Melanoma Clinical Staging (Historical and Current)

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Michael E. Egger and Jeffrey E. Gershenwald

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M. E. Egger
Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

J. E. Gershenwald (✉)
Department of Surgical Oncology, Unit 1484, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Melanoma and Skin Center, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
e-mail: jgershen@mdanderson.org

Abstract

Melanoma staging has evolved as our understanding of clinical and pathological risk factors have improved and surgical staging strategies have matured. The current American Joint Committee on Cancer (AJCC) melanoma staging system is based on the tumor (T), node (N), metastasis (M) system, similar to most other solid tumors; criteria that define TNM

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have changed over time. The T category is determined by primary tumor thickness and presence or absence of ulceration; the N category takes into account both the number of clinically occult and clinically detected lymph node metastases, as well as the presence or absence of non-nodal regional metastases. The M category is defined by anatomic site of disease and lactate dehydrogenase levels. Sentinel lymph node biopsy has become a standard assessment technique by which T2-T4 melanomas, and some T1 melanomas, are staged. Taken together, the melanoma staging system allows for accurate risk stratification of large subsets of melanoma patients that can help guide clinicians and patients regarding prognosis. In the future, melanoma staging may be complemented by validated clinical tools based on multiple clinical, pathological, and molecular risk factors, and may provide a more precise individualized risk assessment for melanoma patients.

Keywords
Melanoma · Staging · Sentinel lymph node biopsy · Prognosis · Metastasis · Lymphadenectomy · Lymph node dissection · Risk assessment

Introduction

The melanoma staging system is based on pathological characteristics of the primary tumor; extent of regional disease, if any; and the absence or presence of distant metastasis. Since the late 1970s, melanoma has been staged according to the American Joint Committee on Cancer (AJCC) melanoma staging system, a TNM-based system that designates tumor (T), regional nodal (N), and distant metastasis (M) classifications based on pathological tumor characteristics of the primary melanoma (T), the number of lymph nodes involved and/or other evidence of regional disease (N), and the presence of distant metastatic disease (M). Stages I and II, Stage III, and Stage IV comprise patients with localized disease, regional disease, and distant metastases, respectively (Table 1). Criteria used to define the AJCC staging system have evolved over time, utilizing an improved understanding of the biology of melanoma, more accurate and less-invasive staging procedures, and identification of factors that better stratify patients according to risk. In this chapter, we review historical aspects of melanoma staging, new changes to the 8th Edition AJCC melanoma staging system and their rationale, future directions in staging classification and risk stratification, and the development of clinical tools that may enhance clinical decision-making.

Primary Tumor Assessment

Primary Tumor Thickness

Solid tumors are most commonly characterized by primary tumor size to determine T category. Melanoma size is assessed by the extent of tumor penetrance from the skin surface, rather than the surface diameter of the lesion. In 1969, Clark et al. first proposed classification of level of invasion based on the relationship of the primary melanoma to the papillary and reticular dermis and which was defined by five levels (I–V) (Clark et al. 1969). Shortly thereafter, Breslow proposed measuring tumor thickness by depth of invasion from the skin surface using an ocular micrometer (Breslow 1970). This measurement, referred to as the Breslow thickness (or, commonly, tumor thickness), is taken from the top of the granular layer of the epidermis to the deepest invasive cell across the broad base of the tumor. When a primary tumor is ulcerated, the tumor thickness measurement is made from the base of the ulcer. Initially, cutpoints of 0.75, 1.50, 2.25, and 3.0 mm were used to stratify patients (Breslow 1970). Breslow thickness provided a more objective, reproducible measure of tumor thickness and could more accurately risk stratify patients with Clark level III and IV primary melanomas, who were observed to have a wide range of prognoses (Breslow 1975).

Initially, Clark level and Breslow thickness complemented each other and were used together to stage patients with primary cutaneous

