MELANOMA CARE
OPTIONS

ISSUE NO. 4 APRIL 2005

FOSTERING AN INTERDISCIPLINARY APPROACH TO MELANOMA CARE

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Before breaking the seal, see how your melanoma management style compares to the styles of experts in the field by following these simple instructions:

- Read the case presentation below
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A Patient With Melanoma on the Back

*Caron M. Grin, MD, and Richard Essner, MD**

A 45-year-old man presented to the dermatologist with a pigmented lesion on his left mid-back, which he first noticed 2 months prior when it bled. Physical examination revealed a 1.9 cm tan-to-brown plaque with asymmetric peripheral black pigmentation. The patient reported no personal or family history of melanoma. Because of the large size of the lesion, a shave biopsy of the darkest portion was taken for pathologic analysis. The pathology report showed atypical melanocytic proliferation and indicated that only a portion of the lesion had been biopsied.

Further biopsy and pathologic analysis revealed malignant melanoma with the following features:

- 2.5 mm depth
- Clark level IV, with small focus of epidermal ulceration
- No regression
- Mitotic rate: 3 mitoses per mm^2
- No lymphocytic infiltration

Before continuing, please answer the questions on the back cover and fax to 973-682-9077.

** The authors wish to thank Marisa Baldassano, MD, Partner, Dermatopathology Consultants, LLC, Haddon Heights, New Jersey, for her commentary on the dermatopathologic aspects of this case. In addition, they thank Rebecca Ferrini, MD, steering committee member, for her comments on techniques for preventing melanoma.*

Chairman's Introduction

Dear Reader,

Welcome to ***Melanoma Care Options,*** an interactive newsletter that will put you in the driver's seat. In this newsletter, we describe a case presentation and you will tell us how you would handle it, using the fax-back form on the back of the newsletter. Then read the newsletter to see what the experts from the **Melanoma Care Consortium** had to say. In a future issue we'll present an analysis of what physicians like you decided and how your answers compared to the opinions of our faculty. The cases will come every month for 8 months, so you will have ample opportunity to cast your vote on melanoma cases across the disease spectrum.

Thank you for taking part in this vital and innovative program. We look forward to your input regarding this and the cases to come.

Sincerely,

John M. Kirkwood, MD
Chairman, **Melanoma Care Consortium** Steering Committee

Editorial

This issue of ***Melanoma Care Options*** deals with a 45-year-old man with an intermediate thickness (2.5-mm) melanoma. Many factors can affect diagnosis, management, prognosis, and follow-up. This case explores factors that influence the choice of biopsy-type, interpretation of the pathology report, selection of margins for surgical excision, timing of sentinel lymph node biopsy (SLNB), role of adjuvant therapy, and appropriate follow-up for the patient with an intermediate-thickness melanoma. We hope you will find something within this issue that is relevant to your practice and that may help you in your care for your patients. As usual, we look forward to hearing your opinions and ideas, through the Web site (www.melanomacare.org) or on the fax-back forms provided.

Regards,

Caron M. Grin, MD

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Continuing Medical Education Information

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To receive up to 1.5 AMA PRA category 1 credits for this activity:

- Read the case summary on the front of the newsletter
- Answer and fax back the questions on the back cover
- Read the remainder of the case study inside the newsletter
- Complete the CME posttest answer and evaluation form at the end of the newsletter, and fax or mail these back to the address listed by April 15, 2006
- Within 4 weeks of successful completion, you may access your credit transcript at http://ccehs.upmc.edu/
- 70% of your posttest answers must be correct for you to receive a certificate of credit

Target Audience:

Dermatologists, dermatologic surgeons, surgical and medical oncologists, oncology nurses, primary care physicians, and other health care professionals who treat or screen for melanoma.

Learning Objectives:

After completing this activity, the participant will be better able to:

- Compare and contrast biopsy methods for evaluation of pigmented lesions
- List prognostic factors that should be reported in the dermatopathology report for pigmented lesions
- Describe relapse and survival rates for intermediate-thickness melanomas
- Propose an approach for the baseline staging and follow-up of a patient with an intermediate-thickness melanoma

Accreditation and Credit Designation:

The University of Pittsburgh School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The University of Pittsburgh School of Medicine designates this continuing medical education activity for a maximum of 1.5 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the educational activity.

**Other healthcare professionals are awarded 0.15 continuing education units (CEUs), which are equal to 1.5 contact hours.*

We gratefully acknowledge an educational grant from Schering-Plough in support of this program.

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Faculty for this activity have been required to disclose all financial or other relationships with pharmaceutical companies, biomedical device manufacturers, and other healthcare-related for-profit entities.

The faculty acknowledges the discussion of off-label use of pharmaceuticals, specifically regarding high-dose interferon alfa-2B.

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A 45-Year-Old Man With Melanoma on the Back

Caron M. Grin, MD

Richard Essner, MD

CASE PRESENTATION

As discussed on the front cover, a 45-year-old man visited his primary care physician with an atypical-appearing pigmented lesion on his left mid-back. On physical examination, he had a 1.9 cm tan-to-brown plaque with an asymmetric area of peripheral black pigmentation. The patient reported no personal or family history of melanoma. The primary care physician performed a shave biopsy of the darkest portion of the skin. The pathology report showed atypical melanocytic proliferation, but not a definitive diagnosis, and noted that only a portion of the lesion had been biopsied.

Subsequent referral to a dermatologist resulted in an excisional biopsy of the lesion, which led to a definitive diagnosis of melanoma. The pathology report also provided the following information:

- 2.5 mm depth
- Clark level IV, with small focus of epidermal ulceration
- No regression
- Mitotic rate: 3 mitoses per mm^2
- No lymphocytic infiltration

Commentary on the Initial Biopsy

When asked what type of biopsy should be performed for a patient presenting with a relatively large bleeding lesion, 71% of the expert panel agreed that adequate biopsy requires full-thickness removal of the entire pigmented lesion. However, some participants (18%) suggested that a biopsy of the area of darkest pigmentation would be sufficient if the lesion was large. Others (12%) thought that the large size of the lesion precludes removal of the entire lesion prior to pathologic confirmation of melanoma.

