Invited review

CUTTING EDGE

Diagnosis, treatment and outcome of adrenocortical cancer

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Background: **Adrenocortical cancer (ACC) is a rare disease with a dismal prognosis. The majority of patients are diagnosed with advanced disease and raise difficult management challenges.**

Methods: **All references identified in PubMed, published between 2004 and 2014, using the keywords 'adrenocortical cancer' or 'adrenal surgery' or both, were uploaded into a database. The database was interrogated using keywords specific for each field studied.**

Results: **In all, 2049 publications were identified. There is ongoing debate about the feasibility and oncological outcomes of laparoscopic adrenalectomy for small ACCs, and data derived from institutional case series have failed to provide an evidence level above expert opinion. The use of mitotane (1-(2-chlorophenyl)-1-(4-chlorophenyl)-2,2-dichloroethane) in combination with chemotherapy in the treatment of metastatic disease has been assessed in an international randomized trial (FIRM-ACT trial) involving patients with ACC. Based on this trial, mitotane plus etoposide, doxorubicin and cisplatin is now the established first-line cytotoxic therapy owing to a higher response rate and longer median progression-free survival than achieved with streptozocin–mitotane. For patients with tumours smaller than 5 cm and with no signs of lymph node or distant metastases, survival is favourable with a median exceeding 10 years. However, the overall 5-year survival rate for all patients with ACC is only 30 per cent.**

Conclusion: **Open and potentially laparoscopic adrenalectomy for selected patients is the main treatment for non-metastatic ACC, but the overall 5-year survival rate remains low.**

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Introduction

Adrenocortical carcinoma (ACC) is an exceedingly rare tumour associated with poor survival. It is frequently referred to as an orphan disease, defined as a condition that affects fewer than 200 000 people nationwide in the USA. Patients with ACC have not benefited as much from the progress in oncological treatments developed for other tumours. Even though recent advances in the genetics of the disease are expected to be translated into new drug treatments for ACC in the coming years[1], radical surgical excision remains the only potentially curative treatment.

Methods

This review summarizes data published between January 2004 and May 2014, identified from the PubMed database using keywords 'adrenocortical cancer', 'adrenal surgery' or both. All references in English were uploaded from PubMed into a database created using EndNote® software (Thomson-Reuters, New York, USA) and the database was interrogated using keywords for the specific fields studied. Cross-checks for further publications were made with reviews written by members of the European Society of Endocrine Surgeons (ESES)[2] and the European Society of Medical Oncology[3], and a recent review by Else and colleagues[4].

Search results

For the time period studied, there were 2049 references in the English language.

Demographics

The estimated annual incidence of ACC is 1–2 patients per million individuals. In the USA, the National Cancer Database[5] recorded 4275 patients with ACC from 1985 to 2007, and concerns were raised that a single patient with ACC was seen at 36 per cent of hospitals whereas three or fewer patients were seen at 72 per cent of hospitals. The Netherlands Cancer Registry[6] included 359 patients

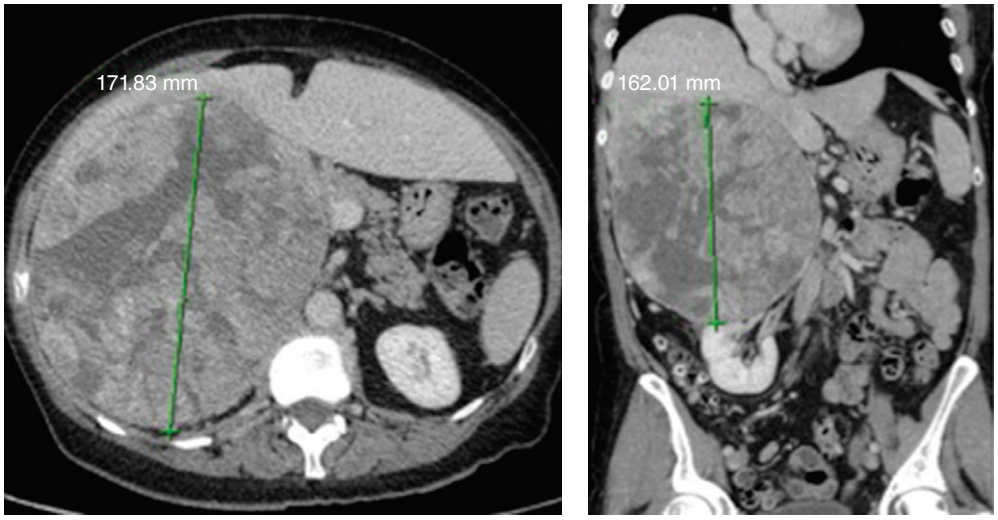


Fig. 1 Appearance of adrenocortical carcinomas on cross-sectional imaging. **a** Transverse and **b** coronal views on CT of a large right adrenocortical tumour in a woman with virilization syndrome

between 1993 and 2010, and demonstrated an increase in the percentage of patients receiving treatment within 6 months after diagnosis, from 76 per cent in 1993–1998 to 88 per cent in 2005–2010. The main reason for this was an increase in surgery for patients with advanced disease. The German ACC registry[7] comprised 492 patients diagnosed between 1986 and 2007, and more recently this was merged with other national registries under the auspices of European Network for the Study of Adrenal Tumours (ENSAT; http://www.ensat.org).

Women appear to be more commonly affected. An analysis of 14 recent publications showed a median female to male ratio of 1·6 (range 0·9–2·6) in a population of 6658 women and 4865 men (*Table S1*, supporting information)[5,6,8–19]; this is similar to the female predominance previously reported for all types of adrenal tumour[20].

Left-sided tumours seem to be more common. Although there is no biological reason to expect a side preference for different types of tumour, an analysis of large series from recent publications confirmed the overall predominance of left-sided tumours (2607 left-sided and 2169 right-sided (*Table S2*, supporting information)[8,12,14,21–24]. It might be that right-sided tumours are less likely to be operated on and are therefore not reported, as they can be associated with liver invasion or invasion of the inferior vena cava (IVC).

