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Adrenocortical carcinoma: modern management and evolving treatment strategies

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Abstract

Adrenocortical carcinoma (ACC) is a rare cancer with a poor prognosis. Unlike many other cancers, there has been little improvement in patient outcome over the past several decades. However, as scientific advancements are made and our understanding of the molecular genetics involved in ACC improve then progress may be achieved in this devastating disease. This review focuses on recent literature published in the field of ACC from 2010 to 2015 with an emphasis on improving diagnosis, staging and treatment for ACC.

Keywords

ACC; adrenal cancer; adrenal surgery; adrenocortical carcinoma; Ki-67; Mitotane; Weiss score

Background

Adrenocortical carcinoma (ACC) is a rare neoplasm characterized by an aggressive course and an overall poor prognosis [1]. Most patients present at an advanced stage, and median survival is less than 12 months, even after complete tumor resection [2,3]. Given the infrequency of its diagnosis and lack of centralized reporting in most countries with modern healthcare systems, the literature is based on sparse data when compared with more common cancers. As such, the benefit for patients with ACC has not been equal with advances in more common cancers [4]. Limited chemotherapeutic options, limited chemotherapeutic efficacy [5] and the perception of limited efficacy and safety of radiation therapy compound the difficulty in treating patients with ACC [6].

However, new diagnostic modalities are being studied to aid in earlier identification of recurrent and/or metastatic disease [7]. Investigation into serum biomarkers for ACC may also provide additional diagnostic and follow-up tools [8].

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A better data collection system and understanding of tumor biology may lead to more effective stratification of patients toward specific therapeutic modalities and improve prognosis. An enhanced molecular understanding of this neoplasm offers the potential for new chemotherapeutic options in the treatment of ACC. Indeed, multiple clinical trials have been performed or are underway in an attempt to evaluate the efficacy of novel agents against ACC. Additionally, new approaches to radiation therapy, along with refined indications for surgery in advanced disease, offer additional tools for utilization by multidisciplinary oncologic teams.

These factors offer some hope that strides can be made toward improving outcomes in this unusual and challenging malignancy. The purpose of this review is to review the current literature relating to the clinical management of ACC, with a focus on aspects of clinical and scientific advances in the understanding of ACC that may lead to more effective treatment of this rare but formidable neoplasm.

Methods

This review summarizes the literature on ACC over a 5-year period, from 19 July 2010 to 19 July 2015. Primary sources and key reviews were obtained via a National Center for Biotechnology Information Pubmed database query, for titles and abstracts containing the terms ‘adrenocortical carcinoma,’ ‘adrenocortical cancer’ or ‘adrenocortical tumor.’ The results were filtered for human subjects and English language of publication.

Search results

For the time period studied, there were 453 references that met the study criteria. These references were uploaded into a database created using EndNote® software (Thompson-Reuters, NY, USA). This database was then interrogated using keywords and abstract for topics of interest by using the ‘Search’ function within the software, gated for keywords found in the title or abstract. Results were then manually screened for relevance, novelty and perceived impact on the management of ACC by the authors. Redundant references were removed. Other seminal works published prior to 2010 were included where applicable. Ultimately, 99 references were included.

Epidemiology

Based on autopsy data combined with data obtained from cross-sectional imaging studies, the prevalence of adrenal tumors in the general population ranges from 4 to 7%, and increases with age [9]. The majority of these are nonfunctioning adrenal adenomas (ACA), and are discovered incidentally while performing imaging workup for other clinical indications. In contrast, malignant cortical tumors are quite rare. As a result, data on their incidence are sparse. Many studies cite the National Cancer Survey data from 1972, which approximates an incidence of 0.5–2 cases per million annually in the USA [10]. A 2006 analysis of the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) database estimates an overall age-adjusted incidence of 7 per million per year [3]. The Netherlands data may be the most convincing given the size of the country and an

effective centralized reporting system: in 2010, they calculate an incidence of 1.0 per million annually [11]. While it is generally assumed that these studies underestimate the true incidence of ACC, both estimated and true incidences are well below the threshold for categorization as a rare disease according to the NIH Office of Rare Diseases, set at a population prevalence of less than 200,000 affected individuals in the USA [12]. A retrospective review of 105 patients treated in a French Hospital from 1963 to 1987 revealed a 2.5 female-to-male incidence ratio. The average age of diagnosis in this study was 46 years [13]. Analysis of the SEER database showed a female-to-male ratio of 1.2:1.0 and a mean age of 51.2 years in the USA [3]. ACC in children is more rare than adults; a SEER database query on data from 1973 to 2008 identified only 85 patients with ACC in the USA, although the SEER database covers approximately 28% of the USA population [14]. It represents 0.2% of all childhood cancers presenting below the age of 15 [15]. However, ACC has bimodal age distribution regarding age of presentation with the first peak occurring in the first decade of life, and the second peak occurring in the fifth or sixth decade of life. Two-hundred and twenty-eight documented cases of pediatric ACC were evaluated in a recent study by Michalkiewicz *et al.* The mean age at diagnosis was 3.2 years, and 60% of the patients were less than 4 years old. Additionally, it was noted that while there was a 1.6:1 female preponderance in the age group less than 4, there was equal preponderance among gender in older children [16]. Interestingly, there is a population of children in southern Brazil that appears to have an incidence of ACC that is approximately 10–15 times greater than that of the USA; this increased incidence is thought to be due to a single R337H germline mutation in the gene encoding p53 [17].

