ABSTRACT  A completely revised staging system for cutaneous melanoma was implemented in 2003. The changes were validated with a prognostic factors analysis involving 17,600 melanoma patients from prospective databases. This major collaborative study of predicting melanoma outcome was conducted specifically for this project, and the results were used to finalize the criteria for this evidence-based staging system. In fact, this was the largest prognostic factors analysis of prospectively followed melanoma patients ever conducted. Important results that shaped the staging criteria involved both the tumor-node-metastasis (TNM) criteria and stage grouping for all four stages of melanoma. Major changes in the staging include: (1) melanoma thickness and ulceration are the dominant predictors of survival in patients with localized melanoma (Stages I and II); deeper level of invasion (ie, IV and V) was independently associated with reduced survival only in patients with thin or T1 melanomas. (2) The number of metastatic lymph nodes and the tumor burden were the most dominant predictors of survival in patients with Stage III melanoma; patients with metastatic nodes detected by palpation had a shorter survival compared with patients whose nodal metastases were first detected by sentinel node excision of clinically occult or “microscopic” metastases. (3) The site of distant metastases (nonvisceral versus lung versus all other visceral metastatic sites) and the presence of elevated serum lactate dehydrogenase (LDH) were the dominant predictors of outcome in patients with Stage IV or distant metastases. (4) An upstaging was implemented for all patients with Stage I, II, and III disease when a primary melanoma is ulcerated by histopathological criteria. (5) Satellite metastases around a primary melanoma and in-transit metastases were merged into a single staging entity that is grouped into Stage III disease. (6) A new convention was implemented for defining clinical and pathological staging so as to take into account the new staging information gained from lymphatic mapping and sentinel node biopsy. (CA Cancer J Clin 2004;54:131–149.) © American Cancer Society, 2004.

INTRODUCTION

It is estimated that 55,100 cases of invasive melanoma will be diagnosed in the United States in 2004 (4% of all cancer cases) and that 7,910 patients will die of the disease (1% to 2% of all cancer deaths). Melanoma is estimated to be the fifth and seventh most common cancers in men and women, respectively, among new cases of cancer in

1Three meetings held by the AJCC Melanoma Staging Committee were partially supported by an unrestricted educational grant from Schering Pharmaceutical, Kenilworth, NJ.
The staging system of melanoma, as with other cancers, is important to clinicians and researchers because it provides: (1) a nomenclature of consistent terms and definitions based on prognosis; (2) compartmentalization of patients into definable risk groups with regard to metastatic risk and survival rates; (3) criteria for stratification and reporting results of melanoma clinical trials; (4) a critical component for comparisons of treatment results among different centers; and (5) a valuable tool for clinical decision making.

The Melanoma Staging Committee of the AJCC was formed in 1998 with experts from all relevant medical specialties, including the leadership of most of the major melanoma centers and cooperative groups from North America, Europe, and Australia, and it convened in March 1999. Members of the Melanoma Staging Committee and additional consultants agreed to an unprecedented collaboration to share prospectively accumulated melanoma outcome data, and at that time they established the AJCC Melanoma Staging Database. This is a single large database involving melanoma patients from 13 cancer centers and cooperative groups created for the purpose of validating the proposed revisions to the melanoma staging system. The data were merged from prospective databases of patients who did not receive any adjuvant systemic therapy and for whom all had quality control measures in place regarding data entry, pathology, and surgery. Details about the data collection, statistical methodologies, and results have been published. The resultant collaborative research project is the largest prognostic factors analysis of melanoma ever conducted. Results from the prognostic factors analyses, as well as input from melanoma clinicians, were used by the AJCC Melanoma Staging Committee to create an evidence-based melanoma staging system that was published in 2001. This staging system became official with publication of the sixth edition of the AJCC Cancer Staging Manual. In addition, these melanoma staging criteria have been approved and adopted by the International Union Against Cancer/Union Internationale Contre le Cancer (IUAC/UICC) TNM Committee, by the World Health Organization Melanoma Program, and by the European Organization for Research and Treatment of Cancer Melanoma Group.

This educational article draws substantially from the original scientific publications on the melanoma staging and prognostic factors analysis as well as from the melanoma staging chapter in the sixth edition of the AJCC Cancer Staging Manual. The staging criteria developed in this AJCC prognostic factors analysis have been independently confirmed by results from melanoma referral centers.

Selection by the AJCC Melanoma Staging Committee of independent prognostic features of melanoma to be used in the revised melanoma tumor-node-metastasis (TNM) classification and the stage groupings was guided by five principles:

1. The staging system must be reproducible and applicable to the practical needs of diverse medical disciplines.
2. The criteria must reflect the biology of melanoma based on consistent outcomes of patients treated at multiple institutions from multiple countries.
3. The criteria used must be evidence-based and reflect the dominant prognostic factors.
consistently identified in Cox multivariate regression analyses.

