How is adrenocortical cancer being managed in the UK?

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ABSTRACT

INTRODUCTION Adrenocortical carcinomas are rare. This case series is reported to give an overview of how adrenocortical carcinoma is currently managed in the UK.

PATIENTS AND METHODS A retrospective review was made of case notes from patients with adrenocortical carcinomas presenting to the authors (TWJL, RDB, BJH, and DS-C) over the past 10 years in Newcastle, Sheffield and Cardiff.

RESULTS Newcastle treated twelve, Sheffield eleven and Cardiff seven cases. The median follow-up was 25.5 months (range, 1–102 months). All tumours were greater than 5 cm in diameter. The majority presented with symptoms of hormone excess. Adrenalectomy was performed in 83% – this was radical in 30% and followed by excision of recurrence in 13%. Adjuvant mitotane was given in 64% of patients, in combination with cytotoxic chemotherapy in 20%. One-third of patients did not receive any adjuvant therapy. There was no significant difference in survival between the three centres. The majority of patients (57%) died during the period of follow-up of this study. The median survival was 37 months (range, 2–102 months).

CONCLUSIONS The size of tumour, stage and mode of presentation, age and overall survival of patients in this study are comparable to published series of adrenocortical carcinomas from major endocrine surgical centres world-wide. Despite controversies about benefits, adjuvant mitotane was used in the majority of cases, whereas cytotoxic chemotherapy was only used in the minority. The exact role of adjuvant therapy in the management of adrenocortical carcinoma is not as well established as for other more common malignancies. Establishing a database for adrenocortical carcinomas in the UK would contribute to our understanding of the management of this disease.

KEYWORDS

Adrenal glands – Adrenal cortex neoplasms – Adrenocortical carcinoma – Mitotane – Surgery – Treatment outcome

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Adrenal cortical cancer (ACC) is a rare tumour with an incidence of 0.5–2 per million/year.¹ It is an aggressive malignancy with a poor prognosis. Five-year survival is reported to be about 30%.² Because of its rarity, single institutions manage only small numbers annually and optimum treatment modalities are less well established than for more common tumours.

Although the majority of ACCs are sporadic of unknown aetiology, they may be associated with rare genetic syndromes such as Beckwith–Wiedemann syndrome (IGFII overexpression), Li–Fraumeni syndrome (p53 mutation) and multiple endocrine neoplasia type 1 (MEN1).³

Pre-operative tissue diagnosis of ACC is not usually possible; therefore, diagnosis relies on a combination of clinical,

biochemical and radiological findings. The majority of ACCs are functioning tumours presenting with Cushing's syndrome, virilisation or feminisation, though the combination of Cushing's syndrome and virilisation is most characteristic. Serum and urinary cortisol, urinary ketosteroids, serum dehydroepiandrosterone sulphate (DHEAS) and sex steroids may be elevated. Due to defective enzyme function in ACC, elevated steroid precursors such as serum DHEAS are a particularly good marker of malignancy.⁴

On computed tomography (CT), ACCs are characteristically large, irregular masses with heterogeneous density showing areas of haemorrhage, calcification and necrosis. High attenuation on unenhanced CT and absence of the rapid enhancement and washout of intravenous contrast help to differentiate ACC from adenomas.⁵ Enhancement on T2-weighted magnetic resonance with chemical shift imaging is also a feature of ACC.⁶ Standard imaging investigations such as CT and magnetic resonance imaging (MRI) have reported sensitivity of 70–80% and specificity of > 90%.^{5,6} PET scan is useful to distinguish benign from malignant adrenal tumours with results from preliminary studies showing high sensitivity (> 95%) and specificity (> 90%).⁷

The pathological distinction between benign and malignant adrenocortical lesions can be difficult. Various scoring systems based on histological criteria have been described to help differentiate ACC from adenoma of which the Weiss criterion is the most widely recognised.^{8,9} Established markers of prognosis are tumour size and stage.¹⁰ There is evidence to support Ki67 and cyclin E expression as tissue immunohistochemical prognostic markers though their exact role is yet to be established.^{11,12}

Surgery is the mainstay of treatment and only hope of cure. The surgical strategy for ACC confined to the adrenal gland, with regional lymph node metastases or with invasion of local organs is complete tumour excision. Radical open surgery excising peri-renal fat, regional lymph nodes and, if necessary, adjacent organs (such as spleen, tail of pancreas and kidney) is often required to achieve clear excision margins. Palliative surgery in metastatic ACC may also have a role in symptom control.¹³ Although laparoscopic adrenalectomy may have a role for potentially malignant adrenal tumours,¹⁴ there are concerns about the incidence of recurrent disease due to incomplete tumour resection or capsular disruption during laparoscopic surgery; most surgeons would, therefore, consider laparoscopy to be contraindicated in ACC.¹⁵

