Final Version of the American Joint Committee on Cancer Staging System for Cutaneous Melanoma

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Purpose: **To revise the staging system for cutaneous melanoma under the auspices of the American Joint Committee on Cancer (AJCC).**

Materials and Methods: **The prognostic factors analysis described in the companion publication (this issue), as well as evidence from the published literature, was used to assemble the tumor-node-metastasis criteria and stage grouping for the melanoma staging system.**

Results: **Major changes include (1) melanoma thickness and ulceration but not level of invasion to be used in the T category (except for T1 melanomas); (2) the number of metastatic lymph nodes rather than their gross dimensions and the delineation of clinically occult (ie, microscopic) versus clinically apparent (ie, macroscopic) nodal metastases to be used in the N category; (3) the site of distant metastases and the presence of elevated serum lactic dehydrogenase to be used in the M category; (4) an upstaging of all patients with stage I, II, and III disease when a primary melanoma is ulcerated; (5) a merging of satellite metastases around a primary melanoma and in-transit metastases into a single staging entity that is grouped into stage III disease; and (6) a new convention for defining clinical and pathologic staging so as to take into account the staging information gained from intraoperative lymphatic mapping and sentinel node biopsy.**

Conclusion: **This revision will become official with publication of the sixth edition of the *AJCC Cancer Staging Manual* in the year 2002.**

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THE AMERICAN JOINT Committee on Cancer (AJCC) has now formally approved the final version of a revised melanoma staging system, which is described herein, along with operational definitions. The final version is similar to the initial recommendations from the AJCC Melanoma Staging Committee published last year.[1] Subsequent to the published recommendations, a number of clinicians made comments and recommendations to members of the AJCC Melanoma Staging Committee. In addition, a major database analysis of prognostic factors involving 17,600 patients from 13 cancer centers and organizations was performed to validate the original proposal.[2] Results from the prognostics factors analyses, as well as input from melanoma clinicians, were used by the AJCC Melanoma Staging Committee to make final adjustments to the melanoma staging system, changes that largely impacted the stage grouping criteria. The AJCC Executive Committee has approved the final version of the melanoma staging system. It will become official with publication of the sixth edition of the AJCC Cancer Staging Manual in the year 2002.

The AJCC Melanoma Staging Committee used the following guidelines to determine which criteria should be used in the tumor-node-metastasis (TNM) classification and the stage groupings. First, the staging system must be practical, reproducible, and applicable to the diverse needs of all medical disciplines. Second, the criteria must accurately reflect the biology of melanoma based on consistent outcome results of patients treated at multiple institutions from multiple countries. Third, the criteria used must be evidence-based and reflect the dominant prognostic factors consistently identified in Cox multivariate regression analyses. Fourth, the criteria must be relevant to current clinical practice and regularly incorporated in clinical trials. Fifth, the required data must be sufficiently easy for tumor registrars to identify in medical records to code staging information.

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Table 1. Melanoma TNM Classification

T classification	Thickness	Ulceration Status
T1	≤ 1.0 mm	a: without ulceration and level II/III b: with ulceration or level IV/V
T2	1.01-2.0 mm	a: without ulceration b: with ulceration
T3	2.01-4.0 mm	a: without ulceration b: with ulceration
T4	> 4.0 mm	a: without ulceration b: with ulceration

N classification	No. of Metastatic Nodes	Nodal Metastatic Mass
N1	1 node	a: micrometastasis* b: macrometastasis†
N2	2-3 nodes	a: micrometastasis* b: macrometastasis† c: in transit met(s)/satellite(s) without metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic node(s)	

M classification	Site	Serum Lactate Dehydrogenase
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

*Micrometastases are diagnosed after sentinel or elective lymphadenectomy.

†Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

Table 2. Proposed Stage Groupings for Cutaneous Melanoma

	Clinical Staging*			Pathologic Staging†		
	T	N	M	T	N	M
0	Tis	N0	M0	Tis	N0	M0
IA	T1a	N0	M0	T1a	N0	M0
IB	T1b	N0	M0	T1b	N0	M0
	T2a	N0	M0	T2a	N0	M0
IIA	T2b	N0	M0	T2b	N0	M0
	T3a	N0	M0	T3a	N0	M0
IIB	T3b	N0	M0	T3b	N0	M0
	T4a	N0	M0	T4a	N0	M0
IIC	T4b	N0	M0	T4b	N0	M0
III‡	Any T	N1	M0			
		N2				
		N3				
IIIA				T1-4a	N1a	M0
				T1-4a	N2a	M0
IIIB				T1-4b	N1a	M0
				T1-4b	N2a	M0
				T1-4a	N1b	M0
				T1-4a	N2b	M0
				T1-4a/b	N2c	M0
IIIC				T1-4b	N1b	M0
				T1-4b	N2b	M0
				Any T	N3	M0
IV	Any T	Any N	Any M1	Any T	Any N	Any M1

*Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

†Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic stage 0 or stage 1A patients are the exception; they do not require pathologic evaluation of their lymph nodes.

‡There are no stage III subgroups for clinical staging.

The final version of the TNM categories is defined in Table 1, and the final stage groupings are in Table 2. All survival rates are actuarial calculations of melanoma-specific survival. Fifteen-year survival rates for patients with stages I to IV melanoma are shown in Fig 1. A summary of survival rates and the demographics of the melanoma patient database used to validate the staging criteria is listed in Table 3 and described in the companion publication (this issue).[2] These definitions, as recommended by the AJCC Melanoma Staging Committee and approved by both the AJCC Executive Committee and the International Union Against Cancer (UICC) TNM Committee, incorporate substantial revisions from the previous (1997) version of the melanoma staging categories and classifications. In addition, the revised melanoma staging system has been approved by the World Health Organization Melanoma Program as well as the European Organization for Research and Treatment of Cancer Melanoma Group in a recent publication.[3]

The major changes in the new version compared with the previous version of the melanoma staging system are summarized in Table 4. For example, this version retains the anatomic compartmentalization, consistent with staging for other cancers, that categorizes patients with localized melanoma (ie, without any evidence of metastases) to stages I and II, those with regional metastases to stage III, and those with distant metastases to stage IV. In the previous (1997) version, patients with thick melanomas (> 4.0 mm in thickness or T4N0M0) were assigned to stage III, whereas in the new version these patients are grouped in stage II. The new staging system also incorporates pathologic information obtained after lymphatic mapping and sentinel lymphadenectomy that is included in the definitions of clinical and pathologic staging.