4. The criteria must be relevant to current clinical practice and regularly incorporated in clinical trials.

5. The required data in medical records must be easily identifiable by tumor registrars who code staging information.

The 2003 versions of the TNM categories and stage groupings are defined in Tables 1 and 2, respectively. Figure 1 shows 15-year survival rates for patients with Stage I to IV melanoma. The major differences between the new (2003) and the previous (1997) versions of the melanoma staging system are summarized in Table 3. For example, the 2003 version retains the anatomic compartmentalization 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. The 1997 version assigned patients with thick melanomas (>4.0 mm in thickness or T4NOMO) to Stage III, whereas in the new version these patients are grouped to Stage II.

**RULES FOR CLASSIFICATION**

The primary difference in the definitions of clinical versus pathological stage grouping is whether the regional lymph nodes are staged by clinical/radiologic examination or by pathologic examination (after partial or complete lymphadenectomy).

**Clinical Staging**

Clinical Stages I and II are confined to those patients who have no evidence of metastases, either at regional or distant sites, based on clinical, radiologic, and/or laboratory evaluation. Stage III melanoma patients are those with clinical or radiologic evidence of regional metastases, either in the regional lymph nodes or intralymphatic metastases manifesting as either satellite or in-transit metastases. Clinical Stage III groupings rely on clinical and/or radiologic assessment of the regional lymph nodes, which is inherently difficult, especially with respect to assessing both the presence and the number of metastatic nodes. The Melanoma Staging Committee therefore made no subgroup definitions of clinically staged patients with nodal or intralymphatic regional metastases. They are all categorized within the group of clinical Stage III disease (Table 2). Clinical Stage IV melanoma patients have metastases at some distant site and are not substaged.

**Pathological Staging**

In contrast to clinical staging, there is greater accuracy (both qualitatively and quantitatively) in defining distinctive prognostic subgroups when combining pathological information about both the primary melanoma and the results of pathological examination of the regional lymph nodes after sentinel or complete lymphadenectomy.

Pathological Stages I and II melanoma comprise those patients who have no evidence of regional or distant metastases, based on absence of nodal metastases after careful pathological examination of the regional lymph nodes, and absence of distant metastases based on routine clinical and radiologic examination. Pathological Stage III melanoma patients have pathological evidence of regional metastases, either in the regional lymph nodes or intralymphatic sites. The quantitative classification for pathological nodal status requires that pathologists perform a careful examination of the surgically resected nodal basin and report on the actual number of lymph nodes examined and the number of nodal metastases identified. Pathological Stage IV melanoma patients have histologic documentation of metastases at one or more distant sites.

The ability to stage melanoma patients more accurately with sentinel node technology has markedly changed our understanding of the natural history of melanoma. This powerful new staging technology has caused a significant stage migration that is now accounted for in this version of melanoma staging. With the widespread use of sentinel node lymphadenectomy, it is clear that there is considerable stage
migration of patients previously staged as "node negative," but who, in fact, had undetected nodal metastases. These previously understaged Stage III patients have revealed an extraordinary heterogeneity of metastatic risk for Stage III melanoma. Thus, the range of survival rates among various subgroups of pathological Stage III patients is quite large, ranging from 9% to 63% 10-year survival.2

Clinical Versus Pathological Staging

The AJCC Melanoma Staging Committee addressed the issue of staging information after sentinel lymphadenectomy or elective lymph node dissection through the definition of clinical and pathological staging. By convention, clinical staging should be performed after complete excision of the primary melanoma (including microstaging) with clinical assessment of regional lymph nodes. Pathological staging will use information gained from both microstaging of the primary melanoma and pathological evaluation of the nodal status after partial (ie, sentinel) or complete lymphadenectomy (ie, after elective or therapeutic lymph node dissection).

Significant differences were identified when survival rates for melanoma patients who were clinically staged were compared with those patients whose nodal disease was staged pathologically (Table 4). These survival differences between clinically and pathologically staged pa-
Primary tumors are classified according to the categories below:

- **Tx**: Primary tumor cannot be assessed (eg, shave biopsy or regressed melanoma).
- **T0**: No evidence of primary tumor.
- **Tis**: Melanoma in situ.
- **T1**: Melanomas ≤1.0 mm in thickness.
- **T2**: Melanomas 1.01 to 2.0 mm.
- **T3**: Melanomas 2.01 to 4.0 mm.
- **T4**: Melanomas >4.0 mm.

Ten-year survival rates for each of the T categories in clinically staged patients are shown in Figure 2.

