WG continues to recommend a 1- to 2-cm surgical margin for T2 CM, taking into account tumor location and functional or cosmetic considerations.[1]

A surgical margin of 2 cm is recommended for CM with a tumor thickness greater than 2.0 mm (ie, T3, >2.0 to 4.0 mm and T4, >4.0 mm). One RCT found

*33,40,87,103-110,112-164

Table XI. Level of evidence and strength of recommendations for the surgical management and SLNB of primary CM

Recommendation	Strength of recommendation	Level of evidence	References
Surgical excision for CM	A	I	103-110
Surgical margins for CM			
MIS	B	II/III	112-117
≤1.0 mm	A	I/II	103,104,118-120
>1.0 to 2.0 mm	A	I	33,103-107,121,123
>2.0 mm	A	I	33,105,108-110,122,124
MMS for MIS, LM type	B	II/III	87,125-142
Caution against sub−1-cm margins for invasive CM	C	III	130,143-145
			Expert opinion
SLNB before/concomitant with WE	C	II	146
SLNB	B	I/II	40,147-164
• No SLNB for MIS or T1a melanoma			
• Discussion of SLNB for T1a melanoma (<0.8 mm) if other adverse features are present			
• Discussion of SLNB for T1b CM (<0.8 mm with ulceration and 0.8-1.0 mm with or without ulceration)			
• Discussion and offering of SLNB for CM >1 mm thickness (≥T2a)			
Discussion of SLNB risks vs benefits with patients	C	III	Expert opinion
Interdisciplinary discussion regarding possible CLND or ultrasound surveillance if positive SLNB			

CLND, Completion lymph node dissection; *CM,* cutaneous melanoma; *MIS, LM,* melanoma in situ, lentigo maligna; *MIS,* melanoma in situ; *MMS,* Mohs micrographic surgery, *WE,* wide excision.

that narrower excision of CM greater than or equal to 2 mm in thickness with a 1-cm margin was associated with a somewhat higher combined local, in-transit, and nodal recurrence rate than wider excision with a 3-cm margin, although SLNB was not used for pathologic staging to exclude occult regional nodal disease at the time of initial WE.[108] No overall survival difference was evident at a median follow-up of 5 years or in long-term follow-up at a median of 8.8 years, though a nonsignificantly higher number of deaths were reported in the narrow-margin group.[109] Surgical complications were higher in the wider-margin group, as was long-term adverse patient perception of the scar site.[124] Another multicenter RCT conducted in 9 European countries from 1994 to 2002 involved 936 patients with clinically staged IIA to IIC CM greater than 2.0 mm, randomized to WE with either 2-cm or 4-cm resection margins.[110] At a median follow-up of 6.7 years, the 5-year overall survival rate in both groups was 65%, supporting the conclusion that the 2-cm resection margin was sufficient and that larger margins did not confer improved patient outcomes.

The evidence regarding depth of WE is less robust than that for peripheral surgical margins, as prior RCTs have not typically standardized depth of excision. Although there is reported variability according to physician specialty,[165] the consensus opinion and that of the WG is that invasive CM should generally be excised to the depth of (but not including) the underlying muscular fascia, except in rare instances of deep primary CM that involves the fascia or underlying structures.[166] No RCTs have specifically explored whether shallower excision to the deep adipose layer affects local recurrence or survival. The WG acknowledges that most melanomas in situ and many thin T1 melanomas are excised to a depth within the adipose layer rather than extending to the muscle fascia. However, no data are available to confirm whether this practice is safe or appropriate, particularly for invasive CM.

As with diagnostic biopsy of the nail apparatus, WE of CM on the digits requires specialized surgical expertise. Because little soft tissue underlies the nail apparatus, partial amputation at the distal interphalangeal joint has typically been recommended for subungual CM on the fingers or toes to avoid complications of degloving the skin on the distal digit. However, partial amputation has not been associated with improved prognosis or survival compared with more conservative techniques,[167,168] although there is no high-level evidence. Narrower surgical margins and digit-sparing surgery have been

proposed to preserve function, particularly for thinner T1 CM (≤0.8 mm) and in situ lesions, and they warrant further investigation.[169,170]

Timing of excision in relation to SLNB

When SLNB is planned, data support its performance during the same operation and before WE of the primary tumor to minimize disruption of the lymphatic channels and optimize the accuracy of lymphatic mapping and identification of the correct SLN(s).[146] In carefully selected patients with a prior WE, the SLN(s) may still be successfully identified and accurately reflect the pathologic status of the regional LN basin(s),[146,171] but this may require more extensive surgery and result in higher morbidity and cost.

Surgical margins for MIS, including the LM type

Although no RCTs of surgical interventions for MIS have been conducted,[112] on the basis of lower-level evidence, the WG recommends a 0.5- to 1-cm margin, recognizing that a 0.5-cm margin is generally adequate and associated with low recurrence rates for MIS, non-LM types, and for most MIS on the trunk and extremities.[113,114] Surgical margins of 0.5 cm were initially recommended for MIS in 1992 through the National Institutes of Health Consensus Development Conference on Diagnosis and Treatment of Early Melanoma,[111] though this statement was not based on any prospective trials and it applied mainly to the more common superficial spreading melanoma subtype, in which the clinical borders of the lesion are usually distinct. The most appropriate depth of excision for MIS has not been studied in a RCT, but surgery is commonly performed to the depth of the deep subcutaneous fat because occult invasive melanoma (generally less than 0.5 mm) has been reported in up to a third of MIS.[172]

Certain MIS subtypes (LM and acral lentiginous) tend to have a higher propensity for subclinical peripheral tumor extension and/or adjacent multifocal microscopic disease. Thus, complete excision may necessitate the use of wider surgical margins and/or margin control techniques that allow comprehensive histologic assessment of the peripheral margins. Because surgical margins wider than 0.5 cm are often necessary to provide histologically clear peripheral margins for MIS, LM type, on the head and neck,[88,113,115,116] a 0.5- to 1-cm surgical margin may be considered. However, microscopic assessment of MIS, LM type, is frequently complicated by the presence of sun-damaged melanocytes (actinic melanocytic hyperplasia), which do not represent MIS but may simulate it.[173-176] Sampling of representative sun-damaged skin may help distinguish true atypical junctional melanocytic proliferations from actinic melanocytic hyperplasia.[1] Although there are limited data to support the use of noninvasive modalities to identify the clinical peripheral margins of MIS, LM type, Wood's lamp,[177] dermoscopy, and/or in vivo RCM[178,179] may aid in preoperative assessment.

MMS and staged excision techniques for MIS, LM type

There is a general lack of high-quality evidence for the surgical treatment of MIS and invasive CM on the head and neck and on acral sites, with only 1 RCT for invasive CM including those on the head and neck[107] and none including acral sites. For MIS with indistinct clinical margins on the head and neck (generally of the LM type), multiple studies have examined the utility of MMS and staged excision with paraffin-embedded permanent sections.[117,125-129] The WG recommends that these surgical techniques be considered for MIS, LM type, to provide tissue-sparing excision on anatomically constrained sites (eg, face, ears, scalp) and exhaustive peripheral margin histologic assessment. For invasive LM melanoma in these locations, comprehensive peripheral margin control (with staged excision or MMS) may be considered for residual MIS, LM type, in addition to complete excision and paraffin-embedded permanent section evaluation of all invasive disease.[130,143,144]

The WG acknowledges the available retrospective data and ongoing efforts to evaluate the benefit of MMS for invasive melanoma on head and neck, acral, and other sites.[130,143,144] Currently, the non-inferiority of narrower surgical margins to those recommended in non–head and neck sites (whether obtained through MMS, staged excision with permanent sections, or conventional WE) has not been prospectively established. The risks of sub–1-cm margins in this setting require further study in light of reported worse prognosis of thicker (T2-T4) CM on the head and neck and on the scalp in particular.[180] The WG reaffirms the general 1-cm minimum surgical margin for invasive CM as espoused in all international guidelines[145] and cautions strongly against the routine use of narrower surgical margins for invasive melanomas at any site, except in rare circumstances for head and neck or acral lesions. However, the WG encourages further study of MMS and alternative surgical techniques for CM on these anatomically constrained areas.

MMS and other staged surgical techniques for MIS, LM type, remain in evolution. As such, WG recommendations are based on several retrospective studies and a single prospective analysis,[128] as well as on expert opinion. A recent retrospective analysis

Table XII. Recommendations for sentinel lymph node biopsy

For all SLNB-eligible patients, careful discussion of the risks and benefits of the procedure involving surgical oncology input is recommended.

SLNB is not recommended for patients with MIS or for most T1a CM (<0.8 mm without ulceration per the eighth edition of the AJCC staging system).

SLNB should be discussed and offered in appropriate patients with CM >1 mm thickness (≥T2a), including T4 CM.

In patients with T1b CM (<0.8 mm with ulceration or 0.8-1.0 mm with or without ulceration per the eighth edition of the AJCC staging system), SLNB should be discussed and considered, though rates of SLN positivity are still relatively low.

SLNB may be considered for T1a CM if other adverse features are present, including young age, presence of lymphovascular invasion, positive deep biopsy margin (if close to 0.8 mm), high mitotic rate, or a combination of these factors.

Interdisciplinary collaboration involving surgical and medical oncologists is recommended for discussion of possible completion lymph node dissection vs regional nodal ultrasound surveillance in the event of a positive SLNB.

