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MELANOMA CARE OPTIONS

Issue 1: Primary Disease

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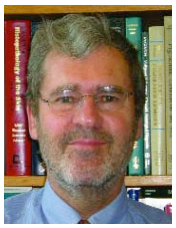
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A note from the Chairmen

Dear Reader,

Welcome to the first issue of the 2006 *Melanoma Care Options* publication series from the **Melanoma Care Coalition**. This coalition, founded in 2004, was formed to foster an interdisciplinary approach to melanoma care. This year, our case discussions have been grouped within disease stage categories—primary, regional, and distant metastatic melanoma. Individual working groups of the coalition contributed these cases, which illustrate salient teaching points for clinical practice. As with previous issues of *Melanoma Care Options*, self-assessment questions are incorporated into each of the cases presented so that you can choose your management approach and compare it against that of our expert panel and review the evidence supporting the recommended strategies.

As you will see from this and subsequent publications, a number of areas of melanoma management remain controversial, and individual strategies are supported by various levels of evidence. We hope that this program illustrates the areas of clear consensus in melanoma management while providing dialogue and insight into the evolving controversies. We welcome your thoughts on this publication series, and we encourage you to participate in the live, interactive **Melanoma Care Coalition** programs—see www.melanomacare.org for a regional program near you. Thank you for participating in the interdisciplinary dialogue that promises to improve our ability to care for patients.

Sincerely,

John M. Kirkwood, MD

Merrick I. Ross, MD, FACS
Co-Chairs, **Melanoma Care Coalition** Steering Committee

Editor's note...

This issue of *Melanoma Care Options* deals with primary disease issues. Self-assessment questions are incorporated into each of the six cases presented so that you can choose your management strategy before reading the available data in support of a specific decision point. The cases described in this publication include the care of a patient with multiple atypical nevi, management of melanocytic tumors of uncertain malignant potential (MELTUMPs), initial biopsy approach, pathology report information, role of surveillance studies, margins of excision, and sentinel lymph node biopsy. The opinions herein are those of the authors and are subject to change dependent on new research findings.

As faculty editor of this issue of *Melanoma Care Options*, I would like to thank you for taking the time to read this newsletter series. I look forward to your input and I welcome your thoughts regarding the management of the cases described in this publication.

Sincerely,

James M. Grichnik, MD, PhD
Melanoma Care Coalition

CONTINUING MEDICAL EDUCATION INFORMATION

Instructions for participation:
- Read the case presentations and comments in the newsletter
- Complete the posttest questions and evaluation form at the end of the newsletter, and fax or mail them to our office

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

To receive up to 1.8 CNE credits for this activity:
- Within 4 weeks of successful completion, a certificate will be mailed to the address provided
- 70% of your posttest answers must be correct for you to receive a certificate of credit

Target Audience
This activity is directed toward dermatologists, dermatologic surgeons, surgical and medical oncologists, general surgeons, oncology nurses, primary care physicians, and other health care professionals who treat or screen for melanoma.

Statement of Need
Primary melanomas are defined as the mass of cells confined to the original site of tumor development. In the absence of clinically evident regional or distant metastatic disease, they are classified as either stage I or stage II melanomas by the American Joint Committee on Cancer (AJCC) staging system. The prognosis for stage I or II patients is generally good if the disease is correctly treated. Therefore, clinicians should be familiar with the appropriate management of primary melanomas to maximize the chance for a cure. This publication describes in detail the management of primary melanomas and highlights important controversies that arise when caring for these patients.

Learning Objectives
After completing this activity, the participants will be able to
- Outline the appropriate management strategies for patients presenting with atypical nevi
- Compare and contrast types of biopsy and describe when each should be used
- Describe the appropriate use of surveillance radiographs and blood tests in patients with early melanoma
- Formulate a pathology report containing the necessary information to allow an informed treatment decision to be made
- Offer appropriate recommendations for excision margins of the primary site based on microstaging information
- Discuss the role of SLN biopsy in localized melanomas
- Explain the rationale for tumor cutoff points for performing SLN biopsy

Continuing Education Credit
The University of Pittsburgh School of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The University of Pittsburgh School of Medicine designates this educational activity for a maximum of 1.5 AMA PRA Category 1 Credits™. Each physician should only claim credit commensurate with the extent of their participation in the activity.

1.8 contact hours of Continuing Nursing Education will be granted by the University of Pittsburgh School of Nursing. The University of Pittsburgh School of Nursing is an approved provider of continuing nursing education by the Pennsylvania State Nurses Association (PSNA), an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.

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

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INTRODUCTION

Despite robust public education efforts concerning the linkage between sun exposure and all types of skin cancers, the incidence of melanoma in the United States is on the rise. In 2006, an estimated 62,000 new cases of melanoma will be diagnosed.[1] An estimated 1 out of every 52 men will develop melanoma within their lifetimes, and women have a 1 in 77 chance of developing the disease.[1] Melanoma is often diagnosed at a younger age than many other cancers, and consequently it ranks as one of the top 3 cancers responsible for the most productive years of life lost. However, if melanoma is caught early and has not progressed past localized disease when diagnosed, the prognosis for these patients is excellent—more than 90% of patients diagnosed with thin melanomas survive longer than 10 years past their initial diagnosis,[2] and the 5-year survival rate for localized melanoma is 98%.[1]

This publication focuses on issues surrounding primary melanoma (stage I and stage II melanoma, as defined by the American Joint Committee on Cancer staging system).[3] In this monograph, we present 6 cases of primary melanoma, followed by a discussion of the relevant issues introduced by each case.

CASE 1: MANAGEMENT OF ATYPICAL NEVI

BY JAMES M. GRICHNIK, MD, PHD, AND DAVID E. ELDER, MB, CHB, FRCPA

BASED ON A CASE SUBMITTED BY CLARA CURIEL-LEWANDROWSKI, MD

CASE PRESENTATION

A 16-year-old girl presented to her dermatologist with multiple atypical (dysplastic) pigmented nevi (Figures 1 and 2). The patient reported using sunscreen whenever she went to the beach and was found to have type 2 skin (burns, then tans moderately). The patient reported no family or personal history of melanoma. One lesion larger than 4 mm was excised and sent to the pathologist. Following histologic examination, the pathologist diagnosed the lesion as a *"lentiginous compound nevus with architectural disorder and slight to focally moderate melanocytic atypia; margins are not involved."*

RE-EXCISING ATYPICAL NEVI

What do you recommend for this patient at this time? (Select all that apply.)

1) Re-excise the lesion with wide margins because atypical lesions have a high risk of progression to melanoma
2) Do not re-excise because these lesions are best understood as risk markers for melanoma rather than high-risk precursors or established malignancies
3) Take a detailed history and perform a total body skin examination because risk for melanoma depends on multiple factors including total number of nevi, number of dysplastic nevi, skin type, and familial/personal history of melanoma
4) Re-excise with the same margins that you would use for a melanoma of similar depth (because there is clinicopathologic suspicion of melanoma)

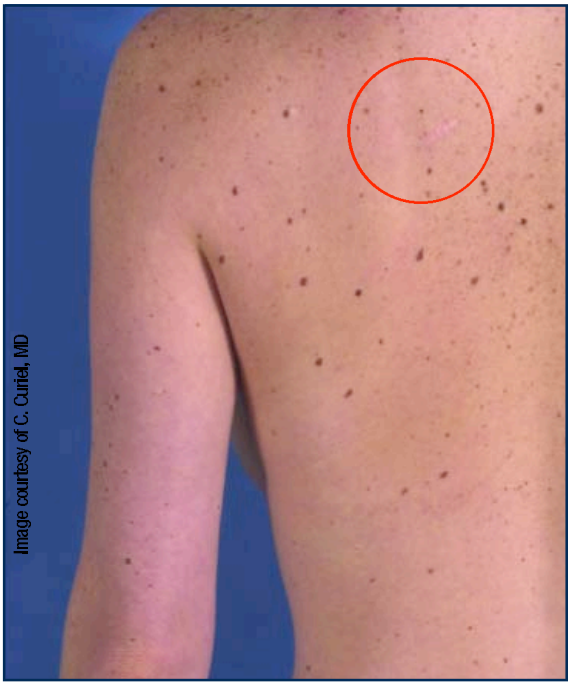

Figure 1. Multiple atypical nevi on the back of an adolescent girl. The site of a previous excision is circled.
Image courtesy of Clara Curiel-Lewandrowski, MD.

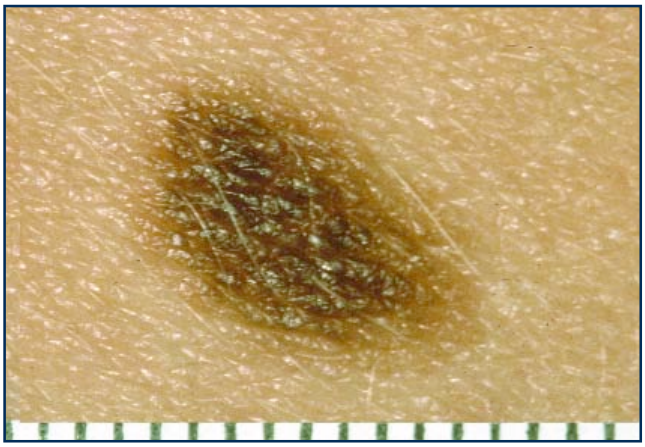

Figure 2. Clinical dysplastic nevus.
Image courtesy of David E. Elder, MB, ChB, FRCPA.

UNDERSTANDING THE RELATIONSHIP BETWEEN DYSPLASTIC NEVI AND MELANOMA

The faculty recommends a detailed history and total body skin evaluation. Re-excision is not recommended, as the original lesion was not malignant and the margins were clear.

The authors only recommend excision of an atypical nevus if the health care provider is concerned that the lesion may actually be melanoma; routine removal of atypical nevi as an approach to decrease melanoma risk is not recommended. Atypical nevi are best viewed as risk markers, not precancers; approximately 3 out of 4 melanomas develop in apparently normal skin.[4] Pathologically, of the melanomas with nevus elements present, only half have atypical nevi; the other half have other nevus types. Based on the number of nevi and annual detection of melanomas in the general population, Tsao and colleagues[4] determined that the annual transformation rate of any single mole into melanoma was on the order of 1 in 200,000 (0.0005%) for men and women under the age of 40. This rate increased to around 1 in 33,000 (0.003%) for men older than 60 years of age. The risk of any single nevus in a 20-year-old patient becoming melanoma by age 80 was found to be approximately 1 in 3154 (0.03%) for men and 1 in 10,800 (0.009%) for women.[4] Therefore, removal of nevi is a very inefficient mechanism to decrease melanoma risk.