STATISTICAL METHODS

Independent prognostic factors were considered by the AJCC Melanoma Committee for defining the TNM catego-

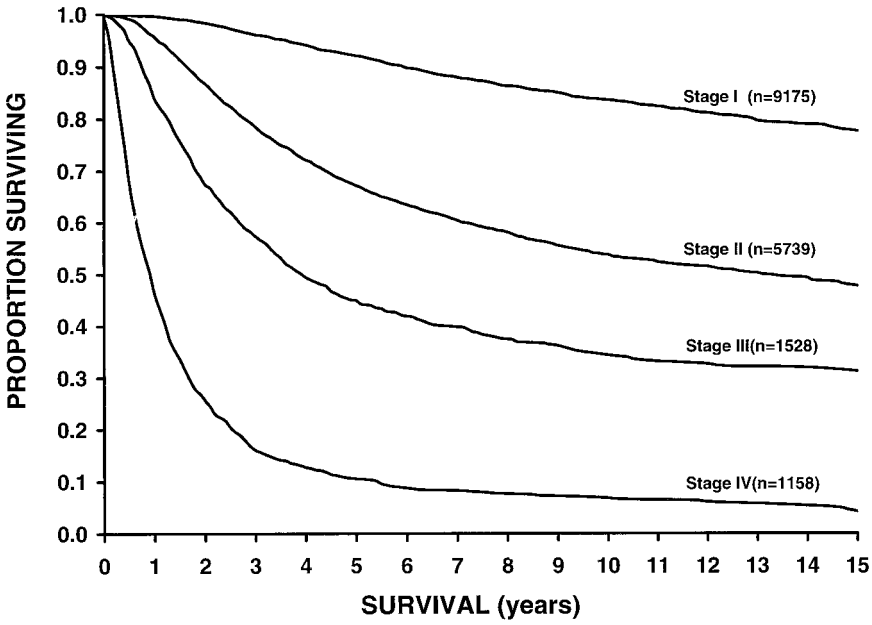

Fig 1. Fifteen-year survival curves comparing localized melanoma (stages II and I), regional metastases (stage III), and distant metastases (stage IV). The numbers in parentheses are patients from the AJCC melanoma staging database used to calculate the survival rates. The differences between the curves are significant ($P < .0001$).

ries and stage grouping based on the results published in literature as well as the prognostic factors analysis described in the companion article (this issue).[2,4] The AJCC Melanoma Database consisted of a total of 30,450 melanoma patients, of which 17,600 patients (58%) had information available for all of the factors required for the proposed TNM classification and stage grouping. Statistical analyses of the AJCC Melanoma Database were based primarily on the methods of survival data analysis. Survival times were calculated from onset of primary melanoma diagnosis and considered censored for patients who were alive at the last follow-up or who died without evidence of melanoma.

Table 3. Survival Rates for Melanoma TNM and Staging Categories

Pathologic Stage	TNM	Thickness (mm)	Ulceration	No. + Nodes	Nodal Size	Distant Metastasis	No. of Patients	Survival ± SE			
								1-Year	2-Year	5-Year	10-Year
IA	T1a	1	No	0	–	–	4,510	99.7 ± 0.1	99.0 ± 0.2	95.3 ± 0.4	87.9 ± 1.0
IB	T1b	1	Yes or level IV, V	0	–	–	1,380	99.8 ± 0.1	98.7 ± 0.3	90.9 ± 1.0	83.1 ± 1.5
	T2a	1.01-2.0	No	0	–	–	3,285	99.5 ± 0.1	97.3 ± 0.3	89.0 ± 0.7	79.2 ± 1.1
IIA	T2b	1.01-2.0	Yes	0	–	–	958	98.2 ± 0.5	92.9 ± 0.9	77.4 ± 1.7	64.4 ± 2.2
	T3a	2.01-4.0	No	0	–	–	1,717	98.7 ± 0.3	94.3 ± 0.6	78.7 ± 1.2	63.8 ± 1.7
IIB	T3b	2.01-4.0	Yes	0	–	–	1,523	95.1 ± 0.6	84.8 ± 1.0	63.0 ± 1.5	50.8 ± 1.7
	T4a	> 4.0	No	0	–	–	563	94.8 ± 1.0	88.6 ± 1.5	67.4 ± 2.4	53.9 ± 3.3
IIC	T4b	> 4.0	Yes	0	–	–	978	89.9 ± 1.0	70.7 ± 1.6	45.1 ± 1.9	32.3 ± 2.1
IIIA	N1a	Any	No	1	Micro	–	252	95.9 ± 1.3	88.0 ± 2.3	69.5 ± 3.7	63.0 ± 4.4
	N2a	Any	No	2-3	Micro	–	130	93.0 ± 2.4	82.7 ± 3.8	63.3 ± 5.6	56.9 ± 6.8
IIIB	N1a	Any	Yes	1	Micro	–	217	93.3 ± 1.8	75.0 ± 3.2	52.8 ± 4.1	37.8 ± 4.8
	N2a	Any	Yes	2-3	Micro	–	111	92.0 ± 2.7	81.0 ± 4.1	49.6 ± 5.7	35.9 ± 7.2
	N1b	Any	No	1	Macro	–	122	88.5 ± 2.9	78.5 ± 3.7	59.0 ± 4.8	47.7 ± 5.8
	N2b	Any	No	2-3	Macro	–	93	76.8 ± 4.4	65.6 ± 5.0	46.3 ± 5.5	39.2 ± 5.8
IIIC	N1b	Any	Yes	1	Macro	–	98	77.9 ± 4.3	54.2 ± 5.2	29.0 ± 5.1	24.4 ± 5.3
	N2b	Any	Yes	2-3	Macro	–	109	74.3 ± 4.3	44.1 ± 4.9	24.0 ± 4.4	15.0 ± 3.9
	N3	Any	Any	4	Micro/macro	–	396	71.0 ± 2.4	49.8 ± 2.7	26.7 ± 2.5	18.4 ± 2.5
IV	M1a	Any	Any	Any	Any	Skin, SQ	179	59.3 ± 3.7	36.7 ± 3.6	18.8 ± 3.0	15.7 ± 2.9
	M1b	Any	Any	Any	Any	Lung	186	57.0 ± 3.7	23.1 ± 3.2	6.7 ± 2.0	2.5 ± 1.5
	M1c	Any	Any	Any	Any	Other Visceral	793	40.6 ± 1.8	23.6 ± 1.5	9.5 ± 1.1	6.0 ± 0.9
Total							17,600				

Table 4. Changes in Melanoma Staging Comparing Previous (1997) and New (2002) Versions

