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

Standards and datasets for reporting cancers

Cancer dataset for the histological reporting of adrenal cortical carcinoma and phaeochromocytoma/paraganglioma (2nd edition)

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Comments	In accordance with the College's pre-publications policy, this document was put on The Royal College of Pathologists' website for consultation from 9 August to 9 September 2011. Nine items of feedback were received. The authors considered them and amended the document as appropriate. Please email publications@rcpath.org if you wish to see the responses and comments. This document replaces the 1st edition of *Dataset for reporting adrenal cortical carcinoma and malignant phaeochromocytoma/paraganglioma*, published in 2006. **Dr Peter Cowling** **Director of Communications**

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Foreword

The cancer datasets published by The Royal College of Pathologists are a combination of textual guidance and reporting proformas that should assist pathologists in providing a high standard of care for patients and facilitate accurate cancer staging. 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 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 assessed by the relevant multidisciplinary team (MDT); 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.

Each dataset contains **core data items** that will be mandated for inclusion in the Cancer Outcomes and Services Dataset (previously the National Cancer Data Set) in England. Core data items are items that are supported by robust published evidence and are required for cancer staging, optimal patient management and prognosis. Core data items meet the requirements of professional standards (as defined by the Information Standards Board for Health and Social Care [ISB]) and it is recommended that at least 90% of reports on cancer resections should record a full set of core data items.

Other, **non-core, data items** are described. These may be included to provide a comprehensive report or to meet local clinical or research requirements. All data items should be clearly defined to allow the unambiguous recording of data.

Authors are aware that datasets are likely to be read by, *inter alia*, trainees, general pathologists, specialist pathologists and clinicians, and service commissioners. The dataset should seek to deliver guidance with a reasonable balance between the differing needs and expectations of the different groups. The datasets are not intended to cover all aspects of service delivery and reference should be made, where possible and appropriate, to guidance on other aspects of delivery of a tumour-specific service, e.g. cytology and molecular genetics.

The guidelines have been approved by the UK Endocrine Pathology Society and the British Association of Endocrine and Thyroid Surgeons (BAETS).

The evidence base has been obtained by consultation of electronic databases, review articles, primary literature, consensus meetings and other guidelines. The level of evidence encompasses C and D. Consensus of evidence in the datasets is achieved by expert review. Gaps in evidence are identified by College Fellows via feedback received from consultation.

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

Each year, the College will ask the authors of the dataset, in conjunction with the relevant sub-specialty adviser to the College, to consider whether or not the dataset needs to be revised. A full consultation process will be undertaken if major revisions are required, i.e. revisions to core data items (the only exception being changes to international tumour grading and staging schemes that have been approved by the College's Specialty Advisory Committee on Histopathology and affiliated professional bodies; these changes will be implemented without further consultation). If minor revisions or changes to non-core data items 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 Fellows' attention. If Fellows do not object to the changes, the short notice of change will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website. All changes will be documented in the 'data control' section at the front of the relevant dataset.

The dataset has been reviewed by the Working Group on Cancer Services and was placed on the College website for consultation with the membership from 9 August to 9 September 2011. All comments received from the Working Group and membership will be addressed by the authors to the satisfaction of the Chair of the Working Group and the Director of Publications.

1 Introduction

Endocrine cancer datasets

The management of endocrine tumours is 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. There is currently no national model for the constitution of MDTs managing endocrine tumours (other than thyroid) that is stipulated by the National Institute for Health and Clinical Excellence (NICE) or Cancer Peer Review. The constitution of these teams should be determined according to local skills, interest and experience. Ideally, the pathologist reporting the cases should have a special interest in endocrine pathology. Alternatively, he/she should have an interest in the endocrine tumours in his/her area of systemic pathology or, if a general pathologist, should participate in a network with the opportunity for specialist pathology review. The reporting pathologist should either be a core member of the appropriate cancer MDT or have access to a pathologist who is a core member. Educational slide circulations relevant to these tumour groups are available through the UK Endocrine Pathology Society (UKEPS) at www.ukeps.com.

