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

Standards and datasets for reporting cancers

Dataset for the histopathological reporting of carcinomas of the parathyroid

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Foreword

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

Each dataset contains core data items (see Appendices C and D) some of which are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – previously the National Cancer Data Set v9.0 in England). Core data items are those that are supported by robust published evidence and are required for cancer staging, optimal patient management and prognosis. Core data items meet the requirements of professional standards and it is recommended that at least 95% of reports on cancer resections should record a full set of core data items. Other non-core data items are described. These may be included to provide a comprehensive report or to meet local clinical or research requirements. All data items should be clearly defined to allow the unambiguous recording of data.

The following stakeholders were contacted to consult on this document:

- UK Endocrine Pathology Society (UKEPS)
- British Association of Endocrine and Thyroid Surgeons (BAETS)
- British Association of Head and Neck Oncologists (BAHNO)
- National Cancer Registration and Analysis Service (NCRAS).

The information used by the authors to develop this dataset was obtained by undertaking a search on PubMed and Google Scholar databases for relevant primary research evidence

and systematic reviews on parathyroid malignancy from January 2016 to October 2022 (inclusive). Key search terms included ‘parathyroid carcinoma’. The recommendations incorporate the core data items and commentary from the International Collaboration on Cancer Reporting (ICCR)[1,2] with additional information from the World Health Organization (WHO) 2022 classification of parathyroid tumours.[3] The level of evidence for the recommendations has been summarised according to modified SIGN guidance (see Appendix E) and the grade of evidence is indicated in the text. No major conflicts in the evidence have been identified and minor discrepancies between studies have been resolved by expert consensus. Gaps in the evidence were identified by College members via feedback received during consultation.

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

A formal revision cycle for all cancer datasets takes place on a 3-yearly basis. However, each year, the College will ask the author of the dataset, in conjunction with the relevant subspecialty adviser to the College, to consider whether or not the dataset needs to be updated or revised. A full consultation process will be undertaken if major revisions are required, i.e. to core data items, apart from changes to international tumour grading and staging schemes that have been approved by the Specialty Advisory Committee on Cellular Pathology and affiliated professional bodies. These changes will be implemented without further consultation. If minor revisions or changes to non-core data items are required, an abridged consultation process will be undertaken whereby a short note of the proposed changes will be placed on the College website for 2 weeks for members’ attention. If members do not object to the changes, the changes will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

The dataset has been reviewed by the Professional Guidelines team, Working Group on Cancer Services and the Lay Advisory Group, and was placed on the College website for consultation with the membership from 19 July to 16 August 2023. All comments received from the Working Group and membership were addressed by the authors to the satisfaction of the Chair of the Working Group and the Clinical Lead for Guideline Review.

This dataset was developed without external funding to the writing group. The College requires the authors of datasets to provide a list of potential conflicts of interest; these are

monitored by the Professional Guidelines team and are available on request. The authors have declared no conflicts of interest.

1 Introduction

1.1 Endocrine cancer datasets

The management of patients with endocrine tumours should be the responsibility of an appropriately experienced and competent multidisciplinary team (MDT). Because these tumours bridge various anatomical divisions, they are the topics of separate cancer datasets. Ideally, the pathologist(s) reporting them should have a special interest in endocrine pathology or, if a general pathologist, should participate in a network with easy opportunity for specialist pathology review.

The dataset has been developed for the reporting of parathyroid specimens containing parathyroid carcinoma. Neck dissections and nodal excisions are dealt with in a separate dataset;[4] this dataset should be used in conjunction, where applicable.

The primary purpose of this document is twofold:

- to define the set of data necessary for the uniform recording and staging of the core pathological features in cancers of the parathyroid
- to describe its application in sufficient detail and clarity that reports from different departments will contain equivalent information, allowing comparison of clinical practice and outcomes.

The core pathological data is summarised as proformas that may be used as the main reporting format or may be combined with free text, as required.

1.2 Design of this dataset and protocol

The RCPath recognises the authority of internationally accepted guidance documents (WHO, American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM and ICCR) and, to promote consistent reporting practice, adopts the recommendations of these organisations. This structured reporting protocol has been developed using the framework and data items specified in the ICCR *Parathyroid Carcinoma and Atypical Parathyroid Neoplasm Histopathology Reporting Guide* (published in 2019).[1,2] This RCPath dataset and protocol includes all of the ICCR cancer dataset elements (core and non-core) and some additional commentary for the UK audience. At

the time of writing, the 5th edition of the *WHO Classification of Endocrine Neoplasms* was unavailable but a review article clearly explains the changes in terminology and reiterates the diagnostic criteria for parathyroid tumours; these have been included.[3] Core references have been updated to include relevant new information from 2016 to October 2022.

