

Guideline Summary: Management of Primary Cutaneous Melanoma

About the Guideline

- This is an update to the 2011 clinical practice guideline and provides recommendations for diagnosis and management of patients with primary cutaneous melanoma (CM), American Joint Committee on Cancer stages 0-IIC and pathologic stage III based on positive sentinel lymph node biopsy (SLNB).
- The guideline covers biopsy techniques, histopathologic reporting, use of laboratory, molecular, and imaging tests for initial work-up, surgery and staged excision, staging of regional lymph nodes (LNs) with SLNB, nonsurgical treatments including imiquimod and radiation therapy (RT) for CM, pregnancy and melanoma, genetic testing for familial melanoma, and management of dermatologic toxicities related to targeted therapies and immunotherapies.
- The guideline was developed in accordance with the American Academy of Dermatology (AAD)/AAD Association “Administrative Regulations for Evidence-based Clinical Practice Guidelines.”

Definition

Primary cutaneous melanoma (CM) is defined as any primary melanoma lesion, regardless of tumor thickness, in patients without clinical or histologic evidence of regional or distant metastatic disease (stage 0-IIC). (See Table II: American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) definitions for invasive CM in the 2018 guidelines of care for the management of primary cutaneous melanoma [<https://www.jaad.org/action/showFullTableImage?isHtml=true&tableId=tbl2&pii=S019096221832588X>]).

Diagnosis and Management

- **Biopsy:** The first step in definitive diagnosis of CM
 - Recommended technique is a narrow excisional/complete biopsy of the entire lesion with clinically negative margins (1- to 3- mm margins, wide and deep enough to ensure the entire lesion is removed), by fusiform/elliptical or punch excision, or deep shave/saucerization (scoop) removal to depth below anticipated level of the lesion.
 - Partial/incomplete sampling (incisional biopsy) may be used in select cases such as facial or acral (peripheral body part) location, very large lesion, low clinical suspicion or uncertainty of diagnosis.
 - Superficial shave biopsies may underestimate the Breslow thickness and clinical stage.
 - Narrow-margin excisional biopsy may be performed if initial partial biopsy is not adequate for diagnosis or micro-staging, but it should not be performed if the

initial specimen meets the criteria for consideration of sentinel lymph node biopsy.

- Biopsy type (incisional or excisional) does not affect positivity, disease recurrence or impact the risk of metastasis.
- **Pathology Report** – when a biopsy is performed the following information should be provided to the pathologist:
 - Must include:
 - Age of patient
 - Gender
 - Anatomic location of the biopsy (including laterality)
 - Strongly recommended to include:
 - Biopsy intent: excisional/complete versus partial/incomplete
 - Technique: elliptical/fusiform, punch, broad shave or deep shave/saucerization
 - Size of lesion
 - Clinical impression/differential diagnosis
 - Macroscopic satellites – may upstage a CM to stage III
 - Clinical photograph (if possible)
 - Optional information:
 - Clinical description and level of suspicion for melanoma including change in the lesion or history of previous biopsy
 - Dermatoscopic features (with or without photograph)
- **Histologic Features of Primary Melanoma to be included in Pathology Report** – the pathology should be read by a provider experienced in the interpretation of pigmented lesions. Most important histologic features are tumor thickness, ulceration, and dermal mitotic rate.
 - Size of specimen
 - Tumor (Breslow) thickness (mm), nearest 0.1 mm, measured from top of granular layer of the overlying epidermis or base
 - Ulceration: loss of epidermis over the melanoma
 - Dermal mitotic rate; “hotspot” method; the number of dermal mitoses/mm²
 - Peripheral and deep margin status
 - Positive or negative (broad versus focal transection at deep margin)
 - Microsatellitosis
 - Redefined from 2011 guideline.
 - Includes any discontinuous microscopic deposit adjacent or deep to a primary melanoma, regardless of size or distance from the main tumor.
- **Optional histologic features:**
 - Gross description of lesion
 - Angiolymphatic invasion/lymphovascular invasion – cancer cells seen in small blood vessels or lymph vessels under the microscope
 - Histologic subtype
 - Neurotropism/perineural invasion – involving the nervous tissue