It is envisaged that the main users of the datasets will be trainee and consultant histopathologists and, on their behalf, the suppliers of IT products to laboratories. Secondary users will include surgeons, oncologists, endocrinologists and nuclear medicine physicians. They will also be of use to cancer registries and the National Cancer Intelligence Network.

Adrenal cancer dataset

This dataset includes guidelines to deal with both adrenocortical carcinoma and phaeochromocytoma. It has also been extended to cover extra-adrenal paragangliomas. Paediatric medullary tumours (neuroblastoma/ganglioneuroblastoma) are not covered in the dataset (an available resource for these tumours is the College's dataset for peripheral neuroblastic tumours – www.rcpath.org).

The World Health Organization (WHO) 2004 classification of endocrine tumours reserves the term 'phaeochromocytoma' for intra-adrenal tumours.[1] Extra-adrenal paragangliomas are defined by type (sympathetic or parasympathetic) and site. Sympathetic paragangliomas arise close to the paravertebral and prevertebral ganglia in the para-axial region of the trunk, or in the connective tissue adjacent to pelvic organs. Therefore, phaeochromocytomas are intra-adrenal sympathetic paragangliomas. Parasympathetic paragangliomas lie close to vascular structures and branches of the glossopharyngeal and vagus nerves in the head and neck. They include what have been defined as carotid body tumours, jugulotympanic, vagal and aortic paragangliomas. Paragangliomas can also arise in other sites that are not necessarily associated with the normal location of sympathetic and parasympathetic paraganglia; these include the small bowel (gangliocytic paraganglioma), nose and nasopharynx, orbit, cauda equina and spine and lesions termed chemodectomas of the lung.

The handling of the gross specimens is broadly similar for both groups of tumours. Reporting proformas have been included that list the key features of these neoplasms. There are several changes incorporated in this dataset that include criteria used to discriminate benign from malignant tumours, a description of the role of immunohistochemistry in differentiating cortical from medullary neoplasms and changes to staging systems. The currently used TNM7/UICC staging system for adrenocortical carcinoma is included along with comments

about a recently proposed staging system that refines the outcome prediction of the UICC system.[2,3] There is currently no staging system for phaeochromocytoma or paraganglioma.

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

1. The most important prognostic feature in adrenal cortical carcinoma is clinical tumour stage and pathological staging is crucial for this.

2. The diagnosis will provide accurate data for cancer registration.

3. They will potentially allow the selection of patients for future clinical trials. This is extremely important as current therapies for these diseases are limited.

2 Clinical information required on the request form

The nature of the specimen and type of surgery should be defined (left/right adrenalectomy or paraganglioma excision from various sites; open or laparoscopic). In addition to excision of primary tumours, adrenalectomy is also performed for removal of metastatic tumour to the adrenal (especially if this represents a solitary metastasis).

Laparoscopic surgery is being used with increasing frequency and this invariably leads to some disruption or even fragmentation of the gland/tumour. This may cause problems in assessing tumour size, integrity of the tumour capsule and completeness of excision and may also cause distortion of vascular channels, making assessment of vascular invasion difficult. In the very rare cases where the specimen has been morcellated, tumour size should be obtained from either the surgeon or from pre-operative cross-sectional imaging studies.

The presence of a clinical syndrome (e.g. Cushing's or Conn's) should be noted. Any history of familial disease (e.g. multiple endocrine neoplasia type 2 [MEN2]) should be included.

3 Preparation of specimens before dissection

The specimen should be measured and described grossly. A digital image may be useful.

Historically, many studies have used 'tumour weight' to try and discriminate between benign and malignant tumours. However, modern stratification systems for adult cortical tumours/ phaeochromocytomas (see section 5) do not utilise tumour weight to make this distinction. Currently, tumour weight is only used as one of many criteria in stratification systems designed to deal with paediatric cortical tumours. While attempts may be made to obtain as accurate a weight as possible, it is advised not to strip the surrounding fat/soft tissue or attached adjacent organs off the tumour in order to obtain an accurate weight. Stripping of surrounding tissues is detrimental to assessment of both completeness of excision (which is a good indicator of the likelihood of local recurrence) and of staging (as it prevents an accurate assessment of local invasion, which is a much more reliable indicator of aggressive behaviour).[2,3]

If the tumour is visible, its size should be measured and it should be noted whether or not the tumour capsule is intact. The specimen margins should be inked.

