PARATHYROID CARCINOMA & ATYPICAL PARATHYROID NEOPLASM

STRUCTURED REPORTING PROTOCOL

(1st Edition 2020)

Incorporating the:

International Collaboration on Cancer Reporting (ICCR)

Parathyroid Carcinoma & Atypical Parathyroid Neoplasm Dataset

www.ICCR-Cancer.org

Core Document versions:

- ICCR dataset: Parathyroid carcinoma & atypical neoplasm 1st edition v1.0[1]
- AJCC Cancer Staging Manual 8th edition[2]
- World Health Organization (2017) Classification of Tumours of Endocrine Organs (4th edition). Volume 10[3]

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The Royal College of Pathologists of Australasia ("College") has developed these protocols as an educational tool to assist pathologists in reporting of relevant information for specific cancers. While each protocol includes "standards" and "guidelines" which are indicators of 'minimum requirements' and 'recommendations', the protocols are a first edition and have not been through a full cycle of use, review and refinement. Therefore, in this edition, the inclusion of "standards" and "guidelines" in each document are provided as an indication of the opinion of the relevant expert authoring group, but should not be regarded as definitive or as widely accepted peer professional opinion. The use of these standards and guidelines is subject to the clinician's judgement in each individual case.

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Contents

Scope

This protocol contains standards and guidelines for the structured reporting of parathyroid resection specimens when the diagnosis is atypical parathyroid neoplasm (atypical parathyroid adenoma or carcinoma). Not included in this protocol are: parathyroid hyperplasia or parathyroid adenoma of usual type, sarcoma, lymphoma, and metastasis.

Structured reporting aims to improve the completeness and usability of pathology reports for clinicians and improve decision support for cancer treatment. This protocol can be used to define and report the minimum dataset, but the structure is scalable and can equally accommodate a maximum data set or fully comprehensive report.

Abbreviations

AJCC	American Joint Committee on Cancer
CT	Computed tomography
FNA	Fine needle aspiration
HPF	High power field
HPT-JT	Hyperparathyroidism jaw-tumour
ICCR	International Collaboration on Cancer Reporting
IHI	Individual Healthcare Identifier
LIS	The laboratory information system
MDT	Multidisciplinary team
MEN	Multiple endocrine neoplasia
mm	Millimetres
MRN	Medical Record Number
NHI	New Zealand National Health Index
NHMRC	National Health and Medical Research Council
PBS	Pharmaceutical Benefits Scheme
PTH	Parathyroid hormone
RCPA	Royal College of Pathologists of Australasia
SI	International System of Units
TNM	Tumour-node-metastasis
UICC	International Union Against Cancer
UK	United Kingdom
UMP	Uncertain malignant potential
WHO	World Health Organization

Definitions

The table below provides definitions for general or technical terms used in this protocol. Readers should take particular note of the definitions for 'standard', 'guideline' and 'commentary', because these form the basis of the protocol.

Ancillary study	An ancillary study is any pathology investigation that may form part of a cancer pathology report but is not part of routine histological assessment.
Clinical information	Patient information required to inform pathological assessment, usually provided with the specimen request form, also referred to as 'pre-test information'.
Commentary	Commentary is text, diagrams or photographs that clarify the standards (see below) and guidelines (see below), provide examples and help with interpretation, where necessary (not every standard or guideline has commentary). Commentary is used to: • define the way an item should be reported, to foster reproducibility • explain why an item is included (e.g. how does the item assist with clinical management or prognosis of the specific cancer). • cite published evidence in support of the standard or guideline • state any exceptions to a standard or guideline. In this document, commentary is prefixed with 'CS' (for commentary on a standard) or 'CG' (for commentary on a guideline), numbered to be consistent with the relevant standard or guideline, and with sequential alphabetic lettering within each set of commentaries (e.g. CS1.01a, CG2.05b).
General commentary	General commentary is text that is not associated with a specific standard or guideline. It is used: • to provide a brief introduction to a chapter, if necessary • for items that are not standards or guidelines but are included in the protocol as items of potential importance, for which there is currently insufficient evidence to recommend their inclusion. (Note: in future reviews of protocols, such items may be reclassified as either standards or guidelines, in line with diagnostic and prognostic advances, following evidentiary review).

Guideline	Guidelines are recommendations; they are not mandatory, as indicated by the use of the word 'should'. Guidelines cover items that are unanimously agreed should be included in the dataset but are not supported by the National Health and Medical Research Council (NHMRC) level III-2 evidence.[4] These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management. Guidelines include 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, block identification key, may be included as either required or recommended elements by consensus of the expert committee. Such findings are essential from a clinical governance perspective, because they provide a clear, evidentiary decision-making trail. Guidelines are not used for research items. In this document, guidelines are prefixed with 'G' and numbered consecutively within each chapter (e.g. G1.10).
Macroscopic findings	Measurements, or assessment of a biopsy specimen, made by the unaided eye.
Microscopic findings	In this document, the term 'microscopic findings' refers to histo-morphological assessment.
Predictive factor	A predictive factor is a measurement that is associated with response or lack of response to a particular therapy.
Prognostic factor	A prognostic factor is a measurement that is associated with clinical outcome in the absence of therapy or with the application of a standard therapy. It can be thought of as a measure of the natural history of the disease.
Standard	Standards are mandatory, as indicated by the use of the term 'must'. Standards 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[4] document). In rare circumstances, where level III-2 evidence is not available an element may be made a Standard where there is unanimous agreement in the expert committee. An appropriate staging system e.g. Pathological TNM staging would normally be included as a required element. These elements must be recorded and at the discretion of the pathologist included in the pathology report according to the needs of the recipient of the report. The summation of all standards represents the minimum dataset for the cancer.

	In this document, standards are prefixed with 'S' and numbered consecutively within each chapter (e.g. S1.02).
Structured report	A report format which utilises standard headings, definitions and nomenclature with required information.
Synoptic report	A structured report in condensed form (as a synopsis or precis).
Synthesis	Synthesis is the process in which two or more pre-existing elements are combined, resulting in the formation of something new. The Oxford dictionary defines synthesis as 'the combination of components or elements to form a connected whole'. In the context of structured pathology reporting, synthesis represents the integration and interpretation of information from two or more modalities to derive new information.

Introduction

Parathyroid carcinoma and atypical parathyroid neoplasms

Parathyroid carcinoma and atypical parathyroid adenomas are extremely rare and account for less than 1% of all causes of hyperparathyroidism. Parathyroid carcinoma is a challenging histologic diagnosis and nearly always requires clinical information such as the presence of significant hypercalcemia, very high parathyroid hormone (PTH) levels, renal or bone disease, and intra-operative findings.[5-9] Rarely, parathyroid carcinoma may arise in ectopic parathyroid glands including intrathyroid glands.