Table 1 TNM staging for cutaneous melanoma, 8th Edition AJCC

T classification	Thickness (mm)	Ulceration status
T0: no evidence of primary tumor	NA	NA
Tis (melanoma in situ)	NA	NA
T1	≤1.0	a: <0.8 mm without ulceration
		b: 0.8–1.0 mm with or without ulceration
T2	>1.0–2.0	a: Without ulceration
		b: With ulceration
T3	>2.0–4.0	a: Without ulceration
		b: With ulceration
T4	>4.0	a: Without ulceration
		b: With ulceration
N classification	**Number of metastatic nodes**	**Nodal metastatic burden**
N0	No regional metastases detected	NA
N1	1 tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	a: Clinically occult (i.e., detected by SLN biopsy)
		b: Clinically detected
		c: No regional nodal disease
N2	2–3 tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with 1 tumor-involved node	a: Clinically occult (i.e., detected by SLN biopsy)
		b: At least one of the two to three nodes clinically detected
		c: 1 clinically occult or clinically detected node with in-transit, satellite, and/or microsatellite metastases
N3	4+ metastatic nodes; in-transit, satellite, and/or microsatellite metastases with 2 or more tumor-involved nodes; or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	a: 4+ clinically occult nodes (i.e., detected by SLN biopsy)
		b: 4+ nodes, at least one of which was clinically detected, or presence of any number of matted nodes
		c: 2+ clinically occult or clinically detected and/or presence of any number of matted nodes in the presence of in-transit, satellite, and/or microsatellite metastases
M classification	**Site**	**Serum LDH**
M0	No distant metastases	NA
M1a	Distant metastasis to the skin and soft tissue including the muscle and/or nonregional nodal metastases	0: not elevated
		1: elevated
M1b	Lung metastases with or without M1a sites of disease	0: not elevated
		1: elevated
M1c	Non-CNS visceral metastases with or without M1a or M1b sites of disease	0: not elevated
		1: elevated
M1d	CNS metastases with or without M1a, M1b, or M1c sites of disease	0: not elevated
		1: elevated

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Clinically occult are diagnosed after sentinel lymph node biopsy

Clinically detected are defined as clinically detectable nodal metastases confirmed pathologically

NA not applicable, *CNS* central nervous system, *LDH* lactate dehydrogenase

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

melanoma (Beahrs et al. 1992; Fleming et al. 1997). Over time, however, Breslow thickness became the more widely used method and is evidenced by a gradual evolution in the importance placed on these two measurements in the AJCC melanoma staging system. In earlier editions, Clark level and Breslow thickness were both used to determine T category (Wanebo et al. 1975; Balch et al. 1978, 1979). In the 6th Edition (2002) AJCC melanoma staging system, Breslow thickness became the primary T category criterion, using tumor thickness cutpoints of 1.0, 2.0, and 4.0 mm. Clark level was used only to subcategorize T1 lesions (Balch et al. 2001a). In the 7th Edition, mitotic rate (discussed below) replaced Clark level of invasion as a criterion to help define a T1b melanoma (Balch et al. 2009; Edge 2010).

In the 8th Edition (2017) AJCC melanoma staging system, tumor thickness cutpoints of 1.0, 2.0, and 4.0 mm continue to define T1, T2, T3, and T4 primary melanoma (Gershenwald et al. 2017a). As in the 7th Edition, T1 tumors are subcategorized according to the presence or absence of primary tumor ulceration, and new to the 8th Edition, a T1b tumor is also defined by any primary melanoma that is 0.8–1.0 mm in tumor thickness regardless of ulceration status (Gershenwald et al. 2017a). Also new to the 8th Edition AJCC melanoma staging system, Breslow thickness measurements are to be recorded to the nearest 0.1 mm (rather than to the nearest 0.01 mm) (Gershenwald et al. 2017a). This change was made in an effort to avoid clustering of reported measurements around critical cutpoints for staging classification, which has been demonstrated to have bias with implications for staging (Ge et al. 2016).

Primary Tumor Ulceration

Primary tumor ulceration is a well-established pathological risk factor associated with adverse survival in patients with cutaneous melanoma. Ulceration is defined microscopically as a full-thickness epidermal defect with evidence of reactive changes and thinning, effacement, or reactive hyperplasia of the surrounding epidermis (Smoller et al. 2016; Edge 2010). The incidence of ulceration increases with increasing Breslow thickness (Balch et al. 2009, 1980; White et al. 2011). The 6th Edition (2002) AJCC melanoma staging system was the first to designate the T category as "a" or "b" based on the absence or presence of ulceration, respectively (Balch et al. 2001a). Multiple studies have found that primary tumor ulceration is associated with worse survival across all tumor thickness groups – essentially "upstaging" a patient to the next highest T category with a tumor that is not ulcerated (Balch et al. 2001a, 2009). For example, a clinically node-negative patient with a T2 primary melanoma that is ulcerated (T2b) has approximately the same survival as a patient with a T3 tumor that is not ulcerated (T3a); stage groupings are discussed below (Balch et al. 2001b, 2009). In patients with tumor-negative sentinel lymph nodes (SLN), ulceration has been shown to be an independent predictor of increased risk of locoregional and distant recurrence and worse melanoma-specific survival, with a relative increase in risk of recurrence or death two to three times that of patients whose primary tumors are non-ulcerated (Balch et al. 2009; Yee et al. 2005; Egger et al. 2016). Primary tumor ulceration is also an important adverse prognostic factor even among patients with Stage III (regional) disease. Primary tumor ulceration has also been shown to impact survival among patients with regional metastasis. Accordingly, in both the 7th and 8th Editions of the AJCC melanoma staging system, the presence or absence of ulceration contributes to the subgrouping of node-positive patients (Gershenwald et al. 2017a; Edge 2010). In summary, primary tumor ulceration is an important staging element for patients with cutaneous melanoma and offers insights into the patient's risk of recurrence and death.

