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Implications of the 2009 American Joint Committee on Cancer Melanoma Staging and Classification on Dermatologists and Their Patients

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The Melanoma Staging and Classification system was recently revised by the American Joint Committee on Cancer (AJCC) and implemented effective January 2010 with changes reflecting new prognostic data gleaned by the significantly larger patient population studied for the 7th edition. This newest analysis yields important long-term outcome data as many of the patients were followed for nearly 2 decades. Additions to edition 7 of the AJCC Melanoma Staging classification highlight several important prognostic factors, particularly the addition of mitotic rate for classifying thin melanomas, the presence of microtumor burden in lymph nodes for stage III disease, and elevated lactate dehydrogenase levels in patients with distant metastatic disease. Although the basic tumor-nodes-metastases (ie, TNM) cancer classification model remains unchanged in this newest edition, the current AJCC Melanoma Staging System has incorporated the latest prognostic data to accurately stratify patients into staging categories. It is important for clinicians and dermatopathologists to familiarize themselves with these changes so that patients are suitably managed and referred to medical and surgical oncologists when appropriate.
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The 7th edition of the American Joint Committee on Cancer (AJCC) Melanoma Staging and Classification was published in December 2009 reflecting a detailed analysis of nearly 60,000 patients from multiple centers worldwide and spanning more than 20 years.[1,2] Although the framework for the staging system and tumor-nodes-metastases (TNM) classification remains largely unchanged, the expanded patient population, as well as longer follow-up, in this newest analysis highlights several important prognostic factors, including the addition of mitotic rate for classifying thin melanomas, the presence of microtumor burden in lymph nodes, and elevated lactate dehydrogenase (LDH) levels in patients with distant metastatic disease (Table 1).[1-3] The inclusion of these new data into the 7th AJCC Staging System is to ensure that all patients within a specific stage of disease have comparable prognosis and survival rates. Appropriate stratification into staging categories will help identify which patients are most likely to benefit from sentinel lymph node (SLN) biopsies, completion lymph node dissections, adjuvant therapies, and eligibility for clinical trials. It is important for clinicians and dermatopathologists to familiarize themselves with the newest AJCC melanoma staging recommendations so that their patients receive the most accurate prognostic information and appropriate therapeutic interventions.

The foundation of melanoma staging is based upon the familiar TNM cancer classification model involving primary tumor thickness (T), regional nodal involvement (N), and the presence or absence of distant metastases (M; Tables 2 and 3). Melanoma is one of the first cancers to link this standard TNM staging model with clinical outcomes and prognosis as was proposed in the 6th AJCC Melanoma Staging System.[2,4,5] The sophisticated interplay between TNM and melanoma staging with prognosis and outcome is constantly evolving as our understanding of melanoma expands. The basic TNM classification for melanoma remains largely unchanged from the 6th AJCC Staging System in that primary tumor thickness remains the most significant prognostic factor in patient survival.[1-3] Thickness intervals remain as ≤1 mm, 1.01 to 2 mm, 2.01 to 4 mm, or >4 mm for T1-T4 classifications, respectively.[1,3-5]

An important new addition is mitotic rate per millimeter squared (mm^2) in distinguishing T1a from T1b disease.[1,3] Previously, T1a and T1b disease had been distinguished by the histopathologic presence of ulceration or by Clark's level

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Table 1 Changes in the Melanoma Staging System Comparing the 6th (2002) Version with the Current Version (2009)

Factor	6th Edition Criteria	7th Edition Criteria	Comments
Thickness	Primary determinant of T staging; thresholds of 1.0, 2.0, 4.0 mm	Same	Correlation of metastatic risk is a continuous variable
Level of invasion	Used only for defining T1 melanoma	No longer used	Clark's levels of IV or V may be used in rare instances as a criterion for defining T1b melanoma *only* if mitotic rate cannot be determined in a nonulcerated T1 melanoma
Ulceration	Included as a second determinant of T and N staging	Same	Signifies a locally advanced lesion; dominant prognostic factor for group stage 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 determinant for defining T1b melanoma
Satellite metastases	In N category	Same	Merged with in transit lesions
Immunohistochemical detection of nodal metastases	Not allowed	Allowed	Must include at least one melanoma-specific marker (eg, HMB-45, Melan-A, Mart 1)
0.2-mm threshold of defined node-positive	Implied	No lower threshold of staging node-positive disease	
Number of nodal metastases	Dominant determinant of N staging	Same	Thresholds of 1 vs 2-3 vs ≥4 nodes
Metastatic "volume"	Included as a second determinant of N staging	Same	Clinically occult ("microscopic") vs clinically apparent ("macroscopic") nodal volume
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 if elevated
Clinical vs 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 and should be required prior to entry into clinical trials

