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Staging and Prognosis of Cutaneous Melanoma

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Keywords

Melanoma; staging; prognosis

Introduction

Formal staging of cancer is fundamental in providing clinicians and patients with prognostic information, developing treatment strategies, and directing and analyzing clinical trials. Staging of cutaneous melanoma continues to evolve through identification and rigorous analysis of potential prognostic factors. The first multivariate analyses of prognostic factors for melanoma were published over three decades ago, and several well-designed reports have subsequently advanced our understanding of important prognostic indicators for this disease.[1–3] Despite these important efforts, need for a unified melanoma staging system applicable to both clinical practice and research became evident.[4–6] In 1998, the American Joint Committee on Cancer (AJCC) Melanoma Staging Committee, which included experts from North America, Europe, and Australia, developed the AJCC melanoma staging database, a first-in-kind international integrated compilation of prospectively accumulated melanoma outcome data from several centers and clinical trial cooperative groups.[7] Analysis of this database resulted in major revisions to the Tumor-Node-Metastasis (TNM) staging system reflected in the 6th edition AJCC Cancer Staging Manual published in 2002. More recently, the committee's analysis of an updated melanoma staging database, including prospective data on over 50,000 patients, led to staging revisions adopted in the 7th edition AJCC Cancer Staging Manual published in 2009.[8,9] This article highlights these revisions, reviews relevant prognostic factors and their impact on staging, and discusses emerging tools that will likely impact future staging systems and clinical practice.

AJCC 7th edition updates and highlighted changes from the 6th addition

Staging systems for melanoma continue to be refined as our understanding of the complex biology of this disease improves. In 2002, the 6th edition AJCC staging system included significant revisions to the prior system based on prognostic factor analysis of the original

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melanoma staging database.[10,11] These included: new strata for primary tumor thickness, incorporation of primary tumor ulceration in the T and N classifications, the distinction of nodal tumor burden as a prognostic factor in patients with regional metastases, and new categories for stage IV disease. Analysis of an updated AJCC melanoma staging database was subsequently performed to provide further insight into the prognostic significance of several biologic factors and to refine the 6th edition. These updates are reflected in the 7th edition melanoma staging system of the AJCC Cancer Staging Manual published in 2009[8] (Tables 1 and 2). While this most recent staging schema remains largely intact compared to the prior version, several noteworthy revisions are briefly highlighted below and further detailed where appropriate throughout this article (Table 3).

A fundamental change to the new staging system is the addition of mitotic rate as a criterion for defining T1b primary melanoma. Mitotic rate of the primary tumor, defined as mitoses/mm^2, was included as a covariate in the staging analysis and was identified to have significant prognostic implications, further discussed below.

A second important change is the formal inclusion of immunohistochemical assessment, rather than just hematoxylin and eosin (H&E) staining, as acceptable in defining the presence of nodal metastases. Importantly, at least one melanoma-specific marker, such as HMB-45, Melan-A, or MART 1, should be used. Furthermore, unlike criteria used in breast cancer staging, there is no lower threshold of tumor burden used to define nodal micrometastases, reflecting the consensus that even small amounts of metastatic disease are potentially clinically relevant.

Historically, patients with melanoma with an unknown primary presenting with metastases arising in the skin, subcutaneous tissue, and/or lymph nodes, have variably been classified as having either stage III or stage IV disease, provided that a staging evaluation does not reveal other sites of disease. However, recent studies focused on patients with melanoma of unknown primary with metastases to lymph nodes have demonstrated a survival profile similar (if not more favorable) to patients with regional nodal disease and a known primary melanoma.[12,13] In the updated staging system, metastatic melanoma to the skin, subcutaneous tissue, or lymph nodes with an unknown primary is classified as stage III disease. Accordingly, such patients should be offered surgical management and participation in adjuvant stage III trials.

