The Ochsner Journal 8:181–185, 2008

Malignant Melanoma of the Head and Neck: A Brief Review of Pathophysiology, Current Staging, and Management

Christian Hasney, MD,* R. Brent Butcher II, MD,† Ronald G. Amedee, MD†

**Department of Otolaryngology–Head and Neck Surgery, Tulane University, New Orleans, LA*
†Department of Otolaryngology–Head and Neck Surgery, Ochsner Clinic Foundation, New Orleans, LA

MELANOCYTE PHYSIOLOGY

Melanoma is a malignant tumor of melanocytes, neural crest derivatives that contain melanin-producing organelles known as melanosomes. Melanocytes are normally found in the basal layer of the epidermis but are also found in the eye, gallbladder, anus, and vagina, and throughout the upper aerodigestive tract. In the skin, there is an extensive interaction between the melanocytes and the adjacent keratinocytes, as melanin is continuously transferred from the melanocytes to the keratinocytes as a result of stimulation by ultraviolet radiation.[1]

BACKGROUND AND EPIDEMIOLOGY

The incidence of malignant melanoma has steadily increased over the last 40 years at a rate of approximately 5% annually. The current worldwide incidence is 10.9 per 100 000 people. Among Americans, the current lifetime risk of developing melanoma is 1 in 75. Although the overall melanoma-specific survival has increased in the last 20 years, the prognosis for those with advanced disease is no better than it was 20 years ago.[2]

RISK FACTORS

Those at greatest risk for developing melanoma are fair-skinned individuals, especially redheads. The risk of developing melanoma is heightened in those living in climates with intense sunlight. Sun exposure is the single greatest risk factor for developing melanoma as both the A and B types of ultraviolet rays are implicated in development of the disease. Patients with pigmented lesions such as junctional nevi, dysplastic nevi, congenital nevi greater than 20 cm in greatest dimension, and those with large numbers of benign nevi are at increased risk for the development of melanoma. Rare congenital syndromes such as dysplastic nevus syndrome (familial atypical mole-melanoma syndrome) and xeroderma pigmentosa carry a nearly 100% risk of developing melanoma. Any childhood sun exposure with sunburn heightens one's risk.

Interestingly, the current thought regarding the relationship between sun exposure and melanoma development favors less frequent, more intense sun exposure as a stronger risk factor than chronic sun exposure. This assertion is based on the hypothesis that those with chronic, in some cases daily, sun exposure compensate for the solar insult in a way that those with less frequent exposure fail to do.[2–4]

CLINICAL PRESENTATION

The hallmark of malignant melanoma is a pigmented lesion that displays the often-cited ABCDE of melanoma: *A* refers to asymmetry of the lesion, *B* to border irregularity, *C* to variegated color, *D* to diameter greater than 6 mm, and *E* to elevation. One should also take the time to evaluate the surrounding skin for recent changes and elicit subjective symptoms such as pain or itching at the lesion site. It is also important to document ulceration of the lesion prior to biopsy as ulceration plays a critical role in the current TNM staging system. Finally, one should be mindful that not all melanoma lesions are pigmented. Up to 10% of melanoma lacks melanin and, rarer still, the pigmented melanoma lesion may spontaneously regress leaving a hypopigmented ''halo.''

DIAGNOSIS

The differential diagnosis of melanoma is vast including an array of benign, sun-induced, vascular, inflammatory, and neoplastic lesions. Because of this overlap and, more importantly, because of the possibility of failing to diagnose a potentially lethal disease, one's threshold for biopsy should be low. As previously stated, one must be sure to document

Address correspondence to:
Christian Hasney, MD
Department of Otolaryngology-Head and Neck Surgery
Tulane University School of Medicine
1430 Tulane Avenue
New Orleans, LA 70112
Tel: (504) 988-5454
Fax: (504) 988-7846
Email: chasney@tulane.edu

Key Words: Clark and Breslow stages, depth-appropriate margins, immunotherapy, lymphoscintigraphy, Melanoma, sentinel node biopsy

Table 1. Clark and Breslow Staging Systems

Clark		Breslow
Confined to epidermis	I	<0.75 mm
Invading papillary dermis	II	0.76–1.5 mm
Abutting papillary-reticular junction	III	1.51–4.0 mm
Invading reticular dermis	IV	>4.0 mm
Subcutaneous invasion	V	—

ulceration prior to biopsy. The preferred method of tissue sampling for the diagnosis of melanoma is excisional biopsy with a margin of normal tissue measuring at least 2 mm. It is, however, acceptable to perform an incisional biopsy in larger lesions or in those in which an excisional biopsy would violate critical structures such as the eyelid or oral commissure. One should never, though, perform a shave or needle biopsy of a suspected melanoma. Once the diagnosis of melanoma has been clinched, work-up should progress based on the clinical stage of the disease.