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LDH, lactate dehydrogenase.

of invasion (IV/V).[4,5] After accounting for mitotic rate and tumor ulceration, the level of invasion no longer correlated with survival outcome for patients with primary melanoma ≤1 mm in multivariate analyses.[1-3] Recent reports detailing the importance of mitoses in predicting survival were confirmed by analysis of the current AJCC melanoma database which found that mitoses, even as few as $1/mm^2$, were an independent predictor of survival after adjusting for other known predictive factors (Table 4) and an inverse relationship between increasing mitotic rate and survival in clinically localized melanomas was found.[1-3] Although patients with mitotically active thin melanomas had worse survival trends, it is unclear whether mitotic rate $\geq 1/mm^2$ is associated with greater rates of occult node−positive disease, although preliminary studies suggest that this frequency may be as high as 5% to 10%.[1,3,6,7] The role of mitoses in regionally metastatic disease was not specifically addressed in the revised AJCC Melanoma Staging guidelines; however, a recent study in which the authors evaluated prognostic factors among patients with stage III disease found mitotic rate second only to number of disease-positive nodes as an independent predictor of survival in patients with microscopic stage III disease.[8] As documentation of mitotic rate in primary tumors becomes universally performed, further studies assessing the significance of mitotic activity in all stages of melanoma will be possible.

It is currently recommended that dermatopathologists use the "hot-spot" approach in determining number of mitoses in melanoma patients.[1-3] This involves locating the most mitotically active area of invasive melanoma on the slide and counting the number of mitoses per millimeter squared, roughly equal to 4 adjacent high power views at 400× magnification.[1-3] In thin melanomas where the total area of vertical growth comprises $<1\ mm^2$, a single mitotic figure can be classified as at least $1/mm^2$ and no mitoses should be documented as $0/mm^2$.[2] Although a mitotic rate of $<1/mm^2$

Table 2 Definitions of TNM for the Revised 7th Edition AJCC Melanoma Staging Classification

Classification		
Primary Tumor (T)	**Thickness (mm)**	**Ulceration Status/Mitoses**
T classification		
T1	≤1.0	a. Without ulceration and mitosis $<1/mm^2$
		b. With ulceration or mitoses $\geq 1/mm^2$
T2	1.01-2.0	a. Without ulceration
		b. With ulceration
T3	2.01-4.0	a. Without ulceration
		b. With ulceration
T4	>4	a. Without ulceration
		b. With ulceration
TX	Primary tumor cannot be assessed (eg, curettaged or severely regressed melanoma)	
T0	No evidence of primary tumor	
Tis	Melanoma in situ	

Regional Lymph Nodes (N)	**No. of Metastatic Nodes**	**Nodal Metastatic Mass**
N classification		
N1	1 node	a. Micrometastasis*
		b. Macrometastasis†
N2	2-3 nodes	a. Micrometastasis*
		b. Macrometastasis†
		c. In transit met(s)/satellite(s) without metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) *with* metastatic node(s)	
NX	Patients in whom the regional nodes cannot be assessed (eg, previously removed for another reason)	
N0	No regional metastases detected	

Distant Metastasis (M)	**Site**	**Serum LDH**
M classification		
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastases	Elevated
M0	No detectable evidence of distant metastases	

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AJCC, American Joint Committee on Cancer Staging; LDH, lactate dehydrogenase; TNM, tumor-nodes-metastases.

*Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed).

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

had previously been used to indicate a mitotic rate of zero, the current AJCC recommendations encourage dermatopathologists to adopt this newer and more specific terminology when assessing mitotic rate.[2]

Unlike the 6th AJCC Staging System, Clark's level of invasion is no longer recognized as an independent predictor of survival in thin primary melanomas after the addition of mitotic rate in defining T1b disease and it is no longer recommended to distinguish T1a and T1b disease.[1,3] This may be attributable to the variability among dermatopathologists in classifying level of invasion, which was often subjective with great inter-reader variability. Today, use of level of invasion in distinguishing more aggressive disease should only be used in thin melanomas in the rare circumstance when mitotic rate cannot be accurately assessed.[1,2] As before, ulceration remains an important distinction between Ta and Tb disease in both the 6th and 7th AJCC staging criteria and its histologic presence is an ominous sign of more aggressive disease (Table 5).[1,3-5]

