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CASE MANAGEMENT

Cutaneous Melanoma of the Head and Neck

An 83-year-old man is referred to Indiana University Health for ongoing work-up and treatment of a newly diagnosed right auricular melanoma. The patient states that the mole, present for "a few years," has recently increased in size and started bleeding. He has no history of skin cancer but grew up on a farm and had considerable sun exposure in his younger years. He is otherwise healthy and has no significant past medical or surgical history. (*continued on page 2*)

ACCREDITATION STATEMENT
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Dr. Cecelia Schmalbach has disclosed that she received an honorarium for teaching from AO North America CMF. Any potential conflict of interest has been resolved.

OBJECTIVES
After reading this article, the reader should be able to:

- Recognize the impact of melanoma with regard to cancer-related mortality in younger and older individuals.
- Identify the predictors of melanoma metastases.
- Describe the clinical evaluation of cutaneous head and neck (HN) lesions.
- Discuss the role of sentinel lymph node biopsy in the management of cutaneous melanoma.
- Summarize the primary and adjuvant therapies for cutaneous melanoma.

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This CME activity does not have any commercial support.

His initial evaluation was done by a local dermatologist, who performed a punch biopsy demonstrating nodular melanoma:

- Depth of invasion – 11 mm
- Clark level – 5 *(Table 1)*
- Mitotic rate – 16/mm^2
- Positive for ulceration, negative for microsatellitosis, perineural invasion,lymphovascular invasion, or regression
- Tumor lymphocyte infiltration – non-brisk
- Pathologic stage – T4b with positive margins

The patient receives a comprehensive head and neck (HN) examination that reveals no additional concerning cutaneous lesions or associated lymphadenopathy in the parotid bed or cervical region. Contrast computed tomography (CT) of the face and neck is performed and is negative.

Melanoma Overview

The incidence of melanoma in the United States continues to rise, with nearly 90,000 new cases projected for 2017,[1] 25 percent of which will occur in people younger than 40 years.[2] Melanoma accounts for just one percent of all skin cancer diagnoses but is the primary cause of skin cancer mortality, responsible for almost 10,000 US deaths annually.[1] Although melanoma can arise *de novo*, approximately half of all cases develop from a preexisting pigmented lesion.

Five major melanoma histologic subtypes have been identified *(Table 2) (Figure 1, see page 4)*: 1) superficial spreading, 2) nodular, 3) lentigo maligna, 4) acral lentiginous, and 5) desmoplastic. Subtype does not impact recurrence or survival nor guide management decisions, and it is not incorporated into the American Joint Committee on Cancer (AJCC) melanoma staging system.

"Melanoma metastasis is predicted by tumor thickness and ulceration, mitotic rate, presence of microsatellites, perineural and/or lymphovascular invasion, regression, and the presence of lymphocyte infiltration,"

TABLE 1. CLARK LEVEL* [13,14]

Level	Description	5-Year Survival Rate†
1	Intraepidermal growth with intact basement membrane	100%
2	Invasion of the papillary dermis	95%
3	Tumor involvement filling the papillary dermis and involvement of the junction between the papillary and reticular dermis	80-85%
4	Invasion of tumor into the reticular dermis	80-85%
5	Invasion of tumor into the subcutaneous fat	55%

**Used to describe the anatomic involvement of the tumor within cutaneous and subcutaneous structures.*
†Clark level is not an independent predictor of melanoma outcome except for the thinnest T1 (<1 mm) tumors.[15]

explains Cecelia Schmalbach, MD, professor of otolaryngology – head and neck surgery at Indiana University School of Medicine and otolaryngology – head and neck surgeon at IU Health.

Cutaneous Head and Neck Melanoma

Approximately one-quarter of all cutaneous melanomas involve the HN region, with primary melanoma of the external ear comprising up to 20 percent of these cases.[3] Diagnosis of cutaneous HN melanoma relies on careful examination of the lesion for asymmetry, border irregularity, color variation, and diameter >6 mm.[1] Any lesion fulfilling the ABCD criteria or whose appearance has recently changed or differs from surrounding nevi should be considered for biopsy. A narrow-margin (1-3 mm) excisional biopsy or incisional/punch biopsy for larger lesions allows comprehensive histologic assessment. Shave biopsy of pigmented lesions is discouraged because the depth of tumor invasion—critical information for staging and treatment—cannot be determined. Wide local excision is not recommended since removal of surrounding tissue can compromise the accuracy of staging using the sentinel lymph node biopsy (SLNB) technique.[4]

Sentinel Lymph Node Biopsy

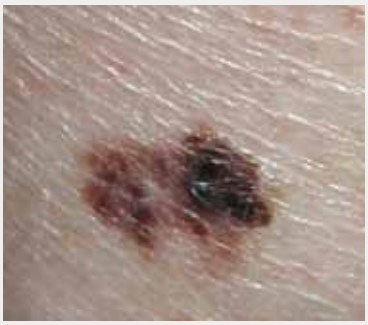
"Wide local excision is the primary treatment for cutaneous head and neck melanoma; elective neck dissection no longer plays a role," reports Dr. Schmalbach. "Regional metastasis is the most important prognostic determinant of melanoma recurrence and survival, and sentinel lymph node biopsy remains our most sensitive and specific modality for accurate regional staging."

