The Royal College of Pathologists
Pathology: the science behind the cure

Standards and datasets for reporting cancers

Dataset for the histopathological reporting of adrenal cortical carcinoma and phaeochromocytoma/paraganglioma

March 2024

Authors: Dr Mufaddal T Moonim, Charing Cross Hospital, London
Dr Dan Berney, Barts Health NHS Trust, London
Dr Alison J Marker, Addenbrooke's Hospital, Cambridge
Dr Thomas Papathomas, Cheltenham General Hospital, Cheltenham & Institute of Metabolism and Systems Research, University of Birmingham

Unique document number	G109
Document name	Dataset for the histopathological reporting of adrenal cortical carcinoma and phaeochromocytoma/paraganglioma
Version number	3
Produced by	Dr Mufaddal T Moonim, Charing Cross Hospital, Imperial College Healthcare Trust, London. Dr Dan Berney, Barts Health NHS Trust, London. Dr Alison J Marker, Addenbrooke's Hospital, Cambridge. Dr Thomas Papathomas, Cheltenham General Hospital, Cheltenham and Institute of Metabolism and Systems Research, University of Birmingham, Birmingham.
Date active	March 2024 **(to be implemented within 3 months)**
Date for full review	March 2027
Comments	This document will replace the 2nd edition of the *Dataset for reporting adrenal cortical carcinoma and malignant phaeochromocytoma/paraganglioma*, published in 2012. In accordance with the College's pre-publications policy, this document was on the College website for consultation from 9 January to 6 February. Responses and authors' comments are available to view on request. **Dr Brian Rous, Clinical Lead for Guideline Review**

The Royal College of Pathologists
6 Alie Street, London E1 8QT
Tel: 020 7451 6700
Fax: 020 7451 6701
Web: www.rcpath.org

Registered charity in England and Wales, no. 261035

Contents

Foreword

The cancer datasets published by The Royal College of Pathologists (RCPath) are a combination of textual guidance, educational information and reporting proformas. The datasets enable pathologists to grade and stage cancers in an accurate, consistent manner in compliance with international standards and provide prognostic information, thereby allowing clinicians to provide a high standard of care for patients and appropriate management for specific clinical circumstances. This guideline has been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every pathological specimen type and clinical scenario. Occasional variation from the practice recommended in this guideline may therefore be required to report a specimen in a way that maximises benefit to the patient. Pathologists should be able to justify any departure from the recommended guidelines.

Each dataset contains core data items (see Appendices D–G) that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – previously the National Cancer Data Set) in England. Core data items are items that are supported by robust published evidence and are required for cancer staging, optimal patient management and prognosis. Core data items meet the requirements of professional standards (as defined by the Information Standards Board for Health and Social Care [ISB]) and it is recommended that at least 95% of reports on cancer resections should record a full set of core data items. Other, non-core, data items are described. These may be included to provide a comprehensive report or to meet local clinical or research requirements (with appropriate consents or other legal grounds). All data items should be clearly defined to allow the unambiguous recording of data.

The following stakeholders were contacted to consult on this document:

- UK Endocrine Pathology Society
- The British Association of Endocrine and Thyroid Surgeons (BAETS).

The guidelines have been approved by the UK Endocrine Pathology Society and the British Association of Endocrine and Thyroid Surgeons (BAETS).

The information used to develop this dataset was obtained by undertaking a 5-year search of the PubMed database for relevant primary research evidence and systematic reviews including the search terms ‘adrenal’, ‘paraganglioma’, ‘cancer’ and ‘pathology’ from November 2016 to June 2023 (inclusive). The recommendations incorporate the core data

items and commentary from the International Collaboration on Cancer Reporting (ICCR),[1,2] with relevant edits as required by the updated 5th edition of the WHO *Classification of Endocrine and Neuroendocrine Tumours*, published in April 2022.[3] The level of evidence for the recommendations has been summarised according to modified SIGN guidance (see Appendix H) and the grade of evidence is indicated in the text. Consensus of evidence in the guideline was achieved by expert review. Gaps in the evidence were identified by College members via feedback received during consultation.

No major organisational changes have been identified that would hinder the implementation of the dataset.

A formal revision cycle for all cancer datasets takes place on a 3-yearly basis. However, each year, the College will ask the author of the dataset, in conjunction with the relevant subspecialty advisor to the College, to consider whether or not the dataset needs to be updated or revised. A full consultation process will be undertaken if major revisions are required, i.e. revisions to core data items (the only exception being changes to international tumour grading and staging schemes that have been approved by the Specialty Advisory Committee on Cellular Pathology and affiliated professional bodies; these changes will be implemented without further consultation).

If minor revisions or changes to non-core data items are required, an abridged consultation process will be undertaken, whereby a short note of the proposed changes will be placed on the College website for 2 weeks for members' attention. If members do not object to the changes, they will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

The dataset has been reviewed by the Professional Guidelines team, Working Group on Cancer Services and the Lay Advisory Group. It was placed on the College website for consultation with the membership from 9 January to 6 February. All comments received from the Working Group and membership were addressed by the authors to the satisfaction of the Chair of the Working Group and the Clinical Lead for Guideline Review.

This dataset was developed without external funding to the writing group. The College requires the authors of datasets to provide a list of potential conflicts of interest; these are monitored by the Professional Guidelines team and are available on request. The authors have declared no conflicts of interest.

1 Introduction

1.1 Endocrine cancer datasets

The management of endocrine tumours is the responsibility of an appropriately experienced multidisciplinary team (MDT). Because these tumours bridge various anatomical sites, they are dealt with by a number of specialist teams. Although there is currently no national model for the constitution of MDTs managing endocrine tumours (other than thyroid), we strongly recommend that patients with these tumours are discussed at specialist adrenal or neuroendocrine MDTs. The constitution of these teams should be determined according to local skills, interest and experience. Ideally, the pathologist reporting the cases should have a special interest in endocrine pathology.

Alternatively, they should have an interest in the endocrine tumours in their area of systemic pathology or, if a general pathologist, should participate in a network with the opportunity for specialist pathology review. The reporting pathologist should either be a core member of the appropriate cancer MDT or have access to a pathologist who is a core member. Educational slide circulations relevant to these tumour groups are available through the UK Endocrine Pathology Society (UKEPS) at www.ukeps.com.

It is envisaged that the main users of the datasets will be trainee and consultant histopathologists. Secondary users will include surgeons, oncologists, endocrinologists and nuclear medicine physicians. They will also be of use to cancer registries and the National Cancer Intelligence Network.

1.2 Adrenal cancer dataset

This dataset includes guidelines to deal with both adrenal cortical carcinoma (ACC) and phaeochromocytoma. It has also been extended to cover extra-adrenal paragangliomas. Paediatric peripheral neuroblastic tumours (neuroblastoma, ganglioneuroblastoma and ganglioneuroma), lymphoma and sarcoma are not covered in the dataset (separate resources for these tumour types are available on the RCPath website).

The 2017 *WHO Classification of endocrine and neuroendocrine tumours* reserves the term ‘phaeochromocytoma’ for adrenal tumours.[4] Extra-adrenal paragangliomas are defined by type (sympathetic or parasympathetic) and site. Sympathetic paragangliomas arise close to the paravertebral and prevertebral ganglia in the para-axial region of the trunk, or in the connective tissue adjacent to pelvic organs. Therefore, phaeochromocytomas are intra-

adrenal sympathetic paragangliomas. Parasympathetic paragangliomas lie close to vascular structures and branches of the glossopharyngeal and vagus nerves in the head and neck. They include what have been defined as carotid body tumours, jugulotympanic, vagal and aortic paragangliomas. Paragangliomas can also arise in other sites that are not necessarily associated with the normal location of sympathetic and parasympathetic paraganglia, including the nose and nasopharynx, orbit and lesions termed 'chemodectomas' of the lung. As per the WHO 2022 classification, the term 'paraganglioma' was a misnomer (i) in the spine, most commonly found in the cauda equina (spinal paraganglioma), (ii) in the small intestine, almost exclusively found in the second part of the duodenum and periampullary region (gangliocytic paraganglioma) and (iii) in the middle ear, a site of paragangliomas that arise from the tympanic paraganglia and of epithelial neuroendocrine tumours that are currently classified as middle ear neuroendocrine tumours.[3,5]

The handling of the gross specimens is broadly similar for both groups of tumours. Reporting proformas have been included (Appendices D and E) that list the key features of these neoplasms. There are several changes incorporated in this dataset that include criteria used to discriminate benign from malignant tumours, a description of the role of immunohistochemistry in differentiating cortical from medullary neoplasms and changes to staging systems. The currently used staging system for ACC – the Union for International Cancer Control's (UICC) *TNM Classification of Malignant Tumours* (*8th edition*) – is included, which has adopted the staging system proposed by the European Network for the Study of Adrenal Tumours (ENSAT).[6] A new staging system for phaeochromocytoma/paraganglioma has now been developed.[7]

These guidelines describe the core data that should be recorded in the histopathology reports from cases of ACC, phaeochromocytoma or paraganglioma. They should be implemented for the following reasons.

- The most important prognostic features in ACC are clinical tumour stage, completeness of primary resection and Ki-67 labelling index. Pathological evaluation is crucial for this.
- Succinate dehydrogenase (SDHx) immunohistochemistry (usually subunit B) is essential for prognostication for phaeochromocytoma/paraganglioma (i.e. SDHx mutated tumours have a high risk of metastasis/malignant behaviour).
- The diagnosis will provide accurate data for cancer registration.

- Accurate diagnosis informs genetic testing.
- The diagnosis informs selection of potential patients for future clinical trials. This is extremely important as current therapies for these diseases are limited.

1.3 Abbreviations used in this guideline

- Adrenal cortical carcinoma (ACC).
- Chromogranin A (CgA).
- Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA).
- Epithelial membrane antigen (EMA).
- Extranodal extension (ENE).
- Grading system for adrenal phaeochromocytoma and paraganglioma (GAPP).
- High power fields (HPFs).
- Labelling index (LI).
- Multidisciplinary team (MDT).
- Multiple endocrine neoplasia type 2 (MEN2).
- Next-generation sequencing (NGS).
- Not otherwise specified (NOS).
- Phaeochromocytoma of the adrenal gland scoring scale (PASS).
- Primary aldosteronism (PA).
- Primary tumour (pT).
- Regional lymph nodes (pN).
- Steroidogenic factor-1 (SF-1).
- Succinate dehydrogenase (SDHx).
- Tyrosine hydroxylase (TH).

2 Clinical information required on the request form

Core clinical information is required for the dataset. This includes the hormonal or functional status of the tumour, imaging findings, relevant preoperative biopsy results,

history of previous surgery/therapy, known relevant family history and the presence of other tumours, germline mutation or a familial syndrome.

The nature of the specimen and type of surgery should be defined (left/right adrenalectomy or paraganglioma excision from various sites; open or laparoscopic). In addition to excision of primary tumours, adrenalectomy is also performed for removal of metastatic tumours to the adrenal. This is therapeutic in a solitary metastasis and/or to acquire tumour tissue for molecular testing (e.g. for metastatic lung cancer).

The presence of a clinical syndrome (e.g. Cushing's or Conn's) should be noted. Any history of familial disease (e.g. multiple endocrine neoplasia type 2 [MEN2]) should be included.

3 Preparation of specimens before dissection

The specimen should be measured and described grossly. A digital image may be useful.

Historically, many studies have used 'tumour weight' to try and discriminate between benign and malignant tumours. However, modern risk stratification systems for adult cortical tumours/phaeochromocytomas (see section 7) do not utilise tumour weight to make this distinction. Currently, tumour weight is only used as one of many criteria in stratification systems designed to deal with adult oncocytic tumours and paediatric cortical tumours. For these reasons, attempts should be made to obtain as accurate a weight as possible. However, it is advised not to strip the surrounding fat/soft tissue or attached adjacent organs off the tumour as this is detrimental to assessment of both completeness of excision (which is a good indicator of the likelihood of local recurrence) and of staging (as it prevents an accurate assessment of local invasion, which is a much more reliable indicator of aggressive behaviour).[6,7]

If the tumour is visible, its size (preferably in mm) should be measured and it should be noted whether or not the tumour capsule is intact. The specimen margins should be inked.

3.1 Morcellated specimens

Advances in imaging have improved early detection of primary and metastatic adrenal tumours. A review of the literature demonstrates the safety and efficacy of laparoscopic adrenalectomy for solitary adrenal tumours (benign functioning and non-functioning adrenal tumours). In primary adrenal malignancies, open surgical excision is recommended.[8] When a laparoscopic approach is used in this context, conversion to an

open procedure should be an early decision, prior to tumour morcellation or fracture of the tumour capsule.[9,10] Patients who have local invasion or tumours that are too large, or who require organ resection, require an open procedure.

While port site and intra-abdominal dissemination of both carcinoma and phaeochromocytoma and the potential of leaving residual disease/high recurrence rate following laparoscopic adrenalectomy are well documented, literature does not discuss the impact of this procedure or the effects of fragmentation/morcellation on the pathologic evaluation of adrenal tumours and its impact on diagnosis and staging of tumour.

From a pathologic standpoint, the fragmentation/morcellation of adrenalectomy specimens impairs the ability of the pathologist to do the following.

- Make a distinction between benign and malignant tumours. While this distinction is multifactorial, pathologic assessment of non-invasiveness (circumscription, intact capsule, presence or absence of capsular invasion) and vascular invasion are difficult or impossible in fragmented/morcellated specimens.
- Evaluate vascular invasion. The process of fragmentation/morcellation allows for dislocation of tumour and creates artefacts that simulate vascular invasion or sinusoidal invasion. The disruption of the tumour–capsule interface precludes assessment of vascular invasion, which is one of the most reliable signs of malignancy as well as an indicator of high risk for subsequent systemic disease.
- Evaluate venous tumour thrombus (pT3, stage 4 disease). The lack of anatomical continuity and piecemeal nature of the specimen make it difficult to determine if venous tumour thrombus is present. This is a feature seen in malignant tumours and required for staging (stage 3–4 disease).
- Assess extra-adrenal extension (pT2/pT3 and stage 3–4 disease). This is often difficult due to distortion of the specimen, crushing artefacts and lack of anatomic continuity.
- Assess margins, completeness of excision and quality assure an oncologic surgical procedure (R0 vs. R1/R2 status). Mutilation/fragmentation/morcellation preclude any of these assessments. An R0 resection is one of the most important indicators of good outcome and long-term survival in ACC.
- Stage the tumour. Tumour size cannot be assessed.

Therefore, mutilation/fragmentation/morcellation of adrenalectomy specimens in patients operated laparoscopically is not advised, as this impairs pathologic diagnosis and

assessment of invasion, prevents proper staging of adrenal tumours and may contribute to tumour dissemination.[8]

4 Specimen handling and block selection

The specimen should be serially sliced and the appearance of the cut surface described, particularly the presence of necrosis. If measurements have not been previously taken, these should now be documented (preferably in mm). If tumour size cannot be obtained from the specimen, it should be obtained from preoperative imaging studies. Acquisition of digital images is useful.

The tumour capsule should be evaluated and presence/absence of apparent invasion into peri-adrenal soft tissue and adjacent organs should be noted separately. The distinction between these is important for staging of ACC. Where the adrenal gland can be identified, its relationship to the tumour and its appearance should be noted.

