Review



# The Management of Adrenocortical Carcinomas in The Era of Precision Medicine

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*Review*

# The Management of Adrenocortical Carcinomas in The Era of Precision Medicine

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**Abstract:** Adrenocortical carcinomas (ACCs) are rare adrenal tumors that occur in hereditary syndromes or sporadically. Even in sporadic cases, somatic alterations in known susceptibility genes are often detected, emphasizing the growing role of genomic profiling. Recent evidence indicates that ACCs vary in their pathogenetic mechanisms, biochemical phenotype, metastatic potential, and prognosis. While surgery remains the primary treatment for localized ACCs, multiple therapeutic options exist for advanced or metastatic disease, although robust prospective data supporting a genomic profiling-oriented approach are still lacking. To enhance personalized management and improve outcomes in this molecularly complex disease, routine genetic testing for germline mutations along with comprehensive genome profiling for somatic mutations and cluster identification should become standard clinical practice. This review summarizes current evidence on ACC diagnosis and treatment, underscoring the need for a more personalized, cluster-based approach in clinical practice.

**Keywords:** adrenocortical carcinoma; rare tumors; multidisciplinary approach; epigenetics; precision medicine

## 1. Introduction

Adrenocortical carcinomas (ACCs) are rare, highly aggressive malignancies originating in the adrenal cortex, with an estimated annual incidence of 0.5-2 cases per million and a median overall survival (OS) of 3-4 years [1,2]. ACC incidence exhibits a bimodal distribution, with the first peak in childhood (ages 1–6) and the second in adults (ages 46–55). While patient sex is generally not considered an important prognostic factor, the impact of age on outcomes remains debated [3-7]. In contrast, tumor stage, assessed by the European Network for the Study of Adrenal Tumors (ENSAT) classification, and tumor grade, determined by the Ki67 index, are clearly linked to prognosis [8-11]. Complete surgical resection is the only curative option for localized disease; however, recurrence rates are high (30-75%). More than half of ACC patients present with advanced or metastatic disease, where 5-year survival drops below 15%. For these patients, mitotane, an adrenocytolytic drug, is the standard systemic therapy, used alone or in combination with the EDP regimen (etoposide, doxorubicin, and cisplatin) [12]. Systemic antineoplastic treatments show limited efficacy in metastatic cases [1,2]. In children, mitotane with or without EDP is also standard, though treatment protocols differ from those in adults, and childhood ACC generally carries a better prognosis [13-15]. Although immunotherapy has demonstrated some tumor burden reduction in selected cases, its overall efficacy remains unproven [16]. Thus, there is an urgent need to explore new therapeutic targets and treatment strategies to improve outcomes in this challenging disease.

## 2. Genetics and Molecular Classification

Weiss et al. first proposed that ACC consists of two pathologic classes that have different mitotic rates and distinct clinical outcomes, developing a proliferation-based two-grade (low and high) system [17]. Further studies on North American patients [18], as well as pediatric ACC patients from North America and Brazil [19], the ENSAT [20] and The Cancer Genome Atlas (TGCA) [21],

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integratively analyzed multiple molecular and genomic platforms, discovering and confirming several important molecular alterations in ACC tumorigenesis and progression.

*2.1. Genomic and Transcriptomic Profiling*

ACC exhibits marked chromosomal instability, underpinning its aggressive behavior and complex molecular pathology [22]. This instability is evident as aneuploidy, with both hypodiploid and hyperdiploid states, and results from recurrent chromosomal amplifications and deletions [21]. A whole-gemome doubling (WGD) is a common event in ACCs, as showed in DNA-copy number analysis [21]. Amplifications frequently involve regions harboring oncogenes such as *MDM2* and *CDK4* on chromosome 12q, which promote unchecked cell cycle progression and tumorigenesis [20,21]. Conversely, deletions cause losses of heterozygosity in tumor suppressor regions, notably affecting *TP53* on 17p13 and *CDKN2A* on 9p. Loss of *TP53*, observed in over 80% of ACCs, compromises DNA repair and apoptosis, correlating strongly with poor prognosis [20,21].

β-catenin (*CTNNB1*) gain-of-function mutations are evident in approximately 25% of both benign and malignant sporadic adrenocortical neoplasms [23]. In adrenocortical adenomas, β-catenin alterations are more frequent in nonfunctioning tumors, suggesting a role in the development of non-secreting adrenocortical adenomas and adrenocortical carcinomas.

A transcriptomic analysis of 51 sporadic adult ACCs revealed that dysregulation of the *TP53* and *CTNNB* pathways significantly contributed to tumor aggressiveness and poor prognosis [24]. The study found that mutations in *CTNNB1*, often altering $Ser^{45}$ of exon 3, leading to β-catenin pathway activation, and *TP53* alterations were mutually exclusive. Among ACCs classified as poor-outcome group, 52% exhibited either *CTNNB1* or *TP53* mutations, while 60% showed abnormal β-catenin or p53 immunostaining [24].

The insulin-like growth factor II gene (*IGF-II*) is involved in the pathogenesis of both familial ACCs, as is the case in Beckwith-Wiedemann syndrome [25], as well as in sporadic ACCs [26,27]. *IGF-II* and *H19*, a gene with a non-translated transcript supposed to be involved in tumor suppression [28,29], mapped contiguously on chromosome 11p15.5, are expressed in a parental origin-specific manner, a phenomenon known as genomic imprinting [30].

Gicquel et al. found that about 80% of the adrenocortical tumors with high IGF-II expression exhibited LOH, which correlated with the abrogation of H19 expression [31].

Dysregulation or rearrangement at 11p15.5 results in significant up-regulation of *IGF2* in ACC, resulting in an autocrine stimulatory loop, fostering cell proliferation and survival [32].

Recent genomic profiling efforts of ACC have identified candidate driver genes such as Zinc and Ring Finger 3 (*ZNRF3*), Telomerase Reverse Transcriptase (*TERT*) and Telomeric Repeat Binding Factor 2 (*TERF2*), identified molecular subgroups with variable clinical outcomes [20,33]. Approximately 20% of ACCs harbor mutations in *ZNRF3*, a gene encoding a transmembrane E3 ubiquitin ligase that normally suppresses Wnt/β-catenin signaling [20,21]. Moreover, telomerase activation is observed in a subset of ACCs, particularly those with mutations in the *TERT* promoter (C228T and C250T). In TCGA study, whole genome doubling analysis led to an evaluation of telomere regulation [21]. *TERT* expression was significantly higher in tumors that underwent the whole genome doubling, leading the authors to postulate that the relationship between the whole-genome doubling and *TERT* expression suggests the important role TERT plays in maintaining telomere length in ACC [20,21].

Interestingly, DNA sequencing of sporadic adrenocortical adenomas recently revealed a recurrent activating L206R mutation in the catalytic subunit of the cAMP-dependent protein kinase A (*PKA*) (*PRKACA*) [34]. This mutation results in constitutive *PKA* activity by disrupting the interaction between *PRKACA* and the regulatory subunits of *PKA* including *PRKAR1A* [35].

In a transcriptomic cluster analysis, de Reniès et al. identified two groups of malignant tumors with very different outcome (C1 and C2) [36]. The study also identified two robust subgroups of tumors in the malignant C1 group. Tumors of the C1A group had a very poor outcome (rate of relapses or metastases, 81%; rate of death, 76%). By contrast, tumors of the C1B group had a much

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better outcome (rate of relapses: 15%; rate of death, 8%). Despite their better outcome, tumors of the C1B group were malignant, as ascertained by the higher rate of recurrences compared to C2 (15% compared with 2%), and the higher pathologic Weiss score (62% ≥ 4 and 85% ≥ 3 in C1B, whereas 69% equal to 0 and 96% ≥ 1 in C2). This study revealed that the combined expression of Discs Large Homolog 7 (DLG7) and PTEN-induced Kinase 1 (PINK1) was the best predictor of disease-free survival (DFS), could overcome the uncertainties of intermediate pathological Weiss scores. Among the malignant tumors, the combined expression of BUB1 Mitotic Checkpoint Serine/Threonine Kinase B (BUB1B) and PINK1 was the best predictor of OS.

