

Clinical Review

Cutaneous Malignant Melanoma: A Synthesis on Updated Guidelines for the Primary Care Perspective

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Abstract

Description

Cutaneous malignant melanoma (CMM) is a condition wherein malignant cells form in the melanocytic cells. CMM is a potentially lethal form of skin cancer, commonly found in sun-exposed areas of the body. There are multiple risk factors for disease development, such as genetic mutation and UV radiation among others. Diagnosis and staging is important in determining disease morbidity and mortality. The United States Preventive Services Task Force (USPSTF) and the American Academy of Dermatology (AAD) have their respective guidelines and consensus on diagnosis, staging and treatment. It is imperative to delineate and educate primary care physicians on CMM, as they serve as the first line of defense in disease diagnosis. The purpose of this article is to provide a concise educational synopsis for primary care physicians.

Keywords

cutaneous malignant melanoma; melanoma; skin neoplasms; neoplasm staging; TNM staging; biopsy; melanocytes; ABCDE; USPSTF; diagnosis

Introduction

Cutaneous malignant melanoma (CMM) is a condition wherein malignant cells form in the melanocytic cells. Melanocytes are found throughout the lower epidermis and are responsible for producing melanin. CMM is a potentially lethal form of skin cancer found most commonly in sun-exposed areas, such as the face, neck, hands and arms, as seen in other skin malignancies. Risk factors are multifactorial, including genetic susceptibility and UV radiation damage.¹ Melanoma comprises 2% of overall skin cancers, with basal and squamous cell carcinoma comprising the remaining 98%. Non-melanoma skin cancer rarely results in death or substantial morbidity, whereas melanoma has notably higher mortality rates.² In 2020 alone, it is estimated that 100,350 US men and women would develop melanoma and 6,850 would succumb to the disease.² Melanoma associated mortality rates are higher among the middle-aged and elderly. Though

the new cases of melanoma of the skin have risen over the last 10 years, the overall mortality rate has declined by 7% on an annual basis between the years of 2013–2017 for both sexes aged 20–64 years.³ In addition, the mortality rate has also dramatically declined for individuals 65 years of age and older by 5 to 6% on an annual basis.³

Prevention is a key criteria of practice for primary care physicians, and a recent Needs Assessment survey by the American Academy of Family Physicians (AAFP) in 2019 indicated that skin cancer management is one of the gaps in knowledge and practice within this field.⁴ As such, it is imperative to delineate and educate primary care physicians on the latest consensus on diagnosis and management of CMM, as they serve as the first line of defense against disease development.⁴ The purpose of this article is to provide a concise educational synopsis for primary care physicians.

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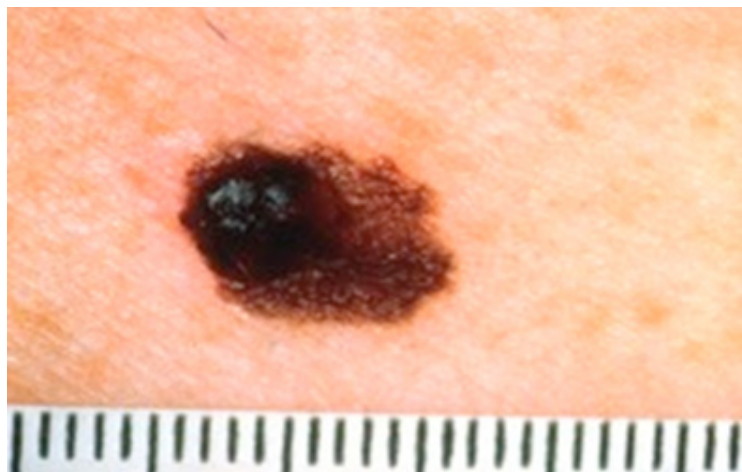


Figure 1. Ugly Duckling Sign, asymmetrical melanoma with uneven color and irregular borders. Source: Skin Cancer Foundation. Retrieved from NIH National Cancer Institute <https://visualsonline.cancer.gov/details.cfm?imageid=2362>.

