Critical to the clinical management of a patient with malignant melanoma is an understanding of its natural history. As with most malignant disorders, prognosis is highly dependent on the clinical stage (extent of tumor burden) at the time of diagnosis. The patient's clinical stage at diagnosis dictates selection of therapy. We review the state of the art in melanoma staging, prognosis, and therapy. Substantial progress has been made in this regard during the past 2 decades. This progress is primarily reflected in the development of sentinel lymph node biopsies as a means of reducing the morbidity associated with regional lymph node dissection, increased understanding of the role of neoangiogenesis in the natural history of melanoma and its potential as a treatment target, and emergence of innovative multimodal therapeutic strategies, resulting in significant objective response rates in a disease commonly believed to be drug resistant. Although much work remains to be done to improve the survival of patients with melanoma, clinically meaningful results seem within reach.


PROGNOSTIC FEATURES AND PATHOLOGIC STAGING

The histologic evaluation of melanoma provides critical staging information. The American Joint Committee on Cancer (AJCC) Melanoma Staging Committee, which comprises major melanoma centers in the United States, Europe, and Australia and national cancer cooperative groups, studied 17,600 melanomas from patients with clinical, pathologic, and follow-up information.2 Cox proportional hazards regression was used to study factors that predict melanoma-specific survival rates.2 Results of this evidence-based study were incorporated into the 2002 AJCC melanoma TNM staging classification (Tables 1 and 2).3,4 The 2002 AJCC staging system incorporates pathologic “microstaging attributes,” including Breslow depth, Clark level, and ulceration.5 Tumor thickness and ulceration were the most powerful predictors of survival.6 The level of invasion had significance only in thin (<1.0 mm) melanomas.7 These and other factors are discussed in the following sections.

DEPTH OF INVASION

The depth of invasion is the most important histologic prognostic parameter in evaluating the primary tumor. The importance of this factor has been recognized for decades.

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TABLE 1. American Joint Committee on Cancer 2002 Melanoma TNM Classification\textsuperscript{a,4}

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Suffix</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed (ie, shave biopsy or regressed melanoma)</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>( \leq 1.0 \text{ mm} )</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>1.01-2.00 \text{ mm}</td>
<td>a: without ulceration and level II or III b: with ulceration and level IV or V</td>
</tr>
<tr>
<td>T3</td>
<td>2.01-4.0 \text{ mm}</td>
<td>a: without ulceration b: with ulceration</td>
</tr>
<tr>
<td>T4</td>
<td>( \geq 4.0 \text{ mm} )</td>
<td>a: without ulceration b: with ulceration</td>
</tr>
<tr>
<td>N1</td>
<td>1 lymph node</td>
<td>a: micrometastasis b: macrometastasis c: distant metastases</td>
</tr>
<tr>
<td>N2</td>
<td>2-3 lymph nodes</td>
<td>a: micrometastasis b: macrometastasis</td>
</tr>
<tr>
<td>N3</td>
<td>( \geq 4 ) metastatic lymph nodes, matted lymph nodes, or combinations of in-transit metastasis or satellite(s) and metastatic lymph node(s)</td>
<td>c: in-transit metastasis or satellite(s) without metastatic nodes</td>
</tr>
<tr>
<td>M1a</td>
<td>Distant skin, subcutis, or lymph node metastases</td>
<td>Normal LDH level</td>
</tr>
<tr>
<td>M1b</td>
<td>Lung metastases</td>
<td>Normal LDH level</td>
</tr>
<tr>
<td>M1c</td>
<td>All other visceral metastases</td>
<td>Normal LDH level</td>
</tr>
<tr>
<td></td>
<td>Any distant metastases</td>
<td>Elevated LDH level</td>
</tr>
</tbody>
</table>

\textsuperscript{a}LDH = lactate dehydrogenase.  
\textsuperscript{b}Micrometastases are diagnosed after elective or sentinel lymphadenectomy.  
\textsuperscript{c}Macrometastases are defined as clinically detectable lymph node metastases confirmed by therapeutic lymphadenectomy or when any lymph node metastasis exhibits gross extracapsular extension.

and evaluated both qualitatively and quantitatively. In 1953, Allen and Spitz\textsuperscript{4} stated that patients with superficial tumors had a greater chance of survival than patients with deeply invasive tumors. Others also recognized depth of invasion as an important prognostic factor in malignant melanoma decades ago.\textsuperscript{4,9} A variety of terms have been used to denote qualitative anatomic levels of invasion, including \textit{stages},\textsuperscript{4} \textit{groups},\textsuperscript{4,9} and \textit{levels}\textsuperscript{4,9} of invasion. The system used today was described by Clark et al.\textsuperscript{9} In level I malignant melanoma, all tumor cells are above the basement membrane (malignant melanoma in situ). Level II tumors invade into the papillary dermis, which extends around skin appendages.\textsuperscript{9} Level III tumors fill and expand the papillary dermis. Importantly, isolated tumor cells between collagen bundles in the upper reticular dermis at the base of level III tumors are still considered level III.\textsuperscript{9} Tumors that invade into the reticular dermis are level IV, and those that invade into the subcutaneous adipose tissue are level V. Stratification of 208 patients with invasive melanoma by Clark level showed that 8.3% with level II, 35.2% with level III, 46.1% with level IV, and 52% with level V tumors died of disease.\textsuperscript{9}

In 1970, Dr Alexander Breslow\textsuperscript{10} provided quantitative measurement of the depth of invasion by measuring the tumor thickness with an ocular micrometer. The measurement (in millimeters) is made from the top of the granular layer of the epidermis to the deepest melanoma cell. If a tumor is ulcerated, the measurement is made from the highest viable melanoma cell to the deepest tumor cell. Adventitial dermal invasion is not measured unless it is the only site of invasion. Then, the measurement is made from

TABLE 2. Pathologic Stage Grouping and Survival\textsuperscript{4,9}

<table>
<thead>
<tr>
<th>Pathologic stage</th>
<th>Tumor</th>
<th>Lymph nodes</th>
<th>Distant metastases</th>
<th>10-y survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
<td>100</td>
</tr>
<tr>
<td>IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
<td>88</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
<td>83</td>
</tr>
<tr>
<td>IIA</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
<td>79</td>
</tr>
<tr>
<td>IIB</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
<td>64</td>
</tr>
<tr>
<td>IIIC</td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
<td>64</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3b</td>
<td>N0</td>
<td>M0</td>
<td>50</td>
</tr>
<tr>
<td>IIIC</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
<td>54</td>
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<td>IIIA</td>
<td>T1-4a</td>
<td>N1a</td>
<td>M0</td>
<td>63</td>
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<tr>
<td>IIIA</td>
<td></td>
<td>N2a</td>
<td>M0</td>
<td>57</td>
</tr>
<tr>
<td>IIIIB</td>
<td>T1-4b</td>
<td>N1a</td>
<td>M0</td>
<td>38</td>
</tr>
<tr>
<td>IIIIB</td>
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<td>N2a</td>
<td>M0</td>
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<tr>
<td>IIIIC</td>
<td>T1-4a</td>
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<tr>
<td>IIIIC</td>
<td></td>
<td>N2b</td>
<td>M0</td>
<td>39</td>
</tr>
<tr>
<td>IV</td>
<td>T1-4b</td>
<td>N2c</td>
<td>M0</td>
<td>...</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
<td>24</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1a</td>
<td>16</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td></td>
<td>M1b</td>
<td>3</td>
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<tr>
<td>IV</td>
<td></td>
<td></td>
<td>M1c</td>
<td>6</td>
</tr>
</tbody>
</table>
the inner luminal surface of the eccrine gland or duct or inner aspect of the outer root sheath epithelium of the hair follicle. Breslow depth is a continuous variable and is the most important prognostic factor in the primary cutaneous melanoma. Clark level remains an independent prognostic factor for thin melanomas. In the 1997 TNM staging system, Clark level was the primary determinant of T staging, with Breslow thickness a second prognostic factor of T stage. In the 2002 AJCC staging classification, Clark level is used only in T1 melanomas. Tumor thickness as measured by the Breslow technique is the primary determinant of T staging. Thin melanomas are now defined by many as those with a depth of invasion of 1.0 mm or less. Staging thresholds of depth have changed from 0.75, 1.50, and 4.0 mm in the 1997 TNM version to 1.0, 2.0, and 4.0 mm in the 2002 TNM version. Although these breakpoints are used in staging classifications, Breslow depth is a continuous variable.

Ulceration
Ulceration is defined in the 2002 AJCC staging classification as the absence of an intact epidermis overlying a major portion of the primary melanoma based on microscopic examination of the histologic sections. Ulceration was second only to tumor thickness as the most powerful independent predictor of survival in 17,600 cases. Although ulceration was an independent predictive factor, it correlated with tumor thickness. Ulceration was identified in only 6% of thin (≤1.0 mm) melanomas but was noted in 63% of thick (>4.0 mm) tumors. Patients with ulcerated melanomas had the same survival rate as those with nonulcerated tumors of the next greater thickness category.

Microsatellites, Satellites, and In-Transit Metastases
Historically, satellites were macroscopic or microscopic discontinuous foci of tumor located within 5 cm of the primary tumor, and in-transit metastases were discontinuous foci located more than 5 cm from the primary tumor. The clinical behavior of satellites or in-transit disease was believed to not impart as poor a prognosis as lymph node metastases. Clinical or microscopic satellites around a primary melanoma and in-transit metastases are considered intralymphatic metastases and portend a poor prognosis. Satellites and in-transit metastases are considered the same clinically, and no survival difference is apparent between these 2 groups. They are both classified as N2c in the absence of nodal metastases because they both have a prognosis similar to multiple lymph node metastases. Patients with both satellites or in-transit metastases and nodal metastases have a worse prognosis than patients who have either satellites or in-transit metastases or nodal metastases alone. When both satellites or in-transit disease and lymph node metastases are diagnosed in the same patient, they are classified as N3 regardless of the number of involved lymph nodes.

