MELANOMA CARE
OPTIONS

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FOSTERING AN INTERDISCIPLINARY APPROACH TO MELANOMA CARE

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

- Read the case presentation below
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A 54-Year-Old Woman With Metastatic Melanoma in a Palpable Inguinal Lymph Node

James Goydos, MD, FACS, and Rosemary Giuliano, ARNP, MSN

A 54-year-old woman presented with a palpable right inguinal lymph node. She had a 5 mm-thick melanoma removed from her anterior right thigh 6 years earlier, without a lymph node evaluation. Fine needle aspiration of the palpable lymph node confirmed metastatic disease. Computed tomography (CT) scans revealed no metastases in the chest, abdomen, or pelvis.

The patient underwent inguinofemoral node dissection. Three of the 15 nodes removed were positive for metastatic melanoma. These included Cloquet's node, the palpable node, and one other node. The palpable node had an extracapsular extension.

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

**The authors wish to thank Rebecca Ferrini, MD, for her review and comments on this manuscript.*

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.

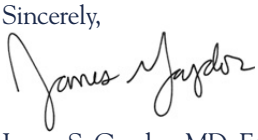
Sincerely,

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

Editorial

This issue follows the case of a woman with metastatic melanoma in a palpable inguinal node. It illustrates several important points about when to perform superficial (inguinofemoral) lymph node dissection, deep (iliac/obturator pelvic) node dissection, or combined lymph node dissection. Faculty members discuss how to weigh morbidity of the procedures, risk of regional and distant recurrence, and chances of increased survival. They debate appropriate adjuvant therapy, given the presence of disease in both superficial and deep nodes. The case illustrates how to prepare for and shepherd patients through the side effects of IFN alfa-2b—eg, depression and severe fatigue—so that they can complete the recommended course of therapy. We hope that you find the case thought provoking and helpful for your practice.

Sincerely,



James S. Goydos, MD, FACS

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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 August 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:

- List factors for and against performing a pelvic node dissection for a palpable inguinal lymph node in a patient with a history of melanoma
- Compare and contrast surgical techniques for groin dissection in a melanoma patient
- Describe the use of IFN alfa-2b adjuvant therapy for high-risk melanoma
- Describe factors to consider in managing toxicities associated with adjuvant IFN alfa-2b therapy in patients 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.*

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

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

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

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Schering-Plough

A 54-Year-Old Woman With Metastatic Melanoma

James Goydos, MD, FACS

Rosemary Giuliano, ARNP, MSN

CASE PRESENTATION

As described, a 54-year-old woman with a history of melanoma presented with a palpable right inguinal lymph node. Fine needle aspiration confirmed this as metastatic disease. She had a 5 mm-thick melanoma removed from her right thigh 6 years earlier with no lymph node evaluation at that time, and she was otherwise healthy. Computed tomography scans of the chest, abdomen, and pelvis did not reveal any metastases.

Metastatic Workup

The decision to assess this patient with fine needle aspiration was in accord with the National Comprehensive Cancer Network (NCCN) 2005 Melanoma Practice Guidelines for stage III melanoma.[1] This document recommends further evaluation for metastatic disease, with at least a chest x-ray and measure of lactate dehydrogenase (LDH) level.[1]

The faculty split on the appropriate additional workup for this patient, with 38% choosing magnetic resonance imaging (MRI) scans of the head, and 30% selecting positron emission tomography (PET)/CT and MRI scans. The NCCN Guidelines recommend a pelvic CT scan for patients with positive inguinofemoral nodes, as already performed in this case, but no further imaging unless indicated by symptoms or abnormalities in a chest x-ray or LDH.[1]

This recommendation derives from findings that an MRI of the brain in patients without symptoms and CT scans of asymptomatic areas rarely detect metastasis.[2,3] A retrospective study of a series of 185 patients with at least 1 sentinel lymph node positive for metastatic melanoma found that an MRI of the brain or CT scan of the chest, abdomen, and pelvis identified metastatic disease in only 1 patient, and this individual had systemic symptoms.[3]

Another report also found that routine CT scans infrequently identified metastatic disease in asymptomatic, clinical stage III melanoma patients. Metastasis was identified by whole body CT alone (ie, chest, pelvis, abdomen) in 6 of 136 patients scanned (4.4%). Pelvic CT scan identified metastases in 7 of 94

(7.4%) patients with groin adenopathy. Authors therefore advised that pelvic CT scan in patients with melanoma in the groin may be useful. Chest CT scan identified metastatic disease in only 1 of 50 (2%) of patients with groin adenopathy.[2]

Case Continued

Many clinicians still scan for distant metastases to rule out patients who are not candidates for lymphadenectomy, said Dr James Goydos. This patient underwent CT scans of the chest and abdomen as well as of the pelvis. Dr Goydos considered the abdominal scan appropriate, given the presence of disease in the pelvis, and the chest CT scan acceptable, as it did not use a contrast agent and added little morbidity. According to Dr Goydos, PET, another option, is sensitive but not specific in the absence of findings on CT. This patient did not undergo further imaging during her workup.

Pelvic Node Dissection?

Inguinofemoral (ie, superficial) node dissection in this patient revealed metastatic melanoma in 3 of the 15 lymph nodes removed. These included Cloquet's node, the palpable node with which the patient presented, and one other node. The palpable node had extracapsular extension.

The next decision involved whether or not to perform pelvic (ie, iliac/obturator or deep) node dissection to reduce risk of regional disease. The goal of this operation is to improve the chance for cure or long-term survival, but it carries notable morbidity. The likelihood of distant metastasis occurring before regional disease would weigh against performing pelvic node dissection.