Localized Melanoma (Stage I&II)

The prognosis for patients with localized melanoma is generally favorable. In the 6th edition AJCC melanoma staging system, tumor thickness and ulceration were identified as the dominant independent predictors of survival.[10] However, based on emerging data from several single institution studies reporting tumor mitotic rate as an adverse prognostic factor,[14–17] mitotic rate was included in the analysis of the updated AJCC melanoma staging database. Importantly, although some investigators predicted that ulceration would no longer maintain its prognostic significance for patients with localized disease, in fact, tumor thickness, mitotic rate, and the presence of ulceration were each found to be significant independent predictors of survival in this group of patients.[8,9] Furthermore, in the 7th edition AJCC melanoma staging system, these three factors were used to define T categories (Tables 1 and 2).[8,9]

Primary tumor thickness was introduced as a prognostic factor by Alexander Breslow in 1970,[18] and has subsequently been validated in multiple studies.[1,19–21] Currently, the AJCC staging system uses tumor thickness cut points of 1.0 mm, 2.0 mm, and 4.0 mm to define T-category strata based on their statistical significance and importantly, their clinical utility in defining tumor thickness as thin (<1 mm), intermediate (1–4mm), and thick (>4mm)

tumors.[4,22] In analysis of over 27,000 patients from the AJCC melanoma staging database with Stage I or II disease, as primary tumor thickness increased, there was a significant decrease in survival (Figures 1A,B).[9]

Ulceration is defined as the lack of an intact dermis overlying the primary tumor on histologic evaluation. Multiple studies demonstrate that the presence of ulceration represents a more aggressive tumor phenotype with a higher likelihood of metastasis and worse prognosis.[23,24] For patients with ulcerated melanomas, survival is significantly lower than for patients with nonulcerated tumors of equivalent depth. Moreover, analysis of the original AJCC melanoma staging database (published in the 2002 AJCC Cancer Staging Manual) demonstrated that survival outcomes for patients with ulcerated tumors were remarkably similar to those of patients with nonulcerated tumors of the next highest T category.[10] This finding was validated in the 2008 database analysis and is reflected in the 2009 AJCC melanoma staging system (Figure 1A and 1B).[8,9]

Primary tumor mitotic rate deserves special mention, as it represents a fundamental change in the revised melanoma staging system. This change is based on a body of data showing a significant correlation between increasing mitotic rate and decreased survival. Salman and Rodgers first suggested the prognostic importance of the mitotic index of the primary tumor, identifying that it was associated with a higher rate of metastasis in patients with thin lesions.[25] Several other investigators have subsequently confirmed tumor mitotic rate as an independent prognostic factor.[14–17] Multivariate analysis of 10,233 patients from the updated AJCC melanoma staging database with localized melanoma (stages I & II) revealed mitotic rate as the second most important predictor of survival, after tumor thickness, and was particularly pronounced among patients with T1 melanoma.[9] Accordingly, in a multivariate analysis of 4,861 patients with T1 melanoma, tumor thickness, mitotic rate, and ulceration were all powerful predictors of survival; level of invasion was no longer statistically significant when mitotic rate and ulceration were included in the analysis.[9] The 10-year survival rate was 95% for nonulcerated T1 melanomas with a mitotic rate of < 1/mm^2, and dropped to 88% if the mitotic rate was ≥1/mm^2 (P<.0001).[9] Although ulcerated T1 melanomas were associated with a mitotic rate ≥ 1/mm^2 in 78% of patients, the 10-year survival rate was the same regardless of whether the mitotic rate was < 1 or ≥1/mm^2 (85% *v* 87%; P=.41). Based on these data, mitotic rate (operationally defined in the 7th edition melanoma staging system as a dichotomous variable) replaced Clark level of invasion as a primary criterion for defining T1b melanoma.[8,9]

The mitotic rate of the primary melanoma should be assessed following biopsy. The suggested approach is detailed in the 7th edition of the AJCC Cancer Staging Manual.[8] Briefly, the recommended technique is to first find the area within the dermis containing the most mitotic figures, the so-called “hot spot”. After counting mitoses in the hot spot, the count is extended to adjacent fields until an area of 1 mm^2 is assessed. The count is then expressed as mitoses/mm^2. If no hot spot can be identified and mitoses are randomly scattered throughout the lesion, then a representative mitosis is chosen, and beginning with that field, the count is then extended until an area corresponding to 1 mm^2 is assessed. Individual microscopes should be calibrated for accurate recording. If the invasive area of a tumor is less than 1 mm^2, then the number of mitoses present in 1 mm^2 of dermal tissue that includes the tumor should be determined and recorded as mitoses/mm^2. Alternatively, in these tumors, the simple presence or absence of a mitosis can be designated as at least 1/mm^2 (i.e., “mitogenic”) or 0/mm^2 (i.e., “nonmitogenic”), respectively.