Although most atypical nevi are benign, many difficulties arise when attempting to distinguish some atypical dysplastic moles from melanomas, both clinically and pathologically. It is important that the pathologist have sufficient experience diagnosing pigmented lesions and that the clinician actively communicate with the pathologist on difficult cases. Secondary opinions may also be sought on difficult cases. In cases where there remains significant concern that the lesion may be melanoma, the faculty recommends considering re-excision with margins similar to what would be used for a melanoma of similar depth.

SAMPLING OF MULTIPLE ATYPICAL NEVI/FOLLOW-UP STRATEGIES

Given the pathology report indicating slight to moderate atypia with no involvement of margins, what care do you offer this patient for follow-up and management of her other lesions? (Select all that apply.)

1) Excise the remaining atypical lesions
2) Biopsy the remaining lesions and have them read by an authoritative dermatopathologist
3) Photograph the nine remaining lesions
4) Obtain total-body photographs (with or without printing a copy for the patient)
5) Arrange follow-up without photographs
6) Advise the patient to inform her relatives of the diagnosis and have their skin checked if they have any concerns about their nevi
7) Reassure the patient that the lesion was benign and discharge her from your care
8) Counsel on sun protection
9) Counsel on thorough skin self examination

The faculty does not recommend excising or biopsying the remaining lesions if they are not suspicious for melanoma. While the American Academy of Dermatology (AAD) recommends excising any clinically suspicious lesion with narrow margins,[5] serial excision of atypical nevi is inappropriate[4]; only those clinically suspicious for melanoma warrant biopsy or excision.

The patient should be carefully followed with regular physical examinations, as the presence of multiple atypical nevi represents an increased risk for melanoma. In one study, individuals with 1 dysplastic nevus were twice as likely to develop melanoma during their lifetime as controls, whereas 10 or more dysplastic nevi increased the risk 12-fold ($P<.001$) (Table 1).[6] Dysplastic nevi in this study were defined as melanocytic nevi with at least 1 diameter of 5 mm or greater that had a macular component or were entirely macular, with 2 of 3 additional criteria (slightly irregular border, indefinite or "hazy" border, pigmentary variation that is generally slight to moderate). This patient, with multiple dysplastic nevi, is at considerable risk of developing a melanocytic lesion within her lifetime.

FAMILIAL LINK TO MELANOMA

Several risk factors for melanoma have a genetic basis, including the presence of multiple atypical nevi, reddish hair, and fair skin.[7] Subjects who reported at least one first-degree relative with melanoma are more than twice as likely to develop the disease as those with no familial history.[8] Likewise, 3 or more first-degree relatives with a history of cutaneous melanoma may increase the likelihood of melanoma by up to 70-fold.[7] The patient may wish to encourage relatives to undergo screening, although this is not as heavily mandated as it would be if the patient or another family member had a history of melanoma. Genetic testing is a developing area and may also be useful to identify some patients at heightened risk for melanoma due to inherited mutations. See Sidebar 1 for a brief discussion of the role of genetic testing in melanoma.

Table 1. Common and dysplastic nevi as melanoma risk factors. From Tucker MA, et al. *JAMA.* 1997;227:1439-1444.[6] Used by permission.

Common Nevi		Dysplastic Nevi	
No. of Nevi	**Relative Risk**	**No. of Nevi**	**Relative Risk**
0-24	1.0	0	1.0
25-49	1.8	1	2.3
50-99	3.0	2-4	7.3
>100	3.4	5-9	4.9
		>10	12.0

FOLLOW-UP STRATEGIES FOR PATIENTS WITH ATYPICAL NEVI

Because patients with multiple atypical nevi are at increased risk of melanoma, the Melanoma Care Coalition faculty recommends that these patients adhere to strict preventive measures and undergo frequent screenings by a dermatologist. Total body photography may be an appropriate follow-up step, as this procedurecan help identify changing lesions and contribute to earlier detection.[9] Advising the patient to inform her relatives of the diagnosis may also be recommended. Prevention strategies recommended by the AAD include a thorough skin self examination every year, avoidance of excessive sun exposure whenever possible (with adequate vitamin D through a healthy diet or vitamin supplements), and the use of a sunscreen with an SPF of 15 or higher.[10] The authors also recommend the regular use and reapplication of sunscreen every 2 hours when exposed to the sun.

CASE 2: MANAGEMENT OF A MELANOCYTIC TUMOR OF UNCERTAIN MALIGNANT POTENTIAL

BY JAMES M. GRICHNIK, MD, PHD, AND DAVID E. ELDER, MB, CHB, FRCPA

BASED ON CASES SUBMITTED BY MARTIN WEINSTOCK, MD, PHD, AND CLARA CURIEL-LEWANDROWSKI, MD

CASE PRESENTATION

A 48-year-old man presented with a pink nodule of recent onset on his back (Figure 3). An excisional biopsy was performed and sent to the pathologist for analysis. The biopsy report indicated a melanocytic tumor of uncertain malignant potential (MELTUMP) and noted that *"while this lesion could represent an atypical Spitz tumor, the differential diagnosis includes malignant melanoma—Clark's level IV, Breslow thickness 4.2 mm, mitotic rate 2, no ulceration or satellites."*

MANAGEMENT OF MELTUMP

What do you recommend for this patient? (Select all that apply.)

1) Obtain a thorough history from the patient, as a history of initial rapid growth followed by no further change for an extended period of time may favor a more benign Spitz lesion
2) Refer slides to a reference pathologist with expertise in Spitz nevi
3) Re-excise with wider margins because this lesion may be a melanoma and could have capacity for metastasis and local recurrence
4) Do not re-excise because these lesions are best understood as risk markers for melanoma rather than high-risk precursors or established malignancies
5) Perform a sentinel lymph node (SLN) biopsy and consider completion lymphadenectomy if the SLN is positive
6) Take a detailed history and perform a total body skin examination, because the risk that this lesion is a melanoma depends on multiple factors, including total number of nevi, total number of dysplastic nevi, skin type, family history, and personal history of melanoma
7) Advise first-degree relatives to undergo total body skin examination
8) Counsel the patient on thorough skin self-examination

The clinician should review the history and clinical findings with the dermatopathologist. Consultation with a reference pathologist with expertise in Spitzoid lesions is also appropriate. If the pathology consult cannot rule out melanoma, then the patient should be offered the appropriate treatment for a deep cutaneous melanoma, which includes wider margins of excision and possibly SLN biopsy.

Sidebar 1: Genetic testing for melanoma

Mutations in the genes encoding p16 (*CDKN2A*) and ARF (*CDK4*) have been linked to the development of certain cancers, including cutaneous melanoma. The lifetime risk of cutaneous melanoma in carriers of a deleterious *CDKN2A* mutation is estimated to be 76% in the United States.[11] Molecular assays can determine whether an individual carries this mutation.

Because of familial predisposition for melanoma in some individuals, commercially available genetic tests have been developed to identify individuals who may be at increased risk. However, routine genetic testing for cutaneous melanoma should only be performed within an experimental protocol, as this procedure's clinical usefulness is the subject of ongoing debate. The chance of a randomly selected individual testing positive is minuscule, and even in a mutation-positive family, a negative test cannot be presumed to indicate an absence of increased risk.[12] Instead of widespread genetic testing, most individuals perceived by virtue of family history and/or cutaneous phenotype to be at high risk for melanoma should be educated regarding preventive strategies and undergo regular screenings and routine self-examination.[13] If genetic testing is performed, informed consent and pretest and posttest genetic counseling are essential.[12]

Patients to consider referring for genetic testing include those with:

- At least 3 family members with melanoma
- 2 family members with melanoma if one has multiple primaries
- 2 family members with melanoma and confirmed pancreatic cancer
- Multiple primaries

Again, a negative test does not rule out increased risk in these settings.

A lesion with uncertain malignant potential should be managed more aggressively than a low-risk Spitz nevus, for which observation alone may be the only warranted therapy.[14] For this lesion, observation alone is not an adequate solution, as it overlooks the possibility that this lesion may already contain melanoma. At a minimum, the authors recommend that the MELTUMP be completely excised after consultation with a reference pathologist.

DEFINING MELTUMPS

MELTUMPs represent a heterogeneous group of melanocytic lesions with varying characteristics (see Sidebar 2). SLN biopsy may also be considered when managing uncertain or borderline cases. Although the presence of melanocytic cells in the SLN does not definitively indicate malignancy, it provides information that may be used to identify a group of tumors with increased risk.

DIAGNOSTIC DIFFICULTIES ASSOCIATED WITH BORDERLINE LESIONS

Spitz nevi/tumors are benign cutaneous melanocytic lesions that histologically mimic malignant melanomas.[20] Even experienced physicians can have trouble distinguishing a Spitz nevus from a melanoma.[21] In 2 reviews of selected "difficult" lesions, expert panels frequently disagreed on diagnosis, with unanimous agreement in only 3% to 29% of cases.[22,23] In one of these studies, some lesions that a majority of panelists categorized as Spitz nevi or atypical Spitz tumors later proved fatal.[23]

With regard to this case, the authors recommend that practicing pathologists who do not report Spitz nevi on a regular basis consider a consultation, particularly when atypical features are observed, as no proven set of criteria can consistently distinguish an atypical Spitz nevus from a melanoma. Several morphologic features help distinguish low-risk from high-risk atypical Spitzoid tumors (Table 2).[14] Specific chromosomal alterations, such as increases in 11p copy number, have been noted in Spitzoid lesions,[24] and in the near future molecular markers may have a role in discriminating malignant from benign Spitzoid lesions. The growth profile of the lesion may be of some benefit, in that Spitz nevi tend to grow rapidly and then enter a static period.[25] Currently, however, differentiation of these lesions on clinical and histologic grounds alone is difficult, and the faculty recommends caution in clinical practice.

