Melanoma Staging: Evidence-Based Changes in the American Joint Committee on Cancer (AJCC) Eighth Edition Cancer Staging Manual

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ABSTRACT

To update the melanoma staging system of the previous (Seventh) edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual published in 2009, a large database was assembled comprising >46,000 patients from 10 centers worldwide with Stages I, II, and III melanoma diagnosed since 1998. Based on analyses of this new database, the existing Seventh Edition AJCC Stage IV database, and contemporary clinical trial data, the AJCC Melanoma Expert Panel introduced several important changes to the TNM classification and stage grouping criteria. These were incorporated into the Eighth Edition AJCC Cancer Staging Manual. Key changes include: (1) tumor thickness measurements to be recorded to the nearest 0.1 mm, not the nearest 0.01 mm; (2) definitions of T1a and T1b revised (T1a, <0.8 mm without ulceration; T1b, 0.8-1.0 mm with or without ulceration, or <0.8 mm with ulceration), with mitotic rate no longer a T category criterion; (3) pathological (but not clinical) Stage IA revised to include T1b N0 M0 (formerly pathological Stage IB); (4) N category descriptors “microscopic” and “macroscopic” for regional node metastasis redefined as “clinically occult” and “clinically apparent”; (5) prognostic Stage III groupings based on N category criteria and T category criteria (i.e., primary tumor thickness and ulceration) and increased from three to four subgroups (Stage IIIA-IIID); (6) definitions of N subcategories revised, with presence of microsatellites, satellites or in-transit metastases now categorized as N1c, N2c or N3c based on number of tumor-involved regional lymph nodes, if any; (7) descriptors added to each M1 subcategory designation for LDH level (LDH elevation no longer automatically upstages to M1c); (8) a new M1d designation for metastases involving the central nervous system. This evidence-based revision of the AJCC melanoma staging system will

guide patient treatment, provide better prognostic estimates, and further refine eligibility and stratification of patients entering clinical trials.

Keywords: American Joint Committee on Cancer (AJCC), melanoma, database, TNM classification, staging, stage groupings, pathology, tumor thickness, ulceration, mitotic rate, regional lymph nodes, sentinel lymph node, visceral metastasis, brain metastasis, prognosis, survival

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International Melanoma Database and Discovery Platform

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INTRODUCTION

To improve the outcomes of patients with cutaneous melanoma, treatment based on accurate staging and patient stratification into clinically-relevant stage groups is fundamental. Not only does staging inform prognostic assessment and clinical decision making, but it also facilitates centralized cancer registry reporting and the design, conduct and analysis of clinical trials.

Since the early 1990s, a major advance in the management of patients with cutaneous melanoma involves the technique of lymphatic mapping and sentinel lymph node (SLN) biopsy;[1] this is now routinely employed as a staging procedure[2] for patients with T1b, T2, T3 and T4 (Eighth Edition) primary cutaneous melanomas and clinically negative regional lymph nodes in most melanoma treatment centers throughout the world.[3] The frequency of SLN metastasis increases with increasing tumor thickness and other adverse clinicopathological prognostic factors.[3-5] Clinical imaging technologies have also advanced, having become more sophisticated and more widely available, facilitating the detection of distant metastatic disease when it is of low volume and asymptomatic.

More recently, based upon improved knowledge of both the molecular pathogenesis of melanoma and cancer immunology, there has been a revolution in the treatment of patients with advanced stage and unresectable melanoma.[6-21] This has already resulted in major improvements in patient outcomes.[3] Two major new classes of effective systemic therapeutic agents are now in widespread clinical use: immunotherapies (e.g., checkpoint inhibitors against cytotoxic T lymphocyte antigen 4 (CTLA-4) and/or programmed death 1 (PD-1)) that enhance the natural host antitumor immune response, and molecularly targeted antitumor therapies (e.g., BRAF inhibitors alone or in combination with MEK inhibitors for the approximately 40 to 50% of patients with $BRAF^{V600}$ mutant melanoma).[22] Moreover, adjuvant therapy with anti-CTLA-4 significantly improves relapse-free survival and overall survival in stage III melanoma patients.[23, 24] It is against this background that the American Joint Committee on Cancer (AJCC) appointed a Melanoma Expert Panel to undertake the task of revising the cutaneous melanoma staging system for the Eighth Edition of the AJCC Cancer Staging Manual.

The Seventh Edition AJCC melanoma staging system (hereafter referred to as the Seventh Edition) has been widely adopted since its publication in 2009 and implementation in 2010.[2, 25] For the Eighth Edition AJCC melanoma staging system (hereafter referred to as the Eighth Edition), a contemporary international database was assembled to provide an evidence-based rationale for revisions to the cutaneous melanoma staging system that would have more current applicability.[3] The objective was to analyze detailed multi-institutional clinicopathological data collected in a standardized fashion to empirically establish T, N, and M categories and stage groupings for the Eighth Edition. We report here the results of analyses using this large melanoma database, supplemented by analyses from the Seventh Edition AJCC Stage IV database and by contemporary clinical trial data. These provided the evidence base for revisions of the Eighth Edition as well as the UICC Eighth Edition TNM Classification of Malignant Tumours.[26] The revised T, N, and M categories and stage groupings are presented below. To ensure that the necessary infrastructure is in place across the cancer care community, the Eighth Edition, originally published in October 2016, will not be formally implemented in the U.S. until January 1, 2018.[27]

DATABASE and METHODS

To assist the Eighth Edition Melanoma Expert Panel in its review of T and N categories and Stage I to III subgroupings, a protocol-based International Melanoma Database and Discovery Platform (IMDDP) was created at The University of Texas MD Anderson Cancer Center (MD Anderson), Houston, TX, USA. This protocol was approved by the MD Anderson Institutional Review Board (IRB) and formal data use agreements were implemented across all participating institutions, each also having obtained approval from their own IRB. This overall approach built upon collaborative efforts of the previous AJCC Melanoma Task Forces (renamed the AJCC Melanoma Expert Panel for the Eighth Edition) and an expanded network of national and international academic melanoma clinician–investigators representing institutions, cooperative groups, and tumor registries. The database included de-identified patient records from 10 institutions in the United States, Europe and Australia, with well-annotated

clinicopathological and follow-up data for patients with Stages I to III melanoma at initial diagnosis, treated since 1998. Importantly, the database reflected a contemporary clinical practice era during which the use of lymphatic mapping and SLN biopsy was well established in nearly all academic medical centers worldwide for patients considered at significant risk for occult regional node metastasis. Patients treated in the pre-SLN era (i.e., pre-1990s) as well as the early SLN era (early through mid-1990s) were deliberately omitted. During this latter period, SLN biopsy surgical techniques had evolved and matured (with development and implementation of a dual-modality intraoperative approach using blue dye and a radiotracer with gamma probe detection) and pathological assessment of the SLN (with widespread implementation of "enhanced" pathological assessment using step or serial sectioning and immunohistochemistry).[1, 2, 28-32]

For the analyses undertaken for the Eighth Edition, the database platform included the records of more than 46,000 melanoma patients (**Supplementary Table 1**), of whom 43,792 qualified for analysis. Only data from patients for whom relevant covariates (**Supplementary Table 2**) were known were included in each analysis.

Comment [TG1]: How many patients did not have complete covariate info? (overall or by institution)

Given the unprecedented changes in the still rapidly evolving landscape of the management of patients with Stage IV melanoma, the Melanoma Expert Panel concluded that it was premature to embark on a broad-based analytic initiative involving data from Stage IV patients treated during the past 8 years. Instead, the legacy 7th Edition AJCC Stage IV international melanoma database containing details of approximately 10,000 patients who presented with or developed Stage IV disease was used as the primary data source for the 8th Edition, supplemented by published contemporary clinical trial data.[6-21]

Statistical Analyses

Melanoma-specific survival (MSS) was calculated from the date of initial melanoma diagnosis. MSS curves were computed using the Kaplan-Meier method. Multivariable analyses were conducted using Cox proportional hazards regression models and recursive partitioning analysis (RPA). Analyses were

performed using S+ (Windows version 8.2, TIBCO, software, Inc.). RPA was performed using the S+ "tree" libraries on the MSS null martingale residuals.

MAJOR CHANGES

Table 1 summarizes the major changes introduced for the T, N, and M categories and stage groupings in the Eighth Edition. The rationale for these changes is described below.

The T Category

Breslow Tumor Thickness

In prior editions of the AJCC Cancer Staging Manual,[2, 25] it was implied (but not explicitly stated) that primary melanoma tumor thickness should be recorded to the nearest 0.01 mm. This has been clarified in the Eighth Edition. Based on consensus recommendations by the International Collaboration on Cancer Reporting[33] and the International Melanoma Pathology Study Group, already widely adopted in the pathology community,[34] thickness measurements should be recorded to the nearest 0.1 mm, not the nearest 0.01 mm, because of the impracticality and imprecision of measurements,[34] particularly for tumors >1 mm thick, and the reality that tumor thickness may vary by 0.1 mm or more between different histological tissue sections cut from the same paraffin tissue block of the tumor.[35] Tumors ≤1mm thick may initially be measured to the nearest 0.01 mm, but should be rounded up or down to be recorded to the precision of a single digit after the decimal (i.e., to the nearest 0.1 mm). The convention for rounding decimal values is to round down those ending in 1 to 4 and to round up those ending in 5 to 9. For example, a melanoma measuring 0.75 mm in thickness would be recorded as 0.8 mm in thickness (i.e., T1b). Tumors measuring 0.95 mm through 1.04 mm would be rounded to 1.0 mm (i.e., T1b). Primary tumor thickness should be measured using an ocular micrometer that has been calibrated to the magnification of the microscope used for the measurement. Microsatellites should not be included in the measurement of tumor thickness. Additional specific recommendations for the measurement of tumor thickness in particular clinical circumstances have been previously documented[33] and will be further

detailed in a planned separate publication on pathological aspects of melanoma staging from the International Melanoma Pathology Study Group.

In the Eighth Edition, the T-category thresholds of melanoma thickness continue to be defined at 1, 2, and 4 mm (**Table 2**).[36] However, the T categories have been revised to promote consistency, with the recommendation that thickness be rounded to the nearest 0.1 mm, as described above. Using these rounding conventions, T2 melanomas include patients with melanomas with a tumor thickness of 1.05 mm to 2.04 mm; T2 is now presented as >1.0–2.0 mm, compared to 1.01–2.0 mm in the Seventh Edition.[37, 38]

Several previously published reports have indicated that survival among patients with T1 melanomas is related to tumor thickness, with a possible clinically important "breakpoint" in the region of 0.7 mm-0.8 mm.[39-42] These observations were explored in the IMDDP database by seeking to identify a subgroup of patients with exceptionally good outcome compared to even the most favorable subcategory (T1a) in the Seventh Edition,[25] and hence in whom SLN biopsy would generally not be indicated. In the T1 cohort, the impact on outcome of a 0.8 mm tumor thickness threshold was evaluated, as well as mitotic rate (as a dichotomous variable, <1 mitosis per mm^2 vs. ≥1 mitosis per mm^2) and ulceration. In a multivariable analysis of factors predicting MSS (including tumor thickness, ulceration, and mitotic rate) among 7,568 T1 N0 patients, tumor thickness ≥0.8 mm had a hazard ratio (HR) of 1.7 vs. <0.8 mm (p = 0.057), ulceration had a HR of 2.6 vs. non-ulcerated (p = 0.035), and mitotic rate ≥1/mm^2 had a HR of 0.85 vs. mitotic rate <1/mm^2 (p = 0.57). Based on these analyses of patients with T1 melanomas, tumor thickness (when dichotomized as <0.8 mm and 0.8-1.0 mm) and ulceration were stronger predictors of MSS than mitotic rate. Accordingly, since mitotic rate was not statistically significant in the model, T1 subcategory definitions have been revised: T1a is now defined as nonulcerated melanomas <0.8 mm in thickness and T1b as melanomas 0.8-1.0 mm in thickness regardless of ulceration status, plus ulcerated melanomas <0.8 mm in thickness (**Table 2**). The Eighth Edition Melanoma Expert Panel also noted that the sub-categorization of T1 melanomas at a 0.8 mm threshold has clinical relevance, particularly for the role of SLN biopsy in patients with T1 melanomas. Overall, SLN metastases are very infrequent (<5%)

Comment [TG2]: Please explain.

Comment [TG3]: What other factors (if any) were included besides thickness, ulceration, and mitotic rate?

Comment [TG4]: Can you briefly describe the analysis that supports combining thickness and ulceration in this way? This combination does not seem to be described in the preceding 2 sentences.

Comment [TG5]: Is it feasible to be more specific?

in melanomas <0.8 mm but occur in approximately 5%-12% of patients with primary melanomas 0.8-1.0 mm,[43-46] and consensus guidelines have recommended that SLN biopsy be considered in this latter group of patients, particularly when other adverse prognostic parameters are also present.[47-49]

As in the Seventh Edition, patients with primary melanoma and no evidence of regional or distant metastasis are stratified into eight T subcategories (T1a through T4b). MSS stratified by T subcategory for 23,001 patients with complete covariate data is shown in **Figure 1**. For these survival curves, patients with T1 melanomas were included if they had clinical or pathological T1 N0 melanomas, but patients with T2-T4 melanomas were included only if pN0 (i.e., no tumor-containing SLNs and no evidence of microsatellites, satellites, or in-transit metastases at diagnosis or following initial treatment). Overall, this approach aligns with the AJCC Principles of Cancer Staging (see chapter 1 of the Eighth Edition AJCC Cancer Staging Manual).[56] An implication of this approach is that patients with T2-T4 melanomas who do not undergo SLN biopsy cannot be pathologically staged. Nonetheless, the Melanoma Expert Panel acknowledges that not all patients with T2-T4 undergo SLN biopsy and improved clinical prognostic models and tools (e.g., clinical calculators, etc.) may be developed to improve prognostic assessment among this cohort of patients in the future.

In the Eighth Edition, five- and ten-year MSS ranged from 99% and 98%, respectively, for patients with T1a N0 melanomas (i.e., primary tumor thickness <0.8 mm, non-ulcerated), to 82% and 75%, respectively, for patients with T4b N0 melanomas (i.e., primary tumor thickness >4.0 mm, ulcerated). MSS for all T subcategories were notably higher than those reported in the Seventh Edition, in which 10-year MSS was 93% and 39% for T1a N0 and T4b N0 melanomas, respectively.[50] The higher survival of patients in the more contemporary patient cohort examined in this Eighth Edition effort is likely a consequence of the widespread use of SLN biopsy, the requirement for SLN biopsy for patients with T2-T4 primary melanoma to be included in AJCC staging, and, to a lesser extent, newer imaging technologies that improve detection of clinically occult metastatic disease, thereby defining more homogenous groups of patients and achieving more accurate staging.[36 38] Some patients, who in the past would have been classified as clinically node negative (cN0), would be expected to harbor clinically

Comment [TG6]: I never thought about this point before, but in reading this sentence, I'm curious whether this approach has been used for other sites as well. If so, it might be worth noting that this is a consistent practice for AJCC.

Comment [TG7]: Some CA readers may not understand this without a more tangible explanation, so it might be useful to explain that some patients who in the past would have been classified as N0 now have a positive SLNB and are classified as N1.

occult nodal metastasis identified on the basis of a positive SLN biopsy and are classified as pN1, pN2, etc., according to the overall number of tumor-involved lymph nodes. In one study, for example, the risk of harboring a positive SLN ranged from 11% in patients with T1a melanoma to 53% in patients with T4b melanoma.[51] Overall, the presence of an ulcerated primary was generally associated with a MSS approximately similar to that of a patient with a nonulcerated primary tumor in the next highest tumor thickness category.

Other T category definitions have been clarified in the Eighth Edition. Patients with melanoma *in situ* are properly categorized as Tis (not T0, which is reserved for an unknown or completely regressed primary site). Since tumor thickness can only be evaluated accurately in histological sections cut perpendicular to the epidermal surface, the T category should be recorded as TX if the thickness cannot be assessed (e.g., in curettage specimens when no tissue fragment shows a complete section of the tumor cut perpendicular to the surface). In some instances, if the tissue has been misembedded, melting the paraffin block and re-embedding the tissue may enable perpendicular sections to be obtained. If there is evidence of regression of part of an invasive melanoma, the thickness should be measured in the usual way to the deepest identifiable viable tumor cell, and the tumor should be assigned to the appropriate T category. Partially regressed melanoma should not be designated TX or T0. T0 should be used if there is no evidence of a primary tumor (e.g., in a patient who presents with nodal or visceral metastasis and no known primary tumor), or if a melanoma has regressed completely. If the invasive component of the melanoma has regressed but overlying in situ melanoma remains, the tumor should be designated Tis.

Ulceration

Primary tumor ulceration is another T category criterion. In the Eighth Edition, as in the Seventh Edition,[38] the absence or presence of ulceration is designated “a” or “b”, respectively, in each T subcategory (e.g., T2a and T2b correspond to non-ulcerated and ulcerated T2 melanomas, respectively)(**Table 2)**. Ulceration is defined as the full thickness absence of an intact epidermis above

any portion of the primary tumor with associated host reaction (characterized by a fibrinous and acute inflammatory exudate) above the primary tumor, based on histopathological examination. If there is no host reaction, this likely represents artefactual loss of an intact epidermis overlying the primary melanoma and the melanoma should not be recorded as ulcerated, since this may have resulted from sectioning artifact caused by the tissue sectioning techniques used in the laboratory. Epidermal loss caused by a prior biopsy should not be recorded as ulceration for staging purposes. If ulceration is present in either an initial partial biopsy or a re-excision specimen of a primary melanoma, then the tumor should be recorded as ulcerated for staging purposes. While the presence of "squared off" edges of a scar can provide a clue to the presence of iatrogenic (prior biopsy related) ulceration, at times it may be difficult or impossible to distinguish between iatrogenic and non-iatrogenic causes of ulceration on the basis of histopathologic assessment alone, and correlation with the clinical history is essential.[52] If doubt remains as to whether ulceration is traumatic or iatrogenic in origin, the tumor should be staged as an ulcerated primary tumor.

Ulceration is an adverse prognostic factor;[25, 36, 37, 41, 53] the presence of an ulcerated primary was generally associated with a MSS similar to that of a patient with a nonulcerated primary in the next highest tumor thickness category **(Figure 1)**. For example, the 5- and 10-year MSS for patients with T2b pN0 and T3a pN0 primary cutaneous melanomas are 93% and 88%, and 94% and 88%, respectively.

Comment [TG8]: This point is also mentioned on the preceding page. Is this duplication intentional?