Factors raising the patient's risk of regional (pelvic/obturator) metastasis include her positive Cloquet's node and her 3 positive inguinal nodes (Table 1).[4,5] The NCCN guidelines advise considering deep groin dissection in the presence of either of these factors.[1] Two characteristics of this patient's disease—the number of positive nodes and extracapsular extension—have also been linked to reduced survival.[6,7]

According to Dr Goydos, her risk of distant metastasis within 5 years is also high—at least 60% to 70% within 5 years for a patient with stage III disease and multiple positive nodes. Still, data do support a reasonable rate of 5-year survival for this patient. In a prognostic factor analysis of 17,600 patients that assessed 5-year survival data for stage III melanoma patients,[8] survival rates ranged widely—from 69% for those with nonulcerated melanomas with a single clinically occult nodal metastasis, to 13% for those with ulcerated melanomas and >4 clinically apparent nodal metastases detected by therapeutic lymphadenectomy.[8] The most significant predictors of reduced 5-year survival for stage III patients were the number of metastatic nodes, presence of clinically palpable diseased nodes, and ulceration of primary melanoma.[8] Even with the negative prognostic impact of >3 positive nodes, this analysis estimated 5-year survival for patients with Stage III melanoma at 27%.[8] Figure 1 summarizes survival figures from the Strobbe study, which specifically examined survival in patients after deep dissection.

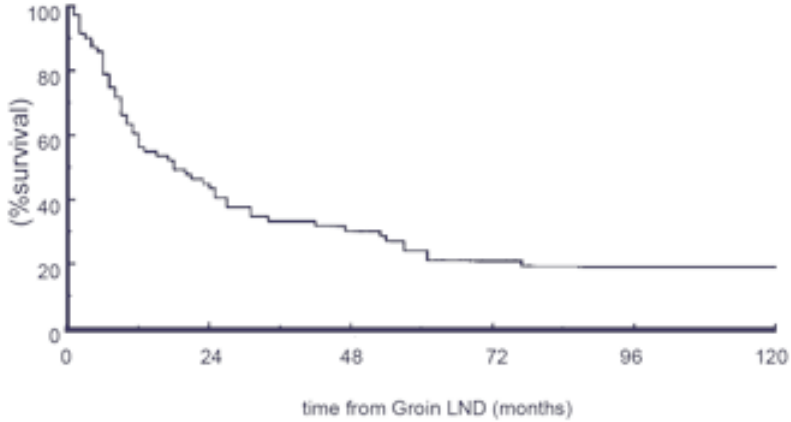
Besides assessing the patient's chances of benefit from deep dissection, the physician must evaluate her risk for complications. Morbidity rates of the combined procedure are relatively high. In one series, more than half (52%) of patients experienced some level of

Table 1

Risk Factors for Regional Pelvic/Obturator Metastasis

Risk Factor	Risk of Deep Node Metastasis
Positive Cloquet's node	67%[5]
	70%[5]
	69%[4]
≥3 positive inguinal lymph nodes	69%[4]

Figure 1



Overall survival rate for 71 patients with positive deep nodes after ilioinguinal lymph node dissection.[27] Reprinted with permission from Strobbe, et al. *Ann Surg Oncol.* 1999.

Table 2

Complication Rates After Combined Inguinofemoral and Iliac/Obturator Lymph Node Dissections[6,28]

Complication	Reported Rate
Overall morbidity	46% to 73%
Lymphedema	
Mild to moderate	19% to 28%
Severe	6% to 24%
Total	25% to 52%
Other	
Seromas	15% to 21%
Infection	11% to 17%
Skin flap necrosis	10% to 15%

lymphedema, and up to 24% developed severe lymphedema (see Table 2).[6]

The risk of lymphedema is not something to enter into lightly, said Dr Goydos, but the chance to cure a patient with high-risk disease makes the procedure worth performing on this woman. The clinician must also consider the patient's age and co-morbidities when deciding whether to recommend the deep surgical procedure. Patients with limited life expectancy or severe co-morbid conditions may not be candidates for deep dissection. Some experts argue that very young patients should not undergo pelvic node dissection because they may have to live a long life with the morbidity of lymphedema, Dr Goydos noted. Table 3 lists factors to consider when evaluating which patients should undergo inguinofemoral dissection only.

Perform the Groin Dissection in One Step or Two?

An overwhelming 81% of faculty voted to perform pelvic node dissection on this patient. There was an animated discussion about whether or not this patient should have undergone combined lymph node dissection of both the superficial and deep nodes in one procedure. One of the panelists stated that in the presence of a palpable node, some physicians would not bother determining the tumor status of Cloquet's node before performing a combined procedure (see Sidebar 1).

Panelist Dr Kenneth K. Tanabe said that on the rare occasions when he performs superficial and deep groin dissection separately rather than as one operation, the dissection of the critical nodes adjacent to the inguinal ligament in the region of Cloquet's node is compromised because of scar tissue. This raises concern about missing more disease with 2 procedures rather than with 1 operation. However, some authorities advocate holding off pelvic dissection until the patient has declared her-/himself either slowly or rapidly progressive in terms of their melanoma, said panelists. The 5-year survival rates cited earlier came from series in which pelvic dissections were performed after patients had declared themselves to be slowly progressive, explained Dr Goydos.

This leads to the contention that before exposing patients to the morbidity of pelvic nodal dissection, one should wait and see if the patient progresses rapidly to distant metastasis. On the other hand, some faculty noted, physicians fear that patients may not comply with follow-up surveillance and may return with uncontrolled metastatic disease.

This patient underwent pelvic/obturator node dissection as a separate dissection. The procedure detected 5 iliac nodes with micrometastatic disease, including the highest common iliac node removed. There was no evidence of gross disease or extracapsular extension during this operation. Post-surgical laboratory test results were within normal ranges.

Follow-up Imaging: Which and How Often?

Faculty members disagreed about appropriate follow-up imaging after pelvic node dissection in this patient. Chest x-ray, CT scan or MRI, multiple imaging, and no imaging drew similar numbers of votes—20% for each option, except 26% for CT scan or MRI. A smaller segment (13%) chose PET scans. Recommended frequency of follow-up imaging formed a rough bell curve—from every 3 months (21%), to every 6 months (35%), to annually (28%).