Although shave and punch biopsies can provide pathologic information, these biopsies may provide insufficient tissue and can lead to an incorrect diagnosis.[1] For example, when assessing a melanoma arising within a nevus, partial biopsies may sample only the benign nevus and overlook the malignant portion of the lesion. In an interview following the convening of the expert panel, Dr Marisa Baldassano, a dermatopathologist, noted that a punch biopsy through a portion of the melanoma precludes the assess-

ment of the complete architecture of the lesion and limits the evaluation of circumscription, important factors in the histopathologic analysis of cutaneous melanoma. In addition, she observed, partial biopsies may change the overall appearance of a lesion, causing it to look more like a nevus than a melanoma. These factors limit the utility of these biopsy methods and may lead to an erroneous diagnosis.[2] Partial biopsies may also prevent the accurate measurement of tumor thickness—an important prognostic factor for outcome of melanoma.[3] A retrospective analysis of 145 initial biopsies performed by experienced dermatologists revealed a 12% inaccuracy rate for superficial shave and punch biopsies, compared with 0% error in full-thickness excisional biopsy.[1]

That said, not all shave biopsies provide inadequate information. A superficial shave biopsy differs from a full-thickness saucerization biopsy. If the lesion appears to be thin, a saucerization biopsy that includes subcutaneous fat can provide a complete specimen for pathologic examination. However, according to Dr Bruce Smoller, saucerization biopsies are probably not indicated for clinically thick melanomas unless the dermatologist is confident the entire skin lesion can be removed.

For situations where the large size or anatomic location of the lesion makes removal of the entire lesion difficult, an incisional biopsy of a portion of the lesion may be performed. However, the biopsy should still be a full thickness biopsy including subcutaneous fat for adequate microstaging.[4] The panel agreed upon the important prognostic value of tumor thickness measurements for melanoma[3] and reinforced the importance of obtaining full-thickness biopsies.

The discrepancy between the initial pathologic findings, which did not reveal melanoma, and the clinical findings, which were suggestive of the presence of melanoma, underscore the importance of correlating the clinical findings with the pathologic findings. This involves choosing a dermatopathologist or pathologist with expertise in melanoma and pigmented lesions of the skin.

Table 1

Prognostic Features of Melanoma

Variable	*P* Value	Risk Ratio	95% CI
Nodal status	<.00001	2.239	1.913–2.621
Thickness	<.00001	1.583	1.433–1.749
Ulceration	<.00001	1.938	1.674–2.242
Site	<.00001	1.483	1.281–1.716
Patient age	.0002	1.095	1.044–1.147
Level of invasion	.01	1.007	0.896–1.131

Cox regression analysis of 4750 pathologically staged, node-negative patients without evidence of nodal metastasis.[3] Adapted from Balch CM et al. *J Clin Oncol.* 2001. Reprinted with permission from the American Society of Clinical Oncology.

Prognostic Value of Histologic Features of Melanoma

When queried about the most important prognostic factor in the pathology report, 64% of the expert panel chose tumor thickness, with 20% selecting ulceration. A minority of panelists felt that regression (8%), Clark level (4%), or lymphocytic infiltration (4%) provided the most prognostic value.

Indeed, multivariate analyses have demonstrated that thickness and ulceration are statistically significant prognostic factors for melanoma. Increasing tumor thickness was highly correlated with 10-year melanoma-specific mortality ($P < .00001$).[3] Ulceration also portends a poorer prognosis, with the presence of ulceration upstaging the melanoma to next greater thickness category without ulceration.[3,5] For example, the survival curve for patients with 1.1 cm to 2.0 cm ulcerated melanomas parallels that of patients with 2.1 cm to 4.0 cm melanomas without ulceration.[3,5] The multivariate analysis conducted by Balch and colleagues of 17,600 patients with melanoma found Clark level to provide less prognostic significance for intermediate-thickness melanomas (Table 1).[3] As a prognostic feature, Clark level is useful in thinner (< 1-mm thickness) melanomas.[3]

Because of the relative importance of these factors, the American Joint Committee on Cancer (AJCC) incorporates tumor thickness and ulceration into its Melanoma Staging System.[7] However, the faculty noted that this multivariate analysis did not include other prognostic factors, such as mitotic rate, lymphocyte infiltration, and regression (Sidebar 1), which may be important in determining prognosis as well (Sidebar 2).[3,7]

Margins for Surgical Excision

When asked what surgical margins they would recommend for an intermediate-thickness melanoma, 87% of participants chose 2-cm margins. A few recommended 1-cm

Sidebar 1

The Potential Importance of Mitotic Rate, Lymphocyte Infiltration, and Regression

Although they are not part of the 2001 AJCC staging criteria, mitotic rate, lymphocyte infiltration, and regression are frequently recorded on the pathology report.

Mitotic rate provides a quantitative measure of the number of mitoses per a high-power microscopic field. Rapidly dividing cells undergo more mitoses and have higher mitotic rates than slowly growing cells. Because cancer cells that divide rapidly tend toward aggressive growth and signify poorer prognosis than those that divide slowly, the mitotic rate may provide prognostic value in melanoma. Indeed, retrospective evaluation of 3,661 patients in the Sydney Melanoma Unit database found mitotic rate to be a statistically significant predictor of survival ($P < .0001$) that exceeded even ulceration in prognostic value.[44] Subsequent analysis of a smaller data set (1,317 patients) at the same center compared the prognostic influence of mitotic rate with stage according to the AJCC 2001 staging system (which includes both tumor thickness and melanoma). The investigators found that, while the prognostic value of mitotic rate did not overtake stage in importance ($P < .0001$), it was an independent predictor of survival ($P = .008$).[45]

In primary melanoma, the invasion of immune cells within the mass of the tumor is qualitatively reported as lymphocyte infiltration.[4,46] These tumor-infiltrating lymphocytes mount an immune attack on the melanoma and have been associated with improved survival and complete or partial regression of the tumor.[46,47]

Regression, characterized by destruction of tumor cells, vascular proliferation, and fibrosis, frequently occurs in melanoma. While regression may be viewed as a positive event, its prognostic value remains controversial.[2,47]

None of these studies represent the rigorous multivariate analysis needed to incorporate a parameter into the staging criteria. However, these types of evolving data suggest the potential for integration of these histologic features into future melanoma staging systems.

