

2010 TNM Staging System for Cutaneous Melanoma... and Beyond

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The American Joint Committee on Cancer (AJCC) has partnered with the *Annals of Surgical Oncology* to publish a series of editorials that highlight revisions in staging criteria for major cancer types from the recently published 7th edition of the *AJCC Cancer Staging Manual*.¹ Cancer registrars nationwide will begin to use these updates when they take effect in January 2010. This editorial, which focuses on the melanoma staging system, is the first in a series designed to outline the revisions of specific staging systems for the *Annals of Surgical Oncology* readership.

2010 TNM STAGING SYSTEM FOR CUTANEOUS MELANOMA

The AJCC 6th edition melanoma staging system was characterized by major revisions to cutaneous melanoma staging that was based on an evidence-based approach that used an international collaborative database developed exclusively for this purpose, and it has been widely adopted over the past 5 years.² On the basis of the success of this collaborative model, and in preparation for making recommendations for the 7th edition, the AJCC Melanoma Staging Committee greatly expanded the AJCC melanoma staging database to include nearly 60,000 patients from 17 cancer centers and organizations. We used this approach to

evaluate an array of contemporary clinicopathologic factors, and recommendations for revisions to the melanoma tumor, node, metastasis system (TNM) categories and stage groupings for the 7th edition were established and validated.^{1,3}

HIGHLIGHTS OF THE 7TH EDITION OF THE AJCC MELANOMA STAGING SYSTEM

Key features of the recommendations to the TNM melanoma staging system for the 7th edition include the following:

1. Melanoma thickness and tumor ulceration continue to define T category strata.
2. Primary tumor mitotic rate (histologically defined as mitoses/mm²) is an important independent adverse predictor of survival. For T1 melanomas, a mitotic rate of at least 1 mitosis/mm² replaces level of invasion as a primary criterion for defining the subcategory of T1b.
3. The presence of nodal micrometastases can be defined by either hematoxylin and eosin or immunohistochemical staining (previously, only hematoxylin and eosin staining could be used for formal staging purposes).
4. There is no lower threshold of tumor burden used to define the presence of regional nodal metastasis. Specifically, as a result of the consensus that volumes of regional metastatic tumor <0.2 mm in diameter (previously used as the threshold for defining nodal metastasis in the AJCC 6th edition) are clinically important, nodal tumor deposits of any size are to be included in staging nodal disease. An evidence-based

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lower threshold of clinically insignificant nodal metastases has not been defined.

5. M-category strata continue to be primarily defined by the site or sites of distant metastases: nonvisceral (i.e., skin/soft tissue/distant nodal, M1a), lung, (M1b), and all other visceral metastatic sites (M1c). An increased serum lactic dehydrogenase level also remains a powerful adverse predictor of survival; patients with such an increase are all categorized as M1c, regardless of the site or sites of distant disease.
6. Survival estimates for patients with intralymphatic regional metastases (i.e., satellite and in-transit metastases) are somewhat better than for the remaining cohort of patients with stage IIIB disease. However, because stage IIIB represents the closest statistical fit for this group, the current staging definition for intralymphatic regional metastasis has been retained.
7. The Melanoma Staging Committee recommended that the relatively uncommon feature known as *microsatellites*—defined as any discontinuous nest of metastatic cells >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—be retained in the N2c category, largely because data in the published literature are insufficient to substantiate a revision of the definitions used in the 6th edition of the staging manual.
8. The staging definition of metastatic melanoma from an unknown primary site was clarified, such that the disease of patients with metastatic melanoma arising in lymph nodes, skin, or subcutaneous tissues without a known associated primary melanoma is to be categorized as stage III rather than stage IV.
9. The definitions of primary tumor ulceration, mitotic rate, and microsatellites were clarified.
10. Lymphoscintigraphy followed by lymphatic mapping and sentinel lymph node biopsy (sentinel lymphadenectomy) remain important components of melanoma staging and should be used (or discussed with the patient) to identify occult stage III regional nodal disease among patients with clinical stage IB or II melanoma.

MITOTIC RATE

Because the introduction of mitotic rate as a T1 category criterion represents an important change in the revised melanoma staging system, additional discussion regarding this primary tumor criterion may be instructive. Primary tumor mitotic rate has been introduced as a required

element for the 7th edition of the AJCC melanoma staging system.¹ Analysis of the AJCC Melanoma Staging database demonstrated that increasing mitotic rate was associated with declining survival rates, especially within thin melanoma subgroups.³ 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.³ On the basis of these data, and because of its inclusion in AJCC staging, mitotic rate should be assessed in all primary melanomas.