Pathologic Staging of Lymph Nodes
Regional lymph node status is a significant prognostic feature of malignant melanoma. Historically, the size of the lymph node metastases was believed to be important, but analysis of the data demonstrated that the number of lymph nodes was the most important feature, followed by the tumor burden within the lymph node. If 1 node is involved, the classification is N1; if 2 to 3 nodes are involved, the classification is N2; and if 4 or more metastatic nodes, natted nodes, or in-transit metastases or satellites with metastatic node(s) are involved, the classification is N3. The presence of an ulcerated tumor in the setting of positive lymph nodes carries a grave prognosis; therefore, an ulcerated melanoma in association with any number of lymph node metastases is classified as N3. N1 and N2 are further classified as micrometastasis, which is diagnosed histologically, and macrometastasis, which is defined as clinically detectable nodal metastases confirmed therapeutically. Patients who have stage III disease are a heterogeneous group with a 5-year survival rate of 13% for a patient with an ulcerated melanoma with 4 or more macroscopically positive lymph nodes to 69% for a patient with a nonulcerated melanoma and 1 microscopically positive lymph node.

Sentinel lymph nodes for melanoma are generally evaluated both histologically and with immunostains. Lymph nodes that are found to have disease identified by immunostains only and are not seen with routine hematoxylin-eosin staining are considered N0. A special designation of N0 (immunohistochemically positive) is preferred, and this information may be important for further staging criteria in the future. Capsular nevi need to be differentiated from metastatic melanoma. The location of the nevic nests in the capsule and the benign cytomorphic findings of the cells are helpful in differentiating these entities. Immunostains are used to increase the detection of melanoma micrometastases in SLNs. Recently, a study of 217 lymph nodes from patients with no history of melanoma showed individual Melan-A or MART-1 (melanoma antigen recognized by T cells) immunoperoxidase cells in the parenchyma of 2.4% and 5.1% of lymph nodes, respectively. Thus, the finding of Melan-A- or MART-1-positive cells without corresponding cytologic atypia or hematoxylin-eosin findings should be interpreted with caution.

Distant Metastases
Distant metastases in the skin, subcutaneous tissue, or distant lymph nodes are classified as M1a. Metastases to the
Prognostic factor. The authors suggested that vertical growth phase evaluation be added to the melanoma histologic report for level II superficial spreading melanomas. In another recent study, 77 patients with thin (<1 mm) cutaneous melanomas underwent SLN biopsy, and 6 patients were found to have positive sentinel nodes. Vertical growth phase (P=0.002), ulceration (P=0.019), and high mitotic rate (P=0.008) were positively correlated with metastatic disease. Although most melanomas that lack vertical growth phase are not associated with metastases, melanomas without identified vertical growth phase have metastasized. Additionally, most melanomas with vertical growth phase are not associated with metastases. The presence of regression also appears to be an important feature in patients with radial growth phase melanomas associated with metastatic disease. Melanomas with epithelioid cells in vertical growth phase tend to have a worse prognosis than those with spindle cells.

Mitotic Rate
Mitotic rate is tabulated as mitoses per square millimeter in the dermal part of the tumor in which most mitoses are identified, as recommended in the 1982 revision of the 1972 Sydney classification of malignant melanoma. Although ulceration is considered the most important prognostic factor after Breslow thickness for localized cutaneous melanoma, many studies have shown that mitotic rate is a significant prognostic factor. In a population-based series of 650 consecutive invasive cutaneous melanomas from the Connecticut tumor registry, tumor thickness and mitotic activity were independent prognostic factors in multivariate regression analysis. After adjustment for mitotic rate, ulceration was no longer significant. When mitotic rate was excluded, ulceration then became an independent prognostic factor. When mitotic rate was excluded, the model showed a relative risk (RR) with ulceration of 2.4 (95% confidence interval [CI], 1.1-5.1). When ulceration was excluded, the model with only a mitotic rate showed an RR of 14.5 (95% CI, 3.9-53.7). Regression analysis, including both ulceration and mitotic rate, showed an RR of 11.6 (95% CI, 3.0-44.6) for mitotic rate and 1.7 (95% CI, 0.8-3.6) for ulceration. In this study, the authors concluded that mitotic rate is a more important prognostic factor than ulceration.

A study of 3661 patients with melanoma from the Sydney Melanoma Unit showed that a mitotic rate of 0 per square millimeter was associated with better survival than those with 1 mitosis per square millimeter, but no significant survival differences were noted for stepwise increases from 1 to 2, 2 to 3, 3 to 4, and 4 to 5 mitoses per square millimeter. Although tumor thickness, ulceration, and mi-
MALIGNANT MELANOMA IN THE 21ST CENTURY

totic rate were closely correlated, Cox regression analysis indicated that mitotic rate was a highly significant independent prognostic factor, second only to tumor thickness. The authors concluded that mitotic rate has the potential to improve the accuracy of melanoma staging and to more rigidly define risk categories for patients entering clinical trials.47

Mitotic rate has also been shown to be a significant independent predictor of clinical outcome in patients with thick41,42,50-52 and thin41,50-54 melanomas. The clinical outcome of 140 patients with thick (>3 mm) stage I cutaneous melano mas was evaluated retrospectively to analyze the prognostic value of a series of clinicopathologic parameters on survival.49 The overall disease-free survival rates at 5 and 10 years were 55.3% and 47.7%, respectively. Multivariate analysis with a Cox proportional hazards model showed that tumor thickness, infiltrating invasive front of the tumor, ulceration, and mitotic rate were significant independent prognostic factors.49 Recent studies have shown mitotic rate to be a significant predictor of lymph node metastases in patients with thin melanomas.41,50-54 A prospective evaluation of 884 patients with thin invasive melanomas showed that growth phase, mitotic rate, and male sex were important prognostic factors and helped identify subgroups at risk for metastases.50

Regression
Malignant melanomas are known to show regression. Histologically, regression is characterized by the absence of melanoma in the epidermis and dermis flanked on one or both sides by melanoma. The dermis in this area shows delicate fibroplasia, scattered lymphocytes, and melanophages. Complete regression is uncommon in malignant melanomas but may explain some cases of metastatic melanoma with an indeterminate primary site.73 Regression has also been identified in cases of malignant melanoma in situ and metastatic disease.60 Although not all studies have found regression to be a statistically significant predictor of survival,55,67,74-76 many studies have found regression to be associated with a worse prognosis and decreased survival.14,19,42,45,56-58 Melanomas with extensive (>75%) or complete regression appear to have a worse prognosis than those with lesser degrees of regression.45,56,60,61 Regression is thought to be particularly important in thin melanomas.42,45,56-60 A case-control study showed that extensive regression was present in 42% of patients with thin (<1 mm) melanomas associated with metastases but only in 5% of matched controls.60 A review of patients with thin (<0.76 mm) melanomas showed that severe histologic regression was present in 40% of primary lesions that metastasized and in only 17% of lesions that did not.60 Another study that evaluated thin malignant melanomas (<0.76 mm) found that 30 of 103 tumors showed partial regression. Six of the 30 patients developed metastases and died.60 These 6 patients had more than 75% regression of their primary tumors.60 None of the 73 patients with thin melanomas without regression had metastases.60

A study evaluating nontumorigenic radial growth phase and tumorigenic vertical growth phase melanomas showed that patients with melanoma without regression and without the tumorigenic vertical growth phase can be given reasonable assurance of survival.41 A retrospective population-based study of 1716 cutaneous melanomas that were 1 mm or smaller identified metastases in 67 cases.42 Thirteen of these 67 melanomas were level II. Eight of the 13 patients with level II melanoma with metastasis were found to have another primary cutaneous melanoma with at least level III invasion before the metastases occurred. All 5 of the remaining tumors showed regression. The authors concluded that metastasis from level II melanoma without regression is rare.42

Tumor-Infiltrating Lymphocytes
Tumor-infiltrating lymphocytes have been found to have prognostic significance.14,67-70 Tumor-infiltrating lymphocytes are currently defined as brisk, nonbrisk, and absent. A study of 72 patients with clinical stage I melanoma of intermediate thickness (1.5-3.99 mm) and at least 5 years of follow-up found that low mitotic rate and an infiltrative lymphocytic response were associated with favorable survival.64 In a model that predicted survival of patients with clinical stage I melanoma, 23 features were evaluated by multivariate analysis, and 6 were found to be independent prognostic factors, including tumor-infiltrating lymphocytes, mitotic rate, tumor thickness, anatomic site of primary tumor, sex, and regression.14 The prognostic value of tumor-infiltrating lymphocytes in the vertical growth phase of 285 primary cutaneous stage I or II melanomas was evaluated.67 The 5- and 10-year survival rates for patients with vertical growth phase melanoma were 77% and 55% for those with a brisk infiltrate, 53% and 45% for those with a nonbrisk infiltrate, and 37% and 27% for those with absent tumor-infiltrating lymphocytes, respectively. Multivariate analysis of thickness, mitotic rate, and tumor-infiltrating lymphocytes showed that thickness and tumor-infiltrating lymphocytes were significant and independent histologic prognostic factors. The authors concluded that when tumor-infiltrating lymphocytes are strictly defined, they have a strong predictive value in vertical growth phase melanomas.67

Angiolympathic Invasion and Angiotropism
The prognostic significance of angiolympathic invasion is difficult to document because it has a close relationship
with tumor thickness,\textsuperscript{63} but it has been found to have independent prognostic significance in some studies.\textsuperscript{54,62,63} Vascular invasion was identified in 15 of 102 nodular melanomas and was significantly associated with tumor thickness, histologic diameter, ulceration, lymph node involvement, and distant metastases.\textsuperscript{63} Vascular invasion had independent prognostic significance in both univariate and multivariate analyses.\textsuperscript{63} A retrospective study of 215 patients with stage I and II melanoma showed that 46 patients had positive SLNs.\textsuperscript{54} Risk factors for node involvement were ulceration, high mitotic rate, tumor angiolymphatic invasion, and microsatellites. Patients with tumors thicker than 1.0 mm with none of these risk factors had only a 14% risk of metastases.\textsuperscript{54} A study of 329 patients with thick (>4 mm) melanomas showed that, when lymph node status was accounted for, tumor thickness, vascular involvement, and ulceration remained independent predictors of survival by multivariate analysis.\textsuperscript{52} Angiotropism has been identified in cutaneous melanoma and shown to be a prognostic factor that predicts risk of metastasis.\textsuperscript{64,66,77} An angiotumoral complex was described in which tumor cells occupy a pericytic location along the endothelium of microvessels without intravasion.\textsuperscript{64,66} This pericyte angiotropism may be a marker of extravascular migration of tumor cells similar to that proposed for glioma migration.\textsuperscript{66}

**MELANOMA CLINICAL STAGING**

The melanoma staging criteria were updated and made official with the publication of the 6th edition of the AJCC Cancer Staging Manual in 2002.\textsuperscript{78} The following section describes the various stages of melanoma and the median survival associated with each stage.

