



AMERICAN SOCIETY OF  
PLASTIC SURGEONS

# Evidence-based Clinical Practice Guideline: Treatment of Cutaneous Melanoma

## INTRODUCTION

### Rationale and Goals

Compared with other cutaneous malignancies, melanoma has the greatest potential for metastasis and, consequently, the highest incidence of mortality. Increased awareness, improved methods of screening, staging, and treatment, and early detection of recurrence are important components of the care continuum that can lead to improved prognosis. Therefore, the aim of this document is to address the assessment and treatment of cutaneous melanoma and to develop a set of recommendations that fairly reflect current accepted medical standards. These guidelines were developed from a comprehensive review of the scientific literature and reflect a consensus of a task force of recognized experts in the field of melanoma treatment, convened by the Health Policy Committee of the American Society of Plastic Surgeons®.

### Scope

Treatment for cutaneous melanoma takes place within a care continuum that includes: (a) diagnosis and risk assessment; (b) active treatment; (c) continuing follow-up; (d) careful surveillance aimed at early detection and treatment of recurrence; and (e) palliative treatment focused on improving the quality of life and relieving suffering, if curative treatment is unlikely. These guidelines specifically address patient assessment; staging and prognosis; treatment; follow-up; and surveillance for recurrence.

### Target Audience

These guidelines are designed for use by any health care practitioner who manages the ongoing care of patients with cutaneous melanoma.

## BACKGROUND

Cutaneous melanoma is a significant public health concern. It is estimated that in 2007 nearly 60,000 Americans will be diagnosed with cutaneous melanoma and over 8100 will die from the disease.<sup>1</sup> Due to its metastatic potential, melanoma accounts for the majority of deaths from cutaneous malignancies. Among all cancers in the United States, the incidence of cutaneous melanoma ranks sixth among both men and women.<sup>1</sup> Although the incidence of melanoma continues to rise in the United States and worldwide, heightened awareness among both physicians and patients and increased opportunities for screening of pigmented lesions have enabled the diagnosis of malignant melanoma at earlier phases of tumor progression, thereby improving patient prognosis.

## DEFINITIONS

**Cutaneous melanoma** is a malignant neoplasm, derived from melanocytes, that arises in the skin.

**Breslow thickness** is a component of staging and is the thickness of the primary melanoma lesion.

**Clark level** is a component of staging and is the level of invasion of primary melanoma into the dermis.

**Lymphoscintigraphy** is scintillation scanning of lymphatics or lymph nodes following intralymphatic or subcutaneous injection of a radionuclide.

**Sentinel lymph node** is the first lymph node to which lymphatic fluid drains from the primary melanoma.

**Sentinel lymph node biopsy** is a staging and treatment technique in which the sentinel lymph node is dissected and evaluated for pathology.

**Complete lymph node dissection** is the full dissection of the regional draining nodal basin of the primary melanoma.

## METHODOLOGY

### Literature Search and Admission of Evidence

This study was carried out with a prospective, systematic method for identifying and evaluating current literature on the treatment of cutaneous melanoma. To identify relevant literature, a comprehensive search of Medline, the Cochrane Database of Systematic Reviews, and the National Guideline Clearinghouse™ was performed by using various combinations of the following search terms: melanoma, cutaneous melanoma, diagnosis, staging, biopsy, treatment, excision margins, sentinel node biopsy, as well as a wide range of indexing terms, free text words and word variants. Search limits restricted results to English-language manuscripts that were published from 1997 to 2007 and also indexed as human studies, clinical trials, randomized controlled trials, systematic reviews, and/or guidelines.

Articles were selected if they were relevant to clinical questions about patient assessment, staging, prognosis, treatment, follow-up and surveillance. Excluded from the literature selection were articles that specifically addressed assessment and treatment of patients with non-cutaneous melanoma.

### Critical Appraisal of the Literature

Relevant articles were categorized by study type: randomized controlled trial, systematic review, cohort study, case-control study, case series, and case report. Each article was critically appraised for study quality according to criteria referenced in key publications

on evidence-based medicine.<sup>2-6</sup> Depending on type (prognostic, diagnostic, or therapeutic) and quality of study, each article was assigned a corresponding level of evidence according to ASPS Evidence Rating Scales (Appendix A), which were modified from scales developed by other surgical specialties and authorities on evidence-based medicine.<sup>2-7</sup>

### **Development of Clinical Practice Recommendations**

Practice recommendations were developed through critical appraisal of the literature and consensus of the ASPS Health Policy Committee. Recommendations are based on the strength of supporting evidence and were graded according to the ASPS Grades of Recommendation Scale (Appendix A), which was modified from scales used by other surgical specialties and authorities in the practice of evidence-based medicine.<sup>2-7</sup> Practice recommendations are discussed throughout this document; however, graded recommendations are summarized in Appendix B.

