

Carcinoma of the Adrenal Cortex Histopathology Reporting Guide



Family/Last name

Date of birth

Given name(s)

Patient identifiers

Date of request

Accession/Laboratory number

Elements in **black text** are CORE. Elements in **grey text** are NON-CORE.

indicates multi-select values indicates single select values

SCOPE OF THIS DATASET

CLINICAL INFORMATION (select all that apply) (Note 1)

- 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 Virilization
- Primary aldosteronism (PA) Feminization
- Conn syndrome
- Other, *specify*

- Imaging findings, *specify*

- Other, *specify*

OPERATIVE PROCEDURE (select all that apply) (Note 2)

- Not specified
- Adrenalectomy, total Adrenalectomy, partial
- Open or laproscopic
- Biopsy (incisional, excisional), *specify*

- Other, *specify*

SPECIMEN(S) SUBMITTED (select all that apply) (Note 3)

- Not specified
- Adrenal tumour
 - Left Right
- Lymph nodes, *specify site(s) and laterality*

- Other (e.g., metastatic site), *specify site(s) and laterality*

TUMOUR SITE (select all that apply) (Note 4)

- Not specified
- Adrenal
 - Left Right
- Other, *specify site(s) and laterality*

SPECIMEN INTEGRITY (Note 5)

- Specimen intact
- Capsule disrupted
- Fragmented specimen
- Cannot be assessed, *specify*

TUMOUR DIMENSIONS (Note 6)

Maximum tumour dimension (largest tumour)

Additional dimensions (largest tumour)

 x

- Cannot be assessed, *specify*

TUMOUR WEIGHT^a (Note 7)

- Cannot be assessed, *specify*

^a With other organs and fat removed.

HISTOLOGICAL TUMOUR TYPE (Note 8)

(Value list based on the World Health Organization (WHO) Classification of Tumours: Pathology and Genetics of Tumours of Endocrine Organs (2017))

- 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 potential^b
- Other, *specify*

^b This is not considered a distinct entity under the WHO Classification.

EXTENT OF INVASION (select all that apply) (Note 9)

- Cannot be assessed
- Confined to adrenal gland
- Invasion into/through adrenal capsule
- Invasion into extra-adrenal structures, *specify*

- Invasion into adjacent organs, *specify*

TUMOUR ARCHITECTURE (Note 10)

- Diffuse (solid or pattern-less)
- Nested/non-diffuse

LIPID RICH CELLS (Note 11)

- ≤25%
- >25%

CAPSULAR INVASION (Note 12)

- Not identified
- Present
- Cannot be assessed, *specify*

LYMPHATIC INVASION (Note 13)

- Not identified
- Present

VASCULAR INVASION (Note 14)

- Not identified
- Present (select all that apply)

- Capillary/lymphatic sized vessels

- Vein size (select all that apply)

- Adrenal vein

- Vena cava

- Other, *specify*

ATYPICAL MITOTIC FIGURES (Note 15)

- Not identified
- Present

NECROSIS (Note 16)

- Not identified
- Present

**Extent**

- Focal
- Extensive

NUCLEAR GRADE (Fuhrman criteria) (Note 17)

- Low (Grade 1 or 2)
- High (Grade 3 or 4)

MITOTIC COUNT AND HISTOLOGICAL TUMOUR GRADE (Note 18)

Mitotic figures/10 mm² ^c
AND

- Low grade (≤20 mitoses)
- High grade (>20 mitoses)
- Cannot be assessed, *specify*

^c 10 mm² approximates 50 HPFs on some microscopes.