The new AJCC staging criteria for melanoma are divided into 4 distinct stages.\textsuperscript{78} Localized melanoma is classified under stage I and stage II, whereas stage III melanoma includes regional metastases, and stage IV encompasses distant metastases. Each stage uses the TNM classifications when determining stage of disease.\textsuperscript{78} Balch et al.\textsuperscript{78} validated the staging system of malignant melanoma on the basis of their results from analysis of a major database of prognostic factors of more than 17,600 patients from 13 cancer centers and organizations.

**DEFINITIONS**

**Stage I.** Stage I cancer is diagnosed in patients who have primary lesions that are 1 mm or less in thickness with no evidence of metastasis.

Stage IA (T1a N0 M0) includes patients whose primary lesions are 1 mm or less in thickness with no ulceration and do not invade the reticular dermis or subcutaneous fat (Clark level <IV or V).

Stage IB (T1b or T2a N0 M0) includes patients whose primary lesions are 1 mm or less in thickness and have ulceration or invasion to Clark level IV or V (T1b) or patients whose primary lesions are 1.01 to 2.0 mm in thickness without ulceration.

**Stage II.** Stage II cancer is diagnosed in patients with thicker primary lesions, without evidence of metastasis.

Stage IIA (T2b or T3a N0 M0) includes patients whose primary lesions are 1.01 to 2.00 mm thick and have ulceration (T2b) or patients whose primary lesions are 2.01 to 4.00 mm thick without ulceration (T3a).

Stage IIB (T3b or T4a N0 M0) includes patients whose primary lesions are 2.01 to 4.00 mm thick and have ulceration (T3b) or patients whose primary lesions are more than 4.00 mm thick without ulceration (T4a).

Stage IIC (T4b N0 M0) includes patients whose primary lesions are more than 4.0 mm thick and have ulceration.

**Stage III.** Stage III cancer is diagnosed when the melanoma spreads to the regional lymph nodes and/or an in-transit or satellite metastasis is present.

Stage IIIA (T1-4a N1a or N2a M0) includes patients whose primary lesions are of any depth without ulceration and who have 1 to 3 nodes involved with microscopic disease as discovered after a sentinel or elective lymphadenectomy.

Stage IIIB (T1-4b N1a or N2a M0, T1-4a N1b or N2b M0, or T1-4a/b N2c M0) includes patients whose primary lesions are of any depth with ulceration and who have 1 to 3 nodes involved with microscopic disease. or

Patients whose primary lesions are of any depth without ulceration and who have 1 to 3 nodes involved with macroscopic disease as discovered on clinical examination and confirmed by therapeutic lymphadenectomy or when nodal metastasis displays gross extracapsular extension. or

Patients whose primary lesions are of any depth with or without ulceration and who have in-transit or satellite metastasis without the presence of metastatic lymph nodes.

Stage IIIC (T1-4b N1b M0, T1-4b N2b M0, or any T N3 M0) includes patients whose primary lesions are of any depth with ulceration and who have 1 to 3 macroscopically involved lymph nodes (N1b or N2b). or

Patients with any depth of tumor with or without ulceration and 4 or more metastatic nodes, matted nodes, or in-transit or satellite metastasis with the presence of metastatic node(s) (N3).

**Stage IV.** Stage IV cancer is diagnosed when the melanoma spreads to distant sites, including the skin, subcutaneous tissue, lymph nodes, and organs. The 3 levels of division of stage IV disease are based on the M status.

M1a (any T, N) includes patients with any depth of tumor, with or without ulceration, with or without nodal involvement, and with distant metastasis limited to distant
TABLE 3. Surgical Management of Melanoma

<table>
<thead>
<tr>
<th>Tumor thickness (mm)</th>
<th>Radius of excision (cm)</th>
<th>Options for lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>In situ ≤ 1.0</td>
<td>0.3-0.5</td>
<td>Observation</td>
</tr>
<tr>
<td>1.1-2.0</td>
<td>1-2</td>
<td>Selective sentinel lymph node biopsy, observation</td>
</tr>
<tr>
<td>2.1-4.0</td>
<td>2</td>
<td>Sentinel lymph node biopsy, observation, elective lymph node dissection</td>
</tr>
<tr>
<td>&gt;4.0</td>
<td>2</td>
<td>Sentinel lymph node biopsy, observation, elective lymph node dissection</td>
</tr>
</tbody>
</table>

skin, subcutaneous tissue, or lymph nodes and a normal lactate dehydrogenase (LDH) level.

M1b (any T, N) includes patients with these same criteria but who also have metastasis to the lungs and a normal LDH level.

M1c (any T, N) includes patients with these same criteria but who also have metastasis to any other visceral site and a normal LDH level or any patient with distant metastasis regardless of the site but with an elevated LDH level.

SURVIVAL

Balch et al1 described the survival rates for 17,600 of 30,450 patients in the AJCC Melanoma Database who had information available for all the factors required for the proposed TNM classification and stage grouping (Table 2).

SURGICAL THERAPY

The most definitive therapeutic intervention in the management of malignant melanoma is primary surgical excision. Most patients with primary tumors of less than 1 mm thickness have a low risk of locoregional or systemic spread. Therefore, preoperative evaluation for occult visceral metastases is usually not required in this population. For patients with a melanoma thicker than 1 mm, a chest x-ray film and baseline liver function tests may be routinely performed, although the yield is low in the absence of symptoms. For patients with stage III disease, further work-up with computed tomography (CT) needs to be performed as clinically indicated. Clinical symptoms should dictate further work-up because extensive imaging studies in the absence of symptoms have a low yield.7980 Positron emission tomography (PET) has no role in patients with clinical stage I or II disease; the sensitivity of identifying involved lymph nodes with PET is only 20%.81 However, PET may be helpful in evaluating patients at high risk for metastatic disease (eg, stage IIC, stage III, or stage IV disease) before planned surgical intervention. One study has shown that findings on preoperative PET (eg, detection of occult metastases) result in changes in therapy plans in only a few patients.82

EXTENT OF EXCISION

Thicker tumors have a higher rate of local recurrences and hence require wider surgical margins when excisions are performed. The width of the margins required for any given thickness of tumor has been studied in several randomized surgical trials. A number of trials have been performed to determine the optimal surgical resection margin for melanomas of various depths. The World Health Organization Melanoma Program randomized patients with melanomas more than 2 mm thick to excision margins of 1 or 3 cm. Clinical outcomes (regional and distant metastatic rates) were comparable in both arms; however, 3 patients in the 1-cm margin group (all of whom had tumors ≥1 mm) had local recurrences. The conclusions of that study are that for patients with thin melanomas (ie, <1 mm), a margin of 1 cm is adequate.83 The Intergroup Melanoma Trial randomized patients with intermediate-thickness melanoma (1-4 mm) to be treated with 2- or 4-cm margins. They concluded that 2- and 4-cm margins were equally effective in achieving comparable rates of local control and survival. The local recurrence rate was influenced by melanoma thickness (2.3% for 1.1- to 2.0-mm thickness, 4.2% for 2.1- to 3.0-mm thickness, and 11.7% for 3.01- to 4.0-mm thickness) and presence or absence of ulceration (10.6% vs 1.5%). On follow-up of 10 years, no difference in survival or local recurrence rates was found between patients who underwent excision with a 2- or 4-cm margin.84 Local recurrence rates were related to the presence of ulceration and site of the melanoma (proximal extremity, 1.1%; trunk, 3.1%; distal extremity, 5.3%; and head and neck, 9.4%).84

No randomized trials have evaluated adequate margins for thick (>4 mm) melanomas. The largest retrospective review to address this issue evaluated outcomes in patients with thick melanomas and detected no differences in outcomes (local recurrences and overall survival) between patients with tumor margins of less or greater than 2 cm.84 The recommendations based on tumor thickness are summarized in Table 3. For locations in which a 2-cm section is impossible, such as in the head and neck area, a negative margin resulting in a reasonable cosmetic result is thought to be acceptable. Removing the fascia is not thought to be necessary and does not improve local recurrence or survival rates. In special circumstances, use of a Mohs resection can only be considered exploratory.85

EVALUATION OF THE LYMPH NODES

In malignant melanoma, as with most solid tumors, the status of lymph nodes is a powerful predictor of recurrence and survival. The overall survival rate of patients with
lymph node metastases (stage III) is between 13% and 69%. The risk of lymph nodal involvement correlates with thickness of the primary lesion and presence of ulceration. The pattern of metastases for melanoma was believed to initially involve the regional lymph nodes, and removal of the regional lymph nodes was believed to have the potential to cure patients with clinically occult lymph nodes. This belief led to the practice of routine elective lymph node dissection (ELND) in all patients who were deemed to have a high risk of regional spread (ie, >1-mm-thick melanomas). Retrospective analyses performed at Duke University, at the Sidney Melanoma Unit, and by Charles Balch suggested a survival advantage for ELND in patients with intermediate-thickness melanoma. Even though ELND was suggested to impart a survival advantage, this advantage was in the most morbid portion of the surgery, and ELND can result in temporary or chronic lymphedema, especially in the lower extremities, seroma formation, infection, and chronic pain.

