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## **Introduction**

Melanoma affects people all over the globe. In the United States, it is the fifth leading cancer in men and the sixth leading cancer in women. The incidence of melanoma has steadily increased over the past few decades, with an annual increase of up to 7% in certain populations. Melanoma was generally known as a disease of the old, but there is a recent trend for earlier age at presentation. This disease is highly curable if found at an early stage, which underscores the importance of patient education and vigilance in physicians when evaluating skin lesions. Melanoma typically occurs in different regions of the body according to sex. In males, the trunk and back, followed by extremities then the head and neck are the predominant patterns. In women, the lower extremities, followed by trunk and back, then the head and neck is the predominant pattern. Treating cutaneous melanoma of the head and neck presents particular problems to the Otolaryngologist because of the complex anatomy of the head and neck, and due to the visual nature of the face, neck and scalp.

## **Skin anatomy**

Melanoma is a disease of the skin or mucosa. Knowledge of skin anatomy is of vital importance in understanding the pathophysiology of this disease. The skin has two components, the epidermis and dermis. The epidermal layer can be further broken down into the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale, or basal layer. Keratinocytes located at the basal layer actively divide and migrate towards the surface of the skin. As they migrate further away from the basement membrane, they begin to keratinize. Melanocytes are also located in the basal layer, and produce melanosomes which contain melanin which they share with the keratinocytes. Other cells within the epidermis include merckel cells, langerhans cells, and intraepidermal T-lymphocytes. Immediately below the

basement membrane is the dermis. The dermal components are the superficial papillary and deep reticular dermis. The papillary dermis contains ground substance, collagen, elastin, and many cell types including macrophages, fibroblasts, mast cells, and inflammatory cells. The reticular dermis is deep to the papillary dermis and contains more intermediate filaments. Below the dermis is the hypodermis, or subcutaneous fat layer.

## **Etiology and Risk factors**

There are many factors that are important to the development of melanoma, but the most important is sun exposure. Sun exposure at a young age places a higher risk of developing melanoma and other skin cancers. The intensity of the sunlight received also places more risk as evidenced by increased incidence in populations living near the equator. Intermittent sun exposure with history of sunburns has a greater affect on the development of melanoma than chronic sun exposure. Despite the common belief that sunblock/sunscreens prevent or decrease the risk of melanoma, two studies have proven this wrong. This could be due to increased sun exposure due to the perceived benefit of sunscreen, or inadequate usage of the sunscreen. (Autier 2007). Other risk factors include Fitzpatrick types I and II, blue/green eyes, adults with more than 100 freckles or children with 50 freckles, blonde/red hair, outdoor summer jobs/hobbies. Genetic factors have also been found to affect the incidence of melanoma. An estimated 5-12% of people with melanoma have a family history of melanoma, and four genes have been found which are associated with increased susceptibility to melanoma. These are inhibitor of cyclin-dependent kinase 4A (*CDKN2A*) also known as *p16*, *ARF (ARF)* or *p14*, cyclin-dependent kinase 4 (*CDK4*), and *melanocortin1 receptor (MC1R)*. *p16* is a tumor suppressor gene and 10-40% of melanoma prone families carry a mutation in this gene. In addition to familial cases of melanoma, virtually all cases of melanoma have a mutation or inactivation of this gene. The *p16* protein is important in cell cycle regulation and plays a central role in the G1 checkpoint by inhibiting phosphorylation of the retinoblastoma protein by *CDK4*. There is high penetrance with rates ranging from 58-91%. *MC1R* is a transmembrane receptor expressed in melanocytes that mediates melanin production after UV irradiation or stimulation by hormones. There have been multiple allelic variations, and they are associated with red hair and fair skin. There appears to be a lower penetrance for this mutation than the others. *Xeroderma pigmentosa* is an autosomal recessive hereditary disorder characterized by multiple skin malignancies, including melanoma. There is reduced or absent ability to repair DNA damaged by ultraviolet light. Giant congenital nevi, nevi that are present at birth and greater than 20 mm, impart a greater risk of developing melanoma, with 5-10% of affected individuals developing melanoma.

