# Diagnosis and Management of Adrenocortical Carcinoma

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**KEYWORDS**

• Adrenal cancer • Advanced disease • Adjuvant therapy • Metastatic disease

**KEY POINTS**

- The presence of an adrenal mass with elevated glucocorticosteroids/precursors *and* androgens/precursors is highly suggestive of adrenocortical carcinoma.
- Adrenocortical carcinoma has a high recurrence rate, especially with a high mitotic rate (Ki67 index >20%).
- Mitotane is associated with multiple endocrine side effects that require careful management, especially adrenal insufficiency, which often needs high-dose glucocorticoid replacement.
- Patients who have disease progression while receiving etoposide, doxorubicin, and cisplatin + mitotane should be considered for clinical trial enrollment when available.
- Immunotherapy, targeted therapies, and cell-based therapies play an emerging role in adrenocortical carcinoma.

## INTRODUCTION

Adrenocortical carcinoma (ACC) is an orphan malignancy, with an annual incidence of approximately 1 case per million people.[1,2] ACC exhibits a bimodal age distribution, with incidence peaks in early childhood and again during the fifth to sixth decades of life.[3–5] To date, no environmental or behavioral factors have been definitively linked to ACC pathogenesis, although a few observational retrospective studies have suggested a potential association with tobacco use in men and oral contraceptives in women.[6–8] Most ACC cases are sporadic; less than 10% of cases occur within the context of familial cancer predisposition syndromes, including Li-Fraumeni syndrome, Lynch syndrome, multiple endocrine neoplasia type 1, and Beckwith–Wiedemann syndrome.[9,10]

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| Abbreviations | |
|---|---|
| $^{18}$F-FDG PET | 18-fluorine fluorodeoxyglucose positron emission tomography |
| ACC | adrenocortical carcinoma |
| CBR | clinical benefit rate |
| CT | computed tomography |
| DHEA | dehydroepiandrosterone |
| ENSAT | European Network for the Study of Adrenal Tumors |
| FDA | Food and Drug Administration |
| ORR | objective response rate |
| OS | overall survival |
| PD-L1 | programmed death-ligand 1 |
| PFS | progression-free survival |
| SF-1 | steroidogenic factor 1 |
| TKIs | tyrosine kinase inhibitors |

ACC is characterized by a high recurrence rate and a highly variable 5-year survival rate, ranging from 13% to 80%, depending on the stage at initial diagnosis.[10,11] Several factors are associated with poor prognosis, such as advanced stage, cortisol-secreting tumors, the presence of tumor thrombus inside major vessels, and incomplete tumor resection.[10–13] A comprehensive approach to diagnosis, treatment, and follow-up is essential, because these factors can significantly influence both prognosis and overall survival. This article reviews the current literature on diagnosis and treatment of ACC, including investigational therapies.

## DIAGNOSIS AND FIRST ASSESSMENT OF ADRENOCORTICAL CARCINOMA

Patients are often diagnosed with ACC when symptoms occur, due to either local mass effects (30%–40%) or hormonal hypersecretion (50%–60%).[10,14,15] However, approximately 15% of cases are identified incidentally during the evaluation of adrenal incidentalomas.[15] Among those with hormonal hypersecretion, hypercortisolism—either isolated or associated with other hormone excess—is present in most patients.[10]

A thorough clinical approach during the initial evaluation is essential. This includes a comprehensive clinical assessment, hormonal workup, radiologic imaging, and histopathologic confirmation. Such an approach not only helps determine hormonal activity at diagnosis and guide perioperative management but also plays a critical role in monitoring disease progression over time (**Table 1**).

In recent years, the urine steroid metabolomics approach has emerged as a promising method to differentiate malignant from benign adrenal tumors, demonstrating acceptable accuracy when combined with tumor diameter and imaging characteristics.[16,17] In a comprehensive analysis of urinary steroid metabolomics, patients with ACC exhibited significantly higher excretion of androgen precursor metabolites (pregnanediol, pregnanetriol, dehydroepiandrosterone [DHEA], and 16α-hydroxy-DHEA) as well as metabolites of active androgens (androsterone and etiocholanolone). Additionally, glucocorticoid precursor metabolites (pregnanediol, pregnanetriol, 17-hydroxyprogesterone, and tetrahydro-11-deoxycortisol) and levels of free cortisol, 6β-hydroxy-cortisol, tetrahydro cortisol, and α-cortisol were significantly elevated in patients with ACC compared to those with benign adrenal tumors.[16]

Adrenal imaging remains a key tool for assessing tumor characteristics and identifying features suggestive of malignancy, such as heterogeneity, irregular margins, necrosis, hemorrhage, and rapid tumor growth.[14,18,19] In addition, findings such as local invasion, venous thrombus, and metastases in lymph nodes and distant organs further

