Parathyroid Carcinoma and Atypical Parathyroid Neoplasm 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

Hyperparathyroidism
- ◯ Information not provided
- ◯ Primary
- ◯ Secondary
- ◯ Tertiary

Previous parathyroid surgery
- ◯ Information not provided
- ◯ No
- ◯ Yes, *specify*

Relevant familial history
- ◯ Information not provided
- ◯ No
- ◯ Yes, *specify*

Presence of clinical syndrome
- ◯ Information not provided
- ◯ No
- ◯ Yes, *specify*

Other clinical information, *specify*

PRE-OPERATIVE BIOCHEMICAL INFORMATION (Note 2)

(select all that apply)

◯ Information not provided
☐ Calcium, *specify level with units and specimen type (serum, other)*
☐ Parathyroid hormone (PTH), *specify level with units*
☐ Other, *specify*

OPERATIVE PROCEDURE (select all that apply) (Note 3)

◯ Not specified
☐ Parathyroidectomy, single gland
☐ Parathyroidectomy, en bloc with thyroid lobe
☐ Other parathyroid gland sampling
- ◯ Unilateral
- ◯ Bilateral

☐ Lymph node sampling, *specify*
☐ Soft tissue of neck, *specify*
☐ Other, *specify*

OPERATIVE FINDINGS (select all that apply) (Note 4)

◯ Not specified
☐ Non-adherent to surrounding structures
☐ Adherent to structure(s)
- ☐ Thyroid
- ☐ Oesophagus
- ☐ Recurrent laryngeal nerve
- ☐ Skeletal muscle
- ☐ Other, *specify*

☐ Cystic
- ◯ Yes
- ◯ No

☐ Other, *specify*

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SPECIMEN(S) SUBMITTED (select all that apply) (Note 5)

- ◯ Not specified
- ☐ Parathyroid
  - ☐ Left
    - ☐ Superior ☐ Inferior ◯ Not specified
  - ☐ Right
    - ☐ Superior ☐ Inferior ◯ Not specified
  - ☐ Other, *specify*
- ☐ Thyroid gland
  - ☐ Left ☐ Right ☐ Isthmus
- ☐ Lymph node(s), *specify site(s) and laterality*
- ☐ Other, *specify site(s) and laterality*

SPECIMEN DIMENSIONS (Note 6)

length mm x width mm x depth mm

SPECIMEN WEIGHT (Note 7)

mg Parathyroid alone

OR

mg Parathyroid with other structure(s), *specify*

◯ Cannot be assessed, *specify*

TUMOUR SITE (select all that apply) (Note 8)

- ◯ Not specified
- ☐ Parathyroid
  - ☐ Left
    - ◯ Superior ◯ Inferior ◯ Not specified
  - ☐ Right
    - ◯ Superior ◯ Inferior ◯ Not specified
  - ☐ Mediastinal
  - ☐ Intrathyroidal, *specify lobe(s)*
- ☐ Soft tissue or muscle, *specify site(s) and laterality*
- ☐ Lymph node(s), *specify site(s) and laterality*
- ☐ Other, *specify site(s) and laterality*

TUMOUR DIMENSIONS (Note 9)

Maximum tumour dimension (largest tumour)

mm

Additional dimensions (largest tumour)

mm x mm

◯ Cannot be assessed, *specify*

BLOCK IDENTIFICATION KEY (Note 10)

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

HISTOLOGICAL TUMOUR TYPE (Note 11)

- ◯ Atypical parathyroid tumour (atypical parathyroid neoplasm/neoplasm of uncertain malignant potential (UMP) or neoplasm of low malignant potential)
- ◯ Parathyroid carcinoma

MITOTIC COUNT (Note 12)

/10 mm^2

◯ Cannot be assessed

TUMOUR NECROSIS (Note 13)

- ◯ Not identified
- ◯ Present

EXTENT OF INVASION (Note 14)

- ◯ Cannot be assessed
- ◯ Confined to parathyroid
- ◯ Invasion into adjacent structure(s) (select all that apply)
  - ☐ Recurrent laryngeal nerve
  - ☐ Thyroid gland
  - ☐ Oesophagus
  - ☐ Skeletal muscle
  - ☐ Major blood vessels
  - ☐ Thymus
  - ☐ Trachea
  - ☐ Spine
  - ☐ Other, *specify*

LYMPHATIC INVASION (Note 15)

