GUIDELINES OF CARE FOR THE MANAGEMENT OF
PRIMARY CUTANEOUS MELANOMA

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Publishable Conflict of Interest Statement

The American Academy of Dermatology (AAD) strives to produce clinical guidelines that reflect the best available evidence supplemented with the judgment of expert clinicians. Significant efforts are taken to minimize the potential for conflicts of interest to influence guideline content. The management of conflict of interest for this guideline complies with the Council of Medical Specialty Societies’ Code of Interactions with Companies. Funding of guideline production by medical or pharmaceutical entities is prohibited, full disclosure is obtained and evaluated for all guideline contributors throughout the guideline development process, and recusal is used to manage identified relationships. The AAD conflict of interest policy summary may be viewed at www.aad.org.

The below information represents the authors disclosed relationships with industry during guideline development. Relevant relationships requiring recusal for drafting of guideline recommendations and content by Work Group members are noted where applicable for each author.

Hensin Tsao, MD served as an advisory board member for Lubax and Epiphany Dermatology receiving honoraria; in another role with Journal Watch Dermatology
receiving honoraria; and as a principal investigator for Relay Therapeutics receiving grant funding.

Clara Curiel-Lewandrowski, MD served as a founder of DermSpectra LLC receiving stock; as a consultant for Amgen receiving honoraria; and has a first-degree relative who received honoraria from Amendia.

David Elder, MB ChB served as a consultant for SciBase and Myriad Genetics receiving honoraria. Dr. Elder was recused from drafting recommendations related to adjunctive pathology tests for equivocal nevi.

Jeffrey E. Gershenwald, MD served as a member of the advisory board for Merck, Syndax Pharmaceuticals, and Castle Biosciences, receiving fees; and in another role for Mercator Therapeutics receiving patent royalties. Dr. Gershenwald was recused from drafting recommendations related to prognostic molecular tests.

Jane M. Grant-Kels, MD was a stockholder for Melafind. Dr. Grant-Kels was recused from drafting recommendations related to diagnostic imaging.

Allan Halpern, MD served as a consultant for Canfield Scientific, Inc., DermTech, International Janssen Research and Development LLC, and SciBase receiving other financial benefits; as a member of the advisory board for Lucid, Inc. and Caliber Imaging and Diagnostics receiving other financial benefits; and in another role for Quintiles Pharma receiving other financial benefits. Dr. Halpern was recused from drafting recommendations related to diagnostic imaging.
Arthur Joel Sober, MD served as a principal investigator for MelaSciences receiving grants/research funding. Dr. Sober was recused from drafting recommendations related to diagnostic imaging.

John A. Thompson, MD served as a consultant for Eisai Pharmaceuticals and Genentech receiving honoraria; and as a member of the data safety monitoring board for Celldex receiving honoraria.

Oliver J. Wisco, DO served as a consultant for MiMedx Group, Inc. and ClearPath Diagnostics receiving fees. Dr. Wisco was also a stockholder for MiMedx Group, Inc. Dr. Wisco was recused from drafting recommendations on topic areas related to ClearPath products.

Shasa Hu, MD served as an advisory board member for Cosmetic Dermatology receiving fees.

Susan M. Swetter, MD, Christopher K. Bichakjian, MD, Valerie Guild, MS, MBA, Timothy M. Johnson, MD, Samantha Wyatt, MD, Jose V. Moyano, PhD, and Wendy Smith Begolka, MBS have no relationships to disclose.
ABSTRACT

The incidence of primary cutaneous melanoma (CM) 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 (AAD) clinical practice guideline (CPG), we provide updated treatment recommendations for patients with primary cutaneous melanoma (American Joint Committee on Cancer (AJCC) stages 0-IIC and pathological stage III by virtue of a positive sentinel lymph node biopsy (SLNB)). Biopsy techniques of a lesion clinically suspicious for melanoma are reviewed as are recommendations for the histopathologic interpretation of CM. The use of laboratory and imaging tests in the initial workup of patients with newly diagnosed melanoma and follow-up of asymptomatic patients are examined. With regard to treatment of primary CM, recommendations for surgical margins and discussion of the concepts of staged excision, including Mohs micrographic surgery (MMS); and nonsurgical treatments for melanoma in situ (MIS), lentigo maligna (LM) type, including topical imiquimod and radiation therapy, are updated. We describe the role of SLNB as a staging technique for CM and offer recommendations for its use. 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.

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 biological 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.

**ABBREVIATIONS**

AAD = American Academy of Dermatology

AJCC = American Joint Committee on Cancer

ART = assisted reproductive technology

BRAF = human gene that encodes a protein called B-Raf (V-Raf Murine Sarcoma Viral Oncogene Homolog B1)

CAP = College of American Pathologists

CPG = clinical practice guideline

CLND = completion lymph node dissection

CM = cutaneous melanoma

CXR = chest radiography

CT = computed tomography

CTLA-4 = cytotoxic T lymphocyte antigen-4
EGFR = epidermal growth factor receptor
GEP = gene expression profiling
HRT = hormone replacement therapy
KA = keratoacanthoma
LDH = lactate dehydrogenase
LN(s) = lymph node(s)
MAPK = mitogen-activated protein kinase
MEK = a kinase enzyme which phosphorylates mitogen-activated protein kinase (MAPK) or a member of the MAPK signaling cascade MAPK/ERK kinase (MAP2K1 and MAP2K2 gene)
MIS, LM type = melanoma in situ, lentigo maligna type
MMS = Mohs micrographic surgery
MRI = magnetic resonance imaging
MSLT = Multicenter Selective Lymphadenectomy Trial
NCCN = National Comprehensive Cancer Network
OCT = oral contraceptive therapy
PAM = pregnancy associated melanoma
PET = positron emission tomography
SCOPE

This guideline addresses the treatment of pediatric, adolescent, and adult patients with AJCC clinical stages 0-IIC primary CM (including melanomas arising from the nail unit), who may also have histologic evidence of regional disease at presentation via 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, skin cancer screening, 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, histopathological and immunohistochemical analysis and pathological reporting of sentinel lymph node specimens, and the use of available systemic adjuvant therapies or those being investigated for patients with CM at higher risk for metastasis (generally 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 melanoma.

**METHOD**

A multidisciplinary Work Group (WG) consisting of academic melanoma specialists in cutaneous, medical, and surgical oncology, dermatopathology, 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 CPG. The WG determined the scope of the guideline, and identified important clinical questions in the management of primary CM (Table I). WG members completed a disclosure of interests that was 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 and available evidence published since the completion of the 2011 melanoma guideline was obtained using a systematic search
and review of published studies from 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 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 (LNs); 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 based on 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.6-10

The available evidence was evaluated using a unified system called the Strength of Recommendation Taxonomy (SORT) developed by editors of the United States family medicine and primary care journals (ie, American Family Physician, Family Medicine, Journal of Family Practice, and BMJ USA).11 Evidence was graded using a 3-point scale based on the quality of methodology (eg, randomized control 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 based on 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 where 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 August 2012), which includes the opportunity for review and comment by the
This guideline is considered current for a period of five 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. 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 LN with SLNB; 3) baseline and surveillance studies, and; 4) surgical and nonsurgical therapy considerations for MIS, LM type. In recognition of advances in CM treatment, this CPG also provides expanded discussion on the use of new technologies and molecular techniques that may aid both diagnosis and prognosis; the impact of the 2017 AJCC 8th Edition melanoma staging system on pathology reporting and SLNB consideration, 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 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- and immuno-therapies for patients with advanced disease.

IMPACT OF THE 8TH EDITION AJCC MELANOMA STAGING SYSTEM
The AJCC 8th Edition Cancer Staging Manual was implemented nationwide on January 1, 2018.\textsuperscript{13} Staging changes that affect CM pathology reporting and management are discussed in the relevant sections below. The AJCC 8th Edition tumor (T), node (N), metastasis (M) categories and stage groupings are listed in Tables 2 and 3.

**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 non-invasive techniques (eg, reflectance confocal microscopy [RCM], as well as electrical impedance spectroscopy, gene expression analysis, optical coherence tomography, and others [see below in “Emerging Diagnostic Technologies”]) can also be considered as these become more readily available.\textsuperscript{14-16} Pre-biopsy 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 healthcare provider and should include a regional photo that encompasses anatomic landmarks and a close-up image, preferably including a dermoscopic image. Recommendations for diagnostic biopsy of primary CM are summarized in Table 4; the level of evidence and the strength of these recommendations are shown in Table 5.
Skin biopsy may occur 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”). Partial biopsy may inaccurately stage CM at the outset and could negatively affect treatment planning. For a lesion clinically suspicious for 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 the lesion is not histologically transected at the deep margin. In general, this can be achieved with a narrow peripheral clinical margin of 1- to 3-mm around the concerning skin lesion.

Diagnostic excisional biopsy can be accomplished in three ways: 1) elliptical (fusiform) excision, 2) punch excision around the clinical lesion, or 3) deep shave/saucerization to a depth below the anticipated plane of the lesion, usually extending to the deep reticular dermis. Saucerization (or “scoop”) biopsy is the most common diagnostic technique employed by dermatologists and other practitioners due to ease of use and time efficiency, and should not be confused with a superficial shave biopsy, which should only be used when invasive melanoma is not suspected. Figure 1 depicts the excisional saucerization technique.

Superficial shave biopsies may underestimate Breslow thickness and clinical stage, and are thus generally discouraged for CM diagnosis. An exception occurs in the setting of a macular lesion suspicious for 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, in
comparison to multiple incisional/partial punch biopsies within the lesion. Figure 2 depicts the broad shave technique.