Further genomic and transcriptomic profiling has refined ACC classification into two distinct subgroups [20,37].

Tumors belongings to poor-outcome group (C1A) present *TP53* inactivating mutations (C1A-p53), *CTNNB1* activating mutations (C1A-β-catenin) or unindentified alteration (C1A-x). These tumors exhibit high mutation burden, chromosomal instability, CpG Island Methylator Phenotype (CIMP) status, resulting in a 5-year survival rate of approximately 20% [24,36,37].

Conversely, the good-outcome group (C1B) displays non-CIMP status and deregulated miRNA clusters, including MIR483 and *DLK1-MEG3*, achieving a 5-year survival rate of 91% [24,36,37]. The C2 group correspond to adrenocortical adenomas [24,36,37].

### *2.2. Epigenetic Modifications: CpG Island Methylator Phenotype*

CpG islands are regions of the genome rich in CpG sites, which consist of deoxycytidine and deoxyguanosine separated by a phosphate group. These CpG sites are particularly susceptible to epigenetic modifications, specifically DNA methylation [38]. When methylation occurs at these sites, often located in the promoter regions of genes, it leads to chromatin condensation and gene silencing. CIMP was first observed in colorectal cancer, with the inactivation of several tumor suppressor genes or genes critical for immune surveillance [39]. A genome-wide methylation study of 51 ACCs and 84 adrenocortical adenomas, classified carcinomas into CIMP-high, CIMP-low and non-CIMP groups [40]. Hypermethylation correlated with poorer prognosis and was more common in carcinomas than adenomas. This study evidenced an inverse correlation between methylation and gene expression, with the presence of *H19* at the top. Among other genes with a strong inverse correlation, detoxification genes, such as Glutathione S-Transferase Pi 1 (*GSTP1*), Glutathione S-Transferase Mu 1 (*GSTM1*) and Glutathione S-Transferase Theta 1 (*GSTT1*), and tumor suppressor genes G0/G1 Switch 2 (*G0S2*), PLAG1 Like Zinc Finger 1 (*PLAGL1*) and NDRG Family Member 2 (*NDRG2*) were identified.

The global methylation analysis showed various levels among the previous identified transcriptome-based subgroups [24,36,37,40]. Within the subgroups of carcinomas of poor prognosis, almost all the carcinomas from the C1A-p53 and the C1A-x subgroups showed a CIMP-status. All the CIMP-high carcinomas belong to these two subgroups. In contrast, a non-CIMP pattern was observed in the poor-prognosis C1A-β-catenin subgroup and the good-prognosis C1B subgroup. This distribution of hypermethylation among the different subgroups of carcinomas is probably responsible for the prognostic value of hypermethylation. However, considering that some tumors of poor prognosis (from the C1A-ß-catenin subgroup) are not hypermethylated, the prognostic value of DNA-methylation based ACCs classification is limited, further suggesting the need to integrated analysis [40].

The mechanisms underlying CIMP remain unclear. Kerdivel et al. demonstrated that overexpression of *DNMT1* and *DNMT3A* [41], driven by gene amplification and proliferation, is key in ACC CIMP development, although no specific CIMP mutations were identified in ENSAT or TCGA cohorts [20,21].

### *2.3. microRNA Expression and Molecular Stratification*

miRNA expression was assessed in 45 ACCs samples (discovery cohort) and 3 normal adrenal samples in the ENSAT study, identifying 3 distinct miRNA expression clusters [20].

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The Mi1 cluster, characterized by the largest differences in miRNA expression compared to normal adrenal samples, was marked by the upregulation of 11 miRNAs from the miRNA-506-514 cluster (Xq27.3), and the downregulation of 38 miRNAs from the imprinted *DLK1-MEG3* cluster (14q32.2) [20].

The *DLK1-MEG3* cluster includes 2 long noncoding RNAs (*MEG3* and *MEG8*) and 54 miRNAs expressed from the maternally inherited homolog. Single nucleotide polymorphism (SNP) array analysis reveals LOH on chromosome arm 14q in all Mi1 tumors, accompanied by a shift in *MEG3* promoter methylation from hemi- to full methylation. This loss of the maternal unmethylated allele silences the *DLK1-MEG3* cluster, contributing to tumorigenesis.

The Mi2 cluster shows only weak overexpression of the miRNA-506-514 cluster, which has demonstrated oncogenic properties in melanoma [42].

The Mi3 cluster showed no peculiar differences between normal adrenal samples. In an integrative analysis with DNA methylation clusters, Mi3 cluster shows hypomethylation in CpG sites, especially outside CpG islands [20].

In the ENSAT study, transcriptome clusters were strongly correlated with subgroups based on DNA methylation and miRNA expression [20]. Indeed, the C1A subgroup with poor prognosis included almost all CIMP and Mi3 tumors. In contrast, C1B tumors with good prognosis were generally non-CIMP and belonged to the Mi1 or Mi2 miRNA cluster. The mutation rate was significantly higher in the C1A group (mean = 0.75 mutations per megabase) than in the C1B group (mean = 0.32 mutations per megabase), and the key genes and pathways identified by exome and SNP analysis were altered primarily in the C1A group. In contrast, miRNA deregulation was mainly observed in the C1B group.

### *2.4. Integrated Genomic Approaches: Subtypes and Clinical Implications*

Integrated DNA copy-number, DNA-methylation, mRNA-expression, miRNA-expression analysis converged into three Cluster of clusters (CoC) ACC subtypes [21]. A comparison between CoC and C1A/C1B showed that the majority of CoC I were classified as C1B, while most CoC II and CoC III were predicted as C1A. Pan-cancer pathway-enrichment analyses showed significant up-regulation of genes in immune-mediated pathways in CoC I tumors and mitotic pathways in CoC III tumors [21]. CoC I tumors, characterized by low CIMP methylation and mutations in genes such as *ZNRF3* and *MEN1*, are associated with a favorable prognosis. CoC II tumors, with intermediate CIMP methylation and mutations in *TP53*, *CTNNB1*, and *ZNRF3*, have intermediate outcomes, whereas CoC III tumors, marked by high CIMP methylation and mutations in *CDK4*, *RB1*, and *TERT*, are linked to the poorest clinical outcomes. TCGA findings underscore the importance of genomic profiling in stratifying ACC patients. Disease progression rates of the three CoCs were 7%, 56%, and 96%, respectively. Survival analysis showed a dismal median event-free survival of 8 months for CoC III, while median event-free survival time was not reached in CoC I. CoC II was more heterogeneous in outcome with an event-free survival of 38 months. Stage III/IV tumors represented 25%, 47%, and 52% of CoC I, II, and III, respectively [21].

### *2.5. Hereditary Predisposition and Genetic Testing*

For adults with ACC, a basic clinical genetic evaluation is recommended, emphasizing family history and signs of hereditary predisposition. ACC is associated with inherited syndromes such as multiple endocrine neoplasia type 1 (MEN1), familial adenomatous polyposis (FAP), neurofibromatosis type 1 (NF1), Li–Fraumeni syndrome (LFS) and Lynch Syndrome (LS) (Table 1) [43,44].

Particularly in ACC patients, *TP53* germline mutations are diverse, either due to low penetrance alleles or due to de novo mutations, which account for up to 20% of new diagnoses of LFS [45]. The relatively high prevalence of *TP53* germline mutations in patients with ACC have led to the general recommendation of genetic testing for *TP53* mutations and deletion/duplication analysis for all ACC patients. This recommendation is part of the Chompret testing criteria [46].

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Because of the high frequency of de novo mutations, *TP53* genetic testing should be recommended even in the absence of a positive family history. Genetic population screening for individuals with the low penetrance p.R337H variant followed by offering screening for ACC has proven advantageous in Southern Brazil, where the prevalence of this founder mutation is high (up to 90% of children with ACC) [46].