Mitotic rate

Mitotic rate, defined as the number of mitoses per square millimeter in the invasive portion of the tumor using the "hot spot" method,[3,36] (i.e., count beginning in a region where mitoses are more frequent and continue in immediately adjacent non-overlapping high power fields), was a T1 category criterion in the Seventh Edition;[37,38] it was included as a dichotomous variable defined as <1/mm^2 versus ≥1/mm^2. In the Eighth Edition, mitotic rate was not included as a T1 staging criterion (based on the T1 analysis described in the tumor thickness section above). Nevertheless, among patients with clinically node negative (cN0) primary melanoma in the Eighth Edition AJCC melanoma database, increasing mitotic

Comment [TG9]: Is it possible to explain this in a brief parenthetical phrase?

rate was significantly associated with decreasing MSS in univariate analysis (**Figure 2**). For example, in a univariate analysis of MSS for patients with T1-4 pN0 melanoma according to mitotic rate (mitoses/mm^2) when categorized as <1, 1-3, 3-10, >10, the 5- and 10-year MSS ranged from 99% and 97% in patients whose primary tumor had <1 mitosis/mm^2 to 84% and 77% in patients whose primary tumors had ≥11 mitoses/mm^2, respectively ($p < 0.0001$, log rank test). As supported by this univariate analysis and previous reports,[54, 55] mitotic rate is likely an important prognostic determinant when evaluated using its dynamic range across melanomas of all tumor thickness categories. Therefore, the AJCC Melanoma Expert Panel strongly recommends that mitotic rate be assessed and recorded for all primary melanomas,[3, 36] even though it is not used for T1 staging in the Eighth Edition. Mitotic rate will likely be an important parameter for inclusion in the future development of prognostic models applicable to individual patients. While not included in the T1 subcategory criteria, mitotic activity in T1 melanomas has been previously shown to be associated with increased risk of sentinel lymph node metastasis.[43, 46, 56, 57]

Comment [TG10]: Please include P values. You may not need P values to accompany all point estimates, but I think they should be included if you are commenting on the importance of a prognostic factor.

Comment [TG11]: Only in univariate analyses or also in multivariable models? Also, why is multivariable analysis mentioned in the discussion on page 12 but not here?

The N category

The N category documents metastatic disease both in regional lymph nodes and in non-nodal loco-regional sites (i.e., microsatellites, satellites and in-transit metastases). For the Eighth Edition, the Melanoma Expert Panel sought to add further granularity throughout the N category by providing clarity of definitions.

Regional Lymph Node Metastasis

In the Eighth Edition, N category criteria continue to include both extent of regional node tumor involvement and number of tumor-involved regional nodes. "Clinically occult" nodal metastasis describes patients with microscopically identified regional node metastasis detected by SLN biopsy and without clinical or radiographic evidence of regional node metastasis (termed "microscopic" nodal metastasis in the Seventh Edition). In contrast, "clinically detected" nodal metastasis describes patients with regional

node metastasis identified by clinical, radiographic or ultrasound examination (termed "macroscopic" nodal metastasis in the Seventh Edition) and usually (but not necessarily) confirmed by biopsy.[58]

Clinically occult (N1a, N2a, N3a) and clinically detected (N1b, N2b, N3b) N subcategories define patients with regional node disease based on extent of regional node involvement and number of tumor-involved regional nodes among patients without satellites, microsatellites, or in-transit metastases (**Table 3)**. If at least one node is clinically detected, and there are additional involved nodes detected only on microscopic examination, the total number of involved nodes (i.e., both those clinically detected and those identified only on microscopic examination of a complete lymphadenectomy specimen) should be recorded for N subcategory based on the total number of tumor-involved regional nodes. If microsatellites, satellites or in-transit metastases are present, patients are assigned to an N "c" subcategory according to the number of tumor-involved regional nodes, regardless of whether clinically occult or clinically detected: N1c, N2c or N3c if 0, 1 or ≥2 regional nodes contain tumor, respectively (**Table 3)**.

As noted in the Seventh Edition, there is no unequivocal evidence that there is a lower threshold for the size of a clinically occult melanoma regional node tumor deposit that defines node-positive disease for staging purposes. Thus, a lymph node in which any metastatic tumor cells have been identified, irrespective of how small the tumor deposit or whether it has been identified on H&E-stained or immunostained sections, should be designated as a tumor-involved lymph node. In the Eighth Edition, it has been clarified that if melanoma cells are found in a lymphatic channel within or immediately adjacent to a lymph node, that node is regarded as tumor-involved for staging purposes.

In the Eighth Edition, the term "gross extranodal extension" is no longer used as an N category criterion, but the presence of matted nodes (defined as two or more nodes adherent to one another through involvement by metastatic disease, identified at the time the specimen is examined macroscopically in the pathology laboratory) is retained as an N3 criterion. Even though it is not formally included as an Eighth Edition N category criterion, the definition of extranodal extension (ENE, also termed extranodal spread or extracapsular extension) has been clarified. In the Eighth Edition, ENE is

defined as the presence of a nodal metastasis extending through the lymph node capsule and into adjacent tissue, which may be apparent macroscopically but must be confirmed microscopically. It is recommended that this factor be recorded, as it may be useful for future analyses.[59]

Patients with clinically occult regional node disease have been shown in several large series to have better survival than patients with clinically evident disease.[50, 60, 61] This was also evident in the AJCC MSS curves according to N category and N subcategory, shown in **Figure 3**. Overall, consistent with our observations in the Seventh Edition,[25, 37, 62] there is marked heterogeneity in prognosis among patients with Stage III regional node disease by N-category designation.

Non-nodal Locoregional Metastases (Microsatellite, Satellite and In-transit Metastases)

The presence or absence of microsatellite, satellite or in-transit metastases, regardless of the number of such lesions, are components of the N category in the Eighth Edition (**Table 3**). They are all thought to represent metastases that are a consequence of intralymphatic or possibly angiotropic tumor spread. S*atellite* metastases have classically and somewhat arbitrarily been defined as clinically evident cutaneous and/or subcutaneous metastases occurring within 2 cm of the primary melanoma.[50, 63] *Microsatellites* have classically been defined as microscopic cutaneous and/or subcutaneous metastases found adjacent or deep to a primary melanoma on pathological examination (see discussion below). *In-transit* metastases have classically and somewhat arbitrarily been defined as clinically evident cutaneous and/or subcutaneous metastases identified at a distance more than 2 cm from the primary melanoma in the region between the primary and the first echelon of regional lymph nodes.[63] Beginning with the Sixth Edition AJCC melanoma staging system, satellite and in-transit metastases were merged into a single staging entity reflective of intralymphatic regional metastases.[63] Occasionally, satellite or in-transit metastases may occur distal to the primary site. An N "c" subcategory has been added into each of the N1, N2 and N3 categories (i.e. N1c, N2c, N3c)(**Table 3**) in the Eighth Edition to incorporate contemporary knowledge of the prognostic importance of non-nodal locoregional metastases, and to simplify the application of staging rules for patients with them. Microsatellites, satellites and in-transit metastases have been shown to portend a relatively poor prognosis.[64-70] In univariate analysis of the

Comment [TG12]: In you discussion of in-transit metastases on the next page you refer to "cutaneous and/or subcutaneous" metastases so I'm just checking whether the distinction between "cutaneous" and "dermal" in intentional.

Eighth Edition database that included patients with or without synchronous regional node involvement, there was no significant difference in survival outcome for these anatomically defined entities (**Figure 4**); hence, they were grouped together for staging purposes (**Table 3**). Planned IMDDP multivariable analyses will further explore the prognostic impact of non-nodal regional disease on MSS.

In the Seventh Edition, a microsatellite was defined as "any tumor nest >0.05 mm in diameter that was separated by normal dermis from the main invasive component of a melanoma by distance of >0.5 mm". The definition of microsatellite has been clarified and refined, so that in the Eighth Edition, there is no minimum size threshold or distance from the primary tumor that defines a microsatellite; it is simply defined as a microscopic cutaneous and/or subcutaneous metastasis adjacent to or deep to and completely discontinuous from a primary melanoma with unaffected stroma occupying the space between, identified on pathological examination of the primary tumor site. Fibrous scarring and/or inflammation noted between an apparently separate nodule and the primary tumor (rather than normal stroma) may represent regression of the intervening tumor; if these findings are present, the nodule is considered to be an extension of the primary tumor and not a microsatellite. Although occasionally seen in the primary melanoma diagnostic biopsy specimen, microsatellites, when present, are more commonly identified in the wide excision specimen.

Metastatic melanoma in lymph nodes without a known primary tumor

Patients presenting with melanoma in one or more lymph nodes without a known primary tumor were not included in the International Melanoma Database constructed for the analyses informing the Eighth Edition. However, based on data from the published literature (including from patients diagnosed before 1998[71-73]) and analysis of patients presenting to Melanoma Institute Australia since 1998,[73] such patients had an equivalent or slightly better survival than patients with a known primary tumor who presented with a similar number of clinically-detected tumor-involved nodes. The AJCC Melanoma Expert Panel recommended that such patients be assigned to the corresponding N category based on the number of lymph nodes containing metastatic disease and the presence or absence of satellite, microsatellite or in-transit metastases. Until additional data are available, melanoma patients with an

unknown primary with N1b disease should be staged as IIIB whereas all other N categories should be staged as IIIC.

The M category

For the Eighth Edition, the Melanoma Expert Panel concluded that because of the rapidly changing and still evolving landscape for the management of patients with Stage IV melanoma, it was premature to embark on a broad-based analytic initiative based on new data from patients treated in recent years. Instead, the legacy Seventh Edition AJCC Stage IV international melanoma database was used for the Eighth Edition as the primary data source (and no new analyses were conducted), supplemented by published contemporary clinical trial data.[6-21] In the Eighth Edition, M category definitions were clarified and refined and a new category for patients with central nervous system (CNS) metastases was added (M1d). For patients with distant metastases, M1 is defined by both anatomic site of distant metastatic disease and serum lactate dehydrogenase level (LDH) for all anatomic site subcategories.

Anatomic site(s) of distant metastatic disease

The anatomic site(s) of metastasis is used to assign patients to one of four (previously three) M subcategories: M1a, M1b, M1c and, new to the Eighth Edition, M1d (**Table 4**). The definition of each M1 anatomic site subcategory was also clarified. Patients with distant metastasis to skin, subcutaneous tissue, muscle or distant lymph nodes, regardless of serum LDH level, are categorized as M1a. Patients with metastasis to lung (with or without concurrent metastasis to skin, subcutaneous tissue, muscle or distant lymph nodes and regardless of serum LDH level) are categorized as M1b. Patients with metastases to any other visceral site(s) (exclusive of the CNS) are designated as M1c. New to the Eighth Edition, patients with metastases to the CNS (i.e., involving the brain, spinal cord, leptomeninges, or other components of the CNS)[36] are designated as M1d (irrespective of the presence of metastatic disease at other sites); these patients were previously designated as M1c in the Seventh Edition. This revision to include an M1d category reflects the expert panel's assessment that, in addition to the

historically poor overall survival outcome for patients with CNS metastases, contemporary clinical trial eligibility and exclusion criteria, as well as stratification and analysis, are often based on the presence/absence of CNS disease.[6-21, 74, 75] This additional level of granularity in the M category therefore better "maps" to contemporary clinical practice and clinical trial decision-making and analysis.

Serum LDH level

In the Seventh Edition, an elevated LDH was used to categorize a patient as M1c, regardless of anatomic site(s) of metastatic disease, given its significance as an independent adverse predictor of survival among patients with Stage IV disease. LDH remains a clinically significant factor associated with response, progression-free survival, MSS and overall survival in the contemporary treatment era of targeted and immune therapies.[76-78] In the Eighth Edition, an elevated LDH level no longer independently defines M1c disease. Instead, in order to better codify the impact of anatomic site and LDH level, descriptors were added to the M1 subcategory designation to indicate LDH status (designated as "(0)" for not elevated and "(1)" for elevated) for each M1 subcategory (**Table 4**).

The Stage Groups

As in prior editions of the AJCC Cancer Staging Manual, both clinical and pathological classifications are employed in melanoma staging. In the Eighth Edition, clinical staging includes microstaging of the primary melanoma – as a standard practice, after resection of the primary melanoma – and clinical/radiologic assessment for regional and distant metastases, as well as biopsies performed to assess for regional and distant metastases as appropriate (**Table 5**). There are no substages for clinical Stage III melanoma. Pathological staging includes all clinical staging information, as well as any additional staging information derived from the wide excision (surgical) specimen that constitutes primary tumor surgical treatment, and pathological information about the clinically node-negative regional lymph nodes after SLN biopsy, with or without completion lymph node dissection (CLND), or therapeutic lymph node dissection for clinically evident regional lymph node disease (**Table 6**). In patients who undergo SLN biopsy and have a clinically occult regional lymph node metastasis identified by SLN biopsy, but

additional surgery in the form of a CLND is not performed, according to the Eighth Edition Principles of Cancer Staging (Chapter 1 of the Eighth Edition AJCC Cancer Staging Manual[55]) and the Eighth Edition melanoma chapter[36], category pN1a(sn) is assigned to specify that CLND was not performed. If a CLND is performed, such patients would be assigned to subcategory pN1a (or another pN>0 subcategory depending on the total number of tumor-involved lymph nodes), to distinguish these two clinical scenarios and to improve granularity in coding for clinical and analytic purposes.[36, 58]

Comment [TG13]: Does this sentence assume that additional nodal mets are not found on CLND?

Due in part to the low overall likelihood of nodal metastasis and lack of uniformly accepted criteria for SLN biopsy in T1 melanoma, neither pathological Stage 0 (melanoma in situ, Tis) nor T1 melanoma requires SLN biopsy to complete pathological staging among patients with clinically node-negative melanomas. Instead, cN information is used to assign the pathological stage for T1 melanomas if SLN biopsy is not performed.

The MSS for all patients stratified by pathological stage groups I to III is shown in **Figure 5**. Patients with Stages I, II, and III disease had 5- and 10-year MSS of 98% and 95%, 90% and 84%, and 77% and 69%, respectively, and were overall slightly improved compared to patients who had similar stages of melanoma in the Seventh Edition analyses.[25, 37]

Stages I and II subgroupings

For pathological T category stage groups, 5- and 10-year MSS ranged from 99% and 98% in patients with Stage IA melanoma, respectively, to 82% and 75% in patients with Stage IIC disease (**Figure 6**). As in the Seventh Edition, patients with clinical T1b N0 melanoma are included in clinical Stage IB. In contrast, patients with pathological T1b N0 melanoma are included in pathological Stage IA (and not IB as in the Seventh Edition) (**Table 6**). This stage grouping reflects the better survival of T1b patients with pathologically negative nodes, since if SLN biopsy was performed it only includes those with a tumor-negative SLN (i.e., T1b pN1 patients would be Stage III), compared with a group of T1b patients who were only clinically staged. Five- and 10-year MSS were 97% and 93%, respectively, for

patients with clinical T1b N0 melanoma, compared to 99% and 96% 5- and 10-year MSS, respectively, for patients with pathological T1b N0 melanoma.

Stage III subgroupings

In the Seventh Edition, both regional node factors (number of nodes involved, microscopic versus macroscopic node involvement) as well as primary tumor ulceration, determined Stage III groups. Although N category alone predicts MSS in the Eighth Edition analysis (**Figure 3**), the Melanoma Expert Panel hypothesized that more accurate prognostic estimates could be obtained by including both T category factors, tumor thickness and ulceration status, along with the number of tumor-involved lymph nodes and whether they were detected clinically or were clinically occult (i.e., positive SLN), and the presence of microsatellite, satellite, and/or in-transit metastases (i.e., 9 N categories; **Table 3**). This was evaluated using recursive partitioning analysis. Initially, 8 pathological Stage III subgroups were created, including three "pairs" of subgroups that had similar 5-year MSS (data not shown). Based on discussions by the Melanoma Expert Panel that explored the relative merits of "grouping" versus "splitting", and the observation that adoption of five N stage groups would result in a total of 11 overall stage groups across T, N, and M (5+5+1=11) which would not conform to the total number of stage groups across the broad AJCC cancer disease site landscape, the 8 subgroups were combined to create four Stage III subgroups that maintained the overall prognostic heterogeneity of the base model (**Figure 7**). As such, these four subgroups stratify patients with Stage III melanoma in the Eighth Edition, compared to the three subgroups that were used to stratify Stage III patients in the Seventh Edition.[25, 37] A clinic workstation guide to combining T and N categories into Stage III subgroups is provided in **Figure 8** (see also **Supplementary Figure 1** for a black and white version). Five-year MSS according to Stage III subgroups ranges from 93% in Stage IIIA patients (1-3 clinically occult tumor-involved SLNs [N1a or N2a] and T1a, T1b or T2a primaries) to 32% for Stage IIID patients (patients with a thick and ulcerated primary [T4b] and either four or more tumor-involved regional nodes [N3a or N3b] or two or more tumor-involved nodes and evidence of microsatellite, satellite or in-transit metastases [N3c]) (**Figure 7**). In the

Seventh Edition, 5-year MSS for Stages IIIA, IIIB, and IIIC disease were 78%, 59% and 40%, respectively.[37] These differences, particularly for patients with Stage IIIA disease, have implications for clinical decision-making and counseling, as well as the design, eligibility, stratification, and analysis of adjuvant therapy clinical trials.

Distant Metastases (Stage IV)

Although revisions to the M category have been implemented in the Eighth Edition, as described in detail above (**Tables 4**, **5** and **6**), no M stage subgroups were proposed and no new data have thus far been analyzed. This is because the availability of contemporary data is limited and because survival differences among patients with Stage IV melanoma historically were small (before the recent revolution in treatment options for patients with advanced melanoma). It is anticipated that, as recently-introduced systemic therapies gain a foothold in the treatment repertoire of patients with advanced disease and even better treatment modalities become available, Stage IV survival outcomes will continue to improve. An international Stage IV melanoma database is planned in the future to explore this new and evolving treatment landscape for patients with advanced disease.

ADDITIONAL RECOMMENDATIONS

Multiple primary melanomas – It is well established that patients may be diagnosed with synchronous or metachronous primary melanomas. In general, according to the Eighth Edition AJCC Principles of Cancer Staging,[58] when patients present with multiple primary cutaneous melanomas, each is considered a different primary site and each is categorized separately. In the uncommon clinical scenario where patients who harbor regional node metastases have multiple primary melanomas draining to the same regional node basin, the primary tumor with the highest T category should be assigned as the originating primary tumor with respect to the nodal metastases; if distant metastases are present, the primary tumor with the highest N category (or the highest T category if N0) should be assigned as the origin of the distant metastases.[58] Moreover, in patients with multiple primary

melanomas, the recorded stage should map to the highest stage group of any of the primary tumors. According to the Principles of Cancer Staging,[58] if there are multiple synchronous melanomas with no evidence of metastatic disease, the assigned category is based on the tumor with the highest T category, and by convention, the *m* suffix is used. For example, T2a(m) would be used to describe a 1.4 mm, non-ulcerated melanoma diagnosed synchronously with a 0.7 mm, non-ulcerated melanoma. Alternatively, another acceptable approach is to designate the number of primary tumors instead of the *m* suffix (i.e., T2a(2) in the above example).[58] To the extent possible, if the number of synchronous multiple primary melanomas at presentation is known, this latter approach is preferred by the Melanoma Expert Panel.

