REVIEW ARTICLE

MEDICAL PROGRESS

Management of Cutaneous Melanoma

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Cutaneous melanoma remains a management challenge. The National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database documents increases of 619 percent in annual diagnoses of cutaneous melanoma and of 165 percent in annual mortality from 1950 to 2000.[1] In 2004, an estimated 55,000 Americans will receive a diagnosis of cutaneous melanoma, and 7900 will die from the disease.[2] Of all cancers in the United States, cutaneous melanoma ranks fifth in incidence among men and seventh among women[2] and is the second leading cause of lost productive years[3,4]; it is also the most common cancer among women 20 to 29 years of age.[5]

MELANOMA SCREENING AND IDENTIFICATION OF HIGH-RISK PERSONS

Efforts to reduce the incidence of cutaneous melanoma have focused on identifying and screening persons at high risk and on promoting sun protection. People with light complexions, an inability to tan, blond or red hair, or blue eyes have a higher risk of melanoma than the general population.[6] Recently, inherited mutations in the melanocortin-1 receptor have been linked to people with red hair, to photosensitivity, and to an increased risk of cutaneous melanoma.[7]

Having many pigmented lesions, including freckles and either common or clinically atypical moles (Fig. 1), is also associated with an increased risk of cutaneous melanoma.[7] Although some moles are precursors to cutaneous melanoma,[8] more often they are markers of an increased risk.[7] Intermittent sun exposure and severe sunburns, especially during childhood, and use of tanning beds have been associated with an increased risk of cutaneous melanoma.[9,10]

Prior cutaneous melanoma is associated with an increased risk of a second primary cutaneous melanoma.[11,12] Recent analysis from the SEER database showed that the rate of subsequent cutaneous melanomas among persons with a history of melanoma was more than 10 times the rate of a first cutaneous melanoma among the general SEER population. Furthermore, the period of greatest risk is the first two years after diagnosis.[12]

Patients with a strong family history of melanoma and multiple clinically atypical moles are at the greatest risk for cutaneous melanoma.[13-17] Inherited mutations in the *CDKN2A* and *CDK4* genes, which have been documented in some families with hereditary melanoma,[7] confer a 60 to 90 percent lifetime risk of melanoma.[18] Although commercially available, genetic testing for hereditary melanoma is currently considered a research tool and is not routinely recommended.

Because skin is readily accessible to direct visual inspection, screening of high-risk persons is strongly recommended. Educational efforts to reduce the incidence of melanoma and the associated mortality promote recognition of early lesions (including an "ABCD" evaluation for asymmetry, border irregularity, color variegation, and a diame-

ter that is greater than 6 mm or increasing in size) and avoidance of sun exposure. The benefit of mass screening has been studied in Australia,[19] the Netherlands,[20] and the United States.[21] The American Academy of Dermatology has long sponsored annual free-access skin checks. In a study conducted from 1992 to 1994, about 2 percent of 282,000 patients screened had suspicious lesions, approximately 8 percent of which proved to be melanoma. Notably, screening through the American Academy of Dermatology program detected a higher percentage of early lesions than were recorded in the 1990 SEER database.[21] Similarly, melanomas that are detected by physicians are diagnosed earlier than lesions that are recognized by patients.[22] Although such efforts have promoted earlier identification of lesions, a direct reduction in mortality has yet to be documented. Nevertheless, for persons at highest risk (i.e., those with a strong family history of melanoma and multiple clinically atypical moles), frequent self-examination and professional evaluation at least once a year are necessary.

IDENTIFICATION OF HIGH-RISK LESIONS

A full skin examination, including mucous membranes, is essential for all people at risk; prior photographs of atypical lesions can be helpful. Clinical recognition of cutaneous melanomas and discrimination from surrounding clinically atypical moles can be difficult (Fig. 1). Melanomas frequently display irregularities in shape, color, and border; however, these features are neither invariant nor specific. Changing or symptomatic lesions or moles that stand out from other surrounding moles deserve prompt histologic evaluation by excision with narrow margins (1 to 3 mm). Subsequent pathological assessment requires multiple sections through the lesion to establish the thickness of the tumor (a measurement, in millimeters, of the distance from the epidermal granular layer to the base of the tumor at its thickest point) and the pathological stage of the disease (Fig. 2 and Table 1). Superficial shave biopsies are suboptimal, since deep margins cannot be fully ascertained.

Melanomas in the nail matrix often produce longitudinal pigmentation and require sampling of the matrix beneath the proximal fold. Nail-bed lesions frequently distort the nail plate, simulating a fungal infection, and require evaluation of both the plate and the underlying tissue bed.

STAGING AND TREATMENT OF PRIMARY MELANOMA

A management schema is shown in Figure 3. After histologic confirmation of cutaneous melanoma, pathological staging of the primary tumor guides the prognosis and decisions regarding further surgery.[23] Increases in the maximal thickness of a tumor and microscopical ulceration are both inversely correlated with survival and can be used to provide reasonable survival estimates. However, nodal status — determined by sentinel-lymph-node biopsy — has emerged as the most powerful predictor of recurrence and survival.[24]

Wide local excision is the treatment for the primary melanoma. Several randomized, controlled trials have determined what the proper resection margin should be according to the thickness of the lesion (Table 2).[25-30] In these trials, patients were enrolled on the basis of the thickness of the tumor and randomly assigned to excision with wide margins (3 to 5 cm) or narrow margins (1 or 2 cm). Because most of the trials showed similar outcomes in the two groups, narrower margins have been accepted for tumors of most thicknesses.

