Ann Surg Oncol (2018) 25:2105–2110
https://doi.org/10.1245/s10434-018-6513-7

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – MELANOMAS

Melanoma Staging: American Joint Committee on Cancer (AJCC) 8th Edition and Beyond

Jeffrey E. Gershenwald, MD[1,2] and Richard A. Scolyer, MD[3,4,5]

[1]Departments of Surgical Oncology and Cancer Biology, Unit 1484, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Melanoma and Skin Center, The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia; [4]Department of Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Camperdown, NSW, Australia; [5]Sydney Medical School, The University of Sydney, Sydney, NSW, Australia

Melanoma staging is a critical tool for communication between physicians and their patients and also assists clinical decision-making and prognostic assessment. It is used for clinical trial design, eligibility, stratification, and analysis. Importantly, it also represents the foundation for reporting in institutional, state, national, and international data registries, which, in turn, facilitate understanding of the broader melanoma landscape.

The 7th edition AJCC melanoma staging system was introduced in 2009 and implemented in 2010. Since that time, there has been a tremendous improvement in our understanding of the molecular and immune biology of melanoma, which has led to the unprecedented introduction and widespread use of a number of effective systemic therapies for patients with advanced disease and in the adjuvant setting.[1–6]

To facilitate an evidence-based approach and to inform revisions for the 8th edition of the AJCC melanoma staging system, we created a contemporary international melanoma database: the International Melanoma Database and Discovery Platform (IMDDP).[7] Given the recent advances in the clinical management of patients with advanced and unresectable disease, rapidly evolving treatment options for such patients and varying approval for use of these new agents in different parts of the world, the AJCC melanoma expert panel considered that it was inappropriate to include stage IV patients in their initial data analyses of the IMDDP. Therefore, patients eligible to be included in the IMDDP were those with stages I–III cutaneous melanoma diagnosed since 1998. This approach allowed us to exclude patients diagnosed during the early and mid-1990s, a period of rapid evolution in surgical, pathological, and nuclear medicine strategies employed to identify, remove, and accurately assess the sentinel lymph node (SLN) in patients with cutaneous melanoma who underwent lymphatic mapping and SLN biopsy. In contrast, the database used for the 7th edition had no restriction on the date of diagnosis and included patients diagnosed as long ago as the 1960s.[8] In addition, for inclusion in the 8th edition analyses, patients were required to have undergone SLN biopsy if their primary was T2 or thicker, and if T1 and a SLN biopsy had been performed, SLN status was incorporated for data analysis and staging purposes.

The TNM- or anatomic-based staging system is effectively constrained by the limited type and number of factors that can be included. However, both anatomic and nonanatomic factors can have significant prognostic importance. As such, the overall 8th edition AJCC strategy embraced inclusion of standard anatomic "TNM" prognostic factors and also considered nonanatomic factors that could help further improve staging and prognostic assessment.[9]

T CATEGORY AND STAGES I/II STAGE GROUPS

In the 7th edition, T-category criteria included tumor thickness (measured to the nearest 0.01 mm) and presence or absence of ulceration across all subcategories; mitoses as a dichotomous variable (< 1 vs. ≥ 1 mitosis/mm^2) also

First Received: 21 March 2018;
Published Online: 30 May 2018

J. E. Gershenwald, MD
e-mail: jgershen@mdanderson.org

was included as a T1 category criterion.[8] However, based on the impracticality of measuring tumor thickness to the nearest 0.01 mm, especially for tumors > 1 mm in tumor thickness, in the 8th edition, the AJCC recommends that tumor thickness be recorded to the nearest 0.1 mm and has provided a formal rounding schema to standardize the approach.[7] For example, patients with melanomas 0.75–0.84 mm in tumor thickness will now be rounded to (and reported as) 0.8 mm (i.e., T1b), and melanomas between 0.95 mm and 1.04 mm in tumor thickness will be reported as 1.0 mm (i.e., T1b). In the 8th edition, the definitions of Tis, T0, and TX have been refined and/or clarified. Tis is used for melanoma in situ (i.e., no invasive component is present). T0 is designated when no evidence of a primary tumor can be found (e.g., a patient presenting with an inguinal nodal metastasis of melanoma with no evidence of a primary tumor). TX is used when the tumor thickness cannot be determined (e.g., in a curettage specimen when there is no sectioning of the tumor perpendicular to the skin surface) or there is no information about the T category for the primary tumor (e.g., a primary melanoma that was resected many years previously and the primary melanoma report cannot be found).