AJCC, American Joint Committee on Cancer; *CM,* cutaneous melanoma; *MIS,* melanoma in situ; *SLN,* sentinel lymph node; *SLNB,* sentinel lymph node biopsy.

of 277 patients treated with MMS and 385 patients treated with conventional WE (mean surgical margins, 0.6 cm) demonstrated no significant differences in local recurrence rates, overall survival, or melanoma-specific survival at a median follow-up of 8.6 years, although significantly more patients with MIS on the face underwent MMS than conventional WE (80.2% vs 36.7%, respectively, [$P < .001$]).[129] Other retrospective analyses and prospectively followed cohorts have demonstrated improved histologic assessment of peripheral margins and lower rates of local recurrence for MIS on the face and ears with MMS versus with conventional WE.[127,130-132] At present, the evidence is insufficient to support use of MMS for MIS elsewhere on the body.[181]

Two main MMS techniques for MIS are commonly described in the dermatologic literature: traditional MMS and modified MMS. The principal difference lies in configuration of the excision and use of frozen versus permanent section assessment. Permanent section analysis of the central debulking specimen is recommended, regardless of the MMS technique, to identify and appropriately stage potential residual invasive CM. Likewise, if invasive CM is identified on a MMS section intraoperatively, the tissue block should be submitted for permanent section analysis and formal pathology review. As with the 2011 AAD CPG, for in situ and invasive CM, permanent paraffin-embedded sections are considered the criterion standard for histologic evaluation of melanocytic lesions.[182]

Several variations of staged excision techniques have been described. Like MMS, they are aimed at providing comprehensive margin control before reconstruction. Specific techniques include the "square" procedure (and associated variations), "spaghetti technique" (and variations), "slow Mohs," staged excision with radial vertical sections, and mapped serial excision techniques.[87,126,133-142] No study directly comparing these staged excision techniques has been conducted. Like MMS, all staged excision techniques involve removal of the majority of the clinically apparent lesion for histologic microstaging. In contrast to MMS, all tissue analysis is performed via paraffin-embedded permanent sections that are read by a pathologist in the various staged excision techniques, which require delayed reconstruction following histopathologic confirmation of negative margins.

Currently, there are limited data to support the use of in vivo imaging technologies for intraoperative, surgical margin assessment of MIS, LM type. Some preliminary data suggest that in vivo RCM can be helpful in identifying the tumor's peripheral margin and therefore guide surgical removal, and this approach remains an active area of investigation.[178,179,183,184]

SLNB
Role of SLNB for staging, regional nodal control, and survival

Current practice guidelines involving every discipline and every major guideline/staging organization worldwide provide relatively uniform recommendations regarding SLNB for CM, and they are consistent in interpretation of its value and limitations.[2,9,145,185] Recommendations for the use of SLNB and the level of evidence and strength of these recommendations are summarized in Tables XII and XI, respectively.

Staging

Accurate staging of CM drives surgical treatment, surveillance intensity, and other therapeutic options including the use of newer systemic adjuvant therapies. The staging accuracy of SLNB is not controversial,[9] though its impact on survival remains

less well defined. It is important to recognize that staging tests are typically validated not on the basis of their ability to improve survival but rather on the basis of their sensitivity and specificity, with SLNB representing the criterion standard for nodal staging in appropriate patients with CM. SLN status is also a key determinant for consideration of systemic adjuvant therapy and clinical trial enrollment.

Pathologic staging of the regional LNs identifies patients with CM with occult metastasis and upstages a patient to AJCC stage III at the outset. SLN status (positive or negative) is widely regarded as the most important prognostic factor for recurrence and the most powerful predictor of survival in patients with CM. A meta-analysis of 71 studies and 25,240 participants estimated an overall 5% or lower risk of regional nodal recurrence following a negative SLNB.[186] Markedly improved survival has been demonstrated in patients with advanced CM with the use of immune checkpoint blockade and therapies targeting the mitogen-activated protein kinase (MAPK) pathway.[187] These agents have recently shown a survival advantage in the adjuvant setting for SLN-node postive patients,[188,189] making accurate staging even more relevant.

Regional LN control

Regional LNs are the most common site of initial metastasis in patients with CM. Surgically uncontrollable regional nodal disease has a major negative impact on quality of life, and it is worth preventing when possible. Lower rates of same-basin LN recurrence and improved disease-free survival occur following lymphadenectomy of clinically occult/ microscopic metastasis compared with delayed lymphadenectomy of clinically detected, palpable nodes—depending on the number of nodes involved, nodal tumor burden, and presence of extracapsular nodal extension.[147,148] The difference in the complexity and morbidity of lymphadenectomy, including lymphedema, for clinically detected versus occult disease is also relevant.[190]

Although the details of SLNB may be beyond the scope of dermatology practice, a brief review of the procedure is included for information and for patient education. Preoperative lymphatic mapping (lymphoscintigraphy), intraoperative vital blue dye injection around the primary CM or biopsy scar, and gamma probe localization with technetium-99 sulfur colloid are used to identify and remove the SLN(s), optimally during the same procedure as the WE. The SLNs are then examined histologically for the presence of tumor involvement by using both routine histology and immunohistochemistry, as well as step

sectioning.[149] The AJCC Melanoma Expert Panel and the International Melanoma Pathology Study Group are working to standardize histologic measurement of SLN tumor burden and other factors that affect survival.[9,40]

Completion LN dissection (CLND) has traditionally been recommended and performed following a positive SLNB, because approximately 8% to 20% of patients will harbor nonsentinel nodal metastases. However, a randomized trial of 483 patients with non—head and neck CM demonstrated no difference in overall survival between SLN-positive patients who underwent CLND and those who did not at a median follow-up of 35 months, regardless of tumor thickness, ulceration, or SLN tumor burden.[191] The larger (N = 1934) randomized Multicenter Selective Lymphadenectomy Trial (MSLT)-II trial[192] assessing CLND versus active nodal observation with ultrasound in patients with a positive SLNB showed that immediate CLND increased the rate of regional disease control and improved staging among patients with a positive SLN but did not increase melanoma-specific survival among all patients with SLN metastasis at a median follow-up of 43 months.

These data and other retrospective studies[193] raise the question of whether CLND is indicated following a positive SLNB, given the associated morbidity. Current National Comprehensive Cancer Network (NCCN) guidelines recommend that CLND versus active nodal basin surveillance with ultrasound be discussed and offered in the setting of a positive SLNB,[2] although CLND may be reasonable in the setting of higher SLN tumor burden, greater number of positive SLNs, and/or adverse histologic features in the primary CM. Surveillance regional nodal ultrasound may also be used to monitor the regional nodal basin in patients who are eligible for SLNB but do not undergo the procedure or in whom SLNB is technically not successful, although ultrasound is not a replacement for the pathologic information provided by either SLNB or CLND.[2,194] The WG recommends interdisciplinary collaboration involving surgical and medical oncologists for discussion of CLND, and radiologists experienced in the use of nodal ultrasound surveillance in patients with CM.

Melanoma-specific survival

SLNB provides the most reliable and accurate means of staging for appropriate patients with primary CM. The Multicenter Selective Lymphadenectomy Trial (MSLT-I) and Sunbelt Melanoma Trial did not demonstrate a therapeutic benefit of SLNB, although the low rates of SLN positivity in these RCTs may have limited their power to detect an overall survival difference between

patients who underwent the procedure and those who did not.[148,150] In the randomized MSLT-I, only 20.8% of patients with CM thickness of 1.2 mm or greater had occult nodal disease, although the subset of SLN-positive patients with tumors 1.2 to 3.5 mm in thickness exhibited a melanoma-specific survival benefit compared with those in the observation arm who subsequently developed regional nodal metastasis (hazard ratio for death from melanoma, 0.56; P = .006).[148] It was thus concluded that for adults with intermediate-thickness CM, delayed detection and treatment of nodal disease appeared to increase the extent of nodal disease when clinically detected (ie, palpable), increase the morbidity of treating that disease, and increase the likelihood of death from CM. As already noted, improved melanoma-specific survival was not demonstrated in the subset of patients who underwent immediate CLND in the second Multicenter Selective Lymphadenectomy Trial.[192]

Although the MSLT-I showed no survival benefit for SLNB in the subset of patients with T3 CM greater than or equal to 3.6 mm in thickness and T4 lesions, staging and regional control benefit is critical in this subgroup at higher risk of regional nodal recurrence and distant metastasis. As noted, accurate staging may promote oncologic consultation and consideration for adjuvant systemic therapy or clinical trials, most of which require SLNB.

Settings in which to discuss, consider, and/or offer SLNB

The WG recommends that pathologic staging with SLNB be discussed and offered for CM at least 1 mm in thickness and states that it may be considered for thinner T1 CM with a Breslow thickness of 0.8 to 1.0 mm (with or without ulceration) or less than 0.8 mm with adverse features (ulceration, lymphovascular invasion, and/or high mitotic rate, particularly in the setting of younger age). Discussion of SLNB and decision making regarding pursuing vs foregoing this staging procedure should be conducted on an individual basis and with appropriate input from surgical oncology.

Consideration of SLNB in T1 CM is more controversial than for thicker CM, and identification of tumors at higher risk of SLN positivity remains an active area of investigation. NCCN guidelines stratify consideration of SLNB in T1 CM according to Breslow thickness,[2] which is the strongest predictor of SLN positivity, particularly at or above the 0.75 mm (now 0.8 mm) threshold.[40] The WG recommends discussion of SLNB in patients with T1b CM, defined per the eighth edition of the AJCC staging system as less than 0.8 mm with ulceration or 0.8 to 1.0 mm with or

without ulceration, although overall rates of SLN positivity in this subset of patients are still relatively low (≤10%). Rates of SLN positivity in T1a CM (<0.8 mm without ulceration) are generally less than 5%.[151,152] Therefore, the WG does not recommend SLNB for patients in the T1a subgroup unless other histologic adverse features are evident.[2,153,154]

Although histologic ulceration, lymphovascular invasion, and high mitotic rate (the threshold for which remains to be established) are relatively uncommon in T1 CM, they have been associated with increased likelihood of SLN positivity in many, but not all studies.[83,153,155-158,195] Further analyses that assess mitotic rate across its continuum for survival-based end points and establish a relevant threshold for consideration of SLNB in T1 melanoma will likely inform clinical decision making.

Younger patients (<40 years) generally have higher rates of SLN positivity than do older patients.[159,196,197] Therefore, age should be taken into consideration for SLNB, particularly when other adverse histologic features are present in T1a or T1b CM. Incomplete/partial biopsy of the primary tumor, with a positive deep margin close to the 0.8 mm T1a/T1b threshold, is another reason to consider SLNB staging in thinner CM.

Contrary to previously held opinions that overall survival in patients with CM greater than 4.0 mm (T4) is determined by high rates of distant metastasis (apart from nodal status), SLN status remains a strong independent predictor of outcome and is essential for adjuvant therapy consideration and clinical trial stratification.[160,161] For all SLNB-eligible patients, the WG recommends careful discussion of the risks and benefits of the procedure, involving surgical oncology input when possible.