(9%) or 0.5-cm margins (4%). None of the panelists voted for 4-cm margins.

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines recommend margins of 1 cm for tumors 1 mm or less, 1 cm to 2 cm for those tumors from 1.01 mm to 2.0 mm, and 2 cm for those thicker than 2 mm. Surgical margins of 0.5 cm are reserved for in situ melanoma.[8] Thus, the majority of the expert panel agreed with the accepted guidelines. Given the melanoma tumor thickness (2.5 mm), Dr Grin queried the panel as to whether there was any value to a 3-cm surgical margin for this patient. In response, Dr Ross cited two relevant studies that addressed this issue: the WHO Melanoma Program, which compared 1-cm surgical margins with 3-cm margins in patients with melanoma thinner than 2 mm,[9] and the Intergroup Melanoma Trial, which compared 2-cm and 4-cm margins in patients with melanomas of 1 to 4 mm in thickness.[10] These studies found no significant difference in overall survival or local recurrence with the narrower margins.[9,10] As Dr Ross pointed out, "If 4-cm margins weren't better than 2-cm margins, then 3-cm margins can't be better than 2-cm margins." In light of the lack of benefit with wider margins, 2-cm margins continues to be the established standard recommendation for this patient.

Staging

The patient underwent wide local excision, lymphatic mapping, and sentinel lymph node biopsy (SLNB). When asked the main factor in deciding whether to perform SLNB, the faculty unanimously agreed that SLNB provides important prognostic information. No participant argued that the lack of palpable lymph nodes could be used to rule out metastasis, nor did any question the merit of SLNB. The undisputed agreement of the panel reflects the widespread acceptance of SLNB as it provides important information for staging.[11]

The panel went on to discuss considerations for optimally performing SLNB. Biopsy of the appropriate lymph node or nodes requires the cooperation of an experienced team that includes a nuclear medicine specialist to perform the lymphoscintigraphy, a surgeon to identify and excise the sentinel lymph nodes, and a pathologist to correctly analyze the nodes. When properly executed by a trained team, SLNB can yield an accurate assessment more than 97% of the time.[11]

Lymph node mapping identifies the lymph node or nodes that drain the affected area. Without lymphoscintigraphy, identification of the nodes that drain the back can be particularly problematic. In 29% of cases, primary melanoma of the trunk drains to multiple lymphatic basins.[12] Furthermore, lesions on the trunk can exhibit unexpected drainage patterns,[11] such as the axilla, groin, or interscapula space. In 32% of melanomas on the trunk, lymphoscintigraphy identifies a different drainage pattern from that predicted by historic anatomic guidelines.[11]

Ideally, lymph node mapping

and biopsy should occur prior to the wide excision. Prior wide excision can affect the lymphatic drainage and diminish the quality of the data obtained.[8] While the faculty concurred that prior surgery may compromise the accuracy of the mapping data, they stressed that patients with previous wide excisions should not be excluded from lymphoscintigraphy and SLNB. The merit of the procedure lies in the identification of positive lymph nodes, and the main downfalls of lymph node mapping following surgery include the potential for removal of more lymph nodes than necessary. Dr Rick Essner stressed that clinicians should explain to patients that the accuracy of lymphoscintigraphy and SLNB decreases with prior surgical procedures especially with unusual flap repairs or other factors that disrupt lymphatic drainage patterns. Many of the faculty agreed that the lack of prospective trials in patients who underwent wide excision prior to lymph node mapping and SLNB further supports offering the procedure to patients at risk for metastatic disease, even if they have had a prior wide local excision.

Tumor thickness generally dictates the appropriateness of SLNB for patients. As a general rule, all patients with intermediate-thickness melanoma (1 mm to 4 mm in Breslow depth) or thick melanoma (>4 mm) should be considered for SLNB. For lesions less than 1 mm, SLNB is generally not recommended unless the tumor has other unfavorable prognostic factors, such as Clark level IV or V, the presence of ulceration, a vertical growth phase, or extensive regression.[8] Contraindications for SLNB include metastatic disease, clinical evidence of lymph node involvement, prior extensive surgery, or other malignancies.

Analysis of SLNB should include routine hematoxylin and eosin (H&E) staining and immunohistochemistry (S-100 and HMB-45).[11] Because of discrepancy in the sensitivity and specificity of immunohistochemical stains, positive staining does not necessarily indicate metastasis. The pathologist must evaluate the lymph node architecture and cellular composition revealed by routine examination in conjunction with immunohistochemical stains to determine true lymph node positivity.[11] The use of diagnostic techniques that involve molecular methods, such as reverse transcriptase polymerase chain reaction (RT-PCR), is currently limited to clinical trials.[13] However, the sensitivity of molecular diagnostics suggests that these methods may be used more frequently in the future as researchers elucidate the appropriate protocols and relative benefits of these types of techniques.

In this case study, the patient underwent lymphoscintigraphy and SLNB. Lymph node mapping identified drainage to one axilla and the contralateral groin. Subsequent analyses of the nodes in both nodal basins were negative by both H&E and immunohistochemical staining.

Based on these results, the faculty was asked to stage the melanoma. The majority of panel participants (74%) correctly staged the melanoma as stage IIB, but some incorrectly classified it as stage IIA (21%) or stage IIIA (5%), perhaps reflecting the major revisions included in the 2001 version of the AJCC staging guidelines. In the new staging guidelines, lymph node negativity (N0) categorizes the melanoma as less than stage III. A tumor thickness falling between 2.01 and 4.0 mm (T3) with ulceration classifies the melanoma as (T3b). Thus, using the TNM system dictated by the guidelines, a T3bN0M0 tumor falls into stage IIB.[7]

Role of Adjuvant Therapy

Following the definitive diagnosis of melanoma, the clinician needs to determine the management of the patient with stage IIB melanoma. The panel was split down the middle when asked if adjuvant therapy should be considered in this patient, with 50% voting yes and 50% voting no.

