Update on Adrenocortical Carcinoma

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KEYWORDS

• Adrenocortical carcinoma • Cancer • Adrenal glands • Adulthood • Pathology

KEY POINTS

- Adrenocortical carcinoma (ACC) is a rare, aggressive cancer with bimodal age distribution, often linked to genetic mutations like TP53 and syndromes such as Li-Fraumeni.
- Accurate diagnosis depends on imaging, molecular profiling, and pathology, with early detection significantly improving prognosis.
- Surgery is the key for localized ACC, but advanced cases require systemic therapies like mitotane and combination of etoposide, doxorubicin, and cisplatin, which have limited survival benefits and high toxicity.
- Immunotherapy and targeted therapies are promising but face challenges like cortisol-induced immunosuppression in hormone-secreting tumors.
- Advancements in genetic understanding, biomarker development, and therapeutic innovations are vital for improving ACC management and outcomes.

INTRODUCTION

Adrenocortical cancer (ACC) is an uncommon and aggressive malignancy originating from the adrenal cortex, presenting a notable public health concern due to its elevated morbidity and mortality rates.[1–4] The heterogeneity of ACC presents challenges in its diagnosis and treatment, as it varies greatly in its clinical manifestation and prognosis.[5] While the exact molecular mechanisms of ACC remain unclear, there have been significant advancements in the understanding of its molecular landscape through genomic and transcriptomic profiling. These discoveries have paved the way for the identification of innovative diagnostic, prognostic, and therapeutic biomarkers, providing new avenues for managing ACC (**Tables 1–6**).[6–8]

Diagnosing and treating ACC remains a challenge due to its rarity and variable clinical presentation. The comprehensive evaluation of clinical presentation, imaging, and pathology is crucial for ACC characterization and diagnosis. The management of ACC is complex due to the disease's rarity and severity; however, a multidisciplinary approach may offer benefits.[9] Surgery remains the fundamental treatment for localized ACC, but effectively treating patients with metastatic ACC remains a major challenge. The roles of adjuvant chemotherapy and radiation therapy in ACC management are still debated. This highlights the urgent need for innovative treatment strategies that can enhance patient outcomes.[10]

This review article aims to provide a thorough overview of the current understanding of ACC

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Abbreviations

ACC	adrenocortical carcinoma
CT	computed tomography
EDP	etoposide, doxorubicin, and cisplatin
FDG	fluorodeoxyglucose
IGF	insulin-like growth factor
SF-1	steroidogenic factor 1
TERT	telomerase reverse transcriptase

pathogenesis, diagnosis, and treatment, with a particular focus on the latest advancements in molecular profiling and the development of novel treatment strategies.

EPIDEMIOLOGY

ACC is a rare malignancy with an annual incidence estimated at 0.5 to 2 cases per million individuals worldwide.[11] ACC exhibits a bimodal age distribution, with peaks in early childhood and middle adulthood.[12,13] In pediatric populations, ACC is particularly rare, representing less than 0.2% of all childhood cancers, with an annual incidence of 0.2 to 0.3 cases per million children.[14] Pediatric ACC commonly presents in 2 distinct age groups: before the age of 5 years and after the age of 10 years, with nearly half of pediatric cases diagnosed before age 4 years.[14,15] In contrast, adult-onset ACC occurs more frequently, peaking around the fifth decade of life.[11]

A notable distinction exists in the gender distribution of ACC. In adults, the female-to-male ratio ranges between 1.17:1 and 1.5:1, with women typically presenting at younger ages and with smaller tumors.[16] Pediatric ACC, however, does not demonstrate a significant gender bias. Geographically, there is a markedly higher prevalence of pediatric ACC in southern Brazil, attributed to a unique germline TP53 mutation (R337H).[17] This mutation, which has a high prevalence (0.3%) in Brazil, is associated with a lower penetrance (2%) than the classical Li-Fraumeni syndrome, which has 100% penetrance. A newborn screening program in southern Brazil for the R337H mutation has proven effective in detecting ACC at early stages in this population.[18]

