Carcinoma of the Adrenal Cortex Histopathology Reporting Guide

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

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 (Note 1)

◯ Information not provided
◯ Information provided (select all that apply)

- ☐ Previous history of endocrine/adrenal tumour or related abnormality, *specify*
- ☐ Relevant biopsy/cytology results, *specify*
- ☐ Imaging findings, *specify*
- ☐ Previous surgery/therapy, *specify*
- ☐ Relevant familial history, *specify*
- ☐ Clinical endocrine status
  - ☐ Non-functioning
  - ☐ Tumour-related, autonomous sex steroid excess
  - ☐ Adrenocorticotropic hormone (ACTH)-independent hypercortisolism
  - ☐ Other, *specify*
  - ◯ Cannot be assessed
- ☐ Other clinical information, *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 node(s), *specify site(s) and laterality*
☐ Other (e.g., metastatic site), *specify site(s) and laterality*

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

◯ Cannot be assessed
☐ Adrenal
  ☐ Left ☐ Right
☐ Other, *specify site(s) and laterality*

SPECIMEN INTEGRITY (Note 5)

◯ Specimen intact
◯ Capsule disrupted
◯ Fragmented/morcellated specimen
◯ Cannot be assessed, *specify*

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TUMOUR DIMENSIONS (Note 6)

Maximum tumour dimension (largest tumour)

mm

Additional dimensions (largest tumour)

mm x mm

- ◯ Cannot be assessed, *specify*

TUMOUR WEIGHT[a] (Note 7)

g

- ◯ Cannot be assessed, *specify*

[a] *With other organs and fat removed.*

BLOCK IDENTIFICATION KEY (Note 8)

(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

HISTOLOGICAL TUMOUR TYPE (Note 9)

(Value list based on the World Health Organization (WHO) Classification of Tumours of Endocrine Organs (2025))

- ◯ 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 10)

- ◯ Cannot be assessed
- ◯ Confined to adrenal gland
- ☐ Invasion into/through adrenal capsule
- ☐ Invasion into extra-adrenal structure(s), *specify*
- ☐ Invasion into adjacent organ(s), *specify*

TUMOUR ARCHITECTURE (Note 11)

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

LIPID RICH CELLS (Note 12)

- ◯ ≤25%
- ◯ >25%

CAPSULAR INVASION (Note 13)

- ◯ Not identified
- ◯ Present

LYMPHATIC (SINUSOIDAL) INVASION (Note 14)

- ◯ Not identified
- ◯ Present

VASCULAR INVASION (Note 15)

- ◯ Not identified
- ◯ Present (select all that apply)
  - ☐ Capillary
  - ☐ Vein
    - ☐ Adrenal vein
    - ☐ Vena cava
    - ☐ Other, *specify*

ATYPICAL MITOTIC FIGURES (Note 16)

- ◯ Not identified
- ◯ Present

TUMOUR NECROSIS (Note 17)

- ◯ Not identified
- ◯ Present

NUCLEAR GRADE (Note 18)

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

MITOTIC COUNT AND HISTOLOGICAL TUMOUR GRADE (Note 19)

Mitotic figures/10 mm^2

AND

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

Ki-67 PROLIFERATION INDEX (Note 20)

%

- ◯ Cannot be assessed, *specify*

RETICULIN FRAMEWORK (Note 21)

- ◯ Intact/preserved
- ◯ Altered/absent

MULTIFACTORIAL SCORING SYSTEMS (Note 22)

- ○ Not used
- ○ Used, *specify scoring system(s) and score(s)* (select all that apply)
  - ☐ 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 neoplasm →

MARGIN STATUS (Note 23)

- ○ Not involved (R0)
- ○ Involved

Extent

- ○ R1 (microscopic), *specify if possible*
- ○ R2 (macroscopic), *specify if possible*

Location of involved margin(s), *specify if possible*

- ○ Cannot be assessed, *specify*

LYMPH NODE STATUS (Note 24)

- ○ Cannot be assessed
- ○ No nodes submitted or found

Number of lymph nodes examined

- ○ Not involved
- ○ Involved

Number of involved lymph nodes

- ○ Number cannot be determined

Extranodal extension[c]

- ○ Not identified
- ○ Present

[c] *Extranodal extension is synonymous with extracapsular extension/spread.*

COEXISTENT PATHOLOGY (select all that apply) (Note 25)

