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LESSON 23

Adrenocortical Carcinoma: Diagnosis and Management

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to describe the basic principles of adrenocortical carcinoma diagnosis and treatment.

This AUA Update aligns with the American Board of Urology Module on Oncology, Urinary Diversion and Adrenal. Additional information on this topic can be found in the AUA Core Curriculum sections on Laparoscopy and Robotic Surgery, and Oncology-Adrenal.



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KEY WORDS: adrenocortical carcinoma, diagnosis, management, adrenalectomy, metastatic disease

INCIDENCE AND EPIDEMIOLOGY

Adrenocortical carcinoma (ACC) is a rare endocrine malignancy that many urologists will not routinely encounter in clinical practice. As ACC is an aggressive cancer associated with poor patient prognosis, early diagnosis and appropriate management of these patients is critical to improving outcomes and ensuring high-quality care. Thus, all urologists must have a good understanding of ACC to evaluate, treat, and refer patients accordingly.

The reported incidence of ACC ranges from 0.7 to 2 per million adults per year in the United States.^{1,2} Despite a greater number of incidental adrenal lesions being detected with increased use of cross-sectional imaging, the incidence of ACC in adults has remained relatively stable over the last 40 years.^{2,3} Approximately 59% of these patients will present with disease localized to the adrenal gland.⁴

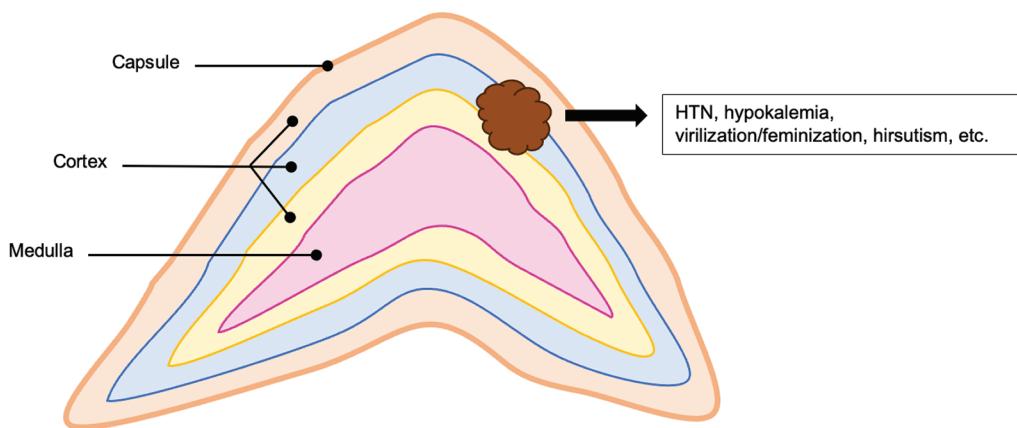
ACC has a 2:1 predilection in females compared to males.⁵ The median age at diagnosis has a bimodal distribution with the first peak in children <5 years old and the second peak in adults in their 40s and 50s.⁶ ACC accounts for 1.2% of pediatric malignancies as compared to 0.02% to 0.2% of adult malignancies.^{5,6} The worldwide incidence in pediatric patients is estimated between 0.2 and 0.3 per million children per year, though geographic region may lead to a higher incidence.^{7,8} For example, each year pediatric ACC affects 2.9 to 4.2 children per million in Southern Brazil, where there is an increased prevalence of p53 tumor suppressor gene mutations.^{9,10}

The most common hereditary syndrome associated with ACC is Li-Fraumeni Syndrome, which is caused by a mutation in p53 and is responsible for 50% to 80% of pediatric and 3% to 7% of adult ACC cases.⁴ In addition, approximately 1% to 3% of adult patients with MEN1 (MENIN) or Lynch Syndrome (MSH2, MSH6) will develop ACC.⁴ To a substantially lesser degree, ACC has also been reported in Beckwith-Wiedemann Syndrome, Familial Adenomatous Polyposis, Neurofibromatosis Type 1, and Carney complex.^{4,11} Given the rarity of this malignancy, genetic testing is recommended in patients with confirmed ACC to screen for associated hereditary syndromes.

HISTORY AND PHYSICAL EXAMINATION

ACC arises from the adrenal cortex where mineralocorticoids, glucocorticoids, and sex hormones are produced (Figure 1). Hypersecretion of these hormones leads to bothersome symptoms in 40% to 60% of patients, which is the primary reason that most patients initially seek medical attention.^{10,12} The importance of a thorough patient history and physical exam cannot be understated as recognition of these signs and symptoms is critical in identifying patients potentially harboring this rare malignancy.