In instances where 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. While spot electrocautery may be necessary to control post-procedural 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 sponge) when hemostasis cannot be achieved with topical agents alone. Hemostasis with ferric subsulfate solution results in brown ferric pigment deposition 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 may be performed of the clinically and/or dermoscopically most atypical portion(s) of the lesion, although the selected area(s) may not represent the greatest Breslow thickness or most atypical pathological regions. There is no evidence that partial/incisional biopsies adversely affect patient outcome by transferring melanoma cells into cutaneous lymphatics or blood vessels. Biopsy type (incisional vs excisional) does not affect rates of sentinel LN positivity or disease recurrence, or impact the risk of metastasis.
When a partial biopsy demonstrates melanoma that meets criteria for SLNB, there is generally no need to remove the residual lesion prior to definitive surgery. The additional procedure may delay definitive surgery and pathological staging of the regional LN, add to procedural costs and patient morbidity, and potentially impact the accuracy of SLNB in instances where 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. When performed on the extremities, diagnostic elliptical/fusiform excisional biopsies should generally be oriented longitudinally (ie, axially) (Figure 3). This permits optimal subsequent WE and, if indicated, SLNB staging.

When a biopsy is performed of a suspicious nail lesion (eg, melanonychia striata, diffuse pigmentation, or amelanotic changes), 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 the biopsy of the nail apparatus. For suspicious subungual lesions, the nail plate should be sufficiently removed to expose the underlying lesion and an excisional or incisional biopsy performed based on the size of the lesion.

**PATHOLOGY REPORT**

When a biopsy is performed of a lesion clinically suspicious for primary CM, 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 6 and 7. The level of evidence and strength of recommendations are shown in Table 5.

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, etc.) of the biopsy site, including laterality, to reduce chances of subsequent wrong-site surgery.\(^{41}\) It is strongly recommended that the clinician include his/her clinical impression and differential diagnosis, size of the lesion, intent of the biopsy (ie, excisional vs partial, noting type of diagnostic biopsy performed [elliptical/fusiform, deep shave/saucerization, broad shave, or punch]), and send a photograph of the lesion, if possible. Macroscopic satellites around the clinical lesion should be noted by the clinician, as they may also be associated with microscopic satellites in the primary tumor.\(^{13}\) 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.\(^{42}\) 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$^{13}$ and College of American Pathologists (CAP)$^{43}$ and various international pathology associations.$^{36}$ Recommendations for histologic factors to be included in the pathology report are shown in Table 7; the level of evidence and the strength of recommendations are listed in Table 5.

There is strong evidence that at least three histologic features of the primary tumor are dominant predictors of outcome: Breslow thickness, ulceration, and dermal mitotic rate.$^{13,44-52}$ Mitotic rate is no longer included in the AJCC 8$^{\text{th}}$ edition CM staging system as a dichotomous variable ($<1/\text{mm}^2$ vs $\geq 1/\text{mm}^2$) 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 7$^{\text{th}}$ edition.$^{13}$ Therefore, T1a CM is now defined as nonulcerated and $<0.8$ mm, while T1b CM is defined as 0.8 to 1.0 mm regardless of ulceration status, or ulcerated CM $<0.8$ mm.$^{13}$ The WG considers it essential for maintenance of an adequate tumor registry that these three primary tumor characteristics are 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 AJCC Cancer Staging Manual 8$^{\text{th}}$ Edition has modified the reporting of thickness to the nearest 0.1 mm rather than the nearest 0.01 mm (eg, thickness of 0.75-0.84 mm will be rounded to 0.8 mm).$^{13}$ Microsatellitosis should not be included in this primary tumor measurement, but commented on separately, as noted below.

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.\textsuperscript{13, 47, 53} 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 square mm (mm\(^2\), with 1 mm\(^2\) approximately equal to 3-4 high-power [\(\times 40\)] microscopic fields, should be calibrated for the individual microscope type, starting in the field with most mitoses – the “hot spot”), was included as a staging attribute in the 7\(^{th}\) Edition AJCC CM staging system to upstage patients with CM \(\leq 1\) mm in thickness from T1a to T1b, replacing Clark level.\textsuperscript{44}

In the 8\(^{th}\) Edition 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-T4 primary CM since it is associated with survival across all thickness categories.\textsuperscript{13, 54}

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.
While the CAP and various international pathology groups 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, both for biopsies and for re-excision specimens. 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 clear peripheral or deep margins. 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 8th Edition AJCC staging system, the presence of in-transit, satellite, and/or microsatellite metastases is categorized as N1c (pathological stage IIIB with a T1a/b – T2a/b-T3a primary tumor and pathological stage IIIC with a T3b, T4a/b primary tumor) in the absence of involved regional LN(s), and N2c or N3c based on the presence of one (N2c) or two 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 2). Therefore, the presence or absence of microscopic satellites must be reported for accurate staging. The AJCC 7th Edition melanoma staging system previously defined microsatellites as the presence of tumor nests >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. The 8th Edition 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. Microsatellite disease is frequently associated with other adverse pathologic features.

The anatomic (Clark) level of invasion was a reportable feature in the 2009 AJCC staging system, but only for tumors ≤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. Therefore, Clark level assessment 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 and the presence or absence of a vertical growth phase, dermal regression, and angiolympathic invasion (also termed “lymphovascular invasion”). Focal or partial histologic regression is commonly observed in T1 CM, previously raising concern that true Breslow thickness may be underestimated. However, most contemporary data support that primary tumor histologic regression is not an adverse prognostic factor for nodal metastasis or survival and is associated with a lower likelihood of SLN positivity and better survival, with the possible exception of extensive or complete regression. Although not essential, it is recommended that these histologic characteristics are 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, 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. Similarly, the lentigo maligna pattern, commonly observed on the head and neck, may be associated with subclinical peripheral and periadnexal extension beyond the visible margins, which may require wider surgical margins to clear histologically. Moreover, histopathological 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, pagetoid scatter, etc. 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. Testing of primary CM for oncogenic (“driver”) mutations such as 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. Other ancillary tests that can be of value in selected cases include HMB45 immunohistochemical staining, where diminution of staining can be a reassuring feature, Ki-67 proliferation marker expression, and staining for p16. If present, the latter marker excludes homozygous chromosome 9p21 loss, which has been associated with aggressive behavior in some tumors, including spitzoid lesions. However, absence of p16 staining is not diagnostic of CM, or reliably predictive
of outcome. Telomerase reverse transcriptase promoter (TERTp) mutations\textsuperscript{79} and protein expression\textsuperscript{80} 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.\textsuperscript{81, 82} These include comparative genomic hybridization (CGH),\textsuperscript{83} fluorescence in situ hybridization (FISH),\textsuperscript{81, 84-86} gene expression profiling (GEP),\textsuperscript{87, 88} and potentially, next generation sequencing (NGS)\textsuperscript{89} in particular situations. 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; Table V for level of evidence).\textsuperscript{82, 90, 91}

Finally, CM is a reportable cancer to central registries, by both the diagnosing clinician and pathologist. Significant rates of under-reporting occur despite the nationwide reporting mandate, which is required by law in all 50 states.\textsuperscript{92-94} Regional and state cancer registries have mechanisms in place to aid practitioners in accurate CM reporting.\textsuperscript{92, 95}

**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
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 recurrence. The latter includes both true local recurrence defined by the presence of in situ and/or radial growth phase (i.e. “persistent disease”), and local, satellite recurrence or metastasis (i.e. intralymphatic deep dermal or subcutaneous fat recurrence without 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 generally excluded head and neck and acral sites); however, prospective RCTs have not been conducted for MIS, including direct comparison of various surgical techniques. 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 9 and 10. The level of evidence and strength of recommendations is shown in Table 11.

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 due to 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 ≤2.0 mm thickness, there is not strong evidence that surgical margins >1 cm favorably affect survival or local recurrence; and 3) current data do not support that surgical margins >2 cm impact 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.\textsuperscript{5,6} It is important to note that most prospective RCTs have mainly included truncal and extremity CM and excluded those 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 ≤1.0 mm in thickness, WE with a surgical margin of 1 cm is recommended for T1 (≤1 mm) CM\textsuperscript{97,105} and may be acceptable for T2 CM (>1.0 mm to 2.0 mm),\textsuperscript{98} although 2 cm margins are also deemed appropriate for T2 lesions based on prospective, randomized trials.\textsuperscript{99-101} Based on available evidence and consensus opinion, the WG continues to recommend a 1-2 cm surgical margin for T2 CM, taking into account tumor location and functional or cosmetic considerations.\textsuperscript{5}

A surgical margin of 2 cm is recommended for CM with a tumor thickness >2.0 mm (T3 [>2.0-4.0 mm], T4 [>4.0 mm]). One RCT found narrower excision of CM ≥ 2 mm 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 pathological staging to exclude occult regional nodal disease at the time of initial WE.\textsuperscript{102} 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 non-significant higher
number of deaths were reported in the narrow-margin group.\textsuperscript{103} Surgical complications were higher in the wider margin group, as were long-term adverse patient perception of the scar site.\textsuperscript{106} Another multicenter RCT conducted in nine European countries from 1994-2002 involved 936 patients with clinically-staged IIA–IIC CM >2.0 mm, randomized to wide excision with either 2 cm or 4 cm resection margins.\textsuperscript{104} At a median follow-up of 6.7 years, the 5-year overall survival in both groups was 65%, supporting 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. While there is reported variability according to physician specialty\textsuperscript{107}, 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.\textsuperscript{108} No RCTs have specifically explored whether shallower excision to the deep adipose layer affects local recurrence or survival.

As with diagnostic biopsy of the nail apparatus, WE of CM on the digits requires specialized surgical expertise. Since 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,\textsuperscript{109, 110} 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 warrant further investigation.\textsuperscript{111, 112}

\textit{Timing of Excision in Relation to Sentinel Lymph Node Biopsy}

When SLNB is planned, data support its performance during the same operation and preceding the primary tumor WE in order to minimize disruption of the lymphatic channels and optimize the accuracy of lymphatic mapping and the identification of the correct sentinel node(s).\textsuperscript{113} 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 lymph node basin,\textsuperscript{113, 114} but may require more extensive surgery, morbidity and cost.