Associated syndromes

Multiple, well-defined genetic syndromes increase susceptibility to ACC. Beckwith–Wiedemann is a disease characterized by overgrowth disorders and increased risk of other malignancies including Wilms tumors, hepatoblastoma and neuroblastoma. Li-Fraumeni syndrome is a well-described familial cancer syndrome stemming from a germline mutation in the *TP53* gene, causing increased susceptibility to breast cancer, leukemia, brain tumors and sarcomas [18]. This mutation is distinct from the previously mentioned *TP53* mutation associated that appears to be regionally restricted to an area in southern Brazil [19]. ACC in children should initiate a germline *TP53* workup [14]. Multiple endocrine neoplasia type 1 (MEN1), classically characterized by hyperparathyroidism, pituitary neoplasms and pancreatic neuroendocrine tumors, is also associated with an increased risk of adrenal lesions, including ACC. Estimates of the incidence of adrenal lesions in MEN1 vary, but a recent French study examining a multicenter database of 715 MEN1 patients evaluated between 1956 and 2008 showed that 10.1% of these patients had adrenal tumors, with an 1.4% overall rate of ACC [20]. Microsatellite instability is the hallmark of Lynch syndrome, and while there is an increased risk of all malignancies in patients with this syndrome, endometrial carcinoma and colorectal carcinoma are most often associated with this disease. The risk of ACC in Lynch syndrome is quite high compared with the general population. A recent study estimates that there is a 3% lifetime risk of ACC in patients with Lynch syndrome [21]. There are multiple reports of cases of ACC in neurofibromatosis, familial adenomatous polyposis, Werner syndrome and Carney complex, but these associations are

less established [22]. Table 1 summarizes the prevalence of familial syndromes associated with ACC.

Clinical presentation

ACC is typically discovered in the context of one of three clinical scenarios in adults. The first scenario involves hormone excess from functional tumors and represents the most common clinical presentation. Approximately 40–60% of patients will present with signs and symptoms of hormone excess, such as hypercortisolism, virilization in women and feminization in men. Paraneoplastic syndromes are rare in ACC; however, tumor-associated hypoglycemia is a well-described phenomenon, presumably secondary to increased levels of IGF-2 [23]. The second common clinical presentation is related to mass effect symptoms such as early satiety or abdominal pain caused by nonfunctioning tumors. Roughly a third of patients will present with symptoms of mass effect [24]. Analysis of the National Cancer Database over a 22-year-period revealed that the mean size of ACC at diagnosis was unchanged at approximately 11.5 cm [25]. Finally, incidentally discovered masses during imaging for other medical issues account for 20–30% of ACC discovery [22].

In contrast, children with ACC have symptoms of hormonal excess in 80–95% of cases, usually manifesting as virilization with or without Cushing's syndrome [26]. Isolated Cushing's syndrome in pediatric ACC patients is rare. Approximately 10% of pediatric patients with ACC have nonfunctional tumors [16], presumably found as a result of workup for a palpable mass, mass effect symptoms or found incidentally on imaging. A single-center review of 23 patients revealed that 14 had a palpable abdominal mass at the time of clinical exam regardless of reason for seeking evaluation [27]. The incidental finding of ACC in children, however, is less common due to the relative infrequency with which children undergo cross-sectional imaging.

Evaluation & work-up

The evaluation of a patient with a new adrenal mass concerning for ACC begins with a complete history and physical, and urine and blood tests to evaluate whether or not the tumor is functional. The only curative treatment for ACC is surgical resection; as such, evaluation of a patient with an adrenal mass should be performed with an initial emphasis on answering the question of whether surgical resection is indicated and technically feasible. The answers hinge on the complete characterization of these tumors with cross-sectional imaging with a focus on size, vascular invasion and whether there is distant disease to determine resectability [24].