ICCR dataset elements for these cancers have been included verbatim and are indicated by the blue ICCR logo. ICCR core elements are mandatory, form part of the COSD data and are therefore represented as standards in this document. ICCR (and RCPath) non-core elements are recommended and may be included as guidelines or used routinely according to local practice.

The ICCR Reporting Guide also covers atypical parathyroid neoplasms/tumours. It is not considered necessary to use the RCPath dataset for these, but the ICCR text is retained for information and completeness. The pathology report should clearly state the considered presence and absence of all the features on which the diagnosis has been made.

1.3 Target users and health benefits of this guideline

The primary target users of the dataset are trainee and consultant cellular pathologists and, on their behalf, the suppliers of IT products to laboratories. The secondary users are surgeons and oncologists, Cancer Registries and the National Cancer Registration and Analysis Service (NCRAS). Standardised cancer reporting and MDT working reduce the risk of histological misdiagnosis and help to ensure that clinicians have all of the relevant pathological information required for tumour staging, management and prognosis. Collection of standardised cancer-specific data also provides information for healthcare providers and epidemiologists and facilitates international benchmarking and research.

2 Clinical information required on the specimen request form

The request form should include patient demographic data, which includes:

- the patient's name
- date of birth
- sex
- hospital

- hospital and NHS numbers (where appropriate), or other patient identification number.

Clinical information should include:

- relevant clinical, biochemical and imaging data
- any history of previous biopsy/sampling or surgery at the site
- operative procedure and findings
- specimens submitted including site and side of parathyroid gland(s)
- ideally, whether a clinically suspicious parathyroid lesion is a single large nodule or is forming multiple nodules, as multiple smaller nodules might favour a diagnosis of parathyromatosis, a benign lesion
- whether surgery is performed for recurrent disease in the neck or metastatic disease; the surgeon must highlight this because histological interpretation may be altered.

Any local arrangements for booking intraoperative frozen sections should be followed.

The request form should enable surgeons to provide annotated diagrams of specimens, if appropriate.

The following should also be recorded:

- the name of the clinician requesting the investigation
- the date and time of the operation
- the date and time at which the specimen was fixed
- the date and time the specimen was received in the laboratory.

3 Receipt and preparation of specimens before dissection

The specimen may be received fresh if intraoperative frozen section is required (see sections 4 and 8). Otherwise, routine fixation in formalin is required (or following sampling, if frozen section is performed). The specimens are nearly always small enough to be fixed intact without needing slicing to aid fixation; such slicing may compromise later assessment of invasion and margins.

4 Specimen handling and block selection

Please refer to the *Tissue Pathways for Endocrine Pathology*.[5] The weight (ideally using a calibrated measuring device that can measure in milligrams if possible, or to the nearest 0.1 g) and the dimensions (in millimetres) should be recorded, together with description of the macroscopic appearances. It is not advised to dissect out the tumour to obtain the weight because this could disrupt evidence of invasion.

The specimens may be received fresh for intraoperative reporting. Appropriate tissue should be taken for frozen section. A block of 5–10 mm in greatest dimension is suggested; for small specimens, this may be the whole specimen but, for larger glands, a block should be taken from the cross-section, including the vascular hilum if possible. After frozen section reporting, the tissue, including any frozen block(s), should be fixed in formalin.

After fixation, the tissue should be sliced and embedded in its entirety for paraffin sections, regardless of whether a frozen section has been performed.

It is helpful to identify 1 block to be used if molecular analysis is needed later but this identification may be better done after microscopic evaluation; the block number should be stated in the report to facilitate future block retrieval.

Where an en bloc resection is done, the nature of the resection and the tissues included should be described and the parathyroid tissue should be identified and measured. Inking the specimen surface before slicing will assist with assessing margins. The whole of the parathyroid tissue should be embedded for histology, with the blocks selected to assess specimen margins and any invasion into attached tissues. All lymph nodes received should be embedded.

5 Core data items

This section sets out to use the ICCR dataset in its current form, with appropriate qualifications and clarifications for implementation in UK clinical practice. In addition to the main dataset items, as outlined below, demographic and clinical data should be collected, as per the ICCR dataset. This includes the patient's name, date of birth, sex, hospital of surgery, hospital number, NHS number (where appropriate) or other patient identification number.

1 ICCR	Descriptor	Core/Non-core	Responses

	Clinical information	Core	Multi-selection value list (select all that apply)/text:
			• Information not provided
			• Hyperparathyroidism
			  – Primary
			  – Secondary
			  – Tertiary
			• Previous parathyroid surgery, specify
			• Relevant familial history, specify
			• Presence of clinical syndrome, specify
			• Other, specify

ICCR commentary: Parathyroid carcinoma is a rare neoplasm representing <1% of cases of primary hyperparathyroidism.[6–9] 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.[10] 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%).[11–13] 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 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.[14] Other information also includes any history of fine needle aspiration, since this procedure may lead to pathologic alterations important to consider during specimen interpretation.