\textit{Surgical Margins for Melanoma in situ, Including Lentigo Maligna Type}

While no RCTs of surgical interventions for MIS have been conducted,\textsuperscript{115} based on lower-level evidence, the WG recommends a 0.5-1 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 (non-facial sites).\textsuperscript{116, 117} Surgical margins of 0.5 cm were initially recommended for MIS in 1992 through the NIH Consensus Development Conference on Diagnosis and Treatment of Early Melanoma,\textsuperscript{105} though this statement was not based on any prospective trials and 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 large RCT, but surgery is commonly performed to the depth of the deep subcutaneous fat since occult invasive melanoma can occur in up to a third of unequivocal MIS.\textsuperscript{118}
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 >0.5 cm are often necessary to histologically clear the peripheral margins for MIS, LM type on the head and neck, a 0.5-1 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. Sampling of representative sun damaged skin may help distinguish true atypical junctional melanocytic proliferations from actinic melanocytic hyperplasia. Although there are limited data to support the use of non-invasive modalities to identify the clinical peripheral margins of MIS, LM type, Wood’s lamp, dermoscopy, and/or in vivo RCM may aid in pre-operative assessment.

*Mohs micrographic surgery 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 acral sites, with only one RCT for invasive CM including those on the head and neck and none including acral sites. For MIS with indistinct clinical margins on the head and neck (generally LM type), multiple studies have examined the utility of MMS and staged excision with paraffin-embedded permanent sections. The WG recommends that these surgical techniques be considered for MIS, LM type where tissue sparing excision due to anatomically constrained sites (eg, face, ears, scalp) and exhaustive peripheral margin histologic assessment are warranted.
For invasive LM melanoma in these locations, exhaustive 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.\textsuperscript{134-136}

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.\textsuperscript{134-136} Currently, non-inferiority of narrower surgical margins than those recommended in non-head and neck sites (whether obtained through MMS, staged excision, 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 scalp in particular.\textsuperscript{137} The WG reaffirms the general 1 cm minimum surgical margin for invasive CM as espoused in all international guidelines\textsuperscript{138} and cautions strongly against the routine use of narrower surgical margins for invasive melanomas at any site, except in rare circumstances for head/neck and acral lesions. However, the WG encourages further study of MMS and other surgical techniques for CM on these anatomically-constrained areas.

MMS and 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,\textsuperscript{131} as well as expert opinion. A recent retrospective analysis 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 median follow-up of 8.6 years, although significantly more patients with MIS on the face underwent MMS compared with
conventional WE (80.2% vs 36.7%, P<.001). Other retrospective analyses and prospectively followed cohorts have demonstrated improved peripheral margin histologic assessment and lower rates of local recurrence for MIS on the face and ears with MMS versus conventional WE. At present, there are no clear data to support use of MMS for MIS elsewhere on the body.

Two main MMS techniques for MIS are commonly described in the dermatologic literature: traditional MMS and modified MMS. The principal difference lies in the configuration of the excision and the 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 intra-operatively, 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 sections are considered the gold standard for histologic evaluation of melanocytic lesions.

Several variations of staged excision techniques have been described. Like MMS, they are aimed at providing comprehensive margin control prior to 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. 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 intra-operative, 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.126, 127, 153, 154

SENTINEL LYMPH NODE BIOPSY

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

Current practice guidelines involving every discipline and major guideline/staging organization worldwide provide relatively uniform recommendations regarding SLNB for CM, and they are consistent in interpretation of its value and limitations.6, 13, 138, 155 Recommendations for the use of SLNB and the level of evidence/strength of these recommendations are summarized in Table 12 and Table 11, respectively.

Staging

Accurate staging of CM drives surgical treatment, surveillance intensity, and other therapeutic options. The staging accuracy of SLNB is not controversial,13 though its impact on survival remains less well defined. It is important to recognize that staging tests are not typically validated based on their ability to improve survival but rather on their sensitivity and specificity, of which SLNB represents the gold standard for nodal staging in appropriate patients with CM. Sentinel lymph node status is also a key determinant for consideration of systemic adjuvant therapy and clinical trial enrollment.
Pathological staging of the regional LN identifies CM patients with occult metastasis and upstages a patient to AJCC stage III at the outset. Sentinel node status (positive or negative) is widely regarded as the most important prognostic factor for recurrence and the most powerful predictor of survival in CM patients. A meta-analysis of 71 studies and 25,240 participants estimated an overall ≤5% risk of regional nodal recurrence following a negative SLNB. Markedly improved survival has been demonstrated in advanced CM patients with the use of immune checkpoint blockade and therapies targeting the mitogen-activated protein kinase (MAPK) pathway. These agents are being studied in the adjuvant setting for SLN-positive and high-risk CM patients, making accurate staging even more relevant.

**Regional lymph node control**

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

While 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 Tc-99 sulfur colloid are used to identify and remove the sentinel lymph node(s), optimally, during the same procedure as the WLE. The SLNs are then examined histologically for the presence of tumor involvement using both routine histology and immunohistochemistry, as well as step sectioning.\textsuperscript{162} 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.\textsuperscript{13, 52}

Completion lymph node dissection (CLND) has traditionally been recommended and performed following a positive SLNB, since approximately 8\%-20\% of patients will harbor nonsentinel nodal metastases. However, a randomized trial of 483 patients with non-head/neck CM demonstrated no difference in overall survival for SLN-positive patients who underwent CLND compared to those who did not at median follow-up of 35 months, regardless of tumor thickness, ulceration, or SLN tumor burden.\textsuperscript{163} The recent publication of the larger (n=1934) randomized Multicenter Selective Lymphadenectomy Trial (MSLT)-II trial\textsuperscript{62} assessing CLND vs active nodal observation with ultrasound in patients with a positive SLNB provides evidence that immediate CLND increased the rate of regional disease control and improved staging among patients with a positive SLN, but it 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\textsuperscript{164} raise the question whether CLND is indicated following a positive SLNB, given the associated morbidity. Current NCCN guidelines recommend that CLND vs active nodal basin surveillance with ultrasound be discussed and offered in the setting of a positive SLNB,\textsuperscript{6} 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.\textsuperscript{6,165} 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. 

\textit{Melanoma-specific survival} 

SLNB provides the most reliable and accurate means of staging for appropriate patients with primary CM. The MSLT-I and Sunbelt Melanoma Trial did not demonstrate a therapeutic benefit of SLNB, although 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 compared with those who did not.\textsuperscript{160,166} In the randomized MSLT-I, only 20.8\% of patients with CM thickness $\geq$1.2 mm had occult nodal disease, although the subset of SLN-positive patients with tumors 1.2-3.5 mm thickness exhibited a melanoma-specific survival benefit compared to those in the observation arm who subsequently developed regional nodal metastasis (hazard ratio for death from melanoma, 0.56; $P=0.006$).\textsuperscript{160} 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, increase the morbidity of treating that disease, and increase the likelihood of dying from CM. As noted above, improved CM-
specific survival was not demonstrated in the subset of patients who underwent immediate CLND in the MSLT-II.\textsuperscript{52}

While the MSLT-I showed no survival benefit for SLNB in the subset of patients with T3 CM $\geq$ 3.6 mm 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.

\textit{Settings in which to discuss, consider and/or offer SLNB}

The WG recommends to discuss and offer pathological staging with SLNB for CM $\geq$ 1 mm, and it may be considered for thinner T1 CM with Breslow thickness 0.8-1.0 mm (with or without ulceration) or $<$ 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 to pursue this staging procedure should be made on an individual basis and with appropriate surgical oncology input.

SLNB consideration in T1 CM is more controversial than for thicker CM, and identification of tumors at higher risk for SLN positivity remains an active area of investigation. NCCN guidelines stratify consideration of SLNB in T1 CM according to Breslow thickness,\textsuperscript{6} which is the strongest predictor of SLN-positivity, particularly at or above the 0.75 mm (now 0.8 mm) threshold.\textsuperscript{52} The WG recommends discussion of SLNB in patients with T1b CM, defined per the AJCC 8\textsuperscript{th} Edition as $<$ 0.8 mm with ulceration or 0.8-1.0 mm with or without ulceration, although overall rates of SLN positivity in this subset of patients are still relatively low ($\leq$ 10\%). Rates of SLN-positivity in T1a CM ($<$ 0.8 mm without ulceration) are generally $<$ 5\%.\textsuperscript{167-169} Therefore, the WG does not recommend
SLNB for patients in the T1a subgroup unless other histologic adverse features are evident.\textsuperscript{6, 170-172}

While 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.\textsuperscript{64, 171, 173-177} Further analyses which assess mitotic rate across its continuum for survival-based endpoints and that establish a relevant threshold for SLNB consideration in T1 melanoma will likely inform clinical decision-making.

Younger age patients (<40 years) generally have higher rates of SLN positivity than older patients.\textsuperscript{178-180} 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 >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 clinical trial stratification.\textsuperscript{181, 182} 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.\textsuperscript{183} While SLNB may have less prognostic
value and may be technically more difficult in older individuals, there is currently no
consensus for an "upper age cut off" to recommend against this procedure. Each case
should be discussed individually, and in conjunction with surgical oncology colleagues,
with the decision to pursue pathological staging of the regional LNs based on patient
comorbidities and how that information may impact further management.

**STAGING WORK-UP AND FOLLOW-UP**

Recommendations for baseline staging and surveillance follow-up of CM are
provided in Table 13. The evidence supporting these recommendations is provided
below and summarized in Table 14 with the strength of the recommendations.

*History and Physical Exam*

Following diagnosis of invasive primary CM, a thorough history and comprehensive
physical exam represent the main components of the diagnostic workup. 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 exam directs need for additional laboratory and imaging
studies. On some occasions, imaging studies might be obtained at baseline in
asymptomatic, high-risk CM patients with equivocal exam 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 exam, total-body skin exam 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 CM diagnosis, 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 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 tests, chemistry panel, complete blood count [CBC]), chest radiography (CXR), 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.\(^ {184-186}\)

Most local, satellite/in-transit and regional nodal recurrences are identified by clinical examination of the skin and LN by the patient and/or health provider.\(^ {187-190}\) 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).\(^ {191}\) Screening CT or PET-CT may be considered if the patient has documented nodal metastasis based on results from the SLNB (stage III), although the yield is low in this setting (0.5-3.7%).\(^ {192}\) 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). A meta-analysis of 74
studies comprising over 10,000 CM patients demonstrated that ultrasonography was
superior for detection of LN metastasis and PET-CT for detection of distant metastasis for
both staging and surveillance in clinically appropriate patients.