Incidence and Mortality

There are multiple factors that affect the incidence of melanoma in the general population. Incidence rates are increased in Caucasian males, especially those 50 years of age and older. In general, the risk of melanoma increases with age, fair complexion and exposure to natural or artificial sunlight over prolonged periods of time.⁵ Alluding to the multifactorial nature of the disease, other risk factors include having a family history of melanoma, a dysplastic nevus, multiple (≥ 100) nevi and/or having prior sunburns or diagnosed skin cancers.⁴ Overall, 5-year survival rates are 91.8% after diagnosis, with a 5-year survival rate of 98% in individuals who have localized disease and are diagnosed earlier. Regional and distant metastatic disease decreases the overall survival rates to 68% and 16% respectively.¹

Diagnosis in the Primary Care Setting

There remains a lack of consensus among primary care physicians on the benefits of whole body skin examination. USPSTF states there is insufficient evidence to assess the balance of benefits versus harm of visual skin examination by a clinician to screen for skin cancer in adults.³ In addition, the USPSTF decided not to continue including a segment about patient skin self-examinations in their updated recommendation statements. However, the USPSTF does recommend that children, adolescents and young adults, ages 10 to 24 years with fair skin be counseled about minimizing exposure

to UV radiation in order to reduce their risk of developing skin cancer.⁶ The American Academy of Dermatology (AAD) recommends that individuals with an exponentially increased risk for melanoma should be checked regularly by a dermatologist.⁶ With these disparate recommendations, it falls to the individual physician to decide who and when to screen by visual inspection.

Visual inspection remains the first tool in examining patients for possible melanoma. The clinical visual screening examination assesses skin lesions using the ABCDE rule.⁷ This clinical tool highlights factors that allow for early identification, which is important for eradication. It includes asymmetry, border, color, diameter and evolution.⁵ Symmetry suggests the shape of one half of a nevus matches the other. Borders should be regular without ragged, notched or blurred edges. Color should be even and can be any shade of red, brown or black. A diameter greater than 6 millimeters is concerning. If the nevus changes over weeks or months, this change refers to evolution of a nevus. Some studies show this change to be the most specific finding that may indicate melanoma.⁷

The ugly duckling sign (**Figure 1**) is another easy and simple method for visual identification of a worrisome nevus. The rule originated since it was observed that nevi in the same person tend to resemble one another, and in a group of nevi, melanoma often strays from the normal pattern.⁸ (**Figure 2**) The ugly duckling sign is part of a process called differential recognition.



Figure 2. Normal mole pattern, round with a distinct border. Source: Skin Cancer Foundation. Retrieved from NIH National Cancer Institute <https://visualsonline.cancer.gov/details.cfm?image-id=2359>.

Studies show that differential recognition of the ugly duckling sign was more discriminatory between CMM than the ABCDE criteria, thus highlighting the importance of looking for an outlier in a group of similar nevi.⁸

Melanoma can have highly specific features that are visualized using a dermatoscope, which ultimately leads to a more accurate diagnosis. A dermatoscope is a skin surface microscope that shines polarized light on the skin and magnifies skin lesions.⁴ It allows the observer to visualize pigmentation and structures on the skin surface that are invisible to the unaided eye without obstruction by skin surface reflections. Interpretation of the structures follows a 2-step algorithm. First, determine the melanocytic vs. the non-melanocytic cells. Then determine the malignant vs. the benign lesions.⁵ This algorithm serves as a guide as to whether to perform a biopsy on the patient, refer them to a specialist or provide them reassurance. Training in this procedure is important for success, as lack of familiarity may result in poorer performance compared with naked eye examination. There are many online tutorials and continuing medical education courses for this training, including an American Academy of Family Physicians guide that provides images as references for visual structures.⁴ Benefits of dermoscopy, when used correctly, can improve diagnostic accuracy from 10 to 27%.⁴ It increases the sensitivity and specificity for the diagnosis of melanoma, is relatively intuitive to use and aids in direct tissue sampling of large lesions and those in surgically sensitive areas.

All clinical evaluations of suspicious lesions should be biopsied. The preferred method is a narrow excisional/complete elliptical biopsy with negative margins of (1–3 mm). Full depth excision is important to prevent transection at the base.⁷ This type of excision can be excluded if the lesion is on the face, in an anatomically sensitive area or is a large lesion. These areas of exception can be sampled with punch, deep shave or partial biopsies. For the importance of time and efficiency, the most common type of biopsy done in dermatology and primary care settings are saucerizations. This type of biopsy uses a scoop technique that removes the entire lesion and allows complete sampling of deep margins. The effectiveness of this method depends on the comfort and skill of the physician as well as the clinical situation.⁷ Biopsy technique must include sample depth below the plane of the anticipated lesion and as such, superficial shave biopsies are not indicated. If a melanoma is transected, the staging tool aspect will be lost. A punch biopsy can be performed on smaller, pigmented lesions to remove the entire lesion. For larger lesions or those in challenging anatomic locations, partial or sampling with a punch, deep shave or elliptical biopsy can be done.⁷ The most important aspect in sampling is to obtain an adequate specimen to allow for definitive diagnosis. In addition, it is imperative to obtain pictures of lesions before and after a biopsy is completed.

