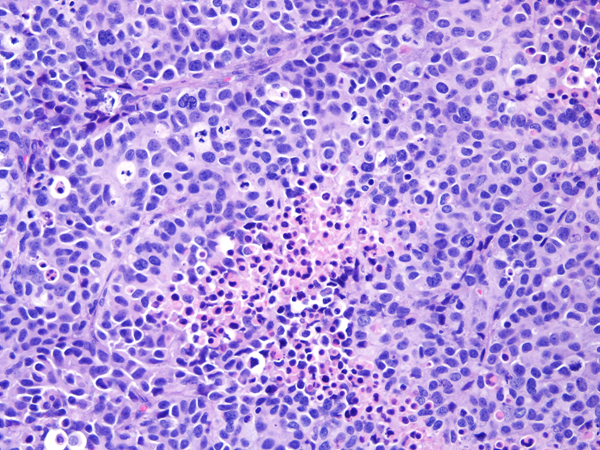
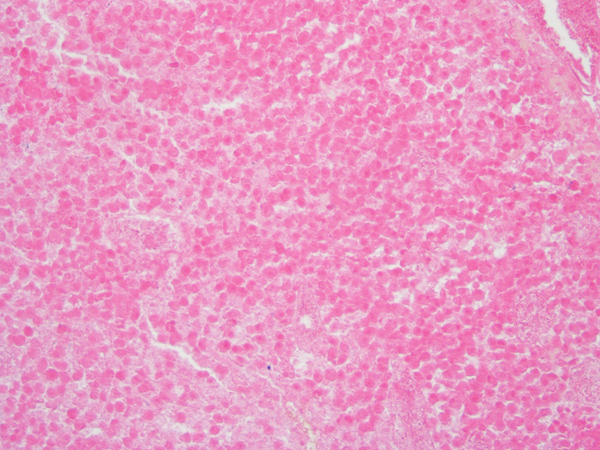
| **Core/**  **Non-core** | **Element name** | **Values** | **Commentary** | **Implementation notes** |
| --- | --- | --- | --- | --- |
| Core | CLINICAL INFORMATION | Multi selection value list (select all that apply)/text:  • Information not provided  • Previous history of endocrine/adrenal tumour or related abnormality, *specify*  • Relevant biopsy/cytology results, *specify*  • Previous surgery/therapy, *specify*  • Relevant familial history, *specify*  • Functional status, *specify*   * Cushing syndrome * Primary aldosteronism (PA) * Virilization * Feminization * Conn syndrome Other, *specify*   • Imaging findings, *specify*  • Other, *specify* | Relevant clinical information (e.g., hypertension, change in body habitus, virilization), the presence of clinical syndromes (e.g., Cushing or primary aldosteronism (PA)) and any evidence (clinical or biochemical) of endocrine hyperfunction or hypofunction should be included. Relevant information regarding familial predisposition to cancer (e.g., Li-Fraumeni, Beckwith-Weidemann and Lynch syndromes), including family history and results of genetic testing, should also be recorded. History of other cancers, which may metastasize to the adrenal glands, should be included.  Any information about prior adrenal biopsy or resection should be included. Relevant information about prior therapy (e.g., chemotherapy) should be included. |  |
| Core | OPERATIVE PROCEDURE | Multi selection value list (select all that apply)/text:  • Not specified  OR  • Adrenalectomy, total  • Adrenalectomy, partial  • Open or laproscopic  • Biopsy (incisional, excisional), *specify*  • Other, *specify* | The type of surgery (open or laparoscopic) should be defined. Laparoscopic surgery is prone to disruption of the gland and tumour capsule, which may lead to difficulties in assessment of tumour size, integrity of the capsule and adequacy of resection, including the evaluation of resection margins.  Regional (para-aortic and peri-aortic) lymph node dissection should be reported when performed under “other”. |  |
| Core | SPECIMEN(S)  SUBMITTED | Multi selection value list (select all that apply)/text:  • Not specified  OR  • Adrenal tumour   * Left * Right   • Lymph nodes, *specify site(s) and laterality*  • Other (e.g., metastatic site), *specify site(s) and laterality* | Specimen laterality is essential. All specimens other than adrenal gland (e.g., lymph nodes, kidney and liver) should also be identified. Gross photography including the cut surface is recommended. | . |
| Core | TUMOUR SITE | Multi selection value list (select all that apply)/numeric/text:  • Not specified  OR  • Adrenal   * Left * Right   • Other, *specify site(s) and laterality* | Tumour site is an important datapoint in fully characterizing any neoplasm. |  |
| Core | SPECIMEN INTEGRITY | Single select value list:  • Specimen intact  • Capsule disrupted  • Fragmented specimen  • Cannot be assessed, *specify* | Documentation of specimen integrity is essential, especially as laparoscopic surgery is being used with increasing frequency and may lead to disruption of the tumour capsule. If the specimen is received intact, with a disrupted capsule, or fragmented should be recorded. |  |
| Core and  Non-core | TUMOUR DIMENSIONS | Numeric/text  • Maximum tumour dimension (largest tumour) \_\_\_ mm  Non-core  • Additional dimensions (largest tumour)  \_\_\_ mm x \_\_\_ mm  OR  • Cannot be assessed, *specify* | Recording tumour dimensions is necessary because all diagnostic systems include tumour size. It is an important component of staging. Documentation of all three dimensions is recommended as it permits determination of tumour volume. If tumour size cannot be obtained from the specimen, it should be obtained from pre-operative imaging studies. |  |
| Core | TUMOUR WEIGHTa | Numeric/text:  • \_\_\_\_g  • Cannot be assessed, *specify* | Accurate determination of tumour weight is essential for complete diagnostic assessment.1 For some of the scoring systems tumour weight is a key element. Tumour weight should be determined after other organs and adipose tissue are removed (trimmed).  **References**  1 Giordano TJ, Chrousos GP, de Krijger RR, Gill AJ, Kawashima A, Koch CA, Medeiros JL, Merino MJ, Papathomas TG, Papotti M, Sasano HR and Weiss LM (2017). Adrenal Cortical Carcinoma. In: *WHO Classification of Tumours of Endocrine Organs, 4th ed*, Lloyd R, Osamura R, Klöppel G and Rosai J (eds), IARC Press, Lyon. | a With other organs and fat removed. |