**Table 1**
**Initial evaluation of a suspected case of adrenocortical carcinoma**

| Evaluation Category | Test or Procedure |
|---|---|
| Laboratory workup | |
| Hypercortisolism | Overnight 1 mg dexamethasone-suppression |
| | Adrenocorticotropic hormone |
| | Midnight salivary cortisol |
| | 24 h urine free cortisol |
| Hyperandrogenism and precursors | DHEA sulfate |
| | 17-OH progesterone |
| | Androstenedione |
| | Testosterone (only in women) |
| | Estradiol (in men and postmenopausal women) |
| | 11-deoxycortisol |
| Hyperaldosteronism (only in patients with arterial hypertension and/or hypokalemia) | Serum electrolytes |
| | Aldosterone/renin ratio |
| Pheochromocytoma (even without symptoms of catecholamine excess) | Metanephrine (plasma or 24 h urine) |
| Imaging assessment | |
| Initial adrenal mass assessment | CT or MRI using abdominal or adrenal protocol |
| Histopathologic confirmation | |
| Surgery or biopsy | Weiss criteria |
| | SF-1 |

*Abbreviation:* CT, computed tomography.

support a diagnosis of malignancy.[20,21] In most cases, ACC is diagnosed as a large adrenal mass, typically greater than 4 cm, showing heterogeneity on computed tomography (CT) scans, including necrosis, irregular margins, and evidence of local invasion (**Fig. 1**).[14]

CT and MRI are both suitable for initial assessment, staging, and follow-up of patients with ACC.[8,14] Adrenal lesions with a precontrast attenuation of 10 Hounsfield units (HU) or less on CT are typically associated with benign clinical course and an extremely low risk of malignancy.[22–24] In contrast, lesions with precontrast attenuation greater than 10 HU, often referred to as atypical adrenal masses, encompass a range of pathologic diagnoses, including lipid-poor adrenal adenomas, pheochromocytomas, and ACC, among others.[19,25–27] Increasing the attenuation cutoff to 20 HU improves the diagnostic accuracy of unenhanced CT for excluding ACC, raising specificity from 64% to 80% while maintaining similar sensitivity (100% vs 99%) compared with the currently recommended 10 HU threshold.[17,28]

Although contrast-enhanced CT can show hemorrhage or necrosis in ACC, MRI provides superior evaluation of tumor borders and local invasion, particularly in relation to surrounding organs.[14] MRI is preferred when vascular involvement is suspected, especially for assessing tumor thrombus.[14,29] Additionally, 18-fluorine

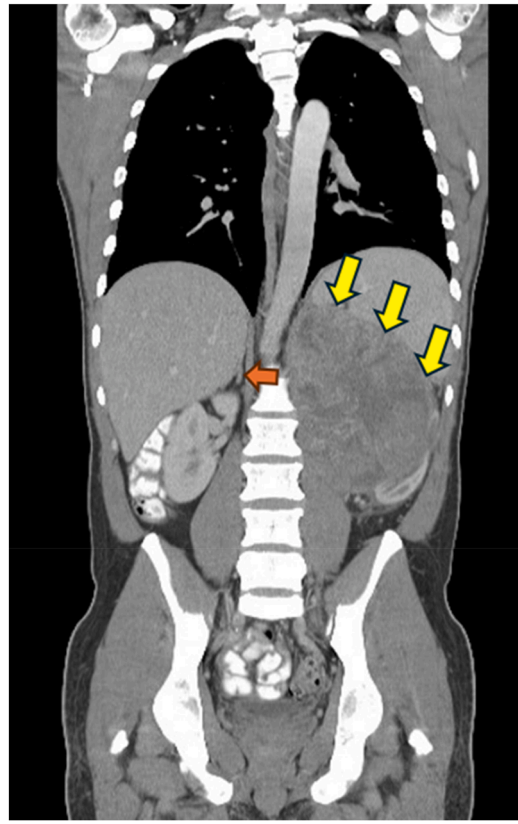

**Fig. 1.** Computed tomography scan of adrenocortical carcinoma. Coronal section of a non-enhanced computed tomography scan showing a large, heterogeneous left adrenal mass consistent with adrenocortical carcinoma (*yellow arrows*), alongside a normal right adrenal gland (*orange arrow*).

fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG PET) is also used for staging and monitoring recurrence, offering high sensitivity and specificity in identifying malignant lesions and metastases that may not be visible on CT.[30–32] Routine use of $^{18}$F-FDG PET is not needed in most cases of adrenal incidentalomas at initial evaluation and has similar clinical benefit to CT in localized ACC, although $^{18}$F-FDG PET can help predict metabolic response and guide clinical decisions in patients with ACC undergoing systemic chemotherapy.[33] A radiomics approach, which employs computational algorithms to extract quantitative features from imaging studies—such as CT scans or MRIs—and creates a dataset for machine learning analysis, has also been explored as a promising tool for evaluating adrenal tumors and predicting ACC prognosis.[34–37]

