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Office Management of Melanoma Patients

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As the incidence of melanoma continues to increase, so does the role of the dermatologist as both medical and surgical oncologist for these patients. The dermatologist holds a key role in all phases of care, including prevention, diagnosis, treatment, and follow-up. The dermatologist is best trained to complete a full and thorough skin examination and is best able to recognize a melanoma in its early stages of growth. Dermatologists have a unique opportunity to prevent melanoma through appropriate patient education concerning sun protection, self skin examinations, and the ABCDEs of melanoma recognition (ie, asymmetry, border irregularity, color variations, dimension and evolution). The dermatologist is well trained to obtain an appropriate full-thickness skin biopsy and is knowledgeable to interpret the pathologist report and understand the significance of the various histologic prognostic indexes. Most patients present with localized disease and with thinner Breslow depth and thus can be skillfully treated in an outpatient setting under local anesthesia by a dermatologist.

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Of all the diagnoses we give our dermatologic patients, none strikes more fear and anxiety than "melanoma." Most patients know that melanoma is the "bad" skin cancer and most seem to know someone (friend or family) who had a melanoma and did poorly, possibly even died. Thus, the initial office visit for a patient with a newly diagnosed melanoma is often lengthy. There are often many misunderstandings and misconceptions about their diagnosis ("Do I need to see a medical oncologist?" "Don't I need a lot of blood work and X rays?" "Don't all patients with melanoma die?"), the initial office visit is very important for the proper discussion of prognosis, treatment plans, and long-term follow-up for the patient. This article will put forth my personal approach for office management of the melanoma patient based on guidelines from the American Joint Committee on Cancer and the National Comprehensive Cancer Network as well as other current scientific literature.

Identifying the Patient at Risk

Early diagnosis is our best chance of curing melanoma. Because prognosis is defined by how deep the melanoma is at the time of initial diagnosis, the sooner the diagnosis is made and the thinner the melanoma, the better the patient will do. To diagnose melanoma early, it is helpful to identify patients at risk so they can be monitored carefully on a regular basis, and educated on self skin examinations, the "ABCDE" of melanoma diagnosis (ie, asymmetry, border irregularity, color variations, dimension, and evolution), appropriate sun protection, and the important fact that they are at increased risk for melanoma. In the same manner that an internist defines cardiac risk factors by multiple criteria (eg, family history, cholesterol, weight, cigarettes, exercise, blood pressure), so too does the dermatologist assess the risk for melanoma in any given patient based on multiple factors. First, skin phenotype characteristics are important. Patients with fair skin (Fitzpatrick's type I and II), freckles, a tendency to burn and not tan, red or blonde hair, and blue or green eyes are at increased risk for melanoma. Likewise, patients with numerous nevi (>100), or atypical nevi of any number, are more likely to develop melanoma. Having 10 or more atypical nevi is associated with a 12× elevation of risk.[1] Keep in mind that most melanomas arise de nova on the skin, so nevi often serve more as a genetic marker for risk than an actual precursor lesion. This said, studies still show as many as 25% of melanomas histologically associated with nevi.[2] Large congenital nevi pose a generally accepted risk of melanoma of approximately 5%-10%, with most of these melanomas developing before puberty.

Besides the genetics of skin type and nevi, family history of melanoma is an independent risk factor, although only about 10%-15% of patients with melanoma have a family history.[3] The association of family history of melanoma with atypical

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nevi is commonly called the "dysplastic nevus syndrome" and these patients generally have earlier onset melanomas and a greater risk of multiple melanomas.[4] A personal history of melanoma increases the risk for another primary melanoma, with approximately 5%-10% of patients developing multiple melanomas. Fortunately, subsequent melanomas are usually thinner than the initial, likely due to better surveillance and follow-up.

Ultraviolet exposure is an established risk factor for melanoma.[5-7] When evaluating the dermatology patient, it is important for the dermatologist to attain a thorough history of blistering sunburns, recreational sun use, occupational sun exposure, and tanning bed usage; all factors for potential melanoma development. One blistering childhood sunburn doubles the risk for melanoma. Melanoma risk increases with the duration of living in sunny areas, as well as locations close to the equator. One only needs to examine fair skinned immigrants to Australia which boasts the highest incidence of melanoma in the world. Tanning bed usage has now been correlated with melanoma risk and the World Health Organization has labeled artificial tanning as a true carcinogen.[8] Young age at first exposure as well as frequency and duration of tanning bed usage elevates the overall risk for melanoma.