Hormonal evaluation

Evaluation of a patient with an adrenal mass should include a biochemical workup of blood and urine to evaluate if the tumor is functional. This evaluation is guided in part by the presence of specific signs and symptoms of hormonal excess such as Cushingoid features, hirsutism, hypertension and/or hyperkalemia [22]. Hypercortisolism is diagnosed by either a dexamethasone suppression test, a midnight salivary cortisol level or a 24-h urine-free cortisol level [22]. Additionally, every patient should have their dehydroepiandrosterone

level (DHEA) measured along with a testosterone level for the purpose of both identifying specific hormone excess requiring treatment and as a benchmark for tumor markers following treatment [22,28]. Additionally, urine metabolites, such as 11-deoxycortisol and DHEA can be used as tumor markers [29].

A potential new approach aiding in the differentiation between adrenocortical adenoma (ACA) and ACC is based on MS profiling of 24-h urine samples. In one study, 32 distinct adrenal-derived steroids were isolated from the urine of patients with ACA and ACC, and the histologies were cross-referenced with the steroid profiles of the patients. While retrospective, this study revealed a pattern of nine immature, early stage steroids that were associated with malignancy with 88% sensitivity and specificity, with obvious implications to aid in the identification of malignant lesions in the presence of an equivocal lesion [30].

Imaging

In addition to diagnostic hormonal evaluation, tumor morphology and metabolic activity obtained by cross-sectional imaging with CT, MRI, ^{18}F -fluorodeoxyglucose PET (FDG-PET) and newer modalities can aid in the diagnosis of ACC. Size of the lesion is predictive of malignancy. Assuming the risk of malignancy in an adrenal incidentaloma is approximately 5%, a lesion measuring greater than 4 cm in its greatest dimension doubles the risk of malignancy to 10%. Furthermore, there is a ninefold increase (47%) in risk of malignancy for tumors greater than or equal to 8 cm [31]. Morphologic characteristic on CT suggestive of ACC include large size, heterogeneous appearance, lack of a well-defined margin, central low attenuation, high density on unenhanced images (more than 10 Hounsfield units), high-contrast washout characteristics and extension into the IVC [32]. Interestingly, despite increases in the frequency of CT scanning in the population at-large and adrenal incidentalomas becoming an increasingly common indication for adrenalectomy, there has been no decrease in mortality associated with ACC [3,25]. MRI using chemical shift can be useful for differentiating lipid-rich ACA from ACC, but this technique is not useful in lipid-poor ACA [33]. MRI is superior compared with CT at evaluating inferior vena cava invasion (IVC), which complicates resection of a right-sided ACC [24]. MRI is also more useful for the detection of liver metastases. Figure 1 illustrates characteristics of ACC seen on conventional cross-sectional imaging.

While CT and MRI are universally regarded as useful in the evaluation of the patient with ACC, other modalities are being investigated for both initial diagnosis and follow-up evaluations. A commonly used imaging modality for the detection of metastatic disease in ACC is FDG-PET. Using a ratio of maximum standardized uptake values (SUV_{max}) of tumor compared with liver, a French study of 23 patients showed that FDG-PET was 100% sensitive and 90% specific in the diagnosis of ACC at an adrenal/liver SUV_{max} ratio of greater than or equal to 1.6 [34]. Another French study of 51 patients confirmed these findings, also noting that the SUV_{max} of the tumor was correlated with Weiss score greater than or equal to 3, IGF-2 expression and loss of heterozygosity (LOH) of the tumor-suppressor gene TP53, all pathologic indicators of malignancy [35]. Tessonier *et al.* also concede that increased SUV_{max} correlates with diagnosis of malignancy, but found no correlation with SUV_{max} of ACC and patient prognosis [36]. The role of FDG-PET in ACC

is evolving, but it appears that it is a useful adjunct to conventional imaging in the diagnosis of adrenal malignancy, especially in the case of intermediate lesions, and/or to evaluate for metastatic ACC.

Proton magnetic resonance spectroscopy (PMRS) is a noninvasive imaging technique used to measure metabolites in living tissue. A prospective study by Faria *et al.* showed that metabolite ratios could be used to differentiate between pheochromocytomas, adenomas, carcinomas and metastatic lesions [37]. Although some criticisms of this study have been raised [38], further refinement of PMRS could be another tool to help discern the identity of indeterminate adrenal lesions preoperatively [39].