### Melanoma Thickness

The T category of melanoma is classified primarily by measuring the thickness of the melanoma. In the 1997 version of the melanoma staging system, the threshold of a T1/T2 melanoma was defined as 0.75 mm, as empirically recommended by Dr. Alexander Breslow in 1970.13,14 The 2003 version defines the T category thresholds of melanoma thickness in even integers (ie, at 1.0, 2.0, and 4.0 mm), because they represent both a statistical “best fit” and are most compatible with current thresholds in making clinical decisions and classifying prognostic groups of node-negative (N0) melanoma patients.

### Melanoma Ulceration

The secondary criterion for T staging is the presence or absence of ulceration above the primary melanoma based on a histopathological examination. Melanoma ulceration is defined histologically as the absence of an intact epidermis.
overlying a significant portion of the primary lesion.\textsuperscript{2,15,16} Survival rates for patients with an ulcerated melanoma are 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 (Figure 2 and Table 5).

Melanoma Level of Invasion

A third criterion, the level of invasion (with regard to the papillary dermis, reticular dermis, and subcutis) as defined by Dr. Wallace Clark,\textsuperscript{17} is used when defining subcategories of T1 melanomas but not for thicker melanomas (ie, T2, T3, or T4). The level of invasion does not reflect prognosis as accurately as tumor thickness for reasons that have been discussed in previous publications.\textsuperscript{3,15,18,19} Nevertheless, level of invasion does provide additional prognostic discrimination in the specific subgroup of thin (ie, T1; \( \leq 1.0 \text{ mm} \)) melanomas.\textsuperscript{2,20,21}

DEFINING T1 MELANOMAS

In this cohort of T1 melanomas, the assignment of T1a is restricted to patients satisfying three criteria: (1) \( \leq 1.0 \text{ mm} \) thick; (2) absence of ulceration; and (3) depth of invasion limited to level II or III. T1b melanomas are defined as those with a thickness of \( \leq 1.0 \text{ mm} \) and with the more aggressive features of level IV or V, or those with ulceration (regardless of level). Both conditions are associated with a significant reduction in survival rates in patients with T1 melanomas.\textsuperscript{20,22–24} About three fourths of patients with T1 melanomas are T1a and have a 95% five-year survival, while the remaining T1 patients have T1b lesions and experience a somewhat lower 91% five-year survival (Figure 2 and Table 5).
### TABLE 3  Differences Between the Previous Version (1997) and the Present Version (2002) of the Melanoma Staging System

| Factor                        | Previous Version                                                                 | Present Version                                                                 | Comments                                                                 |
|-------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Thickness                     | Secondary prognostic factor; 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                  |
| Level of invasion             | Primary determinant of T staging                                                | Used only for defining T1 melanomas                                             | Correlation only significant for thin lesions; variability in interpretation |
| Ulceration                    | Not included                                                                     | Included as a second determinant of T and N staging                            | 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)    | Stage III                                                                        | Stage IIC                                                                         |                                                                           |
| Dimensions of nodal metastases| Dominant determinant of N staging                                               | Not used                                                                         | No evidence of significant prognostic correlation                         |
| Number of nodal metastases    | Not included                                                                      | Dominant determinant of N staging                                               | Thresholds of 1 versus 2 to 3 versus >4 nodes                           |
| Metastatic “volume”*          | Not included                                                                      | Included as a second determinant of N staging                                   | Clinically occult (microscopic) versus clinically apparent (macroscopic) nodal volume |
| Lung metastases               | Merged with all other visceral metastases                                        | Separate category as M1b                                                        | Has a somewhat better prognosis than other visceral metastases           |
| Elevated serum LDH*           | Not included                                                                      | Included as a second determinant of M staging                                   | Included as a second determinant of M staging                             |
| Clinical versus 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; pathologic staging encouraged prior to clinical trials |

*LDH = Lactate dehydrogenase.

### TABLE 4  Five- and 10-year Survival Rates for 5,346 Patients with Clinically Negative Nodal Metastases Receiving Regional Lymph Node Dissection or Sentinel Lymphadenectomy