- ◯ Not identified
- ◯ Present

VASCULAR INVASION (Note 15)

- ◯ Not identified
- ◯ Present
  - **Type of vessel involved** (select all that apply)
    - ☐ Capillary ☐ Vein

PERINEURAL INVASION (Note 16)

- ◯ Not identified
- ◯ Present

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MARGIN STATUS (Note 17)

- ○ Not involved
  - 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*

LYMPH NODE STATUS (Note 18)

- ○ No nodes submitted or found
- Number of lymph nodes examined
- ○ Not involved
- ○ Involved
  - Number of involved lymph nodes
  - ○ Number cannot be determined

COEXISTENT FINDINGS (select all that apply) (Note 19)

- ○ None identified
- ☐ Other finding(s) in same parathyroid gland, *specify*
- ☐ Tissue from another submitted parathyroid gland
  - ○ Normal
  - ○ Hypercellular, *specify*
  - ○ Other, *specify*

ANCILLARY STUDIES (Note 20)

- ○ Not performed
- ○ Performed (select all that apply)
  - ☐ Immunohistochemistry
    - ☐ Ki-67 proliferation index ____ %
    - ☐ Parafibromin (CDC73), *specify results*
    - ☐ PGP9.5, *specify results*
    - ☐ Other, *record test(s), methodology and result(s)*
  - ☐ Molecular testing
    - ☐ CDC73 (parafibromin gene)
      - ☐ Germline testing, *specify results*
      - ☐ Tumour (somatic) testing, *specify results*
    - ☐ Other, *record test(s), methodology and result(s)*

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

HISTOLOGICALLY CONFIRMED DISTANT METASTASES (Note 21)

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

PATHOLOGICAL STAGING (UICC TNM 9th edition)[a] (Note 22)

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

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

Primary tumour (pT)

- ○ TX[b] Primary tumour cannot be assessed
- ○ T0 No evidence of primary tumour
- ○ T1 Limited to the parathyroid gland or any tumour with minimal extra-parathyroid soft tissue extension without direct invasion of the thyroid gland
- ○ T2 Tumour of any size with invasion into the thyroid gland
- ○ T3 Tumour of any size with invasion into adjacent skeletal muscle, recurrent laryngeal nerve, trachea, oesophagus, thymus, or direct invasion into adjacent lymph node(s)
- ○ T4 Tumour of any size with direct invasion into major blood vessels or spine

Regional lymph nodes (pN)

- ○ NX[b] Regional lymph nodes cannot be assessed
- ○ N0 No regional lymph node metastasis
- ○ N1a Metastasis in level VI (pretracheal, paratracheal and prelaryngeal/Delphian lymph nodes) or upper/superior mediastinal lymph nodes
- ○ N1b Metastasis in other unilateral, bilateral or contralateral cervical (level I,II,III,IV, or V) or retropharyngeal node

[a] *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).*

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

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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 parathyroid resection specimens when the diagnosis is atypical parathyroid neoplasm (atypical parathyroid adenoma or carcinoma). No dataset is utilised for parathyroid hyperplasia or parathyroid adenoma of usual type. Biopsies are not included. Sarcoma, lymphoma and metastasis are not covered in this dataset.

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.[2] In development of this dataset, the DAC considered evidence up until August 2025.

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)

Parathyroid carcinoma is a rare neoplasm representing <1% of cases of primary hyperparathyroidism.[3-7] Multiple surgeries may be required for clinical management for some patients with hyperparathyroidism. Clinical syndromes which may be associated with parathyroid disease include multiple endocrine neoplasia (MEN) syndromes (MEN1, MEN2, MEN4 and MEN5), hyperparathyroidism jaw-tumour (HPT-JT), and isolated familial hyperparathyroidism.[8-11] These disorders are more likely to be accompanied by primary hyperparathyroidism-related multiglandular parathyroid disease (multiple multiglandular adenomas) although rare cases of parathyroid carcinoma have been reported.[3,12] The HPT-JT syndrome involving the *CDC73* gene, is an autosomal dominant disorder that is strongly associated with both benign and malignant parathyroid neoplasms, and has a lifetime risk of approximately 15% for the development of parathyroid carcinoma.[3,13-15]

