Impact of standardised reporting in adrenocortical carcinoma: a single centre clinicopathological review

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ABSTRACT

Aims: Structured multicentre efforts are needed if the prognosis of adrenocortical carcinoma (ACC) is to be improved. Data collection may be enhanced through standardised histopathological reporting using criteria such as the recently published Royal College of Pathologists' (UK) minimum dataset (MDS). This study aimed to perform a clinicopathological review of the adult patients treated at the Royal Victoria Infirmary, Newcastle upon Tyne, in the 10 years preceding the MDS.

Methods: Case records were examined for all patients diagnosed with ACC between 1996 and 2006. Pathology was reviewed and compared with the Royal College of Pathologists' MDS along with the original reports. A systematic evaluation of Ki-67 immunolabelling was also performed.

Results: Eleven patients with ACC were diagnosed and treated. Histopathological reporting according to the MDS identified more features of malignancy than in the original reports (8.5 ± 1.2 versus 5.1 ± 0.8, $p<0.02$). The median number of microscopic criteria of malignancy was 7 (range 5–10), with ≥ 5 features occurring in all cases. The most commonly observed features of malignancy were diffuse architecture, <25% clear cells, confluent necrosis, abnormal mitoses and mitotic count ≥ 6 per 50 high-power fields. Capsular invasion and ≥ 8 MDS criteria of malignancy were associated with a worse outcome (each $p<0.01$). Median Ki-67 index was 19.0% (range 3.7–44.1%) and was not apparently related to survival.

Conclusions: Standardised criteria for histopathological reporting of ACC will improve the accuracy of data for cancer registration and may also assist in individual patient stratification. An elevated Ki-67 index is a feature of ACC, although it does not appear to predict individual patient survival.

Adrenocortical carcinoma (ACC) is a highly aggressive malignancy. Metastatic spread is common at presentation (21–52%) and almost invariable on follow up.[1–4] All current medical and surgical treatments carry poor results. For instance, the average survival after diagnosis is only 10–22 months[4–6] and 5-year survival rates vary between 16% and 38% (see review[7]). One of the major restrictions to improving the treatment for ACC is the infrequency of its occurrence, with an incidence of 1–2 per million population per year.[8 9] Thus, even single tertiary care centres may see and treat only one or two patients each year. Accordingly, multicentre collaborations are essential if the prognosis is to be improved. One of the major limitations in this regard has been the lack of standardised data collection between centres.

The histological diagnosis of malignancy in resected adrenocortical neoplasms can be problematic and various combinations of criteria have been proposed.[10–13] In 2006, the Royal College of Pathologists (UK) ((RCPath(UK)) produced a minimum dataset (MDS) for histopathology reports of ACC, based mainly on the Weiss criteria.[14] The MDS also includes comment on involvement of versus clear surgical margins (ie, apparent completeness of resection) and, by encouraging accurate diagnosis and SNOMED coding, it should improve data accuracy for cancer registration. The value of these histological features in predicting outcome and guiding adjuvant therapy has yet to be appraised. Several groups have demonstrated the apparent role of Ki-67 (MIB-1 clone) immunostaining in differentiating benign from malignant adrenocortical neoplasms[15–18] and in predicting outcome in malignancy.[19] Nevertheless, a Ki-67 index is not a criterion included in the current MDS.

This clinicopathological review aimed to retrospectively test the completeness and accuracy of pathological reporting of features listed in the MDS, and to assess the performance of these features and the Ki-67 index in predicting survival for patients with ACC at one centre over 10 years.

METHODS

Histopathology records were interrogated to find all patients who attended the Royal Victoria Infirmary, Newcastle upon Tyne, UK, and who had a diagnosis of ACC made between 1996 and 2006. Patient clinical records were reviewed for age, sex, mode of presentation, pre- and postoperative biochemical and imaging evaluation, and treatment and outcome.

