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MELANOMA CARE
OPTIONS

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Stage IV Melanoma: Surgical and End-of-Life Issues

Kenneth K. Tanabe, MD, and Merrick Ira Ross, MD, FACS

A 63-year-old woman presented with a relatively large pigmented lesion on her shoulder. Initial biopsy revealed a 4.2-mm–thick melanoma with ulceration. The patient underwent wide excision and lymphoscintigraphy, which identified a sentinel lymph node (SLN) in the axilla. Sentinel lymphadenectomy of the SLN was negative for metastatic disease based on H & E and immunohistochemistry. The patient did not receive any adjuvant therapy. She requested computerized tomography (CT) scans to confirm that she was free of disease but was counseled that these scans were not indicated.

Two years following the excision of the primary melanoma, the patient presented with persistent cough of 6 months' duration. She was not taking any other medications, and her physical examination showed neither local recurrence nor any other remarkable findings. A chest X-ray revealed a vague abnormality in the right lung field. This finding prompted a CT scan that identified 2 pulmonary nodules. A full staging workup was negative for other sites of metastatic disease.

Before continuing, please answer the questions on the back cover and fax to 845-398-5108.

Editorial

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

In this issue of *Melanoma Care Options*, we describe the course of a patient who develops metastases following excision of a primary melanoma on the shoulder. Discussions surrounding this case emphasize how the strategy for managing melanoma evolves as the patient progresses through disease stages. The case brings up prognostic features that influence recurrence, survival, and suitability for various therapies; pharmacologic and surgical management of progressive disease; appropriate follow-up measures at various stages of disease; and the role of hospice in end-stage disease. Specifically, this case explores factors that influence the decision to perform a sentinel lymph node biopsy at diagnosis of primary melanoma; issues that influence the decision to recommend adjuvant therapy; the role of biopsy, excision, or palliative surgery for metastatic lesions; and the timing of discussing end-of-life issues. The diagnosis of metastatic melanoma presents a number of difficult decisions for clinicians and their patients. Balancing the relative merit of management options—from aggressive treatments to palliative therapy and hospice care—remains challenging. We hope this case provides insights as you encounter patients with metastatic disease, and we anticipate hearing your thoughts as you consider these issues.

Kenneth T. Tanabe, MD

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Continuing Medical Education Information

Instructions for Participation

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 post-test answer and evaluation form at the end of the newsletter and fax or mail these back to the address listed by September 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 therapies for the management of stage IIC melanoma
- Describe the factors affecting the prognosis of stage IV melanoma
- List the advantages/disadvantages of aggressive staging approaches in stage IV melanoma
- Evaluate the role of palliative surgical techniques in patients with multisite metastatic melanoma
- List the factors to consider in discussing palliative care and hospice with a patient with metastatic melanoma

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

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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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Stage IV Melanoma: Surgical and End-of-Life Issues

Kenneth K. Tanabe, MD

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CASE PRESENTATION

As discussed on the front cover, a 63-year-old woman presented with a relatively large pigmented lesion on her shoulder. Initial biopsy revealed a 4.2-mm–thick melanoma with ulceration. The patient underwent wide local excision and lymphoscintigraphy, which identified a sentinel lymph node (SLN) in the axilla. Following sentinel lymphadenectomy, the SLN was found to be negative for metastatic disease based on H & E and immunohistochemistry. The patient did not receive any adjuvant therapy at this time. According to the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) 2002 staging guidelines, this patient has stage IIC disease.[1]

APPROPRIATENESS OF THE SLN BIOPSY

The expert panel was asked whether a SLN biopsy should have been performed in a patient who presented with a thick, ulcerated melanoma. The overwhelming majority of the expert panel—95%—responded that SLN biopsy was an appropriate measure to undertake. The dissenting 5% likely felt that patients with a thick, ulcerated melanoma were already at high risk of metastasis,[1-3] superseding the need to identify a positive lymph node or nodes.

Dr Kenneth Tanabe, co-moderator of the panel discussion, noted that this philosophy may reflect an outdated paradigm dating back to an era that focused on the possibility that elective lymph node dissection may enhance survival for patients with intermediate thickness melanomas who immediately underwent this procedure.[4-6] Dr Merrick Ross, who also moderated the discussion, suggested that some clinicians may be skeptical about the role of local/regional therapies in patients with this type of high-risk lesion, which may cause them to be reluctant to employ SLN biopsy. However, the majority of the panel agreed that the heterogeneity of disease and outcomes in the patient population with thick melanomas supports the use of SLN biopsy to determine if lymph nodes are involved in order to direct appropriate additional therapy.

ROLE OF ADJUVANT THERAPY

Given the negative status of the SLN, participants were queried whether

they would recommend adjuvant therapy in this patient. The expert panel was split, with 50% voting to offer adjuvant therapy and 50% opting otherwise, reflecting the controversy in the field regarding the suitability of adjuvant therapy in patients with thick lesions but pathologically documented node-negative disease. Dr Steven O'Day pointed out that the literature addressing the influence of SLN positivity on outcomes in patients with thick melanomas runs the gamut, with several publications reporting a high correlation between node-negative disease and improved survival[2,3,7,8] and others showing less impact.[9] Dr Ross cautioned against using SLN status as the only consideration for adjuvant therapy, noting that other tumor parameters can negatively affect outcomes.

