REVIEW ARTICLE

Melanoma for Primary Care

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The incidence of newly diagnosed malignant melanoma is rapidly increasing. In 2016, it is estimated that there will be 76,380 new cases with 10,130 deaths in the United States. Incidence has increased from 1 in 1500 persons born in the early 1900s to 1 in 50 of Caucasian persons born in 2014, 1 in 200 Hispanics, and 1 in 1000 for African-Americans. Unlike basal and squamous cell carcinoma, malignant melanoma correlates more with intense intermittent UV radiation exposure. Malignant melanoma is the aggressive therapy-resistant skin cancer of melanocytes where thickness of the tumor is the most important prognostic factor. The ABCDs (Asymmetry, Border Irregularity, Color Variation, Diameter >6 mm) of melanoma serve as the foundation for patient education, but the use of EFGs (Evolving, Elevation, Firmness, Growth) provide a more comprehensive screening method for malignant melanomas. The authors recommend self-skin examinations and that family physicians maintain a high clinical suspicion in high risk patients since early diagnosis with appropriate treatment significantly impacts survival.

INTRODUCTION

The incidence of malignant melanoma is rapidly increasing in the United States. It is estimated that there will be 76,380 reported new cases with 10,130 deaths in 2016 in the U.S.[1] Incidence has increased from 1 in 1500 persons born in the early 1900s to 1 in 50 of Caucasian persons born in 2014, 1 in 200 Hispanics, and 1 in 1000 for African-Americans. Melanoma is the most common cancer among women ages 25-29.[2] There is a strong correlation between sun exposure and development of malignant melanoma. Unlike basal and squamous cell carcinoma, malignant melanoma correlates better with intense intermittent UV radiation exposure.[3] Survival is directly related to early detection with appropriate treatment.[4] A patient's prognosis remains extremely dependent on the stage present when initially diagnosed.[5]

Melanoma is the 5th leading cancer in men and the 7th in women in the United States.[6] Ultraviolet (UV) light exposure is a major risk factor for development of melanoma. Intense sun or tanning bed exposure, as well as exposure to areas not normally exposed to UV radiation, are risk factors. A history of multiple sunburns in childhood also increases risk for development of melanoma. Those with a family history of melanoma or FAMMM Syndrome (Familial Atypical Multiple Mole and Melanoma Syndrome) are also at increased risk.[7] Six risk factors to watch for in the development of malignant melanoma include the following:

1. Family history of malignant melanoma
2. Blond or red haired individuals
3. Freckling on the skin of the upper back
4. Three or more sunburns with blistering before age 20 years
5. History of an outdoor summer job as a teenager for three or more summers
6. Actinic keratosis present

Anyone with one to two of these six factors has a 3.5 times increased risk as compared to the general population. Anyone with three or more of these factors has a risk 20 times that of the general population. Additional risk factors to consider include location of the patient (those that live closer to the Earth's equator are at an increased risk), and people who have a decreased ability to tan. Also note that a history of a prior melanoma automatically increases the risk for development of an additional melanoma at a future time (Table 1).[8,9]

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Classic cutaneous melanoma exists as four main subtypes:

1. Superficial spreading melanoma,
2. Lentigo maligna melanoma
3. Acral lentiginous melanoma
4. Nodular melanoma

There is also a rare variant amelanotic melanoma. Superficial spreading melanoma is the most common type, most often seen in young people. Lentigo maligna is the most common type in the elderly. When it gets invasive it is referred to as lentigo maligna melanoma. Acral lentiginous melanoma is most common in African-Americans and Asians. It is found under the nails or on the soles of the feet or palms of the hands. Melanoma of the nail bed is a variant of acral lentiginous melanoma, which includes subungual, ungual and periungual melanoma and can affect any finger or toenail. Nodular melanoma is the most aggressive of the melanomas. It has a rapid growth and most commonly occurs on the trunk and limbs in the 5th or 6th decade, more commonly in males. Nodular melanomas are ulcerated and do not have radial growth; they only have vertical growth.[10] It can present as a darkly pigmented papule which may be polypoid or pedunculated.[11]