4 Specimen handling and block selection

The specimen should then be serially sliced and the appearance of the cut surface described, particularly the presence of necrosis. If measurements have not been previously taken, these should now be documented. Again, a digital image may be useful.

The integrity of the tumour capsule and presence/absence of apparent invasion into peri-adrenal soft tissue and adjacent organs should be noted separately. The distinction between these two is important for staging of adrenal cortical carcinoma. Where the adrenal gland can be identified, its relationship to the tumour and its appearance should be noted.

The adrenal vein is usually prominently visible as a clamped structure in adrenalectomy specimens and this, along with other major vessels, should be sampled to determine if tumour thrombus is present within them.[3,4] This is especially important in specimens with an attached kidney, where evaluation of the renal veins/part of the inferior vena cava (if present) is possible. The number of lymph nodes submitted or identified in the main specimen should be recorded. All lymph nodes should be processed. Small nodes should be processed whole. Large nodes may be sampled. Any other tissues submitted should be sampled.

Notes specific for adrenal cortical carcinoma

There are two publications showing that a modified staging system proposed by the European Network for the Study of Adrenal Tumours (ENSAT) is superior to that of TNM7/UICC in predicting outcome in adrenal cortical carcinoma.[3,4] This includes venous tumour thrombus as an additional feature (tumour directly growing into either the adrenal vein, left renal vein or inferior vena cava). We have incorporated the modifications suggested by the ENSAT system in the reporting proforma, so that data are available for routine use and clinical trials until the TNM system is next modified.

Notes specific for phaeochromocytoma/paraganglioma

Most publications suggest that extra-adrenal paragangliomas are more commonly malignant than phaeochromocytoma**.** Coarse nodularity of the cut surface and necrosis are more often found in malignant tumours.[5] There also appears to be genotype/phenotype correlation in inherited disease. Malignancy is very rare in MEN2 and neurofibromatosis type 1 but over 50% of paragangliomas associated with succinate dehydrogenase B (SDHB) mutations are malignant.[6]

Historically, it was usual to examine the adrenal gland for the presence of adrenal medullary hyperplasia as an indicator of MEN2.[7] Normally, the adrenal medulla is confined to the head and body of the gland. Therefore the presence of medullary tissue in the tail of the gland represents medullary hyperplasia. However, it needs to be noted that not all forms of inherited phaeochromocytoma are associated with hyperplasia[8] and that it may not always be possible to identify the tail of the adrenal gland due to distortion by tumour. In current practice, this is not very relevant as most patients would undergo genetic screening to identify various forms of familial disease.[9] Immunohistochemical detection of SDHB is also now feasible if indicated.[10]

Number of blocks

There are no defined protocols for tumour sampling, but we would suggest that lesions <30 mm in diameter should be processed in their entirety and larger lesions should have a minimum of one block for each 10 mm. Blocks should be taken from all morphologically distinct areas, necrotic areas, the tumour capsule and its interface with adjacent tissue to assess invasion and the margins. At least one block should be taken from the adjacent uninvolved adrenal, if identified.

5 Core data items

All tumours

- Nature of specimen.
- Nature of disease (primary diagnosis versus tissue from recurrence or relapse).
- Type of surgery.
- Type of tumour.
- Maximum dimension of tumour.
- Invasion into extra-adrenal/extra-paraganglial tissues and/or adjacent organs.
- Completeness of excision:

  Incomplete excision has been associated with an increased incidence of local recurrence.[3,4] The following is suggested based on the residual (R) tumour classification of TNM7. No tumour identified at any surgical margin (R0), tumour identified microscopically at a surgical margin (R1), tumour identified macroscopically at a surgical margin (R2). It should be noted that to apply the R2 designation, the tumour should actually have been cut through (i.e. visualisation of just the intact capsular surface of the tumour does not confer R2 status).
- Lymph node status.
- Histological evidence of metastasis (if available):

  Due to the ease of performing needle core biopsies of various organs, metastatic disease is now increasingly seen histologically and in many cases may be the only tissue sample available due to the advanced nature of the primary tumour or the co-morbidities associated with surgical resection.