Typically, parathyroid carcinoma shows a thick fibrous capsule and fibrous septae infiltrating into the parenchyma imparting a nodular appearance. The tumour is composed of sheets of follicular cells, though trabecular architecture is also common. Palisading of cells and rosette like patterns may also be seen. Areas with spindle cell appearance can be present. The nuclei are relatively uniform in appearance. Mitoses are present, and mitoses >1/10 high power fields (HPF) should raise concerns for malignancy. Infiltration through the capsule, lymphovascular invasion, perineural invasion or infiltration into adjacent structures, when present, are helpful to confirm a malignant diagnosis.

Somatic mutations in the tumour suppressor gene *HRPT2* or *CDC73 Publication numbers for SPR protocols* gene are seen in 68-100% sporadic parathyroid carcinomas. These somatic mutations are generally truncations or deletions and lead to loss of nuclear expression of parafibromin. Loss of parafibromin expression has 80-100% specificity for parathyroid carcinoma, but lower sensitivity of approximately 60-80%. Another useful marker is PGP 9.5 - a product of the *UCHL1* gene, which is upregulated in parathyroid carcinoma. A Ki-67 labelling index of >4–5% can also be used to distinguish carcinoma from adenoma. Also, those parathyroid carcinomas with higher proliferation rates behave more aggressively. Thus, a combination of immunostains may be more useful than any single stain.

Complete surgical resection is the main stay of therapy. Radiotherapy may help local control. Chemotherapy has a limited role. The average time to recurrence is 2.5–5 years but recurrences may arise after a long disease-free interval requiring a lifelong follow-up. Metabolic complications including severe hypercalcemia also require treatment and can lead to death.

Benefits of structured reporting

The pathology report lays the foundation for a patient's cancer journey and conveys information which:

- Provides the definitive diagnosis
- Includes critical information for Tumour-Node-Metastasis (TNM) staging
- Evaluates the adequacy of the surgical excision
- Provides morphological and biological prognostic markers which determine personalised cancer therapy

However, the rapid growth in ancillary testing such as immunohistochemistry, flow cytometry, cytogenetics, and molecular studies, have made the task of keeping abreast of advances on specific cancer investigations extremely difficult for pathologists. The use of structured reporting checklists by pathologists ensures that all key elements are included in the report specifically those which have clinical management, staging or prognostic implications. Consequently, minimum or comprehensive datasets for the reporting of cancer have been developed[10,11] around the world. Both the United Kingdom,[12] and United States[13] have produced standardised cancer reporting protocols or 'datasets' for national use for many years.

The use of cancer reporting checklists improves completeness and quality of cancer reporting and thereby ensures an improved outcome for cancer patients. This has long term cost implications for public health by ensuring the most effective and timely treatment based on accurate and complete information.

The use of a structured reporting format also facilitates easy extraction of the necessary information by secondary users of the information i.e. cancer registries.

Importance of histopathological reporting

The information contained within a pathology report includes prognostic information for the patient and treating clinical team. The content will assist in subsequent management, whether this may be surveillance, further surgery, radiotherapy or chemotherapy, or a combination of these modalities.

International Collaboration on Cancer Reporting

The International Collaboration on Cancer Reporting (ICCR), founded in 2011 by the Royal College of Pathologists of Australasia (RCPA), United States College of American Pathologists (US CAP) and Royal College of Pathologists United Kingdom (RCPath UK) Colleges of Pathology and the Canadian Association of Pathology - Association Canadienne des Pathologistes (CAP-ACP) in association with the Canadian Partnership Against Cancer (CPAC), was established to explore the possibilities of a collaborative approach to the development of common, internationally standardised and evidence-based cancer reporting protocols for surgical pathology specimens.

The ICCR, recognising that standardised cancer datasets have been shown to provide significant benefits for patients and efficiencies for organisations through the ease and completeness of data capture[14-17] undertook to use the best international approaches and the knowledge and experience of expert pathologists, and produce cancer datasets which would ensure that cancer reports across the world will be of the same high quality – ensuring completeness, consistency, clarity, conciseness and above all, clinical utility.

Representatives from the four countries participating in the initial collaboration undertook a pilot project in 2011 to develop four cancer datasets - Lung, Melanoma, Prostate (Radical Prostatectomy), and Endometrium. Following on from the success of this pilot project, the ICCR was joined by the European Society of Pathology (ESP) in 2013 and in 2014 incorporated a not-for-profit organisation focussed on the

development of internationally agreed evidence-based datasets developed by world leading experts. The ICCR Datasets are made freely available from its website www.ICCR-Cancer.org

Design of this protocol

This structured reporting protocol has been developed using the ICCR Parathyroid Carcinoma & Atypical Parathyroid Neoplasm dataset as the foundation.

This protocol includes all of the ICCR cancer dataset elements as well as additional information, elements and commentary as agreed by the RCPA expert committee. It provides a comprehensive framework for the assessment and documentation of pathological features of parathyroid specimens.

ICCR dataset elements for parathyroid specimens are included verbatim. ICCR Required elements are mandatory and therefore represented as standards in this document. ICCR Recommended elements, that is, those which are not mandatory but are recommended, may be included as guidelines or upgraded to a standard based on the consensus opinion of the local expert committee.

The ICCR elements are identified in each chapter with the ICCR logo placed before the Standard or Guideline number or bullet and the ICCR element description and commentary is boarded by a grey box as shown below:

G3.02	The intraglandular extent should be recorded as a percentage.

Additional commentary by the RCPA expert committee may be added to an ICCR element but is not included in the grey bordered area nor indicated with an ICCR logo e.g.

G2.03	If present, the laterality of the lymph nodes submitted may be recorded as left, right or bilateral.

CS2.03a If present, record site and number. All lymph node tissue should be submitted for histological examination.

Further information on the ICCR is available at www.iccr-cancer.org

Checklist

Consistency and speed of reporting is improved by the use of discrete data elements recorded from the checklist. Items suited to tick boxes are distinguished from more complex elements requiring free text or narrative. A structured or discrete approach to responses is favoured, however the pathologist is encouraged to include free text or narrative where necessary to document any other relevant issues, to give reasons for coming to a particular opinion and to explain any points of uncertainty.

Report format

The structure provided by the following chapters, headings and subheadings describes the elements of information and their groupings but does not necessarily represent the format of either a pathology report (Chapter 7) or checklist (Chapter 6). These, and the structured pathology request form (Appendix 1) are templates that represent information from this protocol, organised and formatted differently to suit different purposes.

Key documentation

- ICCR dataset: Parathyroid Carcinoma & Atypical Parathyroid Neoplasm 1st edition v1.0
- Guidelines for Authors of Structured Cancer Pathology Reporting Protocols, Royal College of Pathologists of Australasia, 2009[18]
- World Health Organization (2017) Classification of Tumours of Endocrine Organs (4th edition). Volume 10[19]

Changes since the last edition

Not applicable

Authority and development

This section provides information about the process undertaken to develop this protocol.