Environmental and genetic risk factors play crucial roles in the pathogenesis of ACC. For adults, cigarette smoking has emerged as an important risk factor, with findings from The Cancer Genome Atlas identifying a smoking-related molecular signature in a subset of ACC cases.[19] Exposure to environmental toxins, such as ionizing radiation, has also been implicated. Genetic syndromes, including Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, and Lynch syndrome, significantly contribute to ACC predisposition across both pediatric and adult populations.[20] In pediatric cases, ACC is often linked to genetic mutations disrupting cellular growth regulation, such as germline TP53 mutations.[21]

The prognosis of ACC is strongly influenced by the stage at diagnosis, with localized disease associated with significantly better outcomes compared to metastatic presentations. The 5-year survival rate for ACC varies widely, ranging

Table 1
Necessary hormonal assessment at baseline

Hormonal Assessment	Essential Laboratory Examinations
Glucocorticoid excess	1 mg dexamethasone suppression test and/or free 24-h urinary free cortisol Morning ACTH level
Sex steroids and steroid precursors	DHEA-S Total testosterone (only in women)
Mineralocorticoid excess	Potassium Aldosterone/renin ratio
Exclusion of a pheochromocytoma	Plasma-free metanephrines

Abbreviations: ACTH, adrenocorticotropic hormone; DHEA-S, dehydroepiandrosterone sulfate.

Adapted from American Association of Clinical Endocrinology Disease State clinical review on the evaluation and management of adrenocortical carcinoma in an adult: a practical approach by Kiseljak-Vassiliades K, et al.[71]

Table 2
New staging system for adrenocortical carcinoma (European Network for the Study of Adrenal Tumors Classification 2008)

Stage	2008 European Network for the Study of Adrenal Tumors-Staging System
I	T1, N0, M0
II	T2, N0, M0
III	T1-2, N1, M0 T3-4, N0-1, M0
IV	T1-4, N0-1, M1

Abbreviations: M0, no distant metastases; M1, presence of distant metastasis; N0, no positive lymph nodes; N1, positive lymph node(s); T1, tumor $\leq$5 cm; T2, tumor greater than 5 cm; T3, tumor infiltration into surrounding adipose tissue; T4, tumor invasion into adjacent organs or venous tumor thrombus in vena cava or renal vein.

Note: (Fassnacht M, et al. (2009), Limited prognostic value of the 2004 International Union Against Cancer staging classification for adrenocortical carcinoma. Cancer, 115: 243-250. https://doi.org/10.1002/cncr.24030.)[72].

Table 3
Genetic syndrome involved in adrenocortical cancer

Syndrome	Genetic Cause	Key Features	Adrenocortical Cancer Prevalence
Li-Fraumeni Syndrome	Germline variants in TP53	Multiple cancer types, including brain cancer, leukemia, and sarcoma	50%–80%
Beckwith-Wiedemann Syndrome	Loss of heterozygosity at 11p15 (IGF2)	Hemihypertrophy, macrosomia, macroglossia, hyperinsulinism, omphalocele	N/A
Multiple Endocrine Neoplasia 1 (MEN1)	Germline heterozygous variants in MEN1	Hyperparathyroidism, entero-pancreatic neuroendocrine tumors, pituitary adenomas	7% (somatic variants)
Lynch Syndrome	Germline variants in MSH2, MSH6, MLH1, PMS2	Colorectal and endometrial cancer, DNA-mismatch repair genes affected	3%
Other Syndromes	Various	Neurofibromatosis type 1, familial adenomatous polyposis, Werner syndrome	N/A

Note that the prevalence percentages in the table are not directly comparable, as they represent different patient populations or study cohorts.
Note: *Adapted from* "Adrenocortical carcinoma" by Else T, et al. Endocr Rev. 2014;35(2):282–326.[45]

from 18% to 82%, depending on the disease stage and the presence of distant metastases. This variability highlights the importance of early detection and accurate staging in improving outcomes for ACC patients.[22]

Future epidemiologic studies are warranted to better understand the regional and global burden of ACC, with a particular focus on environmental and lifestyle factors, such as smoking, which may influence disease incidence and outcomes.