Staging of disease was based on the McFarlane/Sullivan classification:[20] stage I, tumour <5 cm with negative nodes, no local invasion and no metastases; stage II, tumour >5 cm with negative nodes, no local invasion and no metastases; stage III, tumour with positive nodes or local invasion; and stage IV, tumour with positive nodes and local invasion or distant metastases. Stage of disease was based on imaging, intraoperative and pathological findings.

Serum cortisol and testosterone (T) were measured using a competitive chemiluminescence immunoassay (Advia Centaur System, Bayer Diagnostics, Newbury, UK). Follicle stimulating hormone (FSH) and luteinising hormone (LH) were measured by a two-site sandwich chemiluminescence immunoassay (Advia). Urine cortisol was determined by competitive radioimmunoassay

(Orion Diagnostica, Oy, Finland). Dehydroepiandrosterone (DHEAS) and androstenedione were measured by competitive chemiluminscence immunoassay on a DPC Immulite 2000 analyser (DPC, Gwynedd, UK). Oestrone and oestradiol were measured by in-house radioimmunoassay (Leeds SAS steroid centre, UK).

The original histopathology reports were reviewed against the RCPath(UK) MDS. For this evaluation, the reports from two further patients with ACC, treated at another hospital nearby, were also included. The histology slides underwent masked independent review by two pathologists (MSG and SJJ) for features within the MDS including apparent completeness of resection. Differences were resolved by consensus. Immunohistochemistry for Ki-67 was performed retrospectively on formalin-fixed paraffin-embedded tissue using MIB-1 antibody (Dako, Cambridgeshire, UK) at 1 in 300 dilution incubated in Dako autostainer for 30 min at room temperature after pretreatment by pressure cooking in citrate buffer (Menapath, Menarini Diagnostics, Berkshire, UK). The Ki-67 labelling index was assessed independently by the two pathologists. The index was calculated as the percentage of positively stained nuclei out of a minimum of 1000 tumour cell nuclei, and the mean of the two observations was taken.

Statistical analysis

The relationship between the presence of histopathological features and survival was determined by log-rank test and the difference in microscopic features of malignancy on original reports and re-review was determined by paired Student t test. All statistics were done using GraphPad Prism version 3.00 for Windows (GraphPad Software, San Diego, California, USA).

RESULTS

Clinical presentation and endocrine evaluation

Eleven adult patients were diagnosed with ACC at our hospital between 1996 and 2006 (six women, median age of presentation 47 years (range 28–80 years)). The clinical and endocrinological features of each patient are shown in table 1. Autonomous hormone hypersecretion was responsible for the presenting features in seven patients and the most common mode of presentation was with classical features of Cushing syndrome. The median duration of symptoms in all patients presenting with any hormonal manifestations was 3 months (range 1 month to 1 year). There was no relationship between tumour functionality and outcome.

Surgical treatment and extent of disease

Table 2 shows the extent of disease at surgery and on radiological follow-up. Initial assessment of tumour spread by preoperative imaging (ultrasound scan, CT or MRI) and by intraoperative inspection at the time of surgery revealed the presence of definite metastasis in just two patients (table 2). Open adrenalectomy was performed in 10 patients, with one individual (patient I) undergoing laparascopic adrenalectomy. On follow-up, nine patients had radiological evidence of intra-abdominal disease recurrence, with local recurrence in the adrenal bed occurring in four patients, all of whom had had involvement of the original specimen margins (table 2).

Medical treatment

Nine patients received mitotane and three patients received combination chemotherapy (table 2). Despite the attainment of adequate plasma mitotane levels, radiological evidence of a reduction in tumour bulk was present in only two individuals. Reported adverse events on mitotane included gastrointestinal disturbance, dizziness, fixed drug eruption with gynaecomastia, and drug-induced hepatitis.

Survival

Four patients are still alive, of whom only two are free from any evidence of residual or metastatic disease (table 2). Of the seven patients who have died the median survival from presentation was 579 days (range 162–3127 days).