Ki-67 PROLIFERATION INDEX (Note 19)

Ki-67 %

- Cannot be assessed, *specify*

RETICULIN FRAMEWORK (Note 20)

- Intact/preserved
- Altered/absent
- Cannot be assessed, *specify*

MULTIFACTORIAL SCORING SYSTEMS (Note 21)

- 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 →

MARGIN STATUS (Note 22)

Not involved (R0)
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

LYMPH NODE STATUS (Note 23)

No nodes submitted or found
Number of lymph nodes examined

Not involved

Involved
Number of positive lymph nodes

Number cannot be determined

Extranodal extension

- Not identified
- Present
- Cannot be determined

COEXISTENT PATHOLOGY (select all that apply) (Note 24)

- None identified
- Adenoma
- Hyperplasia
- Other, specify

ANCILLARY STUDIES (Note 25)

- Not performed
- Performed, specify

HISTOLOGICALLY CONFIRMED DISTANT METASTASES (Note 26)

- Not identified
- Not assessed
- Present, specify site(s)

PATHOLOGICAL STAGING (UICC TNM 8th edition)^d (Note 27)

TNM Descriptors (only if applicable) (select all that apply)

- m - multiple primary tumours
- r - recurrent
- y - post-therapy

Primary tumour (pT)

- 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 organs^e
- T4 Tumour of any size with invasion of adjacent organs^e

^e Adjacent organs include kidney, diaphragm, great vessels (renal vein or vena cava) pancreas, and liver.

Regional lymph nodes (pN)

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in regional lymph node(s)

^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.

Definitions

CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the NHMRC levels of evidence¹). In rare circumstances, where level III-2 evidence is not available an element may be made a CORE element where there is unanimous agreement in the expert committee. An appropriate staging system e.g., Pathological TNM staging would normally be included as a CORE element.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of the Dataset Authoring Committee.

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Scope

The dataset has been developed for the pathology reporting of malignant adrenal cortical resection specimens. Borderline (low-malignant potential lesions) are included, along with paediatric adrenal cortical carcinomas. Neuroblastoma, sarcoma and lymphoma are not covered in the dataset. Core needle biopsies, benign lesions and tumours and metastasis are not included. Tumours of the adrenal medulla (e.g., phaeochromocytoma) are dealt with in a separate dataset.

This dataset is designed for the reporting of a single laterality of specimen i.e., left or right. If both are submitted then separate datasets should be completed.

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Note 1 – Clinical information (Core)

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.

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Note 2 – Operative procedure (Core)

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”.

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Note 3 – Specimen(s) submitted (Core)

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.

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Note 4 – Tumour site (Core)

Tumour site is an important datapoint in fully characterizing any neoplasm.

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Note 5 – Specimen integrity (Core)

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.

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Note 6 – Tumour dimensions (Core and Non-core)

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.

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Note 7 – Tumour weight (Core)

Accurate determination of tumour weight is essential for complete diagnostic assessment.² 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).

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Note 8 – Histological tumour type (Core)

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.³ 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 system⁴) because it includes a proportional assessment of lipid-rich and lipid-poor cells. Rather, other diagnostic systems⁵ have been developed for these tumours (see **Note 21 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.

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Note 9 – Extent of invasion (Core)

Tumour extension is pathologically distinct from tumour capsular invasion (see **Note 12 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 **Note 21 MULTIFACTORIAL SCORING SYSTEMS & Note 27 PATHOLOGICAL STAGING**).

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Note 10 – Tumour architecture (Core)

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 **Note 21 MULTIFACTORIAL SCORING SYSTEMS**).⁶

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Note 11 – Lipid rich cells (Core)

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 **Note 21 MULTIFACTORIAL SCORING SYSTEMS**).⁶

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Note 12 – Capsular invasion (Core)

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.²

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 **Note 21 MULTIFACTORIAL SCORING SYSTEMS**).

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Note 13 – Lymphatic invasion (Core)

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 **Note 21 MULTIFACTORIAL SCORING SYSTEMS**).

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Note 14 – Vascular invasion (Core)

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.⁷

The assessment of venous invasion is a component of several multifactorial scoring systems (see **Note 21 MULTIFACTORIAL SCORING SYSTEMS**).

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Note 15 – Atypical mitotic figures (Core)

The collective genomic studies of adrenal cortical carcinoma to date indicate the presence of widespread genomic instability with significant copy number changes.^{8,9} 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 **Note 21 MULTIFACTORIAL SCORING SYSTEMS**).