Mitotic Rate

Mitotic rate is a pathological feature of the primary tumor that has also been used to stage patients with primary cutaneous melanoma. Mitotic rate is defined as the number of mitoses

per mm^2 using the dermal "hot spot" method (Edge 2010). Clark et al. identified mitotic rate as an important risk factor in localized cutaneous melanoma in the 1980s (Clark et al. 1989). Mitotic rate was introduced into the 7th Edition AJCC melanoma T category assessment of primary melanoma for patients with "thin" T1 melanoma based on a series of tumor thickness-stratified multivariable models (Balch et al. 2009; Edge 2010). Higher mitotic rate has been shown to be an independent risk factor for death from melanoma and was more important than ulceration in some studies (Barnhill et al. 2005; Azzola et al. 2003). Using both Surveillance, Epidemiology, and End Results (SEER) data and a single-institution database, Gimotty et al. demonstrated that a classification system using mitotic rate greater than zero (i.e., as a dichotomous putative prognostic factor), among other factors, was able to stratify patients with thin, non-ulcerated melanomas into groups with significantly different survival rates (Gimotty et al. 2007). Kesmodel et al. reported that a mitotic rate greater than zero was an independent predictor of a tumor-positive SLN in patients with thin (Breslow thickness $\leq$1.0 mm) melanoma (Kesmodel et al. 2005). Using the 7th Edition AJCC melanoma staging database, Thompson et al. showed that mitotic rate was an independent adverse predictor of survival in localized (Stages I and II) cutaneous melanoma; it was the strongest predictor of survival outcome after Breslow thickness (Thompson et al. 2011). Among patients with Stage III cutaneous melanoma in the same database, Balch et al. observed that mitotic rate was an independent adverse predictor of survival in patients with nodal micrometastases (i.e., from a positive SLN or historically from tumor-involved nodes identified at elective lymph node dissection), but not among patients with nodal macrometastases (i.e., clinically evident) (Balch et al. 2010).

The 7th Edition AJCC melanoma staging committee evaluated mitotic rate as a dichotomous variable (i.e., $<$1 mitosis/mm^2 versus $\geq$1 mitosis/mm^2) within each AJCC tumor thickness group and determined that it was an independent adverse predictor of survival among patients with T1 melanomas. As a result, mitotic rate was introduced into the 7th Edition AJCC staging system as a T1 ($\leq$1.0 mm) primary melanoma criterion; the presence of ulceration and/or a mitotic rate of $\geq$1/mm^2 defined T1b (Balch et al. 2009). However, in the 8th Edition AJCC staging system, mitotic rate is no longer used to subcategorize T1 (Gershenwald et al. 2017a, b). While ulceration continues to be used to subcategorize melanoma, a new approach based on tumor thickness among patients with a thin melanoma is used to define T1 subcategories in the 8th Edition. In particular, mitotic rate was removed as a T1 criterion because analysis of patients with melanomas whose primary tumor thickness was $\leq$1 mm in the international database demonstrated that tumor thickness itself (stratified as $<$0.8 mm vs. 0.8–1.0 mm) was more prognostically important with respect to melanoma-specific survival than was mitotic rate (as a dichotomous variable as employed in the 7th Edition) (Gershenwald et al. 2017a, b).

Importantly, the 8th Edition AJCC melanoma expert panel strongly recommends that mitotic rate continue to be recorded for all patients with a primary cutaneous melanoma and notes that when explored using the mitotic rate continuum, it has been associated with survival across the tumor thickness continuum (Thompson et al. 2011; Gershenwald et al. 2017a, b). Although not a formal component of 8th Edition AJCC melanoma staging system, mitotic rate remains an important component of overall risk assessment and will likely be incorporated into the future development of clinical tools to aid in clinical decision-making through improved risk stratification and prognostic assessment (Gershenwald et al. 2017a).

Regional Lymph Node Assessment

The N category is the next component of melanoma staging and documents the absence or presence of regional lymph node and/or nonnodal locoregional (i.e., microsatellites, satellites, and/or in-transit) melanoma metastasis. The surgical approaches and pathological assessment of the regional lymph nodes have been refined over

the past three decades, with important implications for staging, risk stratification, and assessment for surgical, adjuvant, and other treatment decisions.