TREATING MELTUMPS

Because of the uncertainty associated with these cases, experts recommend that borderline lesions be categorized as "melanocytic tumors of uncertain malignant potential" and that the therapeutic plan consider the worst-case scenario in the differential diagnosis.[15] Health care providers should further remember that agreement among pathologists in the diagnosis of atypical Spitzoid lesions does not necessarily indicate correct diagnosis. The safest action with frank atypia is to treat the lesion as a melanoma of equivalent depth, and at a minimum these lesions should be completely excised with a margin of normal skin around the scar and any residual lesion. Therefore, even though the pathology report indicated a MELTUMP, in this case the authors recommend that the patient described above be offered the consideration of treatment as if this were a stage IIB melanoma (>4 mm, no ulceration), as determined by the AJCC staging guidelines. In cases such as this, the patient should be informed of the uncertainty surrounding his or her diagnosis to avoid a "false assurance of confidence in any given diagnosis."[15]

As mentioned previously, the authors recognize that there is a rationale for using SLN biopsy as part

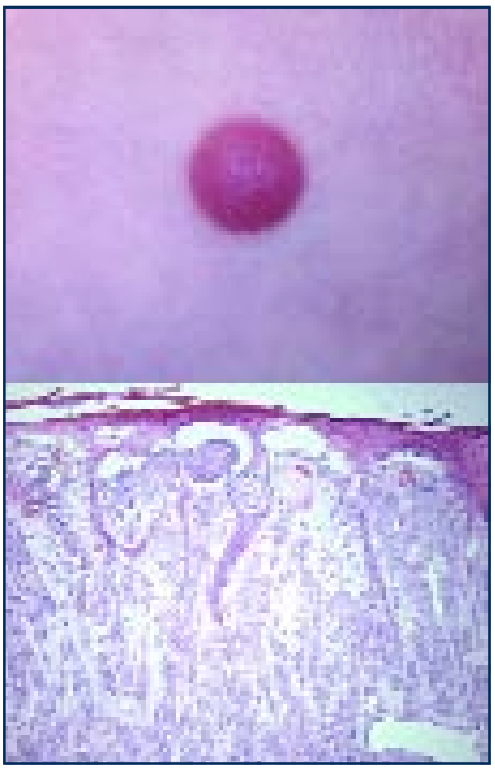

Figure 3. Gross (left) and histologic (right) appearance of a Spitzoid melanocytic tumor. This tumor was of uncertain malignant potential on the back of a 48-year-old patient.
Images courtesy of Clara Curiel-Lewandrowski, MD.

Sidebar 2: Is It a MELTUMP?

While this case focuses on a MELTUMP of the spitzoid family, MELTUMPs represent a heterogeneous group of tumors. In general, the term can be reserved for melanocytic proliferations extending into the dermis.
Lesion types may include[15-18]:

- Dysplastic nevi
- Pigmented epithelioid melanocytoma
- Atypical Spitz nevi
- Cellular nodules in congenital nevi
- Deep penetrating nevi
- Congenital nevi
- Cellular blue nevi

While not all pathologists recognize the value of defining this diagnostic gray zone,[19] the authors of this publication propose that recognizing diagnostically uncertain lesions as a category enables the health care provider to enter into a more frank and active dialogue with the patient about management strategies.[15]

of the differential diagnosis and staging of melanoma. SLN biopsy has identified lymph node metastasis in some lesions categorized as MELTUMPs.[15] In a study of 10 patients with diagnostically controversial melanocytic lesions who underwent SLN biopsy, investigators found tumor deposits in the lymph node parenchyma of 5 of the 10 study subjects.[21] Additional tumor deposits were found in 3 nonsentinel lymph nodes in 1 patient involved in the study, demonstrating the metastatic potential of MELTUMP lesions. An additional study by Su and colleagues[26] identified SLN metastasis in 8 of 18 patients with atypical Spitzoid melanocytic proliferations who underwent SLN biopsy. Although the lymphatic system was involved, 100% of patients in both studies were alive and disease-free at time of publication (follow-up was 10-54 months for Lohmann et al; 3-42 months for Su et al).[21,26]

The authors recommend that many MELTUMPs that have metastasized to the SLN may best be reclassified as "metastatic melanocytic tumor of uncertain malignant potential."[15] However, others contend that a positive SLN "should be taken as evidence of the malignant potential of the tumour," and these lesions should be reclassified as malignant melanoma.[14] In this case, because the lesion was being treated as if it were a deep cutaneous melanoma, the authors would recommend an SLN biopsy.

CASE 3: What Type of Initial Biopsy Should Be Performed?

By James M. Grichnik, MD, PhD, David R. Byrd, MD, and David E. Elder, MB, ChB, FRCPA

Based on a case provided by Ashfaq A. Marghoob, MD, FAAD

CASE PRESENTATION

A 52-year-old white man visited his physician after noticing that a mole that had been on his upper back 10 years had recently changed in both size and color. He reported a history of multiple blistering sunburns and had a familial history of colon cancer. Physical examination revealed an irregularly pigmented 3-cm lesion on the patient's upper back. The lesion had a large diameter, multiple colors, and both macular and papular areas. Dermoscopy revealed an atypical pigment network, blue-white veil, and the presence of irregular blood vessels in the papular component of the lesion. The patient had no palpable lymphadenopathy.

TYPE OF BIOPSY

What type of biopsy procedure would you perform?

1) Random superficial shave biopsy
2) Partial/incisional/punch biopsy of the most apparent clinically relevant region
3) Multiple partial biopsies of different areas
4) Complete/excisional biopsy.

INITIAL BIOPSY

The authors recommend complete excision of the entire lesion in this and the majority of cases. Incisional (punch and superficial shave) biopsy should be reserved for cases in which the clinical suspicion for melanoma is low or the lesion's location or size makes complete excision unfeasible. Exceptions to complete excision arise, such as a lesion of similar diameter on the face, where wound closure after an excisional biopsy may compromise the late reconstruction of a wide excision. In this setting a full-thickness deep shave or punch biopsy of the thickest-appearing (most raised) area would be reasonable for initial diagnosis. A deep shave biopsy is acceptable so long as it removes the deepest margin of the lesion. In this case, the size of the lesion poses a slight problem, but because of its overall complexity, the authors recommend full-excision biopsy.

Because of the increased accuracy of histopathologic analysis and its effect on melanoma staging and treatment strategies, excisional biopsies should be performed whenever possible. The AAD and the National Comprehensive Cancer Network (NCCN) also recommend complete excision of any lesion suspicious for melanoma whenever possible.[5,27]

In cases of thin and intermediate-thickness melanomas where a complete

Table 2. Morphologic features used to differentiate low- and high-risk Spitz nevi. From Dahlstrom JE, et al. *Pathology.* 2004;452-457.[14] Used by permission.

Low Risk	High Risk
<10 years old	>10 years old
No ulceration	Ulceration
Small size (<10mm)	Large size (>10 mm)
Symmetry	Asymmetry
Superficial only	Deep extension
Less cellularity	Hypercellularity
Maturation	No maturation
Minimal or low-grade cytological atypia	Prominent cytological atypia
	Prominent mitotic rate
Few or no mitoses	Deep mitoses
Superficial mitoses only	Atypical mitoses
Typical mitoses	

excision is not possible, a deep shave (saucerization) biopsy that includes subcutaneous fat is preferable to a superficial shave or punch biopsy.[28] When performing a saucerization biopsy, the health care provider should inspect the base of the specimen for any tumor cells, as transection of the lesion base is a potential drawback to this procedure.[29] Deeper tissue should be obtained if any remaining tumor is observed. If an incision biopsy is to be performed, the portion of the lesion most likely to have the greatest Breslow depth should be sampled. Clinically, this may be represented by a firm papular/ nodular region. Dermoscopically (see Sidebar 3), these areas may have a blue-white veil and/ or include an atypical vascular network. Multiple areas may need to be sampled to increase confidence in the extent of the tumor and to prepare for the definitive procedure. Again, if possible, complete excision is the preferred initial procedure.

DETERMINANT OF BRESLOW DEPTH

Because Breslow thickness is an important prognostic factor, a retrospective analysis compared Breslow depth determined by nonexcisional shave or punch biopsy with the "true" Breslow depth obtained from a complete excisional biopsy.[28] Most nonexcisional shave and punch biopsies in this study (88%) accurately determined Breslow depth. However, incisional biopsies became less accurate as lesion thickness increased ($P = .04$).[28]

The NCCN recommends initial margins of 1 mm to 3 mm when performing an excisional biopsy.[27] Removing only a small portion of clinically normal skin around the lesion prevents excess disruption of the draining lymphatics and provides the greatest chance for accurate lymphatic mapping should an SLN biopsy be required for additional staging.[27] A pathologist experienced in pigmented lesions should analyze all biopsy specimens. Based on pathologic analysis, re-excision with wider margins may be recommended.

CASE REVISITED

Because of the size of the lesion, the dermatologist treating this patient decided that an excisional biopsy was not feasible. Based on the clinical examination, he determined what he considered to be the most atypical area of the lesion and performed a shave biopsy of that focus. The biopsy was interpreted by a pathologist who reported the lesion as *"melanoma in situ, extending to specimen margins."* The patient was staged as AJCC stage 0, and the dermatologist recommended definitive excision with 0.5-cm margins, according to the NCCN guidelines for stage 0 lesions.[27]

The patient sought a second opinion, and after a thorough review, the other physician recommended an excisional biopsy to analyze the entire lesion. Prior to the excisional biopsy, the papular areas and regions suggestive of invasive melanoma, as determined by dermoscopy, were marked, and the dermatologist requested that the pathologist evaluate all marked areas (Figure 4).

The new pathologic information revealed a melanoma 2.2 mm in Breslow depth, Clark level IV, with no ulceration and marked regression. Based on this analysis, the patient was upstaged to AJCC Stage IIA. He underwent a therapeutic wide excision with 2-cm margins, and an SLN biopsy was performed. The SLN biopsy was negative for metastatic disease, and after 1 year of follow-up, the patient remained disease-free.

Sidebar 3: Dermoscopy in the Diagnosis of Melanoma

Using directed light and magnification techniques in combination with immersion liquids to render the skin translucent, dermoscopy allows visualization of structures below the skin surface.[30] Dermoscopy can reveal irregular pigment networks and other suspicious features that would otherwise go unnoticed by the physician. In a meta-analysis of 27 individual studies, dermoscopy by experienced physicians increased diagnostic accuracy by 49% vs with visual inspection alone ($P = .001$).[31] However, training is required, as dermoscopy by untrained examiners is no more effective than visual inspection alone.[31]

THE PROBLEM WITH PARTIAL BIPOSIES

Partial biopsies of suspicious lesions are often performed under the assumption that an experienced clinician can predict the most suspicious areas of the lesions by direct examination. These incisional biopsies are intended to spare the patient from increased morbidity of larger excisional biopsies, especially when there is a low index of suspicion for melanoma or the suspicious

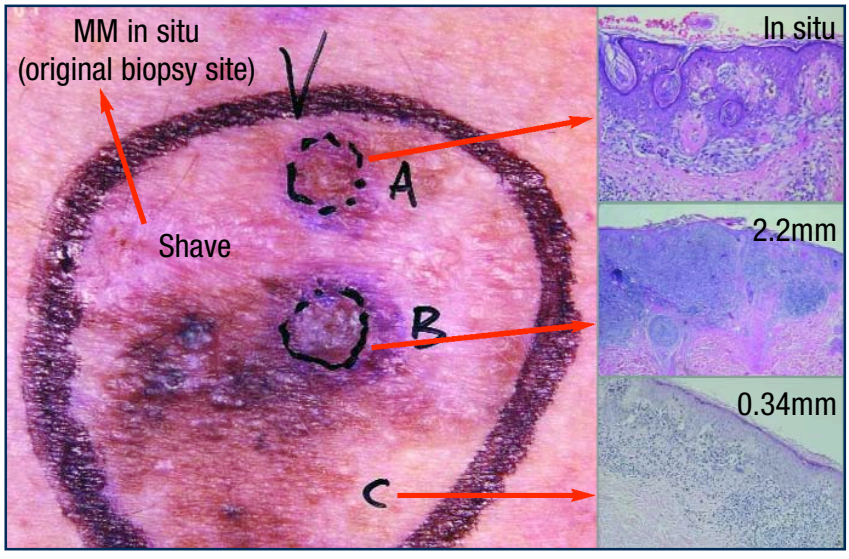

Figure 4. A 3-cm, irregularly pigmented lesion on the upper back of a 52-year-old male. Following an initial shave biopsy, a complete excision was performed and various portions of the lesion were analyzed.

lesion is large.[32] However, as this case demonstrates, clinical examination alone does not always identify the most histologically significant area of the lesion; an excisional biopsy specimen often provides additional pathological staging information that a partial (punch or shave) biopsy cannot.

