A 45-Year-Old Man With Melanoma on the Arm*

Douglas Scott Reintgen, MD; Rosemary Giuliano, ARNP, MSN; Merrick Ira Ross, MD, FACS*

A 45-year-old white man presented to the clinic with an atypical pigmented lesion on his right arm. A shave biopsy was taken for pathologic analysis. Results revealed the following:

- Breslow index thickness of 2.0 mm or greater between top layer of epidermis and deepest point of tumor penetration
- Clark level IV or greater (the melanoma penetrates into the reticular or deep dermis)
- Nonulcerated lesion
- A deep positive microscopic margin.

*The authors wish to acknowledge the contributions of Bruce Averbook, MD, and Marc Ernstoff, MD, in the development of this case.

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

This issue of Melanoma Care Options examines the case of a 45-year-old man with a nonulcerated melanoma lesion. We talk about how best to treat this patient, starting with the margin of surgical incision and then discussing subsequent staging procedures and choice of adjuvant therapy.

This case has an extensive discussion of the roles of sentinel lymph node biopsy and completion lymph node dissection. In addition, we look at emerging practices in the management of micrometastatic melanoma. We will be asking for your opinions regarding this case, and we look forward to your views, which we will review in the next issue.

Because this is the first issue, we have also included a list of melanoma care centers in the United States as a referral resource. I hope you get fully engaged in the cases!

Regards,

Douglas S. Reintgen, MD

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The Melanoma Care Consortium

The Steering Committee and the authors. Pictured from left to right: Rebecca Ferrini, MD; Douglas S. Reintgen, MD; Rosemary Giuliano, ARNP, MSN; John M. Kirkwood, MD; Merrick I. Ross, MD; Ashfaq Ahmed Marghoob, MD, FAAD. Not shown: Susan Swetter, MD.

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Continuing Medical Education Information

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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:
• List appropriate surgical margins for cutaneous melanoma based on tumor depth
• Describe tumor/patient factors that support the use of sentinel lymph node biopsy for evaluation of cutaneous melanoma
• Compare and contrast available adjuvant therapies for the management of surgically-resected pathology positive melanoma lymph node metastases
• Propose a process for following patients after surgical resection of stage III melanoma

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CASE PRESENTATION
A 45-year-old white man presented with an atypical pigmented lesion on his right arm. A shave biopsy revealed the lesion to be nonulcerated, with a deep positive microscopic margin, penetration into the reticular or deep dermis (Clark level 2IV), a Breslow thickness of at least 2.0 mm, and clinically negative lymph nodes.

Commentary on the Biopsy
Dr Merrick Ross, the expert panel moderator, notes that this patient has clinically negative lymph nodes and an intermediate-thickness melanoma. He suggests that a full-thickness biopsy was warranted, although this patient only received a deep shave biopsy, which yielded positive margins. However, Dr Ross does not recommend a formal wide biopsy at this point, as this may be overtreatment for an atypical nevus that is not necessarily melanoma and might negatively affect subsequent sentinel lymph node biopsy (SLNB).

Surgical Management
When asked what surgical therapy they would recommend after the biopsy, 89% of participants agreed on wide local excision (2 cm) plus SLNB. A few recommended 2-cm local excision only (8%) or wide local excision (2 cm) and elective lymph node dissection (ELND, 3%), and none recommended 1-cm local excision.

Why did the faculty make this recommendation? A total of 76% of participants voted that survival benefit, potential for adverse effects, standard of care, local disease control, assessing node status for staging, and risk of melanoma nodal metastasis should all be considered, while 12% considered nodal status the driving factor. Dr Ross stressed that all of the factors are important but agreed that nodal status is the most important.

The panelists recommended a 2-cm local excision based primarily on 5 important studies of the effects of excision margins on local recurrence and survival. These studies tested the assumption that higher-risk melanomas have a higher rate of local satellite metastatic disease, resulting in greater distance of metastases from a thicker primary tumor and the need for a wider excision of the primary melanoma site even though the biopsy may already have clear margins.

The WHO Melanoma Program randomized patients with melanomas thinner than 2 mm to receive...
1-cm or 3-cm margins. There was no difference in overall survival. Local recurrence was slightly, but not significantly, higher with 1-cm excision margin than with a 3-cm margin. The Swedish Group study randomized 989 patients with 0.8-mm to 2.0-mm melanomas to receive 2-cm or 5-cm surgical margins and found no difference in overall survival or recurrence rate.

The Intergroup Melanoma Trial randomized patients with 1-mm to 4-mm melanomas to 2-cm or 4-cm surgical margins. This study found no difference in local recurrence (2.1% vs 2.6%) and an insignificant trend toward improved survival with wider margins (70%, 2-cm group, vs 77%, 4-cm group). The skin graft rate was 46% for the 4-cm group, versus 11% for the 2-cm group (P=.001). Survival was higher (although not significantly) in the 4-cm margin group, in which patients were more likely to need a skin graft, but local recurrence did not differ. This trial emphasizes that skin grafts, but local recurrence did not differ. This trial emphasizes that skin grafts are not necessarily better—one needs to consider the potential for complications or cosmetic defect when choosing the width of surgical margins.

The faculty focused on the more recent UK Melanoma Study Group, which randomized 900 patients with melanomas 2.0 mm or thicker (27% >4 mm) to 1-cm or 3-cm surgical margins. Median follow-up was 60 months. Locoregional recurrences (local, satellite, or in-transit events) were more common in the 1-cm group (168 vs 142 events, P=.05). Melanoma caused 128 deaths in the 1-cm group and 105 in the 3-cm group, a nonsignificant difference (P=.1), with similar overall survival. The authors concluded that 2-mm–thick melanomas require excision margins wider than 1 cm based on a difference in locoregional recurrence.

