Phaeochromocytoma and Paraganglioma Histopathology Reporting Guide

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

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

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

CLINICAL INFORMATION (Note 1)

◯ Information not provided
◯ Information provided

Hormonal status

◯ Cannot be determined (testing status not known)
◯ 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

Relevant biopsy/cytology results

◯ Information not provided
◯ No
◯ Yes, *specify*

Imaging findings

◯ Information not provided
◯ No
◯ Yes, *specify*

Previous therapy

◯ Information not provided
◯ No
◯ Yes, *specify*

Relevant familial history

◯ Information not provided
◯ No
◯ Yes, *specify*

Presence of endocrine or other tumours

◯ Information not provided
◯ No
◯ Yes, *specify*

Presence of germline mutation or familial syndrome

◯ Information not provided
◯ No
◯ Yes, *specify mutation if known*

Other clinical information, *specify*

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

◯ Not specified
☐ Biopsy (core needle, incisional, excisional), *specify*
☐ Open resection (e.g., adrenal resection, liver biopsy), *specify procedure including other organs if present*
☐ Laparoscopic
☐ Organ-sparing
☐ Other (e.g., conversion, laparoscopic to open), *specify*

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

◯ Not specified
☐ Adrenalectomy
- ☐ Left ☐ Right

☐ Other resection, *specify site(s) and laterality*
☐ Biopsy tissue, *specify site(s) and laterality*

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TUMOUR FOCALITY (Note 4)

- ◯ Unifocal
- ◯ Multiple
  - Multifocal (separate tumours in the same organ), *specify number of tumours*
  - Multiple tumours in separate organs, *specify number of tumours*[a]
- ◯ Cannot be assessed, *specify*

TUMOUR SITE[a] (select all that apply) (Note 5)

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

- ◯ Not specified
- ☐ Adrenal
  - ☐ Left
  - ☐ Right
- ☐ Other abdominal or pelvic
  - ◯ Paraaortic
  - ◯ Urinary bladder
  - ◯ Other, *specify*
- ☐ Thorax
  - ◯ Paraaortic
  - ◯ Cardiac
  - ◯ Other, *specify*
- ☐ Head and neck
  - ◯ Carotid body
    - ◯ Left ◯ Right
  - ◯ Middle ear (jugulotympanic)
    - ◯ Left ◯ Right
  - ◯ Vagal
    - ◯ Left ◯ Right
  - ◯ Laryngeal
    - ◯ Left ◯ Right
  - ◯ Other, *specify site(s) and laterality*

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

SPECIMEN INTEGRITY (Note 6)

- ◯ Specimen intact
- ◯ Fragmented specimen
- ◯ Cannot be assessed, *specify*

TUMOUR DIMENSIONS (Note 7)

Maximum tumour dimension (largest tumour)

mm

Additional dimensions (largest tumour)

mm x mm

- ◯ Cannot be assessed, *specify*

BLOCK IDENTIFICATION KEY (Note 8)

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

HISTOLOGICAL TUMOUR TYPE (select all that apply) (Note 9)

(Value list based on the World Health Organization Classification of Endocrine and Neuroendocrine Tumours, 5th Edition (2025))

- ☐ 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* %

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TUMOUR NECROSIS (Note 10)

- ◯ Not identified
- ◯ Present

EXTENT OF INVASION (select all that apply) (Note 11)

- ◯ Cannot be assessed
- ◯ Not identified
- ☐ 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*

LYMPHOVASCULAR INVASION (Note 12)

- ◯ Not identified
- ◯ Present
  - **Type of vessel involved** (select all that apply)
    - ☐ Capillary
    - ☐ Lymphatic
    - ☐ Vein
  - **Location of vessels** (select all that apply)
    - ☐ Periadrenal or peritumoral for extra-adrenal tumours, *specify*
      - ☐ Intracapsular ☐ Extracapsular
    - ☐ Adrenal vein
    - ☐ Vena cava
    - ☐ Other (e.g., adrenal central vein and tributaries), *specify*

MARGIN STATUS (Note 13)

- ◯ Not involved (R0)
  - Distance of tumour from closest margin ____ mm
  - Specify closest margin(s) if possible
- ◯ Involved
  - **Extent**
    - ◯ R1 (microscopic), *specify if possible*
    - ◯ R2 (macroscopic), *specify if possible*
  - Location of involved margin(s), *specify if possible*
- ◯ Cannot be assessed, *specify*