Another emerging imaging modality to aid the diagnosis of ACC, particularly in the setting of a metastatic evaluation, is radioactive iodine-labeled metomidate. Metomidate is a molecule that has a high affinity for 11 β -hydroxylase, an essential enzyme in the biosynthesis of aldosterone and cortisol, which localizes to the adrenal cortex with remarkable specificity. When tagged with radioactive isotopes, namely carbon-11 and iodine-123, differentiation between possible adrenal tumor histologies as well as identification of metastatic disease of adrenocortical origin is possible. In a pilot study of 11 patients with ACC, ¹¹C-metomidate was able to distinguish tumors from adrenocortical origin from noncortical lesions when used as a PET tracer. However, it was not able to distinguish ACA from ACC [7,22]. Similarly, ¹²³I-metomidate was evaluated in the context of single-photon emission CT (SPECT) in a pilot study of four patients with known adrenal masses, and was found to be a highly specific tracer for cortical lesions [40]. ¹²³I-metomidate was also evaluated in a prospective study of 58 patients with metastatic ACC, and was found to have 38% sensitivity and 100% specificity in detecting primary ACC and metastatic ACC lesions, numbers that were favorable compared with FDG-PET. A third of patients had ¹²³I-metomidate uptake in all lesions larger than 2 cm [41].

Staging

The most commonly used staging system is the European Network for the Study of Adrenal Tumours (ENSAT) system, supplanting the International Union Against Cancer (UICC) staging system [42]. The ENSAT classification was proposed by Fassnacht *et al.* in 2009, and is based on a German ACC registry of 492 patients followed for a mean time of 36 months [43]. It was subsequently validated in a North American cohort of 573, and showed improved accuracy in predicting recurrence and survival rates compared with the UICC classification [44]. Both are based on the established tumor, node and metastasis (TNM) classification system proposed by the UICC and the American Joint Committee on Cancer (AJCC) [45]. Table 2 summarizes the different staging systems used in ACC.

Pathologic grading

Tissue examination with light microscopy utilizing the Weiss score remains the standard in determining malignancy in patients with adrenal tumors. This scoring system is based on nine morphologic parameters listed in Table 3 [46]. Tumors with a score of 0–2 do not metastasize, and are defined as ACA [47]. A score from 3 to 6 is suspicious for malignancy,

and a score of greater than 6 defines ACC. Criticisms of this scoring system are that some parameters may be subjective, resulting in high interobserver variability, up to 10% of cases are deemed borderline, and firm diagnoses based on Weiss criteria alone cannot be made [48].

Given the limitations and criticisms of the Weiss criteria, several groups have attempted to refine the criteria to improve the accuracy of diagnosing ACC. A study in 2009 by Volante *et al.* comparing 92 ACC cases to 47 ACA cases was performed to temper the Weiss criteria using additional metrics. Specifically, the addition of the following criteria yielded an algorithm with 100% sensitivity and specificity: >5 mitoses per 50 high-powered fields; presence of necrosis and presence of vascular invasion [49]. Additionally, disruption of the reticulin network of the tumor was present in all 92 ACC and only 2/47 ACA. The diagnostic capability of including reticulin network disruption was further validated by Duregon *et al.*, who also found that the technique was easy to interpret and had high interobserver reproducibility [50]. Inclusion of the modifications to the Weiss score to include mitotic counting and reticulin algorithms may improve accuracy in cases where the diagnosis of malignancy is unclear [50,51].

Along with these advances in classification schema based on morphology, immunohistochemical techniques aid in the pathologic diagnosis of ACC, and are also used to help define the prognosis for patients with this neoplasm, especially in cases where there is tumor spread beyond the adrenal gland and/or the tumor has lost adrenocortical differentiation [22]. The most widely adopted examples of this is the utilization of Ki-67 proliferation index: it is uncommon for ACA to have greater than 5% of its cells stain positively for Ki-67, and conversely almost all ACC have greater than 5% Ki-67 staining. Other immunohistochemical markers useful for differentiation include many proteins commonly expressed in ACC: inhibin pro- α C, calretinin, synaptophysin, melanA and steroidogenic factor 1 [22].

Prognostic factors

Historically, prognostication for patients with established ACC is difficult as the disease course can be quite variable. Interestingly, a select subset of patients have shown prolonged survival despite having advanced and recurrent disease [52]. In the Michigan Endocrine Oncology Repository, about 5% of patients have a disease course of >10 years. Specific factors contributing to increased survival, however, have been incompletely evaluated.

Complete surgical resection is the most powerful prognostic factor in ACC [53]. Schulick *et al.* retrospectively stratified 107 patients who underwent surgery for ACC into two groups: those who had their tumor completely resected in the first operation, and those who had an incomplete resection. Patients who underwent complete resection had a median survival of 74 months with a 5-year survival of 55%. By contrast, patients whose primary operation did not completely resect all evaluable disease had a median survival of 12 months and a 5-year survival of 5% [53].

In addition to its role in ascertaining malignancy in histopathologic analysis of adrenocortical tumors, Ki-67 can be used to aid in prognosis for patients with ACC. A recent study by Bueschlein *et al.* was the largest series to date evaluating the relationship between Ki-67 proliferation index and outcome [54]. In 569 patients who underwent R0 resection for stage I–III disease, Ki-67 proliferation was found to be the single most effective prognostic tool for recurrence-free survival (RFS) and OS. Of note, age, tumor size and venous tumor thrombus were not associated with changes in RFS nor OS [54].

