

## Mitotic count (Core)

Multiple studies indicate that mitotic rate in the invasive portion is an important prognostic factor for localised primary melanomas (including very large studies utilizing the methodology for mitotic count determination described below).<sup>1-13</sup>

The number of mitotic figures can vary greatly between different parts of a tumour. For consistency and reproducibility, a standardised method must be used to assess mitotic count.<sup>14</sup> It is recommended that the field diameter of a microscope be formally calibrated using a stage micrometer to determine the number of high-power fields that equates to a 1 mm<sup>2</sup>.

In the 8<sup>th</sup> edition of the American Joint Commission on Cancer (AJCC)/Union for International Cancer Control (UICC) melanoma staging system, the recommended method to enumerate mitotic figures is to find an area in the dermis with obvious mitotic activity (the “hot spot”), and begin the count in this area, then extending the area counted to immediately adjacent non-overlapping high-power fields in a 1 mm<sup>2</sup> area. If no hot spot is identified and the mitotic figures are sparse and randomly scattered, then the count should begin in a field containing a mitosis, then extended to immediately adjacent non-overlapping high-power fields until a 1 mm<sup>2</sup> area of tissue containing melanoma is assessed. When the invasive component of the tumour involves an area <1 mm<sup>2</sup>, a 1 mm<sup>2</sup> area of dermal tissue that includes the tumour should be assessed and recorded as a number per mm<sup>2</sup>. The number of mitotic figures should be listed as a whole number/mm<sup>2</sup>. If no mitotic figures are identified, the mitotic count may be recorded “none identified” or “0/mm<sup>2</sup>”. This methodology for determining the mitotic count of a melanoma has been shown to have excellent interobserver reproducibility including amongst pathologists with widely differing experiences in the assessment of melanocytic tumours.<sup>1</sup>

It is also recommended in 8<sup>th</sup> edition of the AJCC/UICC melanoma staging manual that the mitotic count should be assessed in all primary melanomas (as whole number/mm<sup>2</sup>) for prognostic purposes.

The data that demonstrated the strong prognostic significance of mitotic count were obtained from the melanoma pathology reports of routinely assessed H&E stained sections. It is therefore not recommended that any additional sections be cut and examined (or immunochemical analysis be performed), in excess of those that would normally be used to report and diagnose the melanoma, to determine the mitotic count (i.e., no additional sections should be cut and examined for the purpose of determining the mitotic count; this includes the situation when no mitotic figures are identified on the initial, routinely examined sections).

## References

- 1 Scolyer RA, Shaw HM, Thompson JF, Li LX, Colman MH, Lo S, McCarthy SW, Palmer AA, Nicoll KD, Dutta B, Slobedman E, Watson GF and Stretch JR (2003). Interobserver reproducibility of histopathologic prognostic variables in primary cutaneous melanomas. *American Journal of Surgical Pathology* 27(12):1571–1576.
- 2 Azzola MF, Shaw HM, Thompson JF, Soong S-J, Scolyer RA, Watson GF, Colman MH and Zhang Y (2003). Tumor mitotic rate is a more powerful prognostic indicator than ulceration in patients with primary cutaneous melanoma. Analysis of 3661 patients from a single center. *Cancer* 97(6):1488–1498.