PROLIFERATIVE FRACTION (Note 14)

Mitotic count ____ /2 mm²

AND/OR

Ki-67 proliferation index ____ %

- ◯ Cannot be assessed, *specify*

LYMPH NODE STATUS (Note 15)

- ◯ No nodes submitted or found
- ◯ Lymph node biopsy, *specify site(s) if applicable*

Number of lymph nodes examined ____

- ◯ Not involved
- ◯ Involved
  - Number of involved lymph nodes ____
  - ◯ Number cannot be determined

ADVERSE HISTOLOGICAL FEATURES (select all that apply) (Note 16)

- ☐ Growth pattern
  - ◯ Large and irregular nests
  - ◯ Diffuse
  - ◯ Pseudorosette (even focal)
- ☐ Cellularity
  - ◯ Moderate (150–250 cells/U)
  - ◯ High (>250 cells/U)
- ☐ Cytologic features
  - ◯ Spindle cells
  - ◯ Other, *specify*
- ☐ Other, *specify*

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ANCILLARY STUDIES (Note 17)

- ◯ Not performed
- ◯ Performed (select all that apply)
  - ☐ Immunohistochemistry
    - ☐ Chromogranin A, *specify result(s)*
    - ☐ Keratins, *specify result(s)*
    - ☐ S100, *specify result(s)*
    - ☐ SDHB, *specify result(s)*
    - ☐ GATA-3, *specify result(s)*
    - ☐ Other, *specify*
  - ☐ Molecular testing, *specify test(s) and result(s)*

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

HISTOLOGICALLY CONFIRMED DISTANT METASTASES (Note 18)

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

PATHOLOGICAL STAGING (UICC TNM 9th edition)[b] (Note 19)
(Applicable only to pheochromocytoma and sympathetic paraganglioma; not applicable to head and neck paraganglioma)

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

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

Primary tumour (pT)

- ◯ TX[c] Primary tumour cannot be assessed
- ◯ T0 No evidence of primary tumour
- ◯ T1 Pheochromocytoma 5 cm or less in greatest dimension, no extra-adrenal invasion
- ◯ T2 Pheochromocytoma greater than 5 cm in greatest dimension, no extra-adrenal invasion
  Paraganglioma of any size, no local invasion
- ◯ T3 Tumour of any size with local invasion, into adjoining tissues or adjacent organs[d]

Regional lymph nodes (pN)

- ◯ NX[c] Regional lymph nodes cannot be assessed
- ◯ N0 No regional lymph node metastasis
- ◯ N1 Regional lymph node metastasis

[b] *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 9th Edition, eds by James Brierley, Meredith Giuliani, Brian O'Sullivan, Brian Rous, Elizabeth Van Eycken. 2025, Publisher Wiley (incorporating errata published 12th October 2025).*

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

[d] *Adjacent organs include kidney, liver, pancreas and spleen.*

Definitions

CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council (NHMRC) levels of evidence[1]). In rare circumstances, where level III-2 evidence is not available an element may be made a CORE element where there is unanimous agreement by the Dataset Authoring Committee (DAC). An appropriate staging system, e.g., Pathological TNM staging, would normally be included as a CORE element.

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

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

NON-CORE elements

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

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

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Scope

The dataset has been developed for the pathology reporting of adrenalectomy/partial adrenalectomy specimens for phaeochromocytoma, other excisions for paragangliomas and biopsies of related specimens.

Sarcoma, lymphoma and metastasis to the adrenal medulla are not covered in this dataset. Neuroblastoma and ganglioneuroblastoma are covered in a separate ICCR dataset.[2] Adrenal cortical tumours are dealt with in a separate ICCR dataset.[3]

The second edition of this dataset includes changes to align the dataset with the World Health Organization (WHO) Classification of Endocrine and Neuroendocrine Tumours, 5th edition, 2025.[4] In development of this dataset, the DAC considered evidence up until August 2025.

