The seventh edition of the American Joint Committee on Cancer (AJCC) staging system for cutaneous melanoma was implemented in 2010 following its introduction in 2009. In 2016, the Melanoma Expert Panel revised and published the eighth edition of the AJCC melanoma staging system, which was formally implemented nationwide January 1, 2018. Based on analyses of a large international melanoma database, key changes have been made in the new system to improve staging and prognostication, risk stratification and selection of patients for clinical trials. With the ever-growing list of increasingly effective treatments available today, it is more important than ever to stage patients accurately so that the monotherapies and combination therapies approved across different stage levels can be used most effectively, and patients can be optimally informed about their options and considered for the most promising and appropriate clinical trials.
Here, we have distilled the most important changes in the new AJCC melanoma staging system, adapting them from the chapter on cutaneous melanoma in the eighth edition and the recently published analyses of the international database by the Melanoma Expert Panel.3,4

<table>
<thead>
<tr>
<th>Change</th>
<th>Summary of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Determinants of Primary Tumor (T) Status</strong></td>
<td>Primary melanoma thickness and ulceration continue to define T category strata, but tumor thickness is to be measured to the nearest 0.1 mm, not the nearest 0.01 mm. The definitions of T1a and T1b have been revised so that T1a melanomas include those &lt;0.8 mm without ulceration while T1b melanomas include those 0.8-1 mm with or without ulceration and those &lt;0.8 mm with ulceration. Mitotic rate is no longer a T1 category criterion but should be documented for all invasive primary melanomas.</td>
</tr>
<tr>
<td><strong>Determinants of Regional Lymph Node (N) Status</strong></td>
<td>The presence or absence of non-nodal regional metastases (i.e., microsatellites, satellites or in-transit metastases) is categorized in the N-category criterion based upon the number (if any) of tumor-involved regional lymph nodes.</td>
</tr>
<tr>
<td><strong>AJCC Prognostic Stage III Groups</strong></td>
<td>Stage III groupings have been redefined and increased from three to four subgroups, with the addition of a stage IIID subgroup. Stage III disease is associated with heterogeneous outcomes; five-year melanoma-specific survival rates range from 93 percent for stage IIIB disease to 32 percent for stage IIID disease.</td>
</tr>
<tr>
<td><strong>Definition of Distant Metastasis (M)</strong></td>
<td>The site of distant metastasis remains the primary component of the M category: non-visceral (distant cutaneous, subcutaneous, nodal), M1a; lung, M1b; non-central nervous system (CNS) visceral, M1c; and a new M1d designation for metastases involving the CNS. M1c no longer includes CNS metastasis. Although an elevated lactate dehydrogenase (LDH) is no longer an M1c criterion, LDH remains an important predictor of survival in stage IV and is now recorded for any M1 anatomic site of disease.</td>
</tr>
</tbody>
</table>

Table 1. Revisions to the Melanoma TNM Melanoma Staging System*  
Changes in Stages I to III Melanoma

In the eighth edition of the AJCC staging system, the Melanoma Expert Panel focused on evidence-based revisions of stages I to III melanoma. These changes were based on analyses of an updated International Melanoma Database, which included de-identified patient records from 10 institutions in the United States, Europe and Australia for over 46,000 patients with stages I through III melanoma who had received treatment since 1998. The data reflect contemporary clinical practice. Thus, clinically node-negative patients with T2 to T4 melanoma were included only if they had undergone sentinel lymph node biopsy (SLNB), while those with T1 melanoma were included with or without undergoing SLNB. With more accurate nodal staging and risk stratification, there was evidence of stage migration between the seventh and eighth editions of the AJCC staging system, as survival outcomes for patients with similar stage groups were generally greater in the eighth edition.

The T Category Criteria

Breslow tumor thickness

In the eighth edition, the T category continues to be defined by melanoma thickness thresholds of 1.0, 2.0 and 4.0 mm (Table 2 and Figure 1a-b). Several previously published studies have suggested that survival among patients with T1 melanoma is primarily related to tumor thickness, with a clinically important threshold in the region of 0.7 to 0.8 mm.\(^5\)\(^6\) In the eighth edition AJCC analyses of the T1 cohort,\(^4\) the panel evaluated survival outcome of a 0.8 mm tumor thickness threshold, primary tumor ulceration and mitotic rate (as a dichotomous variable, <1 mitosis per mm\(^2\) vs ≥1 mm per mm\(^2\)). Multivariable analyses of factors predictive of melanoma-specific survival (MSS) revealed that, among patients with T1 melanoma, tumor thickness and ulceration were stronger predictors of MSS than mitotic rate. Based on these analyses, T1 subcategories were revised so that T1a tumors are nonulcerated primary melanomas <0.8 mm in thickness while T1b are melanomas 0.8 to 1.0 mm in thickness regardless of ulceration status or ulcerated melanomas <0.8 mm in thickness. Mitotic rate is no longer used to subcategorize T1 melanomas.