In the setting of secondary or tertiary hyperparathyroidism due to renal failure or other disorders, individual parathyroid glands may show atypical features that may mimic carcinoma including the presence of pseudoinvasion. Many experts are reluctant to make a diagnosis of parathyroid carcinoma in the setting of secondary/tertiary renal failure or would use more strict criteria by restricting the diagnosis to a parathyroid neoplasm with vascular invasion (blood vessel invasion) and/or metastatic spread. Therefore, knowledge of the presence of renal failure and secondary/tertiary hyperparathyroidism is critical to enable proper pathological assessment.[3]

Discussion with the treating clinician (endocrinologist/surgeon, etc.) for correlative clinical information as described here and under biochemical information is important for characterising this disease. Other relevant information may include detailed family history, imaging findings of lateralisation noted on ultrasound, nuclear medicine (e.g., sestamibi) scan or 4-dimensional CT scans.[16,17] Other information also includes any history of fine needle aspiration (FNA), parathyroid hormone (PTH) washout assays, ethanol ablation, or a former surgery since previous manipulations of the parathyroid glands may lead to worrisome histologic alterations important to consider during specimen interpretation.[3,4,18,19]

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Note 2 – Pre-operative biochemical information (Core and Non-core)

The highest preoperative levels of serum calcium and parathyroid hormone should be recorded. A clinical concern for parathyroid carcinoma is raised when a patient presents with a palpable neck mass (often >30 millimetres (mm)), moderate to severe high serum calcium levels (>3 millimoles (mmol)/litre (L) or >12 milligrams (mg)/declitre (dl)) with significantly elevated PTH levels (more than three times, usually more than 10 times the upper limit of normal).[3-5,20] It remains unclear if the preoperative levels of either calcium or PTH (including a third-to-second generation PTH assay ratio >1) may have a predictive role in this disease,[20-22] although patients with severe hypercalcemia are more likely to meet the criteria for the diagnosis of parathyroid carcinoma.[6,23-26] Documenting this clinical information is important and may also stratify patients' risk of recurrence.[27] In general, standard international (SI) units are preferred which is mmol/L. However, the units used should clearly be stated.

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Note 3 – Operative procedure (Core)

For clinically suspected parathyroid carcinoma, a preoperative biopsy is not recommended. Often the presentation of parathyroid carcinoma overlaps with parathyroid adenoma and the diagnosis is not made until surgical inspection and/or histologic review of the parathyroid resection specimen.[3-5,28,29] When carcinoma is suspected an en bloc resection of the concerning parathyroid gland along with the immediately adjacent or adherent structures such as the ipsilateral thyroid lobe may facilitate complete tumour resection. Advancements in preoperative imaging and the role of intraoperative PTH assays have reduced the need for multigland sampling and it is not often recommended when a parathyroid mass is encountered.[4,5,30] Similarly, lymph node sampling is generally not performed as the rate of regional nodal spread is low. If lymph node sampling is performed, the location of the resected lymph nodes should be specified. Resection of soft tissue of the neck, which may include skeletal muscle and nerve, most often will be encountered in the setting of recurrent disease. Other tissues to be specified may include oesophageal wall, thymus gland, or any structures not otherwise listed. In the unlikely scenario where more than one anatomically primary tumour occurs, a separate dataset should be completed for each tumour.

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Note 4 – Operative findings (Core and Non-core)

The intraoperative findings often are clues to the possible diagnosis of parathyroid carcinoma. Specifically, the observation of the parathyroid mass being adherent to nearby structures (in the absence of prior FNA or surgical procedures) is concerning for parathyroid malignancy and atypical parathyroid tumours. In addition, both atypical parathyroid tumours and parathyroid carcinomas often tend to be firm and have a tan-to-grey appearance. Cystic tumours may be disrupted during surgical intervention. Recognition of involved structures and possible close margins are also important considerations when reviewing the intraoperative and pathologic information together.

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Note 5 – Specimen(s) submitted (Core)

Recording each specimen submitted allows for the extent of surgery to be documented. The location of the excised parathyroid should include laterality as well as correlation with the anatomic position of superior or inferior glands. Parathyroid 'other' may include mediastinal locations or supernumerary glands for which laterality should be included if known/determined. Additional resected specimens may include the thyroid lobe either en bloc with the parathyroid or as a separate specimen. When lymph nodes are submitted their locations should be specified (e.g., level VI, right or left paratracheal, right or left lateral neck). If additional specimens are resected (e.g., such as additional tissue by adjacent to the recurrent laryngeal nerve, muscle, or thymic tissue) these elements are captured in the 'other' specimen field.