The adrenal vein is usually prominently visible as a clamped structure in adrenalectomy specimens; this, along with other major vessels, should be examined and sampled to determine if they contain tumour thrombus.[6,11]

This is especially important in specimens with an attached kidney, where evaluation of the renal veins/part of the inferior vena cava (if present) is possible. The number of lymph nodes submitted or identified in the main specimen should be recorded. All lymph nodes should be processed: small nodes should be processed whole, large nodes may be sampled. Any other tissues submitted should be sampled.

4.1 Number of blocks

There are no defined protocols for tumour sampling, but we would suggest that lesions <30 mm in diameter should be processed in their entirety and larger lesions should have a minimum of one additional block for each 10 mm. Blocks should be taken from all morphologically distinct areas, necrotic areas, the tumour capsule and its interface with adjacent tissue to assess invasion and the margins. At least 1 block should be taken from the adjacent uninvolved adrenal, if identified.

Megablocks may be helpful for assessment of overall tumour architecture, presence of tumour necrosis and capsular invasion. It needs to be emphasised that the entire lesion should not be embedded in megablocks and that part of the lesion should be embedded in smaller blocks to facilitate ancillary testing, e.g. immunohistochemistry.

4.2 Notes specific for adrenal cortical carcinoma

ACC usually appears as a large heterogeneous tumour with the presence of fibrous bands and a nodular cut surface. Haemorrhage, necrosis and calcification may be present. ACC usually has a cream or yellow cut surface, in contrast to oncocytic tumours, which have a tan or brown cut surface.

The UICC has adopted the staging system for ACC proposed by ENSAT (Appendix B). It is emphasised that venous tumour thrombus (in vena cava or renal vein) qualifies as T4 disease.[12]

4.3 Notes specific for phaeochromocytoma/paraganglioma

Specimens should be carefully examined both macroscopically and microscopically to determine whether multiple or multifocal tumours are present. Multifocality applies to the adrenal gland in most cases, but multicentric tumours may also be identified in an adrenalectomy specimen containing a phaeochromocytoma as well as an additional extra-adrenal paraganglioma.[13]

Emerging molecular evidence is in support of the term ‘microphaeochromocytoma’, as opposed to hyperplastic nodule or nodular adrenal medullary hyperplasia, in nodules of <10 mm in maximum diameter in particular genetic backgrounds.[14,15] Normally, the adrenal medulla is confined to the head and body of the gland. Therefore, the presence of substantial medullary tissue in the tail of the gland represents medullary hyperplasia. In addition, thickened medullary tissue, i.e. increased ratio of medulla to cortex (normal ratio 1:3), strongly suggests adrenal medullary hyperplasia.[13] However, it needs to be noted that not all forms of inherited phaeochromocytoma are associated with hyperplasia and that it may not always be possible to identify the tail of the adrenal gland due to distortion by tumour.[16]

5 Adrenal cortical carcinoma

The dataset has been developed for the pathology reporting of potentially malignant adrenal cortical resection specimens. Borderline (low-malignant potential lesions) are included, along with paediatric ACCs. Neuroblastoma, sarcoma and lymphoma are not covered in the dataset. Core needle biopsies, benign lesions/tumours and metastasis are not included.

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.

5.1 Core data items – adrenal cortical carcinoma

1	Descriptor	Responses

ICCR	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
		• Previous surgery/therapy, specify
		• Relevant family history, specify
		• Functional status, specify
		  – Cushing syndrome
		  – Primary aldosteronism (PA)
		  – Conn's syndrome
		  – Virilisation
		  – Feminisation
		  – Other, specify
		• Imaging findings, specify
		• Other, specify

Clinical information – ICCR commentary

Relevant clinical information (e.g. hypertension, change in body habitus, virilisation), the presence of clinical syndromes (e.g. Cushing's or 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 known family history and results of genetic testing, should also be recorded. History of other cancers, which may metastasise 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.

RCPath additional comments:

None.

[Level of evidence – C.]

2	Descriptor	Responses
ICCR	Operative procedure	Multi-selection value list (select all that apply)/text: • Not specified • Adrenalectomy

		– Total – Partial • Open or laparoscopic • Biopsy – Incisional – Excisional • Other, specify
Operative procedure – ICCR commentary: 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 (paraaortic and periaortic) lymph node dissection should be reported when performed under 'other'. **RCPath additional comments:** Please refer to section on morcellation (section 3). *[Level of evidence – C.]*		

3 ICCR	**Descriptor**	**Responses**
	Specimen(s) submitted	Multi-selection value list (select all that apply)/text: • Not specified • Adrenal tumour – Left – Right • Lymph nodes, specify site(s) and laterality • Other (e.g. metastatic site), specify site(s) and laterality
Specimen(s) submitted – ICCR commentary: 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. **RCPath additional comments:** None. *[Level of evidence – C.]*		

4	Descriptor	Responses

ICCR	Tumour site	Multi-selection value list (select all that apply)/text:
		• Not specified
		• Adrenal
		  – Left
		  – Right
		• Other, specify site(s) and laterality

Tumour site – ICCR commentary: Tumour site is an important data point in fully characterising any neoplasm. **RCPath additional comments:** None. *[Level of evidence – C.]*		

5	Descriptor	Responses
ICCR	Specimen integrity	Single-selection value list: • Specimen intact • Capsule disrupted • Fragmented specimen • Cannot be assessed, specify
Specimen integrity – ICCR commentary: 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, it should be recorded. **RCPath additional comments:** Please refer to section on morcellation (section 3). *[Level of evidence – C.]*		

6	Descriptor	Responses
ICCR	Tumour dimensions	Multi-selection value list (select all that apply)/text: • Maximum tumour dimension (largest tumour) in mm • Cannot be assessed, specify
Tumour dimensions – ICCR commentary: 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 preoperative imaging studies.

RCPath additional comments:

Please refer to sections 3 and 4 on macroscopic findings. Provision of the maximum tumour dimension is essential.

[Level of evidence – C.]

7	**Descriptor**	**Responses**
ICCR	Tumour weight	Multi-selection value list (select all that apply)/text: • Tumour weight in grams • Cannot be assessed, specify

Tumour weight – ICCR commentary:

Accurate determination of tumour weight is essential for complete diagnostic assessment.[17] 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).

RCPath additional comments:

It is advised not to strip the surrounding fat/soft tissue or attached adjacent organs off the tumour as this is detrimental to assessment of both completeness of excision (which is a good indicator of the likelihood of local recurrence) and of staging (as it prevents an accurate assessment of local invasion, which is a much more reliable indicator of aggressive behaviour).[6] Please refer to sections 3 and 4 on macroscopic dissection for further comments on tumour weight.

[Level of evidence – C.]

8	**Descriptor**	**Responses**
ICCR	Histological tumour type	Single-selection value list (value list based on the WHO Classification of Tumours: Pathology and Genetics of Tumours of Endocrine Organs, 2017): • ACC, not otherwise specified (NOS) • ACC, oncocytic type • ACC, myxoid type • ACC, sarcomatoid type • Adrenal cortical neoplasm of uncertain malignant potential* • Other, specify * This is not considered a distinct entity under the WHO Classification.

Histological tumour type – ICCR commentary:

All tumours of the adrenal cortex should be given a type based on the most recent edition of the *WHO Classification of tumours of endocrine organs*.[17] Recognition of histological variants of ACC 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) because it includes a proportional assessment of lipid-rich and lipid-poor cells.[18] Rather, other diagnostic systems have been developed for these tumours (see NC7 Multifactorial scoring systems).[19,20]

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 ACC, 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.

RCPath additional comments:

The Lin–Weiss–Bisceglia scoring system for oncocytic tumours should be applied to pure tumours composed of >90% oncocytic cells.

[Level of evidence – C.]

9	**Descriptor**	**Responses**
ICCR	Extent of invasion	Multi-selection value list (select all that apply)/text: • Cannot be assessed • Confined to the adrenal gland • Invasion into/through adrenal capsule • Invasion into extra-adrenal structures, specify • Invasion into adjacent organs, specify

Extent of invasion – ICCR commentary:

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, whether adjacent structures and organs (e.g. kidney, liver, and pancreas) are directly involved, and whether it is a component of pathological staging (see NC7 Multifactorial scoring systems and 22 Pathological staging).

RCPath additional comments:

None.

[Level of evidence – C.]

10	Descriptor	Responses
ICCR	Tumour architecture	Single-selection value list: • Diffuse (solid or pattern-less) • Nested/non-diffuse

Tumour architecture – ICCR commentary:

In contrast to adrenal cortical adenomas, ACCs are typically characterised by diffuse tumour architecture, which is defined as solid or patternless 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 NC7 Multifactorial scoring systems).[20]

RCPath additional comments:

None.

[Level of evidence – C.]

11	Descriptor	Responses
ICCR	Lipid-rich cells	Single-selection value list: • <25% • >25%

Lipid-rich cells – ICCR commentary:

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 NC7 Multifactorial scoring systems).[20]

RCPath additional comments:

None.

[Level of evidence – C.]

12	Descriptor	Responses
ICCR	Capsular invasion	• Not identified • Present • Cannot be assessed, specify

Capsular invasion – ICCR commentary:

The majority of ACCs 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.[17]

Extra-adrenal extension into soft tissue and adjacent organs is evaluated separately. The assessment of capsular invasion is a component of several multifactorial scoring systems (see NC7 Multifactorial scoring systems).

RCPath additional comments:

A full thickness breach of the capsule is required to qualify as capsular invasion.

[Level of evidence – C.]

13	Descriptor	Responses
ICCR	Lymphatic invasion	• Not identified • Present

Lymphatic invasion – ICCR commentary:

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 NC7 Multifactorial scoring systems).

RCPath additional comments:

Involvement of capsular/extracapsular vessels is a major prognostic factor in ACC and is used in various multifactorial stratification systems. The evaluation of intra-tumoural sinusoidal invasion is associated with significant interobserver variability in the experience of the authors.

[Level of evidence – C.]

14	Descriptor	Responses

ICCR	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

Vascular invasion – ICCR commentary:

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.[21]

The assessment of venous invasion is a component of several multifactorial scoring systems (see NC7 Multifactorial scoring systems).

RCPath additional comments:

None.

[Level of evidence – C.]

15	Descriptor	Responses
ICCR	Atypical mitotic figures	• Not identified • Present

Atypical mitotic figures – ICCR commentary:

The collective genomic studies of ACC to date indicate the presence of widespread genomic instability with significant copy number changes.[22,23] 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 NC7 Multifactorial scoring systems).

RCPath additional comments:

None.

[Level of evidence – C.]

16	Descriptor	Responses
ICCR	Necrosis	• Not identified • Present

Necrosis – ICCR commentary:

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 hyalinisation, 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 NC7 Multifactorial scoring systems).[17] There is no accepted definition of focal versus extensive.

RCPath additional comments:
None.

[Level of evidence – C.]

17	Descriptor	Responses
ICCR	Nuclear grade (Fuhrman criteria)	Low (grade 1or 2) High (grade 3 or 4)

Nuclear grade (Fuhrman criteria) – ICCR commentary:
Nuclear grade is a component of the Weiss multifactorial scoring system, using a grading system similar to the Fuhrman criteria for renal cancer; as per the Weiss criteria, grade is assigned based on the most abnormal area.[17,20]

RCPath additional comments:
International Society for Urological Pathology (ISUP) criteria:
As the term Fuhrman grading system is no longer used in renal neoplasia, the basically identical ISUP renal nuclear grading system can also be applied.[24]
Adrenal cortical tumours exhibiting high-grade nuclei show features that would meet the definition of grade 3 or grade 4 in the Fuhrman system, which is based primarily on the simultaneous assessment of nucleolar prominence, nuclear size and nuclear irregularity. To meet the criterion of grade 3, the tumour should demonstrate enlarged irregular nuclei with nucleoli visible at x10 magnification; grade 4 tumours demonstrate, in addition, nuclear pleomorphism, bizarre multilobed giant cells and coarsely granular hyperchromatic chromatin – refer to Figures 3 and 4 in the ICCR document.

[Level of evidence – C.]

17	Descriptor	Responses
ICCR	Mitotic count and histological tumour grade	Multi-selection value list (select all that apply)/text: • Mitotic figures/10 mm^2 AND • Low grade (≤20 mitoses) • High grade (>20 mitoses) • Cannot be assessed, specify 10 mm^2 approximates 50 HPFs on some microscopes.

Mitotic count and histological tumour grade – ICCR commentary:

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 mm^2 is commonly used, as this reflects many microscopes in widespread use.

Architectural grading of ACC 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 NC7 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.[25]

Assessment of mitotic count is prone to reproducibility issues, largely due to variation in interpretation amongst pathologists of what constitutes a mitotic figure and variation between microscopes.[26] 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.

RCPath additional comments:

Mitotic activity is assessed systematically by evaluating areas of highest mitotic/proliferative activity to ensure that at least 50 high power fields/10 mm^2 are evaluated. This may involve assessment of multiple foci across various sections of tumour.

Immunohistochemistry using Ki-67 may be useful to highlight areas of highest mitotic activity.

[Level of evidence – C.]

18 ICCR	Descriptor	Responses
	Ki-67 proliferation index	• Ki-67 % • Cannot be assessed

Ki-67 proliferation index – ICCR commentary:

Significant evidence has accumulated that ACC is a proliferation-driven neoplasm[17–19,23] and the Ki-67 proliferation index, as determined by immunohistochemistry using the Mib-1 antibody,[24] is an important independent prognostic factor.[21–23, 27–32] 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.[33] Estimating the Ki-67 by simple inspection ('eyeballing') has been shown to have some prognostic significance and may be used when image analysis and manual counting is not possible.[34]

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

RCPath additional comments:

Performing Ki-67 on more than one block is valuable in tumours that have borderline morphology/ multifactorial scores.

Visual estimates of Ki-67 % are known to be less standardised and associated with some interobserver variation. However, in practice these still provide valuable prognostic/threshold information.

Mitotic counts and Ki-67 immunohistochemistry provide complimentary information especially in the context of poorly preserved tumours.

At least 500 cells should be assessed.[36]

A significant inflammatory component within the tumour may lead to overestimation of Ki-67 proliferation index.

[Level of evidence – C.]

19	Descriptor	Responses
ICCR	Margin status	• Not involved (R0) • Involved – R1 (microscopic), specify if possible – mm – R2 (macroscopic), specify if possible – mm – Location of involved margin(s), specify if possible • Cannot be assessed, specify

Margin status – ICCR commentary:

Assessment of tumour margins is essential because incomplete resection has been associated with local recurrence and may be an indication for local radiation therapy.[37,38] 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.

RCPath additional comments:

None.

[Level of evidence – C.]

20	Descriptor	Responses
ICCR	Lymph node status	• No lymph nodes submitted or found • Number of lymph nodes examined: – Not involved – Involved

		• Number of positive lymph nodes: – Number cannot be determined
RCPath additional comments: None. *[Level of evidence – C.]*		

21	**Descriptor**	**Responses**
ICCR	Histologically confirmed distant metastases	• Not identified • Not assessed • Present, specify site(s)
Histologically confirmed distant metastases – ICCR commentary: The presence of histologically confirmed distant metastases is a critical component of pathological staging.[6] **RCPath additional comments:** None. [Level of evidence – C.]		