Ulceration

Ulceration is an adverse prognostic factor.\(^7\)\(^8\) Consistently across the 2001, 2008 and 2017 AJCC prognostic factor analyses, patients with ulcerated primary melanomas generally have MSS similar to those of patients with nonulcerated primary melanomas of the next highest tumor thickness category.\(^2\)\(^4\)\(^9\)

In the eighth edition, as in the seventh, the absence or presence of ulceration is designated as “a” or “b”, respectively, in each T subcategory.

No longer a T1 criterion, mitotic rate should still be reported for all primary melanomas

In the eighth edition, though mitotic rate is no longer a T category criterion, it should be documented as a whole number (per mm\(^2\)) for all patients, as it can impact prognosis for patients with stages I to III melanomas. Mitotic rate was removed as a staging criterion for T1 tumors because substratifying T1 tumors using a 0.8 mm cut point showed a stronger association with MSS compared to using presence or absence of mitoses as a dichotomous variable.\(^4\) Nonetheless, increasing mitotic rate among patients with clinically node-negative (cN0) primary melanoma was significantly associated with decreasing MSS in univariate analysis.\(^4\) Mitotic rate remains a major determinant of prognosis across tumor thickness categories and should be documented in all primary invasive melanomas.

Regional lymph node metastasis

The N category delineates the number of tumor-involved regional nodal metastases and the presence or absence of non-nodal regional metastases. Patients without clinical or radiographic evidence of regional lymph node metastasis but who have tumor-involved regional nodal metastasis after a sentinel node biopsy are defined as having “clinically occult” nodal metastasis and represent the majority of patients who present with regional metastasis at diagnosis.\(^3\) Patients with clinically or radiologically detected regional nodal metastases are defined as having “clinically detected” nodal metastasis and have worse survival than those with clinically occult regional metastases.\(^4\) Patients with clinically occult (N1a, N2a, N3a) and clinically detected (N1b, N2b, N3b) regional lymph node metastases without microsatellites, satellites or in-transit metastases are subcategorized based on the number of tumor-involved nodes.

Non-nodal regional metastasis

Microsatellites, satellites and in-transit metastases are associated with similar survival outcomes (Figure 1d). In the AJCC eighth edition, microsatellites are defined as any microscopic focus of metastatic tumor cells in the skin or subcutis adjacent or deep to but discontinuous from the primary tumor.\(^9\) Satellite metastases are classically defined as any foci of clinically evident cutaneous and/or subcutaneous metastases occurring within 2 cm of but discontinuous...
<table>
<thead>
<tr>
<th>N Category</th>
<th>Number of tumor-involved regional lymph nodes</th>
<th>Presence of in-transit, satellite and/or microsatellite metastases</th>
<th>T Category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>T0</td>
</tr>
<tr>
<td>N0</td>
<td>No regional metastases detected</td>
<td>No</td>
<td>-</td>
</tr>
<tr>
<td>N1a</td>
<td>1 clinically occult (i.e., detected by SLN biopsy)</td>
<td>No</td>
<td>-</td>
</tr>
<tr>
<td>N1b</td>
<td>1 clinically detected</td>
<td>No</td>
<td>IIB</td>
</tr>
<tr>
<td>N1c</td>
<td>No regional lymph node disease</td>
<td>Yes</td>
<td>IIB</td>
</tr>
<tr>
<td>N2a</td>
<td>2 or 3 clinically occult (i.e., detected by SLN biopsy)</td>
<td>No</td>
<td>-</td>
</tr>
<tr>
<td>N2b</td>
<td>2 or 3, at least 1 of which was clinically detected</td>
<td>No</td>
<td>IIC</td>
</tr>
<tr>
<td>N2c</td>
<td>1 clinically occult or clinically detected</td>
<td>Yes</td>
<td>IIC</td>
</tr>
<tr>
<td>N3a</td>
<td>≥4 clinically occult (i.e., detected by SLN biopsy)</td>
<td>No</td>
<td>-</td>
</tr>
<tr>
<td>N3b</td>
<td>≥4, at least 1 of which was clinically detected, or the presence of any number of matted nodes</td>
<td>No</td>
<td>IIC</td>
</tr>
<tr>
<td>N3c</td>
<td>≥2 clinically occult or clinically detected and/or presence of any number of matted nodes</td>
<td>Yes</td>
<td>IIC</td>
</tr>
</tbody>
</table>

**T0** — no evidence of primary tumor (e.g., unknown primary or completely regressed melanoma); **Tis** — melanoma in situ; **Tx** — thickness cannot be assessed. (Tis and Tx are not included in the table but are part of the staging system.) **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 clinical N information. (If an SLNB was performed, the results can and should be used for pathological evaluation.)