Adrenal cortical carcinoma

- Tumour weight (see section 3).
- Tumour thrombus in renal vein.
- Tumour thrombus in vena cava.

Phaeochromocytoma and paraganglioma

Presence of other component (neuroblastic/carcinomatous/sarcomatous). Composite phaeochromocytoma/paraganglioma most commonly contain a ganglioneuromatous component, which does not impact on eventual outcome. When they contain a neuroblastic component (neuroblastoma/ganglioneuroblastoma), it is the latter that metastasizes. Rarely admixtures with cortical tumour/carcinoma or sarcoma have been described.

6 Differentiating between benign and malignant tumours

Adrenal cortical tumours

There are no absolute criteria for the diagnosis of malignancy in adrenal cortical tumours apart from invasion of local structures and metastasis. A number of multi-factorial analyses have been proposed to identify malignant potential in intra-adrenal tumours. Some include clinical and biochemical data in addition to histological features and are based on a numerical assessment of risk.[11,12]

Weiss's approach is based solely on histology, with the nine features to be assessed in the original scoring system, each given a score of 1 if present.[13,14] Aubert *et al* recently proposed a modified Weiss scoring system, based on fewer features (which have the advantage of being less susceptible to inter-observer variation).[15] Some of the criteria in the modified system are weighted (i.e. the score of 1 has to be multiplied by the weighting factor). Both systems have been independently validated and a score of three or more in either system indicates malignant potential (>90% lesions will have a risk of local recurrence or distant metastasis).[16,17] Either of these systems can be used, but the report should indicate which. Another feature which correlates with malignancy is the presence of broad fibrous bands.[11]

Table 1: Diagnosis of malignancy in adrenal cortical tumours[13–15]

	Weiss system	**Modified Weiss system**
Clear cells comprising ≤ 25% of the tumour	✓	✓ x 2
Diffuse architecture > one third of the tumour	✓	–
Confluent necrosis	✓	✓
High nuclear grade (Fuhrman grade 3 or 4)	✓	–
Mitotic rate >5/50 HPF	✓	✓ x 2
Atypical mitoses	✓	✓
Venous invasion	✓	–
Sinusoidal invasion	✓	–
Capsular invasion	✓	✓
A score of three or more indicates aggressive/malignant behaviour		

M

Mitosis counting

Mitoses are still counted using a 40X objective (i.e. 40X x 10X = 400X). 50 high power fields (HPF) from areas of greatest mitotic activity are examined. There is insufficient evidence in the literature to move from HPF to a defined area-based counting system. A few publications have stratified adrenocortical carcinoma into low-grade and high-grade variants based on a cut-off of 20 mitoses/50 HPF. A mitotic rate of >20 per 50 HPF is associated with a poorer survival.[14, 18]

Reporting of specimens damaged during surgery

Adrenal carcinoma often shows many of the features included in both of the systems outlined above and a diagnosis of malignancy is possible in most cases, even where there has been surgical trauma to the specimen. The main problem when the tumour is restricted to the adrenal gland is usually the confidence with which the presence or absence of capsular invasion can be diagnosed and the completeness of excision assessed. The problem is the tumour with a score of 2, in which assessment is incomplete. There are no published studies on how to deal with this. Further sampling may be helpful.

Where features contributing to the Weiss or modified Weiss index cannot be assessed, this should be recorded on the proforma. If there is a score of 2, with absent features, it may be necessary to define the lesion as of uncertain malignant potential. However, a mitotic rate of >5 per 50 HPF and the presence of atypical mitoses are highly suggestive of malignancy.

Oncocytic adrenal cortical tumours

There may be a problem in assessing oncocytic tumours when using the Weiss criteria. Oncocytic tumours often have a diffuse pattern of growth, comprise <25% clear cells and

show significant nuclear pleomorphism, resulting in a malignant diagnosis in most cases. However, it is known that many behave in a benign manner. An alternative approach (shown in Table 2) has been suggested, defining major and minor criteria for malignancy.[19] This has now been validated[20] and we recommend its use.