In contrast to pediatric ACC, where up to 80% are linked to *TP53* mutations from LFS, *TP53* screening in adult ACC is less frequent because LFS-related *TP53* mutations occur in only 3-6% of cases [45]. Nevertheless, genetic counseling is advised since about 10% of adult ACC cases have a hereditary basis [48]. The American College of Medical Genetics and Genomics (ACMG) recommends including *TP53*, mismatch repair genes (*MSH2*, *MSH6*, *MLH1*, *PMS2*), and *MEN1* in testing panels [49].

**Table 1.** Syndromic associations with ACCs. NF1: Neurofibromin 1. FLNC: Folliculin.

| Syndrome | Gene/locus | Mechanism | Prevalence | Prevalence of ACC | Other Features |
|---|---|---|---|---|---|
| Li-Fraumeni Syndrome | *TP53* 17p13 | Impaired tumor suppression | 1:20,000 to 1:1,000,000 | 50-80% of children; 3-7% of adults | Breast cancer, brain cancer, sarcoma, lung cancer, leukemia |
| Lynch Syndrome [44] | *MSH2*, *MLH1*, *PMS2*, *MSH6*, *EPCAM* | Microsatellite instability | 1:440 | 3% of adults | Colorectal, endometrial, small bowel, ureteral cancer, pancreatic, prostate cancer |
| Multiple Endocrine Neoplasia Type 1 [50] | *MEN1* | Loss of menin | 1:30,000 | 1-2% of adults | Pituitary adenomas, primary hyperparathyroidism, pancreatic neuroendocrine tumors, other foregut neuroendocrine tumors |
| Familial Adenomatous Polyposis [51] | *APC* | Wnt/β-catenin dysregulation | 1:30,000 | Rare, case reports | Colon polyps, colorectal cancer, thyroid cancer, duodenal adenoma |
| Beckwith-Wiedemann Syndrome [52] | *11p15 Imprinting* | Overexpression of IGF2 | 1:13,000 | Rare, case reports; occur in childhood only | Cancers in childhood, Wilms tumor, hepatoblastoma, rhabdomyosarcoma, neuroblastoma |
| Carney Complex [53] | *PRKAR1A* | Dysregulated cAMP signaling | Rare > 700 patients in the world | Rare, case reports | Pituitary and thyroid tumors, cardiac myxomas, |

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|---|---|---|---|---|---|
| | | | | | schwannomas and other tumors |
| NF1 [54] | *NF1* | Disregulated *RAS* activation | 1:3,000 | Rare, case reports | Gliomas, malignant nerve sheath tumor, benign neural tumors |
| Birth-Hogg-Dube [55] | *FLNC* | mTOR pathway iperactivation | 1:100,000 | Rare, case reports | Skin hamartomas, pulmonary cysts and pneumothoraces, renal oncocytomas and chromophobe renal cell cancers |

## 3. Clinical Presentation, Diagnosis, Staging

### *3.1. Clinical presentation*

ACC may present with a wide range of clinical manifestations or be entirely asymptomatic and discovered incidentally during imaging for other reasons [1-5]. When symptoms occur, they are most often due to hormonal excess. The most common abnormality is hypercortisolism, leading to Cushing syndrome, which typically manifests as a dorsal fat hump, diabetes mellitus, muscle weakness, osteoporosis, hypokalemia, hypertension, mood alterations, insomnia, skin atrophy, and increased susceptibility to infections [56]. Notably, ACC-related Cushing syndrome may present subtly, with primarily muscle weakness, hypokalemia, and constitutional symptoms like fatigue and weight loss. ACC may also cause hyperandrogenism, especially in women, resulting in a virilizing syndrome marked by hirsutism, menstrual irregularities, acne, and temporal balding. In some cases, pure estrogen excess, more common in men, can lead to gynecomastia and testicular atrophy, while hyperaldosteronism may induce hypokalemia and hypertension. In addition to hormonal effects, the tumor's mass effect can produce nausea, vomiting, abdominal fullness, and back pain. Compression or obstruction of the inferior vena cava (IVC) or renal vein may cause leg edema, abdominal collateral circulation, or hydrocele. Although nonspecific malignancy symptoms such as weight loss, night sweats, fatigue, or fever are less common in ACC, they can occur [1-5]. As the tumor progresses, metastasis to regional lymph nodes, lungs, or liver becomes more likely, with bone involvement contributing significantly to morbidity. While brain metastases are relatively rare, they should not be dismissed, especially in patients with neurological symptoms not attributable to treatment side effects. When brain involvement occurs, it most commonly affects the frontal, parietal, and occipital lobes, as well as the meninges and cerebellum, and may present as hemiparesis, seizures, postural instability, headaches, diplopia, ptosis, lethargy, or aphasia [57].

### *3.2. Diagnosis*

Establishing whether an adrenal mass is malignant is critical, as ACC diagnosis is often not obvious. All patients should undergo a comprehensive hormonal work-up to assess for autonomous hormone excess [1,2]. This evaluation includes tests for glucocorticoids, measuring basal ACTH and cortisol, performing a 1 mg dexamethasone suppression test in cases of suspected hypercortisolism or quantifying free cortisol in 24-hour urine when overt Cushing syndrome is present, as well as assessments for sex hormones and their precursors (17-β Estradiol, testosterone, DHEA-S, 17-OH progesterone, and androstenedione) and for mineralocorticoids by evaluating potassium, aldosterone, and the aldosterone/renin ratio in patients with hypertension and/or hypokalemia. In addition, ruling out pheochromocytoma is mandatory through serum and 24-hour urinary metanephrines, keeping in mind that mildly elevated levels (<2 folds) may be non-specific and

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occasionally observed in ACC [1,2]. Urine steroid profiling, particularly via mass spectrometry–based techniques, is increasingly utilized to identify specific steroid metabolites produced by malignant adrenal tumors.

Imaging studies play a central role in distinguishing benign from malignant lesions. CT, MRI, and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) are commonly used, but among these, unenhanced CT is the most reliable for ruling out ACC [1,2]. Benign adenomas typically appear as homogeneous lesions with low CT density (less than 10 to 20 Hounsfield Units [HU]), whereas ACCs are usually large, heterogeneous, low in fat content (resulting in higher HU), with irregular margins and contrast enhancement of solid components [1,2]. An imaging score based on nine parameters, size, attenuation, thin and thick rim enhancement patterns, heterogeneity, calcification, necrosis, fat infiltration, and lymph node prominence, was recently proposed. This score achieved 100% sensitivity and negative predictive value, 80% specificity, and a positive predictive value of 66%, with an area under the curve of 0.974, though further validation is needed [58].

No single imaging modality definitively diagnoses ACC. Malignancy is conclusively determined only by the presence of metastatic lesions in sites normally lacking chromaffin cells [1,2]. Thus, in the absence of such evidence, an adrenal lesion remains only potentially malignant. FDG-PET, for instance, has excellent sensitivity and negative predictive value but limited specificity and positive predictive value, so it is generally reserved for cases with high metastatic risk, such as suspected lesions from other imaging, local invasion, IVC extension, lymph node involvement, tumor size over 5 cm, or known SDHB germline mutations. A recent study tried to determine the prognostic role of the [18F] FDG PET/CT [59]; the authors found that, in treatment-naïve ACC patients, the quantitative PET parameter failed to predict OS, but presence of metastases detected by [18F] FDG PET/CT and Ki-67 index were independently associated with shorter OS. Additional functional imaging techniques include PET with Gallium-68-labelled somatostatin analogues (e.g., DOTATATE, DOTATOC, DOTANOC), particularly useful in SDHB-mutated disease, and CXCR4-directed PET/CT with [68Ga] Ga-pentixafor [60]. The latter has demonstrated uniform CXCR4 expression in both primary tumors and metastases (except in lung lesions), suggesting that CXCR4-directed radioligand therapy could have a broad anti-tumor effect and may help identify patients eligible for such targeted treatment.