## **Types of melanoma**

**Lentigo maligna** is melanoma confined to the epidermis, or melanoma in situ. It is seen in chronically sun exposed areas. In the head and neck, the cheek is the most common location followed by nose, forehead, ears, and neck. It generally occurs in 60 to 70 year olds, with no gender predilection. They range in size from 0.2 cm to greater than 20 cm. Histologically, there is melanocytic proliferation confined to the basal layer of the epidermis, pleomorphism, effacement and thinning of the epidermis, with prominent solar elastosis, and high nuclear to cytoplasm ratio. There also is a mononuclear cell infiltrate and fibroplasia of the papillary dermis. Patterns of spread include pagetoid spread, nesting, and lentiginous melanocytic

proliferation. In pagetoid spread, there is upward migration of melanocytes in a random fashion, single cells predominate over nests of cells, and cells often reach the granular or cornified layer of the epidermis. Nesting pattern is characterized by variations in size and shape of groups of “nested cells,” which replace large portions of normal epithelium. Lentiginous spread is characterized by nesting of melanocytes, and proliferation along adnexal structures. Once the basement membrane is violated, then the **lentigo malignant melanoma** is the diagnosis. Usually, there is hypercellularity with spindle cells in bundles with adjacent stromal dysplasia and accompanied invasion of nerve twigs, neurotropism.

**Nodular melanoma** is characterized by a rapidly enlarging nodule that is black, blue, or pink. The usual age at presentation ranges from 30-70 years old, but typically 40-50. They are 4 mm to 5 centimeters in size with asymmetry and well defined borders. They are unique because they present with a rapid growth phase, two months to four years. Histologically, they are dome-shaped polypoid or sessile tumors with effacement of the epidermis, and host response at the base, or tumor infiltrating lymphocytes present.

**Desmoplastic-neurotropic melanoma** is a rare subtype of melanoma with spindle cells and abundant collagen with a propensity to infiltrate nerves. This is a very aggressive form of melanoma which is locally aggressive and infiltrative. A majority of these lesions are amelanotic, and they typically do not have the features characteristic to most cutaneous melanomas, making diagnosis particularly difficult.

**Mucosal melanoma** is rare and relatively difficult to diagnose at an early stage. It is clinically distinct from cutaneous head and neck melanoma. Most are diagnosed in patients 60 to 70 years old, and there is an equal incidence in all racial groups and no gender predilection. They range in size from 3 mm to 12 cm and are often greater than 7 mm when first diagnosed. Their color can be black, brown, tan, gray, pink, white, or blue. Amelanotic lesions do exist, and contribute to the difficulty in diagnosing these cancers. They are most commonly found in the nasal cavity (anterior septum>inferior/middle turbinate) or the oral cavity (hard palate and maxillary alveolar ridge). Histologically, they show a thickened stratum corneum, prominent acanthosis (elongated epidermal rete), contiguous lentiginous melanocyte proliferation, variable cytologic atypia, nuclear enlargement, hyperchromatism, and prominent pleomorphism. There is a high incidence of desmoplasia, neurotropism, and angiotropism.

## Signs and Symptoms

A comprehensive history should be taken with questions directed towards number of lesions, sun exposure, family history of melanoma or skin cancer, previous skin cancers, history of tanning bed use, history of sunburns, and occupational history. An easy way to remember the signs of a melanoma is the **ABCDE pneumonic**. **Asymmetry**, most lesions do not have a regular shape or symmetry. **Borders** characterized by notched or irregular borders. **Color** characterized by irregular color, variegation of color, or jet black color. **Diameter** greater than 6 mm. **Evolving** lesion characterized by new onset of bleeding, ulceration or pruritis. These signs only serve as a guide and are very helpful in diagnosing melanoma, but not all cutaneous melanomas will fit into these categories. It is important to recognize skin lesions that may look different from surrounding benign lesions, and biopsies should be taken. Review of systems should be thorough, looking for possible sites of distant metastasis. Constitutional, pulmonary,

hepatic, gastrointestinal, musculoskeletal, or neurologic symptoms may warrant further laboratory or radiologic investigation.

## Differential Diagnosis

The differential includes processes with melanocytic proliferation including markedly atypical nevi, halo nevi, Spitz tumors, pigmented spindle cell tumors. Sun damaged skin may also present with actinic keratosis, solar lentigo and solar melanocytic hyperplasia that may be difficult to distinguish from melanoma. Other lesions on the differential include pigmented sarcomas (Kaposi's sarcoma, angiosarcoma, and leiomyosarcoma) and metastatic squamous cell carcinoma.