In 2 studies of patients who had previously undergone incisional biopsies, 21% to 40% were upstaged after the results were examined by full excisional biopsy.[32,33] These data suggest that complete excision provides the most accurate staging and diagnosis for any lesion suspicious for melanoma. Misdiagnosis of melanoma involving partial biopsies is a major source of malpractice claims (Sidebar 4).

DOES THE TYPE OF INITIAL BIOPSY AFFECT SURVIVAL OR TUMOR METASTASIS?

Despite apparent differences in accuracy of incisional and excisional biopsies for initial diagnosis and staging of melanoma, clinical evidence suggests that the type of biopsy does not adversely affect survival.[35,36] The Scottish Melanoma Group identified 761 patients who underwent either incisional biopsy before definitive excision (n = 265) or initial complete excision (matched control group, n = 496). The study measured the time from initial biopsy to recurrence of melanoma and the time to melanoma-related death: the type of initial biopsy had no effect on either endpoint. Even when thick melanomas (>3 mm) were identified, incisional biopsy did not significantly alter time to recurrence or death (P = .87 for recurrence; P = .43 for melanoma-related death).[35]

Nevertheless, because of the increased staging accuracy associated with excisional biopsies, removal of the entire suspicious area is recommended when feasible. Pathologic analysis of the entire lesion allows for a more certain diagnosis and, consequently, a more appropriate therapeutic strategy than would be recommended based solely on the results of an incisional biopsy. Additionally, removal of the entire suspicious lesion may reduce patient anxiety, an important factor to consider when managing patients with melanoma.

CASE 4: PATHOLOGY REPORTS FOR MELANOMA

BY DAVID E. ELDER, MB, CHB, FRCPA

BASED ON CASES SUBMMITTED BY DAVID E. ELDER, MB, CHB, FRCPA, AND CARON M. GRIN, MD

CASE HISTORY

A 52-year-old white man presented with an irregularly pigmented mixed macular and papular 2-cm lesion on his upper back. A complete excision with narrow margins was performed. The pathology report indicated *"Malignant melanoma, tumorigenic vertical growth phase, single dermal mitosis, nonulcerated, Clark level III, Breslow thickness 0.80 mm, with adjacent melanoma in situ extending to specimen margins."*

MANAGEMENT OF A THIN MELANOMA WITH ADVERSE PROGNOSTIC FACTORS

What do you recommend for this patient? (Select all that apply.)

1) Wider excision with additional 5-mm radial margins
2) Wider excision with additional 1-cm radial margins
3) Consideration of SLN biopsy sampling

Based on the information in the pathology report, the authors recommend re-excising with a 1-cm margin and discussing SLN biopsy with the patient. While this melanoma is too thin to warrant an excision wider than 1 cm, the narrower (5-mm) excision margin is reserved for in situ melanomas.[5,27] The health care provider should discuss SLN biopsy with this patient, despite the thinness of the melanoma, as pathologic examination identified 2 prognostic factors that indicate an increased risk for metastasis, namely mitotic activity and the presence of vertical growth phase.[37] For more information regarding the role of SLN biopsy in patients with thin melanomas, refer to Case 6. Observation alone would be inappropriate, as even an in situ melanoma poses serious risk to the patient because of the possibility of persistence followed by future progression, and the Clark level indicates that this melanoma has already spread beyond the epidermis.

FEATURES OF A MELANOMA PATHOLOGY REPORT

This case illustrates the importance of capturing essential pathologic information about a case in a consistent manner. Pathology reports should include information for the

Sidebar 4: Malpractice claims involving partial biopsies

An analysis of malpractice claims filed from 1998 through 2001 revealed that the misdiagnosis of melanoma is a major cause of litigation against dermatologists and pathologists.[34] Seventy percent of claims involved a false-negative diagnosis. Of these, partial biopsies accounted for the majority of cases: 30% of claims involved shave biopsies and 26% involved punch biopsies. An additional 26% of cases were the result of incomplete excision of the lesions in which the type of biopsy was unidentified. *Only 17% of malpractice claims for misdiagnosed melanoma involved completely excised lesions.*[34] Because partial biopsies may not sample the most clinically significant portion of the lesion, they have a greater chance for misdiagnosis than excisional biopsies in which the entire lesion is available for pathologic examination.

optimal management of primary melanoma. Any pathology report describing a melanocytic lesion should include essential information such as the patient's name, date of birth, medical record number, and any other available identifying information. The authors also recommend reporting the anatomical site of the tumor, the diameter of the lesion and/or the biopsy specimen, whether an incisional or excisional biopsy was performed, and any other medically necessary information.

ESSENTIAL MICROSCOPIC INFORMATION

In addition to the pathologist's diagnosis of primary melanoma, the following microscopic information should be included in all pathology reports based on the proven prognostic significance of these characteristics of melanocytic lesions:

Breslow depth and ulceration: Breslow thickness and ulceration have emerged as perhaps the most important predictors of outcome in melanoma patients.[38,39] Tumor thickness is directly related to overall survival: 10-year survival with 0.76-mm melanomas is 90% to 92%; but survival decreases with increasing depth.[38] Likewise, ulceration has a direct "upstaging" effect on overall survival, as "in every instance, the survival rate for ulcerated melanomas was virtually the same as for nonulcerated melanomas of the next greater thickness category."[39] Because of the prognostic significance of both Breslow thickness and ulceration and their importance in the current AJCC criteria (Table 3), these two factors are essential to any pathology report.

Clark level: For melanomas thinner than 1 mm, such as the lesion in this case, Clark level IV invasion is a stage modifier in the current AJCC system and should therefore always be reported.[3] However, as discussed in the Thin Melanoma section of Case 6, Breslow depth is the better predictor of survival, even in lesions less than 1 mm. Still, the authors recommend that Clark level be routinely reported by the pathologist for all melanomas.

Satellites: Microsatellites are defined as nodules of melanoma cells that are separated from the main component of the tumor.[38] Microsatellites are thought to indicate metastatic potential[40] and are used to upstage patients in the latest version of the AJCC staging system for cutaneous melanoma.[3]

Pathology margins: An essential feature of the pathology report for melanoma is a description of the status of the margins of the biopsy specimen; the pathologist's review should include whether the margins were negative or positive for lesional cells. In a final excision procedure, it is mandatory to report the margins as positive or negative. It should be noted, however, that it is not the standard of care to measure margin width in definitive excisions.

DESIRABLE MICROSCOPIC INFORMATION

While the prognostic significance of the features listed above is the basis of the current staging system and is widely accepted, additional microscopic features of melanoma have been suggested to likewise predict patient outcome. These features are not essential for inclusion in a pathology report, but the Melanoma Care Coalition strongly suggests that the following features be reported by the pathologist:

Phase of tumor progression: Tumor progression is recorded as either the vertical or radial growth phase. Melanomas in the vertical growth phase, such as the one described in this case, can proliferate in the dermis and are characterized as mitogenic based on mitotic activity or tumorigenic based on the formation of a tumor mass.[41] Radial growth-phase tumors cannot divide in the dermis; these tumors are limited to the epidermis and unlikely to metastasize.[41] Therefore, vertical stage melanomas are associated with a poorer prognosis.[42]

Mitotic rate: An important marker of tumor proliferation, mitotic rate has been studied as a prognosticator of disease progression. Several studies have identified high mitotic rate as a significant predictor of mortality or SLN positivity.[43-45] Therefore, reporting mitotic rate in the pathology report may help identify patients with thin melanomas who are at the greatest risk for lymph node metastasis and who should undergo SLN biopsy. Mitotic rate should be reported as the number of mitotic cells per mm^2 in the vertical growth phase. However, in thin melanomas this rate may be difficult to determine, and the simpler to estimate property of mitogenicity (the presence of any lesional cells in

Table 3. AJCC staging system for primary melanomas.
Adapted from Balch CM, Buzard AC, Soong S-J, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol.* 2001;19(16):3635-3648.[3]
Adapted with permission from the American Society of Clinical Oncology.

Stage	T Classification	Thickness	Ulceration Status
IA	T1a	≤1.0 mm	No ulceration, Clark level II–III
IB	T1b T2a	≤1.0 mm 1.01 mm – 2.0 mm	Ulceration or Clark level IV–V No ulceration
IIA	T2b T3a	1.01 mm – 2.0 mm 2.01 mm – 4.0 mm	Ulceration No ulceration
IIB	T3b T4a	2.01 mm – 4.0 mm >4.0 mm	Ulceration No ulceration
IIC	T4b	>4.0 mm	Ulceration

mitosis in the dermis) has been demonstrated, along with tumorigenicity, to identify subsets of patients at increased risk within the AJCC stage I category.[46]

Tumor-infiltrating lymphocytes: Lymphocyte infiltration is a marker of the immune response to tumorigenic cells. Tumor-infiltrating lymphocytes should be characterized as "brisk," "non-brisk," or "absent," as these factors are directly correlated to survival. Brisk infiltration of primary tumors or lymph nodes is correlated with a more favorable clinical outcome[47,48] and is characterized by "a dense band of lymphocytes among tumor cells across the entire base or throughout the tumor."[41] Non-brisk lymphocyte infiltration is characterized by the presence of lymphocytes in one or more foci of the vertical growth phase. If no lymphocytes are present or if the lymphocytes do not infiltrate the melanoma, they should be reported as "absent."[47]

Regression: The authors recommend that regression (an area within the tumor that contains no melanocytic cells) be reported. Several studies have suggested that regression correlates with tumor metastasis. Others have failed to find an association.[41] The presence of regression should be reported to allow a fully informed decision.