Despite advances in imaging and hormonal evaluation, the gold standard for ACC diagnosis remains the anatomo-pathological examination of the surgical specimen, utilizing the Weiss score [1,2,17,61]. Biopsy is generally contraindicated due to the risk of tumor spillage and its negative impact on achieving an R0 resection, except when metastatic disease precludes surgery and histopathologic confirmation is necessary for oncological management [1,2,61]. Data from the National Cancer Database, involving 1410 patients with non-metastatic ACC, demonstrated that adrenal biopsy in T1/T2 tumors was associated with decreased overall survival [3]; patients who underwent biopsy had a median survival of 55 months versus 104 months for those diagnosed clinically, with T1/T2 biopsy patients faring similarly to those with clinically diagnosed T3 tumors [3]. The Weiss score, ranging from 0 to 9, is the established tool for differentiating benign from malignant adrenocortical lesions [1,2,17,61]. It comprises nine histopathologic criteria, each assigned 1 point:

(1) High Fuhrman nuclear grade (III or IV)
(2) Mitotic count >5 per 50 high-power fields (10mm$^2$)
(3) Atypical mitosis
(4) Necrosis
(5) Diffuse architecture >30% of tumor volume
(6) Clear cells ≤25% of the tumor volume
(7) Capsular invasion
(8) Venous invasion
(9) Sinusoidal (lymphatic) invasion

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A modified Weiss score focuses on five criteria: mitotic count, clear cells, atypical mitoses, necrosis, and capsular invasion, with the first two weighted double [1,2,61]. A score ≥3 indicates ACC, while scores between 0 and 2 suggest an adenoma (68).

(1) Mitotic count >5 per 50 high-power fields (10 mm2)
(2) Clear cells in ≤25%
(3) Atypical mitosis
(4) Necrosis
(5) Capsular invasion

The 2022 WHO classification of adrenal cortical tumors further refines the diagnosis by recognizing four subtypes of ACC based on cytomorphological features: conventional, oncocytic, myxoid, and sarcomatoid [61]. In some subtypes, such as myxoid ACC, assessing certain Weiss parameters (like diffuse growth, nuclear atypia, or lymphatic invasion) can be challenging [62]. Therefore, supplementary multiparameter diagnostic algorithms have been developed to aid the workup of adrenal cortical neoplasms [61-63]. These include the (a) reticulin algorithm which can be used for conventional, oncocytic and myxoid adrenal cortical neoplasms, (b) Lin–Weiss–Bisceglia system for oncocytic adrenal cortical neoplasms, and (c) Helsinki scoring system which can be used for conventional, oncocytic and myxoid adrenal cortical neoplasms [61]. The reticulin algorithm, noted for its reproducibility, diagnoses ACC when an altered reticulin network, demonstrated by the Gordon-Sweet silver stain, is present along with at least one of the following: a mitotic count greater than 5 per 50 high-power fields, tumor necrosis, or vascular invasion [61]. The Lin-Weiss-Bisceglia system is tailored for oncocytic adrenal cortical neoplasms, which often present with a Weiss score of 3 and pose diagnostic challenges; it requires that more than 90% of the tumor be oncocytic to qualify as a pure oncocytic neoplasm [61-64]. This system categorizes findings into major criteria (high mitotic rate, atypical mitoses, vascular invasion) and minor criteria (large tumor size or weight, necrosis, capsular invasion, sinusoidal invasion), with malignancy diagnosed by the presence of at least one major criterion, whereas a minor criterion indicates uncertain malignant potential [61]. The Helsinki score integrates the Ki-67 proliferation index from the most active area with necrosis and mitotic count, yielding a quantitative score: values from 0 to 8.5 suggest an adenoma, scores above 8.5 indicate carcinoma, and scores over 17 predict an adverse prognosis with a high likelihood of distant metastases [61-63]. A panel of immunohistochemical markers is also recommended to support the diagnosis. Markers such as SF1, inhibin-alpha, calretinin, melan-A help confirm ACC, while chromogranin A is useful for differentiating pheochromocytoma [61]. In pediatric patients, the use of the Weiss criteria, which are effective in adults, tends to overdiagnose tumors that behave benignly [15,61]. Therefore, the Wieneke criteria are currently preferred for diagnosing pediatric ACC, ensuring more accurate classification and management in this population [61,65]. Overall, an integrated diagnostic approach combining hormonal assays, advanced imaging techniques, and detailed pathological evaluation is essential for the accurate diagnosis and appropriate management of ACC.

### *3.3. Staging*

The ENSAT/TNM classification is recommended for assessing ACC stage and is endorsed by the UICC and WHO [1,2]. According to ENSAT, ACC is categorized into four stages (Table 2). Stage I (≤5 cm) and Stage II (>5 cm) tumors remain confined to the adrenal gland. Stage III tumors extend into adjacent tissues, such as para-adrenal fat or nearby organs or involve locoregional lymph nodes, while Stage IV is defined by the presence of distant metastases.

**Table 2.** European Network for the Study of Adrenal Tumors (ENSAT) staging system for ACC. T1: tumor ≤ 5 cm; T2: tumor > 5 cm; T3: tumor infiltration into surrounging tissue; T4: tumor invasion into adjacent organs or venous tumor thrombus in vena cava or renal vein. N0: no positive lymph nodes; N1: presence of positive lymph nodes. M0: no distant metastases; M1: presence of distant metastases.

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| ENSAT Stage | Definition |
|---|---|
| I | T1, N0, M0 |
| II | T2, N0, M0 |
| III | T1-T2, N1, M0 |
| | T3-T4, N0-N1, M0 |
| IV | T1-T4, N0-N1, M1 |

To improve prognostication in advanced cases, a modified ENSAT (mENSAT) system has been proposed. In this system, Stage III includes tumors invading surrounding tissues/organs or the renal/vena cava, and Stage IV is further subdivided into IVa, IVb, and IVc based on the number of metastatic sites (with involvement of two, three, or more than three organs, including nodal metastases) [1,2,11]. Libé et al. demonstrated the prognostic significance of this subclassification, reporting 5-year overall survival rates of 50% for Stage III, 15% for Stage IVa, 14% for Stage IVb, and 2% for Stage IVc (61). Approximately one-fifth of ACC patients present with Stage IV disease, most commonly metastasizing to the lung (≈45%) and liver (≈42%), with bone involvement being less frequent [11]. Therefore, a CT scan covering the chest, abdomen, and bones is indicated for staging, with abdomen MRI added if hepatic or vena cava infiltration is suspected [1,2]. Although the ESE guidelines [2] in 2018 did not recommend routine [18F] FDG PET-CT, recent data challenge this view [66,67]. In a multicenter prospective study, a tumor SUVmax to liver SUVmax ratio greater than 1.5 yielded 87% sensitivity, 86% specificity, 57% positive predictive value, and 97% negative predictive value, suggesting that FDG PET-CT effectively complements adrenal washout CT in evaluating adrenal masses [68]. This recommendation is reinforced by data from a recent meta-analysis [69].

## 4. Therapeutic Options

A multidisciplinary approach is crucial for developing a personalized ACC treatment plan [1,2,66,67]. This plan considers patient factors and tumor characteristics (location, size, extent, biochemical profile, imaging, genetic background). The team must weigh treatment options to ensure optimal outcomes, with surgery remaining the mainstay for most localized ACCs.