Hypercortisolism, commonly known as Cushing's syndrome, occurs in 50% to 80% of hormone-secreting ACCs.⁴ These patients classically present with central obesity, cervical fat deposition, abdominal striae, glucose intolerance, muscle weakness, acne, and psychological disturbances.¹³ High circulating levels of cortisol can also result in glucocorticoid-mediated mineralocorticoid



Anatomy	Histology	Regulated by	Hormone class	Hormone produced	Metabolically active tumor symptoms
Cortex	Zona Glomerulosa	Angiotensin II	Mineralocorticoids	Aldosterone	HTN, hypokalemia
	Zona Fasiculata	ACTH	Glucocorticoids	Cortisol	HTN, hypokalemia
	Zona Reticularis	ACTH	Androgens	DHEA	Virilization/Feminization
Medulla	Chromaffin cells	Preganglionic sympathetic fibers	Catecholamines	Epinephrine, norepinephrine	

Figure 1. Adrenal gland anatomy and hormonal hypersecretion in adrenocortical carcinoma. ACTH indicates adrenocorticotrophic hormone; DHEA, dehydroepiandrosterone; HTN, hypertension.

ABBREVIATIONS: adrenocortical carcinoma (ACC), adrenocorticotrophic hormone (ACTH), European Network for the Study of Adrenal Tumors (ENSAT), ¹⁸F-fluorodeoxyglucose (FDG), inferior vena cava (IVC), positron emission tomography (PET)

receptor activation resulting in sodium reabsorption, hypokalemia, and resultant hypertension.¹³ In addition, 40% to 60% of hormone-secreting tumors produce androgens.¹⁴ As a result, women can exhibit rapid onset of hirsutism, virilization, male pattern baldness, and irregular menstrual cycles. In contrast, men with androgen hypersecretion are often initially asymptomatic. It is not until the peripheral conversion of androgens to estrogens or de novo estrogen production by ACCs that 6% to 10% of men experience gynecomastia, testicular atrophy, and fatigue.^{4,14} Up to 50% of ACC patients will experience concomitant symptoms of both hypercortisolism and androgenism.^{4,14} Interestingly, hypersecretion of aldosterone is uncommon in ACC.¹⁵

Alternatively, one-third of ACC patients will present with symptoms related to tumor mass effect including flank pain, abdominal fullness, and early satiety.⁴ These tumors are silent (non-hormone secreting) or have subclinical hormone secretion leading to delays in diagnosis that allow ACCs to grow unchecked, which likely contributes to the relatively large average tumor size at diagnosis, ranging from 10 to 13 cm.¹⁶ Furthermore, paraneoplastic syndromes and classical constitutional symptoms of malignancy, such as weight loss and night sweats, are rare in ACC. ACC-induced hypoglycemia and endogenous insulin suppression have previously been reported but are uncommon and not well understood.¹⁷

Most patients exhibit some degree of symptoms, with only 20% to 30% of ACCs found incidentally on cross-sectional imaging obtained for other medical reasons.¹⁸ In patients with an incidentally found adrenal mass, biochemical testing and tumor size often dictate the risk of ACC and need for operative intervention.¹⁹

DIAGNOSIS

Radiographic evaluation. Cross-sectional imaging is required for all patients with suspected ACC. Radiographic information such as tumor size, extent of disease, and degree of enhancement can help identify malignant tumors and inform treatment. **There is a linear relationship between adrenal mass size and malignancy risk.** Less than 2% of adrenal masses <4 cm are malignant, while up to 25% of masses >6 cm are malignant. In addition, although only 13% of adrenal masses >4 cm are ACCs, over 90% of ACCs are >4 cm at diagnosis.^{20,21} Prognosis is significantly better for ACC patients with smaller tumors confined to the adrenal gland. Thus, adrenalectomy is often recommended for unilateral masses greater than 4 cm to avoid missing an ACC.²²

Almost all ACC patients will undergo a CT scan during their initial evaluation. **ACCs commonly appear as large, heterogeneous, suprarenal masses that displace other organs with areas of central necrosis (Figure 2).** ACCs will almost never measure <10 Hounsfield units on unenhanced CT.²³ This cutoff has a sensitivity of nearly 100% for adrenal cancers and can be used to distinguish benign adrenal lesions from malignant ones. **Thus, unenhanced CT should be considered a first-line imaging modality in patients with suspected ACC.** Yet approximately one-third of adrenal masses are indeterminate on unenhanced CT. In these cases, an adrenal mass protocol CT consisting of unenhanced (time zero), enhanced (60 to 90 secs), and delayed phases (10 to 15 minutes) can be used to differentiate benign from malignant