Rapidly growing nodular melanomas do not follow the ABCD rule. The EFG rule helps identify these types of melanomas that can go undetected. E refers to elevation and evolving lesion. A mole or lesion that looks different from previous appearance or is changing in size, shape or color.[2] Any lesion that is elevated raises a suspicion and should immediately be referred or biopsied. F refers to firmness- a lesion that feels thick or hard on palpation. G is for any growth, which includes any change in size, shape, color, elevation or new symptom such as bleeding, itching or crusting.[12] These moles do not need to be dark or have any color. They are raised, symmetrical, firm and evolving. It can affect anyone but is more common in men over 50. Rapidly growing nodular melanomas are dangerous because of the very rapid vertical growth.

TABLE 1:

Risk Factors for Melanoma[8,9]

Ultraviolet light exposure	Fair skin
History of atypical moles	Natural light colored hair
History of FAMMM Syndrome	Freckled skin
History of congenital melanocytic nevi	Prior melanoma or other skin cancers
Immunosuppressed status	Male gender
Increasing age	Xeroderma pigmentosum
3 or more sun burns before age 20	Actinic keratosis
Outdoor summer jobs for 3 or more summers	Living closer to the Earth's equator

ILLUSTRATIVE CASE REPORT

A 69-year-old Caucasian male of Irish descent presented for a routine physical examination with no complaints. He had not seen a doctor in 10 years. He had a large facial lesion that was non-painful but pruritic and associated with intermittent bleeding while shaving. Patient stated the lesion had increased in size. He had no history of prior sun exposure or family history of skin cancer. Patient had a five pack years smoking history, denied any alcohol or drug use. Patient was not taking medications. On physical examination the lesion was a 2.5 cm dark pigmented plaque with coalescing center. There was a 3-4 mm thick papule with 2-3 mm satellite lesion (Image 1). A 4-5 mm deep full thickness wedge biopsy was done. Biopsy and pathology showed a 2.4 mm nodular malignant melanoma with ulceration and no metastasis. There was extension into the reticular dermis. The tumor was staged T3b. Nuclear scan and sentinel lymph node biopsy were negative. There was considerable activity and blue staining in the superficial parotid gland. The patient had a wide excision with superficial parotidectomy and local flap closure (Image 2). The patient is being followed closely by oncology. Six months after excision he was found to have a hyperechoic focus in the left occipital area on PET/CT scan. A follow up PET/CT scan six months later showed no abnormalities. It has now been 18 months and the patient is doing well with no current oncological treatment.

IMAGE 1:

Lesion before biopsy

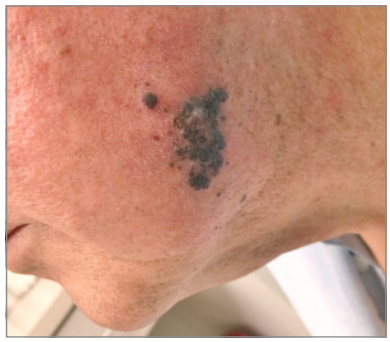
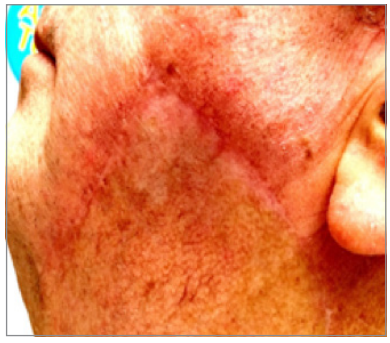


IMAGE 2:

Lesion after flap closure



PROGNOSIS & TREATMENT

Melanomas are aggressive skin cancers that may spread to involve nearly any component of the body. Early diagnosis and appropriate treatment plays a significant role in minimizing morbidity/mortality.[11] Melanoma thickness and extent of metastatic disease are key determinants for the prognosis of a patient with melanoma. Thickness, location of the primary tumor, and sex of the patient are all independent prognostic factors for melanoma. Regarding melanoma of the head/neck areas, a study conducted by the Swedish Melanoma Study Group showed corrected 10-year survival rates to be higher for women at 83%, vs men at 68%, however these were cases of stage I disease. Ten-year survival rates drastically plummeted for patients with higher stage disease with regional and lymph node metastasis.[12]