Angiolymphatic invasion: Melanocytic cells in the blood vessels and lymphatics may indicate metastasis. Angiolymphatic invasion has been correlated with increased SLN positivity, and the factors that allow tumorigenic cells to invade vessels may be related to the tumor's ability to metastasize.[49] Angiolymphatic invasion is associated with an increased risk of relapse and melanoma-associated death ($P<.001$).[50]

Histogenic type: Melanomas fall into 4 main histogenic types: acral lentiginous, lentigo maligna, nodular, and superficial spreading. While each type exhibits unique characteristics, and emerging data suggest that each possesses different biologic mechanisms, the different types of melanoma do not have independent prognostic significance. Lentigo maligna melanomas are generally associated with higher survival than other subtypes, possibly because of earlier diagnosis (or slower progression) and therefore a thinner lesion at the time of diagnosis.[38] Nodular melanomas are likely to be the thickest, while acral lentiginous melanomas have the worst prognosis, perhaps because the thinner dermis present in acral glabrous skin means that a relatively small melanoma can still have a high Clark level.[38] None of these prognostic differences persist after adjustment for thickness.

Associated nevi: A description of any nevus or precursor lesion associated with the melanoma should be included in the pathology report, as it may have epidemiologic significance. The type of associated nevus may help identify other lesions that could develop into melanoma. Additionally, a description of any associated nevi may help identify family members with similar nevi who may be at risk for melanoma.

Actinic elastosis: Chronic sun exposure can lead to actinic damage in the skin, resulting in dermal elastosis. Dermal elastosis in biopsy samples may indicate an increased risk for additional melanoma, especially when observed on the head and neck. An analysis of 141 patients found a significant correlation between head and neck melanomas and the presence of moderate to marked dermal elastosis ($P = .05$).[51]

PROGNOSTIC SIGNIFICANCE OF REPORTING "DESIRABLE" FACTORS FOR THIN MELANOMAS

Thin melanomas (<1.0 mm) are categorized as AJCC stage IA or IB, depending on ulceration and Clark level (stage IB tumors are ulcerated or Clark level IV or V). While most groups offer SLN biopsy to patients with stage IB tumors per the current NCCN guidelines, emerging data suggest that additional factors (tumorigenicity and mitogenicity) may accurately predict risk for metastasis.

While currently not considered essential, mitotic rate and vertical growth phase may be especially important to report as, when combined with sex, they offer a predictive tool for identifying patients with thin melanomas at high risk for metastasis.[46] Patients with a mitotic rate of 0 and radial growth-phase tumors were found to be at the lowest risk for metastasis (0.5%), whereas men with vertical growth-phase tumors exhibiting a mitotic rate higher than 0 were deemed to be at the greatest risk of developing metastasis (31.1% within 10 years for men, 12.5% for women; Figure 5)[46] Overall survival rates for these groups were significantly reduced as the risk status increased ($P<.001$). Gimotty suggests that this prognostic tree is more accurate for predicting metastasis in stage 1 patients than the current AJCC staging system.[46] Therefore, even though these factors are not "essential" for inclusion in a pathology report, they may help identify patients at high risk of metastatic disease.

CASE CONTINUED

The patient underwent a wide local excision with additional 1-cm radial margins. Upon examination of the excised lesion, the pathologist indicated: *"Biopsy-site reaction with adjacent residual melanoma in situ, partial regression present, no satellites or ulceration, excision complete."* The patient underwent SLN biopsy because of the perceived high risk with dermal mitosis, partial regression, and a Breslow depth approaching the thicker side of the less-than-1-mm interval. The SLN biopsy was negative for tumor.

PATIENT FOLLOW-UP

What would you recommend?
1) Review biopsy and remove additional tissue if final margin is less than 1 cm
2) Completion node dissection
3) Observation and watchful waiting

The authors note that the excision with a 1-cm margin was appropriate. As will be discussed more extensively in Case 6, the extent of these margins is defined by the thickness of the primary tumor. For in situ melanoma, the recommendation is for a 5-mm (0.5-cm) margin; for melanomas 1 mm or thinner, a 1-cm margin; and for melanomas thicker than 1 mm, a 2-cm margin may be considered.

Findings in a re-excision may result in additional therapy being offered to the patient, as seen in Case 3. In this case, the excision showed that the melanoma was completely excised, with an appropriate margin based on the depth of the melanoma, and that no adverse prognostic indicators in the re-excision were sufficient to require additional therapy. Because regression is present in the re-excision, it is important to ensure that

the surgical margins are free of regressed or viable melanoma. Because regression is typically a focal finding in a melanoma, a few or many viable cells could easily be present beyond the lateral border of the regression. In short, the entire lesion should be taken out with a "safety margin" of normal skin. The optimal pathology margin width (as opposed to the clinical margin width measured by the surgeon) has never been defined, but as a rule of thumb, we might comment on a margin as "close" and give a measurement if the margin is less than about 1 mm.

Completion lymph node dissection is not indicated for this patient, as no positive SLNs were discovered. Despite the generally low-risk character of this patient's disease (though with some indicators of a potentially worse prognosis), this patient should be followed regularly for life, with attention to the local site, the regional lymph nodes, and any clinical suspicion of systemic metastatic disease. Follow-up should also include skin exams for the possibility of a second primary or of cutaneous metastases. Extensive imaging studies are not generally indicated (for a discussion of appropriate follow-up strategies, please refer to Case 5).

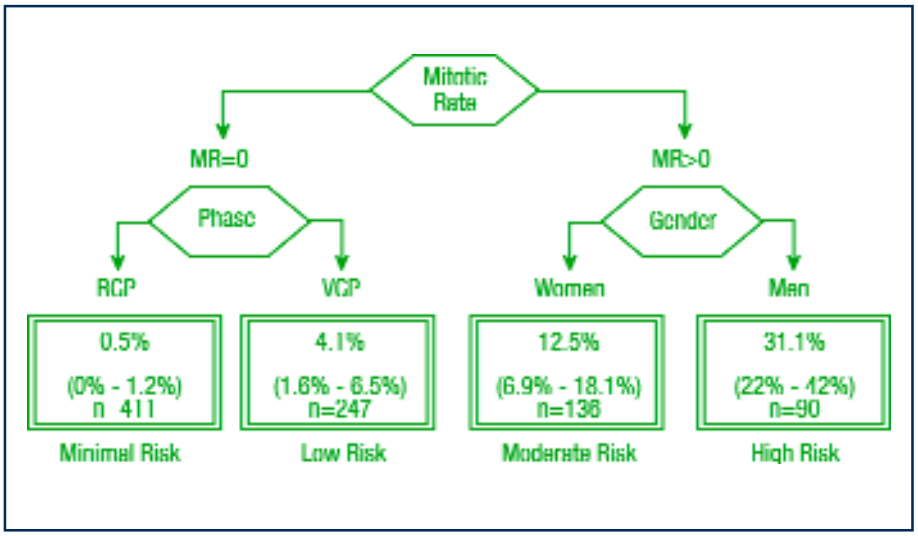

Figure 5. A prognostic tree for 10-year metastasis in patients with AJCC Stage I melanoma. From Gimotty PA, Guerry D, Ming ME, et al. Thin primary cutaneous malignant melanoma: a prognostic tree for 10-year metastasis is more accurate than American Joint Committee on Cancer staging. *J Clin Oncol.* 2004;22(18):3668-3676.[46] Reprinted with permission from the American Society of Clinical Oncology.

CASE CONTINUED

Thirteen years later, the patient presented with multiple cutaneous and visceral metastases. The scar of the definitive therapy of melanoma was not involved (no local recurrence was noted), and a review of the prior histology demonstrated clear margins in the re-excision with a closest margin width of 5 mm.

MANAGEMENT OF METASTATIC MELANOMA

What do you tell the patient?

1) The original management was inadequate
2) Recommend additional excision at primary site
3) The lesion must have metastasized before it was completely excised
4) Metastatic melanoma requires systemic therapy in the hands of an oncologist

Because this patient presented with metastatic melanoma, the authors recommend he be referred to an oncologist for adequate treatment with systemic therapy. Blaming the original surgeon and pathologist is inappropriate, because there is no evidence that any additional local therapy would have affected the outcome. The purpose of re-excision is to prevent local recurrence. Margin width in general has been correlated, to some extent, with local recurrence rates, but not with survival. Therefore, margin widths may be adjusted as necessary to spare important structures. Micrometastases that may be present at the time of excision of the lesion are not, of course, affected by the extent of local therapy, and may serve as the "seeds of systemic metastases" many years later. The lack of local recurrence at the primary site demonstrates that the melanoma must have metastasized before it was completely excised, even though the SLN biopsy performed at the time of original diagnosis was negative.

The finding of a 5-mm margin in the histologic re-examination of the specimen is completely consistent with the 1-cm margin that had been measured clinically at the time of primary treatment. The measured pathology margin will always be less than the measured clinical margin, because of shrinkage artifact in the excised specimen and because the microscopic tumor often extends beyond its clinically detectable edge. Therefore, the goal of treatment is not to obtain a measured margin of 1 cm, or any other arbitrary measurement, in the pathology specimen. It is of course essential for the pathologist to confirm microscopically that the margins are clear, and if they are "close" (in our practice less than about 1 mm is considered close) we recommend that the pathologist alert the clinician to this fact. In this case, a decision may be made whether or not to remove an additional safety margin, depending on all of the clinicopathologic circumstances.

Although the original melanoma was thin (0.80 mm), the pathology report included enough information to classify this patient as higher risk for metastases (presence of mitoses, vertical growth phase, male sex) compared with patients with similar thickness lesions but without these features, according to the prognostic tree developed by Gimotty and colleagues.[46] Therefore, the authors recommend that information in addition to that deemed essential for AJCC staging purposes be routinely reported by the pathologist examining melanocytic lesions to allow an informed decision regarding patient care to be made and to adequately assess the risk for nodal and systemic metastasis. In addition, it should be remembered that a negative SLN, while an excellent predictor of a favorable outcome, is not a perfect predictor.

CASE 5: Role of Surveillance Radiographs and Blood Tests in Early Melanoma

By James M. Grichnik, MD, PhD

CASE INTRODUCTION

Radiologic and laboratory tests are often used to identify metastases, but their role in baseline assessment and surveillance of asymptomatic melanoma remains controversial. The following case describes some of the challenges in interpreting the results of these tests.

CASE DESCRIPTION

A 28-year-old medical oncology pharmacist was diagnosed with a Clark level II, Breslow depth 0.5-mm melanoma. The melanoma was excised with 1-cm margins. Within the subsequent few weeks, the patient had several additional nevi removed and biopsied, all with a benign diagnosis.