Table 4 describes the prognosis for ACC based on the percent of positive Ki-67 cells.

Recently, other studies have identified patient and tumor characteristics that impact patient survival and outcome that may lead to improved prognostic ability for clinicians. In a large retrospective, single-center analysis by Else *et al.*, multiple factors were associated with decreased overall survival (OS): age at diagnosis, increased cortisol production, increased stage and increased tumor grade (>20 mitotic figures per HPF) [28]. A clinical study by Berruti *et al.* found that patients with symptoms of hypercortisolism preoperatively had decreased RFS and OS even after complete surgical resection, suggesting that cortisol excess is associated with more aggressive disease [55]. Miller *et al.* corroborated these findings by showing that muscle loss and increased intra-abdominal fat was associated with worsening survival in ACC [56].

Hofland *et al.* showed that PTTG1 overexpression in tumor tissue is associated with poor survival in ACC [57]. Volante *et al.* identified ribonucleotide reductase large subunit (RRM1) as a factor predicting tumor susceptibility to mitotane [58]. Genome-wide analysis has revealed that less common variants of *TP53* polymorphisms were associated with a decreased OS in ACC [59]. Using data from exome sequencing, miRNA, microarrays and single nucleotide polymorphism analysis in ACC, a 2014 study by Assie *et al.* showed that tumors can be classified as indolent or aggressive based on a pattern of integrated molecular expression [60]. Genomic inquiry identifying relationships between these expression patterns and outcome in ACC is important not only for their potential prognostic value, but also for their attractiveness as potential therapeutic targets as the mechanisms behind their function in ACC tumorigenesis is elucidated.

Treatment

Surgery

Despite advances in multimodality treatment, complete surgical resection with negative pathologic margins remains the only curative treatment for ACC. However, even when an R0 resection is performed, over half of patients with ACC will have a local recurrence [53,61]. All patients considered for surgery should undergo a standard workup to determine their suitability for an operation in addition to their disease-specific evaluation. Additionally, electrolyte abnormalities and hypertension as a result of biochemical functionality of these tumors should be treated prior to surgery [62]. Congruent with much of the literature in ACC, surgical studies of this disease are based on sparse data, and are typically retrospective, single-institution reports. As such, three main controversies persist in the surgical management of ACC: whether laparoscopic surgery is noninferior to open

operations for localized disease; whether a formal lymphadenectomy is required; and the surgical management of metastatic and recurrent disease. Each of these will be briefly summarized.

Historically, open adrenalectomy was advocated for resection of known cases of ACC, but more recently advocates of a minimally invasive approach have noted that for certain patients, a laparoscopic adrenalectomy (LA) may not be inferior to an open adrenalectomy (OA). In a retrospective study of 152 patients, Brix *et al.* indicated that LA was not inferior to OA in the hands of an experienced surgeon for tumors less than 10 cm [63]. LA did not compromise the long-term oncologic outcome for patients with ACC with stage I/II disease and tumors less than 10 cm in a small, single-institution study by Donatini *et al.* [64]. A large multiinstitutional Italian study of 156 patients with ENSAT stage I/II also found no significant difference in 5-year disease-free or overall survival between LA and OA [65]. Criticisms of these studies include the following notions. Because only 23% of patients who were deemed candidates for LA actually underwent LA in the report by Brix *et al.*, there is concern for selection bias, and the follow-up for OA patients was a median of only 32 months compared with 64 months for the LA patients [24]. Given the rarity of ACC, a typical community surgeon may perform 100 LA for incidentalomas for each ACC, and as such they may not have the experience nor an adequate appreciation for the oncologic principles required for a proper resection of these tumors [24]. The feared complication of a resection for ACC is abdominal seeding, leading to local recurrence (LR) and peritoneal carcinomatosis (PC). In a review of 88 patients who underwent adrenalectomy for ACC, Miller *et al.* points out that despite having a decreased tumor size at operation, there was a significantly higher rate of tumor spillage and/or margin positivity as well as local or peritoneal recurrence in LA compared with OA [66]. This is corroborated in a study by Lebouleuz *et al.*, who found an increased risk for PC following LA for ACC [67]. Miller *et al.* also published a review of 156 patients, 46 of which underwent LA, showing that for a mean duration of follow-up of 26 months, OA was significantly superior to LA based on completeness of resection, site and timing of initial tumor recurrence, and survival [68]. Cooper *et al.* also confirmed in a cohort of 302 patients that LA was associated with an increased risk of carcinomatosis and on multivariate analysis LA was associated with worse recurrence-free and overall survival compared with OA [69]. Finally, the issue of whether formal lymphadenectomy should be performed in resection for ACC is still not settled for OA, and transition to resection with LA without a better understanding of this issue is imprudent [70]. Given these findings, it is the opinion of these authors that OA should be the standard of care for known ACC, and that future management of ACC will focus upon standardization of the operation rather than a transition to LA.