Based on previously published studies that reported patients with thicker T1 melanomas have a worse prognosis than those with thinner T1 melanomas, the AJCC melanoma expert panel explored the potential impact of including an additional tumor thickness criterion for subcategorizing T1 melanomas by analyzing our IMDDP melanoma database.[10–13] With the proposal in place to record tumor thickness measurements to the nearest 0.1 mm, a 0.8 mm cut point was explored for patients with T1 melanoma along with ulceration and mitosis (i.e., < 1 vs. ≥ 1 mitosis/mm^2). In this analysis, the addition of a 0.8-mm tumor thickness stratum was a more powerful prognostic factor than mitotic rate (as a dichotomous variable). Principally for this reason, mitotic rate as a dichotomous variable was removed as a T1 subcategory criterion. The subcategorization of T1 melanomas at a 0.8-mm threshold has potential clinical relevance, particularly for the role of SLN biopsy in patients with T1 melanomas. Overall, SLN metastases are very infrequent (< 5%) in patients whose melanoma is < 0.8 mm in thickness and nonulcerated (i.e., AJCC 8th edition T1a) but occur in approximately 5–12% of patients with primary melanomas 0.8–1.0 mm in thickness (i.e., AJCC 8th edition T1b).[14–17] Reflective of these data, consensus guidelines have recommended that SLN biopsy may be considered in this latter group of patients (i.e., patients with a primary tumor thickness 0.8–1.0 mm) and also in patients with thinner ulcerated tumors (i.e., all patients with AJCC 8th edition T1b melanomas).[18,19] Although mitosis was removed as a T1 subcategory criterion, analyses performed for both the 7th and 8th edition AJCC staging systems demonstrated that tumor mitotic rate, when explored across its dynamic range, was a very important prognostic factor and strongly supports that if interrogated in this fashion, will likely be an important covariate going forward as clinical tools are developed. As emphasized by the AJCC melanoma expert panel, for these reasons, mitotic rate should be collected for all invasive melanomas.[7,13]

Comparison of stages I and II substage melanoma-specific survival rates between the AJCC 7th and 8th editions demonstrate more favorable survival in the 8th edition compared with the 7th edition. An important contributing factor was the requirement that to be included in the 8th edition analysis, SLN biopsy had to be performed for patients with T2 and thicker melanomas, and if performed in patients with a T1 melanoma, the status of the SLN was used.[7,8,13,20] This approach ensured that patients with clinically occult nodal metastases (detected by SLN biopsy) were designated as stage III in the 8th edition. In contrast, SLN biopsy was not required for inclusion in the 7th edition survival analyses for any tumor thickness (and indeed many patients included in the dataset were managed before the era of SLN biopsy). As such, in the 7th edition database, many patients with clinically localized melanoma who did not undergo SLN biopsy were characterized as having stage I or II melanoma regardless of whether they harbored clinically occult regional node metastasis, because only clinical staging of their nodal basin was performed. A sequela of this 7th edition approach was that the survival outcomes across multiple T subcategories were likely underestimated and, given the increasing relative risk of tumor-involvement of SLNs with increasing T category, was most evident when comparing outcomes to those of the 8th edition for patients with T4b melanomas (Fig. 1a, b).

N CATEGORY AND STAGE III STAGE GROUPS

For the N category, which includes regional lymph node as well as non-nodal regional disease (i.e., satellites, in-transit metastasis, and microsatellites), the AJCC melanoma expert panel grouped nonnodal regional disease together for staging purposes (because they each had a similar impact on prognosis) and revised the N category criteria.[7] Previously used terms of “microscopic” and “macroscopic” regional disease in the 7th edition have been replaced by “clinically occult” (i.e., detected by SLN biopsy) and “clinical evident” (i.e., detected by clinical examination or radiographic imaging) regional disease to enhance clarity. These correspond to N category designations “a” and “b”, respectively. The presence of microsatellites, satellites, or in-transit metastases is now