Historical: Approach to the Regional Nodal Basin

The role of lymph node dissection for staging purposes, particularly among clinically node-negative patients, has evolved over the years as new surgical techniques evolved, including the technique of lymphatic mapping and sentinel lymph node (SLN) biopsy (Gershenwald et al. 1999). Regional lymph node basins are initially routinely assessed by clinical exam. Clinically suspicious lymph nodes can be biopsied by fine needle aspiration, often using ultrasound guidance, to confirm metastatic disease. In the presence of pathologically confirmed, clinically evident lymph node metastasis, a therapeutic lymph node dissection is generally performed. From a staging perspective, such an approach affords an assessment of the regional nodal basin and an accurate count of the number of nodal metastases to determine N category criteria. Prior to the development of the SLN biopsy technique, an elective lymph node dissection was sometimes performed in patients with intermediate (1–4 mm) tumor thickness primary melanoma and clinically negative nodes to identify microscopic regional nodal metastasis and accurately determine the N category.

Current Approach to the Patient with Clinically Negative Regional Lymph Nodes: Rationale for Lymphatic Mapping and Sentinel Lymph Node (SLN) Biopsy

The technique of lymphatic mapping and SLN biopsy was introduced by Morton and colleagues in 1992, and its prognostic significance was validated by Gershenwald and colleagues in a 1999 multi-institutional study (Morton et al. 1992; Gershenwald et al. 1999). The rationale for this approach is based on the concept that for a given area of the skin, there is at least one regional lymph node that receives direct afferent lymphatic drainage from the primary tumor site – the "sentinel node" – prior to the rest of the regional nodal basin. Morton and colleagues initially demonstrated that the SLN is the most likely first site of metastasis to the regional nodal basin if any are involved, and if the SLN is negative, the remaining regional basin nodes are unlikely to harbor microscopic melanoma metastasis (Ross et al. 1993; Reintgen et al. 1994; Thompson et al. 1995). First incorporated into the 6th Edition (2002) AJCC melanoma staging system, the technique's accuracy has been validated in multiple multi-institutional studies (Balch et al. 2001a; Gershenwald et al. 1999; Morton et al. 1999). Over the past two decades, SLN biopsy has become an important cornerstone for the accurate assessment of many patients with at-risk melanoma who have clinically negative regional lymph nodes.

The principal purpose of the technique of lymphatic mapping and SLN biopsy for staging purposes is to identify microscopic regional lymph node metastases in clinically node-negative patients. The decision to perform lymphatic mapping and SLN biopsy for staging is based on the predicted risk of clinically occult regional node disease. Primary tumor factors, such as Breslow thickness, ulceration, and mitotic rate (discussed above), can be used to inform this decision-making (Kesmodel et al. 2005; Rousseau et al. 2003; McMasters et al. 2001; Sondak et al. 2004). Based on the associations of these primary tumor factors with microscopic regional lymph node metastasis, SLN biopsy is required for staging patients with clinically negative lymph node basins with T2, T3, and T4 melanomas to be included in the 8th Edition AJCC staging system; selective consideration of SLN biopsy for patients with T1b melanoma is permitted (Gershenwald et al. 2017a, b). Metastases identified by SLN biopsy are defined as "clinically occult" and designated with an "a" suffix in the AJCC N category. Metastases that are clinically evident and confirmed pathologically are considered "clinically detected" and designated with a "b" suffix in the

AJCC N category. The 8th Edition AJCC melanoma staging system defines N category as N1 (one positive lymph node), N2 (two to three positive lymph nodes), or N3 (four or more positive lymph nodes); in-transit, satellite, and/or microsatellite metastases can be categorized as N1c, N2c, or N3c, depending on the number of regional lymph nodes involved (see discussion below) (Gershenwald et al. 2017a). As in the 7th Edition, N category suffixes "a" or "b" continue to denote clinically occult or clinically evident, respectively (see also section below on "Non-nodal Locoregional Disease").

Non-nodal Locoregional Disease

Non-nodal regional disease – including microsatellites, satellite lesions, or in-transit metastases – represents an additional component of the AJCC N category staging criteria. In-transit metastases have been classically defined as cutaneous or subcutaneous metastases located greater than 2 cm from the primary tumor site, between the primary tumor and a draining regional nodal basin. Satellite lesions have a similar clinical definition except they are located within 2 cm of the primary tumor. In contemporary practice, however, the distinction between in-transit and satellite metastases is not clinically relevant, as they are equivalent from a staging perspective (i.e., both examples of non-nodal regional disease) and are generally considered in the same context for clinical decision-making. As for patients with regional node metastasis, prognosis in patients with satellite or in-transit metastasis is also informed by primary tumor characteristics and the presence of regional lymph node metastases (Shaikh et al. 2005; Bartlett et al. 2014; Read et al. 2015).