Thickness of the tumor is the most important factor regarding the prognosis. Ten year survival rate is 92% with thickness at or less than 1 mm, however 10-year survival decreases to 50% for tumors thicker than 4mm. Melanomas have vertical and radial phases of growth. Absence of vertical progression, as in a lack of excessive thickness, indicates a better prognosis with a near zero risk for metastatic disease.[13] Early malignant melanoma presents very similarly regardless of location on the body. Melanomas present as asymmetric, borders are often irregular, typically have obvious color variety present and diameters typically greater than 6 mm (usually larger than a pencil eraser). Benign pigmented lesions are typically round, flat, symmetric, nearly uniform in color, and less than 6 mm in diameter. As a melanoma evolves, its cells will begin to invade from the epidermis into the dermis.

Five-year and 10-year survival rates for melanoma are dependent upon the stage of disease when diagnosed (Table 2). As tumor thickness increases, survival rate declines.[14] Those at high risk for melanoma based on family history, past medical history, age 50 years or older, sunburn history, as well as presence of atypical nevi or moles, should perform self-examinations of their skin as well as seek dermatologist examination regularly. If the patient has a finding on self-examination, or notes a mole change, he or she should inform their physician as soon as possible.

The TNM (tumor, node, metastasis) staging system relies on examination of the primary tumor, lymph nodes in the region associated with the primary tumor, as well as distant sites of metastasis. Examination of the primary tumor consists of assessment of thickness, mitotic rate, and presence/absence of ulceration at the site.[15] Lymph node assessment is staged based on the extent of regional lymph node involvement determined from immunohistochemical staining. Presence and extent of distant metastatic sites are also incorporated in the TNM staging system. Key findings are summarized in the Table 3.

Imaging and laboratory studies may be necessary to accurately stage prior to initiation of therapy, as well as for follow-up once initial therapy has been instituted. Extensive imaging is not recommended for localized stage I or II primary melanoma due to low yield and high false positive rates.[16,17] Lymphatic mapping with sentinel lymph node biopsy is recommended for intermediate or high risk lymph node metastatic, however not for low risk. Stage III disease warrants obtaining a CBC, LDH, as well as additional imaging prior to lymphadenectomy.[18] To detect and monitor for any recurrences, a physical exam and additional studies should be conducted every 3-12 months. Regarding stage IV disease, MRI of the brain as well as CT Chest/Abdomen/Pelvis are recommended.[19] A PET/CT may also prove useful if surgical resection is being considered when minimal metastasis consisting of a single site is suspected.[18]

A dermatoscope can aid in distinguishing benign from malignant lesions. A dermatoscope is a handheld device with 10x magnification that uses polarized and nonpolarized light to visualize detailed skin structures. There is a two-step process that can aid in the interpretation of dermoscopic structures (Figure 1).[20] The first step is to differentiate melanocytic lesions from nonmelanocytic lesions, which is done by identifying certain structural features in nonmelanocytic lesions. If these structures are not identified, then the lesion should be biopsied. Once it is determined that a lesion is melanocytic the next step is to determine if it is a benign nevus or malignant melanoma.[20] This can be done by a point system or by pattern analysis. There are certain features typical of a nevus and certain melanoma-specific structures that can help determine if a lesion should be biopsied.

Most biopsies are within the scope of family medicine and can be done in the office. The first step is to determine the type of biopsy. Techniques include shave biopsy, punch biopsy and elliptical biopsy (Table 4). There are two types of shave biopsies: tangential and saucerization. Tangential shave biopsy is not appropriate if a lesion might be malignant since this does not include sufficient depth. Saucerization, also known as scallop shave or deep shave biopsy, is used when depth is required and the lesion is suspicious for melanoma. A deep shave biopsy is recommended by the National Comprehensive Cancer Network for this use. Punch biopsy can also be used for suspicious melanocytic lesions. To obtain adequate tissue for pathology a minimum depth of 3-4 mm should be used. To perform a punch biopsy the clinician should apply the cutting surface of the device perpendicular to the skin and press firmly. The punch biopsy unit should be rotated clockwise and counterclockwise until there is a release that indicates penetration into the dermis. The lesion is then removed. The punch site can be closed with sutures or left to heal by secondary intention.[21]