The NCCN guidelines for imaging

Table 3

Factors Weighing Against Deep Dissection[28]

- No clinical or radiological evidence of deep node disease
- Older age (median age 62 years, compared with median age of 50 years for those undergoing combined dissection)
- Cardiopulmonary risk factors
- A single small groin metastasis
- Thick primary melanomas (>10 mm)
- Presenting with lymph node and locoregional cutaneous metastases along with the palpable groin metastasis

Investigators in one study of melanoma patients with palpable groin nodes used combinations of these factors to select some patients for superficial dissection only.

of stage IB-III melanoma patients advise only chest x-ray every 3 to 12 months at the physician's discretion. Regarding imaging frequency, 84% of faculty who chose one of the options listed above fell within this recommendation.[1] Computed tomography scans should be used only as clinically indicated.[1] Routine scans without an indication do not add to long-term survival or reduced morbidity, Dr Goydos added.

Computed tomography scans also add to patients' long-term anxiety. According to Dr Goydos, they live from scan to scan. Magnetic resonance imaging and PET have not been studied prospectively for their value in follow-up, he said. The NCCN recommendations advise guided MRI of the brain if patients show signs of metastatic disease elsewhere or if they manifest symptoms. Guidelines broadly define the latter to include symptoms such as pain syndromes, but they do not endorse routine MRI scans of asymptomatic patients.

Dr Goydos indicated that some physicians wouldn't even perform chest x-rays, and Dr Tanabe added that LDH may be deleted from the next update of NCCN guidelines. In one series, none of 14 patients with positive sentinel lymph node biopsies (SLNB) had positive or equivocal chest x-rays, and only 3 of those 14 had minimally elevated LDH levels. Lactate dehydrogenase increases are not uncommon.[9] They occurred in 15% of one series of patients with newly diagnosed invasive melanoma, for example, but did not lead to detection of systemic disease or alter initial surgical management.[9] These findings confirm an older report (n = 145) that most recurrent disease was detected by history or physical exam, with a small minority identified by chest x-ray (6%) and none signaled only by an abnormal laboratory test.[10]

Dr Goydos said that the main attraction of LDH for some physicians may be its inclusion on a standard laboratory order. According to one panelist, a positive LDH in an asymptomatic patient at the stage of this case is not likely to be indicative and may force the physician to perform many tests to prove that it's nothing. Dr Goydos concurred, noting that this may subject the patient to needless morbidity, including biopsies.

Case Continued

Follow-up for this patient consisted of physical exam and interim history every 3 months; chest x-ray, blood testing (including liver function tests and LDH), and a dermatologist visit for skin screening every 6 months.

Adjuvant Therapy Options

A spirited discussion ensued about adjuvant therapy. About 87% of faculty recommended use of IFN alfa-2b therapy for this patient. Patients with stage III pelvic/obturator disease, which is likely traveling through the lymphatic system, are among those most likely to benefit from IFN alfa-2b therapy, said Dr Goydos.

The debate focused on whether IFN alfa-2b therapy should be used alone (37% of votes) or in conjunction with radiation to the groin and pelvis (50% of votes). The standard recommendation is not to radiate the pelvis outside of a clinical trial, but this is clearly controversial, said Dr Goydos.[11]

The effect of radiation on overall survival is unknown.[12] Radiotherapy reduces risk of regional recurrence in high-risk cases—defined as those with extracapsular extension, node size 3 cm, 4 involved nodes, cervical location, and therapeutic dissection for clinically apparent disease (as distinguished from subclinical disease discovered upon elective dissection).[12,13] Some authorities argue that adjuvant radiation therapy is justified in patients at high risk of regional recurrence.[14]

Dr Matthew T. Ballo, a panelist and author of several seminal papers in this area, maintained that this patient clearly faced high risk for regional recurrence and therefore would benefit from radiation. Dr Ballo's institution, M. D. Anderson Cancer Center, reserves adjuvant radiation for patients who have undergone therapeutic dissection and who have one of the other aforementioned risk factors for regional recurrence.[12]

Other faculty members noted that radiating the groin adds significant morbidity, including a high risk of lymphedema. Rate of moderate lymphedema requiring medical management after groin dissection and adjuvant radiation was 48% at 4 years in one series.[12,15] In a series of

Sidebar 1

Negative Cloquet's Node Does Not Rule Out Deep Dissection

A positive Cloquet's node raises the suspicion of regional metastasis and therefore indicates the need for deep pelvic dissection (see Table 1). However, a negative Cloquet's node in a patient with palpable inguinal metastasis does not imply that deep dissection isn't necessary.[4] A study analyzing whether Cloquet's node predicts deep pelvic groin metastasis reported that a tumor-negative Cloquet's node meant an 82% (negative predictive value) chance of the absence of additional involved nodes.[4] Authors concluded that too many patients will not be treated for their pelvic lymph node metastases when a tumor-free Cloquet's node is used to justify omission of further dissection.[4] They added that persons with palpable inguinal metastases should undergo iliac/obturator dissection regardless of the tumor status of Cloquet's node.[4] In another series, Cloquet's node was negative in 36% (n = 14) of patients with deep pelvic disease,[27] further corroborating the premise that one cannot use a negative node as an indicator not to perform a deep dissection.