### **PATIENT ASSESSMENT**

Early detection and diagnosis of melanoma is critical for designing appropriate treatment plans and improving patient outcomes. As such, patients presenting with unusual cutaneous lesions should undergo a comprehensive medical history and a focused physical examination to assess the possibility of melanoma. All pigmented skin lesions suspicious for melanoma should subsequently be biopsied.

#### **Patient History**

The patient history should focus on clinical characteristics associated with a higher risk for melanoma,<sup>8-13</sup> including:

- skin type I or II,
- the presence of multiple common nevi (> 30) and atypical nevi ( $\geq 3$ ),
- a personal or family history of melanoma, and
- a history of prior significant sun exposure, particularly blistering sunburns
- In addition, changes in the size, shape, and/or color of clinically suspect lesions should be recorded.

Individuals with high-risk melanoma features should undergo a professional evaluation at least once a year, and these individuals should be instructed on how to perform frequent self-examinations.<sup>10</sup> Furthermore, family members of patients with melanoma should be advised to be screened for melanoma.

#### **Physical Examination**

The physical examination should involve thorough inspection of the entire skin, including mucous membranes, for suspicious pigmented lesions or dysplastic nevi. Pruritis is the most common early symptom of melanoma. Other early signs of melanoma that are useful for diagnosis include the ABCD factors pertaining to pigmented lesions:

- **A**symmetry,
- **B**order irregularity,
- **C**olor variegation or changes, and
- **D**iameter greater than 6 mm.

It is not uncommon for some melanomas, particularly those that are small and that occur in situ, to lack all or most of the ABCD features. For this reason, the mnemonic may be expanded to ABCDEF to increase the sensitivity of the criteria,<sup>14</sup> which includes factors associated with:

- **E**volutionary changes in color, size, symmetry, surface characteristics, and symptoms, and
- **F**unny-looking lesions.

Symptoms associated with late or extensive tumors include bleeding, tenderness, itching, and loss of skin markings. Affected males generally present with primary lesions localized to the trunk, whereas in women most melanomas occur on the lower extremities.

The physical examination should also include careful palpation of major lymph node basins, particularly those likely to be the regional draining nodal basins. Any palpably suspicious lymph nodes should be regarded as potentially malignant.<sup>11</sup>

#### **Biopsy of the Primary Lesion**

Melanoma is often difficult to accurately diagnose based on patient history and physical examination alone. As such, all patients presenting with a pigmented lesion suspected of being melanoma should undergo a biopsy. Pathologic assessment of the biopsied lesion involves determining the maximum thickness of the tumor and staging the disease.

Excision of the entire lesion with narrow margins (1-3 mm) is the most accurate method for determining the thickness of the melanoma.<sup>10, 15-17</sup> Excisional method is the preferred type of biopsy and should be performed except under unusual circumstances when it is not possible to allow histologic assessment of the entire lesion in order to facilitate accurate staging. Shave biopsies and punch biopsies are not recommended since the full depth of the lesion cannot always be fully ascertained, thus preventing pathological staging of the lesion.<sup>15-19</sup> Moreover, wound healing following such biopsies can disrupt the tumor nodule, thereby making accurate staging impossible after subsequent lesion excision.

Although all pigmented lesions should be completely excised during biopsy, special circumstances may warrant the use of incisional biopsy. These are when the suspect lesion is very large, the suspicion for melanoma is low, or when lesion excision is impractical (e.g., of the nail unit). There has existed controversy whether the use of an incisional biopsy can dislodge tumor cells and promote metastasis. Several studies have disproved this concept; use of the incisional biopsy method prior to full excision of the malignant melanoma does not promote metastasis or adversely affect patient outcomes.<sup>20, 21</sup> It should be noted that incisional biopsies that leave at least 50% of the clinical lesion are sometimes inadequate for accurate melanoma staging, and upstaging may be required after complete excision of the residual lesion.<sup>19</sup> For large, suspicious pigmented skin lesions, fusiform incisional biopsy can provide an adequate specimen for accurate histological diagnosis while producing minimal cosmetic or functional impairment.<sup>22</sup> Ultraviolet-assisted punch biopsy mapping has also been shown to be a safe, well tolerated, and accurate technique for determining the true histological margins of lentigo maligna melanoma.<sup>23</sup>

## Other Clinical and Diagnostic Assessments

Patients without symptoms of metastatic disease may be screened by chest x-ray and serum LDH level;<sup>24-26</sup> however, the indications for obtaining these tests remain controversial. Chest x-ray and blood work-up for various protein markers may have limited value in the initial assessment of asymptomatic patients with primary cutaneous melanoma that is 4 mm or less in thickness. These tests may be associated with a high false-positive rate, and initial imaging studies are insensitive and nonspecific for the detection of clinically occult distant disease.<sup>27-29</sup> Although there is no consensus in the literature, many physicians order routine baseline chest x-ray and blood work in all newly diagnosed melanoma patients and some screen only those patients with a higher risk of metastatic disease (i.e. patients qualifying for sentinel node biopsy or node dissection).