Finding the Melanoma: The Physical Examination

Now that we have identified the patient at risk, the next step is a thorough examination. Keep in mind that intermittently exposed areas of the skin have the greatest risk of developing melanoma; the upper back in men and the lower legs in women.[9,10] In elderly patients, the face is more common, especially for the lentigo maligna subtype. However, all patients deserve a thorough and complete skin examination and not just the sun exposed areas. There is no excuse not to do a full skin examination which includes both sun-exposed and nonsun-exposed areas. Melanomas in hidden anatomic sites are likely to be thicker with a poorer prognosis likely because these areas go undetected for longer periods.[11] Patients should be encouraged to undress completely. The skin examination includes viewing the scalp, conjunctiva, oral mucosa, genitalia, perianal area, nails, palms, soles, and interdigital web spaces.

It should be emphasized that a thorough history is important to ask about any changing nevi. Change in color or an increase in size of a new mole is the most common early change noted by patients. These changes are best correlated with early evolving melanoma.[12] Bleeding, itching, and tenderness are later symptoms that are usually indicative of a thicker melanoma. A global evaluation of the skin will identify the degree of sun damage, the number of nevi, the general architecture and distribution of nevi and the possibility of atypical or dysplastic nevi. A pigmented lesion that is "different" from the others (ugly duckling sign), is worrisome for melanoma because of the premise that in a given patient nevi should share a common appearance. At times I have been impressed with how dark and thus suspicious a nevus looks until a global examination reveals that all the nevi are indeed this darkly pigmented. Dermoscopy has become a valuable additional tool for the dermatologist to use because it improves the accuracy of melanoma diagnosis. There is a learning curve involved with becoming skilled at dermoscopy along with evolving criteria and diagnostic algorithms. The future of computerized digital dermoscopic images and automated analysis programs are an exciting next step for accurate and early melanoma diagnosis and are discussed in other articles in this journal.

The Biopsy

If a lesion suspicious for melanoma is identified, an appropriate biopsy is the next step. The initial biopsy is critical for both accurate diagnosis and staging purposes. Nothing is more frustrating than trying to discuss treatment options with the patient when the biopsy is incomplete, that is, there is an inaccurate Breslow depth because of transection at the base of the lesion. If a melanoma is suspected, the biopsy method of first choice is a complete excisional removal into the adipose tissue with a 2-mm margin of adjacent normal-appearing skin. If the pigmented lesion is relatively flat and the suspicion of melanoma is low, then a deep saucerization biopsy may be sufficient. As a general rule, superficial shave biopsies should be avoided. For a larger lesion, an incisional full-thickness biopsy or multiple representative punch biopsies may be acceptable. Incisional biopsies should be performed at the darker, thicker, and more elevated areas of the lesion. Patients can be reassured that there is no risk of "spreading" the melanoma by performing a biopsy. If greater than one-half of the clinical lesion remains after a subtotal biopsy, subsequent excision results in significant upstaging in as high as 20% of these patients.[13]

Establishing the Histologic Diagnosis

The initial step in evaluating a new patient with melanoma is to clearly establish the accuracy of histologic diagnosis. It is imperative that there is a competence level in the histopathologic interpretation of the specimen. My practice is that of a multidisciplinary, university-based practice and it is our protocol to ensure all histologic diagnoses of melanoma have been made by a dermatopathologist that we know and trust. This is not to discredit a general pathologist; however, confirmation of the diagnosis of melanoma by our dermatopathologist allows us a level of comfort and accuracy before recommending final treatment plans to our patients. Because the prognosis is intimately tied to the specific histologic criteria (depth of invasion, ulceration, mitotic rate), an accurate reading is a key starting point. Even among experts, there can be some disagreements in the diagnosis of early melanomas or melanoma variants (eg, desmoplastic, neurotropic, spitzoid, nevoid) and a second opinion is sometimes welcomed. A typical pathology report should include the following: Breslow depth, mitotic rate, ulceration, histologic subtype

(superficial spreading, nodular, acral, lentigo maligna), regression, angiolymphatic invasion, vertical vs. radial growth phase, satellitosis, coexisting nevus, and margins. Clearly, an accurate and complete pathology report is a necessary first step before counseling the patient on prognosis and treatment.