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Note 16 – Necrosis (Core and Non-core)

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 **Note 21 MULTIFACTORIAL SCORING SYSTEMS**).² There is no accepted definition of focal versus extensive.

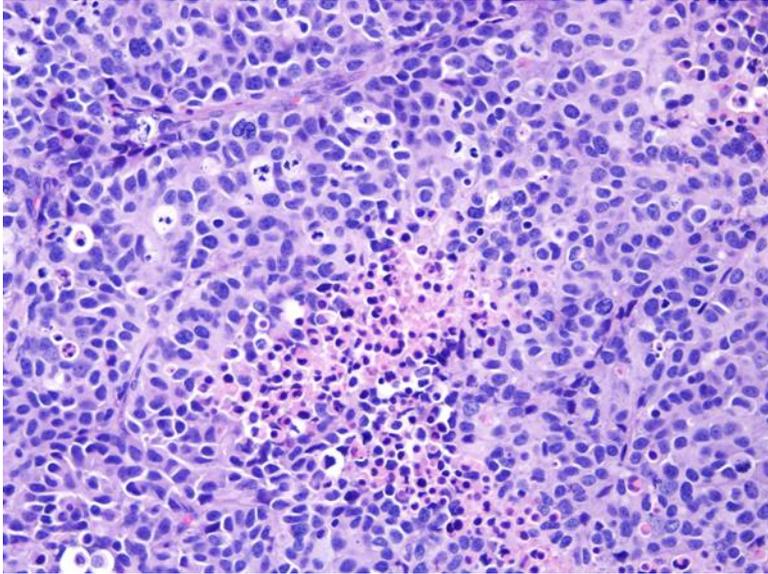


Figure 1: Focal coagulative tumour necrosis. *Reproduced with permission courtesy of Dr Thomas Giordano.*

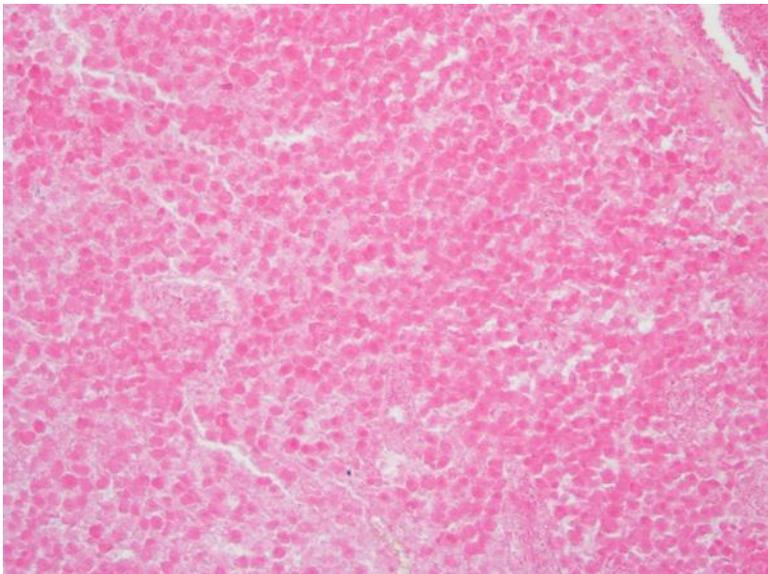


Figure 2: Extensive coagulative tumour necrosis. *Reproduced with permission courtesy of Dr Thomas Giordano.*

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Note 17 – Nuclear grade (Core)

Nuclear grade is a component of the Weiss multifactorial scoring system,⁶ 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.