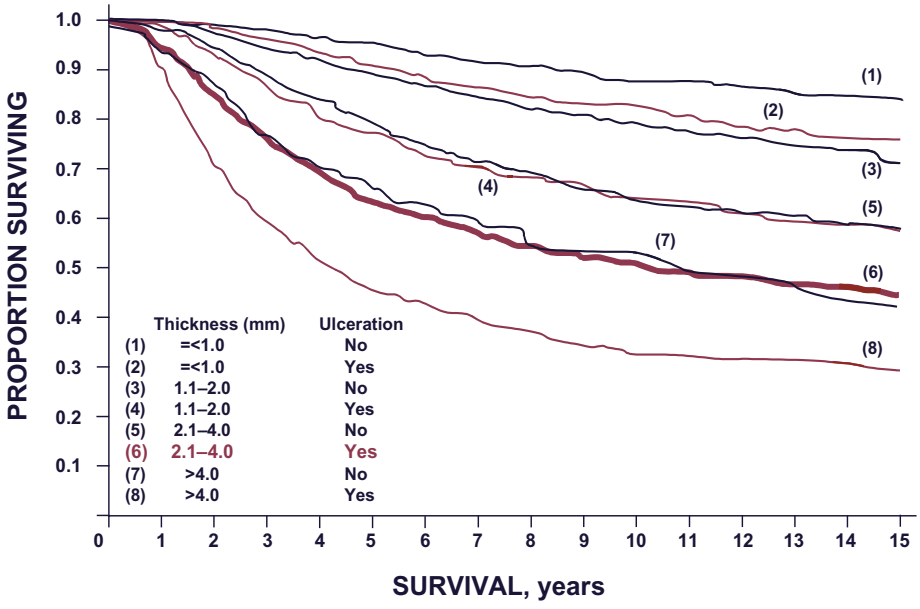
Risk of relapse and death drive management decisions for patients with primary cutaneous melanoma.

Sidebar 2

Components of the Pathology Report

The pathology report for a melanoma biopsy provides important information for diagnosis, staging, prognosis, and appropriateness of adjuvant therapy. What are the components of a typical report for an intermediate-thickness melanoma? NCCN Guidelines recommend Breslow thickness, ulceration status, Clark level, margin status, and evidence of microsatellitosis.[8] Dr Smoller also includes mitotic rate, host immune response rate, presence or absence of regression, and vascular or neural lymphocyte infiltration. However, the extent of reporting varies according to the pathologist, with many reports limiting the information to thickness, ulceration, regression, and margins. Although many of these additional parameters may not appear to be immediately relevant, the potential importance of these factors in the diagnosis and management of melanoma is just beginning to be fully elucidated, leading members of the panel to recommend that practitioners request more complete pathology reports.

Figure 1



The presence of ulceration upstages primary cutaneous melanoma to the next nonulcerated thickness category. Survival curves of 14,914 patients with localized melanoma stratified by melanoma thickness and presence or absence of ulceration: Tumor-node-metastases (TNM) staging provides significant correlation with melanoma-specific survival (P<.0001).[3] Reprinted from Balch CM et al. *J Clin Oncol.* 2001. Reprinted with permission from the American Society of Clinical Oncology.

A retrospective analysis of 17,600 patients with melanoma calculated a 5-year survival rate of 63% for patients with intermediate-thickness melanomas with ulceration (stage IIB T3b).[7] This rate of survival is slightly lower than that found in patients with thick melanomas without ulceration (stage IIB T4a, 67.4%), highlighting the influence of ulceration as an upstaging factor (Figure 1).[7] A different analysis using data obtained from 36,190 patients with melanoma registered in the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) cancer registry validates the impact of ulceration on survival rates.[5] While the study using this SEER data found 10-year survival rates to be significantly higher than those reported in the AJCC data set, analysis of the SEER data set revealed that ulcerated T3 lesions had a 10-year survival probability that approximated that of non-ulcerated T4 lesions.[5]

In addition to tumor thickness and ulceration, SLNB status impacts prognosis. In this case, the patient's negative node status suggests that he is at lower risk for relapse. As reflected in the AJCC 2001 staging criteria, SLN status remains the most significant prognostic factor in patients initially staged as stage I and stage II who underwent successful lymphatic mapping and SLNB.[3] In a study of 580 patients, in whom the median thickness of melanoma was 1.8 mm, only 55.8% of patients who were found to be node-positive by SLNB were relapse-free after 3 years, compared with 88.5% of patients with negative nodes (P < .0001).[14] Likewise, only 69.9% of node-positive patients survived 3 years, in contrast to nearly all of the node-negative patients (96.8%, P < .0001, Figure 2).[14] A negative SLNB, however, does not absolutely preclude relapse, as demonstrated by the 11.5% of patients who do experience relapse within 3 years.[14]

Dr Essner commented that analyses evaluating survival according to node status do not tease out the interaction of thickness and ulceration, which together suggest that stage IIB patients are at high risk for relapse. An increase in primary tumor thickness or presence of ulceration may portend physiologic events, such as angiogenesis, that unfavorably impact disease recurrence and survival.[14] In addition, failure of current histologic techniques to identify occult disease may understage patients in as many as 11% of cases.[15] The faculty noted that, while it is convenient to categorize patients into neatly defined stage categories to determine risk, the reality is that there is a continuum of risk. Every patient—even one classified as having early stage melanoma—has the potential for micrometastasis. Thus, the clinician's evaluation of the risk, the comfort level of the patient with a conservative approach, and the patient's desire to actively manage his or her disease, all contribute to the decision-making process.

Interferon Alfa-2B

Interferon (IFN) alfa-2B is approved by the Food and Drug Administration (FDA) as an adju-

vant therapy for melanoma at high risk for recurrence. However, no clinical studies have been published that specifically assess high-dose IFN alfa-2b in patients with T3bN0 melanoma. Therefore, one must extrapolate from studies of patients with tumors of similar thickness.