Anatomic sites of paraganglia

Paraganglia are neural crest-derived neuroendocrine organs that produce catecholamines as their usual hormonal product. They are typically divided into two groups, associated with sympathetic or parasympathetic nerves. Sympathetic paraganglia, also called sympathoadrenal paraganglia, are divided into two subgroups: the adrenal medulla, and extra-adrenal sympathetic paraganglia. Tumours arising from the adrenal medulla are currently termed phaeochromocytomas, although 'adrenal paragangliomas' is gaining more widespread acceptance as an alternate term accepted by the WHO.[4,5] Tumours arising from extra-adrenal locations are called paragangliomas regardless of their sympathetic or parasympathetic origins. Parasympathetic paragangliomas are also known as head and neck paragangliomas, and most often arise in, or near the carotid body or middle ear. However, sympathetic paragangliomas occasionally (less than 4%) arise from the cervical sympathetic chain.

A list of changes in this dataset edition can be accessed here.

The authors of this dataset can be accessed here.

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Note 1 – Clinical information (Core and Non-core)

Clinical data provide 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, multiple tumours and the presence of additional endocrine or non-endocrine tumours that may be components of a syndrome.[4] Almost 40% of phaeochromocytomas/ paragangliomas are hereditary, making them the most hereditarily determined of all human tumours, and at least 20 hereditary susceptibility genes are now associated with their development.[6] Distinct correlations exist between genotype, biochemical phenotype,[7] tumour distribution, prognosis, and syndrome associations.[8,9]

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.[5] Partial adrenalectomy, which is increasingly utilised in treating patients with pheochromocytomas,[10] might also be expected to cause long term changes in histology of the residual adrenal.

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Note 2 – Operative procedure (Core)

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 pre-operative cross-sectional imaging studies.

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Note 3 – Specimen(s) submitted (Core)

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

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Note 4 – Tumour focality (Core)

The presence of multiple or multifocal tumours is an important clue to the presence of hereditary disease.[11] Multifocality is defined as separate foci of tumour in the same organ, in contrast to multicentric which is multiple tumours in separate organs (e.g., two or three removed paragangliomas or a paraganglioma and a phaeochromocytoma). These designations apply to primary tumours, not metastases, and require histologic confirmation. It may not be possible to determine whether tumour in a a fragmented specimen is multifocal, in which case it would be classified as indeterminate. Specimens should be carefully examined both macroscopically and microscopically to determine whether multifocal tumours are present. As it has been shown that even small, subcentimetre, lesions possess identical molecular abnormalities as their larger counterparts, a size cut-off is no longer endorsed.[12] While nodularity is an indicator for hereditary disease, diffuse thickening of the adrenal medulla is a less clearcut characteristic, due to lack of robust criteria. 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.

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Note 5 – Tumour site (Core)

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.[13]

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.

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Note 6 – Specimen integrity (Core)

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.

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Note 7 – Tumour dimensions (Core and Non-core)

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 millimetres (mm)) correlates to metastatic potential in some studies, although possibly not as an independently useful criterion.[14,15] However, tumour size ≥50 mm is included as a staging criterion in the 9th edition Union for International Cancer Control (UICC) and 8th edition American Joint Committee on Cancer (AJCC) Cancer Staging Manuals.[16,17]

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 10 mm of tumour should be considered.

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

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Note 8 – Block identification key (Non-core)

The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important when further internal or external review arises. The reviewer needs to have unequivocal description of the origin of each block in order to provide an informed specialist opinion. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. It is highly encouraged to have a digital image (photograph) of the specimen and record of the key tumour blocks.

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

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Note 9 – Histological tumour type (Core)

All tumours of the adrenal medulla and extra-adrenal paraganglia should be given a type based on the most recent edition of the WHO Classification of Endocrine and Neuroendocrine Tumours, 5th edition, 2025 (Table 1).[4] 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.[4] There is no specified percentage of the second tumour type.[4] However, complete histoarchitecture of the second tumour type is required. Scattered neuron-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.[4,18]

Table 1: 5th edition of the World Health Organization classification of phaeochromocytomas and paragangliomas.[4]

Descriptor	ICD-O codes[a]
Pheochromocytoma	8700/3
Sympathetic paraganglioma	8681/3
Parasympathetic paraganglioma	8682/3
Extra-adrenal composite paraganglioma	8693/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-0-3.2).[19] Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour: /2 for carcinoma in situ and grade Ill intraepithelial neoplasia; /3 for malignant tumours, primary site: and /6 for malignant tumours, metastatic site. Behaviour code /6 is not generally used by cancer registries.

