MELANOMA CARE OPTIONS™

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SURGICAL EDITION

Issue 2: Update on Therapeutic Options in Melanoma

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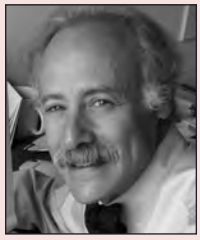

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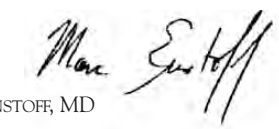
Editor's Note . . .

This issue of *Melanoma Care Options*, the second in our three-part series, tackles issues involved in choosing optimal therapies for patients with melanoma. Emerging data on the progression, prognosis, and therapy of melanoma provide clinicians with new opportunities to optimize the treatment of this disease. In this publication, a single case is followed from initial presentation with high-risk melanoma through progression to metastatic disease. At each stage of progression, therapeutic decisions and relevant controversies are discussed, with a focus on factors that influence patient prognosis, sentinel lymph node staging, adjuvant therapy options, patient selection for metastasectomy, treatment of brain metastases, and the current status of systemic targeted therapies. Self-assessment questions are incorporated at critical junctures so that you can choose your management strategy before reading the faculty's recommendations. The opinions herein are those of the respective authors. They are based on currently available data and clinical experience, and they are likely to evolve as new research findings emerge. In this publication you will also find a section on barriers to care, containing commentary on issues you face as a practitioner managing melanoma.

As faculty editor 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,

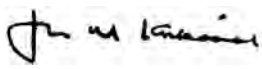


MARC S. ERNSTOFF, MD

A Note From the Chairmen/Steering Committee Editor

Welcome to the second issue of the 2007 *Melanoma Care Options* publication series from the Melanoma Care Coalition. We are pleased that the Melanoma Care Coalition's innovative interdisciplinary programming recently won the 2007 Alliance for Continuing Medical Education Award for Outstanding CME Collaboration. In response to your requests and to the emerging focus of continuing education on systems and barriers affecting provision of optimal patient care, we have incorporated specific material beyond the previous clinical content in these issues. Therefore, alongside the clinical content, you will find articles addressing barriers to care that affect melanoma management in the fields of dermatology, medical oncology, and surgical oncology. In addition, stepping outside of our previous disease-state approach from last year, we have dealt with the clinical content from the perspective of clinical steps in melanoma management, regardless of disease stage. This, the second of a series of 3 publications, focuses on evaluating therapeutic options. The third issue pulls this information together with the identification and profiling of patients with melanoma from the first edition into the management of melanoma in special circumstances. We hope that you find this new approach informative and thought-provoking. As always, we welcome your remarks on the series and encourage you to participate in other Melanoma Care Coalition programs—see www.melanomacare.org for other Melanoma Care Coalition offerings. Thank you for participating in this interdisciplinary dialogue, which promises to improve our ability to care for patients.

Sincerely,



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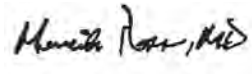

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Instructions for participation:
- Read the case presentations and comments in the newsletter
- Complete the posttest questions and evaluation form at the end of the newsletter, and fax or mail them to our office

To receive a maximum of 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/
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To receive up to 1.5 CNE credits for this activity:
- Within 4 weeks of successful completion, a certificate will be mailed to the address provided
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Target Audience

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

Statement of Need

The prognosis of melanoma worsens significantly with increasing disease stage. A thorough understanding of therapeutic options is particularly important for cases of high-risk primary melanoma, including T4 melanomas (melanomas >4 mm thick), which are likely to progress to metastatic disease. This publication follows a case presentation from the initial diagnosis of T4 melanoma through its progression to distant metastases. Various controversies in patient management are addressed at each stage, and faculty recommendations are provided to help guide practitioners in choosing the optimal therapeutic strategies for patients with melanoma.

Learning Objectives:

After completing this activity, the participants will be better able to:
- Describe the role of sentinel lymph node biopsy in the staging and treatment of cutaneous melanoma
- Compare and contrast adjuvant therapies for the management of melanoma
- List factors to consider in choosing therapeutic approaches to the management of brain metastases and other distant metastases
- Describe the emerging role of targeted therapies in the management of metastatic melanoma

Accreditation and Credit Designation

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 claim only those credits commensurate with the extent of his or her participation in the activity.

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Barriers-to-Care for Patients With Melanoma: Inconsistencies in Spinal Surgery Procedures for Metastatic Melanoma

By Douglas S. Reintgen, MD, and Michael Bihari, MD

Spinal metastasis is common in many types of cancer, not just melanoma. Melanoma accounts for only 4% of all spinal metastases; however, spinal metastases are present in more than half of all patients with metastatic melanoma.

In their review of 133 patients with melanoma metastatic to the spine, Gokaslan and colleagues noted that pain was the most common presenting symptom and palliation should be the goal of treatment.[3] However, the authors recommended that, given a median survival of 4 months for the group, symptom management and treatment should be individualized.

Spinal metastases, especially those causing spinal cord compression, frequently cause severe pain and neurologic complications, which affect quality of life and functional abilities, such as ambulation and urinary sphincter control. A decision about therapy requires a multidisciplinary approach that considers the wishes of the patient and family, the patient's general medical condition and life expectancy, radiosensitivity of the tumor, previous therapy, neurologic condition and severity of symptoms, and extent of spinal involvement, including location and instability.

Spinal Metastasis

Although there is a great deal of information about the management of spinal metastasis in the medical literature, it must be noted that very little of it is specific to melanoma. However, several recent large studies and review articles include some patients with melanoma.[2,4,5]

Klimo and Schmidt,[2] referring to the period prior to the mid 1980s (labeling this time period as "surgery in the old era"), noted that posterior decompressive laminectomy was viewed as the only surgical treatment offered for patients with metastatic spinal cord compression. The authors reviewed a number of studies documenting that laminectomy was of limited value in helping patients regain neurologic function and radiation therapy alone was as effective as laminectomy with adjuvant radiation in controlling pain and retaining or restoring a patient's ambulatory function.

Moreover, significant morbidity is associated with laminectomies, including wound complications such as infections, and the worsening of preexisting spinal instability. Thus, according to the authors, "conventional external beam radiotherapy became and continues to be the first-line treatment in the majority of patients with newly diagnosed metastatic spinal disease."

Additionally, the administration of corticosteroids is an important adjuvant therapy in patients with newly diagnosed spinal metastases

(continued on page 21)

Barriers-to-Care for Patients With Melanoma: Inconsistency in Radiation Oncology Practices

By Douglas S. Reintgen, MD, Thomas E. Olencki, DO, and Michael Bihari, MD

Current treatment guidelines recommend postoperative adjunctive radiation therapy for high-risk patients with melanoma.[1,2] Only a small number of appropriate melanoma patients, however, are treated according to these guidelines.

Based on epidemiologic data and a review of major treatment guidelines for melanoma, Delaney and colleagues[3] calculated that in 23% of patients with melanoma, radiotherapy is indicated at some point in the treatment process of their

(continued on page 22)

Introduction

In the past few years there have been several key advances in the treatment of the patient with melanoma. Prognostic characteristics of the primary lesion have been identified and the importance of sentinel lymph node (SLN) evaluation in guiding therapeutic decisions has been demonstrated. Surgical management remains the cornerstone of therapy for early melanoma, but clinical trials have established the role of interferon (IFN) alfa-2b as adjuvant systemic therapy. An improved understanding of the molecular genetics and immunobiology of melanoma has provided insights into the biologic mechanisms of the disease and suggested new therapeutic approaches.

Despite these advances, there are still critical gaps in our knowledge that impact the care of patients with melanoma. One of the most important of these is an incomplete grasp of factors that influence tumor progression and therapeutic responses. Many of the currently available systemic therapies are associated with significant toxicities, and it is therefore important to identify patients who might benefit from these therapies and to find biomarkers that accurately reflect or predict therapeutic response. In addition, the quest for more effective and better tolerated systemic therapies continues. Patients who fail IFN alfa-2b adjuvant therapy currently have limited options, and systemic and adjuvant therapies for patients with metastatic melanoma are sadly lacking.

This publication discusses both the advances and the gaps in melanoma management as it follows a typical melanoma case, beginning with presentation with localized melanoma, progressing to nodal disease, and culminating with distant metastases. At each step, treatment options and controversies are addressed, with a focus on new findings that may influence patient management.

CASE 1 Management of Localized Advanced Melanoma

By R. Dirk Noyes, MD, FACS, and John M. Kirkwood, MD

CASE PRESENTATION

A 65-year-old man presents with a 4.3-mm ulcerated Clark level IV superficial spreading melanoma of the mid back (Figure 1).

What therapeutic option would you recommend for this patient?

1. Wide excision alone
2. Wide excision plus SLN biopsy
3. Wide excision plus SLN biopsy, with IFN alfa-2b therapy only if positive
4. Wide excision plus SLN biopsy plus IFN alfa-2b regardless of nodal status
5. Wide excision plus SLN biopsy, with IFN alfa-2b only if certain high-risk features are present
6. Wide excision plus IFN alfa-2b (no SLN biopsy)

Figure 1. 4.3-mm ulcerated Clark level IV superficial spreading melanoma of the mid back.

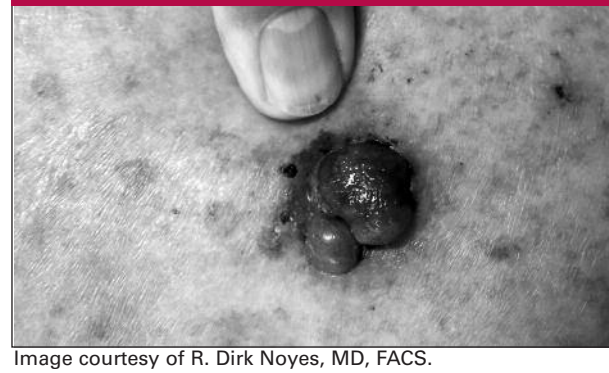


Image courtesy of R. Dirk Noyes, MD, FACS.