CLINICAL PRESENTATION

The clinical manifestations of ACC arise from hormonal excess, tumor mass effects, and incidental findings. Hormonal hypersecretion is the most common presentation and varies between pediatric and adult cases. In adults, hypercortisolism leading to Cushing syndrome is frequently observed, while androgen overproduction is more prevalent in women. Conversely, pediatric patients often exhibit virilization as a dominant clinical feature, with symptoms such as precocious puberty and hirsutism. Mixed hormonal profiles, including cortisol and androgen excess, are also encountered.[23]

Nonfunctional tumors, which do not secrete hormones, may present with symptoms caused by mass effects, such as abdominal pain, early satiety, and a palpable mass. These symptoms arise from the compression or invasion of adjacent structures by the tumor. Pediatric patients, particularly those under 5 years of age, often present with smaller, localized tumors, whereas adults may present with larger, more invasive tumors.[24]

Incidental findings of ACC are increasingly common due to the widespread use of cross-sectional imaging. Incidentally discovered ACCs are typically diagnosed at an earlier stage and are more likely to be nonfunctional, highlighting the importance of vigilance in evaluating adrenal masses identified during imaging for unrelated conditions.[24,25]

Prognostic implications of clinical presentation vary by hormonal activity and tumor characteristics. Patients with functional tumors secreting androgens alone often demonstrate better outcomes than those with cortisol-secreting tumors. The presence

Table 4
Medical management of hormone excess

Hormone	Drug	Dose	Side Effects
Cortisol	Mitotane	0.5 g at bedtime, increase by 0.5 g weekly (2–3 g per day)	Depression, dizziness, skin rash, nausea, vomiting, gynecomastia, hypercholesterolemia, hypertriglyceridemia, hypothyroidism, increased liver function tests, central nervous system toxicity
Cortisol	Metyrapone	250 mg 4 times daily increasing up to 4.5 g per day	Hypertension, skin rash, hirsutism, hypokalemia, adrenal pain, nausea, vomiting
Cortisol	Ketoconazole	200 mg 3 times daily, increasing to up to 400 mg 3 times/day (1200 mg/day)	Reversible hepatotoxicity, gynecomastia, decreased libido, prolongation of the QT interval, nausea, vomiting, abdominal pain, fatigue
Cortisol	Osilodrostat	2 mg twice daily, increase by 2–4 mg/day (max 60 mg/day)	Hypertension, edema, prolongation of the QT interval, nausea, vomiting, headache, hypokalemia, hirsutism
Cortisol	Mifepristone	200 mg daily	HTN, peripheral edema, hypokalemia, abnormal thyroid function tests, diarrhea, nausea, vomiting, vaginal hemorrhage
Testosterone	Bicalutamide	50 mg per day	Edema, gynecomastia, constipation, abdominal pain, diarrhea, hot flashes
Testosterone	Finasteride	5 mg per day	Hypotension, edema, gynecomastia. mastalgia, impotence
Estrogen	Tamoxifen	10 mg daily	Hot flashes, thromboembolic events, ocular effects, uterine malignancies

of hypercortisolism has been associated with immune suppression and a poorer prognosis. Additionally, angioinvasion, a feature observed in some cases, correlates strongly with adverse outcomes and warrants detailed evaluation during diagnosis.[26,27]

ACC arising from ectopic cortical tissue, though rare, should be considered in differential diagnoses, particularly for adrenal-like tumors located in atypical sites. Distinguishing these from other steroidogenic neoplasms, such as pheochromocytomas, is critical for accurate diagnosis and appropriate management.[27,28]

Imaging and Molecular Imaging

In the context of ACC, various imaging modalities such as MRI, computed tomography (CT), and fluorodeoxyglucose (FDG) PET play a critical role in the diagnosis, staging, and follow-up of the disease. Recent studies have provided valuable insights into the unique imaging characteristics of ACC, contributing to a more precise and timely diagnosis.