Reasons not to perform SLNB include advanced age, poor functional status, and/or comorbid conditions that portend a short life expectancy or preclude general anesthesia or subsequent treatment. As age increases, SLNs become more difficult to identify and rates of SLN positivity decline.[198] Although SLNB may have less prognostic value and may be technically more difficult in older individuals, there is currently no consensus for an upper age cutoff to recommend against this procedure. Each case should be discussed individually, and in conjunction with surgical oncology colleagues, with the decision to pursue pathologic staging of the regional LNs based on patient comorbidities and how that information may affect further management.

STAGING WORK-UP AND FOLLOW-UP

Recommendations for baseline staging and surveillance follow-up of CM are provided in

Table XIII. Recommendations for baseline and surveillance studies and follow-up

Baseline radiologic imaging and laboratory studies are not recommended for asymptomatic patients with newly diagnosed stage 0-II primary CM.
Radiologic imaging and laboratory studies for CM at baseline should be performed only to evaluate specific signs or symptoms of synchronous metastasis (regional nodal or distant).
The use of LN ultrasound is encouraged at baseline or in surveillance in the setting of an equivocal LN on physical examination, and for surveillance when • The patient meets criteria for SLNB but does not undergo the procedure; • SLNB is not possible or not technically successful (eg, because of failure of lymphoscintigraphic dye migration and inability to identify a draining SLN); or • CLND is not performed in the setting of a positive SLNB; and • When radiology expertise in the use of nodal ultrasound surveillance for CM is available.
Regular clinical follow-up is recommended as the most important means of detecting CM recurrence. Findings from the history (review of systems) and physical examination should direct the need for further radiologic or laboratory studies to detect local, regional, and distant metastatic disease.
Collaboration with medical oncology is recommended for patients with high-risk CM (stage IIB and IIC) and those with a positive SLNB result for discussion of surveillance imaging and clinical comanagement.
Surveillance follow-up schedule and consideration of radiographic imaging varies according to the risk of disease recurrence (as determined by stage of disease and other factors) and risk of new primary CM (determined by mole pattern, presence of atypical nevi, and family history). Laboratory studies are not recommended for surveillance of asymptomatic patients with CM.
Patient education on self-examination of the skin and LN for the detection of recurrent disease or new primary CM is recommended.
There is insufficient evidence to recommend routine molecular profiling assessment for baseline prognostication. Evidence is lacking that molecular classification should be used to alter patient management outside of current guidelines (eg, NCCN and AAD). The criteria for and the utility of prognostic molecular testing, including GEP, in aiding clinical decision making (eg, SLNB eligibility, surveillance intensity, and/or therapeutic choice) needs to be evaluated in the context of clinical study or trial.

AAD, American Academy of Dermatology; *CLND*, completion lymph node dissection; *CM*, cutaneous melanoma; *GEP*, gene expression profiling; *LN*, lymph node; *NCCN*, National Comprehensive Cancer Network; *SLN*, sentinel lymph node; *SLNB*, sentinel lymph node biopsy.

Table XIII. The evidence supporting these recommendations is provided in this section and summarized in Table XIV[96,97,199-230] with the strength of the recommendations.

History and physical examination

Following diagnosis of invasive primary CM, a thorough history and comprehensive physical examination represent the main components of the diagnostic work-up. Patient history should include a detailed review of systems, focusing on unanticipated major weight loss, new-onset headaches, or other concerning constitutional symptoms. Physical examination should include a total body skin examination, including evaluation of the primary CM biopsy site and surrounding skin for visible and/or palpable satellite/in-transit metastasis and evaluation of regional and distant LN basins. Identification of specific abnormalities on physical examination directs the need for additional laboratory and imaging studies.[1,2] On some occasions, imaging studies might be obtained at baseline in asymptomatic, high-risk patients with CM with equivocal examination findings (eg, regional nodal ultrasound for patients in

whom nodal status cannot be properly evaluated). However, this scenario represents an exception to baseline evaluation.

As with baseline assessment, the key to CM follow-up involves careful physical examination with attention to the WE scar and surrounding skin (between the WE and regional LN basin) to exclude local or satellite/in-transit recurrence, regional and distant LN examination, total-body skin examination to assess for new primary CM, and review of systems for potentially concerning signs or symptoms of disease recurrence (eg, headache, unanticipated weight loss). Following a diagnosis of CM, patients should be educated in the performance of regular skin self-examination for early detection of local recurrence at the scar site, satellite/in-transit metastasis, and new primary CM, as well as in regional LN self-examinations to assess for enlarged LNs.

Baseline and surveillance laboratory and imaging studies to detect occult metastasis

Baseline and surveillance laboratory studies (lactate dehydrogenase [LDH] level, liver function

Table XIV. Level of evidence and strength of recommendations for baseline and surveillance studies, and follow-up schedule

Recommendation	Strength of recommendation	Level of evidence	References
No baseline studies for patients with asymptomatic stage 0-II CM	A	I/II	199-211
Laboratory or imaging studies only to evaluate signs of symptoms of metastasis			
Use of LN ultrasound in the setting of equivocal LN status	A	I/II	202,212
Regular clinical follow-up to detect CM recurrence and metastasis	A	II	201,203,207,213-227
Tailored CM surveillance schedule and testing			
Collaboration with medical oncology for patients with higher-risk CM	C	III	Expert opinion
Patient education on skin self-examination	A	I/II	216,228,229
Use of prognostic molecular techniques, including gene expression profiling	C	II/III	96,97,230

CM, Cutaneous melanoma; *LN*, lymph node.

tests, chemistry panel, complete blood count), chest radiography, and other imaging studies (computed tomography [CT], positron emission tomography [PET], bone scintigraphy, magnetic resonance imaging [MRI]) are not indicated for patients with MIS (AJCC stage 0) or invasive CM (AJCC stages I/II) who present without signs or symptoms of metastasis.[199,200,213]

Most local, satellite/in-transit, and regional nodal recurrences are identified by clinical examination of the skin and LNs by the patient and/or health provider.[214-217] Surveillance imaging is performed to detect clinically occult, surgically or systemically treatable metastasis and is of greatest value in patients at higher risk of disease recurrence (generally stage IIB or higher).[218] Screening CT or PET-CT may be considered if the patient has nodal metastasis in the SLNB (stage III), although the yield is low in this setting (0.5%-3.7%).[231] Detection of occult metastasis tends to correlate with increased primary tumor thickness, ulceration of the primary tumor, and/or large tumor burden in the SLN(s).[201,231] A meta-analysis of 74 studies involving more than 10,000 patients with CM demonstrated that ultrasonography was superior for detection of LN metastasis and PET-CT was superior for detection of distant metastasis for both staging and surveillance in clinically appropriate patients.[202]

Although abnormal laboratory test results are rarely the sole indicator of metastatic disease, serum LDH level was incorporated into the AJCC melanoma staging system in 2002 (sixth edition) for the classification of stage IV (distant) disease, and it remains a key prognostic factor for this subgroup of patients. Elevated LDH levels are associated with worse survival, may predict response to therapy in stage IV patients, and are therefore incorporated across all M categories in the eighth edition of the AJCC staging system.[9] Testing of serum LDH level is not recommended at baseline or for surveillance in patients with lower stages of disease (stage I-III), given the lack of sensitivity or specificity for the detection of metastasis.[199]

The value of serum S100-beta (S100B) levels has been evaluated in multiple European studies, which suggest its role as a potential prognostic biomarker in patients with CM and as a useful tool to identify disease progression.[203,219] A 2008 meta-analysis of 22 studies involving 3393 patients with stages I to IV CM demonstrated worse survival in patients with serum S100B positivity; however, there was significant heterogeneity among study quantification of S100B, and only 2 studies separately evaluated stage I and II patients. One study with 876 clinical stage I patients revealed no significant correlation between S100B levels and survival,[232] and most data suggest potential prognostic value or use as a therapeutic biomarker in patients with stage III and IV disease.[233-235] Serum S100B testing is not routinely used in the United States and is not recommended at baseline or for surveillance of asymptomatic patients with CM on the basis of current evidence.

Routine imaging studies are limited by a low yield of true positive findings in asymptomatic patients with CM and the frequent occurrence of false-positive findings, particularly in earlier-stage disease. As yet, it has not been demonstrated that presymptomatic detection of distant metastasis improves patient outcomes. However, as new therapies for advanced CM continue to evolve, it is possible that systemic

treatments may be more effective in patients with earlier, low-volume metastasis, and surveillance imaging recommendations may change as a result.

Studies consistently indicate that both baseline and surveillance chest radiography evaluation are cost-inefficient and associated with very few true positive findings and high false-positive rates, as well with increased patient anxiety and morbidity related to investigation of spurious findings.[200,204-206,220] As such, chest radiography is not considered a radiologic imaging study of choice; however, it may be considered for surveillance of lung metastasis in patients with stage IIB and higher disease at a 3- to 12-month interval according to the risk of recurrence.[2]

For baseline evaluation in patients with newly diagnosed asymptomatic primary CM of any Breslow thickness, cross-sectional (CT, MRI) and functional/metabolic (PET) or hybrid (PET-CT) imaging is not indicated, except in uncommon situations such as the inability to assess nodal status by regular physical examination, in which case ultrasound evaluation could be obtained.[1,2] Similar to chest radiography, routine cross-sectional imaging in the asymptomatic patient is characterized by false-positive findings, higher cost from additional studies or invasive procedures, and increased patient anxiety, with no proven benefit in terms of overall survival.[218]

The utility of PET-CT, CT, and MRI in CM surveillance is directly correlated to the stage of disease, meaning that patients with stage III and IV CM are more likely to demonstrate clinically occult metastasis than are patients with stage I or II disease. The highest yield of imaging occurs when a patient is symptomatic or has clinical findings suggestive of disease recurrence. Consultation with medical, surgical, and/or cutaneous oncology specialists is recommended to evaluate for suspected metastasis, with imaging to determine the extent of disease before surgical and/or systemic therapy.