Clinical presentation

At the time of presentation, most ACCs are very large, measuring on average 10–15 cm (*Fig. 1*). Despite increasing use of cross-sectional imaging over the past three decades, there has been no decrease in the size of ACC at the time of diagnosis[5], and only a small minority are operated on when smaller than 5 cm. Only two-thirds of patients present with symptoms or signs of excessive hormone secretion, such as rapid onset of hypercortisolism, virilization in women and feminization in men. One-third of patients have large non-secreting tumours and present with symptoms related to the size of the tumour. Paraneoplasic syndromes are rare, the most impressive being tumour-induced hypoglycaemia mediated through excessive secretion of insulin-like growth factor 2.

Because adrenal incidentalomas are present in up to 10 per cent of patients undergoing cross-sectional imaging[25], it is imperative to recognize those with malignant potential. Morphological characteristics of ACC on CT include large size, heterogeneous appearance, lack of a well defined margin, central low attenuation, high density on unenhanced images (more than 10 Houndsfield units), high contrast-washout characteristics and extension into the IVC[26]. The chemical shift on contrast-enhanced MRI can identify the lipid-rich adenomas that have a very low risk of malignancy[27]. The most detailed work demonstrating that size is an important predictor of malignancy was the analysis of 457 patients with ACC recorded in the Surveillance, Epidemiology, and End Results (SEER) database[10]: for tumours smaller than 4 cm, larger than 6 cm, larger than 8 cm and larger than 10 cm, the risk of malignancy increased from 52 per cent to 80,

95 and 98 per cent respectively, and likelihood ratios for tumour size predicting malignancy were 2·0, 4·4, 16·9 and 24·4 respectively. This is the basis of recommending adrenalectomy for non-functional incidentalomas larger than 4 cm.

For tumours smaller than 6 cm, characterization with [^{18}F]fluorodeoxyglucose (FDG) PET–CT has 95 per cent sensitivity and specificity for the diagnosis of ACC[28]. An adrenal-to-liver standardized uptake value (SUV) ratio above 1·6 provides 100 per cent sensitivity and 100 per cent negative predictive value for the diagnosis of ACC[29]. Such findings should be interpreted with caution in patients with a previous diagnosis of malignancy because adrenal metastases also have a high SUV and adrenal-to-liver SUV ratio[17]. Despite good diagnostic accuracy, therapeutic decisions should not be based on FDG-PET uptake values because they have limited prognostic value and do not correlate with survival[30].

A new approach for differentiating adenomas from ACC uses mass spectrometry-based steroid profiling of 24-h urine samples. In a first report[19] comparing 102 adenomas and 45 ACCs, a pattern of predominantly immature, early-stage steroidogenesis was demonstrated in ACC and a subset of nine steroids was found to perform best in identifying patients with ACC. This work is currently being developed further in Eurine-ACT, a pan-European study organized within the ENSAT network.

Imaging with metomidate labelled with ^{123}I (iodometomidate, [^{123}I]IMTO) can diagnose adrenocortical lesions with high specificity. Retention of [^{123}I]IMTO in metastatic lesions can identify patients suitable for specific targeted radioactive treatment. In a prospective study[31] of 58 patients with metastatic ACC, 30 per cent of 430 lesions detected by conventional imaging showed strong, 8 per cent moderate and 62 per cent no tracer accumulation. [^{123}I]IMTO detected primary and metastatic lesions of ACC, with 38 per cent sensitivity and 100 per cent specificity. One-third of patients had radiotracer uptake in all lesions larger than 2 cm[31].

Staging

The ENSAT classification[7] (*Table 1*) is currently used worldwide and has replaced the International Union Against Cancer (UICC) staging classification[32]. This new classification was originally based on 492 patients from the German ACC registry who were followed up for a mean of 36 months[7]. The classification was validated in a North American population-based cohort of 573 patients, and showed higher accuracy in predicting recurrence and survival rates than the UICC classification[33].

Table 1 Staging systems for adrenocortical cancer

	Description
TNM[32]	
T1	≤ 5 cm, no local invasion
T2	> 5 cm, no local invasion
T3	Any size, extension into periadrenal fat
T4	Any size, invasion into neighbouring organs
N1	Metastases into local lymph nodes
M1	Metastatic disease
AJCC/UICC[32]	
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T1–2 N1 M0 or T3 N0 M0
Stage IV	T3 N1 M0 or T4 any N M0 or any T any N M1
ENSAT[7]	
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3–T4 N0 M0 or any T N1 M0
Stage IV	Any T any N M1 (distant metastases)

AJCC, American Joint Committee on Cancer; UICC, International Union Against Cancer; ENSAT, European Network for the Study of Adrenal Tumours.

Genetic mutations and familial syndromes associated with adrenocortical carcinoma

In the past decade, genome-wide expression profile studies, microRNA (miR) profiling and methylation profiling have allowed the identification of subgroups of tumours with distinct genetic markers or molecular pathways related to clinical behaviour[34]. However, this type of analysis is seldom available outside research laboratories and is unlikely to be incorporated into routine clinical decision-making in the immediate future.

Because ACC is a hallmark tumour in families with Li–Fraumeni syndrome caused by mutations in the tumour protein P53 (*TP53*) gene, some advocate *TP53* testing in all patients with ACC regardless of age at diagnosis, or at least in patients whose tumours have aberrant P53 expression[35]. Other authors[36] consider this test justified in all young adults with ACC as one in ten of them might carry such mutations. In a study[37] of 114 patients with confirmed ACC evaluated in the University of Michigan, 94 met with a genetic counsellor and 53 completed *TP53* testing, of whom four (8 per cent) had a *TP53* mutation. None of these patients met the clinical diagnostic criteria for Li–Fraumeni syndrome. For the immediate benefit of a patient with ACC, knowledge of *TP53* polymorphisms predicts overall survival[38] and, for the patient's children and siblings, knowledge of *TP53* status identifies those at risk of developing ACC or other tumours associated with Li–Fraumeni syndrome: soft tissue sarcoma, osteosarcoma, breast cancer, brain tumours and leukaemia.