- T-stage classification (See Table III: Pathologic stage groups according to the eighth edition of the AJCC
[<https://www.jaad.org/action/showFullTableImage?isHtml=true&tableId=tbl3&pii=S019096221832588X>])
- Vertical growth phase: Presence of ≥ 1 clusters of dermal tumor cells bigger than largest epidermal tumor cluster and/or presence of any dermal mitotic activity
- Tumor regression: Apparent loss of dermal tumor with associated fibrosis, cell inflammation, and vascular proliferation
- Tumor infiltrating lymphocytes: White blood cells that have migrated into a tumor
- Anatomic level of invasion
 - Clark level – essential for staging only in tumors ≤ 1 mm in thickness when mitotic rate cannot be assessed; optional for tumors > 1 mm in thickness
 - Level I: Tumor confined to epidermis
 - Level II: Tumor present in papillary dermis
 - Level III: Tumor fills papillary dermis
 - Level IV: Tumor present in reticular dermis
 - Level V: Tumor present in subcutis
- **Diagnostic, prognostic, and therapeutic molecular testing are not recommended**
 - Diagnostic molecular tests (comparative genomic hybridization [CGH], fluorescence in situ hybridization [FISH], gene expression profiling [GEP], are still being researched and may be used as ancillary tests in equivocal melanocytic neoplasms but are not recommended for routine diagnostic use in CM.
 - Testing the primary CM for oncogenic mutations (B-Raf proto-oncogene or NRAS proto-oncogene) is not recommended if metastatic disease is not present.

Surgical Management

- First-line treatment of choice for primary CM of any thickness as well as melanoma in situ (MIS) is surgical excision with histologically negative margins. Surgical margins are based on thickness of the tumor:
 - In situ: 0.5 – 1 cm margin
 - Thickness ≤ 1.0 mm: 1 cm margin
 - Thickness > 1.0 to 2.0 mm: 1-2 cm margin
 - Thickness > 2.0 mm: 2 cm margin
- Surgical margins for invasive CM should be ≥ 1 cm and ≤ 2 cm measured around the primary tumor; however, margins may be narrower to allow for function and/or anatomic location. The excision depth should reach, but not include, the muscle fascia, except in rare incidences of deep primary CM.
- For MIS, wide excision with 0.5 to 1.0-cm margins is recommended; MIS, lentigo maligna (LM) subtype (malignant cells without invasive growth), may need > 0.5 -cm margins to achieve negative margins.
- Perform sentinel lymph node biopsy, if indicated, before wide excision (WE) of the primary tumor, and in the same procedure setting, when possible.

- Mohs micrographic surgery (MMS) or staged excision with paraffin-embedded permanent section may be used for MIS, LM type, on the face, ears, or scalp for tissue-sparing excision and histologic assessment of peripheral margins.
- For MIS, LM type, permanent section analysis of the central MMS debulking specimen is recommended to identify and stage potential invasive CM. If invasive CM is identified on a MMS section intraoperatively, the tissue should be submitted for formal pathology review.
- Sub-1-cm margins (by either WE or MMS) for primary invasive melanomas at constrained sites (i.e. head and neck, acral sites) are generally not recommended until further research is conducted.

Sentinel Lymph Node Biopsy (SLNB)

- Sentinel lymph node (SLN) status (positive or negative) is the most important prognostic indicator for recurrence and predictor of survival in patients with CM.
- Discuss the risks and benefits of the procedure with all SNLB-eligible patients and collaborate with surgical oncology.
- SLNB is not recommended for patients with MIS or for most T1aCM (< 0.8 mm without ulceration).
- SLNB should be discussed and offered to patients with CM > 1 mm in tumor thickness (\geq T2a), including T4 CM.
- Discuss SLNB with patients with T1b CM, (< 0.8 mm with ulceration or 0.8-1.0 mm with or without ulceration), although SLN positivity rates remain relatively low.
- SLNB may be utilized for T1a CM for patients with adverse factors such as young age, lymphovascular invasion, positive deep biopsy margin (close to 0.8 mm), high mitotic rate, or a combination of factors.
- Utilize interdisciplinary collaboration including surgical and medical oncologists to discuss completion lymph node dissection versus regional nodal ultrasound surveillance for positive SLNB.
- **Staging:**
 - Accurate staging will determine surgical treatment, surveillance intervals and use of systemic adjuvant therapies.
 - Staging of the regional lymph nodes (LNs) will help identify metastasis
 - Sentinel lymph node status (positive or negative) is the most important prognostic factor for recurrence and most powerful predictor of survival in patients with CM
- Reasons not to perform SLNB include:
 - Advanced age
 - Poor functional status
 - Comorbidities that may lead to a short life expectancy, adversely affect general anesthesia or other treatments