Table 2. AJCC Eighth Edition T Category, N Category and Pathological Stage Groups for Stages I to III Cutaneous Melanoma


from the primary melanoma. In-transit metastases are defined empirically as clinically evident cutaneous and/or subcutaneous metastases occurring >2 cm from the primary melanoma in the region between the primary melanoma and the regional lymph node basin.

In the eighth edition AJCC international melanoma database, there was no difference in survival outcome among these entities in univariate analysis, and they thus were grouped together for staging purposes (Figure 1d). Patients with microsatellite, satellite and/or in-transit metastases are categorized as N1c, N2c, or N3c based on the number of tumor-involved regional lymph nodes.

**The M Category Criteria**

There are no stage groupings in the eighth edition AJCC melanoma staging system for patients with distant (stage IV) melanoma metastasis. Stage IV subcategories are defined by both anatomic site of metastatic disease (M1a, M1b, M1c and M1d) and the serum lactate dehydrogenase (LDH) level obtained at the time of stage IV diagnosis.

**Central nervous system (CNS) disease defines a new M subcategory, M1d**

In the new staging system, M category definitions are based on both anatomic site of distant metastatic disease and serum LDH level for all anatomic site categories (Table 3). Patients with distant metastasis to the skin, subcutaneous tissue, muscle or distant lymph nodes are categorized as M1a and have a relatively better prognosis compared with patients who have distant metastases located in other anatomic sites. Patients who have lung metastasis (with or without concurrent skin or subcutaneous metastases) have an intermediate prognosis and are categorized as M1b. Those with metastasis to any other visceral sites (excluding the CNS) have a relatively worse prognosis and are categorized as M1c. A new M category (M1d) was added to account for the overall poor prognosis associated with CNS disease as well as to enhance clinical trial design and analysis.

**LDH no longer defines M1c disease**

Although patients with an elevated LDH level no longer automatically categorize to M1c, elevated serum LDH remains an important prognostic factor and identifies stage IV patients with a lower survival rate based upon multiple prospective analyses. Serum LDH is designated within each M category anatomic site based on whether LDH is elevated (designated “0” for “not elevated” and “1” for “elevated” level).

**Stage Groupings Based on TNM Categories**

**Stages I and II disease**

Patients with stages I and II melanoma have localized disease, while those with stages III and IV melanoma have regional and distant metastatic disease, respectively (Table 2 and Figure 1). Although partially defined by the absence of regional disease, patients with stage II melanoma with high-risk features (such as greater tumor thickness and presence of ulceration) may have a worse prognosis than patients with primary melanoma with more favorable features and limited occult regional metastatic (stage IIIA) disease. For example, patients with stage IIC melanoma have worse expected five-year and 10-year survival than those with stage IIIA disease (82 percent and 75 percent versus 93 percent and 88 percent, respectively).

**Heterogeneity of stage III disease**

In the eighth edition, there are four stage III subgroups based on tumor thickness, ulceration status and number of tumor-involved lymph nodes (and whether these were clinically occult versus clinically detected), as well as the presence or absence of non-nodal regional metastases (Table 2). There are significant differences in prognosis across the four stage III subgroups (Figure 1e), with five-year MSS ranging from 93 percent for stage IIIA to 32 percent for stage IIID disease. These rates are significantly better compared with five-year MSS for stages IIIA, IIIB and IIIC disease in the seventh edition (78 percent, 59 percent and 40 percent, respectively), and will have a significant impact on clinical decision-making, patient counseling and clinical trial design.

**Stage IV disease**

There are no stage groupings for stage IV melanoma.

**The Importance of Regional Lymph Node Staging**

The importance of nodal staging and the ultimate benefits of SLNB (sentinel node biopsy) and CLND (completion lymph node dissection) have been a matter of long-standing discussion and debate, culminating in the recent results of two important long-running studies. Thus, we consider it important to include here a review on the topic of regional lymph node staging.