22	**Descriptor**	**Responses**
ICCR	Pathological staging (UICC *TNM 8th edition*)[d]	Multi-selection value list (select all that apply)/text: **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 • T4 Tumour of any size with invasion of adjacent organs 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) Choose if applicable: • m – multiple primary tumours • r – recurrent • y – post-therapy [d] Reproduced with permission. Source: Brierley JD, Mary K. Gospodarowicz, Wittekind C (eds). Union for International Cancer Control *TNM Classification of Malignant Tumours (8th edition).* Oxford, UK: Wiley-Blackwell, 2016.
Clinical information – ICCR commentary: The UICC has adopted the staging system proposed by ENSAT, as outlined in Table 1.[6] It is emphasised that venous tumour thrombus qualifies as T4 disease. Although the ENSAT stage grouping is not considered mandatory, it is listed in Table 1/Appendix B for reference. **RCPath additional comments:** None. *[Level of evidence – C.]*		

Table 1: Staging system for adrenal cortical carcinoma.[6]

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

5.2 Non-core data items – adrenal cortical carcinoma

NC1	Descriptor	Responses
ICCR	Necrosis	Extent • Focal • Extensive
Necrosis – ICCR commentary: There is no accepted definition of focal versus extensive.		

RCPath additional comments:
None.

[Level of evidence – D.]

NC2	Descriptor	Responses
ICCR	Reticulin framework	• Intact/preserved • Altered/absent • Cannot be assessed, specify

Reticulin framework – ICCR commentary:
Histochemical staining to highlight the tumoural reticulin framework (refer to Figures 5 and 6, ICCR dataset) has diagnostic utility and has been incorporated into a diagnostic algorithm (see NC7 Multifactorial scoring systems).[39,40]

RCPath additional comments:
None.

[Level of evidence – C.]

NC3	Descriptor	Responses
ICCR	Margin status	Distance of tumour to closest margin – mm

RCPath additional comments:
None.

[Level of evidence – C.]

NC4	Descriptor	Responses
ICCR	Extranodal extension	• Not identified • Present • Cannot be determined

Extranodal extension – ICCR commentary:
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.

RCPath additional comments: None. *[Level of evidence – C.]*

NC5	Descriptor	Responses
ICCR	Coexistent pathology	• None identified • Adenoma • Hyperplasia • Other, specify
Coexistent pathology – ICCR commentary: It is increasingly becoming evident that ACC may arise from pre-existing lesions such as cortical adenoma. **RCPath additional comments:** The presence of such pathology should be documented. *[Level of evidence – C.]*		

NC6	Descriptor	Responses
ICCR	Ancillary studies	Refer to section 12

6 Phaeochromocytoma and paraganglioma

6.1 Core data items

1	Descriptor	Responses

ICCR	Clinical information	Multi-selection value list (select all that apply)/text:
		• Information not provided
		• Hormonal status
		• Biochemically functioning (select all that apply)
		  – Metanephrine and/or adrenaline
		  – Normetanephrine and/or noradrenaline
		  – Methoxytyramine and/or dopamine
		• Other, specify
		• Biochemically silent
		• Biochemical analysis not performed

		• Cannot be determined (testing status not known) • Imaging findings, specify • Relevant biopsy/cytology results, specify • Previous therapy (including preoperative embolisation, chemotherapy, radiotherapy, targeted therapy, immunotherapy), specify • Relevant familial history, specify • Presence of endocrine or other tumours, specify • Germline mutation or familial syndrome, specify mutation, if known • Other, specify

Clinical information – ICCR commentary:

Clinical data provides important guidance to pathologists for establishing a diagnosis and for assisting clinicians in planning patient management. Optimally, information should be provided on biochemical function, individual and family history (where known), multiple tumours and the presence of additional endocrine or non-endocrine tumours that may be components of a syndrome.[4]

Almost 50% of phaeochromocytomas/paragangliomas are hereditary, making them the most hereditarily determined of all human tumours, and at least 15 hereditary susceptibility genes are now associated with their development.[41] Distinct correlations exist between genotype, biochemical phenotype, tumour distribution, prognosis and syndromic associations.[42–44]

Most phaeochromocytomas and sympathetic paragangliomas are capable of synthesising catecholamines and are also associated with clinical signs and symptoms related to catecholamine excess. In contrast, parasympathetic paragangliomas are rarely symptomatic and often lack tyrosine hydroxylase, the enzyme required for catecholamine synthesis, making them biochemically as well as clinically silent.[45]

There is overwhelming evidence that biochemical testing for phaeochromocytoma/paraganglioma should include metanephrines, measured either in plasma or urine, as these are superior to measurements of catecholamines.[46] Many clinically silent paragangliomas, particularly of the sympathoadrenal type, will produce metanephrines and/or methoxytyramine and therefore are amenable to biochemical testing.[41,42]

Similarly to other neuroendocrine neoplasms, phaeochromocytomas and extra-adrenal paragangliomas are also capable of producing and secreting peptides that can cause clinical syndromes.[47] Production of adrenocorticotropic hormone, ß-endorphin, corticotropin-releasing hormone, calcitonin gene-related peptide, vasoactive intestinal peptide, growth hormone-releasing hormone, neuropeptide Y, peptide YY, insulin-like growth factor-1, galanin, adrenomedullin, serotonin, somatostatin and gastrin-like neuropeptide have been reported.[43]

As with other tumours, previous procedures can alter the microscopic appearance of a tumour, and should be recorded. Fine needle aspiration or core needle biopsy may cause tumour infarction or interfere with assessment of invasion. Preoperative embolisation is an established cause of necrosis in head and neck paragangliomas.[45] Partial adrenalectomy, which is increasingly utilised in treating patients with pheochromocytomas, might also be expected to cause long-term changes in histology of the residual adrenal.[48]

RCPath additional comments:

Provision of appropriate clinical data (especially hormonal status) is essential for multifactorial prognostic scoring, especially the Grading system for Adrenal Phaeochromocytoma and Paraganglioma (GAPP) system (see NC7 Multifactorial scoring systems). *[Level of evidence – C.]*

2	**Descriptor**	**Responses**
ICCR	Operative procedure	Multi-selection value list (select all that apply)/text: • Not specified OR • Biopsy (core needle, incisional, excisional), specify • Open resection, specify procedure, including other organs if present (e.g. adrenal resection and liver biopsy) • Laparoscopic • Organ-sparing • Other (e.g. conversion, laparoscopic to open), specify
Operative procedure – ICCR commentary: Laparoscopic surgery is frequently used and this may lead to some disruption or fragmentation of the gland/tumour. This may cause problems in assessing tumour size, integrity of the tumour capsule and completeness of excision, and may also cause distortion of vascular channels, making assessment of lymphovascular invasion difficult. In the rare cases where the specimen has been morcellated, tumour size should be obtained from either the surgeon or from preoperative cross-sectional imaging studies. **RCPath additional comments:** Please refer to section on morcellation (section 3). *[Level of evidence – C.]*		

3	**Descriptor**	**Responses**

ICCR	Specimen(s) submitted	Multi-selection value list (select all that apply)/text:
		• Not specified
		• Adrenal gland
		  – Left
		  – Right
		• Biopsy tissue, specify site(s) and laterality
		• Lymph nodes, specify biopsy/dissection, site(s) and laterality

		• Other (e.g. right neck mass, midline abdominal mass), specify site(s) and laterality

Specimen (s) submitted – ICCR commentary:

All anatomical structures removed or biopsied as part of the procedure should be identified. Examples of 'other' specimens may include additional tissues or organs (e.g. kidney, larynx), or deposits of recurrent or metastatic tumour.

Laterality information is needed for correct identification of specimens. The designation of laterality may include right, left or midline.

RCPath additional comments:

None.

[Level of evidence – C.]

4	**Descriptor**	**Responses**
ICCR	Tumour focality	Single-selection value list/numeric/text: • Unifocal • Multiple – Multifocal (separate tumours in the same organ), specify number of tumours – Multiple tumours in separate organs,[a] specify number of tumours • Indeterminate • Cannot be assessed, specify [a] If multiple tumours from different organs are present, separate datasets should be used to record all following elements for each tumour.

Tumour focality – ICCR commentary:

The presence of multiple or multifocal tumours is an important clue to the presence of hereditary disease.[49] Multifocality is defined as separate foci of tumour in the same organ, in contrast to multiple tumours in separate organs (e.g. 2 or 3 removed paragangliomas or a paraganglioma and a phaeochromocytoma). These designations apply to primary tumours, not metastases, and require histologic confirmation that tumour is present.

In some cases it may not be possible to determine whether a specimen represents a metastasis or a separate primary (e.g. a suspected lymph node with no residual lymph node architecture or a solitary pulmonary nodule).[50] Similarly, it may not be possible to determine whether a fragmented specimen is multifocal. These examples would be classified as indeterminate.

Specimens should be carefully examined both macroscopically and microscopically to determine whether multiple or multifocal tumours are present. In most cases multifocality specifically applies to the adrenal gland. However, occasional adrenal specimens may contain both a phaeochromocytoma and a nearby extra-adrenal paraganglioma.

Implementation notes: If multiple tumours from different organs are present, separate datasets should be used to record all following elements for each tumour. **RCPath additional comments:** The terms ‘multicentric’ and ‘multiple’ are synonymous. *[Level of evidence – C.]*

5 ICCR	**Descriptor**	**Responses**

	Tumour site	Multi-selection value list (select all that apply)/numeric/text:
		• Not specified
		OR
		• Adrenal
		  – Left
		  – Right
		• Other abdominal or pelvic (single-select)
		  – Paraaortic
		  – Urinary bladder
		  – Other, specify
		• Thorax (single-select)
		  – Paraaortic
		  – Cardiac
		  – Other, specify
		• Head and neck
		• Carotid body
		  – Left
		  – Right
		• Middle ear (jugulotympanic)
		  – Left
		  – Right
		• Vagal
		  – Right
		  – Left
		• Laryngeal
		  – Left
		  – Right
		• Other, specify site(s) and laterality

Tumour site – ICCR commentary:		

This element is defined as the site from which the surgeon has removed tumour tissue, and requires histologic confirmation that tumour is present.

The anatomic location of a paraganglioma has important clinical correlations with predictive value concerning genotype, hormonal function, likelihood of additional and syndromically associated tumours, and risk of metastasis.[51]

Metastatic sites such as bone, liver, lung, lymph node, etc. should specifically indicate which bone(s)/which lung(s)/which lymph node(s), and the number of tumours, independently for each site.

Implementation notes:

Specify number of tumours at any site containing more than one tumour.

If multiple tumours from different organs are present, separate datasets should be used to record all following elements for each tumour.

RCPath additional comments:

None.

[Level of evidence – C.]

6	Descriptor	Responses
ICCR	**Specimen integrity**	Single-select value list: • Specimen intact • Fragmented specimen • Cannot be assessed, specify

Specimen integrity – ICCR commentary:

Tumour fragmentation often results from laparoscopic surgery and may cause problems in assessing tumour size, integrity of the tumour capsule, lymphovascular invasion and completeness of excision.

RCPath additional comments:

None.

[Level of evidence – C.]

7	Descriptor	Responses
ICCR	Tumour dimensions	Numeric/text • Maximum tumour dimension (largest tumour) ___ mm OR • Cannot be assessed, specify

Tumour dimensions – ICCR commentary:

Tumour measurements should not include adjacent fat or other non-neoplastic tissue. The dimensions recorded should be the most complete as determined by accurately assessing gross and microscopic measurements.

Large tumour size (>50 mm) correlates to metastatic potential in some but not all studies, although possibly not as an independently useful criterion.[52,53] However, tumour size ≥50 mm is included as a staging criterion in the American Joint Committee on Cancer (AJCC) TNM *Staging Manual* (*8th edition)*.[54,55]

Tumour sampling for microscopy should represent all variations in the gross appearance and consistency of the tumour, as well as margins and other specific features of interest. The general guideline of at least 1 section per cm of tumour should be considered (see section 4).

In the rare cases where the specimen has been morcellated, tumour size should be obtained from either the surgeon or from preoperative cross-sectional imaging studies.

RCPath additional comments:

None.

[Level of evidence – C.]

8	**Descriptor**	**Responses**
ICCR	Medullary hyperplasia	Applicable to adrenal specimens only. Single-selection value list/text: • Medullary nodules (microphaeochromocytoma) (<10 mm) – Present – Absent – Indeterminate – Cannot be assessed, specify • Diffuse hyperplasia – Present – Absent – Indeterminate – Cannot be assessed, specify

Medullary hyperplasia – ICCR commentary:

Adrenal medullary nodules either coexisting with phaeochromocytoma/paraganglioma, or in a background of diffuse adrenal medullary expansion, are an important clue to the presence of hereditary disease.[56] They most often are associated with MEN2, but have recently been described in other disorders.[15] Historically, nodules <1 cm have been arbitrarily called hyperplastic nodules or nodular adrenal medullary hyperplasia. Current molecular evidence suggests they are more appropriately considered microphaeochromocytomas.[14]

Adrenal gland (or glands) received for diagnosis of possible microphaeochromocytoma or adrenal medullary hyperplasia should be orientated and dissected clean of as much fat/connective tissue as possible and then accurately weighed. Because this would preclude

evaluation of the fat for microscopic involvement by a tumour, it should not be done in cases where invasive tumour is a consideration. Sequential sections of roughly equal thickness are made in the transverse plane to display the distribution and amount of medullary tissue in the general regions – head, body and tail.[57]

Medulla is normally present only in the head and body of the gland, with only minimal extension into the alae but not into the tail. The presence of substantial adrenal medullary tissue in the tail or alae strongly suggests adrenal medullary hyperplasia. Normal medulla usually does not represent more than 1-third of the gland thickness, with cortex on each side comprising the other 2-thirds. However, anatomic variants exist, and definitive diagnosis of medullary hyperplasia in the absence of nodules may require quantitative morphometric analysis.[58]

Although it is sometimes difficult to define the tail of an adrenal gland distorted by a phaeochromocytoma, it should be remembered that adrenal medullary nodules and phaeochromocytomas can occur in adrenals in MEN2 syndrome without an obvious background of diffuse hyperplasia.[58] The adrenal gland adjacent to an apparently sporadic phaeochromocytoma should therefore be sectioned as above and carefully examined for small nodules.[43]

Implementation notes:

Applicable to adrenal specimens only.

RCPath additional comments:

It is advised not to strip the surrounding fat/soft tissue or attached adjacent organs off the tumour as this is detrimental to assessment of both completeness of excision (which is a good indicator of the likelihood of local recurrence) and of staging (as it prevents an accurate assessment of local invasion, which is a much more reliable indicator of aggressive behaviour).[6] Please refer to sections 3 and 4 on macroscopic dissection for further comments on tumour weight.

[Level of evidence – C.]

9	Descriptor	Responses
ICCR	Histological tumour type	Single-selection value list/numeric/text: • Phaeochromocytoma • Extra-adrenal paraganglioma • Composite phaeochromocytoma – Neuroblastoma, specify____% – Ganglioneuroblastoma, specify____% – Ganglioneuroma, specify____% – Malignant peripheral nerve sheath tumour, specify____% • Composite paraganglioma – Neuroblastoma, specify____% – Ganglioneuroblastoma, specify____% – Ganglioneuroma, specify____%

		– Malignant peripheral nerve sheath tumour, specify____% • Other, specify____%

Histological tumour type – ICCR commentary:

All tumours of the adrenal medulla and extra-adrenal paraganglia should be given a type based on the most recent edition of the WHO *Classification of Tumours of Endocrine Organs*.[3] A composite tumour is defined as a tumour that combines morphological features of paraganglioma or phaeochromocytoma with those of a developmentally related neurogenic tumour, including ganglioneuroma, ganglioneuroblastoma, neuroblastoma or malignant peripheral nerve sheath tumour.[3,4]

There is no specified percentage of the second tumour type.[3,4] However, complete histoarchitecture of the second tumour type is required. Scattered neurone-like cells often seen in phaeochromocytomas are not sufficient. This designation is separate from mixed corticomedullary neoplasms, which would be included in 'other'.

