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

Tissue pathways for endocrine pathology

January 2012

Authors: **Dr Debra Milne (Writing Group Lead), City Hospitals, Sunderland**
Dr Sarah J Johnson, Royal Victoria Infirmary, Tyne and Wear
Professor Tim Stephenson, Royal Hallamshire Hospital, Sheffield
Dr David Poller, Queen Alexandra Hospital, Hampshire

Unique document number	G078
Document name	Tissue pathways for endocrine pathology
Version number	2
Produced by	Dr Debra Milne (Lead), City Hospitals, Sunderland; Dr Sarah J Johnson, Royal Victoria Infirmary, Tyne and Wear; Professor Tim Stephenson, Royal Hallamshire Hospital, Sheffield and Dr David Poller, Queen Alexandra Hospital, Hampshire, on behalf of the College's Specialty Advisory Committee on Histopathology and the Working Group on Cancer Services
Date active	January 2012
Date for review	January 2013
Comments	This document supersedes the 2008 version of this document, *Tissue pathways for endocrine pathology.* In accordance with the College's pre-publications policy, this document will be put on The Royal College of Pathologists' website for consultation from 5 December 2011 to 9 January 2012. Nineteen items of feedback were received. The authors considered them and amended the document as was deemed appropriate. Please email publications@rcpath.org if you wish to see the responses and comments. **Dr Peter Cowling** **Director of Communications**

The Royal College of Pathologists
2 Carlton House Terrace, London, SW1Y 5AF
Tel: 020 7451 6700
Fax: 020 7451 6701
Web: www.rcpath.org

Registered charity in England and Wales, no. 261035

Contents

Foreword

The tissue pathways published by The Royal College of Pathologists 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. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. The clinical risk of departing from the guidelines should be carefully considered by the reporting pathologist; just as adherence to the guidelines may not constitute defence against a claim of negligence, so a decision to deviate from them should not necessarily be deemed negligent.

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 guidance has been formulated using published papers of case series and best practice, and expert advice (level D). Consensus of evidence in the tissue pathways is achieved by expert review. Gaps in evidence are identified by Fellows via feedback received from consultation.

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

Each year, the College will ask the author of the tissue pathways, in conjunction with the relevant sub-specialty adviser to the College, to consider whether or not the document needs to be 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 one month for Fellows' attention. If Fellows 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.

The pathway has been reviewed by the Working Group on Cancer Services and was placed on the College website for consultation with the membership from 5 December 2011 to 9 January 2012. 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 Director of Publications.

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 Director of Professional Standards 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 guidance for *Tissue Pathways in Endocrine Pathology* was published in 2008; this has now been revised to ensure that all recommendations are up to date and that the document complies with the revised format of the Tissue Pathway series.

The primary users of the tissue pathway documents are trainee and consultant cellular pathologists, 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.

i. The diagnostic laboratory should have sufficient pathologists, biomedical scientists and clerical staff to cover all of its functions. In general, staffing levels will follow the workload guidelines of The Royal College of Pathologists. 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.

ii. Pathologists should:

- participate in audit
- participate in The Royal College of Pathologists' Continuing Professional Development (CPD) scheme
- 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.

iii. The laboratory should:

- be equipped to allow the recommended technical procedures to be performed safely
- be accredited by Clinical Pathology Accreditation (UK) Ltd, or equivalent
- participate in the UK National External Quality Assurance Scheme for Cellular Pathology Technique
- participate in the UK National External Quality Assurance Scheme for immunocyto-chemistry and fluorescent *in-situ* hybridisation (when these techniques are used in the diagnostic pathway).

iv. Reports should be held on an electronic database that has facilities to search and retrieve specific data items, and that is indexed according to Systematised Nomenclature of Medicine Clinical Terms (SNOMED) T, M and P 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.

v. Workload data should be recorded in a format that facilitates the determination of the resources involved.

3 Site-specific pathways

3.1 Adrenalectomy specimens

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

3.1.1 Indications

(i) Functional or non-functioning adenoma, hyperplasia(s) or dysplasia

Bilateral adrenalectomy as treatment for Cushing's 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's syndrome in primary pigmented nodular dysplasia (PPND, part of Carney's complex).[1]

Bilateral adrenalectomy in Cushing's syndrome associated with nodular hyperplasia and suppressed ACTH.

Occasionally, unilateral adrenalectomy for adrenal adenoma, in Cushing's syndrome or Conn's syndrome.

