

BRIEF ARTICLES

Histopathologic discordance in melanoma can have substantial impacts on patient careAlex Glazer, MD¹, Clay J Cockerell, MD²¹Department of Dermatology, University of Arizona, Tucson, AZ²Cockerell Dermatopathology, Dallas, TX

ABSTRACT

Recommended guidelines for sentinel lymph node biopsy, follow-up, and surveillance for cutaneous melanoma are based upon clinicopathologic staging. In effect, the accuracy of melanoma staging to estimate metastatic risk is critical to subsequent care, neither under-treating or over-treating the patient based on their tumor. Traditional staging continues to evolve based on additional data regarding clinicopathologic features and clinical outcomes. However, such features are subject to inter-observer variability, which puts a limit on their ability to improve prognostication. Reported discordance rates between initial and subsequent pathology review consistently impact both staging and disease management. Newer molecular techniques, such as gene expression profiling, can be used to help define the biology of the primary melanoma tumor and the best course of action after definitive surgical treatment.

INTRODUCTION

Cutaneous melanoma (CM) is a significant and growing health concern in the United States. American Joint Committee on Cancer (AJCC) staging is commonly used to estimate prognosis for patients based on Breslow thickness, presence or absence of ulceration, sentinel lymph node (SLN) status (where appropriate), and nodal tumor burden. Mitotic rate was previously included in the 7th edition of AJCC substaging for thin melanomas, and is still considered by the National Comprehensive Cancer Network as an adverse feature to consider discussion of SLN biopsy (SLNB) for T1a melanomas. While increasing stage is generally associated with poorer prognosis, there are

limitations to its prognostic accuracy such that i) a substantial number of melanoma-related deaths are in patients diagnosed with early stage disease, ii) as many as two-thirds of patients who die from melanoma are SLN-negative, and iii) heterogeneity of risk exists within each stage so that some earlier stages (i.e. stage IIC) may portend a worse prognosis than that of nodal metastatic disease (i.e. stage IIIA).

One possibility to account for such limitations is the inherent subjectivity of traditional staging criteria, as well as other histopathologic features used in the clinical setting. Considerable inter-observer variability has been reported for some of the histopathologic features used in staging and collected as part of pathology reports. While

overall inter-observer concordance of Breslow thickness is higher than that reported for other features, such as ulceration or mitotic rate, its accuracy and interpretation can be impeded by regression and transection at the lesion base. Discrepancies in measuring and reporting histopathologic features can impact melanoma diagnosis and prognostic staging with subsequent effects on definitive surgery, follow-up care and surveillance, SLN biopsy (SLNB) decisions, and treatment eligibility.

As summarized in Table 1, several studies have evaluated the concordance between pathology reports from referring centers that underwent re-review at academic referral centers¹⁻⁵. While it should be noted that these studies evaluated concordance under previous versions of AJCC staging, the histopathologic features they considered are still recommended as additional factors driving clinical care under the current AJCC edition.

REPORTED STUDIES

A single-center study of 420 cases of in situ and thin melanomas that underwent standard re-review upon referral to Moffitt Cancer Center found 24% discordance in pathologic tumor staging, which led to changes in recommended surgical margins for 12% and SLNB for 16%². Notably, 76% of these referrals were originally evaluated by dermatopathologists, suggesting discordance exists even among those with specialized training. Similarly, of 588 cases that underwent routine re-evaluation upon referral to Emory University, 19% of cases had a change in pathologic staging (17% change in clinical stage), resulting in a change in SLNB recommendation for 8% and follow-up for 5% based on national guidelines¹. There was 66% discordance in Breslow thickness alone with an average

difference of 0.38 mm, but the differences in discordant measurements were not numerically statistically significant. A large study of cases referred to the Melanoma Institute of Australia (MIA) found 19% discordance in T stage among 3,620 cases with an agreed-upon diagnosis of invasive melanoma⁶. Of 4,759 cases of in situ and invasive melanoma, changes in excision margins were recommended in 11% of cases after MIA review. Of 4,719 cases with adequate pathology reporting to make recommendations on SLN biopsy, 8.6% underwent a change in SLNB recommendation after MIA review, including both patients for whom SLNB would and would not have been recommended.