That said, SLN status appears to be the most powerful predictor of disease-free survival for clinical stage I and II melanoma patients as a group (Table 1). By determining the patients' true node status via pathologic staging, disease-free survival rates reached 88.5% for confirmed node-negative patients, compared with only 55.8% for patients found to be node positive (*P*<.0001).[7] Likewise, disease-specific survival rates were significantly higher in the SLN-negative patients compared with SLN-positive patients (96.8% vs 69.9%, *P*<.0001).[7] Thus, by multivariate analysis, SLN status was the most powerful prognostic factor that influenced survival. However, within the node-negative population, tumor thickness and ulceration were shown to be independent predictors for disease-free and disease-specific survival, which underscores the importance of basing recommendations for adjuvant therapy not solely on SLN status for patients with stage I or stage II disease.[7]

Restricting the analysis to a patient population with thicker melanomas revealed a similar trend. In a study of 131 patients with lesions ≥ 4 mm, 28% relapsed within 3 years.[8] Three-year, disease-free survival rates varied substantially according to SLN status, reaching 82.4% in patients with node-negative disease but only 58.0% in patients with node-positive disease (*P*<.03).[8] Correspondingly, overall survival in SLN-negative patients was 89.8% compared with 64.4% in node-positive patients (*P* = .006).[8]

While SLN status appears to be a strong predictor of patient outcome across tumor thicknesses, it certainly isn't the only parameter that is predictive of disease course. Nearly 10% of patients in the aforementioned study did not survive 3 years.[8] Other tumor characteristics, such as ulceration, are associated with disease progression and mortality. When assessing the relative merit of adjuvant therapy in node-negative patients with thicker melanomas, other contributing factors should be considered.

But has the role of adjuvant therapy in patients with high-risk primary

Table 1

Survival According to SLN Status

Parameter	Negative SLN	Positive SLN	*P*
Patients with a primary tumor greater than 1 mm or less than 1 mm with ulceration or Clark level IV			
Disease-free survival	88.5%	55.8%	<.0001
Disease-specific survival	96.8%	69.9%	<.0001
Patients with a primary tumor greater than 4 mm			
Disease-free survival	82.4%	58.0%	<.03
Disease-specific survival	89.8%	69.4%	= .006

Sidebar 1

The Role of PET Scans in Detecting Melanoma Metastases

Controversy surrounds the routine use of PET scans for the detection of melanoma metastasis, particularly following initial staging, and the panel was similar split regarding the merit of the approach. Advocates of the technique herald the ease of performing whole body scans to readily detect disease, when patients are most amenable to treatment or able to enter clinical trials. Opponents argue that the rate of false positives combined with the expense of the procedure diminishes the utility of PET scanning as a routine follow-up measure. The literature is equally divided.

The low sensitivity of PET relative to SLN biopsy in identifying lymph node micrometastases argues against PET at initial staging of clinically normal lymph nodes.[38] Clinical studies of the utility of PET in identifying metastatic disease typically employ sensitivity and specificity, calculations which account for the number of false negatives and false positives, respectively. In other words, procedures with a high sensitivity do not overlook lesions, while those with a high specificity do not produce large numbers of false-positive results. In 11 studies of the ability of PET to detect malignant lymph nodes, sensitivities ranged from 0% to 100%, while specificity ranged from 88% to 100%.[38] Thus, PET did not efficiently detect lymph node metastases. However, an aggressive staging regimen involving PET in a pilot study of 43 patients with intermediate-thickness, high-risk primary melanoma, identified 2 patients with secondary primary cancers.[39] These data suggest that larger prospective clinical trials of PET at staging may reveal additional benefit beyond identifying micrometastases.

Most of the panel agreed that PET plays a larger role in evaluating patients prior to surgical resection of metastatic disease, and some studies confirm its utility in this role. Data taken from 7 clinical studies suggests that PET detected metastases with both high sensitivity and specificity in areas as diverse as the abdomen, mediastinum, liver, bones, and skin. Sensitivity of PET in these studies ranged from 71% to 100%, with the exception of the pulmonary and small lesion (<1 cm) subsets in 2 studies, which demonstrated sensitivities of 15% and 13%, respectively. The specificity of PET exceeded 75% in most of the subset analyses of these studies, and was more than 94% in half. Exceptions included lesions under 1 cm, which had 33% specificity, and a study of all foci, which had 56% specificity.[38] Taken together, these data suggest that PET is the most accurate imaging modality for identifying metastases in patients at high risk for harboring distant disease.

Table 2

Clinical Trials of Adjuvant Therapy Enrolling Patients With Surgically Resected, Node-Negative Melanoma[14]

Treatment	Sponsor(s)	Location(s)
CpG 7909 immune stimulant MAGE-3 antigen Montanide ISA-51 gp100 antigen Tyrosinase peptide	University of Southern California, National Cancer Institute (NCI)	Los Angeles, Calif
gp100 antigen GM-CSF-plasmid DNA melanoma vaccine tyrosinase peptide	Memorial Sloan-Kettering Cancer Center, NCI	New York, NY
Human gp100 DNA vaccine Mouse gp100 DNA vaccine	Memorial Sloan-Kettering Cancer Center, NCI	New York, NY
GM2-KLH vaccine QS21 immune stimulant	European Organization for Research and Treatment of Cancer	Numerous worldwide
MART-1 antigen Montanide ISA-51 gp100 antigen GM-CSF tyrosinase peptide	University of Southern California, NCI	Los Angeles, Calif
gp100 antigen Interleukin-2 Montanide ISA-51 Various MART-1 epitopes	National Cancer Institute	Bethesda, Md
IFN alfa	Eastern Cooperative Oncology Group, NCI Southwest Oncology Group Cancer and Leukemia Group B National Cancer Institute of Canada	Numerous worldwide

tumors been firmly established? Many panel participants felt that the hard data supporting its role in stage I and II patients remained lacking. The faculty specifically noted the paucity of data from prospective trials about the efficacy of adjuvant therapy in patients with thick melanoma but node-negative disease. The panel then discussed the data that were available.