For melanoma in situ, margins of 0.5 to 1 cm around the visible lesion or biopsy scar are recommended. For thin melanomas (1.0 mm or less), a 1-cm margin is accepted.[25,26] Although no trials have specifically targeted melanomas that are 1.0 to 2.0 mm thick, most centers recommend a margin of 2 cm if anatomically possible (otherwise, a margin of 1 cm is recommended). This recommendation is derived from two trials showing that margins of 2 cm and 5 cm were equivalent for treating melanomas of 2.0 mm or less[27,28] and one trial that reported a higher, but nonsignificant, rate of local recurrence at 12 years among patients with lesions that are 1.0 to 2.0 mm thick who are treated with a 1-cm excision margin as compared with those treated with a 3-cm margin (4.2 percent vs. 1.5 percent).[25]

For tumors between 2.0 and 4.0 mm in thickness, the U.S. Intergroup Melanoma Surgical Trial established the adequacy of a 2-cm margin.[29] The recent United Kingdom Melanoma Study Group Trial[30] randomly assigned 900 patients with melanomas that had a thickness of 2.0 mm or more to two groups, with excision margins of 1 cm and 3 cm. The study showed no significant difference in the rate of local recurrence or in overall survival between the two groups, although the group with

1-cm margins had more combined locoregional recurrences. Although the findings of the study argue against a 1-cm margin for lesions that are 2.0 to 4.0 mm in thickness, the data do not support a preference for margins of 2 cm versus 3 cm.

Since thick melanomas (larger than 4.0 mm) are associated with a high risk of nodal and distant metastases, more extensive resection is unlikely to mitigate the outcome substantially. One retrospective analysis showed no significant benefit with respect to either local recurrence or overall survival rates among patients with thick tumors who underwent excision with margins greater than 2 cm[31]; thus, a 2-cm margin is probably adequate. On the basis of its recent findings, the United Kingdom Melanoma Study Group does recommend a 3-cm margin for thick tumors,[30] even though its superiority over a 2-cm margin has not been established. Melanomas in unusual sites (e.g., in the nail bed or the nail matrix, on the fingers, and on the soles of the feet) are uncommon and require special surgical attention.[32]

Since patients who are rendered disease-free by surgery are still at risk for regional and distant relapse and for additional primary melanomas, surveillance aimed at early detection of new lesions is needed. Although an optimal follow-up interval has not been determined, at minimum, an annual routine physical examination, including a full skin assessment and palpation of lymph nodes, is important. More frequent visits are appropriate for patients at high risk for multiple primary lesions (i.e., patients with multiple clinically atypical moles or a family history of melanoma) or for relapse (i.e., stage II or III disease). Routine laboratory tests, including serum lactate dehydrogenase, albumin, and plasma hemoglobin measurements and chest radiography,[33,34] have not been shown to be beneficial in screening for visceral disease in asymptomatic patients; therefore, these tests are usually reserved for patients with disease of stage II or higher.

NODAL SAMPLING AND STAGING

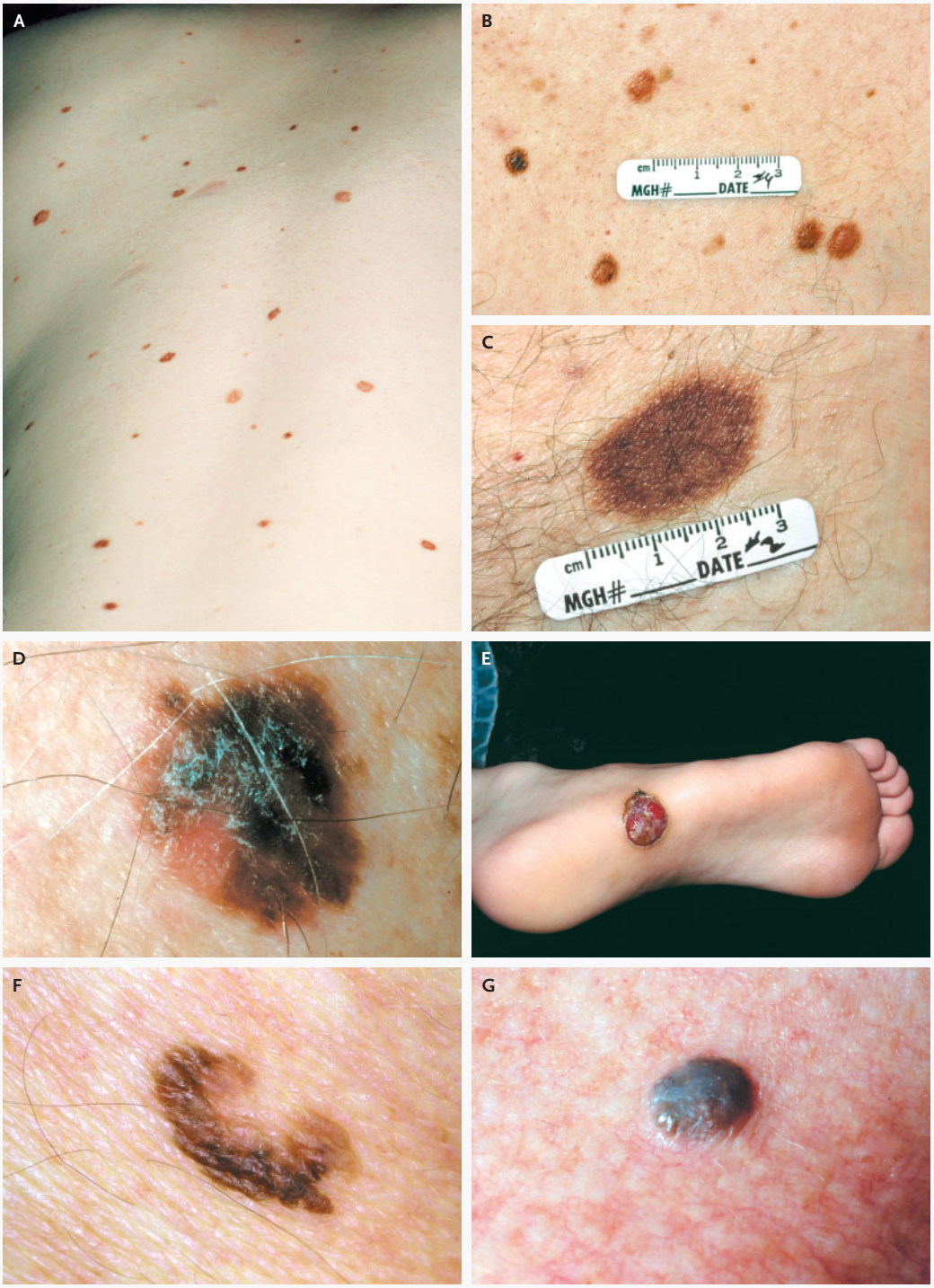
Interest in elective lymph-node dissection grew out of the hypothesis that melanoma cells spread to regional nodal basins before metastasizing widely. Thus, early removal of nodal deposits may prevent subsequent dissemination. Four prospective trials were designed to test this hypothesis,[35-38] and all four failed to show an overall survival benefit. Debate over the merits of elective lymph-node dissection has largely been subsumed by the emergence of sentinel-lymph-node biopsy as a staging, and possibly therapeutic, procedure.