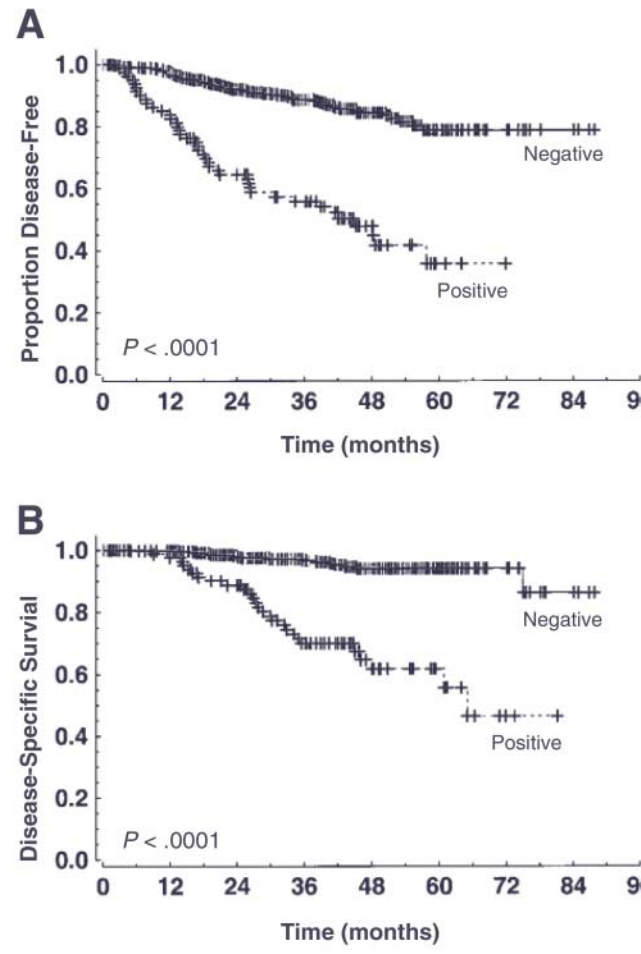
A European study found no benefit for IFN alfa-2b, IFN gamma, or mistletoe extract in node-negative patients with high-risk primary melanoma of thickness greater than 3 mm.[16] Three Eastern Cooperative Oncology Group (ECOG) studies evaluated IFN alfa-2b as adjuvant therapy in nearly 400 patients with T4N0 melanoma, who were free of melanoma following surgery but at high risk for systemic recurrence.[17-19] Many of the faculty, however, felt that it was too far a stretch to compare an ulcerated T3N0 melanoma with T4N0 melanoma. One problem with this comparison lies within the ulceration-dependent range of survival rates for patients with T4N0 melanoma. While 5-year survival of nonulcerated T4N0 melanoma (67.4%) approximately parallels that for T3bN0 (63.0%), the 5-year survival rate for T2bN0 melanoma (77.4%) exceeds that for T3bN0 by 14 percentage points.[7] The studies did not differentiate results according to ulceration.

Nevertheless, data from 3 trials in high-risk patients demonstrated that relapse-free survival was increased by one quarter to one third in patients who received IFN alfa-2b compared with those who were observed or given a vaccine comparator.[17-19] Two studies found an impact of IFN alfa-2b on survival (24% to 38% increase, P = .023–.0237),[17,19] while a third did not.[18] These risk reductions represent results within the overall study population. As Dr Kirkwood explained, the studies were never designed to evaluate efficacy according to patient subsets.

The ongoing ECOG1697 trial hopes to further address the survival benefit of IFN alfa-2B in patients with melanoma. By stratifying randomized patients according to tumor thickness (1.5 mm to 3 mm versus 3.1 mm to 4 mm, or > 4 mm), the trial aims to elucidate impact of IFN alfa-2B specifically in patients with Stage IIB disease.[20] The study will also address whether improvements at 1 year are related to the benefit of continuous dosing or a sustained response to the first month's induction phase.[20] This ongoing study was initially designed to look only at patients with stage IIA melanoma, but was later expanded to include stages IIB and IIIA because of benefits seen in earlier studies. While the melanoma community awaits the results of this trial, the best approach for the clinician and patient is to assess the potential benefit of IFN alfa-2b therapy for that given patient. Obviously, remarked Dr John Kirkwood, patients with the highest risk stand to gain the most from the risk reductions observed with IFN alfa-2b therapy.

Complicating this issue, noted Dr Ross, is that many of the studies that

Figure 2



Negative SLNB is associated with better outcomes for patients with intermediate-thickness melanomas (median thickness 1.80 mm). Kaplan-Meier survival stratified by SLN status. **A.** Disease-free survival for patients with negative (n = 480) and positive (n = 85) SLNB over 8 years. **B.** Disease-specific survival stratified by SLNB status.[14] Reprinted from Gershenwald JE et al. *J Clin Oncol.* 1999. Reprinted with permission from the American Society of Clinical Oncology.

Table 2

Clinical Trials of Vaccine Therapy Enrolling Patients With T3bN0M0 Melanoma[26]

Treatment	Sponsor(s)	Location(s)
GM2-KLH vaccine QS21	European Organization for Research and Treatment of Cancer	Numerous worldwide
gp100 antigen GM-CSF-plasmid DNA melanoma vaccine Tyrosinase peptide	Memorial Sloan-Kettering Cancer Center, National Cancer Institute	New York, NY
Montanide ISA-51 GM-CSF	University of Virginia, Health Sciences Center Cancer Center, National Cancer Institute	Charlottesville, VA
Multi-epitope melanoma peptide vaccine Montanide ISA-51 GM-CSF	University of Virginia, Health Sciences Center Cancer Center, National Cancer Institute	Washington DC Philadelphia, PA Houston, TX Charlottesville, VA
MART-1 antigen Montanide ISA-51 Alum adjuvant gp100 antigen IL-12 GM-CSF Tyrosinase peptide	University of Southern California, National Cancer Institute	Los Angeles, CA
MART-1 antigen Montanide ISA-51 gp100 antigen GM-CSF Tyrosinase peptide	University of Southern California, National Cancer Institute	Los Angeles, CA

provide estimates of the risk of relapse and survival according to stage are older studies, accrued before the advent of SLNB when the node status of patients was determined clinically. For patients with intermediate-thickness primary melanomas without node involvement, reported rates of the likelihood of relapse or death within 5 years ranged from 15% to 50%.[13] Use of this old data may have resulted in the inclusion of many node-positive patients in the N0 staging categories.[7] The faculty agreed upon the need for better data on the real risk for pathologically staged node-negative patients among the various tumor thickness and ulceration categories.