Interferon alfa-2b

The current literature for adjuvant therapy with high-dose interferon alfa-2b (IFN alfa-2b) in melanoma includes studies involving few patients with node-negative disease.[10-13] In Eastern Cooperative Oncology Group (ECOG) trial 1694, 23% of patients had thick primary melanomas; these patients contributed to the 75% relapse-free survival rate observed for patients treated with IFN alfa-2b.[12] However, the node status of these patients was not definitively known. While the vast majority did not have pathologic nodal staging,[12] certainly some—the panel agreed about half—probably had node-positive disease. In a subset analysis over all thickness categories, patients with node-negative disease derived the greatest benefit from IFN alfa-2b therapy.[12] Thus, patients with thick melanomas and negative node status may have benefited from IFN alfa-2b therapy; however, the panel agreed that larger prospective trials in this specific patient population would greatly enhance the ability of clinicians to confidently address the role of IFN alfa in these types of patients. Clinical studies to address this issue are ongoing (Table 2).[14]

Vaccine therapy

Some of the faculty members have had experience using vaccines in both therapeutic and adjuvant settings in patients with stage IIC melanoma. Again, few publications address the issue of vaccine therapy for patients with node-negative disease.[15-20] Currently, no vaccines are approved as adjuvant therapy for melanoma. Thus far, vaccine trials have met varying degrees of success, ranging from no effect[16,18,19] to potential benefit restricted to patients of a particular haplotype.[15,17,20] Numerous ongoing studies are investigating the role of vaccine therapy in patients with surgically resected node-negative melanoma, which may clarify the role of this type of adjuvant approach (Table 2).[14] Through these trials, investigators are trying to refine vaccine therapy and improve immunologic responses by using combinations of peptide vaccines with biologic response modifiers and immune stimulants.

FOLLOW-UP RECOMMENDATIONS

When asked about the appropriate follow-up regimen for patients with stage IIC melanoma, the panel was split on the utility of radiologic and laboratory tests as additional follow-up measures. Approximately one third of participants (37%) elected to follow the patient on an aggressive regimen that includes history, physical exam, PET and/or CT scan, and serum lactate dehydrogenase (LDH) testing. Another third (31%) opted for the same follow-up measures with chest X-ray replacing PET/CT scanning. The remaining third (31%) felt that history and physical examination alone were sufficient. None of the panel voted to leave follow-up to the patient's discretion.

For patients with stage IIC melanoma, National Comprehensive Cancer Network (NCCN) guidelines state that chest X-ray and LDH are optional.[21] Additionally, recent data suggest that elevations in LDH do not aid in early detection of metastases.[22] Furthermore, a study that followed patients who have been previously diagnosed with stage I, II, or III disease found no significant elevation in LDH levels as they initially entered stage IV.[23] These studies question the value of serum LDH testing of patients in early stages of melanoma.

As the polling results show, participants who opted for imaging studies were divided in approach. Dr O'Day reported that PET/CT fusion scans are the approach used at the Los Angeles Clinic and Research Institute in high-risk patients (40%-80% recurrence risk), noting that detecting metastatic disease earlier prompts entry into clinical trials, which may help the individual patient by gaining access to therapy. In addition, entry of suitable patients into the clinical trial setting helps the melanoma population as a whole through the development of improved therapies. He added that most patients prefer to know the status of their disease earlier rather than later, when therapeutic choices are more restricted and time may be more limited. Dr Averbook agreed with the PET/CT scan approach, saying that his institution includes PET/CT scanning as part of the follow-up regimen for patients with lesions greater than 4 mm. He pointed out that negative findings provide patients with great relief. (Sidebar 1 presents more information regarding the role of PET scan in detecting melanoma metastases.) In addition, he noted that this approach has revealed other types of cancers as well. Patients diagnosed with melanoma carry a higher risk of developing subsequent cancer.[24,25] This observation reflects the experience of Dr Ross as well, who noted that while analysis of their data showed PET scanning or CT scanning to have a higher rate of false positives than melanoma-specific true positives, PET/CT scans may actually detect secondary cancers at a higher rate than melanoma metastases. Dr O'Day added that in his experiences, the combined PET/CT fusion scan approach leaves less room for error in interpreting test results and vastly reduces the rate of false positives.

However, not all participants fully endorsed the idea of PET scans or combined PET/CT scanning to detect occult disease. From an economic perspective, the less expensive CT scans alone have the ability to detect metastatic disease, noted Dr Goydos. Along this line, the reduced cost and ease of performing an X-ray perhaps underlies the rationale of those participants who selected this imaging technique in place of the more expensive options.

PATIENT CASE REVISITED

In this case, the patient was concerned about disseminated disease at the time of diagnosis and requested CT scans. She was counseled that these scans were not indicated. Two years later, the patient presented with persistent cough of 6 months' duration. The patient, a heavy smoker, was not taking any medications and her physical examination showed neither local recurrence nor any other remarkable findings. She underwent a chest X-ray, which showed a vague abnormality in the right lung field. This finding prompted a CT scan that identified 2 pulmonary nodules (Figure 1). A full staging workup was negative for other sites of metastatic disease.