Other important primary tumor factors – Although detailed discussion is beyond the scope of this article, in addition to the variables discussed (e.g., tumor thickness, ulceration, mitotic rate), the Melanoma Expert Panel recommends routine collection of multiple other known or putative primary tumor factors: level of invasion, tumor-infiltrating lymphocytes, lymphovascular invasion, and neurotropism**.** The interested reader is referred to a comprehensive description and discussion of these and other factors in the melanoma chapter of the Eighth Edition AJCC Cancer Staging Manual.[36]

SLN microscopic tumor burden – There is significant and growing evidence that microscopic tumor burden in the sentinel node is prognostically important.[79-91] Sentinel node tumor burden can be assessed by a variety of micromorphometric parameters including the maximum size of the largest metastasis, maximum subcapsular depth (also known as tumor penetrative depth[89] of the deposits and measured from the inner surface of the lymph node capsule to the deepest intranodal tumor cell), the microanatomic location of sentinel node tumor deposits, the percentage cross-sectional area of the sentinel node that is involved and the presence of extranodal extension. In various studies, one or more of these parameters has predicted survival in SLN positive patients.[79-91]

The impact of extent of SLN tumor burden (based on largest maximum dimension of the largest discrete metastatic melanoma deposit) was assessed for the subset of patients with known SLN tumor burden in the IMDDP. In univariate analysis, increasing SLN tumor burden was associated with reduced

MSS (**Figure 9**). Although this histopathological parameter is not a formal staging criterion for the N category in the Eighth Edition, documentation of SLN tumor burden is an important prognostic factor that will be included in and likely guide the development of future prognostic models and ultimately validated clinical tools (e.g., calculators, nomograms, etc.) for patients with regional metastatic disease.

Comment [TG14]: "tools" or "trials"? If the former, please explain what a clinical tool is.

Microscopic SLN tumor burden has already been implemented as an inclusion criterion in some clinical trials (e.g., EORTC 18071 - adjuvant ipilimumab in stage III[23, 24] and EORTC1325 - adjuvant pembrolizumab in stage III[24]). In these trials, patients with a single positive SLN must have a microscopic tumor burden >1mm in diameter, based on the relatively worse prognosis of this patient subgroup.

Based on the currently available evidence, the AJCC Melanoma Expert Panel recommends that, as a minimum, the single largest maximum dimension (measured in millimeters to the nearest 0.1 mm using an ocular micrometer) of the largest discrete metastatic melanoma deposit in sentinel nodes be recorded in pathology reports.[36] To further advance this field, the AJCC Melanoma Expert Panel and International Melanoma Pathology Study Group plan to continue efforts to harmonize and standardize assessment and reporting of SLN tumor burden. Planned IMDDP analyses will also further explore the prognostic impact of SLN tumor burden.

Comment [TG15]: Does this refer to the CAP synoptic reporting templates? Does the current melanoma template include size of nodal mets?

Number of distant metastatic sites and extent of distant metastatic disease burden – The number of metastases at distant sites has previously been documented as an important prognostic factor.[77, 92-95] This was also confirmed in previous preliminary multivariable analyses using the Seventh Edition AJCC stage IV melanoma database. However, this feature was not incorporated into the Eighth Edition as a formal staging criterion due in part to significant variability in the deployment of diagnostic imaging to comprehensively search for distant metastases (ranging from a chest x-ray in some centers to high-resolution double-contrast CT, PET/CT, and MRI in others) as well as the heterogeneity with which extent of disease results are codified across databases. Until recording of the indications for and types of investigations used and extent of distant metastatic disease are better standardized, the Melanoma Expert Panel concluded that number of metastases cannot reproducibly be used for staging purposes.

Approach to staging patients following neoadjuvant ("up front") therapy – Historically, surgery represented the mainstay of treatment for patients with cutaneous melanoma. For several solid tumors, neoadjuvant therapy (systemic therapy prior to surgical resection) is often used as part of multidisciplinary treatment approaches for patients with locally advanced and/or regional disease, and for others an "up front" approach using systemic therapy (without a definitive plan for surgery to follow) is employed.[96] The availability of effective systemic therapies has greatly expanded potential treatment approaches for patients with unresectable and regionally advanced melanoma over the past several years and has led to tremendous interest in leveraging these clinical advances to develop neoadjuvant strategies for melanoma patients with locally advanced or metastatic disease. To stage such patients after treatment, the Eighth Edition Principles of Cancer Staging includes a posttherapy or post neoadjuvant therapy classification – yTNM -- that includes T, N, and M categorization after systemic or radiation treatment intended as definitive therapy (ycTNM), or after neoadjuvant therapy followed by planned surgery (ypTNM).[58] Although this has been an infrequently utilized classification in melanoma to date, given that a robust portfolio of neoadjuvant clinical trials in melanoma patients are currently under way, and still more are planned, the "y" classification schema may prove useful in characterizing such patients, and the information can be compared to clinical stages assigned to patients before the start of neoadjuvant therapy. Future analyses will likely allow refinement of this not yet widely used classification schema.

Approach to staging patients following recurrence/retreatment – By definition, clinical and pathological classification according to the AJCC staging system occurs at initial melanoma presentation. Thus, those who have regional node or non-nodal regional metastases at the time of initial presentation are characterized as having Stage III disease, and those who present with distant metastases at the time of initial presentation are characterized as having Stage IV disease. To accommodate staging for patients who have recurred, the Eighth Edition Principles of Cancer Staging also includes an additional classification schema for patients who recur – rTNM – that is further divided into "r-clinical" (rcTNM) and "r-pathological" (rpTNM) stages. Such an approach may be useful to better characterize extent of

disease along an individual melanoma patient's disease continuum.[58] As this staging classification is to date relatively unknown and infrequently used by the global melanoma community, future analyses will likely inform revisions of this classification schema for patients with recurrent melanoma.

CONCLUSIONS

In the Eighth Edition AJCC Staging System for cutaneous melanoma, particular attention was directed to clarifying major themes and terminology, introducing clinically relevant revisions and creating a new, contemporary international database. The Melanoma Expert Panel focused most of its attention on evidence-based revisions of Stages I to III melanoma for the Eighth Edition AJCC Cancer Staging Manual, and established a framework for the development of robust and iteratively refined clinical prognostic models that will assist in the development of clinical tools to ultimately enhance clinical decision making. Importantly, based on analyses of this contemporary melanoma database, survival outcomes for equivalent stage groupings were substantially higher than for similar stage groups of patients in prior Editions, including the Seventh Edition, with implications for clinical decision-making and clinical trial design, eligibility, stratification, and analysis.

Given the rapidly evolving landscape of treatment of Stage IV melanoma in recent years, which already has resulted in significantly improved progression-free and overall survival for patients, the Melanoma Expert Panel strategically paused and did not establish a Stage IV database or perform analyses of Stage IV patients. Instead new, clinically relevant M category criteria were introduced into the Eighth Edition that will facilitate refined collection of Stage IV data including more precise data collection for patients with CNS metastases. These new criteria will be essential to support future assessment of prognosis, as well as clinical trial design, eligibility, stratification, and analysis, for patients with advanced melanoma. Strategic development of analytic efforts for the Stage IV melanoma population in the current new era of effective targeted therapies and immunotherapy is now under way as part of the IMDDP. These analyses are expected not only to improve prognostic assessment for patients

with advanced disease but also to inform further revisions of the staging system, and facilitate the development of clinical tools in the foreseeable future.

Additional enhancements to the Eighth Edition melanoma staging system, including yTNM and rTNM classifications, will enable contemporary melanoma patients to be accurately risk stratified across the disease continuum. This will assist clinicians and patients in clinical management planning and enhance the design, conduct and analysis of clinical trials that should ultimately lead to improved patient outcomes. Undoubtedly, melanoma staging will continue to evolve as new prognostic factors and evidence-based approaches – including integration of clinical, pathological, molecular and immunological endpoints – are developed, refined, and validated.

Tables

Table 1. A summary of the major changes introduced and highlights of the Eighth Edition of the AJCC Melanoma Staging System.

Change	***Details of Change/Highlight***
Definition of Primary Tumor (T)	All principal T category tumor thickness ranges maintained, but **T1** now subcategorized by tumor thickness strata at 0.8mm threshold
Definition of Primary Tumor (T)	Tumor mitotic rate removed as a staging criterion for **T1** tumors • **T1a** melanomas now defined as non-ulcerated and less than 0.8mm in thickness; • **T1b** now defined as melanomas 0.8mm to 1.0mm in thickness regardless of ulceration status OR ulcerated melanomas less than 0.8mm in thickness
Definition of Primary Tumor (T)	**T0** definition has been clarified – **T0** should be used to designate when there is no evidence of a primary tumor, or the site of the primary tumor is unknown (e.g., in a patient who presents axillary metastasis with no known primary tumor); staging may be based on the clinical suspicion of the primary tumor with the tumor categorized as **T0** (**Tis**, not **T0**, designates melanoma in situ)
Definition of Primary Tumor (T)	Tumor thickness measurements now recorded to the nearest 0.1mm, not the nearest 0.01mm, because of impracticality and imprecision of measurements particularly for tumors >1mm thick. Tumors ≤1mm may be measured to the nearest 0.01mm when practical, but should be reported rounded to the nearest 0.1mm (e.g., melanomas measured to be anywhere in the range from 0.75mm to 0.84mm are reported as 0.8mm in thickness (and hence **T1b**)
Definition of Primary Tumor (T)	**Tis** (melanoma in situ), **T0** (no evidence of or unknown primary tumor), and **TX** (tumor thickness cannot be determined) may now be used as the T category designation for stage groupings
Definition of Regional Lymph Node (N)	Number of metastasis-containing regional lymph nodes maintained
Definition of Regional Lymph Node (N)	Previously empirically defined “microscopic” and “macroscopic” descriptors redefined as “clinically occult” (i.e., clinical Stage I-II with nodal metastasis determined at sentinel node biopsy) and “clinically apparent” regional node disease (clinical Stage III), respectively
Definition of Regional Lymph Node (N)	Sentinel node tumor burden is considered a regional disease prognostic factor that should be collected for all patents with positive sentinel nodes, but is not used to determine N category groupings
Definition of Regional Lymph Node (N)	Non-nodal regional disease, including microsatellites, satellites, and in-transit cutaneous and/or subcutaneous metastases more formally stratified by N category according to # of tumor involved lymph nodes (Presence of microsatellites, satellites, or in-transit metastases now categorized as **N1c**, **N2c**, or **N3c** based on number of synchronous tumor-involved regional lymph nodes, if any)
Definition of Regional Lymph Node (N)	“Gross” extranodal extension no longer used as an N staging criterion (but the presence of “matted nodes” is retained)
Definition of Distant Metastasis (M)	**M1** now defined by both anatomic site of distant metastatic disease and serum lactate dehydrogenase (LDH) value for all anatomic site subcategories
Definition of Distant Metastasis (M)	Descriptions of distant anatomic sites of disease clarified in M subcategories

Change	***Details of Change/Highlight***
Definition of Distant Metastasis (M)	Descriptors now added to **M1** subcategory designation that provides LDH values (designated as "0" for "not elevated" and "1" for "elevated" level) for all sites of distant disease; e.g., skin/soft tissue/nodal metastasis with elevated LDH now **M1a(1)**, not **M1c**
Definition of Distant Metastasis (M)	New M1d designation added to include distant metastasis to central nervous system (CNS), with or without any other distant sites of disease; **M1c** no longer includes CNS metastasis
Definition of Distant Metastasis (M)	Elevated LDH level no longer defines **M1c**
AJCC Prognostic Stage Groups	No overall change in T subcategories, but definition of **T1a** and **T1b** refined
AJCC Prognostic Stage Groups	N category now composed of five substages rather than three, and Stage III subgroupings are based on multivariable models including T category elements (tumor thickness and ulceration) and N category elements (# of nodes, satellites/in-transits/microsatellites) demonstrating significant impact of primary tumor factors in assigning N substage
AJCC Prognostic Stage Groups	Clarified that stage IV not further substaged (i.e., **M1c** is stage IV, not stage IVC)

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Gershenwald, J.E., Scolyer, R.A., et al. Melanoma of the Skin. In: Amin, M.B., Edge, S.B., Greene, F.L., et al. (Eds.) AJCC Cancer Staging Manual. 8th Ed. New York: Springer; 2017: 563-585

Table 2. Definition of Primary Tumor (T)

T Category	Thickness	Ulceration status
TX: primary tumor thickness cannot be assessed (e.g., diagnosis by curettage)	Not applicable	Not applicable
T0: no evidence of primary tumor (e.g., unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma *in situ*)	Not applicable	Not applicable
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm 0.8–1.0 mm	With ulceration With or without ulceration
T2	>1.0–2.0 mm	Unknown or unspecified
T2a	>1.0–2.0 mm	Without ulceration
T2b	>1.0–2.0 mm	With ulceration
T3	>2.0-4.0 mm	Unknown or unspecified
T3a	>2.0–4.0 mm	Without ulceration
T3b	>2.0–4.0 mm	With ulceration
T4	>4.0 mm	Unknown or unspecified
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

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Modified from Gershenwald, J.E., Scolyer, R.A., et al. Melanoma of the Skin. In: Amin, M.B., Edge, S.B., Greene, F.L., et al. (Eds.) AJCC Cancer Staging Manual. 8th Ed. New York: Springer; 2017: 563-585

Table 3. Definition of Regional Lymph Node (N)

	Extent of regional lymph node and/or lymphatic metastasis	
N Category	**Number of tumor-involved regional lymph node**	**Presence of in-transit, satellite, and/or microsatellite metastases**
NX	Regional nodes not assessed (e.g., SLN biopsy not performed, regional nodes previously removed for another reason) **Exception**: pathological N category is not required for T1 melanomas, use cN.	No
N0	No regional metastases detected	No
N1	One tumor-involved node or any number of in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (i.e., detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or three tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	
N2a	Two or three clinically occult (i.e., detected by SLN biopsy)	No
N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult (i.e., detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

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Modified from Gershenwald, J.E., Scolyer, R.A., et al. Melanoma of the Skin. In: Amin, M.B., Edge, S.B., Greene, F.L., et al. (Eds.) AJCC Cancer Staging Manual. 8th Ed. New York: Springer; 2017: 563-585

Table 4. Definition of Distant Metastasis (M)

	M Criteria	
M Category	**Anatomic site**	**LDH level**
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Normal
M1d(1)		Elevated

Suffixes for M category: (0) LDH not elevated, (1) LDH elevated.
No suffix is used if LDH is not recorded or is unspecified.

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Table 5. AJCC Clinical Prognostic Stage Groups (cTNM)

When T is…	***And N is…***	***And M is…***	***Then the clinical stage group is…***
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
Any T, Tis	≥N1	M0	III
Any T	Any N	M1	IV

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Table 6. AJCC Pathological (pTNM) Prognostic Stage Groups

When T is…	***And N is…***	***And M is…***	***Then the pathological stage group is…***
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b or N3c	M0	IIIC
T1a/b–T2a	N1a or N2a	M0	IIIA
T1a/b–T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a–N2b	M0	IIIB
T1a–T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N ≥N1	M0	IIIC
T4b	N1a–N2c	M0	IIIC
T4b	N3a/b/c	M0	IIID
Any T, Tis	Any N	M1	IV
Pathological Stage 0 (melanoma *in situ*) and T1 do not require pathological evaluation of lymph nodes to complete pathological staging; use cN information to assign their pathological stage.			

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Supplementary Table 1. Details of the International Melanoma Database and Discovery Platform (IMDDP) – Contributors to Current Analysis

Institution	Location		No. of Patients Contributed to Wave I IMDDP Analysis
	Continent	City, State, Country	
Melanoma Institute Australia	Australia	Sydney, New South Wales, Australia	17,276
Melbourne Melanoma Project	Australia	Melbourne, Victoria, Australia	1,408
Department of Dermatology, National and Kapodistrian University of Athens School of Medicine, Andreas Sygros Hospital	Europe	Athens, Greece	468
Fondazione IRCCS Istituto Nazionale dei Tumori	Europe	Milan, Italy	6,537
Instituto Valenciano de Oncologia	Europe	Valencia, Spain	1,392
National and Kapodistrian University of Athens School of Medicine - General Hospital of Athens – Laiko	Europe	Athens, Greece	1,205
Veneto Institute of Oncology-IOV	Europe	Padova, Italy	2,954
John Wayne Cancer Institute	North America	Santa Monica, California, USA	6,228
The University of Texas MD Anderson Cancer Center	North America	Houston, Texas, USA	8,023
Winship Cancer Institute of Emory University	North America	Atlanta, Georgia, USA	1,495
Total			**46,986**

Supplementary Table 2 - International Melanoma Database and Discovery Platform Data Dictionary. Data elements used for analyses that informed the Eighth Edition (Stages I-III)

Variable	Description	Acceptable Values
Patient Demographics		
Collaborator_Patient_ID	Unique patient identifier for the home institution database (de-identified)	Home institution format
DOB	Patient date of birth	Date
Patient_Sex	Patient sex	Male Female Other/Unknown
Last_Vital_Date	Date of last follow-up	Date
Last_Vital_Status	Status at last follow-up	Alive Deceased
Cause_Death	Cause of death	Melanoma Other Not applicable
T Category		
KnownPrimary_DX_Staging_Date	Date of diagnosis of primary	Date
Primary_Site	Anatomic site of primary	Home institution format
Breslow_Thickness_MM	Breslow thickness (mm)* of primary	Numeric
Ulceration	Ulceration status of primary	Absent Present Unknown
Mitoses_PerMM2	Mitoses/mm^2	Numeric
N Category		
SLNB_Status	Sentinel-lymph node status	Negative Positive Not conducted
Clinical_Detection	If regional nodes are involved, was there clinical detection of regional lymph nodes No = detected by SLN biopsy	Yes No Unknown
Overall_Positive_Nodes	Total number of tumor-involved lymph nodes**	Numeric
Largest_Metastatic_MM	Largest diameter of the largest metastatic deposit in the tumor-involved sentinel node(s) (mm)*	Numeric
Tumor_Nodal_Location	Location(s) of the metastatic deposit(s) in the sentinel node	Subcapsular Intraparenchymal Both Unknown

Variable	Description	Acceptable Values
Extranodal_Extension	Presence of extranodal extension** of regional node(s) at diagnosis	Absent Present Unknown
Microsatellites	Presence of microsatellites in the primary tumor specimen (yes/no) at diagnosis	Absent Present Unknown
Intransit	Presence of in-transit and/or satellite lesions at diagnosis	Absent Present Unknown

*At the level of precision used by your institution and data team.
**Including cumulative results from histopathological assessment of staging lymph node procedures, for example sentinel node biopsy *and* completion lymph node dissection OR lymph node biopsy *and* therapeutic lymph node dissection.

