Final Version of 2009 AJCC Melanoma Staging and Classification


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/mm²), 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 vs visceral) 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.

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...
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 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 1. TNM Staging Categories for Cutaneous Melanoma

<table>
<thead>
<tr>
<th>Classification</th>
<th>Thickness (mm)</th>
<th>Ulceration Status/Mitoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>T1</td>
<td>≤ 1.00</td>
<td>a: Without ulceration and mitosis &lt; 1/mm²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: With ulceration or mitoses ≥ 1/mm²</td>
</tr>
<tr>
<td>T2</td>
<td>1.01-2.00</td>
<td>a: Without ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: With ulceration</td>
</tr>
<tr>
<td>T3</td>
<td>2.01-4.00</td>
<td>a: Without ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: With ulceration</td>
</tr>
<tr>
<td>T4</td>
<td>&gt; 4.00</td>
<td>a: Without ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: With ulceration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>No. of Metastatic Nodes</th>
<th>Nodal Metastatic Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>N1</td>
<td>1</td>
<td>a: Micrometastasis†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: Macrometastasis†</td>
</tr>
<tr>
<td>N2</td>
<td>2-3</td>
<td>a: Micrometastasis†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: Macrometastasis†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c: In transit metastases/satellites without metastatic nodes</td>
</tr>
<tr>
<td>N3</td>
<td>4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>M</th>
<th>Site</th>
<th>Serum LDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastases</td>
<td>NA</td>
</tr>
<tr>
<td>M1b</td>
<td>Distant skin, subcutaneous, or nodal metastases</td>
<td>Normal</td>
</tr>
<tr>
<td>M1c</td>
<td>All other visceral metastases</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Any distant metastasis</td>
<td>Elevated</td>
</tr>
</tbody>
</table>

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

### 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

<table>
<thead>
<tr>
<th>Clinical Staging*</th>
<th>Pathologic Staging†</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>N</td>
</tr>
<tr>
<td>0</td>
<td>Tis</td>
</tr>
<tr>
<td>IA</td>
<td>T1a</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
</tr>
<tr>
<td>IIA</td>
<td>T2a</td>
</tr>
<tr>
<td>IIB</td>
<td>T3a</td>
</tr>
<tr>
<td>III</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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</table>

*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.
Primary tumor thickness. Recommendations for using melanoma thickness in TNM categories and stage groupings in the seventh edition remain unchanged, i.e., 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 ($P < 0.0001$). 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 ($P < 0.0001$).

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 ($P < 0.0001$). 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 ($r^2 = 79.1$; $P < 0.0001$).

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
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% vs 87%; $P = .41$). Therefore, the Melanoma Staging Committee has recommended that mitotic rate

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<thead>
<tr>
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<tbody>
<tr>
<td>Thickness</td>
<td>Primary determinant of T staging</td>
<td>Same</td>
<td>Thresholds of 1.0, 2.0, and 4.0 mm</td>
</tr>
<tr>
<td>Level of invasion</td>
<td>Used only for defining T1 melanomas</td>
<td>Same</td>
<td>Used as a default criterion only if mitotic rate cannot be determined</td>
</tr>
<tr>
<td>Ulceration</td>
<td>Included as a secondary determinant of T and N staging</td>
<td>Same</td>
<td>Signifies a locally advanced lesion; dominant prognostic factor for grouping stages I, II, and III</td>
</tr>
<tr>
<td>Mitotic rate per $mm^2$</td>
<td>Not used</td>
<td>Used for categorizing T1 melanoma</td>
<td>Mitosis $\geq 1/mm^2$ used as a primary criterion for defining T1b melanoma</td>
</tr>
<tr>
<td>Satellite metastases</td>
<td>In N category</td>
<td>Same</td>
<td>Merged with in transit lesions</td>
</tr>
<tr>
<td>Immunohistochemical detection of nodal metastases</td>
<td>Not included</td>
<td>Included</td>
<td>Must include at least one melanoma-associated marker (eg, HMB-45, Melan-A, MART-1) unless diagnostic cellular morphology is present</td>
</tr>
<tr>
<td>0.2 mm threshold of defined N+</td>
<td>Implied</td>
<td>No lower threshold of staging N+ disease</td>
<td>Isolated tumor cells or tumor deposits $&lt; 0.1 mm$ meeting the criteria for histologic or immunohistochemical detection of melanoma should be scored as N+</td>
</tr>
<tr>
<td>Number of nodal metastases</td>
<td>Primary determinant of N staging</td>
<td>Same</td>
<td>Thresholds of 1 v 2-3 v 4+ nodes</td>
</tr>
<tr>
<td>Metastatic volume</td>
<td>Included as a second determinant of N staging</td>
<td>Same</td>
<td>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</td>
</tr>
<tr>
<td>Lung metastases</td>
<td>Separate category as M1b</td>
<td>Same</td>
<td>Has a somewhat better prognosis than other visceral metastases</td>
</tr>
<tr>
<td>Elevated serum LDH</td>
<td>Included as a second determinant of M staging</td>
<td>Same</td>
<td>Recommend a second confirmatory LDH level if elevated</td>
</tr>
<tr>
<td>Clinical v pathologic staging</td>
<td>Sentinel node results incorporated into definition of pathologic staging</td>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: LDH, lactate dehydrogenase.
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/mm². 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 vs 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 < .0001). 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 subgroups 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