Elliptical excision biopsy can be used for larger lesions. When possible the length of the ellipse is 2 to 3 times the width and the angles of the ellipse should be around 30 degrees. The point of the excision should start at one apex and move along the arc of the other apex. Traction on the surrounding tissue allows for a clean and precise cut. Then the lesion should be lifted with a forceps and removed from the surrounding subcutaneous fat with a scalpel.[21] The biopsy specimen should include the underlying subcutaneous fat for melanomas. The wound is then closed with sutures. Undermining the edges of the wound should be avoided in melanocytic lesions since undermining may disrupt lymphatic flow that can impair the ability to perform sentinel node studies.

TABLE 2:

SURVIVAL RATES FOR MELANOMA[14]
Based on 2008 AJCC Melanoma Staging Database

Stage	5-Year Survival Rate	10-Year Survival Rate
IA	97%	95%
IB	92%	86%
IIA	81%	67%
IIB	70%	57%
IIC	53%	40%
IIIA	78%	68%
IIIB	59%	43%
IIIC	40%	24%
IV	15-20%	10-15%

TABLE 4:

Biopsy Techniques[21]

Type of Biopsy	When to Use	Tools Needed
Tangential Shave	Depth not required	Scalpel blade or razor blade
Saucerization Shave	Depth required Removal of entire lesion Suspicious lesions	RazorBlade
Punch	Suspicious lesions Full thickness required Small skin surface	Disposable or nondisposable units with at least 3-4 mm diameter
Elliptical Excision	Larger lesions Complete excision	Scalpel and forceps

FIGURE 1:

TWO-STEP DERMOSCOPY ALGORITHM[20]
With Permission from Dr. Marghoob.

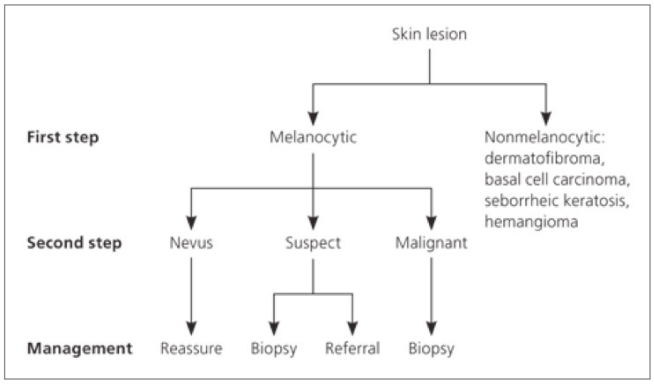


TABLE 3:

2010 AJCC TNM Staging for Cutaneous Melanoma[15]

PRIMARY TUMOR (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Melanoma in situ
T1	Less than or equal to 1.0 mm A: Without ulceration & mitoses <1/mm^2 B: With ulceration and mitoses ≥1/mm^2
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
REGIONAL LYMPH NODES (N)	
NX	Patients in whom the regional nodes cannot be assessed
N0	No regional metastases detected
N1	One lymph node A: Micrometastases B: Macrometastases
N2	Two or three lymph node A: Micrometastases B: Macrometastases C: In-transit met(s) / satellite(s) without metastatic lymph nodes
N3	Four or more metastatic lymph nodes, or matted lymph nodes, or in-transit met(s)/ satellite(s) with metastatic lymph node(s)
DISTANT METASTASIS (M)	
M0	No detectable evidence of distant metastases
M1a	Metastases to skin, subcutaneous, or distant lymph node, normal serum LDH
M1b	Lung metastases, normal LDH
M1b	Metastasis to other visceral metastases with a normal LDH or any distant metastases and an elevated LDH

PATIENT EDUCATION

Education about melanoma encourages behavioral change in terms of sun exposure and also promotes early detection.[22] Screening and prevention decreases the risk of melanoma. Primary prevention refers to decreasing known risk factors. Secondary prevention refers to early diagnosis and treatment.[10] The main goal of follow-up for patients with a history of melanoma is early detection of recurrent disease and additional primary melanoma. There is no specific follow-up interval. Expert opinion recommends follow up at least annually, with a 3-12 month range based on risk for recurrence. Factors include disease stage, multiple primary melanomas, atypical nevi, family history, and patient's awareness. Patients should be educated about monthly self-examinations. The most important part of follow-up for patients with melanoma is a thorough history and total body physical exam with focus on lymph nodes.