Determining mitotic rate is important not only in providing prognostic information, but also in discussing and planning extent of surgery. In the 6th edition of the AJCC Staging Manual, sentinel lymph node (SLN) biopsy was recommended for patients with T1b tumors, based

on an approximately 10% incidence of identifying occult nodal metastasis in patients with thin melanomas that were either ulcerated or had Clark level IV invasion.[10] While the updated AJCC melanoma staging database does not permit a precise estimation of predicting nodal micrometastasis in this cohort, others have demonstrated increased mitotic activity in the primary tumor to be a predictor of SLN positivity.[14–17,26] In a preliminary report based on a multivariate analysis of patients with T1 melanoma who underwent sentinel node biopsy, Caudle and colleagues found that a mitotic rate ≥1/mm^2 was an independent predictor of sentinel lymph node histologic status.[27] Although this clinical question is not yet fully resolved, available data suggests that in addition to using other potential prognostic factors, consideration should be given to offering sentinel lymph node (SLN) biopsy in patients with thin (≤1mm) melanoma if the primary tumor mitotic rate is ≥1/mm^2.

For years, Clark level of invasion has been known to have prognostic significance, and has served as a criterion in several melanoma staging systems.[28] Nonetheless, several investigators have demonstrated that level of invasion is less reproducible among pathologists, and is less accurate in providing prognostic information compared to tumor thickness.[1,29–31] In the 6th edition AJCC melanoma staging system, Clark level of invasion of at least IV (or ulceration) was used to define T1b tumors. However, in the T1 category-specific AJCC multivariate analysis, level of invasion was no longer an independent predictor of survival relative to mitotic rate and ulceration.[9] In the 7th edition AJCC melanoma staging system, level of invasion is only to be used to define T1b tumors in the rare occurrence that mitotic rate cannot be accurately determined.

Stage III Melanoma

Patients with regional metastasis (ie, regional lymph node, satellite, and/or in-transit metastasis) represent a heterogeneous group with regard to staging and prognosis. It is well established that regional lymph nodes are the most common first site of metastasis in melanoma patients.[32] The 6th edition AJCC melanoma staging system identified the number of regional lymph nodes harboring metastatic disease, regional node tumor burden (empirically classified as microscopic versus macroscopic), and ulceration of the primary tumor as independent predictors of survival in this cohort.[10,11] Recent analysis of patients from the AJCC melanoma staging database used for the 7th edition melanoma staging system confirm these criteria as important prognostic factors, and includes patients with long-term follow-up of patients staged in the era of sentinel lymph node biopsy.

Regional lymph nodes

In previous staging systems, the size of metastasis-containing regional lymph nodes was the primary criterion used in stratifying stage III patients.[5] However, more recent analyses have demonstrated that in patients with regional metastasis, the number of nodes harboring metastatic disease is the most important predictor of survival.[4,10,11,33–36] The current AJCC N-category stratifies patients according to number of nodes involved based on best statistical grouping: 1 (N1) versus 2–3 (N2) versus 4 or more (N3) nodes.[8]

Regional node tumor burden, empirically defined in the AJCC melanoma staging system as microscopic or macroscopic metastasis, was the second most important prognostic factor in patients with stage III disease in the AJCC database analysis. Microscopic disease refers to metastatic deposits detected on histologic analysis following elective lymph node dissection, or more commonly, SLN biopsy. Macroscopic disease refers to nodal metastases that are clinically or radiographically apparent and pathologically confirmed. Importantly, these definitions are based on method of detection, not the size or “visibility” of the nodal metastasis. This criterion is used to sub-categorize the N classification in the current staging system. For example, N1a–N3a refers to patients with micrometastasis and N1b-N3b to

patients with macrometastasis. Analysis of patients in the AJCC melanoma staging database demonstrated significant differences in survival when accounting for nodal tumor burden (Figure 1C,D and Table 4).[8,9]