The most common second component of composite tumours is ganglioneuroma (70–80% of cases) followed by ganglioneuroblastoma (15–20%). Although the latter is morphologically comparable to paediatric ganglioneuroblastoma, it differs in molecular and clinical perspectives and confers only a low risk of metastases.[4,57]

RCPath additional comments:

None.

[Level of evidence – C.]

10	Descriptor	Responses
ICCR	Extent of invasion	Multi-selection value list (select all that apply)/text: • Cannot be assessed OR • Microscopic transcapsular penetration of tumour capsule within an organ • Microscopic transcapsular penetration of organ capsule • Invasion into peritumoural soft tissue • Invasion into adjacent structure(s)/organ(s), specify

Extent of invasion – ICCR commentary:

Invasion is a reported risk factor for development of metastases when considered in conjunction with other adverse features. However, invasion is currently categorised and weighted inconsistently.[56] Precise descriptions of the nature and extent of invasion are required in conjunction with other adverse factors in order to optimally guide patient management.

As phaeochromocytomas usually do not have a capsule, the adrenal capsule becomes the capsule of the tumour in most cases.[57] Within other organs an encapsulated tumour may be

more likely. If a tumour capsule is present, invasion of the organ capsule and tumour capsule should be documented separately. Capsular invasion is not assessed in a biopsy.

RCPath additional comments:

None.

[Level of evidence – C.]

11	Descriptor	Responses
ICCR	Lymphovascular invasion	Multi-selection value list (select all that apply)/text: • Not identified • Present (select all that apply) – Periadrenal or peritumoural for extra-adrenal tumours, specify ○ Intracapsular ○ Extracapsular – Adrenal vein – Vena cava – Other (e.g. adrenal central vein and tributaries), specify

Lymphovascular invasion – ICCR commentary:

Vessel invasion is a reported risk factor for development of metastases when considered in conjunction with other adverse features.[49] Precise descriptions of the nature and extent of vascular invasion are required in conjunction with other adverse factors in order to optimally guide patient management.[49]

There are currently no firm data for phaeochromocytoma or paraganglioma to assess whether metastatic risk increases progressively with involvement of small to larger vessels, although extrapolation from other tumours would suggest that is the case. In the adrenal, invasion of one or more tributaries of the central vein may be an important event leading to involvement of the adrenal vein and the vena cava. This may be facilitated by the normal anatomy within the adrenal, where arcades of mural smooth muscle provide gaps through which normal cortex and/or medulla or tumours derived from them can protrude into the vascular space(s).[59]

RCPath additional comments:

None.

[Level of evidence – C.]

12	Descriptor	Responses
ICCR	Margin status	Single-selection value list/text/numeric: • Not involved (R0) • 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

Margin status – ICCR commentary:

Incomplete excision has been associated with local recurrence.[60] Positive margins are defined both grossly, as tumour obviously transected, and microscopically as 'tumour on ink', if the surface is inked. Adrenalectomy specimens especially are frequently damaged and very irregular, often precluding both the application of ink and reliable gross assessment. In these cases the margins cannot be assessed.

RCPath additional comments:

None.

[Level of evidence – C.]

13	Descriptor	Responses
ICCR	Proliferative fraction	Single-selection value list/numeric: • Mitotic count/2 mm^2 AND/OR • Ki-67 ___% • Cannot be assessed

Proliferative fraction – ICCR commentary:

Mitotic count and/or Ki-67 proliferation index is now widely utilised in risk stratification for other neuroendocrine tumours. A high proliferative fraction based on either mitoses or Ki-67 is a reported risk factor for development of metastases for phaeochromocytoma and paraganglioma.[49,61]

Mitotic count should be performed in a minimum area of 2 mm^2, which is equivalent to approximately 10 HPFs in many microscopes. There is currently no standard approach to scoring a Ki-67 labelling index in phaeochromocytoma and paraganglioma, and this has been emphasised. On the basis of established methodology for other neuroendocrine tumours, it is recommended that the Ki-67 index should be reported as percentage of positive tumour cells per x40 HPF (0.2 mm^2) in area of highest nuclear labelling.[4,43,49] Counts should ideally be based on manual counts of printed images or appropriately validated automated image analysis; visual estimates have proven less accurate for multiple tumour types.[4]

RCPath additional comments:

Visual estimates of Ki-67 % are known to be less standardised and associated with some interobserver variation. However, in practice these still provide valuable prognostic/threshold information.

[Level of evidence – C.]

14	Descriptor	Responses

ICCR	Lymph node status	Single-selection value list/text/numeric:
		• No nodes submitted or found
		OR
		• Lymph node biopsy, specify site(s), if applicable
		• Number of lymph nodes examined
		  – Not involved
		  – Involved
		• Number of positive lymph nodes
		• Number cannot be determined

Lymph node status – ICCR commentary:

Regional lymph nodes are found within the anatomic area in which a tumour is located and receive lymphatic drainage from that area. They are, therefore, anatomically related to the tumour and may be the earliest sites of lymph node metastases.

In keeping with practices applied to other tumours to stratify risk of early nodal involvement, the pathology report should state the total number of lymph nodes examined and the number of nodes with metastases. Size of tumour deposit within the lymph node may be correlated with outcome and thus it is recommended to report the greatest tumour dimension identified within the lymph node dissection/biopsy sample.

Lymph node biopsies are sometimes received as intact resections and sometimes as multiple fragments. In the latter, the number of nodes will be known only if specified by the surgeon and otherwise is undetermined.

RCPath additional comments:

None.

[Level of evidence – C.]

15	Descriptor	Responses
ICCR	Histologically confirmed distant metastases	Single-selection value list/text: • Not identified • Not assessed

		• Present, specify site(s)

Histologically confirmed distant metastases – ICCR commentary:

A diagnosis of metastasis is appropriate when phaeochromocytoma or paraganglioma is present in a site where normal paraganglia do not exist. The only such sites a priori are bone and histologically confirmed lymph node. It is crucial to remember the normal anatomic distribution of paraganglia in order to consider the possibility of multiple primary tumours.[62]

The assessment of distant metastasis can be particularly challenging in some cases because primary paragangliomas do also occur in rare anatomic sites such as thyroid, pituitary, gallbladder, liver and lung. Therefore, tumour in these rare locations should not automatically be considered metastatic. In addition, due to the ease of performing needle core biopsies of various organs, metastatic disease is now increasingly seen histologically and, in many cases, biopsies may be the only tissue sample available due to the advanced nature of the primary tumour or the comorbidities associated with surgical resection.

RCPath additional comments:

None.

[Level of evidence – C.]

16	**Descriptor**	**Responses**
ICCR	Pathological staging (AJCC *TNM 8th edition*) TNM descriptors	Primary tumour (pT) Single-selection value list: • TX Primary tumour cannot be assessed • T1 Phaeochromocytoma <5 cm in greatest dimension, no extra-adrenal invasion • T2 Phaeochromocytoma ≥5 cm or paraganglioma – sympathetic of any size, no extra-adrenal invasion • T3 Tumour of any size with invasion into surrounding tissues (e.g. liver, pancreas, spleen, kidneys) Commentary Phaeochromocytoma: within adrenal gland Paraganglioma sympathetic: functional Paraganglioma parasympathetic: often non-functional, and located in the head and neck Note: Parasympathetic paragangliomas are not staged. Regional lymph nodes (pN)

		Single-selection value list: • NX Regional lymph nodes cannot be assessed • N0 No regional lymph node metastasis • N1 Regional lymph node metastasis Choose if applicable: • m – multiple primary tumours • r – recurrent • y – post-therapy
Pathological staging – ICCR commentary: The American Joint Committee on Cancer (AJCC) staging system for phaeochromocytomas and sympathetic paragangliomas was implemented in 2017 in order to guide clinicians in determining the therapies and follow-up that patients require.[7] It is expected that extensive staging and survival data to be collected will also lead to increased understanding of these tumours and to future improvements in patient care.[7,63] **RCPath additional comments:** None. *[Level of evidence – C.]*		

6.2 Non-core data items

NC1	**Descriptor**	**Responses**
ICCR	Tumour dimensions	Numeric/text Additional dimensions (largest tumour) ___mm x ___ mm
RCPath additional comments: None. *[Level of evidence - C.]*		

NC2	**Descriptor**	**Responses**
ICCR	Margin status	• If not involved (R0) – Distance of tumour to closest margin ___ mm – Closest margin, specify if possible

RCPath additional comments: None. *[Level of evidence – C.]*

NC3	**Descriptor**	**Responses**
	Lymph node status	• ENE – Not identified – Present • Number of nodes with ENE – Cannot be determined • Maximum dimension of largest lymph node metastasis
RCPath additional comments: None. *[Level of evidence – C.]*		

NC4	**Descriptor**	**Responses**
	Adverse features	Please see section 7

NC5	**Descriptor**	**Responses**
	Ancillary studies	Please see section 12

7 Predictors of malignancy or metastatic potential

7.1 Adrenal cortical tumours

There are no absolute criteria for the diagnosis of malignancy in adrenal cortical tumours apart from invasion of local structures and metastasis. A number of multifactorial analyses have been proposed to identify malignant potential in intra-adrenal tumours. Some include clinical and biochemical data in addition to histological features and are based on a numerical assessment of risk.[64,65]

NC7	Descriptor	Responses
ICCR	Multifactorial scoring systems	Multi-selection value list (select all that apply)/text: • 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

Multifactorial scoring systems – ICCR commentary:

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 ICCR is unable to recommend any particular approach. The 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.

Weiss system for conventional adrenal cortical neoplasms[20]

- 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 1 point. Tumours with Weiss scores ≥3 are considered to possess malignant potential and should be diagnosed as carcinomas.

Modified Weiss system (Aubert) for conventional adrenal cortical neoplasms[66]

- 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 0–7, with those tumours scoring ≥3 possessing malignant potential. The modified Weiss system is highly correlated with the original Weiss system.[66]

Lin–Weiss–Bisceglia system for oncocytic adrenal cortical neoplasms[19]

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.

Helsinki system for diagnosis and prognosis of conventional and oncocytic adrenal cortical neoplasms[67]

- 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.[68]

Reticulin algorithm for the diagnosis of conventional and oncocytic adrenal cortical neoplasms [39,40]

- 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 on 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.

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 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.[69,70]

Additional efforts to include the Ki-67 proliferation index in the evaluation of paediatric tumours are ongoing.[70,71] For these reasons, evaluation of paediatric tumours with Ki-67 is recommended whenever possible.

RCPath additional comments:

Paediatric tumours with two or fewer Wieneke/AFIP criteria were categorised cortical adenoma, those with 3 as ‘indeterminate’ for malignancy and tumours with 4 or more criteria as ACC.

[Level of evidence – C.]

7.1.2 Reporting of specimens damaged during surgery

ACC often shows many of the features included in both of the systems outlined above and a diagnosis of malignancy is possible in most cases, even where there has been surgical trauma to the specimen. The main problem when the tumour is restricted to the adrenal gland is usually the confidence with which the presence or absence of capsular invasion can be diagnosed and the completeness of excision assessed. The problem is the tumour

with a borderline score on any scoring system, in which assessment is incomplete. There are no published studies on how to deal with this. Further sampling may be helpful.

Where features contributing to any multifactorial scoring system cannot be assessed, this should be recorded within the report. If there is a borderline score with absent features, it may be necessary to define the lesion as of uncertain malignant potential. However, a mitotic rate of >5 per 50 HPF and the presence of atypical mitoses are highly suggestive of malignancy.

7.2 Phaeochromocytoma/paraganglioma

The presence of metastatic disease is the only absolute indicator of malignancy in this group of tumours. Multifactorial scoring systems like the Phaeochromocytoma of the adrenal gland scoring scale (PASS, see Table 2) and GAPP (see Table 3)[49,50] attempt to assess risk of aggressiveness and emerging evidence indicates that the GAPP score performs better than the PASS score, as there is less interobserver variability and better correlation with outcome (higher GAPP scores associated with aggressive phaeochromocytomas/paragangliomas).[49,50,72] SDHB immunohistochemistry (loss of expression) is also a reliable marker of increased risk of aggressive behaviour/metastatic potential.

NC4	**Descriptor**	**Responses**
ICCR	Adverse features	Multi-selection value list (select all that apply)/text: **Histological features** • Necrosis (single-select) – Comedonecrosis – Other, specify • Growth pattern (single-select) – Large and irregular nests – Diffuse – Pseudorosette (even focal) • Cellularity (single-select) – Moderate (150–250 cells/U) – High (>250 cells/U) – Indeterminate • Cytologic features (single-select) – Spindle cells – Other, specify – Other, specify

		Other features • Extra-adrenal abdominal or mediastinal location • Size >50 mm • Negative staining for SDHB • Biochemical testing showing high levels of methoxytyramine

Adverse features – ICCR commentary:

While the cumulative summary of adverse features may be clinically helpful, it is not a required component of the pathology report and is therefore listed as 'Non-core'. Individual features (tumour size and location) that are core are so listed in other sections.

Several categories of histological features are putative risk factors for development of metastases in multiple publications and overlap in the two major proposed scoring systems for risk stratification, PASS (see Table 2) and GAPP (see Table 3).[49,50] However, the individual parameters within the categories are assessed and weighted differently in the two systems. No scoring system is currently required or endorsed, but histologic features may be considered in conjunction with other data for cumulative risk stratification in order to optimally guide patient management.

Comedonecrosis and growth pattern are the most readily recognised and possibly the most predictive parameters, while cellularity is potentially highly subjective. To reduce subjectivity, it was recommended that cellularity be quantitated by counting the number of cells within an area (U) encompassed by a square grid in a 10x ocular viewed with a 40x HPF, corresponding to 0.0625 mm.[41,49] Necrosis does not include ischemic necrosis secondary to therapeutic embolisation or spontaneous infarction.

PASS was designed for phaeochromocytomas, while GAPP was intended for both phaeochromocytomas and sympathetic paragangliomas. No scoring system currently applies to head and neck paragangliomas, although individual parameters may provide useful information for those tumours.[51] Use of either scoring system is optional. A 2019 meta-analysis of multiple papers employing PASS or GAPP concludes that a low score with either histological system is a strong predictor of low metastatic risk but that high scores have little predictive value in the absence of additional features, including genotype and biochemical testing.[52] Poor concordance between expert pathologists has been noted in a PASS study.[53]

Coarse nodularity is a gross finding reported to be associated with metastatic risk.[54]

RCPath additional comments:

Emerging evidence is in support of the GAPP score performing better than the PASS score, with higher GAPP scores associated with aggressive phaeochromocytomas/paragangliomas.[72] Nevertheless, all proposed systems for assessing the malignant potential of paraganglionic tumours need to be further validated.

[Level of evidence – C.]

Table 2: Phaeochromocytoma of the adrenal gland scoring scale (PASS score).[50]

Feature	Score
Large nests of cells or diffuse growth >10% of tumour volume	2
Necrosis (confluent or central in large cell nests)	2
High cellularity	2
Cellular monotony	2
Presence of spindle-shaped tumour cells (even focal)	2
Mitotic figures (>3 per 10 high power fields)	2
Atypical mitotic figure(s)	2
Extension of tumour into adjacent fat	2
Vascular invasion	1
Capsular invasion	1
Profound nuclear pleomorphism	1
Nuclear hyperchromasia	1
Total possible score	**20**

All tumours that metastasised were reported to have scores ≥4.