Pathology

Median tumour weight was 171 g (range 41–1600 g) and median greatest tumour dimension was 85 mm (57–190 mm). Thus, all patients had at least stage II disease. We did not find a relationship between tumour dimension or weight and outcome. Table 3 shows the histological features according to the RCPath(UK) MDS as found on review of the slides. Table 2 shows the Ki-67 indices for proliferation. There was good agreement between the two observers for Ki-67 (mean $\pm$ SD for difference in observer scores, $3.7 \pm 2.2\%$). The median Ki-67 index was 19.0% (range 3.7–44.1%). There was no significant relationship between Ki-67 index and either duration of symptoms prior to diagnosis or outcome.

On histopathological review, the number of MDS microscopic features suggestive of malignancy present in cases ranged from 5–10 (median 7) (for Weiss criteria the median was 6 (range 4–8)) (table 3). Thus, all patients had at least five histological features suggestive of malignancy. The five most commonly observed features of malignancy were diffuse architecture, less than 25% clear cells, confluent necrosis, abnormal mitoses and a mitotic count of six or more per 50 high-power fields (table 3). Sinusoidal invasion was not observed in any of the patients. The presence of $\leqslant 7$ MDS microscopic features of malignancy ($p<0.01$) and the absence of capsular invasion ($p<0.01$) were both associated with an improved survival (fig 1).

Original reporting of features of malignancy

The original histopathology reports were reviewed to determine whether each microscopic feature of malignancy had been commented on in the initial account. In addition to the 11 patients under medical care at our centre, tissue and reports were available for two further patients treated at a neighbouring hospital, and these were included in this analysis. Table 4 shows that only the presence or absence of capsular and extra-adrenal invasion were commented on in all cases in the original reports. Of the five most commonly occurring microscopic features, $<25\%$ clear cells, confluent necrosis and abnormal mitoses were commented on in less than 75% of the original reports (table 4). Re-review of the tissue sections, according to the MDS criteria, not only resulted in more comprehensive reporting but also identified the presence of significantly more microscopic features of malignancy (table 4). For instance, taking into account all 11 of the MDS criteria, the mean ($\pm$SEM) number of times any feature was present on the original report was 5.1 ± 0.8 and on review it was 8.5 ± 1.2 ($p<0.02$).

DISCUSSION

ACC is an aggressive malignancy with poor long-term survival. Low tumour incidence is a major obstacle to identifying effective treatment regimens and accurate prognostic markers. This situation is further compounded by the varied clinical

Table 1 Clinical and biochemical data for 11 patients with adrenocortical carcinoma

Patient	Sex	Age (years)	Clinical presentation	Biochemical evidence of cortisol secretion	Biochemical evidence of androgen/oestrogen secretion	Combined hormone secretion (yes/no)	Post-operative biochemical testing
A	M	45	Mass effect	Not tested	Not tested	Not tested	O/N DST, serum cortisol 38 nmol/l
B	F	28	Oligomenorrhoea	UFC:creatinine ratio 28.5 and 38.0 nmol/mmol	T 3.1 nmol/l, LH 16.1 U/l, FSH 3.3 IU/l, DHEAS 2.9 μmol/l, androstenedione 19.9 nmol/l	No	Not tested
C	F	41	Virilisation	Not tested	T 43.8 nmol/l, DHEAS 36.5 μmol/l, androstenedione 76.0 nmol/l	Yes	UFC 2690 and 1980 nmol/24 h, T 42.2 nmol/l
D	F	42	Cushing syndrome with hirsutism	UFC 3296, 4416 and 6375 nmol/24 h	T 6.8 nmol/l	Yes	UFC 1694 nmol/24 h, T 7.2 nmol/l, androstenedione 23 nmol/l
E	M	62	Cushing syndrome	UFC 364, 442 and 914 nmol/24 h	Not tested: no clinical features of feminisation	No	UFC 159 nmol/24 h O/N DST, serum cortisol 442 nmol/l, oestradiol 234 pmol/l
F	F	46	Cushing syndrome with hirsutism	LDDST, serum cortisol 559 nmol/l; HDDST, serum cortisol 555 nmol/l	T 7.2 nmol/l	Yes	UFC:creatinine ratio 4.8, 9.8 and 9.1 nmol/mmol, T 0.2 nmol/l
G	M	54	Feminisation	LDDST, serum cortisol 291 nmol/l	Oestrone 821 pmol/l, oestradiol 797 pmol/l	Yes	O/N DST, serum cortisol <24 nmol/l, oestrone 95 pmol/l, oestradiol 109 pmol/l
H	M	66	Incidental finding on MRI	UFC 2867 nmol/l; O/N DST, serum cortisol 768 nmol/l	Not tested: no clinical features of feminisation	No	UFC 6803, 5388 and 8666 nmol/24 h
I	M	80	Cushing syndrome	UFC 2584 and 4509 nmol/24 h; LDDST, serum cortisol 864 nmol/l; HDDST, serum cortisol 828 nmol/l	Not tested: no clinical features of feminisation	No	O/N DST, serum cortisol 555 nmol/l
J	F	65	Cushing syndrome with hirsutism	UFC 568 nmol/24 h, LDDST and HDDST reported from another hospital as non-suppressing	T 5.2 nmol/l	Yes	UFC 963, 741 and 1920 nmol/24 h;, LDDST, serum cortisol 566 nmol/l; T 3.0 nmol/l
K	F	47	Mass effect	Not tested	Not tested	Not tested	LDDST, serum cortisol 35 nmol/l; T 0.7 nmol/l

