# Parathyroid Carcinoma & 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 (select all that apply) (Note 1)

- ◯ Information not provided
- ☐ Hyperparathyroidism
  - ◯ Primary
  - ◯ Secondary
  - ◯ Tertiary
- ☐ Previous parathyroid surgery, *specify*
- ☐ Relevant familial history, *specify*
- ☐ Presence of a clinical syndrome, *specify*
- ☐ Other, *specify*

## PRE-OPERATIVE BIOCHEMICAL INFORMATION (select all that apply) (Note 2)

- ◯ 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 ☐ Recurrent laryngeal nerve
  - ☐ Oesophagus ☐ Skeletal muscle
  - ☐ Other, *specify*
- ☐ Other, *specify*

## 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 nodes, *specify site(s) and laterality*
- ☐ Other, *specify site(s) and laterality*

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**TUMOUR SITE** (select all that apply) (Note 6)

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

**SPECIMEN WEIGHT** (Note 7)

mg Parathyroid alone

OR

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

◯ Cannot be assessed, *specify*

**TUMOUR DIMENSIONS** (Note 8)

Maximum tumour dimension (largest tumour)

mm

Additional dimensions (largest tumour)

mm x mm

◯ Cannot be assessed, *specify*

**HISTOLOGICAL TUMOUR TYPE** (Note 9)

- ◯ Atypical parathyroid neoplasm (atypical parathyroid adenoma)/neoplasm of uncertain malignant potential (UMP)[a]
- ◯ Parathyroid carcinoma

[a] *Defined as tumours that are histologically or clinically worrisome but do not fulfill the more robust criteria (i.e., invasion, metastasis) for carcinoma. They generally include tumours that have two or more concerning features, such as fibrous bands, mitotic figures necrosis, trabecular growth, or adherence to surrounding tissues intraoperatively. Atypical parathyroid neoplasms usually have a smaller dimension, weight, and volume than carcinomas and are less likely to have coagulative tumour necrosis.*

**HISTOLOGICAL TUMOUR GRADE** (Note 10)

- ◯ Low grade
- ◯ High grade
- ◯ Not determined
- ◯ Not applicable (i.e., atypical neoplasm/adenoma, UMP[a])

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

- ◯ Cannot be assessed
- ◯ Confined to parathyroid without invasion through tumour capsule
- ☐ Invasion through tumour capsule
- ☐ Invasion into extra-parathyroidal soft tissue
- ☐ Invasion into adjacent structures, *specify*
  - ☐ Recurrent laryngeal nerve
  - ☐ Thyroid gland
  - ☐ Oesophagus
  - ☐ Skeletal muscle
  - ☐ Other, *specify*

**LYMPHOVASCULAR INVASION** (Note 12)

- ◯ Not identified
- ◯ Present
  - ☐ Vascular invasion
  - ☐ Lymphatic invasion

**PERINEURAL INVASION** (Note 13)

- ◯ Not identified
- ◯ Present

**NECROSIS** (Note 14)

- ◯ Not identified
- ◯ Present

**MITOTIC COUNT** (Note 15)

per 2 $mm^2$ [b]

◯ Cannot be assessed

[b] *2 $mm^2$ approximates 10 HPFs on some microscopes.*

**MARGIN STATUS** (Note 16)

- ◯ Not involved (R0)
  - Distance of tumour to closest margin mm
- ◯ Involved
  - ◯ Abutting tissue edge (R1 resection)
  - ◯ Transected, fragmented or ruptured (possible R2 resection)

  *Specify if named structure/location is involved at margin(s)*
- ◯ Cannot be assessed, *specify*


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## LYMPH NODE STATUS (Note 17)

- ◯ No nodes submitted or found

Number of lymph nodes examined ____

- ◯ Not involved
- ◯ Involved

  Number of positive lymph nodes ____

- ◯ Number cannot be determined

## COEXISTENT FINDINGS (select all that apply) (Note 18)

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

## ANCILLARY STUDIES (select all that apply) (Note 19)

- ◯ Not performed
- ☐ Immunohistochemistry performed
  - ☐ Ki-67, *specify results and method* ____ %
  - ☐ Parafibromin (CDC73), *specify results*
  - ☐ PGP9.5, *specify results*
  - ☐ Other immunohistochemistry, *specify*
- ☐ Molecular performed
  - ☐ CDC73 (parafibromin gene)
    - ☐ Germline testing, *specify results*
    - ☐ Tumour (somatic) testing, *specify results*
  - ☐ Other molecular test(s), *specify*
- ☐ Other, *specify*