Baseline, Surveillance Studies and Follow-Up

- Radiologic imaging and laboratory tests are not recommended at baseline for asymptomatic patients with newly diagnosed stage 0-II primary CM.

- Baseline imaging and labs for CM should only be performed to evaluate specific signs or symptoms of metastasis (regional nodal or distant)
- Lymph node ultrasound may be obtained at baseline or in surveillance for an equivocal LN on physical exam, and for surveillance when:
 - SLNB criteria is met but patient does not undergo the procedure
 - SLNB is not possible or unachievable; or
 - Completion lymph node dissection (CLND) is not performed in the setting of SLNB; and
 - When radiology expertise in nodal ultrasound surveillance for CM is available
- Regular clinical follow-up is critical to detect CM recurrence. History (review of symptoms) and physical exam should guide the need for additional radiologic and lab studies.
- Collaborate with medical oncology when managing patients with high-risk CM (stage IIB and IIC) and those with a positive SLNB.
- Surveillance follow-up schedule and radiographic imaging varies based on risk of disease recurrence (determined by stage of disease) and risk of new primary CM (determined by mole pattern, presence of atypical nevi, family history). Lab studies are not recommended for surveillance of asymptomatic patients with CM.
- Educate patients on skin and LN self-examination to detect recurrent disease or new primary CM.
- Molecular profiling assessment cannot be recommended due to insufficient research.
- **Surveillance Intervals and Follow-Up Tests:** while most metastases occur in the first 1 to 3 years after treatment of the primary tumor, skin exams should occur for the entire lifespan.
 - **Stage 0 MIS:**
 - Every 6 – 12 months for 1 – 2 years; then annually
 - Physical exam assessing for local recurrence and full skin check to monitor for new primary CM
 - **Stage IA-IIA:**
 - Every 6 – 12 months for 2 – 5 years; then annually
 - Comprehensive history (review of systems) and physical exam focusing on skin and regional LNs
 - **Stage IIB and higher:**
 - Every 3 – 6 months for first 2 years; at least every 6 months for 3 – 5 years; then annually
 - Comprehensive history (review of systems) and physical exam focusing on skin and regional LNs
 - Radiology exams may be performed for up to 3 – 5 years
- Risk of new primary CM is higher with the following:
 - Increased nevus count
 - Multiple clinical atypical/dysplastic nevi
 - Family history of CM
 - Fair skin/sun sensitivity

- Prior CM
- Male gender
- Local melanoma recurrence in or surrounding the wide excision includes two types:
 - Persistent disease – a recurrence defined by in situ and/or radial growth typically seen at the margin of the prior wide excision scar; may result from incomplete excision of primary CM and is treated with another wide excision, possible SLNB to remeasure Breslow thickness, and/or enrollment into a clinical study.
 - Satellite metastasis – clinically detectable and indicates intralymphatic spread (stage III), usually palpable cutaneous or subcutaneous masses within or surrounding the wide excision scar and is treated with excision, imaging, SLNB, systemic or intralesional therapy.

Nonsurgical Treatments

Nonsurgical therapy for primary cutaneous melanoma should only be considered under select clinical circumstances, when surgical excision is not feasible.