Sidebar 2

Support for Melanoma Patients Receiving IFN alfa-2b Therapy

Crossing Bridges

http://www.melanoma.com/melanoma/crossing_bridges/index.jsp • 800-782-2347 x6003

- Intended to help patients complete IFN alfa-2b therapy
- Supplements information from the patient's medical team
- Website provides patient information about melanoma and practical lifestyle options for adapting to side effects, along with a glossary
- Staffed by oncology nurses specializing in melanoma
- Supported by Schering-Plough Corporation

CancerCare

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- National nonprofit organization
- Provides free professional support services to cancer patients, caregivers, family members, and bereaved
- Offers counseling, education, financial assistance, practical help
- Offers free online and telephone support group for patients with melanoma and their loved ones (http://www.cancercare.org/Melanoma/Melanomamain.cfm#Melanoma_Support)
- Staffed by oncology social workers

40 patients receiving adjuvant radiation after groin dissection, 37% (15) developed lymphedema over a 22-month follow-up period. In 20% (8) of cases, the lymphedema began only after radiation.[11] Other complications of node irradiation include atrophy and loss of subcutaneous fat.[12]

Panelist Steven J. O'Day, MD, concurred with Dr Goydos. A deep dissection gives the best local control, said Dr O'Day. If a patient develops pelvic relapse without system disease, Dr O'Day suggested that repeat surgery might provide a better choice than radiation. There are no data for (survival benefit with) radiation, so first do no harm, he summarized.

The reason to endure the morbidity of radiation is to gain an increase in local control of disease. However, some panelists viewed that argument as less than compelling. Dr Goydos finds that local recurrence in the groin after a complete lymphadenectomy is relatively rare, barring the presence of significant gross disease. There is not much room for gains in local control and a lot of morbidity with radiation, he explained. Further evidence of physician reluctance to choose radiation is that an ECOG trial comparing IFN alfa-2b with and without radiation therapy in metastatic melanoma of the groin, cervical region, and axilla had recruitment difficulties.[16]

Another panelist concurred with Dr Goydos. A deep dissection gives the best local control, and if a patient develops pelvic relapse without system disease, the panelist suggested that repeat surgery might provide a better choice than radiation. There are no data for (survival benefit with) radiation.

Dr Ballo noted that one could reduce morbidity in this patient's case by radiating only the superficial groin, where the node with extracapsular extension was found. If, as Dr Tanabe mentioned earlier, the surgeon is worried about not having removed all the deep nodes in the pelvic node dissection, then the deep nodes also can be radiated.

According to Dr Ballo, the M. D. Anderson Cancer Center would use a hypo-fractionated regimen to radiate such a patient—giving 30 Gy in five 6-Gy fractions delivered over 2 weeks.[12] This is equivalent on paper to a conventional regimen of administering 60 Gy in 6 weeks, he noted. Dr Ballo said that he and his colleagues at M. D. Anderson are not convinced that they see more morbidity with the 2-week course. Patients often appreciate finishing their radiation more quickly.

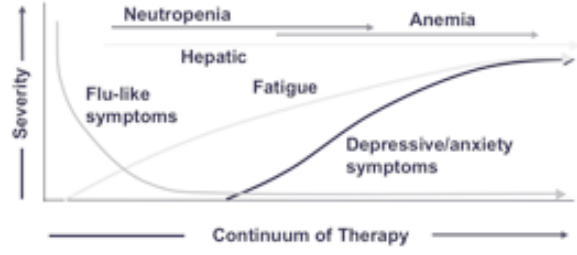
When radiating a patient who will later receive IFN alfa-2b therapy, Dr Ballo said, he and colleagues really try to get the radiation in first, using the hypofractionated regimen, before starting IFN alfa-2b. Other faculty members said that they give 2 weeks of radiation between the 4-week high-dose induction of IFN alfa-2b therapy and the IFN alfa-2b maintenance period.

Faculty noted that a trial examining morbidity and recurrence rates would help resolve the question of when to use radiation after pelvic dissection. A randomized trial in Australia is attempting to answer that question.

IFN alfa-2b: Standard Adjuvant Therapy

Interferon alfa-2b is the only standard adjuvant therapy available for stage IIB/C and III malignant melanoma patients who are disease-free but at high risk for recurrence; neither cytotoxic chemotherapy nor

Figure 2



Course of selected IFN alfa-2b side effects.[21]

interleukin-2 has been found effective in the adjuvant setting.[17] If the patient refuses IFN alfa-2b therapy, vaccines are appropriate in patients fitting this case profile, but one of the panelists noted that patients entering vaccine trials must sign a consent form stating that they have refused IFN alfa-2b therapy.

Interferon alfa-2b has demonstrated efficacy. The pivotal randomized controlled trial of IFN alfa-2b demonstrated significantly longer overall and relapse-free survival compared to observation in patients at high risk of recurrence (stages IIB and III).[18] Another randomized, controlled study has confirmed the benefit of high-dose IFN alfa-2b in relapse-free survival among stage IIB-III patients.[19] A meta-analysis of 12 controlled trials of IFN alfa-2b among high-risk patients also demonstrated significant reduction in recurrence risk (P = .000003).[20]

Depression Detected Prior to IFN alfa-2b Treatment

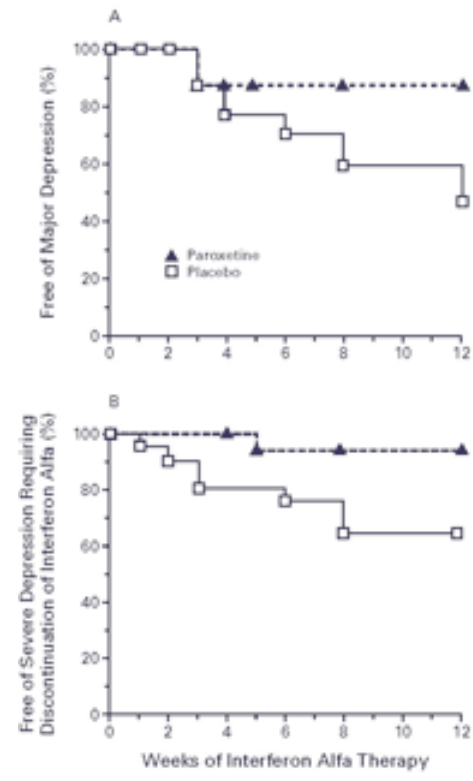
Educating the patient about side effects and coping mechanisms is crucial to completing IFN alfa-2b therapy, a role which falls to the primary care nurse, explained presenter Rosemary Giuliano, ARNP, MSN. Figure 2 shows the time frames during which to expect various side effects; flu-like symptoms are worst at the outset of treatment, then bottom out, she said. Fatigue starts during week 2 or 3 and escalates throughout therapy, and depression and anxiety symptoms worsen with increasing time on therapy. Other side effects include nausea, vomiting, and diarrhea. Besides preparing patients for what to expect and how to handle it, nurses can encourage patients to join a support group for persons receiving IFN alfa-2b therapy (see Sidebar 2).

