CHAPTER 18

Melanoma Review

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INTRODUCTION

Skin cancer continues to affect numerous individuals every year. In fact, from 1982 to 2011 melanoma rates have doubled in the United States (1). The incidence of melanoma continues to both rise and affect various age groups. In the early stages, melanoma is easily treatable. Unfortunately, the advanced stages can spread to organs, more specifically the lung, liver, and brain. Metastatic disease can result in death. It is estimated that 9,940 people will die as a result of melanoma in 2015 (2). Melanoma still presents as a masquerader on the foot. It can be misdiagnosed as a neuropathic ulceration especially among the diabetic population. It can also present in areas that are not easily visualized and advance in staging as a result. Skin cancer awareness, routine screening, and recognition of family history are all key in early detection. This update will focus specifically on the most serious form of skin cancer: melanoma.

EPIDEMIOLOGY

Melanoma rates may be underestimated as many in situ or superficial cases are managed in an outpatient setting. These cases are not routinely reported to the cancer registries (3). The highest incidence rates exist in Northern Europe, New Zealand, Australia, and North America (4). People who live close to the equator where the sunlight is more intense are more likely to develop melanoma than those in other regions (5). As for the United States, the highest rates are seen in the northwestern states. For geographic information and mapping of mortality rates one can refer to the National Cancer Institute.

Incidence increases with age. Incidence is highest among individuals in their 80s. Still, melanoma manifests in younger people as well. Melanoma is one of the leading causes of cancer in women 20 to 29 years of age (6). This form of skin cancer is rare in children. Men are slightly more affected as compared to women with a ratio of 1.3 to 1 (6). Men older than 65 years also have the highest mortality rate (4). In the United States 1 in 50 white, 1 in 200 Hispanic, and 1 in 1,000 African American individuals are at risk in their lifetime (2).

RISK FACTORS

The etiology of melanoma is not completely understood. Research thus far supports a multifactorial etiology. Family history, gene mutations, immunosuppression, physical characteristics, and environmental exposure may all have a role.

Family history is important. The risk of melanoma increases 2.2-fold if at least 1 family member has been diagnosed with melanoma. This risk increases if 2 family members have a history of melanoma. Physical characteristics that place people at risk of melanoma include fair skin, blue or green eyes, and red or blonde hair. Individuals who burn easily are at risk. Exposure to natural or UV light is a risk factor as with all types of skin cancer. Individuals who have a history of more common skin cancers such as squamous cell carcinoma or basal cell carcinoma are at risk for developing melanoma. Further intrinsic risk factors include immunosuppression and maternal-fetal transfer. Melanoma is the most likely to metastasize from the placenta to the fetus, although this is rare.

Several gene mutations have been linked to an increase in risk for melanoma. These gene mutations linked to hereditary melanoma include cyclin-dependent kinase inhibitor 2A and melanocortin-1 receptor gene (7). The major signaling pathway associated with development of melanoma is the mitogen activated protein kinase pathway. Furthermore BRAF mutations have shown to be a link between UV radiation and development of melanoma. Dysplastic nevus syndrome or multiple mole melanoma syndrome increases the risk for melanoma 400-1,000-fold (4).

PATHOPHYSIOLOGY

Morphologic stages include melanocytic atypia, atypical melanocytic hyperplasia, radial growth phase, primary melanoma in the vertical growth phase with or without in-transit metastases, regional lymph node metastatic melanoma, and distant metastatic disease (4). Checkpoint inhibitors have been shown to initiate an anti-tumor immune response directed against melanoma while autoimmune side effects exist. Researchers are studying new checkpoint inhibitors and immunotherapies directed at other parts of the immune

system. Another type of experimental immunotherapy, adoptive cell transfer (ACT), involves altering the patient's white blood cells to increase their ability to fight the tumor. The changed cells are given back to the patient, often in combination with interleukin-2 or other immunotherapies.

STAGING AND MARGINS

There are 4 major types of melanoma: Superficial spreading melanoma, lentigo maligna melanoma, acral lentiginous melanomas, and nodal melanoma. The first 3 types, if detected early, respond well to surgical excision. Unfortunately nodal melanoma can be associated with early metastasis. Metastatic disease is difficult to cure.

The American Joint Committee on Cancer TNM staging system for melanoma contains 3 components: tumor size, lymph node involvement, and metastasis. This staging is utilized to predict both prognosis and survival.

Stage 0: Melanoma in situ (no spreading from epidermis to dermis)

Stage I and II: Melanoma of specific area

Stage 3: Lymph node involvement with no distant spread

Stage 4: Metastasis to distant sites

Clear margins following surgical excision of melanoma are key when treating early stage melanoma. As this disease progresses, lymph node involvement and or metastasis continue to be associated with recurrence and poor prognosis. Research is being conducted to improve survival rates and prognosis for the advanced cases of this disease.

With respect to excision, it is important to remember that melanoma may extend beyond visible margins or have satellite lesions. Breslow's depth classification is helpful with plan of care. MOHs surgery cannot be performed for melanoma. The National Conference of Cancer Network (NCCN) Guidelines are shown in Table 1.

Table 1. NCCN Recommended Margins

Tumor Thickness	Recommended Margin
In situ	0.5 cm
≤1.0 mm	1 cm
1.01-2.0 mm	1-2 cm
>2.01 mm	2 cm

Melanoma most commonly spreads through lymphatics. Hence, for intermediate thickness melanoma (1-4 mm) sentinel lymph node biopsy is also recommended (8). There is insufficient evidence for thin melanomas (<1 mm) with respect to sentinel node biopsy. The biopsy may be considered if high-risk features exist such as ulceration, mitotic rate ≥1 per mm^2, Clark level IV, or positive deep margin on initial biopsy. Completion lymph node dissection is recommended for all patients with positive sentinel node(s) (7).

TREATMENT

The early stages of melanoma can generally be treated with excision provided the margins are appropriate. This often requires a surgical graft application or flap if the deficit is too large for primary closure. Surgical amputations may also be performed to obtain these margins. Unfortunately the advanced stages of melanoma may not be curable. Melanoma can metastasize anywhere. Typically, metastasis is noted to the lungs, liver, and brain. The advanced stages of the disease must be evaluated per each individual and presentation of the disease. If long-term survival is possible with complete resection, then possibly surgery is an option with immunotherapy. Otherwise palliation of symptoms may be an option for patients with advanced disease. There are several prognostic factors for curative resection including: limited number of sites of disease, ability to achieve R0 resection, and long disease-free interval between diagnosis and development of metastasis. As surgeons it is important to allow the biology to be the driving force toward procedure selection.

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