A 10-year prospective analysis of 290 patients with stage IIB, IIC, and III CM assessed the detection rates of imaging with CT of the chest/abdomen/pelvis and brain MRI every 6 months for 5 years after diagnosis, followed by annual chest radiography until year 10.[221] Nearly 40% of patients developed metastasis at a median of 1.4 years. Imaging detected 56.7% of recurrences (mainly visceral), as compared with 41.5% of recurrences initially detected by patient or provider examination. Most clinically detected recurrences were cutaneous. Overall survival was not assessed, however, preventing conclusions as to the merit of this intensive imaging approach in terms of patient outcomes. Another study of surveillance CT in patients with stage IIB and IIC CM concluded that

imaging should be performed only if symptoms of clinical metastatic disease are present.[207]

The WG recommends against surveillance imaging for asymptomatic patients with stages IA, IB, and IIA CM (≤4 mm), unless clinically indicated for work-up of concerning signs and/or symptoms of disease recurrence. Engagement with cutaneous, surgical, and/or medical oncologists is advised for patients with high-risk CM (stages IIB and IIC) for discussion of surveillance imaging and clinical co-management. On the basis of lower-level evidence, surveillance imaging may be considered on an optional basis to screen for recurrent/metastatic disease in asymptomatic patients with stage IIB CM and higher, with frequency determined according to the risk of disease recurrence. However, routine radiologic imaging in patients with asymptomatic CM of any stage is generally not recommended after 3 to 5 years of disease-free follow-up, given timing and patterns of relapse.[2,194,236]

LN ultrasound for regional nodal evaluation and surveillance

Numerous studies have been conducted evaluating LN ultrasound in patients with CM and demonstrate improved assessment of regional LNs compared with palpation alone at both initial diagnosis and during follow-up.[202,212] The use of nodal ultrasound is encouraged at baseline or follow-up in the setting of an equivocal LN on physical examination and for surveillance (1) when the patient meets the criteria for SLNB but does not undergo the procedure; (2) when SLNB is not possible or not technically successful (eg, because of failure of preoperative lymphoscintigraphic dye migration and inability to identify a draining SLN); and (3) when CLND is not performed in the setting of a positive SLNB.[2] Regional nodal ultrasound for melanoma detection requires specific radiologic expertise and understanding of established LN criteria,[237-239] and it has been less commonly used in the United States for this purpose. However, nodal ultrasound is less expensive, noninvasive, and safer than other imaging alternatives, and its use should be encouraged in the appropriate clinical setting and where radiologic expertise is available.

Optimal frequency and duration of clinical dermatologic surveillance for detection of melanoma recurrence and/or additional primary melanomas

Although the optimal interval and duration of follow-up for CM are not well defined, the WG recommends that patients with CM be monitored regularly following diagnosis, particularly for tumors

Table XV. Suggested surveillance intervals and follow-up tests

CM stage	Follow-up interval and duration	Examination	Radiologic* tests
Stage 0 MIS	At least every 6-12 mo for 1-2 y; annually thereafter	Physical examination with emphasis on assessment for local recurrence, particularly for the LM subtype, and full skin check to ascertain for new primary CM	None
Stage IA-IIA	Every 6 to 12 mo for 2-5 y; at least annually thereafter	Comprehensive history (review of systems) and physical examination, with specific emphasis on the skin and regional LNs	None
Stage IIB and higher	Every 3-6 mo for the first 2 y; at least every 6 mo for 3-5 y and at least annually thereafter	Comprehensive history (review of systems) and physical examination, with specific emphasis on the skin and regional LNs	May be performed for up to 3-5 y[†]

CM, Cutaneous melanoma; *LM*, lentigo maligna; *LN*, lymph node; *MIS*, melanoma in situ.
*Including chest radiography (to screen for lung metastasis); computed tomography of the chest, abdomen, and pelvis; brain magnetic resonance imaging; and/or positron emission tomography—computed tomography. The frequency of imaging depends on the risk of recurrence.
[†]Highest risk period for relapse.

at increased risk of recurrence (ie, >2.0 mm in thickness and/or with ulceration, lymphovascular invasion, high mitotic rate). Although most metastases occur in the first 1 to 3 years after treatment of the primary tumor, skin examinations for life are generally recommended. An estimated 4% to 8% of patients with a history of CM develop new primary CM, typically within the first 3 to 5 years following diagnosis.[222] The risk of new primary CM is higher in the setting of increased nevus count, multiple clinical atypical/dysplastic nevi, family history of CM, fair skin/sun sensitivity, prior CM, and male sex.[240] The frequency of dermatologic, surgical, and oncologic surveillance depends on individual patient risk of new primary CM and for recurrent disease.

Surveillance follow-up schedules vary significantly depending on country of location, physician specialty, and stage of disease.[241] In the absence of evidence-based guidelines, many clinicians arrange follow-up according to the schedule with which they and their patients are most comfortable. A suggested surveillance plan is shown in Table XV. On the basis of expert opinion, for patients with stage 0 (MIS), the WG recommends physical examination with emphasis on assessment of local recurrence, particularly for the LM subtype, and a full skin check to evaluate for new primary CM at least every 6 to 12 months for 1 to 2 years and annually thereafter. For stages IA to IIA CM, the WG recommends a comprehensive history, review of systems, and physical examination with specific emphasis on the skin and regional LNs at least every 6 to 12 months

for 2 years and at least yearly thereafter. For patients with stage IIB to IIC, clinical follow-up is recommended every 3 to 6 months for 2 years, then at least every 6 to 12 months for 3 years, and at least annually thereafter.[2] Patients should be promptly evaluated for new concerning skin lesions, change in the CM scar, and/or worrisome signs/symptoms that may indicate recurrent disease.

Additional factors that may influence the follow-up interval include a history of multiple primary CM, the presence of clinically atypical nevi, a family history of or documented genetic predisposition to CM, patient anxiety, and the patient's awareness and ability to detect early signs and symptoms of disease. The WG recommends coordination of surveillance visits across specialty teams to avoid duplication or overlooked testing. This is particularly relevant in the setting of patients with stage IIB or higher CM, a cohort that usually benefits from multidisciplinary surveillance. As noted, available evidence regarding recurrence, surveillance, and survival predates recent breakthroughs in advanced CM treatment. Prospective analyses will likely inform future surveillance recommendations in asymptomatic high-risk patients.

Role of molecular profiling techniques in prognostication and follow-up

There is a need to identify novel biomarkers in CM with improved and/or complementary prognostic ability to conventional clinical and histologic parameters. This approach may be especially relevant to determine thinner CM at increased risk of metastasis.

Gene expression–based prognostic signatures offer promise, but the studies to date have been characterized by heterogeneous sample sizes of high-risk, event-rich cohorts that do not necessarily represent the spectrum of patients who may benefit from the test, as well as by questionable applicability to clinical practice.[96,97,242] Research to develop GEP and other molecular tests (eg, microRNA expression profiles)[243,244] for the accurate and reproducible identification of patients with CM who will experience recurrence is an area of ongoing study[230] that is made more relevant by available systemic adjuvant therapies that improve relapse-free and/or overall survival.[188,189,245]

The majority of the published prognostic GEP studies have compared the predictive accuracy of recurrence or death from CM to SLNB outcome or stage according to the seventh edition of the AJCC staging system.[32,96,97,246-249] These nonoverlapping gene panels have been reported to be as or more predictive of prognosis compared with SLNB status, AJCC stage, and/or traditional histologic factors (Breslow thickness, ulceration, mitotic rate, with the latter usually dichotomized at $1/mm^2$ and not studied as a continuous variable).[97,249] Going forward, GEP assays should be tested against all known histopathologic prognostic factors and contemporary eighth edition of AJCC CM staging to assess their additive value in prognostication. The improved survival for CM on the basis of more accurate pathologic staging in the AJCC worldwide collaborative database of more than 46,000 patients for eighth edition staging supports the prognostic value of SLNB status.[40]

The evidence to date indicates that GEP can stratify patients with CM into distinct categories with some precision.[96,97,230,249] It is not known, however, whether GEP provides more accurate predictions vis-à-vis optimized phenotypic models or whether the addition of GEP can enhance ongoing and planned prognostic assessment with use of known clinicopathologic parameters.[9,40] Importantly, changes to clinical practice (eg, SLNB, intensity of surveillance/imaging, and/or therapeutic choice) based on GEP results should be avoided until more data from the requisite clinical trials and an assessment of clinical utility are available. In addition, the impact of a high-risk prognostic GEP classification on patient quality of life and anxiety over disease recurrence has not been adequately addressed.

Current evidence does not support increased surveillance imaging as a result of available prognostic GEP tests, particularly in node-negative patients who are not yet eligible for newer, more effective adjuvant therapies. Similarly, the frequency of clinical follow-up and indications for imaging in patients with CM are unlikely to be modified by a prognostic GEP result until prospective studies have confirmed a benefit and adjuvant therapy has demonstrated a meaningful impact in earlier-stage disease. In the past, metastatic progression had been largely equated with mortality given the lack of effective therapy. Future prognostic and outcome modeling will need to incorporate the enhanced survival of patients with AJCC stages III to IV CM given the available and emerging systemic treatments.

Lingering questions remain regarding the degree to which the selected gene sets represent genes associated with tumor progression, how they compare with current well-characterized prognostic factors and AJCC eighth edition survival data, and whether they improve prognostic models enough to affect patient management and outcomes. As such, the WG discourages routine baseline GEP for prognostication. Because no surgical or therapeutic RCTs have examined outcome in the context of GEP classification, the WG recommends against using GEP information for management decisions (eg, provision of SLNB, surveillance intensity or imaging, and/or therapeutic choice) outside of a clinical study or trial.[2] A comparative clinical study of molecular profiling platforms is critical to understand the added value of each individual test before its clinical implementation, as is further prospective validation.

Types of local melanoma recurrence and effect on subsequent management

Local CM recurrence within or surrounding the WE consists of 2 types: (1) so-called persistent disease, which corresponds to a recurrence histologically defined by the presence of in situ and/or radial growth phase, and (2) satellite metastasis, which is clinically detectable and represents intralymphatic spread (stage III).[2] Recurrence of persistent disease is generally macular and presents at the margin of the prior WE scar, whereas satellite/in-transit metastases are palpable cutaneous or subcutaneous masses within or surrounding the WE scar (between the scar and regional LN basin). Since satellite and in-transit metastasis both represent intralymphatic (stage III) melanoma, their previous classification based on distance from the WE scar (ie, 2 cm) has been omitted from the eighth edition of the AJCC melanoma staging system.[9,40]

The distinction between local recurrence from persistent disease and local recurrence from satellite metastasis within the WE scar is clinically relevant. The former is presumed to result from incomplete excision of the initial primary CM and is generally

treated with WE, with surgical margins and consideration of SLNB according to histologically remeasured Breslow thickness. The latter is treated as a stage III recurrence in the multidisciplinary setting, which may include excision, imaging, SLNB, systemic or intralesional therapy, and/or enrollment in clinical trials.