The definitive diagnosis of ACC is established through histopathologic evaluation. The Weiss score, which assesses features such as proliferation, tumor architecture, and invasion, is the most commonly used set of pathologic criteria to diagnose ACC, and cases with Weiss score of 3 or greater are considered ACC.[38,39] In challenging cases, pathologic stains for steroidogenic factor 1 (SF-1), Melan-A, synaptophysin, alpha-inhibin, and calretinin can help distinguish adrenocortical tumors from

nonadrenocortical tumors. The immunohistochemical expression of SF-1 is now considered the gold standard in reporting suspected ACC due to its high sensitivity and specificity.[40,41] Tumor proliferation (mitotic count per 10 $mm^2$) and proliferative index (Ki67 labeling index) are part of the initial assessment and are used to determine tumor grade (low-grade: $\leq$20 mitoses per 10 $mm^2$; high-grade: >20 mitoses per 10 $mm^2$) and aggressiveness. The Ki67 index is stratified as less than 10%, 10% to 19%, and 20% or greater in ACC and can predict recurrence in patients following complete (R0) resection.[13,42]

Once the diagnosis is confirmed, staging and recurrence risk assessment are required to guide the next steps in ACC management (**Figs. 2** and **3**).

## ADRENOCORTICAL CARCINOMA MANAGEMENT

The curative treatment of ACC is the initial surgical resection of the primary tumor. This highlights the importance of a meticulous and well-executed surgical procedure by an experienced surgeon to prevent tumor spillage into the abdominal cavity and avoid leaving microscopic residual disease at the resection margins.

Adjuvant therapy, as well as treatment in the context of disease recurrence or progression, aims to prolong overall survival (OS) and progression-free survival (PFS) while maintaining an acceptable quality of life.

Postoperative assessment is essential for stratifying the risk of recurrence. Key tumor and clinical characteristics, including resection status, Ki67 proliferative index, and disease stage, are used to determine the recurrence risk. Low-risk patients include those with European Network for the Study of Adrenal Tumors (ENSAT) stage I or II and Ki67 10% or less.[10,43] Average-risk patients include those with ENSAT stage I or II and Ki67 between 11% and 30%, or ENSAT stage III with Ki67 less than 30%.[43] Patients with a very high risk of recurrence are those with Ki67 30% or greater, a large tumor thrombus in the vena cava, ENSAT stage IV, or microscopically positive (R1) or macroscopically positive (R2) resection margins.[43] This stratification guides the management of ACC and follow-up strategies.

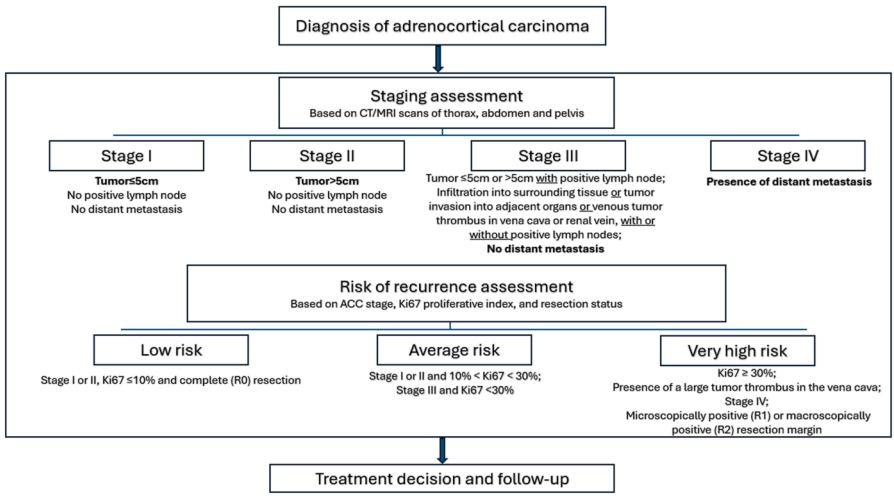


**Fig. 2.** Flowchart summarizing staging and risk assessment in adrenocortical carcinoma (ACC). Staging is performed according to the European Network for the Study of Adrenal Tumors (ENSAT).

