

Malignant Melanoma

What is Malignant Melanoma? Malignant melanoma is a neoplasm of melanocytes or of the cells that develop from melanocytes.¹

Background

One of the most dangerous tumors, malignant melanoma arises from cells of the melanocytic system. Melanoma has the ability to metastasize to any organ, including the brain and heart.² In addition, because Malignant melanoma stems from pigment producing cells (melanocytes), the skin, eyes, ears, GI tract, leptomeninges of the central nervous system (CNS), and oral and genital mucous, membranes may all be sources for this deadly cancer.³

Pathophysiology:

Transformation of melanocytes to melanoma cells is understood poorly. Melanoma is multifactorial and appears to be related to multiple risk factors including: fair complexion, excessive childhood sun exposure and blistering childhood sunburns, increased number of common acquired and dysplastic moles, family history of melanoma, and presence of a changing mole on the skin.³

Melanomas may develop in or near a previously existing precursor lesion or in healthy-appearing skin. A malignant melanoma developing in healthy skin is said to arise de novo, without evidence of a precursor lesion. Many of these melanomas are induced by solar irradiation. The greatest risk of sun exposure–induced melanoma is associated with acute, intense, and intermittent blistering sunburns. This risk is different than that of squamous and basal cell skin cancers, which are associated with prolonged, long-term sun exposure.⁴

Melanomas have 2 growth phases, radial and vertical. During the radial growth phase, malignant cells grow in a radial fashion in the epidermis. With time, most melanomas progress to the vertical growth phase, when the malignant cells invade the dermis and develop the ability to metastasize.¹

Many genes are implicated in the development of melanoma, including *CDKN2A (p16)*, *CDK4*, *RBI*, *CDKN2A (p19)*, *PTEN/MMAC1*, and *ras*. *CDKN2A (p16)* which appears to be especially important in both sporadic and hereditary melanomas. This tumor suppressor gene is located on band 9p21, and its mutation plays a role in various cancers.²

Histopathology

Five different forms or histologic types of melanoma exist, as follows:

Superficial spreading melanomas (SSM)	Approximately 70% of cutaneous malignant melanomas. They often arise from a pigmented dysplastic nevus. SSMs typically develop after a long-standing stable nevus changes; typical changes include ulceration, enlargement, or color changes. A SSM may be found on any body surface, especially the head, neck, and trunk of males and the lower extremities of females.
Nodular melanomas (NMs)	Represent approximately 10-15% of melanomas and also are found commonly on all body surfaces, especially the trunk of males. These lesions are the most symmetrical and uniform of the melanomas and are dark brown or black in color.
Lentigo maligna melanomas (LMMs)	Account for 10-15% of melanomas. They typically are found on sun-exposed areas (eg, hand, neck). LMMs may have areas of hypopigmentation and often are quite large.
Acral lentiginous melanomas (ALM)	Are the only melanomas that have an equal frequency among blacks and whites. They occur on the palms, soles, and subungual areas. Subungual melanomas often are mistaken for subungual hematomas (splinter hemorrhages). Like the NM, ALM is extremely aggressive.
Mucosal lentiginous melanomas (MLMs)	Develop from the mucosal epithelium that lines the respiratory, gastrointestinal, and genitourinary systems. These lesions account for approximately 3% of the melanomas diagnosed annually and may occur on any mucosal surface, including the conjunctiva, oral cavity, esophagus, vagina, female urethra, penis, and anus.

Frequency:

In the US: Malignant melanoma is one of the most increasingly common solid tumors over the last three decades.⁵ Specifically, the incidence of melanoma has more than tripled in the white population during the last 40 years, and melanoma currently is the seventh most common cancer. Approximately 53,600 Americans will develop invasive cutaneous melanoma in 2002, with an additional estimated 30,000-50,000 cases of melanoma in situ. Currently, the lifetime risk for melanoma is 1 in 71

Americans, compared with 1 out of 600 in 1960 and 1 out of 150 in 1985.⁶ The lifetime risk is estimated to rise to 1 in 50 by 2010.

