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

Tissue pathways for endocrine pathology

April 2019

Authors: Dr Debra Milne, Queen Elizabeth Hospital, Gateshead
Dr Sarah J Johnson, Royal Victoria Infirmary, Newcastle upon Tyne
Professor Tim Stephenson, Royal Hallamshire Hospital, Sheffield
Dr David Poller, Queen Alexandra Hospital, Portsmouth

Unique document number	G078
Document name	Tissue pathways for endocrine pathology
Version number	3
Produced by	Dr Debra Milne (writing group lead), Queen Elizabeth Hospital, Gateshead; Dr Sarah J Johnson, Royal Victoria Infirmary, Newcastle upon Tyne; Professor Tim Stephenson, Royal Hallamshire Hospital, Sheffield; and Dr David Poller, Queen Alexandra Hospital, Portsmouth, on behalf of the College's Specialty Advisory Committee on Histopathology and the Working Group on Cancer Services.
Date active	April 2019
Date for review	April 2024
Comments	This document supersedes the 2012 version of this document, *Tissue pathways for endocrine pathology.* In accordance with the College's pre-publications policy, this document was on the Royal College of Pathologists' website for consultation from 5 December 2018 to 2 January 2019. Responses and authors' comments are available to view on request. **Dr Brian Rous** **Clinical Lead for Guideline Review (Cellular Pathology)**

The Royal College of Pathologists
6 Alie Street, London E1 8QT
Tel: 020 7451 6700
Fax: 020 7451 6701
Web: www.rcpath.org

Registered charity in England and Wales, no. 261035
© 2019, The Royal College of Pathologists

This work is copyright. You may download, display, print and reproduce this document for your personal, non-commercial use. All other rights reserved. Requests and inquiries concerning reproduction and rights should be addressed to the Royal College of Pathologists at the above address. First published: 2019.

Contents

NICE accredited
www.nice.org.uk/accreditation

NICE has accredited the process used by the Royal College of Pathologists to produce its tissue pathways. Accreditation is valid for five years from 25 July 2017. More information on accreditation can be viewed at www.nice.org.uk/accreditation.

For full details on our accreditation visit: www.nice.org.uk/accreditation.

Foreword

The tissue pathways published by the Royal College of Pathologists (RCPath) are guidelines that should assist pathologists in providing a high standard of care for patients. Guidelines are systematically developed statements to assist the decisions of practitioners and patients about appropriate health care for specific clinical circumstances and are based on the best available evidence at the time the document was prepared. This guideline has been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every pathological specimen type and clinical scenario. Occasional variation from the practice recommended in this guideline may therefore be required to report a specimen in a way that maximises benefit to the patient.

The guidelines themselves constitute the tools for implementation and dissemination of good practice.

The stakeholders consulted for this document were the UK Endocrine Pathology Society (UKEPS).

The guideline has been formulated using published papers of case series and best practice, and expert advice. Published evidence was evaluated using modified SIGN guidance (see Appendix A). Consensus of evidence in the tissue pathways was achieved by expert review. Gaps in evidence were identified by fellows via feedback received from consultation. The sections of this tissue pathway that indicate compliance with each of the AGREE II standards are indicated in Appendix B.

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

A formal revision cycle for all tissue pathways takes place on a five-yearly basis. However, each year, the College will ask the author(s) of the tissue pathways, in conjunction with the relevant subspecialty adviser to the College, to consider whether or not the document needs to be updated or revised. A full consultation process will be undertaken if major revisions are required. If minor revisions are required, an abridged consultation process will be undertaken whereby a short note of the proposed changes will be placed on the College website for two weeks for members' attention. If members do not object to the changes, the short notice of change will be incorporated into the pathways and the full revised version (incorporating the changes) will replace the existing version on the publications page of the College. All changes will be documented in the data control section of the relevant pathway.

This tissue pathway has been reviewed by the Clinical Effectiveness department, Working Group on Cancer Services and Lay Governance Group and was placed on the College website for consultation with the membership from 5 December 2018 to 2 January 2019. All comments received from the Working Group and membership were addressed by the authors to the satisfaction of the Chair of the Working Group and the Clinical Lead for Guideline Review (Cellular Pathology).