Several prospective randomized trials compared ELND with observation in patients with intermediate-thickness melanomas, and all demonstrated a lack of benefit with routine ELND in patients with intermediate-thickness melanoma. Unfortunately, these trials were underpowered because only 20% of patients with an intermediate-thickness melanoma had lymph node metastases at the time of ELND, and 80% did not benefit from the intervention. Assuming that 25% to 50% of patients with positive lymph nodes would benefit from a lymph node dissection, the procedure would affect only 5% to 10% of the entire study population and would require many more patients than were entered into the trials. The Mayo Clinic trial was faulted for having too few patients with intermediate-thickness (ie, >1.5 mm) melanoma and for technical issues related to insufficient lymph nodule mapping, which may have influenced the outcomes. The World Health Organization study was criticized for unequal ulcerated lesions and a low percentage of male patients (which result in a high risk for nodal involvement). Balch et al reported on a more recent randomized prospective trial to address the same issue in patients with intermediate-thickness melanoma (1-4 mm) and again found no survival advantage in patients undergoing ELND. Subset post hoc analysis revealed that patients with 1- to 2-mm-thick lesions who were older than 60 years had a survival benefit with ELND. These data were reanalyzed with longer follow-up and confirmed the earlier findings. Overall, no survival advantage was seen with ELND vs observation (77% vs 73%; \(P=0.12\)). In subset analysis, patients with nonulcerated lesions (84% vs 77%; \(P=0.03\)), melanomas with a thickness of 1.0 to 2.0 mm (86% vs 80%; \(P=0.03\)), and limb melanomas (84% vs 78%; \(P=0.05\)) had a better overall survival. Subsequently, the World Health Organization Melanoma Program reported the results of another randomized trial that evaluated ELND in patients with truncal melanomas with a thickness of 1.5 to 4.0 mm, which once again demonstrated no advantage for ELND. No statistical difference was seen in overall 5-year survival rates between immediate (61.7%) and delayed (51.3%) lymph node dissection (\(P=0.09\)); however, for patients who were found to be lymph node positive at the time of ELND compared with patients who developed clinically palpable lymph node metastases and underwent a therapeutic lymph node dissection, a 5-year survival benefit was seen (48.2% vs 26.6%; \(P=0.04\)). In summary, randomized surgical trials fail to support a role for ELND in patients with clinically negative lymph nodes.

**SLN Biopsy**

Even though ELND dissection has not been found to have a survival advantage, the patient’s lymph node status carries significant prognostic information and aids in decisions for adjuvant therapy and entry into clinical trials. This has been the impetus for the development of the SLN biopsy procedure. Sentinel lymph node biopsy is a technique used to identify and resect the first lymph node(s) to drain lymphatic flow from the primary tumor site. Sentinel lymph node biopsy allows for staging of the lymph node basin with minimal morbidity and facilitates selection of patients for additional complete lymph node dissection. The concept for using this procedure is that the status of the SLN is reflective of the status of the entire lymph node basin; therefore, therapeutic decisions can be made on the basis of the analysis of the SLN.

The surgical principles of SLN biopsy were developed by Morton et al. The procedure as initially performed used a vital blue dye, 1% isosulfan blue, that was injected intradermally around the primary melanoma. After a brief period, a small incision was made over the primary draining lymphatic basin, and the “blue” node was excised and sent for pathologic analysis. Morton et al initially studied 223 patients with clinical stage I disease. The success in identifying the SLN was 89% in the groin, 81% in the neck, and 78% in the axilla. Nodal metastases were found in 41 (18.4%) of the 223 cases. The SLN accurately predicted the histologic findings of the lymph node basin in 40 (97.6%) of the 41 cases. Complications were minimal and included presence of dye in the urine for 24 hours, retention of blue dye at the injection site up to 2 months, wound edge necrosis (4.0%), seroma (5.5%), and infection (4.8%).

The SLN biopsy technique was further refined by the addition of radiisotope technetium Te 99m sulfur colloid to identify the sentinel node. The radionucleotide is injected intradermally around the primary melanoma at least 2 hours before surgery. Immediately before surgery, 1 mL
TABLE 4. Sentinel Lymph Node Biopsy Series

<table>
<thead>
<tr>
<th>Series</th>
<th>Sample size</th>
<th>Localization successful (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerschenwald et al(^{33})</td>
<td>612</td>
<td>95</td>
</tr>
<tr>
<td>Joseph et al(^{19})</td>
<td>600</td>
<td>99</td>
</tr>
<tr>
<td>Morton et al(^{10})</td>
<td>551</td>
<td>93</td>
</tr>
<tr>
<td>Morton et al(^{10})</td>
<td>584</td>
<td>95</td>
</tr>
<tr>
<td>Leong et al(^{10})</td>
<td>163</td>
<td>98</td>
</tr>
<tr>
<td>Mayo Clinic, Scottsdale, Ariz*</td>
<td>413</td>
<td>98</td>
</tr>
</tbody>
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of 1% isosulfan blue is injected around the tumor. Intraoperatively, a handheld gamma probe is then used along with the vital dye to find the “hot” and/or “blue” node. The ability to find the SLN is increased to 96%. Preoperative lymphoscintigraphy is imperative to determine that the lymph node basin is at risk; patients with nonextremity melanomas may have drainage patterns different from classic anatomical teaching in up to 60% of cases, and more than 1 basin can be at risk 6% to 58% of the time.\(^{92,98}\) Not only can the main lymph node basin be identified but also in-transit lymph node drainage sites (popliteal, epitrochlear, scapular, or brachial) can be defined. Without this preoperative assessment of lymphatic drainage, potential metastatic disease could be missed.

Other institutions, including our own, have used this combined technique with similar success (Table 4).\(^{33,99-102}\) An SLN is positive in approximately 20% of patients (primary tumors >1 mm thick), with the exact risk depending on the thickness of the primary lesion and presence of ulceration. Approximately 10% of all cases are upstaged by a more complete evaluation of the sentinel node with serial sectioning and immunohistochemical analysis (HMB-45 and S100). The average number of SLNs harvested from a lymph node basin ranges from 1.3 to 2.1. Drainage to more than 1 lymph node basin occurred in 15% to 27% of patients. Drainage to in-transit unusual lymph node basins occurred in less than 10% of cases. Head and neck melanomas have the highest localization failure rate. For patients with positive SLNs who have undergone a completion lymph node dissection, the likelihood of finding additional nodes involved is approximately 20%,\(^{103}\) with the risk depending on the thickness of the primary lesion, the size of the involved SLNs, and the number of positive SLNs. The local failure rate after an SLN procedure is low (1.8%-4.8%). The results of SLN analysis are predictive of overall survival. Patients with negative SLNs had a 4-year survival rate of 85% compared with those with positive SLNs who had a 4-year survival rate of 45%. Previous wide local excision of the melanoma does not appear to negate the reliability of the SLN biopsy, provided that a flap rotation was not used to cover the defect.\(^{104}\)

Controversy exists regarding the utility of performing an SLN procedure for thin melanomas (ie, ≤1 mm) and for thick melanomas (>4 mm). Thin melanomas account for approximately 70% of all newly diagnosed cutaneous melanomas. Although most patients with thin melanomas have an excellent long-term prognosis, a small proportion develops metastatic disease. Routinely performing SLN biopsy in these patients yields a positive result in approximately 5%. Attempts are under way to identify prognostic factors to better select these patients to avoid performing SLN procedures in the vast majority who have uninvolved SLNs. Several high risk factors for SLN positivity in these patients have been identified, including a high mitotic rate, tumor ulceration, male sex, and presence of a vertical growth phase, but none have been consistent among studies.\(^{95}\) In contrast, the prognosis of patients with thick melanomas is relatively poor, and the impact of lymph node positivity is unclear. Studies have demonstrated that up to 40% of patients in this group have a positive SLN. Patients with positive SLNs appear to have a worse prognosis, with higher rates of relapse\(^{106}\) and worse survival rates.\(^{106,107}\) On the basis of these data, SLN evaluation should be considered routine in this subset.

Routine evaluation of SLNs is performed using conventional hematoxylin-eosin staining followed by immunohistochemical analysis. No routine immunostaining guidelines exist. Most institutions perform S100 immunostaining with the addition of MART-1 and/or HMB-45 if the hematoxylin-eosin staining result is negative. Recently, reverse transcriptase-polymerase chain reaction (RT-PCR) was used to evaluate SLN tissue and was shown to be more sensitive than immunohistochemical analysis alone. Positivity by RT-PCR was noted in approximately half of patients with pathologic analysis–negative SLNs. Among patients with pathologic analysis–negative SLNs, those with RT-PCR positivity were at a higher risk of disease recurrence and death.\(^{108}\) Subsequent studies have confirmed the value of RT-PCR in predicting a subset of patients with a higher risk of recurrence but do not confirm the value in predicting survival.\(^{109}\) However, RT-PCR is expensive and technically demanding. Moreover, RT-PCR has a high rate of false positivity (ie, most patients who have a negative SLN by immunohistochemical analysis and a positive SLN by RT-PCR do not have disease recurrence). On the basis of these factors, as well as on early reports from the ongoing Sunbelt Melanoma Trial, which addresses the utility of RT-PCR in evaluating lymph nodes, the use of RT-PCR should be considered experimental.

Despite its obvious advantage, the technique of SLN biopsy for melanoma staging has not been widely accepted. Recent analysis of Surveillance, Epidemiology, and End Results data demonstrates that only approximately 50% of
patients with melanoma who are eligible for SLN biopsy undergo the procedure. Most of the controversy relates to the lack of any data demonstrating a survival advantage with SLN biopsy until recently. The interim results of the Multicenter Selective Lymphadenectomy Trial I were reported at the American Society of Clinical Oncology annual meeting in 2005. This trial randomized 1204 patients with larger than 1-mm lesions who underwent wide local excision to immediate SLN biopsy or observation. Patients with positive SLNs underwent a completion lymphadenectomy. No significant overall survival (primary goal) difference was found in patients who underwent the SLN procedure up front compared with those randomized to initial observation. However, several of the secondary aims of the study were positive. Patients randomized to the SLN biopsy arm up front had a better disease-free survival rate compared with those in the observation arm. Moreover, patients who had a positive SLN and underwent an immediate complete lymph node dissection had better survival rates than those in the observation arm who developed lymph nodal involvement subsequently (5-year survival rate, 71% vs 55%; P = .007). Thus, it would appear that routine use of SLN biopsy, followed by complete lymph node dissection if positive, has a prognostic and possibly some therapeutic value, especially in lymph node–positive patients. In light of these data, most melanoma surgeons advocate the use of SLN biopsy to stage their patients’ disease.

SURGERY FOR RECURRENT AND STAGE IV DISEASE

When possible, surgical excision for local recurrences and in-transit metastases is the most effective therapy. The same is true for regional metastases or recurrences in which complete lymph node dissection is the treatment of choice. Surgical resection can also be valuable in patients with metastatic disease, with reports of long-term survival. Current trials are under way to assess the impact of additional systemic therapy after surgical resection for selected patients with stage IV disease. The John Wayne Cancer Institute reported on the long-term survival of 1574 patients with melanoma who underwent surgical resection for stage IV disease. The number and location of metastases were the most powerful factors predicting overall survival. Median survival for those who underwent resection for metastases to skin or distant lymph nodes (35.1 months), lung (28.1 months), and gastrointestinal tract (36.7 months) was much better than for those who underwent resection for metastases to the adrenal gland (27.4 months), brain (21.9 months), and liver (18.2 months). Other studies have reported similar results, with those undergoing resection of lung and subcutaneous metastases or distant lymph nodes having the best long-term survival.