Bilateral adrenalectomy at the stage of adrenal medullary hyperplasia in multiple endocrine neoplasia type 2 (MEN2).

(ii) Adrenalectomy for other indications

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

3.1.2 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 UK Endocrine Pathology Society.

3.1.3 Specimen submission

Usually received in formalin, which should be of adequate volume. If received fresh, formalin is added.

3.1.4 Specimen dissection

Where there is a single nodule, the specimen should be dealt with according to The Royal College of Pathologists' guidelines for reporting of adrenal cortical carcinoma and malignant phaeochromocytoma.[2]

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.[3] 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.

3.1.5 Sectioning and staining

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

3.1.6 Further investigations

None is usually required.

3.1.7 Report content[4]

i. Cortical lesions

Describe the pattern of zonation and thickness of the cortex, and the presence of any nodules. If nodular, the appearance of the intervening cortex should be noted. In pituitary-dependent Cushing's disease, the whole cortex is hyperplastic. Nodular hyperplasia is not common in ectopic ACTH syndrome. In the rare cases of primary pigmented nodular hyperplasia, the intervening cortex is usually atrophic. Describe the medulla, and any additional features or lesions present. Histologically, take note of the different cortical zones; for example in Conn's Syndrome, look for hyperplasia of the zona glomerulosa.

ii. Adrenal medullary hyperplasia

Describe the distribution of medullary tissue and note whether the hyperplasia is nodular or diffuse. An arbitrary limit of 10 mm is the cut-off between nodular hyperplasia and phaeochromocytoma. Document the pattern of zonation of the cortex and the presence of nodules.

3.2 Parathyroidectomy specimens

3.2.1 Indications

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

The surgeon may request intra-operative confirmation of tissue type by frozen section. In some centres, intraoperative blood sampling for parathormone may be used.

3.2.2 Staffing and workload

Confirmation of the nature of the tissue at frozen section can be performed by any consultant pathologist, Reporting of parathyroid frozen sections does not require specialist expertise in endocrine pathology, although familiarity with frozen section appearances of lesions in the head and neck region is required.

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 UK Endocrine Pathology Society.

3.2.3 Specimen submission

These are often received fresh for intra-operative frozen sections. After frozen section examination has been completed, the whole specimen should be placed in formalin.

If no intra-operative consultation is required, the specimen should be sent to the laboratory in formalin, which should be of adequate volume to ensure proper fixation.

3.2.4 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 may be considered when glands are large, have a thick capsule or where the surgeon has indicated difficulty in removing the gland.

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

3.2.5 Sectioning and staining

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

3.2.6 Further investigations

None is usually required.

3.2.7 Report content

For each parathyroid gland, note whether or not the gland is enlarged, has a diffuse or nodular pattern and whether any nodules are encapsulated. Record the presence or absence of fat in nodules and in background parathyroid tissue. Document the cell types.

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 appearances suggest an adenoma or hyperplasia, although it is recognised that the distinction can be unreliable histologically, particularly if only a single gland has been removed.[5]

Where intra-operative 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 in references 5 and 6.

3.3 Thyroidectomy and thyroid lobectomy specimens

3.3.1 Indications

As treatment for thyrotoxicosis when medical treatment has been unsuccessful, to relieve symptoms of compression, or for cosmetic reasons in multinodular goitre or Hashimoto's thyroiditis.

When cytology suggests a follicular neoplasm, in situations where the diagnosis is uncertain or there is a risk of malignancy, refer to the College's guidelines for thyroid cancer specimens.[7]

3.3.2 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 UK Endocrine Pathology Society.

3.3.3 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. Specimens should be sliced to aid fixation.

3.3.4 Specimen dissection

The nature of the specimen and laterality (in lobectomy specimens) are noted. If possible, the specimen is orientated. A search is made for attached parathyroid glands and lymph nodes. The thyroid capsule is examined to assess whether it appears intact. The resection margins are inked. The specimen is weighed, described and the dimensions of each lobe should be recorded. The specimen is cut into 5 mm slices in the horizontal plane. Any parathyroid glands or lymph nodes identified should be processed.

In some cases, it can be useful to have photographs of the specimen for orientation and clinicopathological correlation.

a) Multinodular disease

Submit one block 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 College's guidelines for thyroid cancers.[7] Any unusual foci should be also processed.

b) Inflammatory and diffuse conditions

In addition to Graves' disease and autoimmune thyroiditis, rare inflammatory conditions which can mimic carcinoma, such as Riedel's thyroiditis, will occasionally be encountered. In straightforward cases, submit two representative blocks from each lobe and one from the isthmus. More complex cases will require more extensive sampling.