In individuals with more advanced disease (stage III/IV), various clinical and diagnostic assessments can be useful for identifying metastatic disease. The detection of elevated serum lactate dehydrogenase, alkaline phosphatase levels, and S-100 B protein can indicate melanoma metastasis.<sup>11, 30-32</sup> Screening tests for molecular markers, such as using reverse-transcriptase polymerase chain reaction (RT-PCR) to identify tyrosinase messenger ribonucleic acid (mRNA), have been reported to correlate with disease status and recurrence rates.<sup>11, 33</sup> Patients with advanced-stage disease who have abnormal findings on screening tests, patient history, or physical examination are ideal candidates for directed radiologic examinations, including a chest x-ray, abdominal CT scan, and PET scan to identify possible sites of metastasis. A brain MRI and a chest and abdominal CT scan should be performed if aggressive treatment is undertaken.<sup>28</sup>

## STAGING & PROGNOSIS

### Primary Melanoma Prognosis

Two of the most important features that determine patient prognosis, the risk of metastasis, treatment, work-up, and follow-up for localized cutaneous melanoma include the Breslow depth, indicative of the thickness of the melanoma, and the ulceration status.<sup>34-36</sup> Prognosis worsens as tumor thickness increases. Prognosis is also worse in the presence of ulceration.

Several other histologic features strongly associated with prognosis may be included in the pathology report<sup>11, 27, 37-43</sup>, including the following:

- Tumor location
- Growth phase
- Mitotic rate
- Tumor infiltrating lymphocytes
- Regression
- Microsatellites
- Histologic subtype

### Primary Melanoma Staging

Once a lesion has been histologically confirmed as malignant melanoma, pathological staging (TNM) is essential for determining patient prognosis and guiding treatment decisions. The American Joint Committee on Cancer (AJCC) staging system incorporates

elements related to the primary tumor (T), nodal involvement (N), and distant metastases (M), and this system is often used to determine the disease stage since it has been validated using a population-based cohort.<sup>35, 44</sup> In general, stage I disease encompasses early local disease (thin melanomas without metastasis); stage II comprises more advanced local disease (intermediate-thickness melanomas without metastasis); stage III includes melanomas with regional lymph node and/or in-transit metastasis; and stage IV denotes distant metastatic disease.

The following elements should be included in the pathology report for staging and identification purposes:<sup>11, 27, 35, 45</sup>

- Patient age
- Gender
- Anatomical site of the lesion
- Tumor thickness
- Clark level (indicative of level of invasion)
- Ulceration
- Margin involvement following surgical excision
- Lesion dimensions

### Sentinel Node Biopsy and Prognosis

The presence or absence of sentinel node metastasis is a strong independent predictor of patient outcome after excision of the primary melanoma,<sup>46</sup> particularly for patients diagnosed with clinical stage I or II disease. Hence, sentinel lymph node biopsy is currently the most powerful method for staging and prognosis. Because sentinel lymph node biopsy enables accurate staging of the entire nodal basin, this procedure can provide the same staging information obtained by complete lymphadenectomy but with much less morbidity.<sup>47</sup>

The probability of detecting metastasis in the sentinel lymph node increases with greater tumor thickness. A sentinel node biopsy should be considered for patients with a melanoma 1 mm or greater in thickness.<sup>48, 49</sup> Individuals with thin melanomas less than 1 mm in thickness rarely have nodal disease, and sentinel node biopsy is generally not performed on such patients, except when any of the following features associated with an increased risk of nodal metastasis is found:

- Ulceration<sup>36</sup>
- Clark level IV or V
- Vertical growth phase (VGP)<sup>38-40, 50</sup>
- Small cell melanoma morphology
- No tumor infiltrating lymphocytes and/or an inflammatory reaction<sup>39, 41</sup>
- Mitoses<sup>39</sup>
- Notable regression beneath the tumor<sup>41</sup>

Important prognostic factors to consider in the event of lymph node metastasis include the following:

- The number of involved nodes
- Microscopic versus macroscopic disease
- The presence of extranodal extension

## Lymphatic Drainage Patterns

Preoperative mapping of lymphatic drainage patterns has become an invaluable tool for identifying sites of possible subclinical lymph node metastasis in patients with melanoma. Blue vital dye and radioactive colloid injected into the skin adjacent to the primary tumor or biopsy site enters the lymphatic system and is transported to the tumor-draining lymph nodes. This technique enables visualization of the sentinel lymph nodes, which is imperative for determining which nodes should be removed for sentinel node biopsy. A higher number of radiotracer injections ( $\geq 3$  vs  $< 3$ ) has been shown to improve the sensitivity and accuracy of lymphatic mapping, thereby enabling fewer nodes to be removed during biopsy.<sup>51</sup> Lymphoscintigraphy should be done prior to wide excision but may still be accurate after wide excision.<sup>52</sup>

In patients with truncal melanoma, lymphatic drainage to multiple lymph node basins correlates with poorer survival compared with drainage to a single lymph node basin, irrespective of sentinel lymph node status. The correlation between drainage patterns associated with other melanoma sites and outcome has not been established.

## TREATMENT

### Surgical Excision with Appropriate Margins

Surgery is the gold-standard treatment for melanoma. The goals of surgical treatment are to (1) remove all melanoma cells at the primary site to prevent occult metastases and (2) attain durable local disease control, even if curative treatment is unlikely. Efforts should be made to achieve these goals while causing minimal functional or cosmetic disfigurement during melanoma excision.

Recent analyses have established that tumor thickness, rather than wide excision margins, bears the greatest influence on disease recurrence. Several long-term, randomized, controlled clinical trials demonstrated that narrower margins (1-2 cm) selected in accord with tumor thickness do not compromise the rates of local recurrence, disease-free survival, or overall survival.<sup>34, 53-56</sup> Hence, the currently recommended surgical excision margins for invasive melanoma are based on the thickness of the primary tumor.

According to the combined results of clinical trials,<sup>34, 53-56</sup> excision margins of 0.5-1.0 cm around the biopsy scar or visible lesion are generally accepted for melanoma in situ. A 1-cm margin is accepted for thin melanomas less than 1 mm in thickness. A surgical margin of 2 cm is recommended for melanomas with a thickness of 1-4 mm. No prospective, randomized trials have assessed the appropriate margin for tumors greater than 4 mm in thickness. At the very least, melanomas greater than 4 mm in thickness should be excised with margins of 2 cm. The depth of tumor excision should fully include the dermis as well as some underlying subcutaneous tissue. Following excision, the surgical margins should be analyzed for the presence of tumor cells or atypical melanocytes.

## Recommended Surgical Excision Margins for Primary Melanomas

Tumor Thickness	Recommended Excision Margin
In situ, 0.5-1 mm	0.5 cm
< 1 mm	1 cm
1-2 mm	1-2 cm
1-4 mm	2 cm
> 4 mm	$\geq 2$ cm

The excision margins established in clinical trials and recommended herein should be regarded as guidelines. Every melanoma case requiring excision should be individualized, particularly for individuals with melanomas occurring on the head and neck where cosmetic disfigurement may be profound.

### Sentinel Lymph Node Biopsy

It is well established that examination of the sentinel lymph node, the first lymph node that drains the primary melanoma, enables the identification of individuals in need of selective complete lymph node dissection. Conversely, those with no histologic nodal involvement can be spared from unnecessary surgery since there is a very low probability ( $< 1\%$ ) that other nodes within the same nodal basin harbor metastatic disease. Moreover, it is argued that the sentinel lymph node biopsy procedure is more specific and sensitive for identifying nodal metastases than elective lymphadenectomy due to the smaller size of the specimen requiring examination by a pathologist.<sup>28</sup>

As stated above, a sentinel lymph node biopsy should be considered for patients with a melanoma that is 1 mm or greater in thickness or for patients with a melanoma less than 1 mm thick but with negative prognostic features (e.g., ulceration, Clark level IV/V, VGP).<sup>50, 57</sup> The combined use of vital dyes, radiolocalization, and gamma probe facilitates the identification of the sentinel node in the draining lymph node basin with an accuracy of more than 95%.<sup>10, 58</sup> Clinical reports indicate that 16%-24% of patients undergoing sentinel lymph node biopsy harbor metastatic melanoma cells within the sentinel lymph node.<sup>57-60</sup> Common features associated with metastasis-positive sentinel lymph nodes include:

- Greater Breslow thickness,
- The presence of ulceration, and
- Axial location of the primary tumor.<sup>10, 58</sup>