- ○ None identified
- ☐ Adenoma
- ☐ Hyperplasia
- ☐ Other, *specify*

ANCILLARY STUDIES (Note 26)

- ○ Not performed
- ○ Performed (select all that apply)
  - ☐ Markers of adrenal cortical differentiation
    - ☐ SF-1
    - ☐ Melan-A
    - ☐ Calretinin
    - ☐ Alpha-inhibin
  - ☐ Prognostic/Diagnostic
    - ☐ IGF2
    - ☐ Beta-catenin
    - ☐ p53
    - ☐ CYP11B2
  - ☐ Mismatch repair (MMR) immunohistochemistry
    - ☐ PMS2
    - ☐ MLH1
    - ☐ MSH6
    - ☐ MSH2
  - ☐ Other, *record test(s), methodology and result(s)*

Representative blocks for ancillary studies, *specify those blocks best representing tumour and/or normal tissue for further study*

HISTOLOGICALLY CONFIRMED DISTANT METASTASES (Note 27)

- ○ Not applicable
- ○ Not identified
- ○ Present, *specify site(s)*

PATHOLOGICAL STAGING (UICC TNM 8th edition)[d] (Note 28)

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

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

Primary tumour (pT)

- ○ TX[e] 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[f]
- ○ T4 Tumour of any size with invasion of adjacent organs[f]

Regional lymph nodes (pN)

- ○ NX[e] 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 (incorporating any errata published up until 12th July 2024).*

[e] *TX and NX should be used only if absolutely necessary.*

[f] *Adjacent organs include kidney, diaphragm, great vessels (renal vein or vena cava) pancreas, and liver.*

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 National Health and Medical Research Council (NHMRC) levels of evidence[1]). In rare circumstances, where level III-2 evidence is not available an element may be made a Core element where there is unanimous agreement by the Dataset Authoring Committee (DAC). An appropriate staging system, e.g., Pathological TNM staging, would normally be included as a CORE element.

Molecular and immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world this type of testing is limited by the available resources. In order to encourage the global adoption of ancillary tests for patient benefit, International Collaboration on Cancer Reporting (ICCR) includes the most relevant ancillary testing in ICCR Datasets as CORE elements, especially when they are necessary for the diagnosis. Where the technical capability does not yet exist, laboratories may consider temporarily using these data elements as NON-CORE items.

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. Core needle biopsies, benign adrenal cortical lesions and tumours, as well as sarcoma, lymphoma and metastases are not included. Neuroblastoma and ganglioneuroblastomas are not covered in the dataset. Other tumours of the adrenal medulla (e.g., paraganglioma) 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.

The second edition of this dataset includes changes to align the dataset with the World Health Organization (WHO) Classification of Tumours of Endocrine Organs, 5th edition, 2025.[2]

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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-Wiedemann and Lynch syndromes), including family history and results of genetic testing, should also be recorded. History of other malignant tumours, including melanoma, lung cancer, etc, 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. Any surgical procedure that consistently leads to disruption of the gland and tumour capsule should be avoided, because it 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 characterising 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. The integrity of the specimen should be clearly documented. If the tumour capsule is disrupted or fragmented, this should be recorded. Areas of possible tumour adhesion should be identified and labelled by the surgeon to facilitate pathological evaluation.

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

Recording tumour dimensions is necessary because it is an important component of staging and some diagnostic systems include tumour size. Documentation of all three dimensions is recommended as it permits determination of tumour volume. Reporting of one dimension is a core reporting item, whereas reporting additional dimensions is a non-core reporting item. 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 grossly benign adipose tissue are removed (trimmed). Care should be taken in this process not to disrupt the resection margins.

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Note 8 – Block identification key (Non-core)

The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important should the need for internal or external review arise, in which case a subsequent reviewer would not have seen the gross specimen and would need to know the anatomic sites from which samples were taken for staging purposes. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. It may be useful to have a digital image of the specimen and record of the origin of the tumour blocks in some cases.

Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies, or clinical trials.

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Note 9 – Histological tumour type (Core)

All tumours of the adrenal cortex should be subtyped based on the most recent edition of the WHO Classification of Tumours of Endocrine Organs, 5th edition, 2025 (Table 1).[2] Recognition of histological subtypes 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 system[3]) because it includes a proportional assessment of lipid-rich and lipid-poor cells. Rather, other diagnostic systems[4] have been developed for these tumours (see **Note 22 – MULTIFACTORIAL SCORING SYSTEMS**).