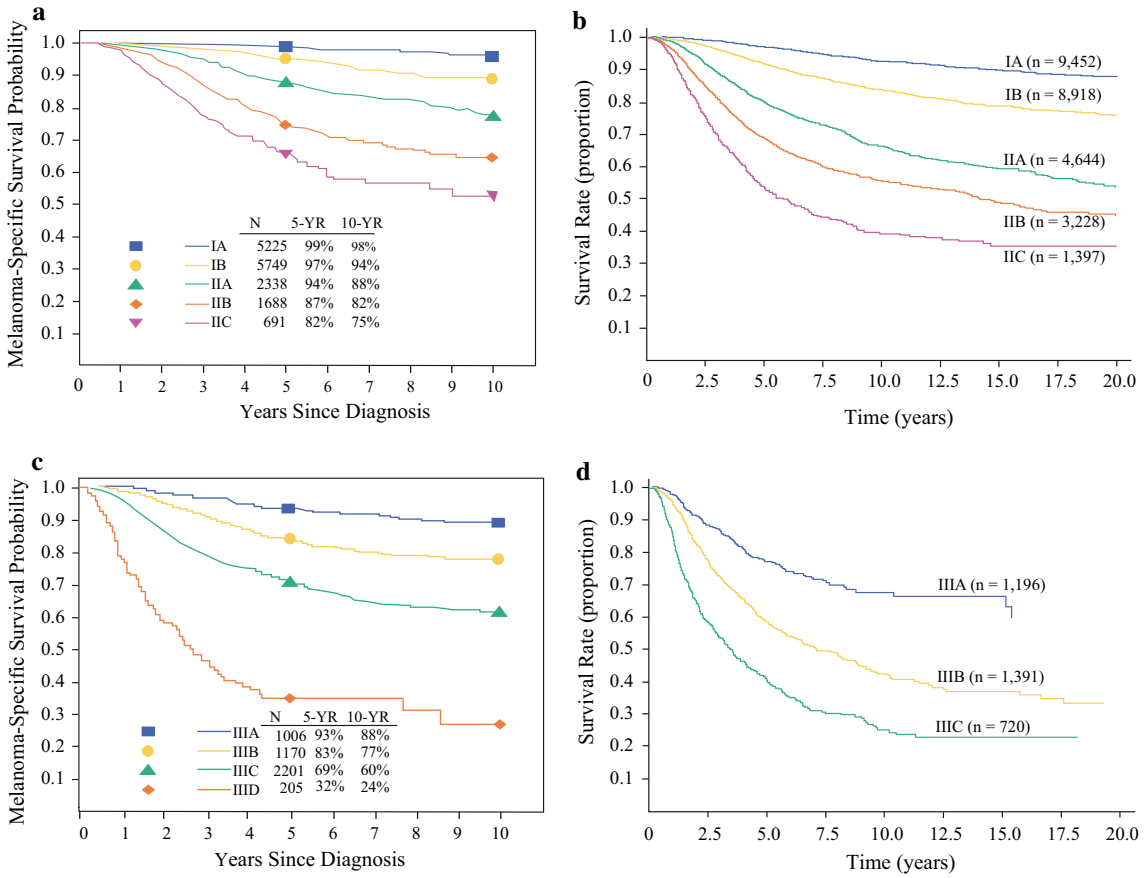

FIG. 1 Comparison of survival curves for 8th edition and 7th edition AJCC stages I, II, and III. **a** 8th edition stages I and II stage groups; **b** 7th edition stages I and II stage groups; **c** 8th edition stage III stage groups; and **d** 7th edition stages III stage groups. Figures **a** and **c** used with permission from Gershenwald, J.E., Scolyer, R.A., Hess, K.R., et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin. 2017;*67:472–92. Figures **b** and **d** used with permission from Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol. 2009;*27:6199–206

categorized as N1c, N2c, or N3c, based on the number of tumor-involved regional lymph nodes, if any.[7] Importantly, the definition of a microsatellite was refined and clarified; a microsatellite is a microscopic cutaneous and/or subcutaneous metastasis adjacent or deep to, but discontinuous from, a primary melanoma detected on pathological examination of the primary tumor site.