ADJUVANT THERAPY

Surgical resection of regionally metastatic stage III melanoma is only partially effective in ensuring long-term disease-free survival. Approximately 60% of these patients ultimately die of metastatic disease. Therefore, additional therapy that eradicates clinically undetectable micrometastases present at the time of primary surgical resection is desirable.

INTERFERON ALFA

The risk of recurrence of melanoma is substantial in deeply invasive primary melanoma and when lymph nodes are involved at diagnosis. The only adjuvant therapy for high-risk melanoma currently approved by the Food and Drug Administration (FDA) is interferon alfa 2b given at a high dose (20 million U/m² for 5 days) for 1 month, followed by a lower dose (10 million U/m² 3 times weekly) for 11 months. Interferon was approved in 1995 on the basis of a pivotal trial (E1684) conducted by the Eastern Cooperative Oncology Group (ECOG). In that trial, 287 patients with either pathologic stage T4 (>4 mm depth) or lymph node positive disease (N1) were randomized to either interferon alfa 2b therapy or observation. At the time of the report, the treatment arm demonstrated improvement in time to progression by an average of 8 months, with a 1-year overall survival benefit (P = .0237). The benefit to the treated patients was associated with significant toxic effects, with dose reductions required in most patients. Subsequent confirmatory studies failed to reproduce the survival benefits noted in the E1684 trial. The North Central Cancer Treatment Group reported a study of 262 patients with earlier-stage disease (stage I and II) who did not receive significant benefit from adjuvant high-dose interferon alfa therapy, although a trend toward prolonged survival was reported (6.6 vs 5.0 years; P = .4). The Intergroup study E1690, using the same eligibility criteria as E1684, initially showed a decreased risk of progression at 5 years of nearly 10% (P = .05), but no overall survival benefit or trend. Potential explanations for this difference include more patients with node-negative disease in E1690, higher rates of salvage therapy with interferon alfa in the observation group after progression, and improvements in surgical techniques compared with patients in E1684.

A pooled analysis of 1916 patients and 716 observational controls from all ECOG trials using high-dose interferon alfa for melanoma (E1684, E1690, E2696) in the adjuvant setting was reported in 2004. The final analysis showed a significant increase in relapse-free survival (P = .006) but not overall survival (P = .42), controlling for poor prognostic factors such as relapse of disease at the time of treatment, ulceration, and enrollment in protocol.
E1684. Despite the positive impact on survival reported by E1694 (high-dose adjuvant interferon therapy vs G2-KLH/ GS-21 vaccine), the results of the pooled data have height-
ened the reluctance of many practitioners and patients to use adjuvant therapy with interferon in light of the substan-
tial toxicity.119 However, a recent report suggested that the subset of patients who developed serologic or clinical evi-
dence of autoimmunity after interferon therapy appeared to achieve survival benefit from treatment.120 These data sug-
gest that improved patient selection may be critical in attaining improved overall survival outcomes with adju-
vant interferon therapy. Efforts to identify these patient characteristics are currently under way.

Concerns about toxicity associated with high-dose adju-
vant interferon alfa therapy have prompted several investi-
gators to evaluate lower-dose therapy for the same clinical settings. Lower-dose adjuvant interferon therapy has dem-
onstrated less toxicity with possible trends toward delay of progression (less effective than high-dose therapy) and no effect on overall survival in node-positive and high-risk node-negative patients.116,121-127 However, prolonged treat-
ments (>1 year) may lengthen time to recurrence, with progression-free survival and overall survival curves ap-
proximating results of untreated controls after cessation of therapy.121,126

**Granulocyte-Macrophage Colony-Stimulating Factor**

In an effort to boost tumor lysis through activation of cytoxic macrophages, granulocyte-macrophage colony-
stimulating factor (GM-CSF) has been used in the adjuvant setting to treat high-risk melanoma. Spitzer et al128 treated 48 patients with resected stage III or IV melanoma with a subcutaneous daily dose of 125 mg/m2 for 2 weeks on, 2 weeks off for at least 1 year. The improvement in progression-
free survival over historical controls was substantial (37 vs 12 months; P<.001). This promising result has led to adjuvant GM-CSF being included in a phase 3 ECOG trial (E4697) to prospectively test its efficacy vs placebo. We eagerly await the results of this trial.

Adjuvant GM-CSF therapy is gaining acceptance in clinical practice for patients at high risk of recurrence who do not wish to undergo adjuvant high-dose interferon alfa therapy or do not qualify for other adjuvant clinical trials. Despite the promising phase 2 data, caution must be used with historical control comparisons.

**Cancer Vaccines**

Both autologous and synthetic vaccine approaches have been used in patients with high-risk melanoma. Many of these vaccines appeared to have clinical activity when results are compared with historical controls129,130 or in pa-
patients with immune responses compared with nonrespond-
ers.129,131,132 Primary avenues of research have focused on the identification of novel melanoma specific/associated anti-
gens (eg, MART-1, gp100, tyrosinase-related protein 1, gangliosides),117 optimization of the use of immune stimu-
lants as vaccine adjuvants (eg, GM-CSF, incomplete Freund adjuvant, interleukin [IL] 2), and development of target-specific measures of efficacy. Vaccines, although unsuccessful to date in the metastatic setting, remain a robust area of research in the adjuvant setting.

**Systemic Therapy for Metastatic Melanoma**

The prognosis of a patient with stage IV metastatic malignant melanoma in the 21st century remains poor. Despite decades of research efforts, the median survival time of a patient with disseminated melanoma is less than 9 months with a less than 5% probability of survival beyond 5 years of diagnosis.128,137,138 To date, the FDA has approved only two agents (dacarbazine and IL-2) for the treatment of stage IV melanoma. Although both agents have demonstrated modest tumor response rates, neither has resulted in a clinically meaningful prolongation of overall survival.

Dacarbazine (5-3,3-dimethyltriazeno-imidazole-4-car-
boxamide), the first drug approved for the treatment of stage IV melanoma, is a parenterally administered DNA-binding agent that undergoes extensive metabolism in the liver and is eliminated primarily by the kidneys. In the liver, dacarbazine is metabolized by the cytochrome P450 isoenzyme system to its active metabolite 5-(3-methyl-1-
triazeno)-imidazole-4-carboxamide, which spontaneously decomposes to the major metabolite 5-aminomidazole-4-
carboxamide. Approximately half a dose is excreted un-
changed in the urine by tubular secretion. Initially reported as a potentially active agent in disseminated melanoma,134 dacarbazine was attributed with an overall response rate of 22%, with the greatest activity in patients with low tumor burden and nonvisceral metastases.135 There was no impact on survival. These early clinical results have been repro-
duced in several subsequent studies and have been the foundation of a variety of chemotherapy and immuno-
therapeutic combination studies using dacarbazine as the primary active agent. In the most recent phase 3 clinical trial comparing dacarbazine with its oral analogue temozolomide for first-line therapy for patients with stage IV melanoma, the response rate for the dacarbazine treatment arm was 12.1%.136 The response rate with temozolomide was comparable at 13.5%. Since the publication of these data, most practicing oncologists have elected to use oral temozolomide vs intravenous dacarbazine because of, among other reasons, ease of administration. Orally active temozolomide, once absorbed (100% bioavailability), is nonenzymatically degraded in normal pH to the same ac-
tive compound as dacarbazine (5-[3-methyl-1-triazeno]-

500
imidazole-4-carboxamide). Elimination is primarily via the kidneys, requiring dose adjustments in patients with severe renal insufficiency. The most common toxic effects of temozolomide therapy are marrow suppression (thrombocytopenia) and constipation. Currently, temozolomide is approved by the FDA for treating anaplastic astrocytoma and glioblastoma multiforme. Approval for treatment of metastatic melanoma is pending.

The second agent approved by the FDA for the treatment of stage IV melanoma is IL-2, a recombinant hormone of the immune system originally described as a T-cell–derived growth factor and initially clinically used in the context of lymphokine activated killer cell therapy. Interleukin 2 received initial FDA approval for use in renal cell carcinoma in 1992, having demonstrated durable responses in select patients. By 1999, similar results were obtained in several studies of advanced-stage melanoma. A pooled analysis of 270 patients treated with high-dose bolus IL-2 (600,000–720,000 IU/kg administered every 8 hours for up to 14 consecutive doses for 5 days) resulted in overall objective response rates of 16% (6% complete responses). Best clinical responses were observed in patients with metastatic disease that involved soft tissues and lymph nodes. The overall median survival time was 11.4 months. Treatment was associated with significant toxic effects, with some patients requiring intensive care support. The more common (≥30%) severe adverse effects (grade 3 and 4) were hypotension (45%), vomiting (37%), diarrhea (32%), and oliguria (39%). Because of the significant treatment-associated toxic effects, this form of therapy is currently used primarily in medical centers with appropriately trained specialized staff.

Encouraged by the results of the high-dose IL-2 data, efforts proceeded in attempting to combine this treatment with other agents that had demonstrated clinical activity in melanoma (dacarbazine, interferon alfa, and cisplatin). The most important of these endeavors was the use of combination biologic (IL-2 and interferon alfa) and chemotherapeutic (cisplatin, vinblastine, and dacarbazine [CVD]) treatments referred to as biochemotherapy. Originally pioneered by Legha et al., this approach was based on the combination of the conventional CVD chemotherapeutic regimen (cisplatin, 20 mg/m² daily for 4 days; vinblastine, 1.6 mg/m² daily for 4 days; and dacarbazine, 800 mg/m² once) followed by biotherapy with high doses of IL-2 (9 × 10⁶ IU/m² intravenous infusion for 4 days) and interferon alfa (5 × 10⁶ IU/m² subcutaneously for 5 days). Initial reports demonstrated remarkable objective responses in the range of 69%. Despite the significant improvement in objective responses and the associated severe adverse effects (15% of the treated patients required intensive care support), the median overall survival was only 13 months (among 62 treated patients). This effort led to a phase 3 randomized clinical trial in which 190 patients with advanced melanoma were randomized to either chemotherapy (CVD) or biochemotherapy (CVD, IL-2, and interferon); greater clinical efficacy was shown in the biochemotherapy arm (overall response rates of 25% vs 48%). Despite significant toxic effects, the median survival time of the biochemotherapy arm was minimally improved (11.9 and 9.2 months). The addition of biotherapy appeared to improve the response rates but had no meaningful impact on overall survival. The final analysis of the benefits of biochemotherapy for the treatment of stage IV melanoma came with Intergroup study E3695, in which CVD was again compared with CVD, IL-2, and interferon. Preliminary analysis of this study demonstrated no overall survival advantage of the CVD, IL-2, and interferon arm. Once again, systemic therapy had failed to change the natural history of metastatic melanoma.

