Background

Adrenocortical carcinoma (ACC) is a rare disease with an age-adjusted incidence of 1.02 patients per million in the United States and an aggressive phenotype with poor outcomes (1). Surgery can be curative, but this is not always possible given advanced stage at presentation and patients often require mitotane along with cytotoxic chemotherapy. Despite increased knowledge of its heterogeneous molecular background, translating that insight to systemic therapies has not been successful. Due to its rarity, conducting clinical trials have also been challenging and the success thus far has been based upon multicenter and international collaboration.

Previously, ACC was expected to have a bimodal distribution with a peak in childhood and the fourth to fifth decade of life, though a recent US population-based study did not describe this and found a median age of 55 years old (1). Most are sporadic tumors, but can also be associated with cancer syndromes such as Li-Fraumeni, Beckwith-Wiedemann, and Multiple Endocrine Neoplasia Type 1 (MEN1) syndrome (2). Lynch Syndrome has also been described as a risk factor (3). ACC in the pediatric age group is most often related to LiFraumeni whereas in adults it is less likely to have a genetic cause.

ACC often presents in an advanced stage, with as many as 70% of patients with stage III or IV disease at the time of diagnosis. The diagnosis is often made due to a rapidly growing mass with compressive symptoms or hormonal excess symptoms.

It is estimated that 60% of ACC patients present with evidence of adrenal hormone excess such as symptoms of Cushing’s syndrome (central weight gain, hypertension, hyperglycemia) as well as virilization or feminization (4). In tumors without hormone secretion, symptoms are related to tumor burden including abdominal pain, back pain, early satiety, and weight loss. Many tumors can be treated surgically restoring normal hormone function.
Cushing’s syndrome in the setting of ACC is a negative prognostic factor (5). Treatments for the Cushing’s syndrome include surgical resection of the primary tumor, mitotane therapy, or therapies such as ketoconazole or metyrapone. Hypertensive therapy with spironolactone or eplerenone is also often necessary as is managing hypokalemia from mineralocorticoid excess. Spironolactone can also be used to treat virilization in female patients.

Less commonly, ACC can be found as an incidental imaging finding. Incidental adrenal lesions measuring 4 cm or larger or lesions with unenhanced CT scan HU >10, or MRI findings showing lack of signal loss on out-of-phase imaging suggest more concern for malignancy. The sensitivity of imaging findings (not tumor size) in a study of 112 patients treated with adrenalectomy for malignant lesions (N=18), including metastasis was 100%, with specificity of 57%, NPV 100%, PPV 33% (6).

Prognosis is quite poor in many advanced stage patients. Survival at 5 years has been reported to be 82% for stage I, 61% at stage II, 50% for stage III and 13% for stage IV in the German registry (7). In the US, recent review of patients suggests median survival of 14 months (SEER-18 review from 2004–2014), but with improved survival (28 months) in those who undergo surgical resection (1). Curative treatment is surgical, though this is not always possible. An open surgical approach has been shown to reduce the likelihood of peritoneal carcinomatosis and local recurrence when compared with laparoscopic approaches (8). En bloc resection of the tumor and involved organs by an open approach in an expert surgeon’s hands is the recommended surgical treatment.

Neoadjuvant chemotherapy

Because of the advanced nature of this disease at diagnosis, some patients have been evaluated for neoadjuvant systemic therapy. For those with borderline resectable tumors, neoadjuvant chemotherapy demonstrated a survival advantage in a small single-center series of 15 patients (9). Eight patients received etoposide, Adriamycin, and cisplatin plus mitotane, 2 received mitotane alone, 3 patients received etoposide/cisplatin and mitotane, and 1 patient received taxol/carboplatin/etoposide. Thirteen of these 15 patients underwent surgical resection. Compared with 38 patients who had immediate surgery, these patients had more advanced disease. However, they also had improved median disease-free survival compared with the immediate surgery group 28.0 vs. 13 months.