| Core | HISTOLOGICAL TUMOUR TYPE | Single selection value list/numeric/text:  • Adrenal cortical carcinoma, not otherwise specified (NOS)  • Adrenal cortical carcinoma, oncocytic type  • Adrenal cortical carcinoma, myxoid type  • Adrenal cortical carcinoma, sarcomatoid type  • Adrenal cortical neoplasm of uncertain malignant potentialb  • Other, *specify* | All tumours of the adrenal cortex should be given a type based on the most recent edition of the World Health Organization (WHO) Classification of Tumours of Endocrine Organs.1 Recognition of histological variants of adrenal cortical carcinoma is vital because some tumour types have distinct diagnostic systems. For example, oncocytic tumours are by definition lipid-poor and therefore should not be evaluated by the most commonly used multifactorial scoring system (i.e., Weiss system2) because it includes a proportional assessment of lipid-rich and lipid-poor cells. Rather, other diagnostic systems3 have been developed for these tumours (see **MULTIFACTORIAL SCORING SYSTEMS**).  In addition, knowledge of the histological type can assist with future diagnostic assessments. For example, knowledge that a particular tumour is the myxoid variant might be useful when evaluating a future metastatic biopsy of a myxoid neoplasm.  Some tumours that do not qualify for an outright diagnosis of adrenal cortical carcinoma yet display unusual features for an adenoma can be diagnosed as *adrenal cortical neoplasm of uncertain malignant potential*. This is not considered a distinct entity under the WHO Classification.  **References**  1 Lloyd R, Osamura R, Klöppel G and Rosai J (eds) (2017). *WHO Classification of Tumours of Endocrine Organs, 4th ed*. IARC Press, Lyon.  2 Lau SK and Weiss LM (2009). The Weiss system for evaluating adrenocortical neoplasms: 25 years later. *Hum Pathol* 40(6):757-768.  3 Bisceglia M, Ludovico O, Di Mattia A, Ben-Dor D, Sandbank J, Pasquinelli G, Lau SK and Weiss LM (2004). Adrenocortical oncocytic tumors: report of 10 cases and review of the literature. *Int J Surg Pathol* 12(3):231-243. | Value list from the WHO Classification  of Tumours: Pathology and Genetics of Tumours of Endocrine  Organs (2017).  Note that permission to publish the WHO classification of tumours may be needed in your implementation. It is advisable to check with the International Agency on Cancer research (IARC).  b This is not considered a distinct entity under the WHO Classification. |
| Core | EXTENT OF INVASION | Multi selection value list (select all that apply)/text:  • Cannot be assessed  • Confined to adrenal gland  OR  • Invasion into/through adrenal capsule • Invasion into extra-adrenal structures, *specify*  • Invasion into adjacent organs, *specify* | Tumour extension is pathologically distinct from tumour capsular invasion (see **CAPSULAR INVASION**). Tumour extension assesses the extent of direct tumour cell invasion beyond the adrenal gland proper and whether adjacent structures and organs (e.g., kidney, liver, and pancreas) are directly involved, and is a component of pathological staging (see **MULTIFACTORIAL SCORING SYSTEMS** & **PATHOLOGICAL STAGING**). |  |
| Core | TUMOUR ARCHITECTURE | Single selection value list:  • Diffuse (solid or pattern-less)  • Nested/non-diffuse | In contrast to adrenal cortical adenomas, adrenal cortical carcinomas are typically characterized by diffuse tumour architecture, which is defined as solid or pattern-less sheets of tumour cells. Non-diffuse growth patterns include trabecular, alveolar and nested. The assessment of tumour architecture is a component of the Weiss multifactorial scoring system and similar systems (see **MULTIFACTORIAL SCORING SYSTEMS**).1  **References**  1 Weiss LM (1984). Comparative histologic study of 43 metastasizing and nonmetastasizing adrenocortical tumors. *Am J Surg Pathol* 8(3):163-169. |  |
