Mitotic count (Core)

The clinical significance of mitotic activity depends on the specific tumour-type involved. Documentation of mitotic activity (highest mitotic count) is required for leiomyosarcoma, smooth muscle tumour of uncertain malignant potential (STUMP) and perivascular epithelioid cell tumour (PEComa), and strongly recommended for uterine tumour resembling ovarian sex cord tumour (UTROSCT), inflammatory myofibroblastic tumour (IMT), solitary fibrous tumour and undifferentiated uterine sarcoma. It is optional for other sarcoma types. The 5th edition of the World Health Organization (WHO) Classification of Tumours[1] considers both high power fields (HPF) and mm^2 for counting of mitoses. In addition, the size of the objective field is mentioned.

For leiomyosarcoma and STUMP, mitotic activity constitutes part of the diagnostic definition together with other histologic features including nuclear atypia and tumour cell necrosis. Mitotic count ≥10 mitoses per 2 mm^2 (≥10 mitoses per 10 HPFs if field diameter is 0.55 mm) is used for spindle cell smooth muscle tumours, whereas mitotic count ≥4 mitoses per 2 mm^2 (≥4 mitoses per 10 HPFs if field diameter is 0.55 mm) and ≥2 mitoses per 2 mm^2 (≥2 mitoses per 10 HPFs if field diameter is 0.55 mm) are used for epithelioid and myxoid smooth muscle tumours, respectively.[1] For STUMP, mitotic activity forms part of the diagnostic definition under two scenarios based on the 2020 WHO Classification:[1] 1) tumours with focal/multifocal or diffuse nuclear atypia, and 5-9 mitoses per 2 mm^2 (5-9 mitoses per 10 HPFs if field diameter is 0.55 mm) but lacking tumour cell necrosis; and 2) tumours showing ≥15 mitoses per 2 mm^2 (≥15 mitoses per 10 HPFs if field diameter is 0.55 mm) and lacking nuclear atypia and tumour cell necrosis. It is important to note that degenerative nuclear changes/karyorrhexis may mimic mitotic figures, particularly atypical mitotic figures. It is generally recommended that a formal mitotic count should rely predominantly if not exclusively on counting of typical bipolar mitoses. For PEComa, the presence of any mitotic activity, together with tumour size (≥50 mm), high grade atypia, necrosis and lymphovascular invasion form the criteria for malignancy in the gynaecologic tract.[2-4] For other rare uterine sarcoma types in which mitotic count is part of the risk stratification (e.g., solitary fibrous tumour), mitotic activity should also be documented.

For IMT, there is limited evidence that mitotic count and large tumour size may be associated with more aggressive clinical behaviour.[5,6] For UTROSCT, there is also limited evidence that elevated mitotic counts and necrosis are associated with malignant behaviour.[7] Mitotic activity is generally brisk for undifferentiated uterine sarcoma and mitotic count has been shown to be prognostically relevant in undifferentiated uterine sarcomas (lacking endometrial stromal sarcoma genetic fusions) with tumours showing a mitotic count of >25 mitoses per 2 mm^2 (>25 mitoses per 10 HPFs if field diameter is 0.55 mm) being associated with decreased survival.[8,9]

For adenosarcoma, most tumours demonstrate stromal mitoses (>1 mitosis per 2 mm^2 (>1 mitosis per 10 HPFs if field diameter is 0.55 mm)) but mitotic activity may be minimal or even absent in some cases.[10,11] There is currently no evidence that mitotic count alone is prognostically significant, in contrast to the presence of sarcomatous overgrowth and/or deep myometrial invasion which are associated with worse prognosis.[12-14] With regard to endometrial stromal sarcomas, while low grade endometrial stromal sarcomas tend to exhibit lower mitotic counts than high grade endometrial stromal sarcomas, there is overlap in the range of mitotic activity and the number of mitoses is not used for diagnostic classification. However, most low grade endometrial stromal sarcomas display a mitotic rate of <5 mitoses per 2 mm^2 (<5 mitoses per 10 HPF if field diameter is 0.55 mm) and a finding of high mitotic rate (particularly >10 mitoses) should prompt more thorough tumour sampling and careful histologic evaluation as well as consideration of ancillary studies to exclude high grade endometrial stromal sarcoma or other tumour types. The degree of mitotic activity has no diagnostic or known prognostic significance for recently recognised entities including *SMARCA4*-deficient uterine sarcoma and *NTRK*-rearranged sarcoma. Mitotic activity is typically high in *SMARCA4*-deficient uterine sarcoma and is variable in *NTRK*-rearranged sarcoma.