Regional lymph nodes represent the most common first site of metastasis in melanoma patients. Nodal staging is valuable for multiple reasons, including:

1. It can provide risk stratification and prognostication for patients at significant risk of harboring occult nodal metastases.
2. It can assist in selecting patients for adjuvant systemic therapies.
3. SLNB and CLND may improve regional disease control.

**Sentinel lymph node biopsy (SLNB)**

The technique of lymphatic mapping and SLNB is associated with a low rate of complications (<5 percent) and has become a standard of care for staging clinically negative regional lymph node
basins in patients deemed to have sufficient risk of occult nodal metastasis. The risk of sentinel lymph node (SLN) metastasis is very uncommon (<5 percent of cases) among patients with T1a melanomas, but rises with increasing primary melanoma thickness: five to 12 percent of T1b (<0.8 mm, ulcerated; 0.8-1.0 mm with or without ulceration) melanomas, and over 50 percent of T4b (>4.0 mm, ulcerated) melanomas.

The Multicenter Selective Lymphadenectomy Trial-I (MSLT-I) was a multi-institutional randomized controlled trial (RCT) comprised of 1269 patients with primary melanoma (≥1.0 mm thick or ≥ Clark level IV with any tumor thickness) randomized to wide excision and regional lymph node observation (with lymphadenectomy at time of nodal relapse) or to wide excision and SLNB with immediate CLND if tumor-involved nodes were identified on SLNB. In this study, patients with positive SLNs had worse five- and 10-year MSS compared with those who had negative SLNs; pathological SLN status was the strongest prognostic factor among all clinical and pathological factors studied. Overall, MSLT-I strongly supported the role of SLNB in early nodal evaluation and confirmed occult SLN involvement as a major prognostic factor associated with patient outcome.

Based on these and other data, the joint ASCO-SSO (American Society of Clinical Oncology–Society of Surgical Oncology) guideline panel recommends SLNB for patients with primary melanomas >1.0 mm. Both the ASCO-SSO and the National Comprehensive Cancer Network (NCCN) guidelines state that for patients with T1b (<0.8 mm with ulceration or 0.8-1.0 mm with or without ulceration) melanomas, SLNB may be considered and discussed with the patient.

Regional lymphadenectomy in the post-MSLT-II era

Until recently, immediate completion lymph node dissection (CLND) has been the standard of care for patients with metastases in one or more SLNs. The goals of CLND among patients with clinically occult regional lymph node metastasis in the SLN have classically been to 1) increase accuracy of staging and assist in clinical decision-making with respect to adjuvant systemic therapy, 2) enhance regional disease control and reduce risk of distant spread of disease and 3) improve MSS.

Although CLND is associated with operative morbidity, such as lymphedema, there is staging value in knowing the non-sentinel nodal status (non-SLN). Multiple retrospective studies have reported that metastatic non-SLNs are an independent negative prognostic

### Table 3. Definition of Distant Metastasis (M)^

<table>
<thead>
<tr>
<th>M Category</th>
<th>Anatomic Site</th>
<th>LDH Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No evidence of distant metastasis</td>
<td>Not applicable</td>
</tr>
<tr>
<td>M1</td>
<td>Evidence of distant metastasis</td>
<td>Not recorded or unspecified</td>
</tr>
<tr>
<td>M1a</td>
<td>Distant metastasis to skin, soft tissue including muscles and/or nonregional lymph node</td>
<td>Not recorded or unspecified</td>
</tr>
<tr>
<td>M1a(0)</td>
<td>Not elevated</td>
<td></td>
</tr>
<tr>
<td>M1a(1)</td>
<td>Elevated</td>
<td></td>
</tr>
<tr>
<td>M1b</td>
<td>Distant metastasis to lung with or without M1a sites of disease</td>
<td>Not recorded or unspecified</td>
</tr>
<tr>
<td>M1b(0)</td>
<td>Not elevated</td>
<td></td>
</tr>
<tr>
<td>M1b(1)</td>
<td>Elevated</td>
<td></td>
</tr>
<tr>
<td>M1c</td>
<td>Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease</td>
<td>Not recorded or unspecified</td>
</tr>
<tr>
<td>M1c(0)</td>
<td>Not elevated</td>
<td></td>
</tr>
<tr>
<td>M1c(1)</td>
<td>Elevated</td>
<td></td>
</tr>
<tr>
<td>M1d</td>
<td>Distant metastasis to CNS with or without M1a, M1b or M1c sites of disease</td>
<td>Not recorded or unspecified</td>
</tr>
<tr>
<td>M1d(0)</td>
<td>Not elevated</td>
<td></td>
</tr>
<tr>
<td>M1d(1)</td>
<td>Elevated</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Kaplan-Meier melanoma-specific survival curves from the eighth edition international melanoma database according to:
(a) T subcategories
(b) pathological stage I and II subgroups
(c) N subcategories
(d) the presence or absence of microsatellites, satellites and/or in-transit metastases
(e) pathological stage III subgroups

