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AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGY DISEASE STATE CLINICAL REVIEW ON THE EVALUATION AND MANAGEMENT OF ADRENOCORTICAL CARCINOMA IN AN ADULT: A PRACTICAL APPROACH

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Abstract

Objective: The aim of this Disease State Clinical Review is to provide a practical approach to patients with newly diagnosed adrenocortical carcinoma, as well as to follow-up and management of patients with persistent or recurrent disease.

Methods: This is a case-based clinical review. The provided recommendations are based on evidence available from randomized prospective clinical studies, cohort studies, cross-sectional and case-based studies, and expert opinions.

Results: Adrenocortical carcinoma is a rare malignancy, often with poor outcomes. For any patient with an adrenal mass suspicious for adrenocortical carcinoma, the approach should include prompt evaluation with detailed history and physical exam, imaging, and biochemical adrenal hormone assessment. In addition to adrenal-focused imaging, patients should be evaluated with chest-abdomen-pelvis cross-sectional imaging to define the initial therapy plan. Patients with potentially resectable disease limited to the adrenal gland should undergo en bloc open surgery by an expert surgeon. For patients presenting with advanced or recurrent disease, a multidisciplinary approach considering curative repeat surgery, local control with surgery, radiation therapy or

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radiofrequency ablation, or systemic therapy with mitotane and/or cytotoxic chemotherapy is recommended.

Conclusion: As most health care providers will rarely encounter a patient with adrenocortical carcinoma, we recommend that patients with suspected adrenocortical carcinoma be evaluated by an expert multidisciplinary team which includes clinicians with expertise in adrenal tumors, including endocrinologists, oncologists, surgeons, radiation oncologists, pathologists, geneticists, and radiologists. We recommend that patients in remote locations be followed by the local health care provider in collaboration with a multidisciplinary team at an expert adrenal tumor program.

INTRODUCTION

Adrenocortical carcinoma (ACC) is a rare malignancy with reported incidence of 0.7 to 2 cases per million per year (1–3). These estimates have recently been confirmed by additional analyses of National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) data from 18 registries (1). The data from the recent SEER-based study from the U.S. reported a total of 2,014 cases in the period between 1973–2014. There were 933 cases reported from 2005–2014, compared to 187 from 1973–1984, with age-adjusted stable incidence of 1 case/million/year (1).

The rarity of ACC and variability in clinical approaches has been a major obstacle in advancing the care for patients with ACC. While significant progress has recently been achieved in understanding the molecular mechanisms of adrenocortical carcinogenesis (2), the scarcity of large randomized trials and evidence-based guidelines as well as the often fragmented care of patients with ACC has resulted in no obvious improvement in survival rates (~35% at 5 years) over the last several decades.

Considering that most patients with ACC will initially present to medical centers with limited expertise in ACC management, the aim of this case-based review is to provide clinically useful information regarding the approach to the management of patients with ACC. In consensus with the recently published European Society of Endocrinology guidelines on management of ACC in adults (3), this review encompasses the management of an adrenal mass, including presurgical evaluation, surgical approach, pathologic assessment, and other therapeutic modalities, based on individual patient presentation.

While the goal of this review is to provide clinical guidance for the approach to the patient with suspected ACC, it is our strong opinion that patients with this and other rare disorders should be managed at expert centers, consisting of a multidisciplinary team, including endocrinologists, endocrine surgeons, medical and radiation oncologists, pathologists, and genetic counselors, experienced and dedicated to the care for patients with ACC. In addition to providing care to patients with ACC, the expert multidisciplinary teams establish recurring tumor board reviews, which provide a platform for the exchange of clinical experience, scientific knowledge, coordination of clinical trials, and translational research activities. Multidisciplinary expert clinics also serve as hubs for building patient networks and interactions.

CLINICAL PRESENTATIONS

CASE 1:

A 32-year-old woman, without significant past medical history, presented to urgent care center with worsening left abdominal pain radiating to her back. The patient stated that the symptoms gradually progressed over the last few weeks, with pain initially intermittent and now constant. Physical exam revealed mild tachycardia and left abdominal tenderness. The work-up revealed mild leukocytosis, and noncontrast abdominal computed tomography (CT) imaging showed a homogeneous right adrenal mass measuring 4.5 cm with a density of 45 HU (Hounsfield units). Subsequently, adrenal labs were ordered: cortisol 17 μg/dL; adrenocorticotropic hormone (ACTH) <5 pg/mL; dehydroepiandrosterone sulfate (DHEAS) 965 μg/dL; 1 mg dexamethasone suppression testing with cortisol 4 μg/dL. Plasma metanephrines were within normal reference range.

1. Is CT imaging indicative of ACC, and is there any further imaging indicated?

   This patient's imaging is indeterminate, and ACC needs to be considered in the differential diagnosis. Additional imaging can be helpful to further characterize initially homogenous lesions. Thoraco-abdominal-pelvic imaging is indicated to evaluate disease extent.