This 1st edition of the protocol is an amalgam of two separate processes:

- This protocol is based on the ICCR dataset – Parathyroid Carcinoma & Atypical Parathyroid Neoplasm 1st edition v1.0. All ICCR elements from this protocol, both core (mandatory) and non-core (optional), are included in this protocol, verbatim. (It should be noted that RCPA feedback from all Anatomical Pathology fellows and specifically the local expert committee was sought during the development process of the ICCR dataset.) Details of the ICCR development process and the international expert authoring committee responsible for the ICCR dataset are available on the ICCR website: iccr-cancer.org.

1. Additional elements, values and commentary have been included as deemed necessary by the local expert committee. In addition, the standard inclusions of RCPA protocols e.g. example reports, request information etc., have also been added.

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Stakeholders

ACT Cancer Registry
ACT Health
Anatomical Pathology Advisory Committee (APAC)
Australian and New Zealand Endocrine Surgeons (ANZES)
Australian Commission on Safety and Quality in Health Care
Australian Digital Health Agency (ADHA)
Australian Institute of Health and Welfare (AIHW)
Australian Pathology
Cancer Australia
Cancer Council ACT
Cancer Council Australia and Australian Cancer Network (ACN)
Cancer Council NSW
Cancer Council Queensland
Cancer Council SA
Cancer Council Tasmania
Cancer Council Victoria
Cancer Council Western Australia
Cancer Institute NSW
Cancer Services Advisory Committee (CanSAC)
Cancer specific expert groups – engaged in the development of the protocols
Cancer Voices Australia
Cancer Voices NSW
Clinical Oncology Society of Australia (COSA)
Department of Health, Australian Government
Endocrine Society of Australia (ESA)
Health Informatics Society of Australia (HISA)
Independent Review Group of Pathologists
Medical Oncology Group of Australia (MOGA)
Medical Software Industry Association (MSIA)
National Pathology Accreditation Advisory Council (NPAAC)
New Zealand Cancer Control Agency
New Zealand Cancer Registry
Northern Territory Cancer Registry

Public Pathology Australia

Queensland Cooperative Oncology Group (QCOG)

Representatives from laboratories specialising in anatomical pathology across Australasia

Royal Australasian College of Physicians (RACP)

Royal Australasian College of Surgeons (RACS)

Royal Australian and New Zealand College of Radiologists (RANZCR)

Royal Australian College of General Practitioners (RACGP)

Royal College of Pathologists of Australasia (RCPA)

South Australia Cancer Registry

Southern Cancer Network, Christchurch, New Zealand

Standards Australia

Tasmanian Cancer Registry

Victorian Cancer Registry

Western Australia Clinical Oncology Group (WACOG)

Western Australian Cancer Registry

Development process

This protocol has been developed following the ten-step process set out in *Guidelines for Authors of Structured Cancer Pathology Reporting Protocols.*[18]

Where no reference is provided, the authority is the consensus of the local expert group for local inclusions and the ICCR Dataset Authoring Committee for ICCR components denoted with the ICCR logo.

1 Pre-analytical

This chapter relates to information that should be recorded on receipt of the specimen in the laboratory.

The pathologist is reliant on the quality of information received from the clinicians or requestor. Some of this information may be received in generic pathology request forms; however, the additional information required by the pathologist specifically for the reporting of parathyroid tumours is outlined in Appendix 1. Appendix 1 also includes a standardised request information sheet that may be useful in obtaining all relevant information from the requestor**.**

Surgical handling procedures affect the quality of the specimen and recommendations for appropriate surgical handling are included in Appendix 1.

S1.01 All demographic information provided on the request form and with the specimen must be recorded.

CS1.01a The Royal College of Pathologists of Australasia (RCPA) *The Pathology Request-Test-Report Cycle — Guidelines for Requesters and Pathology Providers* must be adhered to.[20] This document specifies the minimum information to be provided by the requesting clinician for any pathology test.

CS1.01b Ideally the laboratory information system (LIS) should include documentation as to whether the patient identifies as Aboriginal and/or Torres Strait Islander in Australia, or Māori in New Zealand. This is in support of government initiatives to monitor the health of those who identify as indigenous, particularly in relation to cancer.

CS1.01c The patient's health identifiers may include the patient's Medical Record Number as well as a national health number such as a patient's Medicare number (Australia), Individual Healthcare Identifier (IHI) (Australia) or the National Healthcare Index (New Zealand).

S1.02	**All clinical information as documented on the request form must be recorded verbatim.**

CS1.02a The request information may be recorded as a single text (narrative) field or it may be recorded in a structured format.

CS1.02b In most cases all clinical information should be transcribed: however, in a small number of cases the pathologist may exercise discretion regarding the inclusion of provided clinical information, for instance, possibly erroneous information or information that may impact on patient privacy. In such case reference should be made as to the location of the complete clinical information e.g. 'Further clinical information is available from the scanned request form.'

CS1.02c A diagnosis of parathyroid carcinoma or atypical parathyroid neoplasm requires information regarding intra-operative findings, serum PTH and calcium levels, comorbidities such as chronic renal failure etc. Thus, the option 'Information not provided' should only be used after all means of obtaining this information, including discussion at multidisciplinary team (MDT) meetings, have been exhausted.

G1.01 The copy doctors requested on the request form should be recorded.

S1.03 The pathology accession number of the specimen must be recorded.

S1.04 The principal clinician involved in the patient's care and responsible for investigating the patient must be recorded.

CS1.04a The principal clinician can provide key information regarding the clinical presentation of the patient. Follow up may be required with the principal clinician for several reasons:

- The clinical assessment and staging may be incomplete at the time of biopsy.
- The pathology request is often authored by the clinician performing the biopsy rather than the clinician who is investigating and managing the patient.
- The identity of this clinician is often not indicated on the pathology request form

In practice therefore, it is important in such cases that the reporting pathologist should be able to communicate with the managing clinician for clarification.

CS1.04b The Australian Healthcare identifiers i.e. Healthcare Provider Identifier - Individual (HPI-I) and Healthcare Provider Identifier - Organisation (HPI-O) should be included, where possible, to identify the principal clinician involved in the patient's care.

G1.02	Any clinical information received in other communications from the requestor or other clinician should be recorded together with the source of that information.

2 Specimen handling and macroscopic findings

This section relates to the procedures required after the information has been handed over from the requesting clinician, and the specimen has been received in the laboratory.

Tissue banking

- Pathologists may be asked to provide tissue samples from fresh specimens for tissue banking or research purposes. The decision to provide tissue should only be made if the pathologist is sure that the diagnostic process will not be compromised. As a safeguard, research use of the tissue samples may be put on hold until the diagnostic process is complete.

- If tissue is sampled for banking or research then this should be done in consultation with a pathologist and recorded in the report.