RCPath additional comments: The clinical information should include whether the hyperparathyroidism is primary, secondary or tertiary, and whether there is any concern about the possibility of parathyroid carcinoma. Clinical presentation of parathyroid carcinoma varies but there is nearly always hypercalcaemia, often symptomatic.[13,14] Parathyroid carcinoma and atypical parathyroid tumours are rare in MEN1.[15,16] In the 2022 WHO classification, the traditional term of 'hyperplasia' for primary hyperparathyroidism involving multiple glands is replaced with the terms 'multiglandular parathyroid disease' or 'multiglandular multiple parathyroid adenomas' because the affected glands are composed of multiple clonal proliferations.[3] This may be seen with MEN syndromes and germline genetic testing may be helpful to guide patient management.[3]

[Level of evidence C – The evidence basis for inclusion is well-conducted case-control or cohort studies.]

2 ICCR	**Descriptor**	**Core/Non-core**	**Responses**

	Operative procedure	Core	Multi-selection value list (select all that apply)/text:
			• 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

ICCR commentary: 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.[17,18] 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.[19] 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 1 anatomically primary tumour occurs, a separate dataset should be completed for each tumour.

RCPath additional comments: For any neck dissection or nodal excision, the relevant dataset should be used.[4]

[Level of evidence D – The basis in evidence for inclusion is expert opinion.]

3 ICCR	**Descriptor**	**Core/Non-core**	**Responses**
	Specimens submitted	Core	Multi-selection value list (select all that apply)/text: • 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

ICCR commentary: 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. additional tissue adjacent to the recurrent laryngeal nerve, muscle or thymic tissue) these elements are captured in the 'other' specimen field.

[Level of evidence D – The basis in evidence for inclusion is expert opinion.]

4 ICCR	**Descriptor**	**Core/Non-core**	**Responses**

	Tumour site	Core	Multi-selection value list (select all that apply)/text:
			• 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

ICCR commentary: Parathyroid glands are paired endocrine structures with typically 2 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).[6,20,21]

[Level of evidence D – The basis in evidence for inclusion is expert opinion.]

5 ICCR	Descriptor	Core/Non-core	Responses
	Specimen weight	Core	Numeric/text/single select value list: • ___ mg parathyroid alone • ___ mg parathyroid with other structure(s), specify structure(s) • Cannot be assessed, specify

ICCR commentary: A normal parathyroid gland weighs approximately 40 mg. Glandular size and weight have long been used 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.

[Level of evidence – GPP.]

6 ICCR	Descriptor	Core/Non-core	Responses
	Tumour dimensions		
	Maximum tumour dimension	Core	Numeric/text: • Maximum tumour dimension (largest tumour) ___ mm • Cannot be assessed, specify

ICCR commentary: 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.[6,8,20]

RCPath additional comments: Recent Surveillance, Epidemiology and End Results (SEER) data suggest that tumours more than 4 cm in size are associated with higher mortality.[22]

[Level of evidence – C/D.]

7 ICCR	**Descriptor**	**Core/Non-core**	**Responses**
	Histological tumour type	Core	Single selection value list: • Atypical parathyroid neoplasm (atypical parathyroid adenoma)/neoplasm of uncertain malignant potential (UMP) • Parathyroid carcinoma

ICCR commentary: The histological tumour types to be included for parathyroid neoplasms are those defined in the most recent edition of the *WHO Classification of Tumours of Endocrine Organs*.[23] 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.[24–27]

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 UMP). These lesions lack unequivocal invasion. Parathyroid neoplasms of UMP generally have 2 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.[28–32]

RCPath additional comments: The 5th edition of the *WHO Classification of Parathyroid Tumours* reiterates the features seen in parathyroid carcinomas and atypical parathyroid tumours. The term 'atypical parathyroid tumour' reflects a parathyroid neoplasm of UMP and replaces the previous term of 'atypical parathyroid adenoma'.[3,33] Definite features of malignancy indicating a parathyroid carcinoma are the presence of any 1 of the following: (i) angioinvasion (vascular invasion), (ii) lymphatic invasion, (iii) perineural (or intraneural) invasion, (iv) local malignant invasion into adjacent anatomic structures, or (v) histologically/cytologically documented metastatic disease.[3] In contrast, an atypical parathyroid tumour shows atypical cytological and architectural features but lacks the unequivocal features that would be required for a diagnosis of parathyroid carcinoma.[3] The term atypical parathyroid tumour is reserved for cases where the differential diagnosis is a parathyroid carcinoma.[3] Completion of the dataset is not required for atypical parathyroid tumours but clear specification of the features present or absent is required.