SLNB was introduced in 1992 to accurately identify patients with regional metastasis who may benefit from lymph node dissection and adjuvant therapy.[5] This minimally invasive technique involves the preoperative injection of a radioactive colloid, after which patients undergo lymphoscintigraphy to determine the number, location, and laterality of at-risk draining nodal basins.[2]

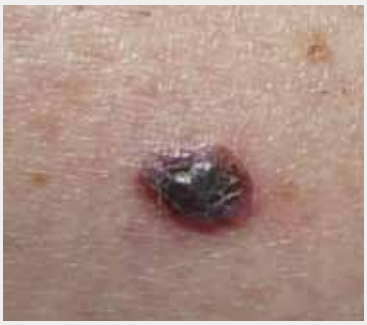
TABLE 2. DESCRIPTION OF MAJOR MELANOMA HISTOLOGIC SUBTYPES[16]

Subtype	Description
Superficial spreading	• Most common subtype, accounting for ~70% of all melanomas • Color variation within the melanoma • >60% are diagnosed as thin, highly curable tumors of <1 mm thickness
Nodular	• Second most common subtype, accounting for 15-30% of all melanomas • Appear as darkly pigmented, pedunculated, or polypoid nodules • Difficult to diagnose at an early stage • ≥50% present as lesions thicker than 2 mm
Lentigo maligna	• Accounts for 10-15% of all melanomas, although US incidence is rising • Melanoma *in situ* that typically arises in sun-damaged areas of the skin • Begins as a tan-brown macule that gradually enlarges and develops darker, asymmetric foci and raised areas • Common in the elderly population
Acral lentiginous	• Accounts for <5% of all melanomas but is the most common subtype among dark-skinned persons • Most commonly develop on palmar, plantar, and subungual surfaces • Appear as dark brown to black irregularly pigmented macules or patches
Desmoplastic	• Rare subtype comprised of spindles with an abundance of collagen • Accounts for only 1% of melanoma cases, but 75% of these cases are diagnosed in the HN region • Typically presents in older individuals • Low rate of regional metastasis but high rate of local recurrence owing to propensity for perineural spread

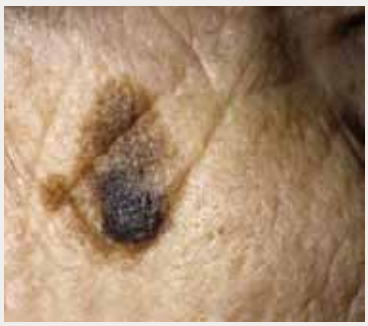
Figure 1. Images of major melanoma histologic subtypes



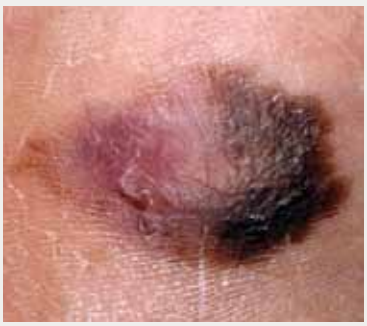
A. Superficial spreading



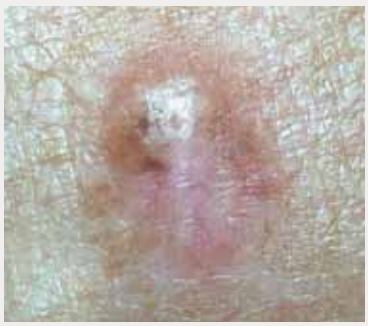
B. Nodular



C. Lentigo maligna



D. Acral lentiginous



E. Desmoplastic

Permission to use these images is granted by DermNet New Zealand (DermNetNZ.org) and Waikato District Health Board under the terms of the Creative Commons License NonCommercial-NoDerivs 3.0 New Zealand (http://creativecommons.org/licenses/by-nc-nd/3.0/nz/).

Fused single-photon emission computed tomography SPECT/CT has emerged as the superior imaging modality, capable of increased anatomic three-dimensional detail and improved resolution as compared with traditional planar lymphoscintigraphy *(Figure 2)*.