### *4.1. Surgery*

Surgical resection remains the primary treatment for localized ACC, particularly in stages I, II, and select stage III cases, as it offers the only potentially curative option [1,2,66,67]. Preoperative hormonal evaluation is essential to assess tumor functionality, especially cortisol secretion, and to identify the risk of postoperative adrenal insufficiency, which may necessitate hormone replacement therapy. Guidelines from the National Comprehensive Cancer Network (NCCN) [70], American Association of Clinical Endocrinologists (AACE) [71], and the Association of Endocrine Surgeons (AAES) [72] recommend open adrenalectomy with en bloc lymph node dissection to reduce peritoneal spread and facilitate removal of adjacent structures when needed. Given ACC's thin-walled capsule, meticulous surgical technique is crucial to prevent tumor rupture and spillage. Achieving an R0 resection, complete removal with negative margins, is key for reducing recurrence and may require resection of surrounding organs such as the kidney, pancreas, spleen, liver, or diaphragm [66,67,70-72]. While laparoscopic adrenalectomy has shown favorable outcomes in high-volume centers, its use is limited outside specialized settings. Both laparoscopic and open approaches can achieve similar R0 resection rates; however, conversions from laparoscopic to open surgery are associated with poorer survival outcomes, underscoring the importance of careful patient selection [66,67,70-72]. Robotic adrenalectomy is emerging as a potential alternative as surgical technology evolves, while retroperitoneoscopic adrenalectomy remains less common due to its complexity, particularly for tumors larger than 4-6 cm [66,67,70-72]. Routine ipsilateral nephrectomy is not recommended unless there is evidence of renal invasion, as adrenal tumors rarely invade the kidney;

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nephron-sparing surgery should be prioritized. Left-sided tumors may require splenectomy if splenic vessels are compromised, while right-sided ACCs with direct IVC involvement may necessitate partial IVC resection [66,67,70-72]. Locoregional lymphadenectomy, involving periadrenal and renal hilum nodes, is recommended for suspected or confirmed ACC, with extended dissection of any suspicious nodes identified preoperatively [66,67,70-72]. Lymph node involvement is a critical prognostic factor: patients with N0 disease have a median OS of 88 months, compared to 35 months for those with 1–3 positive nodes and 16 months for those with more than four positive nodes. Comprehensive lymphadenectomy has been shown to reduce recurrence risk and improve survival [66,67,70-72]. ACC recurrence occurs in up to 75% of cases, necessitating individualized management [73]. For patients with a disease-free interval (DFS) of 12 months or longer, surgical resection or ablation is recommended if complete eradication is feasible. A meta-analysis of 11 studies indicated that reoperation for recurrence yields better survival outcomes than non-surgical treatments, though patients with multiple recurrences or shorter disease-free intervals benefit less [74]. In major referral centers, cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (HIPEC) is increasingly utilized for ACC with peritoneal involvement. HIPEC combines aggressive tumor resection with heated chemotherapy to target residual microscopic disease [75]. Although studies show promising results, such as a median DFS of 19 months in one study and 12 months in another, larger trials are needed to establish its definitive role in ACC management

### *4.2. Neoadjuvant Therapy*

Upfront surgery is effective for early-stage ACC but may be suboptimal for locally advanced or metastatic cases due to high recurrence risk. For patients with resectable or borderline resectable (BR) ACC, neoadjuvant chemotherapy followed by surgery can be considered [66,67,70]. Approximately 50% of patients respond to the standard EDP-M regimen, and neoadjuvant treatment can reduce tumor size, increase the likelihood of achieving an R0 resection, and preserve adjacent organs. It also permits the administration of nephrotoxic drugs prior to nephrectomy, if necessary, and helps identify patients most likely to benefit from radical surgery [76]. BR disease encompasses tumors that are surgically challenging due to anatomical, biological, or patient-related factors. Anatomically, these tumors may require multi-organ resection or are at high risk for positive margins on preoperative imaging. Biologically, BR disease includes tumors with suspected metastases or resectable oligometastatic disease. Patient-related factors, such as significant comorbidities, may contraindicate upfront surgery.

A retrospective study on neoadjuvant EDP-M in BR ACC showed similar rates of margin-positive resections between BR and clearly resectable groups, with a median DFS of 28 months for resected BR ACC compared to 13 months for resectable cases, although OS did not differ significantly [76]. Although randomized studies are lacking, neoadjuvant therapy appears to help select patients likely to benefit from surgery. Multidisciplinary evaluation is essential, as aggressive multimodal treatment can yield promising long-term disease-free outcomes.

### *4.3. Adjuvant Therapy*

Mitotane is the only approved drug with specific cytotoxic activity on adrenal cortical cells and is used both in the adjuvant setting for high-risk, resected ACC and in inoperable or metastatic disease, either alone or combined with chemotherapy [1,2,66,67]. As an isomer of dichlorodiphenyltrichloroethane (DDT), it is directly cytotoxic to adrenal tissue. Mitotane acts by selectively destroying adrenal cortical cells and inhibiting steroidogenesis via the enzyme sterol-O-acyltransferase (SOAT1) [77]. It induces mitochondrial lipid accumulation and endoplasmic reticulum stress, triggering apoptosis and thereby exerting both antitumor and endocrine effects, including control of hormone hypersecretion [77]. Despite its benefits, managing mitotane therapy is challenging. Plasma concentrations above 14 mg/L correlate with efficacy in advanced ACC, yet optimal exposure levels in the adjuvant setting remain debated [1,2]. Endocrine side effects are common; mitotane significantly suppresses adrenal cortical function, necessitating glucocorticoid

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supplementation titrated to individual clinical needs (e.g., fatigue and muscle weakness). It frequently induces central hypothyroidism, which is managed with levothyroxine replacement. In men, hypogonadism is observed in 26–57% of cases, while in women, mitotane may cause menorrhagia, endometrial thickening, and ovarian cysts due to estrogenic effects [1,2].

Mitotane treatment is deemed unsuccessful if disease recurs or progresses in advanced/metastatic cases or if it fails to control Cushing's syndrome secondary to ACC. The benefit of systemic adjuvant treatments in ACC remains unclear due to conflicting study results. Mitotane has demonstrated efficacy in metastatic disease and is frequently employed as adjuvant therapy for high-risk patients (e.g., those with Ki67 >10%, Stage III disease, or R1 resection) [1,2]. A 2007 retrospective analysis by Terzolo et al. reported improved RFS in patients treated with mitotane compared to those untreated [78]. In contrast, a 2016 study by Postelwait et al. found no significant improvement in RFS or OS with adjuvant mitotane in high-risk patients [79]. A meta-analysis of five retrospective studies involving 1249 patients did show significant improvements in both RFS and OS for post-surgical ACC patients receiving mitotane [80].

More recently, the randomized phase III ADIUVO trial, which enrolled low- to intermediate-risk post-surgical patients (target plasma levels 14–20 mg/L), found no significant increase in 5-year recurrence-free survival (79% versus 75%) compared to surveillance; the trial was discontinued prematurely due to slow enrolment [81]. These findings suggest that low- to intermediate-risk patients (Stage I–III, Ki67 <10%) are unlikely to benefit from adjuvant mitotane.

Ongoing trials, such as the ADIUVO-2 phase III study (NCT03583710), aim to compare adjuvant mitotane alone versus mitotane combined with chemotherapy in high-risk post-surgical ACC patients [82]. ACACIA trial (NCT03723941) is evaluating the efficacy of cisplatin/etoposide (EP-M) as compared to observation/mitotane after primary resection of localized ACC. These studies will help clarify the optimal adjuvant approach in ACC management [83].

The role of adjuvant radiotherapy (RT) in localized ACC remains controversial [1,2]. Although several recent studies suggest that adjuvant RT can significantly reduce local recurrences, its impact on RFS and OS is unclear.

A recent study compared 46 patients receiving adjuvant RT after surgery, at the median dose of 45.0 Gy (range: 30-54) with 59 matched, with a median follow up time of 36.5 months. In comparison to the no adjuvant RT group, patients with adjuvant RT had better 3-year OS (87.9% vs 79.5%, P=0.039), especially for patients with ENSAT I/II stage (P=0.004). Adjuvant RT also improved the median DFS time from 16.5months (95%CI, 12.0-20.9) to 34.6months (95%CI, 16.1-53.0). Toxicity of RT was generally mild and moderate with six grade 3 events [84].

Another retrospective analysis of 16 patients found no significant benefit in local recurrence–free survival, distant recurrence-free survival, or overall survival compared to 32 matched patients without RT [85].

Conversely, a study of 20 matched patients demonstrated that adjuvant RT significantly improved local control (hazard ratio [HR] 12.59; 95% CI, 1.62–97.88) but had no effect on overall survival (HR 1.97; 95% CI, 0.57–6.77) [86].