DHEAS, dehydroepiandrosterone; HDDST, high-dose dexamethasone suppression test (2 mg dexamethasone orally, six-hourly for 48 h); LDDST, low-dose dexamethasone suppression test (0.5 mg dexamethasone orally, six-hourly for 48 h); O/N DST, 1.5 mg overnight dexamethasone suppression test; T, testosterone; UFC, urinary free cortisol. Reference ranges: androstenedione 0–13 nmol/l, DHEAS 1.4–11.1 μmol/l, FSH 1–10 IU/l, LH 2–12 U/l, oestradiol 0–180 pmol/l, oestrone <330 pmol/l, random serum cortisol 190–650 nmol/l, T 0–3.2 nmol/l, UFC 0–320 nmol/24 h, UFC/creatinine ratio 5–55 nmol/mmol.

manifestations of the disease and its somewhat unpredictable natural history. Introduction and adherence to standardised microscopic criteria such as the MDS, or Weiss criteria, will lead to more complete histopathological documentation that should impact positively on cancer registration, and possibly also on individual patient prognostication.

Our series illustrates the variety of ways in which an adult patient with ACC may present. Tumour hyperfunctionality occurred in the majority of cases and manifested most commonly as Cushing syndrome. We did not find a relationship between tumour functionality and outcome, which despite the suggestions of some authors[21 22] is consistent with the findings of most studies to date (see review [8]).

Historically, gross examination of the tumour has assisted in the diagnosis of ACC in the presence of haemorrhage or necrosis or if the tumour is especially large.[20] However, with the advent of highly sensitive imaging modalities such as CT and MRI, adrenal tumours are often now identified at a smaller size and, accordingly, standardised histological criteria for malignancy have been advocated. In 1984, Weiss proposed a series of nine histological criteria for adults, with the presence of four (later re-defined to three) or more indicating that a tumour was ACC.[12 13] In 2006, the RCPath(UK) MDS for ACC expanded these criteria with the addition of the presence of ''broad fibrous bands'' and ''extra-adrenal invasion'' and re-classified the term high nuclear grade to ''significant nuclear pleomorphism''.[14] In our series, all cases demonstrated at least five criteria for malignancy with two microscopic features (greater than one-third diffuse architecture and less than 25% clear cells) present in all cases.

While microscopic criteria are undoubtedly of benefit in establishing a diagnosis of malignancy, their role in predicting outcome for patients is a little more contentious. Some studies have demonstrated an inverse relationship between mitotic count and survival.[23 24] However, the results in our patients correspond with those of Wachjenberg *et al*,[8] with no association found. Indeed, only two of our patients had a mitotic rate <6 per 50 high-power fields, both subsequently developing distant metastases. By way of contrast, the total number of MDS microscopic features of malignancy and the presence of capsular invasion were predictive of a worse outcome.