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Note 10 – Tumour necrosis (Core)

Necrosis rarely occurs in phaeochromocytomas and paragangliomas, but is widely known as an adverse histological feature, for example in adrenal cortical carcinoma. It is therefore included in all major proposed scoring systems for phaeochromocytoma and paraganglioma. It is important to note that necrosis pertains to coagulative or comedo-type tumour cell necrosis that is not secondary to therapeutic embolization or spontaneous infarction.

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Note 11 – Extent of invasion (Core)

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.[11] Precise descriptions of the nature and extent of invasion are required in conjunction with other adverse factors to facilitate optimal patient management.

If a tumour capsule is present, invasion of the organ capsule and tumour capsule should be documented. Capsular invasion is not assessed in a biopsy. While this core item is important to document, capsular invasion as discussed in this note does not lead to upstaging of the tumour in the current TNM classification (refer to **Note 19 – PATHOLOGICAL STAGING**).[16,17]

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Note 12 – Lymphovascular invasion (Core)

Vessel invasion is a reported risk factor for development of metastases when considered in conjunction with other adverse features.[11] 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.[11] It is recommended that an attempt be made to separate capillary, lymphatic, and venous invasion, noting that they may coexist.

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).[18]

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Note 13 – Margin status (Core and Non-core)

Margin status is an important variable to record, as incomplete excision has been associated with local recurrence.[20] Positive margins are defined both grossly, as tumour obviously transected and microscopically as 'ink on tumour', 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. The distance of tumour to margin is a non-core item.

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Note 14 – Proliferative fraction (Core)

Mitotic count and Ki-67 proliferation index are now widely utilised in risk stratification for other neuroendocrine tumours. A high proliferative fraction based on either mitoses[21] or Ki-67[22] is a reported risk factor for development of metastases for phaeochromocytoma and paraganglioma.

Mitotic count should be performed in a minimum area of 2 mm^2. There is currently no standard approach to scoring a Ki-67 proliferation index in phaeochromocytoma and paraganglioma. On the basis of established methodology for other neuroendocrine tumours,[4] it is recommended that the Ki-67 proliferation index should be should be recorded as a percent of tumour cells staining in hot spots (the areas with greatest Ki-67 expression). The method used to calculate the Ki-67 percent should be specified (e.g., manual count on a camera captured image and the number of cells evaluated, or automated image analysis nuclear algorithms including the number of cells counted.[23] As in other neuroendocrine neoplasms, selecting multiple hot spots (consisting of at least of 500 neoplastic cells) from multiple regions of the tumour rather than a large area of the tumour is generally recommended.[24]

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Note 15 – Lymph node status (Core)

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..

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.

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Note 16 – Adverse histological features (Non-core)

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, location and necrosis) that are core are listed in other sections.

Several categories of histological features are putative risk factors for development of metastases in multiple publications and overlap in the proposed scoring systems for risk stratification.[22,25-27] 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.

PASS[25] was designed for phaeochromocytomas, while GAPP[22] was intended for both phaeochromomocytomas and sympathetic paragangliomas. No scoring system currently applies to head and neck paragangliomas, although individual parameters may provide useful information for those tumours.[28] Use of either scoring system is optional. A meta-analysis of multiple papers employing PASS or GAPP concluded 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.[29]

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Note 17 – Ancillary studies (Core and Non-core)

Differential diagnostic markers (Core)

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.[30-32] The most frequently utilised positive generic markers of neuroendocrine differentiation 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 GATA-3,[32,33] tyrosine hydroxylase to demonstrate capacity for catecholamine synthesis, and S100 protein and/or SOX10 to demonstrate sustentacular cells. Useful

negative markers include keratins, and, in the adrenal, SF1. A caveat is that head and neck paragangliomas are often completely negative for tyrosine hydroxylase and may occasionally be negative or only focally positive for CgA and synaptophysin.[30] 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,[34] INSM1,[35] and NKX2.2.[36]

Taken together, a minimum diagnostic panel consisting of CgA, GATA-3, and pan-cytokeratin, if resources permit, would be core for the diagnosis. This could be expanded depending on differential diagnostic considerations.

