Workup and Staging of Malignant Melanoma

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KEYWORDS

• Melanoma • Skin neoplasms • Melanoma workup • Melanoma staging

KEY POINTS

- Melanoma is the fifth most common cancer in the United States, and its incidence is increasing.
- Skin lesions with asymmetry, irregular borders, heterogeneous coloration, increasing diameter, or changes over time should be investigated for possible melanoma.
- Pathologic reports after skin biopsy should include important prognostic factors, including histologic subtype, Breslow depth, dermal mitotic rate, and presence of lymphocytic invasion, ulceration, or regression.
- Sentinel lymph node biopsy is important for staging, prognosis, and treatment planning.
- Radiologic assessment for metastases should be performed routinely only in those with symptomatic stage III melanoma.

INTRODUCTION

Melanoma is the fifth most common cancer in the United States, with an estimated 76,100 new cases and 9710 deaths in 2014.[1,2] The incidence has steadily increased over the past 4 decades, with an average increase of 2.6% per year for each of the last 10 years, making it one of the most rapidly rising cancers in terms of incidence.[3] Although the largest number of melanoma cases occurs in individuals aged 55 to 64 years, is it the most common cancer in adults aged 25 to 29 years, and the second most common cancer in adolescents.[4]

Risk factors for melanoma include history of blistering sunburn (particularly at a young age), personal history of melanoma, family history, immune suppression, presence of multiple atypical moles, chronic sun or tanning bed exposure, or genetic syndromes, such as Wiskott-Aldrich syndrome or *xeroderma pigmentosa*. In addition, individuals with red or blond hair, fair complexion, or light eyes are at increased lifetime

The authors have nothing to disclose.
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Surg Clin N Am 94 (2014) 963–972
http://dx.doi.org/10.1016/j.suc.2014.07.001 **surgical.theclinics.com**
0039-6109/14/$ – see front matter

risk for melanoma.[4] Melanoma frequently occurs in existing moles, and early signs of melanoma are described by the mnemonic "ABCDE" (Fig. 1).[5]

PRINCIPLES OF BIOPSY

The first step to accurately staging a patient with suspected melanoma is a complete history and physical examination, including complete examination of the entirety of the skin and all draining lymph node basins. Lesions suspicious for melanoma should be biopsied, taking care to obtain sufficient tissue to allow for accurate assessment of the