As detailed in the 7th edition of the *AJCC Cancer Staging Manual*, the recommended approach to enumerating mitoses is to first find the areas in the dermis containing the most mitotic figures, the so-called hot spot.¹ After counting the mitoses in the hot spot, the count is extended to adjacent fields until an area corresponding to 1 mm² is assessed. If no hot spot can be found and mitoses are sparse and randomly scattered throughout the lesion, then a representative mitosis is chosen, and beginning with that field, the count is then extended to adjacent fields until an area corresponding to 1 mm² is assessed. The count is then expressed as the number of mitoses/mm². To accurately record mitoses, calibration of individual microscopes is recommended; as a guide, 1 mm² corresponds to an area corresponding to approximately four high-power fields at ×400 in most, but not all, microscopes. For classifying T1 (i.e., up to and including 1 mm) melanomas, the threshold for a nonulcerated melanoma to be defined as T1b is ≥1 mitoses/mm². When the invasive component of tumor is <1 mm² (in area), the number of mitoses present in 1 mm² of dermal tissue that includes the tumor should be enumerated and recorded as a number per square millimeter. Alternatively, in tumors whose invasive component comprises an area of <1 mm², the simple presence or absence of a mitosis can be designated as *at least 1/mm²* (i.e., “mitogenic”) or *0/mm²* (i.e., “nonmitogenic”), respectively. At some institutions, when mitotic figures are not found after examining numerous fields, the mitotic count has been described as <1/mm². For most tumor registries, the designation “<1/mm²” is synonymous with zero, as has been customarily used in the past. Although this practice may be continued for historical data, the AJCC Melanoma Staging Committee urges pathologists to use the approach outlined above beginning in 2010.¹

HETEROGENEITY OF STAGE III MELANOMA

Particularly noteworthy is the remarkable heterogeneity of patients with stage III melanoma. On the basis of assessment of three independent predictors of survival for this patient cohort, first introduced in the 6th edition and validated in this 7th edition—including number of lymph

nodes involved, presence or absence of primary tumor ulceration, and assessment of nodal tumor burden (empirically defined as micro- or macroscopic)—5-year survival estimates range from 81.5% in a patient with a single microscopically positive lymph node (by sentinel node biopsy) whose primary tumor was not ulcerated, to 29% for patients with four or more macroscopically involved nodes in a patient whose primary tumor was ulcerated.⁴

BEYOND TNM-BASED STAGING

Despite the robust evidence-based nature of the TNM-based AJCC melanoma staging system, additional survival-based analyses have provided further insight regarding the relative contribution of a multitude of factors, clinicopathologic and otherwise, to patient prognosis and survival. For example, despite the significant predictive capacity of the TNM-based melanoma staging system, it is inherently constrained by its design. AJCC database analyses demonstrate that important predictors of patient survival are provided by factors not currently in the AJCC staging system (e.g., patient age, anatomic site of primary tumor, extent of microscopic nodal tumor burden, number of sites of distant metastases) that combined with the TNM-based system can more accurately reflect an individual patient's prognosis.

In an initial proof-of-concept study outside the scope of the AJCC Melanoma Staging Committee's charge to revise the current staging system, the AJCC has attempted to leverage this enhanced evidence-based appreciation of melanoma prognosis. Individualized patient prognostic models and associated electronic prediction tools for localized (stages I and II) and regional (stage III) melanomas were recently developed.⁵ Despite the limitations of any prognostic modeling endeavor, these electronic prediction tools incorporate lessons learned from the recent AJCC database analysis, as evidenced by inclusion of covariates/key prognostic features not included in the TNM-based AJCC melanoma staging system, and therefore may more accurately estimate survival for melanoma patients than even the validated 7th edition of the AJCC staging system. An initial version of such an individualized patient prognostic model is currently available on the

Internet (<http://www.melanomaprognosis.org>).⁵ Following on-screen prompts, data for key stage-specific prognostic criteria may be directly entered via drop-down menus. On the basis of the data entered, these electronic tools produce, in real time, an individual patient's estimated 1-, 2-, 5-, and 10-year survival with associated 95% confidence intervals.⁵

In the future, it is anticipated that our depth of understanding regarding relevant stage-specific prognostic factors will continue to expand, not only on the basis of currently known or putative prognostic factors, but importantly also on factors not yet known or considered to be important. The increase and expansion of molecular-based profiling studies in melanoma that have begun to define morphogenetic correlates in melanoma, as well as the recently announced inclusion of melanoma in The Cancer Genome Atlas (TCGA) project (http://cancergenome.nih.gov/wwd/tumor_types.asp), will likely allow further refinements in individualized prognosis going forward.

Leveraging our increased knowledge with the ability to harness the Internet will enable individuals to easily use these lessons learned. We are confident that Web-based platforms will facilitate the use of ever more complex, clinically relevant data for patient prognosis, treatment decision making, and clinical trial design and analysis in the foreseeable future.

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