Internationally: Melanoma incidence has continued to increase worldwide with the highest incidence in Australia and New Zealand. The year 2000 rate was 27.9 cases per 100,000 men and 25 cases per 100,000 women internationally compared to 10.9 cases per 100,000 men and 7.7 cases per 100,000 women in North America.³

Mortality/Morbidity:

- United States: An estimated 7400 deaths will occur in 2002 (4700 men, 2700 women). Melanoma is responsible for 75% of skin cancer deaths in the United States. *White males have the highest mortality rates from melanoma.*
- Worldwide: Individuals with cutaneous melanoma have a higher survival rate in developed countries than in developing countries. Increased educational efforts in developed areas result in earlier diagnosis, treatment, and potential cure. Worldwide, 105,000 new cases of melanoma were estimated annually in the year 2000, with 33,000 deaths reported, mostly in males.

Sex: Melanoma is the sixth most common malignancy in women and the seventh most common malignancy in men.¹ In the United States, melanoma has a slight male predilection, occurring in 1 in 70 males compared to 1 in 88 females. Worldwide, in the 105,000 new cases estimated to occur annually, women are affected more frequently than men.³

History and Physical

A changing mole is the most common symptom of melanoma. Thus, on physical exam, a total body skin examination is crucial when evaluating a patient with an atypical nevus or a melanoma. The skin examination should be performed both on initial evaluation of the patient and at all subsequent visits.

Variation in color and/or increase in diameter, height, or asymmetry of borders of a pigmented lesion are noted by more than 80% of patients with melanoma at the time of diagnosis. Physician and

patient education regarding the warning signs of early melanoma has been achieved successfully through the use of the ABCD criteria for a changing mole, which is as follows⁶:

- o **A**symmetry is a common feature of melanoma, whereas most benign tumors tend to be symmetric in shape.
- o **B**order irregularity, although not pathognomonic for melanoma, is a typical finding.
- o **C**olor variegation; Black, blue, and red hues are commonly present. Colors of the brown spectrum (tan to dark brown) are characteristic of benign lesions (nevi, seborrheic keratoses) and are rarely part of a melanoma.
- o **D**iameter >6 mm; melanomas tends to enlarge with time, whereas benign lesions remain stable.

Causes/Risk Factors

The relationship between sun exposure and skin type and the risk of melanoma is complex. Epidemiologic and case control studies suggest that sunlight is the most important environmental factor in the pathogenesis of melanoma, with radiation in the ultraviolet B range (280 to 320 nm) proposed to be the critical component.⁸ Furthermore, melanoma tends to occur at sites of intermittent intense sun exposure (i.e., on trunk in males and legs and back in females). The disease shows an increased worldwide incidence in locations nearer the equator, suggesting a causative role for ultraviolet radiation.

However, not all evidence readily links ultraviolet light to melanoma. Rates of melanoma are relatively uncommon in persons with outdoor occupations. Except for lentigo maligna melanoma subtype, melanoma does not regularly occur on the skin most exposed to the sun such as the face.⁷

Pre-existing conditions also plays a significant role in the development of melanoma. The dysplastic nevus is recognized as an important precursor lesion to melanoma and also as a marker for increased melanoma risk.⁹ Patients with xeroderma pigmentosa, a rare autosomal recessive disorder characterized by deficient repair of ultraviolet B damaged DNA, have higher rates of skin cancer, including melanoma.¹⁰ Certain phenotypes such as blond or red hair have been associated with an

increased risk of melanoma. In one study, blond hair conferred a 7.1-fold increased risk for melanoma compared to black hair.¹¹ Some of the risks associated with development of melanoma have been outlined in Table-1.

Table-1. RISK FACTORS FOR THE DEVELOPMENT OF CUTANEOUS MELANOMA	
Cutaneous phenotype	Fair skin, Hair color--blond/red, Eye color--blue eyes, Freckling
Environmental	Tendency to burn/poor tanning, History of blistering sunburns in childhood Excessive sun exposure
Precursor lesions	Dysplastic nevi, Increased number of benign nevi, Congenital moles Lentigo maligna
Other	Personal history of melanoma, Family history of melanoma, Nonmelanoma skin cancers

The Differential Diagnosis for Malignant Melanoma consists of the following:

Atypical Mole (Dysplastic Nevus)
Basal Cell Carcinoma
Blue Nevi
Cherry Hemangioma
Dermatofibroma
Halo Nevus
Keloid and Hypertrophic Scar
Keratoacanthoma
Lentigo
Metastatic Carcinoma of the Skin
Nevi of Ota and Ito
Nevi, Melanocytic
Seborrheic Keratosis
Spitz Nevus
Squamous Cell Carcinoma
Vitiligo

Lab Study/Evaluation

Expert pathologic interpretation is critical to the management of patients with melanoma.^{1,3,6}

An excisional biopsy with narrow margins is preferred to ascertain the following information:

- Assessment of tumor depth (Breslow depth)
- Ulceration
- Anatomic level of invasion (Clark level)
- Presence of mitoses
- Lymphatic/vessel invasion or vascular involvement
- Host response (tumor-infiltrating lymphocytes)

The prognosis is based on the measured thickness of the tumor in millimeters (Breslow level) more

than any other histologic finding (Table-2). Ideally, the lesion should be excised entirely for diagnosis.

Incisional biopsies may be performed for diagnosis when complete excision is not feasible.

Table-2. 5-Year Survival Rates in Malignant Melanoma	
<i>Breslow tumor thickness (mm)</i>	<i>Survival (%)</i>
<0.75	95-99
.76-1.49	080-95
1.50-4.00	60-75
>4.00	<50

More recently, the use of the sentinel node biopsy has helped identify individuals with micrometastases who would benefit from lymph node dissection or adjuvant chemotherapy.¹² In this procedure, blue dye and radioisotope is injected into the melanoma site to identify the sentinel lymph node (SLN) in the drainage site. Stojadinovic and colleagues found that because the results of positive frozen section biopsy are low, routine frozen sections of SLN is not recommended.¹³ In a study out of England, Acland et al. compared PET scanning versus SLN biopsy. They found that SLN was a better technique for staging melanomas and that PET scanning has little to contribute as a staging procedure.¹⁴ Nevertheless, SLN biopsy is known to offer important prognostic, diagnostic, and therapeutic information.¹

There are several methods of staging melanomas. One method of staging uses Clark's criteria and is listed below.

Clark staging

Level I - All tumor cells above basement membrane (in situ)

Level II - Tumor extends into papillary dermis

Level III - Tumor extends to interface between papillary and reticular dermis

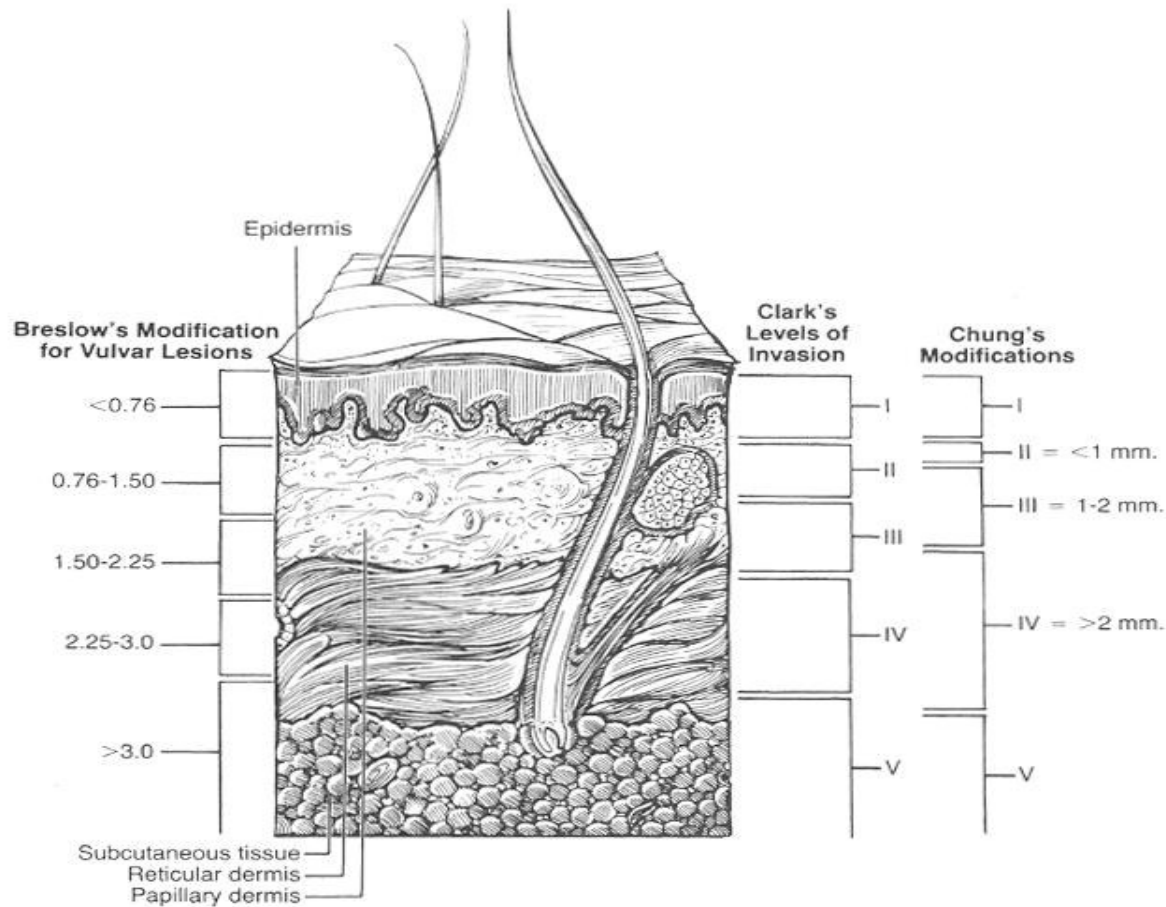
Level IV - Tumor extends between bundles of collagen of reticular dermis (extends into reticular dermis)