Other Therapies

Clinical studies have evaluated a variety of adjuvant therapies for the treatment of melanoma. Thus far, clinical trials have failed to show a survival benefit with other adjuvant therapies including chemotherapy,[21] passive (nonspecific) immunotherapy,[22] preoperative radiotherapy,[23] vitamin A therapy,[24] and/or retinoids.[25] A number of ongoing trials are evaluating biologic modifiers, immunotherapy, and vaccines, alone and in combination, as potential therapies for patients with stage IIB disease (Table 2).[26]

Chemoprevention

Another emerging strategy involves chemoprevention—the use of medications to prevent development of melanoma. Decreased incidence of primary melanoma in patients receiving active treatment was observed in the recently completed Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPs/TexCAPS) trial, designed to evaluate the ability of lovastatin to prevent coronary events. The safety analysis revealed an unanticipated, but statistically significant ($P = .04$) reduction in melanoma incidence in patients receiving the HMG-CoA reductase inhibitor, compared with those receiving placebo.[27] Experimental models of melanoma have demonstrated that statins affect the activation of Rho/Rho-kinase and Akt, which are required for endothelial cell-mediated tissue factor expression.[28] Because tissue factor may be important for melanoma growth and metastasis, there may be a role for lovastatin and other HMG-CoA reductase inhibitors in the chemoprevention of melanoma.[29]

Follow-Up

When asked about the appropriate follow-up regimen for patients with stage IIB melanoma, the panel was split on the utility of radiologic and laboratory tests. Half of the panel (52%) elected to follow the patient with history, physical examination, chest x-ray, and serum lactate dehydrogenase (LDH) testing, while the other half (48%) felt that history and physical examination alone were sufficient. Importantly, none of the panel thought that follow-up should be left to the patient's discretion.

As far as melanoma is concerned, follow-up can refer to immediate

follow-up after the initial diagnosis of melanoma (as part of the staging) or surveillance follow-up. For patients with stage IIB melanoma, NCCN guidelines state that chest x-ray and LDH are optional and that further imaging by computed tomography (CT) scan should be performed with or without positron emission tomography (PET) and/or magnetic resonance imaging (MRI), as clinically indicated.[8] Recent studies demonstrating a high incidence of false-positive results and a lack of significant impact of chest x-ray, CT scan, or LDH testing in the early detection of metastases suggest that these tests have no value in baseline staging.[30-32] For surveillance follow-up, NCCN guidelines recommend examination of the patient every 3 to 6 months for 3 years, then every 4 to 12 months until 5 years postdiagnosis. However, annual follow-up for life is important for detection of another primary melanoma, as patients with the diagnosis of melanoma are at high risk of melanoma.

The NCCN guidelines leave periodic LDH testing and chest x-ray to the discretion of the treating physician.[8] Numerous studies show that LDH testing is almost never the sole indicator of metastatic disease; however, the role of imaging techniques remains controversial.[33,34] Both the expert panel and published literature disagree about the value of imaging techniques as surveillance tools to detect disease recurrence. In a 1995 prospective study of 261 patients, careful patient history and physical examination detected metastases more than 94% of the time, with the remainder revealed by abnormal chest x-ray.[33] A more recent study of 2,008 patients corroborates these results, finding that chest x-ray identified metastatic disease in 5.5% of patients.[34] Furthermore, this study revealed that physical examination led to the detection of metastases in only 47% of relapsing patients, with the next most useful methods involving CT scanning (23.7%) and lymph node sonography (13.7%).[34] In stage II patients only, physical examination was still the most effective diagnostic tool, catching metastases in half of relapsing patients (51.0%), followed by lymph node sonography (22.4%) and CT scanning (14.3%).[34] Based on these results and the relative ease of performance and low cost compared with other imaging techniques, the study authors recommended lymph node sonography as part of routine imaging for stage II patients.[34] Rosemary Giuliano, ARNP, MSN, agreed with a lower-cost approach to follow-up, commenting that PET scan was an over-used, expensive surveillance tool with a high rate of false-positive results, and therefore should not be used for anything but relapsed disease.

After 5 years of follow-up, NCCN guidelines recommend annual examinations for patients who remain free of disease.[8] These should include physical examination, including a full skin examination and lymph node exam. Studies suggest that skin inspections should be conducted by a dermatologist rather than a primary care physician to avoid a high rate of false-positive identification of benign lesions as melanoma; however, specialized training of primary care physicians can reduce the rate of false-positive referrals.[35]

In addition to physician-directed annual skin examinations, the patient should be directed to perform monthly skin self-examinations, using a full-length mirror and assistance from a partner.[36] Mole-mapping programs using digital imaging of the skin may also enhance the ability of a person to detect melanoma by improving self-examination techniques.[37] Availability of a digital image of the skin allows the patient to compare the appearance of the skin over time versus baseline photographs. Patients with melanoma should also be counseled on the importance of sun protection and avoidance. Although the data remain unclear regarding the ability of sunscreens to influence the development and progression of melanoma,[38] sun protection using long-sleeved clothing and hats, as well as avoidance of "prime sunning hours" and sunburn, continue to be prudent recommendations.

The patient's family members should be advised about their increased risk of melanoma, counseled about ultraviolet protection, and educated on skin self-examination. In addition, first-degree relatives may be considered for an initial skin screening, conducted by a dermatologist or physician with specialized training.