Table 3: Grading system for adrenal phaeochromocytoma and paraganglioma (GAPP) scoring scale.[49]

Parameter	Score
Histological pattern	
Zellballen	0
Large and irregular cell nest	1
Pseudorosette (even focal)	1
Cellularity	
Low (<150 cells/U)	0
Moderate (150–250 cells/U)	1
High (more than 250 cells/U)	2
Comedonecrosis	
Absence	0
Presence	2
Vascular or capsular invasion	
Absence	0

Presence			1
Ki-67 labelling index (%)			
<1			0
1–3			1
>3			2
Catecholamine type			
Epinephrine type (E or E+NE)			0
Norepinephrine type (NE or NE+DA)			1
Non-functioning type			0
Total maximum score			**10**
GAPP category	**GAPP score**	**Risk of metastasis (%)**	**5Y OS (%)**
Well differentiated	0–2	3.6	100
Moderately differentiated	3–6	60	66.8
Poorly differentiated	7–10	82.4	22.4
U, number of tumour cells in unit of 10 × 10 mm micrometer under high-power field (×400); E, epinephrine; NE, norepinephrine; DA, dopamine.			

8 SNOMED codes

Details are given in Appendix A.

9 Tumour staging

See sections 6 and 7 for staging systems for phaeochromocytoma and adrenocortical carcinoma.

10 Reporting of small biopsy and cytology specimens

Accurate pathological classification of adrenal tumours requires a multidisciplinary approach. Therefore, every patient with a suspected adrenocortical tumour should undergo careful clinical assessment, appropriate biochemical work-up and adrenal-focused imaging prior to surgery.[73]

Despite improvements in preoperative radiological and biochemical investigations, histopathology remains the gold standard for diagnosis.[73] Histopathological evaluation is

generally performed on adrenal tumour resections because multifactorial scoring systems, developed to separate benign from malignant adrenal tumours, cannot be applied to biopsies. However, tissue can be acquired preoperatively for analysis typically by endoscopic ultrasound-guided fine needle aspiration (EUS-FNA). This is a safe and minimally invasive tool,[74] which can be useful in the evaluation of an adrenal lesion where there is a suspicion of metastatic malignancy with high specimen adequacy and low indeterminate rates.[75] It may not be possible to predict behaviour on such a specimen, especially if the morphology is low grade.

Before performing the procedure it is important to rule out phaeochromocytoma because there is a risk of haemorrhage and hypertensive crisis.[76] Cell block with immunohistochemistry improves specificity and diagnostic accuracy.[77] The majority of adrenal EUS-FNA confirm metastasis, providing useful information for staging and, if required, material for molecular testing.[75]

11 Frozen sections

It is not usual practice to undertake frozen sections on adrenal tumours.

12 Immunohistochemistry

There have been significant advances in the use of immunohistochemistry in the diagnosis, prognosis and determination of the genotypes of adrenal tumours and paragangliomas. The sections below discuss its current utility in diagnostic practice.

12.1 Differentiating between cortical and medullary tumours.

Immunohistochemistry is useful to confirm the diagnosis, particularly in cases where the histological features are ambiguous and a diagnosis of either a cortical tumour or phaeochromocytoma cannot be made on routine H&E staining. Distinction between primary and secondary malignancy is also critical, given that metastatic carcinoma is the commonest malignancy in the adrenal gland.

Adrenocortical carcinomas express markers specific for steroid-producing cells, such as steroidogenic factor-1 (SF-1), as well as inhibin alpha, Melan-A, calretinin and synaptophysin, which are also expressed by other tumour types (Table 4). Staining is variable in intensity and distribution, so markers should be used as part of a panel. Epithelial markers such as pancytokeratin (AE1/3) and epithelial membrane antigen (EMA)

are generally negative; strong diffuse expression of cytokeratin is against a diagnosis of ACC.

Identification of oncocytic adrenocortical neoplasms can be diagnostically difficult. The differential diagnosis includes oncocytic neoplasms arising at other sites (usually kidney or liver) or rarely intra-adrenal tumours, including oncocytic phaeochromocytoma, epithelioid angiomyolipoma (PEComa) and/or metastatic melanoma. Melan-A expression can also be observed in the latter 2.

The immunohistochemical profile of oncocytic, myxoid and sarcomatoid subtypes of ACC largely resembles the profile of conventional ACC. Oncocytic ACCs are generally synaptophysin positive; half of the tumours are alpha-inhibin positive and up to 1 third are Melan-A positive.[78] Sarcomatoid ACCs appear to be negative for SF-1 in the sarcomatoid component and positive for SF-1 in the epithelial component.[79] Furthermore, the sarcomatoid component is usually negative for Melan-A; alpha-inhibin expression is significantly lower and cytokeratin expression can be rarely observed. Aberrant phenotypical differentiation (i.e. melanocytic and neural differentiation) has been rarely observed in the sarcomatoid subtype of ACC.[80]

Phaeochromocytoma and paraganglioma express chromogranin in addition to other neuroendocrine markers, which is helpful in the distinction from ACC. It needs to be noted that synaptophysin expression is not specific for neural/neuroendocrine neoplasms and that up to 2/3 of ACC express synaptophysin.

Paraganglionic tumours and their metastases may need to be distinguished from neuroendocrine tumours arising at other sites. Phaeochromocytomas and paragangliomas do not express cytokeratins, while tyrosine hydroxylase (TH) expression is specific for tumours of adrenal medullary origin and melanocytic neoplasms; however, this is not routinely available in most histopathology departments. In the abdomen, differentiating between a paraganglioma and a neuroendocrine tumour would require demonstration of markers specific for pancreatic and gastrointestinal endocrine tumours (hormones/secretory products specific to those sites). In the thyroid, calcitonin expression should identify medullary carcinoma of thyroid.

Table 4: Immunohistochemical profile of adrenal cortical and medullary tumours and metastases.

	CK	CGA	TH	Syn	SF-1	Inhibin	Calretinin	Melan A	Site-specific markers
Cortical	-/vf	- (0%)	-	+ (67%)	+	+ (97%)	+ (95%)	+ (94%)	-
Medullary	-	+ (100%)	+	+ (100%)	-	+ (6–50%*)	+ (14%)	+ (6%)	-
Metastases	++	-	-	-	-	-	-	-	++

CK: cytokeratins; CGA: Chromogranin A; NSE: Neuron-specific enolase; Syn: Synaptophysin; SF-1 Steroidogenic factor-1; TH: Tyrosine hydroxylase; vf: very focal; * see text.

12.2 Differentiating between primary adrenal and metastatic tumours

The source of metastases to the adrenal gland should be confirmed by appropriate morphology and immunohistochemistry and comparison to the primary tumour, if available. Lymphomas should be characterised by immunohistochemistry and molecular techniques as appropriate.

NC6	**Descriptor**	**Responses**
ICCR	Ancillary studies	• Not performed • Performed, specify

Clinical information – ICCR commentary:

Increasingly, patients with ACC 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 ACC patients have Lynch syndrome, screening for mismatch repair protein defects by immunohistochemistry may be considered.[81,82]

RCPath additional comments:

None.

[Level of evidence – C.]

NC5	Descriptor	Responses

ICCR	Ancillary studies	Multi-selection value list (select all that apply)/numeric/text:
		• Not performed
		OR
		• Immunohistochemistry performed
		  – Chromogranin A, specify result
		  – Synaptophysin, specify result
		  – S-100, specify result
		  – SDHB, specify result
		  – Tyrosine hydroxylase, specify result
		  – Other, specify
		• Molecular testing performed, specify result(s) if available
		• Other, specify

Ancillary studies – ICCR commentary:

The differential diagnosis of phaeochromocytoma or paraganglioma often requires use of generic immunohistochemical markers to establish the neuroendocrine nature of a tumour together with additional more specific markers to confirm the diagnosis or exclude other entities, including other neuroendocrine neoplasms.[45,55,62] The most frequently utilised positive generic markers in most contexts are chromogranin A (CgA) and synaptophysin. However, synaptophysin is expressed in adrenal cortex and must not be used to distinguish phaeochromocytomas from cortical neoplasms.

Additional useful positive markers include tyrosine hydroxylase to demonstrate capacity for catecholamine synthesis and S100 to demonstrate sustentacular cells. Useful negative markers include keratins and inhibin. A caveat is that head and neck paragangliomas are often completely negative for tyrosine hydroxylase and also negative or only focally positive for CgA and synaptophysin.[45] In those cases, the presence of sustentacular cells can be particularly helpful; however, sustentacular-like cells can also be found in other neuroendocrine tumours and are therefore not diagnostic. Additional potentially useful positive markers that have been proposed include dopamine beta-hydroxylase, INSM1, NKX2.2 and GATA-3.[45,59,62,83–85]

In addition to aiding diagnosis, immunohistochemistry is increasingly used as a genetic screen. This particularly applies to staining for loss of SDHB, which also serves as a prognostic marker.[86,87]

RCPath additional comments:

None.

[Level of evidence – C.]

12.3 Ki-67 labelling index assessment in adrenocortical neoplasms

Ki-67 labelling index (LI) typically exceeds 5% in most ACCs, while with regard to prognostication and/or therapeutic decision-making (e.g. adjuvant mitotane therapy),

specific Ki-67 LI thresholds have been proposed in the adult (<10, 10–19, ≥20) and paediatric (>15%) setting.[29,71,88] In this context, Ki-67 LI is a key element as defining the grade, in addition to stage, resection status and symptoms, of the recently validated G-RAS scoring system. The latter appears to have superior prognostic performance to Ki-67 LI and tumour stage in operated patients suffering from adrenocortical cancer, independently from adjuvant mitotane.[89] Please also refer to section 5.18.

12.4 Ki-67 labelling index assessment in phaeochromocytomas & paragangliomas

Ki-67 LI of ≥3% has been documented in approximately 50% of metastatic paraganglionic tumours and Ki-67 LI has been incorporated as a key element of the GAPP system with the following thresholds <1%, 1–3% and >3%.[49,90] Such thresholds have been also significantly correlated with recurrence-free survival.[73] Please also refer to section 6.13.

12.5 SDH immunohistochemistry in phaeochromocytoma and paraganglioma

SDH immunohistochemistry appears to be a valuable tool to triage genetic testing, validate genetic variants of unknown significance emerging from targeted next-generation sequencing analysis and highlight aggressive disease.[91–94] *SDH* mutated phaeochromocytoma and paraganglionic tumours have a high risk of metastasis/malignant behaviour. Tumours with *SDHB, SDHC, SDHD or SDHAF2* mutations display SDHB immunonegativity and SDHA immunoreactivity, while *SDHA* mutated tumours show SDHA and SDHB immunonegativity.[86]

While antibodies to SDHA, SDHB and SDHD are available, in routine practice, evaluation of a single immunohistochemical marker (SDHB) allows determination of SDH mutations across all SDH subunits (see Table 5). SDHD immunohistochemistry might be valuable in the interpretation of inconclusive SDHB immunoexpression patterns as being generally positive in *SDH-x* mutated tumours.[86,95]

Table 5: SDH immunohistochemistry interpretation in paraganglionic tumours harbouring *SDH* mutations.

		Immunohistochemistry		
		SDHA	**SDHB**	**SDHD**
Mutation	***SDHA***	Loss of expression	Loss of expression	Cytoplasmic diffuse (non-mitochondrial) expression
	SDHB	Retention of cytoplasmic granular (mitochondrial) expression	Loss of expression	Cytoplasmic diffuse (non-mitochondrial) expression
	SDHC			Cytoplasmic diffuse (non-mitochondrial) expression
	SDHD			Cytoplasmic diffuse (non-mitochondrial) expression
	SDHAF2			N/A

12.6 Markers of familial origin in phaeochromocytoma and paraganglioma

In current practice, all patients suffering from paraganglionic tumours are expected to be offered genetic screening to identify various forms of hereditary predisposition.[41,46,91,96] From a histopathological standpoint, immunohistochemistry has arisen as a cost-effective approach in the evaluation of germline mutations in patients with phaeochromocytomas/paragangliomas (Table 6).[91,92,97,98] Alpha-inhibin expression has been recently documented in approximately 50% of paraganglionic tumours; particularly in SDH- and VHL-related cases, while a membranous carbonic anhydrase 9 staining has been almost exclusively observed in VHL-related tumours.[97,98] With regard to specific limitations of immunohistochemical markers in endocrine pathology for familial endocrine cancer syndrome identification, the reader is referred to Papathomas and Nose.[92]

Table 6: Immunohistochemistry as a functional tool in phaeochromocytomas/paragangliomas for identification of hereditary tumour predisposition syndromes.

Gene	Molecular cluster	Immunohistochemistry
VHL & SDH-x	Pseudohypoxia	Alpha-inhibin expression
VHL	Pseudohypoxia (non-Krebs cycle-related)	Carbonic anhydrase 9 expression

SDH-x (SDHA, SDHB, SDHC, SDHD & SDHAF2)	Pseudohypoxia (Krebs cycle-related)	SDHB and/or SDHA deficiency and SDHD expression
FH	Pseudohypoxia (Krebs cycle-related)	FH deficiency and 2-succinyl-cysteine (2-SC) expression
MAX	Kinase signalling	MAX deficiency

13 Molecular testing

ACC has been a traditional component of the tumour spectrum of Li-Fraumeni syndrome (LFS).[99] All ACC patients can be referred to clinical genetics for germline inactivating *TP53* mutations (www.england.nhs.uk/publication/national-genomic-test-directories/).

- Although ACC has been proposed as a Lynch syndrome (LS)-associated tumour, currently there is no recommendation for germline mutations in *DNA mismatch repair* (*MMR*) genes according to the NHS rare diseases test directory guidelines.[82,100] Nevertheless, MMR protein immunohistochemistry screening could be an efficient strategy to detect LS in ACC patients. The absence of expression of one or more of the proteins MLH1, PMS2, MSH2 or MSH6 could prompt referral to clinical genetics for LS; the most common inherited colorectal and endometrial cancer syndrome.[82] Of note is that MMR-deficient ACCs arising in the setting of LS do not appear to exhibit high levels of microsatellite instability, contrasting common LS-associated extra-colonic tumours.[92]
- In addition to Li-Fraumeni syndrome and LS, other hereditary syndromes that can manifest with ACC are MEN type 1, familial adenomatous polyposis, Carney complex, Beckwith–Wiedemann syndrome and neurofibromatosis type 1 (NF1). Given this wide variety of syndromes, patients should be screened for hereditary disease.[99,101]

Phaeochromocytomas and paragangliomas carry the highest degree of hereditability among all human neoplasms, as 40–45% are associated with a germline mutation.[91] According to NHS rare diseases test directory, all phaeochromocytoma and paraganglioma patients in England should be referred to clinical genetics based on testing criteria, which can be accessed at www.england.nhs.uk/publication/national-genomic-test-directories/. For those outside of England, please refer to your national guidelines, as appropriate.

