Current Therapy of Cutaneous Melanoma

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Learning Objectives: After studying this article, the participant should be able to: 1. Cite histopathologic and patient-related risk factors associated with an increased risk of melanoma recurrence. 2. Describe the appropriate margin(s) of surgical excision for primary cutaneous melanoma. 3. Discuss the controversies and review current options for management of regional lymph nodes. 4. Describe the current status of adjuvant therapy for melanoma.

Melanoma is a growing public health problem. Optimal care of the melanoma patient is multidisciplinary, but plastic surgeons and other surgical specialties play a central role in the management of these patients. Although surgery remains the mainstay of therapy for melanoma, several recent clinical studies have helped to clarify the biology of the disease and have changed the patterns of care for patients with melanoma. The advent of lymphatic mapping for interrogation of regional lymph nodes and interferon as the first effective postsurgical adjuvant therapy have had a major impact on the care of melanoma in the United States and elsewhere. This article will review the current clinical approach and therapy for cutaneous melanoma. The diagnosis, prognostic variables, staging evaluation, current surgical and medical treatment, and follow-up guidelines for patients with all stages of melanoma are reviewed. Recent studies, controversies, and directions of future investigational therapies will be discussed. (Plast. Reconstr. Surg. 105: 1774, 2000.)

The worldwide incidence of cutaneous melanoma continues to rise about 6 percent per year.1 Melanoma of the skin in now the sixth most common cancer in the United States.2 Melanoma rates are rising faster than any cancer in men and are second only to lung cancer in women.3 An estimated 44,200 new cases of invasive melanoma accounted for 7300 deaths in the United States in 1999.2 It is estimated that approximately 1 in 75 persons born in the United States in the year 2000 will develop melanoma during his or her lifetime;3 about 20 percent of these people will develop advanced disease and die within 5 years of diagnosis. Although improvement in survival rates for early-stage melanoma has been observed, the mortality rate from melanoma in the United States remains stable at about 2.2 per 100,000 annually over the past 9 years.4 By virtue of its metastatic potential, melanoma accounts for the vast majority of deaths from cutaneous malignancies.

Although effective systemic treatment and early diagnosis remain elusive goals, several recent clinical studies have helped to clarify the biology of the disease and have changed the patterns of care for patients with melanoma. Management algorithms for cutaneous melanoma have undergone a paradigm shift over the past 5 years. Although melanoma remains primarily a surgical disease, trends have been toward less radical excision, fewer elective lymph node dissections, and a more aggressive diagnostic approach. The advent of lymphatic mapping of regional lymph nodes and interferon as the first effective postsurgical adjuvant therapy have had a major impact on the care of melanoma in the United States and elsewhere. This article will review the current clinical approach and therapy for cutaneous melanoma.

CLINICAL PRESENTATION AND DIAGNOSIS

Early detection and diagnosis is a critical factor that probably accounts for most of the increase in overall survival rates of melanoma noted over the past several decades. Clinical characteristics (markers) that identify the patient at higher risk for development of melanoma include skin type I or II, presence of...
Melanoma has been devised by Clark et al. from melanocytic nevi to invasive malignant acquired nevus. A stepwise progression leading from a pigmented precursor, usually an actinic nevus, most cutaneous melanomas arise from epidermal melanocytes in the absence of a known primary lesion. However, a distinct minority of cutaneous melanomas arise from a pigmented precursor, usually an acquired nevus. A stepwise progression leading from melanocytic nevi to invasive malignant melanoma has been devised by Clark et al.7

The cell of origin of most cutaneous melanomas is the epidermal melanocyte. Although there is some disagreement, most melanomas (70 to 80 percent) are thought to arise de novo from epidermal melanocytes in the absence of an obvious precursor lesion.6 However, a distinct minority of cutaneous melanomas arise from a pigmented precursor, usually an acquired nevus. A stepwise progression leading from melanocytic nevi to invasive malignant melanoma has been devised by Clark et al. The most common early symptom of melanoma is pruritis. Other early signs of melanoma include the ABCDEs: lesion Asymmetry or border irregularity, Bleeding or crusting, a history of recent Change or variegation in Color (some lesions are nonpigmented), Diameter over 6 mm, and development of an Elevated area (or palpable nodule) in a previously flat nevus. About 1 to 2 percent of primary melanomas arise from melanocytes on mucous membranes. Approximately 5 to 10 percent of patients present with metastatic disease (usually in a lymph node basin) in the absence of an identifiable primary lesion. Less than 2 percent of patients present with visceral metastases in the absence of a known primary lesion.

Although several noninvasive diagnostic techniques for evaluation of skin lesions, such as ultrasound and surface epiluminescence microscopy, are evolving, biopsy is indicated for all suspicious pigmented lesions. Because tumor thickness is the most important histologic feature in determining prognosis and treatment, biopsy technique is critical. Only two approaches should be considered. For most small and medium-sized lesions, the ideal biopsy technique is complete full-thickness excision of the lesion with a 1- to 2-mm surrounding margin of normal skin. The orientation of the biopsy wound closure should consider a possible subsequent wider excision to decrease the necessity for grafting or extensive reconstructive procedures. For example, extremity biopsy incisions should be oriented along a longitudinal axis. Large excisions or reconstructive procedures to improve cosmesis should not be performed at the time of the initial biopsy. If melanoma is confirmed, these maneuvers may unnecessarily enlarge the extent of the wide local excision and may interfere with lymphatic mapping.

If the lesion is large or is anatomically located where total excision would necessitate reconstructive surgery, incisional biopsy is done. Full-thickness removal of the most elevated, thickest, and/or most clinically suspect part of the lesion is the objective. Three types of incisional biopsies are acceptable: full-thickness punch biopsy, full-thickness incisional biopsy, and full-thickness saucerization. Several areas may need to be sampled in large or structurally variable lesions. Partial thickness or shave biopsies are contraindicated in suspected melanoma because these techniques prevent accurate determination of tumor thickness, the primary prognostic variable. When known major prognostic factors are accounted for, incisional biopsies do not seem to worsen the prognosis for melanoma.

Accurate pathologic interpretation of the biopsy specimen is the cornerstone that determines treatment and prognosis for clinically localized melanoma. At a minimum, the pathology report must contain a description of the patient’s age and gender, tumor site, Breslow’s thickness, Clark’s level of invasion, dimensions, and margins. Additional histopathologic characteristics of the primary tumor that may provide important prognostic information should also be included (Table I).

Communication between the clinician and dermatopathologist is essential. Clinical impressions should be conveyed to maximize clinicopathologic correlation. If melanoma is strongly suspected and initial sections are not confirmatory or are equivocal, additional sections and/or immunohistochemical investigations may be indicated. A clinical history of recurrence of a pigmented lesion after prior excision is important to help avoid misinterpretations. In equivocal cases, review of slides from previous excisions may add important clues to the pathogenesis of the lesion.

Several histopathologic characteristics of primary melanoma tumors help predict the prognosis and risk of metastases. Tumor thickness measured in millimeters (Breslow depth) is the strongest predictor of recurrence for primary
cutaneous melanoma and the single most important determinant of patient management.\textsuperscript{11–15} Tumor thickness is a continuous variable associated with increasingly poor prognosis; it forms the primary basis for tumor staging. Numeric breakpoints with respect to tumor thickness and survival statistically stratify patients into subgroups of risk on the basis of large patient series (Fig. 1). Because thickness is so important, melanomas are commonly (and somewhat arbitrarily) referred to as thin (generally those less than 1.0 mm thick), intermediate depth (1.0 to 4.0 mm thick), and thick (generally those greater than 4 mm thick).

The anatomic levels of invasion into the dermal layers of the skin were described by Clark and correlate with survival and recurrence. The Clark level of invasion is strongly correlated with the Breslow depth, but is somewhat less reproducible and therefore adds little prognostic value when tumor thickness is accounted for.\textsuperscript{11} However, the Clark level may be an independent prognostic factor for thin melanomas and for those that arise in thin skin, such as the eyelid and ear.\textsuperscript{16,17} Lymphatic host inflammatory response, histogenetic melanoma subtype, and growth phase correlate with prognosis on univariate analysis but lose their significance after adjustment for tumor thickness.\textsuperscript{11,12,18} Similarly, the presence of angiolymphatic invasion,\textsuperscript{18,19} regression,\textsuperscript{11,20,21} microsatellitosis,\textsuperscript{22,23} neurotropism,\textsuperscript{24,25} and mitotic

| TABLE I |
| Currently Used Prognostic Indicators in Clinically Localized Cutaneous Melanoma with No Evidence of Metastatic Disease |

| Primary predictive variable (always used) | Primary tumor thickness |
| Secondary predictive variables (used in conjunction with tumor thickness) | Ulceration Mitotic index Tumor location Gender Age Clark’s anatomic level Growth phase Host response (tumor infiltrating lymphocytes) |
| Reported prognostic indicators variably correlated with outcome (rarely used) | Neurotropism Regression Angiolymphatic invasion Histologic subtype Satelliteos |

index >6 mitoses per square millimeter²⁶–²⁸ have been variously reported to correlate with worsening prognosis.