The clinical presentation of this patient is unlikely related to the 4.5-cm adrenal mass, and therefore, the lesion is designated as an incidentaloma, where the guiding principles outlined in work-up of incidentally discovered adrenal mass apply (2,4–7). The initial evaluation focuses on imaging features of the tumor with the primary question being suspicion for malignancy. The initial modality for evaluation of an adrenal lesion is usually an unenhanced CT of the abdomen, where a homogenous adrenal mass, size <4 cm and with low radiodensity of <10 HU, is consistent with a benign tumor, usually a lipid-rich adenoma (Table 1). If the lesion is homogeneous but indeterminate by radiodensity (any size with radiodensity >10 HU), a dedicated adrenal contrast-enhanced CT scan can be helpful in further determination of the underlying biology. Lesions with >40% relative or >60% absolute contrast washout at 10 or 15 minutes are most commonly benign with very few exceptions (Table 1). While the advantage of ^{18}F-fluorodeoxyglucose (FDG)–positron emission tomography (PET)/CT has a potential role in determining the overall extent of advanced disease, a high false-positive rate, low specificity, high costs, and additional radiation exposure preclude the routine use in initial work-up (8). The very high negative predictive value, however, can be helpful, as ACCs are invariably ^{18}FDG-PET positive. However, ^{18}FDG-PET–negative ACCs have been reported; most studies only include a limited number of ACCs, and the clinician must be aware that there are rare instances of ^{18}FDG-PET–negative ACCs (9). If initial CT imaging is highly suspicious for malignancy, additional imaging with thoraco-abdominal-pelvic CT is mandatory to determine the extent of disease, as the presence of distant metastasis or local invasion significantly impact the management plan (Table 2), surgical decision, as well as prognosis discussion with the patient.

2. Is the biochemical work-up suggestive of ACC, and is additional biochemical work-up needed?

The initial biochemical results, particularly the high DHEAS, is highly suspicious for ACC, especially in the setting of a large adrenal mass. In addition to excluding pheochromocytoma, work-up should include assessment for autonomous production of glucocorticoids, mineralocorticoids, and adrenal androgens.

In patients presenting with an adrenal mass, a comprehensive history and physical examination are critical to establish the suspicion for autonomous hormone excess. Up to 60% of patients with ACC have evidence of clinical hormone excess, with autonomous glucocorticoid production being the most common (10,11). It is worthwhile mentioning that Cushing syndrome due to ACC can be of rapid onset, and symptoms are often dominated by significant muscle weakness, sometimes lacking other classical features, such as obesity. It is important to note that hypokalemia and hypertension are frequently associated with hormonally active ACC. The high cortisol levels overwhelm the renal HSD11B2 enzyme, which converts cortisol to cortisone, usually preventing access of cortisol to the mineralocorticoid receptors (12). Hyperaldosteronism is rarely associated with ACC, described in around 2 to 7% of patients (12,13). Androgen hormone excess, causing hirsutism, virilization, acne, and irregular periods in women, is seen in 40 to 60% of hormonally active ACCs and is rarely caused by benign lesions (12). Concurrent secretion of glucocorticoid and androgenic hormones in a patient with an adrenal mass is always highly suspicious for ACC. As outlined in Table 2, biochemical work-up in a patient presenting with an adrenal mass suspicious for ACC should include cortisol levels following a 1-mg dexamethasone suppression test to identify autonomous cortisol production and basal ACTH in order to confirm ACTH independence. While an undetectable ACTH level would be expected in patients with autonomous glucocorticoid secretion, it is important to note that in most of the current clinically available assays, ACTH level might not be entirely suppressed even with overt ACTH-independent Cushing syndrome (14). Additional adrenocortical steroid hormone precursors such as 17-hydroxyprogesterone, androstenedione, and particularly 11-deoxycortisol, as well as the steroid sulfate DHEAS, are helpful when evaluating a patient with an adrenal mass suspicious for ACC (3). Urine steroid profiling can further reveal increased steroid precursors and metabolites even in clinically nonfunctioning ACC (15,16). Determining the hormonal phenotype is important for several reasons: a) to confirm adrenocortical tumor biology and diagnosis; b) to serve as a potential prognosticator, as glucocorticoid-producing tumors have been associated with more aggressive disease; c) to guide postoperative management by determining the need for hormone replacement after tumor resection; and d) to establish a potential tumor marker (i.e., unique steroid signature) for surveillance after surgery (although advanced disease might de-differentiate without subsequent hormonal activity) (17). In addition to adrenocortical hormone evaluation, plasma metanephrines are needed in any indeterminate adrenal mass to rule out a pheochromocytoma, as cross-sectional imaging cannot reliably distinguish ACC from pheochromocytoma. The elevated cortisol following a 1-mg dexamethasone suppression test, elevated DHEAS, and normal plasma metanephrines in this patient were suggestive of a combined autonomous cortisol and androgen production and ruled out a hormonally active pheochromocytoma.

3. Is this patient a candidate for surgery?

Surgical resection is the first-line therapy in patients with suspected ACC without evidence of advanced disease and could provide a potential cure.

As a part of pre-operative evaluation, thoraco-abdominal-pelvic CT imaging excluded metastatic disease, and this patient was referred for surgical evaluation (Table 2). For all patients with ACC without evidence of extensive multi-organ involvement or widespread distant metastases, surgical resection is usually the first-line therapy that could provide a potential cure (3,12). The surgical approach to patients with advanced and oligometastatic disease is further discussed in CASE 3. Any surgical resection of an adrenal mass suspicious for an ACC should be performed by an expert surgeon with expertise in adrenal and oncologic surgery (3). The need for surgical and clinical expertise in management of ACC is supported by a recent study from the Netherlands, which showed significantly improved disease-free survival with the establishments of adrenal centers of excellence (18).

An open surgical resection is recommended for all adrenal masses suspicious for ACC. Laparoscopic resection is associated with a higher risk to develop recurrence and should be avoided when a mass is suspicious for ACC (19,20). Upon intra-operative evaluation, complete resection of the adrenal tumor, including adrenal gland, peri-tumoral, and peri-adrenal retroperitoneal fat, is recommended. A detailed assessment of adjacent organs is required with en bloc resection of any organ suspected to be invaded. While the benefit of regional prophylactic lymphadenectomy has not been extensively evaluated, several recent studies suggest a potential benefit of formal lymphadenectomy (21,22). In addition, enlarged or suspicious lymph nodes detected on pre-operative imaging or intra-operative assessment should be removed.