Table 2: Diagnosis of malignancy in oncocytic adrenal cortical tumours[19]

Major criteria		**Minor criteria**
• Mitoses >5/50 HPF (x 400) • Atypical mitoses • Venous invasion		• Large size (>100 mm or >200 g) • Confluent necrosis • Capsular invasion • Sinusoidal invasion
Any one major criterion	Malignant	Oncocytic adrenal cortical carcinoma
Any one minor criterion	Borderline	Oncocytic adrenal cortical neoplasm of uncertain malignant potential
Absence of all major and minor criteria	Benign	Oncocytoma

Paediatric cortical tumours

The systems mentioned above may also be difficult to apply to paediatric cases. Tumours in this age group defined as malignant on histological grounds often have a good outcome. These tumours may be assessed using criteria developed by the Armed Forces Institute of Pathology (AFIP).[21–23]

Table 3: Criteria for malignancy in paediatric adrenocortical tumours [23]

• Tumour weight >400 g • Tumour size >10.5 cm • Extension of tumour into periadrenal soft tissue/adjacent organs • Invasion into vena cava • Venous invasion • Capsular invasion • Presence of tumour necrosis • >15 mitoses per 20 HPF • Presence of atypical mitotic figures
The presence of four or more criteria is associated with malignancy

Phaeochromocytoma/paraganglioma

According to the most recent classification from the WHO, malignancy is defined only by the presence of metastasis to sites where paraganglial tissue is not normally found.[1] However, the classification does recognise the potential lethality of extensive local invasion and such behaviour should be clearly identified in the written report (‘aggressive paraganglioma’). Local invasion (infiltration into adjacent skeletal muscle, soft tissue, nerves, bone and complete/partial incorporation of major blood vessels into the tumour) is often the major

problem associated with head and neck paragangliomas, as these prevent complete resection of what is invariably a slowly growing tumour.

The problem for the pathologist is to recognise tumours with an increased risk of malignant behaviour where metastasis has not been identified at diagnosis. There are no absolute histological criteria for differentiating benign from malignant phaeochromocytomas and these tumours should therefore never be specifically classified as benign. Sympathetic paragangliomas in extra-adrenal locations are more often malignant than phaeochromocytoma.[5] Histological features said to occur more commonly in malignant tumours are coarse nodularity, confluent tumour necrosis, absence of hyaline globules, higher mitotic count (>3 per 20 HPF, x 400),[5] atypical mitotic figures, absence of sustentacular cells as identified by S100 staining[24,25] and a MIB-1 labelling index of >2.5%.[26,27]

A new system for stratifying phaeochromocytoma ('Phaeochromocytoma of the Adrenal gland Scoring Scale' or PASS) uses weighted analysis of a range of features to separate benign from malignant lesions.[28] Although it was found useful in one study,[27] a second study found marked inter- and intra-observer variation in assessing the different features.[29] PASS could be added to the histopathology reports for phaeochromocytoma, but we have not included the features in core items.

Table 4: Phaeochromocytoma of the adrenal gland scoring scale (PASS score)[28]

Feature	**Score**
Large nests of cells or diffuse growth >10% of tumor volume	2
Necrosis (confluent or central in large cell nests)	2
High cellularity	2
Cellular monotony	2
Presence of spindle-shaped tumor cells (even focal)	2
Mitotic figures (>3 per 10 high power fields)	2
Extension of tumor into adjacent fat	2
Vascular invasion	1
Capsular invasion	1
Profound nuclear pleomorphism	1
Nuclear hyperchromasia	1
Total possible score	**20**

All tumors that metastasized were reported to have scores ≥4.

Some tumours, designated composite phaeochromocytoma, have a significant component comprising neuroblastoma, ganglioneuroblastoma, ganglioneuroma or, more rarely, a carcinomatous or sarcomatous component. This should be documented. Again, it may not be possible to predict behaviour on the basis of the nature of the second component.