FOLLOW-UP TESTS FOR PATIENTS WITH PRIMARY CUTANEOUS MELANOMA

What kind of tests would you recommend at this time?
1) Blood work (eg, lactate dehydrogenase [LDH])
2) Chest radiography
3) Chest radiography and blood work
4) PET/CT scan
5) Other
6) No follow-up tests

The authors recommend that no follow-up blood work or imaging studies be performed at this time because of poor sensitivity and specificity. The patient should be assessed every 3 to 12 months with a history and physical examination, and follow-up tests should only be performed when directed by a suspicious physical examination and complete review of systems. This recommendation is consistent with the guidelines of the AAD[5] and the NCCN.[27]

These recommendations are based in part on the poor diagnostic accuracy of blood work and imaging procedures for primary melanoma. In a study of 261 patients undergoing frequent blood testing and other laboratory work, blood tests did not emerge even once as the first sign of melanoma recurrence.[52] Another study found only a few metastases through blood tests, with true-positive rates of 0.5% for lactate dehydrogenase (LDH) and 0.4% for alkaline phosphatase (ALP); however, the false-positive rate associated with these tests was 2.2% for LDH and 2.4% for ALP.[53]

The true-positive rate for chest radiography in asymptomatic melanoma patients ranges from 0% to 0.5%.[54] This procedure is associated with an even higher false-positive rate, ranging from 8% to 15%, often leading to additional costly tests and needless emotional stress for the patient.[54,55]

Computed tomography (CT) is likewise associated with low true-positive and relatively high false-positive rates. In an analysis of 151 patients with AJCC stage I (n = 63), II (n = 61), III (n = 23), or unstageable (n = 4) melanoma, CT scans of the chest and abdomen accurately revealed metastasis in only 2 patients (1.3%).[56] Twenty-four patients (15.9%) had suspicious scans that proved benign when biopsied. Additional studies of CT imaging in patients with local and regional disease found true-positive metastasis in 7% to 15.7% of patients and false-positive results in 11.8% to 22% (Table 4).[56-58]

CASE CONTINUED

The lack of strong evidence supporting routine laboratory tests and imaging studies in metastatic melanoma was discussed with the patient. However, the decision was made to obtain a baseline chest radiograph and blood work in case a comparison should be needed later.

The radiologist's report indicated *"an ill-defined nodular opacity overlying the right mid-lung which may represent a confluence of vessels. Recommend repeat chest radiograph; negative for mediastinal lymphadenopathy. Normal heart."*

FOLLOW-UP SUSPICIOUS CHEST RADIOGRAPHY

In light of the radiologist's report, what procedure would you recommend next?
1) Repeat chest radiography immediately
2) Repeat chest radiography in 3-month intervals
3) Immediate chest CT
4) PET or PET/CT scan
5) None of the above

The authors do not recommend chest radiography for asymptomatic patients with primary cutaneous melanoma; however, the suspicious opacity observed in the radiograph warrants further examination. Therefore, the authors recommend repeating the chest radiography immediately to confirm the results prior to any additional scanning by CT, PET, or PET/CT.

CASE CONTINUED

Despite the recommendation to undergo repeat chest radiography, the patient arranged for immediate additional scanning within the oncology practice where she worked as a pharmacist. The patient received a CT scan of the chest, abdomen, and pelvis, and the report indicated *"innumerable small lesions within the lungs, liver, and spleen which are consistent with metastatic disease."* Likewise, a PET scan identified *"diffusely abnormal uptake within the chest, liver, spleen, and spine,"* and an MRI of the thoracic spine identified *"an 8-mm ovoid lesion . . . in the right caudal third of T3 suggestive of metastatic melanoma."*

Based on these findings, the patient underwent a percutaneous liver biopsy that revealed no evidence of malignancy. She then underwent open liver biopsy, which revealed granulomatous

inflammation and organisms; however, no growth was observed when these were cultured. Based on the pathologic features, the team determined that the patient suffered from histoplasmosis and not metastatic melanoma. No further treatment was recommended.

The Melanoma Care Coalition faculty does not recommend the routine use of imaging procedures in asymptomatic melanoma patients, and evidence suggests that routine screening procedures do not impact patient survival. A recent analysis found no survival advantage of early identification of pulmonary metastasis by radiography.[59] Five-year survival rates for patients whose Stage IV disease was discovered by chest radiography was not significantly different from that in patients with previously identified metastatic disease or known stage IV melanoma at nonpulmonary sites prior to the initiation of the study ($P = .68$).[59]

Most melanoma recurrences are discovered by history and physical examination; imaging studies and blood tests rarely reveal systemic metastasis in asymptomatic patients.[51,60] A "normal" result may only serve to provide a false sense of reassurance, while false-positive results lead to unnecessary anxiety, additional tests, and potentially invasive procedures. Therefore, the Melanoma Care Coalition does not recommend imaging or blood work in the follow-up of asymptomatic patients unless warranted by a suspicious physical examination.

The Melanoma Care Coalition recommends discussing the advantages, disadvantages, and role of follow-up studies with the patient before any relapse is detected. The patient should be informed of the lack of evidence for routine use of these follow-up procedures. The use of additional aspects of surveillance should be emphasized, including the examination of the primary tumor excision site for local or in-transit recurrence; careful physical examination, including nodal examination; and full-body skin examination.

CASE 6: The Role of SLN Biopsy in Primary Melanoma

By David R. Byrd, MD, John M. Kirkwood, MD, and Merrick I. Ross, MD, FACS

Case supplied by Mohammed Kashani-Sabet, MD

CASE PRESENTATION

A 50-year-old man presented to his dermatologist with a suspicious lesion on his right arm. The lesion was 9 mm in diameter and had irregular borders and a raised dark region. Physical examination was otherwise unremarkable. The dermatologist performed an excisional biopsy with 1-mm margins and sent it to a dermatopathologist for analysis. Microscopic examination revealed a nonulcerated Breslow 1.8-mm melanoma with penetration into the reticular dermis (Clark level ≥IV). The biopsy margins were clear.

SURGICAL MANAGEMENT OF PRIMARY MELANOMA

What care would you offer this patient?

1) Nothing further (negative margin biopsy as only treatment)
2) 1-cm excision, no nodal staging
3) 2-cm excision, no nodal staging
4) 1-cm excision, SLN biopsy
5) 2-cm excision, SLN biopsy

The authors recommend a 2-cm excision with SLN biopsy, although a 1-cm excision is acceptable under some circumstances. For melanomas thicker than 2.0 mm, current guidelines recommend a 2-cm excision; for those thinner than 1.0 mm, a 1-cm excision biopsy is recommended.[5,27] For melanomas between 1.0 and 2.0 mm such as the present case, different guidelines disagree—the NCCN recommends a 1.0 or 2.0–cm excision, depending on the location,[27] while the AAD guidelines recommend a 1-cm margin for melanomas thinner than 2 mm.[5]

Several reports have evaluated the difference in local recurrence and survival in patients with melanomas treated with narrow (1 cm or 2 cm) and wide (3 cm to 5 cm) excision margins.[61-65] None of these studies found a significant improvement in local disease control or 5-year survival with the use of wider safety margins. Based on these independent studies, the melanoma community recommends the 1-cm to 2-cm excision margins as described above.

Prospective randomized trials were designed to test the hypothesis that thicker melanomas require wider margins of excision to reduce the incidence of locoregional events. In order for such a paradigm to be valid, one must assume that thicker lesions are more likely to be associated with occult, but clinically relevant, microscopic satellite disease that may remain after a narrow excision as a source of future locoregional relapse. Thin melanomas (≤2 mm) have been evaluated in 3 published trials, comparing 1 cm vs 3 cm or more,[61] 2 cm vs 5 cm,[62] and 2 cm vs 4 cm.[63] Patients with thicker melanomas (>2 mm) have been studied as well in 3 trials, comparing 2-cm vs 4-cm (2 trials)[63,64] and 1-cm vs 3-cm margins.[65]

Table 4. True-positive and false-positive rates associated with computed tomography imaging for the detection of metastatic melanoma.

Study	N	Type	True-Positive Rate	False-Positive Rate
Buzaid[56]	151	AJCC stage I, II, III	1.3%	15.9%
Buzaid[57]	89	Local and regional	7%	22%
Johnson[58]	127	AJCC stage III	15.7%	11.8%

Furthermore, the United Kingdom Melanoma Study Group recently published their experience with treating thicker melanomas with either a 1-cm or 3-cm margin.[65] A significant increase in locoregional events was observed in the 1-cm treatment arm, supporting the hypothesis that for thicker melanomas, 1 cm may be too narrow.

The long-term results from the World Health Organization trial comparing 1-cm vs 3-cm margins for thin melanomas revealed a statistically nonsignificant increase in local recurrence for the subset of patients with primary lesions between 1 mm and 2 mm.[66] It is these data that are responsible for the NCCN margins of excision recommendations in this subset of patients.[27]

VALUE OF SLN BIOPSY

The faculty recommended SLN biopsy for this patient. In patients with primary melanoma the status of the regional lymph nodes draining the primary tumor provides prognostic information that may help determine the subsequent treatment approach. In patients with melanoma of thickness >1.0 mm, lymphatic mapping and sentinel lymphadenectomy has become the method of choice to determine the histopathologic status of the clinically negative regional lymph nodes.[67] Prior to the introduction of SLN biopsy, elective lymph node dissection (ELND) was the only method to identify regional node metastases and stage the nodal basin.[68] However, ELND was not associated with a significant increase in overall survival, except for patients with nonulcerated melanomas, melanomas 1.0 mm to 2.0 mm thick, or melanomas on the extremities.[69] Therefore, routine ELND had limited therapeutic benefit and resulted in unnecessary removal of lymph nodes (and associated morbidity) in histologically node-negative patients.[68] While an overall survival advantage was not demonstrated for the routine use of ELND in the management of intermediate- and high-risk primary melanomas, data from one ELND trial[70] support the hypothesis that removal of regional lymph node metastases, when clinically occult, improves survival compared with waiting until these node-positive patients develop palpable disease. This observation is the result of the analysis performed by the investigators from the World Health Organization as part of the long-term follow-up of patients who participated in a prospective randomized trial evaluating the role of routine ELND in the management of primary trunk melanomas 1.5 mm or thicker. Patients in the ELND arm who were found to have microscopically involved nodes fared better than patients in the wide excision and watchful observation arm who underwent therapeutic node dissection after developing clinical nodal metastases.[70] Such an observation has been recently corroborated by the results from the MSLT-1 trial (detailed below).[68,71] Collectively, these findings support the "selective lymphadenectomy" approach to these primary melanoma patients via SLN biopsy. Such an approach avoids the unnecessary morbidity of ELND in node-negative patients and may optimize the survival of node-positive patients.

IS THERE A SURVIVAL BENEFIT FOR SLN BIOPSY?

It has been suggested that most occult SLN metastases eventually become palpable recurrences in the regional nodal basin that require delayed CLND or other treatment options.[68] In 1994, the international Multicenter Selective Lymphadenectomy Trial (MSLT-I) was initiated to compare the efficacy of SLN biopsy with that of watchful waiting.