CASE 1 (continued):

The patient was referred to a multidisciplinary clinic at a center with adrenal tumor expertise. The imaging and biochemical work-up was reviewed, and surgical resection of primary tumor was recommended. The tumor was resected en bloc, and pathology, read by an experienced endocrine pathologist, was consistent with ACC. There were no positive margins (R0), staining for steroidogenic factor 1 (SF1) was positive, proliferation index Ki67-labeling was 10%, and the pathologic stage was pT2.

1. Does the clinical and pathologic information confirm the diagnosis of ACC and provide a risk categorization?

   Yes, this patient does have a diagnosis of ACC with a low/moderate risk for recurrence.

Following successful open surgery, which is the only potential cure for this disease, the focus should be on a) verification of diagnosis, b) evaluation of prognostic markers, and c) genetic evaluation in order to discuss any adjuvant therapy. The mainstay of a pathologic diagnosis is the review by an experienced endocrine pathologist. The diagnosis can generally be made using routine hematoxylin and eosin staining, from which the Weiss score can be derived (Table 3), providing the final diagnosis of an ACC (Weiss score >3) (23,24). Occasionally, there are neoplasms that are borderline and described as ‘undetermined biological behavior’ (Weiss score of 2 or 3). There are several traditional

immunohistochemical stains that can help in the differential diagnosis and confirm adrenocortical tumor origin, such as inhibin-alpha, Melan-A, and calretinin (Table 4) (25,26). However, SF1 has emerged as the most reliable marker to confirm adrenocortical origin (27).

Once the diagnosis of ACC is made, it is most important to obtain measurements of the proliferative index, preferably Ki67, alternatively mitotic count, obtained from the highest proliferating area of the tumor. A Ki67 index of >10% is regarded as an unfavorable prognostic marker (28,29). As a caveat, it should be mentioned that several institutions are switching from an estimate or count by an individual pathologist to computer-aided image analysis for Ki67 staining. It is important to gain experience with these automated systems, as they often provide different, in our experience, often higher values than traditional estimates (30,31). A careful pathologic review will also provide the correct stage (Table 5) (32,33), with any extra-capsular extension with infiltration of the adipose tissue being the most important differentiator between stage 2 and stage 3, which is not always obvious prior to surgery. Stage >2 or positive (or unknown) R-status increases risk for recurrence. In summary, an experienced pathologist should provide the final diagnosis, a Weiss score, a Ki67 index, resection status, and tumor stage in order to make the correct diagnosis and provide a prognosis estimate.

2. Should adjuvant therapy be recommended for this patient?

While there is no definitive recommendation for adjuvant therapy for this patient, adjuvant mitotane therapy should be considered.

Even following initial resection, disease-specific 5-year survival for patients with ACC is variable, ranging from 60 to 80% for stages 1 and 2 to 40 to 60% for stage 3, with some studies providing even lower estimates. Therefore, a discussion of adjuvant therapies is necessary, taking into account that for any patient with stage 3 disease (Table 5), the risk for a recurrence is likely higher than to remain disease free (34–37). Adjuvant therapy options include mitotane and/or radiation therapy. More recently, for ACCs with a Ki67 index of >20%, a trial has been launched that evaluates adjuvant cytotoxic chemotherapy in addition to mitotane (NCT03583710). All risk factors for recurrence should be considered on an individual basis when making a decision to recommend adjuvant therapy. Following a prognostic assessment, the majority of patients with ACC will be offered mitotane therapy. Although randomized prospective clinical trial data are lacking, large retrospective studies have shown compelling evidence that adjuvant mitotane therapy increases recurrence-free survival and possibly impacts overall survival in advanced disease (stages 3 and 4) (38–41). For patients with stage 1 or 2 disease (Table 5) with low-grade Ki67 (less than 10%) following an R0 resection, there is no evidence-based data on whether adjuvant mitotane may be beneficial due to a lack of prospective and retrospective studies. Individualized decisions to initiate adjuvant mitotane must be made for these instances after weighing a variety of patient-specific factors and balancing them with potential adverse effects. Ongoing trials aim to evaluate the efficacy of adjuvant mitotane in low-/moderate-risk ACC (the ADIUVO trial NCT00777244). The patient described in this case should have a discussion regarding potential benefits versus risks of mitotane therapy with the treating physician. Our practical approach is often to recommend a trial of mitotane therapy and

decide on continuation of therapy based on the side effect profile, which varies significantly between individual patients. Mitotane is initially up-titrated to a dose of ~3 to 6 g per day, with follow-up and monitoring for liver toxicity. Either concurrently or with a delay of a couple of weeks, patients will need to be started on glucocorticoid replacement therapy and monitored for other mitotane-related hormonal disorders (see CASE 2). This patient's tumor was of low/moderate risk with stage 2, free resection margins, and a Ki67 of 10%. Although it remains a matter of debate for which patients radiation therapy should be entertained, and low-level evidence suggests a potential benefit for all stages, radiation is more commonly recommended for patients with high-risk features, particularly those with stage 3 disease and R1 or R2 status (38–41).

3. What surveillance should be recommended to detect recurrences?

The patient should have at least biochemical evaluation and cross-sectional imaging of chest, abdomen, and pelvis in 3-month intervals for 2 years and after that biannually for at least a total of 5 years.

