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ORIGINAL REPORT

Final Version of 2009 AJCC Melanoma Staging and Classification

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ABSTRACT

Purpose
To revise the staging system for cutaneous melanoma on the basis of data from an expanded American Joint Committee on Cancer (AJCC) Melanoma Staging Database.

Methods
The melanoma staging recommendations were made on the basis of a multivariate analysis of 30,946 patients with stages I, II, and III melanoma and 7,972 patients with stage IV melanoma to revise and clarify TNM classifications and stage grouping criteria.

Results
Findings and new definitions include the following: (1) in patients with localized melanoma, tumor thickness, mitotic rate (histologically defined as mitoses/mm^2), and ulceration were the most dominant prognostic factors. (2) Mitotic rate replaces level of invasion as a primary criterion for defining T1b melanomas. (3) Among the 3,307 patients with regional metastases, components that defined the N category were the number of metastatic nodes, tumor burden, and ulceration of the primary melanoma. (4) For staging purposes, all patients with microscopic nodal metastases, regardless of extent of tumor burden, are classified as stage III. Micrometastases detected by immunohistochemistry are specifically included. (5) On the basis of a multivariate analysis of patients with distant metastases, the two dominant components in defining the M category continue to be the site of distant metastases (nonvisceral *v* lung *v* all other visceral metastatic sites) and an elevated serum lactate dehydrogenase level.

Conclusion
Using an evidence-based approach, revisions to the AJCC melanoma staging system have been made that reflect our improved understanding of this disease. These revisions will be formally incorporated into the seventh edition (2009) of the AJCC Cancer Staging Manual and implemented by early 2010.

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INTRODUCTION

The current melanoma staging system was substantially revised in 2001 for the sixth edition of the Cancer Staging Manual, on the basis of an analysis of 17,600 patients in the American Joint Committee on Cancer (AJCC) Melanoma Staging Database.[1,2] For this analysis, we expanded the sample size of the melanoma staging database and added mitotic rate of the primary melanoma as a new covariate because of recent studies demonstrating this to be an important and independent prognostic factor. The database for stage IV patients was expanded five-fold and, for the first time, contained data about the prognostic value of the serum lactate dehydrogenase (LDH) level. During the 7 years since the previous analysis, the sentinel node procedure has become a standard for staging nodal metastases in patients with clinically uninvolved lymph nodes, with the net result that microscopically detected nodal metastases at initial presentation are now detected in many more melanoma patients. It was important, therefore, to verify that the criteria for stage III used in the past, with long-term follow-up, were still valid in this contemporary era of nodal staging. The staging recommendations resulted from an unprecedented collaboration by melanoma centers that contributed the largest data set from melanoma patients ever analyzed.

METHODS

The AJCC Melanoma Staging Committee used previously published guidelines to determine criteria that should be

Table 1. TNM Staging Categories for Cutaneous Melanoma

Classification	Thickness (mm)	Ulceration Status/Mitoses
T		
Tis	NA	NA
T1	≤ 1.00	a: Without ulceration and mitosis < 1/mm^2 b: With ulceration or mitoses ≥ 1/mm^2
T2	1.01-2.00	a: Without ulceration b: With ulceration
T3	2.01-4.00	a: Without ulceration b: With ulceration
T4	> 4.00	a: Without ulceration b: With ulceration
N	No. of Metastatic Nodes	Nodal Metastatic Burden
N0	0	NA
N1	1	a: Micrometastasis* b: Macrometastasis†
N2	2-3	a: Micrometastasis* b: Macrometastasis† c: In transit metastases/satellites without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes	
M	Site	Serum LDH
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

Abbreviations: NA, not applicable; LDH, lactate dehydrogenase.
*Micrometastases are diagnosed after sentinel lymph node biopsy.
†Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically.

used in the TNM classification and the stage groupings.[1] The evidence-based analysis that led to melanoma staging recommendations for the seventh edition of the Cancer Staging Manual was based on the updated AJCC Melanoma Staging Database (data through 2008) containing prospective data on 30,946 patients with stages I, II, and III melanoma and 7,972 patients with stage IV melanoma. Patients were treated at 17 major medical centers, free-standing cancer centers, or cancer cooperative groups (see Appendix, online only). Independent prognostic factors were considered by the AJCC Melanoma Committee for defining the TNM categories and stage groupings on the basis of results published in the literature as well as our prognostic factors analyses of the AJCC Melanoma Staging Database. The statistical approaches and data dictionary definitions are virtually the same as described in our previous publication.[1] Mitotic rate was examined for the first time in this analysis. The Melanoma Staging Committee recommended that mitotic rate be determined by the "hot spot" approach and expressed as the number of mitoses per square millimeter of primary tumor.[3] Statistical analyses of the AJCC Melanoma Staging Database primarily used methods similar to those for survival analysis. Survival times were calculated from the initial melanoma diagnosis (or first distant metastasis for the stage IV analysis) and considered censored for patients who were alive at last follow-up or who died without evidence of melanoma. 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.