Specimen handling

- Detailed fixation and specimen handling instructions are available from the RCPA online Cut-up Manual:

  https://www.rcpa.edu.au/Manuals/Macroscopic-Cut-Up-Manual

- **The specimen must be handled in a systematic and thorough fashion to ensure completeness and accuracy of pathological data.**

Macroscopic findings

S2.01 The labelling of the specimen(s) must be clearly recorded.

S2.02	**Clinical information must be recorded.**	
	CS2.02a	Parathyroid carcinoma is a rare neoplasm representing <1% of cases of primary hyperparathyroidism.[5-8] 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.[21]

		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%).[22-24] 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 computed tomography (CT) scans.[25] 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.
S2.03	**The pre-operative biochemical information must be recorded.**	
	CS2.03a	The highest preoperative levels of calcium and parathyroid hormone should be recorded. (Refer to ICCR guidelines for full commentary.) 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.[7,8,26,27] Documenting this associated clinical information is important and may also stratify patients' risk of recurrence.[28] 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.
	CS2.03b	It is useful to state the normal reference range of the reporting laboratory, in case non-standard units are used.
	CS2.03c	A clinical concern for parathyroid cancer is present if either corrected serum calcium is >3.0 mM or lesion size on ultrasound is >3.0cm.[9]
S2.04	**The operative procedure must be recorded.**	
	CS2.04a	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.[29,30] 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.[31] Advancements in preoperative imaging have reduced the need for multi gland sampling. (Refer to ICCR guidelines for full commentary.) 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 protocol should be completed for each tumour.
	CS2.04b	Ultrasound is recommended when a parathyroid mass is encountered, as characteristic features of malignancy may be identified.[32,33] Lymph node sampling of at least the ipsilateral central compartment should generally be performed as the rate of regional nodal spread is between 5-and 30%.[34]

G2.01	Intraoperative findings should be documented.	
	CG2.01a	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.
S2.05	**The specimen(s) submitted must be recorded.**	
	CS2.05a	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.
S2.06	**The tumour sites must be recorded, where possible.**	
	CS2.06a	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 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.).[8,26,35]
S2.07	**Specimen weight must be recorded in milligrams.**	
	CS2.07a	A normal parathyroid gland weighs approximately 40 mg. Glandular size and weight have long been utilised to aid in defining abnormal parathyroid glands in both benign and malignant conditions. Ideally the weight is of the parathyroid gland only, however 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.
	CS2.07b	Ideally the weight is of the parathyroid gland only, with removal of soft tissue. However soft tissue surrounding the gland should not be removed when a parathyroid atypical adenoma neoplasm or carcinoma is suspected. The soft tissue around the parathyroid allows for the microscopic evaluation of possible extension of parathyroid tumour into the adjacent tissues.
S2.08	**The tumour dimensions must be recorded.**	
	CS2.08a	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.[6,8,26]

S2.09 **A block identification key[12] listing the nature and origin of all tissue blocks must be recorded.**

CS2.09a The origin/designation of all tissue blocks submitted for histologic examination should be recorded and it is preferable to document this information in the final pathology report. This is particularly important should the need for internal or external review arise. The reviewer needs to be clear about the origin of each block in order to provide an informed specialist opinion. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist.

Photography of macroscopic specimens is considered best practice. Annotation of captured images can be very helpful and aids with review of the case later. It can also provide useful information in the context of multidisciplinary meetings.

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

Because of the importance of resection margin status, it is recommended that all surgical surfaces are painted prior to specimen dissection. Occasionally different colours can be used to identify specific surgical margins when possible. This information should also be recorded in the macroscopic description as well as the block key.

G2.02 A descriptive or narrative field should be provided to record any macroscopic information that is not recorded in the above standards and guidelines, and that would normally form part of the macroscopic description.

CG2.02a The traditional macroscopic narrative recorded at the time of specimen dissection is often reported separately from the cancer protocol. Although this remains an option, it is recommended that macroscopic information be recorded within the overall structure of this protocol.

CG2.02b Much of the information recorded in a traditional macroscopic narrative is covered in the standards and guidelines above and in many cases, no further description is required.

CG2.02c A traditional macroscopic description may be required when the LIS does not allow a structured approach.

CG2.02d Where the LIS offers an electronic interface for structured data entry the need for narrative can be significantly reduced to describe only information not otherwise captured.

3 Microscopic findings

This section relates to purely histological or morphological assessment. Information derived from multiple investigational modalities, or from two or more chapters, is described in Chapter 5.

S3.01	**The histological tumour type must be recorded.**	
	CS3.01a	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.[36] 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.[37-40] 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.[41-45]
S3.02	**The histological grade must be reported.**	
	CS3.02a	The division of parathyroid carcinoma into low grade and high grade utilises 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 (>5 mitoses per 50 high power fields).[37,40] 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.
S3.03	**The extent of invasion must be recorded.**	
	CS3.03a	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.[26,28,39,40,46] 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 protocol is for data collection that may aid in future stratification of these tumours for staging and outcome.
S3.04	**The presence of lymphovascular invasion must be recorded.**	
	CS3.04a	Vessel invasion is a reported risk factor for development of metastases when considered in conjunction with other adverse features.[47] Precise descriptions of the nature and extent of vascular invasion are required in conjunction with other adverse factors in order to optimally guide patient management.[47]
S3.05	**The presence of perineural invasion must be recorded.**	
	CS3.05a	The proximity of the parathyroid with the recurrent laryngeal nerve, leads to potential invasion of this structure. Critical review is required of this parameter as proximity without direct nerve involvement would be considered not involved.

S3.06	**The presence or absence of necrosis must be recorded.**	
	CS3.06a	The finding of coagulative necrosis is uncommon outside the diagnosis of atypical parathyroid neoplasm/adenoma or parathyroid carcinoma.[37] Necrosis may also be more common in high grade tumours. It is important to know if an 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.
S3.07	**Mitotic count must be recorded.**	
	CS3.07a	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 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 most microscopes widely used. 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.[26,28,37] 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.
S3.08	**The margin status must be recorded.**	
	CS3.08a	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.[39,44,46,48] 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.
S3.09	**The presence of positive lymph nodes must be recorded.**	
	CS3.09a	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).[44] Metastases to lymph nodes has shown a potential correlation with survival however, this has not been confirmed by retrospective large database studies because of insufficient sampling.[6,7,26,28,49,50] 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 protocol.
G3.01	The presence or absence of coexistent pathological findings should be recorded.	
	CG3.01a	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 protocol. Malignant pathology identified in the thyroid would utilise the corresponding thyroid protocol.
S3.10	**The presence or absence of histologically confirmed distant metastases must be recorded.**	
	CS3.10a	The presence of histologically confirmed distant metastases is a critical component of pathological staging.[51]

G3.02 Any additional relevant microscopic comments should be recorded. For example, the presence of calcification could be mentioned for correlations with radiological findings.

CG3.02a Free text entry to allow any additional, unusual or unexpected findings to be reported.