## HISTOLOGICALLY CONFIRMED DISTANT METASTASES (Note 20)

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

## PATHOLOGICAL STAGING (AJCC TNM 8th edition)[c] (Note 21)

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

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

### Primary tumour (pT)

- ◯ TX Primary tumour cannot be assessed
- ◯ Tis Atypical parathyroid neoplasm (neoplasm of UMP)[a]
- ◯ T1 Localised to the parathyroid gland with extension limited to soft tissue
- ◯ T2 Direct invasion into the thyroid gland
- ◯ T3 Direct invasion into recurrent laryngeal nerve, oesophagus, trachea, skeletal muscle, adjacent lymph nodes, or thymus
- ◯ T4 Direct invasion into major blood vessel or spine

### Regional lymph nodes (pN)

- ◯ NX Regional lymph nodes cannot be assessed
- ◯ N0 No regional lymph node metastasis
- ◯ N1 Regional lymph node metastasis
  - ◯ N1a Metastasis to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes) or superior mediastinal lymph nodes (level VII)
  - ◯ N1b Metastasis to unilateral, bilateral, or contralateral cervical (level I,II,III,IV, or V) or retropharyngeal nodes

[c] *Used with the permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2016) published by Springer Science+Business Media.*


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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 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 in the expert committee. An appropriate staging system e.g., Pathological TNM staging would normally be included as a CORE element.

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

**NON-CORE elements**

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

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

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# Scope

The dataset has been developed for the pathology reporting of parathyroid resection specimens when the diagnosis is atypical parathyroid neoplasm (atypical parathyroid adenoma or carcinoma. No dataset is utilized for parathyroid hyperplasia or parathyroid adenoma of usual type. Biopsies are not included. Sarcoma, lymphoma and metastasis are not covered in this dataset.

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# Note 1 – Clinical information (Core)

Parathyroid carcinoma is a rare neoplasm representing <1% of cases of primary hyperparathyroidism.[2-5] Multiple surgeries are common and may be required for initial diagnosis and/or for recurrence. Clinical syndromes which may be associated with parathyroid disease include multiple endocrine neoplasia (MEN) syndromes and familial hyperparathyroidism. In these disorders it is more likely to find parathyroid hyperplasia or adenoma although rare cases of parathyroid carcinoma have been reported.[6] The hyperparathyroidism jaw-tumour (HPT-JT) syndrome involving the *CDC73* gene, is an autosomal dominant disorder that is strongly associated with parathyroid carcinoma (lifetime risk is approximately 15%).[7-9] In the setting of secondary or tertiary hyperparathyroidism due to renal failure or other disorders, individual parathyroid glands may show highly 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. Therefore, knowledge of the presence of renal failure and secondary/tertiary hyperparathyroidism is important to enable proper pathological assessment. Discussion with the treating clinician (endocrinologist/surgeon, etc.) for correlative clinical information as described here and under biochemical information is important for characterizing this disease. Other relevant information may include detailed family history, imaging findings of lateralization noted on ultrasound, nuclear medicine (e.g., sestamibi) scan or 4-dimensional CT scans.[10] Other information also includes any history of fine needle aspiration (FNA), since this procedure may lead to pathologic alterations important to consider during specimen interpretation.

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

The highest preoperative levels of calcium and parathyroid hormone should be recorded. A clinical concern for parathyroid carcinoma is raised when a patient presents with a palpable neck mass, very high serum calcium levels (>14 mg/dl/3.5 mmol/L) and corresponding significantly elevated parathyroid hormone (PTH) levels. It remains unclear if the preoperative levels of either calcium or PTH may have a predictive role in this disease, although patients with extreme hypercalcemia are more likely to meet the criteria for the diagnosis of parathyroid carcinoma.[2,3,11,12] Documenting this associated clinical information is important and may also stratify patients' risk of recurrence.[13] Different institutions may use different units for measurement of calcium. In general, standard international (SI) units are preferred which is mmol/L. However, the units used should 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.[14,15] 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 have reduced the need for multigland sampling and it is not recommended when a parathyroid mass is encountered.[16] 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 (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. 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 – 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.).[2,11,17]