To date, the patient population from the AJCC melanoma database with stage III disease represents the largest collection of melanoma patients with regional disease ever studied.[1] In addition, these patients were followed for up to 20 years after their diagnosis of melanoma, allowing long-term survival data and prognosis to be gleaned.[1] As before, the number of tumor-involved regional lymph nodes defines the N subclass of the TNM classification with 1 positive node as N1, 2 to 3 positive nodes as N2, and 4 or more positive nodes as N3.[1,3-5] Unlike prior staging classifications, the 7th edition considers any degree of involvement of the lymph nodes as

Table 3 Anatomic Stage/Prognostic Groups for the Revised 7th Edition AJCC Melanoma Staging Classification

Anatomic Stage/Prognostic Groups							
	Clinical Staging*				Pathologic Staging†		
Stage 0	Tis	N0	M0	0	Tis	N0	M0
Stage IA	T1a	N0	M0	IA	T1a	N0	M0
Stage IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
Stage IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
Stage IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
Stage IIC	T4b	N0	M0	IIC	T4b	N0	M0
Stage III	Any T	≥N1	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
Stage IV	Any T	Any N	M1	IV	Any T	Any N	M1

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AJCC, American Joint Committee on Cancer Staging.

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

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

"node involved disease" and therefore stage III, regardless of the extent of tumor burden.[1,2]

In contrast to breast cancer, there has been no definitive lower threshold in which the presence of micro metastatic nodal disease can be considered insignificant in cutaneous melanoma. Stage III disease had previously been divided into clinically evident disease, consisting of macroscopic or radiographically detectable lymph nodes, versus pathologic disease, where microscopic nodal disease is found with standard hematoxylin and eosin staining in patients without clinically evident disease.[2,3]

With the increased frequency of SLN mapping during the past several years, the incidence of pathologic stage III disease at the time of initial diagnosis has increased considerably from the identification of clinically occult node positive disease.[1,3] As SLN biopsies and ease in which laboratories can perform immunohistochemical (IHC) staining on samples have increased worldwide, the most recent recommendations for identifying node-positive disease include microscopic disease visualized with IHC using at least 1 melanoma-specific antibody (HMB-45, Melan-A/MART-1).[1-3]

While the number of nodes involved retains the greatest prognostic significance, the new staging criteria allows for even a single microscopic cell of melanoma on IHC staining to classify a patient with regional or stage III disease.[1-3]

Table 4 Survival Rates for 4861 T1 Melanoma Patients (1.00 mm or less) Subgrouped by Thickness and Mitotic Rate of the Primary Melanoma

Thickness, mm	Mitosis, mm²	n	Survival Rate ± SE 5-Year	Survival Rate ± SE 10-Year
0.01-0.50	<1.0	1194	0.991 ± 0.004	0.974 ± 0.086
0.01-0.50	≥1.0	327	0.970 ± 0.012	0.952 ± 0.017
0.51-1.00	<1.0	1472	0.977 ± 0.005	0.930 ± 0.010
0.51-1.00	≥1.0	1868	0.935 ± 0.006	0.871 ± 0.012

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Table 5 Multivariate Cox Regression Analysis of Prognostic Factors in 10,233 Patients With Localized Cutaneous Melanoma (Stage I and II)

Variable	Chi-Square Values (1 Df)	*P* Value	HR	95% CI
Tumor thickness	84.6	<0.0001	1.25	1.19-1.31
Mitotic rate	79.1	<0.0001	1.26	1.20-1.32
Ulceration	47.2	<0.0001	1.56	1.38-1.78
Age	40.8	<0.0001	1.16	1.11-1.22
Gender	32.4	<0.0001	0.70	0.62-0.79
Site	29.1	<0.0001	1.38	1.23-1.54
Clark's level	8.2	0.0041	1.15	1.04-1.26

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CI, confidence interval; HR, hazard ratio.

Table 6 2008 AJCC Melanoma Staging Database: Five- and Ten-Year Survival Rates for Stage III Melanoma Substages

Stage	n	Survival Rate ± SE	
		5-Year	10-Year
IIIA	1196	0.78 ± 0.02	0.68 ± 0.02
IIIB* (including N2c)	1391	0.59 ± 0.02	0.43 ± 0.02
IIIB (excluding N2c)	992	0.54 ± 0.02	0.38 ± 0.03
IIIC	720	0.40 ± 0.02	0.24 ± 0.03

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AJCC, American Joint Committee on Cancer.
*399 N2c patients (intralymphatic metastases) had 5- and 10-year survival rates of 69% and 52%.