4 Ancillary studies findings

Ancillary studies may be used to determine lineage, clonality or disease classification or subclassification; as prognostic biomarkers; or to indicate the likelihood of patient response to specific biologic therapies.

G4.01	The findings of any ancillary studies, where performed, should be recorded.	
	CG4.01a	Parafibromin is the protein encoded by the *CDC73* gene (previously known as *HRPT2*).[52] 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.[23,37,48,53-55] Somatic only double hit mutation/inactivation also occur frequently in parathyroid carcinomas not associated with HPT-JT.[55] Immunohistochemistry for parafibromin is not widely available and may be technically difficult to perform and interpret.[23] 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.[55-58] 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.[23,55-57,59-61] 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.[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.[60] Ki-67 proliferative index has also been reported as elevated in parathyroid neoplasms though with some overlap with hyperplasia and adenomas.[40,52,58,62,63] 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.[40,64,65]

5 Synthesis and overview

Information that is synthesised from multiple modalities and therefore cannot reside solely in any one of the preceding chapters is described here.

For example, *tumour stage* is synthesised from multiple classes of information – clinical, macroscopic and microscopic.

By definition, synthetic elements are inferential rather than observational, often representing high-level information that is likely to form part of the 'Summary' or 'Diagnosis' section in the final formatted report.

Overarching case comment is synthesis in narrative format. Although it may not necessarily be required in any given report, the provision of the facility for overarching commentary in a cancer report is essential.

S5.01	**The tumour stage and stage grouping must be recorded according to the most recent TNM staging system of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (8th edition) (See Appendix 6).**	
	CS5.01a	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 AJCC Staging Manual will begin the process of systematically gathering data for this rare entity.[51] It is with this goal that the parathyroid protocol is established.
	CS5.01b	A single validated staging system has been developed by an international team, and the criteria used by this system should be recorded and employed to provide interim information.[44]

S5.02 The year of publication and edition of the cancer staging system used in S5.01 must be included in the report.

G5.01 The 'Diagnostic summary' section of the final formatted report should include:

a. Specimen submitted

b. Specimen weight

c. Tumour type

d. Tumour dimensions

e. Extent of invasion

f. Tumour stage

S5.03 The reporting system must provide a field for free text or narrative in which the reporting pathologist can give overarching case comment.

CS5.03a This field may be used, for example, to:

- explain the decision-making pathway, or any elements of clinicopathological ambiguity, or factors affecting diagnostic certainty, thereby allowing communication of diagnostic subtlety or nuance that is beyond synoptic capture
- give recommendations for further action or investigation
- document further consultation or results still pending

CS5.03b Use of this field is at the discretion of the reporting pathologist.

G5.02 The edition/version number of the RCPA protocol on which the report is based should be included on the final report.

CG5.02a For example, the pathology report may include the following wording at the end of the report: 'the data fields within this formatted report are aligned with the criteria as set out in the RCPA document ' XXXXXXXXXX' XXXX Edition dated XXXXXXX'.

6 Structured checklist

The following checklist includes the standards and guidelines for this protocol which must be considered when reporting, in the simplest possible form. The summation of all 'standards' is equivalent to the 'minimum data set' for parathyroid cancer. For emphasis, standards (mandatory elements) are formatted in bold font.

S6.01 The structured checklist provided may be modified as required but with the following restrictions:

a. All standards and their respective naming conventions, definitions and value lists must be adhered to.

b. Guidelines are not mandatory but are recommendations , and where used, must follow the naming conventions, definitions and value lists given in the protocol.

G6.01 The order of information and design of the checklist may be varied according to the LIS capabilities and as described in *Functional Requirements for Structured Pathology Reporting of Cancer* Protocols.[66]

CG6.01a Where the LIS allows dissociation between data entry and report format, the structured checklist is usually best formatted to follow the pathologist's workflow. In this situation, the elements of synthesis or conclusions are necessarily at the end. The report format is then optimised independently by the LIS.

CG6.01b Where the LIS does not allow dissociation between data entry and report format, (for example where only a single text field is provided for the report), pathologists may elect to create a checklist in the format of the final report. In this situation, communication with the clinician takes precedence and the checklist design is according to principles given in Chapter 7.

G6.02 Where the checklist is used as a report template (see G6.01), the principles in Chapter 7 and Appendix 2 apply.

CG6.02a All extraneous information, tick boxes and unused values should be deleted.

G6.03 Additional comment may be added to an individual response where necessary to describe any uncertainty or nuance in the selection of a prescribed response in the checklist. Additional comment is not required where the prescribed response is adequate.

Item descriptions in italics are conditional on previous responses.

Values in all caps are headings with sub values.

S/G	Item description	Response type	Conditional
Pre-analytical			
S1.01	**Demographic information provided**		
S1.02	**Clinical information provided on request form**	**Text** OR **Information not provided*** *Note: A diagnosis of parathyroid carcinoma or atypical parathyroid neoplasm requires information regarding intra-operative findings, serum PTH and calcium levels, comorbidities such as chronic renal failure etc. Thus, this option should only be used after all efforts to obtain this information, including MDT discussion, have been exhausted. OR **Structured entry as below:**	
	Hyperparathyroidism	**Single selection value list:** • Primary • Secondary • Tertiary • Non-functional	
	Previous parathyroid surgery	**Text**	
	Relevant familial history	**Text**	

	Presence of a clinical syndrome	**Text**	
G1.01	Copy To doctors recorded	**Text**	
S1.03	**Pathology accession number**	**Alpha-numeric**	
S1.04	**Principal clinician**	**Text**	
G1.02	Other clinical information received	**Text**	
Macroscopic findings			
S2.01	**Specimen labelled as**	**Text**	
S2.02	**Clinical information**	**Text**	
S2.03	**Pre-operative biochemical information**	**Information not provided*** *Note: This option should only be used after all efforts to obtain this information, including MDT discussion, have been exhausted. OR	
	Calcium	**Text**	**Specify level with units and specimen type (serum, other).**
	Parathyroid hormone (PTH)	**Text**	**Specify level with units.**
	Other	**Text**	
S2.04	**Operative procedure**	Not specified OR **Multi selection value list (select all that apply):** Side • Right	

		• Left
		• Not specified
		Location
		• Superior
		• Inferior
		• Not specified
		Tissue nature
		• Parathyroidectomy, single gland
		• Parathyroidectomy, en bloc with thyroid lobe
		• Other parathyroid gland(s) sampling
		  ○ Unilateral
		  ○ Bilateral
		• Lymph node sampling, *specify*
		• Soft tissue of neck, *specify*
		• Other*, specify*	

G2.01	Intra-operative findings	**Not specified**
		OR
		Multi selection value list (select all that apply):
		• Non-adherent to surrounding structures
		• Adherent to structure(s)
		  ○ Thyroid
		  ○ Recurrent laryngeal nerve	