MELANOMA GROWTH PATTERNS

The natural history of melanoma is characterized by two distinct growth phases: radial (intraepithelial) and vertical (intradermal). The radial growth phase is circumferential in nature, growing within the epidermis to, but not beyond, the dermal-epidermal junction.[5,6] At some point in the radial growth phase, the tumor undergoes a clonal change that confers a survival advantage that allows it to enter the vertical growth phase as it penetrates the dermal-epidermal junction and grows into and beyond the dermis. These two well-described phases serve as the basis for the two classic staging systems for melanoma, those described by Clark and Breslow (Table 1).[7,8]

MELANOMA SUBTYPES

Lentigo Maligna Melanoma

Lentigo maligna melanoma is the name attached to melanoma confined to the epidermis or melanoma in situ. It is a premalignant lesion with a 5% to 33% rate of malignant transformation and is commonly seen in the elderly and in those with chronic sun exposure. Histologically, lentigo maligna is characterized by atypical melanocytes at the dermal-epidermal junction. Lentigo maligna is the least common form of melanoma but is the most readily treatable with a greater than 99% 10-year disease-free survival. Treatment typically includes surgical excision or imiquimod topical cream.

Superficial Spreading Melanoma

Superficial spreading melanoma accounts for 65% to 75% of all melanoma, making it the most common subtype. These lesions may present in a wide variety of colors. The radial growth phase may be extended, lasting between 5 and 7 years. The transition from radial to vertical growth may be heralded by bleeding or ulceration. Rare cases of spontaneous regression, likely via an immune-mediated mechanism, have been described. The standard treatment for the primary lesion is excision with depth-appropriate margins.

Acral Lentiginous Melanoma

Acral lentiginous melanoma is the most common melanoma of African Americans. This subtype represents nearly 90% of all melanoma seen in non-white populations. Lesions frequently appear on the palms, soles, and anogenital mucosa, but rarely in the head and neck.

Nodular Melanoma

Nodular melanoma is the most aggressive subtype of melanoma. It accounts for 10% to 15% of all cases and may occur on sun-exposed and non-exposed areas alike. It is generally seen in those over 50 years of age. Nodular melanoma is remarkable in that it may lack a radial growth phase and may progress rapidly through the vertical phase. Treatment is by excision with depth-appropriate margins.

Rare Melanoma Subtypes

Mucosal melanoma accounts for 2% of head and neck melanoma. More than half of these lesions occur in the nasal cavity. Mucosal melanoma may lack a grossly melanotic appearance. Treatment includes wide local excision with or without adjuvant radiotherapy. Survival is dismal with a 5-year survival of 10% to 45%.

Desmoplastic melanoma represents less than 1% of all melanoma cases; 75% of desmoplastic lesions, however, occur in the head and neck. Like mucosal melanoma, this lesion may be amelanotic. Desmoplastic melanoma may arise from a pre-existing melanoma lesion in the radial growth phase. This lesion has a propensity for neurotropic metastases, which may lead to local recurrence despite excision with apparently disease-free margins.

Neurotropic melanoma is so-called for its histologic resemblance to nerves and neural structures and because of its tendency to infiltrate peripheral nerves. This lesion may arise out of pre-existing melanoma lesions in the vertical growth phase. This tumor is highly aggressive with an exceedingly poor prognosis.