The faculty recommends that the patient undergo wide excision plus SLN biopsy plus IFN alfa-2b therapy regardless of nodal status. On the basis of the presenting symptoms, this tumor is T4b (thickness of >4.0 mm with ulceration), and the patient's clinical stage is currently IIC.[1] A positive nodal status would upgrade this staging to IIIB or IIIC. Both tumor thickness and ulceration are strong negative prognostic variables for patients with primary melanoma. Other factors that suggest a poor

prognosis in patients with primary melanoma include the presence of clinical or microscopic satellite metastases and in-transit metastases between the primary site and the regional lymph nodes.[1] Although the extent of invasion as assessed by Clark level provides important prognostic information for melanomas thinner than 1 mm, this parameter is not predictive of survival in thicker melanomas.[2]

T4b melanomas are frequently aggressive and lethal. Patients with this stage of melanoma are at high risk for regional and distant metastases,[1] and should therefore be assessed by SLN biopsy. Because of the high likelihood that T4 melanomas will progress, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for melanoma recommend that even if the SLN is negative, patients with melanoma thicker than 4 mm should be offered IFN alfa-2b or a clinical trial as options, though observation is also appropriate.[3]

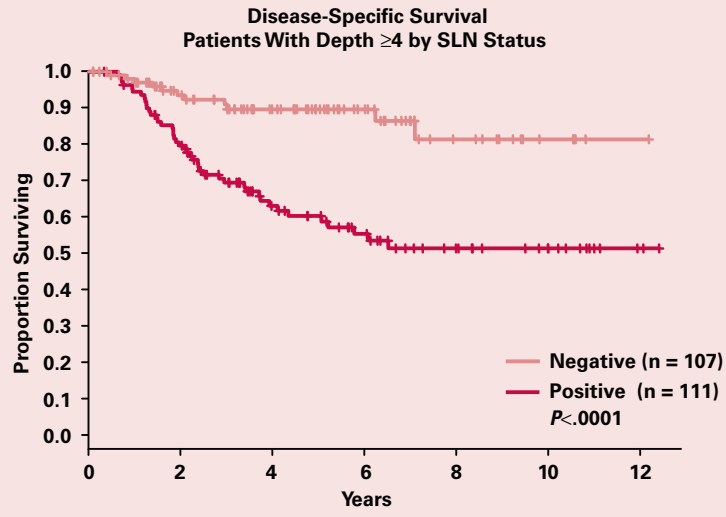
The Rationale for SLN Staging in Melanoma

Metastasis to a regional lymph node is the most important prognostic factor for patients with early melanoma,[1,4] and information on nodal status may impact therapeutic decisions. Patients with T4 melanoma are at a particularly high risk for lymph node involvement: 34% to 50% of patients with T4 melanoma have a positive SLN.[5,6] In addition to Breslow thickness, other factors that have been associated with lymph node metastasis include angiolymphatic invasion, absence of regression, increasing mitotic rate, satellitosis, ulceration, younger age, and location (trunk or lower extremity vs upper extremity).[7,8]

Regional lymph node involvement is associated with significantly reduced survival in T4 melanoma (Figure 2), and this negative effect is further compounded by the presence of ulceration. A study of 329 patients with T4 cutaneous melanoma found that patients with negative lymph nodes and no ulceration had a 5-year overall survival rate of 62%. In contrast, those with positive lymph nodes and ulceration had a 5-year survival rate of only 18% ($P < .0005$).[5]

Genetic probes that detect micrometastatic disease by reverse-transcriptase polymerase chain reaction (RT-PCR) techniques have become available in the last few years. However, the faculty does not recommend molecular staging of SLNs except as part of a clinical trial at this time. In the Sunbelt Melanoma Trial, which involves patients with a primary melanoma site at least 1 mm thick, patients with negative SLN biopsy were tested for micrometastatic disease by RT-PCR. No differences in disease-free or overall survival were observed between patients who were RT-PCR–positive and those who were RT-PCR–negative.[9]

Figure 2. Melanoma-specific survival in patients with T4 melanoma (≥4 mm depth)



From the M.D. Anderson database, courtesy of Merrick I. Ross, MD, FACS.

Therapeutic Impact of SLN Biopsy

Multicenter Selective Lymphadenectomy Trial I (MSLT-I) was designed to address the impact of SLN biopsy in patients with newly diagnosed melanoma of 1.2 to 3.5 mm in thickness.[10] Patients (n = 1269) were randomly assigned to undergo wide excision plus SLN biopsy or wide excision and postoperative observation of the regional nodal basin. A significant improvement in 5-year disease-free survival was observed in the biopsy group compared with the observation group (78.3% vs 73.1%; $P = .009$), but there was no difference in 5-year melanoma-specific survival rate (87.1% vs 86.6%; $P = .58$). However, as discussed below, possible benefits of SLN biopsy were revealed in a subset analysis of node-positive patients. This study did not include patients with T4 melanoma, so it is unclear whether its conclusions apply to thicker, higher-risk melanomas.

Case Revisited: An Alternative Scenario

What if SLN biopsy revealed a

positive lymph node? Would you perform completion lymph node dissection (CLND)?

1. Yes
2. No
3. I would need more information on the status of the SLN

The faculty recommends that CLND be performed for all SLN-positive patients. CLND can potentially improve survival, provide staging information, and optimize regional control in patients with positive SLN biopsy. The faculty noted a disturbing trend in melanoma care in which patients are offered adjuvant therapy without CLND. There are currently no clinical data to support this practice.

Completion Lymph Node Dissection

CLND or treatment according to a clinical trial is currently the standard of care for patients with a positive SLN.[3] Nevertheless, the benefits of this strategy continue to be debated.

Perhaps the most important argument in favor of CLND is that it may confer a survival advantage in patients with nodal metastases. In MSLT-I, patients in the biopsy arm underwent CLND if micrometastases were detected in the SLN. For patients in the observation arm, lymphadenectomy was performed only if nodal involvement was clinically detectable. According to subgroup analysis in patients with known nodal involvement, the immediate-dissection group had a significantly higher 5-year survival rate than the "watch-and-wait" group (72% vs 52%; $P = .004$).[10] These findings indicate that in SLN-positive patients, CLND helps avoid the development of palpable nodal disease, is likely to improve disease-free survival, and may affect overall survival. These benefits are being tested in MSLT-2.

CLND also provides staging information that can be used to guide therapeutic decisions. In patients with nodal metastases, the number of metastatic nodes is the most significant predictor of outcome.[2] It is currently difficult to predict nonsentinel node status in SLN-positive patients in the absence of CLND. Some studies have reported tumor characteristics that are associated with the presence of additional positive lymph nodes,[11,12] but others have been unable to identify any predictive features.[13,14] Prospective studies will be required to further address this issue.

Arguments against routine CLND in patients with positive SLN primarily focus on the current lack of definitive clinical evidence that CLND provides clinical benefit. Although data from MSLT-I suggest improved outcomes with CLND in node-positive patients, subset analyses can be unreliable. A nonrandomized study by Wong and colleagues in 134 SLN-positive patients who did not undergo CLND found no statistically significant difference in recurrence-free or disease-specific survival in these patients compared with a contemporary cohort who had undergone CLND.[15] Another important consideration is that only approximately 14% to 21% of patients with a positive SLN will have additional positive lymph nodes in the CLND specimen.[11,13]

Recent studies have focused on identifying SLN features that predict nonsentinel node involvement. Andtbacka and colleagues analyzed data from 2203 patients who underwent SLN biopsy. Of these, 359 (16%) had a positive SLN. CLND was performed on 343 SLN-positive patients, and additional metastatic lymph nodes were detected in 48 patients (14%). Using univariate and multivariate logistic regression analyses, the authors identified several features associated with additional positive lymph nodes and created a working model for predicting the presence of nonsentinel lymph nodes based on Breslow thickness and the size of the largest SLN metastatic focus (Table 1).[11] Lee and colleagues also identified Breslow thickness and larger SLN tumor size as factors that were significantly associated with the presence of tumor-positive nonsentinel nodes.[12] Another study reported that male gender, Breslow thickness, extranodal extension, and 3 or more positive SLNs were associated with an increased likelihood of additional

Table 1. Model for predicting risk of additional positive lymph nodes in patients with a positive SLN.[11]

Score*	Tumor/SLN Characteristics		Patients With Given Characteristics, n	Patients With Additional Positive Lymph Nodes, n (%)
	Breslow Thickness, mm	Largest SLN Metastatic Focus, mm		
0	<2	≤0.5	47	0 (0)
1	>2 ≤2	≤0.5 >0.5– 2	83	7 (8.4)
2-3	>2 ≤2	>0.5–10 >2	159	31 (19.5)
4	>2	>10	18	9 (50.0)

*The score equals the sum of the score for Breslow thickness (0 for ≤2mm, 1 for >2 mm) and the score for the largest SLN metastatic focus (0 for ≤0.5 mm, 1 for >0.5 mm–2 mm, 2 for >2 mm–10 mm, 3 for >10 mm). SLN indicates sentinel lymph node.

Adapted from Andtbacka et al, 2006.[11]

positive lymph nodes.[16] However, two recent studies did not find any tumor or SLN characteristics that successfully predicted involvement of other nodes, although one suggested that minimal SLN metastatic disease, defined as isolated clusters of cells in the positive SLN, may have use as an indicator against CLND.[13,14]

We hope that data from MSLT-II, a phase 3 clinical trial designed to compare outcomes in SLN-positive patients who have been randomized to CLND vs observation, will provide a definitive answer as to whether CLND provides benefits for patients.[17] Until more clinical information is available, CLND remains the standard of care for SLN-positive patients and should not be omitted except as part of a clinical trial.

Adjuvant Therapy in SLN-Negative Patients

Even if the patient in this case study is SLN negative, the faculty recommends that adjuvant therapy be given strong consideration, as thick primary melanomas with ulceration are associated with a relatively poor prognosis. Adjuvant therapy options include high-dose IFN alfa-2b (standard) and may include clinical trials.

In patients with thick (>4 mm) melanoma, nodal status, ulceration, vascular invasion (tumor cell involvement of the dermal vasculature), and tumor thickness are the major prognostic factors.[5,18] Mitotic rate and microsatellites also influence survival rate in some analyses.[5,19] The patient in this case study has an ulcerated melanoma, which has been found to decrease median overall survival in patients with T4 melanoma from 5.2 years (no ulceration) to 2.9 years (with ulceration).[5] This prognosis argues in favor of adjuvant therapy.