Level V - Tumor invasion of subcutaneous tissue

Other evaluation systems include the Breslow, Chung's and the American Joint Committee on Cancer.

See **Figure-1**.

Figure-1



Management

Surgery is the primary mode of therapy for localized cutaneous melanoma. Surgical margins of 5 mm currently are recommended for melanoma in situ, and margins of 1 cm are recommended for melanomas up to 1 mm in depth (low-risk primaries). Randomized prospective studies show that 2-cm margins are appropriate for tumors in the intermediate-risk group (1-4 mm in Breslow depth), although 1-cm margins have been proposed for tumors of 1- to 2-mm thickness. Margins of at least 2 cm are recommended for cutaneous melanomas greater than 4 mm in thickness (high-risk primaries) to prevent potential local recurrence in or around the scar site. A recently published retrospective study of high-risk primary melanomas showed that excisional margins greater than 2 cm have no effect on local recurrence, disease-free relapse, or overall survival rates; therefore, a 2-cm margin is appropriate in this subgroup.^{2,15}

Because the definitive treatment of cutaneous melanoma is surgery, medical management is reserved for adjuvant therapy and treatment of patients with advanced melanoma. Although controversy surrounds the use of adjuvant therapy in these patients, a recent large, multicenter study showed improvement in both long-term survival and disease-free survival using high-dose interferon-alpha-2b (IFN). Based on this study, the Food and Drug Administration (FDA) approved IFN as adjuvant treatment after excision in patients who are free of disease but are at high risk for recurrence.¹ In addition, Argawala et al. did a study comparing combined treatment of histamine dihydrochloride plus interleukin-2 versus interleukin-2 alone in patients with metastatic melanoma. They found that the use of histamine as an adjunct to interleukin-2 (IL-2) is safe, well tolerated, and associated with a statistically significant prolongation of survival compared with IL-2 alone in metastatic melanoma patients with liver involvement.¹⁶

Other forms of treatment include elective lymph node dissection and sentinel lymph node biopsy/dissection. Prophylactic lymph node dissection for primary cutaneous melanoma of intermediate thickness initially was believed to confer a survival advantage on patients with tumors 1-4 mm in depth. Subsequently, prospective randomized clinical trials have shown no survival benefit for elective lymph node (ELN) excision for melanomas of varying thicknesses on the extremities and marginal, if any, benefit for nonextremity melanomas (See **Figure-2**).³ Gershenwald et al. performed a recent study looking at the efficacy of SLN biopsy. They found that lymphatic mapping and SLN biopsy is highly accurate in staging nodal basins at risk for regional metastases in primary melanoma patients and helps identify those who may benefit from earlier lymphadenectomy.¹⁷