Prognosis

With an adequate biopsy and an accurate reading from an experienced dermatopathologist, the dermatologist is now able to discuss prognosis and staging with the patient. The American Joint Committee on Cancer recently revised the staging system in 2009.[14] Recommendations were based on a multivariate analysis of 35, 946 patients with stages I, II, and III melanomas and 7972 with stage IV melanoma. There are 5 stages: stage 0 is in situ melanoma, stages I and II are localized disease, stage III is regional disease, and stage IV is distant metastatic spread. In patients with localized melanoma, tumor thickness (Breslow depth), mitotic rate (mitoses/mm^2) and ulceration were the most important prognostic factors. The addition of the mitotic rate as an independent prognostic factor is new since the last staging system in 2002. After tumor thickness, mitotic rate was the second most powerful predictor of survival. The most significant correlation with survival was identified at a threshold of 1 mitosis/mm.[2]

Tumor thickness is defined in even integers (1.0, 2.0, and 4.0 mm.) and remains the single most important prognostic factor for survival in localized melanoma. As tumor thickness increases, there is a significant corresponding decline in 5- and 10-year survival rates. Table 1 outlines 10-year survival rates. Of interest, the Clark level invasion is no longer recommended for staging and its significance is purely historical.

Ulceration remains an independent prognostic factor in the new staging system. Survival rates of patients with an ulcerated melanoma are less than those with equivalent nonulcerated thickness but similar to those in the next highest category; thus, evidence of ulceration "upstages" to the next level. Ulceration appears to be more common in thicker melanomas and is rare in thin melanomas <1 mm.

Sentinel lymph node status has become a standard for staging nodal metastases and represents a powerful prognostic indicator for survival.[15-17] In clinically node-negative stage I or II patients, sentinel lymph node status is the most significant prognostic factor for survival. In patients with a negative sentinel lymph node, 5-year survival is between 88% and 93% versus only 51% and 67% for those patients with a positive sentinel lymph node. In stage III patients with regional metastases, the number of metastatic nodes, as well as the tumor burden (micrometastatic vs macrometastatic disease), determines survival rates. Thus, 5-year survival within subtypes of stage III varies from 40% to 78%.[14]

Patients with stage IV disease generally do poorly with a median survival of only 6- to 8 months. Because the overall prognosis for stage IV is so poor, there are no substage groupings. Of interest is the demonstration that an elevated lactate dehydrogenase (LDH) level predicts a poor outcome vs. those with a normal LDH level.[14] The number of metastatic sites also portends a poor prognosis.

Table 1 Breslow Depth and Survival

Breslow Depth	10-Year Survival, %
<1 mm.	92
1-2 mm.	80
2-4 mm.	63
>4 mm.	50

Table 2 Breslow Depth and Sentinel Lymph Node Positivity

Breslow Depth	Sentinel Lymph Node Positivity, %
<1 mm.	5-10
1-2 mm.	15-20
2-4 mm.	25-35
>4 mm.	40-50

Sentinel Lymph Node Biopsy

Currently, the recommendation for sentinel lymph node biopsy and staging is for otherwise-healthy patients with clinically negative nodes and a Breslow thickness of >1 mm. It is also selectively recommended for patients with a Breslow depth <1 mm but with evidence of ulceration and/or mitoses >1/mm.[2,14,18] This is especially highly considered in those patients if the Breslow depth is >0.75 mm. Table 2 outlines the risk of sentinel lymph node positivity in relation to Breslow depth. These data offer some general percentages when counseling patients. Typically both blue dye and technetium-99 radio-colloid solution are used together allowing detection of the sentinel lymph node in >95% of the patients. Ideally, the sentinel lymph node biopsy should be performed at the same time as the wide local excision. It is possible that the sentinel lymph node may not be as accurately defined after a local flap or after a wide local excision in an area of ambiguous drainage.[18]

When discussing the concept of a sentinel lymph node biopsy with the patient, there are 2 aspects of the discussion: prognosis and overall survival. There is little controversy that the sentinel lymph node provides accurate and important prognostic information. In fact, it is usually required for patient entry into clinical trials involving adjuvant therapy or new surgical techniques. However, there is controversy whether a sentinel lymph node biopsy and subsequent completion lymphadenectomy significantly improves overall survival. Although morbidity of the sentinel lymph node biopsy is low, a completion lymphadenecotmy is a much more significant procedure with a higher complication rate, including post operative edema, seroma, infection, and delayed wound healing. Empirically, it would make good sense to remove all nodes when there is only evidence of microscopic disease, but to date studies have shown only a modest improvement in overall melanoma survival between these groups. Certainly, it has saved many patients from an underlying unnec-

essary elective lymph node dissection and it has saved patients from dealing with painful macroscopic disease. Elective lymph node biopsy has more selectively defined the smaller population of patients that may benefit and also helps direct patients who may benefit from adjuvant therapy or clinical trials.