Recent clinical trial data, demonstrating no clear survival benefit for patients with a tumor-involved SLN who underwent completion lymph node dissection (CLND) compared with those who did not, has already begun to transform surgical approaches for patients with tumor-involved SLNs—i.e., fewer patients undergo completion lymph node dissection (CLND) after detection of a tumor-involved SLN.[21,22] It is worth noting that the 8th edition AJCC Cancer Staging Manual provides specific recommendations for documentation of the now common scenario when SLN biopsy identifies tumor-involved SLNs but CLND is not performed.[9] To distinguish patients who have had a CLND from those who have not, the "(sn)" suffix should be appended to the N category for those who did not undergo CLND—i.e., a patient with a single tumor-involved SLN who does not undergo CLND is pN1a(sn).[7,8,13] This approach will likely improve data capture and facilitate future planned analyses in this new era of a more selective approach to CLND.

Recognizing the importance of tumor thickness as a potential prognostic factor among patients with regional disease and expanding on prior analyses demonstrating the importance of primary tumor ulceration among these patients, the AJCC explored the prognostic impact of primary tumor factors (e.g., tumor thickness and ulceration status), as well as regional factors via a T-category- and N-category-based analysis. Based on recursive partitioning analysis, the expert panel agreed on four stage III substages to capture the significant heterogeneity among the stage III population.[13] It is important to note that no direct comparison or "mapping" of the 7th edition and 8th edition

pathological stage III stage groups is possible. First, tumor thickness was included as a component of stage III stage groups for the 8th edition but was not employed as a stage III stage group criterion in the 7th edition melanoma staging system. Furthermore, the N category criteria differ in the 7th and 8th editions and, in several instances, the various N subcategories map to different stage III groupings in the 8th edition. With these important caveats in mind, melanoma-specific survival (MSS) for both AJCC 8th edition stage IIIA and stage IIIB patients was more favorable compared to 7th edition stage IIIA patients (Fig. 1). These observations translate into significant implications for patient counseling, management, and contemporary clinical trial design, stratification, and analysis, because patients in the 8th edition cohort had a more favorable survival profile across stages IIIA, IIIB, and IIIC disease compared with patients with similar stage groupings in the 7th edition (Figs. 1c and d). To facilitate accurate and efficient 8th edition stage III stage group determination, particularly in busy patient clinics, clinic-, desktop-, and phone-friendly stage III subgroup grids are available for download in the supporting information section of reference[13] (reproduced in Fig. 2).

In recent years, multiple studies of patients with tumor-involved SLNs have demonstrated that SLN tumor burden provides important prognostic information.[23,24] SLN tumor burden can be quantitated by a variety of parameters, such as the maximum size of the largest metastasis, the maximum subcapsular depth of extension of the tumor deposit (also known as the tumor penetrative depth), the location of the deposit(s) within the SLN, and the percentage cross-sectional area of the SLN involved by tumor.[25,26] Microscopic tumor burden has already been implemented as an inclusion criterion in some clinical trials of adjuvant therapy.[5] Based on available data and practical considerations, the AJCC melanoma expert panel recommends that the single largest maximum dimension (measured in millimeters using an ocular micrometer) of the largest discrete metastatic melanoma deposit in any tumor-involved SLN be recorded in pathology reports. Although this histopathological parameter is not currently a formal staging criterion, SLN tumor burden will be included in and will likely guide the development of future prognostic models and ultimately validated clinical tools (e.g., calculators, nomograms, etc.) for patients with regional metastatic disease.

M CATEGORY

Patients with distant metastasis continue to be defined by anatomic site of distant metastases and serum lactate dehydrogenase (LDH) level. In the 8th edition, reflective of the importance of central nervous system (CNS) disease in prognosis, clinical management, and clinical trial design, stratification, and analysis, a new M1d designation for distant metastasis to the CNS has been added; M1c no longer includes patients with CNS metastasis. In addition, M1c is no longer defined by any patient with distant metastasis and elevated LDH. Nevertheless, as elevated LDH has been demonstrated to be an adverse prognostic factor both in the 7th edition analyses and recent clinical trials, it remains an M category criterion in the 8th edition.[2,3,7] The revised M category now includes a suffix to signify the absence or presence of an elevated LDH for each M1 subcategory.