While 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 (6th edition) for the classification of stage IV (distant) disease, and remains a key
prognostic factor for this subgroup of patients. Elevated LDH levels are associated with
worse survival and may predict response to therapy in stage IV patients and are therefore
incorporated across all M categories in the AJCC 8th Edition. Serum LDH testing 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.

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 a useful tool to identify disease progression. 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, and most data suggest potential prognostic value
or use as a therapeutic biomarker in patients with stage III and IV disease. Serum
S100B testing is not routinely employed in the US and is not recommended at baseline or for surveillance of asymptomatic patients with CM based on current evidence.

Routine imaging studies are limited by a low yield of true positive findings in asymptomatic CM patients and the frequent occurrence of false positive findings, particularly in earlier stage disease. As yet, it has not been demonstrated that pre-symptomatic 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 CXR evaluation is cost inefficient, associated with very few true positive findings and high false positive rates, as well increased patient anxiety and morbidity to investigate spurious findings. As such, CXR 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 at 3-12 months interval according to the risk of recurrence.

For baseline evaluation in newly-diagnosed asymptomatic primary CM patients of any Breslow thickness, cross-sectional (CT, MRI) and functional/metabolic (PET), or hybrid (PET-CT) imaging is not indicated, with the exception of uncommon situations such as the inability to assess nodal status by regular physical examination, in which case ultrasound evaluation could be obtained. Similar to CXR, 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 on overall survival.
The utility of PET-CT, CT, and MRI in CM surveillance is directly correlated to the stage of disease, meaning that stage III and IV CM patients are more likely to demonstrate clinically occult metastasis than stage I or II patients. The highest yield of imaging occurs when a patient is symptomatic or has clinical findings suspicious for 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 prior to 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 CXR until year 10. Nearly 40% of patients developed metastasis at a median of 1.4 years. Imaging detected 56.7% recurrences (mainly visceral), as compared to 41.5% of recurrences initially detected by patient or provider examination. Most clinically detected recurrences were cutaneous in nature. Overall survival was not assessed, however, preventing conclusions as to the merit of this intensive imaging approach on patient outcomes. Another study of surveillance CT in stage IIB and IIC CM patients concluded that imaging should only be performed if symptoms of clinical metastatic disease are present.

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 medical oncologists is advised for patients with high-risk CM (stages IIB and IIC) for discussion of surveillance imaging and clinical co-management. Based on 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 according to the risk of disease recurrence. However, routine radiologic imaging in asymptomatic CM patients of any stage is generally not recommended after 3-5 years of disease-free follow-up, given timing and patterns of relapse.¹⁶,¹⁷⁰,²⁰⁷

Lymph node ultrasound for regional nodal evaluation and surveillance

Numerous studies have been conducted evaluating LN ultrasound in CM patients and demonstrate improved assessment of regional LNs compared with palpation alone at both initial diagnosis and in follow-up.¹⁹⁴,²⁰⁸ 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 criteria for SLNB but does not undergo the procedure; 2) when SLNB is not possible or not technically successful (eg, due to failure of pre-operative lymphoscintigraphic dye migration and inability to identify a draining SLN); and 3) when CLND is not performed in the setting of a positive SLNB.⁶ Regional nodal ultrasound for melanoma detection requires specific radiologic expertise and understanding of established LN criteria,²⁰⁹-²¹¹ and has been less commonly employed in the US 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

While the optimal interval and duration of follow-up for CM is not well defined, the WG recommends that CM patients be monitored regularly following diagnosis, particularly for tumors at increased risk of recurrence (>2.0 mm thickness, with ulceration,
lymphovascular invasion, and/or high mitotic rate). While most metastases occur in the first 1-3 years after treatment of the primary tumor, skin examinations are generally recommended for life. An estimated 4-8% of patients with a history of CM develop new primary CM, typically within the first 3-5 years following diagnosis.\textsuperscript{212} 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 MIS, nodular or LM subtype of CM; and male sex.\textsuperscript{213} The frequency of dermatologic, surgical, and oncologic surveillance depends on individual patient risk for new primary CM as well as for recurrent disease.

Surveillance follow-up schedules vary significantly depending on country of location, physician specialty, and stage of disease.\textsuperscript{214} In the absence of evidence-based guidelines, many clinicians arrange follow-up according to a schedule with which they and their patients are most comfortable. A suggested surveillance plan is shown in Table 15. Based on expert opinion, for patients with stage 0 (MIS), the WG recommends physical exam with emphasis on assessment of local recurrence, particularly for LM subtype, and full skin check to evaluate for new primary CM at least every 6-12 months for one to two years, then annually thereafter. For stages IA-IIA CM, the WG recommends a comprehensive history, review of systems and physical exam with specific emphasis on the skin and regional LNs at least every 6 to 12 months for two years, then at least yearly thereafter. For patients with stage IIB-IIC, clinical follow-up is recommended every 3-6 months for two years, then at least every 6-12 months for three years, and at least annually thereafter.\textsuperscript{6} 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 stage IIB CM patients and higher, a cohort that usually benefits from multidisciplinary surveillance.

As noted, current evidence regarding recurrence, surveillance, and survival antedates recent breakthroughs in 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 histological parameters. This approach may be especially relevant to determine thinner CM at increased risk of metastasis. Gene expression-based prognostic signatures offer promise, but 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, and questionable applicability to clinical practice.\textsuperscript{90, 91, 215} The development of GEP and other molecular tests (eg, microRNA expression profiles)\textsuperscript{216, 217} that can accurately and reproducibly identify those CM patients who will recur is an ongoing area
of study,\textsuperscript{218} made more relevant by recent advances in systemic adjuvant therapies that improve overall survival.\textsuperscript{219}

The majority of the published prognostic GEP studies compare the predictive accuracy of recurrence or death from CM to SLNB outcome or AJCC 7\textsuperscript{th} Edition stage.\textsuperscript{44,90,91,220-223} These non-overlapping gene panels have been reported to be as, or more predictive of prognosis compared to SLNB status, AJCC stage, and/or traditional histologic factors (Breslow thickness, ulceration, mitotic rate – though usually dichotomized at 1/mm2 and not studied as a continuous variable).\textsuperscript{223} To date, the various GEP assays have not been tested against all known histopathologic prognostic factors or contemporary AJCC 8\textsuperscript{th} edition CM staging to assess their additive value in prognostication. The improved survival for CM based on more accurate pathological staging in the AJCC worldwide collaborative database of >46,000 patients for 8\textsuperscript{th} Edition staging supports the prognostic value of SLNB status.\textsuperscript{52} 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.

Evidence to date does not support increased surveillance imaging as a result of available prognostic GEP tests, particularly in stage I or IIA patients who are not currently eligible for adjuvant therapy trials. Similarly, the frequency of clinical follow-up and potential imaging in high-risk CM patients is unlikely to be modified by a prognostic GEP result, until prospective studies confirm the added value of more intense surveillance in this cohort, and adjuvant therapy demonstrates 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 unresectable AJCC stages III-IV CM given the available and emerging systemic treatments.

As it remains unclear the degree to which the selected gene sets represent genes associated with tumor progression, how they compare to current well-characterized prognostic factors and AJCC 8th edition survival data, and whether they improve prognostic models enough to impact patient management and outcomes, the WG does not recommend prognostic GEP tests at baseline or following SLNB outside of a clinical study or trial. 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.

*Local melanoma recurrence types and effect on subsequent management*

Local CM recurrence within or surrounding the WE consists of two 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). Persistent-disease recurrence is generally macular and occurs at the margin of the prior WE scar, while satellite/in-transit metastases are palpable cutaneous or subcutaneous masses within or surrounding the WE scar (between the scar and regional LN basin). As satellite and in-transit metastasis represent intralymphatic (stage III) melanoma, their previous classification based on distance from the WE scar (ie, 2 cm) has been omitted from AJCC 8th Edition melanoma staging.

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.

NON-SURGICAL MANAGEMENT OF MELANOMA IN SITU, LENTIGO MALIGNA

TYPE

Topical imiquimod as primary or adjuvant therapy

Surgery is the mainstay of therapy for MIS, including 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 reliably be differentiated from true MIS, LM type,
with the use of immunostains (including cytoplasmic and nuclear stains such as Melan-A,
S-100, HMB-45, Sox-10, MitF). However, the limitations of topical treatment over
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, 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, and a single-arm phase II trial investigating the use of topical imiquimod for MIS, LM type have been published. Most studies have shown rates of histological 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 were noted in the setting of sun-damaged skin. Higher pathologic clearance was reported in the subset of patients with both clinical and pathologic response (63.3%) suggesting the importance of treatment duration until clinical clearance is achieved. A randomized trial of 47 patients was conducted to evaluate the addition of tazarotene 0.1% gel to imiquimod 5% cream vs imiquimod monotherapy for MIS, LM type, followed by conservative staged excision. Complete response after 12 weeks was observed histologically in 78% of lesions on combined therapy vs 64% on monotherapy (P=.17), with 22% (8 of 37) vs 36% (15 of 42) of lesions demonstrating residual MIS, LM type, on subsequent staged excision and no recurrences at a mean follow-up of 42 months.

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 histological peripheral margins are narrow or when there is histologic transection at the periphery without clinical correlation of a residual lesion. 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, 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, as well as treat potential subclinical residual LM in a surgically-treated site with histological but not clinical evidence of tumor transection. 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 for at least 12 weeks, 5 or more times per week (>60 treatments) and after an inflammatory response is elicited. 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. It is important to recognize that several months of imiquimod-induced inflammation may be less tolerable for some patients compared to surgical excision, 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 where contraindications to surgery exist, non-surgical 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. Therefore, the WG recommends surgery for eradication of MIS, LM type as first-line
therapy. Alternatives, such as imiquimod or radiation therapy (see below) 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 16. The level of evidence and strength of these recommendations is summarized in Table 17.

Finally, there may be situations in which clinical observation of large MIS, LM type is suitable, particularly in elderly patients with medical co-morbidities where aggressive treatment would be inappropriate. As discussed in the 2011 AAD CPG,\textsuperscript{5} 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.