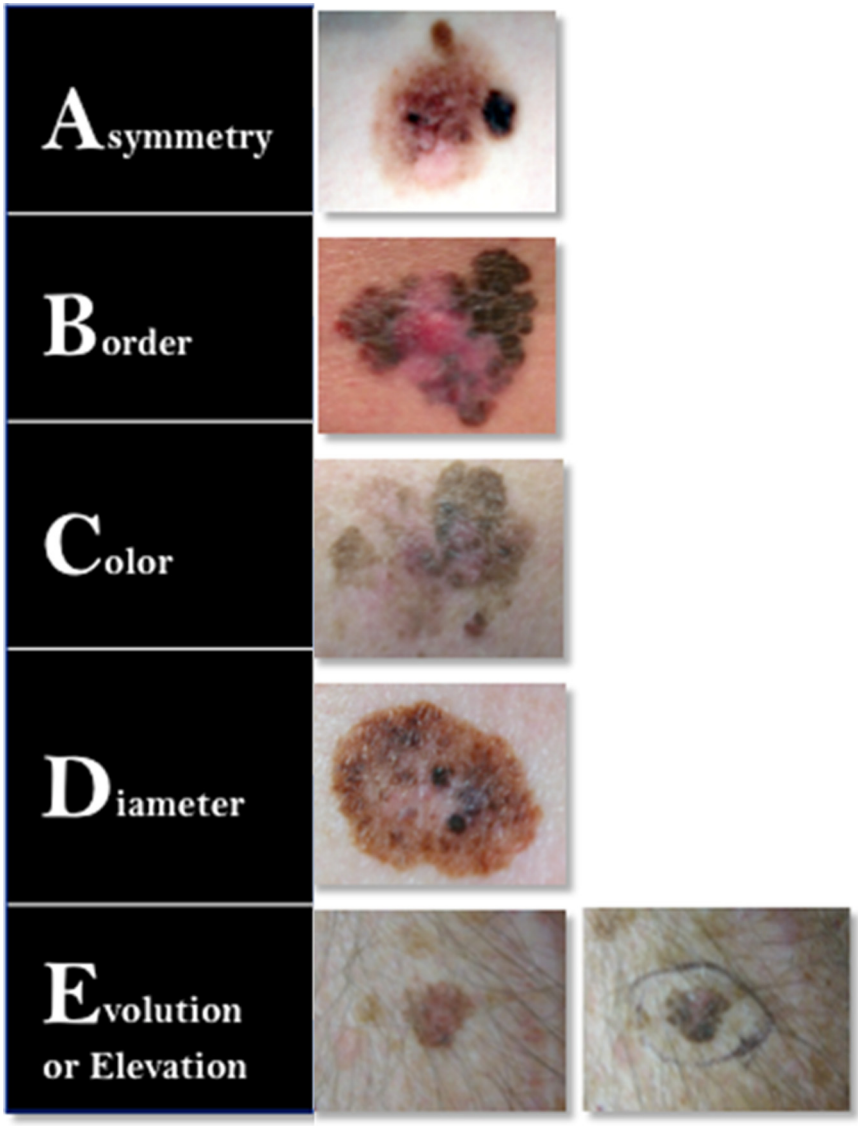

Fig. 1. Early signs of melanoma are described by the mnemonic "ABCDE". (*Courtesy of* Jae Jung, MD, Department of Dermatology, City of Hope Medical Center, Duarte, CA; and Dr Lynn Cornelius, Washington University, St Louis, MO.)

depth of invasion, if present, which in general should be a full-thickness biopsy. Small lesions that are not in cosmetically sensitive locations are amenable to excisional biopsy. An elliptical incision should be oriented to allow for wide excision of the lesion should it reveal melanoma, which is usually along skin lines, or the longitudinal axis of the extremity. Particular attention should be paid to the radial diameter of the lesion, with a 1-mm to 3-mm margin, in addition to ensuring a full-thickness excision.[4] If malignant melanoma is confirmed by pathologic analysis, reexcision to appropriate margins will likely be required, and consideration of the placement of a marking tattoo or leaving a suture in the skin should be made for small lesions, in the event that reexcision is necessary. Shave biopsies should be avoided, as they frequently do not adequately assess the depth of the lesion. Larger lesions or those in cosmetically sensitive areas, such as the face, should be approached via punch biopsy of the area of darkest pigmentation.[4]

PATHOLOGIC ANALYSIS

Biopsy specimens should be submitted to an expert pathologist for analysis. Melanoma is broadly divided into the following subtypes[6–9]:

- Lentigo maligna melanoma: Arises from the premalignant lentigo maligna lesions, but becomes malignant when they break free of the epidermis and invade the dermis. Frequently diagnosed in the elderly, and are often confused with age spots.
- Superficial spreading melanoma: Most common type of melanoma, characterized by a flat or slightly raised lesion with irregular borders and heterogeneous coloration. Demonstrate radial and vertical growth.
- Acral lentiginous melanoma: Rare and aggressive melanoma that occurs more frequently in African American than white individuals, and is often found on the palms of the hands, soles of feet, or mucus membranes. Due to difficulty in detecting the lesion secondary to location, it frequently presents late.
- Mucosal melanoma: Arises on mucus membranes covered by squamous cells.
- Nodular melanoma: Aggressive tumor that assumes a nodular shape, characterized by an early vertical growth phase with little or no radial growth. Comprises approximately 15% of all malignant melanomas, and are typically smooth and a uniform blue/black color.
- Desmoplastic melanoma: Rare melanoma seen in older adults that is characterized by scant spindle cells and minimal cellular atypia.
- Amelanotic melanoma: Flesh-colored melanoma lesions that lack dark pigmentation.
- Pediatric atypical Spitzoid tumor: Lesion most commonly seen in pediatric or adolescent patients, and characterized by melanocytes that assume a spindled or epithelioid shape.
- Uveal melanoma: Occurs on the uvea or conjunctiva.