The false-negative rate of sentinel lymph node biopsy is generally less than 5% when the procedure is performed by skilled clinicians who use multiple imaging techniques to eliminate the dissection of non-sentinel nodes (i.e., blue vital dye, radioactive colloid, and gamma probe) and who perform serial sectioning followed by hematoxylin and eosin staining and immunohistochemistry to

minimize the probability of missed sentinel node metastasis.<sup>10, 46-49, 58, 61, 62</sup> RT-PCR is a precise, rapid, reliable method that can enhance the accuracy of the biopsy results by detecting molecular markers of micrometastases.<sup>63-65</sup> Detection of tyrosinase mRNA, which is synthesized by melanocytes, within a lymph node sample is indicative of the presence of metastatic melanoma cells within that node. The presence of other molecular markers, such as mRNAs for melanoma inhibitory activity (MIA) and Melan-A, also indicate micrometastasis and may improve the sensitivity of RT-PCR when combined with the detection of tyrosinase mRNA.<sup>63, 64</sup>

### **Complete Lymph Node Dissection**

Complete lymph node dissection, or radical lymphadenectomy, is warranted for any patient with a positive sentinel lymph node determined by biopsy, since only full dissection of the nodal basin can illuminate whether other nodes in the same basin also have metastatic disease. Approximately 15%-20% of patients harbor additional metastases within the completely excised specimen. It is unclear whether all patients with a positive sentinel lymph node biopsy need to undergo complete lymph node dissection to attain the best survival outcomes;<sup>66</sup> efforts to identify patient factors predictive of a minimal risk of additional metastasis to non-sentinel lymph nodes have not been fruitful. As such, complete lymph node dissection should be offered to all patients with a positive sentinel node, taking care to discuss the complications of this procedure.<sup>48, 66</sup>

Watch-and-wait observation followed by delayed lymph node dissection of enlarged lymph node metastases (i.e., macrometastases) was formerly proposed as a potential alternative to complete lymph node dissection following a positive sentinel lymph node biopsy. While still unclear, studies have found that early excision of lymphatic metastases revealed by sentinel node biopsy produced a significant survival benefit compared with delayed dissection of enlarged lymph node metastases, and the early excision procedure is also an independent prognostic factor associated with better overall survival.<sup>48</sup>

Prior to widespread use of sentinel node biopsy, immediate elective lymph node dissection for individuals with intermediate-thickness tumors (1-4 mm) was suggested as a prophylactic treatment for the prevention of disease recurrence. Several trials failed to establish an overall survival benefit for patients undergoing this procedure compared with delayed therapeutic dissection, except for those with tumors 1-2 mm thick, those with tumors without ulceration, and those with limb melanomas.<sup>67</sup> The rates of recurrence and overall survival following biopsy-indicated complete lymph node dissection have been shown to be equivalent to or slightly better than elective lymph node dissection, causing the latter procedure to fall out of favor. This procedure also has significant morbidity for patients found to have negative lymphatic metastasis.

Complete therapeutic lymph node dissection is advised for any patient with clinically obvious metastatic melanoma in regional lymph nodes, even when multiple basins are involved. The procedure has been suggested to be curative in about 30% of cases; however, it is unclear if survival is due to the procedure or other factors. Due to the lack of satisfactory treatments, palliative therapeutic lymph node dissection should be considered for individuals with distant metastases in order to ameliorate the potential morbidity from uncontrolled local disease and lymphatic obstruction.<sup>11, 57</sup>

### **Systemic Treatment**

Typically, patients with superficial, early-stage, melanomas can be effectively treated with surgery; however, patients with more advanced disease may require systemic treatment and, therefore, may need a referral to an oncologist. These patients may benefit from available therapeutic agents or investigational agents in clinical trials.<sup>68</sup>

### **POSSIBLE SEQUELAE AND COMPLICATIONS**

#### **Possible Sequelae**

- Local/in-transit recurrence
- Distant recurrence
- Second primary melanoma
- Lymphomas
- Non-melanoma skin cancers
- Brain, bone, lung, liver, and gastrointestinal cancers
- Disfiguring wounds and scars following surgical treatment

#### **Possible Complications**

As with any medical procedure, there are several possible complications that may arise in association with surgical treatment of melanoma:

- Lymphedema
- Hematoma and/or seroma formation
- Wound infection
- Sensory nerve injury, typically transient
- Allergic reactions to isosulfan blue dye
- Edema

### **FOLLOW UP**

Patients who undergo complete disease removal by surgery still remain at risk for regional and distant recurrence, as well as for additional primary melanomas. As such, patient follow-up and surveillance is necessary for the early detection of new lesions and the spread of asymptomatic metastatic disease.

