



Jennifer Eisenpresser. *Downtown*. Oil stick on panel, 8" × 10".

*A new melanoma staging system
allows more precise classification
and improves the accuracy of
predicting the likely prognosis
and outcomes for individuals
with the disease.*

The New Melanoma Staging System

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Background: Classification schemas for cancers are useful for predicting overall survival and selecting patients for treatment. Historically, the most important factors in determining prognosis in patients with melanoma have been tumor thickness and lymph node status. Sentinel lymph node mapping defines a subset of patients with microscopic metastatic disease can be identified, offering greater accuracy in staging.

Methods: The authors reviewed studies evaluating the prognostic factors that are significant in predicting survival in patients with melanoma. The newly revised American Joint Committee on Cancer (AJCC) staging system for melanoma is compared with the 1997 AJCC staging system currently in use.

Results: The changes in the new AJCC melanoma staging system reflect the new prognostic factors that have been found to be important in predicting survival. These include primary tumor thickness (tumor depth in millimeters is more predictive than the level of invasion) and ulceration, number of metastatic lymph nodes, micrometastatic disease based on the sentinel lymph node biopsy technique or elective node dissection, the site(s) of distant metastatic disease and serum LDH levels.

Conclusions: Major revisions have been made to form a new AJCC staging system for melanoma, which will become official in 2002. This system will provide more accurate and precise information regarding patient prognosis. Validation studies are needed to confirm the accuracy of this revised staging system.

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Introduction

The worldwide incidence of malignant melanoma is increasing dramatically. Significant advances have been made over the years in prevention, early detection, and treatment of patients with melanoma. Despite these advances, the death rate continues to increase steadily. Patients with localized, early-stage disease have favorable overall outcome with cure rates of up to 90%. However, the prognosis for those patients with locoregional or metastatic systemic dis-

ease remains poor, with a median survival of 24 months and 6 months, respectively.¹

Classification schemas for cancers are valuable because they allow clinicians to identify those patients who are at high risk of developing advanced disease, compare treatment results, recommend the best therapy, and offer prognostic information to patients and their family members. In predicting overall patient survival, the staging system must take into account the histologic, biologic, and anatomic features of the primary, patterns of growth and metastases, and the natural history of the disease. For melanoma, various clinical and pathologic prognostic factors have been studied, including age, gender, race, tumor thickness, histology,

level of invasion, anatomic location, ulceration of primary lesion, and lymph node status.

Reports over the decades have shown that the most important factors for determining prognosis are thickness of the primary tumor and lymph node status, which were previously integrated into the American Joint Committee on Cancer (AJCC) staging system for melanoma. In addition, other variables have more recently been shown to be significant in predicting survival — ulceration of the primary tumor, number and site of distant metastatic disease, and lactate dehydrogenase (LDH) levels in stage IV disease. Lymphatic mapping with sentinel node biopsy has become a standard of care for melanoma, and yet microscopic vs

Table 1. — 1997 AJCC Melanoma Staging System

Primary Tumor (pT)			
pTX	Primary tumor cannot be assessed		
pT0	No evidence of primary tumor		
pTis	Melanoma in situ (atypical melanocytic hyperplasia, severe melanocytic dysplasia), not an invasive malignant lesion (Clark's level I)		
pT1	Tumor 0.75 mm or less in thickness and invades the papillary dermis (Clark's level II)		
pT2	Tumor more than 0.75 mm but not more than 1.5 mm in thickness and/or invades to papillary-reticular dermal interface (Clark's level III)		
pT3	Tumor more than 1.5 mm but not more than 4 mm in thickness and/or invades the reticular dermis (Clark's level IV)		
pT3a	Tumor more than 1.5 mm but not more than 3 mm in thickness		
pT3b	Tumor more than 3 mm but not more than 4 mm in thickness		
pT4	Tumor more than 4 mm in thickness and/or invades the subcutaneous tissue (Clark's level V) and/or satellite(s) within 2 cm of the primary tumor		
pT4a	Tumor more than 4 mm in thickness and/or invades the subcutaneous tissue		
pT4b	Satellite(s) within 2 cm of the primary tumor		
Regional Lymph Nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis 3 cm or less in greatest dimension in any regional lymph node(s)		
N2	Metastasis more than 3 cm in greatest dimension in any regional lymph node(s) and/or in-transit metastasis		
N2a	Metastasis more than 3 cm in greatest dimension in any regional lymph node(s)		
N2b	In-transit metastasis		
N2c	Both (N2a and N2b)		
<i>Note: In-transit metastasis involves skin or subcutaneous tissue more than 2 cm from the primary tumor but not beyond the regional lymph nodes.</i>			
Distant Metastasis (M)			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
M1a	Metastasis in skin or subcutaneous tissue or lymph node(s) beyond the regional lymph nodes		
M1b	Visceral metastasis		
Stage Grouping			
Stage 0	pTis	N0	M0
Stage I	pT1	N0	M0
	pT2	N0	M0
Stage II	pT3	N0	M0
Stage III	pT4	N0	M0
	Any pT	N1	M0
	Any pT	N2	M0
Stage IV	Any pT	Any N	M1
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macroscopic vs gross nodal disease is not part of the 1997 staging system for melanoma. To assess the prognosis in patients with melanoma with greater accuracy, these factors have been incorporated in the revised AJCC melanoma staging system proposed by the AJCC Melanoma Staging Committee.²