Figure Legends

Comment [TG16]: Please check consistency of font sizes and styles in figures. There seems to be some inconsistency but I can't be certain whether this reflects the original figures or the way they were joined in the pdf.

Figure 1. Kaplan–Meier MSS curves according to T subcategory for patients with Stage I to II melanoma from the Eighth Edition international melanoma database. N0 patients have been filtered so that T2 to T4 patients were included only if SLN negative, whereas patients with T1N0 melanoma are included regardless of whether SLN biopsy was performed.

Figure 2. Kaplan–Meier MSS curves according to mitotic rate (mitoses per square millimeter) in patients with Stage I to II melanoma from the Eighth Edition international melanoma database. N0 patients have been filtered so that T2 to T4 patients were included only if SLN negative, whereas patients with T1N0 melanoma were included regardless of whether SLN biopsy was performed.

Figure 3. Kaplan–Meier MSS curves according to N categories (A) and subcategories (B) from the Eighth Edition international melanoma database

Figure 4. Kaplan–Meier MSS curves according to the presence or absence of microsatellites, satellites, and/or in-transit metastases from the Eighth Edition international melanoma database. (Note: *Intransit* in figure means in-transit and/or satellite metastasis; *both* means microsatellites and/or in-transit and/or satellite metastasis.)

Figure 5. Kaplan–Meier MSS curves according to Stage in patients with Stage I to III melanoma from the Eighth Edition international melanoma database.

Figure 6. Kaplan–Meier MSS curves according to T category stage group for patients with Stage I to II melanoma from the Eighth Edition international melanoma database. N0 patients were filtered so that

T2+ patients are included only if SLN negative, whereas patients with T1N0 melanoma are included regardless of whether SLN biopsy was performed.

Figure 7. Kaplan–Meier MSS curves according to Stage III subgroups from the Eighth Edition international melanoma database.

Figure 8. AJCC Eighth Edition Stage III subgroups based on T and N categories.

Figure 9. Kaplan–Meier MSS curves according to maximum dimension of sentinel node metastatic focus (millimeters) from the Eighth Edition international melanoma database. (Note – insufficient data exists to estimate 10-year MSS for patients with 2 mm to 4 mm maximum sentinel node metastatic focus).

Supplementary Figure 1. AJCC Eighth Edition Stage III subgroups based on T and N categories (black and white version).

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Melanoma Staging: Evidence-Based Changes in the ~~Eighth Edition~~ American Joint Committee on Cancer (AJCC) Eighth Edition Cancer Staging Manual

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ABSTRACT

To update the melanoma staging system of the previous (Seventh) edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual published in 2009, a large database was assembled comprising >46,000 patients from 10 centers worldwide with Stages I, II, and III melanoma diagnosed since 1998. Based on analyses of this new database, the existing Seventh Edition AJCC Stage IV database, and contemporary clinical trial data, the AJCC Melanoma Expert Panel introduced several important changes to the TNM classification and stage grouping criteria. These were incorporated into the Eighth Edition AJCC Cancer Staging Manual. Key changes include: (1) tumor thickness measurements to be recorded to the nearest 0.1 mm, not the nearest 0.01 mm; (2) definitions of T1a and T1b revised (T1a, <0.8 mm without ulceration; T1b, ~~<0.8 mm with ulceration or~~ 0.8-1.0 mm with or without ulceration, or <0.8 mm with ulceration), with mitotic rate no longer a T category criterion; (3) pathological (but not clinical) Stage IA revised to include T1b N0 M0 (formerly pathological Stage IB); (4) N category descriptors “microscopic” and “macroscopic” for regional node metastasis redefined as “clinically occult” and “clinically apparent”; (5) prognostic Stage III groupings based on N category criteria and T category criteria (i.e., primary tumor thickness and ulceration) and increased from three to four subgroups (Stage IIIA-IIID); (6) definitions of N subcategories revised, with presence of microsatellites, satellites or in-transit metastases now categorized as N1c, N2c or N3c based on number of tumor-involved regional lymph nodes, if any; (7) descriptors added to each M1 subcategory designation for LDH level (LDH elevation no longer automatically upstages to M1c); (8) a new M1d designation for metastases involving the central nervous system. This evidence-based revision of the AJCC melanoma

staging system will guide patient treatment, provide better prognostic estimates, and further refine eligibility and stratification of patients entering clinical trials.

Keywords: American Joint Committee on Cancer (AJCC), melanoma, database, TNM classification, staging, stage groupings, pathology, tumor thickness, ulceration, mitotic rate, regional lymph nodes, sentinel lymph node, visceral metastasis, brain metastasis, prognosis, survival

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Eighth Edition AJCC Melanoma Expert Panel

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International Melanoma Database and Discovery Platform

The AJCC Eighth Edition Melanoma Expert Panel acknowledges the following institutions and associated individuals for their data contributions to the Eighth Edition International Melanoma Database of the International Melanoma Database and Discovery Platform to perform analyses that informed the revisions incorporated into the Eighth Edition American Joint Committee on Cancer melanoma staging system (listed below in alphabetical order):

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INTRODUCTION

To improve the outcomes of patients with cutaneous melanoma, treatment based on accurate staging and patient stratification into clinically-relevant stage groups is fundamental. Not only does staging inform prognostic assessment and clinical decision making, but it also facilitates centralized cancer registry reporting and the design, conduct and analysis of clinical trials.

Since the early 1990s, a major advance in the management of patients with cutaneous melanoma involves the technique of lymphatic mapping and sentinel lymph node (SLN) biopsy;[1] this is now routinely employed as a staging procedure[2] for patients with T1b, T2, T3 and T4 (Eighth Edition) primary cutaneous melanomas and clinically negative regional lymph nodes in most melanoma treatment centers throughout the world.[33] The frequency of SLN metastasis increases with increasing tumor thickness and other adverse clinicopathological prognostic factors.[3-5] Clinical imaging technologies have also advanced, having become more sophisticated and more widely available, facilitating the detection of distant metastatic disease when it is of low volume and asymptomatic.

More recently, based upon improved knowledge of both the molecular pathogenesis of melanoma and cancer immunology, there has been a revolution in the treatment of patients with advanced stage and unresectable melanoma.[6-21] This has already resulted in major improvements in patient outcomes.[33] Two major new classes of effective systemic therapeutic agents are now in widespread clinical use: immunotherapies (e.g., checkpoint inhibitors against cytotoxic T lymphocyte antigen 4 (CTLA-4) and/or programmed death 1 (PD-1)) that enhance the natural host antitumor immune response, and molecularly targeted antitumor therapies (e.g., BRAF inhibitors alone or in combination with MEK inhibitors for the approximately 40 to 50% of patients with $BRAF^{V600}$ mutant melanoma).[22] Moreover, adjuvant therapy with anti-CTLA-4 significantly improves relapse-free survival and overall survival in stage III melanoma patients.[23, 24] It is against this background that the American Joint Committee on Cancer (AJCC) appointed a Melanoma Expert Panel to undertake the task of revising the cutaneous melanoma staging system for the Eighth Edition of the AJCC Cancer Staging Manual.

The Seventh Edition AJCC melanoma staging system (hereafter referred to as the Seventh Edition) has been widely adopted since its publication in 2009 and implementation in 2010.[2, 25] For the Eighth Edition AJCC melanoma staging system (hereafter referred to as the Eighth Edition), a contemporary international database was assembled to provide an evidence-based rationale for revisions to the cutaneous melanoma staging system that would have more current applicability.[33] The objective was to analyze detailed multi-institutional clinicopathological data collected in a standardized fashion to empirically establish T, N, and M categories and stage groupings for the Eighth Edition. We report here the results of analyses using this large melanoma database, supplemented by analyses from the Seventh Edition AJCC Stage IV database and by contemporary clinical trial data. These provided the evidence base for revisions of the Eighth Edition as well as the UICC Eighth Edition TNM Classification of Malignant Tumours.[26] The revised T, N, and M categories and stage groupings are presented below. To ensure that the necessary infrastructure is in place across the cancer care community, the Eighth Edition, originally published in October 2016, will not be formally implemented in the U.S. until January 1, 2018.[27]

DATABASE and METHODS

To assist the Eighth Edition Melanoma Expert Panel in its review of T and N categories and Stage I to III subgroupings, a protocol-based International Melanoma Database and Discovery Platform (IMDDP) was created at The University of Texas MD Anderson Cancer Center (MD Anderson), Houston, TX, USA. This protocol was approved by the MD Anderson Institutional Review Board (IRB) and formal data use agreements were implemented across all participating institutions, each also having obtained approval from their own IRB. This overall approach built upon collaborative efforts of the previous AJCC Melanoma Task Forces (renamed the AJCC Melanoma Expert Panel for the Eighth Edition) and an expanded network of national and international academic melanoma clinician–investigators representing institutions, cooperative groups, and tumor registries. The database included de-identified patient records from 10 institutions in the United States, Europe and Australia, with well-annotated

clinicopathological and follow-up data for patients with Stages I to III melanoma at initial diagnosis, treated since 1998. Importantly, the database reflected a contemporary clinical practice era during which the use of lymphatic mapping and SLN biopsy was well established in nearly all academic medical centers worldwide for patients considered at significant risk for occult regional node metastasis. Patients treated in the pre-SLN era (i.e., pre-1990s) as well as the early SLN era (early through mid-1990s) were deliberately omitted. During this latter period, SLN biopsy surgical techniques had evolved and matured (with development and implementation of a dual-modality intraoperative approach using blue dye and a radiotracer with gamma probe detection) and pathological assessment of the SLN (with widespread implementation of "enhanced" pathological assessment using step or serial sectioning and immunohistochemistry).[1, 2, 28-32]

For the analyses undertaken for the Eighth Edition, the database platform included the records of more than 46,000 melanoma patients (**Supplementary Table 1**~~)~~), of whom 43,792 qualified for analysis. Only data from patients for whom ~~all~~ relevant covariates (**Supplementary Table 2**) were known were included in ~~the analyses~~each analysis.

Comment [TG1]: How many patients did not have complete covariate info? (overall or by institution)

Given the unprecedented changes in the still rapidly evolving landscape of the management of patients with Stage IV melanoma, the Melanoma Expert Panel concluded that it was premature to embark on a broad-based analytic initiative involving data from Stage IV patients treated during the past 8 years. Instead, the legacy 7th Edition AJCC Stage IV international melanoma database containing details of approximately 10,000 patients who presented with or developed Stage IV disease was used as the primary data source for the 8th Edition, supplemented by published contemporary clinical trial data.[6-21]

Statistical Analyses

Melanoma-specific survival (MSS) was calculated from the date of initial melanoma diagnosis. MSS curves were computed using the Kaplan-Meier method. Multivariable analyses were conducted using Cox proportional hazards regression models and recursive partitioning analysis (RPA). Analyses were

performed using S+ (Windows version 8.2, TIBCO, software, Inc.). RPA was performed using the S+ "tree" libraries on the MSS null martingale residuals.

MAJOR CHANGES

Table 1 summarizes the major changes introduced for the T, N, and M categories and stage groupings in the Eighth Edition. The rationale for these changes is described below.

The T Category

Breslow Tumor Thickness

In prior editions of the AJCC Cancer Staging Manual,[2, 25] it was implied (but not explicitly stated) that primary melanoma tumor thickness should be recorded to the nearest 0.01 mm. This has been clarified in the Eighth Edition. Based on consensus recommendations by the International Collaboration on Cancer Reporting[33] and the International Melanoma Pathology Study Group, already widely adopted in the pathology community,[34] thickness measurements should be recorded to the nearest 0.1 mm, not the nearest 0.01 mm, because of the impracticality and imprecision of measurements,[34] particularly for tumors >1 mm thick, and the reality that tumor thickness may vary by 0.1 mm or more between different histological tissue sections cut from the same paraffin tissue block of the tumor.[35] Tumors ≤1mm thick may initially be measured to the nearest 0.01 mm, but should be rounded up or down to be recorded to the precision of a single digit after the decimal (i.e., to the nearest 0.1 mm). The convention for rounding decimal values is to round down those ending in 1 to 4 and to round up those ending in 5 to 9. For example, a melanoma measuring 0.75 mm in thickness would be recorded as 0.8 mm in thickness (i.e., T1b). Tumors measuring 0.95 mm through 1.04 mm would be rounded to 1.0 mm (i.e., T1b). Primary tumor thickness should be measured using an ocular micrometer that has been calibrated to the magnification of the microscope used for the measurement. Microsatellites should not be included in the measurement of tumor thickness. Additional specific recommendations for the measurement of tumor thickness in particular clinical circumstances ~~will be~~have been previously documented[33] and will be

further detailed in a planned separate publication on pathological aspects of melanoma staging from the International Melanoma Pathology Study Group.

In the Eighth Edition, the T-category thresholds of melanoma thickness continue to be defined at 1, 2, and 4 mm (**Table 2**).[~~36~~36] However, the T categories have been revised to promote consistency, with the recommendation that thickness be rounded to the nearest 0.1 mm, as described above. Using these rounding conventions, T2 melanomas include patients with melanomas with a tumor thickness of 1.05 mm to 2.04 mm; T2 is now presented as >1.0–2.0 mm, compared to 1.01–2.0 mm in the Seventh Edition.[37, 38]

Several ~~legacy~~previously published reports have indicated that survival among patients with T1 melanomas is related to tumor thickness, with a possible clinically important "breakpoint" in the region of 0.7 mm-0.8 mm~~.~~.[39-42] These observations were explored in the IMDDP database by seeking to identify a subgroup of patients with exceptionally good outcome compared to even the most favorable subcategory (T1a) in the Seventh Edition,[25] and hence in whom SLN biopsy would generally not be indicated. In the T1 cohort, the impact on outcome of a 0.8 mm tumor thickness threshold was evaluated, as well as mitotic rate (as a dichotomous variable, <1 mitosis per mm^2 vs. ≥1 mitosis per mm^2) and ulceration. In a multivariable analysis of factors predicting MSS (including tumor thickness, ulceration, and mitotic rate) among 7,568 T1 N0 patients, tumor thickness ≥0.8 mm had a hazard ratio (HR) of 1.7 vs. <0.8 mm (p = 0.057), ulceration had a HR of 2.6 vs. non-ulcerated (p = 0.035), and mitotic rate ≥1/mm^2 had a HR of 0.85 vs. mitotic rate <1/mm^2 (p = 0.57). Based on these analyses of patients with T1 melanomas, tumor thickness (when dichotomized as <0.8 mm and 0.8-1.0 mm) and ulceration were stronger predictors of MSS than mitotic rate. Accordingly, since mitotic rate was not statistically significant in the model, T1 subcategory definitions have been revised: T1a is now defined as nonulcerated melanomas <0.8 mm in thickness and T1b as melanomas 0.8-1.0 mm in thickness regardless of ulceration status, plus ulcerated melanomas <0.8 mm in thickness (**Table 2**). The Eighth Edition Melanoma Expert Panel also noted that the sub-categorization of T1 melanomas at a 0.8 mm threshold has clinical relevance, particularly for the role of SLN biopsy in patients with T1 melanomas. Overall, SLN metastases are very infrequent (<5%)

Comment [TG2]: Please explain.

Comment [TG3]: What other factors (if any) were included besides thickness, ulceration, and mitotic rate?

Comment [TG4]: Can you briefly describe the analysis that supports combining thickness and ulceration in this way? This combination does not seem to be described in the preceding 2 sentences.

Comment [TG5]: Is it feasible to be more specific?

in melanomas <0.8 mm but occur in approximately 5%-12% of patients with primary melanomas 0.8-1.0 mm,[43-46] and consensus guidelines have recommended that SLN biopsy be considered in this latter group of patients, particularly when other adverse prognostic parameters are also present.[47-49]

As in the Seventh Edition, patients with primary melanoma and no evidence of regional or distant metastasis are stratified into eight T subcategories (T1a through T4b). MSS stratified by T subcategory for 23,001 patients with complete covariate data is shown in **Figure 1**. For these survival curves, patients with T1 melanomas were included if they had clinical or pathological T1 N0 melanomas, but patients with T2-T4 melanomas were included only if pN0 (i.e., no tumor-containing SLNs and no evidence of microsatellites, satellites, or in-transit metastases at diagnosis or following initial treatment). ~~Five~~ Overall, this approach aligns with the AJCC Principles of Cancer Staging (see chapter 1 of the Eighth Edition AJCC Cancer Staging Manual).[56] An implication of this approach is that patients with T2-T4 melanomas who do not undergo SLN biopsy cannot be pathologically staged. Nonetheless, the Melanoma Expert Panel acknowledges that not all patients with T2-T4 undergo SLN biopsy and improved clinical prognostic models and tools (e.g., clinical calculators, etc.) may be developed to improve prognostic assessment among this cohort of patients in the future.

In the Eighth Edition, five- and ten-year MSS ranged from 99% and 98%, respectively, for patients with T1a N0 melanomas (i.e., primary tumor thickness <0.8 mm, non-ulcerated), to 82% and 75%, respectively, for patients with T4b N0 melanomas (i.e., primary tumor thickness >4.0 mm, ulcerated). MSS for all T subcategories were notably higher than those reported in the Seventh Edition, in which 10-year MSS was 93% and 39% for T1a N0 and T4b N0 melanomas, respectively.[50] The higher survival of patients in the more contemporary patient cohort examined in this Eighth Edition effort is likely a consequence of the widespread use of ~~sentinel node~~SLN biopsy, the requirement for SLN biopsy for patients with T2-T4 primary melanoma to be included in AJCC staging, and, to a lesser extent, newer imaging technologies that improve detection of clinically occult metastatic disease, thereby defining more homogenous groups of patients and achieving more accurate staging.[~~36~~ ~~38~~36 38] Some patients, who in the past would have been classified as clinically node negative (cN0), would be expected to harbor clinically

Comment [TG6]: I never thought about this point before, but in reading this sentence, I'm curious whether this approach has been used for other sites as well. If so, it might be worth noting that this is a consistent practice for AJCC.

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Comment [TG7]: Some CA readers may not understand this without a more tangible explanation, so it might be useful to explain that some patients who in the past would have been classified as N0 now have a positive SLNB and are classified as N1.

occult nodal metastasis identified on the basis of a positive SLN biopsy and are classified as pN1, pN2, etc., according to the overall number of tumor-involved lymph nodes. In one study, for example, the risk of harboring a positive SLN ranged from 11% in patients with T1a melanoma to 53% in patients with T4b melanoma.[51] Overall, the presence of an ulcerated primary was generally associated with a MSS approximately similar to that of a patient with a nonulcerated primary tumor in the next highest tumor thickness category. ~~These T-category thresholds also inform substaging in patients both without and with regional disease in the Eighth Edition staging system (see N stage groups below).~~

Comment [TG8]: This point is also mentioned on the next page. Is this duplication intentional?