factor associated with higher recurrence rates following CLND as well as worse disease-free survival, MSS and overall survival. Other studies have demonstrated that the risk for non-SLN metastasis increases as the tumor burden in the sentinel node increases, and exceeds 25 percent if the sentinel node metastatic tumor measures 2 mm or greater.

Two multicenter randomized controlled trials (DeCOG-SLT, MSLT-II) were designed to address the question of whether immediate CLND in patients with nodal metastases identified by SLNB improves survival compared with nodal observation. DeCOG-SLT was a multicenter RCT in which patients with a positive SLNB were randomized to either immediate CLND (N=242) or observation (N=241), with distant metastasis-free survival as the primary endpoint. The sample size of this trial is relatively small and the follow-up is relatively short at 35 months. The MSLT-II trial randomized 1934 patients with SLN metastases to either immediate CLND or nodal observation with ultrasound.

In the follow-up period, neither trial demonstrated an overall survival difference between patients undergoing immediate CLND and those undergoing nodal observation. However, CLND was associated with a slightly higher rate of disease-free survival at three years (68 percent versus 63 percent, p=0.05) and a higher disease control rate in the regional nodes at three years (92 percent versus 77 percent, p=0.001). It is also important to note that in both studies, two-thirds of patients enrolled had a low tumor burden (≤1 mm) in the SLNs. Thus, some have opined that there was a selection bias of patients at lower risk of metastatic non-SLNs.

One logical conclusion of the results is that the SLNB itself may have been therapeutic and sufficient to achieve regional disease control in some patients, and furthermore, that many of those patients with non-SLN metastases also had a higher risk of harboring distant metastases that would negate a putative survival benefit from CLND. As evidence for this conclusion, patients who underwent CLND and were found to have metastatic non-SLNs had a lower MSS compared with patients whose non-SLNs were free of metastases. The MSLT II investigators concluded that “immediate CLND increased the rate of regional disease control and provided prognostic information but did not increase MSS among patients with melanoma and sentinel node metastases.”

The current NCCN guidelines state: “For patients with a positive SLN, two phase 3 studies have demonstrated no improvement in MSS or overall survival in patients undergoing CLND compared to those who underwent active nodal surveillance. CLND did provide additional prognostic information as well as improvement in regional control/recurrence at the expense of increased morbidity.” Thus, the NCCN guidelines recommend either active nodal basin surveillance or CLND for patients with a positive SLNB: “CLND of the involved nodal basin should be discussed and offered” to patients, depending upon the probability of non-SLN metastases, the morbidity of the procedure and the staging value of CLND on adjuvant systemic therapy or clinical trial enrollment.

Conclusions

A standardized and contemporary cancer staging system is essential for meaningful comparisons to be made across patient populations, while accurate staging and risk stratification are important to guide patient treatment and for the selection of patients for clinical trials. The eighth edition of the AJCC melanoma staging system incorporates several notable revisions of the seventh edition. These were derived from the analysis of a large international melanoma database and reflect our contemporary understanding of the natural history of metastatic melanoma and the clinical management of patients with cutaneous melanoma. The AJCC eighth edition cutaneous melanoma staging system was formally implemented in the United States on January 1, 2018.

References


of the considerable changes in the guidelines and explained the motivations for those changes. They have also presented examples exploring the implications for therapy, with an emphasis on surgical management of regional disease.

Given the centrality of staging in clinical communication and care, it is essential that we familiarize ourselves with the new system. Among the many changes, a few include a new approach to measuring and reporting primary tumor thickness, elimination of mitotic rate and LDH as staging factors (though they remain important prognostic factors) and expansion of N stage categories. Taken together, the changes reveal a lowest risk subset of stage III patients who surprisingly have a better overall prognosis than the highest risk subsets of stage II patients.

This latest reworking of the guidelines seeks to provide more accurate prognostication, inform better treatment decisions and improve the efficiency of clinical trials. These goals can be met only if we, the user community, master the challenges of the new system. We thank the authors for helping us to do so.

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