Radical lymph node dissection (LND) has become standard practice in the management of most solid malignancies. In the treatment of ACC, however, the role of LND is incompletely defined. Regional lymph node metastasis is negatively correlated with survival [71], and occurs in as many as 20% of patients with ACC [70], but remains amenable to surgery for curative intent [43]. Formal oncologic operations for ACC, with en bloc resection of surrounding structures is performed to include perinephric fat and Gerota's fascia, often include adequate lymph nodes for staging, but this has not been formally prescribed as standard of care [70]. A retrospective study of 283 patients by Reibetanz *et al.* revealed that

patients who underwent LND had a reduced risk of tumor recurrence as well as a reduced risk of disease-related death [72]. While the definition of what comprised an LND was somewhat arbitrary, and the specific location of the lymph nodes that were removed was not documented, this study lends credence to the idea that similar to other solid malignancies, a formal LND should be included in the surgical treatment of ACC [73].

Despite limited efficacy of existing multimodality options for patients who present with advanced-stage or recurrent ACC, surgical indications for this disease were traditionally limited to patients with early-stage, localized, completely resectable disease, or for palliative reasons. This approach has been challenged by experience from many centers that long-term recurrence-free survival and improved quality of life is possible with surgical extirpations of metastatic lesions and tumor recurrences. In a review of 367 patients with metastatic ACC, surgery was associated with prolonged survival compared with no treatment [74]. A study by Dy *et al.* demonstrated an increased 5-year survival and improved symptoms of pain and hormone hyper-secretion following debulking surgery in patients who recur [75]. In a single-institution study of 28 patients, Gaujoux *et al.* showed that in selected patients with liver metastases, DFS was 7 months and OS was 31.5 months, with 5-year survival at 39% [76]. A 2011 study from the National Cancer Institute demonstrated a mean OS of 40 months and a 5-year survival of 41% in patients who underwent pulmonary resections for metastatic ACC, even in the case of multiple operations for repeat recurrences [77]. Erdogan and colleagues performed a retrospective review of the German Adrenocortical Carcinoma Registry and found a median PFS of 24 months and median OS greater than 60 months among patients with a time to first recurrence interval of more than 12 months and an R0 resection of the recurrence [78]. It has been noted that improved outcomes following repeat resections are related to increased disease-free intervals following initial resection [79]. Indications for surgical management of recurrent and/or metastatic disease are not clearly defined, but given the lack of therapeutic options for advanced ACC, metastectomy in the liver, lung and lymph nodes – along with debulking surgery for palliative indications including those of hormone excess – are emerging as being beneficial in select patients. Future refinements in this area will hinge on identifying which patient and tumor characteristics endow prolonged survival and improved quality of life following surgery for metastatic and/or recurrent ACC.

Chemotherapy

Mitotane has been the standard treatment of ACC for years. It is the best studied and most commonly used chemotherapeutic agent for the treatment of ACC, but the exact mechanism of its antitumor action is unknown [80]. Mitotane is an adrenolytic substance that is thought to act through an apoptotic mechanism secondary to the disruption of mitochondrial processes [81]. It is used both for the primary treatment of metastatic disease and it is used in the adjuvant setting [82]. Additionally, its adrenolytic activity coupled with its inhibition of steroidogenesis through blockade of 5 α -reductase make mitotane useful for the treatment of hormone excess in the palliative setting [83]. There is also some evidence that mitotane sensitizes ACC tumor cells to radiation, but this is not well studied [84].

Monitoring of plasma drug concentrations has become a cornerstone in the administration of mitotane. In a 2011 study by Hermesen *et al.*, plasma concentrations of mitotane and its metabolites measured in 91 patients receiving mitotane for advanced ACC [85]. Univariate and multivariate analysis showed significantly longer survival at 119 months for plasma concentrations greater than or equal to 14 mg/l compared with 18 months for patients receiving mitotane monotherapy in whom a plasma mitotane concentration was less than 14 mg/l. In the adjuvant setting, Terzolo *et al.* showed that plasma concentrations of mitotane greater than 14 mg/l were beneficial in terms of tumor recurrence. In 122 patients who underwent radical resection for ACC and who received adjuvant mitotane, serum concentrations of less than 14 mg/l was associated with longer recurrence-free survival (HR: 0.497) and overall survival (HR: 0.511) [86]. These studies, while retrospective and with a somewhat small sample size, emphasize the point that mitotane has a narrow therapeutic window. Indeed, mitotane therapy is associated with a range of significant toxicity, characterized most commonly by gastrointestinal symptoms and more rarely, by significant neurologic side effects [22]. As such, the question of whether adjuvant mitotane is required following R0 resection in patients with a low-to-intermediate risk of recurrence based on Ki-67 staining is being answered by a multicenter randomized controlled trial (ADIUVO trial, available at [87]). The rarity of ACC makes studying the effects of mitotane in large number of patients, underscoring the desirability of treating patients with ACC at specialized centers. Future directions in the study of mitotane will center on further refinement of its indications in specific clinical scenarios in ACC, as well as in combination with other chemotherapeutic agents.