Lymphatic mapping and sentinel node biopsy is now widely used as the standard method of staging patients deemed to have significant risk of clinically occult regional nodal metastasis. Certainly, most contemporary series reveal that the majority of patients with stage III disease present with micrometastasis, usually detected on SLN biopsy.[9,37–40] Recently, analysis of patients from the AJCC melanoma staging database with stage III disease was performed to identify and compare independent predictors of survival between those with micrometastases and macrometastases.[37] This investigation confirmed significant survival differences based on nodal tumor burden, and remarkable heterogeneity in survival among substages of patients with stage III disease. Multivariate analysis demonstrated differences in independent predictors of survival when stage III patients were stratified by nodal tumor burden (Table 5).[37] In both groups, number of positive lymph nodes remained the most significant predictor of survival. In addition, older age was found to be an independent adverse prognostic factor, regardless of nodal tumor burden. However, in patients with nodal micrometastases, features of the primary tumor including thickness, mitotic rate, ulceration, and anatomic location were found to significantly impact survival. In contrast, these primary tumor features were not independent predictors in patients with nodal macrometastases (Table 5). These results reveal important differences regarding prognosis based on nodal tumor burden (Figures 1C,D and Table 4), and provide the groundwork for further refinement in prognostic assessment of stage III patients, particularly, but not exclusively, among the dominant cohort with nodal micrometastases.

Primary tumor ulceration was first included as a stratification criterion for stage III melanoma in the 6th edition AJCC melanoma staging system based on data demonstrating its significance as an independent adverse predictor of survival in this cohort.[4,10,11,41] This criterion was upheld in the recently published 7th edition AJCC staging system (Tables 4 and 5).[8,9] Similar to its impact on survival estimates for stage I and II melanoma, primary tumor ulceration is associated with decreased survival in stage III, essentially upstaging such a patient whose primary tumor is ulcerated to that of a patient with a nonulcerated primary who has a higher nodal tumor burden category (Figure 1C,D and Table 4). This criterion is therefore again used to define N-category substages (Table 2).[8,9] For example, 5-year survival is 53.9% and 46.6%, respectively, in patients with 2–3 microscopically involved regional nodes and an ulcerated primary melanoma versus 2–3 macroscopically involved lymph nodes in patients whose primary tumor is not ulcerated (Table 4).[37]

The criteria discussed above revealed marked heterogeneity in the prognosis for patients with stage III disease, and are used to define stage III substages into IIIA, IIIB, and IIIC (Figure 1C,D and Tables 2 and 4).[9] Future studies involving staging and management of patients with regional metastases, particularly those with microscopic nodal tumor burden, are likely to be better refined by incorporating other features of the primary tumor, including mitotic rate.

In-transit and satellite disease

The final criterion for defining stage III disease is the presence of intralymphatic metastases in the form of either in-transit disease or satellite lesions. In both the previous and most recent editions of the AJCC melanoma staging system, a designation of N2c is given to patients with in-transit or satellite disease in the absence of nodal metastases, while patients with concomitant nodal metastases and in-transit and satellite lesions are classified as having N3 disease.[8–11] Based on current analyses of the AJCC melanoma staging database, patients with N2c disease have 5- and 10-year survival rates of 69% and 52%, respectively. These

survival rates are actually higher than that of patients with N2a and N2b disease, and more favorable than in prior reports.[4,42–45] Nonetheless, the survival for patients with intralymphatic metastases (in the absence of nodal metastases) still fits best into the stage IIIB category (Tables 1 and 2).

Stage IV Melanoma

The prognosis for patients with distant metastases is generally poor, with historical 5-year survival rates of less than 10%.[46–48] Several factors have been examined in attempt to better predict survival in this group.[3,48–50] Beginning with the 6th edition AJCC melanoma staging system, patients with stage IV melanoma were categorized as having M1a (metastasis to distant skin, subcutaneous tissues, and/or lymph nodes), M1b (metastasis to the lungs), and M1c (metastasis to any non-pulmonary visceral site) disease. In addition, patients with an elevated serum LDH were assigned to the M1c category, regardless of site of distant metastasis. Analysis of the updated database, including over 8000 patients, validated these criteria as significant independent prognostic factors in patients with stage IV disease.[8,9]

Based on this most recent analysis, patients with metastasis to distant skin, subcutaneous tissues, and/or lymph node basins (M1a), have the highest one-year survival rate (62%) among patients with stage IV disease. Patients with pulmonary metastasis (M1b) have an intermediate prognosis (one-year survival rate, 53%). Finally, patients with non-pulmonary visceral metastases and/or an elevated serum LDH (M1c) have the worst one-year survival among stage IV patients (33%) (Table 2 and Figure 2,A,B).[8,9]