NONSURGICAL MANAGEMENT OF MIS, LM TYPE
Topical imiquimod as primary or adjuvant therapy

Surgery is the mainstay of therapy for MIS, including the LM type. However, as this subtype is characterized by larger tumors on chronically sun-exposed skin of the face, scalp, and ears of older individuals who may be poor surgical candidates, alternative therapies, including topical imiquimod cream 5%, have been studied. In addition, complete excision of MIS, LM type, may be confounded histologically by the presence of actinic melanocytic hyperplasia, which cannot be reliably differentiated from true MIS, LM type, even with additional cytoplasmic and nuclear immunostains (eg, Melan-A, S100, HMB45, Sox10, and microphthalmia transcription factor).[173,250] However, the limitations of topical treatment versus surgical excision of MIS, LM type, need to be carefully discussed. In the primary treatment setting, there is a risk of undertreating follicular adnexal extension and potential invasive CM,[172] particularly in the absence of a diagnostic excisional or broad shave biopsy to exclude histologic microinvasion.

Since the 2011 AAD CPG was issued, additional case series, cohort studies, 3 systematic reviews, a randomized trial assessing imiquimod pretreatment with or without tazarotene 0.1% gel before staged excision,[251] and a single-arm phase II trial investigating the use of topical imiquimod for MIS of the LM type have been published.[251-260] Most studies have shown rates of histologic and clinical clearance of at least 75% when topical imiquimod cream is used as primary treatment for LM (in lieu of surgical excision). However, a recent single-arm phase II trial of up to 60 imiquimod applications over 12 weeks followed by surgical resection showed pathologic clearance rates of 37.0% (10 of 27 patients), though the limitations of pathologic assessment in the setting of sun-damaged skin were noted.[261] Higher pathologic clearance was reported in the subset of patients with both clinical and pathologic response (63.3%), suggesting the importance of duration of treatment until clinical clearance has been achieved. A randomized trial of 47 patients was conducted to evaluate the addition of tazarotene 0.1% gel to imiquimod 5% cream versus imiquimod monotherapy for MIS, LM type, followed by conservative staged excision. Complete response after 12 weeks was observed histologically in 78% of lesions treated with combined therapy versus 64% treated with monotherapy (*P* = .17), with 22% of the lesions (8 of 37) versus 36% (15 of 42) demonstrating residual MIS, LM type, on subsequent staged excision and no recurrences at a mean follow-up of 42 months.[251]

Other case series and prospective cohort studies have demonstrated higher rates of clearance (>94%) in the adjuvant setting following attempted complete surgical resection, either when histologic peripheral margins are narrow or when there is histologic transection at the periphery without clinical correlation of a residual lesion.[252,253] However, the level of evidence remains low, with no prospective, randomized trials to assess long-term efficacy of imiquimod for either primary or adjuvant use.

Off-label use of topical imiquimod has been proposed as an adjunctive modality after "optimal" surgical excision,[2] though the term *optimal* is subject to interpretation. One hypothesis is that topical "field" treatment with imiquimod could eradicate sun-damaged melanocytes that serve as a nidus for new or recurrent MIS and also treat potential subclinical residual LM in a surgically treated site with histologic but not clinical evidence of tumor transection.[252] This hypothesis has not been formally tested, and the use of imiquimod field therapy as an adjunct to conventional WE or staged excision (including MMS) warrants further exploration.

Most studies of primary or adjuvant imiquimod for MIS, LM type, have shown improved outcomes, with lower rates of local recurrence when an approximate 2-cm margin of clinically normal-appearing skin is treated 5 or more times per week for at least 12 weeks (>60 treatments) and after an inflammatory response is elicited.[252,254,256,260,262] However, lack of inflammation has been observed with favorable outcomes in the adjuvant setting following surgery, in which case histologic transection may simply represent actinic melanocytic hyperplasia.[252] It is important to recognize that for some patients, several months of imiquimod-induced inflammation may be less tolerable than surgical excision,[261] and the pros and cons of topical imiquimod warrant thorough discussion with patients and their families.

A 2014 systematic review concluded that in selected cases in which contraindications to surgery exist, nonsurgical interventions for MIS, LM type (including topical imiquimod), may be effective and/or preferable but should be used by experienced providers with close, ongoing patient follow-up to observe for potential local recurrence.[112] Therefore,

Table XVI. Recommendations for the use of imiquimod or RT

Topical imiquimod 5% cream may be used as second-line treatment for MIS, LM type, when surgery is not possible at the outset (primary setting) or when optimal surgery has been performed (adjuvant setting).

Careful discussion of the associated risks, benefits, and uncertainties of nonsurgical treatment should take place with the patient and family.

For nonsurgical candidates, RT may be utilized as a second-line therapy for MIS, LM type, though its use is uncommon in the United States.

The use of superficial brachytherapy for MIS, LM type, is not recommended.

Adjuvant RT after WE may be used for desmoplastic CM with high-risk features (eg, Breslow thickness >4 mm, Clark level V, extensive neurotropism/perineural invasion, head and neck location, and/or narrow deep margin resection).

Consultation with a radiation oncologist is recommended to discuss the associated risks and potential benefits of RT.

CM, Cutaneous melanoma; *MIS, LM*, melanoma in situ, lentigo maligna; *RT*, radiation therapy; *WE*, wide excision.

the WG recommends surgery for eradication of MIS, LM type, as first-line therapy. Alternatives, such as imiquimod or RT (see later) can be considered as second-line treatment on a case-by-case basis after a full discussion of the associated risks, benefits, and uncertainties. Recommendations for the use of imiquimod are shown in Table XVI. The level of evidence and strength of these recommendations are summarized in Table XVII.[57,85,112,251-275]

Finally, there may be situations in which clinical observation of large MIS, LM type, is suitable, particularly in elderly patients with medical comorbidities in whom aggressive treatment would be inappropriate. As discussed in the 2011 AAD CPG,[1] treatment of MIS, LM type, with surgical or nonsurgical modalities has not been demonstrated to be superior to observation, although it is reasonable to assume that therapy aimed at reducing tumor burden may improve patient outcomes by reducing the potential for invasive CM development and its associated morbidity.

RT IN PRIMARY MELANOMA
RT for primary treatment of MIS, LM type

Primary RT for MIS, LM type, may be considered when complete surgical excision is not possible, though recent advances in RT have been utilized largely outside the United States.[255] The interpretation of published data is complicated by small sample sizes, varying types of RT, different dosing schedules, and lack of long-term outcome data. Several smaller series from Canada dating back to the 1970s utilized conventional orthovoltage RT for the treatment of in situ and invasive LM with recurrence rates ranging from 0% to 14%.[263-265] Since that time, 3 larger retrospective European studies (N = 64, 150, and 593, respectively) reported the use of superficial/ultrasoft/soft X-ray or Grenz ray (Miescher technique) treatment for in situ and invasive LM with recurrence rates ranging from 0% to 17%.[266-268] Although survival rates for MIS, LM type,

in general were excellent as expected, patient follow-up in these analyses was variable and evaluation of recurrence was based on clinical examination without histopathologic confirmation. Local control and cosmetic results appeared consistently good in the selected populations.

The adequacy of dermal penetration is a concern with low-voltage RT. Superficial RT typically penetrates about 1 mm into the dermis, whereas hair follicles are estimated to extend to a median of 1.5 mm. Other investigators have suggested that a penetration depth of 5 mm is necessary to treat below hair follicles, although this may result in permanent pigmentary changes, dermal fibrosis, and overlying hair loss.[269] Low-voltage superficial X-ray therapy is rarely, if ever, used in the United States for the treatment of MIS, LM type.

A literature review of primary RT for MIS, LM type, was published in 2014; it included 9 clinical studies published through 2009 and involving 537 patients, with a median follow-up of 3 years.[269] In all, 8 studies had outcomes data and showed 18 local recurrences in 349 patients (5%), with progression to invasive LM melanoma in 5 patients (1.4%) who had subsequent poor outcomes. A total of 5 marginal recurrences (4%) and 8 in-field recurrences (5%) were documented, but differing treatments, parameters, and dosages limited specific recommendations regarding primary RT for MIS, LM type. As noted previously, RT may be considered as second-line therapy for MIS, LM type, when surgery is not an option and where expertise with the technique is available. There are no data to support the use of electronic surface brachytherapy for CM, which is not recommended by the WG.[276]

RT as an adjuvant treatment for desmoplastic melanoma with high-risk features

Desmoplastic CM presents unique treatment challenges. Deep tumors with certain high-risk features

Table XVII. Level of evidence and strength of recommendations for (second-line) imiquimod treatment of MIS, LM type, and RT

Recommendation	Strength of recommendation	Level of evidence	References
Imiquimod for MIS, LM type (primary and adjuvant settings)	B	II/III	112,251-262
RT for MIS, LM type	C	II/III	112,255,263-269
Against use of superficial brachytherapy for MIS, LM type	C	III	Expert opinion
Adjuvant RT for high-risk desmoplastic CM	B	II/III	57,85,270-275
Consultation with a radiation oncologist	C	III	Expert opinion

CM, Cutaneous melanoma, *MIS*, melanoma in situ, *LM*, lentigo maligna, *RT*, radiation therapy.

(eg, T4 lesions, extensive neurotropism/perineural invasion, head and neck location) are more difficult to surgically eradicate and have an increased chance of local recurrence and satellite metastasis at the primary site.