Evaluation prior to starting IFN alfa-2b therapy revealed that the patient was experiencing insomnia as well as mild situational depression because of the recent death of her husband. Depression is a serious issue to consider. About 40% of patients receiving IFN alfa-2b therapy in the pivotal trial reported some symptoms of depression; 2% attempted suicide or developed suicidal ideation.[21,22] Patients with a history of mood or psychiatric disorders are at higher risk for developing neuropsychiatric side effects of IFN alfa-2b therapy.[21] In this case, the cause of the mild situational depression was identified, and there was no history of depressive episodes.

Some authorities recommend that all patients receiving IFN alfa-2b therapy undergo baseline screening and ongoing monitoring for depression using scales that rate these symptoms.[23] There are data supporting the use of antidepressant drug therapy to prevent this complication. In a small (n = 40) study, fewer melanoma patients developed symptoms consistent with major depression (2 [11%] vs 9 [45%]) or discontinued therapy due to severe depression (1 [5%] versus 7 [35%]) when undergoing prophylactic antidepressant therapy compared with placebo during IFN alfa-2b treatment (Figure 3).[24]

Based on these findings, prophylactic selective serotonin reuptake inhibitor (SSRI) therapy in conjunction with a formal psychiatric evaluation may be an option when administering IFN alfa-2b treatment to a patient with a history of a mood disorder.[21] Some authorities advocate early intervention with counseling, antidepressant agents, and monitoring if depression develops.[21,23]

Figure 3

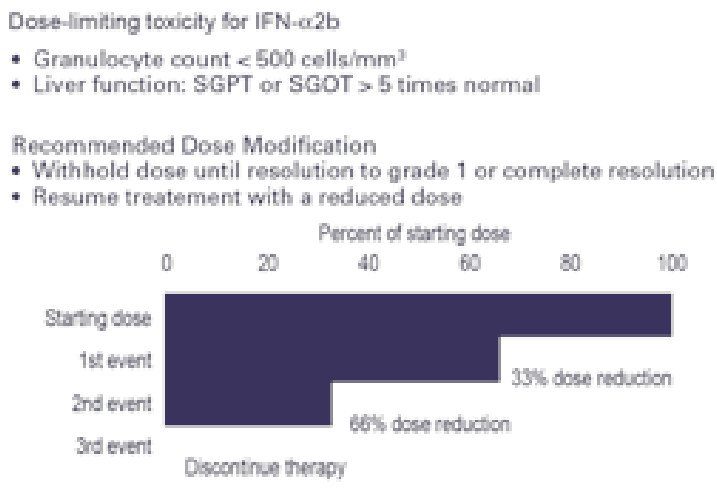


Selective serotonin reuptake inhibitor (SSRI) therapy reduces risk of major depressive disorder symptoms and discontinuation of IFN alfa-2b treatment.[24] Reprinted with permission from Musselman, et al. *N Engl J Med.* 2001.

When to Start an Antidepressant

A large majority (83%) of faculty opted to start an antidepressant agent in this patient. About 47% endorsed initiating antidepressant therapy about 2 to 3 weeks before IFN alfa-2b treatment begins to allow the antidepressant to become effective; the other 36% chose to start the antidepressant concurrently with IFN alfa-2b therapy. Either course is reasonable, as depression and anxiety symptoms develop a few weeks after beginning therapy rather than at the outset (Figure 3). In the aforementioned study, 20 mg paroxetine (Paxil® [GlaxoSmithKline])was started 2 weeks before initiation of IFN alfa-2b induction therapy.[24] Alternate sources of paroxetine include paroxetine HCl controlled-release tablets (Paxil CR®

Figure 4



Three-tiered dose-modification guidelines for adjuvant high-dose IFN alfa-2b therapy.[21] Adapted with permission from Kirkwood, et al. *J Clin Oncol.* 2002.

[GlaxoSmithKline]) and paroxetine mesylate (Pexeva® [Synthon]).

This patient began antidepressant therapy—50 mg qd sertraline (Zoloft® [Pfizer]) titrated to 100 mg qd after 1 week) before starting IFN alfa-2b treatment. Her 4-week induction regimen (31 MIU/d [21 MIU/m²/d] intravenously [IV] 5 times weekly for 4 weeks) included prophylactic oral acetaminophen (650 mg) and diphenhydramine (25 mg) before each IV infusion. The team measured her complete blood count (CBC) and complete metabolic panel (CMP) weekly prior to IFN alfa-2b administration.

IFN alfa-2b Induction: Undiscovered Alcohol Abuse

At week 4, laboratory testing revealed elevated liver function tests (SGOT [AST] = 228; SGPT [ALT] = 394, slightly more than 5 times normal). During discussion after these findings, the patient revealed that she had been drinking 3 to 4 small glasses of wine nightly. This raised her risk for depression as the alcohol likely negated the antidepressant's effect, noted Ms Giuliano. The team referred her for counseling and held the fourth and final week of induction therapy.

One week later, the patient reported abstaining from alcohol entirely. The patient was seen in consultation by the social worker and routine follow-up appointments were scheduled. Repeat CBC and CMP were obtained and revealed slightly elevated liver enzymes, but these were within normal limits.