RESULTS

The TNM categories for the seventh edition of the AJCC Staging Manual are defined in Table 1, and the stage groupings are defined in Table 2. The updated Melanoma Staging Database was used to calculate survival rates for patients with stages I to IV melanoma. Substages for stages I, II, and III are shown in Figure 1A-D and TNM categories for stage IV in are shown in Figure 2. Changes in the melanoma staging system are summarized in Table 3. These recommendations of the AJCC Melanoma Staging Committee have been approved by both the AJCC Executive Committee and the International Union Against Cancer (UICC) TNM Committee. The final recommendations of the melanoma staging criteria will be formally implemented in January 2010.[3]

Staging for Localized Melanoma (stages I and II)

The AJCC Melanoma Staging Database includes prospectively accumulated data on more than 27,000 stage I and II melanoma patients for whom tumor thickness and follow-up information is available. Five-year and 10-year survival rates based on TNM classification range from 97% and 93% for patients with T1aN0M0 melanomas to 53% and 39%, respectively for patients with T4bN0M0 melanomas ($P < .0001$; Fig 1A). By substage, 10-year survival ranged from 93% for stage IA to 39% for stage IIC melanoma ($P < .0001$; Fig 1B).

Table 2. Anatomic Stage Groupings for Cutaneous Melanoma

	Clinical Staging*				Pathologic Staging†		
	T	N	M		T	N	M
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0
III	Any T	N > N0	M0	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	N2c	M0
				IIIC	T1-4b	N1b	M0
					T1-4b	N2b	M0
					T1-4b	N2c	M0
					Any T	N3	M0
IV	Any T	Any N	M1	IV	Any T	Any N	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 (ie, sentinel node biopsy) or complete lymphadenectomy. Pathologic stage 0 or stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