During mitotane therapy, patients should be followed with biochemistry, minimally including positive tumor markers, prior to resection and cross-sectional imaging of the chest, abdomen, and pelvis every 3 months (12). In addition, urine steroid profiling has been emerging as a new tool of recurrence detection and is now available through Mayo Clinic Laboratories, but it has not yet been implemented in routine clinical practice (16,17,42,43). Follow-up continues for at least 2 years at this interval and may be spanned out to biannual screening thereafter. It remains an uncertainty whether there is any benefit in prolonged (>5 years) surveillance. The majority of ACC recurrences occur within a 5-year time frame. However, it is reasonable to continue some surveillance beyond the 5-year mark.

4. Should this patient be offered genetic testing to identify hereditary cancer predisposition syndromes?

The patient should be evaluated for a hereditary syndrome, and genetic testing should be discussed.

Any tumor diagnosis provides the opportunity to evaluate patients for a hereditary cancer syndrome. Identifying patients with a diagnosis of a hereditary cancer syndrome provides the opportunity of tailored future surveillance for other associated tumors, identification of at-risk family members, and might impact therapy (e.g., immunotherapy for Lynch-associated cancers). A cancer-focused family history, careful personal history, and physical exam can provide clues to streamline genetic testing. The main syndromes to consider are Lynch syndrome, Li-Fraumeni syndrome (LFS), and multiple endocrine neoplasia type 1 (MEN1) (12). Lynch syndrome is characterized by germline pathogenic variants in DNA mismatch-repair genes associated with endometrial and colorectal cancer, but also other malignancies (12). Roughly 2 to 4% of ACCs arise in patients with Lynch syndrome, and tumors can be screened by immunohistochemistry for DNA mismatch-repair proteins and microsatellite instability. Alternatively, genetic testing for Lynch syndrome can be recommended based on family or personal history. About 2% of adult ACCs arise in patients with LFS or MEN1. LFS is associated with germline pathogenic variants in *TP53* and, predisposing to multiple different cancers, including early onset breast cancer, sarcoma and

brain cancer (12). Most patients with MEN1 will have other manifestations (e.g., hyperparathyroidism, facial angiofibromas or collagenomas, neuroendocrine tumors, or pituitary adenomas) at the time of diagnosis or a positive family history. The Chompret testing criteria for *TP53* (LFS) suggest testing everyone with a diagnosis of ACC, which is justified because a significant proportion of patients carry de novo mutations, and a family history can be negative (44,45). The patient in this case underwent a direct next-generation sequencing (NGS) panel, including *MSH2*, *MSH6*, *MLH1*, *PMS2*, *TP53*, and *MEN1* testing, which did not reveal a pathogenic variant. In addition, the NGS panel included *APC* and *PRKAR1A*, as familial adenomatous polyposis and Carney complex can be associated with ACC as well. An entirely different question is whether the tumor should be analyzed for potential treatment targets (e.g., somatic mutations analysis). Currently, there is not enough evidence to support any detailed molecular analysis of the tumor, with the exception of overall mutation load and/or microsatellite instability, both of which can be used to justify immunotherapy (3).

CASE 1 (continued):

The patient has been on mitotane for 3 years without recurrence on serial CT imaging. She would like to start a family and presents for consultation on conception.

1. Should fertility counseling be offered to patients diagnosed with ACC?

   Individualized fertility counseling and fertility preservation discussion should be considered in any patient of reproductive age with a diagnosis of ACC.

Fertility counseling should be performed in any man or premenopausal woman diagnosed with ACC at the time of diagnosis. Individualized discussion in light of personal factors, stage of disease, and planned therapy should be considered on an ongoing basis. The impact of surgery, cytotoxic chemotherapy, and the potential impact of mitotane on fetal development should be discussed. Options for preservation of fertility can be considered in certain patients. In addition, given the very limited literature on pregnancy in women with ACC, patients should be aware of the uncertainty in regards to the increased risk of ACC recurrence related to pregnancy (3).

2. When can patients with a history of ACC consider pregnancy?

   While it is unclear at what period post-adrenalectomy patients can consider pregnancy, an individualized approach and risk assessment is recommended with consideration of disease stage, tumor hormonal activity, duration of remission, and length of time since mitotane discontinuation.

Some women may report a history of infertility or amenorrhea at the time of initial diagnosis with ACC due to androgen and/or cortisol excess. However, the initial presentation with ACC during pregnancy has been reported, and in these situations, adrenalectomy is recommended (3). As reported in a study of 12 women with ACC diagnosed during pregnancy or immediately postpartum, fetal outcomes were poor in more than half of cases, with premature birth, intrauterine growth retardation, and even intrauterine death (46). In addition, overall ACC-related mortality was 4 times higher in women diagnosed during or shortly after pregnancy when compared to matched controls. Notably, this cohort

represented mainly patients with advanced disease, and all demonstrated overt hypercortisolism. In contrast, in another study of 17 women with localized disease (majority with stage 1 or 2) treated with adrenalectomy (100%) and mitotane (71%), fetal outcomes were good, and overall survival was not affected by pregnancy when compared to matched controls (47). In this study, none of the women carrying pregnancy to term were treated with mitotane at conception or during pregnancy. It is unclear how long patients should wait after adrenalectomy or mitotane therapy completion prior to considering pregnancy. In 17 patients with treated localized ACC, median duration of ACC remission prior to pregnancy was 48 months (47). The individual risk of pregnancy in a patient with history of ACC is closely related to the overall aggressiveness of disease. It is uncertain whether the physiologic increase in estrogen during pregnancy may be a negative factor contributing to recurrence. As such, guidelines suggest that all patients should be informed on pregnancy-related concerns with ACC (3).