Based on these findings, the panel was asked whether biopsy of one of the lung nodules was necessary. The majority of participants (88%) voted to perform a biopsy. The dissenting 12% of the panel felt that the presence of multiple nodules argued against biopsy. Dr O'Day, who voted against biopsy of the pulmonary nodules, stated that although he would opt to remove a solitary nodule, the presence of multiple small nodules generally makes it difficult to biopsy and obtain relevant pathologic information. He noted that clinical suspicion of a new primary tumor, particularly in the mediastinal nodes or abdomen, might warrant biopsy, but that he does not routinely biopsy multiple nodules. In contrast, Dr. Olencki supported the panel's endorsement of biopsy of a pulmonary nodule, stating that a physician's decisions at this point substantially influences subsequent therapeutic measures for the patient, so it is best to have as much information as possible.

In this case, the patient did have a biopsy of the larger pulmonary nodule, taken via fine needle aspiration, which was positive for melanoma. Thus, according to AJCC/UICC 2002 staging guidelines, the patient had entered stage IV disease.[1]

SITE-SPECIFIC PROGNOSIS OF STAGE IV MELANOMA

According to the AJCC/UICC staging criteria, patients with lung metastases fall into the M1b category. For these patients, the 1-year median survival rate is 57.0%, which falls to 6.7% after 5 years (Table 3).[1] As illustrated in Figure 2, at first, patients with metastases to the skin, subcutaneous tissues, or distant lymph nodes tend to fare the best, with patients with visceral sites outside the lung faring the worst. Patients with lung metastases fall in between the other 2 subclasses in the first few years. However, by 2 years, survival rates of patients with lung metastases begin to parallel those with other visceral metastases or elevated LDH.[2]

With this information in hand, participants were asked what steps they would take in treating this patient. Nearly two thirds of respondents (66%) opted to immediately resect the pulmonary lesions, while a small minority (6%) chose observation and repetition of staging in 2 months. This breakdown of responses does not necessarily reflect what occurs in

actual practice, where many asymptomatic patients are observed and restaged at later times. Immediate resection may not be the best option as it does not allow for time to assess overall tumor biology.

The remainder of participants (29%) chose systemic therapy followed by resection. While neoadjuvant therapy prior to surgery represents an attractive hypothetical approach, no data support this approach nor is there strong consensus regarding the optimal neoadjuvant therapy to employ. Dr Goydos said that he selected this option because the pace of disease was unknown in this patient. He pointed out that even if the metastases were removed in this patient, she could develop additional lesions in a few months, making the initial surgery fruitless. He mentioned IL-2 or dacarbazine (DTIC)-based regimens as proven systemic therapies that improve survival in some patients with metastatic melanoma who can tolerate these agents.[26,27] Providing systemic therapy for a time allows the clinician to assess the rate of metastasis development and the utility of surgery as therapy.

Dr O'Day concurred with waiting prior to surgery, stating that his institution tends to wait a few months to calculate tumor doubling time before surgery. During this time, he might discuss systemic therapy as an option, preferring a clinical trial of a relatively nontoxic agent over more toxic therapies such as biochemotherapy.

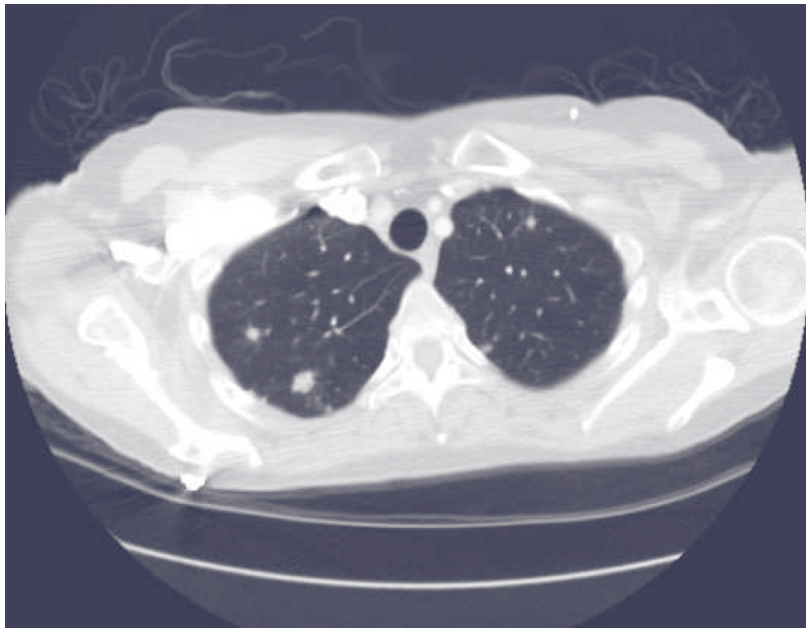
Both tumor-related and host-related factors guide treatment recommendations in patients with metastatic melanoma, particularly in those with minimal metastatic disease, such as was the case for this patient. Tumor-related issues include resectability, the site and number of metastases, disease-free interval between original diagnosis and development of metastases, and tumor doubling time. Host-related factors include performance or functional status, extent and severity of any comorbidities, and risk of the intervention. The panel went on to review the data for selected factors that influence resectability of metastases.

Table 3

Prognosis of Metastatic Melanoma According to Site[1]

AJCC M Category Site	1-Year Survival	5-Year Survival
M1a Skin, SQ tissues, lymph nodes	59.3%	18.8%
M1b Lung	57.0%	6.7%
M1c Liver, bone, brain	40.6%	9.5%

Figure 1



Computerized tomography scan of the chest. Note the 2 pulmonary nodules in the right lung field. Photograph courtesy of author.