Dr Ross noted that in the wide excision group, the N0 electively dissected group (in which 20 to 30 lymph nodes are typically harvested) did worse than the truly node-negative population. The results suggest that ELND may still understage patients (missed metastatic disease), which may explain their lower survival rate, suggesting a need for more careful analysis of lymph nodes.

Dr Ross concludes that “this trial actually supports the sentinel node concept—find the patients who have microscopic disease, and offer those patients more aggressive therapies, and provide careful analysis of the sentinel node—that way, you avoid unnecessary operations for the node-negative patient population.”

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines recommend margins of 1 cm for tumors 1 mm or thinner, 1 cm to 2 cm for those from 1.01 mm to 2.0 mm, and 2 cm for those thicker than 2 mm.

**SLNB Versus ELND**

Most panelists recommended SLNB. They stressed the importance of discussing risks and benefits with the patient and talking about the next steps to take if the node is positive. Very few panelists would recommend ELND. Four prospective randomized trials of ELND showed no survival benefit, although these studies were not powered to examine benefit in patients with positive lymph nodes.

The Intergroup Trial found no difference in overall survival between observed patients and patients with ELND (Figure 1A). These data were updated from the 10-year data published in 2000, when there was not an obvious benefit. However, Dr Ross noted, over time the ELND group tended to improve compared with the observation group. ELND improved survival in patients with 1-mm to 2-mm tumors (Figure 1B), and those without tumor ulceration (Figure 1C). Patients older than 60 tended toward lower survival with ELND.

The WHO Trial also studied ELND. Of 252 patients entered, 122 were randomized to immediate node dissection. In patients with delayed node dissection, 5-year survival was 51.3%, versus 61.7% for patients undergoing immediate node dissection (P=.09). Five-year survival with occult regional node metastases after ELND was 48.2%, versus 26.6% when dissection was delayed until the appearance of nodal metastases (therapeutic lymph node dissection, TLND). Routine node dissection did not impact survival, but regional node status did (P=.007). Patients whose nodes became clinically and histologically positive during follow-up had the poorest prognosis.

Thus, survival rates were similar between patients with wide excision who never developed node metastases (N0) and those with ELND showing no metastatic deposits (N0−, P=.63, Figure 2). Patients with occult node metastases at ELND (N0+) had significantly different survival from those who developed regional node metastases during follow-up, who had delayed dissection (N1, P=.04).

These studies do not conclusively support a survival benefit with ELND, but they suggest that lymph node analysis can provide essential staging information, and there may be improved overall survival in some subgroups with intermediate thickness melanoma. In addition, the surgery itself may help control
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nodal disease. While ELND is not an appropriate therapeutic technique in 2004 and has high morbidity, these studies support the staging benefits of examining lymph nodes, and SLNB represents an effective way to gauge nodal status and make therapeutic decisions.

**Risk for Nodal Metastasis**

When asked what characteristics of this melanoma suggest the need for SLNB, 63.2% of panelists answered thickness, 2.6% Clark level, and 34.2% all factors listed (thickness, ulceration, Clark level, positive deep margins on biopsy). From Dr Ross’ discussion, *thickness* was the main characteristic supporting SLNB for this case. The melanoma was non-ulcerated, and Clark level and positive deep margin are both irrelevant in a 2-mm melanoma. Dr Reintgen stated that there is a defined risk of nodal disease based on tumor thickness. Thinner lesions have a relatively low risk, especially those thinner than 0.76 mm. Dr Reintgen suggests an increased risk of nodal disease with increasing tumor thickness: lesions up to 1 mm thick: 5% risk; lesions 1 mm to 4 mm: 20%; lesions 4 mm or more: 35%. Ulceration is another factor that worsens stage and prognosis regardless of thickness. Some lesions are controversial, such as atypical Spitz nevi in younger patients, and pathologists may disagree on whether they are malignant. The use of SLNB may help determine the likelihood of malignant disease in these patients.

The NCCN Practice guidelines call for SLNB in patients with primary melanomas at least 1 mm thick. Some patients with thinner primary melanomas may also qualify if there is ulceration, Clark level IV invasion, or other factors indicating a higher nodal metastasis rate (axial location, vertical growth phase, deep positive margin, or mitoses). However, SLNB is probably not appropriate for Clark level 2 or 3 melanomas 0.75 mm or thinner, unless other prognostic factors increase the risk of nodal metastases. A number of clinics offer SNLB studies at 0.76mm.

**How SLNB Works**

The panel discussed the procedure for SLNB. Morton first published the rationale and the technique of sentinel lymph node mapping and biopsy in 1999. The rationale is simple. Tumor cells metastasize from the primary efferent channels. Sentinel nodes are immunosuppressed and are the sites of earliest metastases. More than one sentinel node can receive cells. In Dr Reintgen’s practice, approximately 1.8 sentinel nodes are removed per basin on average.