Clearly, many patients previously considered to have had node-negative stage II disease will be up-staged to node-positive stage III disease on the basis of the newest AJCC histopathologic staging recommendations. This change has lead to drastic variability among survival rates in patients with stage III disease, with a range from 40% to 78% 5-year survival (Table 6).[1] Stage III disease has been further partitioned into 3 substages (A-C) on the basis of the number of positive nodes and microscopic versus macroscopic disease burden to help correct for the striking differences in patient survival.[1] At this time, there is no evidence to suggest a threshold for clinically irrelevant node positive disease in melanoma as there is in breast cancer staging (<0.2 mm).[2] Given the profound heterogeneity in survival among patients with node positive disease, there are likely additional important prognostic variables involved beyond number of involved lymph nodes and microscopic versus macroscopic tumor burden. A recent study attempting to characterize these very prognostic factors in stage III disease found that in patients with microscopic nodal disease, features of the primary tumor, such as tumor thickness, mitotic rate, and ulceration, were independent predictors of survival whereas the number of positive nodes and patient age were more predictive of survival in patients with macroscopic nodal disease.[8]

The importance of intralymphatic metastases was again highlighted in the 7th AJCC Staging System with satellite (including microsatellite) and in-transit metastases showing a less favorable prognosis for survival, regardless of the number of lesions.[1,3] These patients are again classified as N2c disease if there are no associated positive regional lymph nodes or N3 if there is regional nodal involvement. Although intralymphatic metastases were once hypothesized and shown in select studies to be an important marker for predicting positive lymph node involvement, these claims have not been validated in subsequent studies.[9] The newest survival analyses by the AJCC melanoma database show a more favorable prognosis than initially believed for satellite and in-transit metastases, even having a more favorable prognosis than other individuals with stage IIIB disease.[1-3] The 5- and 10-year survival for patients with in-transit and satellite metastases (N2c) are 69% and 52%, respectively.[1]

Distant spread of melanoma, or stage IV disease, portends the poorest prognosis in all patients with melanoma ranging from 40% to 60% one-year survival.[1] Some survival differences have been found depending on the site of distant metastases, including distant skin, subcutaneous tissue or distant lymph nodes (M1a) having a slightly more favorable

