



The Royal College of Pathologists

Pathology: the science behind the cure

Standards and Datasets for Reporting Cancers

Dataset for parathyroid cancer histopathology reports

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Foreword

The cancer datasets are **guidelines**. Guidelines are systematically developed statements to assist the decisions of practitioners and patients about appropriate healthcare for specific clinical circumstances and are based on the best available evidence at the time the dataset was prepared. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. Just as adherence to the guidelines may not constitute defence against a claim of negligence, so deviation from them should not necessarily be deemed a failure of duty of care.

This dataset was reviewed by the Cancer Services Working Group and was placed on the College website for consultation with the membership between 23 August and 17 September 2010. All comments received from the Working Group and the membership will be addressed by the authors to the satisfaction of the Chair of the Working Group and the Director of the Professional Standards Unit, and the Director of Communications.

Each year, the authors of the dataset, in conjunction with the sub-specialty advisor to the College, will consider whether or not the dataset needs to be revised.

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

This dataset was developed without external funding to the dataset writing group or lead author.

The remit of The Royal College of Pathologists is to promote the quality of pathology services through training and education. It has no remit to negotiate the terms and conditions of employment for pathologists.

The College requires the authors of datasets to provide a list of potential conflicts of interest and intellectual property deed of assignment; these are monitored by the Professional Standards Unit and are available on request.

1 Introduction

1.1 Endocrine cancer datasets

The management of endocrine tumours should be the responsibility of an appropriately experienced multidisciplinary team (MDT). Because these tumours bridge various anatomical divides, they are dealt with by a number of specialist teams and are the topics of separate cancer datasets.¹⁻³ Ideally, the pathologist(s) reporting them should have a special interest in endocrine pathology. Alternatively, he/she should have an interest in endocrine tumours in his/her area of systematic pathology or, if a general pathologist, should participate in a network with easy opportunity for specialist pathology review.

Although the guidelines of The Royal College of Pathologists are primarily aimed at collecting core data in the reporting of cancers, we suggest that the endocrine guidelines also provide a useful template for the reporting of benign and non-neoplastic endocrine conditions. We have therefore included some of these conditions in the histopathology reporting proforma (see Appendix A).

1.2 Parathyroid carcinoma

Parathyroid carcinoma is responsible for only 0.5–5.2% of cases of primary hyperparathyroidism.⁴⁻¹⁴ The majority of cases of primary hyperparathyroidism are caused by parathyroid adenomas, with most of the remainder being due to parathyroid hyperplasia. These processes may occur in supernumerary and/or ectopically located parathyroid glands. Hyperparathyroidism may arise as part of the multiple endocrine neoplasia (MEN) syndromes MEN1 and MEN2a, and very rarely MEN2b.

Parathyroid carcinoma can be a difficult histological diagnosis but its recognition is important. The best patient outcomes follow early *en-bloc* resection, preferably at first surgery, including ipsilateral thyroid lobectomy (if the parathyroid abuts the thyroid lobe) and removal of any enlarged or abnormal lymph nodes and any adherent tissue, with clear specimen margins.^{4,6,15–18} Involved surgical margins or intra-operative tumour spillage increase the risk of local recurrence.^{6,19}

The natural history of parathyroid carcinomas is variable. These tumours are slow-growing but have potential for multiple recurrences, sometimes after a long disease-free interval; lifelong follow-up is therefore advised.^{5,6,20,21} Local recurrence is common, and there may be later distant metastases.^{6,15,22} Lymph node involvement may occur relatively late.^{6,23} Patient deaths usually result from the metabolic complications of hypercalcaemia.^{6,20,21,23} Chemotherapy has little role, though adjuvant radiotherapy may have value.^{16,21} Surgery is the main initial and palliative treatment, and the only chance of cure, which can be achieved in approximately 50% of patients.^{6,19}

The diagnosis may be suspected pre- or intra-operatively,^{17,24,25} but in practice is most often made post-operatively on paraffin section histology, following which a second operation is needed to clear the surgical field.^{24,25} Pre-operative suspicion may be raised if the patient is young (20–45 years), with a palpable neck mass, hyperparathyroid renal and/or skeletal disease, recurrent laryngeal nerve palsy, and/or extremely high calcium and PTH levels,^{5,6,17,19,20,23,26,27} but these features are not always seen.^{5,24} Intra-operatively, the surgeon may suspect carcinoma if the gland is large, pale and/or adherent, but the surgical findings may be the same as benign parathyroid disease.⁶

Intra-operative frozen section may suggest the diagnosis⁵ and any such glands should not be used for autotransplantation.²⁸ Making a definitive diagnosis of parathyroid carcinoma on frozen sections alone is probably inappropriate, although raising its possibility to the surgeon may help him/her to decide to perform *en-bloc* resection at first surgery.²⁸

The histology of parathyroid carcinoma has been well described elsewhere^{15,19,23,29} In some cases, the diagnosis is obvious but in others it can be very difficult, requiring further specialist opinions to help distinguish it from the more frequently seen adenoma and hyperplasia.