For advanced ACC, multiple combination regimens have been studied. Two seminal studies established the feasibility of these combination regimens. The first of these, by Kahn *et al.*, reported a 36.4% overall response rate in 40 patients with ACC using a combination of streptozocin and mitotane [88]. In a single-institution trial of 28 patients with ACC, the second of these studies, by Berruti *et al.*, evaluated the combination of etoposide, doxorubicin and cisplatin (EDP) with mitotane [89]. With two patients achieving a complete response, and 13 patients achieving a partial response, there was an overall response rate of 53%, accompanied by a mean time to progression of 2 years [89]. The FIRM-ACT Trial, published in 2012, established meaningful data regarding combination therapy for ACC when it compared EDP plus mitotane and streptozocin plus mitotane in a randomized controlled trial [90]. When treated with the regimen as first-line therapy, patients in the EDP-mitotane group had an objective response rate of 23.2% and a median progression-free survival of 5 months, compared with 9.2% response and 2-month progression-free survival for the streptozocin-mitotane group. Notably, the toxicity was similar between the two groups. Overall survival was not significantly different, however [90]. Currently, the combination of EDP and mitotane is the standard treatment, although questions remain about the necessity of mitotane in this scenario [22].

Emerging therapy

Chemotherapeutic options for the treatment of ACC are limited, and many experimental treatments have not shown efficacy. However, an improved understanding of molecular oncogenesis in ACC has led to an array of potential therapeutic targets in ACC, and studies

characterizing these emerging therapies are summarized in detail in a recent review by our group [91]. Molecular pathways that are being studied include the IGF pathway, the WNT/ β -catenin signaling pathway, and the VEGF pathway. Certainly, improvements in the understanding of the mechanisms of tumorigenesis in ACC will be accompanied by novel therapeutic agents to be studied in the treatment of ACC.

Radiation therapy

Historically, the use of external beam radiation therapy (RT) has been relegated to the sidelines in the treatment of malignant adrenal tumors due to the risks of normal tissue toxicity within the irradiated field, specifically to the kidney, stomach, intestine and spinal cord, as well as the opinion by some practitioners that it is relatively ineffective [92]. The development of CT-based planning and intensity-modulated radiation therapy, which uses nonuniform dose distributions, have made RT safe to use as part of a multimodality approach in patients with ACC. Additionally, several recent studies show some promise for the efficacy of RT in both the adjuvant and palliative setting [6,93–94]. Efficacy, however, has not been firmly established with any prospective data. Future inquiry must focus on identifying patients likely to benefit from RT as an adjunct to surgery, as RT alone is not adequate for the treatment of resectable tumors [24].

Radiofrequency ablation

In selected patients with metastatic hepatic disease or localized recurrences not amenable to complete surgical resection, radiofrequency ablation (RFA) and/or cryotherapy have emerged as an adjunct to surgery. While effect of RFA on patient survival is difficult to assess given its usage in combination with surgery, there are reports of RFA being helpful in attempting to render the patient disease free and to aid in palliative tumor debulking [95,96].

Multidisciplinary approach/experienced centers

The debate over surgical approach feeds into the debate about centralization of medical and surgical services for ACC. Fassnacht *et al.* demonstrated lower recurrence rates and superior 5-year survivals in patients with ACC who received early specialized care [61], mirroring findings regarding specialized treatment in other cancers [97]. Experts in the field insist that a multidisciplinary approach by treatment teams experienced in the care of ACC is essential for both optimal individual treatment and for improved data collection needed to advance the field [22]. The results of a 2010 study in Germany by Johanssen *et al.* underscore this concept, where analysis of patients with ACC treated by physicians outside of experienced centers revealed broad patterns of suboptimal care. Twenty-one percent of these patients did not undergo hormonal evaluation. Notably, 48% of patients did not undergo cross-sectional imaging of the chest, despite this being the most likely site of metastasis in ACC. A tenth of patients had no mention of resection margins in their pathologic report following surgical resection [98]. A Dutch study in 2012 by Hermesen *et al.* showed similar findings in surgical patients with ACC. For those who underwent surgical resection at an experienced ACC center, median overall survival was 81 months, compared with a median OS of 20 months for patients who underwent surgical resection at a local hospital [99]. Given these findings,

coupled with the extreme rarity of this disease, these authors strongly recommend referral of these patients to experienced centers.