Factor	Old System	New System	Comments
Level of invasion	Primary determinant of T staging	Used only for defining T1 melanomas	Correlation only significant for thin lesions
Thickness	Second prognostic factor of T staging; thresholds of 0.75, 1.50, 4.0 mm	Primary determinant of T staging; thresholds of 1.0, 2.0, 4.0 mm	Correlation of metastatic risk is a continuous variable
Ulceration	Not included	Included as a second determinant of T and N staging category	Signifies a locally advanced lesion; dominant prognostic factor for grouping stage I, II, and III
Satellite metastases	In T category	In N category	Merged with in-transit lesions
Thick melanomas, > 4.0 mm	In stage IIIA	In stage IIC	Stage III defined as regional metastasis
Dimensions of nodal metastases	Primary determinant of N staging	Not used	No evidence of significant prognostic correlation
No. of nodal metastases	Not included	Primary determinant of N staging	Thresholds of 1 *v* 2-3 *v* $\geq$ 4 metastatic nodes
Metastatic tumor burden	Not included	Included as second determinant of N staging	Clinically occult (microscopic) *v* clinically apparent (macroscopic) burden of nodal metastases
Lung metastases	Merged with all other visceral metastases	Separate category as M1b	Has a somewhat better prognosis than other visceral metastases
Clinical *v* pathologic staging	Did not account for sentinel node technology	Sentinel node results incorporated into definition of pathologic staging	Large variability in outcome between clinical and pathologic staging

Melanoma-specific survival curves were generated according to the Kaplan-Meier product-limit method and were compared using the log-rank test. Multivariate analyses of prognostic factors were based on the Cox proportional hazards model. Both 5- and 10-year survival rates are used to compare statistical relationships of prognostic factors. The *P* values represent overall comparisons based on survival curves and not on any particular time point. Five-year survival rates were used in circumstances where the use of pathologically staged nodal status was critical, because these data reflected more of the experience with sentinel node technology when compared with survival data calculated at 10 years, which used pathologic data more often obtained after elective lymphadenectomy at a time when the sentinel node technology was not as widely used. Additional details about the statistical methods used are described in the companion publication.[2]

STAGING FOR LOCALIZED MELANOMA: STAGES I AND II

The primary criteria for the T classification are tumor thickness (measured in millimeters) and the presence or absence of ulceration (determined histopathologically). Ten-year survival rates for each of the T categories in clinically staged patients are shown in Fig 2. Stage groupings for localized melanomas are defined in Table 2. The sole difference in the definitions of clinical versus pathologic stage grouping is whether the regional lymph nodes are staged by clinical/radiologic examination or by pathologic examination (after partial or complete lymphadenectomy). Fifteen-year survival rates for the entire group of clinically localized melanoma patients are shown in Fig 3.

Melanoma Thickness

In the previous (1997) version of the melanoma staging system, the threshold of a T1/T2 melanoma was defined as 0.75 mm, which was empirically recommended by Alexander Breslow, MD, in 1970.[5] Subsequently, many melanoma investigators have used a threshold of $\leq$ 1.0 mm to define a thin or a good-risk melanoma. In the new staging

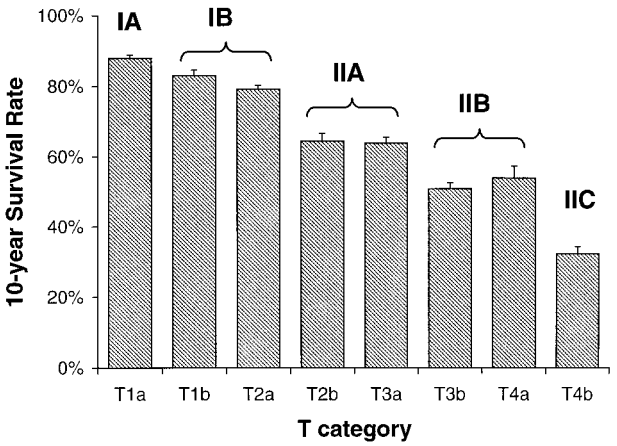

Fig 2. Ten-year survival rates comparing the different T categories and the stage groupings for stages I and II melanoma. Note that the groupings upstage patients with melanoma ulceration with the next level T substage of patients with thicker, nonulcerated melanomas.

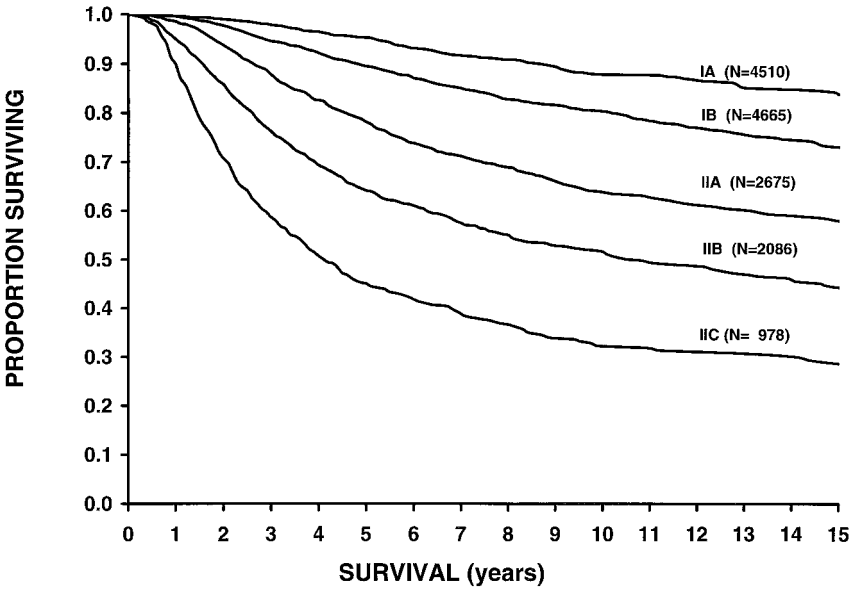

Fig 3. Fifteen-year survival curves for the stage groupings of patients with localized melanoma. See Table 2 for the stage grouping definitions. Numbers of patients from the AJCC melanoma staging database are shown in parentheses. The differences between the survival curves are significant ($P < .0001$)

version, the T-category thresholds of melanoma thickness are defined in even integers (ie, 1.0, 2.0, and 4.0 mm) because they represent both a statistical best fit and are the most compatible with current thresholds in clinical decision making and to classify prognostic groups of node-negative (N0) patients.[6-12]

Because the majority of patients with clinically localized melanoma present with T1 melanomas, a separate statistical analysis was performed to examine different thresholds at 0.1-mm increments of measured thickness between 0.90 mm and 1.1 mm. Because no significant survival differences were observed, a more clinically convenient and widely used threshold of $\leq$ 1.0 mm could appropriately be used for the threshold of T1 melanomas, while T2 melanomas were defined as those measuring 1.01 mm to 2.0 mm in thickness. T3 melanomas are defined as those with a thickness of 2.01 to 4.0 mm and T4 melanomas as those with a thickness of more than 4.0 mm.