| T Stage | Path Nodes (N) | Five-year Survival % ± SE* | 10-year Survival % ± SE* | P Value |
|---------|----------------|----------------------------|--------------------------|---------|
| T1a     | N – (n = 379)  | 94 ± 2.0                   | 86 ± 4.0                 | 0.0035  |
|         | N + (n = 15)   | 64 ± 17.7                  | 64 ± 17.7                |         |
|         | N – (n = 319)  | 90 ± 2.6                   | 84 ± 3.5                 |         |
|         | N + (n = 18)   | 76 ± 14.9                  | 76 ± 14.9                |         |
| T1b     | N – (n = 1480) | 94 ± 0.8                   | 86 ± 1.6                 | <0.0001 |
|         | N + (n = 150)  | 73 ± 5.6                   | 73 ± 5.6                 |         |
| T2a     | N – (n = 408)  | 83 ± 2.3                   | 68 ± 3.7                 | <0.0001 |
|         | N + (n = 62)   | 56 ± 8.8                   | 43 ± 9.7                 |         |
| T2b     | N – (n = 808)  | 86 ± 1.6                   | 73 ± 2.4                 | <0.0001 |
|         | N + (n = 177)  | 59 ± 6.0                   | 53 ± 5.1                 | <0.0001 |
| T3a     | N – (n = 639)  | 72 ± 2.1                   | 61 ± 2.6                 | <0.0001 |
|         | N + (n = 176)  | 49 ± 4.5                   | 32 ± 6.1                 |         |
| T3b     | N – (n = 203)  | 75 ± 3.9                   | 63 ± 6.1                 | 0.0116  |
|         | N + (n = 66)   | 61 ± 7.4                   | 41 ± 11.4                |         |
| T4a     | N – (n = 330)  | 53 ± 3.1                   | 41 ± 3.5                 | 0.2403  |
|         | N + (n = 116)  | 44 ± 5.5                   | 37 ± 5.9                 |         |

*SE = Standard error.

The presence of ulceration (histopathologically) of a primary melanoma (designated Tb) causes upstaging by one stage substage compared with a nonulcerated melanoma (designated Ta).

Adapted from Balch CM, Buzaid AC, Soong SJ, et al. with permission from the American Society of Clinical Oncology.
All T2, T3, and T4 melanomas are defined using thickness and ulceration criteria as described above, but not the level of invasion.

Melanoma In Situ, Indeterminate Melanomas, Multiple Primary Melanomas

Patients with indeterminate melanoma presentations and those who 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. Patients with melanoma in situ are categorized as Tis. For patients with multiple primary melanomas, the T category staging is based on the primary lesion with the worst prognostic features.

Melanoma Growth Patterns

Most of the data used to derive the TNM categories are from cases of melanoma with superficial spreading and nodular growth patterns. There is some evidence that lentigo maligna melanoma, acral lentiginous melanoma, and desmoplastic melanoma may have a different etiology and natural history, with the
former having a more favorable prognosis and the latter two having a less favorable prognosis. Nonetheless, the same staging criteria should be used for melanomas with any of these growth patterns, even though their prognoses may differ somewhat.

**Regional Lymph Nodes (N)**

Regional lymph nodes are classified according to the categories below:

- **N0**: No regional metastases detected.
- **Nx**: Patients in whom the regional nodes cannot be assessed (ie, previously removed).
- **N1 to N3**: Regional metastases based on the number of metastatic nodes and presence or absence of intralymphatic metastases (in-transit or satellite metastases).

**Number of Metastatic Nodes**

This factor is the primary criterion for defining the N category, because the number of metastatic nodes is most strongly associated with 10-year survival compared with all other prognostic factors. Thus, patients with one metastatic node were categorized as N1, those with two to three metastatic nodes as N2, and those with four or more metastatic nodes as N3 (Table 1). Survival rates for these N subgroups are shown in Figures 3 and 4.

**Micrometastases Versus Macrometastases**

The second most significant prognostic feature for patients with lymph node metastases is the tumor burden of nodal metastases. 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. Although such nodal metastases may vary in size (especially for deep-seated nodes or in obese patients), this 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, patients with both clinical evidence of nodal metastases and pathologic examination documenting the number of lymph nodes containing melanoma metastases (after therapeutic lymphadenectomy) are defined as having “macroscopic” or “clinically apparent” nodal metastases. Survival rates for these two patient groups

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![Graph showing five-year survival rates](image-url)
Although previous melanoma staging systems used maximum measured dimensions of lymph node metastases (<5 cm in the 1987 version and <3 cm in the 1992 and 1997 versions), the Melanoma Staging Committee found no compelling evidence in the literature that the measured size of nodal metastases had any independent prognostic value.¹⁸,²⁷

**Intralymphatic Metastases**

The third criterion for defining the N category is the presence or absence of satellites or in-transit metastases, regardless of the number of lesions. Clinical or microscopic satellite lesions around a primary melanoma and in-transit metastases between the primary melanoma and regional lymph nodes represent intralymphatic metastases.¹⁸,²⁸,²⁹ The available data show that these two anatomically defined entities are associated with equally poor survival outcomes.¹⁸ Both satellites and in-transit metastases are, in the absence of synchronous nodal metastases, assigned to a separate N2c classification because both have a prognosis equivalent to multiple nodal metastases (Table 1). The available data also demonstrate that patients with a combination of satellites/in-transit metastases plus nodal metastases have a worse outcome than patients with either event alone, so that these patients were assigned to an N3 classification regardless of the number of synchronous nodal metastases (Table 1).