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## Note 7 – Specimen weight (Core)

A normal parathyroid gland weighs approximately 40 mg. Glandular size and weight have long been utilized to aid in defining abnormal parathyroid glands in both benign and malignant conditions. Ideally the weight is of the parathyroid gland only, however soft tissue surrounding the gland should not be removed when a parathyroid atypical 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 dimensions (Core and Non-core)

The largest dimension of the parathyroid neoplasm is recorded in millimetres (mm). The tumour dimensions may be taken from the gross examination or by microscopic examination as appropriate. Studies are conflicting as to the prognostic value of size.[2,4,11]

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## Note 9 – Histological tumour type (Core)

The histological tumour types to be included for parathyroid neoplasms are those defined in the most recent edition of the World Health Organization (WHO) Classification of Tumours of Endocrine Organs.[18] Parathyroid carcinoma is diagnosed by unequivocal invasion into adjacent soft tissues, muscle or other adjacent organs (e.g., thyroid), lymphovascular or perineural invasion and/or the presence of regional or distant metastases. Parathyroid carcinoma may show a fibrotic tumour capsule as well as broad bands within the substance of the tumour. Cytologically, parathyroid carcinoma may be relatively uniform (low grade) or show high grade features including pleomorphism, macronucleoli, high-mitotic rate, and/or coagulative necrosis.[19-22]

Parathyroid neoplasms that show some histologically worrisome features but do not fulfil the more robust criteria of invasion or metastasis are classified as atypical parathyroid neoplasm (atypical parathyroid adenoma)/neoplasm of uncertain malignant potential (UMP). These lesions lack unequivocal invasion. Parathyroid neoplasms of UMP generally have two or more concerning features, such as fibrous bands, mitotic figures, necrosis, trabecular growth, or adherence to surrounding tissues intraoperatively. Additionally they usually have a smaller dimension, weight, and volume than carcinomas and are less likely to have coagulative tumour necrosis.[23-27]

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## Note 10 – Histological tumour grade (Core)

The division of parathyroid carcinoma into low grade and high grade utilizes cytologic features including pleomorphism necrosis and mitotic activity. High grade parathyroid carcinomas are characterized by the presence of multiple concurrent histologically adverse features including sheets of cells with pleomorphic enlarged nuclei (4x the size of background parathyroid cells) often with macronucleoli, coagulative necrosis, abnormal mitoses, and/or increased proliferation rate.[19,22] Focal cellular atypia or endocrine atypia may be found in benign entities including the characteristic of cells 4x as large and is insufficient to meet criteria for true nuclear pleomorphism.

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## Note 11 – Extent of invasion (Core)

Parathyroid carcinoma and parathyroid neoplasms of uncertain malignant potential may be difficult to diagnose on histologic examination. The extent of tumour involvement has been proposed as one critical factor in diagnosis. Many, but not all, tumours show a fibrotic capsule with invasion. By definition a parathyroid neoplasm of uncertain malignant potential may not invade other structures (i.e., cannot involve adipose tissue, 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.[11,13,21,22,28] Rarely a parathyroid carcinoma may show lymphovascular involvement, a true hallmark of a carcinoma, with minimal to no localized invasive growth. As parathyroid neoplasms are very vascular caution in making the diagnosis of carcinoma is warranted in cases where an invasive growth pattern is not encountered. 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 data collection that may aid in future stratification of these tumours for staging and outcome.

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## Note 12 – Lymphovascular invasion (Core and Non-core)

Lymphovascular invasion is the presence of tumour cells within a lymphatic or vascular space. Identifying this feature in the tumour capsule or in peritumoural soft tissue is a diagnostic criterion to define parathyroid carcinoma. Lymphovascular invasion should not be present in an atypical parathyroid neoplasm/adenoma or parathyroid tumour of uncertain malignant potential. Vascular invasive 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.[26] The presence of fibrin associated with the tumour cells within an endothelial lined space supports the finding of true vascular invasion.[11,13,22,28,29] As an endocrine organ, the parathyroid glands are highly vascular, and it is important not to mistake tumour next to small vessels as representing vascular space invasion. Special stains may be utilized for further visualization/confirmation of vascular invasion though are not essential.