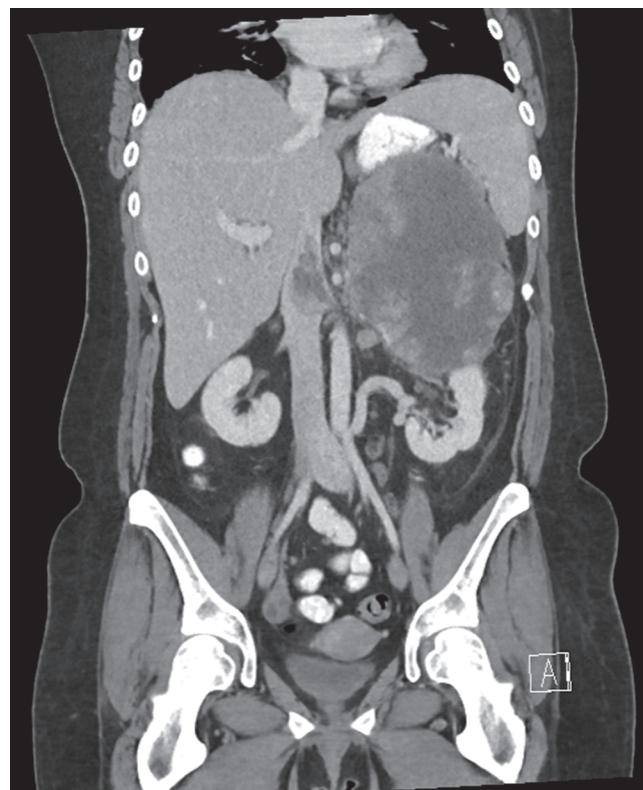


Figure 2. 20-Cm, heterogeneous, left adrenocortical carcinoma with marked central necrosis, inferior vena cava involvement, and mass effect.

tumors (Figure 3, A-C). An absolute or relative washout >50% and >40%, respectively, is consistent with an adrenal adenoma.²⁴ Washout studies have a sensitivity of 96% and specificity of 95% for differentiating benign from malignant masses.²⁵ However, there are important limitations associated with these tests, including increased radiation exposure, medical costs, and false-positive rates.²⁴ For example, pheochromocytomas and metastatic deposits from certain tumors (eg, thyroid and renal cancer) can have similar washout values on adrenal mass protocol CT scans.²⁴ Therefore, a thorough history, physical exam, and biochemical evaluation are also needed for accurate diagnosis. Another benefit of CT scans is the ability to identify locally advanced disease and distant metastasis. The most common sites of metastasis in ACC include liver (48%-96%), lung (45%-97%), lymph nodes (29%-46%), and bone (13%-33%).²⁶ Local invasion into the ipsilateral kidney (26%) and inferior vena cava (25%) can also be seen.²⁷

MRI is considered a second-line imaging modality in ACC. Although MRI may be helpful in identifying inferior vena cava (IVC) invasion, it can be more subject to interpretation and does not provide as robust data as compared to CT.^{24,28} There are special circumstances in which MRI should be pursued including in pregnancy, chronic kidney disease, contrast allergies, and in patients with indeterminate CT scans. ACCs tend to demonstrate high signal intensity on both T1- and T2-weighted sequences, with marked enhancement with contrast, and variable contrast washout values.²⁸

¹⁸F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) CT has a limited role in the initial evaluation of ACC patients. With rare exception, almost all ACCs are FDG PET avid. However, functional adenomas, pheochromocytomas,

and metastatic deposits can also be FDG PET avid, resulting in a low specificity and a high false-positive rate, thus limiting the usefulness of this modality to determine the risk of malignancy