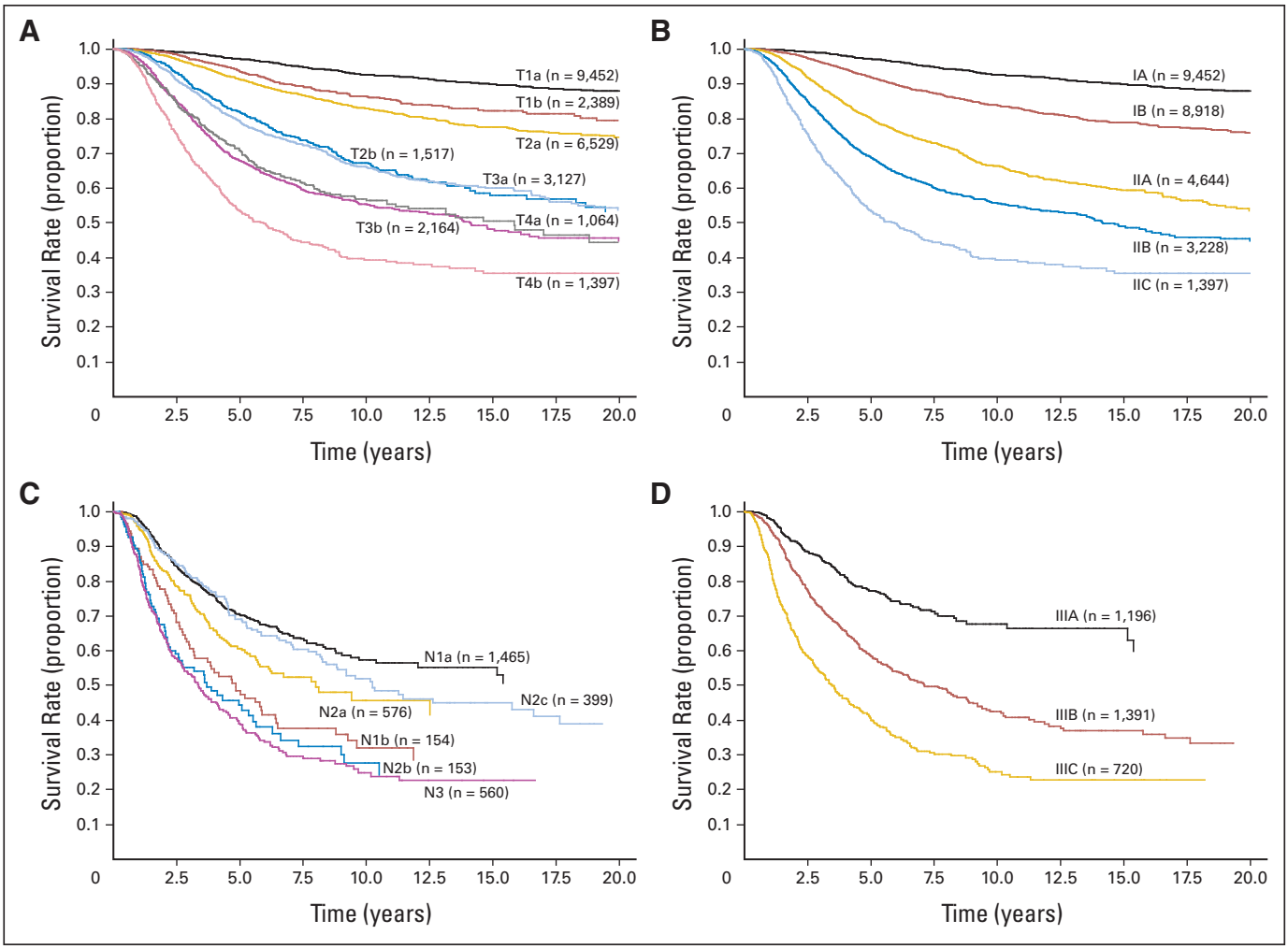

Fig 1. Survival curves from the American Joint Committee on Cancer Melanoma Staging Database comparing (A) the different T categories and (B) the stage groupings for stages I and II melanoma. For patients with stage III disease, survival curves are shown comparing (C) the different N categories and (D) the stage groupings.

Primary tumor thickness. Recommendations for using melanoma thickness in TNM categories and stage groupings in the seventh edition remain unchanged, ie, the T category thresholds of melanoma thickness are defined in even integers (1.0, 2.0, and 4.0 mm). In the 2008 AJCC Melanoma Staging Database, as tumor thickness increased, there was a highly significant decline in 5- and 10-year survival rates ($P < .0001$). Among the 11,841 patients with T1 melanomas ($\leq$ 1.00 mm thickness), the 10-year survival was 92%, while it was 80% in the 8,046 T2 patients with melanomas 1.01 to 2.00 mm thick, 63% in the 5,291 T3 patients with melanomas 2.01 to 4.00 mm thick, and 50% in the 2,461 T4 patients with melanomas more than 4.00 mm thick ($P < .0001$).

Primary tumor ulceration. Recommendations for using ulceration status in defining TNM categories and stage groupings also remain unchanged. Survival rates of 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. For example, 5-year survival was 79% for a T3a nonulcerated melanoma and was 82% for a T2b ulcerated melanoma; both are defined as stage IIA. A T4a nonulcerated melanoma has a 5-year survival of 71%, similar to that of a T3b ulcerated melanoma with a 68% rate; both are defined as stage IIB. A T4b ulcerated melanoma has a 5-year survival of 53% and is categorized as stage IIC.

Primary tumor mitotic rate. Proliferation of the primary melanoma as defined by the mitotic rate was identified as a powerful and independent predictor of survival. As a result, primary tumor mitotic rate is now a required element for the seventh edition melanoma staging system. Multiple thresholds of mitotic rate were examined statistically, and the most significant correlation with survival was identified at a threshold of at least 1/mm^2. Data from the AJCC Melanoma Staging Database demonstrated a highly significant correlation between increasing mitotic rate and declining survival rates ($P < .0001$). In a multifactorial analysis of 10,233 patients with clinically localized melanoma, mitotic rate was the second most powerful predictor of survival, after tumor thickness ($\chi^2 = 79.1$; $P < .0001$).

Defining T1 melanoma. Although melanomas 1 mm or less in thickness constitute a good prognosis group, we found that the 10-year survival outcome was variable, ranging from 85% to 99%, depending on the presence of secondary characteristics of mitotic rate and tumor ulceration. In a multivariate analysis of 4,861 T1 melanomas, tumor thickness, mitotic rate, and ulceration were the most