Role of surgery in the management of adrenocortical carcinoma

Complete tumour resection is the only curative treatment for ACC. Open adrenalectomy has been advocated to ensure local control of the disease. Some experienced surgeons have proposed a laparoscopic approach as a valuable alternative, even for large tumours with malignant potential. This remains a controversial issue because operating on tumours with a diameter over 6–8 cm creates significant technical challenges in not breaching the tumour capsule and fracturing the tumour. Outcomes reported from large units might not be easy to for the 'occasional' adrenal surgeon to match.

This debate feeds into the ongoing effort to centralize surgery for suspected and confirmed ACC in specialized centres[39]. The national audit maintained by the British Association of Endocrine and Thyroid Surgeons (BAETS)[24] recorded only 81 adrenalectomies for ACC during 2005–2012 among over 1700 adrenalectomies performed in the same interval. Based on the estimated incidence of ACC, it was predicted that over 500 patients should have been diagnosed during this time interval. Further proof of a lack of centralization of care of patients with ACC in UK is shown by the publication of the joint experience of managing 30 patients with ACC over a decade at three large centres for endocrine surgery[40]. The number of patients in this report reinforces the hypothesis that most patients with ACC remain unknown to those with an expressed interest and confirmed expertise in the management of this condition. Several studies have demonstrated that patients operated on in a referral centre have better outcomes. For example, disease-free survival was superior in patients who underwent primary resection at the MD Anderson Cancer Center, USA, compared with patients operated on outside this institution, with a median survival of 25 *versus* 12 months, and also better overall survival (median not reached *versus* 44 months)[41]. Similar data from the Netherlands showed that patients operated on in a Dutch Adrenal Network centre had significantly longer overall survival[42].

In the past few years many authors have addressed the question of whether laparoscopic adrenalectomy is acceptable for the surgical treatment of ACC. A systematic review[43] of 23 publications described 673 patients with localized ACC, of whom 112 had laparoscopic surgery. For tumours smaller than 10 cm in size without evidence of invasiveness, laparoscopic adrenalectomy did not seem to be oncologically inferior to open surgery when the operation was performed in a specialized centre. The main recommendation was that open adrenalectomy should still be regarded as standard treatment for ACC and that laparoscopic surgery should be performed within a clinical trial[43].

The published literature was also reviewed at the ESES 2012 symposium. In the absence of any randomized trial there was only qualitative evidence and the data were summarized as follows[44]. The comparison of oncological outcomes remains equivocal as there is an increased risk of local recurrence and peritoneal carcinomatosis when surgery is carried out by the laparoscopic route, although survival and recurrence rates appear to be similar. The conclusion was that laparoscopic resection may be performed in patients with stage I–II ACCs with a diameter smaller than 10 cm, with the aim of including removal of surrounding periadrenal fat to achieve R0 resection without tumour capsule rupture. Most recent publications continue to be divided on whether or not laparoscopic adrenalectomy provides equivalent oncological outcomes, at least for smaller tumours without local invasion (*Table 2*)[13,14,16,18,45–48].

Lymph node dissection (LND) has yet to become a formal component of radical adrenalectomy. Because the lymphatic drainage of the adrenal gland includes the renal hilum lymph nodes, and the para-aortic and paracaval lymph nodes, it is expected that many of these lymph nodes are included when *en bloc* resection of the ACC is performed to include the kidney, perinephric fat and Gerota's fascia.

Some authors have reported that lymph node involvement occurs in about 20 per cent of patients with ACC and is an important prognostic factor[49]. The topic has come under more intense debate following a report based on the retrospective review of medical records of patients followed by the German ACC registry[50]. A formal LND was assumed to have been performed if the histological analysis recorded five or more lymph nodes. Of 283 included patients, only 47 (16·6 per cent) appeared to have had LND and these patients were more often treated by multivisceral resection (48 per cent LND *versus* 18 per cent no LND). Multivariable analysis demonstrated a reduced risk of tumour recurrence (hazard ratio (HR) 0·65, 95 per cent c.i. 0·43 to 0·98) and disease-related death (HR 0·54, 0·29 to 0·99; $P = 0·049$) in patients with LND compared with those without LND. The authors concluded that LND improves tumour staging and leads to a favourable oncological outcome[50]. The methodology used in this study prevents determination of how many of the LNDs were intentional and in how many operations the surgeon failed to retrieve five or more lymph nodes. A further analysis[51] of 320 patients with stage III–IV disease registered in the SEER database showed that LND was performed in 26 per cent of patients with ACC, and was associated with improved survival in univariable analysis of patients with stage IV tumours.