Serum markers are uncommonly used in staging solid tumors. However, multiple reports have consistently demonstrated an elevated serum LDH to represent a highly significant, independent adverse prognostic factor in patients with stage IV melanoma.[51–53] These findings were recapitulated in the 7th edition AJCC melanoma database analysis, and revealed that 1- and 2-year survival rates for stage IV patients with a normal LDH were 65% and 40%, respectively, compared to 32% and 18%, respectively, in those patients with an elevated LDH level (Figure 2A,B).[9] Although the exact pattern of elevated LDH isoforms is nonspecific in melanoma patients, and the mechanism for LDH elevation is not fully understood, an overwhelming amount of clinical data supports its use as a prognostic factor in patients with stage IV disease. Accordingly, it is recommended that serum LDH levels are measured in all melanoma patients when diagnosed with distant metastasis (Table 2 and Figure 2A,B).

Several studies have reported the number of distant metastases to be a relevant prognostic factor in patients with metastatic melanoma.[46,54,55] Although analysis of stage IV patients in the updated staging database confirms this finding,[8,9] the challenge of standardizing the diagnostic modalities used to identify and quantify distant disease makes it difficult to incorporate this as a formal criterion in the current staging system.

Emerging Themes for Staging and Prognosis for Cutaneous Melanoma: Conditional Survival Estimates, Electronic Prognostic Models, and Molecular Profiling

Conditional Survival Estimates

For staging purposes, survival estimates for melanoma patients are determined from the time of melanoma diagnosis and are typically reported using the methods of Kaplan and Meier. Although well-characterized, stage-specific 5-year and 10-year survival estimates based on analysis of large patient populations at time of initial melanoma diagnosis are available,

such traditional survival estimates become less relevant for patients surviving several years beyond diagnosis and treatment, as a patient's cancer-specific risk profile changes over time, particularly for patients with advanced disease at initial presentation. Over the past decade, the concept of conditional survival – ie, having survived "x" years since initial diagnosis, what is "my" predicted survival from that point forward? - has emerged as an important technique to estimate survival for cancer survivors. Conditional survival estimates have been published for a variety of malignancies.[56–63] Recently, analyses of patients with cutaneous melanoma have demonstrated that conditional survival estimates increase over time in patients with advanced disease. [64–66] For instance, in an analysis of melanoma patients using the SEER database, 5-year conditional survival estimates in patients with stage II, III, and IV melanoma improved from 72% to 86%, 51% to 87%, and 19% to 84%, respectively, in which that latter estimate in each range above corresponded to the subset of patients that survived 5 years following initial diagnosis.[66] Furthermore, among stage III patients treated at the University of Texas MD Anderson Cancer Center, 5-year conditional disease-specific survival estimates for patients with stage IIIA, IIIB, and IIIC improved from 78% to 90%, 54% to 79%, and 39% to 78%, respectively.[65]

Understanding that survival estimates are not static, but rather improve for melanoma survivors who initially present with advanced disease, provides an opportunity for more accurate prognostic assessment for patients and clinicians alike. Conditional survival estimates provide quantitative information that educates clinicians, may reduce patient anxiety about risk of cancer recurrence and death, and potentially serve as motivation for clinicians to continue to pursue aggressive treatment strategies in patients with advanced disease.

Beyond TNM-Based Staging

Despite the strong evidenced-based predictive capacity of the current AJCC melanoma staging system, it is de facto constrained by the rigorous structure inherent in its TNM-based design. AJCC database analyses demonstrate several important predictors of survival not included in the current staging system.[9] Variables such as age, gender, primary tumor site, extent of microscopic tumor burden, and number of sites of distant metastases have been shown to have prognostic relevance. Tools that allow clinicians to incorporate these demographic and clinicopathologic data for a specific patient can ultimately yield personalized and ever more accurate estimates of recurrence and survival. As our understanding of the biology of melanoma, as well as stage-specific prognostic factors continues to expand, greater emphasis on development and implementation of individualized patient prognostic models is essential to continue to improve patient care. An ideal system would incorporate state-of-the-art prognostic factor analyses, permit healthcare providers to remotely enter relevant data, and provide real-time feedback.