Figure 1 (facing page). Clinical Images of Pigmented Lesions.

Multiple clinically atypical nevi are distributed over the back of a patient (Panel A). In Panel B, a cluster of clinically atypical moles have central papular components ("fried-egg nevi") and peripheral diffusion of pigment. A large (2.5-cm) nevus has a fuzzy border but relatively symmetric features (Panel C). In Panel D, superficial spreading melanoma is characterized by a dark brown plaque with highly irregular, scalloped borders and extensive color variegation. In Panel E, acral–lentiginous melanoma appears as a large ulcerative nodule on the plantar surface. In Panel F, lentigo maligna melanoma is manifested as an irregular, kidney-shaped, thin brown plaque on the face. In Panel G, nodular melanoma appears as a relatively symmetric, sharply circumscribed nodule with a blue–gray dermal invasive component. Photographs courtesy of Dr. Richard Allen Johnson.

In the early 1990s, Morton et al.[39] developed sentinel-lymph-node biopsy to sample selectively the first draining lymph node (or nodes) from a tumor site. In their initial report, the investigators (with the use of vital blue dye) identified the sentinel lymph node in 82 percent of lymphadenectomies and identified metastases in 21 percent of sentinel lymph nodes; in the absence of involved sentinel lymph nodes, subsequent completion lymphadenectomy revealed melanoma in only 1 percent of the nonsentinel nodes. Current protocols use technetium-99m–labeled radiocolloids in addition to vital dye[40,41] for maximal accuracy. Successful sentinel-lymph-node biopsy requires a multidisciplinary team that includes an experienced surgeon, a nuclear medicine radiologist, and a pathologist. In skilled hands, the sentinel lymph node can be identified more than 95 percent of the time with less than 5 percent false negative results.[41]

Sentinel nodes should be fixed and processed with both hematoxylin and eosin and immunohistochemical stains (e.g., S-100, HMB-45, and MART-1), since hematoxylin and eosin alone will miss up to 12 percent of positive nodes.[42] Since fewer nodes are submitted for examination, more detailed serial analysis, with detection of small micrometastases, is possible. Although benign collections of melanocytes may occasionally be present, the detection of intranodal deposits of melanocytic cells usually indicates metastasis.[43] More recent in-



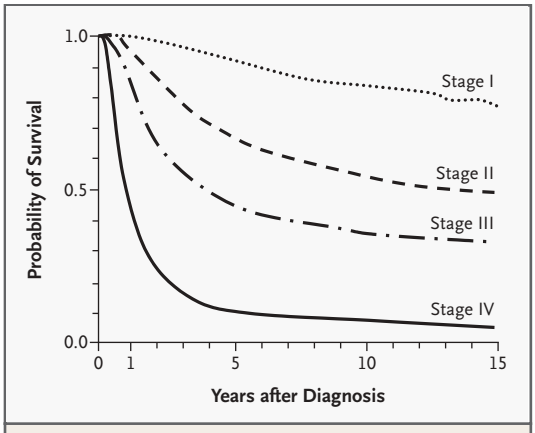


Figure 2. Relationship between the Stage of Melanoma and Survival.

Kaplan–Meier survival curves are adapted from the American Joint Committee on Cancer.[23]

vestigations suggest that the amount and pattern of metastatic deposits in the sentinel lymph node (e.g., tyrosinase messenger RNA [mRNA] molecules and single cells, cell clusters, micrometastases, and macrometastases),[44,45] as well as the function of the immune cells within the nodal basin,[46] may have prognostic significance.

The likelihood of detecting metastatic deposits in the sentinel lymph node is approximately 1 percent if the thickness of the tumor is less than 0.8 mm, 8 percent if it is 0.8 to less than 1.5 mm, 23 percent if it is 1.5 to less than 4.0 mm, and 36 percent if it is 4.0 mm or greater.[47,48] Since many large retrospective studies[24,44,48-52] have shown a strong negative correlation between the presence of metastatic melanoma in sentinel nodes and survival, sentinel-lymph-node biopsy is currently the most powerful staging and prognostic tool. As such, proponents argue that the performance of this minimally invasive procedure provides prognostic information and identifies candidates for systemic adjuvant treatment, such as with interferon alfa-2b. However, critics argue that sentinel-lymph-node biopsy has not been shown to improve survival and that interferon alfa-2b has not been proven effective for microscopical nodal disease. The Multicenter Selective Lymphadenectomy Trial and the Sunbelt Melanoma Trial were designed to address these concerns.[53]

