

## Ki-67 proliferation index (Core)

Significant evidence has accumulated that adrenal cortical carcinoma is a proliferation-driven neoplasm<sup>1-4</sup> and the Ki-67 proliferation index, as determined by immunohistochemistry using the Mib-1 antibody,<sup>5</sup> is an important independent prognostic factor.<sup>6-9</sup> Assessment of the Ki-67 proliferation index should be performed on the area of tumour with the highest mitotic counts (i.e., highest grade component) or ‘hot spots’. Determining the Ki-67 proliferation index should be performed by image analysis when available or manual counting if necessary.<sup>10</sup> Although estimating the Ki-67 by simple inspection (‘eyeballing’) is generally not recommended it has been shown to have some prognostic significance and may be used when image analysis and manual counting is not possible.<sup>11</sup>

Grading individual tumours based on Ki-67 proliferation index is not fully established, but some centres use a 3-class system based on the following cut-offs: ≤15% (low grade), 15-≤30 (intermediate grade), and >30% (high grade).<sup>12</sup> Until there is consensus on Ki-67 cut-offs for individual grades, the absolute Ki-67 proliferative index should be recorded.

## References

- 1 Assie G, Letouze E, Fassnacht M, Jouinot A, Luscap W, Barreau O, Omeiri H, Rodriguez S, Perlemoine K, Rene-Corail F, Elarouci N, Sbiera S, Kroiss M, Allolio B, Waldmann J, Quinkler M, Mannelli M, Mantero F, Papathomas T, De Krijger R, Tabarin A, Kerlan V, Baudin E, Tissier F, Dousset B, Groussin L, Amar L, Claußer E, Bertagna X, Ragazzon B, Beuschlein F, Libe R, de Reynies A and Bertherat J (2014). Integrated genomic characterization of adrenocortical carcinoma. *Nat Genet* 46(6):607-612.
- 2 Giordano TJ, Kuick R, Else T, Gauger PG, Vinco M, Bauersfeld J, Sanders D, Thomas DG, Doherty G and Hammer G (2009). Molecular classification and prognostication of adrenocortical tumors by transcriptome profiling. *Clin Cancer Res* 15(2):668-676.
- 3 Mete O, Gucer H, Kefeli M and Asa SL (2018). Diagnostic and Prognostic Biomarkers of Adrenal Cortical Carcinoma. *Am J Surg Pathol* 42(2):201-213.
- 4 Zheng S, Cherniack AD, Dewal N, Moffitt RA, Danilova L, Murray BA, Lerario AM, Else T, Knijnenburg TA, Ciriello G, Kim S, Assie G, Morozova O, Akbani R, Shih J, Hoadley KA, Choueiri TK, Waldmann J, Mete O, Robertson AG, Wu HT, Raphael BJ, Shao L, Meyerson M, Demeure MJ, Beuschlein F, Gill AJ, Sidhu SB, Almeida MQ, Fragoso M, Cope LM, Kebebew E, Habra MA, Whitsett TG, Bussey KJ, Rainey WE, Asa SL, Bertherat J, Fassnacht M, Wheeler DA, Hammer GD, Giordano TJ and Verhaak RGW (2016). Comprehensive Pan-Genomic Characterization of Adrenocortical Carcinoma. *Cancer Cell* 29(5):723-736.
- 5 Gerdes J (1990). Ki-67 and other proliferation markers useful for immunohistological diagnostic and prognostic evaluations in human malignancies. *Semin Cancer Biol* 1(3):199-206.
- 6 Beuschlein F, Weigel J, Saeger W, Kroiss M, Wild V, Daffara F, Libe R, Ardito A, Al Ghuzlan A, Quinkler M, Osswald A, Ronchi CL, de Krijger R, Feelders RA, Waldmann J, Willenberg HS, Deutschbein T, Stell A, Reincke M, Papotti M, Baudin E, Tissier F, Haak HR, Loli P, Terzolo M, Allolio B, Muller HH and Fassnacht M (2015). Major prognostic role of Ki67 in localized adrenocortical carcinoma after complete resection. *J Clin Endocrinol Metab* 100(3):841-849.

- 7 Duregon E, Molinaro L, Volante M, Ventura L, Righi L, Bolla S, Terzolo M, Sapino A and Papotti MG (2014). Comparative diagnostic and prognostic performances of the hematoxylin-eosin and phospho-histone H3 mitotic count and Ki-67 index in adrenocortical carcinoma. *Mod Pathol* 27(9):1246-1254.
- 8 Morimoto R, Satoh F, Murakami O, Suzuki T, Abe T, Tanemoto M, Abe M, Uruno A, Ishidoya S, Arai Y, Takahashi K, Sasano H and Ito S (2008). Immunohistochemistry of a proliferation marker Ki67/MIB1 in adrenocortical carcinomas: Ki67/MIB1 labeling index is a predictor for recurrence of adrenocortical carcinomas. *Endocr J* 55(1):49-55.
- 9 Renaudin K, Smati S, Wargny M, Al Ghuzlan A, Aubert S, Leteurtre E, Patey M, Sibony M, Sturm N, Tissier F, Amar L, Bertherat J, Berthozat C, Chabre O, Do Cao C, Haissaguerre M, Pierre P, Briet C, Vezzosi D, Lifante JC, Pattou F, Mirallie E, Baudin E, Cariou B, Libe and Drui D (2018). Clinicopathological description of 43 oncocytic adrenocortical tumors: importance of Ki-67 in histoprognostic evaluation. *Mod Pathol* 31(11):1708-1716.
- 10 Lu H, Papathomas TG, van Zessen D, Palli I, de Krijger RR, van der Spek PJ, Dinjens WN and Stubbs AP (2014). Automated Selection of Hotspots (ASH): enhanced automated segmentation and adaptive step finding for Ki67 hotspot detection in adrenal cortical cancer. *Diagn Pathol* 9:216.
- 11 Yamazaki Y, Nakamura Y, Shibahara Y, Konosu-Fukaya S, Sato N, Kubota-Nakayama F, Oki Y, Baba S, Midorikawa S, Morimoto R, Satoh F and Sasano H (2016). Comparison of the methods for measuring the Ki-67 labeling index in adrenocortical carcinoma: manual versus digital image analysis. *Hum Pathol* 53:41-50.
- 12 Papathomas TG, Pucci E, Giordano TJ, Lu H, Duregon E, Volante M, Papotti M, Lloyd RV, Tischler AS, van Nederveen FH, Nose V, Erickson L, Mete O, Asa SL, Turchini J, Gill AJ, Matias-Guiu X, Skordilis K, Stephenson TJ, Tissier F, Feeders RA, Smid M, Nigg A, Korpershoek E, van der Spek PJ, Dinjens WN, Stubbs AP and de Krijger RR (2016). An International Ki67 Reproducibility Study in Adrenal Cortical Carcinoma. *Am J Surg Pathol* 40(4):569-576.