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Note 6 – Specimen dimensions (Non-core)

The specimen dimension is recorded in millimetres (mm) and may be of value when the parathyroid tumour size cannot be determined due to specimen handling or disrupted nature of surgical excision.

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Note 7 – Specimen weight (Core)

A normal parathyroid gland weighs approximately 40-60 mg and measures up to 6-8 mm.[3,5] Glandular size and weight have long been utilised to aid in defining abnormal parathyroid glands in both benign and malignant conditions. Ideally the weight is of the parathyroid gland only; however, unlike parathyroid adenomas, soft tissue surrounding the parathyroid gland should not be removed when a parathyroid atypical tumour (neoplasm) or carcinoma is suspected. This allows for the microscopic evaluation of possible lesional extension into the adjacent tissues. On average parathyroid carcinomas typically weigh over 500 mg; however, there may be considerable variation in gland weight.

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Note 8 – Tumour site (Core)

Parathyroid glands are paired endocrine structures with typically two glands on the right and the left. Based on patterns of embryologic development the glands may also be located in the mediastinum associated with the thymus or partially or fully within a thyroid lobe. Tumour may involve soft tissue that is further specified (i.e., adjacent to recurrent laryngeal nerve) or skeletal muscle (i.e., strap muscles). Other involved structures may include adjacent organs (i.e., thyroid, oesophagus or trachea). Regional tumour metastases to lymph nodes may also occur; the nodal level of involvement and laterality should be recorded (e.g., right paratracheal, or right level VI, etc.).

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Note 9 – Tumour dimensions (Core and Non-core)

The largest dimension of the parathyroid neoplasm is recorded in millimetres (mm). The additional dimensions may also be recorded. The tumour dimensions may be taken from the gross examination (refer to **Note 6 – SPECIMEN DIMENSIONS**) or by microscopic examination as appropriate. In some specimens, it may be difficult to provide the accurate tumour dimension; therefore, the specimen size may be recorded with an explanatory note specifying the estimated size (e.g., at least 40 mm). Studies are conflicting as to the prognostic value of size.[7,26,31]

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Note 10 – 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 of the 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 11 – Histological tumour type (Core)

The histological tumour types to be included for parathyroid neoplasms are those defined in the most recent edition of the WHO Classification of Endocrine and Neuroendocrine Tumours, 5th edition (Table 1).[2,3] The diagnosis of parathyroid carcinoma is restricted to a parathyroid neoplasm that shows one of the following features: (i) angioinvasion (vascular invasion), (ii) lymphatic invasion, (iii) perineural invasion, (iv) malignant invasion into the adjacent structures/organs, or (v) locoregional or distant metastasis. Parathyroid carcinoma may show a fibrotic tumour capsule as well as broad bands within the substance of the tumour. Most parathyroid tumours are unencapsulated. Unlike encapsulated follicular cell-derived thyroid neoplasms, the concept of tumour capsule invasion is not a reliable criterion of malignancy in parathyroid tumours. Therefore, beyond angioinvasion, lymphatic invasion and perineural invasion, tumour invasion that defines malignancy is based on the identification local invasion into adjacent structures/organs. Cytologically, parathyroid carcinoma may be relatively uniform (bland-like parathyroid adenoma) or show nuclear pleomorphism in association with prominent macronucleoli, increased mitotic count (>5 mitoses per 10mm^2), and/or coagulative necrosis.[3,4,25,32-34] The latest WHO Classification does not endorse any grading system for parathyroid carcinomas.

Atypical parathyroid tumours (acceptable terminologies: atypical parathyroid neoplasm; parathyroid tumour of low or uncertain malignant potential) are non-invasive parathyroid neoplasms that show worrisome (atypical) cytological and architectural features.[3] Atypical parathyroid tumours generally have more than one concerning features, such as fibrous bands, increased mitotic figures (>5 mitoses per 10 mm^2), atypical mitotic figure, necrosis, trabecular growth, or adherence to surrounding tissues intraoperatively, as well as aberrant immunohistochemical biomarker expression (refer to **Note 20 – ANCILLARY STUDIES**).[3] Particular care should be taken to distinguish parathyroid carcinoma when identifying an atypical mitotic figure and/or coagulative tumour necrosis in a parathyroid neoplasm.[3] Additional levels may help to identify microscopic invasion in similar cases. Atypical parathyroid tumours usually have a smaller dimension, weight, and volume than carcinomas.