Influence of site of metastasis

As might be expected, the location of the lesion influences the ease of resection and survivability following. Table 4 summarizes the survival statistics garnered from several series of patients who underwent resection of metastases in different sites. In some series, 5-year survival rates approach 40%. With respect to this case, 5-year survival rates for patients who underwent resection of lung metastases reached 29% for patients with a solitary metastasis and 5% to 25% in patients with multiple lesions (JWCI, SMU, unpublished data, 2005).[28,29] Thus, pulmonary lesions represent a type of metastasis amenable to surgery that may improve survival of patients.

Influence of tumor doubling time

Tumor doubling time describes the time required to double the tumor size. Methods used to calculate tumor doubling time vary, but rates for pulmonary lesions can be determined by using serial radiographs to measure the changing diameters of each nodule.[30] Studies of tumor doubling time in melanoma have revealed that metastatic melanomas double in size more

rapidly than do primary melanomas. While primary melanomas have a median and mean tumor doubling time of 94 and 144 days, respectively, the median and mean tumor doubling time of metastatic melanoma diminishes to 33 and 64 days, respectively.[31] Clinicians may use tumor doubling times to determine suitability of patients for resection of lesions.

As might be expected, survival rates for lesions with shorter doubling times are very poor. In addition, 2 studies have demonstrated that shorter tumor doubling times are associated with a worse outcome following surgical resection of pulmonary metastases. In a study of a variety of primary tumor types, 63% of patients with tumor doubling times of greater than 40 days survived 5 years. In stark contrast, no patient with a tumor doubling time of less than 40 days survived even 3 years.[30] A more recent analysis that looked at the pulmonary lesions of metastatic melanoma exclusively produced similar results. In this study of 45 patients, more than 20% of patients with lesions having tumor doubling times of greater than 60 days survived 5 years, compared with 0% of patients with lesions having shorter tumor doubling times ($P < 0.0001$).[32] These data suggest a tumor doubling time cutoff of 40 to 60 days might be used when deciding on the benefit of surgery for metastatic melanoma.

Dr O'Day suggested that formal calculation of tumor doubling time might not be necessary, but that observing the disease for a month or two can provide valuable information about the biology of the existing tumor as well as identify the development of new disease. He noted that lesions that rapidly increase in size tend to occur in conjunction with the development of new lesions, both of which influence the decision to resect. Most patients with surgically resected stage IV disease eventually go on to develop further stage IV disease, which underscores the need for larger prospective randomized trials that precisely identify the impact of tumor doubling times on survival following resection.

Influence of performance status

The performance status of the patient also influences the decision to resect metastases.[33] The exacting nature of many surgical procedures requires that patients have sufficient ability to recover. Patients with Karnofsky performance status greater than 70% (or a World Health Organization status of 0 or 1, who are deemed "functionally independent") fare better following surgery.[34] Correspondingly, patients with decreased performance status are less likely to withstand aggressive surgery.[30]

WHEN TO INTRODUCE END-OF-LIFE ISSUES

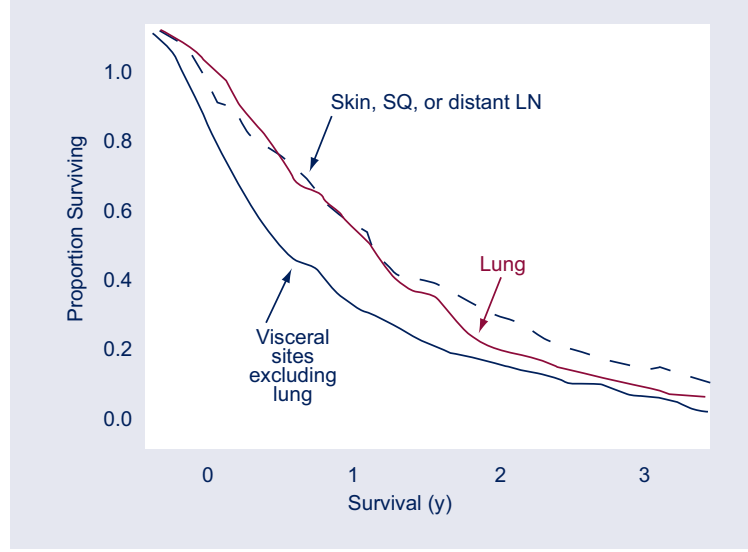
Given the relatively poor prognosis for patients with stage IVB disease, the panel was asked if they would begin discussions of end-of-life issues at this point. While 59% of participants deemed this the appropriate time, a substantial proportion (41%) did not feel that this was the time to introduce end-of-life issues. One of the faculty members suggested that there is never a bad time to discuss these issues in stage IV patients, given that there is a high risk of recurrence even following resection, and that these patients eventually have to face these concerns. Dr Averbook disagreed somewhat, saying that clinicians need to balance realism

Table 4

Survival of Patients Following Resection of Melanoma Metastases[28,29,41]

Site	Median Survival	5-Year Actuarial Survival
Skin, SQ tissues	17 to 48 mo	10% to 30%
Lung	9 to 19 mo	5% to 25%
(Solitary metastasis)	16 to 24 mo	29%
Brain	4 to 17 mo	7%
Gastrointestinal (excluding liver)	8 to 49 mo	28% to 41%
Liver	Not available	29%

Figure 2



Survival curves of 1,158 patients with metastatic melanomas at distant sites. Survival differences are significantly greater for skin, subcutaneous, and distant lymph node metastases compared with lung metastases ($P = .003$) or other visceral sites of metastases ($P < .0001$).[2] Adapted from Balch CM, et al. *J Clin Oncol.* 2001. Adapted with permission from the American Society of Clinical Oncology.

with some degree of optimism for patients with early metastatic disease to help the patients get through the process psychologically. Health care providers should not rush into the end-of-life discussion without consideration of the person's coping mechanisms. Timing is important.