Currently, there are no standard systemic therapeutic regimens that offer significant prolongation of survival for patients with metastatic melanoma. Participation in clinical studies should be considered when possible for patients with advanced melanoma.

**Novel Therapeutics**

It has become increasingly clear that clinically effective therapy for metastatic malignant melanoma will likely involve a combination of cytotoxic drugs with biologic agents directed at inhibiting tumor vasculature (angiogenesis agents) and stimulating antitumor immunity. A multimodal approach is likely to address the deficiencies of individual treatment strategies. A large body of work already exists that describes individual efforts in all these treatment approaches with emerging combination therapeutics.

**Therapeutic Cancer Vaccines.** Therapeutic cancer vaccines represent one of the most heavily investigated and highly anticipated therapeutic strategies in the field of melanoma therapeutics. The basic premise of these interventions is the generation of increased numbers of vaccine- and tumor-specific cytotoxic T lymphocytes using vaccines administered to patients with metastatic melanoma, with the hope of inducing tumor regression or preventing tumor relapse in patients with resected melanoma who have a high risk of recurrence. The types of vaccines and routes of administration have ranged from autologous and allogeneic tumor cell lysates, engineered malignant melanocytes, melanoma tumor-specific peptides, autologous tumor-derived heat shock proteins, intratumoral injection of immune adjuvants, and autologous dendritic cell vaccines. These vaccines have been used either alone or in combination with immune modulators thought to potentiate their efficacy. Most notable (and most studied) of the
therapeutic melanoma vaccines is the polyvalent allogeneic irradiated whole-cell vaccine (PACV), developed from 3 allogeneic melanoma cell lines by Dr Donald L. Morton, and Melacine, a preparation of lyophilized lysates of 2 allogeneic melanoma cell lines combined with a novel immune adjuvant (Detox-PC) developed by Dr Malcolm S. Mitchell. Both vaccines were developed on the premise of multiple antigen targeting directed against both known and unknown melanoma antigens derived from cultured, allogeneic human melanoma cell lines. The experience with PACV demonstrated that patients with resected stage IV melanoma adjuvantly treated with PACV had improved 5-year survival rates compared with historical controls (39% vs 19%).

Interestingly, a subset analysis of 77 patients showed that those exhibiting evidence of immunization (IgM antibodies to TA-90 and positive vaccine-specific delayed-type hypersensitivity) had superior survival compared with immunized patients with no evidence of effective immune response (75% vs 8%), implying a specific therapeutic effect of the vaccine. These nonrandomized data suggested a benefit for adjuvant therapy using the PACV vaccine and gave rise to prospective randomized clinical studies in high- and low-risk patients with melanoma who had undergone resection. Unfortunately, in April 2005, the phase 3 placebo-controlled clinical trial evaluating the clinical benefit of adjuvant PACV therapy in high-risk patients with melanoma was closed before completion of accrual because of lack of clinical benefit. The results of the parallel study in “low risk of relapse” patients have not yet been reported.

Published experience with the Melacine preparation was similar to that of PACV. Initial phase I and phase 2 clinical data in patients with stage IV melanoma suggested effective immunization in 50% and objective responses in almost 20% of treated patients. Unfortunately, a large placebo-controlled phase 3 clinical trial of patients with T3 N0 M0 disease conducted by the Southwest Oncology Group Failed to demonstrate a clinical benefit in the treatment arm. Interestingly, subset analysis showed a disease-free survival benefit in patients expressing HLA-A2 and C3 haplotypes. Whether these data are sufficient to support further clinical studies with Melacine is currently under discussion.

Even though an effective vaccine for melanoma has not yet been developed, the recent FDA approval of a human papillomavirus vaccine for the prevention of cervical cancer provides encouragement for further research in cancer vaccines.

**Angiogenesis Inhibitors.** The recent FDA approval of bevacizumab (anti-vascular endothelial growth factor A) and sunitinib maleate for colon and renal cell carcinoma, respectively, has firmly established the place of angiogenesis inhibitors in cancer therapy. Similar angiogenesis-targeting agents have also been tested in patients with stage IV melanoma. The most notable of this class of agents to be tested in advanced-stage melanoma is thalidomide. Used alone or in combination with temozolomide, thalidomide has been unsuccessful in significantly improving the outcomes of patients with metastatic melanoma. Similar angiogenesis inhibitors (sunitinib malate, carboxyamido-triazole, TNP-470, SU5416, CC-5013, SU5416, BAY 12-9566, squalamine, or CCI-779) used in single-agent phase 1 (and 2) clinical trials have failed to significantly affect the natural history of metastatic melanoma. Agents currently undergoing phase 2 testing either as single angiogenesis agents or in combination with chemotherapy for stage IV melanoma include RAD001 (rapamycin analogue), sunitinib maleate in combination with temozolomide or paclitaxel, and carboplatin in combination with bevacizumab. Early reports on clinical outcomes in these studies are expected by middle to late 2007. To date, the experience with angiogenesis agents in the treatment of stage IV melanoma seems to suggest that combinations of these agents with chemotherapeutic drugs may be of potentially greater utility vs single-agent therapy.

**Novel Cytotoxic Agents.** One of the more unexpected developments in recent years is the reported efficacy of the combination of paclitaxel and carboplatin in the treatment of metastatic melanoma. Although originally tested in 2 small phase 2 clinical trials and deemed not sufficiently clinically active, recent evidence suggests that the combination of paclitaxel and carboplatin may be worth further consideration. This combination has become particularly interesting after early reports of encouraging clinical results emanating from a study in which the addition of sorafenib (BAY 43-9006) to paclitaxel and carboplatin resulted in objective response rates in excess of 50%. Sorafenib is a small molecule, multityrosine kinase inhibitor that, among other mechanisms of action, appears to be cytotoxic in malignant cells bearing b-raf mutations, as has been described in melanoma. The combination of paclitaxel, carboplatin, and sorafenib is currently undergoing phase 3 testing by the US cancer cooperative groups (E2603). The renewed interest in taxanes for the treatment of melanoma has resulted in a number of novel taxanes (ie, ABI-007) being tested in several ongoing phase 2 clinical trials.

Last and certainly not least, another noteworthy agent currently undergoing phase 3 clinical testing in resected and advanced melanoma is anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4). Anti-CTLA4 is a humanized antibody directed at a down-regulatory receptor on activated T cells. The proposed mechanism of action is inhibition of T-cell inactivation, allowing expansion of naturally developed (or vaccine stimulated) melanoma-
specific cytotoxic T cells. Original reports of the use of anti-CTLA4 in patients with metastatic melanoma describe remarkable efficacy in a small group of patients. This agent is currently in phase 3 clinical testing in patients with metastatic melanoma, and planning is under way for phase 3 trials in patients with resected tumors at high risk of disease relapse. We eagerly await the results of these studies.

**Radiation Therapy**

Melanoma is widely believed to be a radioresistant tumor; historically, this has limited the enthusiasm of physicians to use radiation therapy to treat this disease. The concept of radioresistance of melanoma has been interpreted to mean that radiation therapy is not useful for the treatment of melanoma, a perception that is incorrect.

Radiation therapy has been successfully used for primary treatment of ocular melanoma and lentigo maligna melanoma. Melanoma is the most common primary tumor of the eye and was traditionally treated with enucleation. Early reports revealed promising outcomes for patients treated with eye plaques that contained radioisotopes (brachytherapy). These plaques are sewn to the outside of the globe adjacent to the tumor to ensure proximity between the tumor and the radioactive sources. The Collaborative Ocular Melanoma Study was performed to compare enucleation to brachytherapy with the radioisotope iodine 125. Included were melanomas 2.5 to 10 mm in apical height and no more than 16 mm in longest basal diameter. After staging, 1317 patients were randomly assigned to either enucleation or radiation therapy. The dose prescribed to the tumor apex was 85 Gy. The 5-year survival rates were 81% for enucleation and 82% for radiation therapy (P=.48). The primary advantage of radiation therapy was preservation of useful vision, which occurs in approximately half of the patients who have undergone irradiation.

Lentigo maligna melanoma generally occurs in elderly patients in sun-exposed regions of the body. Surgical resection is generally considered the treatment of choice. However, radiation therapy has been used in selected patients who were not optimal candidates for resection. Harwood and Lawson, from the Princess Margaret Hospital, treated 28 patients with lentigo maligna melanoma using radiation therapy, and local failure occurred in 2 patients (7%). They also gave radiation therapy to 23 patients for lentigo maligna, and 2 patients (9%) experienced local disease recurrence. Tsang et al updated the Princess Margaret Hospital experience with patients with lentigo maligna who underwent resection (18 patients) or radiation therapy (36 patients). The 3-year local control rates were 94% for resection and 90% for radiation therapy. They concluded that radiation therapy was an excellent alternative to surgical excision with low morbidity and acceptable long-term cosmesis. Similar results with radiation therapy have been reported at other institutions.

Radiation therapy has been used for the primary treatment of nodular melanomas. Johanson et al described 9 patients treated with radiation therapy for gross residual disease after partial resection. Seven (78%) of the 9 patients achieved local control. Additionally, 9 (39%) of 23 patients with recurrence after resection achieved a complete response with salvage radiation therapy.

Radiation therapy has been used as an adjuvant therapy after resection. Creagan et al reported the results of a phase 3 trial performed at the Mayo Clinic in Rochester, Minn, which compared adjuvant radiation therapy with observation after lymph node dissection in 56 patients with involved regional lymph nodes. The radiation therapy was delivered at a dose of 30 Gy in 28 fractions administered in a split-course fashion with a 3- to 4-week break in the middle of treatment. The median duration of freedom from recurrence was 20 months with adjuvant radiation therapy vs 9 months without radiation therapy (P=.08). The median survival was 33 months with adjuvant radiation therapy vs 22 months without radiation therapy (P=.09). The reported interpretation of this study has been criticized on 3 key points: (1) insufficiently large cohort to detect subtle differences in survival; (2) poorly designed radiation therapy program, which included a break that decreased the treatment efficacy; and (3) no stratification for other significant prognostic variables. However, despite these weaknesses, the findings were provocative and should motivate further investigation.