STAGING

Classically, melanoma lesions have been staged according to the Clark staging system, a description of the histologic level of invasion, and the Breslow

staging system, a measure of the absolute depth of the lesion.[7,8] With the adoption of the American Joint Committee on Cancer (AJCC) TNM staging system (Figure 1),[9] the definition of nodal staging has become increasingly important. Between 10% and 30% of melanoma patients present with clinically detectable cervical metastases. Interestingly, in 55% of patients, the observed drainage patterns are different than those predicted based on the sight of the primary tumor. The strongest predictor of the presence of regional metastases is the thickness of the primary lesion with 65% of those with lesions greater than or equal to 4 mm in thickness presenting with cervical metastases.

Any discussion of nodal disease in melanoma would be remiss without defining the terms satellite lesions and in-transit lesions. Satellite lesions refer to foci of melanoma found within 2 cm of the primary tumor. They are seen in 3% of patients. In-transit lesions are foci of melanoma found greater than 2 cm beyond the primary tumor but not beyond the predicted first echelon of lymph nodes draining the primary tumor. Both satellite and in-transit lesions play a role in the current TNM staging system.

Current modalities for evaluation of regional nodal metastases include computed tomography, magnetic resonance imaging, positron emission tomography, and lymphoscintigraphy. Currently, lymphoscintigraphy coupled with sentinel node biopsy is considered the ''gold standard'' for evaluation of nodal disease in the clinically negative neck. It should be remembered, though, that the lymphoscintigram is merely a snapshot of the dynamic drainage patterns of the head and neck. As previously discussed, lymphatic drainage patterns of melanoma lesions vary from patient to patient. Willis and Ridge, though, asserted that the same discordance exists within individual patients.[10]

Consequently, one should bear in mind that a single lymphoscintigraphy study may not capture all affected nodal basins. This fact and its implications gain added gravity when one recalls the finding of Balch et al that the presence or absence of nodal metastases is the single most important prognostic factor in the survival of melanoma patients.[11]

MANAGEMENT OF THE NECK

The management of the clinically negative neck in melanoma patients has been the subject of some debate in recent years. The current recommendations favor observation in those with primary lesions less than 1 mm in thickness, Clark's level less than IV, and without palpable cervical lymphadenopathy. For all other patients, the options include elective neck dissection and sentinel node biopsy. In a retrospective study, Balch and colleagues demonstrated a significant survival advantage in performing elective neck dissection in those with intermediate thickness (1–4 mm) melanoma.[12–15] The prospective Intergroup Melanoma Surgical Trial narrowed Balch's recommendations to those with stage II and III disease, who are less than 60 years of age, with lesions 1 to 2 mm in thickness.[16] In a 2002 meta-analysis, however, Lens et al scrutinized the three largest prospective trials on the topic and found no survival benefit in those with intermediate-thickness lesions.[17]

The current standard in the diagnosis of cervical metastases in those with intermediate to thick lesions is sentinel node biopsy. The use of this technique was initially shown to improve survival in patients with infraclavicular melanoma. Gershenwald and colleagues found the status of the sentinel node to be the strongest predictor of disease-free survival in melanoma patients. Several other studies have demonstrated the strong negative predictive value of a negative sentinel node biopsy and the benefit of expediting a formal neck dissection following a positive sentinel node biopsy.[18–21]

COMPREHENSIVE MANAGEMENT

The cornerstone of melanoma management is excision with appropriate deep and peripheral margins. The depth of the excision should include the underlying subcutaneous tissue to the level of the deep fascia. Historically, in order for the excision to be considered ''oncologically sound,'' the peripheral margins should measure at least 5 cm. Today, more conservative recommendations prevail (Table 2). When considering surgical margins, one should be wary of frozen section evaluation of melanoma. The disease is not readily identified with this technique and is, thus, not amenable to Mohs micrographic surgery.

Formal cervical lymphadenectomy is recommended in patients with a clinically positive neck or in those with a positive sentinel node biopsy. The extent of neck dissection is tailored to the site of the primary tumor. Radical neck dissection has classically been considered the ''gold standard'' in the management of the melanoma-infiltrated neck. Studies have indicated less frequent recurrence among those undergoing modified radical neck dissection compared to those undergoing radical neck dissection.[22] Though there are little prospective data on the topic, the experience with modified radical neck dissection has been extrapolated to selective neck dissection and this procedure is commonly performed.