Typically, a parathyroid carcinoma has a thick fibrous capsule with dense fibrous septa extending into and dividing the gland.^{15,20,23} The growth pattern is often in the form of diffuse sheets,³¹ but trabecular or spindle cell areas, palisading or rosette-like growth may be seen.^{15,20,23} The nuclei are usually quite monotonous.²³ Mitoses may be present²³ but are not specific to carcinoma, although frequent mitoses (>1 per 10 hpf) should prompt a careful search for other malignant features.²⁰ Abnormal mitotic figures are more suggestive of malignancy.^{15,20} The most specific features are vascular invasion, perineural invasion or direct extension into adjacent soft tissues, but these can be subjective to assess.²⁰ Capsular invasion is also subjective.

A particular pitfall is confusion between carcinoma and degenerative changes in a hyperplastic or adenomatous parathyroid gland,²⁹ with degeneration causing fibrosis and pseudoinvasion of the capsule. Such degenerative changes may result from pre-operative needle sampling for cytology or parathyroid hormone measurements.^{32,33} Other important differential diagnoses are parathyromatosis (multiple rests of hyperfunctioning parathyroid tissue in neck and mediastinum) and the so-called 'atypical adenoma' (showing some worrisome histological features associated with parathyroid carcinoma but not sufficiently for definite diagnosis).

A Ki67 labelling index of >5% has been suggested to distinguish carcinoma from adenoma.^{20,30} Also, those parathyroid carcinomas with higher proliferation rates behave more aggressively.^{34,35} Other markers, such as cyclin D1 or parafibromin, may have future

diagnostic and/or prognostic value but these are not fully accepted yet so are not included here as core items.^{36,37}

It is also useful to be aware of recent developments in pre-operative imaging and parathyroid surgical technique.²⁹ These may lead to increasing removal of only one gland via a targeted surgical approach, with no information or sampling of the remaining glands to contribute to the histological assessment.

Occasionally, immunohistochemistry for parathormone may be required to confirm the parathyroid nature of a nodule, eg. if located intrathyroidally.

1.3 This dataset

These guidelines describe the core data that should be recorded in the histopathology reports from specimens of parathyroid carcinoma. They should be implemented for the following reasons.

1. They will provide feedback to the surgeon on the diagnosis as well as prognostic factors such as completeness of resection.
2. They will provide accurate data for cancer registration.
3. They will potentially allow the selection of patients for future trials of adjuvant therapy.

This document has been devised to include the data required for a careful and thorough assessment of a parathyroid specimen. Where possible, it is evidence based. The document has been widely discussed and has been approved by the UK Endocrine Pathology Society (www.ukeps.com), the British Association of Endocrine and Thyroid Surgeons (www.baes.info) and the British Association of Head and Neck Oncologists (www.bahno.org.uk). Panels of specialist and general histopathologists acting on behalf of the College have also reviewed it. We strongly recommend its use as a dataset.

2 Notes on recording data items

2.1 Specimen request form

In addition to correct patient identification, the specimen request form should contain relevant clinical, biochemical and imaging data, as well as any intra-operative findings. Any local arrangements for booking intra-operative frozen sections should be followed. It should ideally be stated 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.

If surgery is performed for recurrent disease in the neck or metastatic disease, the surgeon must highlight this because histological interpretation may be altered.

2.2 Specimen handling

Best practice in handling parathyroid specimens has been reviewed.³⁸ The specimens may be received fresh for intra-operative reporting. They should be received labelled as to site and the tissue biopsied. The weight (in mg) and the dimensions (in mm) should be recorded, together with description of the macroscopic appearances. Appropriate tissue should be taken for frozen section: we suggest a block of 5–10 mm in greatest dimension, so 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. In addition, imprints may be stained for immediate cytology reporting. After frozen section reporting, the tissue, including any frozen block(s), should be fixed in formalin and embedded in its entirety for confirmation of the diagnosis in paraffin sections.