In addition to histopathologic variables, multifactorial analyses have shown that the clinical factors of anatomic site, ulceration, and gender may be independent prognostic factors for survival.¹¹,¹⁸ Extremity melanomas generally have a better prognosis than those on the head, neck, or trunk. However, distal extremity lesions (foot and hand) have prognoses similar to truncal primaries.²⁹ Mucosal and mucocutaneous melanomas have an overall poor prognosis.³⁰ Ulceration has been shown to be a strong independent prognostic factor in several studies.¹¹,¹²,¹⁸ This might be because tumor thickness may be underestimated in ulcerated lesions, leading to a worse prognosis than would be predicted by the measurable tumor thickness alone. Numerous studies have shown women fare better than men with melanoma.³¹,³² The reasons for gender-related differences in survival are largely unknown. A summary of current histopathologic and patient prognostic factors for clinically localized cutaneous melanoma categorized by relative clinical usefulness is shown in Table I.

Mathematical models for predicting survival that take into account multiple known prognostic variables have been retrospectively derived from several large databases.¹¹,¹²,³² Predictions of 5- and 10-year survival rates based on a mathematical model of several important clinical prognostic factors derived from data from 4568 melanoma patients from the University of Alabama at Birmingham and the Sydney Melanoma Unit are shown in Table II.¹²

### STAGING

Several staging classifications exist for melanoma. The traditional three-stage clinical staging system is still sometimes referred to. Stage I refers to primary disease localized to the skin; stage II denotes regional lymph node metastases; and stage III represents distant metastatic disease. The primary shortcoming of the clinical staging classification is that it fails to account for the wide range of outcomes for the majority of patients who present as clinical stage I.

### TABLE II

Predicted 5- and 10-Year Survival Rates from Initial Diagnosis for Patients with Clinically Localized Melanoma*

<table>
<thead>
<tr>
<th>Tumor Thickness (mm)</th>
<th>Anatomic Site Ulceration</th>
<th>Clark’s Level Sex 5-Year Survival Rate (%)</th>
<th>10-Year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.76</td>
<td>Extremity – – II –</td>
<td>99</td>
<td>97</td>
</tr>
<tr>
<td>Extremity – Other –</td>
<td>97</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>0.76–1.49</td>
<td>Axial – – II –</td>
<td>96</td>
<td>92</td>
</tr>
<tr>
<td>Extremity – Other –</td>
<td>91</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Axial – – Other –</td>
<td>91</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>1.50–2.49</td>
<td>Extremity No – – II –</td>
<td>98</td>
<td>97</td>
</tr>
<tr>
<td>Extremity No Other –</td>
<td>93</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>Extremity Yes – – II</td>
<td>94</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Extremity Yes – Other</td>
<td>82</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Axial No – – II –</td>
<td>95</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Axial No Other –</td>
<td>85</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Axial Yes II –</td>
<td>88</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>2.50–3.99</td>
<td>Axial Yes Other –</td>
<td>64</td>
<td>49</td>
</tr>
<tr>
<td>4.00–7.99</td>
<td>Axial Yes – Male –</td>
<td>80</td>
<td>72</td>
</tr>
<tr>
<td>8.00 –</td>
<td>Axial Yes – Male –</td>
<td>73</td>
<td>62</td>
</tr>
<tr>
<td>≥8.00</td>
<td>Axial Yes – Male –</td>
<td>53</td>
<td>39</td>
</tr>
</tbody>
</table>

The most current standard staging system recommended by the American Joint Commission on Cancer (AJCC) is shown in Table III.\textsuperscript{33} The primary factors in assigning AJCC stage are tumor thickness, nodal status, and distant metastases. Essentially, stage I represents early local disease (thin melanomas without evidence of metastases); stage II is more advanced local disease (intermediate depth melanomas without metastases); stage III comprises thick primary melanomas, regional lymph node and/or intransit metastases; and stage IV denotes the presence of distant metastatic disease. Fifteen-year survival curves by AJCC stage are illustrated in Figure 2.\textsuperscript{11} Survival correlates closely with stage groupings.

The initial clinical evaluation of a patient with melanoma consists of a thorough history and physical examination. The history should focus on prior personal or family history of melanoma; history of sun exposure; and review for neurologic, musculoskeletal, gastrointestinal, pulmonary, and constitutional symptoms. Examination should include careful dermatologic inspection of the entire skin for suspicious pigmented lesions or dysplastic nevi and for synchronous primary lesions (present in 3 to 5 percent of patients). Palpation for satellite or intransit nodules, which may be subcutaneous and nonpigmented, is performed. Careful palpation of the major lymph node basins is performed, with particular attention to the potential regional draining nodal basins. Palpably suspicious lymph nodes are considered to be potentially malignant. The diagnostic approach to the palpable lymph node basin in a patient with melanoma should be fine-needle biopsy, which is satisfactory for diagnosis if positive. If negative or equivocal, open biopsy should be performed through a small incision placed so that it can be excised during a formal lymphadenectomy.

Accurate noninvasive staging of the individual melanoma patient remains problematic. Extensive laboratory and radiographic tests are generally of low yield in the asymptomatic patient with stage AJCC I or II melanoma.\textsuperscript{34–38} Routine blood screening for liver metastases with serum lactate dehydrogenase and alkaline phosphatase is somewhat controversial, but it is generally recommended in patients with significant risk melanoma (\textgreater{}1.0 mm thick). Molecular screening tests, such as blood polymerase chain reaction for tyrosinase messenger ribonuclease, and other melanoma markers have been variably reported to correlate with clinical disease status and recurrence rates.\textsuperscript{39,40} Numerous putative molecular tumor markers are being investigated at this time.

Anatomic imaging studies such as computerized tomography and magnetic resonance imaging rely on morphologic alterations at secondary tumor sites. They are inherently insensitive and nonspecific for locating small metastatic tumor deposits. Gallium scintigraphy and immunoscintigraphy using monoclonal antibodies against melanoma-associated antigens have also been used for primary
melanoma staging without significant improvements in diagnostic sensitivity.41–43 Prospective studies have shown routine computed tomography, magnetic resonance imaging, and nuclear medicine tests to be of no use in asymptomatic patients with primary melanoma who have no physical findings suggestive of metastatic disease.37,40 However, directed radiologic evaluation of symptoms or physical findings suggestive of possible metastatic disease is indicated.

Tissue diagnosis is obtained in patients who present with adenopathy (see above). The extent of radiologic workup in this setting is controversial. In patients with inguinal lymph node metastases, computed tomography has been used to assess for pelvic lymphadenopathy and may be used to guide the decision for pelvic lymphadenectomy.40 In patients with known systemic metastases, the extent of workup depends on the intent of the proposed treatment. For procedures performed with curative intent, a comprehensive evaluation is mandatory. This should include computed tomography of the chest, abdomen, and pelvis or whole-body positron emission tomography. The most sensitive test for brain metastases is magnetic resonance imaging.

Recent interest has been directed toward metabolic imaging with positron emission tomography using fluorodeoxyglucose (FDG-PET), which theoretically can show smaller deposits of metastatic tumor. Retrospective and prospective studies have reported that this method is a sensitive indicator of metastatic melanoma compared with conventional diagnostic imaging modalities.44–52 The improved sensitivity and potential cost-effectiveness of positron emission tomography compared with anatomic imaging modalities are rational arguments for PET staging of patients with recurrent melanoma.53

Until recently, little data existed regarding fluorodeoxyglucose-position emission tomography used for initial staging of patients with primary melanoma. Wagner et al. reported a prospective study of fluorodeoxyglucose-positron emission tomography imaging in 74 patients with clinically localized cutaneous melanoma, comparing preoperative FDG-PET
findings with sentinel node histology and clinical follow-up. Fluorodeoxyglucose-positron emission tomography had only 17 percent sensitivity and only 96 percent specificity for detecting occult regional nodal metastases in the overall group, although its performance was somewhat better in patients with thick (>4.0-mm) melanomas. No patients were correctly upstaged to stage IV (distant metastases) by this method. In contrast to recurrent melanoma, PET does not seem to be useful for initial staging of patients with clinically localized melanoma.

On the basis of these data, initial staging evaluation for patients with clinically localized cutaneous melanoma in the Indiana University Cancer Center Interdisciplinary Melanoma Program includes a detailed history and physical examination, chest radiograph, and serum alkaline phosphatase and lactate dehydrogenase. Abnormal findings on screening tests, physical examination, or history are further investigated with additional directed radiologic examination(s), as indicated.

TREATMENT OF PRIMARY LESION: WIDE EXCISION

In addition to having a prominent role in the diagnosis and staging of melanoma, the surgeon plays a central role in the definitive management of the disease. Wide local excision is the mainstay in treatment of primary melanoma and is appropriate in virtually all cases. Wide excision consists of en bloc removal of the tumor or biopsy site with a margin of normal skin and underlying subcutaneous tissue. The goals of surgical treatment are to remove all of the melanoma cells at the primary site to cure patients at low risk of harboring occult metastases, and to achieve durable local disease control even if there is low likelihood of cure. Without compromising these goals, efforts should directed to excise the tumor with minimal functional or cosmetic disfigurement. Appropriate excision margins have recently become more clearly defined by randomized surgical trials.