Recently, there has been considerable interest in the use of alternative markers of cellular proliferation to predict malignancy and to be used as indicators of prognosis. Proliferating cell

Table 2 Correlation of pathological and clinical features in 11 patients with adrenocortical carcinoma

Patient	Tumour weight (g)	Surgical margins on pathology	Stage	Mean Ki-67 index (%)	Extent of disease at surgery		Medical treatment		Further development of disease		Outcome
					Local	Distant	Mitotane	Chemotherapy	Local	Distant	
A	862	Clear	III	24.0	Adherent to peritoneum, infiltrating right lobe of liver	None	After 4 years	No	No	Liver, lung, mediastinal and intra-abdominal nodes	Alive after 2297 days
B	780	Clear	II	15.5	Capsule not breached	Not evaluated	After 10 months	Single cycle of cisplatin and etoposide	No	Liver and lung	Died 472 days after presentation
C	250	Clear except at surgical breach	III	8.5	Complete excision	None	After 2 years	Six cycles of epirubicin, cisplatin and 5-fluorouracil	No	Liver, lung, brain, perinephric mass, pancreatic head, intra-abdominal nodes, sub-cutaneous tissue	Died 3127 days after presentation
D	700	Clear	IV	30.2	Tumour displacing but not invading kidney and liver	Intra-abdominal nodal mass	Post-operative	No	No	Liver, lung, para-vertebral mass and cervical lymph nodes	Died 162 days after presentation
E	1600	Tumour present at sites of rupture	III	3.7	Invasion of liver and serosa	Not evaluated	After 2 years	No	No	Liver, intra-abdominal nodes, perinephric mass, peritoneal deposits and incisional hernia	Alive after 1683 days
F	160	Clear	II	7.8	Capsule not breached	None	None	No	No	No	Alive after 2287 days
G	145	Clear	II	44.1	Complete excision	None	None	No	No	No	Alive after 939 days
H	177	Involved	IV	19.0	Adherent to inferior vena cava	Liver metastases	Post-operative	No	Yes	Liver	Died 188 days after presentation
I	41	Involved +++	III	26.0	No fragments of adrenal tissue remaining	None	After 9 months	No	Yes	Intra-abdominal nodes, peritoneal and omental deposits	Died 579 days after presentation
J	93	Involved	III	23.1	Adherent to inferior vena cava	None	After 20 months	No	Yes	Liver, lung, bone and scalp	Died 800 days after presentation
K	1655	Involved ++	III	15.8	Invading perinephric tissues	None	After 8 months	Two cycles of cisplatin and etoposide plus trial drugs	Yes	Liver, lung, intra-abdominal nodes and peritoneal deposits	Died 852 days after presentation

Table 3 Summary of histological features present in 11 cases of adrenocortical carcinoma

Patient	>1/3 diffuse architecture*	<25% clear cells*	Significant nuclear pleomorphism*	Confluent necrosis*	Mitoses ⩾6 per 50/HPF (×400)*	Abnormal mitoses*	Broad fibrous bands	Capsular invasion*	Venous invasion*	Sinusoidal invasion*	Extra-adrenal invasion	Number of histological criteria (MDS)	Number of Weiss criteria
A	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No	No	5	4
B	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	8	7
C	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	7	7
D	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	8	6
E	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	7	6
F	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	No	No	6	6
G	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	7	6
H	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	9	7
I	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	No	No	6	6
J	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	7	6
K	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	10	8
Number of patients†	11 (100)	11 (100)	6 (55)	10 (91)	9 (82)	10 (91)	7 (64)	6 (55)	6 (55)	0 (0)	4 (36)		

*Feature also included in the Weiss criteria.[12 13]
†Number of patients with histological feature (%).
HPF, high-power field; MDS, minimum dataset.