**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. For example, nodal metastases in combinations of femoral/iliac, axillary/supraclavicular, cervical/supraclavicular, axillary/femoral, bilateral axillary, or bilateral femoral lymph nodes are considered as
involvement of two contiguous nodal basins. All such patients would be categorized as having Stage III melanoma.

**Distant Metastatic Melanoma (M)**

Distant metastatic melanomas are classified according to the categories below:

- M0: No detectable evidence of distant metastases.
- Mx: Presence or absence of metastases cannot be assessed.
- M1: Metastases to skin, subcutaneous tissue, or distant lymph nodes.
- M2: Metastases to lung.
- M3: Metastases to all other visceral sites.

In patients with distant metastases, the site(s) of metastases and elevated serum levels of lactate dehydrogenase (LDH) are used to delineate the M categories into three groups: M1a, M1b, and M1c, with one-year survival rates ranging from 40% to 60% (Figure 5).

**Site(s) of Distant Metastases**

Patients with distant cutaneous, subcutaneous, or distant lymph node metastasis are categorized as M1a; they have a better prognosis compared with those patients with metastases located in any other anatomic site. Patients with metastasis to the lung are categorized as M1b and have an intermediate prognosis when comparing one-year survival rates. Those patients with metastases to any other visceral sites have a relatively worse prognosis and are designated as M1c.

**Elevated Serum Lactate Dehydrogenase**

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 multivariate analysis of all published studies, even after accounting for site and number of metastases. 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. An elevated serum LDH should be used in staging 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 distant metastases has previously been documented as an important prognostic factor. However, this feature was not incorporated into this version of the staging system because of the significant variability in use of imaging tests to comprehensively search for distant metastases. These may range from a chest x-ray in some centers to positron emission tomography (PET) scanning in others, with obvious implications for sensitivity of this evaluation. Until the indications for various diagnostic imaging modalities are better standardized, the number of metastases cannot reliably be used for staging purposes.

**Stage Groupings**

**Localized Melanoma (Stages I and II)**

Patients with primary melanomas who have no evidence of regional or distant metastases (either clinically or pathologically) are divided into two stages: Stage I for patients at low risk for metastases and melanoma-specific mortality or Stage II for those with intermediate risk for metastases and melanoma-specific mortality. The presence of melanoma ulceration portends a high risk for metastases and “upstages” the prognosis of patients with this finding relative to patients with nonulcerated melanomas of equivalent thickness. For this reason, two subgroups of Stage I patients are defined: (1) Stage IA for T1 melanomas without ulceration or level IV or V depth of invasion (T1aN0M0 melanomas); and (2) Stage IB for either T1 melanomas with histopathological evidence of level IV/V depth of invasion or with surface ulceration (T1bN0M0) or those T2 melanomas without ulceration (T2aN0M0). There are three subgroups of Stage II patients: (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 Figure 2.

Patients with T4bN0M0 melanomas are at particularly high risk for harboring both regional and distant metastases. Mortality rates for patients with these thick, ulcerated melanomas are the same or even higher than mortality rates for some groups of patients with nodal metastases (Figure 2 and Table 5). Based on their risk for melanoma-specific mortality, the 1997 version of the melanoma staging grouped such patients as Stage II. In developing the 2003 version, 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, the 2003 system assigns T4 melanomas to Stage II. This includes T4b melanomas that would still be grouped with other localized melanomas but are designated separately as Stage IIC because of their high risk for clinically occult nodal and systemic metastases. The 10-year survival rate for patients with clinical Stage IIC melanoma is 32% (Table 5 and Figure 2).

**Regional Metastases (Stage III)**

There are no substages for Clinical Stage III melanoma.

There are four major determinants of outcome for pathological 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 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. The five-year survival rates for patients in each of the N categories subgrouped by presence or absence of primary melanoma ulceration are shown in Figure 3 and Table 5.
After accounting for these prognostic features in pathological Stage III melanoma, there are three definable subgroups with statistically significant differences in survival: Stages IIIA, IIIB, and IIIC (Figure 4). Patients with pathological Stage IIIA are defined as those who have one to three microscopic lymph node metastases (detected by sentinel or elective lymphadenectomy) and whose primary melanoma is not ulcerated (T1 to 4aN1aM0 or T1 to 4aN2aM0). Five-year and 10-year survival rates for such patients are 67% and 60%, respectively (Figures 3 and 4, Table 5). Patients with pathological Stage IIIB are those with one to three macroscopic lymph node metastases and a nonulcerated primary melanoma (ie, T1 to 4aN1bM0 or T1 to 4aN2bM0), those with one to three microscopic lymph node metastases and an ulcerated primary melanoma (T1 to 4bN1bM0 or T1 to 4bN2aM0), and those with in-transit or satellite metastases without nodal metastases, regardless of ulceration or T category (T1 to 4bN2cM0) (Figures 3 and 4, Table 5). The estimated five-year survival for Stage IIIB patients is 53% (Figure 3, Table 5). Stage IIIC melanoma comprises those patients with a one to three macroscopic lymph node metastases and an ulcerated primary melanoma (T1 to 4bN1bM0 or T1 to 4bN2bM0) or any patient with N3 disease regardless of T status, including patients with four or more nodal metastases or matted nodes or satellites or in-transit metastases along with nodal metastases (Figures 3 and 4, Table 5). The estimated five-year survival rate for pathological Stage IIIC patients is 26%.4