References

1 WHO Classification of Tumours Editorial Board (2020). *Female Genital Tumours, WHO Classification of Tumours, 5th Edition, Volume 4*. IARC Press, Lyon.

2 Bennett JA, Braga AC, Pinto A, Van de Vijver K, Cornejo K, Pesci A, Zhang L, Morales-Oyarvide V, Kiyokawa T, Zannoni GF, Carlson J, Slavik T, Tornos C, Antonescu CR and Oliva E (2018). Uterine PEComas: A Morphologic, Immunohistochemical, and Molecular Analysis of 32 Tumors. *Am J Surg Pathol* 42(10):1370-1383.

3 Fadare O (2008). Perivascular epithelioid cell tumor (PEComa) of the uterus: an outcome-based clinicopathologic analysis of 41 reported cases. *Adv Anat Pathol* 15(2):63-75.

4 Folpe AL, Mentzel T, Lehr HA, Fisher C, Balzer BL and Weiss SW (2005). Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases and review of the literature. *Am J Surg Pathol* 29(12):1558-1575.

5 Parra-Herran C, Schoolmeester JK, Yuan L, Dal Cin P, Fletcher CD, Quade BJ and Nucci MR (2016). Myxoid Leiomyosarcoma of the Uterus: A Clinicopathologic Analysis of 30 Cases and Review of the Literature With Reappraisal of Its Distinction From Other Uterine Myxoid Mesenchymal Neoplasms. *Am J Surg Pathol* 40(3):285-301.

6 Bennett JA, Nardi V, Rouzbahman M, Morales-Oyarvide V, Nielsen GP and Oliva E (2017). Inflammatory myofibroblastic tumor of the uterus: a clinicopathological, immunohistochemical, and molecular analysis of 13 cases highlighting their broad morphologic spectrum. *Mod Pathol* 30(10):1489-1503.

7 Moore M and McCluggage WG (2017). Uterine tumour resembling ovarian sex cord tumour: first report of a large series with follow-up. *Histopathology* 71(5):751-759.

8 Gremel G, Liew M, Hamzei F, Hardell E, Selling J, Ghaderi M, Stemme S, Pontén F and Carlson JW (2015). A prognosis based classification of undifferentiated uterine sarcomas: identification of mitotic index, hormone receptors and YWHAE-FAM22 translocation status as predictors of survival. *Int J Cancer* 136(7):1608-1618.

9 Hardell E, Josefson S, Ghaderi M, Skeie-Jensen T, Westbom-Fremer S, Cheek EH, Bell D, Selling J, Schoolmeester JK, Måsbäck A, Davidson B and Carlson JW (2017). Validation of a Mitotic Index Cutoff as a Prognostic Marker in Undifferentiated Uterine Sarcomas. *Am J Surg Pathol* 41(9):1231-1237.

10 Howitt BE et al (eds) (2020). Adenosarcoma of the uterine corpus. In: *Female Genital Tumours, WHO Classification of Tumours, 5th Edition, Volume 4*, WHO Classification of Tumours Editorial Board (ed), IARC Press, Lyon.

11 Yemelyanova A et al (eds) (2020). Adenosarcoma of the uterine cervix. In: *Female Genital Tumours, WHO Classification of Tumours, 5th Edition, Volume 4*, WHO Classification of Tumours Editorial Board (ed), IARC Press, Lyon.

12 Clement PB and Scully RE (1990). Mullerian adenosarcoma of the uterus: a clinicopathologic analysis of 100 cases with a review of the literature. *Hum Pathol* 21(4):363-381.

13 Clement PB (1989). Müllerian adenosarcomas of the uterus with sarcomatous overgrowth. A clinicopathological analysis of 10 cases. *Am J Surg Pathol* 13(1):28-38.

14 Zaloudek CJ and Norris HJ (1981). Adenofibroma and adenosarcoma of the uterus: a clinicopathologic study of 35 cases. *Cancer* 48(2):354-366.