In a study of 171 patients, adjuvant RT was more often administered to those with positive resection margins; while no OS difference was seen in the entire cohort, patients with positive margins who received RT experienced a 40% reduction in yearly risk of death (HR 0.60; 95% CI, 0.40-0.92) [87].

A meta-analysis confirmed that adjuvant RT significantly reduces local recurrence (relative risk 0.24; 95% CI, 0.12–0.49) but does not affect disease-specific or overall survival [88].

Most recently, a single-institution propensity-matched analysis reported that adjuvant RT was associated with improved local recurrence-free, overall recurrence-free, and overall survival [89]. The ESE/ENSAT 2018 guidelines did not reach consensus on the routine use of adjuvant RT in ACC [1,2]. They recommend against routine RT in patients with Stage I–II disease and R0 resection but suggest that RT (50-70 Gy over a period of 4 weeks) may be considered on an individual basis, often in combination with mitotane therapy, in patients with Stage III disease or R1/Rx resections [1,2].

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*4.4. Systemic Therapy*

In 2012, Fassnacht et al. showed that combining chemotherapy with mitotane (EDP-M) improved overall response rates (ORR) and PFS compared to streptozocin with mitotane (S-M). The FIRM-ACT trial, the first randomized study in ACC, enrolled 304 patients and evaluated the EDP-M regimen, comprising etoposide (100 mg/m² IV on days 2–4), doxorubicin (40 mg/m² IV on day 1), and cisplatin (40 mg/m² IV on days 3–4) combined with daily oral mitotane targeting plasma levels of 14–20 mg/L. While OS did not differ significantly between arms, ORR was 23.2% for EDP-M versus 9.2% for S-M, and PFS was 5.3 months versus 2.0 months, respectively [90].

Although the combination showed slightly higher adverse events, particularly bone marrow toxicity and infections, EDP-M has become the standard first-line therapy for ACC.

For patients with a low tumor burden or poor performance status, mitotane can be used as a monotherapy [91]. For adult patients, the initiation of mitotane treatment involves two options to attain a therapeutic range, a "low-dose regimen" (starting at 1 g/day and increasing to 3 g/day within 2 weeks) and a "high-dose regimen" (starting at 1.5 g/day and escalating to 6 g/day in 4–6 days). No significant difference was observed in concentration or side effects between the two methods [92].

Other chemotherapy regimens have been explored. A phase II study of docetaxel and cisplatin administered every three weeks in metastatic ACC yielded a 21% ORR, with neutropenia as the most common grade 3-4 toxicity; median PFS and OS were 3 months and 12.5 months, respectively [93].

In a multicenter phase II study of 28 patients, second- or third-line therapy with gemcitabine and 5FU/capecitabine (maintaining mitotane) produced one complete and one partial response, with median PFS of 5.3 months and OS of 9.8 months, accompanied by manageable cytopenia and mucositis [94].

Capecitabine plus bevacizumab, used as salvage therapy in 10 patients, demonstrated no objective responses and a median survival of 4.1 months [95].

In 2016, Kroiss et al. evaluated trofosfamide, a drug belonging to the class of oxazaphosphorines such as cyclophosphamide and ifosfamide, in 27 refractory ACC patients; most experienced only grade 1-2 adverse events, with 23% achieving stable disease, a median PFS of 2.0 months, and OS of 6.6 months [96].

Another study by Kroiss on thalidomide in 27 refractory ACC patients showed no responses, with median PFS of 2.8 months and OS of 9.1 months, and only mild side effects [97].

Retrospective evaluation of temozolomide in 28 patients revealed a 21% ORR, with median PFS of 3.5 months and OS of 7.2 months [98].

A phase II trial with cabazitaxel in 25 patients as second- or third-line therapy reported no objective responses, though 36% had stable disease; median PFS and OS were 1.5 and 6.0 months, respectively, with tolerable nausea and anemia [99].

Ferrero et al. investigated low-dose, metronomic chemotherapy in 5 patients with indolent, refractory ACC who had progressed on gemcitabine/capecitabine. Treatment with daily oral etoposide (50 mg) or cyclophosphamide (50 mg) plus mitotane yielded partial responses or stable disease in two patients, with good tolerability [100].

Turla et al. investigated the efficacy of Megestrol Acetate in addition to EDP-M as first line therapy in 24 patients with metastastic or unresectable adrenocortical carcinoma with low performance status [101]. The association resulted well tolerated and non-inferior to EDP-M administered in patients will good performance status.

There is no established sequence for these therapies. As treatment lines progress, the benefit of mitotane diminishes and may eventually be omitted, especially when metastatic disease overshadows the endocrine component.

4.4.1. Immunotherapy

Immunotherapy has emerged as a potential treatment for advanced ACC, though results have been mixed. While ACC has a high rate of single germline mutations, it exhibits low somatic mutation rates, limiting response to immune checkpoint inhibitors (ICIs) [20,21]. However, recent studies

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suggest that ICIs may benefit certain patient subgroups, particularly those with MMR deficiencies, found in up to 14% of ACC cases [20,21,102].

Several phase II trials have evaluated pembrolizumab, an anti-PD-1 antibody, in advanced ACC. In the NCT02721732 trial, 14 patients were treated, with an overall response rate (ORR) of 14%, including two partial responses (PRs), seven stable disease cases, and five progressing. Notably, six patients had disease stabilization lasting over four months, suggesting a subgroup with indolent disease [103].

Another trial (NCT02673333) with 39 ACC patients reported an ORR of 23% and a disease control rate (DCR) of 52%. Median PFS was 2.1 months, and median overall survival (OS) was 24.9 months [104].

A third study reported an ORR of 15% and a clinical benefit rate of 54% [105], leading to pembrolizumab's inclusion in NCCN guidelines for advanced ACC, especially in chemotherapy unfit patients or with slow-growing disease [70]. However, steroid-induced immunosuppression in ACC patients may limit ICI effectiveness, suggesting that combination therapies should be explored.

Nivolumab, another PD-1 inhibitor, was assessed in a phase II trial (NCT02720484) involving 10 patients who had failed platinum-based therapies. The best response was an unconfirmed PR, with two patients achieving stable disease. Due to the lack of significant responses, the trial was terminated early [106].

Avelumab, a PD-L1 inhibitor, was tested in the JAVELIN phase Ib study (NCT01772004) in 50 ACC patients. ORR was only 6%, with three PRs. Median PFS was 2.6 months, and OS was 10.6 months. While well tolerated, the results were modest [107].

A prospective basket phase II trial, evaluating the combination therapy Atezolizumab plus Cabozantinib, was conducted on 93 patients, of whom 24 had ACC. The ORR was 8.3%, with a median PFS of 2.9 months (95% CI 2.8–5.7) for those with ACC. Adverse reactions of grade ≥ 3 were observed as fatigue (7.5%), neutropenia (6.5%), and increase in liver enzyme levels (6.5%). Two patients died due to drug-induced ischemic stroke and pancreatitis [108].

Notably, no trials have assessed the combination of anti-CTLA-4 and anti-PD-1 blockade in ACC. The CA209-538 study enrolled ACC patients for combination nivolumab and ipilimumab (anti-CTLA-4), but no ACC-specific results have been reported [109].

The phase II basket trial SWOG S1609, evaluated the efficacy of Dual Anti-CTLA-4 and Anti-PD-1 blockade in rare tumors, including 21 patients in an ACC cohort. This cohort included pretreated patients, with a median of 2 previous treatments. The ORR was 14%, 6 months PFS was 24%, 6 months OS was 76% [110]

Despite limited success, pembrolizumab and other ICIs show potential in select patients. Further research is needed to optimize patient selection and explore combination strategies to enhance efficacy.

#### 4.4.2. VEGFs/TKIs

While immunotherapy shows promise in ACC, targeted therapies are under active investigation, though no specific agents have yet been approved.