Distant Metastases (Stage IV)

Because the survival differences between the M categories are small, there are no subgroups of Stage IV melanoma.

Prognostic Factors Analysis

Thirteen institutions and cooperative study groups agreed to contribute prospectively accumulated melanoma patient data to validate the proposed staging system. The AJCC Melanoma Database consisted of a total of 30,450 melanoma patients, of which 17,600 patients (59%) had information available for all of the factors required for the proposed TNM classification and stage grouping.2

In a multivariate analysis of 13,581 patients with localized melanoma (either clinically or pathologically), the two most powerful independent characteristics of the primary melanoma were tumor thickness and ulceration (Table 6). Indeed, no other feature of the melanoma or the patient with localized melanoma had the predictive capability of these two factors. Other statistically significant prognostic factors were patient age, site of the primary melanoma, level of invasion, and gender (Table 6). To determine the relative predictive strength of these prognostic features within cohorts of tumor thickness, the Cox regression analysis was performed within each of the major thickness subgroups used in the melanoma T categories (Table 7). When comparing level of invasion and ulceration within thickness subgroups, there was a pattern of predictive capability for thin melanomas (≤1.0 mm) that was different from all other thickness groups. Thus, for this specific subgroup of patients, level of invasion was more predictive of survival outcome than tumor ulceration. The opposite was true for all melanomas thicker than 1.0 mm, where ulceration was clearly the most predictive, and level of invasion ranked below that of patient age and anatomic site of the primary melanoma (Table 7).

Complete clinical and histopathologic data were available for 1,151 patients with lymph node metastases. A Cox multivariate analysis demonstrated that three factors were most significant (P < 0.0001): (1) the number of metastatic nodes; (2) the tumor burden at the time of staging (ie, microscopic versus macroscopic); and 3) the presence or absence of ulceration of the primary melanoma (Table 8). Melanoma-specific survival (calculated from the onset of primary melanoma diagnosis) decreased significantly with increasing nodal involvement (P < 0.0001; Figure 6). The best grouping for the number of meta-
static nodes that correlated with five-year survival was one versus two to three versus four or more metastatic nodes.

There was a significantly lower survival (calculated from the onset of primary melanoma diagnosis) for those patients who presented with macroscopic (ie, palpable) nodal metastases compared with those with microscopic (ie, nonpalpable) nodal metastases, even after accounting for lead-time bias ($P < 0.0001$; Figure 7). Diminishing five-year survival with increasing tumor burden based on

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**TABLE 6** Cox Regression Analysis for 13,581 Melanoma Patients Without Evidence of Nodal or Distant Metastases

| Variable | Chi-square Value (Wald) | $P$ Value | Risk Ratio | 95% CL* |
|----------|------------------------|-----------|------------|---------|
| Thickness | 244.3 | <0.00001 | 1.558 | 1.473-1.647 |
| Ulceration | 189.5 | <0.00001 | 1.901 | 1.735-2.083 |
| Age | 45.6 | <0.00001 | 1.101 | 1.071-1.132 |
| Site | 42.7 | <0.00001 | 1.214 | 1.136-1.297 |
| Level | 15.1 | 0.001 | 0.836 | 0.764-0.915 |

*CL = Confidence level. Only patients with no missing data in all covariates were included in this multivariate study. Adapted from Balch CM, Soong SJ, Gershenwald J, et al.2 with permission from the American Society of Clinical Oncology.