This pathway was developed without external funding to the writing group. The College requires the authors of tissue pathways to provide a list of potential conflicts of interest; these are monitored by the Clinical Effectiveness department and are available on request. The authors of this document have declared that there are no conflicts of interest.

1 Introduction

This document provides guidance on the specimen handling and reporting of non-cancer specimens from thyroid, parathyroid and adrenal glands. For endocrine tumours in particular, the diagnosis of malignancy may not have been made at the time of tissue resection, and this must be considered when the tissue is examined and sampled for histology. It is

therefore essential that pathologists are also familiar with the corresponding endocrine cancer datasets.

The previous version of *Tissue Pathways in Endocrine Pathology* was published in 2012; this has now been revised to ensure that all recommendations are up to date and that the document complies with the tissue pathway series. In addition to updating references to more recently published guidelines, guidance is included on dealing with thyroid core biopsies.

1.1 Target users of this tissue pathway

The primary users of the tissue pathway documents are trainee and consultant cellular pathologists, advanced practitioners (APs), biomedical scientists (BMSs) and, on their behalf, the suppliers of IT products to laboratories.

2 Generic issues relating to staffing, workload and facilities

The following recommendations should be met for a general level of acceptable practice:

- the diagnostic laboratory should have sufficient pathologists, APs, BMSs and clerical staff to cover all of its functions. In general, staffing levels will follow the workload guidelines of RCPath. For common specimen types, it is not intended to provide detailed guidance in the tissue pathways. For some less common or more specialised specimen types, additional guidance is provided in the relevant section.
- pathologists should:
  - participate in audits
  - participate in an approved CPD scheme, e.g. RCPath
  - participate in relevant external quality assessment (EQA) schemes of a general or specialist nature
  - have access to specialist referral opinions on a local network or national basis.
- the laboratory should:
  - be equipped to allow the recommended technical procedures to be performed safely
  - be accredited by the UK Accreditation Service to the internationally recognised standard 'ISO 15189 Medical Laboratories – requirements for quality and competence'
  - participate in the UK National EQA Scheme for cellular pathology technique
  - participate in the UK National EQA Scheme for immunocytochemistry and fluorescent in situ hybridisation (when these techniques are used in the diagnostic pathway).
- reports should be held on an electronic database that has facilities to search and retrieve specific data items, and that is indexed according to SNOMED CT body structure and morphologic abnormality codes. It is acknowledged that existing laboratory information systems may not meet this standard; however, the ability to store data in this way should be considered when laboratory systems are replaced or upgraded.
- workload data should be recorded in a format that facilitates the determination of the resources involved.

3 Adrenalectomy specimens

Adrenalectomy for suspected adrenal cortical carcinoma and phaeochromocytoma are covered elsewhere in the relevant cancer dataset for adrenal tumours.[1]

3.1 Indications

3.1.1 Functional or non-functioning adenoma, hyperplasia

- Unilateral adrenalectomy for non-functional adrenal adenoma, or for adrenal tumours associated with Cushing syndrome or Conn syndrome.
- Bilateral adrenalectomy as treatment for Cushing disease, where pituitary surgery is not possible or has failed.
- Bilateral adrenalectomy as treatment for ectopic adrenocorticotrophic hormone (ACTH) syndrome, where the source of ACTH has not been identified, or surgical removal of the tumour secreting ACTH is not possible or is incomplete.
- Bilateral adrenalectomy as treatment for Cushing syndrome in primary pigmented nodular dysplasia (part of Carney complex).[1]
- Bilateral adrenalectomy in Cushing syndrome associated with nodular hyperplasia and suppressed ACTH.
- Bilateral adrenalectomy at the stage of adrenal medullary hyperplasia in multiple endocrine neoplasia type 2.

3.1.2 Adrenalectomy for other indications

For example, adrenal mass on imaging, infective lesion, congenital conditions and uncertain diagnosis.

3.2 Staffing and workload

Each department should have access to at least one consultant pathologist with a special interest in endocrine pathology, who is part of a specialist network of endocrine pathologists. Currently, there is no relevant EQA scheme, although occasional adrenal cases may be included in general histopathology EQAs. In addition, pathologists who regularly handle endocrine cases are encouraged to participate in relevant educational slide circulations and meetings, such as those provided by the UKEPS.