[Level of evidence – B/C.]

8 ICCR	Descriptor	Core/Non-core	Responses
	Histological tumour grade	Core	Single selection value list: • Low grade • High grade • Not determined • Not applicable (i.e. atypical neoplasm/adenoma, UMP)

ICCR commentary: The division of parathyroid carcinoma into low grade and high grade uses cytologic features including pleomorphism, necrosis and mitotic activity. High grade parathyroid carcinomas are characterised 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.[24,27] 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.

RCPath additional comments: Recent SEER data suggest that higher grade tumours are associated with higher mortality.[15]

[Level of evidence – B/C.]

9 ICCR	Descriptor	Core/Non-core	Responses
	Extent of invasion	Core	Multi-selection value list (select all that apply)/text: • 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

ICCR commentary: Parathyroid carcinoma and parathyroid neoplasms of UMP may be difficult to diagnose on histologic examination. The extent of tumour involvement has been proposed as 1 critical factor in diagnosis. Many, but not all, tumours show a fibrotic capsule with invasion. By definition a parathyroid neoplasm of UMP 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.[20,26,27,34,35] Rarely a parathyroid carcinoma may show lymphovascular involvement, a true hallmark of a carcinoma, with minimal to no localised 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.

RCPath additional comments: Please see ICCR table 7 above regarding the WHO 2022 classification.

[Level of evidence – C/D.]

10 ICCR	Descriptor	Core/Non-core	Responses
	Lymphovascular invasion	Core	Single selection value list: • Not identified • Present

ICCR commentary: 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 UMP. 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.[31] The presence of fibrin associated with the tumour cells within an endothelial lined space supports the finding of true vascular invasion.[20,27,34–36] 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 used for further visualisation/confirmation of vascular invasion though are not essential.

RCPath additional comments: The WHO 2022 classification explains angioinvasion as tumour invading through a vessel wall and associated thrombus, or intravascular tumour cells admixed with thrombus.[3] This should be assessed at the junction between tumour and non-tumour, not within the tumour.[3] Helpful staining includes GATA3 or parathyroid hormone (PTH) for the epithelial cells, Martius-Scarlet blue or CD61 for the platelet-fibrin thrombus, and D2-40 for lymphatic invasion.[3]

[Level of evidence – B/C.]

11 ICCR	Descriptor	Core/Non-core	Responses
	Perineural invasion	Core	Single selection value list: • Not identified • Present
ICCR commentary: 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. **RCPath additional comments:** There may be invasion of smaller nerves which could be diagnostically helpful. Immunostaining (e.g. S100) may be useful to confirm this but is not essential. The WHO 2022 classification requires at least the involvement of the epineurium.[3] *[Level of evidence – GPP.]*			

12 ICCR	Descriptor	Core/Non-core	Responses
	Necrosis	Core	Single selection value list: • Not identified • Present
ICCR commentary: The finding of coagulative necrosis is uncommon outside the diagnosis of atypical parathyroid neoplasm/adenoma or parathyroid carcinoma.[24] Necrosis may also be more common in high grade tumours. It is important to know if a fine needle aspiration 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. *[Level of evidence D – The basis in evidence for inclusion is expert opinion.]*			

13 ICCR	Descriptor	Core/Non-core	Responses
	Mitotic count	Core	Numeric/single selection value list: • ___ per 2 mm^2 • Cannot be assessed

ICCR commentary: 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.[20,24,34] 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.

RCPath additional comments: Immunostaining for Ki67 can be helpful in identifying the area(s) of the tumour likely to have the highest mitotic rate. The presence of any abnormal mitotic figures should be mentioned.[3] WHO 2022 states that mitoses can be seen in benign and malignant parathyroid disease but mitotic activity exceeding 5 per 50 HPF (about 10 mm^2) in association with coagulative necrosis, macronucleoli, atypical mitoses or a Ki67 rate of more than 5% are highly concerning for malignancy, but a definite diagnosis of parathyroid carcinoma requires at least 1 of the definite diagnostic features described in section 7.[3]

[Level of evidence – B/C.]