Historically, the appropriate margins of wide excision for melanoma have been controversial. The exact origin of wide excision margins of 4 to 5 centimeters is unclear, but it probably dates to anatomic studies published by Handley in 1907. Largely on the basis of a single autopsy examination of a patient with advanced melanoma, he recommended, “for melanotic sarcoma of the skin. . . . When malignant melanoma arises in the digits, amputation should be performed at once. The flaps should never be cut so as to include any skin within, at least, one inch of the tumor.” He also wrote, “a ring incision down to the muscles surrounds and isolates the area of deep fascia and overlying deeper subcutaneous fat to be removed. . . . The excision of the lymphatic gland must be carried out on exactly the same principles as the excision of the primary tumor. In late cases, it may even be right to remove an area of skin over the infected glands.” In apparent support of these recommendations are the propensity of melanomas to recur locally and in the form of intransit nodules and microsatellites arising adjacent to the main tumor mass, suggesting a field effect surrounding some tumors. This aggressive approach became inclusive of all primary melanomas and was not substantially challenged until the late 1970s.

Several retrospective studies published in the 1980s suggested that narrower excision may be appropriate for treatment of some melanomas, particularly thin and in situ lesions. These studies implied that local recurrence was more related to intrinsic biologic factors of the primary tumor than the width of excision. However, other reports suggested that very narrow excision margins were associated with increased rates of local recurrence. These observations suggested that margins could be varied for the risk of local recurrence and could be based on a variety of prognostic factors, primarily tumor thickness. On the basis of the cumulative available data, the National Institutes of Health Consensus Conference on Melanoma in 1992 recommended 1-cm margins to the muscle fascia for lesion 1 mm or less in thickness.

Four prospective randomized studies have addressed the issue of optimal margins of excision for melanomas of varying tumor thickness. These studies are summarized in Table IV. Of particular importance are the complementary World Health Organization (WHO) Melanoma Trial and the Intergroup Melanoma Surgical Trial. The WHO Melanoma trial evaluated 612 patients with melanomas less than 2 mm thick who underwent 1-versus 3-cm radial excision margins. There were no local recurrences in patients with lesions less 1 mm thick regardless of surgical margins, and survival was not different between the narrow- and wide-excision groups. Although the rate of local recurrence was not
statistically different between the two groups, five of the six local recurrences observed in this trial occurred in patients with lesions between 1 and 2 mm thick who were treated with 1-cm excisions. On the basis of these data, the authors of this trial concluded that a 1-cm margin for melanomas less than 2 mm thick was safe. Others have been reluctant to accept these recommendations for patients with 1- to 2-mm thick melanomas because of the trend toward higher local recurrence rates in this subgroup.

The Intergroup Melanoma Surgical Trial addressed the issue of surgical margins for intermediate thickness melanomas. This study randomized 486 patients with melanomas 1 to 4 mm thick to undergo 2- versus 4-cm margins of excision. No statistically significant differences in survival rate, local recurrence rate, or in transit metastases were noted between these groups. Together, these two trials provide the primary basis for current recommendation for wide excision margins for invasive melanomas up to 4 mm of thickness.

There are no prospective data from randomized trials to address the proper surgical margins for patients with thick (>4-mm) melanomas. Many surgeons have used wide excision margins of at least 3 cm in this situation. A recent report from M.D. Anderson and Moffitt Cancer Centers attempted to identify whether a 2-cm margin of excision could be safely applied to patients with thick primary lesions. This retrospective study demonstrated no increase in local recurrence rates and no decrease in overall survival rates when margins of 2 cm were used compared with wider excisions. On the basis of the aggregate data from prospective and retrospective studies, margins beyond 2 to 3 cm do not seem justified for thick melanomas.

Current recommendations for margins of excision are now based primarily on tumor thickness (Fig. 3). When wide excision is performed, the surgical margins should be examined for tumor cells or the presence of atypical melanocytes. We and others have seen local recurrences of invasive melanoma in patients with invasive melanoma excised from within a larger field of lentigo maligna, or positive margins with atypical junctional melanocytic hyperplasia. In cases in which invasive tumor, lentigo maligna, in-situ melanoma, or moderate or severe atypical junctional melanocytic hyperplasia is noted at surgical margins, additional excision should be performed to achieve clear margins.

Because the primary goal of wide excision is local control, and because differences in survival with narrower margins have not been demonstrated, excision recommendations can be individualized somewhat according to the collective importance of prognostic and patient factors and the anatomic location of the primary lesion. Clinical judgment must be used in certain critical areas where melanomas cannot be excised widely without functional or cosmetic impairment. Caution is advised, however, because higher rates of local recurrence are seen with inadequate excision and may, at least theoretically, be the progenitor of regional or distant treatment failure. For this reason, and because treatment tumor recurrences in certain areas may be costly in terms of function and cosmesis, local treatment failure must be avoided.

Very narrow margins of excision, such as frozen section-guided margins or Mohs’ micrographic surgical excision technique, are controversial and have traditionally been considered contraindicated in cases of invasive melanoma. This has recently been questioned. Clinical series have shown similar local recurrence rates after Mohs’ technique compared with historical standard wide local excision for invasive melanomas, suggesting this technique may have a role in the management of some melanomas. To date, randomized trials of Mohs’ technique for melanoma have not been performed; therefore, comparative sur-

### Table IV

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients</th>
<th>Tumor Thickness</th>
<th>Treatment Arms</th>
<th>Recurrence/Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>French</td>
<td>362</td>
<td>≤2 mm</td>
<td>2 cm versus 5 cm</td>
<td>NSD* NSD</td>
</tr>
<tr>
<td>WHO</td>
<td>612</td>
<td>≤2 mm</td>
<td>1 cm versus 3 cm</td>
<td>NSD NSD</td>
</tr>
<tr>
<td>Swedish</td>
<td>769</td>
<td>0.8–2.0 mm</td>
<td>2 cm versus 5 cm</td>
<td>NSD NSD</td>
</tr>
<tr>
<td>Intergroup</td>
<td>486</td>
<td>1.0–4.0 mm</td>
<td>2 cm versus 4 cm</td>
<td>NSD NSD</td>
</tr>
</tbody>
</table>

* NSD, no statistically significant difference.
vival and other outcome data are not available. For this reason, recommended surgical margins should not be compromised routinely. A reconstructive procedure such as a flap or graft is usually favored over possibly inadequate very narrow excision margins.

**Excision of Melanoma in Special Locations**

**Ear**

Efforts should be make to excise melanomas of the ear with margins appropriate for tumor thickness, generally 1 to 2 cm. Lesions on the helical rim can be managed by a full-thickness wedge excision, which can be closed to produce a smaller but otherwise normal-shaped ear. This procedure is not always necessary for thin lesions located on the lateral or medial conchal or antihelical areas. In selected cases, small lesions can often be excised with lateral margins that preserve the helical rim for support. Excision of the underlying cartilage as the deep margin and placing a full-thickness skin graft onto the dermis of the skin of the opposite side of the ear produces a good result. Larger lesions, multifocal lesions, and recurrences may require partial or total ear amputation. Preservation of the upper ear is beneficial for patients who wear glasses.

**Fingers and Toes**

Functional considerations are primary in the hand and foot. Attempts to preserve functional length without compromising adequate margins are made. Melanomas on the distal skin or nail bed of the fingers are managed with amputation just proximal to the distal interphalangeal joint, closing with dorsal or volar oblique flaps. Proximal finger lesions can be managed in most cases without amputation, excising adequate thickness-guided soft tissue margins with full-thickness skin grafts, cross-finger flaps, dorsal hand flaps, or neurovascu-
lar island flaps to reconstruct the defect. Removal of bone provides no oncologic benefit unless it is directly invaded, in which case amputation is necessary. Melanomas of the toes are managed with metatarsophalangeal joint amputation. Removal of the metatarsal heads is rarely necessary and should be avoided particularly in the great toe, because this structure is critical for normal walking. Web-space lesions of the hands or feet usually can be excised with adequate soft tissue margins, using skin grafts or local flaps to manage the wound. The need for formal ray amputations should be rare.

Sole of the Foot

Adequate excision of melanomas on the sole of the foot cannot usually be closed primarily, and some type of reconstructive procedure is needed. For wounds over the dorsal foot and non-weight-bearing plantar surfaces, thick split-thickness skin grafts provide adequate coverage. Lesions of the plantar forefoot can also be managed with a skin graft or a toe fillet flap. Lesions of the weight-bearing heel are problematic. Most large wounds in this location are best managed by one of a variety of plantar arch flaps or by free microvascular transfer, such as a radial forearm fasciocutaneous or skin-grafted muscle flap.

Breast

Melanomas of the skin of the breast do not require mastectomy. These lesions are treated similar to cutaneous melanomas in other locations, with margins of excision appropriate for tumor thickness. The nipple-areola complex may need to be resected if involved or adjacent to the primary tumor. This structure can be reconstructed at a later time.

Anorectal Region

Although rare, anorectal melanoma have a greater than 90 percent mortality owing to the presence of occult distant metastatic disease at presentation. Primary surgical treatment should consist of wide local excision with tumor-free margin. Local skin transposition flaps may be used to reconstruct the anal orifice, and usually the sphincter mechanism can be preserved. Classic abdominoperineal resection does not seem to offer an advantage in survival and should be avoided unless the tumor is too large to be encompassed by a sphincter-preserving local excision.