Melanoma Ulceration

Melanoma ulceration is defined as the absence of an intact epidermis overlying a major portion of the primary melanoma based on microscopic examination of the histologic sections.[6,7,13,14] It can easily be distinguished from artifactual or traumatic disruption of the epidermis. Traumatically induced defects are associated with hemorrhage, brightly eosinophilic fibrin exudation at the site, and an architectural defect that usually defines the agent leading to the trauma, such as an insect bite or an excoriation. In fact, the interpretation of melanoma ulceration among pathologists is one of the most reproducible of all the major histopathologic features.[15,16] This definition encompasses surface defects from a total absence of the epidermis overlying the tumor to an excavated area including the epidermis and a portion of the tumor. The surface may exhibit scattered debris.

Melanoma ulceration heralds such a high risk for metastases that its presence upstages the prognosis of all such patients, compared with patients who have melanomas of equivalent thickness without ulceration. Thus, survival rates for patients with an ulcerated melanoma are proportionately lower than those of patients with a nonulcerated melanoma of equivalent T category but are remarkably similar to those of patients with a nonulcerated melanoma of the next highest T category (Fig 2, Table 3).

Melanoma Level of Invasion

Our prognostic factors analysis in the companion publication demonstrated that the level of invasion, as defined by Wallace Clark, MD,[17] is an independent predictive feature of thin (T1) melanoma but not for thicker lesions.[2] As a result, the level of invasion is incorporated only into the staging definitions of T1 melanomas. In this cohort, the assignment of T1a is restricted to patients who meet the following three criteria: (1) melanoma $\leq$ 1.0 mm thick, (2) absence of ulceration, and (3) depth of invasion limited to level II or level III. Those melanomas with a thickness $>$ 1.0 mm and with the more aggressive features of level IV or V or with ulceration (regardless of level) are defined as T1b melanomas. About three quarters of

patients with T1 melanomas are T1a and have a 95% 5-year survival rate, while the remaining T1 patients have T1b lesions and experience a somewhat lower 91% 5-year survival rate (Table 3).

Melanoma-in-Situ, Indeterminate Melanomas, and Multiple Primary Melanomas

Patients with melanoma-in-situ are categorized as Tis. Those patients with melanoma presentations that are indeterminate or cannot be microstaged should be categorized as Tx. Two examples of indeterminate staging of melanoma would be a diagnosis with a shave or a curettage biopsy that transected the base of the melanoma or when an unknown primary melanoma presents with regional or distant metastases. When patients present with multiple primary melanomas, the T-category staging is based on the melanoma with the worst prognostic features.

Melanoma Growth Patterns

The data used to derive the TNM categories were largely based on melanomas with superficial spreading and nodular growth patterns. There is some evidence that other growth patterns, namely lentigo maligna melanoma, acral lentiginous melanoma, and desmoplastic melanoma, may have a different etiology and prognosis.[9,18-22] At present, the same staging criteria should be used for melanomas with these growth patterns, even though their prognosis may differ somewhat from the more commonly occurring superficial spreading and nodular growth patterns.

Stage Grouping

Patients with primary melanomas with no evidence of regional or distant metastases (either clinically or pathologically) are divided into the following two stages: stage I for early-stage patients with low risk for metastases and melanoma-specific mortality and stage II for those with intermediate risk for metastases and melanoma-specific mortality. Furthermore, stage I patients constitute the following two subgroups: (1) stage IA are T1 melanomas without ulceration or level IV or V depth of invasion (T1aN0M0 melanomas) and (2) stage IB are either T1 melanomas with histopathologic evidence of level IV/V depth of invasion or ulceration of their surface (T1bN0M0) or those T2 melanomas without ulceration (T2aN0M0). Stage II patients constitute the following three subgroups: (1) stage IIA are T2 melanomas with ulceration (T2bN0M0) or T3 melanomas without ulceration (T3aN0M0), (2) stage IIB are either T3 melanomas with ulceration (T3bN0M0) or T4 melanomas without ulceration (T4aN0M0), and (3) stage IIC are T4 melanomas with ulceration (T4bN0M0). Survival rates for these stage groupings are shown in Figs 2 and 3 and listed in Table 3.

The determination of stage grouping for patients with T4bN0M0 melanomas was a dilemma because they are at a particularly high risk for harboring both regional and distant metastases. These thick, ulcerated melanomas are biologically aggressive and are associated with mortality rates that are the same or even larger than those for some groups of patients with nodal metastases (Tables 3 and 5). Such patients were grouped as stage III in the 1997 version of the melanoma staging system because of commensurate risk for melanoma-specific mortality. The Melanoma Staging Committee concluded that such a categorization would add significant complexity to the new stage groupings. To stay within the conventional anatomic definitions, T4 melanomas were therefore assigned to stage II in the final version. This includes T4b melanomas that would still be grouped with other localized melanomas but designated separately as stage IIC, since these patients are at an especially high risk for clinically occult nodal and systemic metastases. The 10-year survival rate for such clinically staged IIC patients is 32% (Table 3, Fig 2).

Data Recording Criteria for Stages I and II Melanoma

When entering melanoma TNM data into tumor registries for the purposes of stage grouping, the electronic data fields must record the measured tumor thickness (in millimeters), the presence or absence of ulceration (based on histopathologic examination), and the level of invasion to derive stage groupings for localized melanomas. In those circumstances where there has been an incisional (or punch) biopsy, generally the maximum tumor thickness in either the biopsy or definitive excision should be recorded (ie, the measurements should not be added). Other prognostic features of localized melanomas were not incorporated into the new TNM categories. Nevertheless, these are potentially important for other types of data analysis and for stratification of patients in clinical trials and should be recorded in medical records and tumor registries. These features include the patient's age and sex, the anatomic site of the primary melanoma (ie, trunk, extremities, or head and neck), regression (if present), and the growth pattern (superficial spreading, nodular, lentigo maligna melanoma, acral lentiginous melanoma, or desmoplastic melanoma).