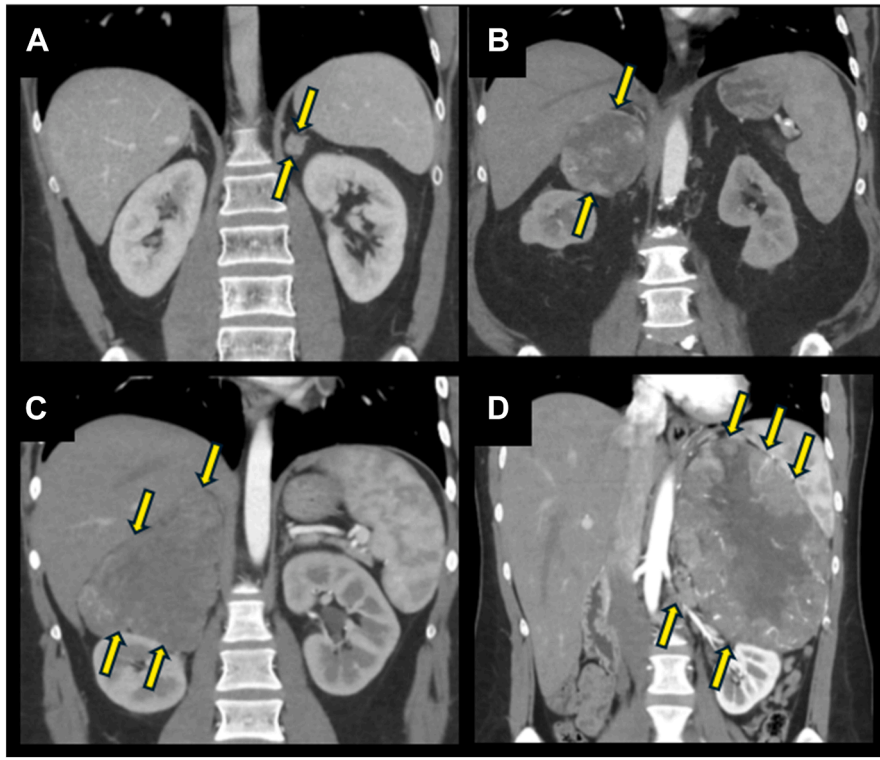


**Fig. 3.** Computed tomography images of adrenocortical carcinoma across ENSAT stages. Coronal sections of computed tomography scans showing adrenal masses consistent with adrenocortical carcinoma (*yellow arrows*). (*A*) Stage I: Small (<5 cm), well-circumscribed adrenal mass without evidence of local invasion or metastasis. (*B*) Stage II: Larger (>5 cm) adrenal lesion with smooth margins and no adjacent organ involvement. (*C*) Stage III: Locally invasive tumor with infiltration into surrounding structures and/or regional lymphadenopathy. (*D*) Stage IV: Advanced disease with distant metastases, including hepatic and pulmonary lesions.

## TREATMENT OF HORMONAL HYPERSECRETION

Patients with established hypercortisolemia require careful preoperative management. Hypercortisolemia increases the risk of opportunistic infections and sepsis, and is also considered a predisposing factor for thromboembolism, often necessitating prophylactic anticoagulation.[44–46] However, retrospective studies of patients with ACC have failed to confirm a direct association between hypercortisolemia and the incidence of venous thromboembolism, which ranges from 13.5% to 23.5% in patients with ACC.[47–49] These studies suggest a multifactorial etiology for venous thromboembolism in the context of ACC.[47–49] Several pharmacologic options have been used for the treatment of hypercortisolemia, including steroidogenesis enzyme inhibitors (ketoconazole, metyrapone, osilodrostat, and abiraterone), glucocorticoid receptor antagonists (mifepristone), and mitotane. In cases of hyperaldosteronism, mineralocorticoid receptor antagonists such as spironolactone and eplerenone in high doses are often needed. Sex steroid excess in ACC may involve androgens or, rarely, estrogens. Androgen-secreting tumors

often cosecrete cortisol and cause markedly elevated testosterone, androstenedione, or dehydroepiandrosterone sulfate (DHEA-S); treatment includes androgen receptor antagonists such as spironolactone, bicalutamide, or flutamide. Estrogen-producing ACCs are rare, and estrogen receptor antagonists or aromatase inhibitors may be considered in severe cases.

## TREATMENT OF LOCALIZED DISEASE

### *Surgical Resection*

Surgical resection of ACC (adrenal mass resection) is the primary and the definitive approach for both diagnosing and treating ACC. Surgical resection enables histopathologic examination of the tumor, as previously discussed. For diagnosing ACC, a surgical specimen is superior to a biopsy specimen because of the heterogeneous nature of the disease, which can lead to misdiagnosis and treatment delays, ultimately impacting survival, especially in stage I and II ACC.[50,51]

The primary goal of the surgery is to achieve an R0 resection, defined as complete tumor resection with no residual disease (microscopically margin-free resection). R0 resection is associated with a lower risk of recurrence and improved OS.[52] Surgical expertise plays a critical role in managing ACC, as a complex and rare disease. However, most adrenal mass resections are performed at institutions that conduct fewer than 6 adrenalectomies per year.[53]