Mucosal Melanomas

Primary melanomas arising from the mucosal epithelial lining of the respiratory, alimentary, and genitourinary tracts comprise about 1 percent of melanomas. The mucosae of the head and neck comprise about 50 percent, with the nasal and oral cavities being most common. Presentation is most often in the form of bleeding or obstruction. No specific factors are sufficiently prognostic that a staging system exists for mucosal melanomas. Most patients present with clinically localized disease, but regional nodal and distant metastatic recurrences are common after excision of the primary site. Treatment of mucosal melanomas has not been standardized, but it generally consists of wide surgical excision with surgical management of the regional nodes if/when metastatic disease is demonstrated. The impact of elective dissection of the regional nodes in mucosal melanomas has not been well studied. Patients with mucosal melanomas of all sites are at high risk for treatment failure, particularly if nodal disease is present, with survival rates ranging from 10 to 50 percent, depending on site.

Unknown Primary Melanoma

Five to 12 percent of melanomas are first noted in the form of metastatic disease. About 70 percent of these presentations occur as nodal metastases in the absence of a primary skin lesion. These cases are thought to represent metastases from regressed or overlooked primary skin lesions, or possibly melanomas arising from intranodal nevi. This situation should generate a systematic search for the primary lesion. A history of prior skin lesion removal or destruction is obtained. A full dermatologic skin survey is performed, and suspicious lesions are biopsied. Depending on the site of regional nodal involvement, inspection of head and neck mucosal sites by fiberoptic endoscopy, ocular examination, anoscopy, and/or pelvic examination may be indicated. Standard staging evaluation is performed. The prognosis of patients with unknown primary melanoma is determined by stage. Accordingly, the patient with an unknown primary melanoma should be treated in the same manner as a similar stage patient with a known primary melanoma.
MANAGEMENT OF REGIONAL LYMPH NODES

The most common site of initial recurrence and metastatic disease in melanoma is the regional lymph nodes. Surgical excision of regional lymph node metastases is the therapy of choice and can be curative. Various series show the 5-year survival rate for patients who undergo lymphadenectomy for nodal disease ranges from 13 to 45 percent.\textsuperscript{72–75} Surgical excision of lymph nodes that are clinically positive for tumor is traditionally referred to as a therapeutic lymphadenectomy. However, by the time regional nodal metastases are clinically obvious, 70 to 85 percent of patients have distant occult metastases, from which they will eventually die. A complete therapeutic lymphadenectomy should be performed in cases of clinically obvious metastatic melanoma in regional lymph nodes even when multiple basins are involved, because it is curative for about 30 percent of patients. Palliative therapeutic lymphadenectomy should also be considered for select patients with distant metastases because the potential morbidity from uncontrolled locoregional disease and lymphatic obstruction has no satisfactory alternative treatment.

Theoretically, excision of occult melanoma nodal metastases at an early stage with a lower tumor burden could prevent progression of disease to distant sites and improve survival. For decades, major controversy has raged over whether early elective lymphadenectomy in patients with clinically negative lymph nodes offers any therapeutic advantage over observation with delayed therapeutic lymphadenectomy in patients who later develop clinically obvious nodal metastases. In support of the elective lymphadenectomy concept are several large, nonrandomized, clinical series that describe patients with occult disease in the nodes who, after undergoing regional lymphadenectomy, showed improved survival rates compared with patients who underwent lymphadenectomy for clinically obvious regional metastatic disease.\textsuperscript{76–82} However, retrospective studies cannot overcome the potential error of lead-time bias that can lead to false conclusions.

Timing of intervention is only one consideration in the elective lymphadenectomy controversy. The other major issue is identification of a subgroup of patients who can potentially benefit from early excision of regional lymph node metastases. Patients with clinically localized melanoma represent a heterogeneous population comprised of at least four subgroups of pathologic disease status. Patients with primary melanomas may have localized disease without regional (lymphatic) or distant metastases. This group will be cured by excision of the primary lesion and will not benefit from any further therapy. A second subgroup will have subclinical lymphatic metastases in the absence of distant disease and may be curable with regional lymphadenectomy. Theoretically, these patients could benefit from elective lymphadenectomy, but identification of this subgroup has been historically problematic. Patients with occult distant metastases (AJCC stage IV) with or without occult regional lymphatic metastases comprise the remainder of clinical stage I patients. These patients are generally considered incurable by current therapies.

In the past 20 years, the understanding of various host and tumor factors as important indicators of probability of occult spread and survival have contributed to therapeutic algorithms of melanoma management. Intermediate Breslow’s depth tumors (1.0 to 4.0 mm) have been identified by retrospective analysis of large databases as having the highest likelihood of occult regional lymphatic spread (15 to 45 percent, depending on depth) without distant metastases.\textsuperscript{57} Tumor thickness, and to a lesser extent, other prognostic factors such as ulceration, gender, age, and location have been the most common criteria for selecting melanoma patients for elective lymphadenectomy.

Four prospective randomized trials of lymphadenectomy in the management of localized cutaneous melanoma have been reported.\textsuperscript{83–86} The results of these studies are summarized in Table V. The WHO Melanoma Group Trial No. 1 included 553 patients with extremity melanomas of all tumor thicknesses.\textsuperscript{83} Neither the intent to treat analysis nor subgroup analyses showed significant improvement in survival. This study has been criticized for failure to stratify patients according to tumor thickness or other prognostic factors, inclusion of only extremity lesions, and the large percentage of female patients. A second study of 171 patients reported by the Mayo Clinic also failed to show a significant difference between early versus delayed node dissections.\textsuperscript{84} The primary criticism of this study has been the high percentage
of patients with extremity lesions and thin primary tumors who would not be expected to benefit from lymphadenectomy. It is important to note that both of these early trials were initiated before the description of major melanoma prognostic factors, including tumor thickness. Although heavily criticized, these two trials clearly show that elective lymphadenectomy does not benefit unselected melanoma patients.

Recently, two more randomized multicenter elective lymphadenectomy trials have been reported. The WHO Melanoma Group Study No. 14 randomized 252 patients with primary truncal melanomas thicker than 1.5 mm to undergo wide local excision plus observation or plus elective lymphadenectomy. Eight-five Five-year overall survival rates were not significantly different between the groups (51 versus 62 percent, \( p = 0.09 \)). However, survival rates were significantly higher in patients undergoing elective lymphadenectomy who were found to have occult node metastases compared with observed patients who developed clinically obvious nodal metastases and required therapeutic lymphadenectomy. Fifty-five Five-year overall survival rates were not significantly different between the groups (51 versus 62 percent, \( p = 0.09 \)). However, survival rates were significantly higher in patients undergoing elective lymphadenectomy who were found to have occult node metastases compared with observed patients who developed clinically obvious nodal metastases and required therapeutic lymphadenectomy (48 versus 27 percent, \( p = 0.04 \)). This study did not require preoperative lymphoscintigraphy to ensure that all node basins at risk were adequately treated.

The Intergroup Melanoma trial evaluated 740 patients with melanomas 1.0 to 4.0 mm deep, randomized to receive wide local excision plus elective lymphadenectomy versus wide local excision plus observation. Eight-six This is the only trial to date that used lymphoscintigraphy to direct elective lymphadenectomy. Subgroup analysis was planned, stratifying for tumor thickness and ulceration. Overall survival was not significantly different between randomized groups (86 versus 82 percent, \( p = 0.25 \), intent to treat analysis). However, subset analysis showed significantly improved survival for patients 1 to 2 mm thick, those without ulcerated tumors, and those younger than 60 years of age. The investigators concluded that this study proved the benefit of elective lymphadenectomy in these subgroups of patients. These conclusions have been controversial because of multiple subgroup analyses and because age was not a prospectively planned subgroup analysis.

Despite these four trials, the elective lymphadenectomy controversy has not been definitively resolved. Collectively, data from the trials show that: (1) not all patients benefit from elective lymphadenectomy (WHO No. 1 and Mayo trials); (2) patients with intermediate-thickness melanomas between 1 and 2 mm seem to have a survival advantage with elective lymphadenectomy, depending on tumor thickness (and possibly other prognostic factors, Intergroup trial); and (3) patients with occult regional lymph node metastases seem to benefit from early versus delayed lymphadenectomy (WHO trial No. 14 and Intergroup trial). However, these studies also show that the survival benefit associated with elective lymphadenectomy as traditionally practiced is small. It is difficult, on the basis of characteristics of the primary tumor and patient, to identify which individuals will actually benefit. In the absence of conclusive data, the decision to perform elective lymphadenectomy must be made on a case-by-case basis.

Lymph node metastases, when present, are the single most important prognostic variable for survival in melanoma, taking priority over all other tumor and host factors. Several prognostic factors have been identified in node positive melanomas. Twelve Eighty-seven to Ninety-one The most important of these is the number of involved nodes. Eighty-seven Microscopic versus macroscopic disease Eighty-eight and Ninety and the presence of extranodal extension Eighty-nine and Ninety also seem to be significant predictors of outcome in some series. Size of nodal metastases is of uncertain significance. Primary tumor char-

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**TABLE V**

Prospective Lymphadenectomy Trials for Melanoma

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients</th>
<th>Tumor Thickness</th>
<th>Sites</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO 1&lt;sup&gt;85&lt;/sup&gt;</td>
<td>553</td>
<td>All</td>
<td>Extremities</td>
<td>OS:NSD*</td>
</tr>
<tr>
<td>Mayo&lt;sup&gt;84&lt;/sup&gt;</td>
<td>171</td>
<td>All</td>
<td>Extremities</td>
<td>OS:NSD</td>
</tr>
<tr>
<td>WHO 14&lt;sup&gt;85&lt;/sup&gt;</td>
<td>252</td>
<td>&gt;1.5 mm</td>
<td>Trunk</td>
<td>OS:NSD†</td>
</tr>
<tr>
<td>Intergroup&lt;sup&gt;86&lt;/sup&gt;</td>
<td>740</td>
<td>1.0–4.0 mm</td>
<td>All</td>
<td>OS:NSD‡</td>
</tr>
</tbody>
</table>

* OS, overall survival; NSD, no statistically significant difference.
† Subgroup analysis showed significantly improved survival for node positive patients treated with elective lymphadenectomy versus delayed therapeutic lymphadenectomy.
‡ Subgroup analysis showed significantly improved survival in patients who underwent elective lymphadenectomy for tumors 1 to 2 mm thick, patients with nonulcerated tumors, and patients < 60 years old.
acteristics such as thickness, ulceration, and location retain some secondary prognostic significance even when lymph nodes are involved. In patients who manifest regional nodal recurrences after wide local excision of the primary tumor, duration of remission may also be important, with early recurrences faring poorer.