The Multicenter Selective Lymphadenectomy Trial assigned 2001 patients whose tumors were 1.0 mm or greater or were classified as Clark level IV or V to undergo wide resection, either alone or with sentinel-lymph-node biopsy. The more complex design of the Sunbelt Melanoma Trial assessed the value of a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay for molecular identification of regional disease and the roles of completion lymph-node dissection and adjuvant interferon alfa-2b therapy on the basis of the extent of regional nodal involvement. Until complete data from these trials become available, judicious use of sentinel-lymph-node biopsy must balance the pretest likelihood of detecting melanoma within a node against the complication rate associated with the procedure and its cost. Early results for 2120 patients in the Sunbelt Melanoma Trial estimate complication rates of 4 percent for sentinel-lymph-node biopsy alone and 23 percent for sentinel-lymph-node biopsy along with completion lymph-node dissection.[54]

Since patients with melanomas that are 1.0 mm or less in thickness rarely have nodal disease,[48] sentinel-lymph-node biopsy is not commonly performed but could be considered if pathological examination showed negative prognostic features such as ulceration or Clark level IV to V invasion.[23] For patients with melanomas that are more than 1 mm thick, sentinel-lymph-node staging can be considered in order to estimate the prognosis and to determine eligibility for clinical trials and the need for adjuvant therapy. Further studies are needed to determine the additional benefit of completion lymph-node dissection in patients who have positive results on sentinel-lymph-node biopsy, the effect of prior wide resection on the accuracy of sentinel-lymph-node biopsy, and the role of sentinel-lymph-node biopsy in patients who are not candidates for completion lymph-node dissection or adjuvant therapy.

ADJUVANT THERAPY

One of the advantages of increasingly accurate staging is that it can identify patients whose risk of recurrence is sufficiently high to justify adjuvant systemic treatment.[23] Attempts to reduce recurrent melanoma with adjuvant therapy date back several decades and have been studied in more than 100 randomized, controlled trials.[55] Recent efforts focus on approaches involving interferon alfa-2b, vaccines, or both.

Although a variety of approaches have been beneficial in comparisons with the use of historical con-

Table 1. Staging Criteria for Melanoma.*

Pathological and TNM Stage	Thickness of Lesion	Ulceration	No. of Involved Lymph Nodes	Nodal Involvement	Distant Metastasis
	mm				
IA	≤1.0	No	0	—	No
IB					
T1b	≤1.0	Yes or Clark level IV or V	0	—	No
T2a	1.01–2.0	No	0	—	No
IIA					
T2b	1.01–2.0	Yes	0	—	No
T3a	2.01–4.0	No	0	—	No
IIB					
T3b	2.01–4.0	Yes	0	—	No
T4a	>4.0	No	0	—	No
IIC	>4.0	Yes	0	—	No
IIIA					
N1a	Any	No	1	Microscopic	No
N2a	Any	No	2 or 3	Microscopic	No
IIIB					
N1a	Any	Yes	1	Microscopic	No
N2a	Any	Yes	2 or 3	Microscopic	No
N1b	Any	No	1	Macroscopic	No
N2b	Any	No	2 or 3	Macroscopic	No
IIIC					
N1b	Any	Yes	1	Macroscopic	No
N2b	Any	Yes	2 or 3	Macroscopic	No
N3	Any	Yes or no	4	Macroscopic or microscopic	No
IV					
M1a	Any	Yes or no	Any	Any	Skin, subcutaneous
M1b	Any	Yes or no	Any	Any	Lung
M1c	Any	Yes or no	Any	Any	Other visceral site

* The 2002 American Joint Committee on Cancer recommends staging melanoma on the basis of the thickness of the lesion, the presence or absence of ulceration, the number of lymph nodes involved, the size of the nodes, and the presence or absence of distant metastases. The commission revised its melanoma staging system in 2002. The revisions included changing the thickness thresholds for lesions from 0.75, 1.5, and 4.0 mm to 1.0, 2.0, and 4.0 mm, respectively; reassigning thick tumors (larger than 4.0 mm) from stage III to stage II; removing Clark's level as a criterion for staging except in the case of lesions that are 1.0 mm or less in thickness; adding new staging criteria, including the presence or absence of microscopical ulceration, number of nodal metastases, metastatic burden, serum lactate dehydrogenase level, and sentinel-lymph-node status; abandoning the use of nodal dimensions; and separating lung metastases from other visceral sites as a secondary determinant of staging, given the improved prognosis. TNM denotes tumor–node–metastasis.

trols, only interferon alfa-2b has been shown to have a reproducible benefit. Three U.S. cooperative group studies showed improvement in relapse-free survival, and two of the three also showed significantly improved overall survival among patients receiving high-dose interferon alfa-2b (Table 3).[56-58] Since therapy with high-dose interferon alfa-2b improved relapse-free survival by 20 to 30 percent and overall survival by as much as 30 percent, the Food and Drug Administration (FDA) approved this treatment for patients with primary lesions thicker than 4 mm (i.e., stage IIB or IIC) or melanoma involving regional lymph nodes that have been rendered disease-free by surgery (i.e., stage III). Although analy-