Regarding the surgical technique, open resection remains the standard for ACC, because it is associated with lower rates of positive margins and recurrence.[54–57] Laparoscopic resection has been performed in select centers by experienced surgeons, showing similar oncologic outcomes to open resection.[58–61] Nevertheless, patient selection for laparoscopic resection must be carefully considered only if high-level surgical expertise is available and tumor diameter is less than 6 cm, because the risk of developing peritoneal carcinomatosis is higher compared with the open resection approach.[61,62]

### *Mitotane Therapy and Adjuvant Treatments*

Mitotane has been the only drug approved by the US Food and Drug Administration (FDA) for the treatment of advanced ACC and remains a cornerstone of treatment. Mitotane was first reported as a therapy for ACC in the 1960s, when it was shown to lead to regression of an ACC lesion and suppression of adrenal function.[63] Mitotane inhibits steroidogenesis and can induce apoptosis in adrenal cells. However, the exact mechanism underlying its therapeutic effect remains unclear, because mitotane can disrupt multiple pathways, including inhibition of sterol-O-acyl-transferase 1, leading to the toxic accumulation of intracellular lipids in the adrenal cortex.[64] Mitotane also induces CYP3A4, accelerating the metabolism of drugs processed by this enzyme, including glucocorticoids.[65] This interaction may require higher doses of glucocorticoid replacement and careful selection of coadministered medications, emphasizing the importance of therapeutic drug monitoring.

Mitotane has been prescribed as adjuvant therapy for patients with ACC at risk of recurrence and those with metastatic disease.[10,43,66–68] The ADIUVO trial, an international, multicenter, randomized phase III study, compared adjuvant mitotane therapy with surveillance in patients classified as having low-to-intermediate risk of recurrence. However, the ADIUVO trial was discontinued early due to slow recruitment and did not confirm the superiority of adjuvant mitotane over observation in patients with low-grade, localized ACC, because no improvement in recurrence-free survival was observed in the mitotane group.

Patients diagnosed with ACC and standard risk of recurrence (ENSAT stage I or II and Ki67 between 11% and 30%, or ENSAT stage III and Ki67 <30%), as well as those with very high risk of recurrence (Ki67 ≥30%, large tumor thrombus in the vena cava, stage IV, or R1 resection), often receive adjuvant mitotane therapy based on expert opinion, retrospective studies, and clinical guidelines rather than prospective evidence.[10,43] Additionally, patients with uncertain resection status (RX) are also often considered for adjuvant mitotane therapy and potentially radiation therapy to reduce recurrence rates.[10]

Regardless of the clinical scenario, adjuvant or metastatic, when mitotane is prescribed, drug levels should be regularly monitored, and adverse events should be carefully assessed. The therapeutic level between 14 and 20 mg/L is predictive of treatment response and is associated with prolonged recurrence-free survival.[66,69] The most common adverse events include gastrointestinal symptoms (nausea, diarrhea, and vomiting), adrenal insufficiency (often requiring concomitant glucocorticoid replacement), and neurologic symptoms (such as dizziness and tremors).[70] Continuous monitoring of mitotane safety through drug level assessments and clinical evaluation is effective in mitigating potential adverse events.[70,71]

Retrospective studies of adjuvant chemotherapy for ACC have shown mixed results. One study reported improved recurrence-free survival with adjuvant platinum-based chemotherapy,[72] whereas a large database-based retrospective study showed no impact on OS among patients who received adjuvant chemotherapy.[73] ADIUVO 2, an ongoing multicenter, pragmatic, randomized phase III clinical trial (NCT03583710), is investigating the use of adjuvant mitotane alone versus mitotane combined with cisplatin/etoposide following primary surgical resection of localized ACC with high risk of recurrence. This trial aims to clarify the role of chemotherapy in adjuvant treatment of ACC.

Adjuvant radiation therapy may be beneficial in patients with positive surgical margins following ACC resection, as suggested by some retrospective studies. These studies indicate a reduction in the risk of local recurrence.[74–77] However, other studies did not show significant improvement in recurrence-free survival or OS with the use of adjuvant radiation therapy.

Neoadjuvant systemic therapy, including mitotane and platinum-based chemotherapy (often cisplatin, etoposide, and doxorubicin; cisplatin and etoposide; or carboplatin and etoposide), has shown outcomes similar to surgery alone in patients with borderline resectable ACC, although available data remain limited. A retrospective study evaluating the use of neoadjuvant chemotherapy (mitotane alone, etoposide/cisplatin-based chemotherapy alone, or a combination of both) showed longer disease-free survival in patients with borderline resectable ACC compared with those with more limited and localized ACC who underwent initial surgical resection.[78]

## TREATMENT OF RECURRENT OR ADVANCED ADRENOCORTICAL CARCINOMA

Recurrence of ACC after the initial surgical procedure frequently occurs.[43] A large retrospective study reported that 39% of ACC patients in a cohort of 621 presented with either recurrent or stage IV disease.[52] Patients with unresectable lesions, including those with recurrences and most patients diagnosed with stage III or IV disease, are classified as having advanced ACC.[43] Although mitotane remains the only FDA-approved drug for ACC, the therapeutic landscape is evolving. Targeted therapies and novel treatment strategies are currently under investigation. Numerous clinical trials are actively recruiting patients,[79] offering promising avenues for improved disease control and survival outcomes.