In addition, knowledge of the histological subtype can assist with future diagnostic assessments. For example, knowledge that a particular tumour is the myxoid subtype 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 or atypical 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.

Table 1: World Health Organization classification of adrenal cortical carcinomas.[2]

Descriptor	ICD-O code[a]
Adrenal cortical carcinoma	8370/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-0-3.2).[5] Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade Ill intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Behaviour code /6 is not generally used by cancer registries.

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Note 10 – Extent of invasion (Core)

Tumour extension is pathologically distinct from tumour capsular invasion (see **Note – 13 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 22 – MULTIFACTORIAL SCORING SYSTEMS** and **Note 28 – PATHOLOGICAL STAGING**).

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Note 11 – Tumour architecture (Core)

In contrast to adrenal cortical adenomas, adrenal cortical carcinomas are typically characterised 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 22 – MULTIFACTORIAL SCORING SYSTEMS**).[6]

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Note 12 – 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 22 – MULTIFACTORIAL SCORING SYSTEMS**).[6]

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Note 13 – 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 22 – MULTIFACTORIAL SCORING SYSTEMS**).

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Note 14 – Lymphatic (sinusoidal) 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. However, a panel including markers positive in lymphatic vessels (e.g., D2-40) and markers positive in blood vessels (e.g., CD31, ERG) may be helpful, but is not required, to distinguish between lymphatics and blood vessels in small vessel invasion.

The assessment of lymphatic (sinusoidal) invasion is a component of several multifactorial scoring systems (see **Note 22 – MULTIFACTORIAL SCORING SYSTEMS**).

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Note 15 – Vascular invasion (Core)

The distinction between small blood vessel invasion (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, attached to the vessel wall, covered with endothelial cells, and admixed with thrombus, are 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 22 – MULTIFACTORIAL SCORING SYSTEMS**).

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Note 16 – 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. Pyknotic or karyorrhexic cells do not qualify as atypical mitoses. The assessment of atypical mitotic figures is a component of several multifactorial scoring systems (see **Note 22 – MULTIFACTORIAL SCORING SYSTEMS**).

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Note 17 – Tumour necrosis (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 22 – MULTIFACTORIAL SCORING SYSTEMS**).[2] There is no accepted definition of focal versus extensive.

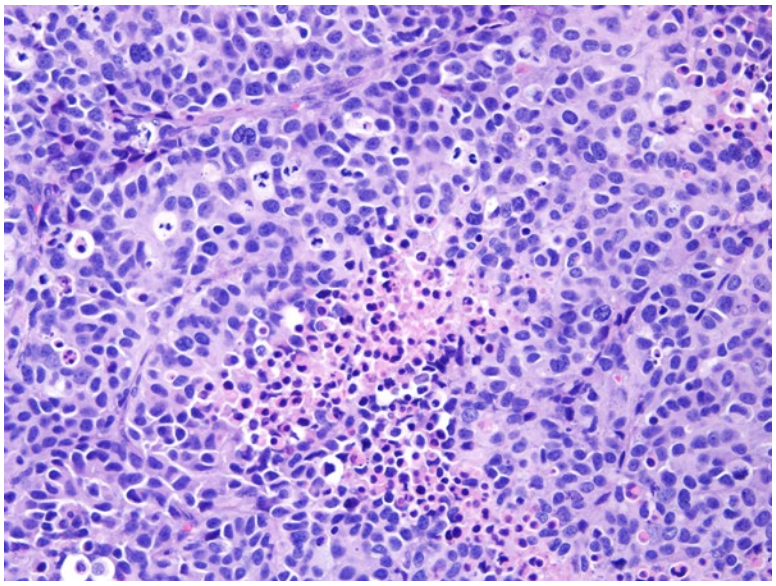

Figure 1: Focal coagulative tumour necrosis. *Reproduced with permission courtesy of Dr Thomas Giordano.*