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

<table>
<thead>
<tr>
<th>T Category</th>
<th>Tumor Thickness</th>
<th>Ulceration</th>
<th>Mitotic Rate</th>
<th>Clark Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>χ²</td>
<td>P</td>
<td>χ²</td>
<td>P</td>
</tr>
<tr>
<td>T1</td>
<td>12.8</td>
<td>.0003</td>
<td>3.8</td>
<td>.05</td>
</tr>
<tr>
<td>T2</td>
<td>4.9</td>
<td>.03</td>
<td>16.2</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>T3</td>
<td>4.1</td>
<td>.04</td>
<td>15.4</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>T4</td>
<td>0.2</td>
<td>.89</td>
<td>14.2</td>
<td>.0002</td>
</tr>
</tbody>
</table>
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 in-
cluded in the analysis. The value of these histologic characteristics
for microstaging strongly supports that the initial biopsy is a criti-
cal 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 mu-
cosal or ocular melanomas.

The AJCC Melanoma Staging Committee recommends that sen-
tinel lymph node biopsy be performed as a staging procedure in
patients for whom the information will be useful in planning subse-
quent 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 unin-
involved regional lymph nodes; the procedure should be recom-
med 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 ≥ 1/
mm² and a thickness of ≥ 0.76 mm are associated with an approxi-
ately 10% risk of occult metastases in their sentinel lymph nodes (J.
Gershwenwald, 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 re-
quired 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 chang-
ing demographic in melanoma, most patients with histologically con-
formed stage III melanoma at diagnosis now present with clinically unin-
involved regional nodes and micrometastases diagnosed by sentinel
lymph node biopsy. Such improved staging translates into more re-
fined (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. Neverthe-
less, 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 inflamma-
tion) 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 Commit-
tee has recommended that this feature of early lymphatic metastases
be retained in the category of N2c melanoma.

The updated AJCC Melanoma Staging Database clearly demon-
strates that an elevated serum LDH is an independent and highly
significant predictor of survival or outcome of stage IV patients, inde-
pendent 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 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 Mel-
anoma Staging Database. However, this feature was not incorporated
into the staging system because of significant variability in the deploy-
ment of diagnostic tests to comprehensively search for distant metas-
tases 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 metas-
tases. In patients with a presumed single skin metastasis from an
unknown primary site, pathology review by an experienced mela-
noma pathologist is appropriate to confirm that the lesion is not a
variant of a primary melanoma, particularly a melanoma with a re-
gressed junctional component. All other presentations (ie, metastases
to a visceral site and no known primary melanoma) should be catego-
rized as stage IV melanoma, using the M1 classification criteria de-
scribed above reflecting metastatic site and serum LDH status.

Finally, the prognostic factors included in the melanoma stag-
ing 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.
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