Ang et al and Ballo et al reported the experiences of the M. D. Anderson Cancer Center investigators who administered postoperative radiation therapy for high-risk patients with melanoma. They recommended the following indications for postoperative radiation therapy to the primary site: desmoplastic melanoma, positive margins, locally recurrent disease, and tumors larger than 4 mm in thickness with either ulceration or satellite lesion. Additionally, they recommended postoperative nodal irradiation for the following indications: extracapsular extension, 4 or more lymph nodes, lymph nodes 3 cm or larger in diameter, recurrent nodal disease, SLN involvement, and complete lymph node dissection not planned. They have used these indications and a program of 30 Gy in 6-Gy fractions, each given twice weekly using primarily electron radiation therapy. This program has been used at many sites and has achieved generally high rates of local-regional control (89% overall). This level of local-regional control was much higher than that of their historical group and that reported in the literature (50%) of high-risk patients undergoing resection alone. Although disease control after resection plus radiation therapy was not site dependent, compli-


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cations appeared related to treatment location. For patients with epitrochlear, cervical, axillary, or groin lymph node disease, the corresponding 5-year rates of symptomatic lymphedema were 0%, 1%, 20%, and 27%, respectively (P<.0001).110 These differences in risk of treatment complications based on location have led Ballo et al to use more stringent criteria that require 2 or more indications for postoperative adjuvant radiation therapy for groin disease and less stringent criteria (>2 lymph nodes or >2 cm in diameter) for cervical disease.

More commonly, radiation therapy has been used for palliation of symptomatic sites of melanoma metastases. One area of great interest is determining the optimal dose-fractionation scheme for use in this setting. Two phase 3 trials have compared various fractionation patterns.210,211 Overgaard et al210 reported on 35 tumors in 14 patients with metastatic or recurrent melanoma who were randomized to receive either 9 Gy 3 times or 5 Gy 8 times, delivered twice weekly. Complete and persistent regression was found in 24 (69%) of 35 tumors and partial response in 10 (29%) of the 35 tumors. The overall response rate was 97%. No difference was observed between the 2 treatment regimens. Sause et al211 reported the results of Radiation Therapy Oncology Group trial 83-05, which randomized patients with measurable lesions to either 8.0 Gy 4 times once weekly (62 patients) or 2.5 Gy 20 times 5 days a week (64 patients). Patients in the 8.0-Gy arm exhibited a complete remission of 24.2% and a partial remission of 35.5%. Those in the 2.5-Gy arm exhibited a complete remission of 23.4% and a partial remission of 34.4%. No difference was found between arms. Although there was much radiobiological-based speculation that melanoma would respond better to programs with fewer larger doses of radiation therapy, this was not the case for metastatic melanoma.

Brain metastases pose special challenges because of the poor associated prognosis. Traditional therapy was whole-brain radiation therapy, which generally resulted in effective palliation and a median survival between 3 and 4 months. Recent studies have suggested that more aggressive management can positively influence survival. Meier et al212 reported on 100 patients who received treatment for brain metastases from melanoma. Their multivariate analysis confirmed that external beam radiation therapy, surgery, stereotactic radiosurgery, chemotherapy, and the location of brain metastases were independent and significant prognostic factors of survival.

Thus, although melanoma is a relatively radioresistant tumor, it is certainly not radioincurable. The utility of radiation therapy depends on the therapeutic index one can achieve using well-reasoned indications and optimal techniques of irradiation. Radiation therapy has been used successfully for primary therapy, adjuvant therapy, and palliation of metastatic melanoma. Further investigation of the use of radiation therapy for melanoma should not be hindered by the notion of radioresistance.

RARE MELANOMAS

Melanoma of the Eye

Uveal melanomas are rare cancers. The incidence of these cancers is approximately 5 to 7 new cases per 1 million persons per year.213 They occur much more commonly in whites than in African Americans.214 There are no known risk factors other than a family history or ocular melanocytosis.215 Ocular melanocytosis causes hyperplasia of deep scleral melanocytes, producing a grayish discoloration of the sclera. Besides uveal melanomas, ocular melanocytosis can cause iris heterochromia, choroidal heterochromia, and glaucoma. The 3 types of uveal melanomas are iris, ciliary, and choroidal. The ciliary and choroidal melanomas are similar, whereas the iris melanoma appears to be different in pathologic findings and metastatic potential. Iris melanomas account for only 3% to 5% of all uveal melanomas.

Chilchordoidal Melanomas

In the eye, the ciliochoroidal melanomas expand and cause visual loss and ultimately pain (Figure 1, A and B). Systemically, they can metastasize. Typical areas of metastasis are the liver, lung, and rarely other organs.216 The diagnosis of ciliochoroidal melanomas depends on certain clinical and echographic findings, and studies have shown that the diagnostic accuracy of these currently available techniques is a 99% ability to make a proper diagnosis. There can be dilatation of vessels on the sclera in the area of the tumor, which are called sentinel vessels. The fundus findings show the presence of a pigmented or mildly pigmented choroidal mass that is dome shaped or mushroom shaped. The mushroom shape occurs if the overlying Bruch membrane, which acts like a barrier to growth, is ruptured in a focal area. There can be an overlying exudative retinal detachment. Orange pigment can also be present on the surface of the tumor. This is caused by lipofuscin pigment collecting in the overlying, poorly functioning retinal pigment epithelium. Fluorescein angiography can show intrinsic vascularity of the tumor and punctate areas of leakage at the level of the retinal pigment epithelium. This leakage is from breakdown of the usual tight junction between the retinal pigment epithelium cells. Ultrasonography typically shows medium to low internal reflectivity of the lesion with a decrescendo pattern of the internal reflectivity and choroidal excavation. These ultrasound findings are distinctly different from other differential possibilities, including choroidal metastases, macular degeneration, choroidal hemangiomas, and choroidal osteomas. These typically show high internal reflectivity by ultrasonography.
Evaluation for metastasis should be made at the time of diagnosis. The most common site for metastasis is the liver, followed by the lung and much less commonly other organs. Evaluation should include liver function tests, including γ-glutamyl-transferase. Either PET/CT or a chest x-ray examination combined with liver ultrasonography should be performed (Figure 1, C).

Risk factors for metastasis have traditionally been size of the tumor, location of the tumor, and the histopathologic type.\textsuperscript{214,216,217} Tumors with a base less than 16 mm and a height less than 8 mm had a 20% rate of metastasis at 10 years.\textsuperscript{218} Tumors with a base less than 16 mm and a height greater than 8 mm had a 35% rate of metastasis at 10 years. Tumors with a base greater than 16 mm have a 60% rate of metastasis at 10 years. Spindle cell tumors have a better prognosis than a mixed cell type, whereas an epithelioid cell type has the worst prognosis\textsuperscript{214,216,217} (Figure 1, D). With molecular techniques, new risk factors are being discovered. At the genetic level, fluorescence in situ hybridization analysis has shown that another more recently noted risk factor for metastasis is monosomy 3.\textsuperscript{219} In addition, at the molecular level, inhibitor of DNA binding 2 (Online Mendelian Inheritance in Man No. 600386) suppression may cause up-regulation of E-cadherin and down-regulation of DNA binding 2, and up-regulation of E-cadherin appears to be related to metastatic potential of the tumor.\textsuperscript{220} How this is related to metastasis is still unknown. More recent studies have shown that periodic acid–Schiff-positive loops are a separate independent risk factor for the development of metastasis.\textsuperscript{221} These loops have been shown to be vascular loops that consist of a combination of endothelial cells and tumor cells. The more of these present, the worse the prognosis.\textsuperscript{222,223} Unfortunately, aside from the size, all the other prognosticators are found at the time of enucleation of the eye. In many patients, the eyes are not removed because studies have shown that, for tumors with a base of less than 16 mm and a height of 10 mm or less, plaque brachytherapy treatment results in the same prognosis as enucleation of the eye.\textsuperscript{217} Vision is ultimately lost because of radiation retinopathy and radiation optic...
neuropathy, but the eye is retained. This allows patients to have the option of retaining their eye and peripheral vision for approximately 2 to 3 years, but there is some concern with retaining the eye since the success rate of brachytherapy in preventing further growth of the tumor is 88% to 90% (Figure 1, E). The treatment of small choroidal melanomas with a tumor height lower than 3 mm is still in question. Many of these grow slowly, and becuase treatment can cause visual loss, treatment should be considered if certain prognostic indicators of further growth are present, namely, documented evidence of growth, orange pigment on the surface, overlying subretinal fluid, proximity to the optic nerve or macula, and a height of at least 2 mm. Previously, the use of transpupillary thermotherapy alone had been considered reasonable treatment for small melanomas, but recent data raise questions about whether these patients develop difficult-to-detect posterior extensions of residual melanoma.224 Because vascularity may be an important and independent indicator for prognosis, methods to determine vascularity short of removal of the eye are needed.

Mueller et al225 attempted to look at the vascularity by using indocyanine green. This approach looks only at the superficial part of the tumor and only qualitatively determines whether there are vessels on the surface of the tumor. The indocyanine green method cannot evaluate or quantify the presence of vessels located deep within the tumor, which may represent the bulk of the tumor vascularity. Buerk et al226 attempted to do this with magnetic resonance imaging by determining the relative enhancement over time. To date, this has been the best attempt to put some quantitation to the vascularity of a choroidal melanoma. The problem with this technique is that it is only a relative enhancement, and so a relative uptake over time is the best that can be accomplished with this technique.

Once metastasis occurs, the prognosis for the patient is poor. The death rate is 80% at 1 year and 92% at 2 years.218 There is no known treatment that is effective for metastatic choroidal melanoma, although multiple therapies are being tried. Because the uveal melanomas express vascular endothelial growth factor, which helps the tumor attract vessels to help nourish the tumor, attempts at the use of vascular endothelial growth factor inhibitors are being considered as well.227 Patients who have had choroidal melanomas should undergo liver function tests, including γ-glutamyltransferase performed every 6 months. Chest x-ray examination or PET/CT should probably be performed on a yearly or every 1.5-year basis.