Microsatellite disease, another type of non-nodal regional metastasis, is a microscopic cutaneous and/or subcutaneous metastasis adjacent or deep to, and discontinuous from, a primary melanoma on pathological examination of the primary tumor site (Gershenwald et al. 2017a, b). The presence of microsatellites is also a risk factor for regional node metastasis (Kimsey et al. 2009).

From a staging perspective, patients with satellite, microsatellite, or in-transit metastasis without regional lymph node metastasis are categorized as N1c, where the "c" designation denotes satellite, microsatellite, or in-transit metastases. In the 7th Edition AJCC melanoma staging system, these patients were all designated as N2c. Patients with regional nodal metastasis who also have satellite, microsatellite, or in-transit metastasis are categorized as N2c or N3c, depending on the number of regional nodal metastases: N2c if there is one regional metastatic node and N3c if there are two or more tumor-involved regional nodes.

Assessment of Distant Metastasis

In the AJCC melanoma staging system, the M category denotes distant metastatic disease: M1 if present and M0 if absent. Overall, M category criteria are based on anatomic site(s) of distant metastasis as well as serum lactate dehydrogenase (LDH) levels.

Site of Distant Metastasis

In the 8th Edition AJCC melanoma staging system, M1a denotes metastatic disease confined to distant skin or subcutaneous tissues (including the muscle) or distant nodal metastasis (Gershenwald et al. 2017a). In general, a nodal metastasis is characterized as M1a disease when located beyond the regional nodal basin(s) of the primary tumor. For example, in the setting of a lower extremity primary, metastasis to the ipsilateral inguinal nodal basin is considered Stage III disease, but metastasis to the axilla is considered M1a. Metastasis confined to distant skin, subcutaneous tissues, or distant lymph nodes is generally associated with a more favorable survival compared to other sites of distant metastasis (Balch et al. 1983, 2009; Bowen et al. 2000; Barth et al. 1995).

M1b is defined as metastasis to the lung, with or without the presence of distant skin or subcutaneous metastasis or distant nodal disease

(Gershenwald et al. 2017a). Overall, these patients have been shown to have a somewhat worse prognosis compared to patients with M1a disease but more favorable survival compared to patients with nonpulmonary visceral metastases (Balch et al. 1983, 2009; Barth et al. 1995).

In the 8th Edition AJCC melanoma staging system, M1c is defined as noncentral nervous system (CNS) visceral metastases (Gershenwald et al. 2017a). Previously, in the 7th Edition, M1c was defined as any nonpulmonary visceral metastasis, including CNS metastasis. The 7th Edition M1c definition was refined as noted above, and a new M subcategory, M1d, has been introduced in the 8th Edition to denote metastasis to the brain, including CNS metastasis. As such, patients with CNS disease, regardless of whether other sites of metastasis are involved, will be categorized as M1d. Overall, patients with CNS metastasis have been noted to have a prognosis worse than patients without CNS metastasis, with median survival historically reported to be less than 1 year and 5-year survival rates $<10\%$ (Barth et al. 1995; Balch et al. 1983). CNS involvement is also frequently used as an inclusion or exclusion criterion for clinical trial eligibility, as well as a component of clinical trial stratification and analysis. In patients with multiple sites of distant metastases, the highest M subcategory corresponding to the anatomic site(s) of distant metastasis is used for staging purposes.

Laboratory Markers

It is generally uncommon for a cancer staging system to use serum markers for staging; however, for patients with melanoma, an elevated serum lactate dehydrogenase (LDH) level at the time of diagnosis of distant metastasis has been shown to be a strong adverse predictor of survival, regardless of anatomic site (Sirott et al. 1993; Eton et al. 1998; Deichmann et al. 1999). In the 8th Edition AJCC melanoma staging system, a suffix of "(0)" or "(1)" further characterizes M1a, M1b, M1c, and M1d disease with non-elevated (0) or elevated (1) LDH levels, respectively. The underlying mechanism for the association of elevated LDH levels with prognosis in metastatic melanoma is incompletely understood, but it remains an important tool to assess prognosis. LDH levels have also been shown to be associated with response to some of the targeted therapies for patients with metastatic or unresectable melanoma; normal LDH levels have been associated with a long-term response without progression to combination BRAF/MEK inhibition (hazard ratio for normal LDH for overall survival in the trial was 0.21) (Long et al. 2016).

Melanoma Stage Groupings

Once the T, N, and M categories are known, a patient's stage grouping (I–IV) can be determined. The 8th Edition AJCC staging system employs both a clinical and pathological classification system (Table 2). Clinical classification is performed after the biopsy of the primary tumor has been performed with clinical or biopsy assessment of the regional lymph nodes. The only assessment of the lymph nodes required for clinical staging is physical examination. The primary tumor pathological features Breslow thickness and ulceration define clinical Stages IA, IB, IIA, IIB, and IIC. Clinically evident regional lymph node and/or non-nodal regional disease identified in the clinical staging of a patient designates a patient as clinical Stage III, without consideration of the number of positive nodes. Clinical Stage IV includes patients who have distant metastasis at the time of diagnosis.