Lymphoscintigraphy is important to determine the correct basin(s) to examine, because lymphatic drainage patterns may not follow the anatomic patterns expected. During lymphoscintigraphy, a radioactive tracer is injected around the primary site, and a γ-camera captures its...
regional nodal drainage. Surgeons use a hand-held γ-probe intraoperatively to find the “hot spot,” or area of high radioactivity, where the sentinel nodes lie. Intraoperatively, vital blue dye is injected and the site massaged, encouraging the dye to migrate to the sentinel node(s). After a few minutes, the surgeon makes a small skin incision at the hot spot and looks for one or more lymph nodes stained bright blue. The node is excised and examined pathologically.17

The Rationale For SLNB

The rational is based on several factors supporting SLNB.14,18 SLNB helps identify patients with clinically inapparent disease—15% to 35% of patients with clinically node-negative melanoma are positive upon SLNB. Therefore, the panel suggests that a “watch-and-wait” philosophy for clinically negative nodes is unacceptable. As discussed earlier, 5% of patients with thinner melanoma lesions (0.76 mm to 1 mm) will test positive on SLNB,18 so patients and physicians may elect to perform the procedure because of its low rate of complications. It is highly accurate and minimally invasive, with a 3% false-negative rate.16

A Strong Indicator

The most relevant prognostic indicator in melanoma is SLNB. The panel cited a retrospective study of 612 patients who underwent SLNB, showing that SLNB status was the most important prognostic factor for disease-free and disease-specific survival.19 Among 580 patients with at least 1 sentinel node identified, 15% were SLNB+ by conventional histology and 85% were SLNB-. The hazard ratio (HR) for disease-specific survival in SLNB+ patients was 6.53. Sentinel node status was more important than tumor thickness (HR=1.23), Clark level, ulceration, axial location, or patient age/sex. According to Dr Reintgen, “the best predictor of recurrence and survival for melanoma is knowing the sentinel node status.” Moreover, SLNB is the most accurate method to define both the node-negative and node-positive populations. The American Joint Committee on Cancer (AJCC) recognizes SLNB as the standard of care for staging high-risk lesions.19

Finally, patients with positive SLNB are candidates for additional therapy such as therapeutic lymphadenectomy, adjuvant interferon (IFN) alfa-2b, vaccine trials, or other clinical trial enrollment. For clinical trial work of the future, SLNB is very important to categorize node status accurately before initiating therapy so that more uniform patient populations are entered.

Survival

Beyond the staging benefits, SLNB may also have a therapeutic benefit. The panel and Dr Reintgen stressed that survival and regional disease control are two important factors to consider in SLNB. Of all considerations, survival is certainly the most important. A recent (2004) German retrospective multicenter trial19 studied 937 patients with regional lymph node metastases. The outcomes of 314 SLNB+ patients were compared with those for 623 patients who received wide local excision and delayed lymph node dissection (DLND) of clinically enlarged nodal metastases. To remove lead-time bias, survival was calculated from time of initial diagnosis and excision of the primary tumor. The estimated 3-year overall survival rate was 80.1% in patients with positive SLNB and 67.6% in those with DLND (P=.002). Dr Reintgen concluded that “you can see the patients did much better if their microscopic nodal disease was removed with the sentinel node procedure.”

Regional Disease Control

The expert panel emphasized that regional disease control is also important in deciding whether to perform SLNB and completion lymph node dissection (CLND). Patients who receive therapeutic lymph node dissection (TLND) for gross nodal disease show 10% to 40% recurrence depending on the number of positive nodes—from
9% with 1 node up to 33% for more than 10 nodes. Following TLND, 25% to 50% of patients still show extracapsular extension in their nodes. In contrast, patients who have microscopic nodal disease resected in the regional basin recur at a much lower rate. A 2000 M.D. Anderson Cancer Study showed 10% regional nodal recurrence in patients with positive SLNB and therapeutic lymphadenectomy. This study echoes the results of a 1994 study in which approximately 9% of patients undergoing ELND had regional in-basin nodal failures (significantly less than that for TLND).

Ultimately, the panel strongly supported SLNB in appropriate patients. This low-morbidity procedure is both the most sensitive and the most specific measure of nodal involvement and helps ensure that high-risk patients receive the treatment they need without forcing an aggressive node dissection on relatively healthy patients. The use of SLNB reduces the risk of regional recurrence, provides the most accurate staging, may contribute to survival benefit, identifies candidates for adjuvant therapy (eg, IFN alfa-2b), and helps reassure the patient. The AJCC has recommended SLNB as a standard of care for appropriate melanomas, and this panel concurs.

When SLNB Is Not Appropriate
Not all patients should have SLNB. If the patient has received a large rotational flap, lymphatics may be altered and SLNB can be inaccurate. If the primary tumor site is directly over the nodal basin, a wide local excision might disrupt the lymphatic channel to the regional basin. Clinically apparent nodal disease or distant disease would preclude SLNB. Finally, as Dr Kirkwood points out, a patient unable or unwilling to undergo subsequent therapies might not opt for SLNB.

Patient Decision Making
According to Dr Kirkwood, the patient needs to be involved in decision-making and understand the benefits and risks. Dr Marghoob stresses the importance of helping the patient weigh benefits and risks and anticipate the decisions that may follow.

STAGING AND NEXT STEPS
The patient received a 2-cm excision at the primary site and underwent lymphatic mapping and SLNB from the right axilla. Dr Reintgen notes that, despite the positive findings from the initial shave biopsy, the excision showed no residual melanoma at the primary site and clear margins. The pathologist reported the following for the SLNB: atypical parenchymal melanocytes in the right axillary sentinel node initially seen on H & E. Positive with S-100, positive with Mel-A, and a few of the cells are positive with HMB-45. Thus, the pathologist called this metastatic melanoma. The primary tumor also stresses the importance of helping the patient weigh benefits and risks and anticipate the decisions that may follow.

CLND is the standard of care in sentinel node metastatic disease. A CLND was completed. The remaining nodes were negative. The melanoma was categorized as IIIA (nonulceration with microscopic involvement in 1 node and no distant metastases).