There are limited data addressing the benefit of adjuvant RT following WE of desmoplastic CM.[85,270-274] An ongoing Trans-Tasman Radiation Oncology Group phase III clinical trial is comparing adjuvant RT with observation following resection of neurotropic CM of the head and neck. The largest (N = 277) and most informative study published to date demonstrated that adjuvant RT was associated with improved local control for desmoplastic CM with negative resection margins, head and neck location, thickness greater than 4 mm, and/or Clark level V.[85] Among 35 patients with positive resection margins, lower rates of local recurrence were also noted in those who received RT than in those who did not. Another study involving 130 patients with desmoplastic CM showed that adjuvant RT was associated with improved local control, but not with CM-specific survival, distant metastasis-free survival, or overall survival.[275] A retrospective study of adjuvant RT in desmoplastic neurotropic CM in 128 patients demonstrated the importance of clear surgical margins for local control.[57] The adjuvant RT−treated group demonstrated recurrence rates similar to those in the surgery-only group, but it generally consisted of patients with high-risk features (head and neck location, greater thickness, higher Clark level, and narrow-margin excision). Limitations of all studies include their retrospective nature that spans decades, different treatment protocols and definitions of histologic desmoplasia, and selection bias.

There is general consensus that adjuvant local RT after WE may provide improved local control for desmoplastic CM with high-risk features, but it has no effect on development of distant metastasis or on overall survival.[2] On the basis of the available evidence, the WG recommends consideration of adjuvant RT for desmoplastic melanoma with high-risk features (eg, Breslow thickness >4 mm, Clark level V, extensive neurotropism/perineural invasion, head and neck location, and/or narrow deep margin resection). Consultation with a radiation oncologist is encouraged to discuss the associated risks and potential benefits of local adjuvant RT.

Recommendations for the use of RT for primary CM are shown in Table XVII. The level of evidence and strength of these recommendations are summarized in Table XVI.

PREGNANCY AND MELANOMA
Pregnancy and risk of developing melanoma

Although CM is on the rise in young women, and in some studies[277] is the most common malignancy reported during pregnancy, evidence is lacking that pregnancy per se increases the risk of developing CM or alters the prognosis. Although the incidence of CM is generally higher in men, it is higher in younger women than in men, most notably during women's reproductive years. A 2009 Norwegian study revealed that the most common malignancy during pregnancy was CM, representing 31% of all malignancies arising during pregnancy.[278]

Whether the increased incidence of CM in young women is related to hormonal factors (including oral contraceptive use before pregnancy) or pregnancy itself has long been debated; the adverse effect of tanning behaviors and tanning bed use, which is particularly common among young women, is clear.[279] Of note is the decreased risk of CM for women with a history of 5 or more live births versus for women with none. Women with a younger age at first birth and higher parity have a lower risk of CM than do women with an older age at first birth and fewer than 5 live births.[280,281] Similar findings were noted in a later study in which it was also demonstrated that women who had their first child earlier in life and who had multiple children were found to be at lower risk of CM.[282] These findings suggest that pregnancy may be protective against CM rather than causative.

Recommended waiting period before a woman with a history of melanoma becomes pregnant

Evidence that future pregnancies will increase the risk of CM recurrence or metastasis is lacking. Several studies have demonstrated no significant impact on prognosis of CM diagnosed before pregnancy.[281] Therefore, if a woman has an early-stage CM (MIS or stage I) with little to no risk of metastasis, there is no rationale to delay subsequent pregnancies. However, in the setting of a higher-risk stage II CM, a 2- to 3-year delay period may be advisable because most recurrences will develop by this time. The suggestion to delay subsequent pregnancy is not based on pregnancy's impact on the mother's CM; controlled studies have consistently revealed no statistically significant difference in survival for CM in pregnant patients versus nonpregnant patients. Rather, this recommendation is based on the desire to avoid the complications of systemic therapy in a pregnant woman with metastatic melanoma and to prevent the loss of the mother, although available effective therapies may reduce this possibility. Additionally, there is the very small risk of placental and fetal CM metastasis if the pregnant mother develops widespread disease.[283]

A population-based study to assess whether cancers (including CM) diagnosed during pregnancy or lactation were associated with an increased risk of death due to the cancer concluded that most cancers during pregnancy and/or lactation do not increase the risk of cancer-specific death, with the exception of breast cancer and ovarian cancer diagnosed during lactation.[278] A systematic review and meta-analysis of 5 studies that met the authors' inclusion criteria concluded that that pregnancy after a successfully treated CM did not worsen prognosis.[284] However, only 1 of the 5 studies included patients beyond stage I disease.

In contrast to these findings, some of the same authors conducted another systematic review of 14 studies and concluded that pregnancy-associated melanoma (PAM) appeared to have a poorer outcome, with a 56% higher mortality risk compared to non-PAM.[285] However, the pooled estimate of mortality risk was performed on only 4 studies that reported hazard ratios and confidence intervals. Several criticisms arose regarding the small number of studies, their varied design and definition of PAM, questionable statistical analysis, and incomplete outcome data. For instance, a postpregnancy study of women 5 years after childbirth was included,[286] as was a population-based study that was missing Breslow thickness in 45% of cases and included proportionally more CM at high-risk sites (head, neck, trunk) in pregnant versus nonpregnant

women.[278] In this latter study, there was no difference in tumor thickness in the 55% of the pregnant women with available Breslow thickness compared with the nonpregnant women. In addition, a prior comprehensive population-based study of the California Cancer Registry demonstrating equivalent maternal and neonatal outcomes for pregnant versus nonpregnant women was excluded from the systematic review because of lack of confidence intervals.[287]

A recent study using tumor proliferative markers (mitotic index and phosphohistone H3 and Ki-67 immunostains) in PAM demonstrated no proliferative activity difference between 50 PAM and 122 non-PAM cases.[288] The authors concluded that the occurrence of the CM during pregnancy should not outweigh other traditional factors (eg, Breslow thickness, AJCC stage, age of the patient) in terms of advice for planning future pregnancies. The WG recommends that timing of future pregnancies in women with PAM consider patient age, CM stage, general reproductive health, and likelihood to conceive before recommending any delay.

Effect of pregnancy on outcome for patients in whom cutaneous versus metastatic melanoma has been diagnosed

Evidence is lacking that pregnancy negatively affects the prognosis of primary CM or more advanced (metastatic) CM. Controlled studies have reported no significant influence of pregnancy on survival, or worse prognosis in pregnant versus nonpregnant women diagnosed with CM.[278,281,287] As noted, the study using proliferative markers in PAM demonstrated no difference in proliferative activity in PAM versus in CM unassociated with pregnancy,[288] supporting the conclusion that prognosis of PAM depends on conventional factors (eg, stage, tumor thickness).

However, 2 contradictory studies have recently been published, including the 2015 systematic review and meta-analysis that reported an increased risk of CM-related death in pregnant patients.[285] Additionally, a retrospective study from a single tertiary care institution demonstrated an increased mortality rate and greater odds of death in woman younger than 50 years with PAM than in nonpregnant women.[289] These findings are incongruent with those of all other studies and are challenging to interpret because of the small number of patients, inconsistent reporting of CM stage, and survival analysis techniques used.

Finally, some studies have addressed the therapeutic approach and outcome for pregnant women in whom CM has been diagnosed. Those with stage I

Table XVIII. Recommendations for management of CM and pregnancy

In a pregnant woman with CM, a tailored, multidisciplinary approach to care that involves the obstetrician and CM specialists relevant to the patient's stage of disease is recommended. A diagnosis of CM during pregnancy does not alter prognosis or outcome for the woman; however, work-up and treatment must take the safety of the fetus into consideration.

In women with a history of CM, a prolonged waiting period before subsequent pregnancy is not recommended. Factors that affect disease recurrence, including CM thickness and stage, as well as age and fertility of the mother, should determine whether a woman with a history of CM should delay becoming pregnant and for how long.

The approach to melanocytic nevi in the pregnant woman should be identical to that in the nonpregnant patient. Any changing nevus during pregnancy should be evaluated and subjected to biopsy if clinically and/or dermoscopically concerning.

Exogenous hormones (eg, oral contraceptives and hormone-containing contraceptive devices/implants, postmenopausal hormone replacement therapy, or hormones associated with assisted reproductive technology) may be used in women in whom CM has been diagnosed.

CM, Cutaneous melanoma.

and II disease have the same outcome and treatment as nonpregnant patients with CM. Those with stage III and IV have also been shown to have the same outcome. However, treatment needs to be individualized and patient specific, depending on several factors (including the timing of CM diagnosis during the pregnancy).[290] Therefore, the WG recommends a tailored, multidisciplinary approach involving the obstetrician and CM specialists relevant to the stage of disease.

There is consensus that WE with local anesthesia can be safely performed throughout pregnancy and that it should usually not be delayed following a CM diagnosis. Regarding SLNB, there is general agreement that this staging procedure should not be performed during the first trimester to avoid exposure to general anesthesia. However, SLNB is considered safe during the second and third trimesters without use of the blue dye to avoid potential anaphylaxis.[283] It is the opinion of the WG that pregnant women with higher-stage CM usually benefit from interdisciplinary care involving an obstetrician, dermatologist, surgeon, and/or medical oncologist.

Skin examination and changing nevi in the pregnant woman

Pregnancy itself does not require more vigilance for development of CM, which instead depends on typical risk factors such as skin phenotype, sun exposure, tanning bed use, number of melanocytic nevi, and/or presence of atypical/dysplastic nevi. Evidence is lacking that melanocytic nevi darken or enlarge during pregnancy, except for those nevi on the breast and abdomen that may appear larger because of stretching of the skin. Melanocytic nevi on the back and legs of pregnant women have not been reported to enlarge. Transient dermoscopic changes have been reported in nevi during

pregnancy, but the nevi returned to normal postpartum, and none was suggestive of CM.[291] The WG recommends that any changing or otherwise concerning melanocytic nevus in a pregnant woman (not as a result of stretching on the breasts or abdomen) be evaluated clinically (optimally with dermoscopy), and if worrisome, be subjected to biopsy as in standard practice. In addition, appropriate sun-protective measures for pregnant women should be similar to those for nonpregnant patients.

Safety of exogenous hormones, oral contraceptives, and other contraceptive devices in women in whom melanoma has been diagnosed

Evidence is lacking that exogenous hormones (oral contraceptive therapy [OCT] or hormone replacement therapy [HRT]) or other contraceptive devices negatively affect prognosis in women with a history of CM, or increase the risk of new primary CM.[281] Therefore, the WG recommends against withholding hormonal therapy when medically appropriate in a patient with a history of CM.