Recently, the first electronic predictive tool for patients with localized melanoma based on the large AJCC melanoma staging database was published.[67] Based on this model, an individual patient's 1-, 2-, 5-, and 10-year survival with associated 95% confidence intervals are available. Refined risk stratification schema to allow for treatment and surveillance planning, selection of patients appropriate for clinical trials, and comparison of effectiveness of therapies for well-defined patient subgroups within trials is possible. An initial version of this model is available on the internet (http://www.melanomaprognosis.org). Following on-screen prompts, data for patients with localized melanoma, as well as those with regional metastases, are entered using drop-down menus, and survival estimates are immediately displayed. This model serves as a template for providing patients and clinicians with prognostic information and a foundation on which to plan future individualized treatment studies.

Molecular-based Profiling and Melanoma Biomarkers

In the future, it is likely that molecular profiling endeavors will provide additional information pertinent to staging and prognosis for cutaneous melanoma. Certainly, recent developments in targeted therapies for patients with metastatic melanoma are based on an improved understanding of disease biology at the molecular level.[68–73] Furthermore, studies attempting to provide "genetic signatures" for individual patients are underway and are beginning to shed light on the potential use of these techniques in prognostic models and treatment planning.[74–76] Of note, the nascent phase II effort of the NIH Cancer Genome Atlas Project (TCGA) specifically includes melanoma, and will hopefully provide invaluable insight into the molecular biology of melanoma in years to come. Further information regarding this exciting initiative can be found at http://cancergenome.nih.gov.

Biomarkers for melanoma identification, prediction of disease progression, prognosis, and treatment planning are lacking. Although serum LDH is part of the current staging system, it is non-specific and cannot readily be used to evaluate response to therapy. While a discussion of emerging melanoma biomarkers is beyond the scope of this article, identification of relevant biomarkers will likely contribute to enhanced prognostic assessment and potentially hasten clinical trial development and evaluation. It is hopeful that this area of intense investigation will yield meaningful surrogates for selecting future therapies, monitoring treatment response, and add to individualized prognostic modeling.

Summary

The AJCC melanoma staging database forms the foundation for the current melanoma staging system; future analyses based on this robust platform will likely continue to serve as a foundation for future improvements in melanoma staging. As our understanding of the biology of this complex tumor system continues to evolve, both clinical and molecular factors that may have significant prognostic implications will undoubtedly be unveiled. Notable updates to melanoma staging published in the 7th edition AJCC melanoma staging system include: incorporation of mitotic rate into T1 criteria, inclusion of immunohistochemical detection of nodal micrometastases, and categorization of patients with melanoma of an unknown primary (ie, metastatic melanoma arising in the skin, subcutaneous tissue, or regional lymph nodes in a patient whose staging evaluation does not reveal other sites of disease) as stage III, rather than stage IV.

Based on the results of the AJCC melanoma staging database analysis, future prognostic factor studies should evaluate the formal impact of mitotic rate across all stages of disease, further assess the influence of microscopic nodal tumor burden in patients with stage III disease in this era of SLN biopsy, and continue to refine staging and prognosis for patients with stage IV melanoma. Moreover, continued development and application of conditional survival estimates in melanoma patients, increased use of prognostic tools which incorporate relevant criteria beyond the scope of TNM-based staging, molecular profiling endeavors (including, for example, lessons learned from the nascent and ongoing NIH-sponsored Cancer Genome Atlas Project [TCGA] which specifically includes melanoma), and identification of melanoma-specific biomarkers, will hopefully provide opportunities for more accurate staging and individualized prognosis for melanoma patients in the future.

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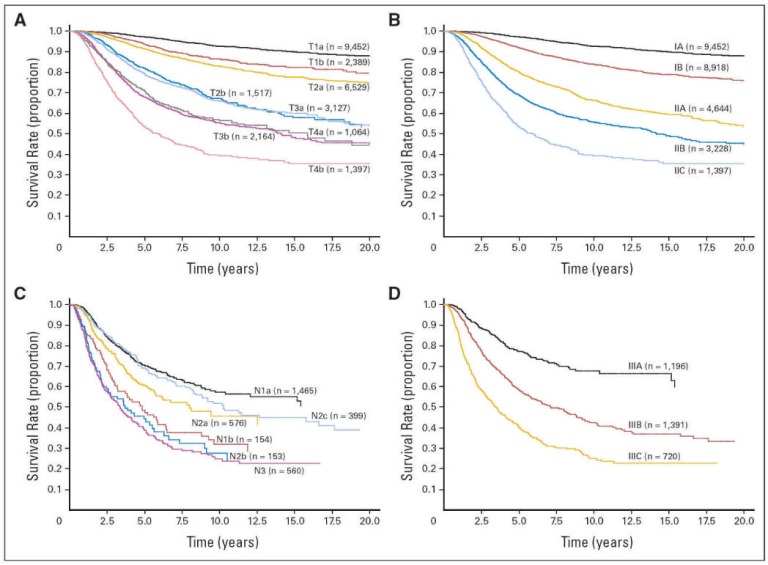

Figure 1.

