



The Royal College of Pathologists

Pathology: the science behind the cure

Standards and Datasets for Reporting Cancers

Dataset for histopathology reporting in adrenal cortical carcinoma and malignant pheochromocytoma/paraganglioma

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This dataset was commissioned by The Royal College of Pathologists' Working Group on Cancer Services. According to the College's pre-publication policy, this document was placed on the College website for consultation from 12 December 2005 – 4 January 2006. No responses were received.

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Director of Publications

INTRODUCTION

Endocrine cancer datasets

The management of endocrine tumours should be the responsibility of an appropriate experienced multidisciplinary team. Because these tumours bridge various anatomical divides, they are dealt with by a number of specialist teams. Ideally the pathologist reporting them should have a special interest in endocrine pathology. Alternatively, he/she should have an interest in endocrine tumours in their area of systematic pathology or, if a general pathologist, should participate in a network with the opportunity for specialist pathology review.

Each group of tumours is dealt with in a separate section. 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 endocrine tumours and for hyperplasia in the parathyroid. We have therefore included some of these options in the forms.

Adrenal cancer dataset

Both adrenal cortical tumours and pheochromocytomas are included in these guidelines and they are extended to cover extra-adrenal paragangliomas. The handling of the gross specimens is broadly similar. Synoptic reporting proformas have been included to include *aides memoire* for the key features of these neoplasms. Medullary tumours specifically associated with childhood and neural tumours are excluded.

These guidelines describe the core data that should be recorded in the histopathology reports from cases of adrenal cortical carcinoma or malignant pheochromocytoma or paraganglioma. They should be implemented for the following reasons:

- they will provide accurate data for cancer registration
- they will provide feedback to the surgeon on the completeness of resection
- they will potentially allow the selection of patients for future trials of adjuvant therapy.

The document has been widely discussed and has been approved by the UK Endocrine Pathology Society and the British Association of Endocrine Surgeons. Panels of specialist and general histopathologists acting on behalf of the College have also reviewed it. We strongly recommend its use as a dataset.

NOTES ON RECORDING DATA ITEMS

Gross examination and specimen handling – general comments

The nature of the specimen should be defined. There is increasing use of laparoscopic surgery, particularly for adrenal cortical tumours. This may result in fragmentation of the gland and cause problems in assessing tumour size and whether the capsule is intact. It may also cause distortion of vascular channels, making the assessment of vascular invasion difficult. This may make the application of current approaches to assessment of malignant potential impossible. The type of surgery should therefore be noted.

The specimen should be weighed, measured and described grossly. It should be noted whether the capsule is intact. The presence of apparent extension into neighbouring soft tissue and organs should be noted separately. The margins should be inked. It is suggested that, although it would be usual practice to dissect the tumour free of fat to obtain an accurate weight, this should not jeopardise the proper assessment of local invasion. Where the adrenal gland can be identified, its relationship to the tumour should be noted. There are no defined protocols for tumour sampling, but we would suggest that lesions less than 3 cm in diameter should be processed in their entirety. Larger lesions should have an additional block for each 1 cm.

In cortical tumours, the appearance of the cut surface should be described, particularly the presence of necrosis. A block should be taken from the adjacent uninvolved adrenal.

Most publications suggest that the location of tumour is important in pheochromocytoma, extra-adrenal tumours being more commonly malignant than intra-adrenal.^{1,2} Coarse nodularity of the cut surface³ and necrosis^{1,3} are more often found in malignant tumours.

Where the adrenal gland is present in a specimen of pheochromocytoma, it is usual to examine it for evidence of medullary hyperplasia as an indicator of multiple endocrine neoplasia Type 2. In the normal gland the medulla is confined to the head and body, so extension into the tail suggests hyperplasia. A block taken from the tail permits assessment. This is now not so important as most patients will undergo a range of genetic testing to identify the various forms of familial disease, some of which are not associated with hyperplasia.⁴

The number of lymph nodes submitted or identified in the main specimen should be recorded. Any grossly involved nodes should be sampled. Where there is no obvious involvement, a random selection should be made.

Note and sample any other tissues submitted.

MICROSCOPIC REPORT

Core data items for all malignancies

- Site of tumour
- Type of tumour
- Maximum dimension of tumour
- Adrenal capsule intact/disrupted
- Invasion of extra-adrenal/extra-paraganglial tissues
- Distance to excision margin
- Lymph node status.