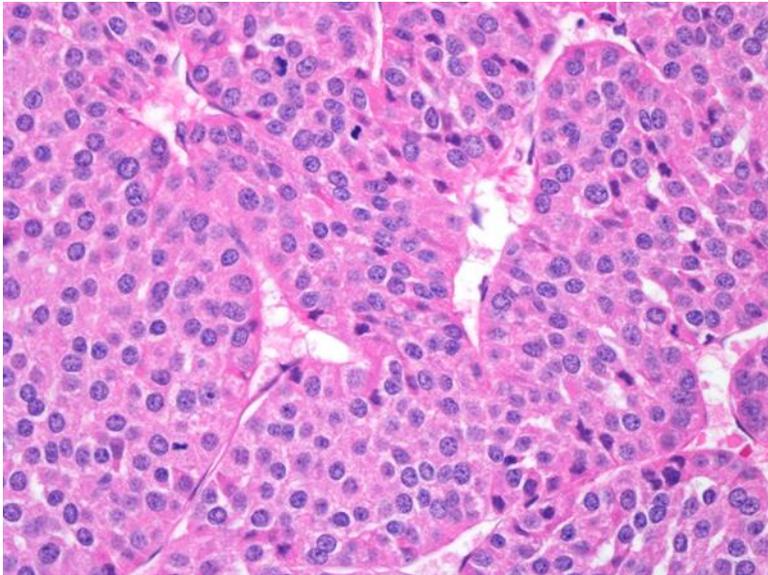


Figure 3: Low nuclear grade. *Reproduced with permission courtesy of Dr Thomas Giordano.*

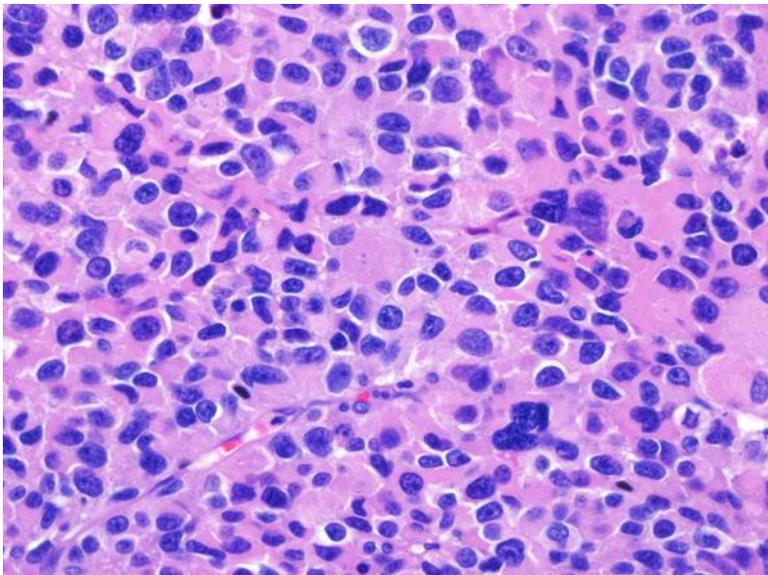


Figure 4: High nuclear grade. *Reproduced with permission courtesy of Dr Thomas Giordano.*

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Note 18 – Mitotic count and histological tumour grade (Core)

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 **Note 21 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.¹⁰

Assessment of mitotic count is prone to reproducibility issues,¹¹ 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.

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Note 19 – Ki-67 proliferation index (Core)

Significant evidence has accumulated that adrenal cortical carcinoma is a proliferation-driven neoplasm^{7-9,12} and the Ki-67 proliferation index, as determined by immunohistochemistry using the Mib-1 antibody,¹³ is an important independent prognostic factor.¹⁴⁻¹⁷ 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.¹⁸ 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.¹⁹

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).²⁰ Until there is consensus on Ki-67 cut-offs for individual grades, the absolute Ki-67 proliferative index should be recorded.

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Note 20 – Reticulin framework (Non-core)

Histochemical staining to highlight the tumoural reticulin framework (refer to Figures 5 and 6) has diagnostic utility^{21,22} and has been incorporated into a diagnostic algorithm (see **Note 21 MULTIFACTORIAL SCORING SYSTEMS**).