Sentinel Lymph Node Biopsy

Morton et al. introduced the concept of sentinel lymph node biopsy in 1992. This concept has its origin in their early work with cutaneous lymphoscintigraphy. Lymphoscintigraphy was initially proposed as a means of localizing lymph node basins draining from a specific melanoma site for elective lymphadenectomy. The value of traditional lymphoscintigraphy for definition of potentially equivocal or multiple draining basins has been clearly demonstrated. Without this test, elective lymphadenectomy may be misdirected in up to 50 percent of axial melanomas. The failure to use lymphoscintigraphy calls into question the results of some elective lymphadenectomy trials.

Subsequent studies in animals and humans have demonstrated that there are well-defined pathways leading from each cutaneous territory (cutaneous lymphosomes) to specific regional node(s), the so-called sentinel nodes. These were first demonstrated by Morton using vital blue dye injected intradermally at the site of the melanoma. Analysis of the sentinel node has been shown to be a sensitive indicator of metastatic melanoma in regional nodes. Importantly, absence of metastatic melanoma in the sentinel nodes indicates probable absence of disease in the remaining nodal basin. Therefore, complete nodal staging can be achieved with sentinel lymph node biopsy. This procedure provides staging information that is essentially equivalent to that obtained by complete lymphadenectomy with less morbidity. With a sensitivity of about 95 percent in experienced hands, sentinel node biopsy can virtually eliminate unnecessary lymph node dissections. Because of its high accuracy and low morbidity, this procedure has essentially replaced elective lymphadenectomy as the technique of choice for staging regional lymph node basins at most major melanoma centers.

Although Morton originally described sentinel node biopsy using blue dye alone, other groups have validated the gamma probe for radiolocalization of the sentinel node. Initially, sentinel node biopsy using blue dye alone was successful in only about 80 percent of patients undergoing the procedure. In experienced hands, success rates now approach 100 percent because of improvements in preoperative lymphoscintigraphy and intraoperative mapping techniques, including use of the gamma probe. The independent evolution of sentinel node biopsy at various centers supports the use of both visual blue dye and radiocolloid for sentinel node localization. The two techniques are complimentary, and most centers now use both. In general, there is good correlation between blue dye localization and radiolocalization for sentinel nodes. In most series, more than one sentinel node exists per basin subjected to sentinel node biopsy. Use of the gamma probe criteria generally results in the removal of more sentinel nodes compared with blue dye alone, but it is not clear that these nodes represent true sentinel nodes.

Considerable variability exists between the protocols at different institutions for sentinel node biopsy with regard to the use of blue dye and/or radiolocalization. Various radiopharmaceuticals, doses, and timing approaches have been successful, but spillover into nonsentinel nodes occurs over time and may lead to unnecessary harvest of nonsentinel nodes. Large particle tracers such as unfiltered technetium sulfur colloid may take slightly longer to visualize the sentinel nodes than small particle tracers such as albumin, but they will demonstrate slower spillover into second-echelon nodes. In high lymphatic flow areas such as the cervical node basin, spillover occurs more rapidly, even when large particle tracers are used. Numerous technical variations have resulted in numerous definitions of what constitutes a sentinel node by radiolabeling criteria, each of which is somewhat arbitrary and subject to our limited knowledge of the intralymphatic kinetics of radiopharmaceutical agents. For this reason, the most reliable indicator (and, in fact, the unequivocal clinical definition) of sentinel node status is the blue-stained afferent channel leading to the blue-stained node(s). Dynamic cutaneous lymphoscintigraphy and the gamma probe are useful adjuncts to localization and harvest of this blue node.

Regardless of which radiotracer is used, the absolute radioactivity counts are of little use in
confirming a node as a sentinel node.\textsuperscript{107,108} The ratio of sentinel node to background or residual node basin is the most useful indicator of sentinel node localization. Radiolabeling is most useful for general localization of lymphatic basins and for intraoperative confirmation of sentinel node identification and removal. Intraoperative use of a handheld gamma probe is extremely useful because it speeds up the procedure considerably and allows a smaller incision with less dissection in pursuit of the blue node(s), which are also usually hot.\textsuperscript{107} Removal of nodes that are hot only (not blue) may be necessary if blue staining is not noted. This occurs most commonly in patients who have primary sites located some distance from the lymph node basin, such as central truncal lesions. During harvest, if the blue-stained sentinel node cannot be found, hot nodes can be removed and count ratios determined. Lymphoscintigraphy is less reliable in predicting the number of sentinel nodes that will be found. Because of the presence of multiple aberrant patterns of lymphatic drainage,\textsuperscript{99,109} the possibility of multiple sentinel nodes, multiple basins, and intransit nodes; and the general facilitation that radiolabeling affords sentinel node biopsy, we use lymphoscintigraphy routinely for this technique.

Despite the excellent results in the literature, sentinel node biopsy has not yet been shown to be reproducible in the hands of the occasional melanoma surgeon. It is a deceptively difficult procedure to master because success depends on the integration of several disciplines, and a gradual learning curve exists. The entire sequence of steps is potentially technically fallible. Experts have variously estimated a learning curve caseload of 25 to 50 sentinel node biopsy cases, with complete lymphadenectomy confirmation or supervision by an experienced surgeon, before the technique should be relied on as a stand-alone diagnostic tool.\textsuperscript{107,108} To confirm success, the learning surgeon should perform complete lymphadenectomy during the learning phase. This is important because the sentinel node is the often the only tumor-containing node in the interrogated basin, and because of the clinical importance of a false-negative diagnosis. With experience, successful harvesting of these nodes should be possible in 98 to 99 percent of cases. Given the relative rarity of melanoma, it may be impractical for many surgeons to acquire these skills.

The importance of cooperation and precise communication between the surgeon, nuclear medicine specialist, and pathologist cannot be overemphasized. The pathologist handling sentinel node tissues must make a diligent search for nodal micrometastases. The median tumor volume in positive lymph nodes after sentinel node biopsy is approximately 4.7 mm\textsuperscript{3}, approximately equivalent to the tumor volume of a solitary 2-mm nodule.\textsuperscript{110} In one large series of recurrences after sentinel node biopsy, the most common reason for false-negative results was pathologic misses.\textsuperscript{111} Pathologists are usually experienced with step sectioning and immunohistochemical (S-100 and/or homatropine methylbromide 45 antigen) staining, but they must be aware of the importance of routinely doing these preparations on sentinel nodes that are negative by standard analysis.\textsuperscript{107,108,112} Enhanced molecular diagnostic assays, such as reverse transcriptase polymerase chain reaction, can upstage patients undergoing sentinel node biopsy and seem to correlate somewhat with clinical outcome.\textsuperscript{113} Reverse transcriptase polymerase chain reaction analysis of sentinel node biopsy specimens and peripheral blood is being tested in ongoing clinical trials, but clinical utility and widespread applicability are uncertain at this time.

Equally crucial to the success of sentinel node biopsy is precise preoperative lymphatic mapping. A variety of tracers are useful in localizing the basin and nodes of drainage. One of the most important technical details is the timing of radiopharmaceutical injection with respect to intraoperative gamma probe localization. Optimal sentinel-to-nonsentinel node ratios are obtained at different times, depending on the agent used.\textsuperscript{102,105} Other important details are the dose and technique of injection, avoidance of tracer spillage, early dynamic images after tracer injection, adequate duration of imaging, and localization using multiple angles of view, shielding, and collimators, if necessary. A familiarity with the various tracers and their characteristics is necessary for the physician team developing a sentinel node biopsy program. The surgeon and nuclear medicine physician must also be aware of possible aberrant patterns of drainage and multiple basins.\textsuperscript{99,109} Lymphoscintigraphy is somewhat less reliable after prior wide excision, particularly if flaps, grafts, incisions, or lymph node biopsies...
have been done. These procedures may disrupt the lymphatic drainage from the melanoma site, making localization of the sentinel node more difficult, and in some cases, impossible. Even if the sentinel node can be localized and harvested, the likelihood that it will accurately reflect the status of the remainder of the basin is diminished.