3.3 Specimen submission

These specimens are usually received in formalin, which should be of adequate volume. If received fresh, formalin is added. Larger specimens may be sliced to aid fixation.

3.4 Specimen dissection

Where there is a single nodule, the specimen should be dealt with according to the RCPath guidelines for reporting of adrenal cortical carcinoma and phaeochromocytoma/ paraganglioma.[1]

The specimen will usually comprise the adrenal gland and surrounding fat. The weight and dimensions of the specimen and, if possible, those of the adrenal tissue, should be recorded. Specimens removed by laparoscopic procedure may be disrupted. If there is any suspicion that there may be a tumour, the specimen surface should be inked. The head, body and tail of the gland should be identified, and the gland sliced from head to tail. The appearance of the cortex should be described, including the presence or absence of nodules (the maximum dimension of large nodules should be recorded). The distribution of the medulla should be noted as extension into the tail indicates hyperplasia.[2] In most cases, one block taken from

each of the head, the body and the tail should be sufficient. However, additional blocks may be required if there are focal abnormalities. In some cases, it can be useful to have photographs of the gross and dissected specimen for orientation and discussion.

[Level of evidence – D.]

3.5 Sectioning and staining

A single haematoxylin and eosin (H&E)-stained section per block is adequate for examination.

3.6 Further investigations

None are usually required.

3.7 Report content

The report should contain a summary of the gross and histological findings, and the diagnosis.

3.7.1 Cortical lesions

For cortical neoplasms, the absence of any adverse features used in the diagnosis of malignancy should be stated.[1] The pattern of zonation and the presence of any nodules should be described. If nodular, the appearance of the intervening cortex should be noted. In pituitary-dependent Cushing disease, the whole cortex is hyperplastic. Nodular hyperplasia is not common in ectopic ACTH syndrome. In cases of primary pigmented nodular hyperplasia, which are rare, the intervening cortex is usually atrophic. The medulla and the presence of any additional features or lesions should be described. Histologically, different cortical zones should be noted; for example, in Conn syndrome, the zona glomerulosa should be examined for hyperplasia.

3.7.2 Adrenal medullary hyperplasia

The distribution of medullary tissue should be described and the type of hyperplasia (nodular or diffuse) noted. An arbitrary limit of 10 mm is the cut-off between nodular hyperplasia and phaeochromocytoma. The pattern of zonation of the cortex and the presence of nodules should be documented.

[*Level of evidence – D.*]

4 Parathyroidectomy specimens

4.1 Indications

- Removal of hyperfunctioning parathyroid tissue in primary, secondary or tertiary hyperparathyroidism.

The surgeon may request intraoperative confirmation of tissue type by frozen section, although this is becoming less frequent with preoperative imaging and targeted surgery (often unilateral). In some centres, intraoperative blood sampling for parathormone may be used.

4.2 Staffing and workload

Reporting of parathyroid frozen sections does not necessarily require specialist expertise in endocrine pathology, but familiarity with frozen section appearances of lesions in the head and neck region is essential.

Each department should have access to at least one consultant pathologist with a special interest or experience in endocrine pathology, who is part of a specialist network of endocrine pathologists. Currently, there is no relevant EQA scheme, although occasional parathyroid cases may be included in general histopathology EQAs. In addition, pathologists who regularly handle endocrine cases are encouraged to participate in relevant educational slide circulations and meetings, such as those provided by the UKEPS.

4.3 Specimen submission

These may be received fresh for intraoperative frozen sections. After frozen section examination has been completed, the whole specimen should be placed in formalin.

If no intraoperative consultation is required, the specimen should be sent to the laboratory in formalin.

4.4 Specimen dissection

For each parathyroid gland, the site, weight, dimensions, colour and consistency must be recorded. Small glands should be bisected. Cut larger glands into parallel slices, cutting through the vascular pole where possible. Glands should have margins inked prior to frozen section if a diagnosis of carcinoma is being considered. Carcinoma should be considered when glands are large, have a thick capsule or where the surgeon has indicated difficulty in removing the gland, although these findings can occur with degenerative changes, and in atypical adenoma.

For frozen sections, one representative block should be taken. All tissue must be processed to paraffin blocks after frozen section examination. If a frozen section is not required, embed all the tissue.