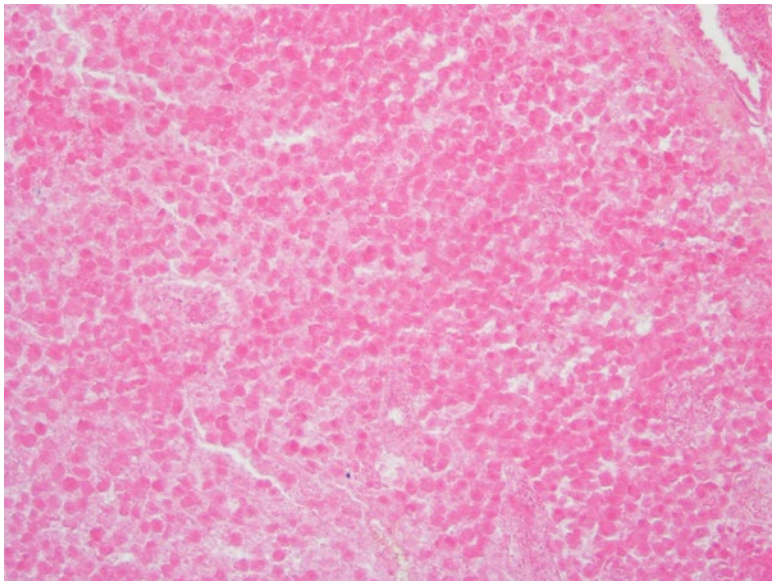

Figure 2: Extensive coagulative tumour necrosis. *Reproduced with permission courtesy of Dr Thomas Giordano.*

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Note 18 – Nuclear grade (Core)

Nuclear grade is a component of the Weiss multifactorial scoring system,[6] using the ISUP four-tier grading system for renal cancer,[10] and as per the Weiss criteria, grade is assigned based the most abnormal area . ISUP grades 1 and 2 are considered low grade and grades 3 and 4 are considered high grade (refer to Figures 3 and 4).

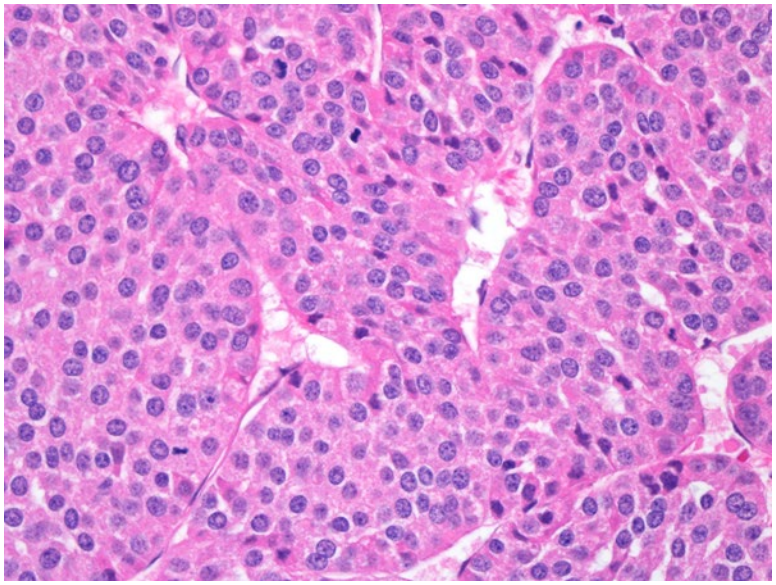

Figure 3: Low nuclear grade. *Reproduced with permission courtesy of Dr Thomas Giordano.*

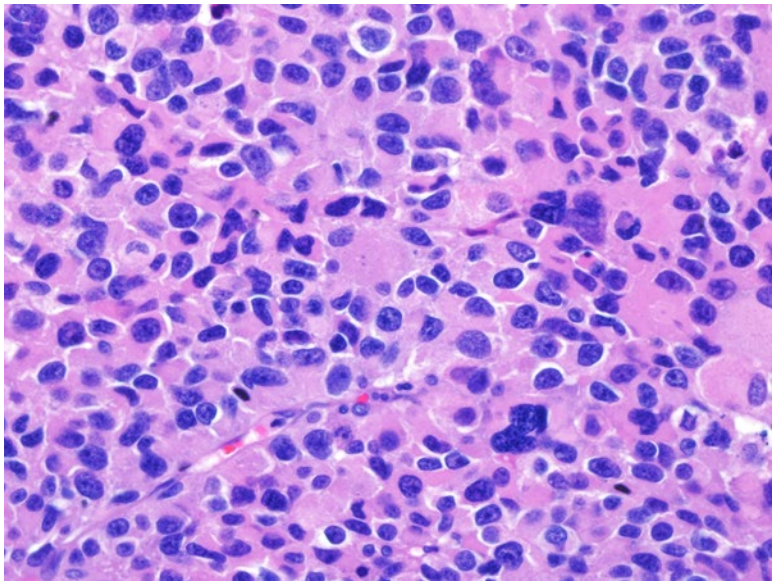

Figure 4: High nuclear grade. *Reproduced with permission courtesy of Dr Thomas Giordano.*