		○ Oesophagus ○ Skeletal muscle ○ Other, *specify* • Other, *specify*	
S2.05	**Specimen(s) submitted**	**Single selection value list:** • Not specified* *Note: This option should only be used when all efforts to obtain this information, including MDT discussion, have been exhausted. OR **Multi selection value list (select all that apply):** • 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*	
S2.06	**Tumour site(s)**	**Single selection value list:** • Not specified OR **Multi selection value list (select all that apply):** • 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*	

S2.07	**Specimen weight**	**Cannot be assessed, specify** OR **Numeric: ___mg** Parathyroid alone OR **Numeric: ___mg** Parathyroid with other structure(s), *specify structure(s)*	
S2.08	**Tumour dimensions**		
	Maximum tumour dimension (largest tumour)	**Numeric: ___mm**	
	Additional dimensions (largest tumour)	**Numeric: __x__x__mm**	
S2.09	**Block identification key**	**Text**	
G2.02	Other macroscopic comments	**Text**	
Microscopic findings			
S3.01	**Histological tumour type**	**Single selection value list:** • Atypical parathyroid neoplasm (atypical parathyroid adenoma)/neoplasm of uncertain malignant potential (UMP)* • Parathyroid carcinoma *Note: Defined as tumours that are histologically or clinically worrisome but do not fulfil 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.	
S3.02	**Histological tumour grade**	**Single selection value list:** • Low grade • High grade • Not determined • Not applicable (i.e. atypical neoplasm/adenoma, UMP*) *Note: Defined as tumours that are histologically or clinically worrisome but do not fulfil 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.	
S3.03	**Extent of invasion**	**Single selection value list:** • Cannot be assessed, specify • Confined to parathyroid without invasion through tumour capsule OR **Multi selection value list (select all that apply):** • Invasion through tumour capsule	

		• Invasion into extra-parathyroid soft tissue
		• Invasion into adjacent structures, *specify*
		  ○ Recurrent laryngeal nerve
		  ○ Thyroid gland
		  ○ Oesophagus
		  ○ Skeletal muscle
		  ○ Other, *specify*	

S3.04	**Lymphovascular invasion**	Not identified
		OR
		Multi selection value list (select all that apply):
		• Present
		  ○ Vascular invasion
		  ○ Lymphatic invasion	

S3.05	**Perineural invasion**	**Single selection value list:** • Not identified • Present	
S3.06	**Necrosis**	**Single selection value list:** • Not identified • Present	
S3.07	**Mitotic count**	**Numeric**: ___ mitotic figures/2 mm^2** **Note: 2 mm^2 approximates 10 high power fields on some microscopes.	
S3.08	**Margin status**	**Single selection value list:**	**If not involved by invasive**

		• Not involved (R0), *specify distance to closest margin*
		• Involved
		  ○ Abutting tissue edge (R1 resection)
		  ○ Transected, fragmented or ruptured (possible R2 resection)
		• Cannot be assessed, *specify*
			carcinoma record the distance of tumour to closest margin
			If involved by invasive carcinoma specify if named structure/location is involved at margin(s)

	Distance to closest margin	***Numeric: __mm***	
	Location of involved margin	***Text***	
S3.09	**LYMPH NODE STATUS**	No nodes submitted or found OR	
		Single selection value list: • Not involved • Involved	**Record the number of LN examined.** **If involved, specify the number of positive LN**
	Number of lymph nodes examined	**Numeric: ___** OR Number cannot be determined	
	Number of positive lymph nodes	**Numeric: ___**	**Not required if number cannot be determined is entered above.**
G3.01	Coexistent findings	**Multi selection value list (select all that apply):** • 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*	
S3.10	**Distant metastases**	**Single selection value list:** • Not identified • Information not available • Present, *specify site(s)*	
G3.02	Additional microscopic comment	**Text**	
Ancillary findings			
G4.01	Ancillary studies	Not performed OR **Multi select value list :** • Immunohistochemistry performed ○ Ki-67, specify results and method _% ○ Parafibromin (CDC73), *specify results* ○ PGP9.5, *specify results* ○ Other immunohistochemistry, *specify* • Molecular testing performed	

		○ *CDC73* (parafibromin gene) ▪ Germline testing, *specify results* ▪ Tumour (somatic) testing, *specify results* ○ Other molecular test(s), *specify* • Other, *specify*	
Synthesis and overview			
S5.01	**PATHOLOGICAL STAGING (AJCC 8TH EDITION)**		
	TNM descriptors	**Multi select value list :** • m - multiple primary tumours • r – recurrent • y – post therapy	
	Primary tumour (T)	**Single select value list :** 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	

		*Note: 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.	
	Regional lymph node (N)	**Single selection value list:** 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	
S5.02	**Year and edition of staging system**	**Numeric:** years **AND** **Text:** Edition e.g.1st, 2nd etc.	
G5.01	Diagnostic summary	**Text**	

	Include: a. Specimen submitted b. Specimen weight c. Tumour type d. Tumour dimensions e. Extent of invasion f. Tumour stage		
S5.03	**Overarching comment**	**Text**	
G5.02	Edition/version number of the RCPA protocol on which the report is based	**Text**	

7 Formatting of pathology reports

Good formatting of the pathology report is essential for optimising communication with the clinician, and will be an important contributor to the success of cancer reporting protocols. The report should be formatted to provide information clearly and unambiguously to the treating doctors, and should be organised with their use of the report in mind. In this sense, the report differs from the structured checklist, which is organised with the pathologists' workflow as a priority.

Uniformity in the format as well as in the data items of cancer reports between laboratories makes it easier for treating doctors to understand the reports; it is therefore seen as an important element of the systematic reporting of cancer. For guidance on formatting pathology reports, please refer to Appendix 2. An example of a pathology report is shown in Appendix 3.

Appendix 1 Pathology request form for parathyroid tumours

This appendix describes the information that should be collected before the pathology test. Some of this information can be provided on generic pathology request forms; any additional information required specifically for the reporting of parathyroid specimens may be provided by the clinician on a separate request information sheet. An example request information sheet is included below. Elements which are in bold text are those which pathologists consider to be required information. Those in non-bold text are recommended.

Also included in this appendix are the procedures that are recommended before handover of specimens to the laboratory.

Patient information

- **Adequate demographic and request information must be provided with the specimen.**
    - Items relevant to cancer reporting protocols include:
        - patient name
        - date of birth
        - gender
        - identification and contact details of requesting doctor
        - date of request
    - Document whether or not the patient identifies as Aboriginal and/ or Torres Strait Islander in Australia, or Māori in New Zealand. This is in support of government initiatives to monitor the health of those who identify as indigenous, particularly in relation to cancer.
- The patient's health identifiers should be provided.
    - The patient's health identifiers may include the patient's Medical Record Number as well as a national health number such as a patient's Individual Healthcare Identifier (IHI) (Australia) or the National Healthcare Index (New Zealand).
- The Australian Healthcare identifiers i.e. Healthcare Provider Identifier - Individual (HPI-I) and Healthcare Provider Identifier - Organisation (HPI-O) should be used, where possible, to identify the requesting doctor.