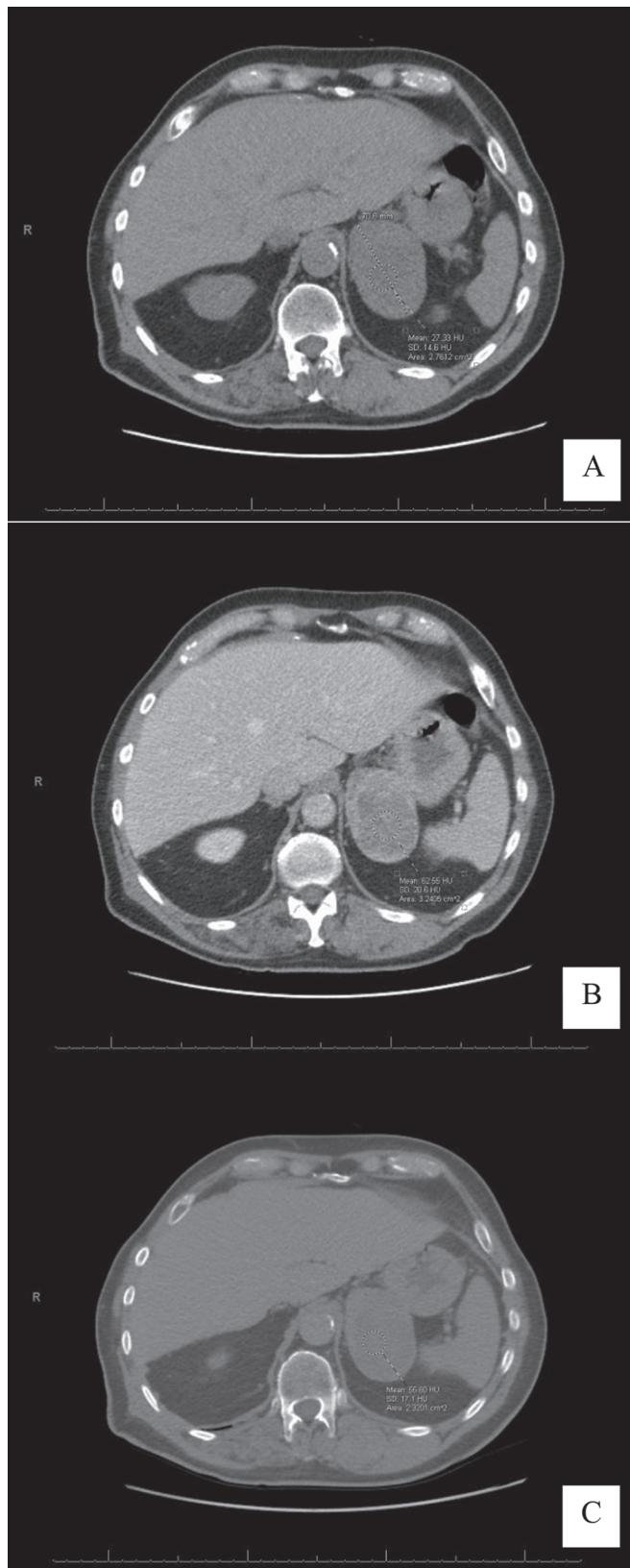


Figure 3. Three-phase adrenal mass protocol CT scan. A, Unenhanced CT scan (time zero). Left adrenal measures at 27 Hounsfield units. B, Contrast-enhanced CT scan (60-90 seconds). Left adrenal measures at 63 Hounsfield units. C, Delayed CT scan (10-15 minutes). Left adrenal measures at 57 Hounsfield units. Absolute washout = 16.7%; relative washout = 9.5%.

in an incidental adrenal mass.²⁹ **FDG PET CT is best used to assess the extent of metastatic disease as well as clinical response to chemotherapeutic treatment (Figure 4).**²⁹ In addition, C-metomidate, a highly selective inhibitor of 11-B-hydroxylase, can be used as a highly specific radiotracer for adrenocortical tissue. Although C-metomidate PET CT scans can be used to differentiate tumors of adrenocortical origin from noncortical origin, they are limited in their ability to distinguish benign from malignant lesions.³⁰ Adrenal scintigraphy using ¹³¹I-6B-iodomethyl-norcholesterol to characterize adrenal lesions has largely fallen out of favor due to its time-consuming nature and high radiation exposure.

All ACC patients should undergo a CT chest to complete their staging evaluation. Cross-sectional imaging of the brain should be obtained in patients presenting with new neurological symptoms or widely metastatic disease at the time of diagnosis.

Biochemical evaluation. A biochemical evaluation is required in all patients with suspected ACC. The European Network for the Study of Adrenal Tumors (ENSAT) has proposed biochemical testing standards for patients with suspected or established ACC (Table 1).¹² There are 4 key components to this evaluation that urologists should be comfortable performing including assessing for glucocorticoid excess, elevated sex steroids, mineralocorticoid overexpression, and presence of pheochromocytomas. These tests can be completed all at once with confirmatory testing completed sequentially. When in doubt, endocrinology can be consulted to assist with a biochemical evaluation.

First, glucocorticoid excess should be evaluated with a low-dose dexamethasone suppression test. For the low-dose suppression test, 1 mg of dexamethasone is given orally at 23:00 hours and then a serum cortisol is drawn at



Figure 4. ¹⁸F-fluorodeoxyglucose positron emission tomography CT demonstrating adrenocortical carcinoma metastasis to the liver (arrow). I indicates inferior; R, left; S, superior.

Table 1. European Network for the Study of Adrenal Tumors Guidelines for Biochemical Evaluation in Suspected or Known Adrenocortical Carcinoma

Biochemical evaluation	Components
Glucocorticoid excess (minimum 3 out of 4 tests)	<ul style="list-style-type: none"> Dexamethasone suppression test (1 mg, 23:00 h) Excretion of free urinary cortisol (24-h urine) Basal cortisol (serum) Basal ACTH (plasma)
Sexual steroids and steroid precursors	<ul style="list-style-type: none"> DHEA-S (serum) 17-OH-progesterone (serum) Androstenedione (serum) Testosterone (serum) 17-Beta-estradiol (serum, only in men and postmenopausal women)
Mineralocorticoid excess	<ul style="list-style-type: none"> Potassium (serum) Aldosterone/renin ratio (only in patients with arterial hypertension and/or hypokalemia)
Exclusion of pheochromocytoma (minimum 1 out of 3 tests)	<ul style="list-style-type: none"> Catecholamine or metanephrine excretion (24-h urine) Meta- and normetanephines (plasma)

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

08:00 hours the next day.³¹ A serum cortisol level <1.8 mcg/dL suggests an intact hypothalamus-pituitary-adrenal axis and excludes autonomous cortisol secretion.³¹ A serum cortisol level >5.0 mcg/dL is indicative of hypercortisolism, which is commonly seen in ACC. A 24-hour urinary free cortisol level or late-night salivary cortisol should be checked to verify hypercortisolism. If confirmed, then a morning adrenocorticotrophic hormone (ACTH) level should be drawn. ACTH-independent hypercortisolism, as seen in ACC, should have a low or undetectable ACTH.