Molecular immunohistochemical markers (Non-core)

In addition to aiding diagnosis, immunohistochemistry is increasingly used as a genetic screen. For several hereditary genetic abnormalities, immunohistochemical stains may be used as surrogate markers for the presence of germline mutations or may be used to strengthen the assessment of pathogenicity of genetic variants (variants of uncertain significance (VUS)). This particularly applies to staining for loss of SDHA and SDHB, the latter of which also serves as a prognostic marker.[37,38] In patients with mutations in any of the *SDH* genes, SDHB staining will be lost, except for that in pre-existent normal cells within the tumour, such as endothelial cells. Loss of expression, non-granular expression or expression that is clearly weaker than that of normal internal control cells all indicate the presence of mutations in *SDH* genes. Similar to SDHA or SDHB, loss of expression of fumarate hydratase and positive staining for 2SC signifies fumarate hydratase mutation (and therefore potentially hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome).[39,40] MAX immunohistochemistry has been proposed as a marker of underlying *MAX* genetic variants, but its utility has been questioned.[41,42] Finally, positive carbonic anhydrase IX staining may signal presence of *VHL* mutations; this may be associated with sporadic as well as germline alterations. Focal CAIX may be found in some SDH deficient tumours and SDHB staining may be weak in some VHL-associated tumours.[43]

Molecular testing (Core)

While this element is deemed core, consideration can be given to temporarily downgrading this to a non-core element until resources allow. As the rate of hereditary pheochromocytomas and paragangliomas has gradually risen from around 10% in year 2,000 to around 40% at the time of writing,[9] it seems prudent to refer every patient to clinical genetics for further genetic counselling and screening. Depending on local resources and routines, somatic molecular analysis may also be performed on tumour tissue, preferably in combination with parallel analyses on blood, to discriminate between hereditary and somatic abnormalities.[44] This may either be done by limited or more extensive next generation sequencing panels or by genome wide approaches, including whole exome or whole genome sequencing.

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Note 18 – Histologically confirmed distant metastases (Core)

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.[32] 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, duodenum, colon, and lung.[45-51] 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.

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Note 19 – Pathological staging (Core)

Tumours of the adrenal medulla and extra-adrenal paraganglia should be staged according to the 9th edition UICC/8th edition AJCC Cancer Staging Manuals.[16,17] 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.[16,17,52]

Reporting of pathological staging categories (pT, pN, pM) is based on the evidence available to the pathologist at the time of reporting. As indicated in UICC TNM9 and AJCC TNM8,[16,17] the final stage grouping of a patient's tumour is based on a combination of pathological staging and other clinical and imaging information.

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References

1 Merlin T, Weston A and Tooher R (2009). Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Med Res Methodol* 9:34.

2 International Collaboration on Cancer Reporting (2023). *Neuroblastoma Histopathology Reporting Guide. 1st edition*. Available from: https://www.iccr-cancer.org/datasets/published-datasets/paediatrics/neuroblastoma/ (Accessed 1st August 2025).

3 International Collaboration on Cancer Reporting (2025). *Carcinoma of the adrenal cortex Histopathology Reporting Guide. 2nd edition.* Available from: https://www.iccr-cancer.org/datasets/published-datasets/endocrine/adrenal-cortex/ (Accessed 1st August 2025).

4 WHO Classification of Tumours Editorial Board. Endocrine and neuroendocrine tumours. Lyon (France): International Agency for Research on Cancer; 2025. (WHO classification of tumours series, 5th ed.; vol. 10). https://publications.iarc.who.int/645.

5 Mete O, Asa SL, Gill AJ, Kimura N, de Krijger RR and Tischler A (2022). Overview of the 2022 WHO Classification of Paragangliomas and Pheochromocytomas. *Endocr Pathol* 33(1):90–114.

6 NGS in PPGL (NGSnPPGL) Study Group, Toledo RA, Burnichon N, Cascon A, Benn DE, Bayley JP, Welander J, Tops CM, Firth H, Dwight T, Ercolino T, Mannelli M, Opocher G, Clifton-Bligh R, Gimm O, Maher ER, Robledo M, Gimenez-Roqueplo AP and Dahia PL (2017). Consensus Statement on next-generation-sequencing-based diagnostic testing of hereditary phaeochromocytomas and paragangliomas. *Nat Rev Endocrinol* 13(4):233–247.

7 Eisenhofer G, Klink B, Richter S, Lenders JW and Robledo M (2017). Metabologenomics of Phaeochromocytoma and Paraganglioma: An Integrated Approach for Personalised Biochemical and Genetic Testing. *Clin Biochem Rev* 38(2):69–100.