Staging

There are several different ways of staging ACC. The American Joint Committee on Cancer (AJCC)/Union for International Cancer Control revised 2017 staging uses the tumor, node, metastases (TNM) system. T1 tumors are confined to the adrenal and are less than 5 cm whereas T4 tumors invade adjacent organs or blood vessels. Stage I and II tumors are confined to the adrenal gland and Stage III includes lymph node positive tumors. Stage IV is any T or N with distant metastasis. The European Network for the Study of Adrenal Tumors utilizes a similar method (4). The University of Michigan proposed a modification of the ENSAT staging tool to include tumor grade as they demonstrated that high grade tumors (>20 mitoses/50 high-power field (HPF)] showed a difference in time to recurrence (10). At this time, the most widely used staging is the ENSAT system.

Pathologic and molecular tools

After staging, using additional pathologic information to predict outcomes and direct treatment in ACC can be challenging and many strategies have been authenticated (11). Pathologic diagnosis of ACC has been evaluated by the Weiss scoring system, introduced in 1984 (12). This 9-factor scoring included nuclear grade, mitotic rate >5/50 HPF, abnormal mitoses, ≤25% clear cells, >1/3 diffuse architecture, necrosis, venous invasion, sinusoidal invasion, and capsular invasion. 1 point was given for each positive finding and a score of 4 or more was initially suggested, but after additional data (1 patient with score of 3 did poorly) decreased to 3 for a diagnosis of malignancy. This was adapted and modified into several different scores with the Modified Weiss system which includes mitotic rate, atypical mitoses, clear cells ≤25%, necrosis, capsular invasion. With this score, a score of 3 or more is consistent with a malignancy. The reticulin algorithm was suggested in 2009 using the disruption of the reticulin network as a portion of the scoring system (11). The Helsinki score was described in 2015 and included a proliferation index (Ki67). This is a calculated score (3x mitotic count + 5x necrosis + Ki-67 index). This has been validated in a large series of patients (13). A novel factor, the cytoskeletal remodeling factor VAV2, which drives cellular invasion, has been more recently identified as an important prognostic indicator (14).

For less common oncocytic ACC, a different criterion
called the Lin-Weiss-Bisceglia criteria was proposed to be better predictive of malignancy in this rare subset of ACC tumors (15). These tumors have a lower likelihood of hormonal production and may grow to very large sizes by the time they are discovered. Since these are even less common than usual ACC, the prognosis is less well understood. Even rarer subtypes of ACC include sarcomatoid and myxoid types.

As future treatments were explored, additional studies to further understand the pathogenesis of ACC were needed. A study of 45 ACC tumors by the ENSAT group demonstrated two groups of molecular signatures. One with a poor outcome had many mutations and DNA hypermethylation (2). The other group with improved outcomes, had deregulation of 2 microRNAs. In 2016, 91 adrenocortical tumors were evaluated from a global cohort of patients. This was part of The Cancer Genome Atlas (TCGA) and was helpful in dividing patients into three categories of molecular findings correlating with clinical outcomes. Five significantly mutated genes included TP53, CTNNB1, MEN1, PPRKAR1A, and RPL22. Whole genome doubling occurred more frequently in aggressive tumors (16). Hypermethylation patterns correlated with worse outcomes.

Molecular targets have been explored for the treatment of ACC as knowledge of the alterations in the molecular genetics of the tumor improved. IGF2 expression is increased in 85% of ACC tumor in adults. Wnt/Beta-catenin signaling pathway is commonly affected in ACC with CTNNB1 Mutations and ZNRF2 gene alterations in 22–37% of cases. TP53 inactivation is found in 16–21% of tumors. Chromatin remodeling genes are also implicated including DAXX, ATRX, MEN1. Inactivation mutations in the protein kinase cAMP-dependent regulatory type I alpha gene (PRKAR1A) are associated with benign pigmented nodular adrenal hyperplasia and Carney complex as well as cortisol –producing adenomas. They have been noted in 8% of patients with ACC, suggesting that there may be a continuum of disease in some patients. Methylagation evaluation have shown that so-called CpG islands can be studied. Hypermethylation of these islands in tumor suppressor genes has been shown in malignancy, and the more hypermethylated the ACC tumor, the more aggressive it is (17).

**Local therapies**

Despite adequate surgical resection, local recurrence and distant metastases are common. 49–90% recurrence rates have been found in various series (5,18). Due to this, radiation to the surgical bed has been suggested.