3.3.5 Sectioning and staining

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

3.3.6 Further investigations

None is usually required. However, if the histological features in a case of Hashimoto's thyroiditis raise the possibility of lymphoma, referral to an expert panel is recommended for review and immunohistochemical and molecular analysis.

3.3.7 Report content[2,3]

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, degenerative and iatrogenic changes (see standard thyroid histology texts for details).

For clinically or radiologically single nodules, it is important to distinguish non-neoplastic disease from neoplasia, not least for comparison with pre-operative cytology.

In some cases, histology should be correlated with the clinical history, e.g. diffuse hyperplastic goitre in keeping with a history of Graves' disease.

4 Criteria for audit of the tissue pathway

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

- completeness of report content
- audit of accuracy and utility of frozen section reporting
- correlation of histology with pre-operative cytology and/or radiological findings
- adherence to minimum histological sampling guidance
- inclusion of clinicopathological comment in report
- turnaround time of histology reports
- accuracy of SNOMED coding.

5 References

1. Shenoy BV, Carpenter PC, Carney JA. Bilateral primary pigmented nodular adrenocortical disease. Rare cause of the Cushing syndrome. *Am J Surg Pathol* 1984;8:335–344.

2. The Royal College of Pathologists. *Dataset for histopathology reporting in adrenal cortical carcinoma and malignant phaeochromocytoma/paraganglioma.* The Royal College of Pathologists, 2006. www.rcpath.org/index.asp?PageID=1535

3. 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.

4. Lloyd RV, Douglas BR, Young WF. *Endocrine Diseases. Atlas of nontumor pathology.* Washington DC: Armed Forces Institute of Pathology, 2002.

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

6. The Royal College of Pathologists. *Dataset for parathyroid cancer histopathology reports.* The Royal College of Pathologists, 2010. www.rcpath.org/index.asp?PageID=1530

7. The Royal College of Pathologists. *Dataset for thyroid cancer histopathology reports.* The Royal College of Pathologists, 2010. www.rcpath.org/index.asp?PageID=1531

8. Lloyd RV, Douglas BR, Young WF. *Endocrine Diseases. Atlas of nontumor pathology*. Washington, DC: Armed Forces Institute of Pathology, 2002.

9. Rosai J, Carcangiu ML, DeLellis RA. *Tumors of the Thyroid Gland. Atlas of tumor pathology, Third series, Fascicle 5*. Washington DC: Armed Forces Institute of Pathology, 1992.

Appendix AGREE monitoring sheet

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

AGREE standard	Section of tissue pathway
SCOPE AND PURPOSE	
1. The overall objective(s) of the guideline is (are) specifically described	Foreword
2. The clinical question(s) covered by the guidelines is (are) specifically described	Introduction
3. The patients to whom the guideline is meant to apply are specifically described	Introduction
STAKEHOLDER INVOLVEMENT	
4. The guideline development group includes individuals from all the relevant professional groups	Foreword
5. The patients' views and preferences have been sought	Not applicable*
6. The target users of the guideline are clearly defined	Introduction
7. The guideline has been piloted among target users	Feedback follows use of first edition
RIGOUR OF DEVELOPMENT	
8. Systematic methods were used to search for evidence	Foreword
9. The criteria for selecting the evidence are clearly described	Foreword
10. The methods used for formulating the recommendations are clearly described	Foreword
11. The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword
12. There is an explicit link between the recommendations and the supporting evidence	A, B, C
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	Sections 3, 4
16. The different options for management of the condition are clearly presented	Sections 3, 4
17. Key recommendations are easily identifiable	Sections 3, 4
18. The guideline is supported with tools for application	No
APPLICABILITY	
19. The potential organisational barriers in applying the recommendations have been discussed	Foreword
20. The potential cost implications of applying the recommendations have been considered	Foreword
21. The guideline presents key review criteria for monitoring and/or audit purposes	Section 5
EDITORIAL INDEPENDENCE	
22. The guideline is editorially independent from the funding body	Foreword
23. Conflicts of interest of guideline development members have been recorded	Foreword

* The Lay Advisory Committee (LAC) of The Royal College of Pathologists has advised the Director of Communications that there is no reason to consult directly with patients or the public regarding this dataset because it is technical in nature and intended to guide pathologists in their practice. The authors will refer to the LAC for further advice if necessary.