Pregnancy should be avoided while on mitotane therapy due to concern of potential teratogenic effects, though available data include only case reports (47–49). If mitotane therapy is discontinued, it may take months for plasma mitotane concentrations to decrease. Discussion of an appropriate contraceptive method while on mitotane is necessary due to several concerns. Mitotane may increase the metabolism and effectiveness of hormonal preparations. In addition, one report suggested that ACC may express estrogen receptors, and as such, both physiologic and exogenous sources of estrogen may theoretically facilitate ACC growth (50). Because of this concern, some experts suggest non–estrogen-containing contraceptive preparations and even avoiding pregnancy altogether.

3. What is the right tumor surveillance for pregnant ACC patients?

   Tumor detection surveillance in pregnant patients with a history of ACC is individualized, based on initial tumor stage and remission status.

Once a well-informed and thoroughly discussed decision on pregnancy is made, pregnancy should be planned only after a comprehensive evaluation that includes complete history, physical exam, and laboratory and imaging work-up to document continuous remission. The frequency of follow-up during pregnancy can be individualized and should at minimum include review of symptoms and physical exam. Regular biochemical and imaging follow-up can be resumed after delivery, with frequency depending on duration of remission and overall prognosis.

CASE 2:

The patient is a 48-year-old woman who presented to her primary care office with worsening abdominal fullness and discomfort, acne, facial hair, and weight gain. On physical exam, she was found to have elevated blood pressure, facial acne and hirsutism, mild leg swelling, and central obesity. The work-up revealed mild hypokalemia and elevated blood glucose, total testosterone = 120 ng/dL, cortisol = 25 μg/dL, ACTH = 6 pg/mL, and DHEAS = 1,250 μg/dL. Abdominal CT imaging showed a 15-cm left adrenal mass, which is likely invading the stomach and possibly the pancreas. Image staging was completed with a chest CT, which did not show any evidence of metastasis. She was referred to an expert surgeon, and en bloc resection of the tumor, left nephrectomy, splenectomy, and distal pancreatectomy was

performed. The pathology was consistent with ACC, and Ki67 was 70%. She was diagnosed with high-grade stage 3 ACC. Postoperatively, she was treated with external radiation to the tumor bed and started on mitotane. She started taking 500 mg daily and increased her dose to 4,500 mg daily by the third week. Although she was initially tolerating mitotane fairly well, after 2 months, the patient started to experience extreme fatigue, nausea, and vomiting with flu-like symptoms and presented to local emergency department. On the work-up, patient was found to be hypotensive, and lab work-up showed hyponatremia, hyperkalemia, TSH = 0.2 mU/L, total thyroxine = 5.1 μg/dL, and ACTH = 120 pg/mL.

1. Is adjuvant therapy with mitotane indicated in this patient?

   Adjuvant therapy with mitotane is indicated in this patient with a high-grade tumor that is stage 3.

Adjuvant therapy should be initiated as soon as possible after surgery, once the patient has fully recovered from their operation. Mitotane and radiation therapy can be administered concurrently; however, given the overlapping gastrointestinal and hematologic side effects, it is often prudent to stagger these therapies sequentially to avoid toxicities that may delay or prevent either or both treatments. Commonly, radiation therapy is administered first and adjuvant mitotane therapy initiated once the course of radiation is completed.

Mitotane is an oral treatment that is available in 500-mg tablets (51). The use of mitotane may confer adrenolytic effects, although more recent data suggests that mitotane may also be adrenostatic in some instances (52). Adjuvant treatment with mitotane is recommended for patients after complete (R0) surgical resection who have either stage 3 or 4 disease (Table 5) and/or high-grade disease of any stage as defined by a Ki67 index of greater than 10%. Therefore, mitotane should be recommended for this patient after a detailed review of the benefits, risks, and limitations of this treatment. High-risk ACC patients are often treated with mitotane alone or with mitotane combined with 3 months of platinum-based chemotherapy. A recently launched clinical trial (ADIUVO-2) aims to prospectively compare 2 years of adjuvant mitotane alone to 2 years of mitotane combined initially with 3 months of chemotherapy (cisplatin and etoposide).

Evidence to support mitotane as an adjuvant therapy stems mainly from retrospective cohort studies. These observational studies demonstrated that adjuvant mitotane therapy was associated with prolonged recurrence-free survival and possibly greater overall survival when compared to no adjuvant therapy amongst patients with locoregional/stage 3 ACC (Table 5) (53). Adjuvant mitotane therapy is generally continued for approximately a minimum of 2 years unless limited by intolerable adverse events and/or substantial recurrences in disease despite optimal mitotane dosing (54,55).

Mitotane levels should be measured in the blood and used to follow the effect of therapy. It is recommended that the therapeutic mitotane level to target resides between 14 and 20 mg/L. Importantly, this therapeutic range is derived from retrospective studies that were not designed to detect an optimal mitotane level. Therefore, this therapeutic range should be considered as a general guidance. Pragmatically, many clinicians titrate mitotane to the highest dose or level a patient can tolerate without substantial adverse sequalae. Some clinicians prescribe a low mitotane dose with a gradual increase in dose over several weeks

(for example: 500-mg tablet daily with increases towards 3 to 6 g per day over the course of a month), whereas others prefer a more aggressive approach of rapidly increasing the dose to a target of 3 to 6 g/day over the course of 2 weeks. Some anecdotal reports, and at least one study, have suggested that a more aggressive approach does not increase adverse events (56); however, patient and physician experiences vary greatly, and there are many unpredictable adverse effects associated with mitotane. An additional complexity is that mitotane is a lipophilic drug with a large volume of distribution, and therefore, it can take weeks to months to achieve therapeutic levels, and conversely, it can take weeks to months for levels and related adverse effects to subside once mitotane has been stopped or the dose decreased. In practice, each dose adjustment can take weeks to be reflected in circulating levels.