Future perspective

ACC is an aggressive tumor with limited treatment options and dismal outcomes. Currently, the best hope for long-term durability remains complete surgical resection. Surgical resection is intimately dependent on the stage at presentation. Ongoing studies of new and different modalities to diagnosis of ACC may significantly improve the number of patients identified at earlier stages. Controversy continues regarding the appropriate use of laparoscopic adrenalectomy and completion lymphadenectomy in ACC patients. Prospective studies to evaluate outcome among minimally invasive surgery and open surgical resection as well as the extent of lymph node dissection is desperately needed. However, given the rarity of this disease and the low propensity of patients to present with early stage disease makes prospective surgical studies difficult to undertake and requires the collaboration of multiple institutions around the world. In addition to understanding the role of surgery in ACC outcomes, the need to improve systemic therapy is crucial to advancing survival among patients with ACC. As scientific technologies and techniques improve, our understanding of the molecular genetics and tumor biology of ACC will also improve giving hope for the discovery of new effective therapies in ACC.

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Practice points

- Continued development of urine and serum steroid-based diagnostic modalities to help aid in the diagnosis of and follow-up in patients with adrenocortical carcinoma (ACC).
- Refinement of experimental imaging techniques may aid in the accurate differentiation of ACA and ACC such that surgical resection may not be necessary for diagnosis.
- Further research into molecular indicators of prognosis may help guide treatment based on accurate risk assessments.
- Prospective surgical trials comparing outcomes in open adrenalectomy and laparoscopic adrenalectomy, as well as standardization of lymphadenectomy, are needed to bring surgical treatment for ACC up to date with other solid malignancies.
- Continued exploration through rigorous clinical trials to evaluate both existing and novel agents, as well as combinations of these agents.
- Radiation and RFA may have an increasingly important role in the treatment of ACC.
- Centralization of medical/surgical services to specialists experienced with the care of patients with ACC is needed to better evaluate outcomes and standardize care.

Figure 1. Radiologic characteristics of adrenocortical carcinoma in a 33-year-old female who presented with abdominal fullness after exercising

Imaging (left to right): CT, MRI, PET-CT.

Courtesy of the National Cancer Institute.

Table 1

Familial syndromes associated with adrenocortical carcinoma.

Syndrome	Prevalence (%)
Li–Fraumeni syndrome	3–7% in adults 50–80% in children
Beckwith–Wiedemann syndrome	<1%
Multiple endocrine neoplasia type I	1.4%
Lynch syndrome	3%
Familial adenomatous polyposis	<1%
Neurofibromatosis type I	<1%
Carney complex	<1%

Table 2

Multiple staging systems for adrenocortical carcinoma.

Staging system	Parameters
TNM:	
T1	<5 cm, no local invasion
T2	>5 cm, no local invasion
T3	Any size, extension into periadrenal fat
T4	Any size, invasion into neighboring organs
N1	Metastasis into local lymph nodes
M1	Metastatic disease
AJCC/UICC:	
Stage I	T1N0M0
Stage II	T2N0M0
Stage III	T1-2N1M0 or T3N0M0
Stage IV	T3N1M0 or T4N0-1M0 or T1-4N0-1M1
ENSAT:	
Stage I	T1N0M0
Stage II	T2N0M0
Stage III	T3-4N0M0 or T1-4N1M0
Stage IV	T1-4N0-1M1

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

Table 3

The Weiss score for diagnosing adrenocortical carcinoma.

Histopathologic criteria	Score
1) Nuclear grade	1
2) Mitotic rate >5 per 50 high-powered field	1
3) Atypical mitotic figures	1
4) Eosinophilic tumor cell cytoplasm (>75% of tumor cells)	1
5) Diffuse architecture (>33% of tumor)	1
6) Necrosis	1
7) Venous invasion	1
8) Sinusoidal invasion (no smooth muscle in wall)	1
9) Capsular invasion	1
Total	9

Nine parameters are evaluated. The presence of a given parameter in a sample gets a score of 1. The absence of that parameter gets a score of 0. A total score of 0–2 is consistent with ACA. A score of greater than 6 defines ACC. Samples with scores between 3 and 6 are suspicious for malignancy.

Table 4

Adrenocortical carcinoma patient outcome based on percentage of Ki-67-positive cells.

Ki-67 index	RFS (months)	OS (months)
<10%	53.2	180.5
10–19%	31.6	113.5
>20%	9.4	42

OS: Overall survival; RFS: Recurrence-free survival.