At a minimum, the presence of elevated sex steroids should be assessed by measuring serum dehydroepiandrosterone sulfate and testosterone levels. Testing for additional metabolites, such as 17-OH-progesterone, androstenedione, and 17-beta-estradiol in men and postmenopausal women, can be helpful when considering hormonal blockade to palliate symptoms.¹² **In hypertensive patients, morning plasma aldosterone and renin levels should be measured to assess for aldosteronism.** An aldosterone/renin ratio ≥20 ng/mL and aldosterone >15 mg/mL is indicative of hyperaldosteronism. Confirmatory testing consists of a 24-hour urine study with salt loading performed in conjunction with endocrinology, but is likely unnecessary in ACC.

Lastly, to avoid a hypertensive crisis, the presence of a pheochromocytoma should be ruled out with either plasma free metanephines and normetanephines (preferred) or 24-hour fractionated urinary metanephines. Elevated plasma free metanephine and normetanephine levels greater than 2 times the upper limit of normal are diagnostic for pheochromocytomas. It is important to recognize that mildly elevated catecholamines and metanephines can be seen in patients taking levodopa, monoamine oxidase inhibitors, benzodiazepines, tetracyclines, or who are withdrawing from clonidine.^{4,12}

Role of tissue biopsy. Adrenal mass biopsies are rarely indicated in patients with a clinical suspicion of ACC. The sensitivity of a transcutaneous biopsy in ACC is <70% and does not improve survival outcomes.³² This suboptimal sensitivity is primarily due to the difficulty in distinguishing an ACC from

a benign adrenal adenoma based on histology from a biopsy (see the section Pathological Analysis regarding Weiss criteria). In addition, biopsies are associated with complications, such as hemorrhage and the potential for biopsy tract seeding.^{18,32} Adrenal mass hemorrhage can add complexity to an otherwise straightforward adrenalectomy. There are special circumstances when an adrenal mass biopsy may be useful, such as in patients with a history of prior non-adrenal malignancy when metastatic disease is suspected, especially when a biochemical evaluation is negative. An adrenal biopsy can reliably distinguish a primary adrenal tumor vs a site of metastatic disease from a non-adrenal primary.

Pathological analysis. As mentioned previously, it is often challenging histologically to distinguish a benign adenoma from a malignant adrenocortical tumor. Thus, the Weiss criteria is the most widely used scoring system to differentiate benign vs malignant adrenocortical tumors (Table 2). **The presence of 3 or more Weiss criteria based on pathological specimens is predictive of ACC with a sensitivity of**

Table 2. Modified Weiss Criteria

Histological criteria	Score	
	0	1
Nuclear grade	1 and 2	3 and 4
Mitoses	≤5 for 50 fields × 400	≥6 for 50 fields × 400
Atypical mitoses	No	Yes
Clear cells	>25%	≤25%
Diffuse architecture	≤33% Surface	>33% Surface
Confluent necrosis	No	Yes
Venous invasion	No	Yes
Sinusoidal invasion	No	Yes
Capsular invasion	No	Yes

The presence of 3 or more histological criteria is predictive of malignancy.

100% and specificity of 96%.³³ These criteria are categorized into 3 domains: (1) tumor structure (cytoplasm appearance, diffuse architecture, and necrosis), (2) cytology (atypia, atypical mitotic figures, and mitotic count), and (3) invasion (veins, sinusoids, and tumor capsule). **The expertise of an adrenal pathologist is required for accurate diagnosis.** In addition, immunohistochemistry staining can be used in the identification of ACCs. Ki-67, a marker of cellular proliferation, is significantly upregulated in ACCs compared to benign adrenal tissue and adenomas.³⁴ Ki-67 expression is now frequently used in histochemical analysis and can be used to predict tumor aggressiveness.

Novel biomarkers. Although seldom used in clinical practice, several biomarkers have been identified that can provide diagnostic and prognostic value in ACC.³⁵ MicroRNAs (miRNA) are small fragments of RNA that regulate post-transcriptional gene expression. miR-483-5p and miR-195 are currently the most promising miRNA biomarkers in ACC. miR483-5p is overexpressed in ACC, while miR-195 is underexpressed.³⁵ Elevated plasma levels of miR483-5p have an 82% to 89% sensitivity and 78% to 93% specificity for ACC; whereas decreased serum levels of miR-195 have a 90.9% sensitivity and 100% specificity for ACC.³⁵ In terms of prognosis, increased levels of miR483-5p and decreased levels of miR-195 at the time of diagnosis are known to be associated with short-term survival. Circulating levels of these miRNAs 3 months after adrenalectomy have also been shown to predict recurrence or death within 3 years of surgery.³⁵

Steroid profiling is another emerging tool that has potential in ACC. Prior research has shown that certain patterns of urine and serum concentrations of steroid precursors and metabolites can be used to differentiate between benign and malignant adrenal tumors. For example, elevated urinary concentrations of tetrahydro-11-deoxycortisol, pregnanediol, 5-pregnanetriol, and 5-pregnadiol have been shown to have a 100% sensitivity and specificity for ACC. Similar findings have been observed for serum concentrations of 11-deoxycorticosterone, progesterone, 17-hydroxyprogesterone, 11-deoxycortisol, dehydroepiandrosterone, dehydroepiandrosterone sulfate, and estradiol.^{35,36} Steroid profiling has also shown some promise in detecting disease recurrence after adrenalectomy.³⁶ However, for steroid profiling to be translated into clinical practice, larger prospective studies using equivalent assays and detection strategies are needed.