Clinical Information

➢ **Surgical handling procedures affect the quality of the specimen.**

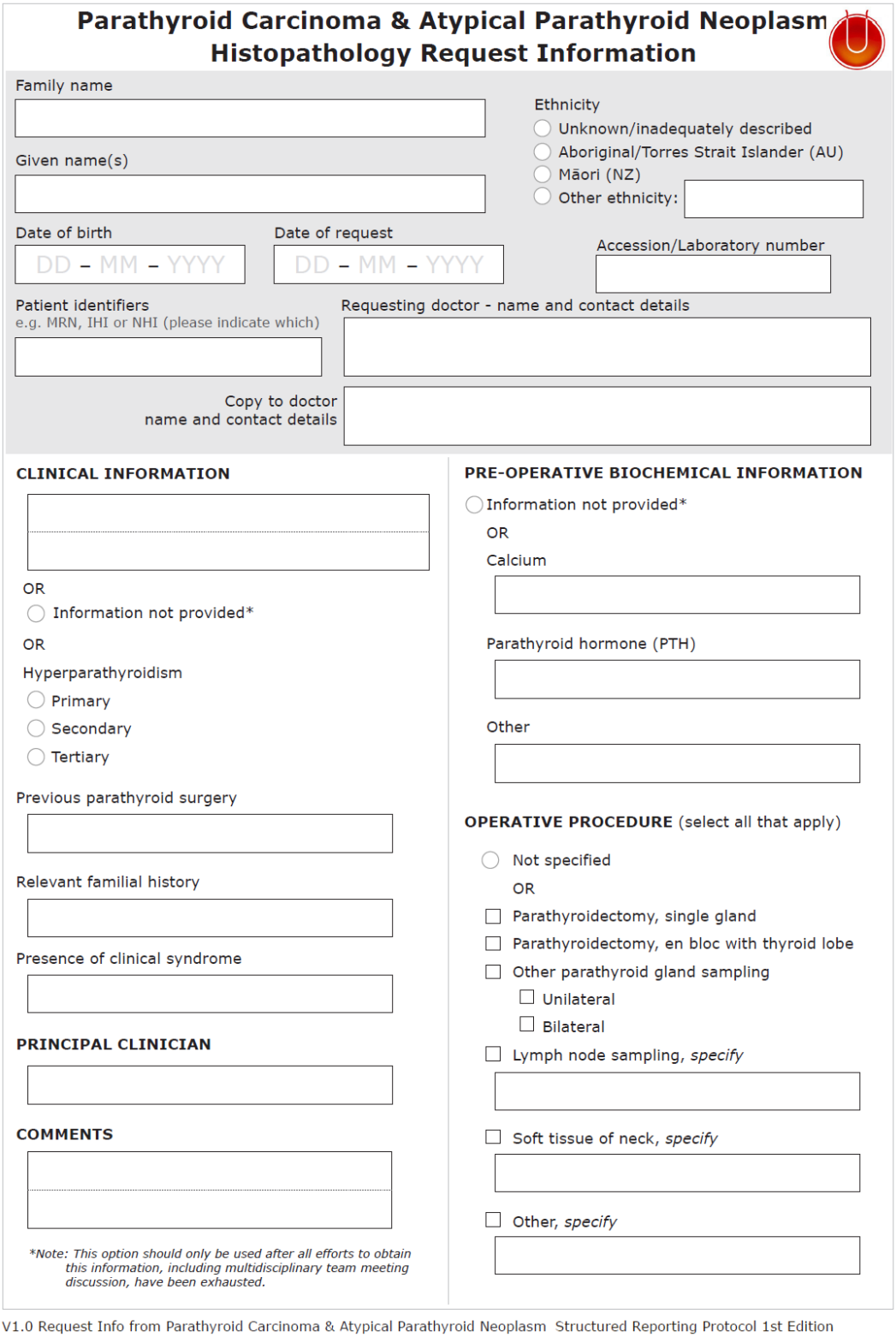
- The specimen should be fixed in 10% neutral buffered formalin as soon as possible after resection or after tissue banking (if applicable).
- It is useful for the surgeon to identify the location of the parathyroid gland (right or left).

	Any hyperparathyroidism must be recorded.
	• 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.
	Any previous parathyroid surgery must be recorded.
	• Multiple surgeries are common and may be required for initial diagnosis and/or for recurrence.
	Any relevant family history must be recorded.
	The presence of a clinical syndrome must be specified.
	• Clinical syndromes which may be associated with parathyroid disease include 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.[21] The HPT-JT) syndrome involving the *CDC73* gene, is an autosomal dominant disorder that is strongly associated with parathyroid carcinoma (lifetime risk is approximately 15%).[22-24]
	Any preoperative biochemical information must be recorded, such as calcium and parathyroid hormone (PTH).
	• 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.
	Any other clinical information should be included, if appropriate.
	• 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.[25] Other

	information also includes any history of FNA, since this procedure may lead to pathologic alterations important to consider during specimen interpretation.

- Space for free text should be included to encourage reporting of ambiguity, or for the addition of other comments.
- All attempts should be made to obtain relevant clinical information from the surgeons. This is important as the pathologist needs to know if tumour is seen infiltrating adjacent structures or if patient has end-stage renal failure, so as to avoid over-reporting hyperplasia as carcinoma.
- It is important to obtain information regarding preoperative fine needle aspiration cytology, which can result in fibrosis, granulation tissue, severe hemorrhage, pseudo capsular invasion, capsule disruption, stellate nodule, or intratumoural band-like septa as a result of the procedure. This can reduce the risk of an erroneous diagnosis of parathyroid carcinoma.

Example Request Information Sheet



Parathyroid Carcinoma & Atypical Parathyroid Neoplasm Histopathology Request Information

Family name

Given name(s)

Ethnicity
- ○ Unknown/inadequately described
- ○ Aboriginal/Torres Strait Islander (AU)
- ○ Māori (NZ)
- ○ Other ethnicity:

Date of birth: DD – MM – YYYY

Date of request: DD – MM – YYYY

Accession/Laboratory number

Patient identifiers
e.g. MRN, IHI or NHI (please indicate which)

Requesting doctor - name and contact details

Copy to doctor name and contact details

CLINICAL INFORMATION

OR
- ○ Information not provided*

OR

Hyperparathyroidism
- ○ Primary
- ○ Secondary
- ○ Tertiary

Previous parathyroid surgery

Relevant familial history

Presence of clinical syndrome

PRINCIPAL CLINICIAN

COMMENTS

*Note: This option should only be used after all efforts to obtain this information, including multidisciplinary team meeting discussion, have been exhausted.