#### **Physical Exam**

Follow-up procedures and frequency can vary depending on stage of disease; however, it is often recommended that a routine physical examination, including full skin assessment and lymph node palpation, be carried out every 3 months for the first year; every 6 months for 5 years, then at least yearly thereafter.<sup>69-72</sup> More frequent visits (i.e., 4 times per year in the first 2-3 years)

are necessary for patients with high-risk melanoma features or poor prognostic indicators:<sup>10, 11, 27, 28, 73, 74</sup>

- Greater tumor thickness
- Multiple melanomas
- The presence of clinically atypical nevi
- A family history of melanoma
- Sentinel lymph node metastasis

### Diagnostic Tests

Consistent with the recommendations for the initial patient assessment, routine laboratory tests such as serum lactate dehydrogenase, serum alkaline phosphatase, serum albumin, plasma hemoglobin, and chest x-ray should be ordered at the discretion of the physician. These tests are generally ineffective at identifying visceral disease in asymptomatic patients, and as such, may be reserved for patients with at least stage II or III disease, or for patients with signs or symptoms of possible systemic involvement based on the medical history and physical examination.<sup>24-33</sup>

### SURVEILLANCE FOR RECURRENCE

Many melanoma metastases and recurrences are identified by patients or their family members. This emphasizes the benefit of educating patients with melanoma on how to perform self-examination of the skin and lymph nodes and encouraging them to bring any unusual skin lesions or symptoms to the attention of their medical provider.<sup>71, 75, 76</sup> Common symptoms associated with melanoma recurrence include local nodularity, satellites, adenopathy, chronic coughing, headaches, bone pain, and gastrointestinal symptoms, among others. Melanoma metastases, local recurrences, and second primary melanomas are also often detected by clinicians during routine physical examinations, thereby stressing the importance of follow-up visits to providers.<sup>27, 28, 73</sup>

Most melanoma recurrences occur within 2-3 years after wide local excision of the primary lesion. The most common site of initial recurrent disease in patients who have not undergone lymphadenectomy is the regional lymph nodes, whereas those who have undergone this procedure tend to develop visceral metastases as the initial site of recurrence.<sup>57, 59</sup> Local and in-transit recurrence portends a particularly poor prognosis. Interestingly, although pediatric patients have a higher incidence of metastasis to sentinel lymph nodes than adult patients, pediatric patients have a lower rate of melanoma recurrence.

Several independent factors associated with the primary melanoma have been associated with an increased risk of melanoma recurrence:<sup>46, 70-72, 77, 78</sup>

- Sentinel lymph node metastasis
- Metastasis to multiple sentinel lymph nodes
- Greater Breslow thickness
- Ulceration
- Clark level IV/V

### DISCLAIMER

Clinical practice guidelines are strategies for patient management and are developed to assist physicians in clinical decision making.

This guideline, based on a thorough evaluation of the scientific literature and relevant clinical experience, describes a range of generally acceptable approaches to diagnosis, management, or prevention of specific diseases or conditions. This guideline attempts to define principles of practice that should generally meet the needs of most patients in most circumstances.

However, this guideline should not be construed as a rule, nor should it be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the appropriate results. It is anticipated that it will be necessary to approach some patients' needs in different ways. The ultimate judgment regarding the care of a particular patient must be made by the physician in light of all circumstances presented by the patient, the available diagnostic and treatment options, and other available resources.

This guideline is not intended to define or serve as the standard of medical care. Standards of medical care are determined on the basis of all facts or circumstances involved in an individual case and are subject to change as scientific knowledge and technology advance, and as practice patterns evolve. This guideline reflects the state of knowledge current at the time of publication. Given the inevitable changes in the state of scientific information and technology, periodic review, updating and revision will be done.

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## APPENDIX A. SCALES FOR RATING LEVELS OF EVIDENCE AND GRADING PRACTICE RECOMMENDATIONS

### Evidence Rating Scale for Diagnostic Studies

Level of Evidence	Qualifying Studies
I	High-quality, multi-centered or single-centered, cohort study validating a diagnostic test (with “gold” standard as reference) in a series of consecutive patients; or a systematic review of these studies
II	Exploratory cohort study developing diagnostic criteria (with “gold” standard as reference) in a series of consecutive patient; or a systematic review of these studies
III	Diagnostic study in nonconsecutive patients (without consistently applied “gold” standard as reference); or a systematic review of these studies
IV	Case-control study; or any of the above diagnostic studies in the absence of a universally accepted “gold” standard
V	Expert opinion; case report or clinical example; or evidence based on physiology, bench research or “first principles”