The AJCC TNM classification is based on the principle that malignant tumor cells follow a certain pattern of timely progression — the primary tumor increases in size, undergoes local invasion, spreads to regional lymph nodes, and finally progresses to systemic invasion via lymphatics or blood vessels.³ Patients with early-stage disease have a highly curative potential, while survival for locoregional and widespread metastatic disease is more guarded. In general, the TNM categories are grouped into five stages (0–IV) with relatively similar survival rates within each stage and disparate survival rates between stages.

The 1997 AJCC Melanoma Staging System

The current AJCC staging system (Table 1) classifies patients into primary tumor (T), regional lymph

nodes (N), and distant metastasis (M). Unlike many other types of tumors, the clinical staging of the primary tumor “length by width” does not correlate well with prognosis in melanoma, and the pathologic microstaging has become more meaningful in determining prognosis.⁴ Therefore, the T stage is based on microstaging of the primary tumor. Two methods of microstaging are used: (1) Breslow’s primary tumor depth,⁵ which measures thickness of the primary tumor in millimeters from top to bottom, and (2) Clark’s level (I–IV),⁶ which categorizes the tumor by the level of invasion into the dermal layers of the skin and subcutaneous fat. Using this system, satellite lesions within 2 cm of the primary tumor are categorized as T4b.

To determine lymph node status, the current staging system uses the greatest diameter of the lymph nodes involved for the classification. However, the actual gross dimensions of metastatic lymph nodes are not absolutely accurate as an independent prognostic variable.^{7,8} In addition, any lesion involving the skin or subcutaneous tissue more than 2 cm from the primary tumor is considered “in-transit metastases” and is categorized as N2 disease rather than T4 stage. In the revised staging system, this concept will

Table 2. — Revised AJCC TNM Classification

T Classification		
T1	≤1.0 mm	a: without ulceration b: with ulceration or level IV or V
T2	1.01–2.0 mm	a: without ulceration b: with ulceration
T3	2.01–4.0 mm	a: without ulceration b: with ulceration
T4	>4.0 mm	a: without ulceration b: with ulceration
N Classification		
N1	One lymph node	a: micrometastasis ^a b: macrometastasis ^b
N2	2–3 lymph nodes	a: micrometastasis ^a b: macrometastasis ^b c: in-transit met(s)/satellite(s) <i>without</i> metastatic lymph nodes
N3	4 or > metastatic lymph nodes,	matted lymph nodes, or combinations of in-transit met(s)/satellite(s) and metastatic lymph node(s)
M Classification		
M1	Distant skin, subcutaneous, or lymph node mets	Normal LDH
M2	Lung mets	Normal LDH
M3	All other visceral or any distant mets	Normal LDH Elevated LDH
mets = metastases		
^a Micrometastases are diagnosed after sentinel or elective lymphadenectomy.		
^b Macrometastases are defined as clinically detectable lymph node metastases confirmed by therapeutic lymphadenectomy or when any lymph node metastasis exhibits gross extracapsular extension.		
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change to better reflect our understanding of the tumor biology of in-transit metastasis. The classification of metastatic disease in the current staging system is simply the absence (M0) or presence (M1) of distant metastatic disease.

The New Melanoma Staging System

Advances in melanoma research and techniques over the past several decades have allowed more detailed and accurate analyses of melanoma tumors. Newer information on emerging prognostic factor (ulceration of the primary) and techniques (lymphatic mapping and sentinel node biopsy) question the accuracy and the validity of the 1997 melanoma staging system.⁷ In June 1999, the AJCC formed a committee of melanoma experts from North America, Europe, and Australia with the objective of revising the 1997 staging system for cutaneous melanoma.² It was the consensus of experts from major melanoma centers worldwide that the current staging system does not incorporate several of the prognostic factors that have been studied in recent years and determined to be important in predicting survival and outcome in patients with melanoma. A critical analysis of the 1997 staging system was published by Buzaid and colleagues,⁷ and a new staging system was proposed.²

The new melanoma staging system, which will become official in 2002, includes five major changes. (1) The level of invasion (Clark's level) is replaced by tumor thickness as the prognostic variable of primary tumor invasion that best predicts survival, (2) ulceration of primary tumor is incorporated into the staging system and patients in each T stage subgroup are upstaged, (3) the size of lymph nodes is replaced by the number of lymph nodes involved in the N staging, (4) patients are categorized into clinical and pathologic staging to incorporate lymphatic mapping data and micrometastatic disease within lymph nodes, and (5) subcategorization of stage IV metastatic disease is based on anatomic site and inclusion of an elevated serum LDH (Table 2).