Although several panel members noted that patients tend to be more focused on treatment and recovery at this stage of disease, the conclusion following subsequent panel discussion was that this is probably the best time to begin early discussions of end-of-life issues. One of the faculty added that the breadth of discussions can be expanded as the patient's condition worsens. Early and balanced introduction of all management options could foster a patient-directed transition between aggressive treatment and hospice care at the appropriate time.

The patient in this case had both nodules removed via a video-assisted thoracoscopic approach. Both nodules were positive for melanoma and clear margins were obtained. Thus, the patient was rendered disease-free.

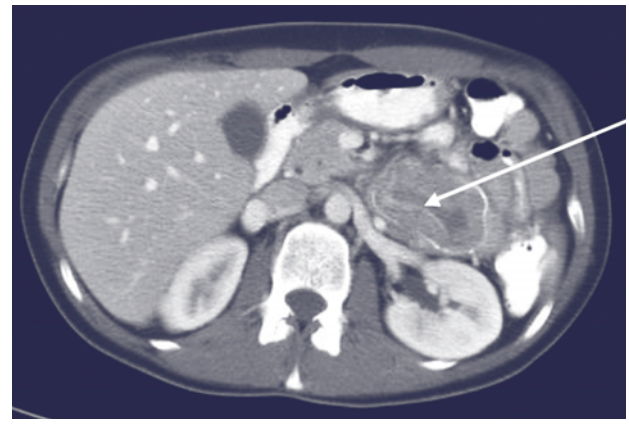
FOLLOW-UP RECOMMENDATIONS REVISITED

Do follow-up recommendations change for a patient with resected stage IV with no evidence of disease? When the choices for follow-up recommendations were resubmitted to the expert panel at this point of the case, about half of the participants (53%) opted for an aggressive approach to follow-up, which includes history and physical examination, PET or CT scan, and serum LDH. This shift in response reflects the realization that disease will likely recur, and attempts to detect recurrence at the earliest possible stage may allow for entry into clinical trials or further resection. An additional 26% chose a similar, but more economic approach, which used X-rays rather than PET or CT scans. The remaining 20% of participants opted to reserve scans for evaluation of symptoms and selected a follow-up approach that involved simply patient history and physical examination.

For patients with stage IV melanoma who are rendered free of disease, NCCN guidelines recommend a follow-up strategy similar to stage III disease.[21] This follow-up approach indicates that chest X-ray and LDH testing are optional and that further imaging by CT scan or PET/MRI should be performed as clinically indicated.[21]

During the course of follow-up, the patient in this case presented with melenic stools. Continued loss of blood led to anemia, which required transfusions every other week. The patient received a full staging workup, which showed a metastasis at the juncture of the distal duodenum and proximal jejunum (Figure 3). Other scans revealed 3 additional asymptomatic brain metastases. Further GI workup demonstrated the presence of 2 adjacent lesions but no other obvious disease in the remainder of the alimentary tract.

Figure 3



A CT scan of the small bowel of a patient with metastatic melanoma revealed a 3.6-cm by 5.0-cm mass at the juncture of the distal duodenum and proximal jejunum of the small bowel. Photograph courtesy of author.

APPROACH TO THE PATIENT WITH MULTISITE DISEASE

Given the presence of symptomatic multisite disease, the panel was polled regarding the next steps for this patient. The consensus (85%) felt that treatment should include resection of the small bowel for palliation and prophylactic irradiation of the brain to prevent development of symptoms. The remainder of the panel (15%) opted for supportive care and referral to hospice. No participants considered systemic therapy to be an appropriate choice at this time.

Management of GI metastases

Melanoma frequently metastasizes to the GI tract, and usually multiple sites in the small intestine harbor disease. Gastrointestinal metastases commonly manifest with chronic bleeding, but may also produce acute complications, including obstruction, massive bleeding, or perforation.[30]

If feasible, resection is the treatment of choice, particularly if all disease can be removed, because it can effectively palliate symptoms.[28] Following surgery, almost all patients experience relief of presenting GI tract symptoms. In a study of 124 patients who underwent surgery for metastases in the stomach, small intestine, colon, or rectum, those patients receiving palliative procedures alone exhibited a median survival of 5.4 to 5.7 months. Palliative procedures do not extend lives substantially because the entire tumor is not removed; however, most patients demonstrate palliation of

symptoms, which improves the quality of their remaining lives. In contrast to palliative procedures, curative resection extended survival to a median of 48.9 months.[35]

Small-bowel resection is the most common operative intervention for melanoma metastasis to the GI tract, carrying a very low postoperative mortality rate of 2.9% and an acceptable postoperative morbidity rate of 8.8%.[36] Thus, surgery improves symptoms in most patients and prolongs survival in patients rendered free of disease. If disease is extensive and unresectable, systemic therapy may be employed.

In this case, the patient elected to not resect. She became anemic and fatigued and experienced substantial abdominal pain. These symptoms forced her to spend most of her time on the couch, which concerned her family and increased their desire for her to have additional treatment. However, the patient did not want further aggressive treatment.

PALLIATIVE CARE AND HOSPICE

In cases such as these, clinicians must use an approach that incorporates the concerns of both patient and family. Reviewing the benefits and toxicities of additional treatment allows the patient and the family to decide if the merit gained is worth the physical, economic, and psychological cost of further treatment. In the same vein, a balanced discussion of the likelihood of benefit from additional treatment and eligibility for clinical trials may help those desiring more therapeutic options. Clinicians also need to discuss patient goals and introduce hospice as part of the overall care plan. (See Sidebar 2 for a discussion of hospice services.)

