Variability in mitotic figures in serial sections of thin melanomas

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Background: T1 melanoma staging is significantly affected by tissue sampling approaches, which have not been well characterized.

Objective: We sought to characterize presence of mitotic figures across a minimum of 5 sequential sections of T1 melanomas.

Methods: A cohort of T1 melanomas with either 5 (single section per slide) or 10 (2 sections per slide) sequential sections (5-μm thickness) per case were prepared and examined for mitotic figures.

Results: In all, 44 of 82 T1 melanomas (54%) were classified as T1b. The number of sections with a mitotic figure present ranged from only 1 of 5 sections (n = 5 of 44 cases, 11.4%) to all 5 (n = 20 of 44 cases, 45.5%). A sequential approach versus a nonsequential approach did not appear to matter.

Limitation: Cases were taken from a single pathology practice in the Pacific Northwest, which may not generalize to other populations in the United States.

Conclusion: The variation in the presence of mitotic figures within sequential sections supports reviewing 3 to 5 sections to fulfill American Joint Committee on Cancer recommendations. The prognostic significance of a T1b melanoma with a rare mitotic figure on a single section versus a T1b melanoma with mitotic figures on multiple sections deserves more attention to see if further subclassification is possible or even necessary. (J Am Acad Dermatol 2014;71:1204-11.)

Key words: accuracy; American Joint Committee on Cancer TNM staging; mitosis; mitotic rate; reproducibility; T1b; variability.

Correct melanoma staging is significantly affected by tissue sampling approaches, as the particular approach one laboratory takes compared with another could influence the prognostic determinants (Breslow depth, mitoses, and epidermal ulceration).[1-6] Mitotic figures can be focal (eg, hot spots) and accurate documentation of their presence then becomes a function of adequate sampling; however, thorough sampling is discouraged because of the need to preserve tissue for future molecular testing and because the studies demonstrating the importance of mitogenicity did not use an exhaustive sampling technique.

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Although prior studies have shown interobserver variability on what constitutes a mitotic figure,[7] we are unaware of any studies that have examined the equivalence of serial sections in noting the presence or absence of a mitotic figure. Without evidence supporting the assumption that mitotic figures are consistently present within sections of T1b melanomas, clinicians cannot safely presume that the biopsy was adequately sampled.

As part of a national study of pathologists' diagnostic interpretation that involved developing a test set of melanocytic lesions, we noted significant variability in the presence of mitotic figures within sequential sections of thin invasive melanomas. Given the importance of mitoses in T1 melanoma classification, we evaluated sequential tissue sections from all thin invasive melanomas specifically to characterize variability in the presence of mitotic figures across sequential sections of thin melanomas. This would allow us to consider implications of sampling on staging criteria.

CAPSULE SUMMARY

- A rigorous approach to accurately capture mitotic activity and expected density of mitoses in T1b melanomas is needed.
- We describe the variability in mitoses between serial sections and the minimum number of sections to review.
- This will increase accuracy and should help prevent under diagnosis.

METHODS

Patient cohort

Skin lesions biopsied in 2010 through 2011 were identified from a private dermatopathology practice in Washington State using their in-house database of patient records. New slides were made for each case, with 5-μm sequential sections transferred onto new slides for each case. All procedures were Health Insurance Portability and Accountability Act compliant, and approval was obtained from the University of Washington Institutional Review Board (#41700).

Identification of thin melanomas—panel dermatopathologists' independent reviews and consensus panel review

Development of study materials, including a histology form designed for independent and consensus panel reviews, for the primary National Institutes of Health—funded study of pathologists is published elsewhere.[8] Briefly, 3 internationally recognized dermatopathologists (the panel) each independently reviewed 1 of the first 3 of 5 sequential sections made for each case, blinded to others' interpretations. The panel subsequently met over the course of 6 days to review each patient case together under a multiheaded microscope with the assistance of a fourth pathologist. During these meetings, agreement was obtained on Breslow depth, mitotic rate, and presence of epidermal ulceration for each case. No T1b melanomas showed epidermal ulceration.

Detailed re-evaluation of all thin melanomas and validation of mitotic figures

All thin invasive melanomas (Breslow depth of $\leq$1.00 mm) (n = 85) were pulled for corroboration of mitoses on every section by the lead author (S. R. K.). Confirmation from the laboratory revealed that 3 of these cases were not sequentially cut because of technical difficulties and were thus eliminated from the current study for a final total of 82 T1 melanoma cases. The re-evaluation was not blinded to the panel's consensus findings, because the goal was to supplement the consensus review by accurately identifying the presence or absence of mitotic figures in all sections for each case. Therefore, cases found to have no mitotic figures or only 1 mitotic figure on 1 of the 3 initially reviewed slides received more attention (up to 30 minutes per section) than those with a mitotic figure identified by all 3 panel members. In addition, the fourth and fifth slides, initially intended as backups for the test set, were included in this review.

When a discrepancy in mitotic rate was noted between the evaluation of cases for this study and the consensus panel review or if it was difficult to determine if a mitotic figure was melanocytic or stromal (valid vs invalid, respectively), these cases were reviewed with one of the panel dermatopathologists (M. W. P.) through a multiheaded microscope for final determination. A total of 23 cases were thus re-evaluated and validated for this study, including 18 T1a cases where the presence of a mitotic figure was questioned and 5 T1b cases where the absence of a mitotic figure was questioned. This re-review found 11 T1a cases (19 total sections) and 5 T1b cases (6 total sections) discrepant with the original panel's consensus diagnosis. Fifteen of these cases (10 T1a and 5 T1b) were part of the slides prepared with 2 sections per slide (10 total sequential sections per case), and during the validation review only 1 of the 2 sections on each slide was reviewed because of time