MRI proves particularly beneficial in differentiating ACC from benign adrenal lesions. ACC typically presents as a sizable, diverse mass with areas of necrosis and hemorrhage. On T1-weighted images, ACC typically exhibits an iso-to hypointense signal compared to the liver. On T2-weighted images, it shows mild hyperintensity. The presence of a signal decrease on out-of-phase images compared to in-phase images suggests malignancy. Furthermore, ACC demonstrates enhancement following contrast administration, which may be heterogeneous due to the presence of necrotic areas.[29]

CT scans are another valuable tool in the assessment of ACC. On unenhanced CT, ACC usually appears as a large, heterogeneous mass with a higher attenuation value compared to benign adrenal adenomas. After contrast administration, ACC shows a

Table 5
Chemotherapy in metastatic/unresectable adrenocortical cancer: second-third line treatment

Treatment	Study Design	Number of Patients	Best Overall Response Rate	Median Progression-Free Survival	Median Overall Survival	Toxicity Details
Etoposide, doxorubicin, and cisplatin[73]	Prospective	101	23.2%	5.6 mo	10.3 mo	FIRM-ACT: No significant toxicities reported.
Streptozocin[73]	Prospective	84	9.2%	2.2 mo	7.4 mo	Mild nausea and vomiting in some patients. 13.4% experienced grade 3, 7.0% had grade 3 liver toxicity.
Temozolomide[74]	Retrospective	28	21%	3.5 mo	7.5 mo	25% of patients developed grade 3 neutropenia.
Gemcitabine[74]	Retrospective	145	5%	3 mo	10 mo	Grade 3 or 4 toxicity in 11.0%: asthenia, edema, nausea, vomiting, fever, reduced appetite, numbness, and diarrhea.
Cabazitaxel[75]	Prospective	25	0%	1.5 mo	6 mo	Asthenia grade 1 or 2 in 88%, hematological toxicity, neutropenia grade 3 (4%), thrombocytopenia grade 4 (4%).

Table 6
Clinical trials and results overview

Trial	Type of Therapy	Patient Count	Best Overall Response Rate	Median Progression-Free Survival and Overall Survival
EDP + Mitotane (FIRM-ACT)	Combination	304	23.2%	mPFS 5.6 mo and OS 14.8 mo
Streptozotocin + Mitotane (FIRM-ACT)	Combination	304	9.2%	mPFS 2.2 mo and OS 12 mo
Avelumab (Javelin)	Combination	50	6%	mPFS 2.6 mo and OS 10.6 mo
Pembrolizumab	Monotherapy	39	23%	mPFS 2.1 mo and OS 24.9 mo
Pembrolizumab MD Anderson	Monotherapy	16	14%	-
DART trial (NCT02834013)	Dual therapy	No results	-	-
Nivolumab	Monotherapy	10	-	mPFS 1.8 mo
Pembrolizumab and Lenvatinib (retrospective)	Combination	8	12.5% (PR)	mPFS 5.5 mo
Pembrolizumab and Relacorilant (NCT04373265)	Open, not yet recruiting	-	-	-
Camrelizumab and Apatinib	Combination	21	52%	mPFS 12.6 mo and OS 20.9 mo

Abbreviations: DART, dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors; EDP, etoposide, doxorubicin, and cisplatin; FIRM-ACT, first international randomized trial in locally advanced and metastatic adrenocortical carcinoma treatment.

heterogeneous enhancement pattern with areas of necrosis and hemorrhage.[30]

18-Fluorodeoxyglucose positron emission tomography (F-FDG PET) represents a highly sensitive diagnostic tool, widely used in assessing both adrenal and extra-adrenal masses, including suspected metastasis. It has been observed that ACC patients, particularly those with tumors characterized by elevated levels of the Ki-67 antigen, exhibit robust FDG uptake.[31,32] Furthermore, Libé and colleagues reported a positive correlation between FDG uptake and the expression of Ki-67, a marker indicating cell proliferation, in ACC. High Ki-67 expression is often linked to aggressive tumor behavior and an unfavorable prognosis. This correlation suggests that FDG PET could serve as a noninvasive method for evaluating tumor aggressiveness and predicting prognosis in ACC patients. The potential application of FDG PET in this regard could significantly enhance current diagnostic and management strategies for ACC.[32,33]

A study by Leboulleux and colleagues emphasized the higher sensitivity and specificity of FDG PET compared to CT scans (90% and 93% for PET/CT and 88% and 82% for CT, respectively) and that the FDG PET can be a complementary modality to CT when diagnosing ACC. This advantage is particularly evident in distinguishing ACC from benign adrenal lesions and detecting metastatic disease.[33]