Preliminary results of the MSLT-I trial failed to show a significant increase in overall survival for the entire population receiving immediate SLN biopsy. This result was not unexpected, as the type of patients included in the study had only a 20% rate of positive nodes, so 80% could not benefit from either SLN biopsy or CLND. However, when the overall survival of node-positive patients who received immediate CLND was compared with those in the delayed CLND group, a significant survival benefit was observed for the SLN biopsy population (71% survival vs 55%, $P = .0033$).[71] DFS was also significantly higher in the SLN biopsy group compared with patients who received delayed CLND. One argument to explain the difference is that some of the SLN-positive patients would not have gone on to develop clinically palpable disease, and this could impact the identified survival difference. However, in this population of patients, the incidence of clinically palpable node development (nodal failure) in the observation arm is actually slightly higher than the SLN positivity rate, suggesting that all positive SLNs will eventually become clinically palpable. Over time this difference may become greater as patients may continue to develop nodal metastases in the observation arm at a higher frequency than what occurs in the SLN arm secondary to false-negative SLN biopsies. Furthermore, the mean number of involved nodes at nodal recurrence was higher in the watch-and-wait group than in the SLN biopsy group, suggesting that removal of the SLN protected against nodal recurrence and development of palpable metastases.[71] Longer follow-up of this trial will be important in determining the survival advantage, if any, associated with early treatment of node-positive patients.

AJCC STAGE AS A PREDICTOR OF SLN POSITIVITY

The sixth edition of the AJCC staging system focuses largely on tumor thickness and ulceration to determine the stage of primary melanomas (Table 3).[3] The presence of ulceration automatically increases these melanomas to the next immediate staging group, whereas Clark level is currently only used to upstage IA melanomas (Clark level II or III) to stage IB (Clark level IV or V). In an attempt to correlate AJCC stage with SLN positivity, the group at the M. D. Anderson Cancer Center conducted a retrospective analysis of 1375 cases of primary cutaneous melanoma.[72] This study demonstrated that SLN positivity correlates with increasing AJCC stage, with positive SLNs found in 2% of patients with stage IA melanoma, 9% for stage IB, 24% for IIA, 34% for IIB, and 53% in patients with stage IIC melanoma. Therefore, AJCC stage may be used to help identify those patients most likely to benefit from SLN biopsy.

PREDICTORS OF SLN METASTASIS IN PATIENTS WITH THIN MELANOMAS

What would you do if the patient were a 21-year-old who presented with a 0.8-mm, nonulcerated, Clark level IV melanoma?

1) Nothing further (negative-margin biopsy as only treatment)
2) 1-cm excision, no nodal staging
3) 2-cm excision, no nodal staging
4) 1-cm excision, SLN biopsy
5) 2-cm excision, SLN biopsy

For patients with thin lesions and negative prognostic factors such as these, the authors recommend that the lesion be definitively excised with 1-cm margins and the option of SLN biopsy be presented to the patient. Historically, SLN biopsy was only offered to patients with melanomas 1 mm or thicker. A relatively low incidence of nodal involvement and a good long-term prognosis for patients with thin melanomas has generally discouraged the use of SLN biopsy in this population.[45,73] However, 10-year melanoma-specific mortality of 12% to 17% for patients with T1a and T1b lesions has prompted a search for a subset of patients with thin melanomas who may benefit from SLN biopsy.[45] To justify the use of SLN biopsy in thin-melanoma patients, investigators have made various attempts to identify prognostic factors that can accurately predict which of these patients are candidates for SLN biopsy. For example, Owen and colleagues found a gradient of survival impact among thin melanomas—at the upper thickness range for thin melanomas, Breslow thickness subgroups (ie, 0.8 mm vs >0.8-1.0 mm, ≤0.9 mm vs >0.9-1.0 mm) correlate with differences in survival to a greater extent than do Clark levels.[74]

The current NCCN guidelines for the management of melanoma recommend that patients with melanomas thinner than 1.0 mm exhibiting a positive deep margin, ulceration, vertical growth phase, or extensive regression should be considered candidates for SLN biopsy.[27] Indeed, when patients were classified based on the presence of primary tumor ulceration, the incidence of SLN metastases in patients with ulceration was nearly 3 times higher than in those without (35% vs 12%, $P<.0001$)[72] Likewise, mitotic rate has recently been shown to be another strong predictor of SLN metastasis: one study of 181 patients with melanomas less than 1.0 mm in Breslow depth showed that a mitotic rate >0 was significantly associated with a positive SLN ($P = .011$).[45] Of 103 patients with a mitotic rate greater than 0, a positive SLN was discovered in 8.7%. Conversely, none of the 78 patients with a mitotic rate of 0 developed nodal involvement.[45] In the same study, those patients with thin melanomas of at least 0.76 mm and a mitotic rate of 1 or greater were found to have an SLN-positive rate of 12.3%.[45]

A recent study by Sondak and colleagues[44] identified patient age as an independent prognostic indicator for SLN metastasis. In a review of 419 patients, the authors found that the rate of nodal involvement decreased as the patient's age increased. The Sunbelt Melanoma Trial also found that SLN metastasis becomes less common with increasing age.[75] Mitotic rate and Breslow thickness were the only other factors identified by Sondak's group to be significantly associated with a positive SLN.[44]

Patients with thin melanomas that contain features associated with SLN metastasis should be considered for SLN biopsy. However, because of the potential morbidity associated with this procedure, the health care provider should discuss the risks and benefits of SLN biopsy with the patient in detail. This conversation involves the patient in the decision-making process and allows the patient to make an informed choice regarding his or her care.

MANAGEMENT OF DEEP CUTANEOUS MELANOMA

What would you do if the patient were a 35-year-old man who presented with a 4.2-mm, Clark level IV, superficial spreading melanoma?

1) Wide excision alone
2) Wide excision plus SLN biopsy
3) Wide excision plus SLN biopsy plus interferon alfa-2b
4) Wide excision plus interferon alfa-2b

The authors recommend a wide excision with 2-cm margins, SLN biopsy, and discussion of interferon alfa-2b with the patient. Some of the arguments for or against SLN biopsy in deep cutaneous melanoma center around the impact of node positivity, since hematogenous spread becomes more likely with deep cutaneous melanoma. Various factors that independently determine the recurrence-free survival and overall survival in patients with thick melanoma include nodal status, ulceration, and vascular invasion. Investigators at M. D. Anderson found a 3-year overall survival in deep cutaneous melanoma of 89.8% for SLN-negative patients, compared with 64.4% for SLN-positive patients ($P = .006$).[76] The 3-year survival was 73.1% for patients with ulceration and 86.7% for those without ($P<.003$).[76] Zettersten and colleagues[77] confirmed the interaction of positive lymph node and ulceration in the prediction of overall survival of 329 patients with T4 melanoma and also found significant impact for tumor thickness and vascular invasion, with median overall survival rates of 5.0 years in patients without vascular invasion and 2.6 years in those with invasion ($P = .0036$). The same median survival rates (5.0 y vs 2.6 y) were found when patients with melanomas from 4 mm to 8 mm thick were compared with those whose tumors were thicker than 8 mm ($P = .0038$).[77] Other studies have also demonstrated the prognostic significance of SLN status in patients with thick melanomas.[76,78-84]

ADJUVANT THERAPY

The high risk of distant microscopic and regional nodal metastases in patients with 4-mm or thicker melanoma[76] would argue in favor of adjuvant therapy after definitive surgical excision and surgical management of the at-risk regional lymph node basin. Adjuvant therapy with high-dose interferon (HDI) for 1 year was approved by the FDA in 1995 based on the results of Eastern Cooperative Oncology Group (ECOG) trial E1684,[85] which showed significant increase in relapse-free survival (RFS) and overall survival (OS) in patients receiving HDI for high-risk melanoma. In this study of 280 patients with high-risk melanoma, 5-year RFS was 37% for patients receiving interferon alfa-2b (95% CI, 30% to 46%), compared with 26% (95% CI, 19% to 34%) for

patients treated with observation alone (one-sided $P = .0023$). The OS at 5 years was 46% in the interferon group (95% CI, 39% to 55%) versus 37% (95% CI, 30% to 40%) in the observation group (one-sided $P = .0237$).[85]

In an attempt to find the optimal dose of IFN alfa-2b to maximize the efficacy/tolerability balance, an additional trial was conducted to compare the profiles of HDI vs low-dose IFN (LDI) alfa-2b. The ECOG-1690[86] trial compared HDI against LDI and observation alone. The HDI regimen consisted of an induction phase of 20 MU/m^2/d for 5 days per week for 4 weeks, followed by a maintenance phase of 10 MU/m^2/d tiw for 48 weeks; patients in the LDI arm of the study received 3 MU/d tiw for 2 years.[86] The ECOG 1690 trial identified 5-year estimated RFS values of 44% for HDI, 40% for LDI, and 35% for observation ($P = .05$ for HDI vs obs groups).[86] However, there was no OS benefit in the E1690 trial.[86]

The ECOG 1694 trial[87] compared an HDI regimen with the ganglioside vaccine (GMK) in 880 high-risk melanoma patients. The trial was closed after the early analysis indicated significant treatment benefit of HDI compared with GMK with respect to both RFS and OS ($P = .0015$ for RFS and .009 for OS). The pooled analysis from ECOG 1684 and 1690 found a significant RFS benefit ($P = .0006$) but no OS benefit in patients treated with HDI vs observation.[88]

All three of the major ECOG studies with HDI included some patients with deep, cutaneous, node-negative melanoma (>4 mm in depth).[85-87] However, relatively small numbers of node-negative patients were enrolled in these studies, making subgroup analysis difficult. In addition, pathologic staging of the nodal basin was only required in 1 of the 3 studies, making interpretation of the risk status of the patients and the results of the intervention difficult. Even with these caveats, the relative benefit of IFN alfa-2b in node-negative vs node-positive patients was variable, making it difficult to assess the relative benefit of IFN alfa-2b in these populations.

In general, the authors agree that although deep cutaneous node-negative melanoma is considered high risk, the indications for adjuvant therapy have been disputed here more than for node-positive patients, partially because this subgroup has been less well studied in the clinical trials. However, it is notable that in the largest and most recent US Intergroup study, the clinically node-negative group derived the largest relative benefit (HR = 2.0), signifying 50% reduction of relapse risk. The health care provider and the patient may have difficulty deciding whether the benefit of IFN is worth the toxicity. Is the patient likely to benefit (are there subsets of patients who are more likely to benefit)? It behooves the physician dealing with such patients to review the data in the context of the risk projected.