### *Surgery and Metastasectomy*

In cases of metastatic ACC, the extent of surgery significantly impacts OS. Patients benefit from resection of the primary tumor alone or in combination with metastasectomy, showing improved survival compared with those who do not undergo surgery.[80,81] Cases involving macroscopically incomplete resection (R2 resection) should be reviewed by a multidisciplinary expert team. If a local recurrence is detected radiologically in the absence of metastases, a new surgery with curative intent should be considered alone or in combination with other therapy (local interventional [metastasectomy or image-guided locoregional therapy, eg, thermal ablation or embolization techniques] or systemic therapy).[10,43]

### *Mitotane Monotherapy*

Mitotane therapy is a treatment option for advanced ACC, particularly in patients with low-grade tumors, late recurrence, and low tumor burden.[82,83] A retrospective study involving 127 patients with advanced ACC who received mitotane monotherapy reported an objective response rate (ORR) of 21%, with median PFS of 4.1 months and median OS of 18.5 months.[83] Patients with rapidly progressing disease and high tumor burden may benefit more from combined systemic therapy.[10]

### *Cytotoxic Chemotherapy*

Patients who have disease progression during mitotane monotherapy or present with rapidly recurrent or progressive disease should receive cytotoxic chemotherapy, for example, platinum-based chemotherapy is one type of regimen.

The FIRM-ACT study was an investigator-initiated, randomized, controlled, open-label, parallel-group trial that evaluated the efficacy of the etoposide, doxorubicin, and cisplatin regimen combined with mitotane (EDP + M) as a treatment of ACC.[67] Participants were randomized to receive EDP + M or streptozocin-mitotane as first-line therapy, with the option to cross over to the alternate regimen upon disease progression. The EDP + M group had a higher objective tumor response (23.2%) and a longer median PFS of 5.3 months, compared with 9.2% and 2.0 months, respectively, in the streptozocin-mitotane group.[67] Among patients who received EDP + M, the median OS was 14.8 months, compared with 12.0 months for those treated with streptozocin-mitotane.

EDP + M is considered the standard cytotoxic chemotherapy for advanced ACC. However, data guiding the selection of second-line or third-line therapies remain limited. For patients who have disease progression during EDP + M therapy, treatment decisions should be individualized, considering comorbidities, performance status, tumor burden, and the availability of therapeutic options. Whenever possible, enrollment in clinical trials should be considered, because this may offer access to novel and potentially effective treatments.

### *Tyrosine Kinase Inhibitors*

Tyrosine kinase inhibitors (TKIs) have been investigated in cohorts of patients with ACC, but the results have been mixed.[84–87] TKIs are primarily metabolized by cytochrome P450 3A4 (CYP3A4) in the liver, and mitotane is a known inducer of CYP3A4, leading to increased clearance and potentially reduced efficacy of TKIs.[65,88] Because many patients receive mitotane as first-line or second-line therapy, TKI activity may be significantly compromised.

This drug–drug interaction was highlighted in a phase II trial in which sunitinib was administered to patients with refractory ACC.[84] The median PFS was 2.7 months, and

the median OS was 5.4 months.[84] Five patients achieved stable disease as their best response. However, the duration of CYP3A4 induction following mitotane discontinuation remains uncertain, with some studies suggesting that it may persist for at least 2 to 8 months.[84,87]

Sorafenib and axitinib have also been evaluated in phase II trials for ACC. The sorafenib trial was prematurely terminated due to a lack of clinical benefit.[85] In contrast, the axitinib trial reported a median PFS of 5.4 months and a median OS of 13.7 months, although no patients could be evaluated according to Response Evaluation Criteria in Solid Tumors.[86]

Another phase II trial assessed cabozantinib in patients with advanced ACC. The median OS was 24 months, with an ORR of 11% and a clinical benefit rate (CBR, defined as the proportion of patients who achieved complete response, partial response, or stable disease during the study period) of 78%.[87] Notably, a post hoc analysis based on prior mitotane exposure revealed that cabozantinib concentrations remained affected in patients who had discontinued mitotane more than 6 months earlier, suggesting a prolonged impact of mitotane on drug metabolism.[87] Despite this, the trial demonstrated promising activity of TKIs in ACC and highlighted a potential immunomodulatory effect of cabozantinib.[87]

The most commonly reported adverse events associated with TKIs included diarrhea, weight loss, fatigue, dysgeusia, palmar-plantar erythrodysesthesia syndrome, hypertension, and nausea.[87] These adverse events were manageable with TKI dose reductions or treatment interruptions.