Other T category definitions have been clarified in the Eighth Edition. Patients with melanoma *in situ* are properly categorized as Tis (not T0, which is reserved for an unknown or completely regressed primary site). Since tumor thickness can only be evaluated accurately in histological sections cut perpendicular to the epidermal surface, the T category should be recorded as TX if the thickness cannot be assessed (e.g., in curettage specimens when no tissue fragment shows a complete section of the tumor cut perpendicular to the surface). In some instances, if the tissue has been misembedded, melting the paraffin block and re-embedding the tissue may enable perpendicular sections to be obtained. If there is evidence of regression of part of an invasive melanoma, the thickness should be measured in the usual way to the deepest identifiable viable tumor cell, and the tumor should be assigned to the appropriate T category. Partially regressed melanoma should not be designated TX or T0. T0 should be used if there is no evidence of a primary tumor (e.g., in a patient who presents with nodal or visceral metastasis and no known primary tumor), or if a melanoma has regressed completely. If the invasive component of the melanoma has regressed but overlying in situ melanoma remains, the tumor should be designated Tis.

Ulceration

Primary tumor ulceration is another T category criterion. In the Eighth Edition, as in the Seventh Edition,[~~38~~38] the absence or presence of ulceration is designated “a” or “b”, respectively, in each T subcategory (e.g., T2a and T2b correspond to non-ulcerated and ulcerated T2 melanomas,

respectively)(**Table 2)**. Ulceration is defined as the full thickness absence of an intact epidermis above any portion of the primary tumor with associated host reaction (characterized by a fibrinous and acute inflammatory exudate) above the primary tumor, based on histopathological examination. If there is no host reaction, this likely represents artefactual loss of an intact epidermis overlying the primary melanoma and the melanoma should not be recorded as ulcerated, since this may have resulted from sectioning artifact caused by the tissue sectioning techniques used in the laboratory. Epidermal loss caused by a prior biopsy should not be recorded as ulceration for staging purposes. If ulceration is present in either an initial partial biopsy or a re-excision specimen of a primary melanoma, then the tumor should be recorded as ulcerated for staging purposes. While the presence of "squared off" edges of a scar can provide a clue to the presence of iatrogenic (prior biopsy related) ulceration, at times it may be difficult or impossible to distinguish between iatrogenic and non-iatrogenic causes of ulceration on the basis of histopathologic assessment alone, and correlation with the clinical history is essential.[~~51~~52] If doubt remains as to whether ulceration is traumatic or iatrogenic in origin, the tumor should be staged as an ulcerated primary tumor.

Ulceration is an adverse prognostic factor;[25, 36, 37, 41, ~~52~~53] the presence of an ulcerated primary was generally associated with a MSS similar to that of a patient with a nonulcerated primary in the next highest tumor thickness category **(Figure 1)**. For example, the 5- and 10-year MSS for patients with T2b pN0 and T3a pN0 primary cutaneous melanomas are 93% and 88%, and 94% and 88%, respectively.

Comment [TG9]: This point is also mentioned on the preceding page. Is this duplication intentional?

Mitotic rate

Mitotic rate, defined as the number of mitoses per square millimeter in the invasive portion of the tumor using the "hot spot" method,[~~3,36~~3,36] (i.e., count beginning in a region where mitoses are more frequent and continue in immediately adjacent non-overlapping high power fields), was a T1 category criterion in the Seventh Edition;[37,38] it was included as a dichotomous variable defined as <1/mm^2 versus ≥1/mm^2. In the Eighth Edition, mitotic rate was not included as a T1 staging criterion (based on the T1 analysis described in the tumor thickness section above). Nevertheless, among patients with clinically

Comment [TG10]: Is it possible to explain this in a brief parenthetical phrase?

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node negative (cN0) primary melanoma in the Eighth Edition AJCC melanoma database, increasing mitotic rate was significantly associated with decreasing MSS in univariate analysis (**Figure 2**). For example, in a univariate analysis of MSS for patients with T1-4 pN0 melanoma according to mitotic rate (mitoses/mm^2) when ~~presented~~categorized as ~~a categorical variable,~~ <1, 1-3, 3-10, >10, the 5- and 10-year MSS ranged from 99% and 97% in patients whose primary tumor had <1 mitosis/mm^2 to 84% and 77% in patients whose primary tumors had ≥11 mitoses/mm^2, respectively~~.~~ (p < 0.0001, log rank test). As supported by this univariate analysis and previous reports,[~~53,~~ 54, 55] mitotic rate is likely an important prognostic determinant when evaluated using its dynamic range across melanomas of all tumor thickness categories. Therefore, the AJCC Melanoma Expert Panel strongly recommends that mitotic rate be assessed and recorded for all primary melanomas,[3, 36] even though it is not used for T1 staging in the Eighth Edition. Mitotic rate will likely be an important parameter for inclusion in the future development of prognostic models applicable to individual patients. While not included in the T1 subcategory criteria, mitotic activity in T1 melanomas has been previously shown to be associated with increased risk of sentinel lymph node metastasis.[43, 46, 56, 57]

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Comment [TG11]: Please include P values. You may not need P values to accompany all point estimates, but I think they should be included if you are commenting on the importance of a prognostic factor.

Comment [TG12]: Only in univariate analyses or also in multivariable models? Also, why is multivariable analysis mentioned in the discussion on page 12 but not here?

The N category

The N category documents metastatic disease both in regional lymph nodes and in non-nodal loco-regional sites (i.e., microsatellites, satellites and in-transit metastases). For the Eighth Edition, the Melanoma Expert Panel sought to add further granularity throughout the N category by providing clarity of definitions.

Regional Lymph Node Metastasis

In the Eighth Edition, N category criteria continue to include both extent of regional node tumor involvement and number of tumor-involved regional nodes. "Clinically occult" nodal metastasis describes patients with microscopically identified regional node metastasis detected by SLN biopsy and without clinical or radiographic evidence of regional node metastasis (termed "microscopic" nodal metastasis in the Seventh Edition). In contrast, "clinically detected" nodal metastasis describes patients with regional

node metastasis identified by clinical, radiographic or ultrasound examination (termed "macroscopic" nodal metastasis in the Seventh Edition) and usually (but not necessarily) confirmed by biopsy.[~~55~~58]

Clinically occult (N1a, N2a, N3a) and clinically detected (N1b, N2b, N3b) N subcategories define patients with regional node disease based on extent of regional node involvement and number of tumor-involved regional nodes among patients without satellites, microsatellites, or in-transit metastases (**Table 3)**. If at least one node is clinically detected, and there are additional involved nodes detected only on microscopic examination, the total number of involved nodes (i.e., both those clinically detected and those identified only on microscopic examination of a complete lymphadenectomy specimen) should be recorded for N subcategory based on the total number of tumor-involved regional nodes. If microsatellites, satellites or in-transit metastases are present, patients are assigned to an N "c" subcategory according to the number of tumor-involved regional nodes, regardless of whether clinically occult or clinically detected: N1c, N2c or N3c if 0, 1 or ≥2 regional nodes contain tumor, respectively (**Table 3)**.

As noted in the Seventh Edition, there is no unequivocal evidence that there is a lower threshold for the size of a clinically occult melanoma regional node tumor deposit that defines node-positive disease for staging purposes. Thus, a lymph node in which any metastatic tumor cells have been identified, irrespective of how small the tumor deposit or whether it has been identified on H&E-stained or immunostained sections, should be designated as a tumor-involved lymph node. In the Eighth Edition, it has been clarified that if melanoma cells are found in a lymphatic channel within or immediately adjacent to a lymph node, that node is regarded as tumor-involved for staging purposes.

In the Eighth Edition, the term "gross extranodal extension" is no longer used as an N category criterion, but the presence of matted nodes (defined as two or more nodes adherent to one another through involvement by metastatic disease, identified at the time the specimen is examined macroscopically in the pathology laboratory) is retained as an N3 criterion. Even though it is not formally included as an Eighth Edition N category criterion, the definition of extranodal extension (ENE, also termed extranodal spread or extracapsular extension) has been clarified. In the Eighth Edition, ENE is

defined as the presence of a nodal metastasis extending through the lymph node capsule and into adjacent tissue, which may be apparent macroscopically but must be confirmed microscopically. It is recommended that this ~~covariate~~factor be recorded, as it may be useful for future analyses.[56~~59~~]

Comment [TG13]: You might substitute "information" or "factor" or another synonym here. Technically, my impression is that it would be called a covatiate only in the context of a multivariable model.

Field Code Changed

Patients with clinically occult regional node disease have been shown in several large series to have better survival than patients with clinically evident disease.[50, ~~57, 58~~60, 61] This was also evident in the AJCC MSS curves according to N category and N subcategory, shown in **Figure 3**. Overall, consistent with our observations in the Seventh Edition,[25, 37, ~~59~~62] there is marked heterogeneity in prognosis among patients with Stage III regional node disease by N-category designation.

Non-nodal Locoregional Metastases (Microsatellite, Satellite and In-transit Metastases)

The presence or absence of microsatellite, satellite or in-transit metastases, regardless of the number of such lesions, are components of the N category in the Eighth Edition (**Table 3**). They are all thought to represent metastases that are a consequence of intralymphatic or possibly angiotropic tumor spread. S*atellite* metastases have classically and somewhat arbitrarily been defined as ~~grossly visible or palpable~~clinically evident cutaneous and/or subcutaneous metastases occurring within 2 cm of the primary melanoma.[50, ~~60~~63] *Microsatellites* have classically been defined as microscopic cutaneous and/or subcutaneous metastases found adjacent or deep to a primary melanoma on pathological examination (see discussion below). *In-transit* metastases have classically and somewhat arbitrarily been defined as clinically evident ~~dermal~~cutaneous and/or subcutaneous metastases identified at a distance more than 2 cm from the primary melanoma in the region between the primary and the first echelon of regional lymph nodes.[~~60~~63] Beginning with the Sixth Edition AJCC melanoma staging system, satellite and in-transit metastases were merged into a single staging entity reflective of intralymphatic regional metastases.[~~60~~63] Occasionally, satellite or in-transit metastases may occur distal to the primary site. An N "c" subcategory has been added into each of the N1, N2 and N3 categories (i.e. N1c, N2c, N3c)(**Table 3**) in the Eighth Edition to incorporate contemporary knowledge of the prognostic importance of non-nodal locoregional metastases, and to simplify the application of staging rules for patients with them. Microsatellites, satellites and in-transit metastases have been shown to portend a relatively poor prognosis.[~~61~~ ~~67~~64-70] In

Comment [TG14]: In you discussion of in-transit metastases on the next page you refer to "cutaneous and/or subcutaneous" metastases so I'm just checking whether the distinction between "cutaneous" and "dermal" in intentional.

univariate analysis of the Eighth Edition database that included patients with or without synchronous regional node involvement, there was no significant difference in survival outcome for these anatomically defined entities (**Figure 4**); hence, they were grouped together for staging purposes (**Table 3**). Planned IMDDP multivariable analyses will further explore the prognostic impact of non-nodal regional disease on MSS.

In the Seventh Edition, a microsatellite was defined as "any tumor nest >0.05 mm in diameter that was separated by normal dermis from the main invasive component of a melanoma by distance of >0.5 mm". The definition of microsatellite has been clarified and refined, so that in the Eighth Edition, there is no minimum size threshold or distance from the primary tumor that defines a microsatellite; it is simply defined as a microscopic cutaneous and/or subcutaneous metastasis adjacent to or deep to and completely discontinuous from a primary melanoma with unaffected stroma occupying the space between, identified on pathological examination of the primary tumor site. Fibrous scarring and/or inflammation noted between an apparently separate nodule and the primary tumor (rather than normal stroma) may represent regression of the intervening tumor; if these findings are present, the nodule is considered to be an extension of the primary tumor and not a microsatellite. Although occasionally seen in the primary melanoma diagnostic biopsy specimen, microsatellites, when present, are more commonly identified in the wide excision specimen.

Metastatic melanoma in lymph nodes without a known primary tumor

Patients presenting with melanoma in one or more lymph nodes without a known primary tumor were not included in the International Melanoma Database constructed for the analyses informing the Eighth Edition. However, based on data from the published literature (including from patients diagnosed before 1998[68-70,71-73]) and analysis of patients presenting to Melanoma Institute Australia since 1998,[70,73] such patients had an equivalent or slightly better survival than patients with a known primary tumor who presented with a similar number of clinically-detected tumor-involved nodes. The AJCC Melanoma Expert Panel recommended that such patients be assigned to the corresponding N category based on the number of lymph nodes containing metastatic disease and the presence or absence of satellite,

microsatellite or in-transit metastases. Until additional data are available, melanoma patients with an unknown primary with N1b disease should be staged as IIIB whereas all other N categories should be staged as IIIC.

The M category

For the Eighth Edition, the Melanoma Expert Panel concluded that because of the rapidly changing and still evolving landscape for the management of patients with Stage IV melanoma, it was premature to embark on a broad-based analytic initiative based on new data from patients treated in recent years. Instead, the legacy Seventh Edition AJCC Stage IV international melanoma database was used for the Eighth Edition as the primary data source (and no new analyses were conducted), supplemented by published contemporary clinical trial data.[6-21] In the Eighth Edition, M category definitions were clarified and refined and a new category for patients with central nervous system (CNS) metastases was added (M1d). For patients with distant metastases, M1 is defined by both anatomic site of distant metastatic disease and serum lactate dehydrogenase level (LDH) for all anatomic site subcategories.

Anatomic site(s) of distant metastatic disease

The anatomic site(s) of metastasis is used to assign patients to one of four (previously three) M subcategories: M1a, M1b, M1c and, new to the Eighth Edition, M1d (**Table 4**). The definition of each M1 anatomic site subcategory was also clarified. Patients with distant metastasis to skin, subcutaneous tissue, muscle or distant lymph nodes, regardless of serum LDH level, are categorized as M1a. Patients with metastasis to lung (with or without concurrent metastasis to skin, subcutaneous tissue, muscle or distant lymph nodes and regardless of serum LDH level) are categorized as M1b. Patients with metastases to any other visceral site(s) (exclusive of the CNS) are designated as M1c. ~~New to the Eighth Edition, patients with metastases to the CNS (i.e., involving the brain, spinal cord, leptomeninges, or other components of the CNS)~~[36]New to the Eighth Edition, patients with metastases to the CNS (i.e., involving the brain, spinal cord, leptomeninges, or other components of the CNS)[36] are designated as

M1d (irrespective of the presence of metastatic disease at other sites); these patients were previously designated as M1c in the Seventh Edition. This revision to include an M1d category reflects the expert panel's assessment that, in addition to the historically poor overall survival outcome for patients with CNS metastases, contemporary clinical trial eligibility and exclusion criteria, as well as stratification and analysis, are often based on the presence/absence of CNS disease.[6-21, 76, 7774, 75] This additional level of granularity in the M category therefore better "maps" to contemporary clinical practice and clinical trial decision-making and analysis.

Serum LDH level

In the Seventh Edition, an elevated LDH was used to categorize a patient as M1c, regardless of anatomic site(s) of metastatic disease, given its significance as an independent adverse predictor of survival among patients with Stage IV disease. LDH remains a clinically significant factor associated with response, progression-free survival, MSS and overall survival in the contemporary treatment era of targeted and immune therapies.[76-78-80] In the Eighth Edition, an elevated LDH level no longer independently defines M1c disease. Instead, in order to better codify the impact of anatomic site and LDH level, descriptors were added to the M1 subcategory designation to indicate LDH status (designated as "(0)" for not elevated and "(1)" for elevated) for each M1 subcategory (**Table 4**).

The Stage Groups

As in prior editions of the AJCC Cancer Staging Manual, both clinical and pathological classifications are employed in melanoma staging. In the Eighth Edition, clinical staging includes microstaging of the primary melanoma – as a standard practice, after resection of the primary melanoma – and clinical/radiologic assessment for regional and distant metastases, as well as biopsies performed to assess for regional and distant metastases as appropriate (**Table 5**). There are no substages for clinical Stage III melanoma. Pathological staging includes all clinical staging information, as well as any additional staging information derived from the wide excision (surgical) specimen that constitutes primary tumor surgical treatment, and pathological information about the clinically node-negative regional lymph

nodes after SLN biopsy, with or without completion lymph node dissection (CLND), or therapeutic lymph node dissection for clinically evident regional lymph node disease (**Table 6**). In patients who undergo SLN biopsy and have a clinically occult regional lymph node metastasis identified by SLN biopsy, but additional surgery in the form of a CLND is not performed, according to the Eighth Edition Principles of Cancer Staging (Chapter 1 of the Eighth Edition AJCC Cancer Staging Manual[55]) and the Eighth Edition melanoma chapter[36], category pN1a(sn) is assigned to specify that CLND was not performed. If a CLND is performed, such patients would be assigned to ~~category~~subcategory pN1a (or another pN>0 subcategory depending on the total number of tumor-involved lymph nodes), to distinguish these two clinical scenarios and to improve granularity in coding for clinical and analytic purposes.[36, ~~55~~58]

Comment [TG15]: Does this sentence assume that additional nodal mets are not found on CLND?

Due in part to the low overall likelihood of nodal metastasis and lack of uniformly accepted criteria for SLN biopsy in T1 melanoma, neither pathological Stage 0 (melanoma in situ, Tis) nor T1 melanoma requires SLN biopsy to complete pathological staging among patients with clinically node-negative melanomas. Instead, cN information is used to assign the pathological stage for T1 melanomas if SLN biopsy is not performed.

The MSS for all patients stratified by pathological stage groups I to III is shown in **Figure 5**. Patients with Stages I, II, and III disease had 5- and 10-year MSS of 98% and 95%, 90% and 84%, and 77% and 69%, respectively, and were overall slightly improved compared to patients who had similar stages of melanoma in the Seventh Edition analyses.[25, 37]

Stages I and II subgroupings

For pathological T category stage groups, 5- and 10-year MSS ranged from 99% and 98% in patients with Stage IA melanoma, respectively, to 82% and 75% in patients with Stage IIC disease (**Figure 6**). As in the Seventh Edition, patients with clinical T1b N0 melanoma are included in clinical Stage IB. In contrast, patients with pathological T1b N0 melanoma are included in pathological Stage IA (and not IB as in the Seventh Edition) (**Table 6**). This stage grouping reflects the better survival of T1b patients with pathologically negative nodes, since if SLN biopsy was performed it only includes those

with a tumor-negative SLN (i.e., T1b pN1 patients would be Stage III), compared with a group of T1b patients who were only clinically staged. Five- and 10-year MSS were 97% and 93%, respectively, for patients with clinical T1b N0 melanoma, compared to 99% and 96% 5- and 10-year MSS, respectively, for patients with pathological T1b N0 melanoma.