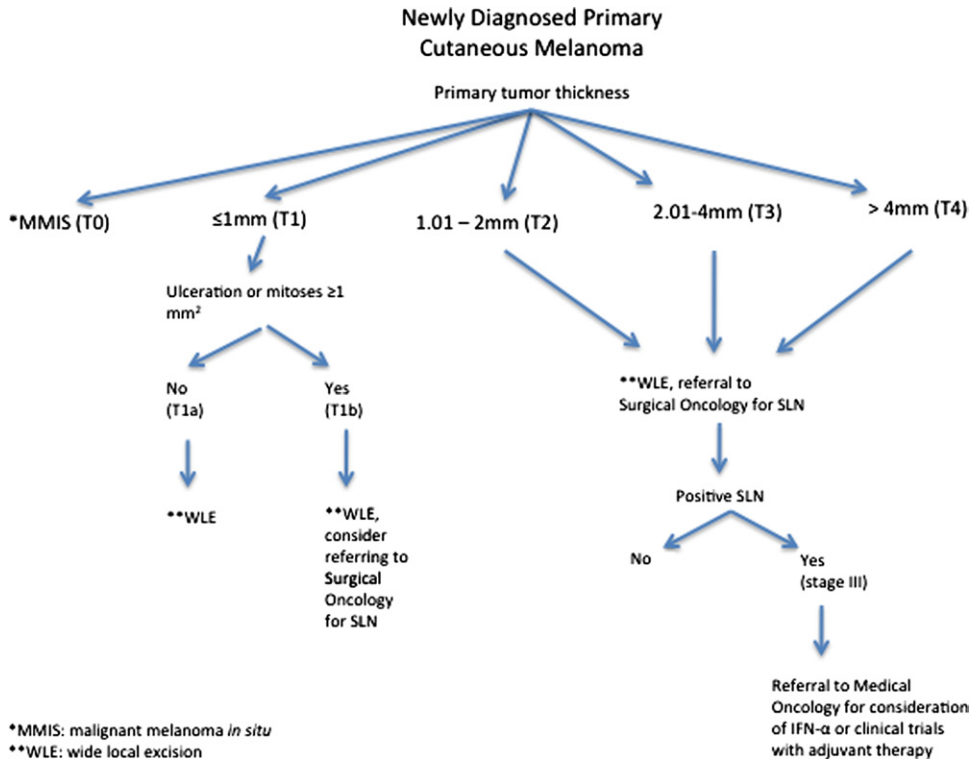

Figure 1 Flow diagram for the management of newly diagnosed primary cutaneous melanoma.

prognosis, pulmonary metastases (M1b) with an intermediate prognosis, and visceral metastases (M1c) with the worst prognosis for stage IV disease. Reaffirmed in the 7th AJCC Staging System is the inclusion of elevated serum LDH in subcategorizing stage IV disease.[1-3]

The pathophysiology and cause of the elevated serum LDH in patients with melanoma is unclear, yet substantial survival differences have been found between patients with distant metastases and normal versus elevated LDH.[1,3,10] An elevated LDH is now considered an independent predictor of worsened survival and poor outcome.[1-3] The current recommendations are to draw an LDH level in patients with stage IV disease at presentation and if this is elevated above the upper limit of normal, repeated 24-48 hours later.[3] All patients with distant metastases and an elevated LDH are automatically classified into M1c disease, regardless of the site of distant metastases.[1-3] In contrast to subclassification of stage III disease based on number of positive nodes, the number of distant metastases is no longer incorporated into the newest staging classification based on lack of standardized methods for locating distant metastases, ranging from chest radiographs, computed tomography, magnetic resonance imaging to positron emission tomography.[4,10]

The 7th edition of the AJCC Melanoma Staging System brings together data from the largest single collection of melanoma patients studied over an extended period of time to accurately stratify patients into staging classes based on survival trends and prognostic factors. Emphasis is placed on the initial biopsies for diagnosing and accurately staging melanoma, and the AJCC recommends, when feasible, complete excisional biopsies with 1- to 2-mm margins for any pigmented lesion in which a melanoma is suspected.[3] The AJCC advocates for SLN mapping to be considered on all patients with T2-T4 disease and clinically uninvolved lymph nodes where the information gained would help guide further treatment (Fig. 1).[1-3] Clinicians should also consider SLN biopsies in patients with thin melanomas ($\leq$1 mm) with worrisome prognostic features, including ulceration or mitoses $\geq$1/mm^2 as well.[1-3] This most recent analysis performed by the AJCC Melanoma Staging Committee was one of the first to assess long-term survival and prognosis in patients after positive SLN biopsies and their data reveal that more accurate pathologic staging has translated into improved survival trends in patients with Stage Ib-IIIA melanomas.[1]

While the recommendations of the 7th edition AJCC Melanoma Staging System identify important independent prognostic variables such as increased mitotic rate and micro tumor burden of disease in regional lymph nodes, a causal relationship, if any, between these prognostic factors and worsened survival rates remains unclear. Whether increased mitotic rate in thin melanomas is associated with clinically occult disease in regional lymph nodes is unknown, although it is now suggested that these patients be offered SLN mapping in the appropriate clinical setting. In addition, more research is needed to determine if all microscopically positive disease in regional lymph nodes is significant, as now, most patients are subjected to the potential morbidity of a completion lymph node dissection. Dermatologists should be aware that all stage III patients warrant evaluation by an oncologist for consideration of high dose interferon alfa therapy or alternatively, ongoing clinical trials with adjuvant therapy.

As our understanding of melanoma expands and our ability to study and follow these patients increases, it becomes clear that melanoma prognosis and survival is much more complex than even reflected in the revised TNM staging system. There are likely a multitude of variables important for patient survival, including patient age, sex, and tumor location, as well as many yet to be discovered factors.[2] The AJCC Melanoma task force and contributors have recently developed a computer-based model which calculates an individual's survival based on an expanded list of prognostic variables.[2] It is hoped that this personalized staging tool, when combined with the standard TNM staging system, will yield more accurate prognostic data and aid physicians in managing patients and formulating treatment plans. While these new prognostic tools and studies are still in inception, the 7th edition AJCC Melanoma Staging guidelines remain the most current and evidence-based prognostic data available for melanoma patients.

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