When bringing up hospice, many people may be under the false impression that hospice replaces medical care. Practitioners need to clarify that hospice is an addition to the treatment plan and that they will be available for consultation and continued access by the patient. One of the faculty pointed out that many patients and their families strongly desire input from their own physician throughout their hospice care, which lessens the feeling of abandonment patients may face when entering end-of-life care under a new treatment team.

Dr Rebecca Ferrini asserted that waiting to bring up palliative care, hospice, and end-of-life issues until all treatment options are exhausted might not be the appropriate mindset. Instead, ongoing discussions of the patient's values and goals over the course of disease management gradually covers these topics, easing the transition of the patient and their loved ones through various stages of disease. One of the faculty, citing the inadequacies of clinicians in giving bad news,[37] suggested that opting for aggressive treatments at the expense of honest discussions may be a shortcoming of those who treat melanoma. She agreed with Dr Ferrini that a continuum of discussion earlier in disease management is more appropriate.

Dr Ferrini recommended an approach for patients with metastatic melanoma in which data regarding treatment options are presented in a positive manner by emphasizing that some patients do well even when survival statistics generally say otherwise. The panel agreed that practitioners must recognize that they must leave the door open for any decision and respect the decision of patients who do not want addi-

Sidebar 2

Hospice Services

Hospice is a health care and support system for terminally ill patients and their families. Typically home-based, hospice care is also provided in freestanding hospice centers, hospitals, and nursing homes and other long-term care facilities. The services provided by hospice include:

- Nursing
- Pastoral care
- Psychosocial support
- Volunteers
- Home care aides
- Hospitalization for acute management of uncontrolled pain and symptoms
- Outpatient services
- Supplies, medications, equipment
- Bereavement services for 1 year after the death

Providing this variety of services requires an multidisciplinary team, which typically includes the patient's personal physician, a hospice physician (or medical director), nurses; home health aides; social workers; clergy or other counselors; trained volunteers; and speech, physical, and occupational therapists, if needed. Medicare, Medicaid, most private insurance plans, HMOs, and other managed care organizations cover hospice care.

Sidebar 3

Introducing Hospice

The faculty agreed that end-of-life issues, including hospice, need to be discussed as patients enter stage IV disease. While many physicians can easily discuss theories and data related to disease recurrence, survival, and therapeutic options, some struggle with more qualitative and holistic issues. Yet, often a patient's best interest lies in ascertaining his or her wants and needs in the face of diagnosis of a terminal disease. The following questions may be used to prompt open-ended discussions[40]:

- What fears or worries do you have about your illness or medical care?
- As you think about your illness, what are the best and worst things that might happen?
- What are your expectations and hopes for the future?

By finding out the answers to these types of questions, clinicians can confidently pursue treatment plans according to the patient's wishes.

tional therapy. Communication allows a physician to ascertain whether a patient wants to take a different tack because he/she is tired of treatment, medical visits, and the uncertainty of their disease. Once patients reach this point, discussions of palliative care and hospice naturally follow. Ultimately, the panel agreed that balanced presentation of the available treatments and end-of-life issues beginning at entry into stage IV disease provides the patient with the greatest ability to transition through management choices. (See Sidebar 3 for ways to prompt patient-directed management choices.)

In this case, the family recognized the value of hospice and home care; hospice allowed the patient to remain at home until she died 1 month later. Despite their earlier reservations about the patient's desire to discontinue aggressive treatment, the family was convinced she received the best care at the appropriate time.

CONCLUSIONS

Based on a review of the literature and panel discussion, our consortium makes the following observations/recommendations:

- Sentinel lymph node biopsy provides important staging information for patients with high-risk primary melanomas
- Adjuvant therapy may benefit patients with thick primary melanomas even if they have node-negative disease
- While some clinicians initially employ aggressive follow-up regimens that include laboratory and imaging tests after diagnosis of a high-risk primary melanoma, there is scant evidence that this approach improves outcomes relative to a strategy that relies on using imaging tests and blood work to investigate specific signs and symptoms
- Prognosis, resectability, site and number of metastases, disease-free interval, and tumor doubling time are tumor-related factors that influence the decision to resect metastases. In addition, clinicians must also weigh the patient's performance status, severity of comorbidities, and the risk of the intervention when deciding to resect
- In an effort to detect subsequent metastases in a stage IV patient with no evidence of disease following surgery, follow-up measures tend to include use of imaging techniques, although there are little data supporting this approach
- Melanoma frequently metastasizes to the GI tract, and curative or palliative resection remains the treatment of choice, when feasible
- As patients enter stage IV, clinicians need to present all of the treatment options, from aggressive therapies to hospice care, in a balanced, honest, and sensitive manner, recognizing that each patient has different goals and values.

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Case Re-evaluation Questions

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 adjuvant therapy for this patient?
   A. Yes
   B. No
3. How would you treat the pulmonary nodules?
   A. Resect the pulmonary nodules
   B. Observe for 2 months then possibly resect the pulmonary nodules
   C. Provide systemic therapy for 2 months then resect the pulmonary nodules
   D. Never resect the pulmonary nodules
4. What surveillance tools would you use in follow-up visits with this patient?
   A. History, physical examination, CT or PET scan, and serum LDH
   B. History, physical examination, X-ray, and serum LDH
   C. History and physical examination alone
5. Do you have any additional comments, questions, or observations about how your management strategy changed? _____

Feedback on Case 5: Micrometastatic Disease Followed by Local Recurrence

Case 5 (May issue) concerned a 43-year-old woman with a 1.72-mm thick, Clark level IV melanoma on the back. Five sentinel lymph nodes (SLNs) were removed. One, an interval node, contained extracapsular micrometastatic disease.