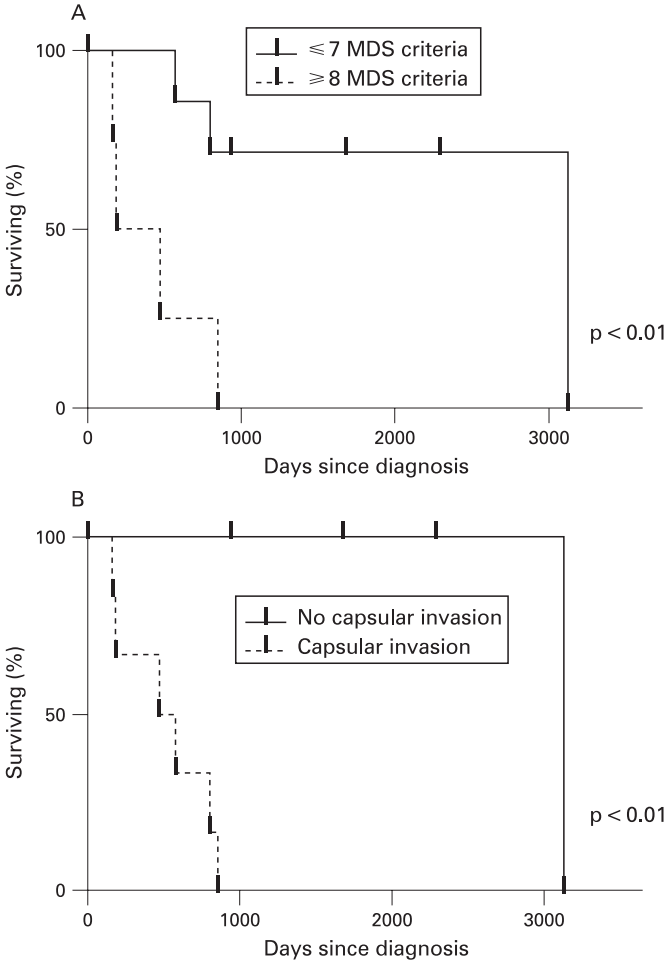

Figure 1 Survival curves according to number of Royal College of Pathologists' (UK) minimum dataset (MDS) microscopic criteria of malignancy (A) and presence or absence of capsular invasion (B).

nuclear antigen has not been shown to differ between benign and malignant adrenal tumours[25] and gradation of staining means it can be difficult to distinguish positive and negative

Table 4 Comprehensiveness of reporting of microscopic features of malignancy in original reports from 13 patients with ACC, prior to the introduction of the Royal College of Pathologists' (UK) minimum dataset

Microscopic feature	Presence or absence of feature documented in original report (%)	Feature documented as present in original reports (%)	Feature present on review (%)
>1/3 diffuse architecture*	10 (77)	10 (77)	13 (100)
<25% clear cells*	3 (23)	3 (23)	13 (100)
Significant nuclear pleomorphism*	12 (92)	6 (46)	8 (61)
Confluent necrosis*	9 (69)	7 (54)	12 (92)
Mitoses ⩾6 per HPF (×400)*	10 (77)	7 (54)	10 (77)
Abnormal mitoses*	7 (54)	5 (38)	11 (85)
Broad fibrous bands	2 (15)	1 (8)	9 (69)
Capsular invasion*	13 (100)	8 (61)	6 (46)
Venous invasion*	12 (92)	5 (38)	7 (54)
Sinusoidal invasion*	6 (46)	2 (15)	1 (8)
Extra-adrenal invasion	13 (100)	3 (23)	4 (31)

*Feature also included in the Weiss criteria.[12 13]
HPF, high-power field.

nuclei at microscopy. The cell cycle marker Ki-67 does appear to be better at distinguishing benign and malignant disease, with a labelling index >2.5% suggestive of ACC.[15 26] The findings in the present series would support this supposition, with the lowest Ki-67 (MIB-1) index being 3.7%. Although not a feature of the RCPath(UK) MDS, we would propose a Ki-67 index as a useful adjunct in establishing a diagnosis of malignancy, with a good inter-observer agreement. However, in order for data to be compared across centres there is a need for standardisation of methods both for Ki-67 (MIB-1) labelling and to ensure a sufficient number of tumour cell nuclei are counted (≥1000 in the present study).