Imiquimod or Radiation Therapy (RT)

- Topical imiquimod 5% cream may be used as second-line treatment for MIS, LM type, when surgery is not possible in early stage or after optimal surgery has been performed (as adjuvant therapy).
- Discuss the risks and benefits of nonsurgical treatment with the patient and family.
- For nonsurgical patients, RT may be used as a second-line therapy for MIS, LM type, though use is not common in the United States.
- Superficial brachytherapy for MIS, LM type is not recommended.
- Adjuvant RT after wide excision may be used for desmoplastic CM with high-risk features (i.e. Breslow thickness > 4 mm, Clark level V, extensive neurotropism/perineural invasion, head and neck location, and/or narrow deep margin resection).
- Consult a radiation oncologist to discuss risks and benefits of RT.

Management of CM and Pregnancy

- CM diagnosis during pregnancy does not change prognosis or outcome for the woman, but work-up and treatment must consider the safety of the fetus.
- Utilize a multidisciplinary team including obstetrics and CM specialists to develop an individualized care plan for the pregnant patient.
- Women with a history of CM do not need to wait a prolonged period of time before subsequent pregnancy. Factors affecting disease recurrence such as CM thickness and stage as well as age and fertility of the mother, should determine if pregnancy should be delayed and for what length of time.
- Treatment of melanocytic nevi in the pregnant women should be the same as the nonpregnant patient. A changing nevus found during pregnancy should be assessed and biopsied if clinically concerning.

- Exogenous hormones (i.e. oral contraceptives, hormone-containing contraceptive devices/implants, postmenopausal hormone replacement therapy or hormones used for reproductive therapy) may be used in women with a CM diagnosis.

Genetic Counseling for Patients with CM

Genetic counseling is recommended for patients with CM who have:

- Family history of invasive CM or pancreatic cancer (≥ 3 affected members on one side of the family)
- Multiple primary invasive CM (≥ 3), including one early-onset tumor (at age < 45 years)
- ≥ 1 melanocytic BRCA1 associated protein 1 (MBAIT) and a family history of mesothelioma, meningioma, and/or uveal melanoma
- ≥ 2 MBAITs

Dermatologic Toxicities of Newer Drugs for Advanced CM (AJCC stages III and IV)

- New drugs that have been approved to treat advanced or unresectable CM include:
 - B-Raf proto-oncogene, serine/threonine kinase inhibitors (BRAFi)s
 - vemurafenib
 - dabrafenib
 - Mitogen-activated protein kinase inhibitors (MEKi)s
 - trametinib
 - cobimetinib
 - Immune checkpoint inhibitors
 - anti-CTLA4 (ipilimumab)
 - anti-PD-1 (pembrolizumab and nivolumab)
 - anti-PDL-1 (atezolizumab)
- Dermatologists and oncologists should collaborate to manage cutaneous toxicity during treatment to recognize and control skin side effects and improve the quality of life of patients.
- Frequency of skin assessment and management depends on the drugs utilized, age of the patient, underlying skin cancer risk factors (i.e. history of actinic damage and/or skin cancer), and/or skin findings as a biomarker for response.
 - Perform skin assessment every 2 – 4 weeks for the first three months of BRAF inhibitor monotherapy in patients with several squamous cell proliferative neoplasms (although BRAF/MEK inhibition combined therapy is standard and has fewer skin toxicities).
 - Perform skin assessment of patients undergoing immune checkpoint inhibitor therapy within the first month of therapy and continue as needed for management of skin side effects.
 - Patients with atopic dermatitis, psoriasis, or other autoimmune dermatoses should be seen before initiation of therapy by a dermatologist for counseling and treatment.

Reference:

Swetter, S.M., Tsao, H., Bichakjian, C.K., Curiel-Lewandrowski, C., Elder, D.E., Gershenwald, J.E.....Lamina, T. (2018). Guidelines of care for the management of primary cutaneous melanoma. *Journal of the American Academy of Dermatology*, 80(1), 208-250. doi: <https://doi.org/10.1016/j.jaad.2018.08.055>

Link to Practice Guideline:

[https://www.jaad.org/article/S0190-9622\(18\)32588-X/fulltext](https://www.jaad.org/article/S0190-9622(18)32588-X/fulltext)