Adjuvant therapy
For adjuvant therapy, 72% suggested 1 year of IFN alfa-2b per the approved label. Nearly 17% recommended enrollment in the US Eastern Cooperative Group (ECOG)-1697 trial (IFN alfa-2b vs 1 month observation), and 8% recommended a melanoma vaccine. A small percentage (3%) answered no adjuvant therapy.

Dr Reintgen notes that because this is a Stage IIIA melanoma, the patient is eligible for the ECOG trial. The group generally endorses clinical trials. However, in this case, Dr Reintgen points out that “the standard of treatment for a Stage IIIA melanoma is one year of IFN,” even though participation in the ECOG trial with the knowledge of the standard of care and alternatives could be an option.

The main point is that the patient must make an informed decision. Note that the observation-only arm of ECOG represents no treatment, choice A. The patient must make this decision with his or her physician, and the physician should make certain the patient understands that the ECOG trial is not some new therapy but the comparison of standard IFN alfa-2b at a reduced duration compared with observation.

The panel discussed the main factors driving their decisions about adjuvant therapy. About 25% answered survival prolongation as the main factor in deciding adjuvant therapy, 6% answered disease...
relapse reduction, and 3% chose quality of life (patient preference). Nobody chose safety considerations for this patient (comorbidities) or clinical trial participation. However, the group recommended that quality of life should have been separated from patient preference. Nearly 67% answered all the above.

Dr Reintgen pointed out the importance of survival considerations and showed the AJCC Staging Committee study, illustrating significant differences in 5-year survival curves of Stage IIIA, IIIB, and IIIC melanomas after year 3 ($P<.001$). Survival is significantly improved with lower volume disease in the regional basin. The high-risk subgroups were defined by the AJCC. This patient with Stage IIIA melanoma (1 microscopic node involvement with no ulceration) has 69% 5-year survival.

**Adjuvant therapy options**
The panel pointed out the importance of estimating the relative risk reduction when discussing the benefits/risks of adjuvant therapy with the patient. The next issue will include some information and resources on this.

### Interferon Alfa-2b

Dr Reintgen suggested that increasingly accurate staging helps identify patients whose risk of recurrence is high enough to justify adjuvant systemic treatment. The panel first focused on adjuvant IFN alfa-2b therapy. Dr Reintgen mentioned that “high-dose interferon is really the only FDA-approved adjuvant therapy for melanoma at high risk for recurrence.”

The faculty reviewed 3 ECOG studies that evaluated IFN alfa-2b as adjuvant therapy in patients who were free of melanoma (postsurgery) but at high risk for systemic recurrence. These studies included patients with melanoma thicker than 4 mm or with primary or recurrent nodal involvement. The three trials showed overall improvement in relapse-free survival at 5 years, and two showed improved overall survival at 5 years with IFN alfa-2b.

In the first controlled trial (ECOG-1684), 143 patients received IFN alfa-2b at a median dose of 19.1 million IU/m² intravenously 5 times per week for 4 weeks (Induction phase) followed by a median dose of 9.1 million IU/m² subcutaneously three times per week for 48 weeks (Maintenance phase). IFN alfa-2b therapy was begun no more than 56 days after surgical resection. The remaining 137 patients were observed. Interferon alfa-2b therapy increased relapse-free survival (median time to relapse 1.72 y for IFN alfa-2b vs 0.98 y for observation, $P=.0023$). Estimated 5-year relapse-free survival was 37% for IFN alfa-2b versus 26% for observation. Patients receiving IFN-alfa-2b also had a prolonged median overall survival time (3.82 y) compared with observed patients (2.78 y, $P=.0237$, stratified Log Rank, Figure 3). Estimated 5-year overall survival was 46% for IFN alfa-2b versus 37% for observation.

In the second IFN study (ECOG-1690), subjects were randomized equally to high-dose IFN alfa-2b therapy for 1 year (same schedule as above, n=203), low-dose IFN alfa-2b therapy for 2 years (3 MU/d sc, n=203), or observation (n=202). Consistent with the earlier trial, high-dose IFN alfa-2b therapy improved relapse-free survival (5-y estimated relapse-free survival was 44% vs 35%, $P=.05$). Relapse-free survival in the low-dose IFN alfa-2b arm did not differ from the observation arm (40% vs 35%, $P=.17$). Dr Reintgen points out that neither high-dose nor low-dose IFN alfa-2b improved overall survival versus observation. However, patients who relapsed on the observation arm were eligible for an IFN alfa-2b regimen, and this regimen provided a survival advantage. Thus, salvage therapy may have confounded the analysis of overall survival.

A third study (ECOG-1694) compared high-dose IFN alfa-2b (n=385) with a GM2 ganglioside GMK vaccine administered via subcutaneous injection (n=389). Relapse-free survival at 2 years was 62% with IFN alfa-2b and 49% with GMK ($P=.002$). This trial showed that high-dose IFN alfa-2b improved overall survival versus observation. However, patients who relapsed on the observation arm were eligible for an IFN alfa-2b regimen, and this regimen provided a survival advantage. Thus, salvage therapy may have confounded the analysis of overall survival.
78% overall survival at 5 years for IFN alfa-2b and 73% for GMK (P=.009). The safety monitoring committee closed this trial early after interim analysis indicated inferiority of GMK vaccine to IFN alfa-2b. For eligible patients, IFN alfa-2b provided a relapse-free and overall survival benefit for both per-protocol and intent-to-treat analysis.