| Core | LIPID RICH CELLS | Single selection value list:  • ≤25%  • >25% | Lipid rich cells, or clear cells, are a marker of adrenal cortical differentiation and should be documented. The assessment of percentage of lipid-rich, or clear cells, is a component of the Weiss multifactorial scoring system and similar systems (see **MULTIFACTORIAL SCORING SYSTEMS**).1  **References**  1 Weiss LM (1984). Comparative histologic study of 43 metastasizing and nonmetastasizing adrenocortical tumors. *Am J Surg Pathol* 8(3):163-169. |  |
| Core | CAPSULAR INVASION | Single selection value list/text:  • Not identified  • Present  • Cannot be assessed, *specify* | The majority of adrenal cortical carcinomas are encapsulated at the periphery of the tumour. Therefore, the presence of local tumour cell invasion into and through the tumour capsule should be evaluated. There is no accepted definition of what constitutes capsular invasion, with some authorities accepting invasion into but not through the capsule as capsular invasion and others requiring full thickness penetration.1  Extra-adrenal extension into soft tissue and adjacent organs is evaluated separately. The assessment of capsular invasion is a component several multifactorial scoring systems (see **MULTIFACTORIAL SCORING SYSTEMS**).  **References**  Giordano TJ, Chrousos GP, de Krijger RR, Gill AJ, Kawashima A, Koch CA, Medeiros JL, Merino MJ, Papathomas TG, Papotti M, Sasano HR and Weiss LM (2017). Adrenal Cortical Carcinoma. In: *WHO Classification of Tumours of Endocrine Organs, 4th ed*, Lloyd R, Osamura R, Klöppel G and Rosai J (eds), IARC Press, Lyon |  |
| Core | LYMPHATIC INVASION | Single selection value list:  • Not identified  • Present | The determination of intra-tumoural lymphatic invasion is prone to artefact and therefore difficult to determine with accuracy and is discouraged. Therefore, assessment of lymphatic (sinusoidal) invasion should be evaluated at the periphery of the tumour in, and around, the tumour capsule. Immunohistochemical markers are generally not helpful in this evaluation.  The assessment of lymphatic (sinusoidal) invasion is a component of several multifactorial scoring systems (see **MULTIFACTORIAL SCORING SYSTEMS**). |  |
| Core | VASCULAR INVASION | Multi selection value list (select all that apply)/text:  • Not identified  • Present (select all that apply)   * Capillary/lymphatic sized vessels * Vein size (select all that apply) * Adrenal vein * Vena cava * Other, *specify* | The distinction between small vessel invasion (lymphatics and capillaries) and invasion of large vessels (i.e., venous) should be determined as invasion of large vessels is associated with a poor prognosis.  Intravascular tumour cells, admixed with thrombus, is thought to be a reliable marker of vascular invasion with the most prognostic significance.1  The assessment of venous invasion is a component of several multifactorial scoring systems (see **MULTIFACTORIAL SCORING SYSTEMS)**.  **References**  1 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. |  |
| Core | ATYPICAL MITOTIC FIGURES | Single selection value list:  • Not identified  • Present | The collective genomic studies of adrenal cortical carcinoma to date indicate the presence of widespread genomic instability with significant copy number changes.1,2 These genomic alterations can be reflected by the presence of atypical mitoses, which should be documented even when only a single unequivocal atypical mitotic figure is identified. The assessment of atypical mitotic figures is a component of several multifactorial scoring systems (see **MULTIFACTORIAL SCORING SYSTEMS**).  **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, Clauser 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 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. |  |
| Core and  Non-core | NECROSIS | Single selection value list:  • Not identified  • Present  **Extent** (Non-core)   * Focal * Extensive | The presence and degree of bona fide tumour necrosis (i.e., coagulative tumour necrosis) should be documented – refer to Figures 1 and 2. Degenerative type changes with hyalinization, as often seen centrally in adrenal cortical adenomas, should not be considered tumour necrosis. Moreover, areas of haemorrhage or blood extravasation in the absence of necrotic tumour cells, single or in clusters, do not qualify as "necrosis". The presence of tumour necrosis is a component of several multifactorial scoring systems (see **MULTIFACTORIAL SCORING SYSTEMS**).1 There is no accepted definition of focal versus extensive.  See the end of the document for figures.  **Figure 1: Focal coagulative tumour necrosis.** *Reproduced with permission courtesy of Dr Thomas Giordano.*  **Figure 2: Extensive coagulative tumour necrosis.** *Reproduced with permission courtesy of Dr Thomas Giordano.*  **References**  1 Giordano TJ, Chrousos GP, de Krijger RR, Gill AJ, Kawashima A, Koch CA, Medeiros JL, Merino MJ, Papathomas TG, Papotti M, Sasano HR and Weiss LM (2017). *Adrenal Cortical Carcinoma. In: WHO Classification of Tumours of Endocrine Organs, 4th ed*, Lloyd R, Osamura R, Klöppel G and Rosai J (eds), IARC Press, Lyon. |  |