Surgical treatment for oligometastatic disease is also potentially helpful in select cases (19). Some patients are treated with liver ablative technologies such as radiofrequency ablation. Resection of liver metastases in patients has been shown to improve survival in a small series with a 5-year survival of 39% in this stage IV group of 28 patients (20). A German series of 43 patients who had resection of liver metastases compared with 34 patients who had liver metastases which were not resected had a median survival of 76.1 vs. 10.1 months. However, disease-free survival after liver resection was only 9.1 months. Again, overall survival was not different (21). Additional ablative techniques have been utilized such as Yttrium-90 microsphere selective internal radiation therapy into the liver with success (22).

**Radiation therapy**

Adjuvant Tumor bed radiation has been suggested for patients with positive surgical margins (R1 or R2 resection) if additional surgery is not possible. It is also suggested for tumor capsule rupture/spillage or Ki-67 >10%. Fourteen patients in the German registry of ACC who received radiation to the tumor bed were matched to 14 patients with same tumor resection, staging, mitotane status, and tumor size. Two of the 14 radiated patients had a recurrence, and 11 of the untreated patients had a local recurrence. Disease-free and overall survival were not different (23). A review of 64 patients in several studies who received post-operative radiation, decreased risk of recurrence was present (24).

The rapidly-growing genomic description of adrenocortical tumors has not been adequate to explain the heterogeneity in tumor biology and response to therapy. In the era of targeted therapy and immunotherapy, ACC treatment remains largely cytotoxic therapy based. The evaluation of systemic therapies has been limited due to the rarity of the tumor. The clinical trial data and retrospective data review will be discussed below.

**Mitotane**

Mitotane, an adrenolytic synthetic derivative of the insecticide dichlorodiphenyltrichloroethane (DDT), has been shown to be effective in reducing recurrence rates (18), but is difficult to tolerate for many patients. It is the only
approved medication for ACC. Mitotane was initially described after DDT was noted to cause atrophy of the adrenal cortical zona fasciculata and zona reticularis in dogs. In 1960, a paper describing the treatment of 18 patients with ACC with o,p′DDD was presented at the American College of Physicians annual meeting and in the Annals of Internal medicine (25). Seven of these 18 original patients described had measurable regression of their metastases with doses of up to 10 grams daily. Seven additional patients had normalization of their urinary steroid levels. The toxicities described remain an issue to this day. In 1960 on these very high doses of mitotane, symptoms included anorexia, nausea, somnolence, lethargy, and abnormal EEG tracings. Unfortunately, despite ongoing efforts, we still rely on this oral medication, albeit with slightly more data to support its use, while our patients complain of the same ailments.

In 2007, a retrospective review of ACC registries in Italy and Germany was done to determine whether adjuvant mitotane was beneficial. Patients who had received surgery with curative intent were included after careful review. Forty-seven Italian patients received mitotane, and 55 Italian patients and 75 German patients did not. In the mitotane group, 23 patients (48.9%) recurred and 50/55 (90.9%) and 55/75 (73.3%) recurred in the other two groups respectively (21). This was confirmed in a continuation study after 9 additional years of follow-up (26).

A retrospective analysis of patients treated at the University of Michigan also demonstrated reduction in recurrence in 105 patients who received mitotane versus 159 who did not. Adjuvant radiation and mitotane together seemed to have additive and benefits, but there was no improvement in overall survival (5).

Two additional retrospective studies failed to show benefit (27,28). One had a recurrence rate of 50% without mitotane, similar to the rates noted above with mitotane, suggesting that surgical completeness of resection was as effective as mitotane adjuvant therapy (27).

In patients with metastatic ACC, a retrospective study of 36 patients who were treated with mitotane alone, identified 3 patients with a complete response and 1 with stable disease (29). Thirty-one patients had progression, and only 3 were within the therapeutic range. Another study suggested that mitotane levels are predictive of outcomes (30). Of the patients who achieved therapeutic levels of mitotane (14–20 mg/L) 22 of the 63 (35%) recurred, and 36/59 (61%) in the non-therapeutic group recurred. Therapeutic levels were associated with recurrence free survival, but not overall survival. Toxicities of grade 3–4 were present in 9% of the patients.

Currently, an international, multicenter, prospective, randomized trial (ADIUVO trial, clinicaltrials.gov ID: NCT007777244) is ongoing enrolling low risk ACC patients (stage I–III after complete surgical resection, Ki67 <10%). This trial is to determine the role of adjuvant mitotane in low risk disease.