Stage III subgroupings

In the Seventh Edition, both regional node factors (number of nodes involved, microscopic versus macroscopic node involvement) as well as primary tumor ulceration, determined Stage III groups. Although N category alone predicts MSS in the Eighth Edition analysis (**Figure 3**), the Melanoma Expert Panel hypothesized that more accurate prognostic estimates could be obtained by including both T category factors, tumor thickness and ulceration status, along with the number of tumor-involved lymph nodes and whether they were detected clinically or were clinically occult (i.e., positive SLN), and the presence of microsatellite, satellite, and/or in-transit metastases (i.e., 9 N categories; **Table 3**). This was evaluated using recursive partitioning analysis. Initially, 8 pathological Stage III subgroups were created, including three "pairs" of subgroups that had similar 5-year MSS (data not shown). Based on discussions by the Melanoma Expert Panel that explored the relative merits of "grouping" versus "splitting", and the observation that adoption of five N stage groups would result in a total of 11 overall stage groups across T, N, and M (5+5+1=11) which would not conform to the total number of stage groups across the broad AJCC cancer disease site landscape, the 8 subgroups were combined to create four Stage III subgroups that maintained the overall prognostic heterogeneity of the base model (**Figure 7**). As such, these four subgroups stratify patients with Stage III melanoma in the Eighth Edition, compared to the three subgroups that were used to stratify Stage III patients in the Seventh Edition.[25, 37] A clinic workstation guide to combining T and N categories into Stage III subgroups is provided in **Figure 8** (see also **Supplementary Figure 1** for a black and white version). Five-year MSS according to Stage III subgroups ranges from 93% in Stage IIIA patients (1-3 clinically occult tumor-involved SLNs [N1a or N2a] and T1a, T1b or T2a primaries) to 32% for Stage IIID patients (patients with a thick and ulcerated

primary [T4b] and either four or more tumor-involved regional nodes [N3a or N3b] or two or more tumor-involved nodes and evidence of microsatellite, satellite or in-transit metastases [N3c~~]).]~~) (**Figure 7**). In the Seventh Edition, 5-year MSS for Stages IIIA, IIIB, and IIIC disease were 78%, 59% and 40%, respectively.[37] These differences, particularly for patients with Stage IIIA disease, have implications for clinical decision-making and counseling, as well as the design, eligibility, stratification, and analysis of adjuvant therapy clinical trials.

Distant Metastases (Stage IV)

Although revisions to the M category have been implemented in the Eighth Edition, as described in detail above (**Tables 4**, **5** and **6**), no M stage subgroups were proposed and no new data have thus far been analyzed. This is because the availability of contemporary data is limited and because survival differences among patients with Stage IV melanoma historically were small (before the recent revolution in treatment options for patients with advanced melanoma). It is anticipated that, as recently-introduced systemic therapies gain a foothold in the treatment repertoire of patients with advanced disease and even better treatment modalities become available, Stage IV survival outcomes will continue to improve. An international Stage IV melanoma database is planned in the future to explore this new and evolving treatment landscape for patients with advanced disease.

ADDITIONAL RECOMMENDATIONS

Multiple primary melanomas – It is well established that patients may be diagnosed with synchronous or metachronous primary melanomas. ~~In general, according to the Eighth Edition AJCC Principles of Cancer Staging,[55]~~In general, according to the Eighth Edition AJCC Principles of Cancer Staging,[58] when patients present with multiple primary cutaneous melanomas, each is considered a different primary site and each is categorized separately. In the uncommon clinical scenario where patients who harbor regional node metastases have multiple primary melanomas draining to the same regional node basin, the primary tumor with the highest T category should be assigned as the

originating primary tumor with respect to the nodal metastases; if distant metastases are present, the primary tumor with the highest N category (or the highest T category if N0) should be assigned as the origin of the distant metastases.[5558] Moreover, in patients with multiple primary melanomas, the recorded stage should map to the highest stage group of any of the primary tumors. According to the Principles of Cancer Staging,[5558] if there are multiple synchronous melanomas with no evidence of metastatic disease, the assigned category is based on the tumor with the highest T category, and by convention, the *m* suffix is used. For example, T2a(m) would be used to describe a 1.4 mm, non-ulcerated melanoma diagnosed synchronously with a 0.7 mm, non-ulcerated melanoma. Alternatively, another acceptable approach is to designate the number of primary tumors instead of the *m* suffix (i.e., T2a(2) in the above example).[5558] To the extent possible, if the number of synchronous multiple primary melanomas at presentation is known, this latter approach is preferred by the Melanoma Expert Panel.

Other important primary tumor factors – Although detailed discussion is beyond the scope of this article, in addition to the variables discussed (e.g., tumor thickness, ulceration, mitotic rate), the Melanoma Expert Panel recommends routine collection of multiple other known or putative primary tumor factors: level of invasion, tumor-infiltrating lymphocytes, lymphovascular invasion, and neurotropism**.** The interested reader is referred to a comprehensive description and discussion of these and other factors in the melanoma chapter of the Eighth Edition AJCC Cancer Staging Manual.[3636]

SLN microscopic tumor burden – There is significant and growing evidence that microscopic tumor burden in the sentinel node is prognostically important.[81-9379-91] Sentinel node tumor burden can be assessed by a variety of micromorphometric parameters including the maximum size of the largest metastasis, maximum subcapsular depth (also known as tumor penetrative depth[89] of the deposits and measured from the inner surface of the lymph node capsule to the deepest intranodal tumor cell), the microanatomic location of sentinel node tumor deposits, the percentage cross-sectional area of the sentinel node that is involved and the presence of extranodal extension. In various studies, one or more of these parameters has predicted survival in SLN positive patients.[81-9379-91]

The impact of extent of SLN tumor burden (based on largest maximum dimension of the largest discrete metastatic melanoma deposit) was assessed for the subset of patients with known SLN tumor burden in the IMDDP. In univariate analysis, increasing SLN tumor burden was associated with reduced MSS (**Figure 9**). Although this histopathological parameter is not a formal staging criterion for the N category in the Eighth Edition, documentation of SLN tumor burden is an important prognostic factor that will be included in and likely guide the development of future prognostic models and ~~the development of~~ ultimately validated clinical tools (e.g., calculators, nomograms, etc.) for patients with regional metastatic disease.

Comment [TG16]: "tools" or "trials"? If the former, please explain what a clinical tool is.

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Microscopic SLN tumor burden has already been implemented as an inclusion criterion in some clinical trials (e.g., EORTC 18071 - adjuvant ipilimumab in stage III[23, 24] and EORTC1325 - adjuvant pembrolizumab in stage III[24]). In these trials, patients with a single positive SLN must have a microscopic tumor burden >1mm in diameter, based on the relatively worse prognosis of this patient subgroup.

Based on the currently available evidence, the AJCC Melanoma Expert Panel recommends that, as a minimum, the single largest maximum dimension (measured in millimeters to the nearest 0.1 mm using an ocular micrometer) of the largest discrete metastatic melanoma deposit in sentinel nodes be recorded in pathology reports.[~~36~~36] To further advance this field, the AJCC Melanoma Expert Panel and International Melanoma Pathology Study Group plan to continue efforts to harmonize and standardize assessment and reporting of SLN tumor burden. Planned IMDDP analyses will also further explore the prognostic impact of SLN tumor burden.

Comment [TG17]: Does this refer to the CAP synoptic reporting templates? Does the current melanoma template include size of nodal mets?

Number of distant metastatic sites and extent of distant metastatic disease burden – The number of metastases at distant sites has previously been documented as an important prognostic factor.[~~71, 72, 74, 75, 79~~77, 92-95] This was also confirmed in previous preliminary multivariable analyses using the Seventh Edition AJCC stage IV melanoma database. However, this feature was not incorporated into the Eighth Edition as a formal staging criterion due in part to significant variability in the deployment of diagnostic imaging to comprehensively search for distant metastases (ranging from a chest x-ray in

some centers to high-resolution double-contrast CT, PET/CT, and MRI in others) as well as the heterogeneity with which extent of disease results are codified across databases. Until recording of the indications for and types of investigations used and extent of distant metastatic disease are better standardized, the Melanoma Expert Panel concluded that number of metastases cannot reproducibly be used for staging purposes.

Approach to staging patients following neoadjuvant ("up front") therapy – Historically, surgery represented the mainstay of treatment for patients with cutaneous melanoma. For several solid tumors, neoadjuvant therapy (systemic therapy prior to surgical resection) is often used as part of multidisciplinary treatment approaches for patients with locally advanced and/or regional disease, and for others an "up front" approach using systemic therapy (without a definitive plan for surgery to follow) is employed.[94,96] The availability of effective systemic therapies has greatly expanded potential treatment approaches for patients with unresectable and regionally advanced melanoma over the past several years and has led to tremendous interest in leveraging these clinical advances to develop neoadjuvant strategies for melanoma patients with locally advanced or metastatic disease. To stage such patients after treatment, the Eighth Edition Principles of Cancer Staging includes a posttherapy or post neoadjuvant therapy classification – yTNM -- that includes T, N, and M categorization after systemic or radiation treatment intended as definitive therapy (ycTNM), or after neoadjuvant therapy followed by planned surgery (ypTNM).[55,58] Although this has been an infrequently utilized classification in melanoma to date, given that a robust portfolio of neoadjuvant clinical trials in melanoma patients are currently under way, and still more are planned, the "y" classification schema may prove useful in characterizing such patients, and the information can be compared to clinical stages assigned to patients before the start of neoadjuvant therapy. Future analyses will likely allow refinement of this not yet widely used classification schema.

Approach to staging patients following recurrence/retreatment – By definition, clinical and pathological classification according to the AJCC staging system occurs at initial melanoma presentation. Thus, those who have regional node or non-nodal regional metastases at the time of initial presentation

are characterized as having Stage III disease, and those who present with distant metastases at the time of initial presentation are characterized as having Stage IV disease. To accommodate staging for patients who have recurred, the Eighth Edition Principles of Cancer Staging also includes an additional classification schema for patients who recur – rTNM – that is further divided into "r-clinical" (rcTNM) and "r-pathological" (rpTNM) stages. Such an approach may be useful to better characterize extent of disease along an individual melanoma patient's disease continuum.[5558] As this staging classification is to date relatively unknown and infrequently used by the global melanoma community, future analyses will likely inform revisions of this classification schema for patients with recurrent melanoma.

Field Code Changed

CONCLUSIONS

In the Eighth Edition AJCC Staging System for cutaneous melanoma, particular attention was directed to clarifying major themes and terminology, introducing clinically relevant revisions and creating a new, contemporary international database. The Melanoma Expert Panel focused most of its attention on evidence-based revisions of Stages I to III melanoma for the Eighth Edition AJCC Cancer Staging Manual, and established a framework for the development of robust and iteratively refined clinical prognostic models that will assist in the development of clinical tools to ultimately enhance clinical decision making. Importantly, based on analyses of this contemporary melanoma database, survival outcomes for equivalent stage groupings were substantially higher than for similar stage groups of patients in prior Editions, including the Seventh Edition, with implications for clinical decision-making and clinical trial design, eligibility, stratification, and analysis.

Given the rapidly evolving landscape of treatment of Stage IV melanoma in recent years, which already has resulted in significantly improved progression-free and overall survival for patients, the Melanoma Expert Panel strategically paused and did not establish a Stage IV database or perform analyses of Stage IV patients. Instead new, clinically relevant M category criteria were introduced into the Eighth Edition that will facilitate refined collection of Stage IV data including more precise data

collection for patients with CNS metastases. These new criteria will be essential to support future assessment of prognosis, as well as clinical trial design, eligibility, stratification, and analysis, for patients with advanced melanoma. Strategic development of analytic efforts for the Stage IV melanoma population in the current new era of effective targeted therapies and immunotherapy is now under way as part of the IMDDP. These analyses are expected not only to improve prognostic assessment for patients with advanced disease but also to inform further revisions of the staging system, and facilitate the development of clinical tools in the foreseeable future.

Additional enhancements to the Eighth Edition melanoma staging system, including yTNM and rTNM classifications, will enable contemporary melanoma patients to be accurately risk stratified across the disease continuum. This will assist clinicians and patients in clinical management planning and enhance the design, conduct and analysis of clinical trials that should ultimately lead to improved patient outcomes. Undoubtedly, melanoma staging will continue to evolve as new prognostic factors and evidence-based approaches – including integration of clinical, pathological, molecular and immunological endpoints – are developed, refined, and validated.

Tables

Table 1. A summary of the major changes introduced and highlights of the Eighth Edition of the AJCC Melanoma Staging System.

Change	***Details of Change/Highlight***
Definition of Primary Tumor (T)	All principal T category tumor thickness ranges maintained, but **T1** now subcategorized by tumor thickness strata at 0.8mm threshold
Definition of Primary Tumor (T)	Tumor mitotic rate removed as a staging criterion for **T1** tumors • **T1a** melanomas now defined as non-ulcerated and less than 0.8mm in thickness; • **T1b** now defined as melanomas 0.8mm to 1.0mm in thickness regardless of ulceration status OR ulcerated melanomas less than 0.8mm in thickness
Definition of Primary Tumor (T)	**T0** definition has been clarified – **T0** should be used to designate when there is no evidence of a primary tumor, or the site of the primary tumor is unknown (e.g., in a patient who presents axillary metastasis with no known primary tumor); staging may be based on the clinical suspicion of the primary tumor with the tumor categorized as **T0** (**Tis**, not **T0**, designates melanoma in situ)
Definition of Primary Tumor (T)	Tumor thickness measurements now recorded to the nearest 0.1mm, not the nearest 0.01mm, because of impracticality and imprecision of measurements particularly for tumors >1mm thick. Tumors ≤1mm may be measured to the nearest 0.01mm when practical, but should be reported rounded to the nearest 0.1mm (e.g., melanomas measured to be anywhere in the range from 0.75mm to 0.84mm are reported as 0.8mm in thickness (and hence **T1b**)
Definition of Primary Tumor (T)	**Tis** (melanoma in situ), **T0** (no evidence of or unknown primary tumor), and **TX** (tumor thickness cannot be determined) may now be used as the T category designation for stage groupings
Definition of Regional Lymph Node (N)	Number of metastasis-containing regional lymph nodes maintained
Definition of Regional Lymph Node (N)	Previously empirically defined “microscopic” and “macroscopic” descriptors redefined as “clinically occult” (i.e., clinical Stage I-II with nodal metastasis determined at sentinel node biopsy) and “clinically apparent” regional node disease (clinical Stage III), respectively
Definition of Regional Lymph Node (N)	Sentinel node tumor burden is considered a regional disease prognostic factor that should be collected for all patents with positive sentinel nodes, but is not used to determine N category groupings
Definition of Regional Lymph Node (N)	Non-nodal regional disease, including microsatellites, satellites, and in-transit cutaneous and/or subcutaneous metastases more formally stratified by N category according to # of tumor involved lymph nodes (Presence of microsatellites, satellites, or in-transit metastases now categorized as **N1c**, **N2c**, or **N3c** based on number of synchronous tumor-involved regional lymph nodes, if any)
Definition of Regional Lymph Node (N)	“Gross” extranodal extension no longer used as an N staging criterion (but the presence of “matted nodes” is retained)
Definition of Distant Metastasis (M)	**M1** now defined by both anatomic site of distant metastatic disease and serum lactate dehydrogenase (LDH) value for all anatomic site subcategories
Definition of Distant Metastasis (M)	Descriptions of distant anatomic sites of disease clarified in M subcategories

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Definition of Distant Metastasis (M)	Descriptors now added to **M1** subcategory designation that provides LDH values (designated as "0" for "not elevated" and "1" for "elevated" level) for all sites of distant disease; e.g., skin/soft tissue/nodal metastasis with elevated LDH now **M1a(1)**, not **M1c**
Definition of Distant Metastasis (M)	New M1d designation added to include distant metastasis to central nervous system (CNS), with or without any other distant sites of disease; **M1c** no longer includes CNS metastasis
Definition of Distant Metastasis (M)	Elevated LDH level no longer defines **M1c**
AJCC Prognostic Stage Groups	No overall change in T subcategories, but definition of **T1a** and **T1b** refined
AJCC Prognostic Stage Groups	N category now composed of five substages rather than three, and Stage III subgroupings are based on multivariable models including T category elements (tumor thickness and ulceration) and N category elements (# of nodes, satellites/in-transits/microsatellites) demonstrating significant impact of primary tumor factors in assigning N substage
AJCC Prognostic Stage Groups	Clarified that stage IV not further substaged (i.e., **M1c** is stage IV, not stage IVC)

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Table 2. Definition of Primary Tumor (T)

T Category	Thickness	Ulceration status
TX: primary tumor thickness cannot be assessed (e.g., diagnosis by curettage)	Not applicable	Not applicable
T0: no evidence of primary tumor (e.g., unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma *in situ*)	Not applicable	Not applicable
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm 0.8–1.0 mm	With ulceration With or without ulceration
T2	>1.0–2.0 mm	Unknown or unspecified
T2a	>1.0–2.0 mm	Without ulceration
T2b	>1.0–2.0 mm	With ulceration
T3	>2.0-4.0 mm	Unknown or unspecified
T3a	>2.0–4.0 mm	Without ulceration
T3b	>2.0–4.0 mm	With ulceration
T4	>4.0 mm	Unknown or unspecified
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

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Table 3. Definition of Regional Lymph Node (N)

	Extent of regional lymph node and/or lymphatic metastasis	
N Category	**Number of tumor-involved regional lymph node**	**Presence of in-transit, satellite, and/or microsatellite metastases**
NX	Regional nodes not assessed (e.g., SLN biopsy not performed, regional nodes previously removed for another reason) **Exception**: pathological N category is not required for T1 melanomas, use cN.	No
N0	No regional metastases detected	No
N1	One tumor-involved node or any number of in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (i.e., detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or three tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	
N2a	Two or three clinically occult (i.e., detected by SLN biopsy)	No
N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult (i.e., detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

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Table 4. Definition of Distant Metastasis (M)

M Criteria		
M Category	**Anatomic site**	**LDH level**
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Normal
M1d(1)		Elevated

Suffixes for M category: (0) LDH not elevated, (1) LDH elevated.
No suffix is used if LDH is not recorded or is unspecified.

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Table 5. AJCC Clinical Prognostic Stage Groups (cTNM)

When T is…	***And N is…***	***And M is…***	***Then the clinical stage group is…***
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
Any T, Tis	≥N1	M0	III
Any T	Any N	M1	IV

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Table 6. AJCC Pathological (pTNM) Prognostic Stage Groups

When T is…	***And N is…***	***And M is…***	***Then the pathological stage group is…***
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b or N3c	M0	IIIC
T1a/b–T2a	N1a or N2a	M0	IIIA
T1a/b–T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a–N2b	M0	IIIB
T1a–T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N ≥N1	M0	IIIC
T4b	N1a–N2c	M0	IIIC
T4b	N3a/b/c	M0	IIID
Any T, Tis	Any N	M1	IV
Pathological Stage 0 (melanoma *in situ*) and T1 do not require pathological evaluation of lymph nodes to complete pathological staging; use cN information to assign their pathological stage.			