The panel presented the ongoing ECOG-1697 trial.27 As discussed previously, this trial examines the effect of 1-month, intravenous, high-dose IFN alfa-2b treatment on the relapse-free and overall survival of patients with stage II or III malignant melanoma that has been completely excised. IFN alfa-2b will be compared with observation. The trial will also assess toxicity in these patients and compare the effect of treatment on quality-adjusted survival.

To summarize, adjuvant IFN alfa-2b therapy in high-risk melanoma has been studied in several trials.24-26,28-31 A recent meta-analysis of these studies shows that only high-dose IFN alfa-2b therapy prolongs relapse-free survival, with a 26% risk reduction for recurrence at 5 years (Figure 4a).32 Overall survival was prolonged with high-dose IFN alfa-2b in 2 trials, resulting in an overall 15% reduced risk of death with IFN alfa-2b across the three trials, which fell just short of statistical significance (Figure 4b, P=.06). Low-dose IFN alfa-2b is less effective. Ongoing IFN alfa-2b studies are examining modified dosing regimens, treatment of intermediate and high-risk melanoma, and the mechanism of action.

IFN Alfa-2b Safety and QOL

Safety
The panel discussed typical side effects of IFN alfa-2b such as flu-like symptoms, neutropenia, anorexia, nausea, and fatigue. Because of known adverse reactions, the FDA mandated a warning on the label:

*Alfa interferons cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many but not all cases these disorders resolve after stopping interferon therapy.*

The panel remarked that in clinical studies, IFN alfa-2b dose was modified because of adverse events in 65% (n=93) of the patients.

No data show a survival benefit with melanoma vaccines.

Therapy was discontinued because of adverse events in 8% of patients during the Induction phase and 18% of patients during the Maintenance phase. The most frequently reported event was fatigue, observed in 96% of patients. Reduced discontinuation rates over time in the three ECOG IFN alfa-2b trials suggest that with experience, health care providers can provide support and dose reductions to keep patients on therapy.

Quality of Life
The panel discussed a number of quality-of-life (QOL) studies with IFN alfa-2b. Dr. Reintgen said that while the efficacy of adjuvant IFN alfa-2b has been tempered by its toxicity, patient preferences for treatment have supported its use and recurrence-free survival is highly valued by patients.

The panel discussed the study by Kilbridge and colleagues that assessed QOL associated with adjuvant IFN alfa-2b among 107 low-risk melanoma patients.33 The study included 4 possible IFN alfa-2b toxicity scenarios, disease-free health, and melanoma recurrence leading to cancer death (with or without IFN alfa-2b). Patients reported the improvement in 5-year disease-free survival required to tolerate IFN alfa-2b. A majority of patients were willing to tolerate mild-to-moderate toxicity for a 4% improvement in 5-year disease-free survival and severe toxicity for a 10% improvement. Generally, patients rated their QOL with recurrent melanoma far lower than the QOL with severe IFN alfa-2b toxicity.

To confirm this finding, Kilbridge and colleagues performed a QOL-adjusted survival analysis of 2 cooperative group phase III trials, E1684 and E1690/S9111/C9190.34 Most patients experienced improvement in QOL-adjusted survival in both trials, but this benefit was statistically significant in only 16% of patients in one study. In the other study, 77% of patients experienced a benefit but 23% felt a detriment, and neither group reached significance. Change in QOL-adjusted survival depends more on the utility for IFN alfa-2b toxicity than on the utility for melanoma recurrence. Patients with cancer are most likely willing to accept greater IFN alfa-2b toxicity than the general population and will tend to favor IFN alfa-2b treatment.

Vaccines
Dr. Reintgen briefly reviewed a number of clinical trials currently studying different vaccines in melanoma. Overall, the panel points out that “to date, no randomized phase 3 trial data show a survival benefit with melanoma vaccines.”

The panel made a brief mention of trials in patients with Stage III melanoma. Colony-stimulating fac-
tors (CSFs) may increase the number of immune cells found in bone marrow or peripheral blood. Combining vaccine therapy with sargramostim, a CSF, may produce a stronger immune response and kill more tumor cells. The Memorial Sloan-Kettering Cancer Center is enrolling patients in a phase 1 study of multi-epitope peptide vaccine with sargramostim (GM-CSF) plasmid DNA immune adjuvant in patients with Stage IIB, IIC, III, or IV melanoma.34 Also, Craig Slingluff’s group at the University of Virginia is conducting a phase 2 trial of vaccine therapy with or without the CSF sargramostim in patients with Stage IIB, IIC, III, or IV melanoma.34

A phase 3 trial of melacine vaccine for HLA-A2, C3–positive melanoma is being planned. One completed trial in clinically node-negative cutaneous melanoma demonstrated statistically significant improvement in relapse-free survival in class I MHC HLA-A2 or aHLA-C3–positive patients receiving melacine ($P = .0002$). These results validate a previous observation in Stage IV disease.35

Finally, the John Wayne Cancer Institute in Santa Monica, California, has completed accrual of 1148 patients with resected Stage III melanoma in a phase 3 trial of immunotherapy with a polyvalent melanoma vaccine (canvaxin plus BCG) versus placebo plus BCG as postsurgical treatment.34

**Ongoing Studies of SLNB and Adjuvant Therapy**

The panel again emphasized that SLNB is accepted as a method of staging the regional lymph nodes for patients with melanoma.36 As a staging method, SLNB can identify very early nodal metastases: single microscopically positive nodes are present in 80% to 90% of node-positive patients. The debate continues whether patients with regional nodal disease should receive CLND, adjuvant IFN alfa-2b, or enrollment in a clinical trial.