STAGING FOR REGIONAL METASTATIC MELANOMA: STAGE III

Stage III melanoma patients include those with regional metastases, either in the regional lymph nodes or intralymphatic metastases manifesting as either satellite or in-transit

metastases. The definitions for clinical and pathologic staging for stage III are more complicated than for the other stages because of the need to accommodate advances in staging for lymph node metastases (Table 2). In response to more precise nodal staging of melanoma patients using the technology of sentinel node biopsy, separate designations must be applied for patients who have clinical/radiologic staging of the regional lymph nodes compared with the more accurate method of pathologic staging using lymphatic mapping and sentinel node lymphadenectomy.

Clinical Staging of Regional Mesastases

Clinical stage III groupings rely on clinical and/or radiologic assessment of the regional lymph nodes. Clinical staging of nodal metastases is inherently difficult, especially with respect to assessing the number of metastatic nodes present. The Melanoma Staging Committee, therefore, made no subgroup definitions of clinically staged patients with nodal or intralymphatic regional metastases. They are all categorized as clinical stage III disease (Table 2)

Pathologic Staging of Regional Mesastases

In contrast to clinical staging of regional metastases, there is greater accuracy (both qualitatively and quantitatively) in finding distinctive prognostic subgroups within pathologic stage III using information from pathologic examination of the regional lymph nodes after lymphadenectomy. The numerical classification for pathologic staging requires that pathologists perform a careful examination of the surgically resected nodal basin and report on the actual number of nodal metastases identified.

These are the following four major determinants of outcome for pathologic stage III melanoma: (1) the number of metastatic lymph nodes, (2) whether the tumor burden is microscopic (ie, clinically occult and detected pathologically by sentinel or elective lymphadenectomy) or macroscopic (ie, clinically apparent by physical or radiologic examination and verified pathologically), (3) the presence or absence of ulceration of the primary melanoma, and (4) the presence or absence of satellite or in-transit metastases.[2,4,9,23-36] The effect of ulceration on survival rates of stage III patients is shown in Fig 4, with additional data described in the companion publication.[2] The stage groupings for stage III melanoma are defined in Table 2 and survival rates for these patients are shown in Fig 5.

Number of Metastatic Nodes

Based on the data analysis in the companion publication concluding that the number of metastatic nodes best correlated with 10-year survival,[2] this factor was used as the primary criterion for defining the N category. Originally, the thresholds for defining N1, N2, and N3 categories were one versus two to four versus ≥ five metastatic nodes based on the literature. However, the pooled data analysis demonstrated that the threshold for the N3 category should be at ≥ four metastatic nodes.[2] Thus, patients with one metastatic node were categorized as N1, those with two to three metastatic nodes as N2, and those with ≥ four metastatic nodes as N3. Survival rates for these N subgroupings, including the impact of melanoma ulceration on survival and stage grouping, are shown in Fig 4.

Micrometastases Versus Macrometastases

The second most significant prognostic feature for patients with nodal metastases is the tumor burden of nodal metastases, so designated operationally but not by actual measurements. Thus, those patients without clinical or radiologic evidence of lymph node metastases but who have pathologically documented nodal metastases are defined by convention as having microscopic or clinically occult nodal metastases. It is recognized that such nodal metastases may vary in dimensions (especially for deep-seated nodes or in obese patients), but such a delineation can be identified in the medical record, based on the preoperative clinical examination and the operative notation about the intent of the lymphadenectomy (ie, whether it is an elective, sentinel, or therapeutic lymphadenectomy). In contrast, melanoma patients with both clinical evidence of nodal metastases and

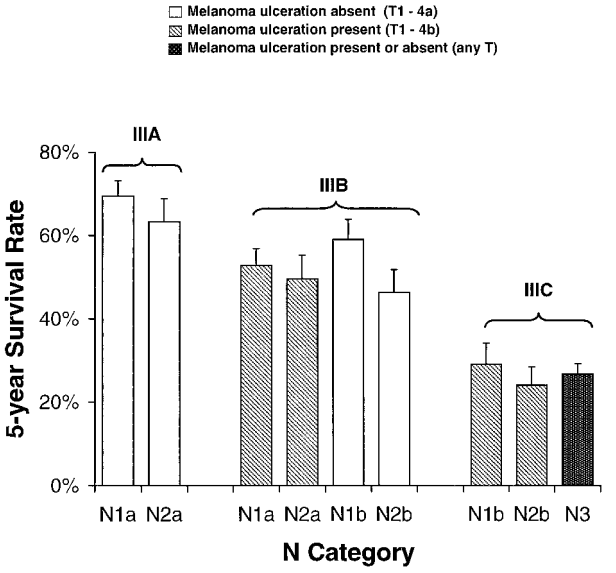

Fig 4. Five-year survival rates from the AJCC melanoma staging database comparing the different N categories and the stage groupings for stage III melanoma. The survival results are significantly different when the primary melanoma is ulcerated compared with equivalent N category of patients without ulceration.

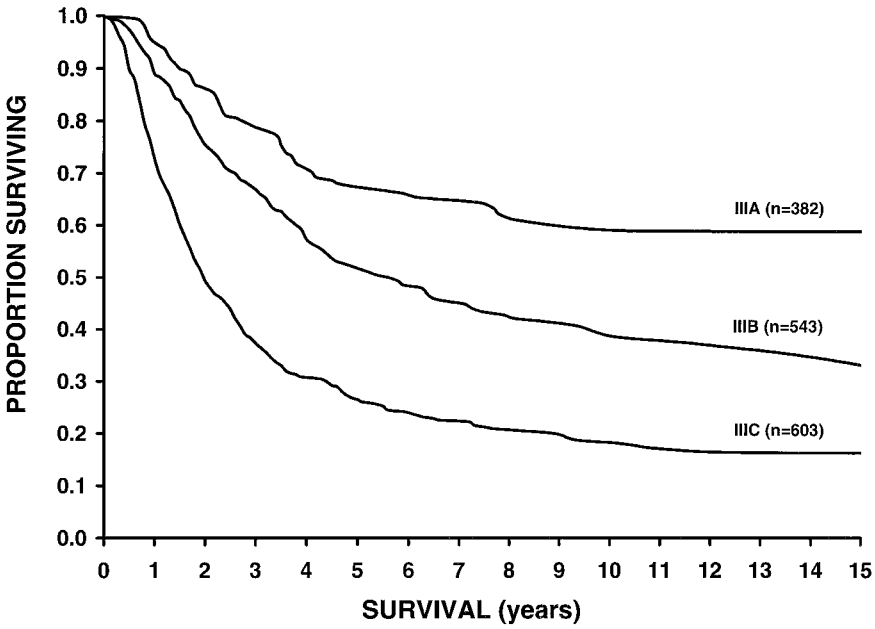

Fig 5. Fifteen-year survival curves for stage groupings of regional metastatic melanoma patients (pathologic stage III). Numbers of patients from the AJCC melanoma staging database are shown in parentheses. The differences between the survival curves are significant ($P < .0001$).