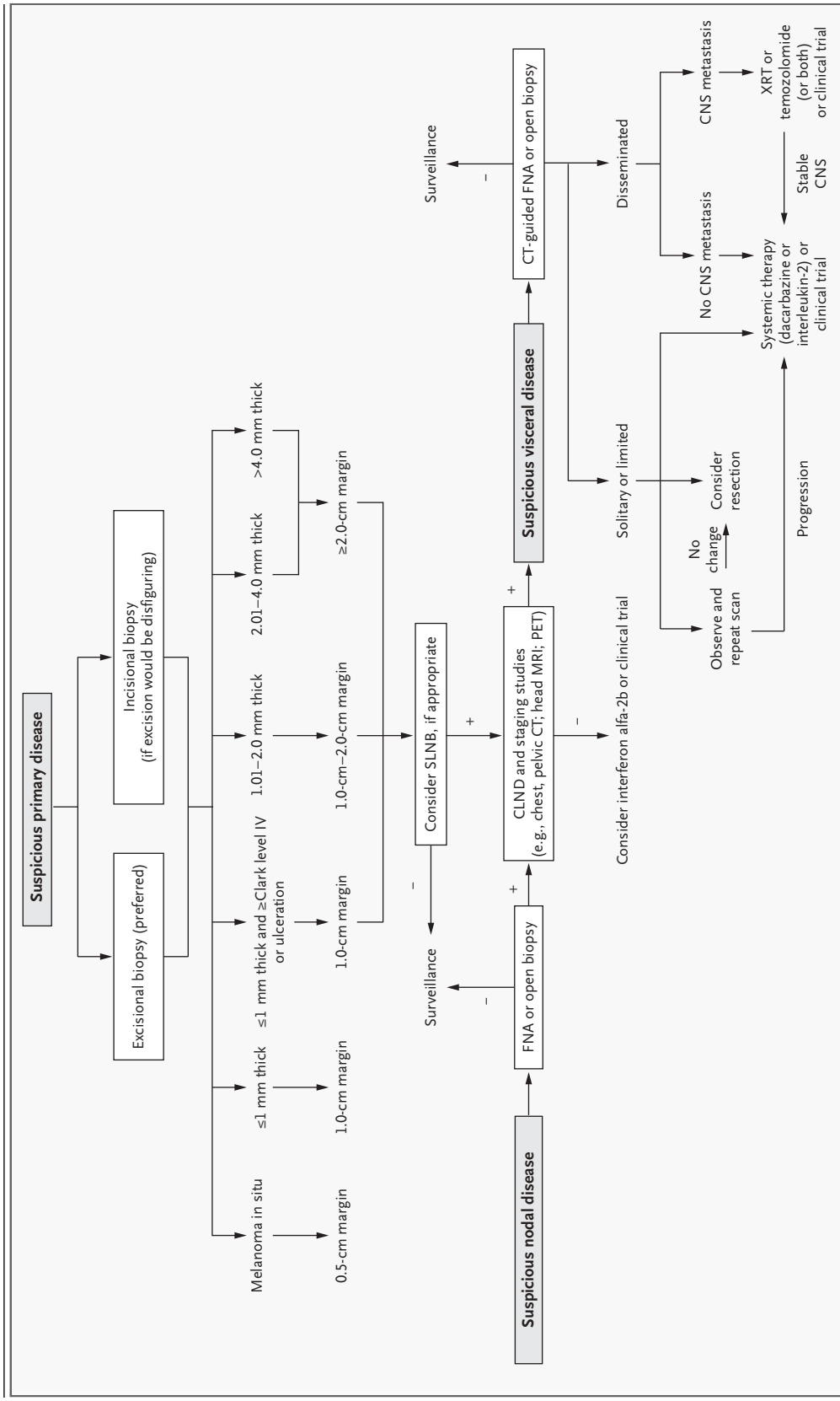


Figure 3. Algorithm for the Management of Cutaneous Melanoma.
SLNB denotes sentinel-lymph-node biopsy, FNA fine-needle aspiration, CLND completion lymph-node dissection, CT computed tomography, MRI magnetic resonance imaging, PET positron-emission tomography, CNS central nervous system, and XRT external radiation therapy. A minus sign indicates no evidence of disease, and a plus sign evidence of metastasis. Patients who are candidates for sentinel-lymph-node biopsy should be referred to a surgeon experienced in performing the procedure so that the benefits and complications can be fully discussed.

Table 2. Rates of Recurrence and Overall Survival in Randomized, Prospective Studies of Excision Margins in Patients with Primary Melanoma.

Study	Tumor Thickness	Excision Surgical Margin	No. of Patients	Rate of Recurrence	Overall Survival
	mm	*cm*		%	%
World Health Organization[25,26]	≤2.0	1	305	Local recurrence at 12 yr, 2.6	At 12 yr, 87.2
		3	307	Local recurrence at 12 yr, 0.98	At 12 yr, 85.1
French Cooperative Trial[27]	≤2.0	2	161	Local recurrence at 10 yr, 0.62	At 10 yr, 87
		5	165	Local recurrence at 10 yr, 2.4*	At 10 yr, 86†
Swedish Melanoma Trial Group[28]	≤2.0	2	476	Local recurrence at 10 yr, 0.6	At 10 yr, 79
		5	513	Local recurrence at 10 yr, 1	At 10 yr, 76
United States Intergroup Trial[29]	1.0–4.0	2	238	Local recurrence at 10 yr, 2.1	At 10 yr, 70
		4	230	Local recurrence at 10 yr, 2.6	At 10 yr, 77‡
United Kingdom Melanoma Study Group Trial[30]	>2.0	1	453	Local recurrence at 5 yr, 3.3; locoregional recurrence at 5 yr, 37.1	At 5 yr, 68.2
		3	447	Local recurrence at 5 yr, 2.8; locoregional recurrence at 5 yr, 31.0§	At 5 yr, 70¶

* P=0.22.
† P=0.56.
‡ P=0.07.
§ P=0.05 for locoregional recurrence only.
¶ P=0.60.

ses in individual studies suggested that the benefit of high-dose interferon alfa-2b may be restricted to certain patient populations on the basis of the number of nodes that are involved, no consistent pattern has been observed. Thus, it is reasonable to propose that the benefit of interferon alfa-2b is proportional to the risk of recurrence and that therapy can be considered for all patients in whom the potential benefit outweighs the expected toxic effects, regardless of the number of diseased nodes. In general, this would include patients with stage IIB, IIC, or III disease, no serious coexisting illnesses, and a life expectancy of more than 10 years.[59]

High-dose interferon alfa-2b has many side effects, including acute constitutional symptoms, chronic fatigue, headache, nausea, weight loss, myelosuppression, and depression.[60] Although these side effects can often be managed with appropriate supportive care,[61,62] most patients will require an adjustment of the dose during therapy. Thus, high-dose interferon alfa-2b should be administered by health care professionals who are familiar with its side effects.