14 ICCR	**Descriptor**	**Core/Non-core**	**Responses**
	Margin status	Core	Single selection value list/text/numeric: • Not involved (R0) • 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
Margin status – ICCR commentary: Parathyroid neoplasms have a potential to locally recur if incompletely excised. Disruption of the gland intraoperatively, rupture, piecemeal removal and involved surgical margins all place a patient at increased local risk of recurrence.[26,31,35,36] 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. *[Level of evidence – C/D.]*			

15 ICCR	**Descriptor**	**Core/Non-core**	**Responses**
	Lymph node status	Core	Single selection value list/text/numeric: • No nodes submitted or found • Number of lymph nodes examined – Not involved – Involved ○ Number of positive lymph nodes ○ Number cannot be determined
ICCR commentary: 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).[31] Metastases to lymph nodes has shown a potential correlation with survival however this has not been confirmed by large database studies.[7,8,20,34,37,38] 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.			

RCPath additional comments: For any neck dissection or nodal excision, the relevant dataset should be used.[4]

[Level of evidence – C/D.]

16 ICCR	Descriptor	Core/Non-core	Responses
	Histologically confirmed distant metastases	Core	Single selection value list/text: • Not identified • Not assessed • Present, specify site(s)
ICCR commentary: The presence of histologically confirmed distant metastases is a critical component of pathological staging.[39] **RCPath additional comments:** The presence of distant metastases is 1 of the definite criteria of malignancy as stated by WHO 2022;[3] please see section 7 above. Recent SEER data suggest that distant metastases are associated with higher mortality.[14] *[Level of evidence C – The basis in evidence for inclusion are well-conducted case-control or cohort studies.]*			

6 Non-core data items

NC1 ICCR	Descriptor	Core/Non-core	Responses
	Pre-operative biochemical information	Non-core	Multi-selection value list (select all that apply)/text: • Information not provided • Calcium, specify level with units and specimen type (serum, other) • Parathyroid hormone (PTH), specify level with units • Other, specify
ICCR commentary: 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 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 hypercalcaemia are more likely to meet the criteria for the diagnosis of parathyroid carcinoma.[6,7,20,40] Documenting this associated clinical information is important and may also stratify patients' risk of recurrence.[34] Different institutions may use different units for measurement of calcium. In general, standard international units are preferred which is mmol/L. However, the units used should be stated.

[Level of evidence – B/C.]

NC2 ICCR	Descriptor	Core/Non-core	Responses

	Operative findings	Non-core	Multi-selection value list (select all that apply)/text:
			• Not specified
			• Non-adherent to surrounding structures
			• Adherent to structure(s)
			  – Thyroid
			  – Oesophagus
			  – Recurrent laryngeal nerve
			  – Skeletal muscle
			  – Other, specify
			• Other, specify

ICCR commentary: 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 fine needle aspiration 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.

RCPath additional comments: Any intraoperative findings should be included but adherence can relate to degenerative changes rather than malignancy. It has recently been suggested that absence of near-infrared autofluorescence may help to increase the intraoperative suspicion of parathyroid carcinoma.[41]

[Level of evidence – GPP.]

NC3 ICCR	Descriptor	Core/Non-core	Responses
	Tumour dimensions		
	Additional dimensions (largest tumour)	Non-core	Additional dimensions (largest tumour) ___ mm x ___ mm

ICCR commentary: 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.[6,8,20]

[Level of evidence – C/D.]

NC4 ICCR	Descriptor	Core/Non-core	Responses
	Lymphovascular invasion	Non-core	When present, multiselect value list: • Vascular invasion • Lymphatic invasion

ICCR commentary: 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 UMP. 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.[31] The presence of fibrin associated with the tumour cells within an endothelial-lined space supports the finding of true vascular invasion.[20,27,34–36] 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 used for further visualisation/confirmation of vascular invasion though are not essential.

RCPath additional comments: The WHO 2022 classification explains angioinvasion as tumour invading through a vessel wall and associated thrombus, or intravascular tumour cells admixed with thrombus.[3] This should be assessed at the junction between tumour and non-tumour, not within the tumour.[3] Helpful staining includes GATA3 or PTH for the epithelial cells, Martius-Scarlet blue or CD61 for the platelet-fibrin thrombus and D2-40 for lymphatic invasion.[3]

[Level of evidence – B/C.]

NC5 ICCR	Descriptor	Core/Non-core	Responses
	Margin status	Non-core	If not involved, distance of tumour to closest margin ___ mm

Margin status – ICCR commentary: Parathyroid neoplasms have a potential to locally recur if incompletely excised. Disruption of the gland intraoperatively, rupture, piecemeal removal and involved surgical margins all place a patient at increased local risk of recurrence.[26,31,35,36] 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.

[Level of evidence – C/D.]

NC6 ICCR	Descriptor	Core/Non-core	Responses

	Coexistent findings	Non-core	Multi-selection value list (select all that apply)/single select/text:
			• 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

ICCR commentary: 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. if specific for hyperplasia or adenoma), or other features seen as relevant to this dataset. Malignant pathology identified in the thyroid would use the corresponding thyroid dataset.