**TABLE 7** Cox Regression Analysis by Tumor Thickness Category for Stages I and II Primary Melanoma

| Variable | Chi-square Value (Wald) | $P$ Value | Risk Ratio | 95% CL* |
|----------|------------------------|-----------|------------|---------|
| Thickness <1.00 (n = 5,299) | | | | |
| Level | 24.778 | <0.00001 | 1.451 | 1.253-1.680 |
| Ulceration | 17.239 | <0.00001 | 2.073 | 1.469-2.924 |
| Age | 12.563 | 0.0004 | 1.156 | 1.067-1.253 |
| Site | 6.940 | 0.0084 | 1.394 | 1.089-1.784 |
| Gender | 5.506 | 0.0189 | 0.744 | 0.581-0.952 |

Thickness 1.01 to 2.00 mm (n = 3,943)

| Ulceration | 57.215 | <0.00001 | 1.965 | 1.650-2.341 |
| Age | 24.085 | <0.00001 | 1.567 | 1.310-1.876 |
| Site | 11.613 | 0.0007 | 1.348 | 1.042-1.614 |
| Level | 6.536 | 0.0099 | 1.211 | 1.047-1.400 |
| Gender | 2.668 | 0.1024 | 0.764 | 0.581-1.030 |

Thickness 2.01 to 4.00 mm (n = 2,959)

| Ulceration | 62.291 | <0.00001 | 1.766 | 1.634-2.034 |
| Age | 12.529 | 0.0004 | 1.087 | 1.038-1.138 |
| Site | 12.342 | 0.0004 | 1.306 | 1.125-1.516 |
| Level | 4.451 | 0.0349 | 1.143 | 1.010-1.294 |
| Gender | 3.165 | 0.2226 | 0.872 | 0.705-1.077 |

Thickness >4.00 mm (n = 1,380)

| Ulceration | 47.246 | <0.00001 | 1.932 | 1.601-2.331 |
| Age | 8.745 | 0.0031 | 1.087 | 1.028-1.148 |
| Level | 4.065 | 0.0438 | 1.139 | 1.004-1.293 |
| Gender | 2.675 | 0.0951 | 0.858 | 0.716-1.027 |
| Site | 2.547 | 0.1106 | 1.154 | 0.968-1.376 |

*CL = Confidence level. Only patients with no missing data in all covariates were included in this multivariate analysis. Adapted from Balch CM, Soong SJ, Gershenwald J, et al.2 with permission from the American Society of Clinical Oncology.
increasing number of metastatic nodes present was observed for all subgroups ($P < 0.0001$; Table 9).

Ulceration of a primary melanoma was the only primary tumor feature that still predicted an adverse outcome in Stage III disease (Table 8). This was true even within each of the Stage III subgroups examined, including a two-way survival analysis correlating presence or absence of ulceration with the number of metastatic lymph nodes ($P < 0.0001$), or a three-way analysis that integrated subgroups according to all three of the most important prognostic factors: ulceration of the primary melanoma, nodal tumor burden, and the number of metastatic nodes (Table 9).

The prognostic influence of different distant metastatic sites was analyzed in 1,158 Stage IV patients using various combinations of sites of metastases. The most significant

| Table 8 Cox Regression Analysis for 1,151 Stage III (Nodal Metastases) Patients |
|--------------------------|-----------------|-----------------|------------------|-----------------|
| Variable                | Chi-square Value (Wald) | $P$ Value | Risk Ratio | 95% CL* |
| No. of metastatic nodes | 57.616           | <0.000001    | 1.257       | 1.185-1.334   |
| Tumor burden            | 40.301           | <0.000001    | 1.792       | 1.497-2.146   |
| Ulceration              | 23.282           | <0.000001    | 1.582       | 1.313-1.906   |
| Site                    | 17.843           | 0.0001       | 1.461       | 1.225-1.746   |
| Age                     | 13.369           | 0.0003       | 1.118       | 1.053-1.187   |
| Thickness               | 1.964            | 0.1611       | 1.091       | 0.966-1.233   |
| Level                   | 0.219            | 0.6396       | 1.033       | 0.901-1.186   |
| Gender                  | 0.006            | 0.9407       | 1.007       | 0.836-1.213   |

*CL = Confidence level. Only patients with no missing data in all covariates were included in this multivariate analysis. Adapted from Balch CM, Soong SJ, Gershenwald J, et al.² with permission from the American Society of Clinical Oncology.

FIGURE 6 Survival Curves of 1,528 Melanoma Patients with Lymph Node Metastases Subgrouped by the Actual Number of Metastatic Nodes. The correlation is highly significant ($P < 0.0001$). Adapted from Balch CM, Soong SJ, Gershenwald J, et al.² with permission from the American Society of Clinical Oncology.
differences were noted when visceral versus nonvisceral sites (ie, skin, subcutaneous tissue, and distant lymph nodes) were compared. Although significant one-year survival differences were observed when patients with lung metastases were compared with those patients with metastases in other visceral sites ($P < 0.0001$), no differences were noted when two-year survival data were compared (Figure 8).