8 Mete O, Tischler AS, de Krijger R, McNicol AM, Eisenhofer G, Pacak K, Ezzat S and Asa SL (2014). Protocol for the examination of specimens from patients with pheochromocytomas and extra-adrenal paragangliomas. *Arch Pathol Lab Med* 138(2):182–188.

9 Turchini J, Cheung VKY, Tischler AS, De Krijger RR and Gill AJ (2018). Pathology and genetics of phaeochromocytoma and paraganglioma. *Histopathology* 72(1):97–105.

10 Asher KP, Gupta GN, Boris RS, Pinto PA, Linehan WM and Bratslavsky G (2011). Robot-Assisted Laparoscopic Partial Adrenalectomy for Pheochromocytoma: The National Cancer Institute Technique. *European Urology* 60(1):118–124.

11 Tischler AS and deKrijger RR (2015). 15 YEARS OF PARAGANGLIOMA: Pathology of pheochromocytoma and paraganglioma. *Endocr Relat Cancer* 22(4):T123–133.

12 Korpershoek E, Petri BJ, Post E, van Eijck CH, Oldenburg RA, Belt EJ, de Herder WW, de Krijger RR and Dinjens WN (2014). Adrenal medullary hyperplasia is a precursor lesion for pheochromocytoma in MEN2 syndrome. *Neoplasia* 16(10):868–873.

13 Benn DE, Robinson BG and Clifton-Bligh RJ (2015). 15 YEARS OF PARAGANGLIOMA: Clinical manifestations of paraganglioma syndromes types 1-5. *Endocr Relat Cancer* 22(4):T91–T103.

14 Pacak K, Eisenhofer G, Ahlman H, Bornstein SR, Gimenez-Roqueplo AP, Grossman AB, Kimura N, Mannelli M, McNicol AM, Tischler AS and International Symposium on P (2007). Pheochromocytoma: recommendations for clinical practice from the First International Symposium. October 2005. *Nat Clin Pract Endocrinol Metab* 3(2):92–102.

15 Eisenhofer G, Lenders JW, Siegert G, Bornstein SR, Friberg P, Milosevic D, Mannelli M, Linehan WM, Adams K, Timmers HJ and Pacak K (2012). Plasma methoxytyramine: a novel biomarker of metastatic pheochromocytoma and paraganglioma in relation to established risk factors of tumour size, location and SDHB mutation status. *Eur J Cancer* 48(11):1739–1749.

16 Brierley JD, Giuliani M, O'Sullivan B, Rous B and Van Eycken E (eds) (2025). *TNM Classification of Malignant Tumours, 9th Edition*. Wiley.

17 Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM and Meyer LR (eds) (2017). *AJCC Cancer Staging Manual. 8th ed.*, Springer, New York.

18 deKrijger RR, Tischler AS, Asa SL Lack EE, Volante M (2025). *Tumors of the Adrenal Glands and Extra-Adrenal Paraganglia*. American Registry of Pathology, Washington, DC.

19 Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM and Whelan S (eds) (2020). *International Classification of Diseases for Oncology, Third edition, Second revision ICD-O-3.2*. Available from: http://www.iacr.com.fr/index.php?option=com_content&view=category&layout=blog&id=100&Itemid=577 (Accessed 1st August 2025).

20 Li M, Fitzgerald P, Price D and Norton J (2001). Iatrogenic pheochromocytomatosis: a previously unreported result of laparoscopic adrenalectomy. *Surgery* 130(6):1072–1077.

21 Strong VE, Kennedy T, Al-Ahmadie H, Tang L, Coleman J, Fong Y, Brennan M and Ghossein RA (2008). Prognostic indicators of malignancy in adrenal pheochromocytomas: clinical, histopathologic, and cell cycle/apoptosis gene expression analysis. *Surgery* 143(6):759–768.

22 Kimura N, Takayanagi R, Takizawa N, Itagaki E, Katabami T, Kakoi N, Rakugi H, Ikeda Y, Tanabe A, Nigawara T, Ito S, Kimura I and Naruse M (2014). Pathological grading for predicting metastasis in phaeochromocytoma and paraganglioma. *Endocr Relat Cancer* 21(3):405–414.

23 Cree IA (2022). From Counting Mitoses to Ki67 Assessment: Technical Pitfalls in the New WHO Classification of Endocrine and Neuroendocrine Tumors. *Endocr Pathol* 33(1):3–5.