Ki-67 immunopositivity as a marker of cellular proliferation is useful in predicting outcome in other malignancies[19] and can be used to guide treatment of neuroendocrine tumours.[27] That we found no relationship between Ki-67 index and survival was largely due to the highest Ki-67 index occurring in a patient who presented with signs of feminisation. The biochemistry of aromatase expression in this man's tumour is the subject of a separate report (manuscript in preparation). Nevertheless, the case illustrates the complex relationship between histopathological features of malignancy and clinical manifestations in ACC.

In summary, ACC is a heterogeneous condition with a grim prognosis. Although the condition is rare, it is possible to positively impact on clinical care through multicentre collaborations, as evidenced by the results of the recent study of adjuvant mitotane.[28] Standardised histopathological criteria ensure comprehensiveness of reporting, offer advantages in predicting outcome and should facilitate future multicentre endeavours.

Take-home messages

- Adrenocortical carcinoma is a rare malignancy with a poor prognosis and a heterogeneous clinical presentation.
- Standardised microscopic criteria such as the Royal College of Pathologists' (UK) minimum dataset or Weiss criteria are useful in assisting in the diagnosis of malignancy and also possibly in predicting outcome.
- An elevated Ki-67 index is a feature of adrenocortical carcinoma although is not included in either the Royal College of Pathologists' (UK) minimum dataset or Weiss criteria, and may not necessarily correlate with prognosis.
- Given the rarity of the condition, multicentre efforts are essential if the prognosis of the malignancy is going to be improved. Standardised methods of histopathological data collection will assist future collaborations.

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Competing interests: SJJ is a co-author of the RCPath(UK) minimum dataset for histological reporting in adrenal cortical carcinoma and malignant phaeochromocytoma/paraganglioma.