pathologic examination documenting the number of nodal metastases (after therapeutic lymphadenectomy) are defined by convention as having having macroscopic or clinically apparent nodal metastases. Survival rates for these two patient groups are significantly different.[2,37,38]

The previous melanoma staging systems used maximum measured dimensions of nodal metastases ($<$ 5 cm in the 1987 version and $<$ 3 cm in the 1992 and 1997 versions). However, the Melanoma Staging Committee found no compelling evidence in the literature that the measured size of nodal metastases had any independent prognostic value.[4,39]

Primary Melanoma Ulceration

The third most significant prognostic factor in defining pathologic stage III melanoma is the presence or absence of melanoma ulceration.[2] Based on the analysis described in the companion publication and in the literature, the presence or absence of ulceration is the only prognostic feature of a primary melanoma that independently predicts outcome in stages I and II as well as in stage III melanoma.[2,4,23,33] The AJCC Melanoma Staging Committee accounted for this by upstaging all pathologic stage III patients by one substage when the primary melanoma was ulcerated. The survival correlation was remarkable when the stage subgroupings were analyzed using these definitions (Fig 4, Table 5).

Intralymphatic Metastases

The fourth criterion for defining pathologic stage III melanoma is the presence or absence of satellites or in-transit metastases, regardless of the number of lesions. The presence of clinical or microscopic satellite metastases around a primary melanoma as well as in-transit metastases between the primary melanoma and the regional lymph nodes represent intralymphatic metastases and portend a poor prognosis.[4,40-43] The available data show no substantial difference in survival outcome for these two anatomically defined entities.[4] Therefore, they are both assigned to a separate N2c classification in the absence of synchronous nodal metastases because both have a prognosis equivalent to multiple nodal metastases (Tables 2 and 3). Furthermore, the available data demonstrate that patients with a combination of satellites and in-transit metastases plus nodal metastases have a worse outcome than patients who experience either event alone, so these patients were assigned to a N3 classification regardless of the number of synchronous metastatic nodes (Tables 2 and 3).[4]

Table 5. Five-Year Survival Rates (%) of Pathologically Staged Patients Showing Upstaging Effect of Melanoma Ulceration

	IA	IB	IIA	IIB	IIC	IIIA	IIIB	IIIC
Nonulcerated melanoma	T1 95	T2 89	T3 79	T4 67		N1a N2a 67	N1b N2b 54	N3 28
Ulcerated melanoma		T1 91	T2 77	T3 63	T4 45		N1a N2a 52	N1bN2b N3 24

Stage Groupings for Pathologic Stage III Melanoma

After these prognostic features in pathologic stage III melanoma are accounted for, there are the following three definable subgroups with statistically significant differences in survival: stages IIIA, IIIB, and IIIC (Fig 5, Table 3). Patients with pathologic stage IIIA are confined to those who have one to three microscopic lymph node metastases (detected by sentinel or elective lymphadenectomy), and whose primary melanoma is not ulcerated (T1-4aN1aM0 or T1-4aN2aM0). The 5- and 10-year survival rates for such patients are 67% and 60%, respectively (Fig 4, Table 5). With respect to pathologic stages IIIB and IIIC, the final version of the melanoma staging criteria varies slightly from that originally proposed.[1] In the prior proposal for stage grouping, all patients with pathologic evidence of lymph node metastases and an ulcerated melanoma would have been upstaged to N3 regardless of the number of metastatic nodes or the tumor burden, on the basis of the published literature at that time.[1] However, the actual data analysis demonstrated that patients with one to three macroscopic lymph node metastases and a nonulcerated primary melanoma (ie, T1-4aN1bM0 or T1-4aN2bM0) had approximately the same prognosis as those with one to three microscopic lymph node metastases and an ulcerated primary melanoma (T1-4bN1bM0 or T1-4bN2aM0) (Fig 4, Table 5).[2] In the final version, such patients are now grouped as pathologic stage IIIB melanoma, along with N2c patients (intralymphatic metastases without nodal metastases). The estimated 5-year survival rate for stage IIIB patients is 53% (Figs 4 and 5, Table 5). Patients grouped as stage IIIC melanoma are defined as those with a one to three macroscopic lymph node metastases and an ulcerated primary melanoma (T1-4bN1bM0 or T1-4bN2bM0) or any patient with N3 disease regardless of T status or whether the nodal metastases are microscopic or macroscopic (Table 2). The estimated 5-year survival rate for pathologic stage IIIC patients is significantly lower at 26% (Table 5, Figs 4 and 5).

In summary, the stage grouping for pathologic stage III melanoma uses these four criteria to assign patients with regional metastases into one of three groups designated as stage IIIA, IIIB, or IIIC. Pathologic stage IIIA patients have three or fewer microscopic (clinically occult) nodal metastases and a nonulcerated melanoma (T1-4aN1aM0 and T1-4aN2aM0) identified after sentinel or elective lymphadenectomy (Table 2). Pathologic stage IIIB patients comprise the following three subgroups with equivalent survival rates: (1) those with three or fewer microscopic (clinically occult) nodes and an ulcerated primary melanoma (T1-4bN1aM0 and T1-4bN2aM0), (2) those with three or fewer macroscopic metastatic nodes and a nonulcerated primary (T1-4aN1bM0 and T1-4aN2bM0), or (3) those with satellite or in-transit metastases but no evidence of nodal or distant metastases (T1-4a/bN2cM0) (Table 2). Pathologic stage IIIC patients comprise the following three subgroups: (1) those with $\geq$ four metastatic nodes or matted nodes regardless of tumor burden or ulceration status (T1-4N3M0), (2) those with one to three macroscopic nodes and an ulcerated primary (T1-4bN1bM0, T1-4bN2bM0), or (3) any patient with any combination of satellites or in-transit metastases and nodal metastases.