Where an *en-bloc* resection is done, the nature of the resection and the tissues included should be described, and the parathyroid tissue identified and measured. Inking the specimen surface before slicing will assist with assessing margins.

2.3 Intra-operative reporting

Intra-operative reporting is used to confirm that the tissue sampled is parathyroid.²⁸ It is sometimes possible to identify histological features suggestive of malignancy, although definitive diagnosis is usually made on paraffin histology. The surgeon should be asked about additional information from intra-operative findings (e.g. the appearance of other parathyroid glands) and this should be documented.

The frozen section findings should be documented, including the verbal report, the name of the reporting pathologist, the name of the surgeon receiving the report, the date and the time.

3 Final report

3.1 Core data items

- Tumour capsule – intact, breached or cannot be assessed
- Surgical margins – involved, clear or cannot be assessed, plus measurement
- Lymph nodes – number and site(s) of those identified
- Lymph nodes – number and site(s) of those involved

The margin is regarded as clear if tumour cells are not seen at the surgical margin of the specimen, which may have been painted at original macroscopic handling. Adequate clearance has not been defined so the distance between the margin and the closest tumour cells should be recorded, ie an involved margin would have a distance of 0mm.

Other relevant data are non-core items and their inclusion is suggested to provide a complete report. For example, where other parathyroid glands are submitted, the pathologist should attempt to distinguish parathyroid hyperplasia from parathyroid adenoma although it is recognised that there is inter-observer variation in interpreting these features.³⁹

The final written report should include the macroscopic findings, the intra-operative frozen section report and by whom and to whom this was given (with date and time), and any additional clinical information obtained from the surgeon. When thyroid tissue is submitted during surgery for parathyroid disease, it should include comment on the presence or otherwise of any thyroid pathology. Audit may target completeness of reports as to these data and the core data items stated above, and/or inter- and intra-observer studies in the diagnosis of parathyroid carcinoma cases.

4 TNM classification

There is no TNM staging classification for parathyroid carcinomas.^{40,41}

5 SNOMED codes

All primary parathyroid carcinomas should be coded as T97000 or TB7000, M81403.

Other relevant SNOMED codes are:

M00100 Normal

M72000 Hyperplasia

M09350 Uncertain

M81400 Adenoma.

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Appendix B Parathyroid carcinoma dataset monitoring sheet

The Cancer Datasets of The Royal College of Pathologists comply with the AGREE standards for good quality clinical guidelines (www.agreecollaboration.org). The sections of this dataset that indicate compliance with each of the AGREE standards are indicated in the table.

AGREE standard	Section of dataset
SCOPE AND PURPOSE	
1. The overall objectives of the guideline are specifically described	1
2. The clinical questions covered by the guidelines are specifically described	1
3. The patients to whom the guideline is meant to apply are specifically described	1
STAKEHOLDER INVOLVEMENT	
4. The guideline development group includes individuals from all the relevant professional groups	1
5. The patients' views and preferences have been sought	N/A
6. The target users of the guideline are clearly defined	1
7. The guideline has been piloted among target users	Feedback follows use of a previous edition
RIGOUR OF DEVELOPMENT	
8. Systematic methods were used to search for evidence	1
9. The criteria for selecting the evidence are clearly described	1
10. The methods used for formulating the recommendations are clearly described	1
11. The health benefits, side effects and risks have been considered in formulating the recommendations	1
12. There is an explicit link between the recommendations and the supporting evidence	1–3, 6
13. The guideline has been externally reviewed by experts prior to its publication	1
14. A procedure for updating the guideline is provided	Foreword
CLARITY OF PRESENTATION	
15. The recommendations are specific and unambiguous	2–3
16. The different options for management of the condition are clearly presented	1
17. Key recommendations are easily identifiable	2–3
18. The guideline is supported with tools for application	Appendix A
APPLICABILITY	
19. The potential organisational barriers in applying the recommendations have been discussed	1,2
20. The potential cost implications of applying the recommendations have been considered	N/A
21. The guideline presents key review criteria for monitoring and/audit purposes	3
EDITORIAL INDEPENDENCE	
22. The guideline is editorially independent from the funding body	1
23. Conflicts of interest of guideline development members have been recorded	Foreword