Depth of invasion is an important prognostic factor, and is described by Breslow depth as determined by an ocular micrometer to determine maximal tumor thickness and Clark level (**Table 1**).[10,11]

A complete pathologic report by an experienced pathologist is required for accurate histologic analysis of a melanotic lesion. Gross analysis includes a description of the lesion's symmetry, as well as maximum lesion diameter. Complete microscopic assessment should include detailed information regarding the histologic subtype, Clark level, Breslow depth, dermal mitotic rate per square millimeter, degree of atypia,

Table 1
Clark level

Level	Anatomic Depth
Level 1	Melanoma confined to epidermis (in situ)
Level 2	Invasion into the papillary dermis
Level 3	Invasion to the junction of the papillary and reticular dermis
Level 4	Invasion into the reticular dermis
Level 5	Invasion into the subcutaneous fat

From Weedon D. Skin pathology. 2nd edition. Sydney (Australia): Churchill-Livingstone; 2002.

presence of lymphocytic invasion, presence of ulceration or tumor regression, presence of lymphovascular or perineural invasion, microsatellitosis, and margin assessment.[12,13] Tumor thickness/depth of invasion is the most important independent predictor of survival from melanoma, but multiple studies have shown that a high dermal mitotic rate is related to decreased survival, and is second only to tumor thickness in predicting survival.[14–16] The importance in defining mitotic rate accurately is particularly important in thin melanoma, where a single mitosis changes the tumor stage from T1a to T1b.[17] Immunohistochemistry staining for HMB-45, Melan-A protein, anti-phospho-histone 3, and S-100 is frequently performed.[14] If the diagnosis remains in question after routine hematoxylin-eosin (H&E) staining and immunohistochemistry, fluorescent in situ hybridization or comparative genomic hybridization to detect mutational subtypes found in melanocytic tumors can be performed.[18]

ROLE OF SENTINEL LYMPH NODE BIOPSY

The presence of tumor in the lymph nodes is a key prognostic indicator, and accurate identification is paramount for both accurate staging and decision-making on further therapy. If metastases to lymph nodes are identified, lymph node dissection is both prognostic and therapeutic, with improvements in local control and melanoma-specific survival.[19–21]

Initially described by Morton and colleagues,[22] sentinel lymph node biopsy has resolved most of the previous controversies surrounding elective lymph node dissection for clinically node-negative patients. This technique is based on the concept of orderly progression of tumor metastasis through lymphatic channels that are specific to each area of skin that can be followed with appropriate tracers, such as isosulfan blue and Tc-99 labeled sulfur colloid. The sensitivity for detection of tumor in sentinel lymph nodes using blue dye alone is 93%, but approaches 100% when a second tracer (lymphoscintigraphy) is added.[3]

In the setting of clinically nonpalpable nodes, sentinel lymph node biopsy with lymphoscintigraphy is now considered the standard of care in the workup of intermediate-thickness melanoma with a large multicenter randomized study demonstrating its importance in obtaining prognostic information and decreasing regional recurrence.[23] A number of others advocate its use for melanomas with a thickness of 0.76 mm or more, balancing the relative risks of sentinel node biopsy with the information gained.[13,24–26] In addition to lymph node status, the use of sentinel node mapping allows for ultrastaging of the lymph nodes with serial sectioning and immunohistochemistry, which could be impractical with elective lymph node dissections that yield substantially higher numbers of nodes excised. The burden of tumor in the sentinel lymph node is related to melanoma survival, and can be used to

determine which patients require completion lymph node dissection. Patients in whom submicrometastases (<0.1 mm) are found in the sentinel node have the same recurrence and survival as sentinel lymph node–negative patients, and can be spared completion lymph node dissection.[27] Patients with micrometastatic deposits (0.1–0.2 mm) in the sentinel node require completion lymph node dissection, because 10% of patients will have additional positive nodes, portending a poorer prognosis and increased risk of death.[27,28] More recently, the utility of completion lymphadenectomy has been questioned as well. A study from the National Cancer Database found that as many as 50% of patients with positive sentinel node dissections do not undergo definitive lymph node dissection.[29] The Multicenter Selective Lymphadenectomy Trial II (MSLT-II), which randomizes patients to completion dissection or observation for positive nodes, has recently finished accruing and will help to answer this question.[30]