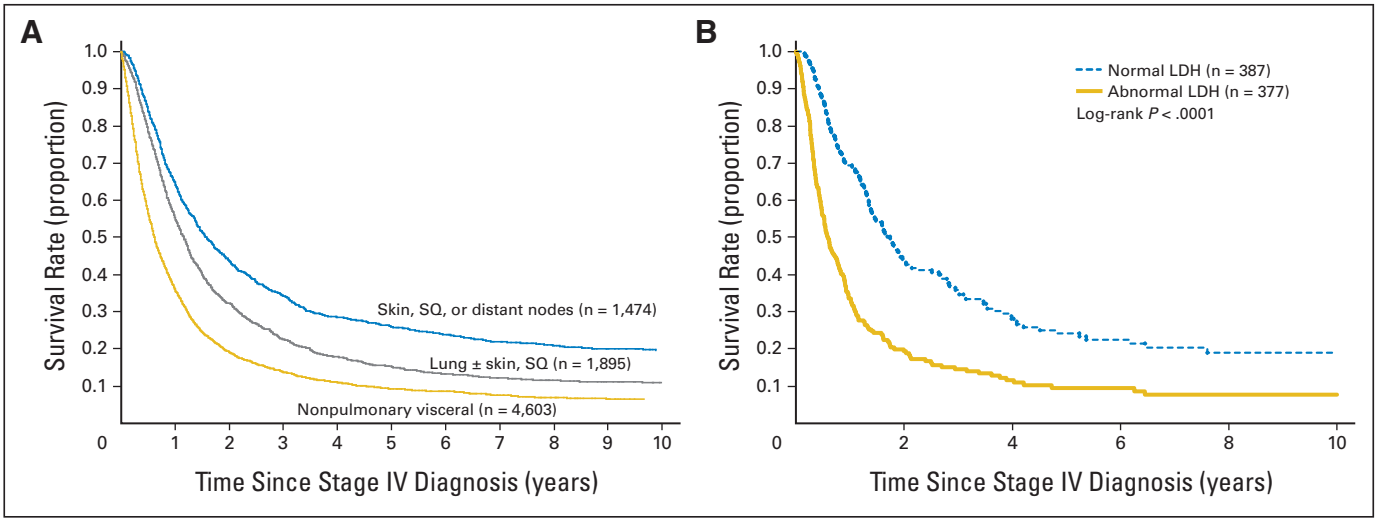

Fig 2. Survival curves of 7,635 patients with metastatic melanomas at distant sites (stage IV) subgrouped by (A) the site of metastatic disease and (B) serum lactose dehydrogenase (LDH) levels. LDH values are not used to stratify patients. Curves in (A) are based only on site of metastasis. The number of patients is shown in parentheses. SQ, subcutaneous.

powerful predictors of survival outcome for T1 melanoma patients, and the level of invasion was no longer statistically significant when mitotic rate and ulceration were included in the analysis (Table 4). The 10-year survival rate was 95% for nonulcerated T1 melanomas with a mitotic rate of less than 1/mm^2 and dropped to 88% if the mitotic rate was at least 1/mm^2 ($P < .0001$). Ulcerated T1 melanomas were associated with a mitotic rate of $\geq$ 1/mm^2 in 78% of patients, but the 10-year survival rate was the same regardless of whether the mitotic rate was less than 1 or $\geq$ 1/mm^2 (85% *v* 87%; $P = .41$). Therefore, the Melanoma Staging Committee has recommended that mitotic rate

Table 3. Differences Between the 6th Edition (2002) and the Recommended 7th Edition (2009) of the Melanoma Staging System

Factor	6th Edition Criteria	Recommended 7th Edition Criteria	Comments
Thickness	Primary determinant of T staging	Same	Thresholds of 1.0, 2.0, and 4.0 mm
Level of invasion	Used only for defining T1 melanomas	Same	Used as a default criterion only if mitotic rate cannot be determined
Ulceration	Included as a secondary determinant of T and N staging	Same	Signifies a locally advanced lesion; dominant prognostic factor for grouping stages I, II, and III
Mitotic rate per mm^2	Not used	Used for categorizing T1 melanoma	Mitosis $\geq$ 1/mm^2 used as a primary criterion for defining T1b melanoma
Satellite metastases	In N category	Same	Merged with in transit lesions
Immunochemical detection of nodal metastases	Not included	Included	Must include at least one melanoma-associated marker (eg, HMB-45, Melan-A, MART-1) unless diagnostic cellular morphology is present
0.2 mm threshold of defined N+	Implied	No lower threshold of staging N+ disease	Isolated tumor cells or tumor deposits < 0.1 mm meeting the criteria for histologic or immunohistochemical detection of melanoma should be scored as N+
Number of nodal metastases	Primary determinant of N staging	Same	Thresholds of 1 *v* 2-3 *v* 4+ nodes
Metastatic volume	Included as a second determinant of N staging	Same	Clinically occult (microscopic) nodes are diagnosed at sentinel node biopsy *v* clinically apparent (macroscopic) nodes diagnosed by palpation or imaging studies, or by the finding of gross (not microscopic) extracapsular extension in a clinically occult node
Lung metastases	Separate category as M1b	Same	Has a somewhat better prognosis than other visceral metastases
Elevated serum LDH	Included as a second determinant of M staging	Same	Recommend a second confirmatory LDH level if elevated
Clinical *v* pathologic staging	Sentinel node results incorporated into definition of pathologic staging		Large variability in outcome between clinical and pathologic staging; sentinel node staging encouraged for standard patient care, should be required prior to entry into clinical trials

Abbreviation: LDH, lactate dehydrogenase.