High-dose IFN alfa-2b is currently the only adjuvant therapy approved by the US Food and Drug Administration (FDA). Three Eastern Cooperative Oncology Group (ECOG) trials have shown that this therapy, given at a dose of 20 MU/m^2 intravenously (IV) 5 times per week for 4 weeks, followed by 10 MU/m^2 subcutaneously (SC) 3 times per week for 48 weeks, significantly improves relapse-free survival compared with observation (ECOG 1684 and 1690)[20,21] or GM2-KLH-QS21 (GMK, Progenics, Tarrytown, NY) antiganglioside vaccine (ECOG 1694)[22] in patients with high-risk melanoma (Table 2). Two trials, ECOG 1684 and 1694, also showed a statistically significant improvement in overall survival (Table 2).[20,22]

The trials reported inconsistent data on the effect of high-dose IFN alfa-2b in node-negative vs node-positive patients. In ECOG 1684, the benefit of IFN alfa-2b was greater in node-positive patients,[20] while ECOG 1694 found a greater benefit in the node-negative strata,[22] and ECOG 1690 reported no difference between the two.[21] It should be noted that the studies were not designed for subset analysis. More recent data from EORTC 18952 and EORTC 18991 indicate that the effects of IFN adjuvant therapy may be greater at earlier stages of microscopic disease,[23,24] providing additional support for the significant effects observed in node-negative patients in ECOG 1694.[22]

Subgroup analyses performed in patients with stage IIB/IIC melanoma (T4N0) identified a significant relapse-free and overall survival advantage in the IFN alfa-2b arm in the largest trial (ECOG 1694),[22] but not the others[20,21] (Table 2). The ability of IFN alfa-2b to improve outcomes in patients with T4 melanoma is therefore suggested by these trials but has not yet been definitively demonstrated. Treatment-related toxicities, including flulike symptoms, fatigue, depression and other neuropsychiatric symptoms, myelosuppression, and hepatotoxicity,[20,21] should also be considered before initiating adjuvant therapy with high-dose IFN alfa-2b.

Table 2. HDI therapy in patients with high-risk melanoma. For relapse-free and overall survival, data shown are for HDI vs observation (ECOG 1684 and 1690) or GMK vaccine (ECOG 1694) in the ITT population.

Study	ECOG 1684[20]	ECOG 1690[21]	ECOG 1694[22]
Treatment arms	HDI vs obs	HDI vs LDI vs obs	HDI vs GMK vaccine
Number of patients			
All	287	642	880
Stage IIB/IIC (%)	31 (10.8%)	163 (25.4%)	202 (23.0%)
Relapse-free survival			
Est. survival rate[a]	37% vs 26%	44% vs 35%[b]	62% vs 49%
Hazard ratio (*P* value)			
All patients	1.40 (*P* = .0023)	1.28 (*P* = .054)[b]	1.49 (*P* = .00045)
Stage IIB/IIC	NR (*P* = .12)	1.46 (*P* = .20)[b]	2.06 (*P* = .012)
Overall survival			
Est. survival rate[a]	46% vs 37%	52% vs 55%[b]	78% vs 73%
Hazard ratio (*P* value)			
All patients	NR (*P* = .024)	1.0 (*P* = .995)	1.38 (*P* = .023)
Stage IIB/IIC	NR	NR	1.88 (NR)

[a]5-year survival estimates for ECOG 1684 and 1690; 2-year survival estimates for ECOG 1694.
[b]HDI vs obs. ECOG indicates Eastern Cooperative Oncology Group; GMK, GM2-KLH-QS21 antiganglioside vaccine; HDI, high-dose IFN alfa-2b; IFN, interferon; LDI, low-dose IFN alfa-2b; NR, not reported.

CASE 2 Management of Localized Advanced Melanoma

By Marc Ernstoff, MD, and John M. Kirkwood, MD

CASE CONTINUED

The patient decides against SLN biopsy and adjuvant therapy. One year later, he develops palpable nodal disease in the left axilla. Fine needle aspiration biopsy is positive for metastatic melanoma. The patient is scheduled for radical resection of the left axilla.

Should the patient receive SLN biopsy at the same time as the radical resection?

1. Yes
2. No

The faculty recommends that the patient also receive SLN biopsy at this time. This patient's lymph nodes have not yet been mapped, and evaluation of other sites of spread is important so that additional surgical procedures, if necessary, can be performed at the same time as the radical node dissection.

The reliability of SLN biopsy following a wide local excision (WLE) and repair has recently been assessed in a controlled study by Ariyan and colleagues.[25] Nineteen patients underwent SLN mapping prior to WLE and again following WLE. Postoperative SLN mapping concurred with pre-WLE mapping in 13 of the 19 patients. Additional nodal sites were noted in 5 patients postoperatively, and 1 patient had loss of a nodal drainage site following surgery. Thus, it appears that post-WLE SLN mapping can reliably identify the clinically relevant nodal drainage site in approximately 90% of patients.

SLN biopsy is particularly helpful in mapping sites with indeterminate drainage. In a study of 266 patients with truncal melanoma and clinically negative regional lymph nodes who underwent SLN mapping and biopsy, 29% of patients had lymphatic drainage to multiple basins, and this feature was associated with a lower 5-year survival rate than drainage to a single lymphatic basin (68% vs 78%, $P = .04$).[26]

SLN mapping revealed involvement of only the left axilla. Radical axillary resection was performed, revealing 2 metastatic nodes out of 18.

Would you discuss adjuvant therapy with this patient now?

1. Yes
2. No

The faculty is strongly in favor of discussing adjuvant therapy with the patient. The patient now has pathologic stage IIIC melanoma (T4b, clinically detectable metastasis to 2 nodes), with a 5-year predicted survival rate of 24%.[1] However, there still may be time to induce immunity and prolong survival.

The immune system has the capacity to respond to the tumor with a T-helper type 1 (Th1) immune response, which is critical to induction of the cytotoxic T lymphocyte antitumor response. The immune response to tumor-associated antigens has been assessed in patients with melanoma or renal cell carcinoma. Patients with active disease were found to have an immune response that is skewed toward T-helper type 2 (Th2) cells, which dampen the Th1 response. In contrast, cancer patients with no current evidence of disease and healthy subjects showed either a strong Th1 response or a mixed Th1/Th2 response to these antigens.[27] These findings suggest that agents capable of stimulating the anti-tumor Th1 response could induce tumor immunity.

Adjuvant Therapy in SLN-Positive Patients: Emerging Options

Options for adjuvant therapy include high-dose IFN alfa-2b (discussed above) or clinical trials. Because high-dose IFN alfa-2b is the only agent to show survival benefits in phase 3 clinical trials, several adjuvant therapy trials are focusing on identifying the optimal dose and duration of IFN alfa-2b. Other studies are examining different agents as adjuvant therapy, including immunostimulants, cytokines, and vaccines, with the goal of identifying more effective or better-tolerated agents or combinations of agents.

Interferon alfa-2b: Optimizing dose and duration

The ECOG trials that served as the basis for IFN alfa-2b approval are discussed in the previous section. An update of the data from extended follow-up of these trials (median of 2.1 to 12.6 years) was reported by Kirkwood and

colleagues in 2004.[28] All three trials showed durable improvements in relapse-free survival in the IFN alfa-2b arm compared with observation or GMK vaccine. This difference remained significant for ECOG 1684 (*P*=.02) and ECOG 1694 (*P*=.006) and approached significance in ECOG 1690 (*P*=.09). ECOG 1690 still showed no benefit to overall survival (*P*=.98) at a median follow-up of 6.6 years, and the benefit initially observed in ECOG 1684 on reanalysis is no longer nominally significant in this unplanned additional analysis at a median follow-up of 12.6 years (*P*=.18). Benefits to overall survival were still noted in ECOG 1694 at a median follow-up of 2.1 years (*P*=.04).[28]

ECOG 1690 also included an arm in which patients were given low-dose IFN alfa-2b (3 MU IV 3x/wk) for 2 years. Compared with the observation arm, the low-dose IFN alfa-2b group did not show significant improvements in relapse-free or overall survival.[21] Data from this study and others[23,29] therefore suggest that lower doses of IFN are ineffective at durably halting disease progression or improving survival in patients with high-risk melanoma.

However, one recent study subset analysis has suggested that long-term treatment (25 months) with intermediate doses of IFN alfa-2b may be beneficial to patients with node-negative early-stage disease, although the authors concluded that this treatment was not to be recommended.[23]

Nevertheless, the optimal administration of IFN alfa-2b to reduce toxicity and improve efficacy remains a critical concern. A recent study compared IFN alfa-2b induction therapy at a lower dose than normally used (15 MU/m^2 IV 5 consecutive days per week for 4 weeks) with the same induction regimen followed by maintenance therapy with 10 MU (flat dose) SC 3 times weekly for 48 weeks in 353 patients with stage IIB, IIC, or III melanoma.[30] An observation arm was not included in this trial. No significant differences in disease-free or overall survival were observed between the two regimens, but the induction-only group had a lower rate of grade 3–4 toxicity, possibly because of the shorter duration of therapy.[30] An ongoing trial, ECOG 1697, is currently evaluating a high-dose induction regimen using the standard dose of 20 MU for 5 consecutive days per week for 4 weeks, compared with observation only.[31] We hope that outcome and toxicity information from this trial will provide guidance in choosing the optimal IFN alfa-2b dosing regimen.

European Organization for Research and Treatment of Cancer (EORTC) trial 18991 was designed to assess the effects of long-term pegylated IFN (Peg-IFN) alfa-2b therapy for 5 years as adjuvant therapy after regional lymph node dissection in patients with stage III melanoma.[24] Peg-IFN can be self administered and is given on a weekly schedule; these features may make long-term therapy less onerous for some patients. The treatment regimen consisted of an 8-week induction phase in which Peg-IFN alfa-2b was administered at 6 µg/kg/wk SC for 8 weeks, followed by a maintenance phase of 3 µg/kg/wk for 5 years or until distant metastasis occurred. The primary end points in this study were distant metastasis–free survival and overall survival later amended to include relapse-free survival. Compared with observation (n = 629), the Peg-IFN alfa-2b arm (n = 627) demonstrated a significant improvement in relapse-free survival (median of 34.8 months vs 25.5 months, *P* = .011) but not in distant metastasis–free survival (45.6 months vs 36.1 months, *P* = .07) or overall survival (median survival not reached, *P* = .78). Patients with only microscopic nodal involvement (N1a) appeared to experience a greater benefit than those with N1b or N2 melanoma but it is notable that median follow-up is only 4.3 years and treatment is planned for 5 years, so follow-up off-treatment will be of interest. The typical IFN alfa-2b side effect profile was observed although 30% of patients appear to tolerate treatment past 3 years.[24] Ongoing trials in Europe are comparing the efficacy and safety of Peg-IFN alfa-2b or Peg-IFN alfa-2a with low-dose IFN alfa-2b.[32,33]

Granulocyte-macrophage colony–stimulating factor

The ECOG 4697 phase 3 trial is evaluating the effect of granulocyte-macrophage colony–stimulating factor (GM CSF) as adjuvant therapy in patients with locally advanced or metastatic melanoma.[34] GM-CSF may exert antitumor effects by stimulating peripheral blood mononuclear cells, inhibiting angiogenesis, and activating dendritic cells. An earlier phase 2 trial reported that, compared with historical controls, GM-CSF significantly increased overall and disease-free survival in 48 patients with stage III or IV melanoma.[35] ECOG 4697 is currently closed, and results are likely to be reported in the next several months.