A systematic review of 36 studies involving 5626 patients with CM found no increased risk of CM with OCT or HRT, suggesting that exogenous hormones are not associated with an increased risk of CM.[282] A pooled analysis of 10 controlled studies found no relationship between OCT use and CM (including current and/or past use and long duration of use), supporting the conclusion that OCT is not a risk factor for CM.[280] A randomized trial of postmenopausal women given HRT likewise demonstrated no increased risk of CM in this group versus in the placebo group.[292]

Women who required assisted reproductive technology (ART) (n = 113,226) were compared with women who did not (53,859) regarding incidence of all cancers. For those women who underwent ART, a

Table XIX. Level of evidence and strength of recommendations for CM and pregnancy, genetic counseling/testing, and dermatologic toxicities

Recommendation	Strength of recommendation	Level of evidence	References
Multidisciplinary work-up and treatment approach for the pregnant patient with CM	C	III	Expert opinion
Pregnancy waiting period	B	II	278,281,284,285,287,289
Evaluation and treatment of melanocytic nevi in the pregnant patient	C	III	291
Use of exogenous hormones and oral contraceptives in women with a history of CM	B	I/II	280-282,292,293
Referral for genetic counseling and possible germline genetic testing for select patients with CM	C	III	294
Frequency of dermatologic assessment for patients with advanced/metastastic CM	C	III	Expert opinion
Dermatologic assessment for patients with CM on who are undergoing BRAFI and other targeted therapy	A	I/II	295-304
Dermatologic assessment for patients with CM who are undergoing therapy with immune checkpoint inhibitors	A	I/II	305-311

BRAFI, B-Raf proto-oncogene, serine/threonine kinase inhibitor; *CM*, cutaneous melanoma.

statistically significantly lower risk of all cancers was noted compared with that for women without prior ART therapy. Parenthetically, the authors noted a non−statistically significant higher risk of CM in the women treated with ART, but there appeared to be no contraindications to ART-related hormone use in terms of CM risk.[293]

Recommendations for CM and pregnancy are shown in Table XVIII. The level of evidence and strength of these recommendations are summarized in Table XIX.[†]

GENETIC COUNSELING FOR PATIENTS WITH FAMILIAL MELANOMA AND MULTIGENE TESTING
Genetic testing for prediction of germline risk for patients or families at high risk of CM development

The spectrum of CM tumor syndromes is rapidly expanding. In addition to cyclin dependent kinase inhibitor 2A gene (*CDKN2A*) and cyclin-dependent kinase 4 gene (*CDK4*), germline variants in multiple genes (eg, *TERT* promoter, microphthalmia-associated transcription factor gene [*MITF*] E318K, and BRCA1 associated protein 1 gene [*BAP1*]) potentially predispose individuals to melanoma, among other cancers.[312] Features of cancer predisposition traditionally involve early onset of disease (at age <40 years), having multiple cancers or cancer types, multigenerational familial involvement down 1 lineage, and/or an aggregation of other rare malignancies beyond statistical chance. These features are critical to discern for possible hereditary CM, with history of familial CM and early onset of cancer in the individual or family as key features of cancer predisposition. For instance, a 70-year-old sun-damaged individual who develops 2 CMs within 5 years is less likely to harbor a germline mutation than is a 30-year-old who develops 2 CM within 5 years.

Because "familial" CM may result from heritable mutations or shared environmental risk, the actual prevalence of true "hereditary" CM is not known. A population-based estimate examining only *CDKN2A* found that 1.2% and 2.9% of patients with a single primary melanoma or multiple primary melanomas (MPMs), respectively, harbor germline *CDKN2A* mutations.[313] Compared with noncarriers, carriers of the *CDKN2A* mutation developed CM at an earlier age and more often reported a family history of CM. Although the number of high-quality studies examining the benefits of genetic counseling and testing in hereditary CM is extremely limited, several studies[314] of *CDKN2A* germline testing found improved adherence to total body skin examinations among unaffected carriers without inducing distress in either carriers or noncarriers; all participants reported at least 1 perceived benefit of genetic testing, whereas only 15.9% reported a negative aspect.[315] It is important to note that many of the published studies have predominantly focused on *CDKN2A* and have been from specialized centers with strong expertise in the management of hereditary CM. Thus, the role of genomic profiling using multigene panels and for a wider spectrum of cancers remains an active area of exploration.

A summary of the data and support for *CDKN2A/p16* testing, in which the rule of 3s was first proposed, has been published by the International

Table XX. Recommendations for genetic counseling of patients with CM

Cancer risk counseling by a qualified genetic counselor is recommended for patients with CM who have
- A family history of invasive CM or pancreatic cancer (≥3 affected members on 1 side of the family)
- Multiple primary invasive CM (≥3), including 1 early-onset tumor (at age <45 y)
- ≥1 MBAIT and a family history of mesothelioma, meningioma, and/or uveal melanoma
- ≥2 MBAITs

CM, Cutaneous melanoma, *MBAIT,* melanocytic BAP1-mutated atypical intradermal tumor.

Melanoma Genetics Consortium.[294] This concept involves 3 or more invasive CMs or a mix of 3 or more invasive CMs and pancreatic cancer diagnoses in an individual or family. Individuals who meet this criterion have a relatively high associated risk of *CDKN2A* mutation carriage (~30%). However, the penetrance of the p16 mutation depends on whether CM incidence is low or high in the geographic area and population, as well as on other factors (eg, skin phenotype, age of diagnosis, and degree of ultraviolet exposure). Those with pancreatic cancer in the family may benefit from earlier screening of this occult malignancy by gastroenterology specialists.[316]

More recently, the BAP1 tumor syndrome has been recognized as a rare but important cause of hereditary melanoma, including both cutaneous and ocular melanoma. *BAP1* is a tumor suppressor gene located on chromosome 3p21. Although the complete spectrum of tumors associated with *BAP1* mutations is unknown, germline mutations of *BAP1* are associated with increased risk of uveal melanoma, atypical Spitz tumors (also termed *melanocytic* BAP1-*mutated atypical intradermal tumors* [MBAITS]), CM renal cell carcinoma, and mesothelioma.).[317,318] Data support the conclusion that *BAP1* is a high-penetrance gene for ocular melanoma but a medium-penetrance gene for CM because only 13% of carriers of *BAP1* mutation develop CM.[317,319] Somatic *BAP1* mutations are also observed in cutaneous melanocytic neoplasms (atypical Spitz tumors and CM), uveal melanoma, mesothelioma, clear cell renal cell carcinoma, and other tumors.

Selection criteria for referral for multigene testing for familial melanoma

Patients with newly diagnosed CM should be queried regarding their personal and family history of CM and other cancers, as CM may present as the first cancer within mixed cancer syndromes. For patients with CM who have a family history of CM, those with 2 or more relatives affected by CM and/or pancreatic cancer (ie,. ≥3 in the kindred) should undergo genetic risk assessment, especially if a first-degree relative is involved. For patients with MPMs (≥3 invasive CMs), early age of onset of the initial CM (<45 years) is more consistent with a hereditary melanoma phenotype

than for those who develop MPMs later in life as a result of excessive sun exposure.

For dermatologists, 1 of the cardinal features of the BAP1 tumor syndrome is the presence of small red-orange papules that are histologically diagnostic of a *BAP1*-associated tumor.[320] Patients with at least 1 histologically proven MBAIT and a personal or family history of mesothelioma, meningioma, or uveal melanoma or individuals with 2 or more MBAITs should receive genetic counseling by a qualified counselor (see National Society of Genetic Counselors [https://www.nsgc.org/page/find-a-genetic-counselor]). Patients with a *BAP1* mutation should be offered regular skin and ocular examinations and may require referral to other specialists for internal malignancy screening.[312]

The ultimate decision to pursue genetic testing for germline mutations is a complex decision based on pedigree structure, cancer patterns, patient wishes, and perceived risks versus benefits. The WG suggests that genetic counseling be considered if the aforementioned criteria are met, with testing optional because not all individuals need to undergo formal genetic evaluation, and there is no strong evidence that genetic evaluation is either harmful or helpful. Recommendations for genetic counseling with possible multigene testing for hereditary melanoma are shown in Table XX. The level of evidence and strength of these recommendations are summarized in Table XIX.

DERMATOLOGIC TOXICITIES OF NEWER MELANOMA DRUGS
Follow-up for patients with metastatic melanoma for cutaneous side effect management

A multitude of novel drugs and combination drug regimens have been US Food and Drug Administration (FDA) approved for advanced or unresectable CM since the 2011 AAD CM CPG was issued. There is strong evidence derived from seminal RCTs regarding the incidence of dermatologic toxicities associated with newer CM drugs, including those targeting the MAPK pathway (BRAF inhibitors [BRAFIs] and mitogen-activated protein kinase kinase

Table XXI. Dermatologic toxicities of newer drugs for advanced CM (AJCC stages III and IV)

Dermatologists should collaborate with oncologists for management of cutaneous toxicity during BRAF/MEK kinase or immune checkpoint inhibitor therapy because appropriate recognition and control of skin side effects may improve the quality of life of patients with CM and avoid unnecessary interruption of medication.

The frequency of dermatologic assessment for cutaneous toxicity diagnosis and management depends on the agent(s) being used, age of the patient, underlying skin cancer risk factors (eg, history of actinic damage and/or skin cancer), and/or potential role of skin findings as a biomarker for response.
- Dermatologic assessment every 2-4 wk for the first 3 mo of BRAF inhibitor monotherapy is recommended for patients with numerous squamoproliferative neoplasms, although combination BRAF/MEK inhibition is standard and associated with less skin toxicity.
- Dermatologic assessment of patients undergoing therapy with immune checkpoint inhibitors should occur within the first mo of therapy and continue as needed for management of skin side effects.
- Patients with atopic dermatitis, psoriasis, or other autoimmune dermatoses should be seen before initiation of therapy by a dermatologist for pre-emptive counseling and treatment.