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Supplementary Table 1. Details of the International Melanoma Database and Discovery Platform (IMDDP) – Contributors to Current Analysis

Institution	Location		No. of Patients Contributed to Wave I IMDDP Analysis
	Continent	City, State, Country	
Melanoma Institute Australia	Australia	Sydney, New South Wales, Australia	17,276
Melbourne Melanoma Project	Australia	Melbourne, Victoria, Australia	1,408
Department of Dermatology, National and Kapodistrian University of Athens School of Medicine, Andreas Sygros Hospital	Europe	Athens, Greece	468
Fondazione IRCCS Istituto Nazionale dei Tumori	Europe	Milan, Italy	6,537
Instituto Valenciano de Oncologia	Europe	Valencia, Spain	1,392
National and Kapodistrian University of Athens School of Medicine - General Hospital of Athens – Laiko	Europe	Athens, Greece	1,205
Veneto Institute of Oncology-IOV	Europe	Padova, Italy	2,954
John Wayne Cancer Institute	North America	Santa Monica, California, USA	6,228
The University of Texas MD Anderson Cancer Center	North America	Houston, Texas, USA	8,023
Winship Cancer Institute of Emory University	North America	Atlanta, Georgia, USA	1,495
Total			**46,986**

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Supplementary Table 2 - International Melanoma Database and Discovery Platform Data Dictionary. Data elements used for analyses that informed the Eighth Edition (Stages I-III)

Variable	Description	Acceptable Values
Patient Demographics		
Collaborator_Patient_ID	Unique patient identifier for the home institution database (de-identified)	Home institution format
DOB	Patient date of birth	Date
Patient_Sex	Patient sex	Male Female Other/Unknown
Last_Vital_Date	Date of last follow-up	Date
Last_Vital_Status	Status at last follow-up	Alive Deceased
Cause_Death	Cause of death	Melanoma Other Not applicable
T Category		
KnownPrimary_DX_Staging_Date	Date of diagnosis of primary	Date
Primary_Site	Anatomic site of primary	Home institution format
Breslow_Thickness_MM	Breslow thickness (mm)* of primary	Numeric
Ulceration	Ulceration status of primary	Absent Present Unknown
Mitoses_PerMM2	Mitoses/mm^2	Numeric
N Category		
SLNB_Status	Sentinel-lymph node status	Negative Positive Not conducted
Clinical_Detection	If regional nodes are involved, was there clinical detection of regional lymph nodes No = detected by SLN biopsy	Yes No Unknown
Overall_Positive_Nodes	Total number of tumor-involved lymph nodes**	Numeric
Largest_Metastatic_MM	Largest diameter of the largest metastatic deposit in the tumor-involved sentinel node(s) (mm)*	Numeric
Tumor_Nodal_Location	Location(s) of the metastatic deposit(s) in the sentinel node	Subcapsular Intraparenchymal Both Unknown

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Variable	Description	Acceptable Values
Extranodal_Extension	Presence of extranodal extension** of regional node(s) at diagnosis	Absent Present Unknown
Microsatellites	Presence of microsatellites in the primary tumor specimen (yes/no) at diagnosis	Absent Present Unknown
Intransit	Presence of in-transit and/or satellite lesions at diagnosis	Absent Present Unknown

*At the level of precision used by your institution and data team.
**Including cumulative results from histopathological assessment of staging lymph node procedures, for example sentinel node biopsy *and* completion lymph node dissection OR lymph node biopsy *and* therapeutic lymph node dissection.

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Figure Legends

Figure 1. Kaplan–Meier MSS curves according to T subcategory for patients with Stage I to II melanoma from the Eighth Edition international melanoma database. N0 patients have been filtered so that T2 to T4 patients were included only if SLN negative, whereas patients with T1N0 melanoma are included regardless of whether SLN biopsy was performed.

Figure 2. Kaplan–Meier MSS curves according to mitotic rate (mitoses per square millimeter) in patients with Stage I to II melanoma from the Eighth Edition international melanoma database. N0 patients have been filtered so that T2 to T4 patients were included only if SLN negative, whereas patients with T1N0 melanoma were included regardless of whether SLN biopsy was performed.

Figure 3. Kaplan–Meier MSS curves according to N categories (A) and subcategories (B) from the Eighth Edition international melanoma database

Figure 4. Kaplan–Meier MSS curves according to the presence or absence of microsatellites, satellites, and/or in-transit metastases from the Eighth Edition international melanoma database. (Note: *Intransit* in figure means in-transit and/or satellite metastasis; *both* means microsatellites and/or in-transit and/or satellite metastasis.)

Figure 5. Kaplan–Meier MSS curves according to Stage in patients with Stage I to III melanoma from the Eighth Edition international melanoma database.

Figure 6. Kaplan–Meier MSS curves according to T category stage group for patients with Stage I to II melanoma from the Eighth Edition international melanoma database. N0 patients were filtered so that

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T2+ patients are included only if SLN negative, whereas patients with T1N0 melanoma are included regardless of whether SLN biopsy was performed.

Figure 7. Kaplan–Meier MSS curves according to Stage III subgroups from the Eighth Edition international melanoma database.

Figure 8. AJCC Eighth Edition Stage III subgroups based on T and N categories.

Figure 9. Kaplan–Meier MSS curves according to maximum dimension of sentinel node metastatic focus (millimeters) from the Eighth Edition international melanoma database. (Note – insufficient data exists to estimate 10-year MSS for patients with 2 mm to 4 mm maximum sentinel node metastatic focus).

Supplementary Figure 1. AJCC Eighth Edition Stage III subgroups based on T and N categories (black and white version~~) ..~~).

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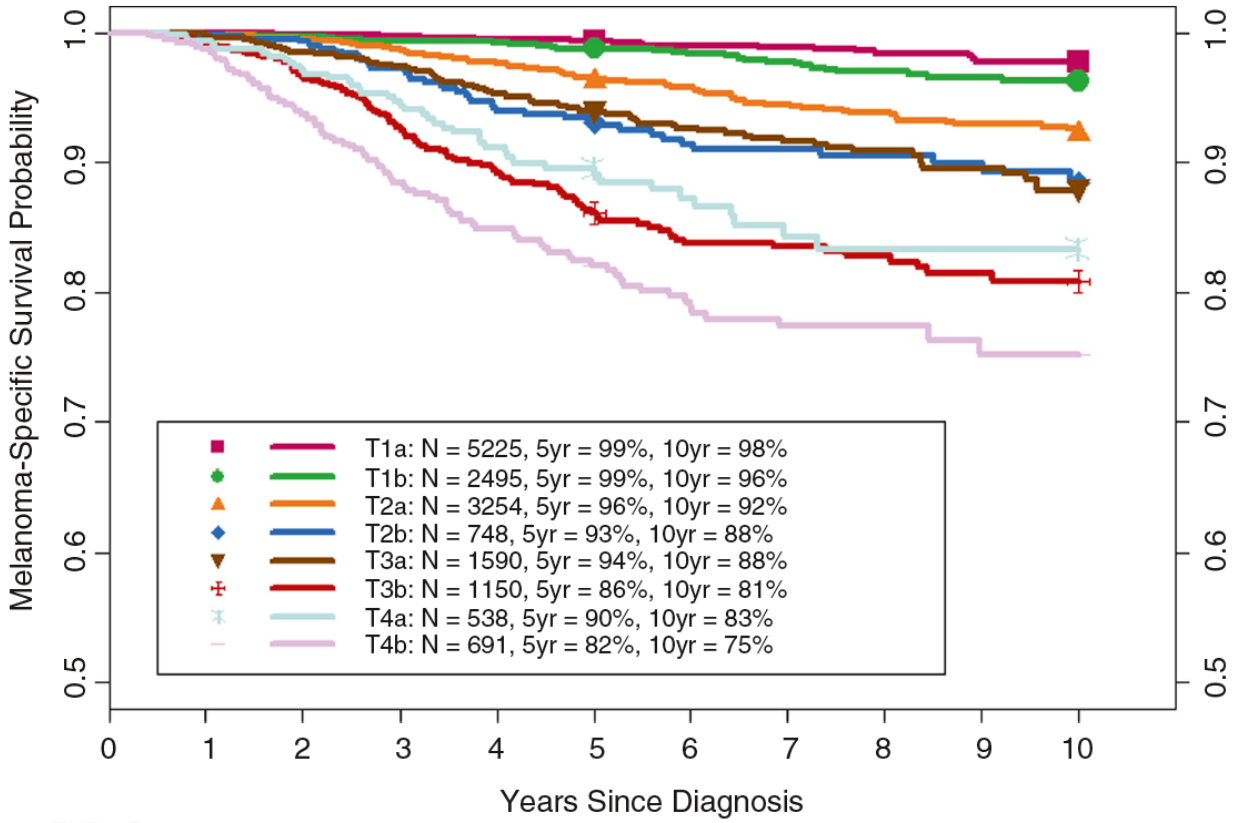
FIGURES

Figure legends included in manuscript file

Figure 1



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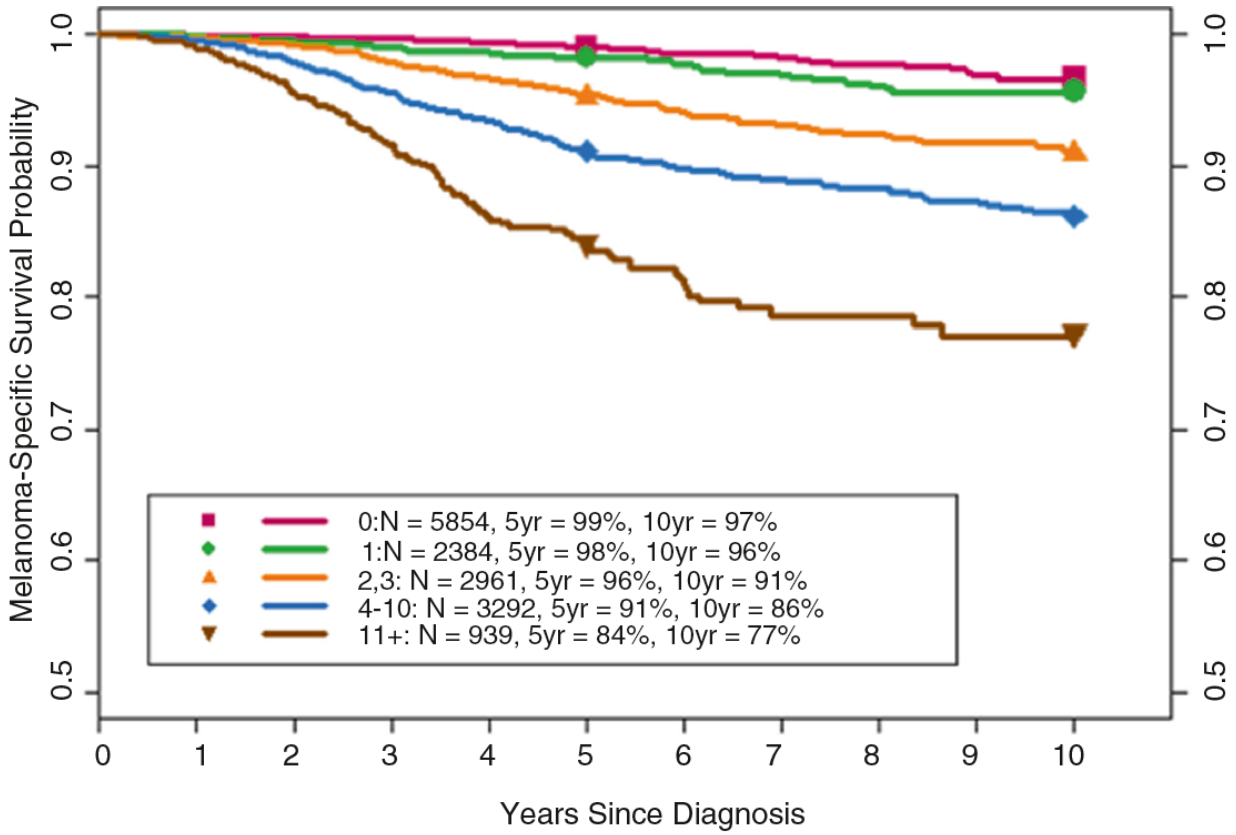
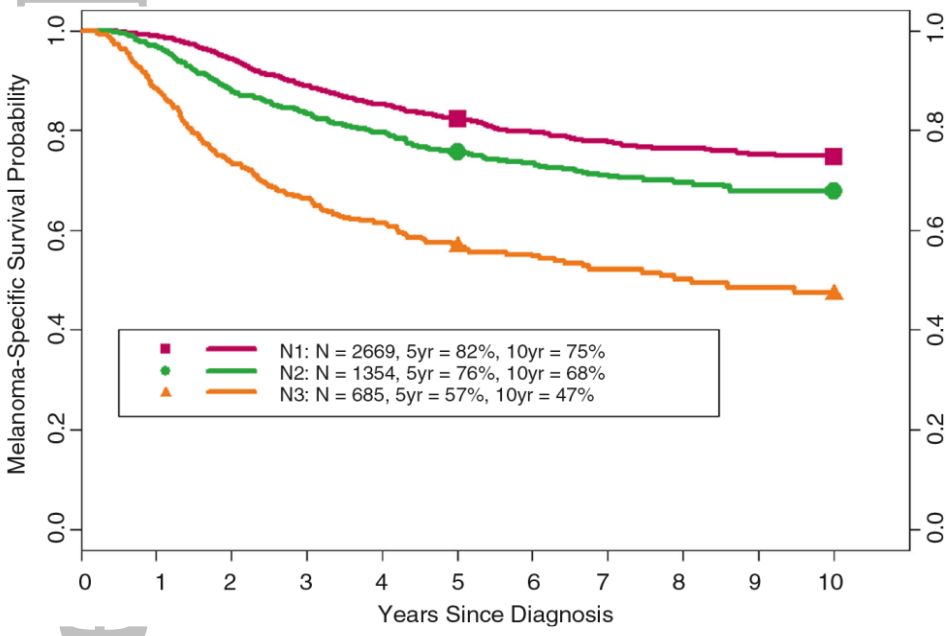
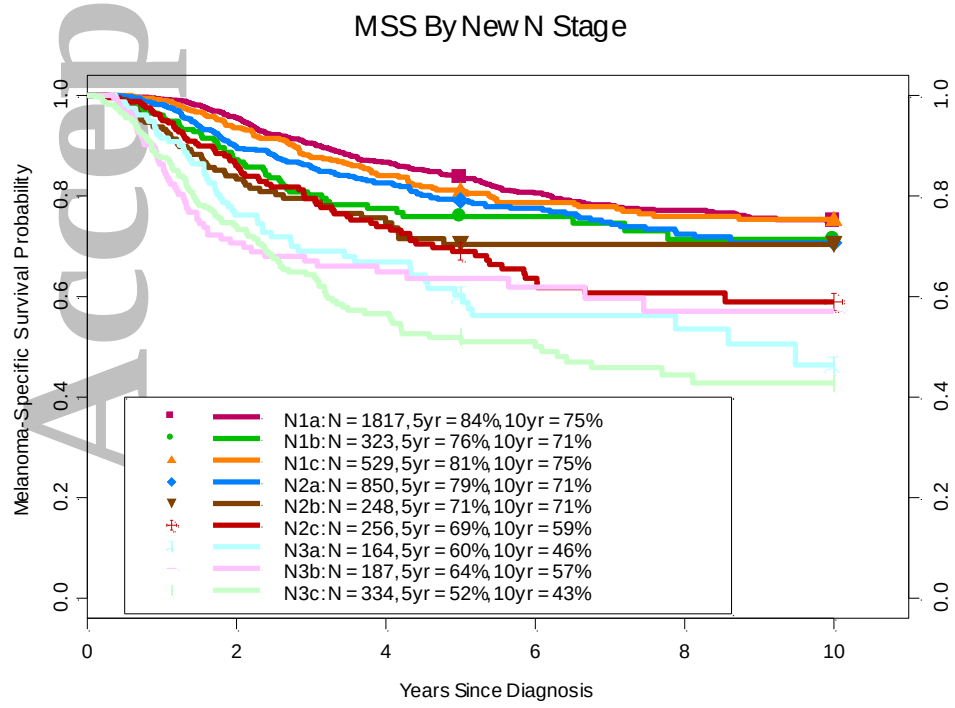


Figure 3

A- N categories - 3 curves



B. N subcategories - 9 curves



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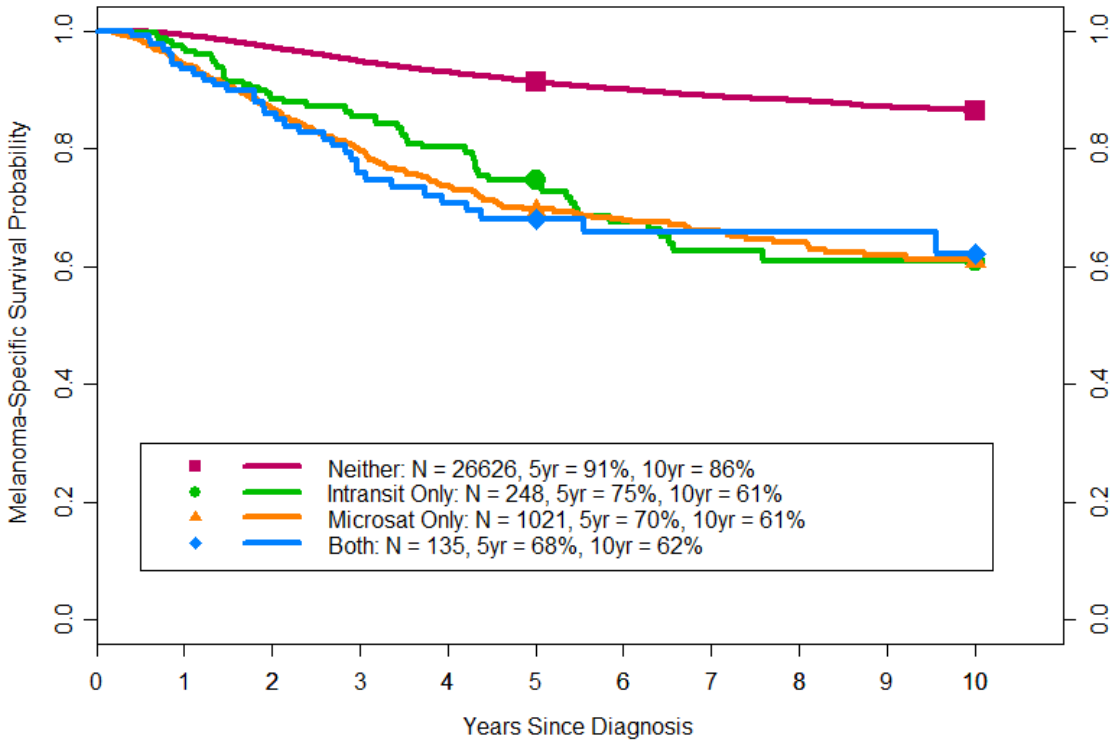