2. What are common side effects of mitotane?

While side effect of mitotane include common systemic adverse effects such as fatigue and gastrointestinal disturbances, mitotane is also associated with multiple endocrinopathies (adrenal insufficiency, hypothyroidism, hypercholesterolemia, and reproductive dysfunction), which need to be closely monitored and treated.

Mitotane side effects include nonendocrine adverse effects and endocrinopathies. Common nonendocrine adverse effects of mitotane treatment include nausea, vomiting, diarrhea, and fatigue; however, these side effects can overlap with signs and symptoms of adrenal insufficiency and hypothyroidism (discussed below) (3). At higher levels or doses of mitotane, the risk of neurologic side effects increases, including ataxia, memory loss, and depression. Hepatotoxicity can occur at any level or dose of mitotane and can range from a mild increase in liver enzymes to severe hepatic synthetic dysfunction. Mitotane can cause substantial hypercholesterolemia, bone marrow suppression, and drug-induced rash. In addition, mitotane is known to cause several complicated endocrinopathies, which are discussed below.

Mitotane-Induced Adrenal Insufficiency—Mitotane can have an adrenolytic or adrenostatic effect on the residual contralateral adrenal gland, where endogenous adrenal steroidogenesis is insufficient or deficient. For this reason, mitotane-treated patients require treatment with glucocorticoids, and at times, mineralocorticoids as well. The patient in CASE 2 presented with an adrenal crisis during a flu-like illness with hyponatremia, hyperkalemia, and an elevated ACTH, suggesting primary adrenal insufficiency. This patient should be treated with isotonic intravenous fluids and stress-dose hydrocortisone, and once stabilized, with maintenance glucocorticoid therapy (such as hydrocortisone) and fludrocortisone. Mitotane can induce an increase in hepatic synthesis of cortisol-binding globulin (as well as other globulins, discussed below), thereby resulting in a greater requirement of glucocorticoid dosing and false reassurance when measuring total serum cortisol levels. In addition, and more important, mitotane increases activity of CYP3A4, which metabolizes exogenous glucocorticoids, thereby further necessitating a higher glucocorticoid dose (and other hormone replacement, discussed below). These effects of mitotane mean that most patients treated with long-term mitotane usually require higher doses of maintenance glucocorticoid (for example: hydrocortisone 50 to 100 mg per day). Doses of glucocorticoids have to be titrated based on symptoms of adrenal insufficiency, in

response to elevated levels of ACTH and/or renin, and/or hyponatremia or hyperkalemia. Patients should be educated regarding stress-dosing of glucocorticoids, be provided with intramuscular glucocorticoid emergency injections, and taught to recognize symptoms that warrant emergency care.

Mitotane-Induced Hypothyroidism—Mitotane-treated patients should have thyroid function monitored regularly, since hypothyroidism is very likely to occur. Thyroid laboratory patterns can reflect either primary or secondary hypothyroidism. Thyrotropin levels are often low, which may reflect a sick-euthyroid pattern or a direct effect of mitotane on thyrotroph cells. Total thyroxine levels and free thyroxine levels can vary and are not always reliably measured while on mitotane therapy. Mitotane increases thyroid-binding globulin and increases metabolism of exogenous levothyroxine by increasing CYP3A4 activity; therefore, patients often require higher doses of levothyroxine than are predicted by body weight. Monitoring of thyroid function is most reliably done by total thyroxine or a reliable free-thyroxine assay (for example by equilibrium dialysis).

Mitotane-Induced Reproductive Abnormalities—Mitotane can induce male hypogonadism and gynecomastia. This can manifest as a primary or secondary hypogonadism. Furthermore, mitotane increases sex hormone–binding globulin levels and reduces 5-alpha reductase activity; therefore, replacement therapy with testosterone in men can be challenging (57). Monitoring in men should involve measurement of total testosterone, sex hormone–binding globulin, and luteinizing hormone. Anecdotal cases of endometrial hyperplasia have been reported, and ovarian cysts are very common in women on long-term mitotane therapy, and therefore, regular assessment of menstrual regularity and/or pelvic ultrasounds should be considered in the setting of symptoms.

CASE 2 (continued):

On the 6-month follow-up imaging, the patient was noted to have a new liver lesion, as well as two subcentimeter lesions in the lung. Despite therapeutic mitotane level, the lesions have progressed at follow-up CT scan 6 weeks later.

1. What is the imaging and treatment approach to this patient?

   This patient’s presentation is highly suggestive of new metastatic lesions with an overall poor prognosis. The patient should undergo 18FDG-PET to confirm the malignant nature of the new lung and liver masses and to look for additional lesions. In the absence of other metastasis, surgical resection of oligometastatic disease in liver and lung should be discussed with the patient.