In the selection of patients for nodal staging with sentinel node biopsy, tumor thickness is the primary criteria. The sentinel node positivity rate in various reports ranges between 12 and 36 percent. A positive correlation between sentinel node positivity with tumor thickness has generally been observed, with positivity rates for sentinel node biopsy less than 5 percent for AJCC T1 melanomas and approaching 50 percent for AJCC T4 lesions. Thus, sentinel node biopsy is likely to be a low-yield procedure in most thin melanomas. Conversely, studies have shown nodal status is an independent significant prognostic factor in patients with thick melanomas. A rational argument can be made for considering patients with thick melanomas, who ordinarily would not be offered elective lymphadenectomy, for staging with sentinel node biopsy. The ideal Breslow criteria for selection for this technique is not known, and cut points are therefore somewhat arbitrary. In the Indiana University Cancer Center Interdisciplinary Melanoma Program, approximately 95 percent of all positive results of sentinel node biopsy were noted in patients with tumor thickness of 1.2 mm or greater.

Tumor ulceration has been shown to be an important prognostic factor for melanoma recurrence, and it is also an independent predictor of a positive result of sentinel node biopsy in several series. Our experience with this technique shows that Breslow’s depth, tumor ulceration, and a high mitotic index are independent predictors of a positive sentinel node biopsy. This finding suggests that patients with ulcerated tumors and those with high mitotic index should be considered for sentinel node biopsy, regardless of tumor depth. In the Indiana University Cancer Center Interdisciplinary Melanoma Program, we advocate this technique for patients with clinically localized melanomas at significant risk for occult regional metastases. Other patients with thin lesions thought to be at higher risk for recurrence than would be predicted by tumor thickness alone may be considered for sentinel node biopsy on a case-by-case basis.

Lymphadenectomy performed after a positive sentinel node biopsy result is termed selective complete lymphadenectomy. The positivity rate for nonsentinel nodes removed by selective complete lymphadenectomy following a positive sentinel node biopsy is from 7 to 35 percent in various series. These numbers probably underestimate the true positivity rate for selective lymphadenectomy, because analysis of these specimens has not been as rigorous as for sentinel node biopsy specimens. The relatively low incidence of positive nodes in selective lymphadenectomy specimens has led to speculation that selective lymphadenectomy may be unnecessary after a positive sentinel node biopsy result for some patients, such as those with thin melanomas.

In a recent report, our group was unable to demonstrate a convincing correlation between tumor thickness and regional lymph node basin tumor burden, or between nonsentinel node positivity and the number of positive sentinel nodes or the presence of multiple sentinel node micrometastases. This illustrates the difficulty in accurately predicting the status of the residual nodal basin after a positive sentinel node biopsy. Because recent prospective clinical trials suggest that occult melanoma nodal micrometastases are clinically important and that early therapeutic lymphadenectomy may favorably impact survival, selective lymphadenectomy is probably the most appropriate therapy after a positive result from sentinel node biopsy. The question of subsequent therapy after a positive result from this technique is the subject of two ongoing prospective clinical trials.

Technical and therapeutic controversies notwithstanding, the status of the sentinel node is clinically relevant for at least three major reasons. First, the status of the sentinel node has been shown to be an important independent prognostic factor, with a positive result predictive of high risk for treatment failure. A recent multicenter study showed the histologic status of the sentinel node to be a more important prognostic factor than tumor thickness in patients with clinically negative nodes before sentinel node biopsy. The predictive value of a negative result after this technique is less certain at this time, but it probably identifies patients with significantly lower risk of recurrence than would be predicted by tumor char-
acteristics. Second, sentinel node biopsy identifies with minimal morbidity those high-risk patients who may benefit from additional therapy, such as selective complete lymphadenectomy or adjuvant interferon, or who may be eligible for participation in clinical trials. The technique allows surgeons to perform selective lymphadenectomy on the basis of histologic confirmation, essentially eliminating the problem of false-negative selection for elective lymphadenectomy. Third, the psychological benefit for the patient whose sentinel node biopsy does not reveal metastases seems significant. For these reasons, this procedure in experienced hands is the ideal clinical approach for staging and management of patients with significant-risk melanoma today.

Whether sentinel node biopsy has become the standard of care for melanoma or is still under investigation is debatable. Despite the confirmed diagnostic accuracy and increasing use of this technique for melanoma staging, it is important to emphasize that the efficacy of lymphatic mapping and sentinel node biopsy as a therapeutic procedure for patients with melanoma is unproven. Despite the valuable staging information it provides, this procedure cannot directly identify patients who will experience recurrence because of undetected stage IV disease. The possible therapeutic benefits of the procedure itself and therapeutic decisions based on it (including selective complete lymphadenectomy) are currently unknown. Lack of procedural standardization, questions about general reproducibility, and absence of prospective clinical trials showing efficacy of therapy using the technique have caused some experts to recommend against the routine use of therapy based on sentinel node biopsy outside the investigational setting at this time.

**Adjuvant Therapy**

**Interferon**

Until 1996, no systemic or adjuvant therapy had been demonstrated by prospective randomized trial to provide a significant overall survival benefit in patients with melanoma. A wide variety of agents have been investigated, including nonspecific immunostimulants such as bovine mycobacterium, single agent and multiagent chemotherapy, isoprinosine, megestrol acetate, retinoids, levamisole, vaccinia melanoma oncolysates, and several interferon trials. In 1996, Kirkwood et al. reported the results of the Eastern Cooperative Oncology Group (ECOG) trial 1684, a phase III trial comparing a 1-year course of high-dose adjuvant interferon-α-2b with observation in a randomized group of 287 patients rendered without evidence of disease surgically. The study population was comprised of patients with melanomas >4.0 mm thick and patients with surgically resected regional nodal metastases. There were statistically significant improved 5-year relapse-free survival rates (37 versus 26 percent) and overall survival rates (46 versus 37 percent) in the high-dose interferon group compared with untreated patients. This study is currently the only trial to show an overall survival benefit for any regimen in the adjuvant treatment of melanoma, and it was the primary basis for Food and Drug Administration approval of interferon-α-2b for adjuvant therapy of resected high-risk melanoma in 1996.

The ECOG trial 1684 study represents a significant advance in the treatment of melanoma, and has changed the standard of care for stage III disease. However, several points and questions have been raised. First, the high-dose regimen is very toxic and expensive. Patients must have a good performance status to tolerate the full course of therapy. Other trials employing lower doses of interferon or different regimens have not shown similar efficacy. Second, the study showed survival benefit for the entire group and for analyzed subsets of recurrent and node-positive melanoma (both occult and overt nodal metastases). However, it included only 31 patients with node-negative melanomas, and this was the only subset not to show statistically significant benefit. This small number of node-negative patients obviates any meaningful conclusions regarding efficacy in this subgroup. Third, patients with other forms of lymphatic metastases, such as local recurrences, extracapsular nodal disease, intransit metastases, and satellite nodules, were excluded from this study. The role of adjuvant interferon in this population of patients is unknown.

A follow-up interferon study has recently been reported. ECOG trial 1690 was a three-arm study comparing the same high-dose interferon regimen used in ECOG trial 1684 with a low-dose interferon regimen and an observation arm. At a median follow-up of 52 months, preliminary analysis confirmed the relapse-free survival benefit for the high-dose interferon
regimen but did not show an overall survival benefit. The low-dose treatment arm showed no significant benefit for either relapse-free or overall survival. These findings have not yet been explained, but they may have resulted from a higher survival rate in the observation arm compared with the ECOG 1684 trial, earlier diagnosis and treatment of regional nodal metastases, or improved treatment of recurrent disease in the observation arm with interferon. Although these results are preliminary, they raise questions about the efficacy of adjuvant interferon in resected stage III melanoma.

At this time, the role of interferon in the treatment of melanoma is not clear. The cumulative observations from several trials do not suggest survival benefit for interferon regimens other than the high-dose regimen used in ECOG trials 1684 and 1690. The strongest evidence for efficacy is in node-positive melanoma patients. At this time, there is no direct proof of survival efficacy of interferon therapy in node-negative patients. Because patients with melanomas are a heterogeneous population, some have argued not to submit node-negative patients to the toxicity and expense of high-dose interferon therapy. The clinical importance of accurate nodal staging and the attractiveness of sentinel node biopsy are highlighted by this controversy. Furthermore, because intransit metastases, satellite nodules, and local recurrences all represent various forms of lymphatic metastases with a prognosis similar to that of nodal metastases, it has been argued these patients should be offered adjuvant interferon therapy, despite the lack of direct evidence showing efficacy. Ongoing clinical trials testing interferon and other forms of immune modulation should clarify the appropriate treatment groups and refine the optimal agents, dosage, and duration of this adjuvant therapy.

Figure 3 summarizes the current clinical care guidelines for clinically localized cutaneous melanoma in the Indiana University Cancer Center Interdisciplinary Melanoma Program. These guidelines continue to be modified as new information is gained.

**Management of Recurrent and Metastatic Disease**

Although most patients with melanoma are cured, approximately 25 percent of patients presenting with clinical stage I melanoma will develop a recurrence. Groups of patients at high risk for treatment failure can be identified at the time of initial presentation. Among patients who experience recurrent disease, 55 to 67 percent of recurrences appear within the first 2 years and up to 80 percent appear by 3 years after treatment of the primary tumor. Thick tumors and ulcerated lesions tend to recur earlier and thin melanomas at later posttreatment intervals. Patterns of recurrence are similar for early and late recurrences. Rarely, recurrent melanoma may present 10 years or later after apparently successful treatment of the primary lesion.