Table 1: 5th edition of the World Health Organization Classification of parathyroid tumours.[2]

Descriptor	ICD-O codes[a]
Parathyroid adenoma	8140/0
Parathyroid lipoadenoma	8324/0
Atypical parathyroid tumour	8140/1
Parathyroid carcinoma	8140/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-0-3.2).[35] 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 12 – Mitotic count (Core)

In primary hyperparathyroidism, the presence of mitoses is uncommon in benign parathyroid disorders and should raise concern for a parathyroid malignancy or atypical parathyroid tumour. The literature commonly refers to mitotic rates per 50 high power fields (HPF) without always defining the diameter of the HPFs. For this reporting protocol mitotic count should be evaluated as number of mitoses per 10 mm^2. It is recommended that reporting pathologists know their field diameter when calculating mitotic rates. The estimate of 10 HPFs equating to 2 mm^2 is commonly used as this reflects many microscopes in widespread use. The area of the tumour with the highest mitotic activity, i.e., 'hot-spot', should be preferentially counted if identified. While absolute mitotic count does not definitively separate adenomas from carcinomas, an increased mitotic activity in parathyroid tumours refers to a mitotic count that exceeds 5 per 10 mm^2 in the latest WHO Classification.[3] Limited studies to date have evaluated the prognostic significance of this histologic factor.[27,31,32] The use of supplemental techniques such as phosphoHistone-H3 for identifying mitosis is not established in parathyroid neoplasms. The finding of atypical mitoses may be remarked upon in the pathology report.

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Note 13 – Tumour necrosis (Core)

The finding of coagulative necrosis is uncommon outside of the diagnosis of atypical parathyroid tumour or parathyroid carcinoma.[32] Particular care should be taken to distinguish parathyroid carcinoma when identifying coagulative tumour necrosis in a parathyroid neoplasm.[3] In such situations, additional levels may help to identify microscopic invasion to render the diagnosis of carcinoma. It is important to know if a previous manipulation (e.g., FNA, PTH washout, ethanol ablation therapy) may have been performed as this may lead to secondary necrosis or infarction in a parathyroid adenoma and should not be reported as an atypical tumour or carcinoma without other supporting criteria.

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Note 14 – Extent of invasion (Core)

Parathyroid carcinoma and atypical parathyroid tumours may sometimes be difficult to diagnose on histologic examination. The extent of tumour involvement has been proposed as one critical factor in diagnosis and also determines the pT stage (refer to **Note 22 – PATHOLOGICAL STAGING**). By definition an atypical parathyroid tumour may not invade other structures (i.e., cannot involve adipose tissue beyond the gland, muscle or adjacent organs as these features are restricted to parathyroid carcinomas). Documentation of tumour extent may also imply severity of local disease; however, studies correlating tumour extent with prognosis are conflicting.[25,27,31,34,36,37]

Rarely a parathyroid carcinoma may only show angioinvasion or lymphatic invasion, a true hallmark of a carcinoma, with minimal to no localised invasive growth (as in pT1 disease).[3,4,37] The assessment of vascular invasion should not be done within the tumour substance, but it is assessed at the tumour periphery or the tumour (pseudo) capsule. Overall, the documentation of the presence and extent of local tissue involvement in parathyroid carcinomas is inconsistently presented in the literature for this rare disease. The importance of including these findings in this dataset is for compliance with the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) TNM staging,[38,39] as well as to collect data that may further refine the future stratification of these tumours for staging and outcome.

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Note 15 – Lymphatic invasion (Core) and Vascular invasion (Core)