The most important ability of ^{18}FDG-PET is to detect additional distant metastases, which may impact surgical decision making in this patient (58). In addition, the study provides whole-body imaging beyond the chest, abdomen, and pelvis, where a minority of metastases may occur. In a retrospective analysis of patients with ACC, ^{18}FDG-PET changed the management plan in 9% of patients at restaging (8). Accordingly, there is a strong argument for obtaining ^{18}FDG-PET at this point. Establishing a reference uptake for all metastases during ^{18}FDG-PET for future comparison to evaluate any evolution of the disease has been

suggested by some expert panels (3). The counter arguments for routine use of ^{18}FDG-PET include the additional cost of the study and the false-positive results.

After radical surgery, more than 50% of patients with ACC will develop recurrence within 5 years. This is associated with a poor prognosis, since the 5-year survival rate for patients with metastatic disease is less than 15% in most series. The question of further treating patients with recurrent ACC depends on several factors, including the site of recurrence, the number of organs harboring metastases, local expertise, the progression slopes, and individual patient considerations. A thorough discussion with patients about the prognosis and their preferences is very important. The palliative character of any therapy for stage 4 ACC should be conveyed to the patient in order to balance quality of life, which is mainly determined by disease extent, hormone excess, and side effects of therapies. Regardless of therapeutic modalities, cure is a rare exception for stage 4 ACC, and the majority of patients will die of their disease. Most patients, however, desire active therapy rather than choosing supportive care only. A minimum recurrence-free period of 6 to 12 months has been suggested to select patients who are likely to benefit from further metastasis surgery (59–61). Although metastases to the lungs tend to occur earlier, they are associated with longer survival, making a case for pulmonary metastatectomy in patients in whom complete resection is possible (62). In a heterogeneous cohort of 28 patients with ACC and either synchronous or metachronous liver metastasis, surgical treatment of recurrence was an independent prognosticator of overall survival after adjusting for tumor laterality, hormone secretion, and the extent of initial hepatectomy (63).

A history of a very high Ki67, presence of metastatic lesions 6 months after initial therapy, along with disease progression despite therapeutic mitotane level, is associated with overall poor prognosis in this patient. Any therapy at this stage will be palliative; however, aggressive resection of distant disease may provide higher long-term survival rates compared to those who do not undergo surgery (61,64). Furthermore, very long survival has been reported in patients with oligometastatic disease with considerable intervals between recurrences (65). Accordingly, resection of limited, potentially resectable hepatic or pulmonary metastases (60) needs to be discussed with this patient. The discussion should include morbidity and mortality associated with re-operation as well as time needed for recovery after surgery, including its impact on quality of life (66). Different therapy algorithms have been suggested based on the site, size, and number of metastases (67). Surgery will likely not offer any benefit for patients with rapidly progressive tumors and may be worse than the disease itself if only a minimal increase in survival is expected.

2. Are there alternative local therapy approaches available for this patient?

Local therapy approaches may provide additional alternatives for patients with metastatic ACC in the presence of significant comorbidities, unresectable tumors, or patient preference of not having more surgeries.

For patients with unresectable recurrences or metastatic lesions or for those who opt against surgery, local therapies such as radiofrequency ablation, percutaneous laser ablation, cryoablation, microwave ablation, and transcatheter arterial chemoembolization approaches may provide local control (68,69). The decision on the mode of therapy depends on a

number of factors, including residual tumor location, prognostic factors, benefit/risk ratio, local expertise, and patient preference. It is important to emphasize the need for systemic therapy in most patients with distant metastases because the occurrence of metachronous metastases is not uncommon (70). Local therapies can provide tumor control for selected patients, particularly for those with limited progression and few organ involvements. Percutaneous radiofrequency ablation has been used successfully in patients with metastatic liver disease (70). Some data suggests better outcome for tumors less than 3 to 5 cm in size that are not near sensitive tissues or large blood vessels (69,71). In selected cases, a partial tumor debulking may be attempted if it facilitates successful local therapy. Local therapies generally have a good safety profile, but side effects may include bleeding, infection, and injury to adjacent tissues.

3. What follow-up and surveillance is indicated in patients following oligometastatic lesion local therapy?

   Close monitoring of the patient with contrast CT of chest, abdomen, and pelvis after surgical resection or local therapy of a metastatic lesion is necessary to assess for disease progression.

All patients with metastatic ACC who undergo active therapy including surgery or local therapies need close follow-up with contrast CT studies of chest, abdomen, and pelvis to monitor the progression of the disease. This will cover the majority of metastatic lesions in patients with ACC. There is no well-standardized approach for the frequency of imaging after surgical resection of metastatic lesions. Along with recent expert opinions, we recommend serial imaging every 3 months for 2 years and then every 3 to 6 months for an additional 3 years (3). The best imaging interval depends on a number of factors, including the dynamics of the disease, patient symptoms, toxicity and type of ongoing treatment, and the overall prognosis (72). Additional imaging after each surgical intervention to establish a baseline for future comparison should be considered. In a minority of patients with metastatic disease who are alive beyond 5 years, adapting the survey based on the clinical picture is reasonable. CT imaging is the study of choice, but magnetic resonance imaging (MRI) may provide better resolution on venous tumor thrombus, venous invasion, and small hepatic metastasis. Other additional imaging such as CT of head and bone are indicated in cases of clinical suspicion of metastatic lesions. The addition of ^{18}FDG-PET to routine follow-up CT studies is suggested by some groups but not endorsed by the current guidelines (73). Patients should have a physical examination at each visit and be closely monitored for any new or worsening respiratory and abdominal complaints, including any signs or symptoms of mass effect.