Clinical Versus Pathologic Nodal Staging

Historically, the distinction between clinical staging and pathologic staging has not been emphasized because the definitions did not delineate any specific prognostic groups. With the widespread use of sentinel node lymphadenectomy, the range of survival rates among various subgroups of pathologic stage III patients is enormous (ranging from 13% to 69% 5-year survival rates and 9% to 63% 10-year survival rates) because of upstaging based on a direct examination of the sentinel lymph nodes by histopathologic examination.[2]

Our own prognostic factors analysis and those from many other institutions have consistently demonstrated that the nodal status is a significant prognostic feature of melanoma.[2,30,32-34] Thus, significant differences were identified using the survival rates for melanoma patients who were first clinically staged as having no evidence of nodal metastases and who were subsequently staged pathologically after either sentinel or elective node dissection (Table 6). These survival differences were statistically significant among all T substages except for T4b (Table 6). The differences were most striking in patients with clinical T2aN0M0, T2bN0M0, T3aN0M0, T3bN0M0, and T4aN0M0 disease, where 5-year survival rates for the clinically node-negative patients when staged based on their pathologic nodal status varied significantly, with diminished survival rates ranging from 14% to 30% among clinically versus pathologically staged patients of equivalent T categories (Table 6). These results highlight the compelling prognostic value of knowing the nodal status as identified by lymphatic mapping and sentinel lymphadenectomy in those situations where accurate staging is important.

Contiguous or Multiple Nodal Basins and Staging

By convention, regional nodal metastases refer to disease confined to one nodal basin or two contiguous nodal basins, such as patients with nodal disease in combinations of femoral/iliac, axillary/supraclavicular, cervical/supraclavicular, axillary/femoral or bilateral axillary, or femoral me-

Table 6. Five-Year Survival Rates for 5,346 Patients With Clinically Negative Nodal Metastases Who Were Pathologically Staged After Either RND or SLN

T Stage	Pathologic Nodal Status	No. of Patients	5-Year Survival, % ± SE	P*
T1a	N−	379	94 ± 2.0	.0035
	N+	15	64 ± 17.7	
T1b	N−	319	90 ± 2.5	.0039
	N+	18	76 ± 14.9	
T2a	N−	1,480	94 ± 0.8	< .0001
	N+	150	73 ± 5.6	
T2b	N−	408	83 ± 2.3	< .0001
	N+	62	56 ± 8.8	
T3a	N−	808	86 ± 1.6	< .0001
	N+	177	59 ± 6.0	
T3b	N−	639	72 ± 2.1	< .0001
	N+	176	49 ± 4.5	
T4a	N−	203	75 ± 3.9	.0116
	N+	66	61 ± 7.4	
T4b	N−	330	53 ± 3.1	.2403
	N+	116	44 ± 5.5	

Abbreviations: RND, regional lymph node dissection; SLN, sentinel lymphadenectomy.

*P value based on the comparison of survival curves using the log rank test.

tastases. All such patients would be categorized as having stage III melanoma.

Data Recording Criteria for Stage III Melanoma

Electronic data fields for melanoma should incorporate all the information listed above for the primary melanoma. In addition, they should incorporate the number of metastatic lymph nodes identified by the pathologist (out of a total number of lymph nodes examined), the presence or absence of intralymphatic metastases (satellites or in-transits), and the intent of the surgical procedure that led to the detection of the nodal metastases (ie, a therapeutic lymphadenectomy for clinically detectable metastatic lymph nodes or either a sentinel or elective lymphadenectomy that detected clinically occult metastases). The former would define macroscopic nodal disease while the latter would define microscopic nodal disease. It is acknowledged that these terms are operational definitions simply used for communicating a level of tumor burden and are not intended to be used as a more strict definition of microscopic disease that cannot be observed without a microscope. It is not necessary to measure the dimensions of the nodal metastases for the purposes of staging. Nevertheless, the extent of tumor involvement in a sentinel lymph node should be noted (and measured where possible) to examine whether future subgroups should account for this, which has been suggested by some investigators.[44]

With the availability of immunohistochemical staining, it is now possible to detect nodal metastases at a level of less than 0.1 mm in tumors or even aggregates of a few cells.[45] The reverse transcriptase polymerase chain reaction technique may even be able to detect metastases not identified by the light microscope.[46-48] Such sophisticated detection procedures may be incorporated into future staging criteria but are not sufficiently available or standardized to warrant their inclusion at this time. Immunohistochemical staining does help direct pathologists to suspicious areas and does help distinguish melanoma cells from other cell types in a lymph node. Nevertheless, for the purposes of staging for nodal metastases, there must be histopathologic confirmation using standard hematoxylin and eosin staining.

STAGING FOR DISTANT METASTATIC MELANOMA: STAGE IV

In patients with distant metastases, the site(s) of metastases and elevated serum levels of lactic dehydrogenase (LDH) are used to delineate the M categories into three groups: M1a, M1b, and M1c, with 1-year survival rates ranging from 41% to 59% (Fig 6). Because the survival differences between the M categories are small, there are no subgroups of stage IV melanoma.

Site(s) of Distant Metastases

Patients with distant metastasis in the skin, subcutaneous tissue or distant lymph nodes are categorized as M1a; they have a relatively better prognosis compared with those patients with metastases located in any other anatomic

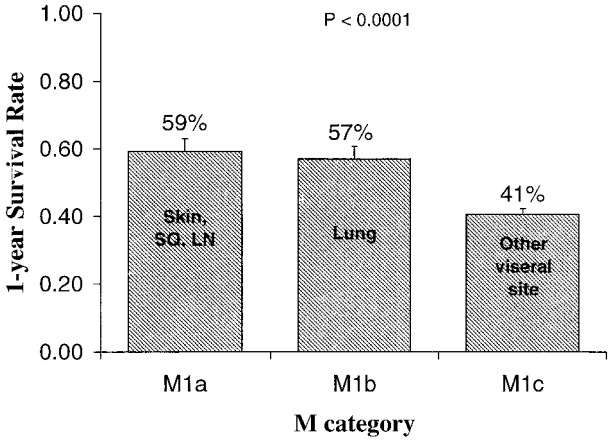

Fig 6. One-year survival rates from the AJCC melanoma staging database comparing the different M categories. There is a significant difference comparing skin, subcutaneous, and lung metastases to all other sites (P < .0001).

site.[2,9,23,49-51] Patients with metastasis to the lung are categorized as M1b and have an intermediate prognosis when 1-year survival rates are compared. Those patients with metastases to any other visceral sites have a relatively worse prognosis and are designated as M1c.

Elevated Serum LDH

Although it is uncommon in staging classifications to include serum factors, an exception was made for elevated levels of serum LDH. This factor was among the most predictive independent factors of diminished survival in all published studies when it was analyzed in a multivariate analysis, even after accounting for site and number of metastases.[52-56] Therefore, when the serum LDH is elevated above the upper limits of normal at the time of staging, such patients with distant metastases are assigned to M1c regardless of the site of their distant metastases. The use of an elevated serum LDH should be used only when there are two or more determinations obtained more than 24 hours apart because an elevated serum LDH on a single determination can be falsely positive due to hemolysis or other factors unrelated to melanoma metastases.