The panel separately discussed each of 3 trials involving SLNB: the Multicenter Selective Lymphadenectomy Trial (MSLT), the Sunbelt Melanoma Trial, and the Florida Melanoma Trial (II). The MSLT will address whether wide resection alone or in combination with SLNB will have a survival benefit; the Sunbelt trial looks at molecular staging and the role of IFN alfa-2b in people with minimal disease in the regional basin; and the Florida Melanoma Trial addresses the need for CLND in patients with positive SLNB.

The **Multicenter Selective Lymphadenectomy Trial (MSLT)** is a national trial that will address whether CLND provides a survival benefit for patients.37 This study assigned 2001 patients with melanomas at least 1.0 mm thick or Clark level IV to undergo

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**Figure 4A**

<table>
<thead>
<tr>
<th>High-Dose Trials</th>
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<tbody>
<tr>
<td>ECOG 1684</td>
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<tr>
<td>Intergroup E1690</td>
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<tr>
<td>NCCTG 83-7052</td>
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<td>ECOG 2696</td>
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<td><strong>Subtotal:</strong></td>
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<td><strong>Low-Dose Trials</strong></td>
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<td>WHO 16</td>
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<tr>
<td>ECOG 1690 (L)</td>
</tr>
<tr>
<td>UKCCCR A1M-High</td>
</tr>
<tr>
<td>French CGM</td>
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<tr>
<td>Austrian MMCG</td>
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<td>Scottish MG</td>
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**Figure 4B**

Meta-analysis of results of 12 trials of adjuvant IFN alfa-2b in melanoma. A. Rates of recurrent melanoma with high- and low-dose IFN alfa-2b. High-dose IFN alfa-2b reduced the risk of disease recurrence by 26% ($P = .00009$). Low-dose IFN showed a trend to increased benefit ($P = .02$). B. Risk of death with high-dose IFN alfa-2b. High-dose IFN alfa-2b reduced the risk of death by 15% (2-sided $P = .06$). Adapted from Wheatley K, et al. *Cancer Treat Rev.* 2003.31
wide resection, either alone or with SLNB. Investigators hope to determine whether wide excision of the primary melanoma with intraoperative lymphatic mapping followed by selective lymphadenectomy will prolong overall and disease-free survival compared with wide excision and clinical surveillance of regional nodal basins. The MSLT II trial (initiated 2004) also asks whether patients with minimal microscopic disease in resected sentinel lymph node require CLND.

The panel discussed the Sunbelt Melanoma Trial, a more complex, ongoing trial involving 79 US and Canadian centers and over 3600 patients. This trial looks at the usefulness of reverse transcriptase polymerase chain reaction (RT-PCR) in evaluating sentinel lymph nodes. Dr Reintgen suggests that this trial will help define the role of ultrastaging to identify patients who will most benefit from adjuvant therapy. The trial hypothesizes that adjuvant IFN alfa-2b plus regional lymphadenectomy is more effective than lymphadenectomy alone at prolonging disease-free and overall survival for patients with early nodal metastasis (single microscopically positive sentinel node).

Preliminary results from the Sunbelt trial indicate that patients without regional disease according to routine histologic analysis, immunohistochemistry, and PCR analysis enjoy a high disease-free survival independent of their original tumor thickness or ulceration status. These patients are closer to being defined as “cured” of their disease than was possible using criteria from the old staging system. However, patients whose sentinel node is histologically negative but PCR positive have a significantly lower overall survival rate over nearly 1.7 years. Histologically positive patients have a far worse disease-free survival.

The Sunbelt Melanoma Trial also evaluates morbidity associated with SLNB alone compared with SLNB followed by CLND. In this analysis, 96 of 2120 patients (4.6%) experienced complications with SLNB, while 103 of 444 patients (23.2%) developed complications with SLNB followed by CLND. No deaths were associated with either procedure. The authors conclude that SLNB plus CLND has significantly more morbidity than SLNB alone. However, Dr Reintgen emphasized that the investigators in the Sunbelt Melanoma Trial could not identify factors that predict minimal risk of non–sentinel node metastasis. For this reason, the group reconfirms that CLND is the preferred way to manage nodal metastasis for patients with positive SLNB, despite its potential complications.

The Florida Melanoma Trial is a regional trial that will further address the role of CLND. Patients with a positive SLNB are randomized to (1) CLND and adjuvant IFN alfa-2b or (2) no further surgery and adjuvant IFN alfa-2b.

**Molecular Staging by PCR Analysis**

Rosemary Giuliano points out that RT-PCR analysis of lymph nodes is extremely sensitive, detecting 1 melanoma cell in 1 million lymphocytes. Immunohistochemistry (S-100 antigen) detects 1 in 100,000 cells, while H & E stain detects only 1 melanoma cell in 10,000 lymphocytes.

While RT-PCR shows great promise as a staging tool in clinical trials, Dr McMasters points out several issues to resolve before RT-PCR analysis can be used clinically:

1. The assay methods for RT-PCR analysis should be standardized across laboratories.
2. The best combination of markers must be found to exclude the possibility of a false-positive RT-PCR test caused by the finding of benign nevus cells, in sentinel nodes in 5% of patients. Patients with benign nevus cells in the sentinel nodes might not also have melanoma cells and this test must discriminate between the two.
3. The value of quantitative or semiquantitative analysis of mRNA expression to improve specificity must be evaluated. For example, the newer real-time quantitative PCR test may improve the results.
4. The value of additional treatment for patients with RT-PCR–positive SLNB has yet to be established, which is one of the goals of the ongoing Sunbelt Melanoma Trial.