Differential diagnosis

There are a few cases where the histological features are ambiguous and a confident diagnosis of either a cortical tumour or phaeochromocytoma cannot be made on routine haematoxylin and eosin (H&E) staining. Immunohistochemistry is useful in this situation. Table 5 illustrates the utility of various markers currently used to make this distinction.

General neuroendocrine markers (e.g. synaptophysin, NSE) are not helpful as they may be positive in adrenal cortical tumours.[30] However, chromogranin is negative in cortical tumours and almost always positive in phaeochromocytoma. Conversely, the majority of cortical tumours will be positive for inhibin α and/or with Melan A (clone A103); note that a small minority of phaeochromocytomas/paragangliomas also express the latter two markers.[31–33]

Table 5: Immunohistochemical profile of adrenal cortical and medullary tumours

	Keratin	CGA	TH	Syn	NSE	Inhibin	Calretinin	Melan A
Cortical	-/vf	- (0%)	-	+ (67%)	+	+ (97%)	+ (95%)	+ (94%)
Medullary	-/~ 29%	+ (100%)	+	+ (100%)	+	+ (6%)	+ (14%)	+ (6%)

CGA Chromogranin A
TH Tyrosine hydroxylase
Syn Synaptophysin
NSE Neuron specific enolase
vf very focal

Paragangliomas and their metastases may need to be distinguished from neuroendocrine tumours arising at other sites. Tyrosine hydroxylase expression is specific for tumours of adrenal medullary origin and melanocytic lesions; however, this is not routinely available in most histopathology departments. In the abdomen, differentiating between a paraganglioma and a neuroendocrine tumour would require demonstration of markers specific for pancreatic and gastrointestinal endocrine tumours (hormones/secretory products specific to those sites). In the neck, calcitonin expression would identify medullary carcinoma of thyroid.

The source of metastases to the adrenal gland should be confirmed by appropriate morphology and immunohistochemistry and comparison to the primary tumour if available. Lymphomas should be characterised by immunohistochemistry and molecular techniques as appropriate.

7 Non-core data items

All tumours

- Tumour capsule intact/disrupted.
- Distance to closest excision margin.
- Other tissues included.

Adrenal cortical tumours

- The presence or absence of broad fibrous bands.
- The histological features of the adjacent adrenal, especially the cortex should be documented. These may have functional significance (e.g. atrophy in Cushing's syndrome or presence of spironolactone bodies in previously treated Conn's syndrome).

Phaeochromocytoma

- The presence of coarse nodularity within the tumour.
- The presence/absence of sustentacular cells, identified by immunostaining for S100 protein. This has been quoted by several studies, but may not correlate well with outcome.[24, 25]

- Ki-67 (MIB-1) index.[26] Studies have documented that benign tumours are associated with a proliferation index of <1%, while those that were aggressive/malignant had indices of >2.5%.
- The presence or absence of adrenal medullary hyperplasia.
- PASS – phaeochromocytoma of the adrenal gland scoring scale.

8 SNOMED codes

Details are shown in Appendix A.

9 Tumour staging

Adrenal cortical carcinoma

The UICC introduced a staging system for adrenal cortical carcinoma in the 7th edition.[2] Details are shown in Appendix B.

The European Network for the Study of Adrenal Tumours (ENSAT) proposed a modified staging system in 2008 that refines the prognostic predictive power of the UICC/TNM7 staging system (data presented in Table 6).[3,4] The major changes are to stage 3 (tumour with any one of the following: positive lymph nodes, extra-adrenal tissue infiltration, venous tumour thrombus in renal vein/IVC) and stage 4 (any tumour with distant metastasis). In addition, this system highlights that patients with tumour spillage at the time of surgery or tumours that have been incompletely excised (R1/R2) have a worse prognosis as compared to stage matched controls.