MUCOSAL MELANOMA

Uncommonly, melanomas arise in sun-sheltered internal sites, usually in the mucosa of the head and neck, gastrointestinal tract, urinary tract, and vagina. One epidemiological study determined that 1.3% of all melanomas arose in such mucosal locations.221 Because of their rarity, the pathophysiology, etiology, risk factors, epidemiology, and clinical behavior of these tumors have not been well characterized.

Mucosal melanomas arise from resident melanocytes that are normally present in the mucosa. Benign melanocytic lesions occur in some of these sites (eg, nevi can be found in oral mucosa) and may represent precursor lesions.232 The genetic pathway followed by mucosal melanomas is somewhat distinct from that of UV radiation–induced dermal melanomas. For example, the genetic abnormalities typical of dermal melanomas (eg, BRAF and N-Ras mutations) are rarely found in mucosal melanomas.233-236 Biographical differences between mucosal and dermal melanoma result in several differences in clinical behavior. For example, compared with their dermal counterparts, mucosal melanomas (1) are not etiologically linked to UV exposure (correspondingly the population incidence has remained stable), (2) develop in older patients, (3) have a much worse prognosis, and (4) are disproportionately more common in populations other than white people.231,237,238

The most common sites of involvement of mucosal melanomas are the head and neck region (oropharynx, 55%), followed by the anus (24%), genitilia (vagina, 18%), and the urinary tract (3%). The mean age at diagnosis is 67 years, with a female preponderance (mainly because the male genital counterpart to vaginal melanomas is exceedingly rare).231,239 Clinically, these tumors manifest with local symptoms (eg, bleeding, ulceration, mass effect) or with signs of metastatic disease. Because these tumors are found in inaccessible locations and the index of clinical suspicion for melanoma at these sites is low, internal melanomas are often diagnosed later in the disease course. When a mucosal melanoma is detected, an obvious initial
diagnostic approach is to rule out a mucosal metastasis from a dermal primary lesion. However, some pathological features have been recognized that are typical for primary mucosal lesions; therefore, the diagnosis of a mucosal primary tumor is not always a diagnosis of exclusion.

Overall, the prognosis of patients with mucosal melanoma is relatively poor, with an overall 5-year survival rate of only 25% (compared with 80% for all skin melanomas). The prognosis of those with anal and rectal melanomas is even worse, with a 5-year survival rate of only 20%. Clinically, mucosal melanomas are more aggressive and deeper than dermal melanomas; it is unclear whether this finding is the result of a delay in diagnosis (ie, the inverse of a lead-time bias) or represents an underlying biological difference. The most important prognostic features are depth and lymph nodal involvement. Mucosal lesions have a higher propensity to metastasize than dermal lesions of similar thickness; presumably, the lack of mucosal fat allows for early lymphatic spread. Lymph nodal involvement is common in mucosal melanomas (40%) and is even more common in anal melanomas (60%).

Lymph nodal involvement portends a poor prognosis.

Because of the rarity of these tumors, no clinical trials are available on which to base treatment decisions. Therefore, therapy for mucosal melanoma presents a challenge. Ideally, the goals of local therapy are to achieve complete local excision with wide margins and removal of involved lymph nodes. Achieving wide surgical margins is difficult in tumors close to vital organs; therefore, local recurrences are common. Adjunct radiation to the tumor bed or to the draining lymph node has been advocated by some clinicians. The specific role of adjuvant interferon as it applies to mucosal sites is unclear and, given the marginal benefit of such therapy in general, may best be deferred.

Chemotherapy may have a palliative role in these patients, and responses to systemic chemotherapy and biochemotherapy have been described. Currently, several novel signal transduction inhibitors are being developed to treat metastatic melanoma based on genetic abnormalities commonly noted in dermal melanoma. One example is the development of the raf-kinase inhibitor sorafenib in melanoma based on the presence of activating mutations of the MAP kinase/ras pathway. Because these mutations are rarely found in these tumors, it is unclear whether such agents would be effective in mucosal melanoma.

**Melanoma of Unknown Primary Lesion**

Approximately 2% to 4% of all patients with melanoma and 9% of patients with melanoma with metastatic lymph node involvement do not have an identifiable primary lesion. The predominant site of involvement tends to be the axilla, and most patients are males. However, in females, there appears to be a greater preponderance of metastases in the extremities, consistent with the pattern of primary melanomas. It is unknown whether these clinical settings represent a regressed primary lesion or a primary tumor originating in a typically metastatic site. A few patients with this presentation report regression of a pigmented nevus.

Despite the presumed presence of a primary undetected lesion, the 5-year survival rate when lymph node metastases are resected is 40% to 55% and as high as 85% for in-transit or cutaneous metastases that are resected. Indeed, at least one series showed a survival advantage when a primary tumor could not be located. Patients who present with widespread or visceral metastases, however, have an equally poor prognosis as those with known primary tumors, with survival measured in a few months. However, when a patient presents with skin or lymphatic metastases from melanoma, an aggressive search for the primary lesion is indicated to remove all disease, with dermatologic examination mandatory and ophthalmic examination recommended, especially for liver metastases. If possible, all underlying disease should be surgically resected given the possibility of long-term survival. In addition, PET is a potential option for initial staging, although is unlikely to locate the primary tumor.

Management for patients with lymph node metastases in one nodal basin should be considered similar to that for patients with a known primary lesion. Patients with multiple areas of involvement or visceral disease should be managed as those with metastatic melanoma. If disease can be resected, interferon or GM-CSF therapy can be considered, as can enrollment in a clinical trial if the patient is eligible.

**CONCLUSION**

The key factor in the management of patients with melanoma is the recognition of the need for a dedicated cadre of clinicians, researchers, and statisticians to deal with these patients and their families. This disease is too complicated, too unpredictable, and too deadly to be managed without comprehensive prospective clinical trials. The Mayo Clinic has established some suggested practice guidelines (Table 5), but questions still remain.

So what has been accomplished? Where have we come during the past decades? The advances in the management of patients with metastatic melanoma have been frustratingly slow. However, we are now poised on the cusp of treatment such as targeted molecules and “designer...
### TABLE 5. Mayo Clinic Suggested Practice Guidelines *

<table>
<thead>
<tr>
<th>Stage</th>
<th>Surgical therapy</th>
<th>Imaging</th>
<th>Systemic therapy</th>
<th>Clinical follow-up</th>
<th>Laboratory or imaging tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (A and B)</td>
<td>Wide local excision. SLN biopsy is recommended for depths of ≥ 1 mm, if ulceration is present, or if suspicion of regional disease is high. If SLN biopsy result is positive, proceed with lymph node dissection</td>
<td>No</td>
<td>None (consider clinical trials)</td>
<td>Comprehensive history and physical examination, with special emphasis on the skin and lymph areas every 3-4 mo for year 1, every 6 mo for year 2, and yearly thereafter up to year 5; yearly thereafter as clinically indicated. Patient should be seen by a dermatologist annually for life</td>
<td>At discretion of treating physician</td>
</tr>
<tr>
<td>II (A, B, and C)</td>
<td>Wide local excision, with SLN biopsy; if SLN biopsy result is positive, proceed with lymph node dissection</td>
<td>Further imaging as clinically indicated (PET, CT, MRI, chest x-ray examination)</td>
<td>None (consider clinical trials)</td>
<td>Comprehensive history and physical examination, with special emphasis on the skin and lymph areas every 3-4 mo for years 1-3, every 6 mo for years 4 and 5, and yearly thereafter as clinically indicated. Patient should be seen by a dermatologist annually for life</td>
<td>CBC, chemistry panel, and LDH</td>
</tr>
<tr>
<td>III (A, B, and C)</td>
<td>Wide local excision followed by SLN biopsy or elective lymph node dissection for clinically involved regional lymph nodes; if SLN biopsy result is positive, proceed with lymph node dissection</td>
<td>Further imaging with PET and/or CT should be considered</td>
<td>IIIA (consider clinical trials); IIB (adjuvant high-dose interferon alfa for 1 y [controversial]); IIC (high-dose interferon for 1 y [controversial]) or low-dose GM-CSF for 1 y [controversial])</td>
<td>Comprehensive history and physical examination, with special emphasis on the skin and lymph areas every 3-4 mo for years 1-3, every 6 mo for years 4 and 5, and yearly thereafter as clinically indicated. Patient should be seen by a dermatologist annually for life</td>
<td>CBC, chemistry panel, LDH; additionally: IIIA–none; IIB—if prior PET and/or CT for further staging, repeated scanning at physician’s discretion. IIC—additional PET and/or CT every 3-6 mo for first 5 y and then yearly thereafter</td>
</tr>
<tr>
<td>IV</td>
<td>After diagnosis of stage IV disease, decision needs to be made whether patient can be surgically rendered disease free. If possible, complete surgical resection should be considered</td>
<td>Further imaging with PET, CT, and/or MRI highly recommended</td>
<td>No standard therapy for stage IV disease and all patients should be considered for participation in clinical trials. For patients who are surgically resectable to NED, consider adjuvant GM-CSF. ** For patients ineligible for surgery and/or clinical trials, the following palliative therapy options may be offered: (1) Interleukin 2, (2) temozolomide or dacarbazine, (3) paclitaxel and carboplatin</td>
<td>Comprehensive history and physical examination, with special emphasis on the skin and lymph areas every 3-4 mo for patients who are surgically rendered NED and are not proceeding with further adjuvant therapy. For all patients receiving adjuvant or palliative therapy, frequency of follow-up determined by the regimen prescribed and left to discretion of treating physician</td>
<td>CBC, chemistry panel, LDH; repeated PET and/or CT every 2-4 mo for the first 5 y and then yearly thereafter for patients rendered NED (high risk of relapse). For all patients receiving adjuvant or palliative therapy, frequency of repeated scanning determined by regimen prescribed and left to discretion of treating physician</td>
</tr>
</tbody>
</table>

*Practice guidelines are institution specific and not exclusively evidence based. CBC = complete blood cell count; CT = computed tomography; GM-CSF = granulocyte-macrophage colony-stimulating factor; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NED = no evidence of disease; PET = positron emission tomography; SLN = surgical lymph node.

**An anonymous author once made the comment, “The best way to predict the future is to create the future.” With this phrase in mind, with the interest and the commitment of dedicated clinicians, researchers, and scientists, we are creating a future that is positive and hopeful for individuals dealing with malignant melanoma. The future is not down the road. The future is today. The future is now....
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