Phaeochromocytoma/paraganglioma

There are no absolute criteria for differentiating benign from malignant phaeochromocytomas and they should therefore never be defined as histologically benign. According to the most recent classification from the World Health Organization, malignancy is defined only by the presence of metastasis. However, the classification does recognise the potential lethal behaviour of tumours with extensive local invasion and such behaviour should be clearly identified in the written report. The problem for the pathologist is to recognise tumours with an increased risk of malignant behaviour. Histological features said to occur more commonly in malignant tumours are confluent tumour necrosis, absence of hyaline globules, higher mitotic count (3 per 20 high power fields [HPF] versus 1)³ and absence of sustentacular cells as identified by S100 staining.⁵ A new system for intra-adrenal tumours (PASS – Pheochromocytoma of the Adrenal gland Scaled Score) uses weighted analysis of a range of features to separate benign from malignant lesions. However, it requires validation before it can be recommended for general use.⁶

Some tumours, designated composite phaeochromocytoma, have a significant component resembling neuroblastoma, ganglioneuroblastoma or ganglioneuroma.⁷ This should be documented. Again, it is not possible to predict behaviour on the basis of the nature of the second component.

The presence or absence of medullary hyperplasia should be noted where possible.

Tumour staging

There are no staging criteria for phaeochromocytoma or paraganglioma.

Adrenal cortical tumours

There are no absolute criteria for the diagnosis of malignancy in adrenal cortical tumours apart from extensive invasion of local structures and metastasis. A number of multifactorial analyses have been proposed to identify malignant potential,⁸⁻¹¹ but none is perfect. Some include clinical and biochemical data in addition to histological features and are based on a numerical assessment of risk.^{9,11} Weiss's approach is based solely on histology,^{8,10} with the nine features to be assessed shown in Table 1 below.

The presence of three or more of these indicates malignant potential. This is the easiest system to apply in practice. We have added to the synoptic report the presence of broad fibrous bands, which features in the other systems. A mitotic count of more than 20 per 50 HPF has been reported to correlate with shorter disease-free survival.⁸ The utility of this approach has recently been confirmed in a number of studies.^{12,13} Aubert *et al*¹³ recently proposed a modified scoring system, based on fewer features, but this requires further testing. These systems are sometimes difficult to apply to paediatric cases.⁷

Table 1 Histological features to be assessed

Diffuse architecture	Atypical mitoses
Clear cells ≤ 25% of total	Capsular invasion
Significant nuclear pleomorphism	Sinusoidal invasion
Confluent necrosis	Venous invasion
Mitotic count ≥ 6 per 50 HPF	

The histological features of the adjacent cortex should be documented. These may have functional significance (e.g. atrophy in Cushing's syndrome or presence of spironolactone bodies in Conn's syndrome).

Tumour staging

The American Joint Committee on Cancer/International Union Against Cancer do not have a TNM staging system for adrenal malignancies. However, there is a published system for adrenal cortical tumours^{14, 15} and the pathology data contributes to staging. This is shown below.

pT1 ≤ 5 cm, no invasion
pT2 > 5 cm, no invasion
pT3 Any size, locally invasive but not involving adjacent organs
pT4 Any size with invasion of adjacent organs

N0 No nodes involved
N1 Regional nodes involved
NX Cannot assess regional nodes

M0 No distant metastases
M1 Distant metastases
MX Cannot assess distant metastases

SNOMED CODES

Malignant pheochromocytoma T93 M87003
Malignant paraganglioma (any site) T95 M86933
Adrenal cortical carcinoma T93 M83703

DISTINCTION BETWEEN ADRENAL CORTICAL TUMOURS AND PHAEOCHROMOCYTOMA

There are a few cases where the histological features are difficult to interpret and a confident diagnosis as a cortical tumour or pheochromocytoma cannot be made on routine haematoxylin and eosin staining. Immunohistochemistry may be of use. General neuroendocrine markers (e.g. synaptophysin, neuron specific enolase, PGP 9.5) are not helpful as they may be positive in adrenal cortical tumours.¹⁶ However, chromogranin is negative in cortical tumours and almost always positive in pheochromocytoma. Conversely, the majority of cortical tumours will be positive for inhibin α ¹⁷ and/or with melanA (clone A103).¹⁸

OTHER TUMOURS

The source of metastases should be confirmed by appropriate immunohistochemistry and lymphomas characterised by immunohistochemistry and molecular techniques.

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