Table 2 Outcome of laparoscopic and open adrenalectomy for adrenocortical cancer

Reference	Study group	No. of patients	Median follow-up (months)	Results
OA was superior to LA				
Miller *et al.*[13]	Single institution (2005–2011) 217 patients overall 156 patients with stage I–III cancer	46 LA 110 OA	27	Positive margins or intraoperative tumour spill for 30% of LAs and 16% of OAs. Time to visible tumour bed recurrence or peritoneal recurrence in patients with stage II disease shorter after LA. Overall survival for patients with stage II cancer longer after OA
Mir *et al.*[45]	Single institution (1993–2011) 44 patients	18 LA 26 OA	22	2-year recurrence-free better for OA (60 *versus* 39%; $P = 0{\cdot}7$), but overall survival similar (54 *versus* 58%; $P = 0{\cdot}6$). OA associated with lower risk of recurrence (HR 0·4, 95% c.i. 0·2 to 1·2; $P = 0{\cdot}099$) and improved overall survival (HR 0·5, 0·2 to 1·2; $P = 0{\cdot}122$)
Cooper *et al.*[14]	Patient review at single institution (1993–2012) 402 patients 46 LA at an outside institution 210 OA at an outside institution 46 OA at referring institution	46 LA 256 OA		Despite smaller tumour size, patients who had LA developed peritoneal carcinomatosis more frequently than those treated with OA. After controlling for tumour stage, OA had superior recurrence-free and overall survival
Leboulleux *et al.*[18]	Institutional practice (2003–2009) Stage I 2 Stage II 32 Stage III 7 Stage IV 21 Unknown stage 2	6 LA 58 OA		4-year rate of peritoneal carcinomatosis 67 (95% c.i. 30 to 90)% for LA and 27 (15 to 44)% for OA ($P = 0{\cdot}016$)
OA and LA had comparable outcomes in selected patients				
Porpiglia *et al.*[46]	43 patients with stage I and II ACC	18 LA 25 OA	30 LA 38 OA	Recurrence rate 64% after OA and 50% after LA. Median recurrence-free survival 18 months after OA and 23 months after LA ($P = 0{\cdot}8$). During follow-up, 28% in OA group and 5% in LA group died. No difference in survival time ($P = 0{\cdot}3$)
Miller *et al.*[47]	Retrospective review (2003–2008)	17 LA 71 OA	37	Recurrent disease in 63% after LA and 65% after OA. Mean(s.d.) time to first recurrence 9·6(14) months after LA and 19·2(37·5) months after OA ($P < 0{\cdot}005$). Positive margins or intraoperative tumour spill in 50% of LAs and 18% of OAs. Local recurrence in 25% of LA and 20% of OA group ($P = 0{\cdot}23$).
Lombardi *et al.*[16]	Italian multi-institutional surgical survey 156 patients (stage I/II) who had R0 resection	30 LA 126 OA		Local recurrence rate 19% for OA and 21% for LA. Distant metastases recorded in 31% after OA and 17% after LA (*P* not significant). Mean(s.d.) time to recurrence 27(27) months after OA and 29(33) months after LA (*P* not significant). No significant differences in 5-year disease-free survival between LA and OA (38·3 *versus* 58·2%) and 5-year overall survival (48 *versus* 67%).
Brix *et al.*[23]	Retrospective analysis of patients registered with German ACC registry 152 patients with stage I–III ACC < 10 cm	35 LA 117 OA		No difference between LA and OA in disease-specific survival. No difference in adjusted recurrence-free survival (HR 0·91, 0·56 to 1·47; $P = 0{\cdot}69$). Frequency of tumour capsule violation and peritoneal carcinomatosis comparable between groups
Donatini *et al.*[48]	Single institution 34 patients with stage I/II ACC < 10 cm	13 LA 21 OA	66(52) LA* 51(43) OA*	Disease-specific and disease-free survival identical in both groups

*Values are mean(s.d.). OA, open adrenalectomy; LA, laparoscopic adrenalectomy; HR, hazard ratio; R0, complete resection with no microscopic residual tumor; ACC, adrenocortical carcinoma.

Patients with locally advanced disease treated without surgery have poor survival. In a cohort of 320 patients registered in the SEER database[51] the 1-year survival rate for stage III was only 13 per cent if not operated and 77 per cent after surgical treatment. For stage IV disease these figures were 16 and 54 per cent respectively. In this context there are three separate issues to be addressed: the extent of the initial surgery for locally invasive tumours, the surgical treatment of local recurrence and the operative management of metastatic disease.

The radical surgical approach to locally invasive tumours should include a multivisceral resection. Such *en bloc* resections are done to prevent breaching of the tumour capsule with control of the large vessels, even though direct invasion into adjacent organs is rare. There are no published data demonstrating improved survival or lower local recurrence rates, but multivisceral resection allows safer vascular control and potentially complete venous tumour thrombus resection that could improve long-term disease-free survival[49].

Involvement of the IVC is a major challenge for surgical treatment of ACC. A first report[52] from Cochin Hospital, Paris, was based on 15 patients, in whom the upper limit of extension was the intrahepatic IVC in two patients, retrohepatic IVC in six, and suprahepatic IVC in seven patients, including four with extension into the right atrium. The operative technique was thrombectomy (13 patients), partial resection with direct closure (1) and total resection with replacement of the IVC (1). Median survival time was 8 months. Three patients were still alive after 24, 25 and 45 months of follow-up, one of whom was reoperated on for local recurrence at 17 months.

A subsequent publication[53] from New York reported the outcome of 57 patients undergoing resection with curative intent for ACC, and for whom large-vessel extension was defined as vascular wall invasion or intraluminal extension of the neoplasm into the IVC or renal vein. Compared with those without large-vessel extension, patients with such extension had a higher rate of tumour-positive surgical margins, shorter median overall survival (18 *versus* 111 months) and shorter median recurrence-free survival (11 *versus* 64 months).

A survey of members of ESES[54] received replies from 18 centres in nine countries and reported the outcome of 38 patients with ACC invading the IVC. Open adrenalectomy was associated with resection of surrounding viscera in 24 patients. Complete resection (R0) was achieved in 20 patients, seven patients had persistent microscopic disease (R1) and four had macroscopic residual disease (R2). Five patients died within 30 days, 25 died after a median 5 (range 2–61) months after surgery and 13 patients were alive at median of 16 (2–58) months, seven with metastatic disease and six with no signs of distant disease.

Some ACCs may have characteristics at presentation that argue against immediate surgery because of an unacceptable risk of morbidity or death, incomplete resection or recurrence. A recent publication[55] from MD Anderson Cancer Center introduced the concept of 'borderline resectable adrenal tumours'. The authors compared 38 patients with ACC considered for immediate surgery with 15 patients who had borderline resectable ACC and received neoadjuvant therapy (mitotane and etoposide or cisplatin-based chemotherapy). Thirteen patients with borderline resectable ACC underwent surgical resection, of whom five had a partial response, seven had stable disease and one had progressive disease. Median disease-free survival for patients with borderline resectable ACC was 28 months, compared with 13 months for those who had initial surgery. Five-year overall survival rates were similar at 65 and 50 per cent respectively.

Histological assessment of adrenocortical carcinoma

The Weiss scoring system remains the standard for differentiating adrenocortical adenomas from ACC. This score is based on the assessment at light microscopy of nine morphological parameters (*Table 3*); a score of less than 3 defines benign adenomas, a score greater than 6 is associated with ACC, and a score of 3–6 raises suspicion of malignancy[56]. There are, however, significant limitations as the score is observer-dependent, has low reproducibility, and its diagnostic applicability is low among non-expert pathologists. In an attempt to mitigate some of these limitations, a programme was initiated to improve the reproducibility of pathological diagnosis of ACCs in France. For the Weiss score separating malignant (score 3 or higher) from benign (2 or lower) tumours, interobserver reproducibility increased from the first to the second reading. With increased experience, the pathologists involved reached an improved sensitivity for the diagnosis of ACCs from 86 to 95 per cent[57].