Cytotoxic T lymphocyte–associated antigen 4 blockade

Monoclonal antibodies are being studied as a way to prevent T-cell deactivation by blocking cytotoxic

Table 3. Selected clinical trials of vaccines as adjuvant therapy in patients with melanoma.[32,34,44,45]

Phase	Trial Designation	Vaccine	Treatment Arms	Key Eligibility Criteria
Phase 3[a]	ECOG-4697	Tyrosinase:368-376, gp100:209-217 (210M), MART-1:27-35	1) GM-CSF + vaccine 2) Placebo + vaccine 3) GM-CSF + placebo vaccine 4) Placebo + placebo vaccine	HLA-A2 positive (for vaccine portion of trial)
Phase 1/2	UVACC-HIC-11491	Multiepitope melanoma peptides	1) Vaccine + tetanus toxoid helper peptide 2) Cyclophosphamide + vaccine + tetanus toxoid helper peptide 3) Vaccine + multiepitope helper peptides 4) Cyclophosphamide + vaccine + multiepitope helper peptides	At least 2 intact (undissected) axillary and/or inguinal lymph node basins HLA-A1, -A2, or -A3 positive AND HLA-DR1, -DR4, -DR11, -DR13, or -DR15 positive
Phase 2	2004-0502	gp100 and MAGE-3	1) Vaccine 2) Vaccine + leuprolide, a luteinizing hormone–releasing hormone agonist	HLA-A2 positive
Phase 2	NCI-06-C-0069	gp100:209-217(210M)	1) Vaccine emulsified in Montanide ISA-51 2) Vaccine emulsified in Montanide ISA-51 + imiquimod at site of injection 3) Vaccine mixed in NaCl 4) Vaccine mixed in NaCl + imiquimod at site of injection	HLA-A0201 positive
Phase 1/2	NYU-RUH-NBH-0428-0401	Melanoma antigen-pulsed dendritic cells	1) Melanoma antigen-pulsed dendritic cells 2) Melanoma antigens + QS21 adjuvant	HLA-A0201 positive
Phase 2	LAC-USC-10M036	Tyrosinase, gp100, and MART-1	Open-label trial: vaccine emulsified in Montanide ISA-51 + ipilimumab	HLA-A0201 positive and positive for at least one of the following: gp100, tyrosinase, MART-1

*Trial is closed. ECOG indicates Eastern Cooperative Oncology Group; GM-CSF, granulocyte-macrophage colony–stimulating factor; HLA, human leukocyte antigen; MAGE, melanoma antigen–encoding gene; MART, melanoma antigen recognized by T cells; NaCl, sodium chloride; NCI, National Cancer Institute.

T lymphocyte–associated antigen 4 (CTLA-4), a molecule that inhibits T-cell responses, although most of the research to date has been conducted in patients with metastatic melanoma. Two different fully human anti–CTLA-4 monoclonal antibodies are being investigated: ipilimumab (formerly known as MDX-010), an immunoglobulin G1 (IgG1) antibody, and ticilimumab (formerly known as CP-675,206), an IgG2 antibody.[36-39] Early, small-scale studies indicate that approximately 4% to 8% of patients with metastatic melanoma experience a complete response to CTLA-4 blockade (given in combination with interleukin-2 [IL-2] in one study), and 13% to 22% experience an objective response.[38,40,41] Responses may be delayed, occurring after more than 12 weeks of treatment in about 10% of patients, and are frequently highly durable, sometimes lasting more than 12 months.[42]

Autoimmune breakthrough events (ABEs), including colitis, uveitis, dermatitis, and vitiligo, are common and may be associated with clinical benefit.[37,38,41] In one study, 5 of 14 patients with grade 3/4 autoimmune toxicity (36%) experienced a clinical response. In contrast, a clinical response occurred in only 2 of the 42 patients who had not experienced autoimmune toxicity (5%).[41] ABEs can be successfully managed with corticosteroids without interfering with clinical benefit.[41]

Preliminary data therefore suggest that the immunostimulatory activity associated with CTLA-4 blockade may improve outcomes in patients with metastatic melanoma and perhaps in those with other cancers as well. A trial of ipilimumab as adjuvant therapy in melanoma patients who have failed IFN alfa-2b therapy is currently being planned. Data from a study of 9 patients with melanoma suggest that CTLA-4 blockade is even more effective in patients previously vaccinated with irradiated, autologous tumor cells that had been genetically engineered to secrete GM-CSF. In contrast, a synergistic effect was not observed in patients vaccinated with melanoma antigens.[43] Other upcoming studies will explore the possibility of synergistic activity between anti–CTLA-4 agents and other immunotherapies, including IFN alfa-2b.

Vaccines

Several trials are investigating the use of vaccines as adjuvant therapy

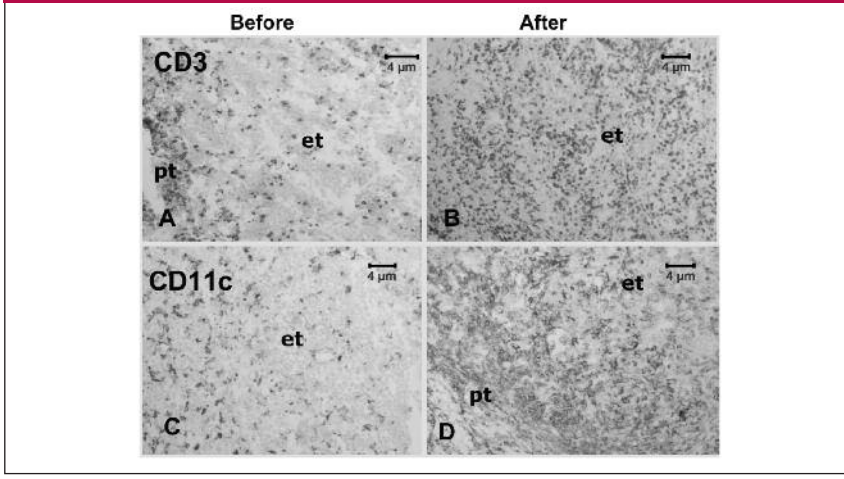
for melanoma; some of these are listed in Table 3,[32,34,44,45] and others can be found at www.clinicaltrials.gov. Most of the currently available trials involve patients with specific human leukocyte antigen (HLA) subtypes. The ECOG 4697 trial mentioned above is also evaluating a peptide vaccine consisting of 3 melanoma-specific antigens, either alone or in combination with GM-CSF, in HLA-A2–positive patients.[34] The combination of anti–CTLA-4 agents and vaccines is also being assessed in clinical trials.[45] Although most trials involve peptide vaccines, some are examining the use of dendritic cells derived from the patient's peripheral blood mononuclear cells that have been exposed to various melanoma antigens. The use of various adjuvant agents is another area of active inquiry.

Vaccines composed of melanoma cell lysates have also been assessed as adjuvant therapy. Vaccinia melanoma cell lysates failed to improve disease-free or overall survival in 2 trials.[46,47] A recent study compared 2 years of low-dose IFN alfa-2b plus Melacine, a combination of melanoma cell lysates from two melanoma cell lines and the adjuvant Detox PC, vs 1 year of high-dose IFN alfa-2b.[48] This study found no difference between the two treatment arms in overall or relapse-free survival. The data from this trial suggest that although immunotherapy plus low-dose IFN alfa-2b may not improve survival compared with standard treatment regimens, it may offer a less toxic alternative.

Predicting Response to IFN Alfa-2b

Adjuvant therapy with IFN does not benefit everyone, and the associated toxicities can be significant.

Figure 3. Immunohistochemical staining for CD3 (A, B) and CD11c (C,D) in melanoma-infiltrated lymph nodes from a clinical responder before (A, C) and after (B, D) treatment with high-dose IFN alfa-2b for 4 weeks. Peritumoral (pt) and endotumoral (et) compartments are shown.



Adapted with permission from Moschos et al, 2000.[49]

Predictors of prognosis and response therefore have the potential to play a key role in guiding adjuvant therapy decisions.