Pathological stage groups are determined after the status of the regional lymph nodes is determined after either SLN biopsy or completion lymph node dissection. Pathological classification uses information from additional microstaging of the primary tumor after biopsy and wide excision and from assessment of the regional nodal basin by either SLN or complete lymph node dissection; although SLN biopsy may be performed for some patients with T1 melanoma and clinically negative lymph nodes, SLN biopsy is not required for AJCC staging for patients with a T1 melanoma. Primary tumor thickness and ulceration define pathological Stages IA, IB, IIA, IIB, and IIC.

Table 2 Stage groupings for cutaneous melanoma, 8th Edition AJCC

Clinical stage				Pathological staging			
	T	N	M		T	N	M
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
					T1b	N0	M0
IB	T1b	N0	M0	IB	T2a	N0	M0
	T2a	N0	M0				
IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0
III	Any T	N ≥1	M0	IIIA	T1a/b-T2a	N1a or N2a	M0
				IIIB	T0	N1b or N1c	M0
					T1a/b-T2a	N1b/c or N2b	M0
					T2b/T3a	N1a-N2b	M0
				IIIC	T0	N2b, N2c, N3b, or N3c	M0
					T1a-T3a	N2c or N3a/b/c	M0
					T3b/T4a	Any N ≥ N1	M0
					T4b	N1a-N2c	M0
				IIID	T4b	N3a/b/c	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

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Pathological Stage III is reserved for patients with nodal or non-nodal regional disease. Stages IIIA, IIIB, IIIC, and IIID are determined by primary tumor thickness, ulceration, and the N categorization for nodal or non-nodal regional disease. Pathological Stage IV is for any M1 disease; there are no Stage IV substages.

Future Directions

Current staging criteria and classification continue to evolve. Reflective of the desire to develop and mature a framework by which additional known or putative prognostic elements can be collected for analysis and the development of improved clinical tools, the AJCC charges each of its expert panels to recommend which additional primary tumor, nodal, and/or distant disease factors be collected. Although these factors are not used to assign stage grouping, they may be of relevance to individual risk assessment; several such elements are discussed below. Prognostic models that take into account a multitude of patient and tumor characteristics can be used to personalize risk assessment and for the development of validated clinical tools.

Primary Tumor Assessment

Pathological assessment of the primary tumor includes more features than are included to define the AJCC T category. Some such factors include mitotic rate as a continuous variable and across all tumor thickness categories, level of invasion, regression, lymphovascular invasion, tumor-infiltrating lymphocytes, and neurotropism. While these factors may contribute information to risk assessment for an individual patient,

their influence on survival, independent of the more established pathological prognostic factors – Breslow thickness, mitotic rate, and ulceration – has not been unequivocally established. As such, these factors are not included in AJCC staging, but should continue to be collected for ongoing and future research into individual risk assessment models.

Efforts have also been made to subclassify cutaneous melanoma based on histologic subtypes and molecular profiles. Cutaneous melanoma has been classically divided into five histologic subtypes: superficial spreading, nodular, lentigo maligna, acral lentiginous, and desmoplastic. The most common subtype is superficial spreading. While AJCC staging does not currently incorporate these histologic subtypes, variations in biological behavior of the different subtypes can potentially be used to inform future staging and development of clinical tools. In exploratory studies, molecular classification of primary melanomas (e.g., by differential gene expressions) has identified possible strategies to inform clinical outcome (Bittner et al. 2000; Jaeger et al. 2007; Gerami et al. 2015; Koh et al. 2012; Rajkumar and Watson 2016). These approaches have not been sufficiently validated for clinical use nor have they been implemented into AJCC staging criteria, but taken together represent an area of opportunity to develop clinical tools that may improve risk stratification and enhance clinical decision-making.