Lymphatic and vascular invasion (angioinvasion) is the presence of tumour cells within a lymphatic or vascular space, respectively. Identifying this feature at the tumour periphery or in peritumoural soft tissue is a diagnostic criterion to define parathyroid carcinoma. Lymphatic or vascular invasion should not be present in an atypical parathyroid tumour. Angioinvasive parathyroid carcinomas have a worse prognosis than carcinomas diagnosed solely on the basis of other forms of invasive growth and appear to have a higher risk of recurrence.[25,37,40] The presence of fibrin associated with the tumour cells within an endothelial lined space supports the finding of true vascular invasion.[3,4,25,27,31,34,36,41] As an endocrine organ, the parathyroid glands are highly vascular and have fenestrated endothelium, and it is important not to mistake tumour next to small vessels as representing vascular space invasion. Moreover, peliosis (extravasated erythrocytes) is a common finding in parathyroid tumours and may also mimic vascular invasion. Special stains (e.g., ERG, CD34, CD31) may be utilised to highlight vascular structures. When the morphological distinction of small blood vessels from lymphatic channels poses a challenge, special stains may also be used (e.g., D2-40 to highlight lymphatic channels, CD34 for endothelial cells lining blood vessels). In addition, the use of Martius-Scarlet Blue histochemistry or CD61 immunohistochemistry can be used to highlight platelets (fibrin) admixed with intravascular tumour cells when rendering the diagnosis of angioinvasion (vascular invasion).[3] When the status of blood vessel or lymphatic invasion is indeterminate due to technical issues (e.g., the area of interest not being present in subsequent levels), the option of 'other, specify' can be used to document challenges.

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Note 16 – Perineural invasion (Core)

Histologically confirmed perineural invasion is documented as a part of this reporting guide. In some cases, perineural invasion can be a microscopic finding unrelated to recurrent laryngeal nerve invasion. However, the close proximity of the parathyroids with the recurrent laryngeal nerve, leads to potential gross invasion of this structure. Critical review is required of this parameter as close proximity without direct nerve involvement would be considered not involved.

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Note 17 – Margin status (Core and Non-core)

Parathyroid neoplasms have a potential to locally recur if incompletely excised. Since secondary changes including fibrosis or desmoplastic tissue reaction may be mistaken for macroscopic involvement of margins (R2 margin status), histologic confirmation of the R2 margin status is needed. Disruption of the gland intra-operatively, rupture, piecemeal removal and involved surgical margins all place a patient at increased local risk of recurrence.[25,36,40,41] Such disruption of parathyroid specimens, which often requires clinical, biochemical and imaging correlations for the completeness of the tumour excision, would be considered as R2 margin status when gross residual disease may remain (transected margins). However, in the absence of intraoperative and postoperative biochemical and imaging data, pathologists can select the option of cannot be assessed to document the margin status of disrupted parathyroid specimens. Often the proximity to the adjacent nerve may lead to the tumour abutting the margin either focally or with possible circumscribed nests approximating the margin. These scenarios are consistent with a R1 microscopic surgical margin. As parathyroid masses are often without orientation the location of the margin involved may not be determined; however, if known should be specified. Currently surgery is the only modality to effectively treat parathyroid tumours.

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Note 18 – Lymph node status (Core)

Regional lymph node metastasis from parathyroid carcinoma is uncommon with involvement mostly in the central neck (levels VI or VII) and rarely lateral neck (levels II, III, and IV).[40] Metastases to lymph nodes has shown a potential correlation with survival however this has not been confirmed by large database studies.[6,7,27,31,42,43] Although the evaluation of lymph node metastasis for extranodal extension (ENE) is encouraged for other head and neck malignancies, there is currently limited data on ENE specific to parathyroid carcinoma and so it is not included in this dataset.

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Note 19 – Coexistent findings (Non-core)

Coexistent findings enable documentation of other histologic features identified in either the same parathyroid gland as the neoplasm or in other parathyroid gland tissue submitted for evaluation. As coexisting parathyroid conditions may be encountered in other parathyroid glands submitted it is important to detail whether the histology has normal, hypercellular (i.e., specifying if diagnostic of adenoma or multiglandular parathyroid disease), or other features seen as relevant to this dataset. Malignant pathology identified in the thyroid would utilise the corresponding thyroid dataset.

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Note 20 – Ancillary studies (Core and Non-core)

The confirmation of parathyroid origin is required when dealing with non-functional parathyroid carcinomas. PTH expression can be variable but GATA3 and GCM2 are diffusely positive in parathyroid neoplasms.[44] Since there is no single marker that can distinguish parathyroid carcinomas from atypical parathyroid tumours and adenomas, the use of multiple immunohistochemical markers in a panel has been recommended.[3,44] Unlike most parathyroid adenomas, parathyroid carcinomas tend to show loss of parafibromin, APC, BCL2, p27, E-cadherin, MDM2, and 5-hydroxymethylcytosine, and tend to be more frequently positive for PGP9.5, p53 (overexpression), galectin-3, as well as Ki-67 proliferation index >5%.[4,25,34,37,44-55] Atypical parathyroid tumours may also show aberrant biomarker expression indistinguishable from carcinomas.[3]

Similar to other neuroendocrine neoplasms, the assessment of the proliferative activity of all parathyroid carcinomas by undertaking a formal Ki-67 proliferation index and mitotic count is required.[3] It is also desirable to perform other immunohistochemical biomarkers. Some key immunohistochemical biomarkers are discussed in this section.