**RADIATION THERAPY IN PRIMARY MELANOMA**

*Radiation therapy for primary treatment of MIS, LM type*

Primary radiation therapy (RT) for MIS, LM type may be considered when complete surgical excision is not possible, though recent advances in RT have largely been utilized outside the US.\textsuperscript{229} 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 LM and LMM with recurrence rates ranging from 0-14%.\textsuperscript{237-239} Since that time, 3 larger retrospective European studies (n=64,
150 and 593, respectively) reported the use of superficial/ultra-soft/soft X-ray or Grenz ray
(Miescher technique) treatment for LM and LMM with recurrence rates ranging from 0-
17%. 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 to 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
depth of 5 mm RT penetration is necessary to treat below hair follicles, although this may
result in permanent pigmentedary changes, dermal fibrosis, and overlying hair loss. Low-
voltage superficial X-ray therapy is rarely, if ever, used in the US for the treatment of MIS,
LM type.

A literature review of primary RT for MIS, LM type was published in 2014, which
included 9 clinical studies published through 2009 involving 537 patients, with median
follow-up of 3 years. Eight 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. Five 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.$^{244}$

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

Desmoplastic CM presents unique treatment challenges. Deep tumors with certain high-risk features (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 wide excision of desmoplastic CM.$^{70,245-249}$ An ongoing Trans-Tasman Radiation Oncology Group (TROG) 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 >4 mm, and/or Clark level V.$^{70}$ Among 35 patients with positive resection margins, lower rates of local recurrence were also noted in those who received RT compared with 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 OS.$^{250}$ A retrospective study of adjuvant RT in desmoplastic neurotropic CM in 128 patients demonstrated the importance of clear surgical margins for local control.$^{251}$ The adjuvant RT-treated group demonstrated similar recurrence rates to the surgery-only group, but 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. Based on 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 radiation therapy for primary CM are shown in Table 17. The level of evidence and strength of these recommendations are summarized in Table 16.

**PREGNANCY AND MELANOMA**

**Pregnancy and risk of developing melanoma**

Although CM is on the rise in young women, and in some studies is the most common malignancy reported during pregnancy, there is no evidence 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 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.\textsuperscript{253}

Whether the increased incidence of CM in young women is related to hormonal factors (including oral contraceptive use prior to pregnancy) or pregnancy itself has long been debated; the adverse effect of tanning behaviors and tanning bed use, particularly common among young women, is clear.\textsuperscript{254} Of note is the decreased risk of CM for women with a history of five or more live births compared to women with none. Women with earlier age at first birth and higher parity have a lower risk of CM compared to women with later age at first birth and fewer than five live births.\textsuperscript{255, 256} Similar findings were noted in a later study where 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 for CM.\textsuperscript{257} These findings suggest that pregnancy may be protective against CM, rather than causative.

\textit{Recommended waiting period before a woman with a history of melanoma becomes pregnant}

There is no evidence that future pregnancies will increase the risk of CM recurrence or metastasis. Several studies have demonstrated no significant impact on prognosis of CM diagnosed prior to pregnancy.\textsuperscript{256} 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 since most recurrences will develop by this time. The suggestion to delay subsequent pregnancy is not because of its impact on the mother’s CM; controlled studies consistently reveal no statistically significant difference in survival
for CM in pregnant patients compared with non-pregnant patients. Rather, this recommendation is based upon the desire to avoid the complications of systemic therapy in a pregnant woman and to prevent the loss of the mother, although better treatment options may reduce this possibility. Additionally, there is the very small risk of placental and fetal CM metastasis if the pregnant mother develops widespread disease.\textsuperscript{258}

A population-based study to assess if 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.\textsuperscript{253} A systematic review and meta-analysis of five studies that met the authors’ inclusion criteria concluded that that pregnancy after a successfully treated CM did not worsen prognosis.\textsuperscript{259} However, only one of the five 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) compared with non-PAM appeared to have a poorer outcome (56% increased mortality risk for PAM).\textsuperscript{260} 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 post pregnancy study was included which studied women 5 years after childbirth,\textsuperscript{261} as well as a population-based study missing Breslow thickness in 45% of cases and with proportionally more CM at high risk sites (head, neck, trunk) in pregnant vs non-pregnant
women.\textsuperscript{253} In this latter study, there was no difference in tumor thickness in the 55\% of the pregnant women with available Breslow thickness compared with non-pregnant women. In addition, a prior comprehensive population-based study of the California Cancer Registry demonstrating equivalent maternal and neonatal outcomes for pregnant vs non-pregnant women was excluded from the systematic review due to lack of confidence intervals.\textsuperscript{262}

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.\textsuperscript{263} The authors concluded that the occurrence of the CM during pregnancy should not outweigh other traditional factors (eg, Breslow thickness, AJCC stage, age of 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.

\textit{Effect of pregnancy on outcome for patients diagnosed with cutaneous versus more advanced melanoma}

There is no evidence that pregnancy negatively affects the prognosis of primary CM or more advanced CM. Controlled studies have reported no significant influence of pregnancy on survival, or poorer prognosis in pregnant women diagnosed with CM versus women not pregnant at the time of diagnosis.\textsuperscript{253, 256, 262} As noted, the recent study using proliferative markers in PAM demonstrated no proliferative activity difference in PAM versus CM unassociated with pregnancy,\textsuperscript{263} supporting that prognosis of PAM depends on conventional factors (eg, stage, tumor thickness).
However, two contradictory studies have recently been published, including the 2015 systematic review and meta-analysis that reported an increased risk for CM-related death in pregnant patients. Additionally, a retrospective study from a single tertiary care institution demonstrated an increased mortality rate and greater odds of death in woman <50 years of age with PAM compared to non-pregnant women. These findings are incongruent with all other studies and are challenging to interpret due to the small number of patients, inconsistent reporting of CM stage, and survival analysis techniques employed.

Finally, some studies have addressed the therapeutic approach and outcome for pregnant women diagnosed with CM. Those with stage I and II disease have the same outcome and treatment as non-pregnant CM patients. Those with stage III and IV have also been shown to have the same outcome. However, treatment needs to be individualized and is patient-specific depending on several factors, including the timing of CM diagnosis during the pregnancy. 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 safely be performed throughout pregnancy and 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 trimester without the use of the blue dye to avoid potential anaphylaxis. It is the opinion of the WG that pregnant women
with higher stage CM usually benefit from interdisciplinary care involving the 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 rather 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. There is no evidence that melanocytic nevi change during pregnancy, except for those nevi on the breast and abdomen which may appear larger due to the stretching of skin. Melanocytic nevi on the back and legs of pregnant women have not been reported to enlarge. There is also no evidence that melanocytic nevi darken during pregnancy. Transient dermoscopic changes have been reported in nevi during pregnancy but return to normal post-partum, and none were suggestive of CM.\(^{266}\) The WG recommends that any changing or otherwise concerning melanocytic nevus in a pregnant woman (not due to stretching on the breasts or abdomen) be evaluated clinically, and optimally by dermoscopy, and if worrisome, biopsied as in standard practice. In addition, appropriate sun protective measures for pregnant women should be similar to those in nonpregnant patients.

**Safety of exogenous hormones, oral contraceptives, and other contraceptive devices in women who have been diagnosed with melanoma**

There is no evidence that exogenous hormones (oral contraceptive therapy [OCT] or hormone replacement therapy [HRT]) or other contraceptive devices negatively impact prognosis in women with a history of CM, or increase the risk for new primary CM.\(^{256}\) 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 CM patients found no increased risk of CM with OCT or HRT, suggesting that exogenous hormones are not associated with an increased risk of CM.\textsuperscript{257} A pooled analysis of 10 controlled studies found no relationship between OCT use and CM (including current/past use and long duration of use), supporting that OCT is not a risk factor for CM.\textsuperscript{255} A randomized trial of postmenopausal women given HRT likewise demonstrated no increased risk of CM in this group versus the placebo group.\textsuperscript{267}

Women who required assisted reproductive technology (ART) ($n = 113,226$) were compared to women who did not ($53,859$) regarding incidence of all cancers. For those women who underwent ART, a statistically significantly lower risk for all cancers was noted compared to 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.\textsuperscript{268}

Recommendations for CM and pregnancy are shown in Table 18. The level of evidence and strength of these recommendations are summarized in Table 19.

**GENETIC COUNSELING FOR PATIENTS WITH FAMILIAL MELANOMA AND MULTI-GENE TESTING**

Genetic testing for germline risk prediction for patients or families at high risk of CM development

The spectrum of CM tumor syndromes is rapidly expanding. In addition to CDKN2 and CDK4, germline variants in multiple genes (eg, TERT promoter, MITF[E318K], and
BAP1) potentially predispose individuals to melanoma, among other cancers. Features of cancer predisposition traditionally involve early onset of disease (<40 years), having multiple cancers or cancer types, multigenerational familial involvement down one 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 two CMs within 5 years is less likely to harbor a germline mutation than a 30-year-old who develops two CM within 5 years.

Since “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 (SPM) or multiple primary melanomas (MPMs), respectively, harbor germline CDKN2a mutations. Compared to noncarriers, carriers of CDKN2A mutations developed CM at an earlier age and more often reported a family history of CM. While the number of high-quality studies examining the benefits of genetic counseling and testing in hereditary CM is extremely limited, several studies with 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 one perceived benefit of genetic testing while only 15.9% reported a negative aspect. 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 multi-gene 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 has been published by the international melanoma genetics consortium, where the “rule of 3’s” was first proposed.\textsuperscript{273} This concept involves 3 or more invasive CM or a mix of 3 or more invasive CM 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 other factors (eg, skin phenotype, age of diagnosis, and degree of UV exposure). Those with pancreatic cancer in the family may benefit from earlier screening of this occult malignancy by gastroenterology specialists\textsuperscript{274}

More recently, the BRCA1-Associated Protein 1 (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. While 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.\textsuperscript{275, 276} Data support that BAP1 is a high-penetrance gene for ocular melanoma but a medium-penetrance gene for CM, since only 13% of BAP1 mutation carriers develop CM.\textsuperscript{275, 277} 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 multi-gene 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 CM patients with 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 those who develop MPMs later in life due to excessive sun exposure.

For dermatologists, one of the cardinal features of the BAP1 tumor syndrome is the presence of small red/orange papules that are histologically diagnostic of a BAP-1 associated tumor. Patients with at least one 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](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.