The expert panel agrees that until such information is available, RT-PCR analysis of SLN should not be used outside of a clinical trial.

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**Overall Evaluations of Adjuvant Therapies**

The group concluded that the weight of evidence supports the use of IFN alfa-2b in this patient based on established efficacy. The relative efficacy of vaccines has not been established in this patient type, and a watchful-waiting approach was not recommended because of the risk for recurrence. From a safety perspective, vaccines are well tolerated, while IFN alfa-2b has clear safety/tolerability issues. However, several outcomes studies show that patients are willing to tolerate the IFN alfa-2b therapy if they believe it provides a reduced risk of recurrence and increased likelihood of survival. The comparative impact of vaccines and IFN alfa-2b on QOL is not known, so
the group could not evaluate the therapies on this basis. The group also encouraged enrolling patients in clinical trials wherever possible. They emphasized providing all options to the patient and assessing his or her goals and desires after carefully evaluating all the options.

**Discussion of Patient Follow-up**

The panel then explained how this patient was followed. He was started on high-dose IFN alfa-2b therapy, and, at the last analysis, showed no regional disease. According to Rosemary Giuliano, such patients should be seen every 3 months for the first year, every 6 months for years 2 through 5, and annually after year 5. A positron emission tomography (PET) scan might also be performed annually through year 5, but chest x-rays and blood tests are not necessary after the first year. This assessment is largely consistent with, though not identical to, the NCCN guidelines, which recommend a complete physical and dermatologic examination every 3 to 6 months for the first 3 years and every 4 to 12 months for years 4 and 5, with annual visits thereafter. The guidelines leave x-rays, blood counts, and lactate dehydrogenase measurements up to the clinician, acknowledging that x-rays and blood work are relatively ineffective screening tools in this population.

**Conclusion**

The panel then summarized by making several recommendations and drawing conclusions from this case study and the literature:

- The refined new recommendations for surgical margins and SLNB have lowered morbidity and improved staging for patients with melanoma.
- Optimal methods for pathologic assessment of the sentinel node are under investigation.
- This patient should be offered adjuvant therapy, and IFN alfa-2b is the only approved adjuvant therapy for patients with Stage III melanoma.
- CLND following positive SLNB is standard of care for patients with Stage III melanoma.

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**CME Questions—Case Report, Stage III Melanoma**

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

1. For a patient with a nonulcerated melanoma with Breslow thickness of ≥2 mm, Clark level IV, what surgical margins would you recommend?
   a. 1 cm
   b. 2 cm
   c. 4 cm
   d. not recommended to perform a local excision.

2. For a melanoma of 0.8 mm, what surgical margin would you recommend?
   a. 1 cm
   b. 2 cm
   c. 4 cm
   d. 1 cm

3. Which of the following melanoma patient groups has the poorest prognosis based on nodal status?
   a. Patients who never develop nodal metastasis (N0)
   b. Patients with no metastatic deposits at end lymph node dissection (N0-)
   c. Patients with occult nodal metastasis at elective node dissection (N0+)
   d. Patients who develop regional node metastases during follow-up and have delayed lymph node dissection (N1)

4. According to the NCCN guidelines, which patients are appropriate candidates for sentinel lymph node biopsy?
   a. Those with primary melanomas ≥1 mm thick
   b. All patients with Clark level 2 melanomas
   c. Those with Clark level I melanoma 0.8 mm thick
   d. Those with nonulcerated Clark level 2 tumors
   e. All of the above

5. In melanoma, a complete lymph node dissection:
   a. Is the standard of care for a patient showing any evidence of metastatic disease
   b. Is always recommended in a Stage II melanoma
   c. Is the standard of care for a patient with a melanoma of Clark level IV
   d. All of the above

6. Providing adjuvant therapy with IFN alfa-2b for 1 year:
   a. Is the standard of care for resected Stage III melanoma
   b. Is the standard of care for resected Stage II melanoma
   c. Is the standard of care for resected Stage IV melanoma
   d. Is shown to result in an unacceptable quality-of-life decrement in all patients
   e. None of the above

7. The meta-analysis for high-dose IFN alfa-2b shows:
   a. No improvement in relapse-free survival but improvement in overall survival in patients receiving IFN alfa-2b compared with observation alone
   b. Improvement in relapse-free survival in patients receiving IFN alfa-2b compared with observation alone
   c. Overall survival rate similar to low-dose IFN alfa-2b
   d. Relapse-free survival similar to that of GMK vaccine
   e. None of the above

8. The current efficacy and safety data with melanoma vaccines have shown:
   a. Some vaccines, but not others, have a similar survival benefit to IFN alfa-2b
   b. Significant safety concerns with vaccines
   c. No survival benefit for GMK vaccine compared with IFN alfa-2b
   d. Extensive documentation of efficacy in patients with Stage III melanoma

9. Preliminary data from the Sunbelt Melanoma Trial have shown:
   a. PCR-RT does not provide any additional diagnostic benefit over histologic analysis
   b. Patients showing no histologic evidence of disease in a sentinel lymph node but testing positive for PCR have a lower overall disease-free survival than patients who are negative for disease by histologic and PCR methods
   c. Patients who show no regional disease by routine histologic analysis, immunohemistry, and PCR analysis show a disease-free survival that varies depending on their original Breslow tumor thickness or ulceration levels
   d. Analysis of lymph nodes using PCR is the standard of care for sentinel lymph node biopsy