The latest WHO Classification recommends the application of parafibromin immunohistochemistry in parathyroid carcinomas and atypical parathyroid tumours.[3] Parafibromin is the protein encoded by the *CDC73* gene (previously known as *HRPT2*). Germline mutations and deletions in the *CDC73* gene occur in the autosomal dominant HPT-JT syndrome with somatic second hits occurring in carcinomas and adenomas arising in this setting. Patients presenting with apparently sporadic parathyroid carcinoma may have occult HPT-JT syndrome.[14,32,41,56-58] Somatic only double hit mutation/inactivation also occur frequently in parathyroid carcinomas not associated with HPT-JT.[58] Immunohistochemistry for parafibromin is not widely available and may be technically difficult to perform and interpret.[14] Immunohistochemical evaluation of parafibromin shows nuclear staining in normal parathyroid cells and most benign parathyroid tumours.[59] Loss of nuclear expression of parafibromin occurs in most but not all tumours associated with biallelic *CDC73* mutation/deletion.[58,60-62] Some tumours may show nucleolar parafibromin loss which an abnormal parafibromin expression and this finding requires further molecular testing to rule out *CDC73* alterations.[3,63,64] Loss of nuclear parafibromin expression is not completely sensitive for *CDC73* mutation but may be used to triage genetic testing for HPT-JT syndrome in patients with atypical parathyroid tumours and parathyroid carcinoma. Parafibromin loss may be associated with a higher likelihood of recurrence in parathyroid carcinoma.[14,49,50,58,60,61,65] Atypical parathyroid tumours with parafibromin deficiency are regarded to be high-risk neoplasms.[46,65] It has been suggested that tumours which demonstrate loss of parafibromin expression may show subtle morphological clues including sheet like growth, eosinophilic cytoplasm, perinuclear cytoplasmic clearing and nuclear enlargement.[8,58] Genetic testing is considered in any patients with parafibromin-deficient parathyroid tumours (adenomas, atypical parathyroid tumours, parathyroid carcinomas) since a fraction of sporadic looking manifestations occurs in the setting of pathogenic constitutional *CDC73* variants.

As mentioned above, parathyroid carcinomas are required to be assessed with Ki-67 immunohistochemistry. Ki-67 proliferative index has also been reported as elevated (often >5%) in parathyroid neoplasms though with some overlap with hyperplasia and adenomas.[34,44,45,52,62,66,67] Evaluation of Ki-67 immunohistochemical staining of the parathyroid neoplasm 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).[68] 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.[69]

Protein Gene Product 9.5 (PGP9.5) is also overexpressed in the majority of parathyroid carcinomas and has shown similar performance in parathyroid carcinomas as parafibromin immunohistochemical evaluation.[50] Other markers of worth mentioning might include galectin-3 overexpression, E-cadherin and retinoblastoma (Rb) loss of expression which has also been studied with an association in carcinomas compared to adenomas.[34,44,45,70-72]

At this time, no routine diagnostic tumour (somatic) molecular testing algorithms have been developed in parathyroid carcinoma. Germline testing is indicated in all patients with primary hyperparathyroidism-related multiglandular parathyroid disease, and *CDC73* testing should be considered in parafibromin-deficient parathyroid tumours.[3,8,11] However, as a clinical tool theranostic molecular testing in advanced parathyroid carcinoma has been promising in modern endocrine oncology practice.[73-76]

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Note 21 – Histologically confirmed distant metastases (Core)

The presence of histologically confirmed distant metastases is a critical component of pathological staging.[38,39]

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Note 22 – Pathological staging (Core)

A prognostic staging system has now been adopted for parathyroid carcinomas. The standardised data collection as proposed in the former version of this guide (outlined in the 8th edition of AJCC Cancer Staging Manual[39]) is now being updated with the UICC TNM 9th edition.[38]

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,[38,39] 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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