Melanoma is traditionally considered a radioresistant tumor, though some studies support the use of hypofractionated radiation as an adjunct to surgery.[23] At this time, radiation is reserved for adjuvant treatment following definitive surgical treatment and

TX	Primary tumor cannot be assessed (e.g., shave biopsy or regressed melanoma)
T0	No evidence of primary tumor
Tis	Melanoma *in situ*
T1	Melanoma ≤ 1.0 mm in thickness with or without ulceration
T1a	Melanoma ≤ 1.0 mm in thickness and level II or III, no ulceration
T1b	Melanoma ≤ 1.0 mm in thickness and level IV or V or with ulceration
T2	Melanoma 1.01–2 mm in thickness with or without ulceration
T2a	Melanoma 1.01–2.0 mm in thickness, no ulceration
T2b	Melanoma 1.01–2.0 mm in thickness, with ulceration
T3	Melanoma 2.01–4 mm in thickness with or without ulceration
T3a	Melanoma 2.01–4.0 mm in thickness, no ulceration
T3b	Melanoma 2.01–4.0 mm in thickness, with ulceration
T4	Melanoma > 4.0 mm in thickness with or without ulceration
T4a	Melanoma > 4.0 mm in thickness, no ulceration
T4b	Melanoma > 4.0 mm in thickness, with ulceration

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one lymph node
N1a	Clinically occult (microscopic) metastasis
N1b	Clinically apparent (macroscopic) metastasis
N2	Metastasis in two to three regional nodes or intralymphatic regional metastasis without nodal metastases
N2a	Clinically occult (microscopic) metastasis
N2b	Clinically apparent (macroscopic) metastasis
N2c	Satellite or in-transit metastasis *without* nodal metastasis
N3	Metastasis in four or more regional nodes, or matted metastatic nodes, or in-transit metastasis or satellite(s) *with* metastasis in regional node(s)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis to skin, subcutaneous tissues or distant lymph nodes
M1b	Metastasis to lung
M1c	Metastasis to all other visceral sites or distant metastasis at any site associated with an elevated serum lactic dehydrogenase (LDH)

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage III	Any T	N1	M0
	Any T	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

Figure 1. American Joint Committee on Cancer staging for melanoma.[9]

Table 2. Appropriate Surgical Margins Based on Tumor Thickness

Tumor Thickness	Margin Size
CIS	0.5 cm
1–2 mm	1 cm
2–4 mm	2 cm
>4 mm	>2 cm

CIS = carcinoma in situ.

as a primary treatment in those who are poor surgical candidates, with extensive facial lentigo maligna melanoma, neurotropic lesions, extracapsular spread, multiple node involvement (>4), or recurrence.[24]

Systemic chemotherapy or immunotherapy is reserved for those who have completed locoregional therapy and are at high risk for recurrence. These patients include those with ulcerated primary lesions, lesions greater than 4 mm in thickness, and those with in-transit, nodal, or distant metastases. Currently, systemic chemotherapy plays a principally palliative role in the treatment of melanoma.

The wave of the future in systemic therapy for melanoma is immunotherapy. Immunomodulators such as interferon-alpha are already in use. These factors work by attempting to induce an immune response to the tumor leading to spontaneous regression. Meta-analysis data suggest that biochemotherapy with interferon and the cytokine interleukin-2 coupled with standard chemotherapeutic regimens may improve response rates but does not affect overall survival.[25]