Once the patient is in the operating room and under anesthesia, lymphatic mapping continues, with vital blue dye injected intradermally into the four quadrants surrounding the primary melanoma lesion. Following wide local excision, sentinel nodes are identified using a combination of auditory cues from the handheld gamma probe and visual clues from the blue dye.

"By definition, a lymph node is considered 'sentinel' if it measures 10 percent or greater than the hottest node ex vivo." Dr. Schmalbach describes. "Each sentinel lymph node is sent separately for microsectioning and permanent histologic evaluation that includes melanoma-specific immunohistochemistry.

"The mean number of sentinel lymph nodes obtained per head and neck melanoma patient is 2.4, allowing a more practical, thorough, and comprehensive histologic assessment than does an entire elective lymphadenectomy specimen, which can contain more than 20 nodes," Dr. Schmalbach continues. "Patients with a positive biopsy return to the operating room within two weeks of diagnosis for definitive therapeutic lymph node dissection; those whose biopsies are negative are followed clinically."

SLNB is regarded as one of the most important advances in the management of melanoma to date. It is now considered the standard of care for selected cases of HN cutaneous melanoma and has been incorporated into the AJCC staging system, the National Comprehensive Cancer Network practice guidelines, and numerous national and international consensus statements.[2]

"All patients with localized melanomas having a depth of invasion of 1.0 mm or more should be offered sentinel lymph node biopsy," recommends Dr. Schmalbach. "Some thinner melanomas associated with poor prognostic variables (see previously described predictors of metastasis) may also benefit from this staging modality."

The patient undergoes wide local excision and staging SLNB, which reveals micrometastatic melanoma in the parotid sentinel node; the cervical SLN is negative.* Because he has regional disease, a metastatic work-up is performed that includes magnetic resonance imaging (MRI) of the brain and full-body fused SPECT/CT, both of which are negative. Diagnosis/stage: T4bN1M0 stage IV melanoma.

One week later, the patient undergoes right parotidectomy and neck dissection. The surgical site is closed primarily with a cervical facial advancement flap. Final pathology reveals 0/4 positive nodes in the parotid gland and 1/23 positive nodes in the right neck.

**The cervical and parotid nodal basins are the most common sites of metastasis for HN cutaneous melanoma.[6]*

Adjuvant Therapy

Radiation Therapy

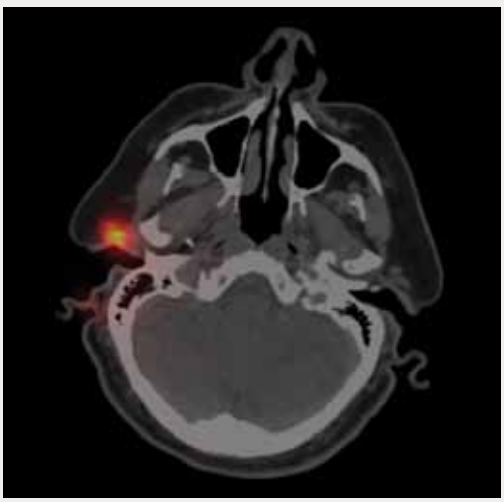
Radiation can be used as adjuvant therapy following wide local excision and/or regional lymphadenectomy to improve local and regional control rates in patients with melanoma.

Radiation to the primary melanoma site is usually recommended for deep desmoplastic melanoma associated with narrow surgical margins, extensive neurotropism, or local recurrence. In the setting of extranodal extension, ≥1 parotid or ≥2 cervical metastatic nodes, or a node measuring ≥3.0 cm, radiation is given to the draining nodal basins. The most common regimen involves hypofractionated doses.

Systemic Therapy

Because melanoma is relatively chemoresistant, the primary role of chemotherapy is as palliative treatment for stage IV disease. Traditionally, high-dose interferon alpha-2B has been used as adjuvant systemic therapy in patients with advanced local and regional disease.

Figure 2. SPECT/CT imaging of a right auricular melanoma



While this drug improves disease-free survival, it has not been shown to impact overall survival and has significant side effects, in particular flu-like symptoms, liver dysfunction, and depression.

Today, the systemic management of advanced melanoma has expanded to include immunotherapy using targeted therapies and checkpoint inhibitor drugs, the first of which was approved by the US Food and Drug Administration in 2011.

"Analysis of the genetic characteristics of melanoma can reveal potential targets for treatment," Dr. Schmalbach notes. "Approximately 40 to 50 percent of melanomas have a mutation in BRAF V600.[7] Single-agent therapy with vermurafenib (Zelboraf®) or dabrafenib (Tafinlar®) or a combination of BRAF/MEK-directed treatment are all acceptable for adjuvant systemic therapy in patients with advanced, mutated melanoma."