| Core | NUCLEAR GRADE (Fuhrman criteria) | Single selection value list:  • Low (Grade 1 or 2)  • High (Grade 3 or 4) | Nuclear grade is a component of the Weiss multifactorial scoring system,1 using a grading system similar to the Fuhrman criteria for renal cancer,2 and as per the Weiss criteria, grade is assigned based the most abnormal area – refer to Figures 3 and 4.  See the end of the document for figures.  **Figure 3: Low nuclear grade.** *Reproduced with permission courtesy of Dr Thomas Giordano.*  **Figure 4: High nuclear grade.** *Reproduced with permission courtesy of Dr Thomas Giordano.*  **References**  1 Weiss LM (1984). Comparative histologic study of 43 metastasizing and nonmetastasizing adrenocortical tumors. *Am J Surg Pathol* 8(3):163-169.  2 Giordano TJ, Chrousos GP, de Krijger RR, Gill AJ, Kawashima A, Koch CA, Medeiros JL, Merino MJ, Papathomas TG, Papotti M, Sasano HR and Weiss LM (2017). Adrenal Cortical Carcinoma. In: *WHO Classification of Tumours of Endocrine Organs, 4th ed*, Lloyd R, Osamura R, Klöppel G and Rosai J (eds), IARC Press, Lyon. |  |
| Core | MITOTIC COUNT AND HISTOLOGICAL TUMOUR GRADE | Numeric/single selection value list:  • Mitotic figures/10 mm 2 c  AND  • Low grade (≤20 mitoses)  • High grade (>20 mitoses)  • Cannot be assessed, *specify* | It is recommended that reporting pathologists know their field diameter when calculating mitotic count. The literature commonly refers to mitotic count per 50 high power fields (HPFs) without always defining the diameter of the HPFs. The estimate of 50 HPFs equating to 10 mm2 is commonly used as this reflects many microscopes in widespread use.  Architectural grading of adrenal cortical carcinoma is not feasible. Rather, tumour grade has been based on tumour cell proliferation, initially based on mitotic count. Mitotic count is essential for the diagnostic and prognostic evaluation of adrenal cortical tumours and should be performed and reported whenever possible. Mitotic count is also a component of all multifactorial scoring grading systems (see **MULTIFACTORIAL SCORING SYSTEMS**). One of the initial and most established mitotic grading schemes consists of two classes; low grade and high grade, where low grade carcinomas contain ≤20 mitoses/50 HPF and high grade carcinomas contain >20 mitoses/50 HPF.1  Assessment of mitotic count is prone to reproducibility issues,2 largely due to variation in interpretation amongst pathologists of what constitutes a mitotic figure and variation between microscopes. To reduce this variation, only unequivocal mitotic figures should be counted. Pyknotic nuclei from apoptotic bodies should not be counted. In addition, the area of HPFs varies amongst different microscope brands. To reduce this variation, pathologists should determine the number of HPFs that represents 10 mm2 and adjust the number of fields counted accordingly.  **References**  1 Weiss LM, Medeiros LJ and Vickery AL, Jr. (1989). Pathologic features of prognostic significance in adrenocortical carcinoma. *Am J Surg Pathol* 13(3):202-206.  2 Yigit N, Gunal A, Kucukodaci Z, Karslioglu Y, Onguru O and Ozcan A (2013). Are we counting mitoses correctly? *Ann Diagn Pathol* 17(6):536-539. | c 10 mm2 approximates 50 HPFs on some microscopes. |
| Core | Ki-67 PROLIFERATION INDEX | Numeric/single selection value list/text:  • Ki-67 \_\_\_ %  • Cannot be assessed, *specify* | Significant evidence has accumulated that adrenal cortical carcinoma is a proliferation-driven neoplasm1-4 and the Ki-67 proliferation index, as determined by immunohistochemistry using the Mib-1 antibody,5 is an important independent prognostic factor.6-9 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.10 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.11  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).12 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, Clauser 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, Feelders 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. |  |