When sending the specimen out for pathology, it is important to document pertinent information for the pathologist. This information

includes the patient ID, sex and the anatomical location of the biopsy—including laterality, the dimension of the lesion and the surgical margins. It is also helpful to include clinical impression, differential diagnosis and lesion size.⁷ If macroscopic satellites are observed, this information should be documented as it may play a role in staging. The method of removal and the use of hemostatic agents during a biopsy should be documented. This information serves as a guide for what margins may be needed if melanoma is confirmed.⁷

Disease Staging

Proper staging is based on a combination of histological and clinical features. Staging is based on the tumor, nodes and metastasis (TNM) classification, which is primary tumor classification, regional lymph nodes and distant metastasis.⁷ When reviewing the pathology report, histological features of a primary tumor that are strong predictors of outcome are Breslow thickness, ulceration and dermal mitotic rate. Breslow thickness refers to the maximum tumor thickness from the top of the granular layer to the deepest layer of malignant cells. Of these histological features, ulceration is a negative indicator wherein the tumor induces full thickness loss of epidermis and results in dermal changes.⁷ The biopsy report should also include the status of microsatellites as well as peripheral and deep margins. This will indicate whether the entire lesion was available and subsequently provides guidance for further management.⁷ The patient may have biopsies to determine primary skin lesions or to confirm possible metastatic disease that does not have definitive morphological indicators on routine stains, thus requiring additional immunohistochemistry analysis in order to confirm the presence of melanoma.

When completing the initial evaluation of a patient with newly diagnosed melanoma, it is important to take time and consideration for a thorough history and physical exam. The examiner should include a detailed review of symptoms by documenting any unanticipated weight loss, new onset headaches or constitutional symptoms.⁷ A total skin exam should be performed. It is also important to evaluate the primary biopsy site for satellite metastasis and to evaluate local and distant lymph nodes. Abnormal laboratory results should also be

documented. Lactate dehydrogenase (LDH) levels were added to the staging system for stage 4 (distant) disease, as high LDH is associated with a worse survival rate and may predict the response to therapy in stage 4 patients, but rarely is a sole indicator of metastatic disease.⁷

The *Journal of the American Academy of Dermatology* has a grade A recommendation, which states that at baseline, radiological imaging and lab studies are not recommended for asymptomatic patients with a newly diagnosed stage 0–2 primary melanoma.¹⁰ They should only be obtained to evaluate specific signs or symptoms of metastasis. It is also reported that a lymph node ultrasound is proven to be better than palpation alone at the time of disease diagnosis and follow-up. Furthermore, routine imaging in patients with an asymptomatic melanoma at any stage is not recommended after 3–5 years of disease-free follow-up. This recommendation is supported by evidence that most metastasis occurs in the first 1–3 years after treatment.¹⁰

Treatment

Surgical

The primary treatment of a cutaneous malignant melanoma is surgery with a goal of local control and cure in patients with occult regional or distant metastasis. After the initial biopsy, a wider and deeper excision is performed to ensure complete removal of the lesion.⁷ This procedure serves to confirm histologically clear margins and reduce the risk of local recurrence. Surgical margins differ based on melanoma staging. A stage T1 melanoma should have a wide excision allowing a surgical margin of 1 cm. The recommendations for a T2 melanoma, however, varies from 1–2 cm based on tumor location as well as functional or cosmetic factors. In areas such as the face, ears, scalp and fingers—where functional and cosmetic factors must be taken into consideration—a tissue sparing excision, such as Mohs micrographic surgery, should be considered.⁷

A sentinel lymph node biopsy (SLNB) provides the most reliable and accurate means of staging for appropriate patients with primary melanoma.⁷ When indicated, it should be performed before or concomitantly with a wide excision of the primary tumor to minimize disruption of

lymphatic channels and optimize accuracy of mapping. Discussion of SLNB starts for stage T1 melanoma depending on other adverse features, and SLNB should be offered for patients with stage T2.⁷