Testing of individual (proband) affected with cancer where the individual +/- family history meets one of the following criteria. The proband has:

- phaeochromocytoma <60 years, OR
- any paraganglioma at any age, OR
- phaeochromocytoma/paraganglioma with loss of staining for SDH proteins on immunohistochemistry, OR
- bilateral phaeochromocytoma (any age), OR
- phaeochromocytoma and renal cell carcinoma (any age), OR
- phaeochromocytoma/paraganglioma (any age) AND ≥1 relative (first/second/third degree relative) with phaeochromocytoma/paraganglioma/renal cell cancer (any age)/gastrointestinal stromal tumour.

Note:

- the proband's cancer and majority of reported cancers in the family should have been confirmed.
- testing under this clinical indication does not include NF1.

It should be noted that occasional tumours that appear SDH negative on immunohistochemistry may show discordant findings on standard molecular panels and further genetic/epigenetic investigations are warranted.

In the sporadic setting, a subset of aggressive tumours harbour mastermind-like transcriptional coactivator 3 (*MAML3*) fusions.[102,103] These fusion-positive paraganglionic tumours are characterised by intense MAML3 nuclear staining and increased β-catenin immunoexpression.[103]

14 Criteria for audit

The following are recommended by the RCPath as Key assurance indicators (see *Key assurance indicators for pathology services*, November 2019) and key performance indicators (see *Key Performance Indicators – Proposals for implementation*, July 2013):

- cancer resections should be reported using a template or proforma, including items listed in the English COSD, which are, by definition, core data items in RCPath cancer

datasets. English trusts were required to implement the structured recording of core pathology data in the COSD

  - standard: 95% of reports must contain structured data

- histopathology cases must be reported, confirmed and authorised within 7 and 10 calendar days of the procedure

  - standard: 80% of cases must be reported within 7 calendar days and 90% within 10 calendar days.

15 References

1. Giordano T, Berney D, de Krijger R, Erickson L, Fassnacht M, Mete O *et al. Carcinoma of the Adrenal Cortex Histopathology Reporting Guide (1st edition).* International Collaboration on Cancer Reporting 2019. Accessed October 2022. Available at: www.iccr-cancer.org/datasets/published-datasets/endocrine/adrenal-cortex/

2. Tischler A, Asa S, Clifton-Bligh R, de Krijger R, Kimura N, Komminoth P *et al. Phaeochromocytoma and Paraganglioma Histopathology Reporting Guide.* International Collaboration on Cancer Reporting 2019. Accessed October 2022. Available at: www.iccr-cancer.org/datasets/published-datasets/endocrine/phaeochromocytoma/

3. WHO Classification of Tumours Editorial Board. *WHO Classification of Endocrine and Neuroendocrine Tumours*. Lyon, France: IARC Press, 2022.

4. Lloyd R, Osamura R, Klöppel G, Rosai J (eds). *WHO Classification of Tumours of Endocrine Organs (4th edition).* Lyon, France: IARC Press, 2017.

5. Rindi G, Mete O, Uccella S, Basturk O, La Rosa S, Brosens LAA *et al.* Overview of the 2022 WHO Classification of Neuroendocrine Neoplasms. *Endocr Pathol* 2022;33:115–154.

6. Fassnacht M, Johanssen S, Quinkler M, Bucsky P, Willenberg HS, Beuschlein F *et al.* Limited prognostic value of the 2004 International Union Against Cancer staging classification for adrenocortical carcinoma: proposal for a Revised TNM Classification. *Cancer* 2009;115:243–250.

7. Amin MB, Edge S, Greene FL, Byrd DR, Brookland RK, Washington MK *et al. AJCC Cancer Staging Manual (8th edition)*. New York, USA: Springer, 2017.

8. Zografos G, Vasiliadis G, Farfaras NA, Aggeli C, Digalakis M. Laparoscopic surgery for malignant adrenal tumors. *JSLS* 2009;13:196–202.

9. Mpaili E, Moris D, Tsilimigras DI, Oikonomou D, Pawlik TM, Schizas D *et al.* Laparoscopic versus open adrenalectomy for localized/locally advanced primary adrenocortical carcinoma (ENSAT I-III) in adults: Is margin-free resection the key surgical factor that dictates outcome? A review of the literature. *J Laparoendosc Adv Surg Tech A* 2018;28:408–414.

10. Hue JJ, Ahorukomeye P, Bingmer K, Drapalik L, Ammori JB, Wilhelm SM *et al.* A comparison of robotic and laparoscopic minimally invasive adrenalectomy for adrenal malignancies. *Surg Endosc* 2022;36:5374–5381.

11. Lughezzani G, Sun M, Perrotte P, Jeldres C, Alasker A, Isbarn H *et al.* The European Network for the Study of Adrenal Tumors' staging system is prognostically superior to the International Union against Cancer-Staging system: A North American validation. *Eur J Cancer* 2010;46:713–719.

12. Brierley JD, Mary K. Gospodarowicz, Wittekind C (eds). *Union for International Cancer Control TNM Classification of Malignant Tumours (8th edition).* Oxford, UK: Wiley-Blackwell, 2016.

13. Thompson LDR, Gill AJ, Asa SL, Clifton-Bligh RJ, de Krijger RR, Kimura N *et al*. Data set for the reporting of pheochromocytoma and paraganglioma: explanations and recommendations of the guidelines from the International Collaboration on Cancer Reporting. *Hum Pathol* 2021;4:83–97.

14. Korpershoek E, Petri BJ, Post E, van Eijck CH, Oldenburg RA, Belt EJ *et al*. Adrenal medullary hyperplasia is a precursor lesion for pheochromocytoma in MEN2 syndrome. *Neoplasia* 2014;23:868–873.

15. Romanet P, Guerin C, Pedini P, Essamet W, Castinetti F, Sebag F *et al*. Pathological and genetic characterization of bilateral adrenomedullary hyperplasia in a patient with germline MAX mutation. *Endocr Pathol* 2017;28:302–307.

16. Koch CA, Mauro D, Walther MM, Linehan WM, Vortmeyer AO, Jaffe R *et al.* Pheochromocytoma in von Hippel–Lindau disease: distinct histopathologic phenotype compared to pheochromocytoma in multiple endocrine neoplasia type 2. *Endocr Pathol* 2002;13:17-27.

17. Giordano TJ, Chrousos GP, de Krijger RR, Gill AJ, Kawashima A, Koch CA *et al*. Adrenal Cortical Carcinoma*. In*: Lloyd R, Osamura R, Klöppel G, Rosai J (eds). *WHO Classification of Tumours of Endocrine Organs (4th edition).* Lyon, France: IARC Press, 2017.

18. Lau SK, Weiss LM. The Weiss system for evaluating adrenocortical neoplasms: 25 years later. *Hum Patho* 2009;40:757-768.

19. Bisceglia M, Ludovico O, Di Mattia A, Ben-Dor D, Sandbank J, Pasquinelli G *et al*. Adrenocortical oncocytic tumors: report of 10 cases and review of the literature. *Int J Surg Pathol* 2004;12:231-243.

20. Weiss LM. Comparative histologic study of 43 metastasizing and nonmetastasizing adrenocortical tumors. *Am J Surg Pathol* 1984;8:163–169.

21. Mete O, Gucer H, Kefeli M, Asa SL. Diagnostic and prognostic biomarkers of adrenal cortical carcinoma. *Am J Surg Pathol* 2018;42:201–213.

22. Assie G, Letouze E, Fassnacht M, Jouinot A, Luscap W, Barreau O *et al.* Integrated genomic characterization of adrenocortical carcinoma. *Nat Genet* 2014;46:607–612.

23. Zheng S, Cherniack AD, Dewal N, Moffitt RA, Danilova L, Murray BA *et al.* Comprehensive pan-genomic characterization of adrenocortical carcinoma. *Cancer Cell* 2016;29:723–736.

24. Delahunt B, Cheville JC, Martignoni G, Humphrey PA, Magi-Galluzzi C, McKenney J *et al.* The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. *Am J Surg Pathol* 2013;37:1490–1504.

25. Weiss LM, Medeiros LJ, Vickery Jr AL. Pathologic features of prognostic significance in adrenocortical carcinoma. *Am J Surg Pathol* 1989;13:202–206.

26. Yigit N, Gunal A, Kucukodaci Z, Karslioglu Y, Onguru O, Ozcan A. Are we counting mitoses correctly? *Ann Diagn Pathol* 2013;17:536–539.

27. Giordano TJ, Kuick R, Else T, Gauger PG, Vinco M, Bauersfeld J *et al.* Molecular classification and prognostication of adrenocortical tumors by transcriptome profiling. *Clin Cancer Res* 2009;15:668–676.

28. Gerdes J. Ki-67 and other proliferation markers useful for immunohistological diagnostic and prognostic evaluations in human malignancies. *Semin Cancer Biol* 1990;3:199–206.

29. Beuschlein F, Weigel J, Saeger W, Kroiss M, Wild V, Daffara F *et al.* Major prognostic role of Ki67 in localized adrenocortical carcinoma after complete resection. *J Clin Endocrinol Metab* 2015;100:841-849.

30. Duregon E, Molinaro L, Volante M, Ventura L, Righi L, Bolla S *et al.* Comparative diagnostic and prognostic performances of the hematoxylin-eosin and phospho-

histone H3 mitotic count and Ki-67 index in adrenocortical carcinoma. *Mod Pathol* 2014;27:1246–1254.

31. Morimoto R, Satoh F, Murakami O, Suzuki T, Abe T, Tanemoto M *et al.* Immunohistochemistry of a proliferation marker Ki67/MIB1 in adrenocortical carcinomas: Ki67/MIB1 labeling index is a predictor for recurrence of adrenocortical carcinomas. *Endocr J* 2008;55:49–55.

32. Renaudin K, Smati S, Wargny M, Al Ghuzlan A, Aubert S, Leteurtre E *et al.* Clinicopathological description of 43 oncocytic adrenocortical tumors: importance of Ki-67 in histoprognostic evaluation. *Mod Pathol* 2018;31:1708–1716.

33. Lu H, Papathomas TG, van Zessen D, Palli I, de Krijger RR, van der Spek PJ *et al.* Automated Selection of Hotspots (ASH): enhanced automated segmentation and adaptive step finding for Ki67 hotspot detection in adrenal cortical cancer. *Diagn Pathol* 2014;9:216.

34. Yamazaki Y, Nakamura Y, Shibahara Y, Konosu-Fukaya S, Sato N, Kubota-Nakayama F *et al.* Comparison of the methods for measuring the Ki-67 labeling index in adrenocortical carcinoma: manual versus digital image analysis. *Hum Pathol* 2016;53:41–50.

35. Papathomas TG, Pucci E, Giordano TJ, Lu H, Duregon E, Volante M *et al.* An international Ki67 reproducibility study in adrenal cortical carcinoma. *Am J Surg Pathol* 2016;40:569–576.

36. WHO Classification of Tumours Editorial Board. *Digestive System tumours: WHO Classification of Tumours (5th edition).* Lyon, France: IARC Press, 2019.

37. Glenn JA, Else T, Hughes DT, Cohen MS, Jolly S, Giordano TJ *et al.* Longitudinal patterns of recurrence in patients with adrenocortical carcinoma. *Surgery* 2019;165:186–195.

38. Sabolch A, Else T, Griffith KA, Ben-Josef E, Williams A, Miller BS *et al.* Adjuvant radiation therapy improves local control after surgical resection in patients with localized adrenocortical carcinoma. *Int J Radiat Oncol Biol Phys* 2015;92:252–259.

39. Duregon E, Fassina A, Volante M, Nesi G, Santi R, Gatti G *et al.* The reticulin algorithm for adrenocortical tumor diagnosis: a multicentric validation study on 245 unpublished cases. *Am J Surg Pathol* 2013;37:1433–1440.

40. Volante M, Bollito E, Sperone P, Tavaglione V, Daffara F, Porpiglia F *et al*. Clinicopathological study of a series of 92 adrenocortical carcinomas: from a proposal of simplified diagnostic algorithm to prognostic stratification. *Histopathology* 2009;55:535–543.

41. Toledo RA, Burnichon N, Cascon A, Benn DE, Bayley JP, Welander J *et al*. Consensus statement on next-generation-sequencing-based diagnostic testing of hereditary phaeochromocytomas and paragangliomas*. Nat Rev Endocrinol* 2017;13:233–247.

42. Eisenhofer G, Klink B, Richter S, Lenders JW, Robledo M. Metabologenomics of phaeochromocytoma and paraganglioma: An integrated approach for personalised biochemical and genetic testing. *Clin Biochem Rev* 2017;38:69–100.

43. Mete O, Tischler AS, de Krijger R, McNicol AM, Eisenhofer G, Pacak K *et al.* Protocol for the examination of specimens from patients with pheochromocytomas and extra-adrenal paragangliomas. *Arch Pathol Lab Med* 2014;138:182–188.

44. Turchini J, Cheung VKY, Tischler AS, De Krijger RR, Gill AJ. Pathology and genetics of phaeochromocytoma and paraganglioma. *Histopathology* 2018;72:97–105.

45. Tischler AS. Pheochromocytoma and extra-adrenal paraganglioma: updates. *Arch Pathol Lab Med* 2008;132:1272–1284.

46. Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH *et al.* Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2014;99:1915–1942.

47. Neumann HPH, Young WF Jr, Eng C. Pheochromocytoma and paraganglioma. *N Engl J Med* 2019;381:552–565.

48. Asher KP, Gupta GN, Boris RS, Pinto PA, Linehan WM, Bratslavsky G. Robot-assisted laparoscopic partial adrenalectomy for pheochromocytoma: The National Cancer Institute Technique. *European Urology* 2011;60:118–124.

49. Kimura N, Takayanagi R, Takizawa N, Itagaki E, Katabami T, Kakoi N *et al.* Pathological grading for predicting metastasis in phaeochromocytoma and paraganglioma. *Endocr Relat Cancer* 2014;21:405–414.

50. Thompson LD. Pheochromocytoma of the adrenal gland scaled score (PASS) to separate benign from malignant neoplasms: a clinicopathologic and immunophenotypic study of 100 cases. *Am J Surg Pathol* 2002;26:551–566.

51. Ellis RJ, Patel D, Prodanov T, Nilubol N, Pacak K, Kebebew E. The presence of SDHB mutations should modify surgical indications for carotid body paragangliomas. *Ann Surg* 2014;260:158-162.

52. Stenman A, Zedenius J, Juhlin CC. The value of histological algorithms to predict the malignancy potential of pheochromocytomas and abdominal paragangliomas–A meta-analysis and systematic review of the literature. *Cancers (Basel)* 2019;11:225.

53. Wu D, Tischler AS, Lloyd RV, DeLellis RA, de Krijger R, van Nederveen F *et al.* Observer variation in the application of the pheochromocytoma of the adrenal gland scaled score. *Am J Surg Pathol* 2009;33:599–608.

54. Linnoila RI, Keiser HR, Steinberg SM, Lack EE. Histopathology of benign versus malignant sympathoadrenal paragangliomas: clinicopathologic study of 120 cases including unusual histologic features. *Hum Pathol* 1990;21:1168–1180.

55. Kimura N, Takekoshi K, Naruse M. Risk stratification on pheochromocytoma and paraganglioma from laboratory and clinical medicine. *J Clin Med* 2018;7:242.

56. Tischler AS, de Krijger RR. 15 years of paraganglioma: Pathology of pheochromocytoma and paraganglioma. *Endocr Relat Cancer* 2015;22:123–133.

57. Lack E. *Tumors of the Adrenal Gland and Extraadrenal Paraganglia (Volume 8).* Washington DC, USA: American Registry Of Pathology, 2007.

