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 (select all that apply)
  - ☐ 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, *specify*
  - ☐ Imaging findings, *specify*
  - ☐ Previous therapy, *specify*
  - ☐ Relevant familial history, *specify*
  - ☐ Presence of endocrine or other tumours, *specify*
  - ☐ Presence of germline mutation or familial syndrome, *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*

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*

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

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TUMOUR SITE[a] (select all that apply) (Note 5)
(Specify number of tumours at any site containing more than one tumour)

- ◯ Cannot be assessed
- ☐ 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 Tumours of Endocrine Organs (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* → %

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

LYMPH NODE STATUS (Note 15)

- ◯ Cannot be assessed
- ◯ 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*

ANCILLARY STUDIES (Note 17)

- ◯ Not performed
- ◯ Performed (select all that apply)
  - ☐ Immunohistochemistry
    - ☐ Chromogranin A, *specify result*
    - ☐ Keratins, *specify result*
    - ☐ S100, *specify result*
    - ☐ SDHB, *specify result*
    - ☐ GATA-3, *specify result*
    - ☐ 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 8th 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
- ◯ 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, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley (incorporating any errata published up until 12th July 2024).*

[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. Adrenal cortical tumours are dealt with in a separate ICCR dataset.

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

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 termed phaeochromocytomas, while 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.

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Note 1 – Clinical information (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.[2] 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.[3] Distinct correlations exist between genotype, biochemical phenotype,[4] tumour distribution, prognosis, and syndrome associations.[5,6]

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 embolization is an established cause of necrosis in head and neck paragangliomas.[7] Partial adrenalectomy, which is increasingly utilised in treating patients with pheochromocytomas,[8] 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.[9] 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.[10] 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.[11]

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.[12,13] However, tumour size ≥50 mm is included as a staging criterion in the Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) TNM8 Staging Manual.[14,15]

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 Tumours of Endocrine Organs, 5th edition, 2025 (Table 1).[2] 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.[2] There is no specified percentage of the second tumour type.[2] 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.[2,16]

Table 1: World Health Organization classification of phaeochromocytomas and paragangliomas.[2]

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).[17] 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.[9] 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 (see **Note 19 – PATHOLOGICAL STAGING)**.[14,15]

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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.[9] 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.[9]

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).[16]

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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.[18] 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[19] or Ki-67[20] 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,[2] it is recommended that the Ki-67 proliferation index should be reported as a percentage of positive tumour cells in the area of highest nuclear labelling (so called hotspots).[5,20] 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.[2]

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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.[21-24] 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[22] was designed for phaeochromocytomas, while GAPP[21] 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.[25] 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.[26]

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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.[27-29] 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,[29,30] 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.[27] 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,[31] INSM1,[32] and NKX2.2.[33]

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.[34,35] 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).[36,37] MAX immunohistochemistry has been proposed as a marker of underlying *MAX* genetic variants, but its utility has been questioned.[38,39] 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.[40]

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 2000 to around 40% currently, it seems prudent to refer every patient to clinical genetics for further genetic counseling 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.[41] 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.[29] 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.[42-48] 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 8th editions of the UICC/AJCC Cancer Staging Manuals.[14,15] 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.[14,15,49]

Reporting of pathological staging categories (pT, pN, pM) is based on the evidence available to the pathologist at the time of reporting. As indicated in UICC TNM8 and AJCC TNM8,[14,15] the final stage grouping of a patient's tumour is based on a combination of pathological staging and other clinical and imaging information.

The reference document TNM Supplement: A commentary on uniform use, 5th edition (C Wittekind et al. editors) may be of assistance when staging.[50]

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References

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