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/benefits. The WG suggests that genetic counseling be considered if the above
criteria are met, with only possible testing since 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 multi-gene testing for hereditary melanoma are shown in Table 20. The level of evidence and strength of these recommendations are summarized in Table 19.

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 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 mitogen-activated protein kinase (MAPK) pathway (BRAF and MEK inhibitors), and those resulting in immune checkpoint blockade to activate T-lymphocytes (eg, monoclonal antibodies against cytotoxic T lymphocyte antigen-4 [CTLA-4], programmed death-1 [PD-1], and its ligand 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.

Over 90% of patients on BRAF inhibitor (BRAFi) monotherapy will develop cutaneous toxicity and about 40% of patients on checkpoint inhibitors will develop autoimmune-related skin conditions. However, many of the key trials that resulted in
FDA approval for these agents\textsuperscript{282-287} 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 BRAF inhibitor 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 21. The level of evidence and strength of these recommendations is summarized in Table 19.

\textit{BRAF and MEK inhibitor therapy}

FDA-approved BRAF inhibitors include vemurafenib and dabrafenib; FDA approved MEK inhibitors 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 [KA] type), hypertrophic actinic keratosis, verrucal keratosis, keratosis pilaris-type eruption, hand-foot skin reaction (painful palmoplantar keratosis), and xerosis, which are frequently observed on BRAFi monotherapy.\textsuperscript{280, 281, 288} 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).\textsuperscript{289} Cutaneous SCC/KA development generally occurs in older patients with pre-existing actinic damage and/or history of skin cancer, within 8 weeks of starting therapy. With continuation of BRAFi therapy beyond 4-6 months, the incidence of new cSCC/KA lesions often decreases.
Baseline dermatologic assessment and pre-BRAFi treatment of actinic keratosis is warranted. Complete surgical excision for most cSCC/KAs 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. Many of these side effects are attenuated, or even reversed with the addition of MEK inhibitors, although MEK inhibition can promote the development of acneiform papulopustular skin eruptions and paronychia, analogous to treatment with epidermal growth factor receptor (EGFR) inhibitors. NCCN Melanoma Guidelines currently recommend combined BRAF and MEK inhibitor as first-line therapy for those patients with metastatic CM and a BRAF V600 activating mutation in whom molecularly targeted therapy is indicated, because combination therapy results in improved response rates and survival and reduced toxicity, in comparison to monotherapy.

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. Pre-treatment podiatric evaluation for paring of existing corns, calluses, and hyperkeratotic areas may reduce symptoms. Acneiform eruptions on MEKi therapy can be managed with topical steroid ointments or oils for pruritus, topical or oral antibiotics (typically tetracyclines, or cephalaxins to avoid potential phototoxicity), and/or dilute bleach soaks. Severe papulopustular eruptions may require treatment with isotretinoin or drug cessation.
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. The combined BRAF/MEK inhibitor therapy was associated with rash and acneiform dermatitis in 24% and 12%, respectively, but these toxicities were usually less than grade 3 in severity.

**Immune Checkpoint Inhibitor Therapy**

FDA-approved immune checkpoint inhibitors include anti-CTLA-4 (ipilimumab), anti-PD-1 (pembrolizumab and nivolumab) and anti-PDL-1 (atezolizumab). 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. Unmasking or worsening of atopic dermatitis, psoriasis, sarcoidosis, or autoimmune bullous disease (bullous pemphigoid-like) has been reported on both PD-1 and PD-LI inhibitors, with more frequent flare of pre-existing autoimmune disease if active at treatment initiation. Onset of vitiligo-like CM-associated hypopigmentation may correlate with improved immune response, particularly for patients on anti-PD-1 therapy, in whom dermatologic recognition of this finding may therefore aid in oncologic management.
Anti-CTLA-4 antibody therapy induced skin toxicity is dose-related and generally reversible, with onset generally within the first month of therapy, as opposed to later onset with PD-1 or PD-L1 inhibitors. While an overall survival benefit was observed in patients treated with high-dose ipilimumab in the adjuvant setting for surgically resected stage III melanoma, the severity of associated immune related adverse events have 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 compared to high-dose ipilimumab, resulting in FDA approval of nivolumab in the adjuvant setting. The incidence 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 anti-pruritic 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. Importantly, no difference in CM survival has been demonstrated between patients requiring immunosuppressive therapy for immune-related adverse events and those who do not.

**Viral oncolytic immunotherapy**

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

*Role of the dermatologist in the 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, and so chronic skin and systemic toxicities may be observed. Early recognition and control of dermatologic toxicities may prevent unnecessary medication interruption and improve patient quality of life during treatment. It is important to note that any systemic treatments for cutaneous reactions (eg, oral corticosteroids) should be undertaken with the partnership of medical oncology in order 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, high-frequency
ultrasound – some of which are already FDA-approved)\textsuperscript{305, 306} and novel software technologies (eg, artificial intelligence-based deep learning algorithms\textsuperscript{307}) 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.\textsuperscript{308, 309} The uptake of one or more of these technologies will eventually depend on cumulative evidence regarding their effectiveness, clinical utility, cost benefit and competing strategies.

**GAPS IN RESEARCH**

Gaps in research were identified, including, but not limited to the 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 multi-gene somatic and germline mutational analysis; and the value of ancillary molecular tests in comparison to well-established clinicopathologic predictors of outcome. Efforts to standardize the histopathologic diagnosis and categorization of melanocytic neoplasms are underway to reduce the significant interobserver variability among pathologists.\textsuperscript{310} Ongoing advances in genomic medicine may make many of the above 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 high-level evidence. Management of primary CM should therefore always be tailored to meet the needs of the individual patient.
REFERENCES

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258. Schwartz JL, Mozurkewich EL, Johnson TM. Current management of patients with melanoma who are pregnant, want to get pregnant, or do not want to get pregnant. Cancer 2003;97:2130-3.


266. Bieber AK, Martires KJ, Driscoll MS, Grant-Kels JM, Pomeranz MK, Stein JA. Nevi and pregnancy.


Table 1. Clinical Questions Used to Structure the Evidence Review

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>• What biopsy techniques are effective in establishing accurate histopathologic diagnosis of CM?</th>
</tr>
</thead>
</table>
| 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, either before or after SLNB? |
| **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 for patients diagnosed with cutaneous versus more advanced CM?  
• 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, other contraceptive devices safe in women who have been diagnosed with CM? |
| **Germline Mutations and Multi-gene 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 by which individuals with CM or at risk should be referred for multi-gene testing for familial CM? |
| **Dermato-Oncology Considerations** | • How often should patients with metastatic CM on newer systemic therapies be followed for cutaneous side effect management?  
• What is the role of the dermatologist in the surveillance of patients with advanced CM? |
### Table 2. AJCC TNM definitions for invasive CM (Adapted from the AJCC 8th Edition melanoma staging system (2017))

<table>
<thead>
<tr>
<th>T Classification</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 ≤1.0mm</td>
<td>a. &lt;0.8 mm without ulceration</td>
</tr>
<tr>
<td></td>
<td>b. &lt;0.8 mm w/ulceration or 0.8-1.0 mm +/- ulceration</td>
</tr>
<tr>
<td>T2 &gt;1.0-2.0mm</td>
<td>a. Without ulceration</td>
</tr>
<tr>
<td></td>
<td>b. With ulceration</td>
</tr>
<tr>
<td>T3 &gt;2.0-4.0mm</td>
<td>a. Without ulceration</td>
</tr>
<tr>
<td></td>
<td>b. With ulceration</td>
</tr>
<tr>
<td>T4 &gt;4.0mm</td>
<td>a. Without ulceration</td>
</tr>
<tr>
<td></td>
<td>b. With ulceration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N and M Classification</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N1 1 node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes</td>
<td>a. Clinically occult*</td>
</tr>
<tr>
<td></td>
<td>b. Clinically detected†</td>
</tr>
<tr>
<td></td>
<td>c. Intralymphatic metastases§ without regional lymph node disease</td>
</tr>
<tr>
<td>N2 2-3 nodes or in-transit, satellite, and/or microsatellite metastases with one tumor-involved node</td>
<td>a. Clinically occult*</td>
</tr>
<tr>
<td></td>
<td>b. Clinically detected (at least 1)†</td>
</tr>
<tr>
<td></td>
<td>c. Intralymphatic metastases§ with 1 occult or clinically detected regional LN</td>
</tr>
<tr>
<td>N3 4 or more tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases</td>
<td>a. ≥4 metastatic clinically occult nodes with no intralymphatic metastases</td>
</tr>
<tr>
<td></td>
<td>b. ≥4 metastatic nodes (at least one clinically detected), or matted nodes (any number) with no intralymphatic metastases</td>
</tr>
<tr>
<td></td>
<td>c. ≥2 clinically occult or clinically detected nodes and/or presence of matted nodes (any number) with intralymphatic metastases</td>
</tr>
<tr>
<td>M1a Distant skin, soft tissue (including muscle), and/or non-regional lymph nodes</td>
<td>+/- ↑LDH§</td>
</tr>
<tr>
<td>M1b Lung metastasis +/- M1a</td>
<td>+/- ↑LDH§</td>
</tr>
<tr>
<td>M1c Distant non-CNS visceral +/- M1a or M1b</td>
<td>+/- ↑LDH§</td>
</tr>
<tr>
<td>M1d Distant metastasis to CNS +/- M1a or M1b or M1c</td>
<td>+/- ↑LDH§</td>
</tr>
</tbody>
</table>

*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 on 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.
&Suffix: (0) LDH not elevated, (1) LDH elevated.
**CNS = central nervous system
Table 3. 8th Edition AJCC pathological stage groups\textsuperscript{13}