PRE-OPERATIVE BIOCHEMICAL INFORMATION
- ○ Information not provided*

OR

Calcium

Parathyroid hormone (PTH)

Other

OPERATIVE PROCEDURE (select all that apply)
- ○ Not specified

OR
- ☐ 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*

V1.0 Request Info from Parathyroid Carcinoma & Atypical Parathyroid Neoplasm Structured Reporting Protocol 1st Edition

The above Request Information Sheet is also available on the RCPA Cancer Protocols webpage.

Appendix 2 Guidelines for formatting of a pathology report

Layout

Headings and spaces should be used to indicate subsections of the report, and heading hierarchies should be used where the LIS allows it. Heading hierarchies may be defined by a combination of case, font size, style and, if necessary, indentation.

- Grouping like data elements under headings and using 'white space' assists in rapid transfer of information.[67]

Descriptive titles and headings should be consistent across the protocol, checklist and report.

When reporting on different tumour types, similar layout of headings and blocks of data should be used, and this layout should be maintained over time.

- Consistent positioning speeds data transfer and, over time, may reduce the need for field descriptions or headings, thus reducing unnecessary information or 'clutter'.

Within any given subsection, information density should be optimised to assist in data assimilation and recall. The following strategies should be used:

- Configure reports in such a way that data elements are 'chunked' into a single unit to help improve recall for the clinician.[67]

- Reduce 'clutter' to a minimum.[67] Thus, information that is not part of the protocol (e.g. billing information or SNOMED codes) should not appear on the reports or should be minimised.

- Reduce the use of formatting elements (e.g. bold, underlining or use of footnotes) because these increase clutter and may distract the reader from the key information.

Where a structured report checklist is used as a template for the actual report, any values provided in the checklist but not applying to the case in question must be deleted from the formatted report.

Reports should be formatted with an understanding of the potential for the information to 'mutate' or be degraded as the report is transferred from the LIS to other health information systems.

As a report is transferred between systems:

- text characteristics such as font type, size, bold, italics and colour are often lost
- tables are likely to be corrupted as vertical alignment of text is lost when fixed font widths of the LIS are rendered as proportional fonts on screen or in print
- spaces, tabs and blank lines may be stripped from the report, disrupting the formatting
- supplementary reports may merge into the initial report.

Appendix 3 Example of a pathology report

Citizen, Gerald W.
C/O Paradise Close
Wreck Bay Resort
Nar Nar Goon East, 3181

Male

DOB 1/7/1971
MRN M1196788

Lab Ref: **18/P28460**
Referred: 28/4/2020

Copy to: Dr N.G.Chappie
Rainforest Cancer Centre.
46 Smith Road,
Woop Woop, 3478

Referred by: Dr E. Throat
Suite 3, AJC Medical Centre,
Nose Drive
Nar Nar Goon West, 3182

Parathyroid Carcinoma & Atypical Parathyroid Neoplasm
STRUCTURED REPORT

Diagnostic Summary

Right Lower Parathyroid and Right Lobe of Thyroid Gland:

Parathyroid Carcinoma (T=45mm)

The tumour infiltrates the thyroid gland (pT2)

Perineural invasion is present

The tumour is present at the inferior margin of resection

21 lymph nodes show no evidence of malignancy (0/21)

AJCC 8th Edition Staging Parameters: pT2, pN0

Supporting Information

CLINICAL INFORMATION RECEIVED

(Provided on the request form and obtained at the Endocrine MDT 30 April 2020):

Hyperparathyroidism:	Primary hyperparathyroidism
Previous parathyroid surgery:	Nil
Relevant familial history:	Nil
Presence of a clinical syndrome:	Nil
Other clinical information received:	None

MACROSCOPIC

Specimen labelled as:	Right Lower Parathyroid and Right Lobe of Thyroid
Preoperative biochemical information:	
Calcium:	14.2 mg/dl (ref 2.2-2.5 mg/dl)
Parathyroid hormone:	425 pmol/L (ref: 1.0-7.0 pmol/L)
Other:	Nil
Operative procedure:	Right Lower Parathyroidectomy and Right Hemithyroidectomy with right neck dissection levels 2-4.
Intra-operative findings:	Parathyroid adherent to the thyroid gland
Specimen submitted:	Right Inferior Parathyroid and Right Lobe of Thyroid

Tumour sites:	Right inferior parathyroid with infiltration into the right thyroid gland and attached soft tissues.
Specimen weight:	560 mg including the parathyroid and the thyroid lobe and attached soft tissues
Tumour dimensions:	45mm from Superior to Inferior x 20mm Superficial to deep x 20mm right to left
Maximum tumour dimension (largest):	45 mm
Additional dimensions (largest tumour):	20mm Superficial to deep x 20mm right to left
Block identification key:	A: Superior pole of thyroid.
	B, C: Tumour infiltrating the thyroid gland
	D, E: Tumour infiltrating the soft tissues
	F, G: Tumour in the parathyroid gland
	H: Tumour at the superficial margin
	J: Tumour at the inferior margin
	K-M: 2 lymph nodes in each block
	N-Q: Single lymph node bisected in each
	R-V: 3 lymph nodes in each block
	Photographs taken: M/PTH1234
Other macroscopic comments:	Specimen inking: Superficial: blue, deep: black, Medial aspect: red stripe.
	Macroscopic observations: Specimen serially sectioned from superior to inferior in to 20 slices. The cut surface shows a firm tan lesion with a multinodular appearance infiltrating into the thyroid gland. The tumour extends from slice 3 to slice 18.

MICROSCOPIC

Histologic tumour type:	Parathyroid carcinoma
Histological tumour grade:	High grade
Extent of invasion:	The tumour infiltrates the right lobe of the thyroid gland.
Lymphovascular invasion:	Not identified
Perineural invasion:	Present
Necrosis:	Coagulative necrosis present
Mitotic count:	4/10hpf

Margin status

Invasive carcinoma:	Involved - the tumour abuts the inferior and superficial margins of resection.
Distance to closest margin:	0.5 mm
Location of involved margin:	Tumour is present at the inferior margin of resection.

Lymph node (LN) status	Not involved
Number of nodes examined:	21
Number of nodes positive:	0
Coexistent findings:	None identified
Distant metastases:	Not identified
Additional microscopic comments:	Appearance of the tumour: Tan, multinodular lesion
	Sheets and trabecular growth pattern

ANCILLARY TESTS

Immunohistochemistry performed:	PTH: Positive in the neoplastic cells
	TTF1: Negative
	Calcitonin: Negative
	Parafibromin: Loss of nuclear staining
	PGP 9.5: Positive
	Ki67 proliferation index: 10%

Reported by Dr Bernadette Beckstein Authorised 1/5/2020

Appendix 4 WHO histological classification of parathyroid tumours

Parathyroid carcinoma	8140/3
Parathyroid adenoma	8140/0

Secondary, mesenchymal and other tumours

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O).[68] Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours.
The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.

From WHO Classification of Tumours Pathology and Genetics. Tumours of Endocrine Organs 2017, Volume 10, 4th Edition. IARC.

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