**Regional Lymph Nodes**

Regional lymph nodes represent the most common site of initial recurrent disease in patients treated without prior lymphadenectomy. In patients treated with a prior lymphadenectomy, visceral metastases are more common as the initial site(s) of treatment failure. Therapy of clinically obvious nodal recurrences is complete regional therapeutic lymphadenectomy, which is curative for 25 to 30 percent of patients. Even in the presence of distant metastases, palliative therapeutic lymphadenectomy should be considered because this is a potentially morbid condition that has no satisfactory alternative treatment. It is important to excise all tumor tissue, and radical procedures are sometimes justified. In the neck, complete radical or modified radical lymphadenectomy is generally indicated, sometimes with parotidectomy, depending on the location of the primary tumor and clinical involvement. Axillary recurrences generally merit complete axillary therapeutic lymphadenectomy, removing all three levels of nodes and, if necessary for complete tumor extirpation, sacrifice of long thoracic and thoracodorsal neurovascular structures. Inguinal recurrences should be treated by complete inguinofemoral therapeutic lymphadenectomy. In the presence of palpable inguinal disease or multiple positive superficial inguinal nodes, more than 40 percent of patients will also have metastases to the ipsilateral pelvic nodes. Many surgeons routinely perform ipsilateral iliac and obturator lymphadenectomy in this situation. Others use computed tomography or other imaging modalities to guide this decision.

Recurrence in the lymph node basin after therapeutic lymphadenectomy for bulky adenopathy, particularly in the head and neck region, has been reported as high as 44 to 50
percent at 2 years. This indicates that surgery alone frequently fails to control metastatic disease. Because reoperation for local relapse after surgery is difficult and frequently results in morbidity, measures to improve locoregional control in selected patients are justified. Nonrandomized studies suggest that the use of adjuvant radiotherapy may improve local control after therapeutic lymphadenectomy in the head and neck. The role and optimal protocol for use of postoperative adjuvant radiotherapy are currently subjects of a prospective Intergroup study.

As previously noted, patients with nodal metastases are at high risk for treatment failure due to distant metastases. Therefore, patients with regional nodal recurrence should be considered for adjuvant interferon therapy.

Local Recurrence

Local recurrence is defined as recurrence within 2 cm of an excision scar. With prolonged follow-up, local recurrence after wide local excision is seen in 3 to 5 percent of patients. Prospective clinical trials show it to be largely preventable with proper wide excision. Ulceration and microsatellitosis are associated with a higher rate of local recurrences, as is increasing tumor thickness. Local recurrence is strongly associated with the appearance of intransit, nodal, and distant metastases. Local recurrence also portends a grave prognosis, with 82 percent of patients with local recurrence in the Intergroup trial dying of the disease. However, patients with local recurrence related to true regrowth of a tumor not excised (i.e., after a missed diagnosis) seem to have a somewhat better prognosis, which more closely related to tumor thickness. The management of local recurrence with generous surgical resection (1 to 3 cm) is the simplest, most common, and most locally effective form of therapy. The high risk of occult metastatic disease and poor prognosis in this group of patients is a rational argument for considering adjuvant interferon therapy.

Intransit Recurrence

Intransit metastases appear in 2 to 38 percent of patients surgically treated for primary melanoma. Intransit disease is defined as dermal or soft tissue nodules located at least 2 cm from the primary lesion. Local recurrences after prior wide excision of at least 2 cm can also be considered intransit metastases. Factors predisposing to this pattern of recurrence include increasing thickness of primary lesion, ulceration, presence of involved lymph nodes, and locally recurrent disease. Intransit disease is viewed as a continuum of lymphatic disease and carries a prognosis similar to that of regional nodal and locally recurrent melanoma. Management of solitary intransit metastases is usually with generous wide excision. However, with excision alone, additional regional cutaneous recurrences can be expected in up to 67 percent of patients.

When multiple or recurrent intransit metastases appear in an extremity, a potentially morbid and limb-threatening situation exists. Isolation limb perfusion should be considered in these scenarios. Although prospective studies have not shown adjuvant isolation limb perfusion to be of benefit in primary melanoma of the extremity, the procedure seems to have some palliative benefit in the therapeutic setting. A variety of agents and protocols have been employed, but melphalan perfused with mild hyperthermia has been used most commonly. Overall response rates of 60 to 100 percent have been reported with melphalan isolated limb perfusion, with about half of these responses being complete, and about half of the complete responses being durable. These rates are superior to those of systemic therapy with substantially less morbidity. A successful isolation limb perfusion usually maintains control of disease in a limb, preserving a functional extremity. Because most of these patients eventually succumb to distant metastatic disease, this procedure is the treatment of choice in the setting of multiple or recurrent intransit metastases.

Recently, isolation limb perfusion with cytokine tumor necrosis factor has been reported with 90 to 100 percent response rates. A phase III clinical trial reported by Fraker et al., which randomized patients to hyperthermic isolation limb perfusion with melphalan versus melphalan plus tumor necrosis factor and interferon, showed an overall response rate of 100 percent in the melphalan arm versus 90 percent in the three-agent arm. However, complete responses were more common in the three-agent group (80 versus 61 percent), suggesting that tumor necrosis factor may be useful in bulky disease. Substantial potential for systemic and limb-threatening toxicity exists with isolation limb perfusion, but morbidity in
large series from experienced centers is acceptable.

Extensive recurrent/intransit melanoma of the extremity is an aggressive disease with long-term survival rates of about 10 to 20 percent. Historical literature on major limb amputation for recurrent extremity melanoma shows 5-year survival rates of 21 to 35 percent. The poor overall prognosis, morbidity of major limb amputation, and good response rates with isolation limb perfusion are strong arguments against performing amputation of otherwise functional limbs. The highly select patient population in whom amputation is sometimes recommended are patients with locally extensive, symptomatic distal limb recurrences after a previously unsuccessful isolation limb perfusion, and those patients with severe comorbidity who are not candidates for that technique. With the advent of isolation limb perfusion, the indications for major limb amputation for melanoma are exceedingly rare.

Distant Metastases

Remote soft tissue or nodal metastases are seen as the initial site of relapse in about 2 to 16 percent of patients. Visceral metastases are seen in about 20 percent of patients as the initial site of recurrence. Although visceral metastases may be seen in any organ, the most common sites are lung, liver, brain, bone, and gastrointestinal tract. Most patients with visceral or soft tissue metastases are asymptomatic or have findings at physical examination. Lung metastases, which are typically asymptomatic, are usually found by radiography.

Stage IV melanoma is generally considered to be incurable by currently available therapies, with median survival times of 6 to 9 months for patients with multiple visceral metastases. Patients with skin, subcutaneous, nonregional lymph node and pulmonary metastases fare somewhat better, with median survival times of 12 to 15 months. Patients with bone, brain, and liver metastases do very poorly, with median survival of 3 to 4 months. The most realistic goal for the surgeon treating stage IV melanoma is palliation and preservation of quality of life. Mature surgical judgment and careful patient selection are important to prevent excessive morbidity while maximizing quality of remaining life.

A small group of patients with stage IV melanoma have what appears to be limited disease and can be deemed candidates for potentially curative surgical resection. In most cases, surgical resection with curative intent is performed for solitary lesions of the skin and distant nodal sites. Similarly, curative resection of isolated pulmonary metastases can result in long disease-free survival time in carefully selected patients. Resection of brain and gastrointestinal metastases is usually performed with palliative intent, with very few long-term survivors. Even in apparently localized stage IV disease, most patients who undergo resection (80 to 90 percent) will eventually suffer treatment failure owing to the presence of undetected, frequently widespread metastases. Randomized trials evaluating the impact of surgical resection on survival in patients with stage IV melanoma have not been reported.

Systemic therapies for stage IV melanoma are generally unsatisfactory. Melanoma is a relatively chemotherapy-resistant disease. Responses to cytotoxic agents are relatively infrequent, incomplete, and not durable. Single-agent response rates are generally about 10 to 20 percent, with the most active single agent being dacarbazine. Other agents with activity against melanoma include the nitroso-ureas, platinum-based compounds, and the taxanes.

A variety of combination chemotherapy regimens have been developed for the treatment of melanoma, with response rates approaching 50 percent in phase II trials. Several randomized trials have examined the utility of single and multiagent chemotherapy for stage IV melanoma. None have demonstrated an improvement in overall survival compared with dacarbazine alone. Early detection and therapy of distant metastatic disease has not been clearly demonstrated to improve patient outcomes. Because of toxicity, poor response rates, and lack of survival benefit, chemotherapy for melanoma is considered to be palliative. The use of toxic chemotherapy regimens is difficult to justify in asymptomatic melanoma patients. At present, no consensus exists on the utility of any chemotherapy regimen for stage IV melanoma.

Interleukin-2 is a T-cell growth factor with antitumor and immunomodulatory activity. High-dose interleukin-2 produces overall responses similar those from chemotherapy (15 to 20 percent), with complete responses in about 4 to 6 percent of patients. Interleukin-2 has a broad toxicity profile with a sepsis-like syndrome. It has been approved for use in stage IV melanoma and is most often employed...
as a second-line agent after cytotoxic therapies have failed.