As previously mentioned, the cellular proliferation marker Ki-67 is significantly upregulated in ACC and is frequently used to help distinguish benign from malignant adrenal tumors. However, Ki-67 also has substantial prognostic value in ACC. In a large cohort of 568 ACC patients, Ki-67 expression was found to be the single most important factor in predicting disease recurrence and survival after adrenalectomy.³⁷ In this same study, Ki-67 also outperformed Weiss, Van Slooten, and Hough criteria in identifying ACCs.³⁷ These findings have been independently confirmed by multiple studies, resulting in adoption of Ki-67 into clinical practice to risk-stratify patients and inform treatment.

MANAGEMENT OF LOCALIZED ACC

ACC patients should be managed at health care facilities with expert multidisciplinary teams dedicated to treat-

ing this rare malignancy. From a surgical perspective, urologic oncologists or endocrine surgeons with extensive experience in performing adrenalectomies should be sought out in order to prevent tumor spillage and obtain negative margins, both of which are critical to achieve an optimal outcome for the patient. These are often complex cases due to tumor size and local invasion, which necessitates collaboration between surgical specialties as often multi-organ resection is required to achieve a good result. As such, ACC patients should be referred to high-volume centers and experienced surgeons after diagnosis.

Treatment for ACC is based on cancer stage. Two primary staging systems exist for ACC (Table 3). The ENSAT and American Joint Committee on Cancer staging systems are equivalent. Adrenalectomy with the goal of achieving negative margins is the gold standard for ACC treatment. All stage I and II patients who are operative candidates should undergo adrenalectomy. Similarly, stage III patients who have surgically resectable disease should undergo adrenalectomy with wide local excision, which may include a lymph node dissection and/or resection of surrounding structures (kidney, spleen, etc). **Multidisciplinary input from medical oncology, urology, endocrinology, and other surgical subspecialties is often required to determine the likelihood of achieving negative surgical margins in locally advanced disease. Adrenalectomy should not be performed in the setting of widespread metastatic disease, though in rare cases adrenalectomy can be performed in patients who have mass effect, substantial local pain, or refractory symptomatic hypercortisolism.** Adrenalectomy can also be considered in patients with locally advanced disease with low-volume visceral metastasis if resection with negative margins is feasible.

There is some controversy about the optimal surgical approach. In general, the choice should be based on the

Table 3. World Health Organization, European Network for the Study of Adrenal Tumors, and American Joint Committee on Cancer Staging Criteria for Adrenocortical Carcinoma

Stage	WHO 2004	ENSAT/AJCC
I	T1, N0, M0	T1, N0, M0
II	T2, N0, M0	T2, N0, M0
III	T1-2, N1, M0 T3, N0, M0	T1-2, N1, M0 T3-4, N0-1, M0
IV	T1-4, N0-1, M1 T3, N1, M0 T4, N0-1, M0	T1-4, N0-1, M1

Abbreviations: AJCC, American Joint Committee on Cancer; ENSAT, European Network for the Study of Adrenal Tumors; WHO, World Health Organization.

T1, tumor ≤ 5 cm; T2, tumor > 5 cm; T3, local invasion but not into surrounding organs; T4, tumor invasion in adjacent organs (ENSAT/AJCC: venous tumor thrombus in vena cava/renal vein); N0, no positive regional lymph nodes; N1, positive regional lymph node(s); M0, no distant metastases; M1, distant metastasis.

clinical features of the tumor as well as the technical ability and experience of the operating surgeon. Multiple approaches exist, including minimally invasive/robotic transperitoneal and retroperitoneal adrenalectomy, as well as open surgery through flank, thoracoabdominal, or chevron incisions. Considerable controversy exists regarding open vs laparoscopic adrenalectomy in ACC, with some groups advocating solely for an open approach as prior research has shown that laparoscopic surgery may be associated with a higher risk of tumor spillage, local recurrence, and carcinomatosis.¹² However, more recent data suggest that disease-free and overall survival does not differ significantly between open and laparoscopic approaches in tumors <10 cm.¹² It is the opinion of the authors that, in general, open surgery is favored and a laparoscopic resection should only be attempted in smaller tumors (typically <6 cm) where the surgeon is confident this can be performed with negative margins and no tumor spillage. We have found that open adrenalectomy through a thoracoabdominal incision provides excellent exposure and reduces overall risk of tumor spillage.