Despite the toxicity, modest efficacy, and considerable expense of interferon alfa-2b, retrospective analyses show that the agent is associated with improved quality-of-life-adjusted survival[63] and is relatively cost-effective.[64] Additional evidence suggests that patients at high risk for a recurrence of melanoma prefer interferon alfa-2b therapy and its attendant toxic effects to even a slight increase in the risk of relapse.[65] Critics, however, have expressed concern about toxicity and the lack of a consistent survival advantage.[66] For example, the significant survival benefit with interferon alfa-2b, as compared with observation alone, in the initial report of the E1684 trial was no longer apparent when the data were reanalyzed at a median follow-up of 12.6 years.[67] Furthermore, other investigators have suggested without substantiation that the marked survival advantage observed in the more recent E1694 trial may be due, in part, to a deleterious effect of the experimental ganglioside vaccine rather than to a therapeutic effect of interferon alfa-2b.[66] Finally, meta-analyses of many randomized, controlled trials involving treatment with interferon at various doses failed to show a survival advantage in the aggregate.[68]

Since high-dose interferon alfa-2b has considerable toxic effects and prevents recurrence and death in only a minority of the patients at risk, it is not currently accepted worldwide and is inconsistently used in the United States. In addition, the intensity and duration of the regimen make it difficult to combine with other approaches. Efforts to improve the efficacy and toxicity profiles of inter-

Table 3. Relapse-free and Overall Survival in Trials of Interferon Alfa for Stage III Melanoma.

Trial and Regimen*	No. of Patients	Relapse-free Survival at 5 Years	P Value	Overall Survival at 5 Years	P Value
		%		%	
ECOG 1684[56]					
High-dose interferon†	143	37	0.002	46	0.02
Observation	137	26		37	
ECOG 1690[57]					
High-dose interferon	203	44	0.07	52	0.74
Low-dose interferon‡	203	40	0.12	53	0.67
Observation	202	35		55	
ECOG 1694[58]					
High-dose interferon	385	62§	0.002	78¶	0.009
GMK vaccine‖	389	49		73	

* ECOG denotes Eastern Cooperative Oncology Group.
† The dose of interferon was 20 million units per square meter of body-surface area per day, given intravenously five times a week for 4 weeks; then 10 million units per square meter per day, given subcutaneously three times per week for 48 weeks.
‡ The dose of interferon was 3 million units per day, given subcutaneously three times a week for two years.
§ Relapse-free survival is given for two years.
¶ Overall survival is given for two years.
‖ The dose of GMK vaccine was 1 ml administered by means of a deep subcutaneous injection on days 1, 8, 15, and 22, and then every 12 weeks through week 96.

feron have included the use of lower-dose regimens and combination with various vaccines.

Low-dose interferon has been extensively tested in Europe. Several trials have failed to show that low-dose interferon, as compared with observation alone, results in an increase in recurrence-free survival or overall survival in patients with high-risk stage II or III disease,[57,69,70] although two trials did report an increase in recurrence-free survival among patients with intermediate-risk melanoma.[71,72] This benefit led to approval, in several European countries, of low-dose interferon alfa-2b for patients with lesions of intermediate thickness. Nevertheless, no studies have yet shown that regimens of low-dose interferon alfa-2b provide an overall survival advantage; therefore, such regimens cannot be routinely recommended.

Other trials have evaluated interferon regimens that omit either the high-dose intravenous induction phase or the subcutaneous maintenance phase. A recent European trial suggested a significant delay in distant recurrence, but not an improvement in overall survival, with interferon alfa-2b (5 million units) administered subcutaneously three times a week for two years.[66] This delayed rate of relapse prompted European investigators to study longer durations of interferon therapy with the use of a pegylated interferon. In contrast, the early improvement in recurrence-free survival but not overall survival that is consistently seen with high-dose interferon prompted U.S. investigators to compare the four-week intravenous induction phase alone with observation alone in patients with stage IB to IIIA melanoma (in the E1697 study) and in those with regional nodal disease detected only by RT-PCR for melanoma-associated mRNA (in the Sunbelt Melanoma Trial).[73]

Other investigators have attempted to improve the efficacy of interferon therapy in patients with stage III disease by combining intermediate-dose interferon with Melacine (a vaccine comprising melanoma-cell lysates mixed in an adjuvant called Detox[74]) or by incorporating intermediate-dose interferon into a regimen that includes several chemotherapy drugs and interleukin-2 (biochemotherapy). A trial of high-dose interferon as compared with Melacine plus intermediate-dose interferon has completed enrollment, and a preliminary analysis showed no significant difference in efficacy between the two study groups.[75] Studies comparing a nine-week course of intensive biochemotherapy with a year of therapy with high-dose interferon are under way as a joint effort among the various U.S. oncology cooperative groups.

The appropriate adjuvant treatment for patients with intermediate- or high-risk melanoma remains controversial. Since interferon alfa-2b is the only FDA-approved therapy, it is reasonable to inform patients for whom this therapy would be appropriate about its potential risks and benefits and known adverse effects. Patients who are not able to tolerate interferon or who prefer treatments that are less toxic or more aggressive should be encouraged to consider participating in controlled clinical trials. Such studies ideally enroll patients who have undergone adequate staging and whose disease has been stratified accordingly.