| Non-core | RETICULIN FRAMEWORK | Single selection value list/text:  • Intact/preserved  • Altered/absent  • Cannot be assessed, *specify* | Histochemical staining to highlight the tumoural reticulin framework (refer to Figures 5 and 6) has diagnostic utility1,2 and has been incorporated into a diagnostic algorithm (see **MULTIFACTORIAL SCORING SYSTEMS**).  See the end of the document for figures.  **Figure 5: Intact reticulin framework in adrenal cortical adenoma.** *Reproduced with permission courtesy of Dr Thomas Giordano.*  **Figure 6: Altered reticulin framework in adrenal cortical carcinoma.** *Reproduced with permission courtesy of Dr Thomas Giordano.*  **References**  1 Duregon E, Fassina A, Volante M, Nesi G, Santi R, Gatti G, Cappellesso R, Dalino Ciaramella P, Ventura L, Gambacorta M, Dei Tos AP, Loli P, Mannelli M, Mantero F, Berruti A, Terzolo M and Papotti M (2013). The reticulin algorithm for adrenocortical tumor diagnosis: a multicentric validation study on 245 unpublished cases. *Am J Surg Pathol* 37(9):1433-1440.  2 Volante M, Bollito E, Sperone P, Tavaglione V, Daffara F, Porpiglia F, Terzolo M, Berruti A and Papotti M (2009). Clinicopathological study of a series of 92 adrenocortical carcinomas: from a proposal of simplified diagnostic algorithm to prognostic stratification. *Histopathology* 55(5):535-543. |  |
| Non-core | MULTIFACTORIAL SCORING SYSTEMS | Single selection value list/numeric:  • Not used  • Specify scoring system(s) used and score(s)   * Weiss system for conventional adrenal cortical neoplasms * Modified Weiss system (Aubert) for conventional adrenal cortical neoplasms * Lin-Weiss-Bisceglia system for oncocytic adrenal cortical neoplasm * Helsinki system for diagnosis and prognosis of conventional and oncocytic adrenal cortical neoplasms * Reticulin algorithm for the diagnosis of conventional and oncocytic adrenal cortical neoplasms Wieneke/AFIP algorithm for paediatric adrenal cortical neoplasms | Several multifactorial scoring systems have been developed for assessment of malignant potential in adrenal cortical neoplasms. Some of the more commonly used ones are presented below along with their intended uses. There is ongoing debate around the validation and reproducibility of these systems so the International Collaboration on Cancer Reporting (ICCR) is unable to recommend any particular approach. ICCR has therefore chosen to ensure that pathologists record as consistently as possible the individual data items that contribute to the scoring systems (core data). Pathologists should use their judgement to select the appropriate system for their practice and individual tumour types.  *1. Weiss system1 for conventional adrenal cortical neoplasms*   * + - High-nuclear grade (yes/no)     - Mitotic count of >5 mitoses per 50 HPFs (yes/no)     - Presence of atypical mitotic figures (yes/no)     - <25% lipid-rich (clear) cells (yes/no)     - Presence of diffuse architecture (yes/no)     - Presence of tumour necrosis (yes/no)     - Presence of venous invasion (yes/no)     - Presence of lymphatic (sinusoidal) invasion (yes/no)     - Presence of capsular invasion (yes/no)   The Weiss system can be deployed for the majority of conventional adrenal cortical tumours, but should not be used for oncocytic tumours because they consistently display densely eosinophilic cytoplasm, a diffuse architecture and high nuclear grade. The Weiss system consists of 9 elements, each worth one point. Tumours with Weiss scores ≥3 are considered to possess malignant potential and should be diagnosed as carcinomas.  *2. Modified Weiss system (Aubert)*2 *for conventional adrenal cortical neoplasms*   * + - 2 x Mitotic count of >5 mitoses per 50 HPFs (yes/no)     - 2 x <25% lipid-rich (clear) cells (yes/no)     - Presence of atypical mitotic figures (yes/no)     - Presence of tumour necrosis (yes/no)     - Presence of capsular invasion (yes/no)   The modified Weiss system can be also deployed for the majority of conventional adrenal cortical tumours, but should not be used for oncocytic tumours. The modified Weiss system places twice the weight on mitotic rate and percent lipid-rich cells and eliminates nuclear grade, architecture, venous invasion and lymphatic invasion. Tumours are thereby graded from 0 to 7, with those tumours scoring ≥3 possessing malignant potential. The modified Weiss system is highly correlated with the original Weiss system.2  *3. Lin-Weiss-Bisceglia system*3 *for oncocytic adrenal cortical neoplasms*  Major criteria   * + - Mitotic count of >5 mitoses per 50 HPFs (yes/no)     - Presence of atypical mitotic figures (yes/no)     - Presence of venous invasion (yes/no)   Minor criteria   * + - Tumour size >10 cm and/or weight <200 g (yes/no)     - Presence of tumour necrosis (yes/no)     - Presence of lymphatic (sinusoidal) invasion (yes/no)     - Presence of capsular invasion (yes/no)   The Lin-Weiss-Bisceglia system is used specifically for oncocytic adrenal cortical neoplasm. Under the Lin-Weiss-Bisceglia system, pathologic features are divided into Major and Minor criteria. The presence of any Major criterion indicates malignant potential. In the absence of Major criteria, the presence of 1-4 Minor criteria indicates uncertain malignant potential.  *4. Helsinki system*4 *for diagnosis and prognosis of conventional and oncocytic adrenal cortical neoplasms*   * + - 3 x Mitotic count of >5 mitoses per 50 HPFs (yes/no)     - 5 x Presence of tumour necrosis (yes/no)     - + Ki-67 proliferation index (percentage)   Tumours with Helsinki scores >8.5 predict metastatic behaviour. The Helsinki score was evaluated and validated using conventional and oncocytic tumours.5  *5. Reticulin algorithm6,7 for the diagnosis of conventional and oncocytic adrenal cortical neoplasms*   * Abnormal/absent Reticulin framework (yes/no)   + - Presence of tumour necrosis (yes/no)     - Mitotic rate of >5 mitoses per 50 HPFs (yes/no)     - Presence of venous invasion (yes/no)   The Reticulin algorithm employs a two-step process. First, the reticulin framework is evaluated by silver-based histochemical staining for reticulin (see **RETICULIN FRAMEWORK**). If disruption of the framework is observed, then the tumour is evaluated for the presence of the criteria above. Tumours with both disrupted reticulin framework and at least one of the other diagnostic criteria are considered to possess malignant potential and can be diagnosed as carcinoma.  *6. Algorithm for paediatric adrenal cortical neoplasms*   * Tumour weight >400 g (yes/no) * Tumour size >10.5 cm (yes/no) * Extra-adrenal extension (yes/no) * Invasion into vena cava (yes/no) * Presence of venous invasion (yes/no) * Presence of capsular invasion (yes/no) * Presence of tumour necrosis (yes/no) * Mitotic count of >15 mitoses per 20 HPFs (yes/no) * Presence of atypical mitotic figures (yes/no)   The above Wieneke/Armed Forces Institute of Pathology (AFIP) algorithm8 reflects the observation that paediatric adrenal cortical neoplasms generally behave better than their adult counterparts despite similar histologic features, which also may reflect their different genomic landscapes.9 Additional efforts to include the Ki-67 proliferation index into the evaluation of paediatric tumours are ongoing.9,10 For these reasons, evaluation of paediatric tumours with Ki-67 is recommended whenever possible.  **References**  1 Weiss LM (1984). Comparative histologic study of 43 metastasizing and nonmetastasizing adrenocortical tumors. *Am J Surg Pathol* 8(3):163-169.  2 Aubert S, Wacrenier A, Leroy X, Devos P, Carnaille B, Proye C, Wemeau JL, Lecomte-Houcke M and Leteurtre E (2002). Weiss system revisited: a clinicopathologic and immunohistochemical study of 49 adrenocortical tumors. *Am J Surg Pathol* 26(12):1612-1619.  3 Bisceglia M, Ludovico O, Di Mattia A, Ben-Dor D, Sandbank J, Pasquinelli G, Lau SK and Weiss LM (2004). Adrenocortical oncocytic tumors: report of 10 cases and review of the literature. *Int J Surg Pathol* 12(3):231-243.  4 Pennanen M, Heiskanen I, Sane T, Remes S, Mustonen H, Haglund C and Arola J (2015). Helsinki score-a novel model for prediction of metastases in adrenocortical carcinomas. *Hum Pathol* 46(3):404-410.  5 Duregon E, Cappellesso R, Maffeis V, Zaggia B, Ventura L, Berruti A, Terzolo M, Fassina A, Volante M and Papotti M (2017). Validation of the prognostic role of the "Helsinki Score" in 225 cases of adrenocortical carcinoma. *Hum Pathol* 62:1-7.  