<table>
<thead>
<tr>
<th>Pathological (pTNM) Stage Groupings</th>
<th>When T is:</th>
<th>And N is:</th>
<th>And M is:</th>
<th>Pathologic Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis\textsuperscript{*}</td>
<td>N0</td>
<td>M0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>T1a\textsuperscript{*}</td>
<td>N0</td>
<td>M0</td>
<td>IA</td>
<td></td>
</tr>
<tr>
<td>T1b\textsuperscript{*}</td>
<td>M0</td>
<td>M0</td>
<td>IA</td>
<td></td>
</tr>
<tr>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
<td>IB</td>
<td></td>
</tr>
<tr>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
<td>IIA</td>
<td></td>
</tr>
<tr>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
<td>IIA</td>
<td></td>
</tr>
<tr>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
<td>IIB</td>
<td></td>
</tr>
<tr>
<td>T4b</td>
<td>N0</td>
<td>M0</td>
<td>IIC</td>
<td></td>
</tr>
<tr>
<td>T0\textsuperscript{†}</td>
<td>N1b, N1c</td>
<td>M0</td>
<td>IIIB</td>
<td></td>
</tr>
<tr>
<td>T0\textsuperscript{†}</td>
<td>N2b, N2c, N3b or N3c</td>
<td>M0</td>
<td>IIIC</td>
<td></td>
</tr>
<tr>
<td>T1a/b-T2a</td>
<td>N1a or N2a</td>
<td>M0</td>
<td>IIIA</td>
<td></td>
</tr>
<tr>
<td>T1a/b-T2a</td>
<td>N1b/c or N2b</td>
<td>M0</td>
<td>IIIB</td>
<td></td>
</tr>
<tr>
<td>T2b/T3a</td>
<td>N1a-N2b</td>
<td>M0</td>
<td>IIIB</td>
<td></td>
</tr>
<tr>
<td>T1a-T3a</td>
<td>N2c or N3a/b/c</td>
<td>M0</td>
<td>IIIC</td>
<td></td>
</tr>
<tr>
<td>T3b/T4a</td>
<td>Any N ≥N1</td>
<td>M0</td>
<td>IIIC</td>
<td></td>
</tr>
<tr>
<td>T4b</td>
<td>N1a-N2c</td>
<td>M0</td>
<td>IIIC</td>
<td></td>
</tr>
<tr>
<td>T4b</td>
<td>N3a/b/c</td>
<td>M0</td>
<td>IIID</td>
<td></td>
</tr>
<tr>
<td>Any T, Tis</td>
<td>Any N</td>
<td>M1</td>
<td>IV</td>
<td></td>
</tr>
</tbody>
</table>

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

\textsuperscript{†}T0 = primary tumor cannot be assessed.

Table 4. Recommendations for diagnostic biopsy of suspected melanoma

| Preferred biopsy technique is a narrow excisional/complete biopsy with 1-3 mm clinical margins that encompass the entire breadth of lesion, and 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 anticipated plane of 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 should not generally be performed if the initial specimen meets criteria for consideration of sentinel lymph node biopsy.

Table 5. Level of evidence and strength of recommendations for biopsy of suspected CM, clinical information and pathology report.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
<th>Level of Evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biopsy</strong></td>
<td></td>
<td></td>
<td>17-34</td>
</tr>
<tr>
<td>• Excisional biopsy with 1-3mm clinically negative margins</td>
<td>B</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>• Partial biopsy in select circumstances</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Follow-up excisional biopsy to partial biopsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical information provided to the pathologist</strong></td>
<td>C</td>
<td>III</td>
<td>Expert opinion</td>
</tr>
<tr>
<td><strong>Pathology Report</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical information</td>
<td>C</td>
<td>III</td>
<td>41</td>
</tr>
<tr>
<td>Tumor (Breslow) thickness</td>
<td>A</td>
<td>I/II</td>
<td>13, 44-52, 56, 58</td>
</tr>
<tr>
<td>Ulceration</td>
<td>A</td>
<td>I/II</td>
<td>13, 44-53, 56, 58</td>
</tr>
<tr>
<td>Mitotic rate</td>
<td>A</td>
<td>I/II</td>
<td>13, 44-52, 54, 56, 58, 311</td>
</tr>
<tr>
<td>Level of invasion (Clark)</td>
<td>B</td>
<td>II</td>
<td>48, 50, 51, 57</td>
</tr>
<tr>
<td>Microsatellitosis</td>
<td>B</td>
<td>II</td>
<td>55, 311-315</td>
</tr>
<tr>
<td>Angiolympathic invasion</td>
<td>B</td>
<td>II</td>
<td>62, 63, 311, 312, 316</td>
</tr>
<tr>
<td>Histologic subtype</td>
<td>B</td>
<td>II</td>
<td>48, 71, 312, 316, 317</td>
</tr>
<tr>
<td>Neutrotropism/perineural invasion</td>
<td>C</td>
<td>III</td>
<td>251, 318</td>
</tr>
<tr>
<td>Regression</td>
<td>B</td>
<td>I/II</td>
<td>58, 61, 65-68</td>
</tr>
<tr>
<td>Tumor-infiltrating lymphocytes</td>
<td>B</td>
<td>II</td>
<td>58, 59, 319</td>
</tr>
<tr>
<td><strong>Use of ancillary molecular diagnostic techniques for equivocal melanocytic neoplasms</strong></td>
<td>C</td>
<td>III</td>
<td>81-88</td>
</tr>
<tr>
<td><strong>Against testing for oncogenic mutations in the absence of metastatic melanoma, or outside of a clinical study</strong></td>
<td>C</td>
<td>III</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>
### Table 6. Recommended clinical information to be provided to the pathologist

<table>
<thead>
<tr>
<th>Essential</th>
<th>Strongly Recommended</th>
<th>Optional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of patient</td>
<td>Biopsy intent/technique</td>
<td>Clinical description/Level of suspicion for melanoma/prior change or biopsy (if applicable)</td>
</tr>
<tr>
<td>Sex</td>
<td>Size of lesion</td>
<td>Dermoscopic features (with or without photograph)</td>
</tr>
<tr>
<td>Anatomic location (including laterality)</td>
<td>Clinical impression/differential diagnosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Macroscopic satellites</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinical photograph (if possible)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 7. Recommended histologic features of primary CM for inclusion in the pathology report

<table>
<thead>
<tr>
<th>Essential</th>
<th>Optional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of specimen</td>
<td>Gross description of lesion</td>
</tr>
<tr>
<td>Tumor thickness (Breslow); mm (nearest 0.1)</td>
<td>Angiolymphatic invasion/lymphovascular invasion</td>
</tr>
<tr>
<td>Ulceration</td>
<td>Histologic subtype</td>
</tr>
<tr>
<td>Dermal mitotic rate; “hotspot” method; # mitoses per square mm</td>
<td>Neurotropism/perineural invasion</td>
</tr>
<tr>
<td>Peripheral and deep margin status (positive (broad or focal)/negative)</td>
<td>Regression</td>
</tr>
<tr>
<td>Microsatellitosis</td>
<td>Tumor (T) category for staging</td>
</tr>
<tr>
<td></td>
<td>Tumor infiltrating lymphocytes</td>
</tr>
<tr>
<td></td>
<td>Anatomic level of invasion (Clark level)</td>
</tr>
<tr>
<td></td>
<td>Vertical growth phase</td>
</tr>
</tbody>
</table>

### Table 8. Recommendations for diagnostic, prognostic, and therapeutic molecular testing for primary CM

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

Prognostic molecular testing, including GEP, 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.
Table 9. Surgical margin recommendations for primary cutaneous melanoma

<table>
<thead>
<tr>
<th>Tumor thickness</th>
<th>Surgical margin*</th>
</tr>
</thead>
<tbody>
<tr>
<td>In situ</td>
<td>0.5-1 cm**</td>
</tr>
<tr>
<td>\leq 1.0 mm</td>
<td>1 cm</td>
</tr>
<tr>
<td>&gt; 1.0 – 2.0 mm</td>
<td>1 – 2 cm</td>
</tr>
<tr>
<td>&gt; 2.0 mm</td>
<td>2 cm</td>
</tr>
</tbody>
</table>

*Recommended surgical excision margins are clinically measured from the edge of the lesion or prior biopsy at the time of surgery; they are not histological margins as measured by the pathologist. Margins may be modified for functional considerations or anatomic location.

**Margins wider than 0.5 cm may be necessary for MIS, LM-type.

Table 10. Recommendations for surgical management of primary cutaneous melanoma

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical excision with histologically negative margins is the recommended and first-line treatment for primary CM of any thickness, as well as MIS. Surgical margins should be based on tumor thickness.</td>
</tr>
<tr>
<td>Surgical margins for invasive CM should be at least 1 cm and no more than 2 cm clinically measured around the primary tumor, although margins may be less to accommodate function and/or anatomic location. Depth of excision is recommended to (but not including) the fascia.</td>
</tr>
<tr>
<td>For MIS, wide excision with 0.5- to 1.0-cm margins is recommended; LM subtype may require &gt;0.5-cm margins to achieve histologically negative margins because of subclinical extension.</td>
</tr>
<tr>
<td>SLNB, when indicated, should be performed prior to wide excision of the primary tumor, and in the same operative setting, whenever possible.</td>
</tr>
<tr>
<td>MMS 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 peripheral margin histologic assessment.</td>
</tr>
<tr>
<td>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 intra-operatively, the tissue should be submitted for formal pathology review.</td>
</tr>
<tr>
<td>Sub-1 cm margins (either by WE or MMS) for primary invasive melanomas at anatomically-constrained sites (e.g. head and neck, and acral sites) are generally not recommended until further studies are available.</td>
</tr>
</tbody>
</table>
### Table 11. Level of evidence and strength of recommendations for the surgical management and SLNB of primary CM