24 Volynskaya Z, Mete O, Pakbaz S, Al-Ghamdi D and Asa SL (2019). Ki67 Quantitative Interpretation: Insights using Image Analysis. *J Pathol Inform* 10:8.

25 Thompson LD (2002). 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* 26(5):551–566.

26 Koh JM, Ahn SH, Kim H, Kim BJ, Sung TY, Kim YH, Hong SJ, Song DE and Lee SH (2017). Validation of pathological grading systems for predicting metastatic potential in pheochromocytoma and paraganglioma. *PLoS One* 12(11):e0187398.

27 Pierre C, Agopiantz M, Brunaud L, Battaglia-Hsu SF, Max A, Pouget C, Nomine C, Lomazzi S, Vignaud JM, Weryha G, Oussalah A, Gauchotte G and Busby-Venner H (2019). COPPS, a composite score integrating pathological features, PS100 and SDHB losses, predicts the risk of metastasis and progression-free survival in pheochromocytomas/paragangliomas. *Virchows Arch* 474(6):721–734.

28 Ellis RJ, Patel D, Prodanov T, Nilubol N, Pacak K and Kebebew E (2014). The presence of SDHB mutations should modify surgical indications for carotid body paragangliomas. *Ann Surg* 260(1):158–162.

29 Stenman A, Zedenius J and Juhlin CC (2019). 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)* 11(2):225.

30 Tischler AS (2008). Pheochromocytoma and extra-adrenal paraganglioma: updates. *Arch Pathol Lab Med* 132(8):1272–1284.

31 Kimura N, Takekoshi K and Naruse M (2018). Risk Stratification on Pheochromocytoma and Paraganglioma from Laboratory and Clinical Medicine. *J Clin Med* 7(9):242.

32 Asa SL, Ezzat S and Mete O (2018). The Diagnosis and Clinical Significance of Paragangliomas in Unusual Locations. *J Clin Med* 7(9):280.

33 Miettinen M, McCue PA, Sarlomo-Rikala M, Rys J, Czapiewski P, Wazny K, Langfort R, Waloszczyk P, Biernat W, Lasota J and Wang Z (2014). GATA3: a multispecific but potentially useful marker in surgical pathology: a systematic analysis of 2500 epithelial and nonepithelial tumors. *Am J Surg Pathol* 38(1):13–22.

34 Kimura N, Miura Y, Nagatsu I and Nagura H (1992). Catecholamine synthesizing enzymes in 70 cases of functioning and non- functioning phaeochromocytoma and extra-adrenal paraganglioma. *Virchows Arch A Pathol Anat Histopathol* 421(1):25–32.

35 Rooper LM, Bishop JA and Westra WH (2018). INSM1 is a Sensitive and Specific Marker of Neuroendocrine Differentiation in Head and Neck Tumors. *Am J Surg Pathol* 42(5):665–671.

36 McCuiston A and Bishop JA (2018). Usefulness of NKX2.2 Immunohistochemistry for Distinguishing Ewing Sarcoma from Other Sinonasal Small Round Blue Cell Tumors. *Head Neck Pathol* 12(1):89–94.

37 van Nederveen FH, Gaal J, Favier J, Korpershoek E, Oldenburg RA, de Bruyn EM, Sleddens HF, Derkx P, Riviere J, Dannenberg H, Petri BJ, Komminoth P, Pacak K, Hop WC, Pollard PJ, Mannelli M, Bayley JP, Perren A, Niemann S, Verhofstad AA, de Bruine AP, Maher ER, Tissier F, Meatchi T, Badoual C, Bertherat J, Amar L, Alataki D, Van Marck E, Ferrau F, Francois J, de Herder WW, Peeters MP, van Linge A, Lenders JW, Gimenez-Roqueplo AP, de Krijger RR and Dinjens WN (2009). 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* 10(8):764–771.

38 Papathomas TG, Oudijk L, Persu A, Gill AJ, van Nederveen F, Tischler AS, Tissier F, Volante M, Matias-Guiu X, Smid M, Favier J, Rapizzi E, Libe R, Curras-Freixes M, Aydin S, Huynh T, Lichtenauer U, van Berkel A, Canu L, Domingues R, Clifton-Bligh RJ, Bialas M, Vikkula M, Baretton G, Papotti M, Nesi G, Badoual C, Pacak K, Eisenhofer G, Timmers HJ, Beuschlein F, Bertherat J, Mannelli M, Robledo M, Gimenez-Roqueplo AP, Dinjens WN, Korpershoek E and de Krijger RR (2015). 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* 28(6):807–821.