58. DeLellis RA, Wolfe HJ, Gagel RF, Feldman ZT, Miller HH, Gang DL *et al.* Adrenal medullary hyperplasia. A morphometric analysis in patients with familial medullary thyroid carcinoma. *Am J Pathol* 1976;83:177–196.

59. Kimura N, Miura Y, Nagatsu I, Nagura H. Catecholamine synthesizing enzymes in 70 cases of functioning and non- functioning phaeochromocytoma and extra-adrenal paraganglioma. *Virchows Arch A Pathol Anat Histopathol* 1992;421:25–32.

60. Li M, Fitzgerald P, Price D, Norton J. Iatrogenic pheochromocytomatosis: a previously unreported result of laparoscopic adrenalectomy. *Surgery* 2001;130:1072–1077.

61. Strong VE, Kennedy T, Al-Ahmadie H, Tang L, Coleman J, Fong Y *et al.* Prognostic indicators of malignancy in adrenal pheochromocytomas: clinical, histopathologic, and cell cycle/apoptosis gene expression analysis. *Surgery* 2008;143:759–768.

62. Asa SL, Ezzat S, Mete O. The diagnosis and clinical significance of paragangliomas in unusual locations. *J Clin Med* 2018;7:280.

63. Roman-Gonzalez A, Jimenez C. Malignant pheochromocytoma-paraganglioma: pathogenesis, TNM staging, and current clinical trials. *Curr Opin Endocrinol Diabetes Obes* 2017;24:174–183.

64. Hough AJ, Hollifield JW, Page DL, Hartmann WH. Prognostic factors in adrenal cortical tumors. A mathematical analysis of clinical and morphologic data. *Am J Clin Pathol* 1979; 72:390–399.

65. van Slooten H, Schaberg A, Smeenk D, Moolenaar AJ. Morphologic characteristics of benign and malignant adrenocortical tumors. *Cancer* 1985;55:766–773.

66. Aubert S, Wacrenier A, Leroy X, Devos P, Carnaille B, Proye C *et al*. Weiss system revisited: a clinicopathologic and immunohistochemical study of 49 adrenocortical tumors. *Am J Surg Pathol* 2002;26:1612–1619.

67. Pennanen M, Heiskanen I, Sane T, Remes S, Mustonen H, Haglund C *et al.* Helsinki score-a novel model for prediction of metastases in adrenocortical carcinomas. *Hum Pathol* 2015;46:404–410.

68. Duregon E, Cappellesso R, Maffeis V, Zaggia B, Ventura L, Berruti A *et al.* Validation of the prognostic role of the "Helsinki Score" in 225 cases of adrenocortical carcinoma. *Hum Pathol* 2017;62:1–7.

69. Wieneke JA, Thompson LD, Heffess CS. Adrenal cortical neoplasms in the pediatric population: a clinicopathologic and immunophenotypic analysis of 83 patients. *Am J Surg Pathol* 2003;27:867–881.

70. Pinto EM, Chen X, Easton J, Finkelstein D, Liu Z, Pounds S *et al.* Genomic landscape of paediatric adrenocortical tumours. *Nat Commun* 2015;6:6302.

71. Picard C, Orbach D, Carton M, Brugieres L, Renaudin K, Aubert S *et al.* Revisiting the role of the pathological grading in pediatric adrenal cortical tumors: results from a national cohort study with pathological review. *Mod Pathol* 2019;32:546–559.

72. Wachtel H, Hutchens T, Baraban E, Schwartz LE, Montone K, Baloch Z *et al.* Predicting metastatic potential in pheochromocytoma and paraganglioma: A comparison of PASS and GAPP scoring systems. *J Clin Endocrinol Metab* 2020;1:105.

73. Fassnacht M, Dekkers OM, Else T, Baudin E, Berruti A, de Krijger R *et al*. European Society of Endocrinology clinical practice guidelines on the management of

adrenocortical carcinoma in adults, in collaboration with the European network for the study of adrenal tumors. *Eur. J. Endocrinol* 2018;1:179.

74. Patil R, Ona MA, Papafragkakis C, Duddempudi S, Anand S, Jamil L. Endoscopic ultrasound-guided fine-needle aspiration in the diagnosis of adrenal lesions. *Ann Gastroenterol* 2016;29:307–311.

75. Point du Jour KS, Alwelaie Y, Coleman A, Tadros T, Aneja R, Reid MD. Adrenal gland fine needle aspiration: A multi-institutional analysis of 139 cases. *J Am Soc Cytopathol* 2021;10:168–174.

76. Casola G, Nicolet V, van Sonnenberg E*,* Withers C, Saba MR, Bret PM *et al*. Unsuspected pheochromocytoma: risk of blood-pressure alterations during percutaneous adrenal biopsy. *Radiology* 1986;159:733–735.

77. Mukherjee S, Sengupta M, Das RN, Chatterjee U, Kanjilal B, Basu K *et al.* Diagnostic utility of cytology smears and cell block in adrenal lesions. *Diagn Cytopathol* 2020;48:1003–1012.

78. Kanitra JJ, Hardaway JC, Soleimani T, Koehler TJ, McLeod MK, Kavuturu, S *et al.* Adrenocortical oncocytic neoplasm: A systematic review. *Surgery* 2018;164:1351–1359.

79. Papathomas GT, Duregon E, Korpershoek E, Marion van R, Cappellesso R, Sturm N *et al.* Sarcomatoid adrenocortical carcinoma: a comprehensive pathological, immunohistochemical, and targeted next-generation sequencing analysis. *Hum Pathol* 2016;58:113–122.

80. de Krijger RR, Papathomas TG. Adrenocortical neoplasia: evolving concepts in tumorigenesis with an emphasis on adrenal cortical carcinoma variants. *Virchows Arch* 2012;460:9–18.

81. Challis BG, Kandasamy N, Powlson AS, Koulouri O, Annamalai AK, Happerfield L *et al.* Familial adrenocortical carcinoma in association with lynch syndrome. *J Clin Endocrinol Metab* 2016;101:2269–2272.

82. Raymond VM, Everett JN, Furtado LV, Gustafson SL, Jungbluth CR, Gruber SB *et al.* Adrenocortical carcinoma is a Lynch syndrome-associated cancer. *J Clin Oncol* 2013;20:3012.

83. Rooper LM, Bishop JA, Westra WH. INSM1 is a sensitive and specific marker of neuroendocrine differentiation in head and neck tumors. *Am J Surg Pathol* 2018;42:665–671.

84. McCuiston A, Bishop JA. Usefulness of NKX2.2 immunohistochemistry for distinguishing Ewing sarcoma from other sinonasal small round blue cell tumors. *Head Neck Pathol* 2018;12:89–94.

85. Miettinen M, McCue PA, Sarlomo-Rikala M, Rys J, Czapiewski P, Wazny K *et al*. GATA3: a multispecific but potentially useful marker in surgical pathology: a systematic analysis of 2500 epithelial and nonepithelial tumors. *Am J Surg Pathol* 2014;38:13–22.

86. Papathomas TG, Oudijk L, Persu A, Gill AJ, van Nederveen F, Tischler AS *et al.* SDHB/SDHA immunohistochemistry in pheochromocytomas and paragangliomas: a multicenter interobserver variation analysis using virtual microscopy: a Multinational Study of the European Network for the Study of Adrenal Tumors (ENS@T). *Mod Pathol* 2015;28:807–821.

87. van Nederveen FH, Gaal J, Favier J, Korpershoek E, Derkx P, Pollard PJ *et al.* An immunohistochemical procedure to detect patients with paraganglioma and phaeochromocytoma with germline SDHB, SDHC, or SDHD gene mutations: a retrospective and prospective analysis. *Lancet Oncol* 2009;10:764–771.

88. Mete O, Erickson LA, Juhlin CC, de Krijger RR, Sasano H, Volante M *et al.* Overview of the 2022 WHO Classification of Adrenal Cortical Tumors. *Endocr Pathol* 2022;33:155–196.

89. Elhassan YS, Altieri B, Berhane S, Cosentini D, Calabrese A, Haissaguerre M *et al.* S-GRAS score for prognostic classification of adrenocortical carcinoma: an international, multicenter ENSAT study. *Eur J Endocrinol* 2021;186:25–36.

90. van der Harst E, Bruining HA, Jaap Bonjer H, van der Ham F, Dinjens WN, Lamberts SW *et al.* Proliferative index in phaeochromocytomas: does it predict the occurrence of metastases? *J Pathol* 2000;191:175–180.

91. Papathomas TG, Suurd DPD, Pacak K, Tischler AS, Vriens MR, Lam AK *et al.* What have we learned from molecular biology of paragangliomas and pheochromocytomas? *Endocr Pathol* 2021;32:134–153.

92. Papathomas TG, Nosé V. New and Emerging Biomarkers in Endocrine Pathology. *Adv Anat Pathol* 2019;26:198–209.

93. Velusamy A, MRCP UK, Moonim M, FRCPath, Hubbard J, McGowan B *et al.* SDHB immunostaining: Still an indispensable tool in characterising pheochromocytoma and paraganglioma*. J Endocrine Soc* 2019. Available at: doi.org/10.1210/js.2019-SUN-344

94. Velusamy A, Izatt L, Moonim M, McGowan B, Hubbard J, Obholzer R *et al*. Using SDHB immunostaining in characterising pheochromocytoma and paraganglioma. Endocrine Abstracts 2015. Accessed October 2022. Available at: www.endocrine-abstracts.org/ea/0038/ea0038p23

95. Menara M, Oudijk L, Badoual C, Bertherat J, Lepoutre-Lussey C, Amar L *et al.* SDHD immunohistochemistry: a new tool to validate SDHx mutations in pheochromocytoma/paraganglioma. *J Clin Endocrinol Metab* 2015;100:287–291.

96. Plouin PF, Amar L, Dekkers OM, Fassnacht M, Gimenez-Roqueplo AP, Lenders JW *et al*. European Society of Endocrinology Clinical Practice Guideline for long-term follow-up of patients operated on for a phaeochromocytoma or a paraganglioma. *Eur J Endocrinol* 2016;174:G1–G10.

97. Mete O, Pakbaz S, Lerario AM, Giordano TJ, Asa SL. Significance of alpha-inhibin expression in pheochromocytomas and paragangliomas. *Am J Surg Pathol* 2021;45:1264–1273.

98. Favier J, Meatchi T, Robidel E, Badoual C, Nguyen AT, Gimenez-Roqueplo AP *et al.* Carbonic anhydrase 9 immunohistochemistry as a tool to predict or validate germline and somatic VHL mutations in pheochromocytoma and paraganglioma–a retrospective and prospective study. *Mod Pathol* 2020;33:57–64.

99. Else T, Kim AC, Sabolch A, Raymond VM, Kandathil A, Caoili EM *et al.* Adrenocortical carcinoma. *Endocr Rev* 2014;35:282–326.

100. Domènech M, Grau E, Solanes A, Izquierdo A, Del Valle J, Carrato C *et al*. Characteristics of adrenocortical carcinoma associated with Lynch syndrome. *J Clin Endocrinol Metab* 2021;106:318–325.

101. Petr EJ, Else T. Adrenocortical carcinoma (ACC): When and why should we consider germline testing? *Presse Med* 2018;47:e119–e125.

102. Fishbein L, Leshchiner I, Walter V, Danilova L, Robertson AG, Johnson AR *et al.* Comprehensive molecular characterization of pheochromocytoma and paraganglioma. *Cancer Cell* 2017;31:181–193.

103. Alzofon N, Koc K, Panwell K, Pozdeyev N, Marshall CB, Albuja-Cruz M *et al.* Mastermind like transcriptional coactivator 3 (MAML3) drives neuroendocrine tumor progression. *Mol Cancer Res* 2021;9:1476–1485.

Appendix A SNOMED codes

Topographical codes are used in SNOMED to indicate the organ/site of lesions and morphological codes (M) are used to indicate the morphological diagnosis.

Topographical codes	SNOMED 2 or 3	SNOMED-CT terminology	SNOMED-CT code
Adrenal gland	T-B3000	Adrenal structure (body structure)	23451007
Glomus	T-B5300	Glomus jugulare (body structure)	80595007
Aortic body	T-B5400	Aortic body (body structure)	75061007
Carotid body	T-B4000	Carotid body structure (body structure)	51345006

Morphological codes	SNOMED 2 or 3	SNOMED-CT terminology	SNOMED-CT code
Adrenal cortical carcinoma	M83703	Adrenal cortical carcinoma (morphologic abnormality)	2227007
Malignant phaeochromocytoma	M87003	Phaeochromocytoma, malignant (morphologic abnormality)	29370006
Paraganglioma	M86933	Extra-adrenal paraganglioma, malignant (morphologic abnormality)	32512003
Jugular paraganglioma	M86901	Glomus jugulare tumour (morphologic abnormality)	32037004
Aortic body paraganglioma	M86911	Aortic body tumour (morphologic abnormality)	53320004
Carotid body tumour	M86921	Carotid body tumour (morphologic abnormality)	30699005
Gangliocytic paraganglioma	M86830	Gangliocytic paraganglioma (morphologic abnormality)	72787006

Procedure codes (P) Local P codes should be recorded. At present, P codes vary according to the SNOMED system used in different institutions.

Appendix B Staging for adrenal cortical carcinoma

TNM8/UICC staging for adrenal cortical carcinoma

pTX Primary tumour cannot be assessed

pT0 No evidence of primary tumour

pT1 Tumour ≤5 cm, no extra-adrenal invasion

pT2 Tumour >5 cm, no extra-adrenal invasion

pT3 Tumour of any size with local invasion, but not involving adjacent organs*

pT4 Tumour of any size with invasion of adjacent organs.

*Adjacent organs are defined as: kidney, diaphragm, great vessels (renal vein/vena cava), pancreas and liver.

pNX Regional nodes cannot be assessed.

pN0 No regional lymph node metastasis

pN1 Metastasis in regional lymph nodes**

**Regional lymph nodes are the hilar, abdominal para-aortic and paracaval lymph nodes. Laterality does not affect the N categories.

M0 No distant metastasis

pM1 Distant metastasis.

Stage grouping

	TNM8/UICC		
Stage 1	T1	N0	M0
Stage 2	T2	N0	M0
Stage 3	T1/T2	N1	M0
	T3/T4	N0	M0
Stage 4	Any T	Any N	M1

Brierley JD, Mary K. Gospodarowicz, Wittekind C (eds). UICC *TNM Classification of Malignant Tumours* (*8th edition)*. Oxford, UK: Wiley-Blackwell, 2016.

Appendix C Staging for phaeochromocytoma and sympathetic paragangliomas

TNM8/UICC staging for phaeochromocytoma and sympathetic paragangliomas

pTX Primary tumour cannot be assessed

pT1 Phaeochromocytoma <5 cm in greatest dimension, no extra-adrenal invasion

pT2 Phaeochromocytoma ≥5 cm or paraganglioma – sympathetic of any size, no extra-adrenal invasion

pT3 Tumour of any size with invasion into surrounding tissues (e.g. liver, pancreas, spleen, kidneys)

Applicable to:

- phaeochromocytoma: within adrenal gland
- paraganglioma sympathetic: functional
- paraganglioma parasympathetic: often non-functional, and located in the head and neck.

Note: Parasympathetic paragangliomas are not staged.

pNX Regional lymph nodes cannot be assessed

pN0 No regional lymph node metastasis

pN1 Regional lymph node metastasis

Choose if applicable:

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

Appendix D Histopathology reporting proforma for adrenal cortical carcinoma

Surname……Forenames…… Date of birth……....Sex....