## Diagnosis

In order to obtain a diagnosis, tissue must be obtained. Biopsy should be full thickness and can be excisional with 1-2 mm margins or incisional for larger lesions. Shave biopsy should be avoided because the depth of the melanoma will not be obtained, and this is important for staging and treatment. Punch biopsy that is full thickness through the lesion is also acceptable. The patient should have a full body examination by a physician that is familiar with skin lesions and skin cancer. Any other suspicious lesions need to be biopsied at the same time. If there is lymph node enlargement, an FNA of the suspicious lymph node is warranted. Other screening tests such as chest x-rays, CT scans, lactate dehydrogenase, and depend on the stage of disease, or clinical findings that may warrant their use.

Histologic examination of the specimen should show proliferation of melanocytes. Other features include cytologic atypia, intraepidermal proliferation with extension down to the papillary dermis, and polypoid morphologies. They have enlarged nuclei and nucleoli with pleomorphism present, and a high nuclear to cytoplasm ratio. The cytoplasm has a pink, granular quality with a clear space around the nuclei. Staining with S-100, HMB-45, vimentin, and *MART1* positivity and cytokeratin negativity help confirm diagnosis of melanoma when hematoxylin and eosin staining is equivocal.

## Staging and Prognostic factors

The most important prognostic factors for localized melanomas are **tumor thickness** and presence of **ulceration**. There are two microstaging systems to assess tumor thickness. These are the Clark qualitative systems, and the Breslow quantitative system. The Clark system is based on depth into histological layers of skin, while the Breslow system is based on depth in millimeters. The new AJCC staging system uses the Breslow system because it better predicts outcome, but the Clark scale is used to differentiate T1a and T1b melanomas.

### Clark Quantitative System

- I. In situ; all tumor cells within the epidermis, superficial to basement membrane
- II. Tumor involves but does not completely fill the papillary dermis
- III. Tumor fills the interface between the papillary and reticular dermis

IV. Tumor cells invade the reticular dermis

V. Tumor involves subcutaneous tissue

### **Breslow Quantitative System**

- < 0.75 mm
- 0.76-1.49 mm
- 1.50-3.99 mm
- > 4.0 mm

Low risk lesions are less than 1 mm in thickness and they have a greater than 90 percent cure rate with wide local excision. Lesions that are between 1.5 mm and 3.99 mm are considered intermediate risk and have a greater than 70 to 85 percent cure rate with definitive surgery. For thick lesions, the cure rate falls to 50 to 70 percent. The other prognostic factor for local melanomas is ulceration. Ulceration refers to the microscopic evaluation of the epidermis, not gross ulceration. The presence of ulceration signifies a more aggressive melanoma and up stages that lesion. These lesions have no gross nodal disease, and sentinel lymph node biopsy is negative for micrometastasis. If there is gross nodal disease or micrometastasis is found from sentinel lymph node biopsy, then the patient has stage III (regional) disease. The most important prognostic factors are number of metastatic nodes, tumor burden, and ulceration. For staging, the total number of metastatic lymph nodes determines N stage, and not the gross lymph node size. N1 disease is confined to one lymph node, N2 is confined to two to three lymph nodes, while N3 has four or more positive lymph nodes or distant nodes. Sentinel lymph node biopsy helps determine the tumor burden and lymph nodes status. Microscopic (occult) metastasis has better prognosis than macroscopic or gross metastatic disease. In addition to the above, lesions with satellite metastasis or in-transit metastasis are defined as stage IIIB. As with stage I and II disease, the presence of ulceration has a negative impact on survival. Stage IV disease is metastatic disease. The anatomic site of metastasis, and lactate dehydrogenase levels affect prognosis. M1a lesions are confined to the skin, subcutaneous tissue and distant lymph nodes, M1b lesions are patients with lung metastasis, and M1c have visceral organ metastasis or elevated levels of lactate dehydrogenase. Disseminated disease has the worst prognosis with survival time of 6 to 8 months. One year survival for metastatic disease to the skin or lungs is around 57 percent, this drops to 41 percent if other visceral organs are involved. For distant disease, imaging of the thorax, abdomen, pelvis, and head need to be obtained, as well as lactate dehydrogenase levels.