RCPath additional comments: In the 2022 WHO classification, the traditional term of 'hyperplasia' for primary hyperparathyroidism involving multiple glands is replaced with the terms 'multiglandular parathyroid disease' or 'multiglandular multiple parathyroid adenomas'.[3] Please see section 1 of the core data items above.

[Level of evidence – GPP.]

NC7 ICCR	Descriptor	Core/Non-core	Responses
	Ancillary studies	Non-core	Multi-selection value list (select all that apply)/numeric/text: • 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

ICCR comments: Parafibromin is the protein encoded by the CDC73 gene (previously known as HRPT2).[42] 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.[12,24,36,43–45] Somatic only double-hit mutation/inactivation also occur frequently in parathyroid carcinomas not associated with HPT-JT.[45] Immunohistochemistry for parafibromin is not widely available and may be technically difficult to perform and interpret.[12] 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.[45–48] 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.[12,45–47,49–51] 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.[45]

Ki-67 proliferative index has also been reported as elevated in parathyroid neoplasms though with some overlap with hyperplasia and adenomas.[27,42,48,52,53] 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.[28,54,55] 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]

RCPath additional comments: In the overview article on the 2022 WHO classification, immunostaining is discussed usefully and at some length.[3] No individual markers are definite but careful use of a panel of immunostains can help to support a morphological diagnosis of parathyroid carcinoma.[3] Adenomas tend to retain parafibromin and APC staining, be negative for PGP9.5 and galectin3, and have a low Ki67 labelling index. Loss of parafibromin, APC, retinoblastoma, e-cadherin, p27, bcl-2a, mdm-2 and 5-hmC, and positivity for PGP9.5, galectin3, hTERT, and p53 overexpression, with a raised Ki67 rate (often over 5%) tend to correlate with carcinoma.[3,56,57] Atypical parathyroid tumours tend to have an intermediate expression of these markers, and there is particular overlap with Ki67 indices.[3] A meta-analysis has shown good specificity of loss of parafibromin immunohistochemical staining for the diagnosis of parathyroid carcinoma but limited sensitivity; there was heterogeneity between the studies.[58]

WHO 2022 also expands on the concept of 'parafibromin deficiency' in parathyroid neoplasms, which is the complete loss of nuclear immunostaining in all tumour cells.[3] This correlates highly with a CDC73 mutation, which may be somatic or germline, though staining may be retained with some germline pathogenic variants.[3] Parafibromin deficiency is rarely seen in adenomas (e.g. HPT-JT syndrome), is seen more often in atypical parathyroid tumours and is frequent in carcinomas.[3] Routine germline CDC73 mutation testing is advised for patients with parafibromin-deficient neoplasms.[3] Parafibromin deficiency has prognostic value in carcinoma with increased recurrence, metastasis and mortality,[57,59] and also in atypical parathyroid tumours.[3] Long-term follow-up of patients with parafibromin deficiency is advised.[3] Subsets of tumours may show loss of nucleolar staining with retained nuclear staining; germline molecular testing is also advised for these patients.[3]

[Level of evidence – A.]

7 Diagnostic coding and staging

7.1 Coding

See Appendix B.

7.2 Staging

There is no UICC TNM staging classification for parathyroid carcinomas, therefore the AJCC 8th edition of TNM staging is advised.[39]

17 ICCR	Descriptor	Core/Non-core	Responses
	Pathological staging (AJCC TNM 8th edition)	Core	See Appendix A
ICCR commentary: 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 recognised that standardised data collection as proposed here and outlined in the 8th edition of the AJCC Staging Manual will begin the process of systematically gathering data for this rare entity.[39] It is with this goal that the parathyroid dataset is established. *[Level of evidence C – The basis in evidence for inclusion is well-conducted case-control or cohort studies.]*			

8 Reporting of small biopsy specimens

Small biopsy samples are rarely taken deliberately from a parathyroid tumour but the possibility of parathyroid carcinoma may need to be considered in the differential diagnosis, if a neck tumour of unknown type or an extra-cervical metastatic deposit is biopsied for diagnosis.

9 Reporting of frozen sections

Intraoperative reporting may be used to confirm that the tissue sampled is parathyroid.[60] It is sometimes possible to identify histological features suggestive of malignancy, although definitive diagnosis is usually made on paraffin histology.

The frozen section findings should be documented in the final report, including the verbal report, the name of the reporting pathologist, the name of the surgeon receiving the report, the date and the time, plus any additional information provided by the surgeon (e.g. intraoperative findings, appearance of other parathyroid glands).