Table 6: Comparison of TNM7/UICC and ENSAT staging systems

Stage	TNM7/UICC[2]			ENSAT system[3]		
	Criteria	Five-year survival rate (%)		Criteria	Five-year survival rate (%)	
		Ref 3	Ref 4		Ref 3	Ref 4
1	pT1 N0 M0	82	74	Same as TNM7	82	74
2	pT2 N0 M0	58	64	Same as TNM7	61	64
3	pT1-2 N1 M0 pT3 N0 M0	55	57	Tumour with any one of the following: • involved lymph nodes • extra-adrenal tissue infiltration • venous tumour thrombus in renal vein or IVC	50	44
4	pT3 N1 M0 pT4 N0 M0 pT1-4 N0-1 M1	18	12	Any tumour with distant metastasis	13	7

Malignant phaeochromocytoma/paragangliomas

There are no staging criteria/systems for phaeochromocytoma or paraganglioma.

10 Reporting of small biopsy specimens

The usual reason for a biopsy of an adrenal lesion would be to differentiate between a primary adrenal cortical tumour and metastasis. This is dealt with under differential diagnosis above. It is not possible to predict behaviour on such a specimen.

Biopsy of a phaeochromocytoma or functioning paraganglioma is contraindicated. However, specimens may be received from non-functional extra-adrenal paragangliomas in order to make a specific diagnosis. These should have H&E histology and an immunohistochemical panel of neuroendocrine markers as outlined above. Differentiation from other neuroendocrine tumours is discussed in differential diagnosis.

11 Frozen sections

It is not usual practice to have frozen sections.

12 Criteria for audit of the dataset

In keeping with the recommended key performance indicators published by The Royal College of Pathologists (www.rcpath.org/index.asp?PageID=35), reports on adrenocortical carcinoma and phaeochromocytoma/paraganglioma should be audited for the following.

- The inclusion of SNOMED or SNOMED-CT codes:
  - standard: 95% reports should have T, M and P codes.
- It is recommended that at least 90% of reports on cancer resections should record a full set of core data items
- The use of electronic structured reports or locally agreed proformas (it is assumed that these processes will ensure that 90% of core data items are recorded):
  - standard: 80% of resection specimens will include 100% data items presented in a structured format.
- Turnaround times for biopsies and resection specimens:
  - standard: 80% diagnostic biopsies will be reported within seven calendar days of the biopsy being taken.
  - standard: 80% of all histopathology specimens (excluding those requiring decalcification) will be reported within ten calendar days of the specimen being taken.

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Appendix A SNOMED codes

Adrenal gland	T93000	
Adrenal cortical carcinoma	M83703	
Phaeochromocytoma	M87000	
Malignant phaeochromocytoma	M87003	
Paraganglioma	M86931	
Malignant paraganglioma	M86933	
Jugular paraganglioma	T95300	M86901
Aortic body paraganglioma	T95400	M86911
Carotid body tumour	T94000	M86921
Gangliocytic paraganglioma		M86830

Comment:

The coding system has been designed with the following suffixes to code for various outcomes:

0 indicates benign behaviour

1 indicates uncertain behaviour/outcome

3 indicates malignant behaviour.

Thus due to the uncertain outcome of head and neck paragangliomas, these are routinely coded with suffixes ending in 1. If, however, a malignant head and neck paraganglioma is encountered, the M code should end with a 3 (i.e. for a malignant carotid body paraganglioma the M code would be M86923).

Appendix B Staging for adrenal cortical carcinoma

TNM7/UICC staging for adrenal cortical carcinoma

pTX Primary tumour cannot be assessed

pT0 No evidence of primary tumour

pT1 ≤5 cm, no extra-adrenal invasion

pT2 >5 cm, no extra-adrenal invasion

pT3 Any size, locally invasive but not involving adjacent organs *

pT4 Any size with invasion of adjacent organs.

* Adjacent organs are defined as: kidney, diaphragm, great vessels, pancreas and liver.

pN0 No nodes involved

pN1 Regional nodes involved **

pNX Cannot assess regional nodes.

** Regional lymph nodes are the local aortic and retroperitoneal lymph nodes.

pM0 No distant metastases

pM1 Distant metastases.