### *Immune Checkpoint Inhibitors*

Pembrolizumab has been evaluated in multiple clinical trials involving patients with ACC.[89,90] In a phase II trial that enrolled 39 patients, with a median follow-up of 17.8 months,[89] the ORR was 23%, the CBR was 46.1%,[89] the median PFS was 2.1 months, and the median OS was 24.9 months.[89] Notably, immunohistochemical expression of tumor programmed death-ligand 1 (PD-L1) and the presence of high microsatellite instability or mismatch repair deficiency was not associated with objective response, in contrast to findings reported in other solid tumors studies.[91–97]

Another phase II study of pembrolizumab monotherapy, which included 23 patients and reported a longer median follow-up of 66.9 months, reported a median PFS of 4.0 months and a median OS of 15.5 months.[90] The ORR at 27 weeks or greater was 20%, and the CBR at 27 weeks was 30%.[90] No correlation was observed between PD-L1 expression or tumor-infiltrating lymphocyte scores and treatment response (ORR or CBR). Microsatellite instability status was not available for this cohort. The most commonly reported adverse events included elevated aspartate aminotransferase/alanine aminotransferase, fatigue, pruritus, hypocalcemia, and increased alkaline phosphatase, supporting the favorable safety profile of the drug.[89,90]

Avelumab was investigated in a phase Ib trial, achieving an ORR of 6%, with 42% of patients experiencing stable disease.[98]

Nivolumab monotherapy was evaluated in a phase II trial that was terminated early due to failure to meet its primary endpoint.[99] Only 2 patients achieved stable disease.[99] However, the safety profile was acceptable, with no unexpected adverse events reported.

The combination of nivolumab and ipilimumab (anti-CTLA-4 antibody) showed activity in ACC. In a phase II trial, a CBR of 60% was observed among 6 enrolled patients.[100] Another phase II study involving 16 patients with advanced ACC reported an ORR of 6.25% and a CBR of 50%.[101] A separate trial with 21 patients showed

an ORR of 14% and a CBR of 24%.[102] The most common adverse events were fatigue and rash, and the most frequent grade 3 or 4 immune-related adverse events included hepatic dysfunction and adrenal insufficiency.[100–102]

### *Combination of Tyrosine Kinase Inhibitors and Immune Checkpoint Inhibitors*

A phase II basket trial evaluated the combination of cabozantinib and atezolizumab in 24 patients with ACC.[103] The ORR was 15.4%, including 2 patients who achieved partial responses.[103] Notably, both responders were microsatellite-stable, and 1 was PD-L1–negative. The median PFS was 2.9 months, and the median OS was 13.5 months.[103] The most common adverse events reported in the trial included fatigue, diarrhea, hepatic dysfunction, oral mucositis, nausea, and hypertension.

### *Image-Guided Locoregional Therapies and Radiation Therapy*

Image-guided locoregional therapies have been investigated in ACC and show promise in the management of advanced disease. These modalities include radiofrequency ablation, microwave ablation, cryoablation, chemoembolization, and radioembolization. Image-guided locoregional therapies may be used as standalone treatments or in combination with surgical resection and systemic therapies.[104] Compared with traditional surgery or metastasectomy, image-guided locoregional therapies offer several advantages, including minimally invasive approaches and lower complication rates.[104,105]

Retrospective studies in advanced ACC cohorts have reported a reasonable safety profile, acceptable disease control rates, prolonged life expectancy in patients with metastatic disease, and prolonged time to next line of systemic therapy.[104–107] The disease control rate ranged from 69.7% to 81.4%, with complete response rates between 20.5% and 66.3%, partial response rates between 8.1% and 20.5%, stable disease rates between 7.0% and 28.8%, and progressive disease rates between 18.6% and 30%.[104,107]

Radiation therapy, including conventional radiation therapy, stereotactic body radiation therapy, and brachytherapy, has also shown efficacy in advanced ACC. In a retrospective study of 80 patients with 132 lesions (local recurrences and metastases to the lung, liver, bone, lymph nodes, brain, and soft tissue), responses included 4.5% complete response, 39.4% partial response, and 45.5% stable disease.[106]

The most commonly reported adverse events across these studies were grade 3 complications, such as bleeding, biloma, diarrhea, pneumonitis, intrahepatic hematoma, atrial fibrillation, and electrolyte imbalance, as well as grade 2 events, including bleeding, abscess formation, and pneumothorax.