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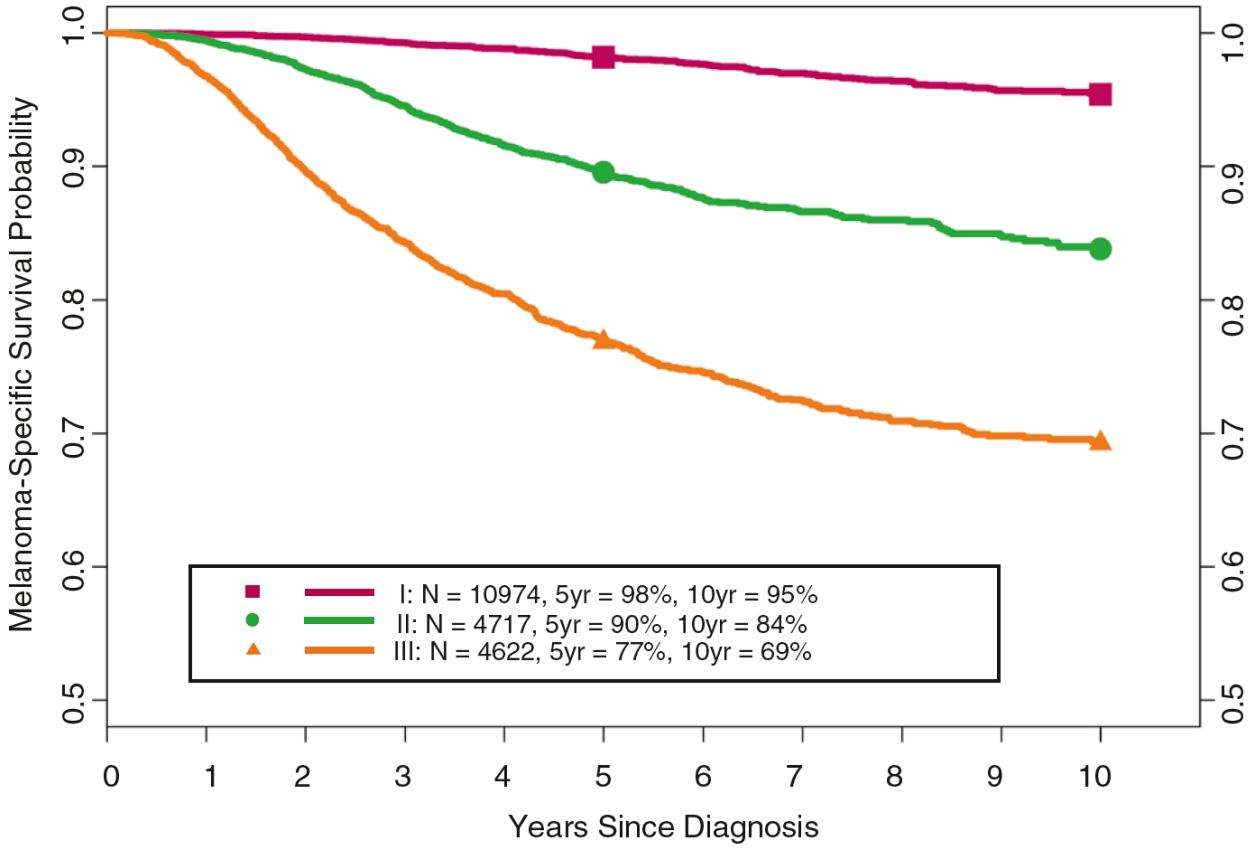

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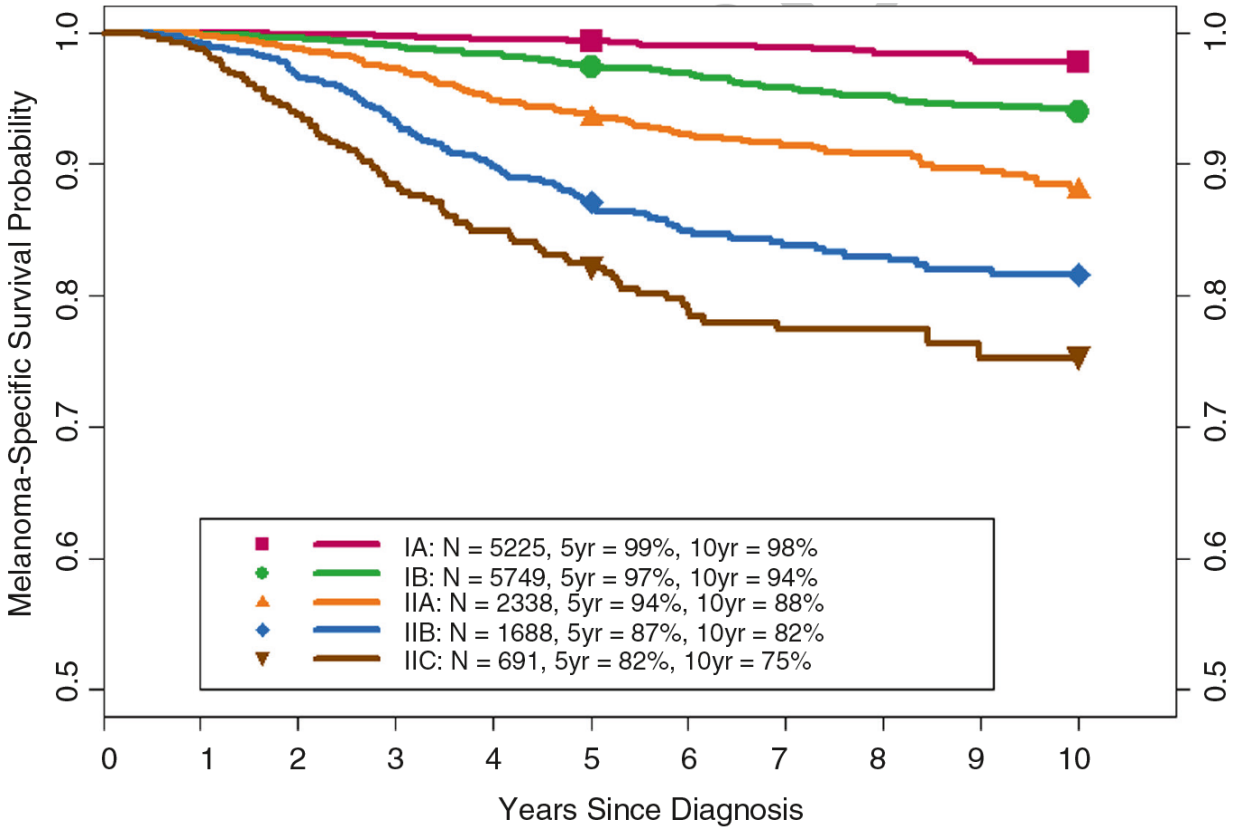

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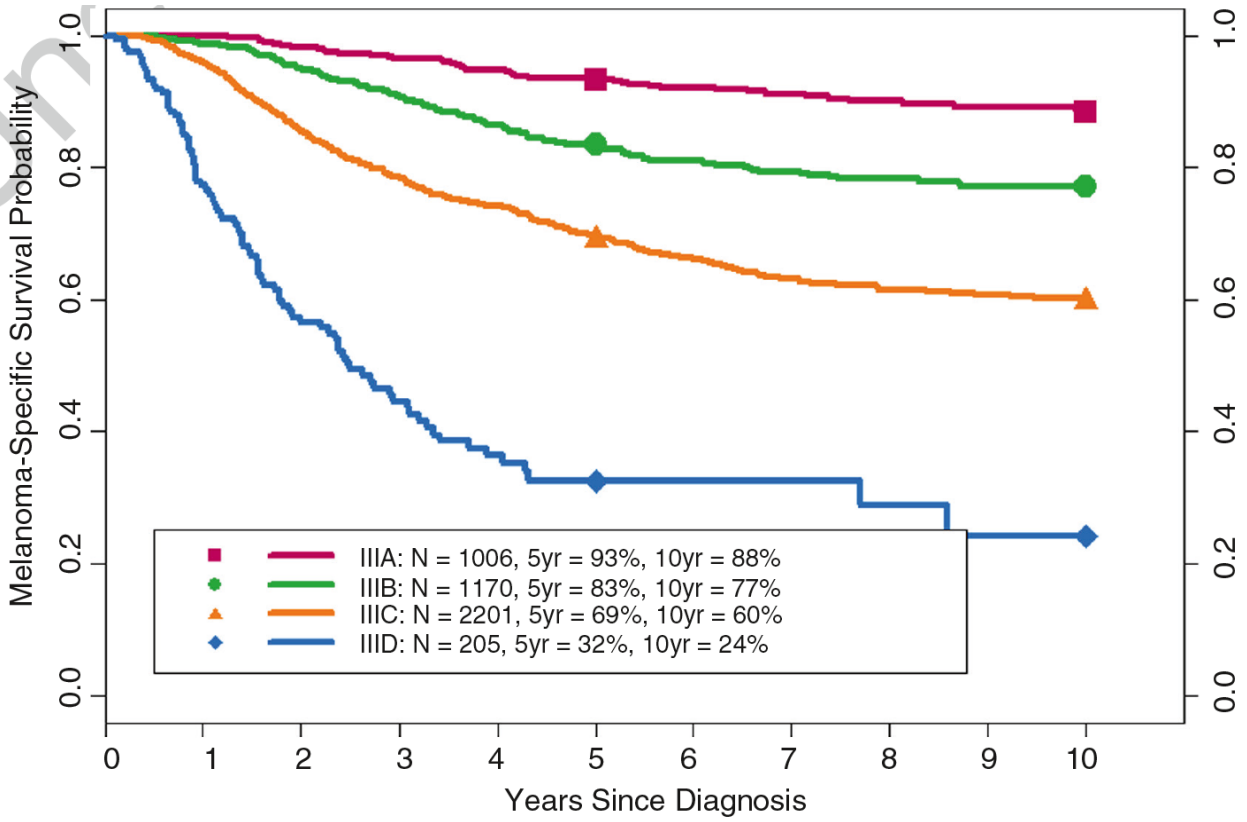

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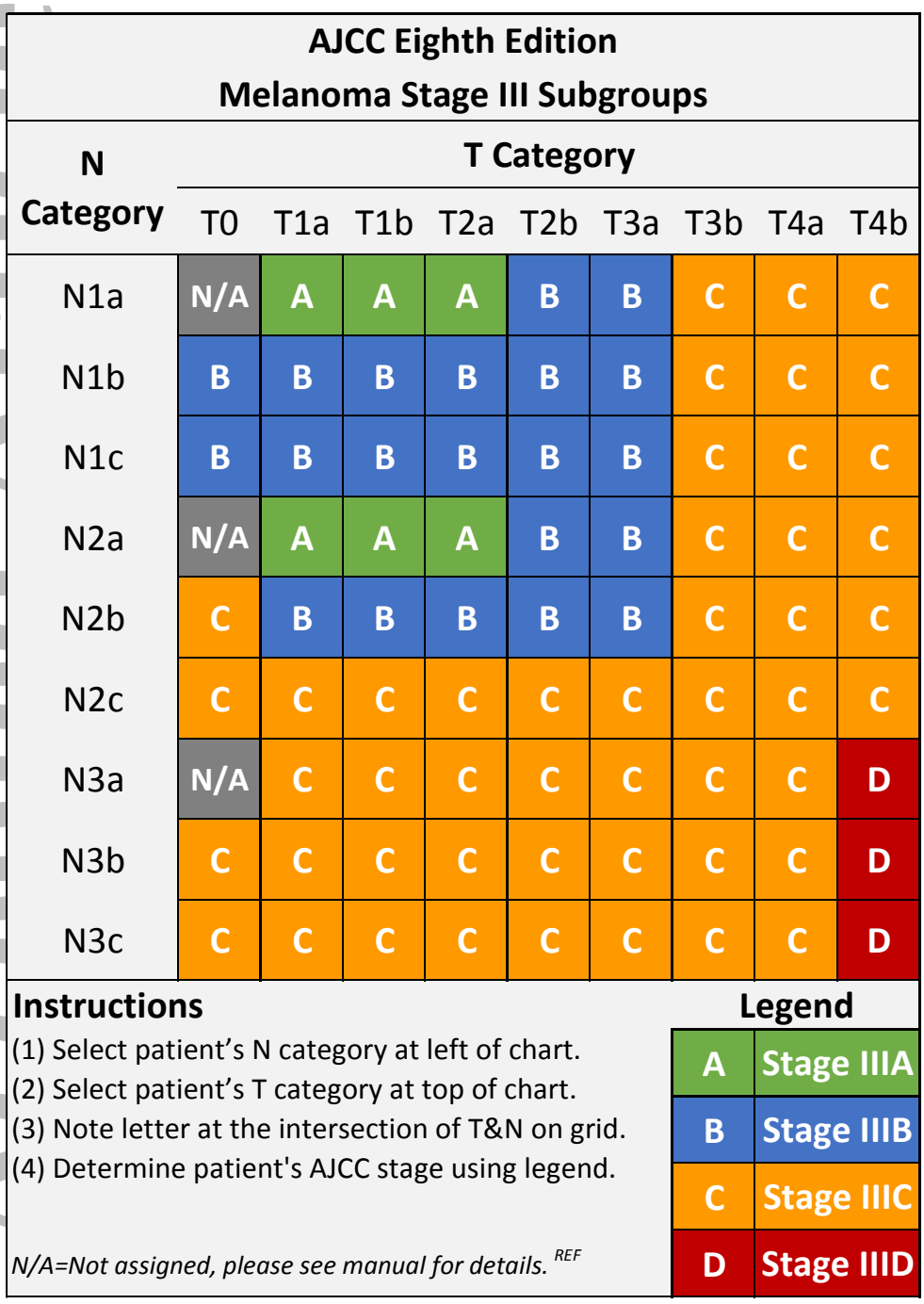


AJCC Eighth Edition
Melanoma Stage III Subgroups

N Category	T Category								
	T0	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b
N1a	N/A	A	A	A	B	B	C	C	C
N1b	B	B	B	B	B	B	C	C	C
N1c	B	B	B	B	B	B	C	C	C
N2a	N/A	A	A	A	B	B	C	C	C
N2b	C	B	B	B	B	B	C	C	C
N2c	C	C	C	C	C	C	C	C	C
N3a	N/A	C	C	C	C	C	C	C	D
N3b	C	C	C	C	C	C	C	C	D
N3c	C	C	C	C	C	C	C	C	D

Instructions

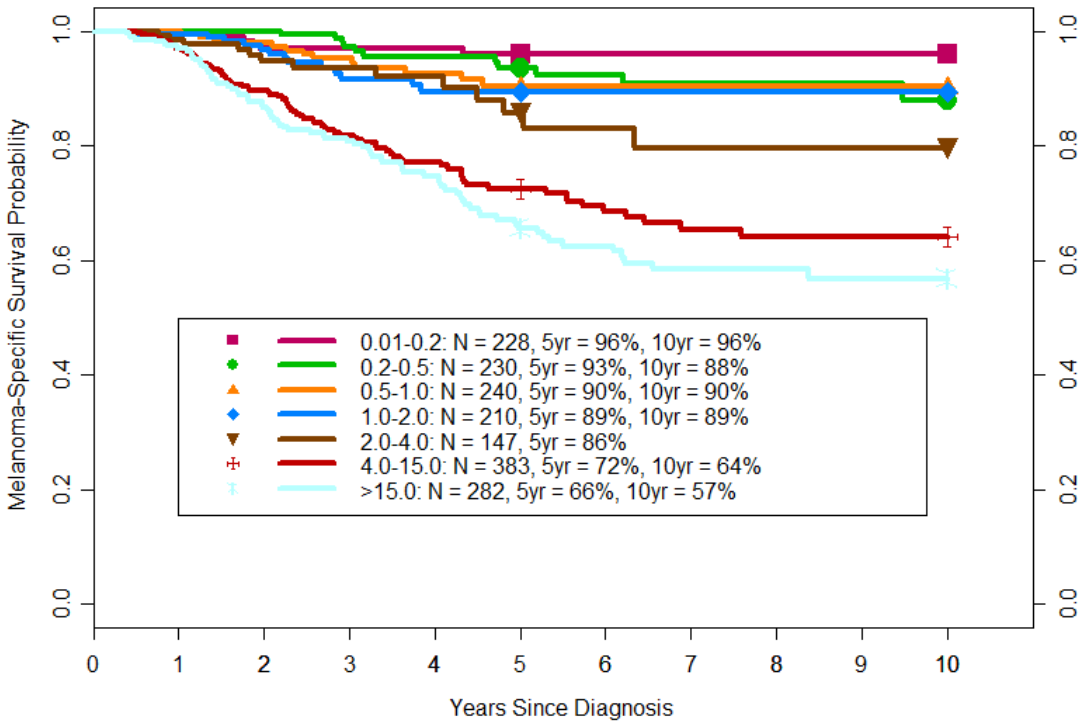
(1) Select patient's N category at left of chart.
(2) Select patient's T category at top of chart.
(3) Note letter at the intersection of T&N on grid.
(4) Determine patient's AJCC stage using legend.

N/A=Not assigned, please see manual for details. REF

Legend

A	Stage IIIA
B	Stage IIIB
C	Stage IIIC
D	Stage IIID

Figure 9



Supplementary Figure 1

AJCC Eighth Edition
Melanoma Stage III Subgroups

N Category	T Category								
	T0	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b
N1a	NA	A	A	A	B	B	C	C	C
N1b	B	B	B	B	B	B	C	C	C
N1c	B	B	B	B	B	B	C	C	C
N2a	NA	A	A	A	B	B	C	C	C
N2b	C	B	B	B	B	B	C	C	C
N2c	C	C	C	C	C	C	C	C	C
N3a	NA	C	C	C	C	C	C	C	D
N3b	C	C	C	C	C	C	C	C	D
N3c	C	C	C	C	C	C	C	C	D

Instructions

(1) Select patient's N category at left of chart.
(2) Select patient's T category at top of chart.
(3) Note letter at the intersection of T&N on grid.
(4) Determine patient's AJCC stage using legend.

NA=Not assigned, please see manual for details. [REF]

Legend	
A	Stage IIIA
B	Stage IIIB
C	Stage IIIC
D	Stage IIID