Mitotane, an insecticide which was found to induce necrosis of adrenal cortex,¹⁶ is a lipophilic compound which is concentrated in the adrenal cortex where it causes necrosis by inducing degeneration of mitochondria.¹⁷ Mitotane is used for advanced ACC with one-quarter to one-third of patients showing tumour response.¹⁸ Gastrointestinal and neurological side-effects are common and plasma mitotane

levels need to be monitored during therapy. In order to maximise tumour response and minimise side-effects, a plasma mitotane level of 14–20 mg/l is necessary. Mitotane therapy induces adrenal insufficiency requiring endocrine surveillance and steroid replacement therapy.¹⁹ The role of adjuvant mitotane for ACC is controversial,²⁰ although recent data from a multicentre European study have supported the adjuvant use of mitotane for ACC and highlighted the uncertainties in the management of this rare disease.²¹

Review of the available data from small, retrospective, non-randomised studies of cytotoxic chemotherapy with or without mitotane in advanced ACC has shown a tumour response rate in about one-quarter of patients.¹⁹ However, the optimum chemotherapeutic regimen is unknown. In order to investigate this, the FIRM-ACT trial has been established. This prospective, randomised, European trial is comparing the use of mitotane and streptozotocin with mitotane, cisplatin, etoposide, and doxorubicine for the treatment of advanced ACC.²² Tumour bed irradiation following resection may have a role in reducing local recurrence.²³

Due to the lack of up-to-date published data on this topic, it is pertinent to describe how ACC is currently being managed in the UK. This study reports the presentation and management of 30 patients with ACC referred over the past decade to the co-authors (RDB, TWJL, BJH and DS-C) at three major tertiary endocrine surgical units in the UK (Royal Victoria Infirmary, Newcastle upon Tyne; Royal Hallamshire Hospital, Sheffield; University Hospital of Wales, Cardiff).

Patients and Methods

A retrospective search was made through patient records of all cases of adrenocortical cancer referred to the co-authors at these three institutions over the past decade.

Results

Newcastle contributed twelve, Sheffield eleven and Cardiff seven cases. Length of follow-up varied from 1–102 months. Median length of follow-up was 25.5 months and the mean was 30.4 months. All the tumours were greater than 5 cm diameter. The age at presentation rose in the fourth decade and remained high until seventh decade of life (Fig. 1).

In the cohort, 48% presented with Cushing's syndrome. Of these, 30% had Cushing's syndrome alone and in 18% this was accompanied by virilisation. One case (3%) presented with feminisation and two cases (6%) with pure virilisation. Approximately one-third (34%) presented with abdominal symptoms and in about one in ten (9%) the ACC was an incidental finding (Fig. 2).

Metastatic disease was apparent at diagnosis in one-third (34%), became apparent at operation in 7% and during

follow-up in a further 38%. During the period of follow-up in this study, approximately one in five (21%) did not develop metastatic disease. Adrenalectomy was performed in 83% of patients. This was described as a radical adrenalectomy in 30% and included excision of recurrence in 13%. One in ten patients had only a diagnostic laparoscopy and in 7% no operation was performed (Fig. 3).

Adjuvant therapy was given to two-thirds of these patients. Mitotane was the mainstay of adjuvant therapy, being used in 64%. Chemotherapy was given to 20% in conjunction with mitotane and radiotherapy in addition to mitotane and chemotherapy in 7%. Chemotherapy was the sole adjuvant treatment in one case (Fig. 4).

The majority of patients (57%) died during the period of follow-up of this study and only one in five were alive and disease-free. There was no significant difference in the survival between these three centres; the median survival of the 30 cases was 37 months (range, 2–102 months) and the overall 5-year survival was about 40% (Figs 5 and 6).

Discussion

The size and stage at presentation, the mode of presentation (with functioning tumours accounting for over half of cases), the age at diagnosis, and the overall 5-year survival found in this study are comparable to previous published case series of ACC. This implies that the management and survival from this condition in these three UK centres is comparable to that reported from major endocrine surgical centres world-wide.^{10,24–27}

Adjuvant mitotane following surgery for ACC is used empirically based on its efficacy in advanced ACC although retrospective studies investigating the benefit of adjuvant mitotane have reported conflicting results.²⁸ Despite the high proportion of patients with operable ACC reported in this surgical case series (83% underwent adrenalectomy), mitotane was still used in the majority (64%). This suggests that mitotane is being used commonly as adjuvant therapy in these three centres.

Cytotoxic chemotherapy is reserved for patients with advanced ACC. In this study, 79% of patients developed metastatic disease during the follow-up period yet only 20% received cytotoxic chemotherapy. This suggests a reluctance to use cytotoxic chemotherapy, perhaps due to uncertainty about optimal regimens and tumour response rates. The results of the FIRM-ACT trial should help establish the role of cytotoxic chemotherapy in the management of this condition.

Conclusions

This case series of 30 patients represents a decade's experience of ACC from three major endocrine surgical centres.

Because of its rarity, progress in our understanding of the management of ACC is unlikely to occur unless these tumours are managed in specialist centres and every effort is made to enrol these patients in multicentre prospective trials (such as FIRM-ACT) or collect data on the management and outcome of ACC in national databases. In continental Europe, ACC databases exist such as GANIMED in Germany, COMETE in France, and NISGAT in Italy. A recent publication from these databases has helped to consolidate the role of adjuvant mitotane in the treatment of this disease.²¹ We should be encouraged to establish our own database of ACC in the UK.

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