10 Support of research and clinical trials

Awareness of any local or national tissue banking initiatives and clinical trials is advised, with consideration of submission of material, with appropriate consent. Targeted therapy may be a possibility in the future but is beyond the remit of this dataset.[61]

11 Specific aspects of individual tumours not covered elsewhere

Some tumours may be challenging, especially oncocytic/oxyphilic types, with the differential diagnosis including tumours of parathyroid or thyroid origin, which may be benign or malignant, or metastatic carcinoma from elsewhere. Immunostaining can be helpful here; TTF1, thyroglobulin and PAX8 (ideally monoclonal) can help identify thyroid tissue, with PTH, GATA3 and chromogranin staining parathyroid tissue.[3]

12 Criteria for audit

The following is recommended by the RCPath as key performance indicators (see Key Performance Indicators – Proposals for implementation, July 2013):

- histopathology cases must be reported, confirmed and authorised within 7 and 10 calendar days of the procedure
  - standard: 80% of cases must be reported within 7 calendar days and 90% within 10 calendar days.

The RCPath recommends as a key assurance indicator[62] that there should be a statement of agreement between the laboratory and the users of the laboratory services regarding turnaround times for specific patient pathways. The laboratory also needs to provide evidence that the needs of different users are balanced. There should be audit of performance against these agreed turnaround times (audit to be performed at least annually) with published results.

The following criteria are additional examples of what could be assessed in periodic reviews of histological reports on parathyroid cancers:

- completeness of reports for the core data items stated above (the standard being that 95% of reports contain a full set of core data items)

- turnaround times for reporting intraoperative frozen sections
- turnaround times for reporting paraffin sections
- inter- and intra-observer studies in the diagnosis of parathyroid carcinoma cases.

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Appendix A AJCC TNM staging and grading

The AJCC TNM 8th edition staging system should be used and it is a core item.[39]

Definitions of AJCC TNM

Definitions of primary tumour (T)

T category	T criteria
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Atypical parathyroid neoplasm (neoplasm of uncertain malignant potential)*
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

*Defined as tumours that are histologically or clinically worrying but do not fulfil the more robust criteria (i.e. invasion, metastasis) for carcinoma. They generally include tumours that have 2 or more concerning features, such as fibrous bands, mitotic figures, necrosis, trabecular growth or adherence to surrounding tissues intraoperatively.[27,63]

Atypical parathyroid neoplasms usually have a smaller dimension, weight and volume than carcinomas and are less likely to have coagulative tumour necrosis.[17]

Definitions of regional lymph node (N)

N category	N criteria
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) ore superior mediastinal lymph nodes (level VII)

N1b	Metastasis to unilateral, bilateral or contralateral cervical (level I, II, II, IV, or V) or retropharyngeal nodes

Definitions of distant metastasis (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

AJCC prognostic stage groups (page 908)

There is not enough data to propose anatomic stage and prognostic groups for parathyroid carcinoma.

Histologic grade (G)

G	G definition

Low grade (LG): round monomorphic nuclei with only mild to moderate nuclear size variation, indistinct nucleoli and chromatin characteristics resembling those of normal parathyroid or of adenoma.

High grade (HG): more pleomorphism, with a nuclear size variation greater than 4:1, prominent nuclear membrane irregularities, chromatin alterations, including hyperchromasia or margination of chromatin, and prominent nucleoli. High-grade tumours show several discrete confluent areas with nuclear changes.

Residual tumour (R)

In addition to the AJCC TNM above, it can be useful to include an R classification to record the presence/absence of tumour remaining after curative therapy.

RX	Presence of residual tumour cannot be assessed
R0	No residual tumour
R1	Microscopic residual tumour
R2	Macroscopic residual tumour

Appendix B SNOMED coding

A SNOMED topography code should be recorded for the site of the tumour and a SNOMED morphology code for the diagnosis.

Versions of SNOMED prior to SNOMED-CT will cease to be licenced by the International Health Terminology Standards Development Organisation from 26 April 2017. It is recognised that versions of SNOMED 2, SNOMED 3/RT and SNOMED CT are in use in the UK; these are, therefore, currently considered acceptable.

SNOMED Procedure codes (P codes in SNOMED 2/3/RT) should be recorded for the procedure. P codes vary according to the SNOMED system in use in different organisations, therefore local P codes should be recorded and used for audit purposes.