PATHOLOGIC DIAGNOSIS

The pathologic evaluation of ACC is pivotal for its diagnosis and prognostication. In adult ACC, the Weiss scoring system remains a widely used diagnostic tool. This system evaluates 9 histopathological features, including mitotic rate, necrosis, and capsular invasion, with a score of 3 or more suggesting malignancy.[34,35] However, advancements in diagnostic criteria have introduced ancillary biomarkers that complement the Weiss score. Steroidogenic factor 1 (SF-1), a nuclear receptor expressed in adrenocortical cells, has emerged as a highly specific and sensitive marker for ACC diagnosis.[36] Immunohistochemical staining for Ki-67, a marker of cellular proliferation, is now standard practice, with a threshold of 15% associated with malignancy in both pediatric and adult cases.[37]

For pediatric ACC, the Wieneke classification, initially the primary diagnostic algorithm, has seen updates with the validation of newer criteria tailored to pediatric cohorts.[35] Recent studies highlight the role of algorithms integrating Ki-67 indices and other markers for enhanced diagnostic accuracy.[38] Ancillary biomarkers, such as insulin-like growth factor 2 (IGF2) and other steroidogenic markers, are increasingly incorporated into routine pathologic assessment, aiding in differentiation from other adrenal or metastatic tumors.[39,40]

Angioinvasion, an important pathologic feature, not only aids in diagnosis but also serves as a critical prognostic factor.[41] Its presence correlates strongly with disease aggressiveness and poorer outcomes, emphasizing the necessity of its thorough evaluation.[7,42] Additionally, ACC arising from ectopic cortical tissue presents unique pathologic challenges, requiring differentiation from other adrenal-like neoplasms through a combination of histopathological and molecular analyses.[5]

Incorporating molecular pathology, recent advances highlight the importance of identifying somatic alterations, including TP53 and CTNNB1 mutations, through next-generation sequencing. These findings not only refine diagnosis but also guide therapeutic strategies, paving the way for personalized medicine in ACC management.[43–45]

Molecular Pathology

MicroRNA (miRNA) has emerged as a potential diagnostic biomarker in ACC. Several studies have investigated the diagnostic value of circulating miRNA, such as long noncoding RNAs and circular RNAs, in patients with ACC. For instance, miR-483-5p and miR-210 have been shown to be upregulated in ACC and may serve as potential diagnostic biomarkers.[46,47] Further studies are needed to validate these findings and to determine the clinical utility of noncoding RNAs in ACC diagnosis and management.

Genetic Alterations in Adrenocortical Carcinoma

ACC exhibits diverse genetic alterations that play significant roles in its pathogenesis.[48] These alterations can be classified into germline (constitutional) and somatic mutations. Differentiating between these categories provides a clearer understanding of the molecular underpinnings of ACC and their implications for diagnosis, prognosis, and management.

Germline (constitutional) mutations

Germline mutations predispose individuals to ACC, particularly in syndromic contexts. Key mutations include as follows:

- *TP53 Mutations:* Germline TP53 mutations are a hallmark of Li-Fraumeni syndrome, which significantly increases the risk of ACC, especially in children. This underscores the importance of early genetic screening in families with a history of Li-Fraumeni syndrome.[49,50]
- *FLCN Mutations:* Mutations in the folliculin gene (FLCN), associated with Birt-Hogg-Dubé syndrome.[51,52]
- *Succinate dehydrogenase (SDHx)Mutations:* Germline mutations in SDHx genes, traditionally associated with pheochromocytomas and paragangliomas, have been identified in some ACC cases.[52]
- *Other Germline Mutations:* Emerging evidence links mutations in genes such as MEN1, APC, and PRKAR1A to syndromic forms of ACC. These mutations often coincide with distinct molecular phenotypes, emphasizing the heterogeneity of ACC.[53,54]

SOMATIC MUTATIONS

Somatic alterations are acquired mutations that contribute to the tumorigenesis of ACC. Notable mutations include as follows:

- *CTNNB1 Mutations:* Mutations in CTNNB1, encoding β-catenin, are among the most frequently observed in ACC. These mutations lead to aberrant activation of the Wnt/β-catenin signaling pathway, promoting cellular proliferation and survival. The Wnt pathway plays a crucial role in both benign and malignant adrenal cortical neoplasms.[27]
- *ZNRF3 Mutations:* Alterations in ZNRF3, a negative regulator of Wnt signaling, further implicate the dysregulation of this pathway in ACC. Loss of ZNRF3 is associated with aggressive tumor behavior and poor prognosis.[55]
- *TP53 and CDKN2A Alterations:* Somatic TP53 mutations are common in sporadic ACCs and are associated with genomic instability. Additionally, deletions or mutations in CDKN2A, a tumor suppressor gene, contribute to dysregulated cell cycle control.[56,57]
- *IGF2 Overexpression:* Loss of imprinting at the IGF2 locus on chromosome 11p15 leads to overexpression of this oncogenic growth factor, which is a hallmark of many ACCs. This alteration is often accompanied by loss of heterozygosity at the same locus.
- *Telomerase reverse transcriptase (TERT) and SF1 Amplifications:* Amplifications of TERT and encoding steroidogenic factor 1 drive

tumor proliferation and survival by enabling telomere maintenance and promoting steroidogenesis.[57,58]

MOLECULAR PROFILING AND CLINICAL IMPLICATIONS

Advances in next-generation sequencing have provided a comprehensive view of the genetic landscape of ACC.[59] Pediatric and adult ACCs exhibit distinct profiles, with pediatric cases predominantly harboring TP53 mutations, while adult ACCs display a broader array of alterations, including frequent somatic mutations in Wnt pathway regulators and IGF2 overexpression. These findings underscore the importance of tailoring diagnostic and therapeutic approaches to the age-specific genetic landscapes of ACC.

TREATMENT

The treatment of ACC is multifaceted and often involves a combination of resection and systemic therapies. Surgical resection remains the primary treatment for localized ACC. Complete surgical resection, also known as R0 resection, offers the best chance for long-term survival. However, ACC is often diagnosed at an advanced stage, and in such cases, surgery alone is not sufficient.[9]

Systemic therapies are typically used in the adjuvant setting or for patients with metastatic or unresectable disease. Mitotane (1.1 dichloro-2[o-chlorophenyl]-2-[p-chloro-phenyl] ethane, o,p'-DDD), an adrenolytic drug, has been the most prevalent drug to treat ACC for over half a century. It can be used both as an adjuvant treatment following surgery and for inoperable or metastatic ACC. Mitotane has been shown to improve recurrence-free survival in patients with ACC, but its impact on overall survival is less clear.[60]

In addition to mitotane, cytotoxic chemotherapy, particularly the combination of etoposide, doxorubicin, and cisplatin (EDP), is often used in patients with advanced ACC. This regimen has been shown to improve response rates and progression-free survival compared to mitotane alone. However, it is associated with significant toxicity, and its impact on overall survival is uncertain.[61]

Targeted therapies, including inhibitors of the insulin-like growth factor (IGF) pathway and immune checkpoint inhibitors, are emerging as promising options for the treatment of advanced ACC. Immune checkpoint inhibitors such as pembrolizumab, nivolumab, and avelumab have been evaluated in clinical trials, primarily targeting the programmed cell death protein 1 (PD-1) and programmed cell death ligand 1(PD-L1) axis. Early results indicate that these agents may offer benefits for certain patient subsets, particularly those with high tumor mutational burden or microsatellite instability, characteristics that correlate with increased immunogenicity.[62,63]

However, the efficacy of immunotherapy in ACC is often hindered by unique challenges. In patients with cortisol-secreting tumors, elevated cortisol levels have been linked to immunosuppressive effects, resulting in reduced efficacy of immune checkpoint blockade. The immunosuppressive environment in these cases is characterized by a dampened T-cell response and increased regulatory T-cell activity, which can promote resistance to immunotherapy. Consequently, strict monitoring and management of cortisol levels during immunotherapy are critical for optimizing therapeutic outcomes.