Table 4. Multivariate Cox Regression Analysis of Pathologic Factors by T Category for Stage I and II Melanoma Where Mitotic Rate Data Are Available

	Tumor Thickness		Ulceration		Mitotic Rate		Clark Level	
T Category	χ^2	*P*	χ^2	*P*	χ^2	*P*	χ^2	*P*
T1	12.8	.0003	3.8	.05	20.8	< .0001	1.9	.17
T2	4.9	.03	16.2	< .0001	15.9	< .0001	0.2	.65
T3	4.1	.04	15.4	< .0001	12.2	.0005	1.4	.24
T4	0.2	.69	14.2	.0002	9.1	.003	2.7	.10

replace Clark level of invasion as a primary criterion for defining T1b melanoma.

Since mitotic rate will replace level of invasion in defining T1 categories, the Melanoma Staging Committee redefined the criteria for T1a and T1b melanomas. T1a melanomas (approximately 60% of T1 patients in the AJCC Melanoma Database) will be restricted to those meeting the following three criteria: ≤ 1.0 mm thick, no ulceration, and mitotic rate of less than 1/mm^2. T1b melanomas (approximately 40% of T1 patients) are now defined as those whose tumor thickness is ≤ 1.0 mm and that have at least one mitosis per square millimeter or tumor ulceration present. In contrast to the sixth edition of the AJCC staging system, level of invasion is no longer routinely considered in defining T1 melanomas, except in the rare circumstances when mitotic rate cannot be accurately determined.

Staging for Regional Metastatic Melanoma (stage III)

The 2008 AJCC Melanoma Staging Database contains 3,307 stage III patients who had information available to define stage, the vast majority of whom presented with micrometastases identified by a sentinel node biopsy and completion lymphadenectomy. A Cox multivariate analysis of the database demonstrated that the number of tumor-bearing nodes, tumor burden at the time of staging (ie, microscopic *v* macroscopic), presence or absence of primary tumor ulceration, and thickness of the primary melanoma were the most predictive independent factors for survival in these patients (all *P* values < .001). These characteristics were incorporated into the stage grouping criteria.

Five-year survival rates based on TNM classification ranged from 70% for patients with T1-4N1aM0 melanomas to 39% for patients with T1-4N3M0 melanomas (*P* < .0001; Fig 1C). In the absence of nodal metastases, patients with intralymphatic metastases (N2c) have 5- and 10-year survival rates of 69% and 52% , respectively (Fig 1C), while those with combined intralymphatic metastases and nodal metastases (N3) have survival rates of 46% and 33%, respectively. Five-year survival within substages of stage III were 78%, 59%, and 40% for patients with stage IIIA, IIIB, and IIIC melanoma, respectively (*P* < .0001; Fig 1D).

Immunohistochemical detection of micrometastases. With the current widespread availability of immunohistochemical (IHC) staining, it is possible to consistently detect nodal metastases at a microscopic level consisting of aggregates of only a few cells.[4-6] The availability and widespread use of IHC methods to detect melanoma-associated antigens is sufficiently available worldwide that the AJCC Melanoma Staging Committee considers it acceptable to classify nodal metastases solely on the basis of IHC staining of melanoma-associated markers. Although some IHC markers are sensitive but not specific for melanoma cells (eg, S100 protein, tyrosinase), IHC alone will be accepted if the diagnosis is based on at least one melanoma-associated marker (eg, HMB-45, Melan-A/MART 1) and the cells have malignant morphologic features that can be detected in the IHC stained tissue.[4]

Staging for Distant Metastatic Melanoma (stage IV)

In patients with distant metastases, the site(s) of metastases and elevated serum levels of LDH are used to delineate the M1 stage into three M categories: M1a, M1b, and M1c. One-year survival rates among 7,972 stage IV patients were 62% for M1a, 53% for M1b, and 33% for M1c melanomas (*P* < .0001; Fig 2A).

Patients with distant metastasis in the skin, subcutaneous tissue, or distant lymph nodes and a normal LDH level are categorized as M1a; they have a relatively better prognosis compared with those patients with metastases located in any other distant anatomic site (Fig 2A). Patients with metastasis to the lung (or with a combination of lung and skin or subcutaneous metastases) and a normal LDH level are categorized as M1b and have an intermediate prognosis. Those patients with metastases to any other visceral sites or at any location with an elevated LDH level are designated as M1c and have the worst prognosis (Fig 2A and 2B).