A phase II trial evaluated dovitinib, a fibroblast growth factor receptor (FGFR) inhibitor, in 17 patients with metastatic or locally advanced ACC. This study reported no objective responses, a median PFS of 1.8 months, and only 23% of patients achieving stable disease at 6 months [111]. The FGF/FGFR pathway plays a key role in both embryogenesis and adrenal tumorigenesis; preclinical and clinical studies demonstrate that FGFR 1-4 are upregulated in ACC, and high expression is linked to poor prognosis, making them potential targets.

Several trials are investigating anti-angiogenic agents, particularly those targeting vascular endothelial growth factor (VEGF).

Axitinib, a VEGF inhibitor, was studied in 13 patients with metastatic ACC in a phase II trial, where the median PFS was 5.48 months and OS was 13.7 months [112].

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Cabozantinib, which inhibits c-MET, VEGF, AXL, and RET, has also been explored. In a single arm, phase II study enrolling 18 patients with progressive ACC after mitotane treatment, after a median follow up of 36,8 months, median PFS was 6 months, suggesting some benefit from this multi-targeted agent [113]. The ongoing CaboACC phase II trial (NCT03612232) is further evaluating cabozantinib in advanced ACC [114].

Another promising combination involves lenvatinib, a multikinase VEGF inhibitor, and pembrolizumab. A small retrospective case series reported that this regimen was well tolerated, with 25% of patients achieving partial responses and 12.5% showing stable disease [115]. This proof-of-concept supports further investigation, with the Accomplish phase II trial (NCT05036434) planned in advanced ACC.

Sunitinib, a multi-tyrosine kinase inhibitor, was evaluated in a phase II trial of 35 patients with refractory ACC, yielding a median PFS of 2.8 months and OS of 5.4 months, indicating modest benefit [116]. Ongoing research continues to explore these targeted approaches in ACC treatment.

#### 4.4.3. IGF2/IGF1-R Pathway Inhibitors. Insulin-Like Growth Factor 1 Receptor

IGF overexpression and activation of IGF receptor (IGFR) and mTOR pathways are frequently observed in ACC, leading to the development of targeted therapies. However, clinical trials have yielded limited success.

In a phase I study, figitumumab, an anti-IGF-1R antibody, was tested in 14 patients with refractory ACC [117]. While no objective responses were observed, 57% achieved stable disease, with mild toxicities like hyperglycemia, nausea, and fatigue.

In 2013, a phase II trial combined cixutumumab, another IGF-1R antibody, with the mTOR inhibitor temsirolimus in 26 patients [118]. No objective responses occurred, but over 40% of patients achieved stable disease. Side effects included mucositis, thrombocytopenia, and hyperglycemia.

A phase II trial by Lerario et al. examined cixutumumab with mitotane as a first-line therapy in 20 patients, but due to slow enrollment and limited efficacy, it was discontinued. Only one partial response was recorded (5% ORR), with a median PFS of 1.5 months [119].

Linsitinib, an oral dual IGF-1R/insulin receptor inhibitor, initially showed promise in early trials [120]. However, The GALACCTIC trial, a phase III randomized study, by Fassnacht et al., in 139 patients with advanced ACC found no survival benefit for linsitinib over placebo (median OS: 323 vs. 356 days, $p = 0.77$) [121]. Despite these disappointing results, strategies targeting alternative pathways, such as Wnt/β-catenin or CDK overexpression, may offer new therapeutic avenues for ACC.

#### 4.4.4. mTORC1 Inhibitors

Hyperactivation of kinase activity (*RAS*/*RAF*/*ERK* or *PI3K*/*AKT*/*mTOR* pathways) is a common finding in patients with ACCs. Everolimus, a derivative of rapamycin, acts as a signal transduction inhibitor, targeting mTOR. In a small exploratory study, no clinically meaningful response was observed with everolimus in four patients with advanced ACC [122].

#### 4.4.5. EGFR Inhibitors

Presence of EGFR in adrenocortical tumors has been demonstrated in the past. The expression of EGFR in adrenal tumors indicates a malignant phenotype, which can be used to differentiate carcinomas from adenomas and is a potential target for treatment. Erlotinib showed poor activity in combination with gemcitabine in advanced refractory ACC, in a study enrolling 10 patients with progressive ACC after two to four previous systemic therapies [123]. So, its use as salvage therapy should not be considered. Although EGFR expression level did not correlate with the clinical outcome in patients, in vitro experiments demonstrated that inhibition of EGFR signaling lead to moderate growth inhibition in ACC cells

#### 4.4.6. PI3Kγ Inhibitor

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Eganelisib (IPI-549) is an orally consumed PI3Kγ inhibitor with remarkable anticancer properties, both individually and when combined with PD-1/PD-L1 inhibitors, as demonstrated in preclinical research. A phase I/Ib study evaluated the safety and tolerability of eganelisib as monotherapy and in combination with nivolumab, although one patient with ACC achieved PR in the dose escalation cohort with combination treatment, none out of five patients with advanced ACC showed response in the dose expansion cohort [124].

#### 4.4.7. PLK-1 Inhibitor

PLK1 is prominently expressed during cell division, and its elevated expression is observed in various cancer types [125]. TKM-080301 is a PLK1-targeted small interfering RNA (siRNA). In a phase I/II study, 16 patients received treatment doses of 0.6 or 0.75 mg/kg/week for up to 18 cycles, and tumor responses were evaluated in 8 of them. A significant decrease in tumor size was detected in a 51-year-old man with metastatic intraperitoneal nonfunctional ACC, and the removed tumor exhibited almost total necrosis [126]. Several patients stopped the treatment for various reasons, including disease progression, and frequently reported side effects that included fever, chills, back discomfort, reactions to infusion, and nausea.

#### 4.4.8. Other Drugs

Gossypol (AT-101). AT-101, the levorotatory enantiomer of gossypol from cottonseed oil, is a BH3 mimetic that inhibits BCL-xL, BCL-2, BCL-w, and MCL-1. It disrupts their function, promoting apoptosis in cancer cells [127]. Although AT-101 has been tested in several malignancies, including glioma, breast, lung, and colorectal cancer, a phase II trial in 29 patients with advanced ACC showed no clinical benefit [128].

Progesterone (Pg) has demonstrated anti-tumor activity in multiple cancers, including ACC. Preclinical studies showed that Pg reduced viability in ACC cell lines (NCI-H295R) and primary ACC cultures by interacting with progesterone receptors (PgRs) through genomic and non-genomic pathways [129]. Additionally, Pg inhibited β-catenin nuclear translocation, a key oncogenic pathway in ACC, and enhanced mitotane's antitumor effects.

Nevanimibe, a selective SOAT-1 inhibitor, demonstrated some preclinical activity but failed to show significant objective responses in a phase I trial with 48 ACC patients [130].

Around 50% of ACCs produce glucocorticoids (GC), and hypercortisolism is associated with worse survival outcomes. Blocking the glucocorticoid receptor (GR) could enhance immune-related gene expression and stimulate an anti-tumor immune response. The phase Ib trial (NCT04373265) is currently investigating the combination of relacorilant, a nonsteroidal GR antagonist, with pembrolizumab in advanced ACC patients with hypercortisolism [131].

Although promising, these novel strategies require further investigation to determine their efficacy in ACC treatment.

#### 4.4.9. Radioisotopes

Radiolabeled Metomidate has been used for adrenocortical imaging, showing high uptake in primary and metastatic ACC [132]. Hahner et al. developed I131-Metomidate to target metastatic lesions [133]. In a study of 11 patients evaluated with I123-Metomidate, with advanced ACC not amenable to radical surgery and exhibiting high uptake of [123I]IMTO in their tumor lesions were offered treatment with [131I]IMTO (1.6-20 GBq in one to three cycles of [131I]IMTO) [133]. Stable disease was achieved in 5 patients, with a median PFS of 14 months. Adverse effects were mild (grade 1–2), primarily affecting bone marrow [133].

Theragnostic approaches are supported by growing evidence of efficacy in pre-treated advanced ACC [134,135].