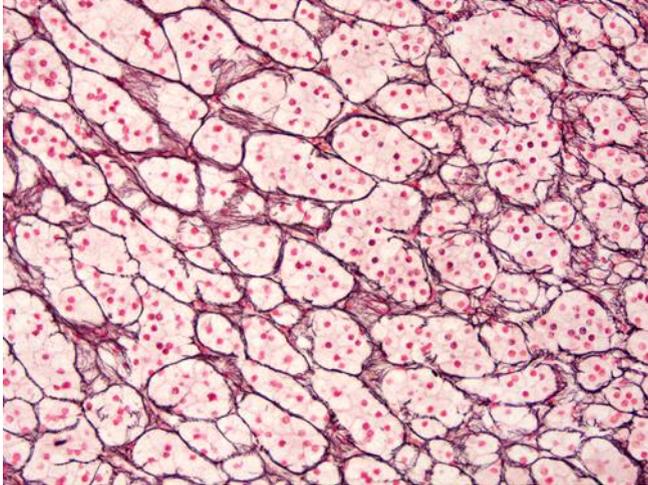


Figure 5: Intact reticulin framework in adrenal cortical adenoma. *Reproduced with permission courtesy of Dr Thomas Giordano.*

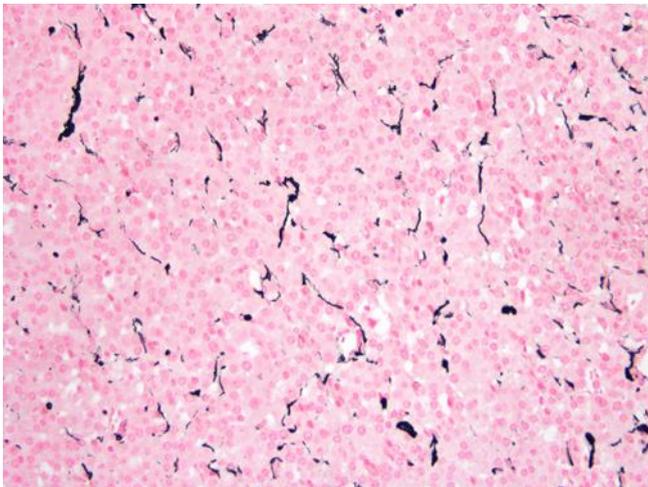


Figure 6: Altered reticulin framework in adrenal cortical carcinoma. *Reproduced with permission courtesy of Dr Thomas Giordano.*

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Note 21 – Multifactorial scoring systems (Non-core)

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 system⁶ 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)²³ 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.²³

3. *Lin-Weiss-Bisceglia system*⁵ 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*²⁴ 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.²⁵

5. *Reticulin algorithm*^{21,22} 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 **Note 20 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) algorithm²⁶ 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.²⁷ Additional efforts to include the Ki-67 proliferation index into the evaluation of paediatric tumours are ongoing.^{27,28} For these reasons, evaluation of paediatric tumours with Ki-67 is recommended whenever possible.

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Note 22 – Margin status (Core and Non-core)

Assessment of tumour margins is essential because incomplete resection has been associated with local recurrence²⁹ and may be an indication for local radiation therapy.³⁰ 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.

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Note 23 – Lymph node status (Core and Non-core)

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.

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Note 24 – Coexistent pathology (Non-core)

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.

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Note 25 – 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,^{31,32} screening for mismatch repair protein defects by immunohistochemistry may be considered.

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Note 26 – Histologically confirmed distant metastases (Core)

The presence of histologically confirmed distant metastases is a critical component of pathological staging.³²

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Note 27 – Pathological staging (Core)

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 1.³³ 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.³³

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

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References

- 1 Merlin T, Weston A and Tooher R (2009). Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Med Res Methodol* 9:34.
- 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.
- 3 Lloyd R, Osamura R, Klöppel G and Rosai J (eds) (2017). *WHO Classification of Tumours of Endocrine Organs, 4th ed*. IARC Press, Lyon.
- 4 Lau SK and Weiss LM (2009). The Weiss system for evaluating adrenocortical neoplasms: 25 years later. *Hum Pathol* 40(6):757-768.
- 5 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.
- 6 Weiss LM (1984). Comparative histologic study of 43 metastasizing and nonmetastasizing adrenocortical tumors. *Am J Surg Pathol* 8(3):163-169.
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