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## Note 13 – Perineural invasion (Core)

The close proximity of the parathyroids with the recurrent laryngeal nerve, leads to potential 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 14 – Necrosis (Core)

The finding of coagulative necrosis is uncommon outside of the diagnosis of atypical parathyroid neoplasm/adenoma or parathyroid carcinoma.[19] Necrosis may also be more common in high grade tumours. It is important to know if a FNA may have been performed as this may lead to secondary

necrosis in a parathyroid adenoma and should not be reported as an atypical neoplasm or carcinoma without other supporting criteria.

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## Note 15 – Mitotic count (Core)

The presence of mitoses is uncommon in benign parathyroid disorders and should raise concern for a parathyroid malignancy. However, absolute mitotic count does not definitively separate adenomas from carcinomas. The literature commonly refers to mitotic rates per 50 or 10 high power fields (HPFs) without always defining the diameter of the HPFs. For this reporting protocol mitotic count should be evaluated as number of mitoses per 2 $mm^2$. 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. Limited studies to date have evaluated the prognostic significance of this histologic factor.[11,13,19] The use of supplemental techniques such as PHH3 for identifying mitosis is not established in parathyroid neoplasms. The finding of abnormal mitoses may be remarked upon in the pathology report.

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## Note 16 – Margin status (Core and Non-core)

Parathyroid neoplasms have a potential to locally recur if incompletely excised. Disruption of the gland intra-operatively, rupture, piecemeal removal and involved surgical margins all place a patient at increased local risk of recurrence.[21,26,28,29] Such disruption of parathyroid specimens would be considered as R2 margin status when gross residual disease may remain (transected margins). 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 17 – 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).[26] Metastases to lymph nodes has shown a potential correlation with survival however this has not been confirmed by large database studies.[3,4,11,13,30,31] 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 18 – Coexistent findings (Non-core)

Coexistent findings enables 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 encounted in other parathyroid glands submitted it is important to detail whether the histology has normal, hypercellular (i.e., specifying if specific for hyperplasia or adenoma), or other features seen as relevant to this dataset. Malignant pathology identified in the thyroid would utilize the corresponding thyroid dataset.

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## Note 19 – Ancillary studies (Non-core)

Parafibromin is the protein encoded by the *CDC73* gene (previously known as HRPT2).[32] 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.[8,19,29,33-35] Somatic only double hit mutation/inactivation also occur frequently in parathyroid carcinomas not associated with HPT-JT.[35] Immunohistochemistry for parafibromin is not widely available and may be technically difficult to perform and interpret.[8] Immunohistochemical evaluation of parafibromin shows nuclear staining in normal parathyroid cells and most benign parathyroid tumours. Loss of nuclear expression of parafibromin occurs in most but not all tumours associated with biallelic *CDC73* mutation/ deletion.[35-38] Loss of 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 neoplasms and parathyroid carcinoma. Parafibromin loss may be associated with a higher likelihood of recurrence in parathyroid carcinoma.[8,35-37,39-41] 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.[35]

Ki-67 proliferative index has also been reported as elevated in parathyroid neoplasms though with some overlap with hyperplasia and adenomas.[22,32,38,42,43] If performed, 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 and the number of cells evaluated, or automated computer assisted calculation including the number of cells counted).

Other markers might include Cyclin D and/or galectin-3 overexpression or retinoblastoma (Rb) loss of expression which has also been studied with an association in carcinomas compared to adenomas.[22,44,45] 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.[40]

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## Note 20 – Histologically confirmed distant metastases (Core)

The presence of histologically confirmed distant metastases is a critical component of pathological staging.[46]

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## Note 21 – Pathological staging (Core)

A prognostic staging system has not been formally adopted for parathyroid carcinomas. The rarity of this disease has limited standard review and comparison for meaningful stratification. However, it is recognized that standardized data collection as proposed here and outlined in the 8th edition of American Joint Committee on Cancer (AJCC) Staging Manual will begin the process of systematically gathering data for this rare entity.[46] It is with this goal that the parathyroid dataset is established.

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