About three-quarters (77%) of pre-test participant votes and a plurality of the faculty (44%) supported treatment with completion lymph node dissection (CLND) with adjuvant interferon (IFN) alfa-2b. Other options drawing faculty votes were observation (36%), systemic IFN alfa-2b alone (15%), and CLND only (5%).

Case presenters explained that the patient did not undergo CLND for 2 reasons. Metastasis beyond the SLN was considered unlikely, given the patient's low disease volume and absence of metastasis in other SLNs. Additionally, drainage patterns from the affected node were uncertain.

The patient instead was enrolled in a clinical trial with IFN alfa-2b (Eastern Cooperative Oncology Group [ECOG] 1697) examining the efficacy of IFN alfa-2b treatment for patients with and without micrometastatic disease.

Readers' views after reading the newsletter moved closer to the actual management of the patient (see graph). Post-tests, a smaller proportion chose CLND with IFN alfa-2b. A larger percentage opted for enrollment in a clinical trial with IFN alfa-2b (ECOG 1697) or for systemic IFN alfa-2b therapy.

Faculty then discussed a hypothetical scenario in which the same patient developed palpable neck nodes containing metastatic melanoma 6 months after terminating IFN alfa-2b therapy and underwent functional neck dissection. This procedure removed 2 nodes positive for melanoma, including one measuring 3 cm with extracapsular extension (ECE).

Participants' pre- and post-test votes clustered in either radiation or IFN as adjuvant therapy options, but the proportions favoring each alternative shifted. Post-test scores showed a movement toward selecting radiation therapy (31% pre-test vs 69% post-test) and a shift away from IFN therapy (46% pre-test vs 12% post-test).

These changes moved the respondents' views closer to those of the panel. About half the faculty (45%) chose radiation therapy. IFN therapy (27%) and investigational alternatives (27%) drew the same proportions of faculty votes. No panelist chose observation.

One-third (33%) of respondents said that reading the case changed their opinion about management of micrometastatic nodal disease. This is roughly the size of the shift from CLND plus IFN alfa-2b to other IFN alfa-2b options for initial post-SLN biopsy.

CME Post-test Questions

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

1. The most powerful predictor of disease-free survival for clinical stage I and II melanoma patients is:
   A. Clark level
   B. SLN status
   C. tumor thickness
   D. ulceration

2. Which factors predict disease-free and disease-specific survival according to rigorous multivariate analysis of node-negative patients with thick melanomas?
   A. Clark level and thickness
   B. tumor doubling time and vertical growth phase
   C. tumor doubling time and ulceration
   D. thickness and ulceration

3. A subset analysis of ECOG trial 1694 found:
   A. no benefit of IFN-alfa in patients with thicker melanomas
   B. improved survival only in patients with >4 positive lymph nodes
   C. the greatest benefit of IFN-alfa in node-negative patients
   D. greater efficacy of GM-2-KLH/QS-21 vaccine than IFN alfa

4. According to AJCC/UICC 2002 staging guidelines, patients with metastases to the lung have an M subcategory of:
   A. M1a
   B. M1b
   C. M1c
   D. M1d

5. The overall 5-year survival rate of patients with stage IV melanoma with lung metastases is:
   A. 6.7%
   B. 16.7%
   C. 26.7%
   D. 36.7%

6. The 5-year survival rates for patients who underwent resection of a solitary lung metastasis is:
   A. 9%
   B. 19%
   C. 29%
   D. 39%

7. Better outcomes have been observed following resection of metastases with a tumor doubling time of:
   A. 10 to 20 days
   B. 20 to 40 days
   C. 40 to 60 days
   D. tumor doubling time has not been shown to influence outcomes

8. According to NCCN guidelines, which of the following follow-up procedures is considered optional in stage IV patients rendered free of disease?
   A. Chest X-ray
   B. LDH testing
   C. CT scans
   D. all of the above

9. Surgical resection of GI metastases is the treatment of choice because:
   A. it almost always palliates symptoms
   B. it invariably extends lives
   C. it is usually curative
   D. none of the above

10. According to the expert panel, the best time to bring up end-of-life issues is:
    A. at the initial diagnosis of melanoma of any stage
    B. when patients enter stage IV disease
    C. prior to any treatment
    D. when patients can no longer withstand aggressive therapies

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 63-year-old woman with metastatic melanoma, outlined on the front cover. Please circle the answer that most represents your opinion, detach this perforated page, and fax to 845-398-5108. Or, if you prefer, you can visit the Melanoma Care Consortium at www.MelanomaCare.org.

1. Would you recommend adjuvant therapy following wide excision of a thick primary melanoma in a patient with pathologically node-negative disease?
   A. Yes
   B. No

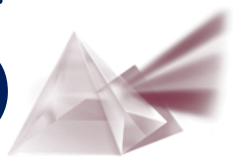
2. Would you recommend a biopsy of one of the pulmonary nodules of this patient?
   A. Yes
   B. No

3. What approach would you recommend for this patient following development of 2 pulmonary nodules?
   A. Resect the pulmonary nodules
   B. Observe for 2 months then possibly resect the pulmonary nodules
   C. Provide systemic therapy for 2 months then resect the pulmonary nodules
   D. Never resect the pulmonary nodules

4. Once a patient has been diagnosed with metastatic disease and rendered disease-free via surgical excision, which follow-up measures would you recommend?
   A. History, physical examination, PET or CT scan, and serum LDH testing
   B. History, physical examination, X-ray, and serum LDH testing
   C. History and physical examination only

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

MELANOMA CARE OPTIONS



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