Work-Up

Once a diagnosis of melanoma is made, the foundation of the work-up is a thorough and complete review of systems and physical examination. To a great extent this will help determine further diagnostic tests. The patient should be asked about unusual "lumps, bumps, or swelling" which would represent cutaneous metastatic lesions or enlarged lymph nodes. Likewise, specific questions pertaining to neurologic, pulmonary, and gastrointestinal symptoms, as well as constitutional symptoms, should be explored to look for potential symptoms of metastatic spread. As previously discussed, a full skin examination should be performed, lymph nodes carefully palpated with special attention to the primary echelon nodes, and palpation of those areas between the primary melanoma site and nodal basins to look for interval nodes. If there is evidence of a clinically palpable lymph node, then the patient should be referred for a lymph node aspirate or open biopsy.

In the past, routine complete blood count, liver function tests, and chest X-rays were ordered for all patients with melanoma. However, it has become clear that these studies provide little helpful staging information unless directed by a positive finding on review of systems or physical examination. The true positive rate in an asymptomatic patient is 0.5% for chest X-ray, 0.07% for a computed tomography scan of the chest, abdomen, and pelvis, and 0% for a brain magnetic resonance imaging.[18-21] However, false-positive rates can be in the range of 15%-18% and lead to additional costly studies, as well as increased patient anxiety. As pointed out, LDH can be helpful prognostically but only for stage IV disease. Positron emission tomography/computed tomography scans are indicated if the sentinel lymph node biopsy is positive primarily to look for distant stage IV disease before subjecting the patient to a completion lymphadenectomy. If the sentinel lymph node biopsy is positive and staging imaging studies are negative, then completion lymphadenectomy is recommended, as well as referral to medical oncology for consideration of adjuvant interferon or enrollment in clinical studies.

Interferon is the only adjuvant therapy approved by the Food and Drug Administration for stage III melanoma, but the overall benefit is small and adverse symptoms significant.[22-24] Nonetheless, patients should be given the chance to discuss this with the medical oncologist. Because sentinel lymph node biopsy provides the most accurate prognostic information, there is usually little indication for additional imaging studies if the sentinel lymph node biopsy is negative and the patient is otherwise asymptomatic. Overall, sentinel lymph node biopsy negative patients have an excellent prognosis and thus routine imaging studies are typically not helpful or warranted.[18]

If a patient does have a positive finding on positron emission tomography/computed tomography scan, then appropriate referral for a confirmation biopsy is recommended. Resection can be considered for solitary or limited stage IV disease and radiation is often recommended for central nervous system metastatic melanoma. The concept of a multidisciplinary melanoma group within a comprehensive cancer center is very helpful for the management of these more complex stage III and stage IV disease patients.

Surgery

Although the incidence of melanoma and the absolute number of patients dying from melanoma continues to increase every year, the percentage of melanoma patients dying has decreased. To a large extent this is the result of more melanomas being diagnosed earlier and thinner with an improved prognosis. A total of 85% of melanoma patients at presentation have localized disease and most of these patients have melanomas that are <1 mm deep.[14] These patients can be easily treated on an outpatient basis with negligible morbidity and a very high success rate.

The primary treatment for melanoma is surgery. Fortunately, during the past several decades, well-controlled studies have shown that narrower excision margins give excellent cure rates and thus the need for any resection margins >2 cm is unwarranted.[25-28] Hopefully, the days of 3- to 5-cm margins are behind us. When feasible, a primary closure should be used, but at times functional or cosmetic considerations require a skin graft or a local flap. Currently, recommended margins for melanoma excisions are outlined in Table 3. For in situ melanomas, 5-10 mm is recommended, except for lentigo maligna subtype, which often requires >5 mm. For stage Ia (<1 mm), a 1-cm margin is adequate. For melanomas 1-2 mm, at least a 1 cm and up to a 2-cm margin is recommended if anatomically feasible. For melanomas >2 mm, a 2-cm margin is recommended.[29] Dissection should be carried to the level of the deep subcutaneous tissue at the level of the fascia, but muscle fascia is usually not removed. Special consideration is given for subungual melanomas and melanoma of the finger or toe. The recommended surgical treatment for melanoma of the digit is a joint disarticulation at the joint proximal to the tumor. Subungual melanomas usually require a partial or full amputation.[29]