REFERENCES

1. **Soreide JA,** Brabrand K, Thoresen SO. Adrenal cortical carcinoma in Norway, 1970–1984. *World J Surg* 1992;**16**:663–7. Discussion in *World J Surg* 1992;**16**:668.
2. **Icard P,** Goudet P, Charpenay C, *et al*. Adrenocortical carcinomas: surgical trends and results of a 253-patient series from the French Association of Endocrine Surgeons study group. *World J Surg* 2001;**25**:891–7.
3. **Didolkar MS,** Bescher RA, Elias EG, *et al*. Natural history of adrenal cortical carcinoma: a clinicopathologic study of 42 patients. *Cancer* 1981;**47**: 2153–61.
4. **Icard P,** Chapuis Y, Andreassian B, *et al*. Adrenocortical carcinoma in surgically treated patients: a retrospective study on 156 cases by the French Association of Endocrine Surgery. *Surgery* 1992;**112**:972–9. Discussion in *Surgery* 1992;**112**: 979–80.
5. **Langer P,** Bartsch D, Moebius E, *et al*. Adrenocortical carcinoma – our experience with 11 cases. *Langenbecks Arch Surg* 2000;**385**:393–7.
6. **Luton JP,** Cerdas S, Billaud L, *et al*. Clinical features of adrenocortical carcinoma, prognostic factors, and the effect of mitotane therapy. *N Engl J Med* 1990;**322**:1195–201.
7. **Allolio B,** Fassnacht M. Clinical review: Adrenocortical carcinoma: clinical update. *J Clin Endocrinol Metab* 2006;**91**:2027–37.
8. **Wajchenberg BL,** Albergaria Pereira MA, Medonca BB, *et al*. Adrenocortical carcinoma: clinical and laboratory observations. *Cancer* 2000;**88**:711–36.
9. **Dackiw AP,** Lee JE, Gagel RF, *et al*. Adrenal cortical carcinoma. *World J Surg* 2001;**25**:914–26.
10. **Hough AJ,** Hollifield JW, Page DL, *et al*. Prognostic factors in adrenal cortical tumors. A mathematical analysis of clinical and morphologic data. *Am J Clin Pathol* 1979;**72**:390–9.
11. **van Slooten H,** Schaberg A, Smeenk D, *et al*. Morphologic characteristics of benign and malignant adrenocortical tumors. *Cancer* 1985;**55**:766–73.
12. **Weiss LM.** Comparative histologic study of 43 metastasizing and nonmetastasizing adrenocortical tumors. *Am J Surg Pathol* 1984;**8**:163–9.
13. **Weiss LM,** Medeiros LJ, Vickery AL Jr. Pathologic features of prognostic significance in adrenocortical carcinoma. *Am J Surg Pathol* 1989;**13**:202–6.
14. **Royal College of Pathologists**. Dataset for histopathology reporting in adrenal cortical carcinoma and malignant phaeochromocytoma/paraganglioma. http://www.rcpath.org/index.asp?PageID = 1023 (accessed 5 June 2008).
15. **Goldblum JR,** Shannon R, Kaldjian EP, *et al*. Immunohistochemical assessment of proliferative activity in adrenocortical neoplasms. *Mod Pathol* 1993;**6**:663–8.
16. **Vargas MP,** Vargas HI, Kleiner DE, *et al*. Adrenocortical neoplasms: role of prognostic markers MIB-1, P53, and RB. *Am J Surg Pathol* 1997;**21**:556–62.
17. **Wachenfeld C,** Beuschlein F, Zwermann O, *et al*. Discerning malignancy in adrenocortical tumors: are molecular markers useful? *Eur J Endocrinol* 2001;**145**:335–41.
18. **Terzolo M,** Boccuzzi A, Bovio S, *et al*. Immunohistochemical assessment of Ki-67 in the differential diagnosis of adrenocortical tumors. *Urology* 2001;**57**:176–82.
19. **Hoos A,** Stojadinovic A, Mastorides S, *et al*. High Ki-67 proliferative index predicts disease specific survival in patients with high-risk soft tissue sarcomas. *Cancer* 2001;**92**:869–74.
20. **Schteingart DE,** Doherty GM, Gauger PG, *et al*. Management of patients with adrenal cancer: recommendations of an international consensus conference. *Endocr Relat Cancer* 2005;**12**:667–80.
21. **Karakousis CP,** Rao U, Moore R. Adrenal adenocarcinomas: histologic grading and survival. *J Surg Oncol* 1985;**29**:105–11.
22. **Hogan TF,** Gilchrist KW, Westring DW, *et al*. A clinical and pathological study of adrenocortical carcinoma: therapeutic implications. *Cancer* 1980;**45**:2880–3.
23. **Harrison LE,** Gaudin PB, Brennan MF. Pathologic features of prognostic significance for adrenocortical carcinoma after curative resection. *Arch Surg* 1999;**134**:181–5.
24. **Stojadinovic A,** Ghossein RA, Hoos A, *et al*. Adrenocortical carcinoma: clinical, morphologic, and molecular characterization. *J Clin Oncol* 2002;**20**:941–50.
25. **Suzuki T,** Sasano H, Nisikawa T, *et al*. Discerning malignancy in human adrenocortical neoplasms: utility of DNA flow cytometry and immunohistochemistry. *Mod Pathol* 1992;**5**:224–31.
26. **Sasano H,** Suzuki T, Moriya T. Recent advances in histopathology and immunohistochemistry of adrenocortical carcinoma. *Endocr Pathol* 2006;**17**:345–54.
27. **Vilar E,** Salazar R, Perez-Garcia J, *et al*. Chemotherapy and role of the proliferation marker Ki-67 in digestive neuroendocrine tumors. *Endocr Relat Cancer* 2007;**14**:221–32.
28. **Terzolo M,** Angeli A, Fassnacht M, *et al*. Adjuvant mitotane treatment for adrenocortical carcinoma. *N Engl J Med* 2007;**356**:2372–80.