Consultations to medical, radiation, and surgical oncologist may also be warranted. A patient with a suggestive lesion should be referred to a dermatologist or surgical oncologist for excisional biopsy. If diagnosis of melanoma is made, the patient should be referred to an oncologist after definitive surgery is performed.¹

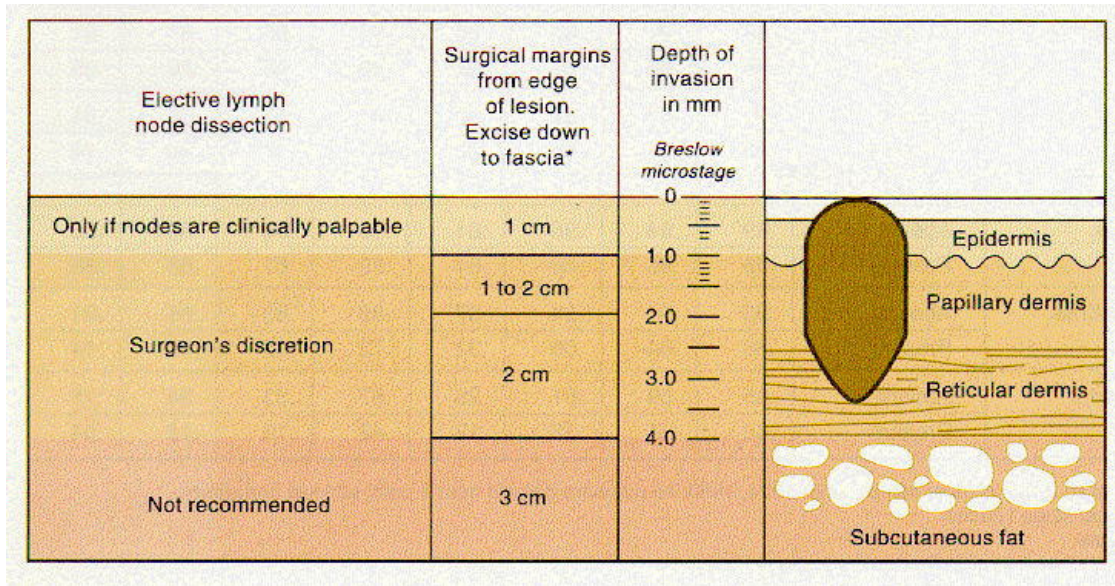


Figure-2
Surgical Management of ELN

Prognosis

Prognosis is multifactorial and primarily depends on, tumor thickness, presence or absence of histologic ulceration, and lymph node involvement (most important), See Table-2. Despite advances in the treatment of metastatic disease, detection and treatment of cutaneous melanoma in its thin early phase remains the best chance for cure.⁶

Prevention

Sun-avoidance behavior is currently the main emphasis in melanoma prevention. Protecting young children from sun exposure may be the most important factor that can be monitored. Early detection of melanoma can be lifesaving. The skin self-examination is now recommended to all patients with increased risk of melanoma.¹⁸ Even still, it has been difficult to prove that regular use of sunscreen can protect against melanoma. In fact, the majority of retrospective epidemiologic studies have failed to show that regular use of sunscreen protects against melanoma.⁷ First-degree relatives of a patient diagnosed with familial melanoma should be encouraged to have annual skin examinations.

Follow-up

Follow-up care of a patient with melanoma is based on the stage of the primary. The follow-up examination should be performed with the knowledge that the patient has an increased risk for a second primary and that, of all solitary sites of visceral recurrence, the lungs are the most frequent. Although no absolute guidelines exist, the patient with a primary less than 1 mm in thickness should be examined every 6 months for the first 2 years and every year after that for the next 8 years. Blood chemistries should be obtained at every other visit, and chest x-rays should be obtained yearly for 5 years and then every 2 years for the next 5 years. Suggested follow-up care for patients with primaries 1-4 mm in thickness consists of a physical examination every 3-4 months for the first 3 years, every 6 months for the 2 years after that, and yearly for the next 5 years. Blood chemistries should be obtained at every other visit, and chest x-rays should be obtained yearly for the first 5 years and every other year for the 5 years after that.^{1,3}

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David M Isaacs MS3

UHS Class of 2005

Family Practice Rotation #1

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Dr. Lewis Rosenblatt, DO