T Classification

A number of clinical, histopathologic, and microstaging parameters have been studied to determine prognosis, including tumor thickness, Clark's level, ulceration, histology, S phase, mitotic index, primary site, lymphocytic infiltration, and expression of a number of different molecular markers of the primary. These studies have consistently shown that the most important independent predictors of outcome are primary tumor thickness

and ulceration.^{9,10} Analysis of histopathologic features of melanoma comparing Clark's level and Breslow's depth have shown that the actual tumor thickness is more predictive of outcome and that there are no natural breakpoints of survival, as believed previously.¹¹⁻¹⁴ Tumor thickness is best treated as a continuous variable. There is an instance in which Clark's level invasion continues to carry prognostic information: In patients with "thin" (<1.0 mm) melanoma, Clark's level IV or V lesion portends a worse prognosis. For this reason, pathologists need to continue to include Clark's level along with tumor thickness and ulceration in the histology report of the primary melanoma.

Ulceration of primary melanoma tumor carries a worse prognosis compared to non-ulcerated lesions. Multivariate analyses have shown that ulceration is an independent risk factor for developing advanced disease even when tumor thickness is taken into account.^{15,16} For each T classification, there is now a subclassification designated "a" for absence of ulceration and "b" for the presence of ulceration within the primary tumor. The T stage of the primary will be initially calculated by tumor thickness, and the presence of ulceration of the primary will increase the T stage by one level.

N Classification

Lymph node metastasis (N) is one of the most important predictors of survival in melanoma patients. Currently, the 10-year survival rates for stage III patients vary widely, ranging from 12% to 69%.¹⁷ The new classification system includes six subgroups for node-positive patients, making it somewhat more complicated but much more predictive. The 1997 staging system uses the size of metastatic lymph nodes as a predictor of survival, although it is unclear why this variable was incorporated. However, most studies have shown that the number of lymph nodes involved with tumor is a more accurate predictor of prognosis and survival than the actual gross dimensions of the involved lymph node.⁸

The emergence and improvements in the technique of sentinel lymph node (SLN) mapping and biopsy have permitted a more accurate assessment of the lymphatic drainage site from the primary site of the melanoma.¹⁸ It has been possible to identify more precisely a subset of patients with micrometastatic locoregional disease within the lymph nodes. With lymphatic mapping and a more detailed examination of the SLNs with serial sectioning and immunohistochemistry staining, more accurate staging is achieved. Other studies have shown that patients with clinically nega-

tive but microscopically occult metastatic who undergo elective lymph node dissection do better than those who undergo resection of macroscopic (clinically evident) disease.¹⁹ An accumulation of experience and long-term follow-up data is becoming available in the use of lymphatic mapping and SLN biopsy.¹⁷ SLN status is a strong predictor of survival, with an overall 93% survival rate at 3 years if the SLN was negative and a 67% survival rate if the SLN was positive.²⁰ A second major change was necessary to incorporate data from this new surgical technique. Microscopic disease is designated “a” and macroscopic disease as “b” for each classification of lymph node (N) disease. Furthermore, more data are becoming available on the optimal technique of identifying micrometastatic disease. The conventional method uses hematoxylin-eosin (H&E) histology and immunohistochemistry staining of the SLNs. However, reverse transcriptase-polymerase chain reaction (RT-PCR) is another emerging method that may further improve the accuracy rate in detecting nodal metastases.²¹⁻²³ The Sunbelt Melanoma Trial is currently evaluating conventional histology vs RT-PCR techniques for detection of nodal micrometastasis. The AJCC Melanoma Staging Committee elected not to include RT-PCR work in the regional basin staging until the data from this more sensitive assay mature. Nodal disease is defined as metastases identified with an H&E stain. Immunohistochemistry, with S-100 and HMB-45 stains of the SLN, may initially find the metastases, but a patient is considered to have node-positive disease only if it can be confirmed with an H&E stain.

In addition, patients with in-transit metastases or satellite lesions without lymph node disease have a similar prognosis⁷ to those with lymph node metastases. In the revised staging system, these patients are now upstaged as having N2c disease compared to the 1997 staging system in which these patients were considered as having T4 disease.