RESPONSE MARKERS

In order to permit selection of patients most likely to benefit from the treatment, various investigators have studied the mechanism of action of interferon alfa-2b and sought to identify the potential markers of response to IFN. The recent study led by Dr Kirkwood's group on neoadjuvant IFN alfa-2b treatment of high-risk melanoma patients measured the expression of signal transducers and activators of transcription (STAT1 and STAT3) in tumors pre and post therapy.[89] Since STAT3 expression is associated with suppression of the immune response and STAT1 is associated with promotion of an effective immune response, the increase in the STAT1/STAT3 ratio in tumor samples obtained after IFN compared with pretreatment biopsies supports the elicitation of an effective immune response with IFN.[89] These findings support the STAT1/STAT3 ratio as a potential important biomarker of responsiveness to IFN. STAT1 and STAT3 may be involved with the development of atypical nevi (with STAT3 expression increasing with the degree of atypia). As in the case of melanoma, high-dose IFN also increases the STAT1/STAT3 ratio in these lesions, potentially pointing to a role for "STAT-modifying" agents in melanoma prevention strategies.[90,91]

Methylthioadenosine phosphorylase (MTAP), which catalyzes the phosphorylation of methylthioadenosine, is expressed to a greater degree in normal cells and tissues than in tumors, especially malignant melanomas. This is either due to the selective deletion of the region of the chromosome that codes for MTAP or hypermethylation of the promoter.[92] In a subgroup analysis of 26 patients with MTAP-positive melanoma, 18 patients who received interferon therapy had a significant benefit compared with 8 who did not receive interferon therapy ($P = .009$), while in the subgroup of 13 MTAP-negative patients, no survival benefit was observed with interferon ($P = .8$).[92] These data suggest that MTAP expression may be a potential marker of responsiveness to interferon.

Development of autoimmunity is a well characterized marker of response to IFN alfa-2b in patients with melanoma. However, in patients with metastatic melanoma the appearance of vitiligo or other autoimmune manifestations indicated longer survival than expected.[93,94] In a study by Gogas and colleagues[94] involving 200 patients with high-risk melanoma (stage IIB, IIC, and III) who received adjuvant HDI, the development of autoantibodies in 26% of patients was associated with significantly longer RFS (hazard ratio, 0.12; 95% confidence interval, 0.05 to 0.25; $P<.001$) and overall survival (hazard ratio, 0.02; 95% confidence interval, <0.01 to 0.15; $P<.001$) upon multivariate analysis. At the time the study was published, the median relapse-free and overall survival values were not reached in the autoimmunity group. Antithyroid antibodies were the most frequently observed antibodies.[94]

Induction of autoimmunity is a strong marker of response to interferon therapy. While we are not yet to the point where we can prospectively determine which patients will respond to therapy, cessation of treatment in individuals who fail to develop autoimmunity soon after initiation of therapy may spare these patients from the excess toxicity associated with this treatment. The identification of factors that can be used to predict response to interferon therapy will help melanoma clinicians target individuals to specific therapies, and the identification of clinical markers and biomarkers of response brings us closer to achieving this goal.

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Posttest Questions

Please answer each question on the space provided on page 24.

1. The presence of more than 10 dysplastic nevi has been demonstrated to increase an individual's lifetime risk of developing melanoma by a factor of ___?

   A. 2
   B. 8
   C. 12
   D. 23

2. All of the following are routine measures that should be taken by an individual with multiple atypical (dysplastic) nevi, EXCEPT:

   A. Undergo regular total body skin examinations
   B. Use sunscreen with an SPF of 15 or higher
   C. Undergo genetic testing for a p16 mutation
   D. Avoid excessive sun exposure whenever possible

3. The concept of melanocytic tumor of uncertain malignant potential (MELTUMP) is best defined as:

   A. A borderline lesion that may or may not be malignant
   B. Any melanoma greater than 3 mm in Breslow thickness that forms a visible "lump"
   C. A term for metastatic melanocytic cells that are found in the SLN
   D. A scale used to define the severity of atypia in any given nevus

4. When a patient presents with a lesion in which Spitzoid features are identified upon pathologic examination, which of the following would be an appropriate course of action to take?

   A. Do nothing; no further treatment is warranted
   B. Perform chest radiography to identify any potential metastases as soon as possible
   C. Completely excise the lesion
   D. Immediately begin the patient on a regimen of interferon alfa-2b

5. Each of the following is an essential piece of microscopic information to include on the pathology report, EXCEPT:

   A. Breslow thickness
   B. Clark level
   C. Presence of satellites
   D. Exact measurement of surgical margin width

6. Which of the following follow-up procedures is most practical for identifying melanoma recurrence in a patient with primary melanoma?

   A. Routine detailed history and physical examination
   B. Routine blood tests
   C. Routine chest radiography
   D. Routine PET/CT scan

7. For a tumor 2.8 mm in Breslow thickness, which of the following management strategies is recommended?

   A. 1-cm excision, no SLN biopsy
   B. 1-cm excision, SLN biopsy
   C. 2-cm excision, no SLN biopsy
   D. 2-cm excision, SLN biopsy

8. Each of the following is an established advantage of performing SLN biopsy, EXCEPT:

   A. Accurate staging
   B. Low morbidity relative to elective CLND for the node-negative patient
   C. Significantly improved overall survival vs observation and therapeutic node dissection

9. Given similarities in all other risk factors and pathologic features, which of the following patients with melanoma would be more likely to have a positive SLN?

   A. A 15-year-old boy with 3 mitoses in the pathology report
   B. A 62-year old man with 0 mitoses in the pathology report

10. Which of the following have been studied as potential markers of clinical response to interferon alfa-2b?

    A. STAT1/STAT3
    B. MTAP
    C. Autoimmune response
    D. All of the above

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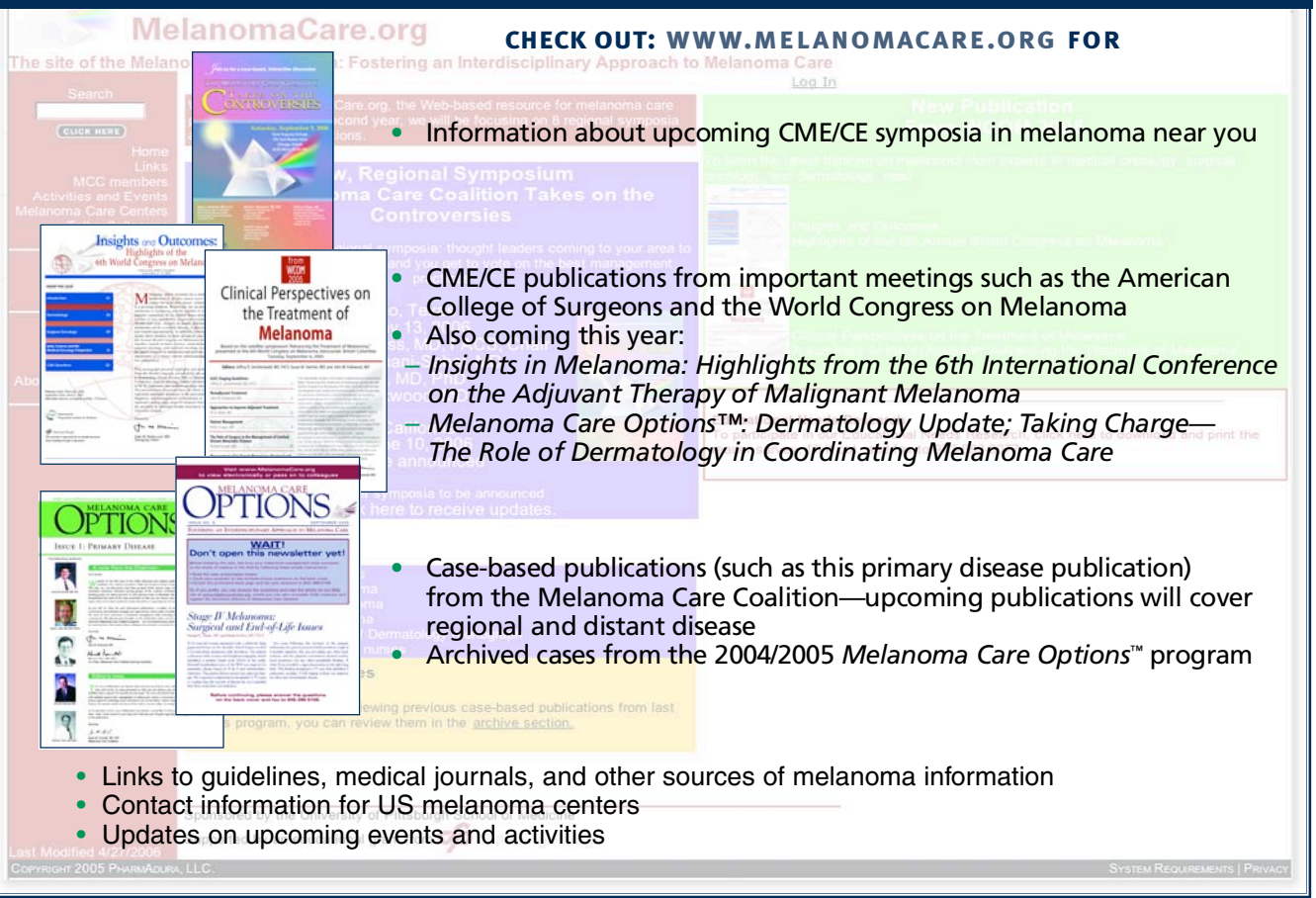

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Evaluation Form

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 following educational objectives achieved?

A. Outline the appropriate management strategies for patients presenting with atypical nevi
0 0 0 0 0

B. Compare and contrast types of biopsy and describe when each should be used
0 0 0 0 0

C. Describe the appropriate use of surveillance radiographs and blood tests in patients with early melanoma
0 0 0 0 0

D. Formulate a pathology report containing the necessary information to allow an informed treatment decision to be made
0 0 0 0 0

E. Offer appropriate recommendations for excision margins of the primary site based on microstaging information
0 0 0 0 0

F. Discuss the role of SLN biopsy in localized melanomas
0 0 0 0 0

G. Explain the rationale for tumor cutoff points for performing SLN biopsy
0 0 0 0 0

Very Low Low Moderate High Very High

2. To what extent were you satisfied with the overall quality of the educational activity?
0 0 0 0 0

3. To what extent was the content of the program relevant to your practice or professional responsibilities?
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4. To what extent did the program enhance your knowledge of the subject area?
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7. To what extent did the activity present scientifically rigorous, unbiased, and balanced information?
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Answer the Posttest Questions Here

1. ☐ 2. ☐ 3. ☐ 4. ☐ 5. ☐ 6. ☐ 7. ☐ 8. ☐ 9. ☐ 10. ☐

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AUGUST 2006

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