As mentioned, the lentigo maligna subtype of melanoma in situ presents a surgical challenge. Lentigo maligna is usually

Table 3 Excision Margins

Breslow Depth, mm	Margin, cm
Melanoma in situ*	0.5-1.0
<1	1
1-2	1-2
>2	2

*Excludes lentigo maligna

seen on the sun exposed head and neck sites in an older population. These pigmented lesions can be large, very ill-defined, have a background of diffuse actinic damage, and significant subclinical spread. A typical margin of 5 mm will provide clear margins in only approximately 50% of patients. Closer to a 1-cm margin is usually required, but even margins of 2-3 cm may be necessary. Various surgical approaches have been recommended for the treatment of lentigo maligna and lentigo malignas melanomas.[30-32] Mohs surgery has been documented to be effective, but frozen section slides can be difficult to accurately interpret even using immunostains. Complete peripheral mapping with rapid (24 hours) permanent section histology interpreted by an experienced dermatopathologist (slow or modified Mohs surgery) may be the most accurate method, although it is certainly more work and time for both the patient and the surgeon.

Follow-Up

The final phase of the office management of the patient with melanoma is appropriate follow-up. All melanomas, including thin melanomas, can recur late and therefore, at minimum, annual visits for life are recommended. Thicker melanomas are more likely to recur during the first 1 to 3 years and thus more frequent follow-up (every 3-6 months) is typically recommended.[18] Patients with localized Stage IA disease can probably be seen every 6-12 months for the first 2-3 years and then yearly thereafter. However, if the patient is at risk for multiple melanomas as the result of family history or atypical nevi, then more frequent follow-up, at least every 6 months, is suggested. The purpose of the follow-up examination is first to detect local or distant recurrences or to look for additional melanomas. The patient should have a melanoma-focused review of systems and a complete skin examination and lymph node examination as previously discussed. The follow-up visit is also a time to educate the patient on how to perform monthly skin examinations, how to do a self lymph node examination, and to discuss ongoing sun protection measures. It is also an appropriate time to discuss the potential need to have family members screened.

Many patients with the diagnosis of melanoma will be quite anxious about the diagnosis and will need significant reassurance. Follow-up visits can be tailored to their individual needs for consultation, examination and reassurance by the dermatologist. The overall yield and potential value of routine imaging studies or hematologic tests in asymptomatic patients is very low and not usually necessary. Again, this should be directed by findings on the review of systems and the physical examination. Although unfortunate, there are no data that shows improved survival if metastatic melanoma is detected when clinically asymptomatic vs. symptomatic for stage IV disease.[18]

Summary

Accurate Breslow staging will require an accurate biopsy usually a complete excision with narrow margins and not a superficial shave biopsy. With thin melanomas, excision with a 1-cm margin to the deep subcutaneous tissue at the level of the fascia is recommended usually with a primary closure. Lentigo maligna is a special case of melanoma in situ that requires more than the standard 5 mm margin and is probably best treated with complete peripheral mapping. For thin melanomas in asymptomatic patients with a negative review of systems and normal lymph nodes, no imaging studies or hematologic studies are required. Sentinel lymph node biopsy should be discussed fully for patients with melanomas >1 mm or if >0.75 mm with evidence of ulceration or a mitotic rate of >1 mm/mm^2. Ideally, the sentinel lymph node biopsy and wide local excision should be performed at the same time, preferably by an experienced surgical oncologist. The patients should be aware that sentinel lymph node biopsy gives excellent prognostic information but data on significant overall survival benefit is lacking. In follow-up the dermatologist should provide continuity of care and should be knowledgeable in appropriate interval examinations. It is important that dermatologists continue to work closely with their medical and surgical oncological colleagues and have a ready referral pattern established to provide optimal patient care for those with stage III and IV disease. Finally, early diagnosis and better cure rates depend upon the identification of patients at risk with regular complete cutaneous examinations and appropriate patient education.

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