Stage grouping

<table>
<tr><th></th><th colspan="3">TNM7/UICC</th><th>ENSAT</th></tr>
<tr><td>Stage 1</td><td>T1</td><td>N0</td><td>M0</td><td>Same as TNM7/UICC</td></tr>
<tr><td>Stage 2</td><td>T2</td><td>N0</td><td>M0</td><td>Same as TNM7/UICC</td></tr>
<tr><td rowspan="2">Stage 3</td><td>T1/T2</td><td>N1</td><td>M0</td><td rowspan="2">Tumour with any of the following:
• lymph node involvement
• extra-adrenal tissue infiltration
• venous tumour thrombus in renal vein or IVC</td></tr>
<tr><td>T3</td><td>N0</td><td>M0</td></tr>
<tr><td rowspan="3">Stage 4</td><td>T3</td><td>N1</td><td>M0</td><td rowspan="3">Any tumour with distant metastasis</td></tr>
<tr><td>T4</td><td>N0</td><td>M0</td></tr>
<tr><td>Any T</td><td>Any N</td><td>M1</td></tr>
</table>

Appendix C Histopathology reporting proforma for adrenal cortical carcinoma

Surname…… Forenames…… Date of birth……..... Sex....

Hospital…….…….…… Hospital no…….…..... NHS/CHI no……..

Date of receipt…….…….. Date of reporting……..…..... Report no…….....

Pathologist……..……... Surgeon…….……

Clinical details

Nature of specimen Right adrenalectomy □ Left adrenalectomy □
Tissue from metastatic deposit □ Site ……

Nature of disease Primary diagnosis □ Recurrence/relapse □

Type of surgery Open □ Laparoscopic □ Not known □

Pathologic findings

Maximum dimensions of tumour …….. mm

Weight …… gm (only if possible, see section 3).

Invasion into extra-adrenal soft tissue Yes □ No □

Invasion into adjacent organs Yes □ No □

Venous tumour thrombus Yes □ No □

Vein involved Renal □ Vena cava □ Not identified □

Lymph nodes Yes □ No □ Cannot assess □

Lymph nodes involved Yes □ No □ Number involved.....

Excision complete R0 □ R1 □ R2 □

Histological evidence of metastasis: Yes □ No □ Site .....

Diagnosis

Adrenocortical carcinoma □ [M83703]

Adrenocortical tumour of uncertain malignant potential □
(based on an incomplete Weiss/modified Weiss score) [M83701]

Pathological stage (TNM7/UICC) .....

Pathological stage (ENSAT) .....

Signature ……..... Date……..…. SNOMED code …….

Appendix D Histopathology reporting proforma for phaeochromocytoma and paraganglioma

Surname…… Forenames…… Date of birth……..... Sex....
Hospital…….…….…… Hospital no…….…..... NHS/CHI no……..
Date of receipt…….…….. Date of reporting……..…..... Report no…….....
Pathologist…….…….... Surgeon…….……

Clinical details

Nature of specimen Right adrenalectomy □ Left adrenalectomy □
Other □ Site ……..
Tissue from metastatic deposit □ Site ……

Nature of disease Primary diagnosis □ Recurrence/relapse □

Type of surgery Open □ Laparoscopic □ Not known □

Pathologic findings
Maximum dimensions of tumour …… mm

Invasion into extra-adrenal soft tissues Yes □ No □
Invasion into adjacent organs Yes □ No □

Lymph nodes identified Yes □ No □ Cannot assess □
Lymph nodes involved Yes □ No □ Number involved.....

Excision complete R0 □ R1 □ R2 □

Presence of other component Yes □ No □
If yes, state type: ……..

Histological evidence of metastasis: Yes □ No □ Site .....

Diagnosis .....

Signature ……..... Date……..…. SNOMED code …….

Appendix E AGREE 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 objective(s) of the guideline is (are) specifically described	Introduction
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	Foreword
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	N/A*
6. The target users of the guideline are clearly defined	Foreword
7. The guideline has been piloted among target users	Introduction
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	References
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	2–11
16. The different options for management of the condition are clearly presented	2–11
17. Key recommendations are easily identifiable	2–11
18. The guideline is supported with tools for application	Appendices
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/audit purposes	12
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.