Changes in SLNB results have also been reported after review of the same SLN pathology slides of melanoma cases referred to the University of Michigan³. Thirteen out of 167 (8%) SLN cases had discordant interpretations between the original pathology review and subsequent review at the University of Michigan. It is possible that a lack of expert review prior to referral contributed to these discrepancies, as only 3 out of the 13 discordant cases were initially reviewed by dermatopathologists. Five of the 13 discordant cases were re-diagnosed as SLN negative, permitting the majority of these patients avoidance of completion lymph node dissection (CLND), and one patient discontinued interferon therapy as a result of down-staging. Eight of the discrepant cases were upstaged to SLN positive; two of these patients had additional nodal disease upon CLND and subsequently developed distant metastatic disease, from which one patient died.

While numerous studies have shown that Breslow thickness, ulceration, SLN status, and other clinicopathologic features have significant prognostic value in melanoma, the

Table 1. Summary of reported histopathologic discordance and changes in recommended management.

Study	Design referral center; number of cases and type; years evaluated	Discordance in staging % (n/total)	Change in patient care recommendations (%)
Santillan et al. J Clin Oncol 2010; 28(3): 481-6	Moffitt Cancer Center; 420 in situ and invasive melanoma cases; 2006-2009	24% (97/420)	Surgical margins: 12% (52/420) SLNB: 16% (67/420)
Patrawala et al. J Am Acad Derm 2016; 74(1):75-80	Emory University Hospital; 488 in situ and invasive melanoma cases; 2009-2014	19% (114/598; pathologic stage) 17% (101/598; clinical stage)	Surgical margins: 10% (58/588) SLNB: 8% (45/588) Follow-up: 5% (29/588)
Niebling et al. Ann Surg Onc 2014; 21:2245-51	Melanoma Institute Australia; 5011 consecutive in situ and invasive melanoma cases; 2002-2011	22% (945/4269; melanoma T stage) 20% (712/3620; invasive melanoma T stage)	Surgical margins: 11% (531/4759) SLNB: 9% (407/4719)
Dandekar et al. Ann Surg Onc 2014; 21:3406-11	University of Michigan; 167 SLNs; 2006-2009	8% (13/167) SLN+ to SLN-: 3% (5/167) SLN- to SLN+: 5% (8/167)	SLNB: 8% (13/167)
Monshizadeh et al. Pathology 2012; 44(5): 441-7	Western Australian Melanoma Advisory Service; 721 cases of in situ and invasive melanoma cases; 2000-2009	18% (N/R; pathologic stage) 16% (N/R; clinical stage)	N/R
Murali et al. Ann Surg 2009; 249(4):641-7	Sydney Melanoma Unit; 912 cases; 2-year study period (2002 AJCC staging)	3.8% (pathologic stage I-II) 17.7% (T stage) 16.3% (AJCC substage)	N/R

N/R: not reported SLN: sentinel lymph node; SLNB: sentinel lymph node biopsy

subjectivity of histopathologic evaluation can have serious implications for melanoma patient care. National guidelines make recommendations based on AJCC stage and substage for decision-making on SLNB, frequency of follow-up visits, surveillance imaging, and adjuvant therapy. Therefore, pathologic assessment plays a critical role in driving management decisions for melanoma patients. In several cancers, molecular testing through gene expression profiling has been developed and implemented clinically as an additional, objective tool for use in conjunction with traditional staging methods to guide informed and individualized decisions on disease management. In cutaneous melanoma, a 31-gene expression profile (31-GEP) test has been well-validated for its prognostic accuracy⁷⁻⁹. It has demonstrated a high degree of technical reliability, with 99% inter-assay and 100% intra-assay concordance in classifying melanomas as low (Class 1) or high (Class 2) risk for metastasis¹⁰. The 31-GEP test result can be used to enhance the sensitivity of traditional staging for the identification of high-risk patients, providing additional assurance of appropriate risk stratification and subsequent development of optimal individualized management plans^{11,12}. Additionally, in melanoma cases with equivocal histopathology for staging, such as those described in the literature summarized herein (Table 1), the 31-GEP test also has clinical value in objectively interrogating tumor biology at the molecular level.