39 Udager AM, Magers MJ, Goerke DM, Vinco ML, Siddiqui J, Cao X, Lucas DR, Myers JL, Chinnaiyan AM, McHugh JB, Giordano TJ, Else T and Mehra R (2018). The utility of SDHB and FH immunohistochemistry in patients evaluated for hereditary paraganglioma-pheochromocytoma syndromes. *Hum Pathol* 71:47–54.

40 Fuchs TL, Luxford C, Clarkson A, Sheen A, Sioson L, Elston M, Croxson MS, Dwight T, Benn DE, Tacon L, Field M, Ahadi MS, Chou A, Clifton-Bligh RJ and Gill AJ (2023). A Clinicopathologic and Molecular Analysis of Fumarate Hydratase-deficient Pheochromocytoma and Paraganglioma. *Am J Surg Pathol* 47(1):25–36.

41 Seabrook AJ, Harris JE, Velosa SB, Kim E, McInerney-Leo AM, Dwight T, Hockings JI, Hockings NG, Kirk J, Leo PJ, Love AJ, Luxford C, Marshall M, Mete O, Pennisi DJ, Brown MA, Gill AJ, Hockings GI, Clifton-Bligh RJ and Duncan EL (2021). Multiple Endocrine Tumors Associated with Germline MAX Mutations: Multiple Endocrine Neoplasia Type 5? *J Clin Endocrinol Metab* 106(4):1163–1182.

42 Cheung VKY, Gill AJ and Chou A (2018). Old, New, and Emerging Immunohistochemical Markers in Pheochromocytoma and Paraganglioma. *Endocr Pathol* 29(2):169–175.

43 Mete O, Pakbaz S, Lerario AM, Giordano TJ and Asa SL (2021). Significance of Alpha-inhibin Expression in Pheochromocytomas and Paragangliomas. *Am J Surg Pathol* 45(9):1264–1273.

44 Flores SK, Estrada-Zuniga CM, Thallapureddy K, Armaiz-Peña G and Dahia PLM (2021). Insights into Mechanisms of Pheochromocytomas and Paragangliomas Driven by Known or New Genetic Drivers. *Cancers (Basel)* 13(18):4602.

45 Kawanabe S, Katabami T, Oshima R, Yanagisawa N, Sone M and Kimura N (2022). A rare case of multiple paragangliomas in the head and neck, retroperitoneum and duodenum: A case report and review of the literature. *Front Endocrinol (Lausanne)* 13:1054468.

46 Kimura N, Ishikawa M and Shigematsu K (2022). Colorectal paragangliomas with immunohistochemical deficiency of succinate dehydrogenase subunit B. *Endocr J* 69(5):523–528.

47 Tayara A, Townsend WR, 3rd, Umar A, Parker KG, Manucha V, Kane AC, Jackson L and Taylor CS (2024). Paragangliomas Arising From the Laryngeal Paraganglia: Thyroid and Laryngeal Paragangliomas With Radiology-Pathology Correlation. *Cureus* 16(4):e57613.

48 Bo JP, Zhou N, Sun MX and Zhou J (2023). Primary hepatic paraganglioma with megacolon: A case report. *Oncol Lett* 25(5):183.

49 Mehra S and Chung-Park M (2005). Gallbladder paraganglioma: a case report with review of the literature. *Arch Pathol Lab Med* 129(4):523–526.

50 Stojanoski S, Boldt HB, Kozic D, Patócs A, Korbonits M, Medic-Stojanoska M and Casar-Borota O (2021). Case Report: Malignant Primary Sellar Paraganglioma With Unusual Genetic and Imaging Features. *Front Oncol* 11:739255.

51 Tobón A, Velásquez M, Pérez B, Zúñiga V, Sua LF and Fernández-Trujillo L (2020). Pathologic features and clinical course of a non-functioning primary pulmonary paraganglioma: A case report. *Ann Med Surg (Lond)* 55:185–189.

52 Roman-Gonzalez A and Jimenez C (2017). Malignant pheochromocytoma-paraganglioma: pathogenesis, TNM staging, and current clinical trials. *Curr Opin Endocrinol Diabetes Obes* 24(3):174–183.