## AJCC 2003 MELANOMA TNM CLASSIFICATION

<b>T Classification</b>	<b>Thickness</b>	<b>Ulceration Status</b>
T1	≤1.0 mm	a: without ulceration and level II/III
		b: with ulceration or level IV/V
T2	1.01–2.0 mm	a: without ulceration
		b: with ulceration
T3	2.01–4.0 mm	a: without ulceration
		b: with ulceration
T4	> 4.0 mm	a: without ulceration
		b: with ulceration
<b>N Classification</b>	<b>No. of Metastatic Nodes</b>	<b>Nodal Metastatic Mass</b>
N1	1 node	a: micrometastasis *
		b: macrometastasis †
N2	2–3 nodes	a: micrometastasis *
		b: macrometastasis †
		c: in transit met(s)/satellite(s) without metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic node(s)	
<b>M Classification</b>	<b>Site</b>	<b>Serum Lactate Dehydrogenase</b>
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

\* Micrometastases are diagnosed after sentinel or elective lymphadenectomy.

† Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

## Pathologic Staging of Cutaneous Melanoma

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 IIIA	T1–4a	N1a	M0
	T1–4a	N2a	M0
Stage IIIB	T1–4b	N1a	M0
	T1–4b	N2a	M0
	T1–4a	N1b	M0
	T1–4a	N2b	M0
	T1–4a/b	N2c	M0
Stage IIIC	T1–4b	N1b	M0
	T1–4b	N2b	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

## Treatment

Current treatment guidelines for surgical excision are based on depth of invasion in millimeters for the lesion. For melanoma in situ, a 0.5 millimeter margin is recommended, but may not be adequate. Margins are taken until they are negative because up to 12% of melanoma in-situ will be upstaged to invasive melanoma on permanent pathology. For lesions less than 1.0 mm, a 1.0 cm margin is recommended. Intermediate lesions are 1.01-2.0 mm and require a 1.0-2.0 cm margin. Lesions greater than 2.0 mm require a 2.0 cm margin. Non-surgical ablative techniques such as Nd:Yag laser, imiquimod, and fluorouracil have been tried, but high recurrence rates are problematic. These techniques have no role in the management of melanoma. Moh's micrographic surgery is another alternative for initial excision. Wide local excision with adequate margins is usually deferred until permanent pathology results are received.

There is a 20% rate of occult neck disease in patients with cutaneous melanoma of the head and neck. Because of this, the neck needs to be evaluated for metastatic disease. Elective neck dissection was carried out for many years, but recent randomized control trials showed no survival benefit of performing elective neck dissection. The morbidity associated with elective neck dissection and performing this procedure in four out of five people that did not need it, prompted researchers to look at other means of evaluating lymph nodes. In 1992, Morton used lymphoscintigraphy to map sentinel lymph nodes for cutaneous melanoma. It was a well established practice for most sites in the body, but there was concern about using SLNM in the head and neck due to complex drainage patterns and the number of lymph nodes in the head and neck.

Studies performed by Schmalbach and Agnese found that SLNB in the head and neck was comparable to other sites in the body. There are more lymph nodes in the head and neck region and more sentinel nodes are found during surgery. Also, there is a 26% rate of finding sentinel lymph nodes in non-predicted sites. Currently, sentinel lymph node biopsy has supplanted elective neck dissection for staging of the clinically negative neck. Certain criteria must be met before performing sentinel lymph node mapping and biopsy. These include Breslow depth equal to 1 mm in the setting of tumor extension to the deep margin, ulceration, extensive regression to 1 mm, young age, high mitotic rate, and Clark level IV. SLN mapping requires preoperative lymphoscintigraphy approximately two to four hours preoperatively. A radioactive colloid is injected into the dermis surrounding the primary melanoma and a scan is performed. This scan aides the surgeon in focusing on specific nodal groups during surgery. Intraoperatively, isosulfan blue dye is injected intradermally around the melanoma. Wide local excision of the primary lesion is performed, followed by using the gamma probe to isolate the sentinel node or nodes. Sentinel node biopsy is complete when the gamma probe demonstrates only minimal background radioactivity. Permanent section is the gold standard for finding micrometastasis, thus it may be necessary to perform therapeutic neck dissection at a later date.