Some parathyroid glands are intrathyroidal. If a thyroid lobectomy or partial lobectomy specimen is received, it should be weighed and measured. The specimen is then sliced (3–4 mm thickness) and any nodule(s) embedded. If no nodules are identified, embed all the slices.

4.5 Sectioning and staining

A single H&E-stained section per block is adequate for examination.

4.6 Further investigations

None are usually required.

4.7 Report content

The report should contain a summary of the gross and histological findings, and the diagnosis.

For each parathyroid gland, the site should be stated (if provided by the surgeon), and a note made of whether or not the gland is enlarged, has a diffuse or nodular pattern and whether any nodules are encapsulated. The presence or absence of fat in nodules and in background parathyroid tissue should be recorded, and the cell types documented.

Other specimens may be submitted as possible parathyroid glands (e.g. thyroid or lymph node); the nature of the submitted tissue and any abnormality should be reported.

The main purpose of the histology report is to confirm that parathyroid tissue has been removed, to assess the extent of any enlargement and to exclude malignancy. The gland

architecture and types of cells present should be described. It is useful to suggest whether the appearance indicates an adenoma or hyperplasia, although it is recognised that the distinction can be unreliable histologically, particularly if only a single gland has been removed.[3]

[*Level of evidence – D.]*

Where intraoperative frozen section has been performed, the final report should document who gave the result to whom and should specify the date and time of the verbal report.

More detailed instructions on handling can be found elsewhere.[3,4]

5 Thyroid specimens

5.1 Indications

- Total thyroidectomy as treatment for thyrotoxicosis when medical treatment has been unsuccessful.
- Total or hemithyroidectomy to relieve symptoms of compression, or for cosmetic reasons in multinodular goitre or Hashimoto thyroiditis.
- Diagnostic hemithyroidectomy (lobectomy), or occasionally isthmusectomy, when cytology suggests a follicular neoplasm, where the diagnosis is uncertain or where there is a risk of malignancy. In these situations, refer to the College's guidelines for thyroid cancer specimens.[5]
- Core biopsy of thyroid, usually ultrasound guided, after repeated unsatisfactory cytology, or in suspected inflammatory versus neoplastic conditions, e.g. lymphoma, anaplastic carcinoma or metastasis.[6]

5.2 Staffing and workload

Each department should have access to at least one consultant pathologist with a special interest or experience in thyroid pathology, who is part of a specialist network of thyroid pathologists. Currently, there is no thyroid EQA scheme, although thyroid cases are included in the head and neck pathology EQA, and occasional endocrine cases may be included in general histopathology EQA schemes. In addition, pathologists who regularly handle thyroid cases are encouraged to participate in relevant educational slide circulations and meetings, such as those provided by the UKEPS.

5.3 Specimen submission

These specimens are usually sent in formalin, which should be of adequate volume to ensure proper fixation. If received fresh, formalin must be added. Larger specimens should be sliced to aid fixation.

5.4 Specimen dissection

The nature of the specimen and laterality (in lobectomy/hemithyroidectomy specimens) should be noted and, if possible, the specimen orientated. The specimen should be inspected for attached parathyroid glands and lymph nodes. The thyroid capsule should be examined to assess whether or not it appears intact, and the resection margins inked if there is suspicion of neoplasia. The specimen should be weighed, described and the dimensions of each lobe recorded. The specimen should be serially sectioned into 5 mm slices in the horizontal plane. Any possible parathyroid glands or lymph nodes identified should be processed.

In some cases, specimen photography is valuable to aid clinicopathological correlation.

5.4.1 Multinodular disease

One block should be submitted from representative nodules, up to a maximum of five from each lobe. Any encapsulated nodule should be treated as a potential follicular tumour and sampled according to the College's guidelines for thyroid cancers.[7] Any unusual foci should be also processed.

5.4.2 Inflammatory and diffuse conditions

In addition to Graves disease and autoimmune thyroiditis, rare inflammatory conditions that can mimic carcinoma, such as Riedel thyroiditis, will occasionally be encountered. In straightforward cases, two representative blocks from each lobe and one from the isthmus should be submitted. At least one representative block from each lobe should be taken. More complex cases will require more extensive sampling.

[*Level of evidence – D.*]

5.4.3 Core biopsies

These should be embedded in their entirety.