Somatostatin receptors are highly expressed in ACC. Grisanti et al. evaluated Ga-68 DOTATOC uptake in 19 patients, with two showing significant metastatic site uptake. One patient treated with

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Lu177-DOTATOC had stable disease for 12 months; another had 4 months of disease stabilization and symptom improvement [136].

### *4.5. Epigenetic Therapies*

#### 4.5.1. HDAC Inhibitors

Histone tails, as they have some positively charged amine groups on their lysine and arginine amino acids, interact with DNA backbone composed of phosphate groups (negatively charged). Acetylation is used to neutralize the positive charges previously cited, so that the binding to the DNA is compromised. This decreased binding allows chromatin expansion, permitting genetic transcription to take place. Histone deacetylases have the role to remove the acetyl groups, so that the histone tails can bind against the DNA backbone. The increased DNA binding condenses DNA structure and prevents the transcription. Hyperacetylated chromatin is active in transcription, while hypoacetylated chromatin is silent.

Michael J. Demeure et al. [137], McKale R. Davis et al. [138], and McKale R. Montgomery et al. [139] investigated the effects of HDAC inhibitors (HDACi) in ACC.

In Demeure's study, ACC cell lines (NCI-H295R and SW13) were analyzed for gene expression and biomarkers. Dysregulation of the p53 pathway and G2/M transition was identified, particularly overexpression of *PTTG1*, which encodes securin, an anaphase-promoting complex (*APC*) substrate that associates with a separin until activation of the *APC*. *PTTG1* overexpression was inversely correlated with survival [137]. To assess its potential as a therapeutic target, researchers treated ACC cells with Vorinostat (SAHA), an HDAC inhibitor known to reduce *PTTG1* expression in colorectal cancer. Vorinostat binds the active site of HDACs, chelating zinc ions necessary for their function. It inhibited ACC cell growth, causing a dose-dependent reduction in securin protein levels in both lines [137].

McKale R. Davis et al. studied HDAC inhibition in SW13 cell subtypes: SW13+ (expressing vimentin) and SW13- (lacking vimentin, *BRM*, and *BRG1*, key ATPase subunits of the *SWI/SNF* chromatin remodeling complex). *BRM* and *BRG1* function as tumor suppressors but are often silenced in cancer [138]. Trichostatin A (TSA), an HDACi, induced a phenotypic switch from SW13- to SW13+, restoring *BRM* expression. This reinstated *BRM*'s role in suppressing glucocorticoid receptor-induced transcription, ultimately reducing cell proliferation [138]. Montgomery et al. found FK228 to be the most effective HDACi in this model. However, a key challenge with HDAC inhibition was the induction of epithelial-mesenchymal transition (EMT), caused by vimentin re-expression and glycosylation alterations affecting glycan synthesis and binding proteins [139]. These changes complicate therapeutic outcomes.

Despite these challenges, epigenetic modifications are reversible, making HDACi an attractive therapeutic target in ACC. Further research is needed to refine these approaches and mitigate EMT-related resistance.

#### 4.5.2. DNA Methyltransferase Inhibitors

As previously said, CpG islands are genomic regions with high CpG site density, often found in gene promoter regions. Methylation of these sites leads to chromatin condensation and gene silencing. ACC cells exhibit three distinct methylation phenotypes: non-CIMP, low-CIMP (l-CIMP), and high-CIMP (h-CIMP), with increased methylation correlating with worse OS [20,21].

The primary regulators of this phenotype are *DNMT1* and *DNMT3A* [20,21]. The h-CIMP phenotype is associated with high expression of genes involved in cell proliferation and survival, while genes related to immune response are hypermethylated and silenced, resulting in poor immune cell infiltration and reduced immune response. This contributes to a poor prognosis. Based on these findings, a combination of demethylating agents (e.g., 5-Azacitidine) and immunotherapy has been proposed as a potential treatment strategy for h-CIMP ACC.

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Suh I et al. [140] investigated Decitabine, a DNA methyltransferase inhibitor that removes methyl groups from silenced promoter sequences. Decitabine has a dose-dependent mechanism: at low doses, it inhibits methylation and reactivates gene expression, while at high doses, it induces cytotoxicity by trapping DNA methyltransferases. Treatment of NCI-H295R ACC cells with Decitabine demonstrated antineoplastic effects across key hallmarks of ACC, including reduced cortisol secretion, decreased cell proliferation, lower cellular invasion [140]. To confirm its demethylating effects, the study examined gene expression at chromosomal region 11q13, known for LOH in 70-100% of sporadic ACCs. Six underexpressed genes (*DDB1*, *MRPL48*, *NDUFS8*, *PRDX5*, *SERPING1*, *TM7SF2*) were analyzed. *NDUFS8* and *PRDX5* showed significant re-expression after Decitabine treatment. *NDUFS8* is a mitochondrial respiratory chain subunit, with mutations linked to Leigh disease. *PRDX5* encodes an antioxidant enzyme, peroxiredoxin, with genome-protective functions. Interestingly, *DDB1* and *TM7SF2* expression decreased post-treatment, an unexpected result requiring further investigation. This paradoxical response highlights the complexity of epigenetic regulation and suggests that while demethylation is a promising therapeutic approach, additional studies are needed to refine its application in ACC.

## 5. Locoregional Procedures

Lung metastases occur in over 40% of ACC patients and can be managed surgically when isolated. Pulmonary metastasectomy, radiofrequency ablation (RFA), and thermoablation have shown favorable outcomes, with early surgical intervention improving long-term survival. For inoperable cases, RFA and thermoablation serve as effective alternatives [1,2,66,67].

Liver metastases are also present in over 40% of ACC patients. Surgical resection is viable for limited metastases or when performed during initial surgery, but recurrence rates are high (80-100%) with significant morbidity (50%). Better outcomes are associated with non-functioning primary tumors, fewer metastases, longer disease-free intervals, and R0 resection. A multicenter study confirmed improved survival in patients with longer disease-free intervals and non-functioning tumors. For non-surgical candidates or those with recurrent liver disease, locoregional treatments such as RFA, transarterial chemoembolization (TACE), and selective internal radiation therapy (SIRT) offer promising results. Ablative therapies are most effective for oligometastatic disease with tumors ≤3 cm, especially when combined with systemic treatments. TACE and SIRT have been linked to longer survival, and SIRT combined with systemic or other local therapies has shown tumor reduction and extended disease-free survival, with some patients achieving disease control for up to two years [1,2,66,67].

Bone metastases are less common, affecting about 10% of patients. A retrospective study found that most patients were treated with mitotane and chemotherapy, with only 23% undergoing surgery. Survival outcomes were better for patients with single bone metastases, suggesting that early intervention with surgery or RFA may improve survival, particularly in those with a longer disease-free interval [1,2,66,67].

## 6. Conclusions

ACC continues to pose a formidable clinical challenge, largely attributable to its pronounced aggressiveness, underlying molecular complexity, and limited responsiveness to standard therapeutic regimens. Recent advances in genomic, transcriptomic, and epigenetic profiling have expanded our understanding of ACC pathobiology, enabling more precise diagnostic algorithms and refined risk stratification; nevertheless, patient outcomes, particularly in advanced disease, remain suboptimal.

Looking ahead, transitioning toward a precision medicine paradigm is imperative. Personalized, multimodal approaches that integrate surgical resection with molecularly targeted therapies, immunotherapeutic agents, and epigenetic modulators hold considerable promise. Furthermore, emerging innovations in imaging technologies and radioligand therapies have the potential to

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enhance both diagnostic accuracy and therapeutic efficacy. However, given the rarity and intrinsic complexity of ACC, comprehensive management is best delivered in specialized referral centers, where multidisciplinary teams can collaboratively tailor and optimize multidisciplinary treatment strategies.

Ultimately, robust translational research will be key to identifying novel therapeutic targets and refining existing interventions. By fostering closer ties between bench research and clinical application, and by leveraging the capabilities of dedicated ACC centers, the field may achieve substantive improvements in survival and quality of life for patients confronting this challenging malignancy.

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