In addition to the Weiss score, a diagnostic algorithm has been proposed based on the observation that the tumoral reticulin framework is consistently disrupted in malignant tumours, but only in a small subset of benign tumours. This score has not been adopted or validated in large cohorts of patients[58].

Prognostic markers

The Ki-67 proliferation index is the best predictor of malignant behaviour, with a value of more than 10 per cent

Table 3 Weiss score

	Comments
Nuclear grade	Grade 3 or 4 according to the Fuhrman criteria[115]
Mitotic rate	> 5 per 50 HPFs (×40 objective, counting the greatest numbers of mitotic figures in areas with greatest number of mitoses)
Atypical mitotic figures	Abnormal distribution of chromosomes, excessive number of mitotic spindles
Cytoplasm	Presence of clear or vacuolated cells resembling normal zona fasciculata
Diffuse architecture	Over one-third of the tumour forms patternless sheets of cells; trabecular, columnar, alveolar or nesting patterns are regarded as non-diffuse
Necrosis	
Venous invasion	Tumour cells within endothelium-lined vessel, with smooth muscle as a component of the wall
Sinusoid invasion	Tumour cells within endothelium-lined vessel in adrenal gland with little supportive tissue
Invasion of tumour capsule	

Nine parameters are assessed on haematoxylin and eosin-stained sections from representative areas of the tumour. Each parameter is scored zero when absent and 1 when present in the tumour. HPF, high-power field.

being associated with shorter disease-free survival. Factors associated with decreased survival or poor outcomes include high steroidogenic factor 1 expression and mitotic index[59], somatic mutations of the tumour suppressor gene *TP53* and loss of retinoblastoma protein expression[60].

A nomogram predicting cancer-specific and all-cause mortality was developed in 205 patients with ACC using three variables (age, stage and surgical status), and provided 72–80 per cent accuracy for prediction of cancer-specific or all-cause mortality at 1–5 years[61]. A prognostic score with five co-variables (hormone status other than isolated hyperandrogenism, tumour size larger than 75 mm, primary tumour classified as T3/T4, presence of microscopic venous invasion and a mitotic index of more than 5 per 50 high-power fields) has also been proposed for estimating the risk of metastasis and recurrence[62]. To date, neither of these prognostic models has been reproduced or tested by any other research group.

In contrast to this potentially widely applicable risk stratification, some laboratories have reported that specific biological markers could be used to identify patients with poor prognosis, including tumour overexpression of pituitary tumour transforming gene 1 (*PTTG*), which encodes securin, a negative regulator of P53[63], low expression of the transforming growth factor β signalling mediator SMAD3 and diminished expression of GATA-6 (a member of a family of transcription factors)[64], high circulating levels of miR-483-5p and low circulating levels of miR-195[65,66], or high expression level of miR-503, miR-1202 and miR-1275[67].

Adjuvant mitotane treatment

Mitotane is the first-line treatment for metastatic ACC and is also used regularly in the adjuvant setting. Mitotane is an adrenolytic substance that acts through an apoptotic process activated by the disruption of mitochondria[68]. The drug is also an inhibitor of steroidogenesis. Cytochrome P450-3A4 induction by mitotane results in rapid inactivation of more than 50 per cent of administered hydrocortisone. Strong inhibition of 5α-reductase activity leads to relative inefficiency of testosterone replacement in mitotane-treated men[69]. Its prolonged inducing effect on CYP3A4 activity results in clinical interactions with multiple drugs metabolized by this enzyme, such as macrolide antibiotics, simvastatin and sunitinib[70].

The aim of mitotane therapy is to reach the target concentration of 14 mg/l. In a single-centre prospective study[71] of 21 patients treated with a high-dose mitotane strategy (4 g/day or more) the therapeutic threshold of 14 mg/l was reached within 1 month in 27 per cent. This target concentration has been shown to be beneficial in some studies. In a retrospective analysis[72] of 122 patients from six European referral centres the threshold of 14 mg/l was reached and maintained in 63 patients during a median follow-up of 36 months; these patients had a lower recurrence rate (35 *versus* 61 per cent) and prolonged recurrence-free survival (HR 0·4, 95 per cent c.i. 0·22 to 0·79) compared with 59 patients who did not reach the target mitotane concentration.

The acceptance of mitotane as an adjuvant treatment, rather than being restricted to metastatic disease, was based on favourable data published by several groups. A retrospective evaluation[41] of 218 patients followed at a single institution after surgery for ACC identified the lack of adjuvant mitotane treatment as a significant risk factor for recurrence on multivariable analysis, with HR 1·95. The selection of patients for adjuvant mitotane treatment is limited by the ability to diagnose ACC in patients without metastatic disease. This issue is currently being addressed by the ADIUVIO trial, a multicentre randomized trial that is recruiting patients with a low to intermediate risk of recurrence, and comparing adjuvant mitotane with observation alone (http://www.adiuvo-trial.org)[73].

Postoperative radiotherapy

A systematic review[74] in 2009 identified only ten articles that covered radiotherapy in a total of 129 patients with

ACC: 64 patients received postoperative irradiation and 65 had palliative therapy for advanced disease. In an adjuvant setting, postoperative radiotherapy was able to prevent local recurrence in the majority of patients. Among those with advanced disease, a response to radiotherapy was observed in 57 per cent of patients. Based on these data, recommendations were made to consider adjuvant radiotherapy to the tumour bed in patients at high risk of local recurrence (for example after R1 resection), and radiotherapy in a palliative setting may be used to treat symptomatic metastases to bone, brain or vena cava obstruction[74].

Subsequent data in favour of adjuvant radiotherapy, in a study[75] from the University of Michigan, was based on the analysis of 58 patients with ACC who underwent a total of 64 therapeutic episodes, in which 38 had surgery alone, ten had surgery plus adjuvant radiotherapy, and 16 received definitive radiotherapy for unresectable disease. Lack of radiotherapy was associated with 4·7 times the risk of local failure compared with treatment regimens that involved radiotherapy. In contrast, a retrospective cohort study from the MD Anderson Cancer Center[76] showed discouraging results. Local recurrence was not affected by adjuvant radiotherapy and the 5-year local recurrence-free rate was similar to that in the no-radiotherapy group (53 *versus* 67 per cent).