**The First International Randomized Trial in Locally Advanced and Metastatic Adrenocortical Carcinoma Treatment (FIRM-ACT) (31)**

A randomized prospective trial of 304 adult patients with advanced ACC not amenable to surgical resection was completed in 2012. Mitotane plus etoposide, doxorubicin, and cisplatin every 4 weeks or mitotane plus streptozocin every 3 weeks was compared. There was a cross over if progression. Overall survival was not different (likely due to the cross over design), but EDP plus mitotane demonstrated improved response rate (23.2% vs. 9.2%). Three patients in the study had a complete response and 6 patients after the study medication were surgically treated and disease free. Progression-free survival was 5.0 months in the EDP plus mitotane group and 2.1 months in the streptozocin-mitotane group. This data lead to EDP plus mitotane as the systemic therapy of choice. Only 54 patients in the study had mitotane levels within therapeutic range of 14–20 mg/L with both groups having equal patients with these levels. Thus far additional treatments have not been as promising as this trial and it remains the standard of care for advanced ACC. Multiple small studies using novel and targeted agents are described.

**Insulin-like growth factor IGF-2 and IGF1-receptor agents**

Since 80–90% of ACC have IGF-2 signalling pathway abnormalities, it seemed logical to attempt targeting this pathway. IGF-2 overexpression is common in ACC, present in over 80% (32).

**Cixutumumab and mitotane 2014**

Twenty patients were treated with the combination of mitotane plus cixutumumab (IGF-1R inhibitor) IV every 2 weeks for unresectable recurrent/metastatic ACC in this
phase II study. It was terminated before randomization so this single arm trial has minimal information. However, there were 3 significant toxicities and the medial PFS was 6 weeks (33).

**Linsitinib 2015**

An oral small molecular inhibitor of IGF-1R and insulin receptor was studied in a Phase III double-blind, randomized, phase 3 study in patients with locally advanced or metastatic ACC (34). One hundred thirty-nine patients were studied, 90 receiving study medication, 49 assigned to the placebo arm. No benefit to progression-free survival or overall survival was found. However, there were 3 patients who had a partial response, suggesting some potential benefit to a subset of patients with low grade tumors (low Ki67) perhaps explained by the particular tumor genetic profile.

Figutumumab, another IGF-1R targeted therapy, also failed in clinical trials (35).

**VEGF inhibitor therapy**

Since ACC commonly express vascular endothelial growth factor receptor (VEGFR), it seemed possible that inhibition of VEGF signal could improve outcomes. This was another attempt that is successful in other tumors, but was not so in these 3 trials.

**Bevacizumab plus capecitabine**

In a study of patients who had failed at least one line of chemotherapy, salvage treatment was offered and reviewed as a small case series of 10 patients. Most of these patients were in the FIRM-ACT trial and progressed. Treatment with the monoclonal antibody to vascular endothelial growth factor (VEGF) bevacizumab, was chosen due to presence of VEGF staining in adrenal tumors. This approach has been successful in other cancers. Capecitabine was chosen as an oral prodrug of 5-flourouracil which is noted to have adrenolytic impacts (36). Unfortunately, none of the 10 patients had stable disease or had any response to treatment.

**Gemcitabine plus metronomic 5-flourouracil or capecitabine 2010**

In advanced ACC patients progressing after mitotane plus 1 or 2 previous chemotherapy cycles, 5FU (first 6 patients) or oral capecitabine was used with gemcitabine in this phase II multicenter study (37). 46.3% of patients were not progressing after 4 months. Median time to progression was 5.3 months with an overall survival of 9.8 months. This was purported to be moderately active.

**Sunitinib 2012**

Because adrenal hemorrhage and possible adrenal dysfunction was reported with use of sunitinib and it has tyrosine kinase inhibitor targets including VEGFR1 and 2, c-KIT, PDGFR, it was utilized in patients with ACC in this clinical trial. In 38 refractory patients progressing after mitotane and at least one type of cytotoxic chemotherapy, sunitinib was used (38,39). Thirty-five patients were evaluable. Unfortunately, 6 patients died before the first evaluation could be performed. Stable disease was noted in 5 patients and 24 had progressive disease. Median progressive-free survival was 2.8 months, but in patients with stable disease, it was 5–11 months. Interestingly, the use of mitotane appeared to have caused an increased metabolism of the drug and lower responses in patients on mitotane.