Ipilimumab (Yervoy®), a monoclonal antibody directed at the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) receptor, has also been shown to confer a survival advantage in metastatic melanoma and does not require the BRAF mutation.[8] Nivolumab (Opdivo®) and pembrolizumab (Keytruda®), both of which block the programmed cell death ligand 1 (PD-L1), demonstrate efficacy in the treatment of advanced disease.[9,10]

"When these drugs work, they are very effective," says Dr. Schmalbach. "However, all of them can cause significant side effects and should be administered by medical oncologists very familiar with immunotherapy."

The case is presented at the IU Health multidisciplinary melanoma oncology board and is evaluated by medical and radiation oncologists. Adjuvant local and regional radiation (total 48 Gy delivered in two fractions) is given. The patient elects to receive high-dose interferon alpha-2B rather than ipilimumab or enrollment in a clinical trial.

Follow-Up

"Five to 10 percent of patients with melanoma develop a second primary cancer at some point in their lives,[11] making long-term follow-up critical," emphasizes Dr. Schmalbach. "The goals of follow-up are: 1) early detection of locoregional recurrence, 2) early detection of a second skin cancer (melanoma or nonmelanoma), 3) identification of distant metastasis, and 4) patient/family education and psychosocial support."

When melanoma recurs, it usually does so within the first 24 months after treatment. At IU Health, a baseline CT or fused SPECT/CT is obtained after surgery, and follow-up visits are scheduled every 12 weeks for the first two postoperative years or more frequently for high-risk individuals, such as those who are immunosuppressed. These visits may be alternated among the multidisciplinary care team, composed of a dermatologist, medical oncologist, and surgeon.

The patient returns to IU Health every 12 weeks for follow-up visits. Photodocumentation is performed at each appointment to follow existing nevi. He is currently disease-free 13 months after completing treatment. Additional imaging will be performed if symptoms develop.

"The leading cause of melanoma remains intense sun exposure, making it a cancer of young and older adults, and it ranks second only to testicular cancer in loss of average adult life-years per fatality.[12] These startling statistics underscore the importance of prevention, accurate staging, and appropriate care and follow-up," Dr. Schmalbach concludes.

Outrun the Sun

Outrun the Sun, Inc.® (OTS) is a nonprofit organization dedicated to building awareness of melanoma and other skin cancers, educating communities about preventive measures to reduce the incidence of melanoma, and raising funds for melanoma research.

Since its inception, OTS has supported 22 melanoma investigators at major US medical centers. In partnership with IU School of Medicine, the organization helped establish a novel dermatology curriculum to ensure that *all* medical students receive the necessary training to detect skin cancer in its earliest stages, paving the way to better patient outcomes. And the group's fundraising efforts have included the Outrun the Sun Race Against Melanoma, which is held annually in Indianapolis. As a result of these and other activities, OTS has been recognized by the American Academy of Dermatology and the Indiana Cancer Consortium for its achievements.

For more information, visit outrunthesun.org or contact the OTS office at 317-253-2121.

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Dr. Schmalbach received her medical degree from the Jefferson Medical College in Philadelphia, PA; completed a residency in otolaryngology – head and neck surgery at the University of Michigan in Ann Arbor, where she also earned a masters of science in clinical research design and statistical analysis; and took her fellowship training in microvascular and skull base surgery at Vanderbilt University in Nashville. Her clinical interests include cutaneous HN cancers, mucosal neoplasms, and HN trauma. Her research interests focus on the use of SLNB in the staging of high-risk HN cutaneous cancers and cutaneous cancer in immunosuppressed patients.

Dr. Schmalbach currently serves as vice chair of clinical affairs in the Department of Otolaryngology and head of the Division of Head & Neck Surgery at IU School of Medicine and is co-director of the Multidisciplinary Endocrine Center at IU Health. A fellow of the American College of Surgeons and member of American Head and Neck Society, she is the deputy editor of *Otolaryngology Head and Neck Surgery*, an editorial reviewer for several other medical journals, and the author of more than 50 peer-reviewed articles, books, and book chapters.

Dr. Schmalbach served eight years of active duty in the United States Air Force (USAF), achieving the rank of lieutenant colonel. She was deployed to Afghanistan in support of Operation Enduring Freedom and was awarded the USAF Meritorious Service Medal. In 2016, she was named a Connolly Top Doctor by her peers and an Indianapolis Top Doctor by *Indianapolis Monthly.*

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