The role of palliative radiotherapy for control of local symptoms and prevention of complications from large metastases remains undisputed[77]. Despite these results, the use of radiotherapy remains limited. In an analysis of data from the Dutch ACC registry (1990–2008)[78], only 13 of 159 patients had radiation therapy, of whom six received irradiation for the palliation of painful bone metastases and four for unresectable tumour recurrence or metastases.

Treatment of recurrent and metastatic disease

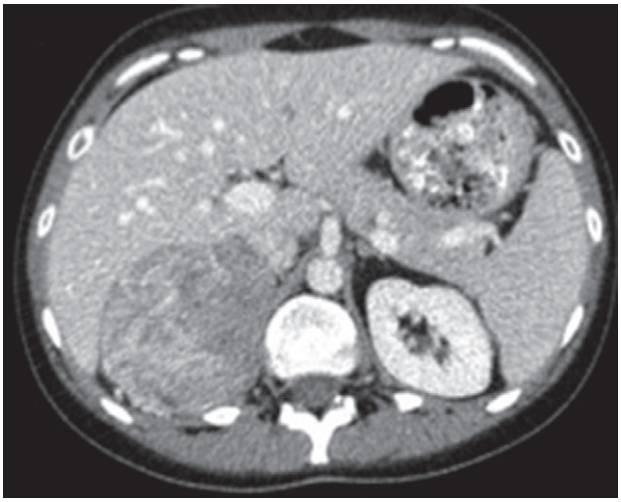
In 1999, a study[79] reported a median survival of 74 months, with a 5-year survival rate of 57 per cent, in patients undergoing complete second resections for recurrent disease, compared with 16 months and zero respectively in those who had incomplete second resection (discussed by Else and colleagues[4]). In a retrospective analysis from the German ACC registry[80] of 154 patients with first recurrence after initial radical resection, 101 underwent repeat surgery, with radical resection in 78; 99 patients received additional non-surgical therapy. After a median of 6 (range 1–221) months, 144 patients experienced progression. The best predictors of prolonged survival after first recurrence were time to first recurrence over 12 months and R0 resection. These data suggest that radical reoperation should be offered to patients with delayed recurrence.

Surgeons at the Mayo Clinic[81] reported recurrence in 93 of 125 patients who had an initial R0 resection. The median time to recurrence was 15 (range 2–150) months. Of the 67 patients who underwent reoperation for recurrence, 48 had R0 resection. Median survival was 179 days for those who had no therapy, 226 days for patients managed without surgery and 1272 days for those who had debulking surgery. Radical resection (R0) for recurrence and a disease-free interval longer than 6 months were associated with survival after operation. Based on these data, patients with recurrent ACC may benefit from operative intervention, with improvement in survival and symptoms.

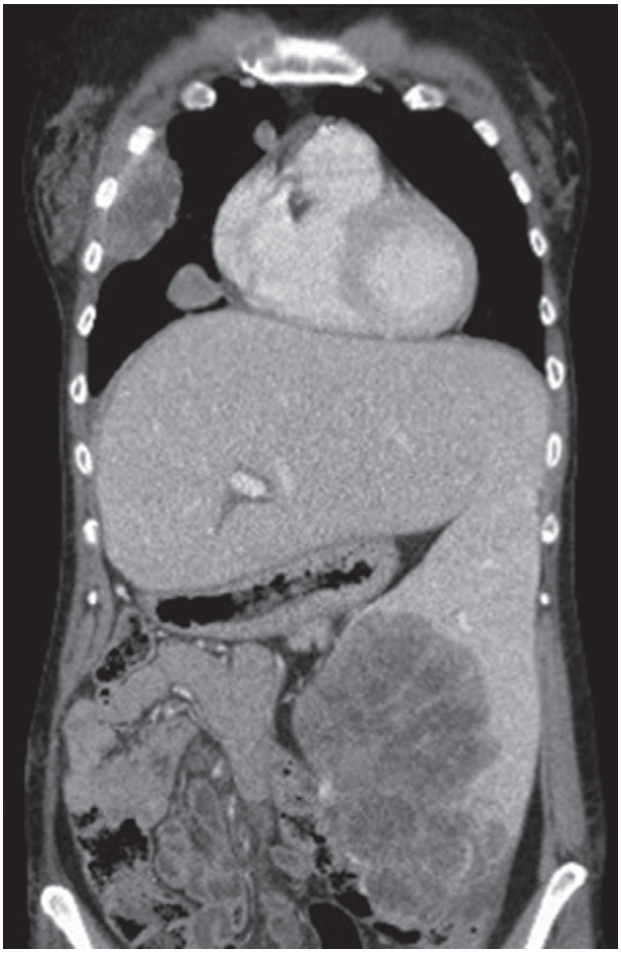
Mitotane monotherapy is indicated in the management of patients with metastatic disease with a low tumour burden or more indolent disease, whereas patients with aggressive disease need cytotoxic chemotherapy[82]. The aim of mitotane treatment is to reach a therapeutic concentration between 14 and 20 mg/l. This can be achieved after a median of 7 weeks when using a high-dose loading regimen[83]. Occasional patients have a significant clinical response despite never achieving the 14-mg/l threshold and many patients show disease progression despite maintaining appropriate levels for many months.

The FIRM-ACT trial (the first international randomized trial for adrenocortical cancer treatment)[84] randomly assigned 304 patients with advanced ACC to receive mitotane plus either a combination of etoposide, doxorubicin and cisplatin (EDP) every 4 weeks or streptozocin every 3 weeks. The primary endpoint was overall survival. For first-line therapy, patients in the EDP–mitotane group had a significantly higher response rate than those in the streptozocin–mitotane group (23 *versus* 9 per cent) and longer median progression-free survival (5·0 *versus* 2·1 months; HR 0·55, 95 per cent c.i. 0·43 to 0·69), but there was no difference in overall survival (14·8 *versus* 12·0 months). Among the 185 patients who received the alternative regimen as second-line therapy, the median duration of progression-free survival was 5·6 months in the EDP–mitotane group and 2·2 months in the streptozocin–mitotane group. Patients who did not receive the alternative second-line therapy had better overall survival with first-line EDP–mitotane than with streptozocin–mitotane (17·1 *versus* 4·7 months).