Elevated serum LDH. The updated AJCC Melanoma Staging Database demonstrated that an elevated serum LDH is an independent and highly significant predictor of survival outcome among patients with stage IV disease. Thus 1- and 2-year overall survival rates for those stage IV patients in the 2008 AJCC Melanoma Staging Database with a normal serum LDH were 65% and 40%, respectively, compared with 32% and 18%, respectively, when the serum LDH was elevated at the time of staging (*P* < .0001; Fig 2B). Therefore, serum LDH should be measured at the time stage IV disease is documented, and if the LDH level is elevated, those patients are assigned to M1c regardless of the site of their distant metastases.

The survival differences among M categories will be useful for clinical trial stratification; however, the overall prognosis of all patients with stage IV melanoma remains poor, even among patients with M1a. For this reason, the Melanoma Staging Committee recommended no stage groupings for stage IV.

DISCUSSION

Histological features of the primary melanoma—tumor thickness, mitotic rate, and ulceration—are important hallmarks of melanoma prognosis and staging. Most notably, the mitotic rate has emerged in this analysis as a powerful predictive factor of survival.[7-10] After 40

years of being an integral component of melanoma staging, the Clark level is no longer recommended as a staging criterion, since it is not an independent prognostic factor when mitotic rate is included in the analysis. The value of these histologic characteristics for microstaging strongly supports that the initial biopsy is a critical component of both diagnosis and staging. An excisional biopsy of the entire clinically apparent lesion, with a narrow 1- to 2-mm margin of adjacent normal-appearing skin, is the biopsy technique of choice when melanoma is suspected, and shave biopsies should be avoided. An incisional biopsy may be acceptable for larger lesions. A deep saucerization biopsy may be satisfactory when the lesion is flat and the suspicion of melanoma is not high.[11] These staging criteria of the primary melanoma should be used for all growth patterns of cutaneous melanoma but do not apply to mucosal or ocular melanomas.

The AJCC Melanoma Staging Committee recommends that sentinel lymph node biopsy be performed as a staging procedure in patients for whom the information will be useful in planning subsequent treatments and follow-up regimens. Specifically, the procedure should be discussed with (and recommended for) otherwise healthy patients who have T2, T3, and T4 melanomas and clinically uninvolved regional lymph nodes; the procedure should be recommended selectively for patients with T1b melanomas.[12-21] The use of mitotic rate for the purpose of classifying thin melanomas as T1b was based on a survival analysis. The AJCC Melanoma Staging Database did not contain sufficient data to assess risk of occult nodal micrometastases in this population. However, preliminary evidence from several other large studies suggests that T1 melanomas with a mitotic rate of $\geq 1/mm^2$ and a thickness of ≥ 0.76 mm are associated with an approximately 10% risk of occult metastases in their sentinel lymph nodes (J. Gershenwald, personal communication, March 2009). These data may be helpful when discussing the indications for sentinel lymph node biopsy for staging with individual patients with T1b melanoma. Furthermore, staging with sentinel node technology should be required as an entry criterion for all melanoma patients presenting with clinical stage IB or II disease before entry into clinical trials involving new surgical techniques or adjuvant therapy.

This staging system is the first to contain long-term follow-up of patients staged with sentinel lymph node biopsy. Reflective of a changing demographic in melanoma, most patients with histologically confirmed stage III melanoma at diagnosis now present with clinically uninvolved regional nodes and micrometastasis diagnosed by sentinel lymph node biopsy. Such improved staging translates into more refined (and favorable) survival estimates for patients with stages IB-IIIA melanoma (Fig 1).

Intralymphatic metastases (ie, satellites or in transit metastases) are another criterion in the N category, regardless of the number of lesions.[22] For the first time, there are prospective data and survival rates in the 2008 AJCC/UICC melanoma staging database for patients who manifest intralymphatic metastases. The results were somewhat better than those previously reported in the literature and are higher than those in the remaining cohort of stage IIIB patients. Nevertheless, the category of stage IIIB was still the closest fit statistically, and the AJCC Melanoma Committee recommended that the sixth edition staging definition be retained. Microscopic satellites are defined as any discontinuous nest of metastatic cells more than 0.05 mm in diameter that are clearly separated by normal dermis (not fibrosis or inflammation) from the main invasive component of melanoma by a distance of at least 0.3 mm. Data from the literature show that survival outcome are comparable to that of patients with clinically detectable satellite metastases.[23-26] Accordingly, the AJCC Melanoma Staging Committee has recommended that this feature of early lymphatic metastases be retained in the category of N2c melanoma.