The importance of family counseling lies in the observation that parents, siblings, and offspring of patients with melanoma carry a 2.24 times higher risk of cutaneous melanoma than people without an immediate family member with melanoma.[39] Genetic factors are complex and likely encompass heritability of a combination of phenotypic traits (e.g., fair skin, eye and hair color, nevus formation and number) as well as genotypic variation in cell senescence, cell division, and immunity. Analyses of large databases of melanoma patients and their families have identified both highly penetrant autosomal dominant and low-penetrance genes, which correlate to melanoma in these families. Shared environmental parameters may also contribute to the risk. Family members may also have similar lifestyle habits and similar levels of sun exposure, known contributors to the development of melanoma.[40]

Genetic screening tests are not commonly used in current practice,

despite their availability. One such test (MELARIS®, Myriad Genetics, Salt Lake City, Utah) identifies p16 mutations, a candidate gene for melanoma development. While approximately 5 to 10% of melanomas occur in the setting of familial malignant melanoma,[41] up to 40% of patients with familial melanoma have mutations in the p16 gene (also called CDKN2A or INK4A) located on chromosome 9p21.[42] The p16 gene encodes a cell cycle regulator that normally acts as a tumor suppressor. The p16 plays a key role in senescence and a protective role against the development of tumors.[43] Thus, although frequently mutated in families with melanoma, mutations in p16 that occur with other cancers means that the specificity of p16 screening tests for melanoma remains quite low. Another cell cycle regulator, p53, is abnormally expressed in 20% to 40% of primary melanomas,[40] but again the specificity of mutations in p53 is not limited to a specific type of cancer.[40] Thus, specific genetic markers for melanoma that may lead to the development of more accurate genetic susceptibility tests have yet to be found.

Conclusions

The panel discussion and review of the literature provide the following recommendations for the patient with ulcerated intermediate-thickness melanoma:

- Adequate biopsy requires full-thickness excision and removal to ensure proper diagnosis.
- It is important to coordinate clinical and pathologic findings by having the biopsy assessed by a qualified pathologist or dermatopathologist with experience in pigmented lesions of the skin.
- Ideally, lymphatic mapping and SLNB should be performed prior to the wide excision, but these techniques should not be excluded as an option for patients who have already undergone wide excision.
- Patients with intermediate-thickness melanoma have a moderate risk for recurrence.
- There is no recommended adjuvant therapy for ulcerated intermediate-thickness melanoma. High-dose IFN alfa-2b may be of benefit to these patients, and suitable patients should be considered for adjuvant therapy clinical trials.

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CME Evaluation Form

Please use the scale below to answer these questions.
Fill in the circle completely. You may use pen or pencil to fill in the circles.

Very Low Low Moderate High Very High

1. To what extent were the objectives of the educational activity achieved?
   O O O O O
2. To what extent were you satisfied with the overall quality of the educational activity?
   O O O O O
3. To what extent was the content of the program relevant to your practice?
   O O O O O
4. To what extent did the activity enhance your knowledge of the subject area?
   O O O O O
5. To what extent did the activity change the way you think about clinical care/professional responsibilities?
   O O O O O
6. To what extent will you make a change in your practice/professional responsibilities as a result of your participation in this educational activity?
   O O O O O
7. Which of the following best describes the impact of this activity on your performance? **(Please use the scale below in answering this question.)**
   - O This program will not change my behavior because I am already currently conducting my professional responsibilities in a manner consistent with the information presented in this educational activity.
   - O This activity will not change my behavior because I do not agree with the information presented.
   - O I need more information before I can change my practice behavior.
   - O I will immediately implement the information into my practice.
8. What action(s) will you take as a result of participating in this activity?
   (Please use the scale below in answering these questions.)
   - O None.
   - O Discuss new information with other professionals.
   - O Discuss with industry representative.
   - O Participate in another educational activity.
9. To what extent did the activity present scientifically rigorous, unbiased, and balanced information?
   O O O O O
10. To what extent was the presentation free of commercial bias?
    O O O O O
11. Please indicate your degree:
    O MD/DO O Physician Assistant
    O Nurse O Nurse Practitioner O Other
12. Was there any particular content that was irrelevant to your practice? If yes, why? _____
13. What types of information should be used to determine topics for this activity if repeated? _____
14. Would you prefer a different learning format (discussions, skills training, formal course)? _____
15. In the event that content exhibited commercial bias, please describe the specifics. _____
16. Do you have any other comments or suggestions for improving this education activity? Please discuss. _____

Answer CME Questions Here

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Case Re-evaluation

Please circle the answer that best describes your current view of the case.

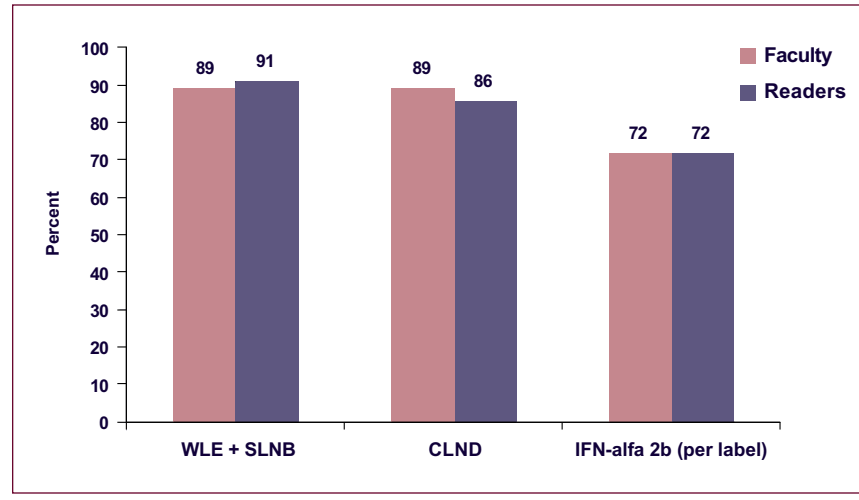
1. Did your opinion on patient management change after you completed this exercise?
   A. Yes B. No
2. Would you now consider this a high-risk patient?
   A. Yes B. No
3. What adjuvant therapy would you have offered this patient?
   A. Chemotherapy
   B. High-dose interferon alfa-2b
   C. Melanoma vaccine or other vaccine trial
   D. Chemoprevention
   E. Watch and wait
4. What surveillance tools would you use in follow-up visits with this patient?
   A. History, physical examination, chest x-ray, and serum lactate dehydrogenase
   B. History and physical examination alone
   C. Patient-directed follow-up only
5. Do you have any additional comments, questions, or observations about how your management strategy changed as a result of reading this article?