Survival curves from the 7th edition 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. Note that survival outcomes for patients with ulcerated tumors were remarkably similar to those of patients with nonulcerated tumors of the next highest T category. For patients with stage III disease, survival curves are shown comparing (C) the different N categories and (D) the stage groupings. Note in particular the marked heterogeneity in survival among these patients with stage III disease.

From Balch CM, Gershenwald JE, Soong S, et al, Journal of Clinical Oncology 27(36): 6199-206, 2009; with permission.

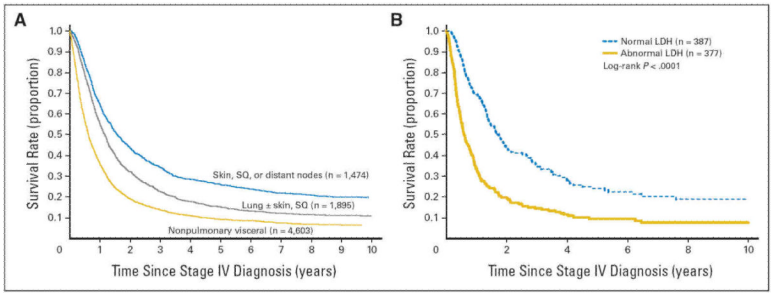

Figure 2.

Survival curves of 7,635 patients with metastatic melanoma at distant sites (stage IV) subgrouped by (A) the site of metastatic disease and (B) serum lactate 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. From Balch CM, Gershenwald JE, Soong S, et al, Journal of Clinical Oncology 27(36): 6199-206, 2009, with permission.

Table 1

TNM staging categories for cutaneous melanoma (7th edition).

T classification	Thickness	Ulceration Status
Tis	NA	NA
T1	≥1.00 mm	a: w/o ulceration and mitosis ≥1/mm2
		b: with ulceration or mitoses ≥1/mm2 n/mm2
T2	1.01 – 2.0 mm	a: w/o ulceration
		b: with ulceration
T3	2.01 – 4.0 mm	a: w/o ulceration
		b: with ulceration
T4	>4.0 mm	a: w/o ulceration
		b: with ulceration

N classification	# 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 met(s)/satellite(s) without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in transit metastases/ satellites with metastatic nodes	

M classification	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

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* Micrometastases are diagnosed after sentinel lymph node biopsy.

** Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically.

Table 2

Anatomic stage groupings for cutaneous melanoma (7th edition).

	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	Tl-4a	N1a	M0
					Tl-4a	N2a	M0
				IIIB	Tl-4b	N1a	M0
					Tl-4b	N2a	M0
					Tl-4a	N1b	M0
					Tl-4a	N2b	M0
					Tl-4a	N2c	M0
				IIIC	Tl-4b	N1b	M0
					Tl-4b	N2b	M0
					Tl-4b	N2c	M0
					Any T	N3	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

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*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 lymph 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.

Table 3

Differences between the previous (2002) and the current (2009) versions of the AJCC melanoma staging system

Factor	2002 Criteria	2009 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 melanomas	No longer used	Clark levels 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 melanoma
Ulceration	Included as a second determinant of T and N staging	Same	Signifies a locally advanced lesion; dominant prognostic factor for grouping Stage I,II and III
Mitotic rate per mm^2	Not used	Used for categorizing T1 melanoma	Mitosis ≥ /mm^2 used as a primary determinant for defining T1b melanoma
Satellite metastases	In N category	Same	Merged with in transit lesions
Immunochemical detection of nodal metastases	Not allowed	Allowed	Must include at least one melanoma-specific marker (e.g., HMB-45, Melan-A, MART 1)
0.2 mm threshold of defined N-positive disease	Implied	No lower threshold of staging N-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 pathological staging; sentinel node staging encouraged for standard patient care and should be required prior to entry into clinical trials

From Balch CM: Melanoma of the Skin. *In* Edge SB, Byrd DR, Compton CC, et al (eds): AJCC Cancer Staging Manual ed 7th. New York: Springer Verlag, 2009; with permission.