Pretreatment cytokine levels may help identify patients who will respond to IFN alfa-2b. Concentrations of several cytokines, including IL-1α, IL-1β, IL-6, macrophage inflammatory protein (MIP)-1α, MIP-1β, and tumor necrosis factor (TNF)-α, are higher in patients with melanoma than in healthy controls.[49] Analyses of blood samples from patients in ECOG 1694, the trial in which high-dose IFN alfa-2b was compared with GMK vaccine, showed that high pretreatment levels of these proinflammatory cytokines were correlated with the duration of relapse-free survival in patients treated with high-dose IFN alfa-2b but not in those who received GMK vaccine. There were no significant associations between posttreatment cytokine levels and survival.[49]

Moschos and colleagues evaluated predictors of IFN response in a study in which high-dose IFN alfa-2b was used as neoadjuvant therapy (eg, prior to lymphadenectomy) in patients with stage III melanoma.[50] Biopsy samples were obtained from 20 patients with palpable lymph nodes, and these patients were treated with standard high-dose IFN alfa-2b induction therapy for 4 weeks. Patients then underwent radical regional lymphadenectomy, followed by IFN alfa-2b maintenance therapy. Neoadjuvant high-dose IFN alfa-2b was found to be highly effective: 11 patients (55%) showed an objective clinical response, and 10 patients (50%) had no sign of recurrent disease at a median follow-up of 18.5 months. Immunohistochemical analyses of pretreatment and posttreatment tissue samples demonstrated that more mononuclear immune cells infiltrated the endotumoral compartment associated with treatment efficacy in clinical responders than in nonresponders. Specifically, endotumoral CD11c+ and CD3+ cells were elevated (Figure 3) and CD83+ cells were decreased in clinical responders compared with nonresponders. There were no changes in the expression of melanoma-associated antigens, tumor cell proliferation, angiogenesis, or apoptosis in

responders compared with nonresponders.[50] A subsequent study using tissue samples from these patients found that the signal transducers and activators of transcription (STAT) signal pathway was also altered by high-dose IFN alfa-2b treatment.[51] The expression of STAT1, a signaling molecule associated with reduced tumor growth, was increased in response to high-dose IFN alfa-2b, while the expression of STAT3, a molecule associated with immunosuppression and tumor progression, was reduced. The STAT1-STAT3 ratio at baseline may predict clinical outcome, and changes in this ratio mediated by immunotherapies may predict therapeutic effect.[51]

Autoimmunity may also have prognostic significance in patients receiving IFN alfa-2b. In a study of 200 patients treated with IFN alfa-2b, autoantibodies or clinical manifestations of autoimmunity, including vitiligo and hypothyroidism, were associated with statistically significant improvements in relapse-free and overall survival. Autoimmunity did not occur immediately after the initiation of IFN alfa-2b treatment; the median time to the detection of autoantibodies was 3 months, and median time to autoimmune clinical manifestations was 9 months.[52] Contrary to these findings, no association between the presence of autoantibodies and response to IFN adjuvant therapy was found in an analysis of patients enrolled in EORTC 18952.[53]

Although further research is required, there is growing evidence that autoimmunity may act as a general prognostic indicator for immunomodulatory therapies, including CTLA-4 blockade and high-dose IFN alfa-2b therapy. In particular, vitiligo, thyroiditis, and antibodies to endocrine targets are frequently noted in patients with favorable clinical responses to therapy, suggesting that autoimmunity to endocrine and pigment cell targets may be a surrogate for an immune response to tumor antigens that have yet to be defined.

CASE 3 Management of Distant Metastatic Disease

By R. Dirk Noyes, MD, FACS, and Keith Flaherty, MD
With contributions from Wolfram Samlowski, MD (brain metastasis), Richard L. White, Jr, MD, FACS (role of metastasectomy), and Vernon K. Sondak, MD (role of metastasectomy)

CASE CONTINUED

Two years later the patient develops a solitary pulmonary nodule. Positron emission tomography (PET) and computed tomography (CT) scans show no other evidence of stage IV disease. The staging workup is otherwise negative, and the patient's performance status is 0.

What would you do next?

1. Biopsy; if positive, treat with systemic therapy
2. Resect without biopsy

The faculty recommends resecting without biopsy. This option has the highest likelihood of extending the patient's survival, and the faculty considers it to be the treatment of choice for patients with solitary metastases.

The use of surgery for metastatic melanoma has received renewed interest in the past several years because of improvements in imaging, the availability of minimally invasive surgical approaches, decreased morbidity and mortality after major surgery, the failure of nonsurgical treatments to improve overall survival for patients with metastatic melanoma, and reports of long-term survival following resection.[54]

Potential Benefits of Metastasectomy

The lung is a common site of metastatic involvement in patients with melanoma and the first site of metastasis in 36% of patients with metastases.[55] Patients with melanoma have a 13% risk of developing a pulmonary metastasis in the first 5 years following diagnosis and a 23% risk over 20 years.[56]

Patients with distant metastatic disease have a poor prognosis. In a meta-analysis of studies involving more than 6000 patients with stage IV melanoma, Lee and colleagues reported a median survival time of 8.9 months and a 5-year survival rate of 2.3%.[57] In drafting the American Joint Committee on Cancer staging system, Balch and colleagues reported on survival for melanoma patients with lung metastases versus other visceral or skin/subcutaneous sites.[1] The 1-year survival rate for patients with lung metastases was 57%, which was

Sidebar

Metastasectomy: Survival Benefit or Selection Bias?

There seems to be little doubt that patients who undergo metastasectomy have improved melanoma survival compared with historical cohorts. The question, however, is how many patients would be long-term survivors *without* surgery. Both retrospective and prospective studies are influenced by a selection bias, and comparing resected patients with nonresected patients can be misleading. For instance, only patients who are able to undergo surgery and who are considered likely to benefit from this procedure are treated with resection for metastatic melanoma.[54]

Findings from Southwest Oncology Group study 9430, a prospective evaluation of surgery for metastatic melanoma that allowed any site of disease and any prior therapy or postoperative adjuvant therapy, suggest that certain cases of melanoma have a favorable "biosignature," and that this may contribute to the improved survival observed in resected patients. In the 63 patients analyzed, the time to disease progression was relatively short (median of 6 months), but the median overall survival (21 months) was prolonged compared with survival for patients treated nonoperatively in other studies.[54,59] The biosignature of patients with prolonged survival is characterized by indolent disease or a more favorable response to systemic salvage therapy. It is possible that these attributes, rather than the removal of the metastatic lesion, may account for improved survival in patients selected for resection.[54]

comparable to skin (59%) and higher than other visceral sites (41%). However, by 5 years, the survival rate for patients with lung metastases was 6.7%, compared with 18.8% for skin and 9.5% for other visceral sites. These differences in prognosis provide the basis for classification of metastatic disease, with M1a including metastases to distant skin or subcutaneous or nodal metastases, M1b encompassing lung metastases, and M1c referring to all other visceral metastases *or* to any distant metastasis with elevated serum lactate dehydrogenase levels.[1]

Survival benefits

There is evidence that metastasectomy can significantly improve survival time, particularly for patients with only a single metastatic site. Reported median survival time after a complete metastasectomy ranges from 10 to 29 months for patients with skin, soft-tissue, or lymph node metastases, 15 to 49 months for patients with gastrointestinal metastases, and 11 to 20 months for patients with pulmonary metastases (reviewed by Ollila, 2006).[58] In a survey of patients with pulmonary melanoma metastases who had been evaluated at the Duke Comprehensive Cancer center between 1970 and 2004, the performance of a pulmonary metastasectomy was found to be a significant predictor of overall survival ($P < .001$), resulting in a 12-month survival advantage in patients with a disease-free interval longer than 5 years and a 10-month survival advantage in patients with no evidence of extrathoracic

Table 4. Factors associated with an improved prognosis in patients undergoing metastasectomy for melanoma

Factor	Reference	Comments
Primary stage (I vs II)	Essner et al, 2004[61]	Stage I primary is associated with a better outcome than stage II
Prior lymph node metastases	Essner et al, 2004[61]	Patients with no intervening regional lymph node metastases had better outcomes
First site of metastasis	Essner et al, 2004[61]	Low-risk sites include skin/subcutaneous/distant lymph nodes and lung. High-risk sites include adrenal, brain, and liver.
Histologic type	Petersen et al, 2007[56] Harpole et al, 1992[62]	Nodular histology is associated with a poorer outcome
Number of metastatic sites	Petersen et al, 2007[56] Andrews et al, 2006[63] Essner et al, 2004[61] Leo et al, 2000[64] Tafra et al, 1995[65] Harpole et al, 1992[62]	Fewer lesions is associated with an improved outcome
Progression-free survival	Essner et al, 2004[61] Leo et al, 2000[64] Harpole et al, 1992[62]	Longer time between stages I/II and IV is associated with a better outcome
Complete resection of disease	Olilla et al, 1998[66] Harpole et al, 1992[62]	Complete resection improves survival over palliative care
Tumor doubling time	Olilla et al, 1998[66] Tafra et al, 1995[65]	Patients with tumor doubling time >60 days had a significant survival advantage

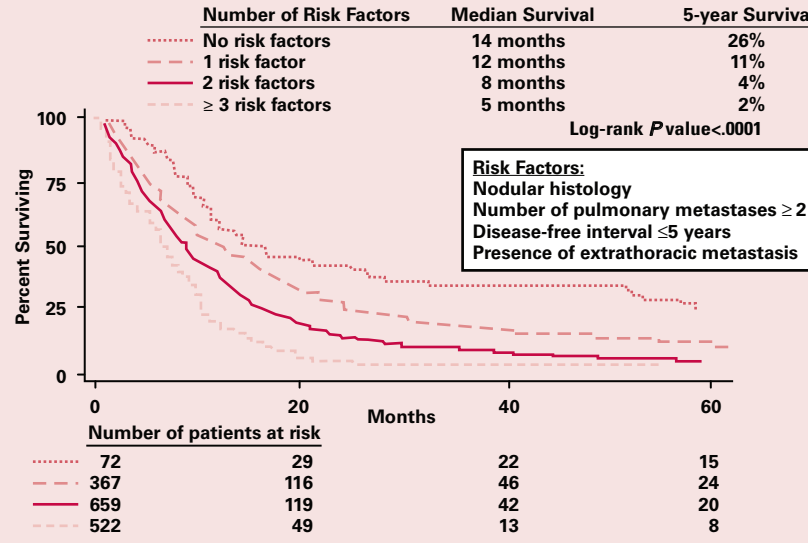
metastasis.[56] It is possible, however, that the dramatic improvements in survival in patients undergoing metastasectomy may be due to a selection bias for patients who would have a favorable disease course even in the absence of surgery (see Sidebar).

Even repeated metastasectomy may improve survival of selected patients with melanoma. A study of 131 patients whose stage IV melanoma recurred following metastasectomy reported that patients undergoing a repeat complete metastasectomy had a median survival of 18.2 months, compared with 12.5 months for palliative surgery and 5.9 months for nonsurgical management.[60] The study from Duke found no significant difference in survival between patients undergoing a single metastasectomy and those receiving repeated metastasectomies.[56]

Prognostic factors

Several studies have identified prognostic features to aid in patient selection for metastasectomy (Table 4).[56,61-66] Some of these factors, such as site of metastasis, disease-free interval, and number of metastatic sites, are prognostic features for all patients with stage IV melanoma.[67] Others, such as complete resection, are specific to patients who have had a metastasectomy. As might be expected, the more risk factors a patient has, the less likely the patient is to benefit from metastasectomy (Figure 4).[56] Leo and colleagues reached a similar conclusion by analyzing patient outcomes on the basis of prognostic groupings. The most favorable grouping, patients who had undergone a complete resection after a single metastasis at longer than 36 months, had a survival rate of 29% at 5 years.[64] The presence of 1 risk factor (time to metastasis <36 months or >1 metastasis) decreased the 5-year survival rate to 20%, and 2 risk factors reduced it to 7%. There were no 5-year survivors among patients with an incomplete resection.[64]

Figure 4. Overall survival of patients undergoing pulmonary metastasectomy on the basis of preoperative risk factors. Reprinted with permission from Petersen et al, 2007.[56]



Role of metastasectomy in the treatment of metastatic melanoma

In appropriately selected patients, metastasectomy can result in long-term survival and, in rare cases, a surgical cure. Various institutions have reported 10-year survival rates of 10% to 15% following metastasectomy, compared with less than 5% for nonresected patients (J. M. Kirkwood, personal communication). It is not clear to what extent these favorable outcomes apply to nonsurgical modalities targeted at solitary metastases, such as radiofrequency ablation or embolization.