6 Duregon E, Fassina A, Volante M, Nesi G, Santi R, Gatti G, Cappellesso R, Dalino Ciaramella P, Ventura L, Gambacorta M, Dei Tos AP, Loli P, Mannelli M, Mantero F, Berruti A, Terzolo M and Papotti M (2013). The reticulin algorithm for adrenocortical tumor diagnosis: a multicentric validation study on 245 unpublished cases. *Am J Surg Pathol* 37(9):1433-1440.  7 Volante M, Bollito E, Sperone P, Tavaglione V, Daffara F, Porpiglia F, Terzolo M, Berruti A and Papotti M (2009). Clinicopathological study of a series of 92 adrenocortical carcinomas: from a proposal of simplified diagnostic algorithm to prognostic stratification. *Histopathology* 55(5):535-543.  8 Wieneke JA, Thompson LD and Heffess CS (2003). Adrenal cortical neoplasms in the pediatric population: a clinicopathologic and immunophenotypic analysis of 83 patients. *Am J Surg Pathol* 27(7):867-881.  9 Pinto EM, Chen X, Easton J, Finkelstein D, Liu Z, Pounds S, Rodriguez-Galindo C, Lund TC, Mardis ER, Wilson RK, Boggs K, Yergeau D, Cheng J, Mulder HL, Manne J, Jenkins J, Mastellaro MJ, Figueiredo BC, Dyer MA, Pappo A, Zhang J, Downing JR, Ribeiro RC and Zambetti GP (2015). Genomic landscape of paediatric adrenocortical tumours. *Nat Commun* 6:6302.  10 Picard C, Orbach D, Carton M, Brugieres L, Renaudin K, Aubert S, Berrebi D, Galmiche L, Dujardin F, Leblond P, Thomas-Teinturier C and Dijoud F (2018). Revisiting the role of the pathological grading in pediatric adrenal cortical tumors: results from a national cohort study with pathological review. *Mod Pathol* 32(4):546-559. |  |
| Core and  Non-core | MARGIN STATUS | Single selection value list/text/numeric:  • Not involved (R0)  Non-core   * Distance of tumour to closest margin \_\_\_ mm   • Involved  **Extent**   * R1 (microscopic)*, specify if possible*   \_\_\_ mm   * R2 (macroscopic)*, specify if possible* \_\_\_ mm * Location of involved margin(s), *specify if possible*   • Cannot be assessed, *specify* | Assessment of tumour margins is essential because incomplete resection has been associated with local recurrence1 and may be an indication for local radiation therapy.2 R0 is defined as no tumour identified at any margin, R1 as microscopically involving a margin, and R2 as gross involvement of a margin. Large tumours should be generously sampled to adequately assess margin status.  Margin assessment is difficult or error prone in fragmented specimens. In this case use the “cannot be assessed” option.  **References**  1 Glenn JA, Else T, Hughes DT, Cohen MS, Jolly S, Giordano TJ, Worden FP, Gauger PG, Hammer GD and Miller BS (2019). Longitudinal patterns of recurrence in patients with adrenocortical carcinoma. *Surgery* 165(1):186-195.  2 Sabolch A, Else T, Griffith KA, Ben-Josef E, Williams A, Miller BS, Worden F, Hammer GD and Jolly S (2015). Adjuvant radiation therapy improves local control after surgical resection in patients with localized adrenocortical carcinoma. *Int J Radiat Oncol Biol Phys* 92(2):252-259. |  |
| Core and  Non-core | LYMPH NODE STATUS | Single selection value list/text/numeric:  • No nodes submitted or found  • Number of lymph nodes examined  • Not involved  • Involved   * Number of positive lymph nodes * Number cannot be determined   **Extranodal extension (ENE)** (Non-core)  • Not identified  • Present  • Cannot be determined | Extranodal extension (ENE) is defined by unequivocal direct involvement of soft tissue (usually adipose) beyond the capsule of a given lymph node. Involvement of efferent lymph vessels should not be considered ENE. |  |
| Non-core | COEXISTENT PATHOLOGY | Multi selection value list (select all that apply)/text:  • None identified  OR  • Adenoma  • Hyperplasia  • Other, *specify* | It is increasingly becoming evident that adrenal cortical carcinoma may arise from pre-existing lesions such as cortical adenoma. The presence of such pathology should be documented. |  |