**Axitinib 2014**

A selective inhibitor of VEGFR-1, 2, and 3, axitinib, was used in a phase II, open-label clinical trial. Thirteen patients were enrolled. There were no RECIST responses in any of the patients. However, it appeared to slow the growth rate in 4 of the patients (40).

**Thalidomide (2018)**

Thalidomide is an immunomodulatory agent, used in multiple myeloma.

Twenty-seven patients with progressive disease after a median of 4 systemic treatments for ACC were treated with thalidomide. This review of patients from the European Network for the Study of Adrenal Tumours registry demonstrated disease control in only 2 patients. Twenty-five patients had progressive disease after a median PFS of 11.2 weeks. Two had stable disease. The treatment was well-tolerated (41).

**Targeting Wnt-beta-catenin**

A basket trial for solid tumors using celecoxib (which
regulates beta-catenin) and bortezomib (ubiquitin-proteasome pathway inhibitor) included 1 patient with ACC among the 18 patients studied was found to have stable disease. One additional patient (renal cell carcinoma) had stable disease, but the other 16 had progressive disease (39).

**Immunotherapy**

Immunotherapy has offered hope and improved survival for many cancers that previously had poor outcomes. Evaluation of ACC for immunotherapy response seemed like a promising idea. However, recent trials suggest disappointing results for immunotherapies in ACC. Avelumab (a PD-L1 antibody) was studied in a Phase IB trial in patients with progressive ACC. The response rate in these 50 patients was 6%. Twenty-one patients had stable response. Progression free survival was 2.6 months and overall survival was 10.6 months. It was relatively well tolerated (42).

Ten patients with metastatic ACC were treated with nivolumab 240 mg IV every 3 weeks. After a follow-up of 4.5 months and median number of doses of 2, 2 patients had stable disease for 48 and 11 weeks and 1 patient had a partial response. Median PFS was only 1.8 months (43).

Pembrolizumab was utilized in a group of 16 patients with ACC who had failed previous line of therapy within the past 6 months. This was a phase II study with pembrolizumab 200 mg every 3 weeks. Two patients had a partial response, 7 patients had stable disease (6 for 4 months or longer) of the 14 patients who were evaluable. Five of the patients had progressive disease. At the end of 27 weeks, 5 were alive (44).

Pembrolizumab plus mitotane was used in 6 patients with ACC who had progressed on mitotane alone (N=3) or mitotane plus EDP (N=3). 200 mg or 2 mg/kg IV pembrolizumab was given every 3 weeks along with mitotane. In this group, 2 had a partial response, and 4 had stable disease and received therapy for 8 to 31 months. This suggests there is potential for improved outcomes with the use of mitotane in addition to PD-1 inhibitor (45).

**Metformin**

Metformin is a biguanide used to treat type 2 diabetes mellitus by improving insulin sensitivity and glucose levels. It has been shown to reduce development of cancer in patients with diabetes (46). Metformin reduces insulin/insulin-like growth factor I (IGF-1) signaling and inhibits mammalian target of rapamycin (mTOR), both important in ACC. It also activated AMP-activated kinase, reduces endogenous production of reactive oxygen species with its associated DNA damage (47). A recent study with EGFR mutated lung cancer has shown improved progression-free survival and overall survival benefit by combining metformin with EGFR-tyrosine kinase inhibitors compared with tyrosine-kinase inhibitor alone (48). Many other studies are ongoing.

Metformin has been tested in cell culture and xenograft with ACC cell model H295R demonstrating anti-proliferative and pro-apoptotic effects (49). Perhaps the addition of metformin to other systemic therapies will have additive benefit?

Systemic therapies for ACC remain focused on mitotane, a treatment we have utilized for more than 5 decades to treat this disease. Unfortunately, although we now understand much more than ever in the pathogenesis of ACC, we have not yet identified the perfect therapy for this aggressive disease. Due to the rarity of this tumor and its devastating nature, collaborative and imaginative work must continue to push for improved outcomes for our patients.

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None.

**Footnote**

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**References**