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
<th>Level of Evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical excision for CM</td>
<td>A</td>
<td>I</td>
<td>97-104</td>
</tr>
<tr>
<td>Surgical margins for CM:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIS</td>
<td>B</td>
<td>II/III</td>
<td>115-117, 119, 120, 132</td>
</tr>
<tr>
<td>≤1.0 mm</td>
<td>A</td>
<td>I/II</td>
<td>97, 98, 320-322</td>
</tr>
<tr>
<td>&gt;1.0 – 2.0 mm</td>
<td>A</td>
<td>I</td>
<td>45, 97-101, 323-325</td>
</tr>
<tr>
<td>&gt;2.0 mm</td>
<td>A</td>
<td>I</td>
<td>45, 99, 102-104, 106, 324</td>
</tr>
<tr>
<td>MMS for MIS, LM-type</td>
<td>B</td>
<td>II/III</td>
<td>72, 128-131, 133, 135, 139, 140, 143-152</td>
</tr>
<tr>
<td>Caution against sub-1 cm margins for invasive CM</td>
<td>C</td>
<td>III</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>SLNB prior to/concomitant with WE</td>
<td>C</td>
<td>II</td>
<td>113</td>
</tr>
<tr>
<td>- No SLNB for MIS or T1a melanoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Discussion of SLNB for T1 melanoma (&lt;0.8 mm) if other adverse features present</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Discussion of SLNB for T1b CM (&lt;0.8 mm with ulceration and 0.8-1.0 mm with or without ulceration)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Discussion and offering of SLNB for CM &gt;1 mm thickness (T2a and higher)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discussion of SLNB risk/benefits with patients</td>
<td>C</td>
<td>III</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>Interdisciplinary discussion regarding possible CLND or ultrasound surveillance if positive SLNB</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 12. Recommendations for sentinel lymph node biopsy (SLNB)

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>For all SLNB-eligible patients, careful discussion of the risks and benefits of the procedure involving surgical oncology input is recommended.</td>
</tr>
<tr>
<td>SLNB is not recommended for patients with MIS or for most T1a melanoma (AJCC 8th Edition).</td>
</tr>
<tr>
<td>SLNB should be discussed and offered in appropriate patients with CM ≥1 mm thickness (T2a and higher), including T4 CM.</td>
</tr>
<tr>
<td>In patients with T1b CM (&lt;0.8 mm with ulceration and 0.8-1.0 mm with or without ulceration per AJCC 8th Edition), SLNB should be discussed and considered, though rates of SLN positivity are still relatively low.</td>
</tr>
<tr>
<td>SLNB may be considered for T1a CM (&lt;0.8 mm) if other adverse features are present, including young age, presence of lymphovascular invasion, positive deep biopsy margin (if close to 0.8 mm), or high mitotic rate – or a combination of these factors.</td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>
**Table 13. Recommendations for baseline and surveillance studies and follow-up for primary cutaneous melanoma**

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline radiologic imaging and laboratory studies are not recommended for asymptomatic patients with newly-diagnosed Stage 0-II primary CM.</td>
</tr>
<tr>
<td>Radiologic imaging and laboratory studies for CM at baseline should only be performed to evaluate specific signs or symptoms of synchronous metastasis (regional nodal or distant).</td>
</tr>
</tbody>
</table>
| 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, due to 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 history (review of systems) and physical exam 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 for discussion of surveillance imaging and clinical co-management. |
| 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 for 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. |
| Outside of use in a clinical study or trial, there is insufficient evidence to recommend molecular profiling assessment to aid in determining patient prognosis at baseline, optimal treatment following SLNB, or in surveillance to predict CM recurrence. |
Table 14. Level of evidence and strength of recommendations for baseline and surveillance studies, and follow-up schedule for primary CM.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
<th>Level of Evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>No baseline studies for asymptomatic Stage 0-II CM patients</td>
<td>A</td>
<td>I/II</td>
<td>184, 185, 193-195, 201, 203, 204, 206, 329-332</td>
</tr>
<tr>
<td>Laboratory or imaging studies only to evaluate signs of symptoms of metastasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of LN ultrasound in the setting of equivocal LN status</td>
<td>A</td>
<td>I/II</td>
<td>194, 208</td>
</tr>
<tr>
<td>Regular clinical follow-up to detect CM recurrence and metastasis</td>
<td>A</td>
<td>II</td>
<td>186-191, 193-196, 202, 205, 206, 212, 333-337</td>
</tr>
<tr>
<td>Tailored CM surveillance schedule and testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collaboration with medical oncology for patients with higher-risk CM</td>
<td>C</td>
<td>III</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>Patient education on SSE</td>
<td>A</td>
<td>I/II</td>
<td>189, 338, 339</td>
</tr>
<tr>
<td>Insufficient evidence for prognostic molecular techniques, including GEP</td>
<td>C</td>
<td>II/III</td>
<td>90, 91, 218</td>
</tr>
</tbody>
</table>
Table 15. Suggested surveillance intervals and follow-up tests for CM

<table>
<thead>
<tr>
<th>CM Stage</th>
<th>Follow-up interval and duration</th>
<th>Exam</th>
<th>Radiologic* Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0 MIS</td>
<td>at least every 6-12 months for 1-2 years; annually thereafter</td>
<td>physical exam with emphasis on assessment for local recurrence, particularly for LM subtype, and full skin check to ascertain for new primary CM</td>
<td>None</td>
</tr>
<tr>
<td>Stage IA-IIA</td>
<td>every 6 to 12 months for 2-5 years; at least annually thereafter</td>
<td>comprehensive history (review of systems) and physical exam with specific emphasis on the skin and regional LNs</td>
<td>None</td>
</tr>
<tr>
<td>Stage IIB and higher</td>
<td>Every 3-6 months for the for 2 years; at least every 6 months for years 3-5; at least annually thereafter</td>
<td>comprehensive history (review of systems) and physical exam with specific emphasis on the skin and regional LNs</td>
<td>May be performed for up to 3-5 years**</td>
</tr>
</tbody>
</table>

*chest x-ray [to screen for lung metastasis], CT of the chest/abdomen/pelvis, brain MRI, and/or PET-CT; frequency of imaging depends on the risk for recurrence

**highest risk period for relapse

Table 16. Recommendations for the use of imiquimod or radiation therapy in CM

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 of uncertainties of nonsurgical treatment should take place with the patient and family.

For non-surgical candidates, RT may be utilized as a second-line therapy for MIS, LM type*, though its use is uncommon in the US.

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 neurotopism/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.
**Table 17.** Level of evidence and strength of recommendations for (second-line) imiquimod treatment of MIS, LM type (primary and adjuvant setting), and radiation therapy in primary CM.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
<th>Level of Evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imiquimod for MIS, LM type</td>
<td>B</td>
<td>II/III</td>
<td>115, 225-236</td>
</tr>
<tr>
<td>RT for MIS, LM type</td>
<td>C</td>
<td>II/III</td>
<td>115, 229, 237-243</td>
</tr>
<tr>
<td>Against use of superficial brachytherapy for MIS, LM type</td>
<td>C</td>
<td>III</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>Adjuvant RT for high-risk desmoplastic CM</td>
<td>B</td>
<td>II/III</td>
<td>70, 245-251</td>
</tr>
<tr>
<td>Consultation with a radiation oncologist</td>
<td>C</td>
<td>III</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

**Table 18.** Recommendations for management of CM and pregnancy

In a pregnant woman with CM, a tailored, multidisciplinary approach to care is recommended, involving the obstetrician and CM specialists relevant to the patient’s stage of disease. A CM diagnosis 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 prior to subsequent pregnancy is not recommended. Factors that impact 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 with CM should be identical to that in the non-pregnant patient. Any changing nevus during pregnancy should be evaluated and biopsied if clinically and/or dermoscopically concerning.

Exogenous hormones (eg, oral contraceptives and hormone-containing contraceptive devices/implants, post-menopausal hormone replacement therapy or hormones associated with assisted reproductive technology) may be used in women who have been diagnosed with CM.
Table 19. Level of evidence and strength of recommendations for CM and pregnancy, genetic counseling/testing, and dermatologic toxicities

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
<th>Level of Evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multidisciplinary work-up and treatment approach for the pregnant CM patient</td>
<td>C</td>
<td>III</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>Pregnancy waiting period</td>
<td>B</td>
<td>II</td>
<td>253, 256, 259, 260, 262, 264</td>
</tr>
<tr>
<td>Evaluation and treatment of melanocytic nevi in pregnant CM patient</td>
<td>C</td>
<td>III</td>
<td>266</td>
</tr>
<tr>
<td>Use of exogenous hormones, oral contraceptives in women with a history of CM</td>
<td>B</td>
<td>I/II</td>
<td>255-257, 267, 268</td>
</tr>
<tr>
<td>Referral for genetic counseling and possible germline genetic testing for select CM patients</td>
<td>C</td>
<td>III</td>
<td>273</td>
</tr>
<tr>
<td>Frequency of dermatologic assessment for advanced CM patients</td>
<td>C</td>
<td>III</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>Dermatologic assessment for CM patients on BRAFi therapy</td>
<td>A</td>
<td>I/II</td>
<td>279-288</td>
</tr>
<tr>
<td>Dermatologic assessment for CM patients on immune checkpoint inhibitors</td>
<td>A</td>
<td>I/II</td>
<td>294-298, 300, 301</td>
</tr>
</tbody>
</table>
Table 20. Recommendations for genetic counseling of CM patients

Cancer risk counseling by a qualified genetic counselor is recommended for CM patients with:
- a family history of invasive CM or pancreatic cancer (3 or more affected members on one side of the family)
- multiple primary invasive CM (3 or more) including one early onset tumor (<45 years)
- at least one MBAIT and a family history of mesothelioma, meningioma, and/or uveal melanoma
- 2 or more MBAITs*

*MBAITs = melanocytic BAP1-mutated atypical intradermal tumors, BAP-1 = BRCA1-Associated Protein 1

Table 21. Dermatologic toxicities of newer drugs for advanced CM (stages III and IV)

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

The frequency of dermatologic assessment for cutaneous toxicity diagnosis and management depends on the agent(s) being used, age of the patient and 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 weeks for the first 3 months 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 on immune checkpoint inhibitors should occur within the first month of therapy and continue as needed for skin side effect management.
- Patients with psoriasis or other autoimmune dermatoses should be seen before initiation of therapy by a dermatologist for pre-emptive counseling and treatment.
Figure 1. Diagnostic excisional biopsy with deep shave/saucerization technique

Superficial shave biopsy leads to partial sampling

Saucerization or “scoop” technique removes entire lesion and allows sampling of deep margins
2532 **Figure 2.** Diagnostic broad shave biopsy for suspected MIS, LM type
Figure 3. Longitudinal/axial orientation of diagnostic elliptical/fusiform excisional biopsy on the extremity.