The faculty recommends that surgery should be offered to all patients with a solitary melanoma metastasis who are capable of undergoing the procedure. Improvements in imaging have increased the ability to detect metastatic sites, and advances in surgical technologies, including the use of minimally invasive video-assisted thoracic surgery, have decreased the morbidity associated with resection. Although this discussion has focused mainly on pulmonary metastases, mean 5-year postsurgery survival rates of 22% to 28% have also been reported for patients with skin/subcutaneous/lymph node, gastrointestinal, brain, or liver metastases.[61]

In addition to solitary lesions, metastasectomy should also be strongly considered for limited disease after immunotherapy, symptomatic disease such as gastrointestinal bleeds or obstruction, painful subcutaneous lesions, and easily accessible brain metastases.

Case Continued

The patient's pulmonary lesion is removed via a video-assisted procedure and there is no evidence of residual disease.

What systemic therapy should be given to the patient?

1. None
2. Dacarbazine or temozolomide
3. Biochemotherapy
4. IL-2
5. IFN
6. GM-CSF
7. Clinical trial

The faculty recommends a clinical trial or no treatment for this patient. Currently, there are no randomized data to support any available agent in the stage IV setting.[68,69] Although IFN alfa-2b therapy is sometimes offered to these patients, IFN trials in melanoma were confined to patients with stage II/III disease, and to date only a minimal effect has been detected in patients with stage IV melanoma.[28,68] IL-2 has shown some benefit in patients with metastatic melanoma, including durable responses in approximately 5% of patients.[70] However, IL-2 has not been tested as adjuvant therapy in stage IV melanoma, and a study with IL-2 as adjuvant therapy for metastatic renal cell carcinoma reported negative results (reviewed by Lawson, 2005).[71] As discussed above, GM-CSF has shown some promise as adjuvant therapy for patients with stage IV melanoma in one small study.[35] A phase 3 clinical trial has been conducted and completed to determine whether this result can be confirmed, but the data are not yet mature enough for publication.

No adjuvant therapy is given, and the patient presents 6 months later with a single brain lesion.

What would be your next step?

1. Systemic therapy with IL-2
2. Metastasectomy of the brain lesion
3. Stereotactic radiosurgery (SRS) of the brain metastasis
4. Systemic therapy with other agent(s)

The faculty recommends SRS, as this option is associated with low morbidity and may improve survival time. Although some patients with brain metastases respond to IL-2 therapy, the response rate in patients with untreated brain metastases is less than one third of that seen in patients without brain metastases (5.6% vs 19.8%).[72]

Management of Brain Metastases

Brain metastases can be identified by autopsy in up to 75% of patients who die of melanoma and are the cause of death in approximately 20% to 55% of patients with melanoma (reviewed by McWilliams et al, 2003).[73] The median time from primary diagnosis to cerebral metastasis is approximately 3 years, and the median survival from the time of diagnosis of cerebral metastasis is about 4 months.[74] Patients who receive surgery and postoperative therapy have somewhat longer median survival (8.9 months) than those receiving surgery alone (8.7 months), radiotherapy alone (3.4 months), or palliative care (2.1 months), but the prognosis is nonetheless grim.[74]

SRS involves the use of 3-dimensional imaging to deliver a concentrated dose of radiation to a specific area. This procedure is capable of reaching areas not accessible by conventional surgery. Other advantages of SRS include minimal invasiveness, reduced morbidity, and cost-effectiveness. SRS is generally performed during a single session. Local control rates of 75% to 94% have been reported for patients with melanoma brain metastases treated by SRS.[75]

A recent retrospective study of 44 patients with melanoma found that aggressive therapy with SRS as the primary treatment modality resulted in improved survival time. Patients with stage IIIB or IV melanoma were screened with magnetic resonance imaging (MRI) or CT of the brain, and follow-up imaging was performed annually for 2 years, or sooner if warranted by symptoms. If brain metastases were diagnosed, SRS was usually employed for 5 or fewer lesions, and whole-brain radiotherapy was generally used for more than 5 lesions. Systemic therapy with chemotherapeutic or biologic agents was offered as appropriate. Brain images were assessed at least every 2 months, and salvage treatment, including SRS, whole-brain radiotherapy, or palliative surgery, was employed as necessary.[76]

Median survival in this study was 11.1 months. Statistical analyses indicated that survival was significantly correlated with number of SRS treatments (median survival of 7.4 months with 1 SRS treatment vs 16.2 months with more than 1 treatment, $P = .02$) and surgical resection ($P = .02$).[76] The improved survival associated with this aggressive, SRS-based approach suggests that this treatment should be the therapy of choice for patients with brain metastases of melanoma.

Case Continued

The patient undergoes SRS for the single metastatic brain lesion. Three months later, he presents with a single liver metastasis and multiple pulmonary metastases deemed unresectable.

Would you offer this patient systemic therapy now?

1. Yes
2. No

The faculty would recommend systemic therapy, with an emphasis on clinical trials of targeted therapies.

CASE 4 Systemic Therapy for Distant Metastatic Disease: Focus on Targeted Therapies

By Keith Flaherty, MD

The discovery of oncogene mutations in melanoma has provided a rational basis for the investigation of targeted therapies in melanoma (Figure 5). These genetic events result in the activation of signal transduction pathways that are essential for cellular proliferation, metastasis, and resistance to chemotherapy. It has become apparent that melanomas that arise on skin, mucosa, or uvea differ with regard to the pattern of genetic abnormalities. Even melanomas that arise from the skin will differ in their genetic make-up, with some association between pattern of sun exposure and mutations.[77] As an example, BRAF is mutated in the vast majority of superficial spreading melanomas that arise on intermittently sun-exposed skin, but is infrequently mutated in lentigo maligna and acral lentiginous melanomas, and rarely mutated in uveal melanoma. Thus, it is likely that certain targeted therapies and targeted therapy combinations will be suited to distinct subsets of melanoma patients, defined by the pathways that are activated (Figure 6).

Recent preclinical and clinical investigations suggest that single-pathway inhibition will not be sufficient to eradicate advanced melanoma. It is more likely that clinical efficacy in melanoma will require simultaneous inhibition of several critical targets. There remain several potential therapeutic targets for which pharmacologic

Figure 5. Oncogenes and signal transduction pathways in melanoma.

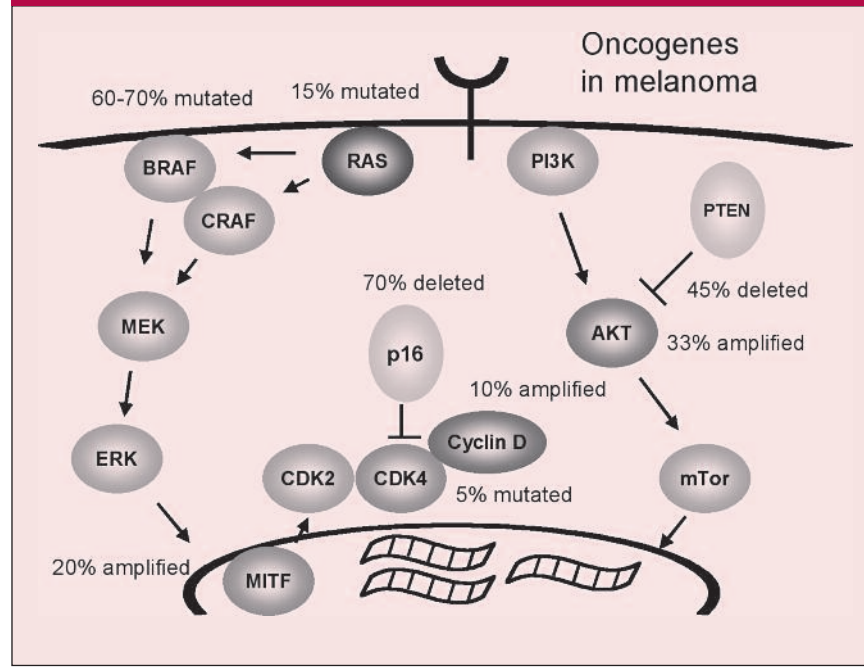
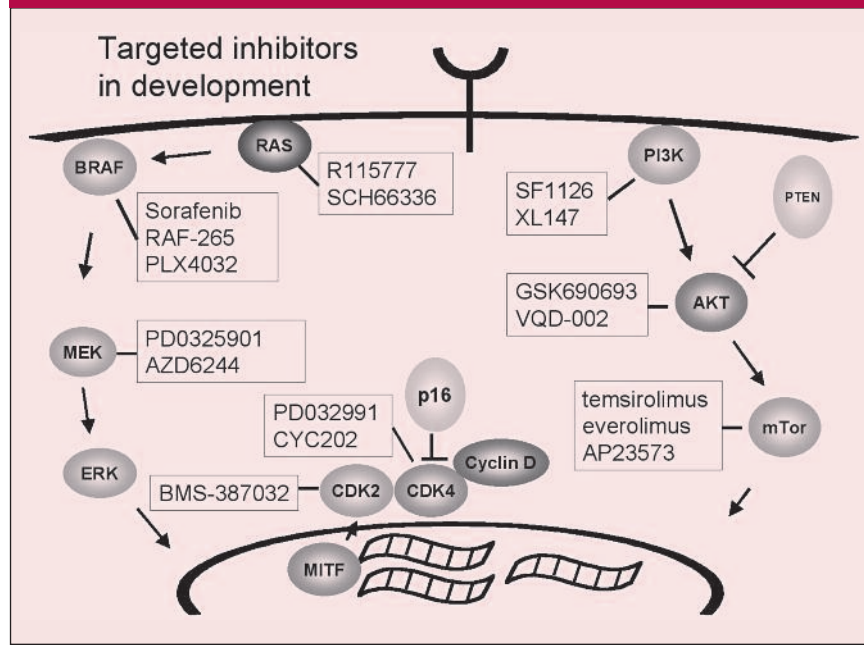


Figure 6. Targeted inhibitors in clinical development.



inhibitors do not yet exist. The molecular targets that have been identified can be grouped in the following categories: the mitogen-activated protein (MAP) kinase pathway, the PI3 kinase pathway, growth factor receptors, and cell cyclecontrol/pigmentation pathways.