### Evidence Rating Scale for Prognostic Studies

Level of Evidence	Qualifying Studies
I	High-quality, multi-centered or single-centered, prospective cohort study with adequate power; or a systematic review of these studies
II	Lesser-quality prospective cohort study; retrospective study; untreated controls from a randomized controlled trial; or a systematic review of these studies
III	Case-control study; or systematic review of these studies
IV	Case series
V	Expert opinion; case report or clinical example; or evidence based on physiology, bench research or “first principles”

### Evidence Rating Scale for Therapeutic Studies

Level of Evidence	Qualifying Studies
I	High-quality, multi-centered or single-centered, randomized controlled trial with adequate power; or systematic review of these studies
II	Lesser-quality, randomized controlled trial; prospective cohort study; or systematic review of these studies
III	Retrospective comparative study; case-control study; or systematic review of these studies
IV	Case series
V	Expert opinion; case report or clinical example; or evidence based on physiology, bench research or “first principles”

## Scale for Grading Recommendations

Grade	Descriptor	Qualifying Evidence	Implications for Practice
A	Strong Recommendation	Level I evidence or consistent findings from multiple studies of levels II, III, or IV	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
B	Recommendation	Levels II, III, or IV evidence and findings are generally consistent	Generally, clinicians should follow a recommendation but should remain alert to new information and sensitive to patient preferences.
C	Option	Levels II, III, or IV evidence, but findings are inconsistent	Clinicians should be flexible in their decision-making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role.
D	Option	Level V; little or no systematic empirical evidence	Clinicians should consider all options in their decision-making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.

**APPENDIX B. SUMMARY OF RECOMMENDATIONS**

RECOMMENDATIONS FOR PATIENT ASSESSMENT	SUPPORTING EVIDENCE	GRADE
<p><b>Patient History</b> Assess risk factors:</p> <ul style="list-style-type: none"> <li>• Skin type I or II</li> <li>• Presence of multiple common nevi (&gt; 30)</li> <li>• Presence of atypical nevi (≥ 3)</li> <li>• Personal or family history of melanoma</li> <li>• Prior significant sun exposure (blistering sunburns)</li> </ul>	8, 12, 13	<b>B</b>
<p><b>Physical Exam</b> Exam should include:</p> <ul style="list-style-type: none"> <li>• Thorough inspection of entire skin, including mucous membranes, for pigmented lesions</li> <li>• Focused exam of pigmented lesions (ABCDE criteria)</li> <li>• Careful palpation of major lymph node basins</li> </ul>	14, 79	<b>B</b>
<p><b>Biopsy of the Primary Lesion</b> For pigmented lesions suspect for melanoma:</p> <ul style="list-style-type: none"> <li>• Excisional biopsy recommended when possible</li> <li>• Only when excisional biopsy is impractical, should incisional biopsy be considered</li> </ul>	18-20	<b>B</b>
<p><b>Other Clinical and Diagnostic Assessments</b> For all patients, consider:</p> <ul style="list-style-type: none"> <li>• Blood work (serum lactate dehydrogenase, alkaline phosphatase)</li> <li>• Chest x-ray</li> </ul> <p>For patients with more advanced disease, consider:</p> <ul style="list-style-type: none"> <li>• Blood work (serum lactate dehydrogenase, alkaline phosphatase, S100B)</li> <li>• Radiologic exams (chest x-ray, chest and abdominal CT, PET scan, brain MRI)</li> <li>• Screening tests for molecular markers (RT-PCR)</li> </ul>	25-26, 29	<b>C</b>