Based on the FIRM-ACT trial, mitotane plus EDP is now the established first-line cytotoxic therapy. However, most patients experience disease progression and will require salvage therapies. There are ongoing international efforts, including comprehensive 'omic' approaches, to improve understanding of the pathogenesis and develop better therapies[85].



a Primary disease



b Metastatic disease

The therapeutic potential of metomidate ([^{131}I]IMTO) has been assessed only in a preliminary study[86] of ten patients; only four had disease progression and median progression-free survival in the others was 14 months. Based on these data, a prospective trial[31] is being conducted to determine whether therapy using [^{131}I]IMTO will be of value to patients with metastatic ACC.

A number of drugs developed for other malignant diseases have been assessed as potential therapies for ACC, but the results to date have been disappointing (*Table S3*, supporting information)[87–97].

A common theme to recent advances in the treatment of malignant disease is a personalized approach based on genetic mutations. This approach was attempted for ACC by using hotspot gene sequencing and comparative genomic hybridization in adult stage III–IV ACC to screen for mutations and copy number abnormalities of potential interest for therapeutic use. No simple targetable molecular event emerged, although it appeared that drugs targeting the cell cycle and inhibitors of the fibroblast growth factor receptor pathway could be the most relevant therapeutic approach for advanced ACC[98]. A different approach was used at the National Cancer Institute[99]. A quantitative high-throughput proliferation assay of 2816 clinically approved drugs was performed in the NCI-H295R ACC cell line, which validated the antineoplastic effect of bortezomib, ouabain, methotrexate and pyrimethamine. This work has yet to be translated in clinical trials.

Surgery for metastatic disease

Radical surgery for metastatic disease is seldom reported as the number of such patients referred for surgery in each centre remains low (*Fig. 2*). In a retrospective cohort study[100] of 124 consecutive patients with metastatic ACC from the Gustave–Roussy Institute and Cochin Hospital, Paris, the presence of hepatic and bone metastases, number of metastatic lesions, number of organs that were the site of metastasis, a high mitotic rate (more than 20 per 50 high-power fields) and atypical mitoses in the primary tumour were predictors of survival. Similarly, a report from the National Cancer Institute[101] included

Fig. 2 Cross-sectional imaging of a patient with sequential resection of primary tumours and metastatic disease. **a** Right adrenocortical cancer associated with severe Cushing's syndrome; *en bloc* excision of the adrenal tumour, right kidney and tumour thrombus in the inferior vena cava was performed. **b** CT image 3 years after the initial operation in the same patient, when extensive metastatic disease affecting the spleen, pleura and right lung was demonstrated. There was no local recurrence of tumour

over 100 procedures in 57 patients over three decades (1977–2009); there were 23 resections for liver metastases, 48 for pulmonary metastases, 22 for abdominal disease including local recurrences, and 13 for metastases at other sites. Median and 5-year survival rate from time of first metastasectomy were 2·5 years and 41 per cent respectively. Patients with a disease-free interval of more than 1 year had better survival (median 6·6 *versus* 1·7 years).

Surgery for liver metastases from ACC is rarely considered. A review[102] published in 2006 identified only 48 reports, with complete clinical data available for analysis in only nine patients. Based on this limited information, the impression was that metachronous metastases that developed after a minimum of 1 year following resection of the primary tumour, and were completely removable, may represent an indication for surgery. A series from the US National Cancer Institute[103] reported only 19 liver resections from 1979 to 2009. Of the 19 patients, 13 had synchronous extrahepatic disease. The status 'disease in the liver only' was reached in 18 of 19 patients after surgery, and in six of 17 patients after a median follow-up of 6 years. A disease-free interval greater than 9 months after primary resection was associated with longer survival (median 4 *versus* 1 year). The median overall survival (1·9 years) and 5-year survival rate (29 per cent) were encouraging.

Similar outcomes were reported from Memorial Sloan–Kettering Cancer Center[104] in 28 patients with liver metastases who had surgery between 1978 and 2009. The median disease-free and overall survival after hepatectomy were 7 and 32 months respectively, with a 5-year survival rate of 39 per cent. Even though it is rarely curative, liver resection appears to be justified if can be done with minimal morbidity.

Pulmonary metastasectomy for primary ACC, recorded in the German national registry over two decades (1989–2009)[105], was performed in only 24 patients who had a total of 56 pulmonary metastasectomies. The 5-year survival rate was 25 per cent, with median survival of 50 months. Age younger than 41 years at the time of first pulmonary metastasectomy was associated with improved survival. The data also showed that recurrence of pulmonary metastases should not preclude repeated surgical resection of these lesions.

Similar results were reported from US National Cancer Institute[106], following analysis of 26 patients who underwent 60 pulmonary metastasectomies over three decades (1979–2010). After resection of a median of six metastases, 23 patients were rendered free from disease in the lung and 14 became completely disease-free. Median overall and 5-year actuarial survival from initial pulmonary metastasectomy were 40 months and 41 per cent respectively. Time to first recurrence after adrenalectomy and T category of the primary tumour were associated with increased overall survival after pulmonary metastasectomy.

The most recent publication[107] on this topic summarizes the experience of the Mayo Clinic and MD Anderson Cancer Center over a decade (2000–2012). Synchronous resection of the primary ACC and metastatic disease was performed in 27 patients with lung (19 patients), liver (11) and brain (1) metastases. Complete resection (R0) was achieved in 11 patients. Median overall survival was improved in patients with R0 resection compared with those who had R2 resection (860 *versus* 390 days). Patients undergoing neoadjuvant therapy had a trend towards better survival than those who had no neoadjuvant therapy. Adjuvant therapy was associated with improved recurrence-free survival at 6 months and 1 year, but not improved overall survival. The authors emphasized that the response to neoadjuvant chemotherapy may be of use in defining which patients may benefit from surgical intervention.