The MAP kinase pathway has been the focus of most attention as a therapeutic target in melanoma since the identification of BRAF mutations in the majority of metastatic melanomas.[78,79] NRAS mutations are found in a mutually exclusive subset of melanomas.[80] The therapeutic relevance of BRAF and NRAS is supported by several lines of evidence. Depletion of mRNA for either oncogene with RNA interference inhibits the growth of melanoma cell lines in vitro.[81,82] Pharmacologic inhibition of RAS remains technically challenging. Farnesyltransferase inhibitors (FTIs) are nonspecific inhibitors of RAS that inhibit the post-translational modifications required to produce membrane-localized, activated RAS. However, the abundance of other farnesylated proteins inherently limits the therapeutic index of this type of agent. One FTI, R115777, was evaluated as a single agent in melanoma patients in a phase 2 trial from Cancer and Leukemia Group B, but failed to produce a partial response among the first 14 patients treated.[83] An upcoming cooperative group phase 2 trial will evaluate the efficacy of R115777 in combination with sorafenib.

There are several BRAF inhibitors in development. Sorafenib (BAY 43-9006) is the only BRAF inhibitor that has been evaluated in phase 2 trials. The spectrum of kinases inhibited by sorafenib includes BRAF, CRAF, VEGF receptor 2, PDGF receptor β, p38, flt-3, and c-kit.[84] Both wild-type and mutant BRAF are potently inhibited. In vitro, sorafenib markedly inhibits MEK and ERK phosphorylation and induces apoptosis in melanoma cell lines.[85] Sorafenib has similar effects on BRAF wild-type cells, suggesting that inhibition of targets other than BRAF may account for some of the cytotoxicity. In a mouse xenograft model with BRAF mutant cell lines, sorafenib significantly inhibits growth, but does not cause established tumors to regress.[86] In 2 single-agent phase 2 trials with sorafenib in melanoma, 2 partial responses were observed among 59 patients, and 18 patients had stable disease.[87,88] It is unclear whether sorafenib maximizes the therapeutic potential of BRAF inhibition. Two more potent and specific BRAF inhibitors, RAF265 and PLX4032, are currently being evaluated in phase 1 trials.

The combination of sorafenib, carboplatin, and paclitaxel produced a promising objective response rate in patients with metastatic melanoma, and more pronounced impact on progression-free survival than in historical controls in a single-arm phase 2 trial.[89] This combination is being further evaluated in 2 randomized trials. ECOG 2603 is a randomized phase 3 trial comparing the 3-drug regimen against chemotherapy alone in patients with metastatic melanoma who have not received previous chemotherapy. This study has overall survival as the primary end point and is intended to accrue 800 patients. Over 450 patients have been accrued to date. A smaller randomized trial evaluated the same regimen among patients who have failed treatment with dacarbazine or temozolomide.[90] The end point of this study was progression-free survival, and 270 patients were accrued. The addition of sorafenib to carboplatin and paclitaxel did not improve progression-free survival or objective response rate. However, the progression-free survival and overall response rate of the control arm were superior to what would be expected in a treatment-refractory group. An even smaller randomized phase 2 trial has been completed comparing sorafenib and dacarbazine vs dacarbazine alone.[91] One hundred and one patients were randomized between the two treatments, with progression-free survival as the primary end point. Median progression-free survival for the sorafenib/dacarbazine group was 21.1 weeks, compared with 11.7 weeks in patients receiving dacarbazine alone, but this difference did not reach statistical significance. The percentage of patients progression free at 6 months was higher for the sorafenib/dacarbazine group (41% vs. 18%) and the objective response rate was doubled (24% vs. 12%). Thus, among chemotherapy-naïve patients, the addition of sorafenib to chemotherapy appears to confer a benefit. ECOG 2603 may confirm that finding and define the impact of sorafenib on overall survival.

MEK offers another point of intervention in the MAP kinase pathway, given that it is downstream of BRAF in the MAP kinase pathway. Two highly specific inhibitors of MEK, PD0325901 and AZD6244, are currently in phase 2 trials. Given the lack of cross-reactivity with other kinases, these agents offer a purer test of the efficacy of MAP kinase pathway suppression than FTIs or sorafenib. In preclinical models PD0325901

induces cell cycle arrest in BRAF mutant cells but not BRAF wild-type cells.[92] In BRAF mutant xenografts, PD0325901 arrests growth and induces a minor degree of tumor regression. This agent has been evaluated in a phase 1 clinical trial.[93] The majority of patients treated (27 of 41) had metastatic melanoma. Serial biopsies were performed on all patients and revealed greater than 80% inhibition of ERK phosphorylation at all dose levels but the lowest two. Despite target inhibition, partial responses were observed in only 1 patient with melanoma, and an additional 4 patients with melanoma had stable disease.[94] These results echo those with the less specific MAP kinase pathway inhibitor sorafenib. Sorafenib and earlier-generation MEK inhibitors appear to enhance the effects of cytotoxic chemotherapy in a broad range of tumor types, supporting their investigation in combination with conventional chemotherapeutics.[85,94,95]

The loss of PTEN, in a large subset of melanomas, eliminates an important mechanism of negative regulation on Akt and downstream components of the PI3 kinase pathway. Thus, PI3 kinase, Akt, and mTOR represent potential therapeutic targets in melanoma. The lack of PI3 kinase and Akt inhibitors for clinical use has turned attention to mTOR, for which numerous inhibitors are in clinical development. In favor of this approach, the mTOR inhibitor rapamycin inhibits the proliferation of melanoma cell lines and demonstrates synergy with sorafenib.[96] However, a phase 2 clinical trial with temsirolimus, another mTOR inhibitor, resulted in only one objective response among 33 melanoma patients and early closure of the study.[97] A cooperative group phase 2 trial investigating the combination of sorafenib and temsirolimus will begin this year.

Platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) are overexpressed in melanoma, and both are well-described mediators of tumor angiogenesis. The therapeutic potential of VEGF and PDGF inhibition has been explored in single-agent phase 2 trials. Imatinib mesylate, a potent PDGF receptor–β inhibitor, failed to demonstrate significant clinical activity as a single agent in patients with metastatic melanoma.[98] Bevacizumab, a monoclonal antibody against VEGF, also produced few objective responses when used as monotherapy in this patient population.[99] Unfortunately, neither of these trials explored the impact of these therapies on tumor perfusion with noninvasive imaging or angiogenesis histology in biopsy samples. Therefore, it is not possible to say whether or not angiogenesis was impacted in the absence of clinical activity.

Dysregulation of cell cycle control has been well described in melanoma and is mediated by p16 deletions, activating mutations of CDK4, and amplification of cyclin D. Pharmacologic inhibition of CDK4 is an attractive yet, to date, untested strategy. CDK inhibitors are currently in early clinical development and should be evaluated in melanoma. MITF has been defined as the master regulator of pigmentation and is amplified in approximately 15% of metastatic melanomas.[100] The upregulation of MITF in some melanomas is tightly correlated with CDK2 expression and sensitive to CDK2 inhibition.[101] This raises the potential therapeutic strategy of using a CDK2 inhibitor in conjunction with a BRAF inhibitor to treat the subset of melanomas with MITF amplification and BRAF mutation. This genetic subset of melanoma represents a unique population for the investigation of CDK2 inhibitors.

Signal transduction pathways that are activated via mutation in melanoma represent rational therapeutic targets. However, it is becoming increasingly clear that each melanoma harbors multiple mutations, resulting in simultaneous activation of several pathways. Therefore, combinations of targeted therapies are presumably needed to effectively alter the natural history of the disease. Recent analyses have given some insight into the best strategy for designing targeted therapy treatment regimens. For example, NRAS mutations are typically mutually exclusive with PTEN loss, while BRAF mutation is not.[102,103] Since NRAS activates signaling through the MAP and PI3 kinase pathways at the same time, in the absence of an effective agent against NRAS itself, inhibition of NRAS signaling will require simultaneous inhibition of both pathways. Similarly, melanomas that harbor BRAF mutations and PTEN loss will require simultaneous blockade of both pathways. Because of the lack of specific inhibitors for some of the identified targets and the limited availability of some of the newer compounds for widespread preclinical testing, many of the theoretically attractive combinations have yet to be investigated. In the next 3 to 5 years, we expect the critical phase 1 and phase 2 trials to be completed, clarifying the potential therapeutic contribution of each of these molecular targets.

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Barriers-to-Care for Patients With Melanoma: Inconsistencies in Spinal Surgery Procedures for Metastatic Melanoma

(continued from page 4)

causing spinal cord compression. Although the mechanism of action of corticosteroids is not completely understood, these agents often improve neurologic status.[6,7]

Traditionally, decompressive laminectomy has been performed in an effort to alleviate cord compression. However, Patchell and colleagues suggest that laminectomy is not the best surgical procedure for metastatic spinal disease.[5] Most malignancies causing compression can be found in the vertebral body, which is anterior to the spinal cord. Laminectomy, which involves removal of posterior elements of the spinal column, is likely to exacerbate spinal instability. Additionally, laminectomy does not involve removal of the tumor and, therefore, the procedure does not provide adequate decompression of the spinal cord and nerve roots in many patients.

Surgical Management

Klimo and colleagues defined a "new era" in the surgical management of spinal metastases beginning in the 1980s with the development and eventual acceptance of approaches that allowed surgeons to directly decompress the spinal cord.[4] In many of these procedures, often performed through an anterior approach, the tumor is removed, achieving circumferential decompression of the spinal cord. And, when needed, the spine may be reconstructed and immediately stabilized with the placement of internal fixation devices.