| Non-core | ANCILLARY STUDIES | Single selection value list/text:  • Not performed  • Performed, *specify* | **Ancillary studies** (Non-core)  Increasingly, patients with adrenal cortical carcinoma are undergoing significant ancillary testing, not limited to histochemical stains (e.g., reticulin), immunohistochemistry for a variety of lineage-specific (e.g., SF-1), diagnostic and prognostic biomarkers, and next-generation sequencing (NGS)-based panel genotyping. The significance of such testing should be interpreted in the general context of the specific case.  Given the recent recognition that a small percentage of adrenal cortical carcinoma patients have Lynch syndrome,1,2 screening for mismatch repair protein defects by immunohistochemistry may be considered.  **References**  1 Challis BG, Kandasamy N, Powlson AS, Koulouri O, Annamalai AK, Happerfield L, Marker AJ, Arends MJ, Nik-Zainal S and Gurnell M (2016). Familial Adrenocortical Carcinoma in Association With Lynch Syndrome. *J Clin Endocrinol Metab* 101(6):2269-2272.  2 Raymond VM, Everett JN, Furtado LV, Gustafson SL, Jungbluth CR, Gruber SB, Hammer GD, Stoffel EM, Greenson JK, Giordano TJ and Else T (2013). Adrenocortical carcinoma is a lynch syndrome-associated cancer. *J Clin Oncol* 31(24):3012-3018. |  |
| Core | HISTOLOGICALLY CONFIRMED DISTANT METASTASES | Single selection value list/text:  • Not identified  • Not assessed  • Present, *specify site(s)* | The presence of histologically confirmed distant metastases is a critical component of pathological staging.1  **References**  1 Raymond VM, Everett JN, Furtado LV, Gustafson SL, Jungbluth CR, Gruber SB, Hammer GD, Stoffel EM, Greenson JK, Giordano TJ and Else T (2013). Adrenocortical carcinoma is a lynch syndrome-associated cancer. *J Clin Oncol* 31(24):3012-3018. |  |
| Core | PATHOLOGICAL STAGING (UICC TNM 8th edition)d  TNM descriptors | Choose if applicable:  • m - multiple primary tumours  • r - recurrent  • y - post-therapy | The Union for International Cancer Control (UICC) has adopted the staging system proposed by The European Network for the Study of Adrenal Tumours (ENSAT), as outlined in Table 1.1 It is emphasized that venous tumour thrombus qualifies as T4 disease. Although the ENSAT stage grouping is not considered mandatory, it is listed in Table 1 for reference.  **Table 1: Staging system for adrenocortical carcinoma**.1   |  |  | | --- | --- | | **ENSAT stage** | **Definition** | | I | T1, N0, M0 | | II | T2, N0, M0 | | III | T1-T2, N1, M0  T3-T4, N0-N1, M0 | | IV | T1-T4, N0-N1, M1 |   **References**  1 Fassnacht M, Johanssen S, Quinkler M, Bucsky P, Willenberg HS, Beuschlein F, Terzolo M, Mueller HH, Hahner S and Allolio B (2009). Limited prognostic value of the 2004 International Union Against Cancer staging classification for adrenocortical carcinoma: proposal for a Revised TNM Classification. *Cancer* 115(2):243-250. | Note that permission to publish the TNM cancer staging tables may be needed in your implementation. It is advisable to check.  d Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley-Blackwell |
| Core | PRIMARY TUMOUR (pT) | Single selection value list:  • TX Primary tumour cannot be assessed  • T1 Tumour 5 cm or less in greatest dimension, no extra-adrenal invasion  • T2 Tumour greater than 5 cm, no extra-adrenal invasion  • T3 Tumour of any size with local invasion, but not invading adjacent organse  • T4 Tumour of any size with invasion of adjacent organse |  | e Adjacent organs include kidney, diaphragm, great vessels (renal vein or vena cava) pancreas, and liver. |
| Core | REGIONAL LYMPH NODES (PN) | Single selection value list:  • NX Regional lymph nodes cannot be assessed  • N0 No regional lymph node metastasis  • N1 Metastasis in regional lymph node(s) |  |  |

**Figures**

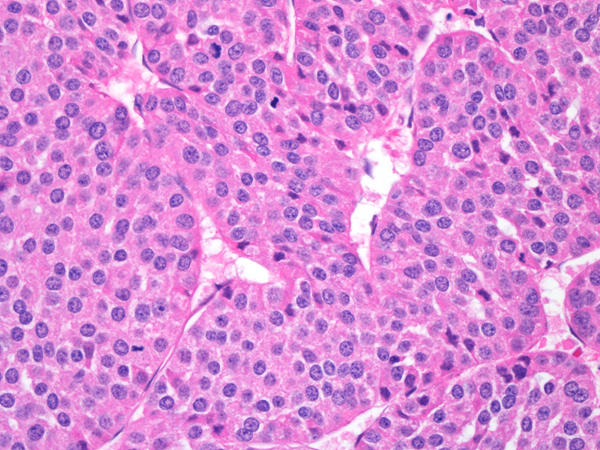
**Figure 1: Focal coagulative tumour necrosis.** *Reproduced with permission courtesy of Dr Thomas Giordano.*

****

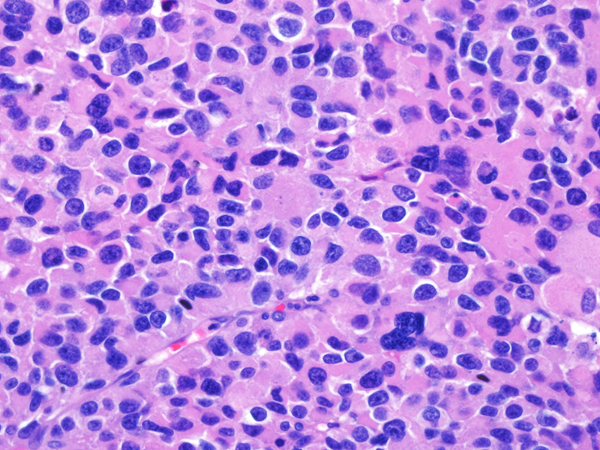
**Figure 2: Extensive coagulative tumour necrosis.** *Reproduced with permission courtesy of Dr Thomas Giordano.*



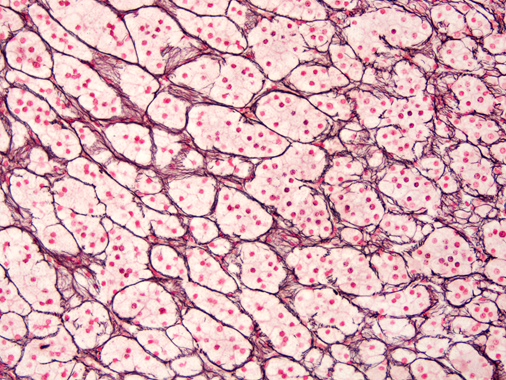
**Figure 3: Low nuclear grade.** *Reproduced with permission courtesy of Dr Thomas Giordano.*

****

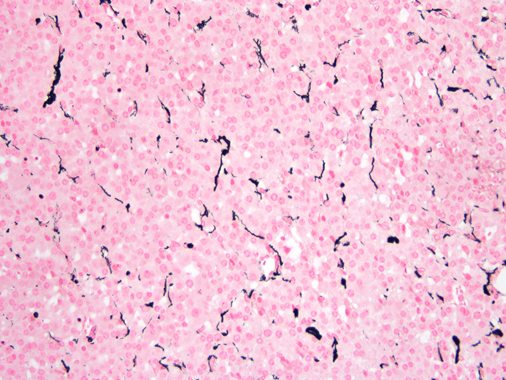
**Figure 4: High nuclear grade.** *Reproduced with permission courtesy of Dr Thomas Giordano.*

****

**Figure 5: Intact reticulin framework in adrenal cortical adenoma.** *Reproduced with permission courtesy of Dr Thomas Giordano.*

****

**Figure 6: Altered reticulin framework in adrenal cortical carcinoma. *Reproduced with permission courtesy of Dr Thomas Giordano.***

****