DISCUSSION

As recognized by AJCC, melanoma staging, just as it has in the past, will continue to change as contemporary data supports additional prognostic features. In light of the studies summarized here, additional factors, including molecular analysis, could improve the reliability of staging and positively

influence patient care by facilitating accurate and objective assessment of the tumor and its biological potential for metastasis.

Conflict of Interest Disclosures: AG participated in a research fellowship that was partially funded by Castle Biosciences, Inc. CJC has served as a consultant and speaker for Castle Biosciences, Inc. Editorial assistance was provided by Kristen Plasseraud, PhD, an employee and options holder of Castle Biosciences, Inc..

Funding: None.

Corresponding Author:

Alex Glazer, MD
University of Arizona
Tucson, AZ
alexglazer@gmail.com

References:

1. Patrawala S, Maley A, Greskovich C, et al. Discordance of histopathologic parameters in cutaneous melanoma: Clinical implications. *Journal of the American Academy of Dermatology*. 2016;74(1):75-80.
2. Santillan AA, Messina JL, Marzban SS, Crespo G, Sondak VK, Zager JS. Pathology review of thin melanoma and melanoma in situ in a multidisciplinary melanoma clinic: impact on treatment decisions. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2010;28(3):481-486.
3. Dandekar M, Lowe L, Fullen DR, et al. Discordance in histopathologic evaluation of melanoma sentinel lymph node biopsy with clinical follow-up: results from a prospectively collected database. *Annals of surgical oncology*. 2014;21(11):3406-3411.
4. Monshizadeh L, Hanikeri M, Beer TW, Heenan PJ. A critical review of melanoma pathology reports for patients referred to the Western

- Australian Melanoma Advisory Service. *Pathology*. 2012;44(5):441-447.
5. Murali R, Hughes MT, Fitzgerald P, Thompson JF, Scolyer RA. Interobserver variation in the histopathologic reporting of key prognostic parameters, particularly clark level, affects pathologic staging of primary cutaneous melanoma. *Annals of surgery*. 2009;249(4):641-647.
 6. Niebling MG, Haydu LE, Karim RZ, Thompson JF, Scolyer RA. Pathology review significantly affects diagnosis and treatment of melanoma patients: an analysis of 5011 patients treated at a melanoma treatment center. *Annals of surgical oncology*. 2014;21(7):2245-2251.
 7. Gastman BR, Gerami P, Kurley SJ, Cook RW, Leachman S, Vetto JT. Identification of patients at risk for metastasis using a prognostic 31-gene expression profile in subpopulations of melanoma patients with favorable outcomes by standard criteria. *Journal of the American Academy of Dermatology*. 2018;In press.
 8. Hsueh EC, DeBloom JR, Lee J, et al. Interim analysis of survival in a prospective, multi-center registry cohort of cutaneous melanoma tested with a prognostic 31-gene expression profile test. *Journal of hematology & oncology*. 2017;10(1):152.
 9. Greenhaw BN, Zitelli JA, Brodland DG. Estimation of Prognosis in Invasive Cutaneous Melanoma: An Independent Study of the Accuracy of a Gene Expression Profile Test. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]*. 2018.
 10. Cook RW, Middlebrook B, Wilkinson J, et al. Analytic validity of DecisionDx-Melanoma, a gene expression profile test for determining metastatic risk in melanoma patients. *Diagnostic pathology*. 2018;13(1):13.
 11. Dillon LD, Gadzia JE, Davidson RS, et al. Prospective, Multicenter Clinical Impact Evaluation of a 31-Gene Expression Profile Test for Management of Melanoma Patients. *SKIN, The Journal of Cutaneous Medicine*. 2018;2(3):111-121.
 12. Schuitevoerder D, Heath M, Cook RW, et al. Impact of Gene Expression Profiling on Decision-Making in Clinically Node Negative Melanoma Patients after Surgical Staging. *Journal of drugs in dermatology : JDD*. 2018;17(2):196-199.