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 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

Legend

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

FIG. 2 American Joint Committee on Cancer (AJCC) eighth edition stage III subgroups based on T and N categories. Used with permission from Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017; 67:472–491

BEYOND TNM, ASSESSMENT OF CLINICAL PROGNOSTIC TOOLS, AND NEXT STEPS

Additional prognostic factors that are not staging criteria but are recommended for recording clinical care, emerging prognostic factors for clinical care, as well as

recommendations for clinical trial stratification are also presented in the 8th edition AJCC Cancer Staging Manual and/or on the AJCC website.[7,27]

Despite its success over the past several decades, TNM/anatomic-based staging systems have been constrained in their ability to accommodate prognostic factors that may emerge from an improved understanding of cancer biology. To be useful, any staging system needs to be clinically relevant, reflect contemporary practice, and be refined as our understanding of the disease matures. In an effort to foster clinical relevance, the AJCC has expanded its principles of cancer staging to include nonanatomic-based factors. Nevertheless, it is essential that before such factors are introduced as staging criteria (and therefore adopted in routine clinical settings), they are demonstrated to have independent prognostic significance, are validated in independent patient cohorts, and are practical to measure in routine clinical practice. Using a systematic search of the published literature, a priori criteria were used to evaluate quality and clinical relevance of 17 clinical prognostic tools for primary cutaneous melanoma; a principal conclusion was that there "is a great opportunity to improve these tools and to foster the development of new, validated tools by the inclusion of contemporary clinicopathological covariates and by using improved statistical and methodological approaches."[28] Formal criteria also have been recently developed by the AJCC 8th edition Precision Medicine Core to serve as a framework for approval of contemporary risk models by the AJCC.[29] These changes are overall reflective of a strategic evolution from population-based staging to a more personalized approach.[29,30]

Given the ongoing advances in our understanding of the clinical, pathological, molecular, and immunological underpinnings of melanoma, a less "staccato" approach to cancer staging is likely to be embraced and implemented by the AJCC. Strategically configured iterative or "rolling" updates can more efficiently exploit integration of clinically relevant advances into the cancer staging arena. It is important to note that while there is tremendous enthusiasm to integrate molecular and/or immune-based biomarkers into melanoma staging and other clinical prognostic tools, there are as yet no formally validated schema. In addition, some biomarkers may have predictive significance but not prognostic significance. Overall, no molecular or immune biomarkers or signature currently fulfill the necessary criteria for inclusion into the AJCC melanoma staging system or as a component of a validated clinical tool.

Opportunities abound to leverage the expanding repertoire of electronic data collection efforts to facilitate development, validation, implementation, and use of clinically relevant clinical calculators and tools to more accurately stage patients. Such approaches will enable individualizing prognostic—and even predictive—assessment and enhance clinical decision making for patients with melanoma.[29,31] Failure to maintain relevance in this exciting and unprecedented era of cancer discovery that is translating into improved patient outcomes will eventually render any staging system or prognostic model less relevant and potentially obsolete.

ACKNOWLEDGEMENT This work was supported in part by The University of Texas MD Anderson Cancer Center Melanoma Moon Shots Program; by the Robert and Lynne Grossman Family Foundation; and by the Michael and Patricia Booker Melanoma Research Endowment. Support from the Australian National Health and Medical Research Council and colleagues at Melanoma Institute Australia and Royal Prince Alfred Hospital is also gratefully acknowledged.

REFERENCES

1. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med. 2015;*373:23–34.
2. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med. 2014;*371:1877–88.
3. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med. 2015;*372:2521–32.
4. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med. 2017;*377:1345–56.
5. Long GV, Hauschild A, Santinami M, et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. *N Engl J Med. 2017;*377:1813–23.
6. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N Engl J Med. 2017;*377:1824–35.
7. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the skin. In: Amin MB, et al. (eds) *AJCC cancer staging manual*. Switzerland: Springer, 2017:563–85.
8. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol. 2009;*27:6199–206.
9. Gress DM, Edge SB, Greene FL, et al. Principles of cancer staging. In: Amin MB, et al. (eds) *AJCC cancer staging manual*. Switzerland: Springer, 2017:3–30.
10. Gimotty PA, Elder DE, Fraker DL, et al. Identification of high-risk patients among those diagnosed with thin cutaneous melanomas. *J Clin Oncol. 2007;*25:1129–34.
11. Green AC, Baade P, Coory M, et al. Population-based 20-year survival among people diagnosed with thin melanomas in Queensland, Australia. *J Clin Oncol. 2012;*30:1462–7.
12. Lo SN, Scolyer RA, Thompson JF. Long-term survival of patients with thin (T1) cutaneous melanomas: a Breslow thickness cut point of 0.8 mm separates higher-risk and lower-risk tumors. *Ann Surg Oncol. 2018;*25:894–902.
13. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin. 2017;*67:472–92.
14. Andtbacka RH, Gershenwald JE. Role of sentinel lymph node biopsy in patients with thin melanoma. *J Natl Compr Canc Netw. 2009;*7:308–17.