Feedback on Case 1: 2.0 mm Melanoma

Check here each month for the polling results from our previous cases. We will report on the answers given by you, our readers, to the pre test and post test questions, so that you see how your management style compares to the styles of your peers and our faculty.

Case 1 (January issue) concerned a 45-year-old man with a 2.0 mm thick, Clark level, nonulcerated melanoma on the arm. At the time of this writing, the management approach of the participants matched that of the faculty in most instances.

See the graphic for a comparison of the pre-test questions. Most faculty and readers would elect for a wide local excision (WLE) and sentinel lymph node biopsy (SLNB) rather than a simple local excision or WLE without SLNB. Also, if the SLNB was positive, most faculty and readers would opt for a CLND. If the remaining nodes were negative, the majority would recommend 1 year of IFN alfa-2b per label, although a notable percentage (18% of faculty and 15% readers) would consider enrollment in the ECOG 1697 clinical trial (IFN alfa-2b vs. 1 month observation). Fewer (8% of faculty and 4% of readers) would recommend a melanoma vaccine.



Strategy: 2.0 mm, Clark Level IV melanoma.

Since so many of the readers were in accord with the faculty, it was not surprising that only a small percentage (15%) would change their management strategy based on reading the newsletter. After reading the article, 100% of readers would have performed a SLNB (up from 91%), while the percentage who would recommend IFN-alfa 2b per protocol after CLND were similar pre and post poll (72% vs. 74%).

These results are consistent with an aggressive approach to high-risk melanoma that includes SLNB, CLND, and adjuvant therapy for micrometastatic nodal disease among the faculty and the readers.

CME Post-test Questions

Please answer each question on the space provided on page 14.

1. Which of the following is the best type of initial biopsy for patients with pigmented lesions suspicious for melanoma?
   A. Punch biopsy
   B. Saucerization biopsy
   C. Superficial shave biopsy
   D. Full-thickness excisional biopsy

2. For patients with intermediate-thickness melanoma, which of the following histologic features of melanoma has been shown to be a significant prognostic feature by rigorous multivariate analysis?
   A. Lymphocyte infiltration
   B. Mitotic rate
   C. Regression
   D. None of the above

3. The recommended surgical margins for excision of melanoma of 2.5 mm Breslow depth are:
   A. 0.5 cm B. 1 cm C. 2 cm D. 4 cm

4. A patient with stage IIB melanoma without ulceration has a 5-year survival rate of:
   A. 23% B. 43% C. 63% D. 83%

5. Lesions located on the trunk:
   A. Primarily drain to a single nodal basin.
   B. Have drainage that is unaltered by prior wide excision.
   C. Can drain to the axilla, groin, or other basins.
   D. Very rarely metastasize to the lymph nodes.

6. Even when melanoma is staged as node-negative by sentinel lymph node biopsy (SLNB), the study by Gershenwald and colleagues revealed that ___ of patients had relapsed within 3 years:
   A. Nearly 5%. B. Nearly 12%.
   C. Nearly 25%. D. Nearly 40%.

7. The IFN alfa-2B study(ies) that enrolled patients with T2bN0 melanoma is/are:
   A. ECOG Trial 1684 B. ECOG Trial 1690
   C. ECOG Trial 1697 D. All of the above

8. An agent that has been associated with chemoprevention in melanoma as shown in the AFCAPs/TexCAPS trial is:
   A. Alum B. GM-CSF
   C. Lovastatin D. Retinoids

9. A caveat in using estimated survival rates listed in the AJCC 2001 in patients with stage IIB disease is that:
   A. The worldwide data set for this stage of patients is too small.
   B. Not all of the patients classified as stage IIB underwent pathologic staging.
   C. The worldwide data set did not include patients with ulcerated melanoma.
   D. A subsequent analysis using SEER data found the survival rates to be substantially lower than those reported by AJCC 2001.

10. Which of the following follow-up procedures has been shown to be the most effective indicator of metastatic disease in asymptomatic patients?
    A. Chest x-ray
    B. Lactate dehydrogenase testing
    C. Physical examination
    D. Ultrasound

Visit www.MelanomaCare.org to view electronically or pass on to colleagues

Please answer these questions BEFORE OPENING this newsletter.

The following questions refer to the case study of a 45-year-old man with a bleeding lesion, as outlined on the front cover. Please circle the answers that most represent your opinion, detach this perforated page, and fax to 973-682-9077. Or, if you prefer, you can visit the Melanoma Care Consortium at www.MelanomaCare.org.

1. Without evidence of melanoma, what type of initial biopsy is appropriate for this lesion?

A. Punch biopsy
B. Shave biopsy
C. Excisional biopsy
D. All of the above

2. Given the pathology report, what is the next step for this patient?

A. Narrow excision
B. Wide local excision alone
C. Wide local excision with sentinel lymph node biopsy (SLNB)
D. No further treatment

3. If SLNB indicates negative lymph nodes, is this person at high risk for relapse?

A. Yes
B. No

4. What therapy would you recommend for this patient if it is determined that the sentinel lymph node is negative?

A. Chemotherapy
B. High-dose IFN alfa-2b
C. Melanoma vaccine or other vaccine trial
D. Chemoprevention trial
E. Watch and wait

5. What surveillance tools would you use in follow-up visits with this patient?

A. History, physical examination, chest x-ray, and serum lactate dehydrogenase
B. History and physical examination alone
C. Patient-directed follow-up only

Please retain this sheet because it includes the CME post test questions on page 15.

MELANOMA CARE OPTIONS

APRIL 2005

Fostering an Interdisciplinary Approach to Melanoma Care

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