The updated AJCC Melanoma Staging Database clearly demonstrates that an elevated serum LDH is an independent and highly significant predictor of survival or outcome of stage IV patients, independent of other factors. Furthermore, 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.[27-30]

The mechanisms or sources of elevated LDH isoenzymes are unknown, and generally the there is a nonspecific pattern of elevation among the various LDH isoenzymes. Survival rates are significantly reduced in patients with an elevated serum LDH at the time of initial assignment to stage IV. Therefore, when serum LDH is elevated above the upper limits of normal at the time of staging, those patients who also have distant metastases are assigned to M1c, regardless of the site of their distant metastases.

The number of metastases at distant sites has previously been documented as an important prognostic factor.[27,31,32] This was also confirmed by preliminary multivariate analyses using the AJCC Melanoma Staging Database. However, this feature was not incorporated into the staging system because of significant variability in the deployment of diagnostic tests to comprehensively search for distant metastases among institutions that contributed data. Tests range from a simple chest x-ray in some centers to high-resolution double-contrast computed tomography, positron emission tomography/computed tomography, and/or magnetic resonance imaging in others.

In patients who present with metastases and no known primary site, it is difficult to assign a staging category. When patients have an initial presentation of metastases in the lymph nodes, these should be presumed to be regional (stage III instead of stage IV) if an appropriate staging workup does not reveal any other sites of metastases. These patients have a prognosis and natural history that is similar to, if not more favorable than, patients with the same staging characteristics from a known primary cutaneous melanoma.[33,34] When there are localized metastases to the skin or subcutaneous tissues, these should also be presumed to be regional (ie, stage III instead of stage IV) if an appropriate staging workup does not reveal any other sites of metastases. In patients with a presumed single skin metastasis from an unknown primary site, pathology review by an experienced melanoma pathologist is appropriate to confirm that the lesion is not a variant of a primary melanoma, particularly a melanoma with a regressed junctional component. All other presentations (ie, metastases to a visceral site and no known primary melanoma) should be categorized as stage IV melanoma, using the M1 classification criteria described above reflecting metastatic site and serum LDH status.

Finally, the prognostic factors included in the melanoma staging system should be the primary stratification criteria and end results reporting criteria of melanoma clinical trials. The use of a consistent set of criteria will facilitate the reporting of melanoma treatment outcomes and comparability of melanoma clinical trials and thereby accelerate the progress of multidisciplinary melanoma treatment approaches.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Balch CM, Buzaid AC, Soong SJ, et al: Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. J Clin Oncol 19:3635-3648, 2001

2. Balch CM, Soong SJ, Gershenwald JE, et al: Prognostic factors analysis of 17,600 melanoma patients: Validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol 19:3622-3634, 2001

3. Edge SE, Byrd DR, Compton CC, et al (eds): AJCC Cancer Staging Manual. New York, NY, Springer, 2009

4. Ohsie SJ, Sarantopoulos GP, Cochran AJ, et al: Immunohistochemical characteristics of melanoma. J Cutan Pathol 35:433-444, 2008

5. Scolyer RA, Mihm MC Jr, Cochran AJ: Pathology of melanoma, in Balch CM, Houghton AN, Sober AJ, et al (eds): Cutaneous Melanoma. St. Louis, MO, Quality Medical Publishing, 2009, pp 205-250

6. Spanknebel K, Coit DG, Bieligk SC, et al: Characterization of micrometastatic disease in melanoma sentinel lymph nodes by enhanced pathology: Recommendations for standardizing pathologic analysis. Am J Surg Pathol 29:305-317, 2005

7. Gimotty PA, Elder DE, Fraker DL, et al: Identification of high-risk patients among those diagnosed with thin cutaneous melanomas. J Clin Oncol 25:1129-1134, 2007

8. Kesmodel SB, Karakousis GC, Botbyl JD, et al: Mitotic rate as a predictor of sentinel lymph node positivity in patients with thin melanomas. Ann Surg Oncol 12:449-458, 2005

9. Francken AB, Shaw HM, Thompson JF, et al: The prognostic importance of tumor mitotic rate confirmed in 1317 patients with primary cutaneous melanoma and long follow-up. Ann Surg Oncol 11: 426-433, 2004

10. Busam KJ: The prognostic importance of tumor mitotic rate for patients with primary cutaneous melanoma. Ann Surg Oncol 11:360-361, 2004

11. Sober AJ, Balch CM: Method of biopsy and incidence of positive margins in primary melanoma. Ann Surg Oncol 14:274-275, 2007

12. Balch CM, Cascinelli N: Sentinel-node biopsy in melanoma. N Engl J Med 355:1370-1371, 2006

13. Balch CM, Morton DL, Gershenwald JE, et al: Sentinel node biopsy and standard of care for melanoma. J Am Acad Dermatol 60:872-875, 2009