AJCC, American Joint Committee on Cancer; *BRAF*, B-Raf proto-oncogene, serine/threonine kinase; *CM*, cutaneous melanoma; *MEK*, mitogen-activated protein kinase kinase.

inhibitors [MEKIs]), and those resulting in immune checkpoint blockade to activate T lymphocytes (eg, monoclonal antibodies against cytotoxic T lymphocyte antigen-4 [CTLA4], programmed death-1 [PD-1], and its ligand programmed death ligand 1 [PD-L1]). As these agents are being used in other cancers, recognition of both common and rare cutaneous side effects is critical for appropriate management by dermatologists and other practitioners. It is important to recognize that the management of skin toxicity from the newer cancer agents is an actively evolving area of investigation and practice.

More than 90% of patients undergoing BRAFI monotherapy will develop cutaneous toxicity and about 40% of patients taking checkpoint inhibitors will develop autoimmune-related skin conditions.[295-297] However, many of the key trials that resulted in FDA approval for these agents[298-303] did not further classify cutaneous side effects beyond nonspecific terms such as *rash* or *pruritus*, with the exception of cutaneous squamous cell carcinoma (cSCC) development, which is most commonly associated with the use of BRAFI monotherapy. Subsequent characterization of dermatologic toxicities has resulted from numerous case series and review articles. Recommendations for assessment of dermatologic toxicities during treatment for advanced CM are shown in Table XXI. The level of evidence and strength of these recommendations are summarized in Table XIX.

BRAFI and MEKI therapy

FDA-approved BRAFIs include vemurafenib and dabrafenib; FDA-approved MEKIs include trametinib and cobimetinib. The most common cutaneous side effects for MAPK inhibitors include severe ultraviolet A–induced photosensitivity,

hyperproliferative epidermal neoplasms (including cSCC [usually keratoacanthoma-type]), hypertrophic actinic keratosis, verrucal keratosis, keratosis pilaris–type eruption, hand-foot skin reaction (painful palmoplantar keratosis), and xerosis, which are frequently observed during BRAFI monotherapy.[296,297,304] Less common BRAFI-associated skin findings include telogen effluvium and textural hair changes (course, brittle hair), eruptive nevi, panniculitis (namely, erythema nodosum), and BRAF wild-type new primary CM (generally superficial in nature).[321] Cutaneous SCC/keratoacanthoma development generally occurs in older patients with pre-existing actinic damage and/or a history of skin cancer, within 8 weeks of starting therapy. With continuation of BRAFI therapy beyond 4 to 6 months, the incidence of new cSCC/keratoacanthoma lesions often decreases.

Baseline dermatologic assessment and pre-BRAFI treatment of actinic keratosis is warranted. Complete surgical excision for most cSCCs/keratoacanthomas is generally not indicated, and they can generally be managed with liquid nitrogen cryotherapy or deep shave/saucerization followed by electrodessication and curettage during the first few months of therapy.[322] Many of these side effects are attenuated or even reversed with the addition of MEKIs, although MEK inhibition can promote the development of acneiform papulopustular skin eruptions and paronychia analogously to treatment with epidermal growth factor receptor inhibitors.[296,323,324] The NCCN melanoma guidelines currently recommend combined BRAFI and MEKI therapy as first-line treatment for those patients with metastatic CM and a *BRAF* V600 activating mutation in whom molecularly targeted therapy is indicated,[2] because compared with monotherapy, combination therapy

results in improved response rates and survival and reduced toxicity.

Hyperkeratosis and thickening of skin on the palms and soles (hand-foot skin reaction) is often painful and can be managed with topical keratolytic agents (ammonium lactate 12%, urea 20%-40%, or salicylic acid 6%) and emollients. Pretreatment podiatric evaluation for paring of existing corns, calluses, and hyperkeratotic areas may reduce symptoms.[322]

Acneiform eruptions during MEKI therapy can be managed with topical steroid ointments or oils for pruritus, topical or oral antibiotics (typically tetracyclines, or cephalexins to avoid potential phototoxicity), and/or dilute bleach soaks. Severe papulopustular eruptions may require treatment with isotretinoin or drug cessation.[325] As MEKI therapy is being studied in conjunction with checkpoint blockade in *BRAF* wild-type CM, recognition of the associated skin toxicities is important.

A recent RCT of dabrafenib in combination with trametinib versus matched placebos in patients with resected stage III CM showed statistically significant improvements in relapse-free and overall survival for patients who received dabrafenib/trametinib therapy, which is now FDA approved in the adjuvant setting.[189] The combined BRAFI and MEKI therapy was associated with rash and acneiform dermatitis in 24% and 12% of patients, respectively, but these toxicities were usually less than grade 3 in severity.

Immune checkpoint inhibitor therapy

FDA-approved immune checkpoint inhibitors include anti-CTLA4 (ipilimumab), anti−PD-1 (pembrolizumab and nivolumab), and anti−PDL-1 (atezolizumab) drugs. The most common dermatologic findings from immune checkpoint blockade include nonspecific morbilliform dermatitis with or without pruritus; pruritus with or without dermatitis; vitiligo (vitiligo-like CM-associated hypopigmentation); and lichenoid skin eruptions mimicking lichen planus, mucocutaneous lichen planus, lichenoid drug eruption, lichen sclerosis, or lichenoid keratosis.[305-308] Unmasking or worsening of atopic dermatitis, psoriasis, sarcoidosis, or autoimmune bullous disease (bullous pemphigoid-like) has been reported during treatment with both PD-1 and PD-LI inhibitors, with more frequent flare of pre-existing autoimmune disease if active at treatment initiation.[309,326] Onset of vitiligo-like CM-associated hypopigmentation may correlate with improved immune response, particularly for patients undergoing anti−PD-1 therapy,[310,311] in whom dermatologic recognition of this finding may therefore aid in oncologic management.

Anti-CTLA4 antibody therapy−induced skin toxicity is dose related and generally reversible, with onset generally occurring within the first month of therapy, as opposed to later onset with PD-1 or PD-L1 inhibitors.[307] Although an overall survival benefit was observed in patients treated with high-dose ipilimumab in the adjuvant setting for surgically resected stage III melanoma,[245] the severity of associated immune-related adverse events has limited its use in practice. A recent RCT showed that in the adjuvant therapy of resected stage IIIB, IIIC, and IV melanoma, the anti−PD-1 agent nivolumab resulted in improved recurrence-free survival and lower toxicity than did high-dose ipilimumab,[188] resulting in FDA approval of nivolumab in the adjuvant setting. The incidences of pruritus and rash with nivolumab were 23% and 20%, respectively, and were somewhat lower than reported with ipilimumab.

Immune checkpoint inhibitor−related morbilliform or maculopapular eruptions are generally treated with topical steroids, topical antipruritic lotions, and/or oral antihistamines. Systemic steroids may be necessary for more severe skin involvement, and prompt cessation of the drug is mandatory for onset of suspected Stevens-Johnson syndrome or toxic epidermal necrolysis.[307] Importantly, no difference in CM survival has been demonstrated between patients requiring immunosuppressive therapy for immune-related adverse events and those not requiring it.[327]

Viral oncolytic immunotherapy

Oncolytic virus immunotherapy is a new approach to treating metastatic CM, including satellite/in-transit metastasis. Talimogene laherparepvec is an oncolytic immunotherapy based on herpes simplex virus type 1. Administered via intratumoral injection, talimogene laherparepvec induces viral lysis of CM cells, followed by stimulation of a tumor-specific immune response.[328] There is a risk of spread to people in close contact with the patient following administration, to vulnerable populations, or through accidental exposure. Specific biosafety procedures and processes are required to mitigate this risk.

Role of the dermatologist in surveillance of patients with advanced melanoma

Dermatologists play a major role in the diagnosis and management of cutaneous side effects related to treatment of CM and other cancers. As yet, the most appropriate duration of PD-1/PD-L1 or MAPK inhibition is unclear, so chronic skin and systemic toxicities may be observed.[329] Early recognition and control of dermatologic toxicities may prevent

unnecessary interruption of medication and improve patient quality of life during treatment.[6] It is important to note that any systemic treatments for cutaneous reactions (eg, oral corticosteroids) should be undertaken with the partnership of medical oncology to avoid conflicts in therapeutic intent. An interdisciplinary approach to care is recommended by the WG. As CM survivorship increases in the era of novel therapeutics, dermatologists should work closely with oncologists and other practitioners on this front.

EMERGING DIAGNOSTIC TECHNOLOGIES

In review of the currently available highest-level evidence, the expert WG acknowledges that although much is known about the management of primary CM, much has yet to be learned. Bedside diagnosis will continue to improve with further investigation of existing, noninvasive imaging/electrical data acquisition and evaluation tools (eg, RCM, electrical impedance spectroscopy combined with digital dermoscopy, optical coherence tomography, cross-polarized light and fluorescence photography, and high-frequency ultrasound, some of which are already FDA approved)[330,331] and novel software technologies (eg, artificial intelligence–based deep learning algorithms[332]) that can inform and target those lesions most concerning for malignancy. Noninvasive genomic methods (eg, adhesive patch "biopsy") are being investigated to further classify melanocytic lesions as either benign or malignant to guide the need for further biopsy.[333,334]

The uptake of 1 or more of these technologies will eventually depend on cumulative evidence regarding their effectiveness, clinical utility, cost versus benefit, and competing strategies.

GAPS IN RESEARCH

Gaps in research have been identified; they include, but are not limited to, standardization of the interpretation of mitotic rate in primary CM; lack of RCTs for the surgical and nonsurgical treatment of MIS, LM type; the need for further study regarding MMS and other exhaustive margin control techniques for both invasive and in situ CM; the clinical utility and prognostic significance of various biomarkers and molecular tests; optimal clinical situations in which to pursue multigene somatic and germline mutational analysis; and the value of ancillary molecular tests in comparison with well-established clinicopathologic predictors of outcome. Efforts to standardize the histopathologic diagnosis and categorization of melanocytic neoplasms are under way to reduce the significant

interobserver variability among pathologists.[335] Ongoing advances in genomic medicine may make many of the aforementioned issues obsolete before the next AAD melanoma CPG is issued.

Because of these and other gaps in knowledge, the recommendations provided by the expert WG are occasionally based on consensus expert opinion rather than on high-level evidence. Management of primary CM should therefore always be tailored to meet the needs of the individual patient.

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