Faculty members were divided about whether to administer her final week of induction therapy at full dose (46%) or with a 33% reduction (40%). The remainder (13%) voted to discontinue IFN alfa-2b therapy. According to one panelist, the majority's recommendation to continue therapy likely reflects the opinion that her elevated liver enzymes stemmed from alcohol use rather than IFN alfa-2b. The speed with which liver function tests normalized supports this assessment, he added.

The 33% dose reduction increment reflects the protocol used in the Eastern Cooperative Oncology Group (ECOG) trials of IFN alfa-2b therapy (Figure 4).[21] No faculty opted for the more conservative 50% dose reduction specified in the package insert.[22]

The patient received her full dose at week 5. Ms Giuliano explained this decision by noting that it was the patient's final dose, and that the high-dose induction phase is thought to be the crucial element of therapy. Discontinuation rates related to side effects in ECOG clinical trials have become less frequent as clinician awareness and ability to predict side effects has increased. Rates of discontinuation due to adverse events (AEs) fell from 26% in the first IFN alfa-2b trial (ECOG 1684) to 10% in the most recent one (ECOG 1694).[18,25]

Some panelists questioned whether or not it is standard practice to make up a skipped IFN alfa-2b dose during induction. At one institution, patients do not make up a missed week of induction therapy but rather move into the maintenance phase. Other faculty indicated that, according to protocol ECOG 1697, the current methodology allow 6 weeks to give 4 doses of induction therapy.

Faculty had differing views about the patient's psychological state. Dr Goydos explained that counseling sessions are led by a psychiatrist. Ms Esper suggested that the patient may have had a more significant depression and co-morbid psychiatric and alcohol abuse history than her management reflects and that this patient may not belong on IFN alfa-2b therapy due to her psychosocial issues. Ms Giuliano responded that the patient's depression was being monitored closely and pointed out that the patient did abstain from alcohol after counseling. Laboratory test were normal and the LFTS remained within the normal range. It is important to note that a detailed history had been taken, and this mood disturbance was determined to be a situational depression. The patient had no history of life problems, legal difficulties, or other alcohol related problems and reported she had increased alcohol use to assist in sleep. She denied a psychiatric history and did not meet criteria for major depression, although she did have insomnia and a sad affect.

IFN alfa-2b Maintenance: Managing Fatigue

The patient then entered her maintenance phase (15 MIU/d [10 MIU/m^2/d] subcutaneously 3 times weekly for 48 weeks), self-administering IFN alfa-2b treatment with a multidose pen that became available within the last 2 years. This device allows for adjustable dosing from 1 MIU to approximately 20 MIU, in 1-MIU increments. Overfills can be corrected easily without wasting the drug by turning a wheel so that the drug is drawn back into the pen. The 30-gauge needle causes less discomfort for the patient than the more typical 27-gauge needle. According to Ms Giuliano, patients are more compliant with this easy-to-use delivery method.

Regarding follow-up, faculty overwhelmingly agreed (88%) that the patient should be monitored monthly during the maintenance phase with physical exam, CBC, and CMP. The package insert for IFN alfa-2b treatment recommends monthly monitoring of liver function and differential white blood cell counts during maintenance.[22] Small subgroups of panelists (5% each) opted for the same follow-up testing or the same follow-up plus staging studies every 3 months. The patient was in fact followed monthly. Her laboratory results remained within normal limits, and she reported no feelings of depression and continued taking sertraline 100 mg daily (Zoloft® [Pfizer]).

At month 5, she complained of severe fatigue such that she could not continue treatment. She spoke of feeling in a constant state of exhaustion. Fatigue beyond the early weeks of IFN alfa-2b therapy use may result from central nervous system effects, said Ms Giuliano. The agent's impact on the HPA and HPG axes may account for fatigue as well as depression (Figure 5).[21] Fatigue may worsen with continued therapy and can be accompanied by malaise, anorexia, weight loss, and cognitive deficits such as mental slowing, moderate depression, persistent somnolence, and severe headache.[21]

Constitutional symptoms such as fatigue are not considered an objective indication for dose reduction, said Ms Giuliano.[21] Nonetheless, it is the most common dose-limiting chronic toxicity associated with high-dose IFN alfa-2b therapy.[21] Grade 3/4 fatigue affected about 25% of patients in the 3 ECOG randomized trials of IFN alfa-2b.[21] Rest is not completely restorative for this type of fatigue, and the resulting exhaustion can diminish the patient's overall sense of well-being, activities of daily living, ability to participate in relationships, and, most importantly, compliance with treatment.

Faculty members were divided about whether to hold the IFN alfa-2b treatment until the patient's fatigue improved (44%) or to consider adding a CNS stimulant such as methylphenidate HCl (Ritalin® [Novartis]; Concerta® [McNeil]; Metadate® [Celltech]) or methylphenidate HCl extended-release (Ritalin LA® [Novartis]) (50%). A small percentage (5%) voted to stop the IFN alfa-2b treatment.

Nurse education and support is pivotal in helping patients manage fatigue (see Table 4). Assessment of depression is especially important, Ms Giuliano said. Clinicians can reassure patients that if these methods do not alleviate fatigue sufficiently, then IFN alfa-2b therapy can be interrupted or dose reduced. Knowing that alternatives exist may help patients feel empowered to cope with potential fatigue.[21]

There is little information about using drugs to relieve fatigue in patients taking IFN alfa-2b. In one study of melanoma patients receiving IFN alfa-2b treatment, methylphenidate sustained-release; 20 mg qd plus exercise (n = 8) was associated with lower rates of fatigue, cognitive slowing, and therapy discontinuation compared with exercise alone (n = 4).[26] Sources of methylphenidate sustained-release include (Ritalin® SR [Novartis]; Concerta® [McNeil]; Metadate® ER or Metadate® CD [UCB Celltech];