Although the available evidence is limited and primarily derived from retrospective studies, both image-guided locoregional therapies and radiation therapy appear to be viable options for patients with advanced ACC—particularly those with slow disease progression (defined as a disease-free interval >9 months after primary ACC resection) and low tumor burden (lesions <5 cm), or for symptom management related to pain, local mass effect, or neurologic symptoms.[10,108] However, caution is warranted regarding the low frequency of reported adverse events, which may reflect reporting bias inherent to retrospective study designs.

### *Cell-Based Therapy*

Cell-based therapy is an evolving field and has emerged as a promising strategy for treating aggressive neoplasia. In the context of ACC, studies are limited and primarily based on preclinical models, although one clinical trial (NCT04897321) is currently recruiting pediatric patients.[109–111]

The identification of new tumor neoantigens, such as ROR-1 and B7-H3 (CD276),[109,111] may enable the development of cell-based therapies for patients for ACC. However, significant barriers remain to progress to clinical use, including the localization of T cells to tumor sites, heterogeneity of the tumor microenvironment, and sustained T-cell functionality.[111,112] These challenges are further compounded by the heterogeneity of ACC, particularly in terms of hormonal production and its impact on the tumor microenvironment.

## FOLLOW-UP RECOMMENDATION FOR PATIENTS WITH ADRENOCORTICAL CARCINOMA

Patients diagnosed with ACC should undergo a structured follow-up to monitor disease recurrence and progression. Current guidelines recommend follow-up every 3 months during the first 2 years after diagnosis, followed by evaluations every 6 months until the completion of 5 years.[9,10] After this initial 5 year period, the frequency of follow-up should be individualized based on disease status and therapy, with annual assessments considered appropriate for patients in remission.

Follow-up care should be coordinated by a multidisciplinary health care team to ensure optimal outcomes. Each visit should include a comprehensive clinical and physical examination aiming to identify early signs of recurrence, new hormone excess, or adverse events related to therapy. Biochemical evaluation is recommended, because the hormonal profile serves as a disease-specific fingerprint and may reveal changes in tumor activity.[10]

Imaging studies are essential for the detection of recurrence. Cross-sectional imaging of the chest, abdomen, and pelvis should be performed routinely during follow-up, given that most recurrences are locoregional or involve metastases to the lungs or liver.[10] In selected cases, particularly those with inconclusive findings on conventional imaging, $^{18}$F-FDG PET may provide additional diagnostic information.

## SUMMARY

ACC is a rare and aggressive malignancy that often presents with symptoms related to mass effect or hormonal excess, particularly hypercortisolism. Accurate diagnosis requires a comprehensive evaluation—clinical, hormonal, radiologic, and histopathologic. Surgical resection remains the only curative treatment, highlighting the importance of surgical expertise to prevent tumor spillage and ensure complete removal.

Adjuvant therapies aim to prolong survival and maintain quality of life. Treatment decisions are guided by risk stratification, based on stage, Ki67 index, and resection margin status. Mitotane, the only FDA-approved drug for advanced ACC, is commonly used in patients with intermediate-to-high recurrence risk.

Advanced ACC includes unresectable, recurrent, or metastatic disease. The standard first-line treatment is EDP + M, although second-line options are limited. Investigational therapies include TKIs, immune checkpoint inhibitors, image-guided locoregional therapies, radiation therapy, and cell-based therapies.

## CLINICS CARE POINTS

- The presence of adrenal mass with elevated glucocorticosteroids/precursors *and* androgens/precursors is highly suggestive of ACC.
- Genetic counseling is recommended, especially with a family history of cancer.

- Surgical resection is the only curative treatment.
- Open surgery is the preferred approach for suspected ACC, particularly for adrenal masses greater than 6 cm. Surgical expertise is essential to avoid tumor spillage and ensure complete removal.
- ACC has a high recurrence rate, especially with a high mitotic rate (Ki67 index >20%).
- Mitotane, the FDA-approved treatment of advanced/metastatic ACC, is associated with multiple endocrine side effects that require careful management, especially adrenal insufficiency, which often needs high-dose glucocorticoid replacement.
- Adjuvant mitotane in low-risk ACC (Ki67 <10%) has unproven benefit, as shown in the ADIUVO trial.
- Etoposide, doxorubicin, and cisplatin + mitotane (EDP + M) is the standard first-line regimen for advanced ACC, although response rates are suboptimal.
- Patients who have disease progression during EDP + M therapy (or are ineligible) should be considered for clinical trial enrollment.
- Image-guided locoregional therapies are best suited for patients with slow progression and low tumor burden.
- The role of immunotherapy, targeted therapies, and cell-based therapies in ACC is emerging.
- Follow-up visits (including clinical and physical examinations, hormonal profiling, and routine imaging) should occur every 3 months for the first 2 years, every 6 months until year 5, and annually thereafter, based on disease status.

## DISCLOSURE

The authors have nothing to disclose.

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