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Note 19 – Mitotic count and Histological tumour grade (Core)

It is recommended that reporting pathologists know their field diameter when calculating mitotic count. The literature and the multifactorial scoring systems (see **Note 22 – MULTIFACTORIAL SCORING SYSTEMS**) commonly refer 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 millimetres $(mm)^2$ 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 22 – 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.[11]

Assessment of mitotic count is prone to reproducibility issues,[12] 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 mm^2 and adjust the number of fields counted accordingly.

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Note 20 – Ki-67 proliferation index (Core)

Significant evidence has accumulated that adrenal cortical carcinoma is a proliferation-driven neoplasm[7-9,13] and the Ki-67 proliferation index, as determined by immunohistochemistry using the Mib-1 antibody,[14] is an important independent prognostic factor.[15-18] 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.[19] Estimating the Ki-67 by simple inspection ('eyeballing') is not recommended.

Although there is strong evidence that the Ki67 proliferative index is a key factor in assigning grade, different studies have used different Ki-67 proliferative cut-offs to assign grade groups. Some studies have used a three-tiered system based on the following cut-offs: ≤15% (low grade), >15-≤30 (intermediate grade), and >30% (high grade).[20] Recent studies and consensus statements have used a cutoff of ≤10% as an inclusion criterium for low grade.[21-24] Until there is consensus on Ki-67 cut-offs for individual grades, the actual Ki-67 proliferative index should be recorded.

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Note 21 – Reticulin framework (Non-core)

Histochemical staining to highlight the tumoural reticulin framework (refer to Figures 5 and 6) has diagnostic utility[25,26] and has been incorporated into a diagnostic algorithm (see **Note 22 – MULTIFACTORIAL SCORING SYSTEMS**). It has also been evaluated and shown to be useful in the assessment of paediatric adrenal cortical tumours.[27]

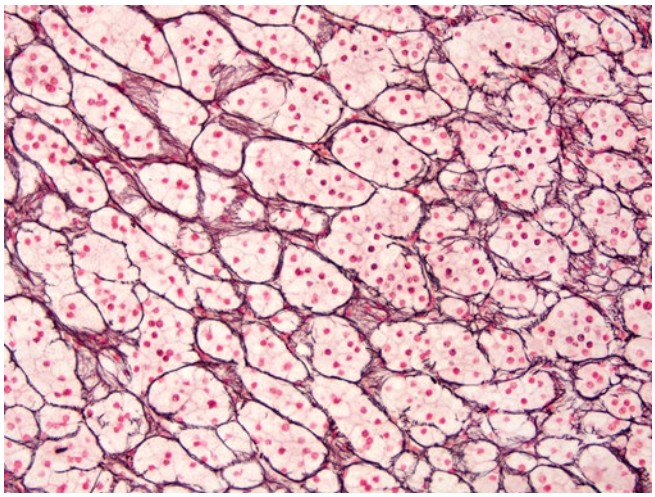

Figure 5: Intact reticulin framework in adrenal cortical adenoma. *Reproduced with permission courtesy of Dr Thomas Giordano.*

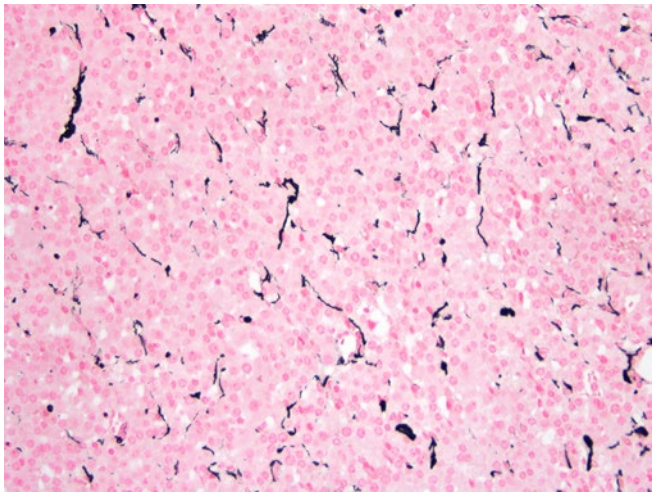

Figure 6: Altered reticulin framework in adrenal cortical carcinoma. *Reproduced with permission courtesy of Dr Thomas Giordano.*