Special attention to tumor laterality is also important for surgical planning. The right adrenal vein is short, small caliber, and typically inserts into the IVC just inferior to the liver. As such, there is an increased risk of venotomy and avulsion of the right adrenal vein, which can result in hemorrhage that is difficult to control. Early identification and ligation of the right adrenal vein is recommended by the authors, even at the expense of resultant venous congestion. The right adrenal vein should be dissected circumferentially and its insertion at IVC should be adequately exposed before it is clipped and divided. Surgeons should also appreciate that up to 20% of patients have an accessory right adrenal vein that is commonly located just superior to the main vessel.³⁸

Concomitant ipsilateral radical nephrectomy at the time of adrenalectomy should be performed if there is concern for local invasion into the kidney. **However, in the absence of local invasion, an ipsilateral radical nephrectomy is not indicated, as there is no oncologic benefit.**³⁹ In certain circumstances (eg, tumors >10 cm), radical nephrectomy may be necessary to gain adequate exposure to the adrenal gland. In these cases, it would be prudent for surgeons to consent for the potential need for radical nephrectomy at the time of adrenalectomy. However, every effort should be made to preserve the ipsilateral kidney if possible.

Adjuvant therapy should be considered based on a patient's individual risk of disease recurrence.^{40,41} Low-risk patients, those with stage I to III disease, negative surgical margins, and Ki-67 expression ≤10% are typically observed following surgery. Patients at high risk for recurrence, those with Ki-67 >10 and <20%, positive surgical margins, and intraoperative tumor spillage should be offered adjuvant mitotane therapy, an adrenolytic chemotherapeutic agent. Patients with Ki-67 ≥20%, IVC thrombus, and vascular invasion are at the highest risk for recurrence, and a combination of mitotane and cisplatin-based chemotherapy can be considered in this subset.^{40,41} External beam radiation to the resection bed can also be considered in patients at high risk of local recurrence. In a 2019 study by Gharzai et al, a median radiation dose of 55 Gy to the resection bed was associated with almost a 30% improvement in overall survival 3 years after surgery.⁴²

Interestingly, a 2018 systematic review of 5 retrospective studies by Tang et al found that adjuvant mitotane was associated with longer recurrence-free survival and overall survival in patients with high risk of recurrence after adrenalectomy.⁴³ However, the first randomized controlled trial of ACC patients with low- to intermediate-risk disease showed no difference in recurrence-free survival and overall survival between patients who were randomized to adjuvant mitotane or observation.⁴⁴ Since the efficacy of adjuvant mitotane in low- to intermediate-risk ACC has not been established, it is forgone in most centers.

Lastly, patients who undergo adrenalectomy +/– adjuvant mitotane and chemotherapy or radiation therapy should undergo a period of surveillance for at least 5 years with a combination of cross-sectional imaging (chest and abdomen) and biochemical testing (if the tumor was initially functional) every 3-6 months. Currently, there is no role for neoadjuvant therapy in ACC.

MANAGEMENT OF RECURRENT ACC

Surgical resection is favored in patients with disease recurrence whether localized or oligometastatic if excision with negative margins is possible. Radiofrequency ablation and targeted radiation therapy are viable alternatives. These patients are known to have significantly improved 5-year overall survival compared to those who do not undergo surgical resection of their recurrent disease (57% vs 0%).⁴⁵ Adjuvant mitotane can be considered in these patients to reduce the risk of further recurrence. Patients who present with disease recurrence >2 years after adrenalectomy have the best response to resection compared to those with early relapse. If surgical resection is not feasible, then these patients should be treated as having metastatic disease.

MANAGEMENT OF ADVANCED ACC

Patients with metastatic disease require treatment with systemic therapy. Chemotherapeutic regimens have historically included mitotane monotherapy and combinations of mitotane with cisplatin, carboplatin, etoposide, doxorubicin, or streptozocin. **First-line therapy currently consists of a combination of mitotane, etoposide, doxorubicin, and cisplatin, particularly in patients with aggressive disease characteristics (eg Ki-67 expression >20%, rapid tumor growth, and spread).** This combination of chemotherapeutics is associated with a response rate between 23% and 49%.⁴⁶ For patients who are not candidates for platinum-based chemotherapy or cannot tolerate its side effects, single-agent mitotane is an option. In addition, mitotane monotherapy may be considered in patients with low-volume metastatic disease and low-grade tumor features, with multi-agent chemotherapy reserved as a second-line therapy. Unfortunately, single-agent mitotane is associated with a poor partial response rate, ranging from 10% to 30%.⁴⁷ Another available option is pembrolizumab, a monoclonal antibody directed against PD-1 receptors on T-cells, used as monotherapy or in combination with mitotane. Small phase II studies have shown an overall response rate of 14% to 23% and disease control rates ranging from 52% to 54% with pembrolizumab.^{47,48} In general, patients with metastatic ACC should be considered for clinical trials when available. There are several promising therapeutics

under investigation in metastatic ACC, including IGF1R, VEGF, and EGFR inhibitors.