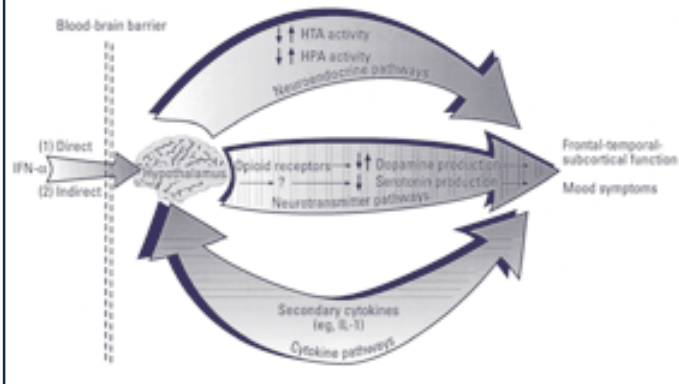
Table 4

Helping Patients Manage Fatigue With IFN alfa-2b Therapy[21]

Suggest patients:

- Engage in strenuous activities when their strength is at its apex
- Identify and approach potentially helpful persons about assisting them in cases of need when debilitating fatigue is not present
- Engage in regular, light exercise
- Plan a routine alternating activity and rest
- Maintain at least some involvement in normal daily activities and social outlets

Figure 5



Possible mechanisms by which IFN alfa-2b may cause neurotoxicity.[29] Adapted with permission from Valentine, et al. *Semin Oncol.* 1998.

Methylin® ER [Mallinckrodt]) Exercise alone appeared to alleviate fatigue when compared with historical controls; however, patients in the exercise-only group all reported disruptions in their work and activities. Those also taking methylphenidate sustained-release indicated that they maintained their usual work and activity patterns during the study period.[26]

The patient was started on methylphenidate 5 mg (Ritalin® [Novartis]) twice daily. An alternative source of methylphenidate is Concerta® (McNeil). She completed the maintenance phase without a dose reduction. Support from family and friends, the primary care nurse, and the social worker, as well as therapy with methylphenidate (Ritalin® [Novartis]), and sertraline (Zoloft® [Pfizer]) helped her finish the therapy successfully.

Conclusions

Patients with multiple positive inguinofemoral lymph nodes are at high risk for regional (pelvic/obturator node) involvement, regardless of whether Cloquet's node is positive. Five-year survival for patients with metastatic melanoma and the negative prognostic factor of >3 positive lymph nodes is only 27% in one large analysis.[28] Therefore, it is appropriate to recommend adjuvant therapy in such individuals.

Appropriate adjuvant therapy in patients at high risk of pelvic/obturator node involvement still needs to be defined. Clinical trials are underway to address this issue. Trials are needed to address the value of resection, IFN alfa-2b, chemotherapy, IL-2, and radiation. Faculty members agree that the current standard of care includes surgical resection, IFN alfa-2b, and close monitoring, as was done here. Managing AEs of IFN alfa-2b therapy is challenging. However, with assistance, many patients can complete full-dose treatment.

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   O O O O O
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   O O O O O
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   O O O O O
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   O O O O O
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10. To what extent was the presentation free of commercial bias?
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Case Re-evaluation Questions

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

1. Would you now recommend pelvic node dissection?
   A. Yes
   B. No
2. What adjuvant therapy would you now recommend?
   A. Radiation to groin and pelvis
   B. IFN alfa-2b therapy
   C. Both A and B
   D. Other
3. If you changed your adjuvant therapy choice after completing this exercise, what influenced you most?
   A. Morbidity of groin radiation
   B. Patient's elevated risk of locoregional metastasis
   C. Other (please specify)_____
4. Did your opinion about management of IFN alfa-2b side effects change after completing this exercise?
   A. Yes
   B. No
5. If you answered "yes" to question 4, what influenced you most?
   A. Data supporting use of pharmacologic support
   B. Concern about patient risk
   C. Other (please specify)_____
6. Do you have any additional comments, questions, or observations regarding how your management strategy changed? _____

Feedback on Case 4: Melanoma on the Back

Case 4 (April issue) concerned a patient with 2.5-mm-depth melanoma on the back. It presented as a tan-to-brown plaque with an asymmetric area of peripheral black pigmentation and covered an area of 1.9 cm. The pathology report rated it a Clark level IV with a small focus of epidermal ulceration, no regression, and a mitotic rate of 3 mitoses per mm^2. There was no lymphatic infiltration.

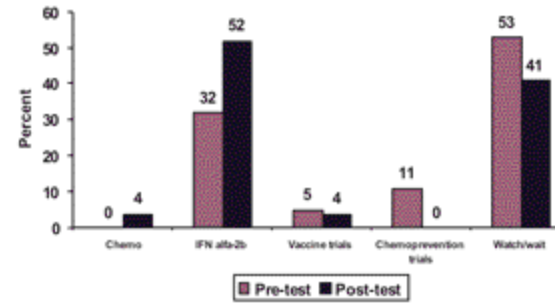
Solid majorities of both readers (pre-case reading; 68%) and faculty (71%) recommended an excisional biopsy as initial evaluation of this lesion. Small proportions of readers advised punch or shave biopsy (5% for each option). The balance of readers (21%) stated that all 3 types of biopsies were appropriate in first assessment of this lesion.

All responding readers (100% pre-case reading) and faculty (100%) also agreed that the next step in evaluation after confirmation of melanoma should be wide local excision with sentinel lymph node biopsy (SLNB). This reflects the widespread acceptance of SLNB for staging.

Most respondents agreed that the patient was at high risk of relapse despite having negative lymph nodes on SLNB. This was true both before (90%) and after reading the case (88%). Faculty assessment of risk in this case was mixed. Lymph node negativity pointed to lower risk. The interaction of thickness and ulceration suggested high risk.