N Category

The 8th Edition AJCC staging system incorporates the pathological status of SLNs without consideration for the extent of microscopic tumor burden in positive SLNs. Several studies support that both volume and distribution of microscopic disease have prognostic significance and that all positive SLNs should not therefore be considered at equal risk for non-SLN metastases and death from melanoma. Various measures of metastatic SLN tumor burden have been proposed, including measurement of the diameter of the SLN metastasis, depth of SLN tumor invasion, and anatomic distribution of the metastasis within the SLN (Ranieri et al. 2002; Carlson et al. 2003; Debarbieux et al. 2007; van Akkooi et al. 2008; Dewar et al. 2004; Starz et al. 2004). In general, several assessments of microscopic tumor burden have been shown to be associated with non-SLN metastases among patients who have a completion lymph node dissection, as well as survival. Maximum diameter of the largest metastatic focus has become the most common measurement used in clinical practice, given its reported prognostic significance, ease of measurement, and reproducibility. Although such measurements are currently not yet incorporated into AJCC melanoma staging, the 8th Edition AJCC melanoma staging system recommends that the SLN tumor burden be recorded. In the future, these measures may be incorporated into prognostic models and clinical tools (Gershenwald et al. 2017a, b).

Molecular and immunological analyses have been explored to further refine the assessment of SLNs in an attempt to identify patients at high and low clinical risk. Reverse transcriptase polymerase chain reaction (RT-PCR)-based and other techniques have been employed over the past two decades as a way to detect submicroscopic and otherwise undetectable metastatic melanoma using putative surrogate markers of melanoma (Wang et al. 1994; Van der Velde-Zimmermann et al. 1996; Goydos et al. 1998). Early observational studies evaluating the use of RT-PCR-based techniques suggested that this type of so-called molecular staging was prognostically significant. Confounding such early reports, however, other studies reported contrary findings, suggesting that RT-PCR-based analysis does not refine prognostic abilities beyond standard pathological analysis (Shivers et al. 1998; Bostick et al. 1999; Blaheta et al. 2000; Hochberg et al. 2002; Kuo et al. 2003; Ribuffo et al. 2003; Ulrich et al. 2004; Romanini et al. 2005; Kammula et al. 2004; Mangas et al. 2006; Hilari et al. 2009). A multi-institutional randomized clinical trial reported no difference in overall survival between patients with pathologically negative SLNs whose SLNs were "RT-PCR positive" only and whose regional nodal basins were observed and similar patients who

underwent complete lymph node dissection of the mapped nodal basin, with or without adjuvant interferon therapy (Scoggins et al. 2006; McMasters et al. 2016). Currently, this molecular approach is not employed for risk stratification for routine clinical care in cutaneous melanoma and is not a component of AJCC staging guidelines. The immunological milieu of the SLN has also been explored. Tumor-mediated immune modulation may, for example, render a lymph node more or less susceptible to the establishment of metastases (Cochran et al. 2006). Moreover, markers of immune response in the SLN may identify patients at increased risk of recurrence (Ma et al. 2012; Vallacchi et al. 2014). Currently, neither RT-PCR-based nor immunologic assessment of the SLN is included in AJCC melanoma staging; studies are ongoing using contemporary approaches such as next-generation sequencing, etc., to further assess possible roles for molecular profiling in the risk assessment of patients with cutaneous melanoma.

M Category

The melanoma M staging category currently includes site of disease and serum LDH levels. Novel ways to assess the risk of progression and potential response to therapy have been proposed for patients with metastatic disease. In the rapidly evolving era of mutation-targeted therapy and immunotherapy, genomic profiling of metastatic melanoma plays an important role in the assessment of patients with Stage IV melanoma to determine suitability for enrollment in clinical trials or other treatment options. These measures may someday play a role in staging.

Estimates of metastatic tumor burden (e.g., number of metastases, size of metastases, change in tumor burden over time) have been shown to correlate with prognosis in patients with Stage IV melanoma (Gaudy-Marqueste et al. 2014; Panasiti et al. 2013). The AJCC melanoma expert panel recognizes that the number of distant metastases has prognostic value; however, such measures have not been incorporated into the staging system because of the variability in the use of imaging to identify metastatic disease and inconsistent and nonuniform inclusion in many institutional melanoma databases that have been used to inform AJCC staging. Fold elevation of serum LDH and exploratory studies of alternative tumor markers such as S100B and YKL-40 have also been associated with prognosis and treatment response (Egberts et al. 2012; Dick et al. 2016; Simeone et al. 2014). Changes in the serum levels of these tumor markers have been shown to be associated with responses to targeted BRAF agents and immunotherapy (Abusaif et al. 2013; Diem et al. 2016). Elevated LDH has been shown to correlate with poor survival in patients treated with the anti-CTLA-4 immunotherapy drug ipilimumab (Kelderman et al. 2014).

Contemporary molecular techniques may also risk stratify patients with metastatic melanoma. Investigators have attempted to correlate circulating markers of immune response, such as neutrophil to lymphocyte ratio, or receptor expression on $CD4^+$ and $CD8^+$ T lymphocytes, with survival (Jacquelot et al. 2016; Gandini et al. 2016). Sera samples can be tested using RT-PCR or melanoma-specific antigen-detecting platforms to quantify minute expression levels of melanoma-associated cells. This so-called "liquid biopsy" approach can identify circulating tumor cells, cell-free circulating DNA, or cell-free circulating microRNA that has been shown to correlate with survival in Stage III and Stage IV patients (Huang and Hoon 2016).