15. Cordeiro E, Gervais MK, Shah PS, et al. Sentinel lymph node biopsy in thin cutaneous melanoma: A systematic review and meta-analysis. *Ann Surg Oncol. 2016;*23:4178–88.
16. Han D, Zager JS, Shyr Y, et al. Clinicopathologic predictors of sentinel lymph node metastasis in thin melanoma. *J Clin Oncol. 2013;*31:4387–93.
17. Murali R, Haydu LE, Quinn MJ, et al. Sentinel lymph node biopsy in patients with thin primary cutaneous melanoma. *Ann Surg. 2012;*255:128–33.
18. Wong SL, Faries MB, Kennedy EB, et al. Sentinel lymph node biopsy and management of regional lymph nodes in melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Clinical Practice Guideline Update. *Ann Surg Oncol. 2018;*25:356–77.
19. Wong SL, Faries MB, Kennedy EB, et al. Sentinel lymph node biopsy and management of regional lymph nodes in melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Clinical Practice Guideline Update. *J Clin Oncol. 2018;*36:399–413.
20. Melanoma of the skin. In: Edge SB, et al. (eds) *AJCC cancer staging manual*. Philadelphia: Springer, 2010:325–46.
21. Faries MB, Thompson JF, Cochran AJ, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. *N Engl J Med. 2017;*376:2211–22.
22. Leiter U, Stadler R, Mauch C, et al. Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. *Lancet Oncol. 2016;*17:757–67.
23. Gershenwald JE, Andtbacka RH, Prieto VG, et al. Microscopic tumor burden in sentinel lymph nodes predicts synchronous nonsentinel lymph node involvement in patients with melanoma. *J Clin Oncol. 2008;*26:4296–303.
24. van der Ploeg AP, van Akkooi AC, Haydu LE, et al. The prognostic significance of sentinel node tumour burden in melanoma patients: an international, multicenter study of 1539 sentinel node-positive melanoma patients. *Eur J Cancer. 2014;*50:111–20.
25. Scolyer RA, Li LX, McCarthy SW, et al. Micromorphometric features of positive sentinel lymph nodes predict involvement of nonsentinel nodes in patients with melanoma. *Am J Clin Pathol. 2004;*122:532–9.
26. Murali R, Cochran AJ, Cook MG, et al. Interobserver reproducibility of histologic parameters of melanoma deposits in sentinel lymph nodes: implications for management of patients with melanoma. *Cancer. 2009;*115:5026–37.
27. American Joint Committee on Cancer. https://cancerstaging.org/references-tools/deskreferences/Pages/Supplementary-Material.aspx. Accessed 2 March 2018.
28. Mahar AL, Compton C, Halabi S, et al. Critical assessment of clinical prognostic tools in melanoma. *Ann Surg Oncol. 2016;*23:2753–61.
29. Kattan MW, Hess KR, Amin MB, et al. American Joint Committee on Cancer acceptance criteria for inclusion of risk models for individualized prognosis in the practice of precision medicine. *CA Cancer J Clin. 2016;*66:370–4.
30. Amin MB, Edge SB, Greene FL, et al. Organization of the AJCC cancer staging manual. In: Amin MB, et al. *AJCC cancer staging manual*. Switzerland: Springer, 2017) 31–7.
31. Compton CC, Hess, K.R., Halabi, S., et al. Risk models for individualized prognosis in the practice of precision oncology. In: Amin MB, et al. (eds) *AJCC cancer staging manual*. Switzerland, Springer, 2017:47–52.