Survival rate

ACC remains a disease with a dismal prognosis. For the very few patients with stage I disease (tumours 5 cm or smaller with no sign of lymph node or distant metastases), median survival is in excess of 10 years, but those with stage IV disease (distant metastases) are unlikely to survive more than 1 year after the initial diagnosis. Recent survival estimates are summarized in *Table 4*[5,6,8,12,15,22,51,108–110].

Adrenocortical carcinoma in children – a different disease?

The SEER database[111] registered only 85 patients under the age of 20 years between 1973 and 2008, suggesting an annual incidence of 0·21 per million. Patients younger than 4 years appeared to have more favourable features than older patients, and better 5-year survival (91·1 *versus* 29·8 per cent).

Most ACCs in childhood are sporadic, but they can be a manifestation of Beckwith–Wiedemann and Li–Fraumeni syndromes. There is therefore a need to consider paediatric ACC as a useful sentinel cancer for initiating a germline *TP53* detection programme[112].

In an analysis[113] of 29 children treated at Great Ormond Street Hospital, London, between 1987 and 2011 there was a strong association between high Weiss score and large tumour size and adverse outcome, suggesting that the same histological criteria can be used as in adult ACC. In very young children aged less than 3 years, however, a discrepancy between adverse pathological features and a positive

Table 4 Survival data for patients with adrenocortical carcinoma reported in recent publications

Reference	Centre or data source	Study interval	No. of patients	Median survival	Comments
Canter *et al.*[108]	National Cancer Database	1985–2000	2248		Clinically insignificant relationship between tumour size and advanced disease at presentation
Bilimoria *et al.*[8]	National Cancer Database	1985–2005	3982	32 months	Overall 5-year survival rate 38·6% for all patients who underwent resection. Higher risk of death with increasing age, poorly differentiated tumours, involved margins, and nodal or distant metastases. Overall survival unchanged from 1985 to 2000
Kutikov *et al.*[5]	National Cancer Database	1985–2007	4275	24 months	No stage migration. No statistical trends in tumour size changes over the years in patients who underwent surgery for localized disease. No shift toward lower stage or smaller tumour size. No improvement in 5-year survival during study period
Else *et al.*[109]	Ann Arbor, USA		391	35 months	Cortisol production, stage III tumour and tumour grade were negative prognostic factors. Improved overall survival with open adrenalectomy
Ayala-Ramirez *et al.*[12]	MD Anderson Cancer Center, Texas, USA	1998–2011	330	38 months Stage I 24 years Stage II 6 years Stage III 3·5 years Stage IV 0·9 years	Older age, functioning tumours, higher disease stage and incomplete resections associated with poor survival
Kerkhofs *et al.*[6]	Netherlands Cancer Registry	1993–2010	359	Stage I–II 159 months Stage III 26 months Stage IV 5 months	Percentage receiving treatment within 6 months after diagnosis increased from 76% in 1993–1998 to 88% in 2005–2010 ($P = 0·047$), mainly owing to an increase in surgery for stage III–IV tumours. No improvement in survival, as reflected by lack of association between survival and time of diagnosis
Kerkhofs *et al.*[110]	Netherlands Cancer Registry	1999–2009	189	Stage I–III 5-year survival 63%	Median survival of patients with stage I–III disease significantly longer for 46 patients operated on in a DAN hospital than for 37 operated on in a non-DAN hospital
Fassnacht *et al.*[15]	German ACC registry		149 with stage II	5-year survival 96%	Recurrence rate lower (30 *versus* 74%; $P < 0·01$) and 5-year survival rate better (96 *versus* 55%; $P < 0·05$) for 30 patients followed up prospectively compared with 119 in the retrospective group. Adjuvant mitotane associated with improved survival (HR 0·35, 95% c.i. 0·13 to 0·97; $P = 0·04$)
Lombardi *et al.*[22]	Multi-institution Italian cohort		263	Mean time to recurrence 25 months	Lower local recurrence rate (6 *versus* 19%) and longer mean time to recurrence (25 *versus* 10 months) in 172 patients who underwent adrenalectomy at high-volume centre (≥ 10 patients) compared with 91 at low-volume centres (< 10 patients)
Tran *et al.*[51]	SEERS database	1988–2009	320	1-year survival Stage III 77% Stage IV 54% 5-year survival Stage III 40% Stage IV 28%	Poor survival at 1 year without surgery for patients with stage III (13%) and stage IV (16%) disease

DAN, Dutch Adrenal Network; ACC, adrenocortical carcinoma; HR, hazard ratio; SEERS, Surveillance, Epidemiology, and End Results.

clinical outcome was observed, suggesting that adrenocortical tumours in this age group should be classified as neoplasms of unknown malignant potential[114].

Discussion

This review aimed to present the current topics of interest related to the management of patients with ACC. Most published data are based on retrospective reviews of practice in institutions that attract enough patients for meaningful information to be generated. Most case series cover a long time interval, in which it is likely that surgical practice varied significantly. The outcome in the majority of patients, who are likely to have been operated on in centres with minimal experience in the treatment of ACC, remains unknown. The surgical community in Europe will have the opportunity to contribute to future studies through EUROCRINE®, a newly developed pan-European registry for rare endocrine tumours (http://www.eurocrine.eu), whose launch in 2015 will provide the infrastructure for comprehensive data collection for patients with ACC operated on across several EU countries.

It is unlikely that the role of surgery as a single treatment option with potential for cure will be challenged in the next decade. In this context, the surgical community will have to debate many ongoing questions. Should surgery for ACC be centralized and what defines an expert centre? Is the outcome of laparoscopic surgery comparable to that after open surgery in patients with stage I–II ACC? Is LND required in all patients with suspected or proven ACC? Is surgery of the primary tumour or debulking surgery of benefit in patients with non-secreting metastatic ACC? Many of these questions are currently being addressed by a joint group established as a collaboration between ESES and ENSAT, with the aim of ensuring a less heterogeneous approach to the operative management of ACC.

Disclosure

The author declares no conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Predominance of adrenocortical carcinoma in women (Word document)

Table S2 Predominance of left-sided tumours as determined in seven recent publications (Word document)

Table S3 Drugs being evaluated as potential treatments for advanced adrenocortical carcinoma (Word document)