The patient in this case had a stage IIB (T3bN0) tumor. Faculty members were evenly split on the question of management. Half (50%) chose to watch and wait; the other half (50%) would consider adjuvant therapy. This may reflect the lack of treatment data specific to patients with this type of melanoma. High dose interferon (IFN) alfa-2b is approved for use in melanoma cases at high risk of recurrence, but published clinical studies do not specifically assess its efficacy in patients with T3bN0 disease. Until results of an ongoing trial are available, faculty generally suggest that clinicians and patients must assess the potential benefit of IFN alfa-2b on a case-by-case basis. Patients at the highest risk of recurrence stand to gain the most from therapy. Faculty noted that there is a continuum of risk and that all patients have the potential for micrometastasis.

Survey participants changed their views regarding adjuvant therapy after reading the case (see graphic). A larger proportion (32% pre-test vs 52% post-test) chose IFN alfa-2b after reading the newsletter, and fewer opted to watch and wait (53% pre-test vs 41% post-test). Fewer (11% pre-test vs 0% post-test) chose chemoprevention trials. The newsletter noted that evidence for HMG Co-A reductase inhibitors in chemoprevention of melanoma is in early stages.



Faculty and readers largely agreed upon how to follow the patient. About half (52%) of the faculty chose surveillance using history, physical examination, chest x-ray, and serum lactate dehydrogenase testing. The rest (48%) opted for history and physical exam only. A smaller proportion of readers chose the more aggressive follow-up approach after reading the newsletter (63% pre-test vs 52% post-test). Post-test reader scores mirrored those of the faculty (52% for the more aggressive approach, 48% for the more conservative). No respondents recommended patient-directed follow-up before or after reading the case. Similarly, no faculty member chose this option.

Given the frequency with which readers and faculty concurred, it is not surprising that reading the case did not alter the view of most (71%) respondents.

CME Post-test Questions

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

1. Metastatic workup in the presence of positive inguinofemoral nodes includes:
   A. Pelvic CT scan
   B. PET/CT scan
   C. MRI of the head
   D. All of the above

2. Disease characteristics associated with reduced 5-year survival include:
   A. Positive Cloquet's node
   B. >3 positive inguinal nodes
   C. Extracapsular spread
   D. Both B and C
   E. All of the above

3. Reported 5-year survival rate(s) for patients with positive groin nodes is/are:
   A. 40%
   B. 25% to 30%
   C. 10%
   D. Both A and B
   E. All of the above

4. Routine postsurgical follow-up of patients with stage III melanoma includes:
   A. History and physical exam, dermatologic exam
   B. Chest x-ray
   C. CT scan
   D. PET scan
   E. Both A and B

5. Standard adjuvant therapy for stage III melanoma in the pelvic lymph nodes includes:
   A. IFN alfa-2b therapy
   B. Radiation therapy
   C. Interleukin-2 therapy
   D. Chemotherapy

6. Which of the following is not true of adjuvant radiation therapy?
   A. Improves locoregional control in patients at elevated risk of regional metastasis
   B. Improves survival in patients at elevated risk of regional metastasis
   C. Course of therapy can be delivered within 2 weeks
   D. Can be given in a patient also scheduled for IFN alfa-2b adjuvant therapy

7. Depression as a side effect of IFN alfa-2b therapy typically begins:
   A. Within the first week
   B. Within the first month
   C. Midway through the maintenance period
   D. Late in the maintenance period
   E. Depression is not a side effect of IFN alfa-2b therapy

8. IFN alfa-2b dose-reduction increments used in the Eastern Cooperative Oncology Group trials call for which of the following after resolution of first dose-limiting toxicity?
   A. Resume at 33% dose reduction
   B. Resume at 50% dose reduction
   C. Resume at 66% dose reduction
   D. Discontinue therapy

9. Factors weighing against performing therapeutic deep pelvic dissection include:
   A. Cardiopulmonary risk factors
   B. Primary melanoma >10-mm thick
   C. Negative Cloquet's node
   D. Both A and B
   E. All of the above

10. Recommended options for managing severe fatigue during IFN alfa-2b therapy include:
    A. Counsel to engage in light exercise
    B. Bed rest
    C. Immediate cessation of IFN alfa-2b therapy
    D. Pharmacologic support using methylphenidate
    E. Both A and D
    F. Both B and C

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 54-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 973-682-9077. Or, if you prefer, you can visit the Melanoma Care Consortium at www.MelanomaCare.org.

1. Given an inguinofemoral node dissection with positive findings, would you recommend a pelvic node dissection?
A. Yes B. No

2. What factors would you consider in making your decision?
A. Tumor status of Cloquet's node
B. Number of positive nodes discovered on inguinofemoral dissection
C. Surgical risks (morbidity, etc.)
D. Patient characteristics (eg, age, comorbidity)
E. Rate of disease progression
F. All of the above

3. If pelvic node dissection revealed micrometastatic disease, what adjuvant treatment would you recommend?
A. Radiation to groin and pelvis
B. IFN alfa-2b therapy
C. Systemic chemotherapy
D. Interleukin-2 therapy
E. Both A and B
F. Vaccine
G. Other

4. If evaluation of the patient prior to starting IFN alfa-2b therapy revealed situational depression, would you:
A. Start IFN alfa-2b therapy?
B. Postpone IFN alfa-2b therapy and observe the patient closely?
C. Start antidepressant therapy concurrent with IFN alfa-2b therapy?
D. Start antidepressant therapy 2 to 3 weeks before initiating IFN alfa-2b therapy, in order to allow the antidepressant to take effect?

5. If the patient developed fatigue during IFN alfa-2b maintenance therapy and wished to terminate treatment, would you:
A. Stop IFN alfa-2b therapy?
B. Postpone IFN alfa-2b therapy until the patient's fatigue improved?
C. Refer patient for counseling about exercise and other behavioral ways to manage fatigue?
D. Consider starting a CNS stimulant such as Ritalin® (methylphenidate)?
E. Continue IFN alfa-2b therapy and recommend strict bed rest?
F. Both C and D

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

MELANOMA CARE OPTIONS

AUGUST 2005

Fostering an Interdisciplinary Approach to Melanoma Care

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