In a review of the literature dealing with the treatment of spinal metastases, Klimo and colleagues note that many published reports indicate a superior rate of preserving and restoring neurologic function with the use of newer surgical methods.[6] However, Patchell and colleagues state that, "the standard treatment for spinal cord compression caused by metastatic cancer is corticosteroids and radiotherapy" and "the role of surgery has not been established."[5] To determine the value of surgery for the management of spinal cord compression, the authors conducted a randomized trial comparing the value of direct decompressive therapy followed by radiotherapy with radiotherapy alone. Using ability to walk as the primary endpoint, with urinary continence, need for corticosteroids and opioid analgesics, and survival time as secondary end points, the authors determined that surgery plus radiotherapy is superior to radiotherapy alone.

In a related study, Thomas and colleagues evaluated the cost-effectiveness of the two approaches.[8] Looking at costs related to treatment and posttreatment care, the authors concluded that surgery plus radiotherapy is cost-effective.

A Multidisciplinary Approach

The management of metastatic spinal disease has advanced significantly over the past 20 years, largely because of improvements in decompressive surgical techniques, spinal instrumentation capabilities, and greater clarification of the role of radiation therapy. These advances have improved our ability to provide meaningful palliation for patients with improvement in quality of life and neurologic function.

Unfortunately, there continues to be variability in the treatment of melanoma metastases to the spine, which may indicate continuing and significant uncertainty among specialists caring for patients with metastatic melanoma as to what constitutes the most appropriate care. Although the best approach for management must be based on the condition and needs of the individual patient, there is clear evidence that radiation alone should not automatically be considered the treatment of first choice, and laminectomy should not be considered the appropriate surgical method.

Treatment decisions should be multidisciplinary for all patients with newly diagnosed metastatic spine disease and include input from a medical oncologist, a radiation oncologist, and a spine surgeon.

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Barriers-to-Care for Patients With Melanoma: Inconsistency in Radiation Oncology Practices

(continued from page 4)

illness. The authors noted, however, that actual utilization rates of radiation therapy for melanoma were 1% according to SEER data and 6% according to data from the American College of Surgeons.

These numbers suggest that many patients with melanoma do not have ready access to centers offering appropriate radiation techniques and that there may be significant regional differences in the use of radiation therapy for melanoma. Part of the issue is that melanoma has historically been regarded as radioresistant, a notion that may limit the interest of surgical oncologists to recommend radiation therapy to treat the disease. Several authors note this perception and refute the idea that radiation therapy is not useful for the treatment of melanoma.[4,5] Additionally, in a recent review article, the Melanoma Study Group of the Mayo Clinic Cancer Center clearly documented that, "using well-reasoned indications and optimal techniques of irradiation, radiation therapy has been used successfully for primary therapy, adjuvant therapy, and palliation of metastatic melanoma."[6]

Adjuvant Radiation Therapy

Ballo and Ang[4] reviewed the indications for radiation therapy in melanoma patients focusing on the postsurgical excision of the primary tumor site or dissection of lymph nodes as well as elective radiation therapy for patients with clinically node-negative disease who are at high risk of nodal involvement.

Local excision remains the standard treatment for patients with melanoma stages I and II. Indications for adjuvant radiotherapy include desmoplastic melanoma, inoperable tumors or those where excision may require extensive reconstruction, Breslow thickness ≥4 mm with ulceration and/or satellitosis, locally recurrent disease, and positive margins. While local recurrence is rare after adequate resection, Ballo and Ang state that, "although prospective studies are lacking, the available data support a strategy of adjuvant irradiation when local recurrence is of concern."

Ballo and Ang also outline the indications for radiation therapy for melanoma patients with documented nodal disease (or nodal recurrence) following the local excision of a primary tumor who are at high risk based on pathologic characteristics of involved nodes. These recommended indications include extracapsular extension, 4 or more lymph nodes, lymph nodes 3 cm or larger, cervical lymph node location, recurrent nodal disease, and sentinel lymph node involved but complete lymph node dissection not planned.

The authors refer to 7 retrospective studies that suggest significant improvements in regional recurrence rates when radiation therapy is used following surgery.

Radiation Dosage and Fractionation

Because of the positive experience within their institution (M.D. Anderson Cancer Center, in Houston) and based on their confidence that some melanoma cell lines are intrinsically more radiosensitive, Ballo and Ang promote the use of hypofractionation rather than a more conventional fractionation regimen.

Conventional Fractionation Versus Hypofractionation

Conventional fractionation involves dividing a total dose of external beam radiation therapy into several smaller doses, or fractions, over a period of days. Typically, treatment is delivered 5 days a week over the course of several weeks. Hypofractionation is the delivery of higher doses of radiation in fewer treatments than conventional therapy. Usually, hypofractionation is administered 2 days a week over 2 to 3 weeks.

However, the use of hypofractionation remains somewhat controversial for the treatment of patients with cutaneous melanoma. In a recent article, Chang and colleagues[7] examined locoregional control of cutaneous melanoma after adjuvant radiation therapy in 56 patients with high-risk disease and compared outcomes between conventional fractionation and hypofractionation. The authors concluded that while surgery and adjuvant radiation therapy provide excellent locoregional control, hypofractionation and conventional fractionation are equally efficacious.

Additionally, some radiation oncologists may be concerned about side effects and safety of hypofractionation. Marnitz and colleagues[5] assert that conventional fractionation is safer than

hypofractionation because of a decrease in the incidence and duration of reactions, especially in cases of irradiation of the head, neck, and brain. Ballo and Ang also limit total radiation to the brain, brainstem, or spinal cord and suggest that for these patients a conventional fractionation regimen may be used.

The Bottom Line

Multiple studies clearly document that radiation therapy is useful for the treatment of melanoma and should put to rest the perception that the disease is radioresistant. Based on appropriate indications, both conventional fractionation and hypofractionation regimens are efficacious for the treatment of cutaneous melanoma.

It is important for surgical oncologists to be aware of these indications and to work closely with medical oncologists and radiation oncologists to ensure that patients are offered a full and appropriate spectrum of services.

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CE Posttest Questions

Please answer each question in the space provided on the back cover.

1. Which factor is *not* associated with a negative prognosis in patients with T4 melanoma?
A. Clark level
B. Lymph node involvement
C. Ulceration
D. Tumor thickness
E. Vascular invasion

2. The MSLT-I study:
A. Was conducted in patients with thick (>4.0 mm) melanomas
B. Examined the use of IFN alfa-2b in node-positive patients
C. Found that in node-positive patients, SLN and CLND (for patients with a positive SLN) resulted in a survival benefit compared with "watch and wait"
D. Found a higher melanoma-specific survival rate in patients who underwent SLN biopsy compared with those who did not
E. All of the above

3. Which of the following statements concerning IFN alfa-2b therapy is true?
A. IFN alfa-2b should not be used in node-negative patients
B. IFN alfa-2b is highly effective in the treatment of stage IV melanoma
C. Low-dose and high-dose IFN alfa-2b regimens are equally effective
D. High-dose IFN alfa-2b is the only adjuvant therapy approved by the FDA for melanoma
E. All of the above

4. Anti–CTLA-4 therapies:
A. Block inhibition of T-cell responses
B. Result in a complete response in 4% to 8% of patients with metastatic melanoma
C. May cause autoimmune reactions
D. All of the above
E. None of the above

5. Metastasectomy
A. Is only an option for patients with lung metastases
B. Should not be used to treat symptomatic disease
C. Is more likely to be successful in patients with a single metastasis and a prolonged disease-free interval
D. Should not be repeated
E. All of the above

6. In a study of melanoma patients with brain metastases, patients who received more than one SRS treatment experienced:
A. Increased memory loss
B. Improved survival
C. Loss of treatment effectiveness
D. Nausea
E. All of the above

7. MEK offers a point of intervention in which pathway?
A. The MAP kinase pathway
B. The PI3 kinase pathway
C. Cell cycle control/pigmentation pathways
D. All of the above
E. None of the above

8. Which pathways does NRAS use to activate signaling?
A. MAP and PI3
B. MAP and cell cycle control/pigmentation pathways
C. PI3 and cell cycle control/pigmentation pathways
D. MAP, PI3, and cell cycle control/pigmentation pathways
E. None of the above

9. Local excision is the standard treatment for patients with melanoma stages I and II. Which of the following is *not* an indication for adjuvant radiotherapy?
A. Desmoplastic melanoma
B. Inoperable tumors or those where excision may require extensive reconstruction
C. Breslow thickness ≤4 mm without ulceration or satellitosis
D. Locally recurrent disease
E. Positive margins

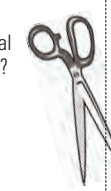
10. Based on epidemiologic data and a review of major treatment guidelines for melanoma, Delaney and colleagues calculated that in 23% of patients with melanoma, radiotherapy is indicated at some point in the treatment process of their illness. The authors noted, however, that actual utilization rates of radiation therapy for melanoma were:
A. Less than 10%
B. 11% to 20%
C. 21% to 40%
D. 41% or more

Evaluation Form

Please use the scale below in answering these questions. Fill in the circle completely. You may use pen or pencil.

Very Low Low Moderate High Very High

1. To what extent were the following objectives of the educational activity achieved?
   - A. Describe the role of sentinel lymph node biopsy in the staging and treatment of cutaneous melanoma
     ❍ ❍ ❍ ❍ ❍
   - B. Compare and contrast adjuvant therapies for the management of melanoma
     ❍ ❍ ❍ ❍ ❍
   - C. List factors to consider in choosing therapeutic approaches to the management of brain metastases and other distant metastases
     ❍ ❍ ❍ ❍ ❍
   - D. Describe the emerging role of targeted therapies in the management of metastatic melanoma
     ❍ ❍ ❍ ❍ ❍
2. To what extent were you satisfied with the overall quality of the educational activity?
   ❍ ❍ ❍ ❍ ❍
3. To what extent was the content of the program relevant to your practice or professional responsibilities?
   ❍ ❍ ❍ ❍ ❍
4. To what extent did the program enhance your knowledge of the subject area?
   ❍ ❍ ❍ ❍ ❍
5. To what extent did the program change the way you think about clinical care and/or professional responsibilities?
   ❍ ❍ ❍ ❍ ❍
6. To what extent will you make a change in your practice and/or professional responsibilities as a result of your participation in this educational activity?
   ❍ ❍ ❍ ❍ ❍
7. To what extent did the activity present scientifically rigorous, unbiased, and balanced information?
   ❍ ❍ ❍ ❍ ❍
8. To what extent was the presentation free of commercial bias?
   ❍ ❍ ❍ ❍ ❍



Posttest Answer Sheet

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

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