5.5 Sectioning and staining

A single H&E-stained section on each block is adequate for examination.

5.6 Further investigations

None are usually required in total and hemithyroidectomy specimens. However, if the histological features in a case of Hashimoto thyroiditis or a core biopsy raise the possibility of lymphoma, expert haematopathological review is required.

5.7 Report content

The report should provide a summary of the gross and histological features and include a diagnosis.

There is a wide range of histological appearances in non-malignant thyroid disease, including thyroiditides (often autoimmune), colloid and hyperplastic nodules, diffuse and multinodular goitre, and degenerative and iatrogenic changes (see standard thyroid histology texts for details). The reporting pathologist should have access to the full clinical history, preoperative cytology and imaging, together with the opportunity to review previous cytology and histology slides, radiology reports, and any other relevant investigations. For encapsulated follicular-patterned lesions, accurate and up-to-date diagnostic classification hinges on the identification of papillary thyroid carcinoma-like nuclei, and whether there is capsular and/or vascular invasion.[7–9]

[Level of evidence – D.]

Core biopsies have an important role when used selectively, such as after unsatisfactory or inconclusive fine needle aspirations, and to enable histological assessment in anaplastic carcinoma, metastasis and lymphoma. Ideally, core biopsies should be undertaken only after discussion with members of the multidisciplinary team. The histological report should consider relevant radiology and previous cytology and, when a nodule has been biopsied, should state if there is evidence of a capsule. It may be helpful to categorise core biopsies in a manner similar to those used for thyroid cytology.[6]

[Level of evidence – D.]

6 Criteria for audit

Implementation of this tissue pathway may be monitored by audit of:

- completeness of report content (100% of cases)
- accuracy of frozen section reporting (100% of cases)
- correlation of histology with pre-operative cytology and/or radiological findings
- correlation of core biopsy reporting with subsequent resection histology
- adherence to minimum histological sampling guidance (100% of cases)
- turnaround time of histology reports
- accuracy/completion of SNOMED coding (100% of cases).

7 References

1. Moonim MT, Johnson SJ, McNicol AM. *Cancer dataset for the histological reporting of adrenal cortical carcinoma and phaeochromocytoma/paraganglioma (2nd edition)*. London, UK: The Royal College of Pathologists, 2012. Available at: www.rcpath.org/profession/publications/cancer-datasets.html

2. DeLellis RA, Wolfe HJ, Gagel RF, Feldman ZT, Miller HH, Gang DL *et al*. Adrenal medullary hyperplasia. A morphometric analysis in patients with familial medullary thyroid carcinoma. *Am J Pathol* 1976;83:177–196.

3. Johnson SJ. Changing clinicopathological practice in parathyroid disease. *Histopathology* 2010:56;835–851.

4. Johnson SJ, Stephenson TJ. *Dataset for parathyroid cancer histopathology reports (3rd edition)*. London, UK: The Royal College of Pathologists, 2016. Available at: www.rcpath.org/profession/publications/cancer-datasets.html

5. Stephenson TJ, Johnson SJ. *Dataset for thyroid cancer histopathology reports*. London, UK: The Royal College of Pathologists, 2014. Available at: www.rcpath.org/profession/publications/cancer-datasets.html

6. Na DG, Baek JH, Jung SL, Kim JH, Sung JY, Kim KS *et al.* Core needle biopsy of the thyroid: 2016 consensus statement and recommendations from Korean Society of Thyroid Radiology. *Korean J Radiol* 2017;18:217–237.

7. Johnson SJ, Stephenson TJ, Poller DN. *NIFTP addendum to the RCPath Dataset for thyroid cancer histopathology reports*. London, UK: The Royal College of Pathologists, 2016. Available at: www.rcpath.org/profession/publications/cancer-datasets.html

8. Hung YP, Barletta JA. A user's guide to non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). *Histopathology* 2018;72:53–69.

9. Lloyd RV, Osamura RY, Kloppel G, Rosai J (eds). *WHO Classification of Tumours of Endocrine Organs.* Lyon, France: International Agency for Research on Cancer, 2016.

Appendix A Summary table – Explanation of grades of evidence

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

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

Appendix B AGREE II guideline monitoring sheet

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

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