Morphological item	**SNOMED code**	**SNOMED-CT terminology**	**SNOMED-CT code**
Parathyroid carcinoma	M81403	Adenocarcinoma, no subtype (morphologic abnormality)	35917007
Atypical parathyroid tumour/neoplasm or parathyroid tumour of uncertain malignant potential (UMP)	M81401	Atypical adenoma (morphologic abnormality)	24482001
Topography items	**SNOMED code**	**SNOMED-CT terminology**	**SNOMED-CT code**
Parathyroid	T97000	Parathyroid structure (body structure)	111002
Thyroid	T96000	Thyroid structure (body structure)	69748006

Appendix C Reporting proforma for carcinomas of the parathyroid

Surname…… Forenames…… Date of birth……..... Sex.....
Hospital…… Hospital no……..... NHS/CHI no……..
Date of surgery…… Date of receipt…… Date of reporting……..…....
Report no……..... Pathologist……....Surgeon…….

Clinical information provided (select all that apply)

Information not provided □

Hyperparathyroidism: primary □ secondary □ tertiary □

Previous parathyroid surgery, specify □ ……..……..

Relevant familial history, specify □ ……..…..

Presence of a clinical syndrome, specify □ ……..……..

Other, specify (e.g. imaging, pre-operative FNA) □……..…...

Operative procedure (select all that apply)

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 □……..……..

Specimen(s) submitted (select all that apply)

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 □ ……..……..

Tumour site (select all that apply)

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

Parathyroid alone ……mg

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

Cannot be assessed, specify □ ……..

Tumour dimensions

Maximum tumour dimension (largest tumour) ……mm

Cannot be assessed, specify □ ……

Histological tumour type

Atypical parathyroid tumour □

Parathyroid carcinoma □

Histological tumour grade

Low grade □

High grade □

Not determined □

Not applicable (i.e. atypical neoplasm tumour) □

Extent of invasion (select all that apply)

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

Not identified □

Present □

Perineural invasion

Not identified □

Present □

Necrosis

Not identified □

Present □

Mitotic count

…… per 2 mm^2

Cannot be assessed □

Margin status

Not involved (R0) □

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 □ ……

Lymph node status

Number of lymph nodes examined ……

Number of positive lymph nodes ……

Number cannot be determined □

Histologically confirmed distant metastases

Not identified □

Not assessed □

Present, specify site(s) □ ……

Pathological staging (AJCC TNM 8th edition)[c]

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 □

Appendix D Reporting proforma for carcinomas of the parathyroid in list format

Element name	Values	Implementation notes	COSD v9
Clinical information provided	Multi-selection value list (select all that apply): Information not provided □ Hyperparathyroidism: Primary □ Secondary □ Tertiary □ Previous parathyroid surgery, specify □ …….. Relevant familial history, specify □ …….. Presence of a clinical syndrome, specify □ …….. Other, specify (e.g. imaging, pre-operative FNA) □……..		
Operative procedure	Multi-selection value list (select all that apply) 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 □……..		
Specimens submitted	Multi-selection value list (select all that apply) 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 □ ……..		

Tumour site	Multi-selection value list (select all that apply) 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	Parathyroid alone ……mg or Parathyroid with other structure(s), ……mg, specify structure(s) …… Cannot be assessed, specify □ ……..		
Tumour dimensions	Maximum tumour dimension (largest tumour) ……mm Cannot be assessed, specify □ ……		pCR0830
Histological tumour type	Atypical parathyroid tumour □		

	Parathyroid carcinoma □		
Histological tumour grade	Low grade □ High grade □ Not determined □ Not applicable (i.e. atypical neoplasm tumour) □		pCR0860 • Low grade = G1 Well differentiated • High grade = G3 Poorly differentiated • Not determined = GX Grade of differentiation is not appropriate or cannot be assessed
Extent of invasion	Multi-selection value list (select all that apply) 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	Not identified □ Present □		pCR0870 • Not identified = NU No – vascular/lymphati

			c invasion not present • Present = YU Yes – vascular/lymphatic invasion present
Perineural invasion	Not identified □ Present □		
Necrosis	Not identified □ Present □		
Mitotic count	…… per 2 mm^2 Cannot be assessed □		
Margin status	Not involved (R0) □ 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 □ ……		pCR0880 • Not involved = 01 Excision margins are clear (distance from margin not stated) • Abutting tissue edge (R1 resection) = 05 Tumour reaches excision margin • Transected, fragmented or ruptured (possible R2 resection = 05 Tumour reaches excision margin
Lymph node status	Number of lymph nodes examined …… Number of positive lymph nodes …… Number cannot be determined □		Number of lymph nodes examined = pCR0890 Number of positive lymph nodes = pCR0900

Histologically confirmed distant metastases	Not identified □ Not assessed □ Present, specify site(s) □ ……		
Pathological staging (AJCC TNM 8th edition)	TNM descriptors (only if applicable) (select all that apply): m – multiple primary tumours r – recurrent y – post-therapy		pCR0910
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 □		pCR0920

Appendix E Summary table – explanation of grades of evidence

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

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

Appendix F AGREE II guideline monitoring sheet

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

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