- 3 Barnhill RL, Katzen J, Spatz A, Fine J and Berwick M (2005). The importance of mitotic rate as a prognostic factor for localized cutaneous melanoma. *J Cutan Pathol* 32(4):268–273.
- 4 Gimotty P, Elder D, Fraker D, Botbyl J, Sellers K, Elenitsas R, Ming ME, Schuchter L, Spitz FR, Czerniecki BJ and Guerry D (2007). Identification of high-risk patients among those diagnosed with thin cutaneous melanomas. *Journal of Clinical Oncology* 25(9):1129–1134.
- 5 Ostmeier H, Fuchs B, Otto F, Mawick R, Lippold A, Krieg V and Suter L (1999). Can immunohistochemical markers and mitotic rate improve prognostic precision in patients with primary melanoma? *Cancer* 85(11):2391–2399.
- 6 Retsas S, Henry K, Mohammed MQ and MacRae K (2002). Prognostic factors of cutaneous melanoma and a new staging system proposed by the American Joint Committee on Cancer (AJCC): validation in a cohort of 1284 patients. *European Journal of Cancer* 38(4):511–516.
- 7 Gimotty P, Van Belle P, Elder DE, Murry T, Montone KT, Xu X, Hotz S, Raines S, Ming ME, Wahl P and Guerry D (2005). Biologic and prognostic significance of dermal Ki67 expression, mitoses, and tumorigenicity in thin invasive cutaneous melanoma. *Journal of Clinical Oncology* 23(31):8048–8056.
- 8 Nagore E, Oliver V, Botella-Estrada R, Morena-Picot S, Insa A and Fortea J (2005). Prognostic factors in localized invasive cutaneous melanoma: high value of mitotic rate, vascular invasion and microscopic satellitosis. *Melanoma Res* 15(3):169–177.
- 9 Francken AB, Shaw HM, Thompson JF, Soong SJ, Accortt NA, Azzola MF, Scolyer RA, Milton GW, McCarthy WH, Colman MH and McGovern VJ (2004). The prognostic importance of tumor mitotic rate confirmed in 1317 patients with primary cutaneous melanoma and long follow-up. *Annals of Surgical Oncology* 11(4):426–433.
- 10 Clark W, Jr, Elder D, Guerry D, Braitman L, Trock B, Schultz D, Jynnestvedt M and Halpern A (1989). Model predicting survival in stage I melanoma based on tumor progression. *Journal of the National Cancer Institute* 81(24):1893–1904.
- 11 Thompson JF, Soong SJ, Balch CM, Gershenwald JE, Ding S, Coit DG, Flaherty KT, Gimotty PA, Johnson T, Johnson MM, Leong SP, Ross MI, Byrd DR, Cascinelli N, Cochran AJ, Eggermont AM, McMasters KM, Mihm MC Jr, Morton DL and Sondak VK (2011 Jun 1). Prognostic significance of mitotic rate in localized primary cutaneous melanoma: an analysis of patients in the multi-institutional American Joint Committee on Cancer melanoma staging database. *J Clin Oncol.* 29(16):2199–2205.
- 12 Mandala M, Galli F, Cattaneo L, Merelli B, Rulli E, Ribero S, Quaglini P, De Giorgi V, Pigozzo J, Sileni VC, Chirco A, Ferrucci PF, Occelli M, Imberti G, Piazzalunga D, Massi D, Tondini C and Queirolo P (2017). Mitotic rate correlates with sentinel lymph node status and outcome in cutaneous melanoma greater than 1 millimeter in thickness: A multi-institutional study of 1524 cases. *J Am Acad Dermatol* 76(2):264–273.e262.

- 13 Tejera-Vaquerizo A, Ribero S, Puig S, Boada A, Paradela S, Moreno-Ramirez D, Canueto J, de Unamuno B, Brinca A, Descalzo-Gallego MA, Osella-Abate S, Cassoni P, Carrera C, Vidal-Sicart S, Bennassar A, Rull R, Alos L, Requena C, Bolumar I, Traves V, Pla A, Fernandez-Orland A, Jaka A, Fernandez-Figueres MT, Hilari JM, Gimenez-Xavier P, Vieira R, Botella-Estrada R, Roman-Curto C, Ferrandiz L, Iglesias-Pena N, Ferrandiz C, Malveyh J, Quaglino P and Nagore E (2019). Survival analysis and sentinel lymph node status in thin cutaneous melanoma: A multicenter observational study. *Cancer Med* 8(9):4235-4244.
- 14 Scolyer RA and Thompson JF (2013). Mitotic rate in melanoma should be recorded as the number of mitoses per mm<sup>2</sup> (not per high power field): surgeons tell your pathologists! . *Am J Surg Pathol* 206(1):142-143.