Hospital…….……Hospital no…….....NHS/CHI no……..

Date of receipt…….Date of reporting…….…....Report no…….....

Pathologist……...Surgeon…….…….

Clinical information

……

Operative procedure

(select all that apply)

- □ Not specified □ Adrenalectomy, total/partial □ Open/laparoscopic
- □ Biopsy (incisional, excisional) □ Other, specify ……..

Macroscopic findings

Specimens submitted

□ Not specified □ Adrenal tumour [□ Left □ Right] □ Lymph nodes, specify site(s) and laterality

□ Other (e.g. metastatic site), specify site(s) and laterality
……

Specimen integrity

□ Specimen intact □ Capsule disrupted □ Fragmented specimen □ Cannot be assessed, specify

Maximum tumour dimension (largest tumour) ……..mm. □ Dimension cannot be assessed

Tumour weight ……g □ Weight cannot be assessed

Microscopic findings

Histological tumour type

□ Adrenal cortical carcinoma (select from options below)

□ Not otherwise specified (NOS) □ oncocytic type □ myxoid type □ sarcomatoid type

□ Adrenal cortical neoplasm of uncertain malignant potential

□ Other, specify ……

Lipid rich cells: □ ≤25% □ >25%

Necrosis: □ Not identified □ Present

Nuclear grade: □ Low (Grade 1 or 2) □ High (Grade 3 or 4)

Mitotic figures/10 mm^2: ……..

Histological grade: □ Low grade (≤20 mitoses) □ High grade (>20 mitoses)

Atypical mitotic figures: □ Not identified □ Present

Ki-67 proliferation index: ……% □ Cannot be assessed, specify …….

Capsular invasion: □ Not identified □ Present □ Cannot be assessed, specify ……

Lymphatic invasion: □ Not identified □ Present

Vascular invasion

□ Not identified □ Present (select all that apply below)

□ Capillary/lymphatics □ Veins [□ Adrenal vein □ Vena cava □ Other, specify ……]

Extent of invasion

□ Cannot be assessed □ Confined to adrenal gland

□ Invasion into/through adrenal capsule □ Invasion into extra-adrenal structures, specify

□ Invasion into adjacent organs, specify ……

Margin status

□ Not involved (R0) □ Involved (R1, microscopic) □ Involved (R2, macroscopic)

□ Location of involved margin(s), specify if possible ……. □ Cannot be assessed, specify ……

Number of lymph nodes examined …… Number of involved lymph nodes ……..

Histologically confirmed distant metastasis (specify site) ……..

Pathological staging (UICC *TNM 8th edition*)

□ 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*
- ☐ T4 Tumour of any size with invasion of adjacent organs

*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)

SNOMED topography code

- ☐ May have multiple codes; look up from SNOMED tables

SNOMED morphology code

- ☐ May have multiple codes; look up from SNOMED tables

Signature …… Date……..…. SNOMED code …….

Appendix E Histopathology reporting proforma for phaeochromocytoma and paraganglioma

Surname…… Forenames…… Date of birth……....Sex....

Hospital…….……Hospital no…….....NHS/CHI no……..

Date of receipt…….Date of reporting…….…....Report no…….....

Pathologist……...Surgeon…….…….

Clinical information

……

Operative procedure

□ Not specified □ Biopsy (core needle, incisional, excisional), specify ……..

□ Open resection, specify procedure, including other organs if present (e.g. adrenal resection and liver biopsy) ……..

□ Laparoscopic □ Organ-sparing □ Other (e.g. conversion, laparoscopic to open), specify ……..

Macroscopic findings

Specimen submitted:

□ Adrenal gland (□ Left □ Right) □ Biopsy tissue, specify site(s) and laterality ……

□ Lymph nodes, specify biopsy/dissection, site(s) and laterality ……..

□ Other, specify site(s) and laterality ……..

Tumour focality

□ Unifocal □ Indeterminate □ Cannot be assessed, specify……..

□ Multiple

□ Multifocal (separate tumours in the same organ), specify number of tumours

□ Multiple tumours in separate organs, specify number of tumours

Tumour site, specify site and laterality

…….

Specimen integrity □ Specimen intact □ Fragmented specimen □ Cannot be assessed, specify

Maximum tumour dimension (largest tumour) ……mm □ Cannot be assessed

Microscopic findings

Histological tumour type:

□ Phaeochromocytoma □ Extra-adrenal paraganglioma □ Composite phaeochromocytoma

□ Composite paraganglioma □ Other, specify …….

If composite tumour, histologic second component is:

□ Neuroblastoma □ Ganglioneuroblastoma □ Ganglioneuroma □ Malignant peripheral nerve sheath tumour

Medullary hyperplasia: □ Present □ Absent □ Cannot be assessed

Mitotic count ……. / 2mm^2

Ki-67 ……% □ Cannot be assessed

Lymphovascular invasion

□ Not identified □ Present [□ Adrenal vein □ Vena cava □ Other, specify …….]

Extent of invasion

□ Cannot be assessed □ Microscopic transcapsular penetration of tumour capsule within an organ

□ Microscopic transcapsular penetration of organ capsule □ Invasion into peritumoural soft tissue

□ Invasion into adjacent structure(s)/organ(s), specify …….

Margin status

□ Not involved (R0) □ Involved (R1, microscopic) □ Involved (R2, macroscopic)

□ Location of involved margin(s), specify if possible ……. □ Cannot be assessed, specify

Number of lymph nodes examined …… Number of involved lymph nodes ……..

Histologically confirmed distant metastasis (specify site) ……..

Pathological staging (UICC *TNM 8th edition*)

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

Primary tumour (pT)*

- □ TX Primary tumour cannot be assessed
- □ T1 Phaeochromocytoma <5 cm in greatest dimension, no extra-adrenal extension
- □ T2 Phaeochromocytoma ≥5 cm or paraganglioma – sympathetic of any size, no extra-adrenal invasion
- □ T3 Tumour of any size with invasion into surrounding tissues (e.g. liver, pancreas, spleen, kidneys)

*Phaeochromocytoma: within adrenal gland; paraganglioma sympathetic: functional; paraganglioma parasympathetic: often non-functional, and located in the head and neck.

Note: Parasympathetic paragangliomas are not staged.

Regional lymph nodes (pN)

- □ NX Regional lymph nodes cannot be assessed
- □ N0 No regional lymph node metastasis
- □ N1 Regional lymph node metastasis

SNOMED topography code

- □ May have multiple codes; look up from SNOMED tables

SNOMED morphology code

- □ May have multiple codes; look up from SNOMED tables

Signature ……..... Date……..…. SNOMED code …….

Appendix F Histopathology reporting proforma for adrenal cortical carcinoma in list format

Element name	Values	Implementation comments	COSD v9
Operative procedure	Select all that apply • Not specified • Adrenalectomy, total/partial • Open/laparoscopic • Biopsy (incisional, excisional) • Other, specify …….		pCR0760 • Not specified = 99 • Adrenalectomy, total/ partial = EX • Open/laparoscopic = 99 • Biopsy (incisional, excisional) = BU • Other, specify = 99…….
Macroscopic findings	Specimens submitted: • Not specified • Adrenal tumour – Left – Right • Lymph nodes, specify site(s) and laterality • Other (e.g. metastatic site), specify site(s) and laterality …….. Specimen integrity: • Specimen intact • Capsule disrupted • Fragmented specimen • Cannot be assessed, specify Maximum tumour dimension (largest tumour) ……..mm. • Dimension cannot be assessed Tumour weight ……g • Weight cannot be assessed		

Microscopic findings	Histological tumour type:
	• Adrenal cortical carcinoma (select from options below)
	  – Not otherwise specified (NOS)
	  – Oncocytic type
	  – Myxoid type
	  – Sarcomatoid type
	• Adrenal cortical neoplasm of uncertain malignant potential
	• Other, specify ……
	
	Lipid rich cells:
	• ≤25%
	• >25%
	
	Necrosis:
	• Not identified
	• Present
	
	Nuclear grade:
	• Low (Grade 1 or 2)
	• High (Grade 3 or 4)
	
	Mitotic figures/10 mm^2:
	……
	
	Histological grade:
	• Low grade (≤20 mitoses)
	• High grade (>20 mitoses)
	
	Atypical mitotic figures:
	• Not identified
	• Present
	
	Ki-67 proliferation index:
	……%
	• Cannot be assessed, specify …….
	
	Capsular invasion:
			pCR0860
			• Low grade (≤20 mitoses) = G1
			• High grade (>20 mitoses) = G4
			
			pCR7010

	• Not identified
	• Present
	• Cannot be assessed, specify ……
	
	Lymphatic invasion:
	• Not identified
	• Present
	
	Vascular invasion:
	• Not identified
	• Present (select all that apply below)
	  – Capillary/
	  – lymphatics
	  – Veins
	  ○ Adrenal vein
	  ○ Vena cava
	  ○ Other, specify …….
	
	Extent of invasion:
	• Cannot be assessed
	• Confined to adrenal gland
	• Invasion into/through adrenal capsule
	• Invasion into extra-adrenal structures, specify
	• Invasion into adjacent organs, specify
	
	Margin status:
	• Not involved (R0)
	• Involved (R1, microscopic)
	• Involved (R2, macroscopic)
	• Location of involved margin(s), specify if possible …….
	• Cannot be assessed, specify
		Note: If lymphatic and vascular Invasion are present, use value ‘YB’	pCR0870
			• Not identified = NU
			• Present = YL
			
			pCR0870
			• Not identified = NU
			• Present = YL
			
			pCR0880
			• Not involved (R0) = 01
			• Involved (R1, microscopic) = 05
			• Involved (R2, macroscopic) = 05
			• Cannot be assessed, specify = 06

	Number of lymph nodes examined …… Number of involved lymph nodes …….. Histologically confirmed distant metastasis (specify site) …….		 pCR0890 pCR0900
Pathological Staging (UICC TNM 8th edition)	• 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* • T4 Tumour of any size with invasion of adjacent organs *Adjacent organs include kidney, diaphragm, great vessels (renal vein or vena cava) pancreas and liver		pCR0910
Regional lymph nodes (pN)	• NX Regional lymph nodes cannot be assessed • N0 No regional lymph node metastasis • N1 metastasis in regional lymph node(s)		pCR0920
SNOMED Topography code	• May have multiple codes; look up from SNOMED tables		pCR6410
SNOMED Morphology code	• May have multiple codes; look up from SNOMED tables		pCR6420

Appendix G Histopathology reporting proforma for phaeochromocytoma and paraganglioma in list format

Element name	Values	Implementation comments	COSD v9
Operative procedure	• Not specified • Biopsy (core needle, incisional, excisional), specify …….. • Open resection, specify procedure, including other organs if present (e.g. adrenal resection and liver biopsy) …….. • Laparoscopic • Organ-sparing • Other (e.g. conversion, laparoscopic to open), specify		pCR0760 • Not specified = 99 • Biopsy (core needle, incisional, excisional) = BU • Open resection = RE • Laparoscopic = 99 • Organ-sparing = PE • Other (e.g. conversion, laparoscopic to open), specify = 99
Macroscopic findings	Specimen submitted: • Adrenal gland – Left – Right • Biopsy tissue, specify site(s) and laterality …… • Lymph nodes, specify biopsy/dissection, site(s) and laterality …… • Other, specify site(s) and laterality …….. Tumour focality: • Unifocal • Indeterminate • Cannot be assessed, specify…… • Multiple – Multifocal (separate tumours		

	in the same organ), specify number of tumours – Multiple tumours in separate organs, specify number of tumours Tumour site, specify site and laterality …… Specimen integrity • Specimen intact • Fragmented specimen • Cannot be assessed, specify Maximum tumour dimension (largest tumour) ……mm • Cannot be assessed		
Microscopic findings	Histological tumour type: • Phaeochromocytoma • Extra-adrenal paraganglioma • Composite phaeochromocytoma • Composite paraganglioma • Other, specify …… If composite tumour, histologic second component is: • Neuroblastoma • Ganglioneuroblastoma • Ganglioneuroma • Malignant peripheral nerve sheath tumour Medullary hyperplasia: • Present • Absent		

	• Cannot be assessed Mitotic count ……. / 2mm^2 Ki-67 ……% • Cannot be assessed *Lymphovascular invasion:* • Not identified • Present – Adrenal vein – Vena cava – Other, specify……..… *Extent of invasion:* • Cannot be assessed • Microscopic transcapsular penetration of tumour capsule within an organ • Microscopic transcapsular penetration of organ capsule • Invasion into peritumoural soft tissue • Invasion into adjacent structure(s)/organ(s), specify ……. *Margin status:* • Not involved (R0) • Involved (R1, microscopic) • Involved (R2, macroscopic) • Location of involved margin(s), specify if possible ……. • Cannot be assessed, specify		pCR7010 pCR0870 Not identified = NU Present = YL pCR0880 Not involved (R0) = 01 Involved (R1, microscopic) = 05 Involved (R2, macroscopic) = 05 Cannot be assessed, specify = 06 pCR0890 pCR0900

	Number of lymph nodes examined …… Number of involved lymph nodes …….. Histologically confirmed distant metastasis (specify site) ……		
Pathological staging (UICC *TNM 8th edition)*	• m – multiple primary tumours • r – recurrent • y – post-therapy		
Primary tumour (pT)* *Phaeochromocytoma: within adrenal gland; Paraganglioma sympathetic: functional; Paraganglioma parasympathetic: often non-functional, and located in the head and neck. Note: Parasympathetic paragangliomas are not staged.	• TX Primary tumour cannot be assessed • T1 Phaeochromocytoma <5 cm in greatest dimension, no extra-adrenal extension • T2 Phaeochromocytoma ≥5 cm or paraganglioma – sympathetic of any size, no extra-adrenal invasion • T3 Tumour of any size with invasion into surrounding tissues (e.g. liver, pancreas, spleen, kidneys)		pCR0910
Regional lymph nodes (pN)	• NX Regional lymph nodes cannot be assessed • N0 No regional lymph node metastasis • N1 Regional lymph node metastasis		CR0920

SNOMED Topography code	• May have multiple codes; look up from SNOMED tables		pCR6410
SNOMED Morphology code	• May have multiple codes; look up from SNOMED tables		pCR6420

Appendix H Summary table – Explanation of grades of evidence

(modified from Palmer K *et al. BMJ* 2008; 337:1832)

Grade (level) of evidence	Nature of evidence
Grade A	At least one high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target population or A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target cancer type.
Grade B	A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target population or Extrapolation evidence from studies described in A.
Grade C	A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high- quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target population or Extrapolation evidence from studies described in B.
Grade D	Non-analytic studies such as case reports, case series or expert opinion or Extrapolation evidence from studies described in C.
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group.

Appendix I AGREE II guideline monitoring sheet

The autopsy guidelines of The Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of this autopsy guideline that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	Introduction
2 The health question(s) covered by the guideline is (are) specifically described	Introduction
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	Foreword
6 The target users of the guideline are clearly defined	Introduction
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Foreword
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword and Introduction
12 There is an explicit link between the recommendations and the supporting evidence	All sections
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	All sections
16 The different options for management of the condition or health issue are clearly presented	All sections
17 Key recommendations are easily identifiable	All sections
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	Appendices
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	Section 14
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interest of guideline development group members have been recorded and addressed	Foreword