RECOMMENDATIONS FOR TREATMENT	SUPPORTING EVIDENCE	GRADE
<p><b>Surgical Excision of Primary Melanoma</b></p> <ul style="list-style-type: none"> <li>• In situ, 0.5-1mm lesion: 0.5 cm margin</li> <li>• &lt; 1 mm lesion: 1 cm margin</li> <li>• 1-2 mm lesion: consider 1-2 cm margin</li> <li>• 1-4 mm lesion: 2 cm margin</li> <li>• &gt; 4 mm lesion: ≥ 2 cm margin</li> </ul>	34, 53-56	<b>A</b>
<p><b>Sentinel Lymph Node Biopsy</b></p> <p>SLNB should be considered for patients with:</p> <ul style="list-style-type: none"> <li>• Primary melanoma ≥ 1mm</li> <li>• Primary melanoma &lt; 1mm, but with negative prognostic features (i.e., ulceration, Clark level IV/V, VGP)</li> </ul> <p>Recommend use of multiple imaging techniques:</p> <ul style="list-style-type: none"> <li>• Blue vital dye</li> <li>• Radioactive colloid</li> <li>• Gamma probe</li> </ul> <p>Measures to minimize probability of missed sentinel node metastasis include:</p> <ul style="list-style-type: none"> <li>• Serial sectioning</li> <li>• Hematoxylin and eosin staining</li> <li>• Immunohistochemistry</li> <li>• RT-PCR</li> </ul>	46-50, 57, 80	<b>B</b>
<p><b>Complete Lymph Node Dissection</b></p> <p>CLND is recommended for patients with:</p> <ul style="list-style-type: none"> <li>• Positive sentinel lymph node (determined by biopsy)</li> <li>• Clinically obvious metastatic melanoma in regional lymph nodes, even when multiple basins are involved</li> <li>• Distant metastasis (as palliative treatment)</li> </ul>	46-49, 58, 61, 62, 80	<b>B</b>
<p><b>Systemic Treatment</b></p> <ul style="list-style-type: none"> <li>• Patients who cannot be successfully treated with surgery should be referred to an oncologist for further treatment options</li> </ul>	46-49, 58, 61-65, 80	<b>B</b>
<p><b>Complete Lymph Node Dissection</b></p> <p>CLND is recommended for patients with:</p> <ul style="list-style-type: none"> <li>• Positive sentinel lymph node (determined by biopsy)</li> <li>• Clinically obvious metastatic melanoma in regional lymph nodes, even when multiple basins are involved</li> <li>• Distant metastasis (as palliative treatment)</li> </ul>	48, 66, 67, 80, 81	<b>C</b>
<p><b>Systemic Treatment</b></p> <ul style="list-style-type: none"> <li>• Patients who cannot be successfully treated with surgery should be referred to an oncologist for further treatment options</li> </ul>	Expert Opinion	<b>D</b>



**APPENDIX C. CODING**

<b>Procedure</b>	<b>CPT Code</b>
Excision, malignant lesions	11600-11646
Repair, intermediate layer closure of wounds	12031-12057
Repair, complex wound closure	13100-13153
Adjacent tissue transfer or rearrangement	14000-14061
Split thickness skin graft	15050-15121
Full thickness skin graft	15200-15261
Radical resection of tumor (e.g., malignant neoplasm), soft tissue of face or scalp	21015-52
Radical resection of tumor (e.g., malignant neoplasm), soft tissue of neck or thorax	21557-52
Radical resection of tumor (e.g., malignant neoplasm), soft tissue of back or flank	21935-52
Radical resection of tumor (e.g., malignant neoplasm), soft tissue of shoulder area	23077-52
Radical resection of tumor (e.g., malignant neoplasm), soft tissue of upper arm or elbow area	24077-52
Radical resection of tumor (e.g., malignant neoplasm), soft tissue of forearm and/or wrist area	25077-52
Radical resection of tumor (e.g., malignant neoplasm), soft tissue of hand or finger	26117-52
Radical resection of tumor, soft tissue of pelvis and hip area (e.g., malignant neoplasm)	27049-52
Radical resection of tumor (e.g., malignant neoplasm), soft tissue of thigh or knee area	27329-52
Radical resection of tumor (e.g., malignant neoplasm), soft tissue of leg or ankle area	27615-52
Radical resection of tumor (e.g., malignant neoplasm), soft tissue of foot	28046-52
Biopsy or excision of lymph node(s)	38500-38542
Cervical lymphadenectomy	38700-38724
Axillary lymphadenectomy	38740-38745
Inguinofemoral lymphadenectomy	38760-38765
Injection procedure; for identification of sentinel node	38792
<b>Diagnosis</b>	<b>ICD-9 Code</b>
Malignant melanoma of skin	172.0-172.9
Unqualified visual loss, one eye (e.g., restricted or obstructing vision)	369.8
Hemorrhage, unspecified (e.g., bleeding)	459.0
Chronically irritated with evidence of inflammation (e.g., purulence, oozing, edema, erythema)	682.0-682.9
Unspecified pruritic disorder (e.g., itching)	698.9
Dyschromia (abnormal pigmentation of skin)	709.0
Disturbance of skin sensation (e.g., painful)	782.0
Other symptoms involving skin and integumentary tissues (e.g., changing lesions, including: enlarging or changing colors)	782.9
Malignant melanoma of skin	V10.82
Other malignant neoplasm of skin	V10.83
Infections and parasitic diseases, other (e.g., infected lesion)	V12.09
Previous exposure to therapeutic or other ionizing radiation (i.e., therapeutic or sun exposure, sunburn, or tanning salons)	V15.3
Observation for suspected malignant neoplasm	V71.1