Treatment of the neck with therapeutic neck dissection with or without superficial parotidectomy depends on tumor location, and evidence of gross disease. Scalp lesions anterior to the external auditory canal and lesions to the lateral forehead, cheek, and auricle, typically drain to the periparotid lymph nodes and deep cervical lymph nodes. Therapeutic neck dissection for these lesions involves superficial parotidectomy and modified radical neck dissection. Melanomas on the nose, lips, or chin will drain to level I, as well as the deep jugular nodes and require a modified radical dissection of levels I-IV. Posterior and mid scalp lesions generally metastasize to occipital nodes, postauricular nodes, and posterior neck nodes. For these lesions, occipital and level II-V lymphadenectomy is performed without parotidectomy. Lesions of the auricle or ear canal may present with extensive local disease prompting auriculectomy with lateral temporal bone resection in addition to the superficial parotidectomy and modified radical neck dissection.

Closure of the resultant defect follows the reconstructive ladder. The face causes particular concerns because defects may violate the facial units. With undermining, most defects can be closed primarily with minimal tension. Skin grafting, local flaps, pedicled flaps, and free flaps may also be needed. If the facial nerve is involved with melanoma, then static procedures may be necessary as well as nerve grafting.

Patients with disseminated melanoma have a grave prognosis, and surgery only plays a palliative role in their care. Adjuvant treatments for head and neck cutaneous melanoma have not yielded improvements in survival. Melanomas are relatively radioresistant as well as chemoresistant. Radiation treatments are generally reserved for stage IV disease, and patients with significant negative prognostic factors such as neurotropism, greater than 4 node metastasis, extracapsular spread, or recurrence. The Radiation Oncology group is in a randomized phase III clinical trial. The only chemotherapeutic option for stage IV disease is *Dacarbazine (DTIC)*. Less than 5% of people experience a complete response, and only 10% to 20% of people have any type of response. Immunotherapeutic agents are currently being studied and may be the adjuncts to the treatment of stage III and IV diseases. Currently, interferon alpha-2B is FDA approved for stage IIB and IIC, as well as stage III disease and has shown improvements in

disease free survival but not overall survival. Other immunotherapeutic technologies that are under investigation include vaccinations, cytokines, and antibodies.

## **Summary**

Cutaneous melanoma of the head and neck accounts for approximately 25-35% of all melanomas. This disease has seen an increase in incidence of 3% per year over the past year, with those born in 2005 having a 1 in 38 chance of developing melanoma over their lifetime. Traditionally, this was a disease of the elderly, but now melanomas are found in all age groups. With early detection, wide local excision carries a greater than 90% cure rate. Tumor thickness, the presence of ulceration, nodal status, and distant metastasis are the most important prognostic factors. Sentinel lymph node biopsy now plays a major role in detecting micrometastasis and providing information about the necessity of therapeutic neck dissection. Stage IV disease has a grave prognosis with survival measured in months. There are currently many investigational studies looking to improve survival in this group of patients.

## **DISCUSSANT: Dr. C. Berlingeri-Ramos, Dept. UTMB Dermatology**

The question was asked on the difference between UVA and UVB.

UVA penetrates more into the skin, while UVB's shorter wavelength penetrates less and it is limited to the dermis and the papillary dermis. It is thought that UVB is responsible for the mutations involved in causing cancer.

Malignant melanoma does occur in negroes but is much more common in fair-skinned patients especially those with red hair and blue eyes.

Dr. Quinn remarked that while in Victorian times, a tanned skin was evidence of an occupation requiring manual work outdoors and therefore a mark of membership in the laboring classes. Today a "healthy tan" signifies that the wearer has sufficient leisure and discretionary funds to enjoy days of recreational activity at the seashore, and hence is a claim to enhanced social status and relative affluence.

Dr. Berlingeri-Ramos then remarked that "there is no such thing as a healthy tan except for the ones that are sprayed on. With respect to tanning salons, Dr. Berlingeri-Ramos believes that in some States, a minor must have a parent's consent before being admitted for a tanning session.

She was asked about the dimensions of a so-called "giant nevus." She replied that the usual minimum diameter is considered to be 20 cm. and in these, some 10% become malignant.

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