SENTINEL LYMPH NODE PROCEDURE

- Preoperative lymphoscintigraphy (particularly for truncal lesions) to localize which nodal basin(s) is/are draining the primary tumor
- Induction of general anesthesia
- Patient positioning and padding of pressure points, with lesion and draining lymph node basins accessible
- Subdermal injection of blue dye around lesion
- Incision over first draining lymph node basin as determined by radioactivity counts
- Identify and isolate blue channel and blue/radioactive lymph node
- Clip lymphatic channels to avoid lymphatic leak
- Remove sentinel lymph nodes, send to pathology

Unlike sentinel lymph node biopsy for breast cancer, sentinel lymph nodes should not typically be sent for frozen section pathologic analysis, but rather sent in their entirety for permanent pathologic examination, as the false-negative rate of frozen analysis of sentinel lymph nodes in melanoma is high.[14] Pathologic evaluation includes standard H&E and immunohistochemistry with staining for HMB-45 and S100[31] and fluorescence in situ hybridization is helpful in distinguishing whether melanocytes in lymph nodes are metastatic melanoma or benign nodal nevi.[32]

IMAGING WORKUP

Chest X-Ray

Routine chest x-ray is frequently used in the initial staging of patients diagnosed with melanoma. However, a number of studies have questioned the cost-effectiveness of this approach. A 2011 study of patients scheduled to undergo sentinel lymph node biopsy for melanoma showed the preoperative chest x-ray did not identify lung metastases, did not change the planned treatment, and did not add any valuable information to the staging workup in any of the 248 patients studied.[33] In the asymptomatic patient, the specificity and sensitivity of routine chest x-ray is low, with a true-positive rate of 0% to 0.5% and false-positive rate of 8% to 15% in large series.[3,34] Furthermore, the performance of routine chest x-rays for patients with asymptomatic, localized melanoma in the United States exceeds $5 million.[3]

Ultrasound

Although the use of ultrasound has been widely used in the preoperative evaluation of lymph nodes in patients with breast cancer, the value of this modality in the

assessment of lymph nodes in melanoma is debatable. A small study by De Giorgi and colleagues[35] evaluated the use of contrast-enhanced ultrasound in patients with early-stage melanoma, and reported a negative predictive value of 100%, with all ultrasonographically negative lymph nodes corresponding to sentinel lymph nodes without metastatic disease. However, the study was small, with only 15 patients evaluated. A larger prospective study of 107 patients with melanoma and clinically negative nodes used ultrasound with fine-needle aspiration cytology in the initial assessment of patients with melanoma. The investigators reported a sensitivity of 34% and specificity of 87% in detecting lymph node involvement by ultrasound alone. When fine-needle aspiration and cytology were added to ultrasonographic evaluation, the sensitivity and specificity were 4.7% and 100%, respectively. The investigators concluded that the yield of this diagnostic technique is insufficient for routine use in the evaluation of patients eligible for sentinel lymph node biopsy for melanoma.[36] A study by Marone and colleagues[37] used high-resolution ultrasound before sentinel lymph node biopsy in 623 patients, and showed a positive predictive value of 100% and negative predictive value of 87%. However, the sensitivity of detecting micrometastases was extremely small, and the risk of missing these small melanoma deposits in lymph nodes precludes the use of high-resolution ultrasound as a substitute for sentinel lymph node biopsy.