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Note 22 – 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. Therefore, the DAC is unable to recommend any particular approach but pathologists are encouraged to use the system that seems most appropriate. The DAC 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.
Evaluation of these systems for paediatric tumours is an area of active investigation.[27-31]

1. Weiss system[6] 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 (defined as adrenal cortical tumours composed of >90% oncocytic cells) 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)[32] 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.[32]

3. Lin-Weiss-Bisceglia system[4] 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[33] for diagnosis and prognosis of conventional and oncocytic adrenal cortical neoplasms

Parameter	Score
• Mitoses >5 per 50 high power fields (10 mm^2)	• 3
• Necrosis	• 5
• Ki-67 proliferation index (%)	• Numeric value of the Ki-67 proliferation index from the highest proliferative area

Score 0 to 8.5: adrenal cortical adenoma

Score >8.5: adrenal cortical carcinoma

Score >17: adverse prognosis

5. Reticulin algorithm[25,26] 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 21 – 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) algorithm[34] 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.[35] Additional efforts to include the Ki-67 proliferation index into the evaluation of paediatric tumours are ongoing.[35,36] For these reasons, evaluation of paediatric tumours with Ki-67 is recommended whenever possible.

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Note 23 – Margin status (Core and Non-core)

Assessment of tumour margins is essential because incomplete resection has been associated with local recurrence[37] and may be an indication for local radiation therapy.[22,38] 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 24 – Lymph node status (Core and Non-core)

Extranodal extension (ENE), defined by unequivocal direct involvement of soft tissue (usually adipose) beyond the capsule of a given lymph node, is a non-core reporting item. Involvement of efferent lymph vessels should not be considered ENE.

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Note 25 – Coexistent pathology (Non-core)

It is increasingly becoming evident that adrenal cortical carcinoma may arise from pre-existing lesions such as cortical adenoma or in the context of adrenocortical nodular disease. The presence of such pathology should be documented.

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Note 26 – Ancillary studies (Non-core)

Increasingly, patients with adrenal cortical carcinoma are undergoing significant ancillary testing when available, not limited to histochemical stains (e.g., reticulin), immunohistochemistry for a variety of lineage-specific (e.g., SF-1 when available, or alpha-inhibin, Melan-A, calretinin, and synaptophysin when SF-1 is not available), diagnostic (e.g., IGF2) and prognostic biomarkers (beta-catenin and p53), and next-generation sequencing

(NGS)-based panel genotyping. The significance of such testing should be interpreted in the general context of the specific case. For example, CYP11B2 immunohistochemistry can be useful to determine if an adrenal neoplasm is the cause of hyperaldosteronism.[39]

Given the recent recognition that a small percentage of adrenal cortical carcinoma patients have Lynch syndrome,[40,41] screening for mismatch repair (MMR) protein defects by immunohistochemistry may be considered.

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Note 27 – Histologically confirmed distant metastases (Core)

The presence of histologically confirmed distant metastases is a critical component of pathological staging.[41-43]

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Note 28 – Pathological staging (Core)

Adrenal cortex tumours should be staged according to the 8th editions of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) Cancer Staging Manuals.[42,43]

The UICC has adopted the staging system proposed by the European Network for the Study of Adrenal Tumours (ENSAT), as outlined in Table 1.[44] It is noted that venous tumour thrombus qualifies as T4 disease, although it is noted that under this system venous thrombus only refers to gross infiltration of the vena cava or large veins. Although the ENSAT stage grouping is not considered a requirement of this dataset, it is listed in Table 2 for reference.

Table 2: Staging system for adrenocortical carcinoma.[44]

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

Reporting of pathological staging categories (pT, pN, pM) is based on the evidence available to the pathologist at the time of reporting. As indicated in UICC TNM8 and AJCC TNM8,[42,43] the final stage grouping of a patient's tumour is based on a combination of pathological staging and other clinical and imaging information.

The reference document TNM Supplement: A commentary on uniform use, 5th edition (C Wittekind et al. editors) may be of assistance when staging.[45]

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