Non-surgical

In older individuals who may be poor surgical candidates, topical imiquimod 5% cream has been studied as a potential therapy. However, in the primary treatment setting, there is a risk of undertreating with imiquimod alone. When combined with topical tazarotene 0.1%, a complete response was observed histologically in a 12-week treatment period in 78% of patients, whereas only 64% of patients achieved complete response when treated with imiquimod alone for the same length of time.⁷ In addition to combination therapy, an important factor in the eradication of the cancer is the duration of treatment until a clinical and pathologic response is achieved.⁷

Radiation therapy for non-surgical candidates may be used as second line, though the practice is uncommon in the United States.⁹ Adequacy of dermal penetration is a concern with low voltage radiation. Investigators suggest that a penetration depth of 5 mm is needed in order to receive radiation treatment. However, that depth may result in permanent pigment changes, dermal fibrosis and overlying hair loss.⁹ Adjuvant radiation therapy is associated with improved local control for desmoplastic melanoma, though there is no observed effect on metastasis-free survival. A consult with a radiation oncologist is encouraged to discuss risks and benefits of radiation therapy.⁵

Special Consideration

Pregnancy and cutaneous malignant melanoma

In some studies, CMM is the most commonly reported malignancy during pregnancy. CMM rates are higher in men than women, but when it does present in women, CMM is usually more prevalent during reproductive years.¹⁰ Evidence is lacking on whether nevi darken or enlarge during pregnancy, except for those on the breast and abdomen, which may appear larger due to stretching. In pregnant women, a tailored multidisciplinary approach is required, involving the obstetrician, dermatologist, mel-

noma specialist and medical oncologist.¹⁰

Diagnosis of melanoma during pregnancy does not change the prognosis for women. In women with a history of melanoma, a prolonged waiting period before the subsequent pregnancy is not recommended.¹⁰ Factors that detect disease recurrence include melanoma thickness, stage, advanced age and fertility level. The approach to a melanocytic nevus should be the same as in a non-pregnant patient. In treatment, exogenous hormones may be used in women diagnosed with this disease.¹⁰

Surveillance and Follow-Up Care

Annual skin examinations are recommended for life and regular clinical follow-up is the most important means of detecting recurrence. Serum S-100B protein is a potential prognostic biomarker and is a useful tool to identify disease progression.¹⁰ Patients should be educated on regular skin self-exams for early detection of recurrent or new disease. A grade C recommendation from the AAD states that for high risk melanoma and +SLNB requires collaboration with medical oncology for multidisciplinary care.¹⁰

A dermatological assessment should be done for patients with melanoma who are undergoing BRAF1-kinase specific treatment or other targeted therapies with immune checkpoint inhibitors.¹⁰ The spectrum of melanoma tumor subtypes is rapidly expanding, including mutations in CDKN2A, CDK4, TERT, BRCA1 and BAP1 cell lines.¹⁰ It is imperative to look for familial lineage with early onset of disease less than or equal to 40 years of age, multiple cancers or cancer types, multigenerational involvement, aggregation or rare cancers. Genetic counseling should be recommended in patients with melanoma that have a family history of invasive disease, pancreatic cancer (3 or more on one side of the family) and multiple primary invasive melanomas (3 or more), early age of tumor onset less than or equal to 45 years of age in conjunction with a family member with mesothelioma, meningioma or uveal melanoma. The role of genomic profiling remains an active area of exploration.¹⁰

The 2019 review from the AAD on CMM has additional guidance, which has been included

since 2011, such as further randomized control trials (RCTs), case reports and, more importantly, novel therapeutic agents approved by the Food and Drug Administration (FDA) for advanced or surgically inoperable melanoma.¹⁰ These novel therapeutic agents include immune checkpoint inhibitors, such as ipilimumab and pembrolizumab. Hence, the new update on CMM recognizes the importance of determining side effects of these medications, which is critical for dermatologists and other specialties to recognize.¹⁰ However, some of the key aspects of CMM recognition, diagnosis and management are still under continuous review and investigation, such as noninvasive biopsy techniques using a high-frequency ultrasound and optical coherence tomography among others. The 2019 update also highlights the need for further research in CMM, including treatment (surgical vs. nonsurgical), appropriate margin control definitions, prognostic biomarkers and the utilization of genomic medicine in genetic counseling of high risk patients. Thus, the overall take home message is the multifactorial nature of this disease and the requisition for a personalized approach to management for each patient.¹⁰

Conflicts of Interest

The authors declare they have no conflicts of interest.

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