Combination strategies are under active investigation to enhance the effectiveness of immunotherapy in ACC. For instance, integrating immune checkpoint inhibitors with other targeted therapies, such as insulin-like growth factor 1 receptor (IGF-1R) inhibitors, aims to overcome resistance mechanisms and create a more favorable tumor microenvironment. Additionally, preclinical studies have suggested that combining immunotherapy with radiotherapy or mitotane could potentiate immune responses by increasing tumor antigen presentation and modulating the immune milieu.[64]

The role of novel biomarkers to predict response to immunotherapy is gaining attention in ACC research. For example, high expression of PD-L1 and increased infiltration of CD8 + T-cells are being explored as potential predictors of favorable outcomes. Understanding these biomarkers could enable more personalized treatment approaches and improve the selection of patients most likely to benefit from immune checkpoint blockade.[62,65,66]

While immunotherapy offers hope for improved management of advanced ACC, further research is needed to elucidate the mechanisms underlying treatment resistance and to refine combination strategies. Large-scale clinical trials are essential to validate these approaches and establish the safety and efficacy profiles of immunotherapy in diverse patient populations.

Adjuvant Therapy and Metastasectomy

Adjuvant therapy is essential in managing high-risk ACC patients following surgical resection, particularly those with positive resection margins, advanced stage, or high Ki-67 proliferation indices. Mitotane remains the cornerstone of adjuvant treatment, providing benefits in recurrence-

free survival, especially when therapeutic plasma levels are achieved. Recent studies suggest combining mitotane with platinum-based chemotherapy, such as EDP regimen, for enhanced outcomes in high-risk patients, though evidence remains limited to retrospective data and clinical trials like ADIUVO-2.[10,61,67] Radiotherapy can improve local control in patients with residual microscopic disease or close surgical margins, but its role in improving overall survival remains uncertain due to the risk of distant micrometastases.[10,67] Emerging evidence also highlights the potential of incorporating immunotherapy in the adjuvant setting, though its use currently is limited to clinical trials in metastatic cases.

Metastasectomy is a critical surgical option for managing recurrent or metastatic ACC, with both therapeutic and palliative implications. Complete resection of isolated metastases, particularly in the lungs, liver, or bones, has been associated with prolonged survival in well-selected patients who have limited disease burden and good performance status.[67,68] For patients with unresectable metastases, metastasectomy can alleviate symptoms, improve quality of life, and reduce tumor burden when integrated with systemic therapies. However, the efficacy of this approach varies, emphasizing the need for multidisciplinary evaluation to tailor interventions based on tumor characteristics, disease distribution, and patient factors.[69,70] Ongoing advancements in imaging and surgical techniques continue to refine the role of metastasectomy in improving outcomes for ACC patients.

CHALLENGES AND FUTURE DIRECTIONS

While acknowledging the influential role of genetic predisposition in the development of adrenocortical carcinoma (ACC), it is imperative to address several challenges that currently persist. The inadequate availability of comprehensive studies at a large scale poses hindrances in the advancement of robust diagnostic and therapeutic strategies. Furthermore, restricted access to genetic testing may be attributed to financial constraints or a lack of awareness among health care professionals.

To overcome these obstacles, future research should diligently concentrate on broadening our comprehension of the genetic foundation of ACC. Subsequently, it is essential to refine and authenticate diagnostic algorithms that integrate genetic information. Additionally, concerted endeavors are required to augment awareness regarding the significance of genetic testing among health care providers and patients alike. Such endeavors shall ultimately lead to an improvement in the diagnosis and management of ACC.

CLINICS CARE POINTS

- Timely detection of ACC through comprehensive imaging and pathology is crucial for improving outcomes, particularly in localized disease.
- Baseline evaluation for hormone excess (eg, cortisol, androgens, and mineralocorticoids) is essential to guide diagnosis and treatment strategies.
- Complete surgical resection (R0 resection) offers the best prognosis for localized ACC, emphasizing the need for experienced surgical teams.
- Incorporating Ki-67 proliferation index into diagnostic protocols is critical for risk stratification and prognosis in both pediatric and adult cases.
- Patients with a family history of cancer syndromes or early-onset ACC should undergo genetic testing for targeted interventions and family counseling.

DISCLOSURE

None.

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