Number of Metastases

The number of metastases at distant sites has previously been documented as an important prognostic factor.[9,23,50,51] However, this feature was not incorporated into this version of the staging system as a result of the significant variability in the deployment of diagnostic tests to comprehensively search for distant metastases. These may range from a chest x-ray in some centers to positron emission tomography scanning in others. Until the indications and types of tests used are better standardized, the number of metastases cannot reliably be used for staging purposes.

Data Recording Criteria for Stage IV Melanoma

Electronic fields for patients with stage IV melanoma should include all the information listed above for the primary melanoma and regional metastases, plus the site(s) of distant metastases as well as the serum LDH level (normal *v* abnormal). Additional data to be considered include the number of distant metastases, and the patient's age, sex, and performance status.

DISCUSSION

Over the past 3 years, the AJCC Melanoma Staging Committee held a series of meetings to revise the melanoma staging system. They used an evidence-based methodology to create the TNM criteria and stage groupings, based on their own data and information published in the medical literature. The membership of the Committee included a representative of the UICC TNM Committee and comments were solicited from other UICC, World Health Organization Melanoma Program, and European Organization for Research and Treatment of Cancer representatives.

The proposed melanoma staging system was published in 2000.[1] Some changes to the original proposal were made, based on the prognostic factors analysis. These included (1) adding level of invasion to define T1a and T1b categories, and (2) incorporating primary melanoma ulceration into the stage grouping criteria for stages IIIB and IIIC instead of moving all patients with nodal metastases and an ulcerated primary melanoma into stage IIIC, and (3) eliminating all subgroups of clinical stage III.

A highly significant and underreported feature of melanoma is the presence or absence of ulceration overlying the primary melanoma. An ulcerated melanoma (as defined histopathologically) is associated with such aggressive metastatic behavior that such lesions should be considered in the same category as a poorly differentiated or locally advanced cancer.[6,7,13,14,33,36,37,57-68] The term ulceration is a descriptive term for this biologic event, in which the melanoma tumor invades through the overlying epidermis rather than pushing it upward, manifesting as an absent epidermis overlying the tumor (Fig 7). Such an event can clearly be distinguished from traumatic or artifactual events leading to a partial absence of the overlying epidermis. In most instances, an ulcerated melanoma does not have an ulcer crater[13] (Fig 7). The results demonstrated, once again, a significant impact of melanoma ulceration that had to be accounted for in the stage groupings because ulceration negatively impacted survival rates in stages I, II, and III disease compared with nonulcerated melanomas. This was true for every

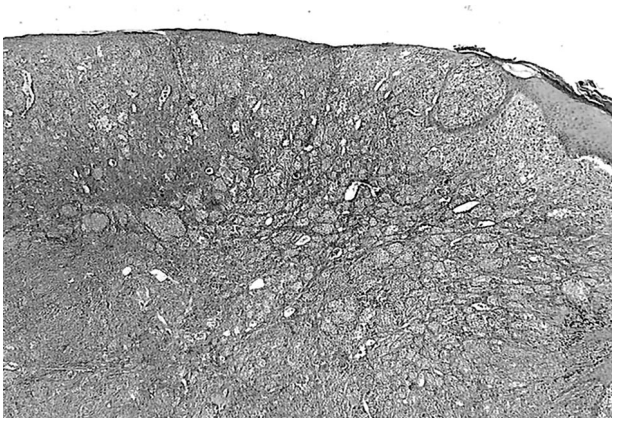

Fig 7. Photomicrograph of a typical ulcerated melanoma. The epidermis above the primary melanoma is absent, with a tapering of the epidermis at the periphery of the lesion.

combination of prognostic factors used to assemble various substages.

The technologic advance of lymphatic mapping and sentinel lymphadenotomy was incorporated into this staging system through the definitions of clinical and pathologic staging. The ability to stage patients more accurately with sentinel node technology has changed our understanding of the natural history of melanoma.[69-74] The information obtained from examining the sentinel node has had an important impact on the staging of the disease, treatment planning, and the conduct of clinical trials in melanoma patients.[33,34,45,64,68,75-79] This powerful new staging technology caused a significant stage migration that is now accounted for in this version of melanoma staging. The marked diversity in the natural history of stage III melanoma is demonstrated by fivefold differences in 5-year survival rates for defined substages that ranged from 69% for patients with a nonulcerated melanoma (regardless of thickness) who had a single clinically occult nodal metastasis (detected by sentinel or elective lymphadenectomy) to 13% for patients with an ulcerated melanoma (regardless of thickness) with four or more clinically apparent nodal metastases (detected by therapeutic lymphadenectomy).[2] The importance of having pathologic information was demonstrated by the 14% to 30% differences in 5-year survival rates for patients with clinically node-negative lymph nodes when staged based on their pathologic nodal status (Table 6). These differences were so great that the AJCC Melanoma Committee strongly recommended that all patients with clinical T2N0M0, T3N0M0, and T4N0M0 melanomas have pathologic nodal staging with sentinel lymphadenectomy before entry onto melanoma clinical trials.

Finally, the prognostic factors used to validate the melanoma staging system should be the primary stratification criteria and end-results reporting criteria of melanoma clinical trials. The AJCC Melanoma Committee recommends that all melanoma patients with clinically negative regional lymph nodes and who may be considered for later entry onto surgical and adjuvant therapy clinical trials should have pathologic staging with sentinel lymphadenectomy to ensure prognostic homogeneity within assigned treatment groups. In this way, investigators will be better able to discern between the impact of natural history and treatment when interpreting results of melanoma clinical trials. Moreover, the use of a consistent set of criteria will facilitate the comparability of melanoma clinical trials and thereby accelerate the progress of multidisciplinary melanoma treatment approaches.

It is evident that the next phase of staging melanoma will evolve as new technology allows the clinician to reliably diagnose metastatic melanoma at a level of tumor burden better than that achievable with the light microscope or routine x-rays. These include molecular diagnostic approaches, such as reverse transcriptase polymerase chain reaction, to detect relevant gene expression, positron emission tomography scanning, use of antimelanoma antibodies, and serum markers of tumor-related DNA and RNA species that will more accurately detect and stage metastatic melanoma.[46-48,52,80-83] Some of these advances will no doubt be incorporated into subsequent revisions of the melanoma staging system.

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