REFERENCES

1. Elder DE, Murphy GF. Benign melanocytic tumors. In: Rosai J, Sobin LH, eds. *Atlas of Tumor Pathology: Melanocytic Tumors of the Skin*. Washington, DC: Armed Forces Institute of Pathology; 1991:103–205.
2. Bailey BJ, Johnson JT, Newlands SD, eds. *Head and Neck Surgery-Otolaryngology,* 4th ed. Philadelphia: Lippincott. 2006.
3. Armstrong BK, English DR. Epidemiologic studies. In: Balch CM, et al, eds. *Cutaneous Melanoma,* 2nd ed. Philadelphia: Lippincott; 1992:12–26.
4. Zitsch RP, Renner GJ. *Cutaneous Melanoma of the Head and Neck*. Alexandria, VA: AAO-HNS SIPAC. 2005.
5. Barnhill RL, Mihm MC Jr. Histopathology of malignant melanoma and its precursor lesions. In: Balch CM, et al, eds. *Cutaneous Melanoma,* 2nd ed. Philadelphia: Lippincott; 1992:234–263.
6. Kurban RS, Kibbi A-G, Mihm MC Jr. Histogenic types of primary skin melanoma. In: Lejune FJ, Chaudhuri PK, Das Gupta TK, eds. *Malignant Melanoma: Medical and Surgical Management*. Columbus, OH: McGraw-Hill; 1994:127–134.
7. Clark WH Jr, From L, Bernardino EA, Mihm MC. The histogenesis and biologic behavior of primary human malignant melanoma of the skin. *Cancer Res*. 1969;29:705–727.
8. Breslow A. Thickness, cross-sectional area and depth of invasion in the prognosis of cutaneous melanoma. *Ann Surg*. 1970;172:902–908.
9. American Joint Committee on Cancer. *Manual for Staging of Cancer.* 6th ed. Philadelphia: Lippincott; 2002:209–220.
10. Willis AI, Ridge JA. Discordant lymphatic drainage patterns revealed by serial lymphoscintigraphy in cutaneous head and neck malignancies. *Head Neck*. 2007;29:979–985.
11. Balch CM, Soong SJ, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol*. 2001;19:3622–3634.
12. Balch CM, Soong S, Ross MI, et al. Long-term results of a multi-institutional randomized trial comparing prognostic factors and surgical results for intermediate thickness melanoma (1.0 to 4.0 mm). *Ann Surg Oncol*. 2000;7:87–97.
13. Balch CM, Soong SJ, Bartolucci AA, et al. Efficacy of an elective regional lymph node dissection of 1 to 4 mm thick melanomas for patients 60 years of age and younger. *Ann Surg*. 1996;224:255–263; discussion 263–266.
14. Veronesi U, Adamus J, Bandiera DC, et al. Inefficacy of immediate node dissection in stage 1 melanoma of the limbs. *NEJM*. 1977;297:627–630.
15. Sim FH, Taylor WF, Pritchard DJ, Soule EH. Lymphadenectomy in the management of stage I malignant melanoma: a prospective randomized study. *Mayo Clin Proc*. 1986;61:697–705.
16. Balch CM, Soong SJ, Smith T, et al. Long-term results of a prospective surgical trial comparing 2 cm vs. 4 cm excision margins for 740 patients with 1–4 mm melanomas. *Ann Surg Oncol*. 2001;8:101–108.
17. Lens MD, Dawes M, Goodacre T, Newton-Bishop JA. Elective lymph node dissection in patients with melanoma: systematic review and meta-analysis of randomized controlled trials. *Arch Surg*. 2002;137:458–461.
18. Gershenwald J, Colome MI, Lee JE, et al. Patterns of recurrence following a negative sentinel lymph node biopsy in 243 patients with stage I or II melanoma. *J Clin Oncol*. 1998;16:2253–2260.
19. Chao C, Wong SL, Edwards MJ, et al. Sentinel lymph node biopsy for head and neck melanomas. *Ann Surg Oncol*. 2003;10:21–26.
20. Patel SG, Coit DG, Shaha AR, et al. Sentinel lymph node biopsy for cutaneous head and neck melanoma. *Arch Otolaryngol Head Neck Surg*. 2002;128:285–291.
21. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. *NEJM*. 2006;355:1307–1317; Erratum in: *N Engl J Med*. 2006;355:1944
22. Mack LA, McKinnon JG. Controversies in the management of metastatic melanoma to regional lymphatic basins. *J Surg Oncol*. 2004;86:189–199.
23. Ang KK, Byers RM, Peters LJ, et al. Regional radiotherapy as adjuvant treatment for head and neck malignant melanoma, *Arch Otolaryngol Head Neck Surg*. 1990;116:169–172.
24. Ang KK, Geara FB, Byers RM, et al. Radiotherapy for melanoma. In Balch CM, et al, eds. *Cutaneous Melanoma,* 4th ed. St Louis, MO: Quality Medical Publishing, Inc.; 2003:389.
25. Ives NJ, Stowe RL, Lorigan P, Wheatley K. Chemotherapy compared with biochemotherapy for the treatment of metastatic melanoma: a meta-analysis of 18 trials involving 2,621 patients. *J Clin Oncol*. 2007;25:5426–5434.