The U.S. Preventative Task Force (USPSTF) concludes that skin cancer screening in asymptomatic adults is a grade I recommendation meaning there is insufficient evidence to assess the benefits and harms of visual skin examination by a clinician. USPSTF recommends counseling children, adolescents, and young adults 10 to 24 years who have fair skin about minimizing their exposure to ultraviolet radiation and gives this a grade B recommendation. For adults older than 24, this is a grade I recommendation. The current evidence is insufficient.[23]

The authors recommend self-skin examinations and maintaining high clinical suspicion in high-risk patients. A thorough self-skin examination requires a well-lit room, in addition to full length, hand held mirrors and a hair dryer (Figure 2).[24] It is necessary to examine areas of skin that are hard to see during self-examination. These areas include portions of the back, scalp, buttocks, and perineal area. A spouse, relative or friend can help with the examination of these areas. The self-skin exam should be carried out step-by-step, and assistance obtained to ensure full viewing of areas difficult to view otherwise.[25]

SUMMARY

The incidence of malignant melanoma is increasing at an alarming rate. Melanoma affects nearly every body part from the eyes to the nail beds. Early diagnosis and treatment requires education by primary care providers to patients. Increased patient education and provider awareness may be able to decrease incidence and mortality. This means maintaining an elevated clinical suspicion in asymptomatic patients. The ABCDs along with the EFGs of melanoma can be used as a guideline and screening for melanomas. A dermatoscope can help in the diagnosing of suspicious melanocytic lesions. Patients with suspicious lesions should have a biopsy or be referred to a dermatologist for additional evaluation. Patients with a personal and/or family history of melanoma require particularly close follow up. By the time a melanoma is palpable it is often too late, therefore early detection is key. Fortunately most melanomas grow slowly and can be detected early to prevent morbidity and mortality.

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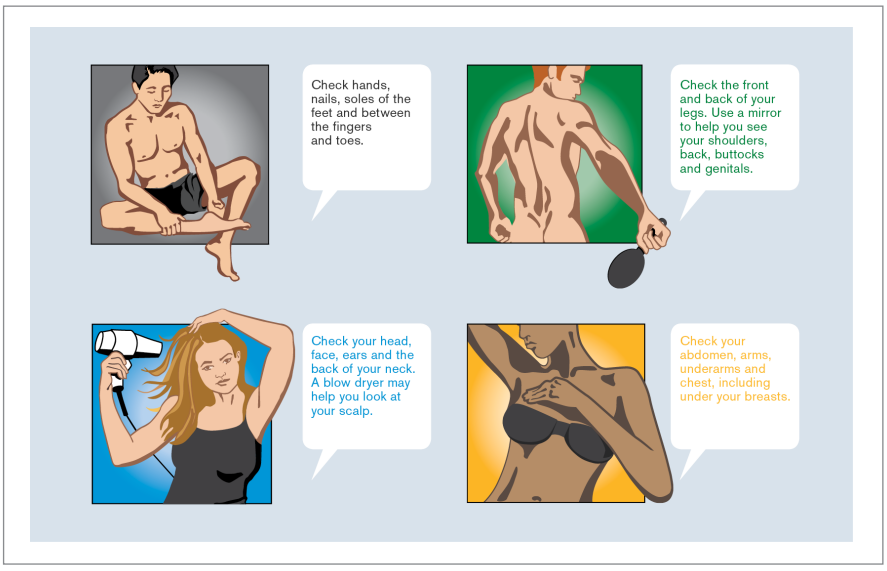
FIGURE 2:

How to Do a Self-Skin Examination[24]
With permission from Melanoma Research Foundation



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