10. According to the NCCN guidelines, which of the following is an appropriate follow-up strategy for a patient with a surgically resected Stage III melanoma?
    a. Follow-up every 6 months for the first year
    b. Follow-up every year for years 2 through 5
    c. Serial chest x-rays and blood test every 6 months for year 2 through 5
    d. Follow-up every year starting at year 5
CME Evaluation Form

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

Very Low Low Moderate High Very High

1. To what extent were the objectives of the educational activity achieved?
   0 0 0 0 0

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

3. To what extent was the content of the program relevant to your practice?
   0 0 0 0 0

4. To what extent did the activity enhance your knowledge of the subject area?
   0 0 0 0 0

5. To what extent did the activity change the way you think about clinical care/professional responsibilities?
   0 0 0 0 0

6. To what extent will you make a change in your practice/professional responsibilities as a result of your participation in this educational activity?
   0 0 0 0 0

7. Which of the following best describes the impact of this activity on your performance? (Please use the scale below in answering this question.)
   O This program will not change my behavior because I am already currently conducting my professional responsibilities in a manner consistent with the information presented in this educational activity.
   O This activity will not change my behavior because I do not agree with the information presented.
   O I need more information before I can change my practice behavior.
   O I will immediately implement the information into my practice.

8. What action(s) will you take as a result of participating in this activity? (Please use the scale below in answering these questions.)
   O None.
   O Discuss new information with other professionals.
   O Discuss with industry representative.
   O Participate in another educational activity.

9. To what extent did the activity present scientifically rigorous, unbiased, and balanced information?
   0 0 0 0 0

10. To what extent was the presentation free of commercial bias?
    0 0 0 0 0

11. Please indicate your degree:
    O MD/DO  O Physician Assistant
    O Nurse  O Nurse Practitioner  O Other

12. Was there any particular content that was irrelevant to your practice? If yes, why? __________________________________________________________

13. What types of information should be used to determine topics for this activity if repeated? ____________________________________________

14. Would you prefer a different learning format (discussions, skills training, formal course)?
   _________________________________________________________________

15. In the event that content exhibited commercial bias, please describe the specifics._____________________________________________

16. Do you have any other comments or suggestions for improving this education activity? Please discuss._________________________

If you wish to receive credit for this activity, please fill in your name and address and send to:

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☐ I completed the activity and claim _____ credit hours

Case Re-evaluation

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

1. Did your opinion on patient management change after you completed this exercise?  a. Yes  b. No

2. Would you have performed a sentinel lymph node biopsy?
   a. Yes  b. No

3. What adjuvant therapy would you have provided?
   a. Clinical trial of investigational adjuvant agent
   b. High-dose interferon alfa-2b
   c. High-dose interferon alfa-2b plus isolated limb perfusion
   d. Observation

4. If you did change your opinion about question 3, which data influenced you most?
   a. Patient preference
   b. Evidence base
   c. Patient’s psychological status
   d. All of the above

5. Do you have any additional comments, questions, or observations regarding how your management strategy changed?
Below is a list of melanoma care centers in the United States where you can refer your patients and access other resources to improve your practice.

**NORTHEAST**
- **Specialized Melanoma Program**
  - Buffalo, NY: 716-845-7614
  - New Haven, CT: 860-679-4600

**MIDWEST**
- **Melanoma Center**
  - University of Cincinnati Medical Center: 513-475-7630
  - Chicago, IL: 312-902-9999

**SOUTH**
- **The Melanoma and Pigmented Lesion Center**
  - Johns Hopkins Hospital: 410-614-1022
  - Vanderbilt University Medical Center: 615-343-2990

**OUTSIDE THE UNITED STATES**
- **Dartmouth-Hitchcock Medical Center**
  - Lebanon, NH: 603-650-5175

**References**
Please answer these questions BEFORE OPENING this newsletter.

These questions refer to the case outlined on the front cover. Please circle the answer that best represents your opinion, detach this perforated page, and fax it to 973-682-9077. Or, if you prefer, you can answer these questions and read the article online at www.MelanomaCare.org.

1. What do you recommend as initial definitive surgical therapy based on the clinical picture and pathology report?
   A. Wide local excision (2-cm margin)
   B. Simple local excision (1-cm margin)
   C. Wide local excision (2-cm margin) and elective lymph node dissection
   D. Wide local excision (2-cm margin) and Sentinel Lymph Node Biopsy (SLNB)

2. What factors would you consider in making this first decision?
   A. Risk of melanoma nodal metastasis
   B. Importance of assessing nodal status for staging
   C. Local disease control
   D. Standard of care for melanoma
   E. Potential adverse events associated with surgical techniques
   F. Possible survival benefit
   G. All of the above

3. What characteristics of this melanoma suggest the need for SLNB?
   A. Thickness
   B. Ulceration status
   C. Clark level
   D. Positive deep margin on the shave biopsy
   E. All of the above

4. If the SLNB were positive, what would you recommend next?
   A. No further treatment
   B. A complete lymph node dissection (CLND)
   C. No further surgery, 1 month of interferon (IFN) alfa-2b
   D. No further surgery, 1 year of IFN alfa-2b

5. If, upon CLND, all remaining nodes were negative, what adjuvant therapy would you recommend?
   A. None
   B. 1 year of IFN alfa-2b according to approved FDA label
   C. Enrollment in clinical trial ECOG-1697 (IFN alfa-2b vs. 1 month observation)
   D. Melanoma vaccine

6. What are the main factors in your decision?
   A. Survival prolongation
   B. Disease relapse reduction
   C. Quality of life (patient preference)
   D. Safety considerations for this patient (comorbidities)
   E. Clinical trial participation
   F. All of the above