Various tumor-specific vaccines have been investigated as potential adjuvant therapy for patients with high-risk melanoma. These vaccines include a GM_2-ganglioside–based vaccine[76]; a shed melanoma-antigen vaccine[77]; a polyvalent whole-cell vaccine, Canvaxin[78]; a dinitrophenyl-conjugated autologous tumor vaccine, M-Vax[79]; and the aforementioned Melacine vaccine.[74] When administered

as adjuvant therapy, many of these vaccines have been reported to produce responses in some patients with advanced disease and to prolong survival significantly in comparison with historical controls.

Given the evolution in the methods for staging melanoma (including high-resolution computed tomography, positron-emission tomography, and sentinel-lymph-node biopsy), contemporary controls are essential to evaluate adjuvant treatments. To date, few large-scale, randomized, controlled trials of vaccine efficacy have been reported. Livingston et al. initially reported a small phase 3 trial comparing a GM_2 ganglioside vaccine administered along with bacille Calmette–Guérin (BCG) with BCG alone in patients with stage III disease.[76] Immunoglobulin M antibodies developed in 80 percent of patients who received the GM_2 vaccine, whereas 10 percent of patients in both groups had antibody present at enrollment. When patients with preexisting antibodies were excluded from the analysis, a significant improvement in recurrence-free survival was observed in patients receiving the GM_2 vaccine. Unfortunately, a modified, more immunogenic version of this vaccine fared poorly when compared with high-dose interferon.[58]

When treatment with Melacine was compared with observation alone in patients with stage II disease, the vaccine did not increase either recurrence-free or overall survival in the treated population as a whole. However, a prospectively defined subgroup of patients with expression of either the HLA-A2 haplotype or the HLA-C3 haplotype, or both, had significantly longer disease-free and overall survival, as compared with patients with other HLA types who received the vaccine and with patients who were followed by observation alone.[80] However, prospective confirmation of this intriguing result is lacking.

Investigators have identified HLA-restricted melanoma antigens recognized by CD8 T cells in patients who have a response to T-cell–derived immunotherapy.[81] These peptide antigens have been cloned and are being tested in patients with stage IV melanoma, either alone or in combination with dendritic cells,[82] anti–cytokine-T-lymphocyte–associated protein 4 (CTLA-4) antibody,[83] or cytokines, such as interleukin-2,[84] interferon, and granulocyte–macrophage colony-stimulating factor (GM-CSF).[85] Many of these promising strategies are also being investigated in the adjuvant setting. Although vaccines are less toxic than some other treatments, their efficacy relative to that of interferon and their ability to synergize with interferon remain to be established.

TREATMENT OF DISTANT DISEASE

For patients with stage IV melanoma, no randomized, controlled trials have shown a significant survival advantage with the use of any specific drug or combination of drugs, including dacarbazine and a high-dose bolus of interleukin-2, both of which have been approved by the FDA for the treatment of stage IV disease (Table 4).[86] Although surgical resection can result in five-year survival rates of up to 25 percent,[87] these results have usually been achieved in highly selected patients with isolated metastases or stage M1a disease. The usual outcome for patients with distant metastases remains bleak, with median survival of 6 to 10 months and less than 5 percent of patients surviving for more than 5 years.[23,88]

High-dose bolus interleukin-2 (600,000 or 720,000 U per kilogram of body weight, administered intravenously three times daily on days 1 to 5 and 15 to 19) received FDA approval in 1998 because the regimen led to durable responses in a meaningful proportion of patients with stage IV disease.[89] Updated information regarding these patients, which was presented to the FDA, confirms the durability of the response in this patient population. Although a tumor response occurred in only 16 percent of patients, the median duration of the response has yet to be reached among those with a complete response, and disease progression has not been noted in any patient with a response lasting for more than 30 months. Unfortunately, high-dose bolus interleukin-2 therapy is associated with many severe toxic effects (including hypotension, the capillary-leak syndrome, myocarditis, transient renal insufficiency, and catheter-related sepsis[90]). These effects have restricted the use of this therapy to highly selected patients being treated by experienced clinicians in specialized programs that are equipped to manage the potential complications.

Efforts to improve on the therapeutic index associated with the administration of interleukin-2 have included altered dose levels and schedules, measures to block the toxic effects of high-dose bolus interleukin-2, and combinations with other cytokines (e.g., interferon alfa and interleukin-12), immune protectors (e.g., histamine), and various vaccines.[84,91-94] Despite a promising preclinical