Melanoma has historically been considered to be a relatively radioresistant tumor, but this concept has recently been challenged. Although not useful as a primary treatment for cutaneous melanoma or surgical resectable nodal metastases, radiation can be useful for palliation. Indications for radiotherapy in selected stage IV melanoma patients include impending spinal cord compression (in combination with surgical decompression and stabilization); bone metastases; localized, unresectable symptomatic visceral metastases; and treatment of extensive cutaneous metastases not amenable to surgical resection or isolation limb perfusion. Radiosurgical treatment of brain metastases with the gamma knife has shown promise for local control of brain metastases. Treatment guidelines for recurrent and metastatic melanoma currently used in the Indiana University Cancer Center Interdisciplinary Melanoma Program are illustrated in Figure 4.

Because most standard therapies for stage IV melanoma are ineffective, experimental therapies may often be considered in the first-line therapeutic approach. A variety of novel approaches for treatment of metastatic melanoma are currently in clinical trials. Combinations of cytotoxic chemotherapy and biologic therapy have come to the forefront of melanoma research. Initial trials with biochemotherapy regimens demonstrate increased toxicity but suggest enhanced antitumor activity in stage IV melanoma. A variety of vaccine therapy approaches continue to generate heightened interest as potential therapy for metastatic melanoma. Although initial response rates for vaccines alone are not significantly better than standard chemotherapy, these agents carry substantially less toxicity, suggesting potential utility as therapy for both measurable disease and as postresection adjuvant therapy. Combinations of vaccines with other immunomodulatory agents suggest that response rates of up to 40 percent may be possible. Ongoing and future clinical trials are important to define the role of these and other investigational approaches for the treatment of metastatic melanoma.

**Follow-Up and Surveillance**

The basic assumptions in follow-up of any cancer patient are that early detection of recurrence will lead to treatment, which will ulti-

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**FIG. 4.** Clinical care guidelines for recurrent and/or metastatic melanoma (AJCC stages III and IV), histologically confirmed. LND, lymphadenectomy; ILP, hyperthermic isolation limb perfusion with melphalan; interferon, high dose interferon-α-2b; CTX, single or multiagent chemotherapy or interleukin-2 therapy; XRT, external beam irradiation therapy; INV, investigational therapies; PAL, palliative/supportive care.
mately impact favorably on outcome. However, recurrences of melanoma are not always treatable, and if treatable, not always curable. It is difficult to define the relationship between intensity of follow-up for melanoma and outcome. There is currently no consensus on the frequency of follow-up or recommendations for surveillance testing for all patients with melanoma. It is unlikely that the optimal follow-up program will be defined by prospective trial. It has become common to arrange follow-up schedules on the basis of risk, timing, and patterns of relapse, as well as the treatment options available if a recurrence is detected. For example, thick melanomas or patients with nodal metastases are commonly followed at more frequent intervals than patients with low-risk melanomas. If recurrence is detected, it is reasonable to offer more intensive follow-up to patients where more treatment options are available (i.e., academic centers specializing in the multimodality management of advanced disease). Less rigorous strategies are probably appropriate in the setting of a local community and for patients who are not interested in pursuing investigational therapies.

The goals of follow-up are twofold: detection of second primary lesions (seen in 3 to 5 percent of primary melanomas), and detection of locoregional and distant recurrent disease. In the setting of careful surveillance, most second primary melanomas that are discovered are thin and have a good prognosis. A number of reviews have appeared in the literature describing current practices in the follow-up of patients after surgical treatment for melanoma. Most treatable recurrences are noted by the patient and are detectable by physical examination or are hinted at by a careful history. The exception is pulmonary metastases, which are commonly found by plain chest radiographs. Routine surveillance radiography has not otherwise been shown to be of benefit. Likewise, routine laboratory testing is of limited clinical utility in finding asymptomatic visceral metastases. Because most recurrences appear within the first 2 to 3 years, are locoregional, and are treatable surgically, follow-up visits should be more frequent during this time. The optimal duration of follow-up is unknown. Late recurrences more than 10 years after initial treatment are well recognized, and the risk of second primary melanomas is lifelong. On the basis of these facts, the current Indiana University Cancer Center Interdisciplinary Melanoma Program follow-up guidelines are outlined in Table VI.

**SUMMARY**

The melanoma epidemic continues to pose a serious public health problem in the United States, and it is expected to increase. Care of the melanoma patient has evolved rapidly over the past decade, fueled by good cooperative clinical trials. Surgery remains the mainstay of therapy for most melanoma patients. Adjuvant therapy is now available for the postsurgical patient at high risk for relapse. For these reasons, a multidisciplinary approach represents the optimal means of patient care delivery for melanoma today. Dissemination of new knowledge from each specialty in a coordinated and

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### TABLE VI

Current Clinical Follow-Up Guidelines at the Indiana University Interdisciplinary Melanoma Program

<table>
<thead>
<tr>
<th>AJCC Stage</th>
<th>Physical Examination</th>
<th>Laboratory</th>
<th>CXR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0 (in situ)</td>
<td>Initial and yearly up to 10 yrs</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Stage Ia (&lt;1.75 mm)</td>
<td>Every 6 mo × 2 yr, yearly to 10 yrs</td>
<td>Initial</td>
<td>Yearly</td>
</tr>
<tr>
<td>Stage Ib (1.75–4.0 mm)</td>
<td>Every 6 mo × 4 yrs, yearly to 10 yrs</td>
<td>Yearly</td>
<td>Yearly</td>
</tr>
<tr>
<td>Stage IIa (4.1–6.0 mm, node-negative)</td>
<td>Every 3 mo × 4 yrs, every 6 mo × 1 yr, yearly to 10 yrs</td>
<td>Yearly</td>
<td>Every 6 mo × 2 yrs, yearly to 10 yrs</td>
</tr>
<tr>
<td>Stage III (node-positive or recurrent)</td>
<td>Every 3 mo × 4 yrs, every 6 mo × 1 yr, yearly to 10 yrs</td>
<td>Yearly</td>
<td>Every 6 mo × 3 yrs, yearly to 10 yr</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Every 1–3 mo, depending on disease status, symptoms, etc.</td>
<td>Every 6 mo, if NED; otherwise, as clinically indicated</td>
<td></td>
</tr>
</tbody>
</table>

* Patients at high risk for second primary melanomas may require more frequent visits. Symptoms, physical examination, or abnormal surveillance laboratory results or CXR direct additional laboratory or radiographic tests.
† Laboratory serum alkaline phosphatase and lactate dehydrogenase; CXR, posteroanterior and lateral chest radiographs; NED, no evidence of disease after therapy.
collaborative manner is necessary to ensure optimal patient care in this changing field. Enrollment of patients with melanoma into prospective randomized trials is important to optimal patient care in this changing field. A collaborative manner is necessary to ensure Vol. 105, No. 5 / CURRENT THERAPY OF CUTANEOUS MELANOMA 1795

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Ringborg, U., Andersson, R., Eldh, J., et al. Resection margins of 2 versus 5 cm for cutaneous malignant melanoma with a tumor thickness of 0.8 to 2.0 mm: Randomized study by the Swedish Melanoma Study Group. Cancer 77: 1809, 1996.


129. McCarthy, W. H., Shaw, H. M., Thompson, J. F., and Hart, A. A. Results of radical dissection of the


Self-Assessment Examination follows on page 1800.
1. The single most important factor that determines prognosis, treatment, and follow-up recommendations in melanoma is:
   A) Mitotic index of the tumor
   B) Clark's level of invasion
   C) Histologic tumor subtype
   D) Breslow's depth of invasion
   E) Presence of ulceration

2. Approximately what percentage of patients with melanoma localized to the skin who undergo surgical nodal staging with sentinel lymph node biopsy have micrometastases found by standard pathologic and/or immunohistochemical techniques?
   A) <10 percent
   B) 20 percent
   C) 35 percent
   D) 50 percent
   E) 65 percent

3. The most common initial site of melanoma metastasis is:
   A) Liver
   B) Lung
   C) Lymph nodes
   D) Skin
   E) Brain

4. Objective responses to dacarbazine occur in what percentage of patients with stage IV melanoma?
   A) 0 percent
   B) 10 percent
   C) 20 percent
   D) 35 percent
   E) 55 percent

5. The most appropriate margin of excision for a patient with a 2.9-mm-deep melanoma on the face is:
   A) 1.0 cm
   B) 2.0 cm
   C) 3.0 cm
   D) 0.5 cm
   E) Complete excision with Mohs' micrographic technique

6. Multifactorial analysis has demonstrated that each of the following factors may be an independent prognostic variable for survival in melanoma patients except:
   A) Lymphocytic tumor infiltrate
   B) Ulceration
   C) Sentinel lymph node status
   D) Anatomic site
   E) Tumor thickness
7. Which of the following is most likely to be of value in the initial staging evaluation of a patient presenting with an 1.8-mm melanoma of the back?
   A) Physical examination
   B) Computed tomographic scan of the abdomen, chest, and pelvis
   C) Chest radiograph
   D) Whole-body fluorodeoxyglucose-positron emission tomography scan
   E) Magnetic resonance imaging of the brain

8. Which is the most appropriate therapy for a patient presenting with a 3.0-mm-deep ulcerated melanoma of the forearm with no palpable adenopathy and a normal chest x-ray?
   A) Excision with 1-cm margins and elective axillary lymph node dissection
   B) Excision with 3-cm margins and sentinel lymph node biopsy
   C) Excision with 2-cm margins and treatment with high-dose interferon
   D) Excision with 2-cm margins and sentinel lymph node biopsy
   E) Excision with 2-cm margins with isolated limb perfusion using melphalan

To complete the examination for CME credit, turn to page 1916 for instructions and the response form.