Table 4

Five-year survival rates for stage III (nodal metastases) patients stratified by number of metastatic nodes, primary tumor ulceration, and nodal tumor burden (microscopic or macroscopic) (n=2313).

Primary tumor ulceration	No. of Nodal Micrometastases % ±S.E. (n=1,872)			No. of Nodal Macrometastases % ± S.E. (n=441)		
	1	2–3	≥4	1	2–3	≥4
Absent	81.5 ± 1.9 (777)	73.2 ± 3.7 (246)	38.0 ± 8.5 (46)	51.6 ± 7.2 (75)	46.6 ± 7.9 (67)	45.4 ± 9.1 (50)
Present	56.6 ± 2.9 (531)	53.9 ± 4.2 (223)	34.0 ± 8.3 (49)	49.4 ± 6.2 (88)	37.7 ± 6.2 (93)	29.2 ± 6.7 (68)

From Balch CM, Gershenwald JE, Soong SJ, et al: Multivariate analysis of prognostic factors among 2,313 patients with stage III melanoma: comparison of nodal micrometastases versus macrometastases. J Clin Oncol 28:2452, 2010; with permission.

Table 5

Multivariate Cox regression analyses for nodal micrometastases and for nodal macrometastases with mitotic rate data available (N=1338)

		Nodal Micrometastases (n=1070)			Nodal Macrometastases (n=268)		
Variable	**d.f.**	**Chi-Square(χ^2)**	**P-value**	**Hazard Ratio**	**Chi-Square(χ^2)**	**P-value**	**Hazard Ratio**
# of Positive Nodes	2	43.0	>0.001		6.1	0.0480	
1**	—	—	—	1.00	—	—	1.00
2–3	1	2.2	0.1343	1.25	0.2	0.6800	1.11
≥4	1	43.0	>0.001	3.59	5.7	0.0172	1.83
Thickness (mm)	3	21.4	>0.001		5.7	0.1267	
0–2.00**	—	—	—	1.00	—	—	1.00
2.01–4.00	1	7.0	0.0083	1.62	0.8	0.3842	0.74
4.01–6.00		4.3	0.0380	1.58	0.3	0.5811	1.22
>6.00	1	21.2	>0.001	3.00	0.6	0.4210	1.34
Ulceration	1	11.1	0.001		2.8	0.0959	
Absent**	—	—	—	1.00	—	—	1.00
Present	1	11.1	0.001	1.59	2.7	0.0959	1.45
Clark Level	1	0.003	0.9597		0.4	0.5140	
II/III**	—	—	—	1.00	—	—	1.00
IV/V	1	0.003	0.9597	1.01	0.4	0.5140	1.27
Mitotic Rate	2	23.4	>0.001		2.71	0.2582	
<1**	—	—	—	1.00	—	—	1.00
1–19.99	1	0.02	0.8993	0.96	2.6	0.1085	0.45
≥20	1	6.1	0.0134	2.69	2.4	0.1239	0.41
Age (year)	2	12.7	0.0018		13.8	0.0010	
<50**	—	—	—	1.00	—	—	1.00
50 — 69	1	2.5	0.1160	1.26	1.6	0.2121	0.75
≥70	1	12.6	0.0004	1.83	6.3	0.0118	1.92
Site	1	5.0	0.0251		0.4	0.5413	

		Nodal Micrometastases (n=1070)			Nodal Macrometastases (n=268)		
Variable	**d.f.**	**Chi-Square(χ^2)**	**P-value**	**Hazard Ratio**	**Chi-Square(χ^2)**	**P-value**	**Hazard Ratio**
Extremity**	—	—	—	1.00	—	—	1.00
Axial	1	5.0	0.0251	1.36	0.4	0.5413	1.13
Gender	1	1.1	0.2959		0.9	0.3435	
Male**	—	—	—	1.00	—	—	1.00
Female	1	1.1	0.2959	0.86	0.9	0.3435	0.79

From Balch CM, Gershenwald JE, Soong SJ, et al: Multivariate analysis of prognostic factors among 2,313 patients with stage III melanoma: comparison of nodal micrometastases versus macrometastases. J Clin Oncol 28:2452, 2010; **with permission.**