M Classification

Metastasis classification (M) identifies patients with distant and systemic metastatic melanoma. Studies have shown that there are variables identifying population of patients even within the stage IV group who have better prognoses than others. Three factors are important in determining prognosis for advanced stage melanoma: the site of metastasis, the number of metastatic sites, and serum level of LDH. An analysis by the Eastern Cooperative Oncology Group (ECOG) database showed that patients with skin, subcutaneous tissue, or distant lymph node involvement have better survival than those with metastases to the lung or other visceral

organs.²⁴ The proposed new melanoma staging system incorporates three subcategories of the M classification: M1 disease includes distant skin, subcutaneous, or lymph node metastases, M2 disease includes lung metastasis, and M3 includes all other visceral organ or distant metastases. Patients with elevated serum LDH levels have a poorer prognosis, and the presence of this variable in patients with stage IV melanoma will cause them to be classified as M3 disease.²⁴⁻²⁶

Staging: Clinical vs Pathologic

In the past, the TNM classification of melanoma has been grouped more broadly into a staging system divided into three general categories: localized melanoma (stage I and II), regional disease (stage III), and distant metastatic disease (stage IV).

Table 3. — New Stage Groupings for Cutaneous Melanoma

	Clinical Staging ^a			Pathologic Staging ^b			
0	Tis	N0	M0	Tis	N0	M0	
IA	T1a	N0	M0	T1a	N0	M0	
IB	T1b	N0	M0	T1b	N0	M0	
		T2a	N0	M0	T2a	N0	M0
IIA	T2b	N0	M0	T2b	N0	M0	
		T3a	N0	M0	T3a	N0	M0
IIB	T3b	N0	M0	T3b	N0	M0	
		T4a	N0	M0	T4a	N0	M0
IIC	T4b	N0	M0	T4b	N0	M0	
III ^c	Any T	N1	M0				
		N2					
		N3					
					T1-4a	N1a	M0
IIIA				T1-4a	N2a	M0	
					T1-4b	N1a	M0
IIIB				T1-4b	N2a	M0	
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a/b	N2c	M0
IIIC				T1-4b	N1b	M0	
					T1-4b	N2b	M0
					Any T	N3	M0
					Any T	Any N	Any M1
IV	Any T	Any N	Any M1	Any T	Any N	Any M1	

^a 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.

^b Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy, except for *pathologic stage 0* or *stage 1A* patients, who do not need pathologic evaluation of their lymph nodes.

^c There are no stage III subgroups for clinical staging.

From the American Joint Committee on Cancer Staging System for Cutaneous Melanoma.

SLN mapping/biopsy for the identification of micrometastatic disease within a draining lymph node was a major technologic advancement in the care of patients with melanoma. This new information was addressed and incorporated into the new staging system by defining two types of staging — clinical and pathologic (Table 3). The AJCC Melanoma Staging Committee recommends that when possible, nodal staging should be performed and that for any clinical trial work, nodal staging is important.

Early-stage (I and II) localized melanoma is based on the T classification without evidence of lymph node metastasis. Ulceration of the primary tumor “upstages” patients for each T stage. A new staging category of IIC is designated to ulcerated T4 lesions. These patients are at increased risk of developing metastatic disease compared with node-negative patients, and they have a prognosis equivalent to those with multiple metastatic lymph nodes.^{27,28}

The hallmark of locoregional disease (stage III) is involvement of regional lymph nodes. The presence of microscopic lymph node disease identified by SLN sampling is differentiated by the pathologic staging. The subgroup of patients with micrometastatic disease in one node still has an excellent prognosis. Patients with multiple metastatic lymph nodes and ulcerated primary tumors have a poorer prognosis and are designated into a new classification of stage IIIC. Likewise, satellite or in-transit metastases have a poor prognosis and are upstaged to IIIB in the revised system compared with the 1997 staging system. Stage IV disease remains the same; patients in this category have distant metastatic disease.

Conclusions

Major revisions have been made to form a new AJCC staging system for malignant melanoma. The changes reflect of a number of new prognostic factors that are significant independent variables, including melanoma primary tumor thickness and ulceration, number of metastatic lymph nodes, micrometastatic disease based on SLN biopsies or other nodal staging procedure (elective lymph node dissection), the site(s) of distant metastatic disease, and serum LDH levels. The new melanoma staging system is designed to allow more precise classification and to improve the accuracy of predicting the overall prognosis and outcome in patients with melanoma. Follow-up validation studies will confirm the accuracy of this new staging system. The new staging system has received the endorsement of the entire Melanoma Staging Committee and the AJCC. As new treatments in gene therapy

and immunotherapy become available, this more accurate staging system will be essential for conducting future clinical trials.

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