**DISCUSSION**

The results of multivariate analyses using a database derived from records of 17,600 pa-

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**TABLE 9** Five-year Survival Rates for Stage III (Nodal Metastases) Patients Stratified by Number of Metastatic Nodes, Ulceration, and Tumor Burden

| Melanoma Ulceration | Microscopic % ± SE* | Macroscopic % ± SE* |
|---------------------|---------------------|---------------------|
|         | 1+ Nodes | 2 to 3 Nodes | >3+ Nodes | 1+ Nodes | 2 to 3 Nodes | >3+ Nodes |
| Absent   |           |             |            |           |             |            |
| (n = 252) | 69 ± 3.7  | 63 ± 5.6    | 27 ± 9.3   | (n = 122) | 59 ± 4.7    | 46 ± 5.5   |
| Present  |           |             |            |           |             |            |
| (n = 217) | 52 ± 4.1  | 50 ± 5.7    | 37 ± 8.8   | (n = 109) | 29 ± 5.0    | 25 ± 4.4   |

*SE = Standard error.
†n = Number of patients.

Adapted from Balch CM, Soong SJ, Gershenwald J, et al.2 with permission from the American Society of Clinical Oncology.
Patients with melanoma from 13 cancer centers and cooperative groups showed: (1) tumor thickness and ulceration were the most powerful predictors of survival in patients with localized melanoma (Stages I and II), while level had a significant impact only within the subgroup of thin (ie, T1; ≤1.0 mm) melanomas; (2) the number of metastatic nodes, the tumor burden (microscopic versus macroscopic nodal metastases), and the presence or absence of melanoma ulceration and of intralymphatic metastases (satellite or in-transit metastases) were the most powerful predictors of survival in patients with nodal metastases (Stage III); and (3) the number and anatomic site of distant metastases and the presence of an elevated serum LDH were the most significant predictor of survival in patients with distant metastases (Stage IV). Subsequent to the publication of the AJCC melanoma staging articles, several institutions have independently validated these prognostic criteria as the most predictive from among currently available clinical and pathological criteria. The major limitation of the AJCC data is that patients with early Stage I melanoma may not have been referred to major cancer centers or entered into clinical trials, so that the survival rates for the Stage IA patients in the AJCC analysis may likely have a somewhat lower five- and 10-year survival rate compared with results from a comprehensive regional referral institution such as the Sydney Melanoma Unit, Sydney, Australia. In addition, several studies have demonstrated the highly significant value of mitotic rate as an independent predictive factor but this parameter is more interpretive and would be difficult to fold into a TNM criterion.

Patients with nodal metastases should not be considered as a homogeneous group, and
recommendations to enter patients into intensive clinical trials should take into account the marked diversity in the natural history of Stage III melanoma. In fact, some Stage III patients actually have a good prognosis (or intermediate risk for distant metastases). This prognostic heterogeneity is demonstrated by more than fivefold differences in five-year survival rates for defined substages, ranging from 69% for patients with nonulcerated melanomas (regardless of thickness) who had a single clinically occult nodal metastasis (detected by sentinel or elective lymphadenectomy) to 13% for patients with ulcerated melanomas (regardless of thickness) who had four or more clinically apparent nodal metastases (detected by therapeutic lymphadenectomy). Stage III patients are sometimes incorrectly assumed to be at uniformly high risk for distant metastases and therefore may be offered very intensive forms of systemic therapy (eg, biochemotherapy). Understanding their differences in clinical outcome will be important not only in the design and analysis of clinical trials but also in calibrating therapeutic intensity to metastatic risk.

Survival rates for patients with Stage IV melanoma are, unfortunately, more often measured more in months than in years, and only a minority of Stage IV patients survive beyond one year. None of the prognostic features in this analysis was able to stratify Stage IV patients into subgroups with median survival separated by more than a few months. In general, the only Stage IV patients who live beyond one or two years are those with limited disease who have had a complete surgical resection of the distant metastases. Whether the long-term results reflect a more favorable biology of disease or a therapeutic benefit of surgery (or a combination of the two) is a difficult issue to address in the absence of any randomized trials.

The prognostic factors identified by this analysis 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 entry into surgical and adjuvant therapy clinical trials should have pathological staging with sentinel lymphadenectomy to ensure prognostic homogeneity within assigned treatment groups. In this way, investigators will be better able to discern between the natural history impact and the treatment impact being studied in 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 well below that achievable with the light microscope or routine x-rays. These include molecular diagnostic approaches, such as reverse transcription polymerase chain reaction to detect relevant gene expression, PET scanning, use of radiolabeled antimelanoma antibodies, serum markers, and genetic/molecular markers that will more accurately detect and stage metastatic melanoma. Some of these advances in molecular-based staging will no doubt supplant those prognostic features of melanoma now determined largely with the light microscope.

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