18-Fluoro-Deoxyglucose Positron Emission Tomography/Computed Tomography

Like other imaging modalities, the use of 18-Fluoro-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) has a narrowly defined role in the workup of patients with melanoma. The yield of routine, preoperative radiographic staging (including chest x-ray, bone and liver scans, head CT, upper gastrointestinal series with small-bowel follow-through, or capsule endoscopy) in asymptomatic patients with early-stage melanoma is low.[38,39] Even in asymptomatic patients with stage III melanoma, the *routine* use of staging CT (CT chest/abdomen/pelvis and magnetic resonance imaging [MRI] of the brain) is questionable, with 11 false-positives for every 1 true unsuspected metastasis that is detected.[38] Radiographic workup for occult metastases is indicated in patients presenting with advanced melanoma (late stage III and stage IV), symptomatic patients, or those with persistently elevated lactate dehydrogenase (LDH) levels after initial excision, which suggests the presence of metastatic disease.[40,41] For patients with stage III and IV melanoma, the addition of FDG-PET and whole-body CT to the diagnostic workup was predictive of melanoma-specific survival and disease-free survival.[42] In the setting of palpable lymph nodes, PET/CT was useful in identifying patients whose lymph node disease burden was sufficiently limited as to allow for surgery for local control.[42] In 12% of patients with what was thought to be surgically treatable metastatic melanoma, PET/CT identified metastases missed in conventional imaging, such as CT chest/abdomen/pelvis or brain MRI, ultimately altering the surgical plan.[42] Although PET/CT is not a substitute for sentinel lymph node biopsy in patients with nonpalpable nodes, it does detect macrometastases, and is a useful surgical planning tool.[43] Another study showed that in patients with stage III melanoma, unsuspected metastases were identified by PET/CT in 15% of patients, with a sensitivity of 92% and specificity of 90%.[44] A total of one-third of patients evaluated were upstaged, and two-thirds were downstaged by FDG-PET/CT.[44] Furthermore, a positive PET/CT was the most important predictor of melanoma-specific survival (hazard ratio 2.52) in multivariate analysis, when controlling for gender, lymph node positivity, and extranodal extension. Patients with negative PET/CT scans had 47.6% 5-year melanoma-specific survival, compared with 16.9% for PET/CT-positive patients.[42]

LABORATORY TESTS

Several laboratory tests have been shown to provide prognostic information in selected patients with melanoma. LDH has long been known to be an important predictor of melanoma prognosis. However, a recent study by Wevers and colleagues[45] identified *preoperative* levels of S100-B to be a stronger prognostic biomarker than LDH in patients undergoing lymph node dissection for bulky macrometastatic involvement. Persistent elevated *postoperative* values of LDH remain useful in determining the need for metastatic workup.[40]

For patients with metastatic melanoma, treatment options are few. Recent advances in targeted therapies have identified the BRAF mutation as a potential target, and BRAF inhibitors (ipilimumab) are a therapeutic option in these difficult patients. For patients with stage IV melanoma, evaluation for a BRAF mutation should be performed on the tumor to determine if BRAF inhibitors could be used.[14,46] Surgical excision for oligometastatic disease has also been advocated by some for those with slower doubling times.[47]

Table 2
American Joint Committee on Cancer, seventh edition, staging criteria for cutaneous melanoma

Stage	Description	5-y Survival
Stage 0	In situ	99.9%
Stage I (A/B) T1a: $\leq$1.0 mm thick, no ulceration, mitosis <1/mm^2 T1b: $\leq$1.0 mm thick, with ulceration or mitoses $\geq$1/mm^2 T2a: 1.01–2.0 mm thick, no ulceration	Invasive	89%–95%
Stage II (A, B, C) T2b: 1.01–2.0 mm thick, with ulceration T3a: 2.01–4.0 mm thick, without ulceration T3b: 2.01–4.0 mm thick, with ulceration T4a: >4.0 mm thick, without ulceration T4b: >4.0 mm thick, with ulceration	High risk	45%–79%
Stage III (A, B, C) N1: Single positive lymph node N1a: Micrometastasis N1b: Macrometastasis N2: Two to 3 positive lymph nodes or regional in-transit metastases N2a: Micrometastasis N2b: Macrometastasis N2c: In-transit metastasis/satellites *without* metastatic nodes N3: Four positive lymph nodes, matted nodes, or in-transit metastases/satellites *with* metastatic nodes	Regional metastases	24%–70%
Stage IV M1a: Metastases to skin, subcutaneous or distant lymph nodes, normal LDH M1b: Lung metastases, normal LDH M1c: Other visceral metastases or any distant metastases with elevated LDH	Distant metastases	7%–19%

Data from Balch CM, Gershenwald JE, Soong SJ, et al. Melanoma of the skin. In: Edge SB, Byrd DR, Compton CC, editors. AJCC cancer staging manual. 7th edition. New York: Springer; 2010. p. 325–44.

SUMMARY STAGING

Staging of melanoma is based on the 2010 American Joint Committee on Cancer (AJCC) seventh edition TNM system. Unlike previous editions, the most recent AJCC melanoma staging system accounts for the importance of dermal mitotic rate in the prognosis of malignant melanoma. In particular, stage T1b now does not focus solely on ulceration, but includes the presence of one or more mitotic figures per square millimeter and/or ulceration (**Table 2**).[14,48,49]

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