Table 4. Key Randomized Trials for Stage IV Melanoma.*

Study	Trial Regimen	No. of Patients	Response Rate	Median Survival
			%	*mo*
Costanzi et al.	Carmustine, hydroxyurea, and dacarbazine with or without BCG	256	29	With BCG, 6.7; without BCG, 6
	versus			
	Dacarbazine and BCG	130	18	6.9
Buzaid et al.	Cisplatin, vinblastine, and dacarbazine	46	24	6
	versus			
	Dacarbazine	45	11	5
Chapman et al.	Cisplatin, dacarbazine, carmustine, and tamoxifen	108	18	7
	versus			
	Dacarbazine	118	10	7
Cocconi et al.	Dacarbazine and tamoxifen	60	28†	10.7‡
	versus			
	Dacarbazine	52	12	6.4
Rusthoven et al.	Cisplatin, dacarbazine, carmustine, and tamoxifen	98	30	Men, 6.4; women, 6.9
	versus			
	Cisplatin, dacarbazine, and carmustine	97	21	Men, 6.4; women, 7.1
Falkson et al.	Dacarbazine and interferon alfa	30	53	17.6§
	versus			
	Dacarbazine	30	18	9.6
Falkson et al.	Dacarbazine, interferon alfa with or without tamoxifen	126	16	With tamoxifen, 9.5; without tamoxifen, 9.3
	versus			
	Dacarbazine with or without tamoxifen	129	21	With tamoxifen, 8; without tamoxifen, 10
Keilholz et al.	Interleukin-2 (decrescendo regimen) and interferon alfa	66	18	9
	versus			
	Cisplatin, interleukin-2, and interferon alfa	60	35; overall survival same	9
Rosenberg et al.	Cisplatin, dacarbazine, and tamoxifen	52	27	15.8
	versus			
	Cisplatin, dacarbazine, tamoxifen, high-dose interleukin-2, and interferon alfa	50	44; overall survival worse	10.7
Eton et al.	Cisplatin, vinblastine, and dacarbazine	92	25	9.5
	versus			
	Cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa (sequential)	91	48	11.8
Keilholz et al.	Cisplatin, dacarbazine, and interferon alfa	180	23	9.0
	versus			
	Cisplatin, dacarbazine, interferon alfa, and interleukin-2	183	21	9.0
Atkins et al.	Cisplatin, vinblastine, and dacarbazine	201	11	8.7
	versus			
	Cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa (concurrent)	204	17	8.4

* All study data are taken from Atkins et al.[86] BCG denotes bacille Calmette–Guérin.
† P=0.03.
‡ P=0.02.
§ P<0.01.

rationale and encouraging findings in a few small clinical trials, these approaches have yet to yield activity that is sufficient to justify either FDA approval or routine clinical administration.

Among cytotoxic agents, dacarbazine remains the benchmark, since it produces responses in 15 to 20 percent of patients and the median duration of the response is four months.[54,95] The major side effects of dacarbazine are limited to nausea and vomiting. Response rates and the duration of the

response do not appear to be affected by administration schedules. The availability of potent antiemetic agents has permitted outpatient administration of dacarbazine at a dose of 1 g per square meter of body-surface area in a convenient schedule of one day every three to four weeks. Temozolomide, an analogue of dacarbazine, is characterized by significant central nervous system penetration and can be absorbed orally.[96] Clinical trials have suggested that temozolomide has activity that is equal to that of dacarbazine[97] and may be associated with a lower frequency of central nervous system relapse.[98,99] However, FDA approval has not been forthcoming. Investigations continue into temozolomide used alone in various dosing schedules and in combination with other therapies. For patients with brain metastases, the combination of temozolomide with thalidomide,[100] especially in conjunction with radiation therapy, has generated particular interest; however, data supporting the superiority of these approaches to standard therapy have yet to be produced.

A variety of regimens combining dacarbazine with other cytotoxic agents, tamoxifen, or interferon alfa have shown promising response rates in single-institution phase 2 trials and potential survival advantages in small phase 3 trials.[86] Unfortunately, despite extensive investigation, no randomized, controlled trials have shown these approaches to be superior to dacarbazine alone (Table 4).

Recent attention has focused on combinations of dacarbazine and cisplatin with interleukin-2 and interferon alfa (i.e., biochemotherapy). Phase 2 studies of such regimens have typically shown tumor responses in 40 to 50 percent of patients,[90] and meta-analyses suggest their superiority to regimens involving cytotoxic chemotherapy and immunotherapy alone.[101,102] In addition, a single-institution phase 3 trial showed that as compared with chemotherapy, biochemotherapy resulted in a doubling of the response rate and the time to progression, with a prolongation of median survival that approached significance (from 9.2 to 11.9 months).[103] Unfortunately, several other phase 3 trials, including two recent studies of the Eastern Cooperative Oncology Group[104] and the European Organization for the Research and Treatment of Cancer,[105] showed no survival benefit with biochemotherapy as compared with chemotherapy or immunotherapy alone.[104-107] Consequently, routine use of these more toxic combination approaches can no longer be justified.

FUTURE DIRECTIONS

Ongoing therapeutic investigations focus on vaccine-based immunotherapy and targeted-chemotherapy approaches. Although many melanomas carry distinct tumor-associated antigens that can be recognized by the immune system, recent studies have suggested that most patients become tolerant to these antigens early in the course of their disease.[108] Efforts to overcome immune tolerance include the use of dendritic-cell or heat-shock-protein–based vaccines,[109] concurrent use of immune adjuvants (interleukin-12, cytidine phosphate guanosines, GM-CSF, and anti-CTLA-4 antibody) and gene therapy (intratumoral injection of Allovectin-7 and GM-CSF),[110,111] and adoptive transfer of tumor-specific cytolytic T cells after the use of lymphocyte-depleting chemotherapy to eliminate regulatory T cells.[112] Although these approaches have begun to show encouraging immunologic activity — including vitiligo,[113] enhanced reactivity of tumor-specific T cells in the peripheral blood,[85] and occasional clinical responses[112] — much work is required before they can be used in the majority of patients with stage IV disease.

Recent advances in our understanding of the biologic features of melanoma indicate that many tumors evolve strong defenses against chemotherapy-induced apoptosis, including methylation-mediated silencing of the *APAF-1* gene,[114] sustained expression of Bcl-2, and activating mutations of the *BRAF* gene.[115] Investigations combining chemotherapy with demethylating agents (e.g., 5-aza-2′-deoxycytidine), antisense Bcl-2 oligonucleotides, or RAF inhibitors (e.g., BAY 43-9006) have been initiated, with some encouraging early results.[116,117] It is hoped that this better understanding of the biologic features of melanoma and the mechanisms underlying tumor-induced immune suppression will lead to more precisely targeted treatment approaches and rational treatment selection. Given the promise of these new approaches and the limited value of existing standard therapies, advanced disease is best managed by encouraging participation in clinical trials.

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