The current (8th) edition AJCC melanoma staging system does not provide specific recommendations regarding the use of mutational testing for staging; nonetheless, it is clear that there is utility in assessing for somatic mutations among patients with unresectable disease or distant metastasis to help inform therapeutic options. High-throughput gene sequencing, termed next-generation sequencing, can identify genetic mutations that can be used to select targeted therapy, potentially classify patients into prognostic groups, and predict response to immunotherapy (Castiglione et al. 2016). These approaches, while not part of the current (8th) AJCC staging system, represent areas of ongoing investigation that may improve individualized

risk assessment for patients to help guide decision-making in the future.

Personalized Risk Assessment Versus Staging

The complex interplay between multiple risk factors, the wide range of prognoses within stage groups (e.g., heterogeneity of Stage III melanoma), and the power of computer-based analysis provide opportunities to further refine individualized risk assessment beyond TNM. One must understand that cancer staging and personalized risk assessment serve different roles. Staging classifies patients into large groups of generally similar risk. Staging is useful to inform clinical decision-making, to compare patients across clinical trials, and for other research and reporting efforts. The current staging system is necessarily constrained under a TNM-based system and therefore does not allow the inclusion of other risk factors that can potentially provide a more personalized individual risk assessment. This precise (or imprecise) estimation is more suitably determined by clinically validated prognostic tools (Collins et al. 2015; Kattan et al. 2016). These tools use multiple clinical and pathological features to estimate a single individual's risk of melanoma recurrence and death.

Several risk calculators are available online that use a composite of clinical and pathological factors to provide patients and clinicians with personalized risk assessment (Soong et al. 2010; Callender et al. 2012). In principle, such models can be useful clinical tools to improve clinical decision-making and risk assessment. However, one must be mindful of the shortcomings of currently available clinical prognostic tools and discuss such limitations with patients (Mahar et al. 2016). Issues include both the internal and external validity of the studies used to build the predictive models, either of which may limit the applicability of the tools to certain patient populations. Moreover, the data used to build the models may be somewhat dated, and the clinical risk assessments do not take into account newer therapies and improved diagnostic techniques. The 8th Edition AJCC Precision Medicine Core has developed criteria by which clinical prognostic tools can be critically assessed in an effort to inform both the professional and lay users of these tools (Kattan et al. 2016). Moving forward, AJCC staging guidelines and clinical prognostic tools will likely both play important roles in the study and management of patients with cutaneous melanoma.

The AJCC melanoma staging system is based on estimates of survival at the time of diagnosis based on clinicopathological data available at that time. A complementary approach to survival analysis is the concept of conditional survival. This type of survival estimation is based on a premise that a patient has already survived for a specific period of time following initial diagnosis. Given that they are alive for a certain period of time after diagnosis, their likelihood of survival has improved. Conditional survival has been explored for melanoma across all AJCC stages. These studies demonstrate improved conditional survival over time for AJCC Stage II, III, and IV patients, but not for Stage I patients (Xing et al. 2010; van der Leest et al. 2014). The implication is that the prognosis for localized Stage I disease is overall quite favorable and generally constant over time, while for patients with more advanced locoregional or distant metastatic disease, prognosis improves over time as a patient survives longer following the initial diagnosis. Conditional survival models can be used for all stages in melanoma to improve risk assessment. This approach takes advantage of information gained over time and offers a dynamic complement to the AJCC staging system and associated prognostic models based on the time of diagnosis. It is likely that conditional survival analyses will be explored using contemporary analytic approaches going forward.

Conclusion

Contemporary AJCC staging for cutaneous melanoma incorporates a TNM-based assessment of the primary tumor (T), nodal and non-nodal regional metastasis (N), and distant metastases (M). Primary tumor thickness and ulceration are

important prognostic factors that are important to prognosis in both localized and regionally advanced disease. Regionally metastatic disease exists across a spectrum of microscopic tumor deposits in single lymph nodes to non-nodal regional metastases and bulky, clinically apparent nodal metastases. N stage groups stratify these differences in an effort to risk cohort patients with Stage III disease. Patients with distant metastatic melanoma can be risk stratified according to their anatomic site of disease and serum LDH levels. Taken together, these factors can be used to predict the risk of melanoma-related death. As our understanding of melanoma evolves, so too will the potential factors – clinical, pathological, molecular, immunologic, etc. – and tools that can be utilized to assess risk. Clinicians must continue to collect data on clinical and pathological risk factors so that predictive models and staging system can be critically appraised and updated.

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