14. Carlson GW, Murray DR, Hestley A, et al: Sentinel lymph node mapping for thick (> or = 4-mm) melanoma: Should we be doing it? Ann Surg Oncol 10:408-415, 2003

15. Cascinelli N, Belli F, Santinami M, et al: Sentinel lymph node biopsy in cutaneous melanoma: The WHO Melanoma Program experience. Ann Surg Oncol 7:469-474, 2000

16. Cascinelli N, Bombardieri E, Bufalino R, et al: Sentinel and nonsentinel node status in stage IB and II melanoma patients: Two-step prognostic indicators of survival. J Clin Oncol 24:4464-4471, 2006

17. Gershenwald JE, Mansfield PF, Lee JE, et al: Role for lymphatic mapping and sentinel lymph node biopsy in patients with thick (> or = 4 mm) primary melanoma. Ann Surg Oncol 7:160-165, 2000

18. Dessureault S, Soong SJ, Ross MI, et al: Improved staging of node-negative patients with intermediate to thick melanomas (> 1 mm) with the use of lymphatic mapping and sentinel lymph node biopsy. Ann Surg Oncol 8:766-770, 2001

19. Ferrone CR, Panageas KS, Busam K, et al: Multivariate prognostic model for patients with thick cutaneous melanoma: Importance of sentinel lymph node status. Ann Surg Oncol 9:637-645, 2002

20. Gershenwald JE, Thompson W, Mansfield PF, et al: Multi-institutional melanoma lymphatic mapping experience: The prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. J Clin Oncol 17:976-983, 1999

21. Rousseau DL Jr, Ross MI, Johnson MM, et al: Revised American Joint Committee on Cancer staging criteria accurately predict sentinel lymph node positivity in clinically node-negative melanoma patients. Ann Surg Oncol 10:569-574, 2003

22. Buzaid AC, Ross MI, Balch CM, et al: Critical analysis of the current American Joint Committee on Cancer staging system for cutaneous melanoma and proposal of a new staging system. J Clin Oncol 15:1039-1051, 1997

23. Balch CM: Microscopic satellites around a primary melanoma: Another piece of the puzzle in melanoma staging. Ann Surg Oncol 16:1092-1094, 2009

24. Kimsey TF, Cohen T, Patel A, et al: Microscopic satellitosis in patients with primary cutaneous melanoma: Implications for nodal basin staging. Ann Surg Oncol 16:1176-1183, 2009

25. Rao UN, Ibrahim J, Flaherty LE, et al: Implications of microscopic satellites of the primary and extracapsular lymph node spread in patients with high-risk melanoma: Pathologic corollary of Eastern Cooperative Oncology Group Trial E1690. J Clin Oncol 20:2053-2057, 2002

26. Shaikh L, Sagebiel RW, Ferreira CM, et al: The role of microsatellites as a prognostic factor in primary malignant melanoma. Arch Dermatol 141: 739-742, 2005

27. Neuman HB, Patel A, Ishill N, et al: A single-institution validation of the AJCC staging system for stage IV melanoma. Ann Surg Oncol 15:2034-2041, 2008

28. Bedikian AY, Johnson MM, Warneke CL, et al: Prognostic factors that determine the long-term survival of patients with unresectable metastatic melanoma. Cancer Invest 26:624-633, 2008

29. Keilholz U, Martus P, Punt CJ, et al: Prognostic factors for survival and factors associated with long-term remission in patients with advanced melanoma receiving cytokine-based treatments: Second analysis of a randomised EORTC Melanoma Group trial comparing interferon-alpha2a (IFNalpha) and interleukin 2 (IL-2) with or without cisplatin. Eur J Cancer 38:1501-1511, 2002

30. Manola J, Atkins M, Ibrahim J, et al: Prognostic factors in metastatic melanoma: A pooled analysis of Eastern Cooperative Oncology Group trials. J Clin Oncol 18:3782-3793, 2000

31. Barth A, Wanek LA, Morton DL: Prognostic factors in 1,521 melanoma patients with distant metastases. J Am Coll Surg 181:193-201, 1995

32. Balch CM, Soong SJ, Murad TM, et al: A multifactorial analysis of melanoma. IV. Prognostic factors in 200 melanoma patients with distant metastases (stage III). J Clin Oncol 1:126-134, 1983

33. Cormier JN, Xing Y, Feng L, et al: Metastatic melanoma to lymph nodes in patients with unknown primary sites. Cancer 106:2012-2020, 2006

34. Lee CC, Faries MB, Wanek LA, et al: Improved survival after lymphadenectomy for nodal metastasis from an unknown primary melanoma. J Clin Oncol 26:535-541, 2008