Patients with metastatic ACC typically experience symptoms from hypercortisolism, tumor mass effect, and bony involvement. **Mitigating hypercortisolism not only improves quality of life but can also prolong survival by reducing the infection risk associated with hypercortisolism.** Metyrapone is an 11-beta-hydroxylase inhibitor that blocks the conversion of 11-deoxycortisol to cortisol, and 11-deoxycorticosterone to corticosterone and aldosterone. It is considered a first-line therapy in the treatment of hypercortisolism and can reduce serum cortisol levels to a normal range in 3 to 7 days.^{12,40} The recommended dosing of metyrapone is 250 mg 4 times a day increasing up to 6 g per day depending on therapeutic response. Ketoconazole and mitotane can be added to or substituted for metyrapone in refractory cases or when metyrapone is not tolerated. The state of adrenal insufficiency induced by these medications must be closely monitored and managed with glucocorticoid (eg hydrocortisone) and mineralocorticoid (eg fludrocortisone) replacement. Patients on metyrapone monotherapy may also require treatment with spironolactone or amiloride to address hypertension that is induced by the buildup of deoxycorticosterone. The virilization effects of androgen hormone hypersecretion can be mitigated with androgen blockage with bicalutamide or 5-alpha-reductase inhibition with finasteride. Similarly, symptoms caused by rare estrogen hypersecretion (eg, gynecomastia) can be reduced by antiestrogens, such as tamoxifen.^{12,40} Again, in rare cases, palliative adrenalectomy and radiation therapy can be pursued in patients with symptoms from tumor mass effect or recalcitrant excessive hormone production.

In general, cytoreductive adrenalectomy in the setting of widespread metastatic disease is not recommended. However, this may be revisited in the future as a recent

multicenter retrospective study found that patients who underwent cytoreductive adrenalectomy had a significantly higher 5-year overall survival compared to patients who did not (22% vs 5%).⁴⁹ These findings have yet to be reproduced in an independent or prospective study.

PROGNOSIS

Prognosis in ACC is dependent on stage and is generally poor. Five-year relative survival based on National Cancer Institute data is 74%, 54%, and 38% for local, regional, and distant disease, respectively. Using the ENSAT staging system, 5-year survival is 84% for stage I, 63% for stage II, 51% for stage III, and 15% for stage IV.¹² Additional negative prognostic markers include large tumor size (>12 cm), high Ki-67 expression, high mitotic rate, tumor necrosis, and p53 mutations.¹²

DID YOU KNOW?

- Early diagnosis and management are critical to improving outcomes and ensuring the delivery of high-quality care in patients with ACC.
- Most, but not all, ACC patients suffer from symptoms related to adrenal hormone hypersecretion.
- ACC patients should be managed at health care facilities with expert multidisciplinary teams dedicated to treating this rare malignancy.
- Surgeons with extensive experience in performing adrenalectomies should be sought out in order to reduce perioperative morbidity, prevent tumor spillage, and obtain negative margins, all of which are critical to achieving optimal outcomes.

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Study Questions Volume 42 Lesson 23

1. The inherited genetic condition or syndrome most commonly associated with ACC is
 - a. Beckwith-Wiedemann
 - b. Li-Fraumeni
 - c. Neurofibromatosis Type II
 - d. MEN Type I
2. A 50-year-old woman has a 5-cm left adrenal mass, measuring 30 Hounsfield units, discovered on CT following minor trauma. Biochemical evaluation is negative. The risk that this mass is an ACC is
 - a. ~1%
 - b. ~10%
 - c. ~25%
 - d. ~35%
3. A 68-year-old woman has a left adrenalectomy for a 4.9-cm ACC confined to the adrenal gland. Margins are negative. Ki-67 expression is 8%. Preoperative metastatic evaluation is negative. The next step is
 - a. Surveillance
 - b. Radiation therapy to the tumor bed
 - c. Adjuvant mitotane
 - d. Adjuvant mitotane, etoposide, doxorubicin, and cisplatin
4. A 70-year-old woman with metastatic ACC to the bones and lung completes 2 cycles of mitotane, etoposide, doxorubicin, and cisplatin. A restaging CT shows stable disease in the lungs and bone, but the primary tumor has increased from 13 cm to 14 cm. The patient is bothered by weight gain, easy bruising, and recurrent intertrigo. The next step is
 - a. Continue mitotane chemotherapy alone
 - b. Start metyrapone
 - c. Stereotactic radiation therapy to the adrenal
 - d. Robotic-assisted laparoscopic adrenalectomy
5. A 63-year-old man has a left en bloc adrenalectomy and nephrectomy for a 12-cm ACC that on final pathology invades the perinephric fat but not the substance of the kidney. Preoperative PET CT showed no evidence of metastasis. His 5-year survival is approximately
 - a. 15%
 - b. 30%
 - c. 50%
 - d. 70%