CASE 3:

The patient is a 52-year-old man who initially presented to his primary care provider with back pain. On assessment, the patient was also found to be hypertensive, and on follow-up visits, the blood pressure was higher despite an aggressive three-drug regimen antihypertensive therapy. Retroperitoneal ultrasound with Doppler was ordered for secondary hypertension work-up and revealed a large solid mass at the upper pole of right kidney. Subsequent adrenal CT and PET/CT skull-to-thigh imaging showed an 8-cm left adrenal mass (standard uptake value = 5), thrombus in left renal vein extending into inferior

vena cava, without lesions in lungs or liver. CT angiography showed no inferior vena cava (IVC) thrombus above the diaphragm or right atrium.

1. Is there a role for neoadjuvant systemic therapy in borderline-resectable ACC (BRACC)?

   Based on limited data, administration of neoadjuvant therapy prior to surgery in patients with BRACC was associated with a trend increase in 5-year survival rates.

The majority of patients with ACC present with locally advanced disease (34% with stage 3) or metastatic disease (26% with stage 4) (74). Thus, a radical resection with curative intent is not always possible. When there is a radiologic suspicion of locally advanced ACC or evidence of invasion of surrounding organs, the surgical field is large, and multi-organ resection is often required. It is also common to observe small-volume metastases to other organs, which can complicate surgical decision making. In addition, patients with poor performance status secondary to hormone excess have a higher risk for perioperative complications. The term BRACC has been retrospectively defined as clinical stage where extent of tumor burden at presentation or patient's characteristics oppose immediate surgical approach. In patients with BRACC, there is either a need for multi-organ or major vascular resection with high risk for a margin-positive resection based on pre-operative imaging review, and/or there is radiographic suspicion for low-volume metastatic disease that is often outside the planned surgical field. In some BRACC cases, poor performance status secondary to patient's related comorbidities also prevents immediate surgical intervention. In a retrospective study of 15 patients with BRACC treated with neoadjuvant chemotherapy and 38 patients with ACC treated with primary surgical resection, there was no statistically significant difference in median overall survival between the two groups, despite a more advanced disease in patients with BRACC; 5-year survival of 65% and median time to progression of 28 months in patients with BRACC, versus 5-year survival of 50% and median time to progression of 14 months in patients with localized ACC (75).

The complexity of care for patients with BRACC is best approached by an experienced team, coordinating all aspects of care, including the supportive, hormonal, oncologic, and surgical care. The use of systemic therapy in these cases can result in clinically meaningful improvements to make surgery possible as well as remarkable improvement in comorbidities associated with autonomous hormone production through tumor burden reduction. These patients require close monitoring, assessment, and frequent adjustment of the anti-hormonal medications (i.e., ketoconazole or metyrapone) used to control the concomitant autonomous hormone production associated with ACC. The use of ^{18}FDG-PET/CT is very helpful in these cases to predict metabolic response of ACC that can precede the anatomic changes in some cases (8).

In a few cases, a multiphase surgical approach is considered, starting with removal of the primary tumor, followed by a planned resection of metastases outside the surgical field (for example, isolated metastases in liver or lungs). The combined use of multiple treatment options including systemic chemotherapy, surgery, transarterial chemoembolization, and

radiofrequency ablation carries the best hope to improve the long-term outcomes of patients with ACC.

CASE 3 (continued):

The patient was referred to a local community cancer center where surgical resection of the primary tumor was attempted with intra-operative tumor rupture. The pathology of core biopsy was consistent with ACC, with Ki67 of 20%. Patient was subsequently referred to an adrenal tumor center for further management.

1. Does intra-operative tumor rupture carry a higher risk of recurrence?

   Unfortunately, patients with ACC who had tumor rupture and intra-operative tumor spillage often develop peritoneal carcinomatosis with limited ability to achieve permanent remission.

Laparoscopic resection in particular is associated with a higher risk to develop recurrence, tumor rupture, and carcinomatosis (19,20). Once peritoneal seeding occurs, there is little meaningful therapy. Cytoreductive surgery can be combined with heated intraperitoneal chemotherapy in an attempt to reduce disease load. In a phase II clinical trial setting, 9 patients with recurrent ACC, in the peritoneum only, received intraperitoneal heated chemotherapy in addition to surgery. It is unclear if this approach yielded any clinical benefit, as 2 patients died of disease within 2 years of follow-up, and the remaining 7 patients had evidence of disease recurrence (76).

CASE 3 (continued):

The patient was evaluated in an adrenal tumor multidisciplinary center and underwent second surgery, which included IVC thrombectomy, IVC venoplasty, and periaortic lymphadenectomy for enlarging lymph nodes. The pathology was consistent with ACC. The patient underwent external radiation therapy to adrenal bed and was subsequently started on mitotane. At 3 months postoperatively, the patient presented with shortness of breath, and imaging revealed a pulmonary embolism, new lung nodules, and a right atrium lesion most likely consistent with metastatic disease. The lung metastases all progressed on subsequent imaging 6 weeks later.

1. What are therapy options for recurrent and advanced disease?

   In addition to mitotane, in patients with progressive systemic disease, chemotherapy with etoposide, doxorubicin, cisplatin (EDP) is recommended.

ACC is a systemic disease in most cases. In addition to patients with ACC presenting with stage 4 disease, almost 60 to 70% of patients with localized ACC develop local and more commonly distant recurrence after having surgery with curative intent (62,77,78).

Mitotane is the only approved drug to treat metastatic ACC, although it is associated with low response rates (12). Thus, systemic chemotherapy has been used in combination with mitotane to enhance efficacy. One of the only phase III studies in ACC (FIRM-ACT) compared the two most commonly used regimens (EDP with mitotane vs. streptozocin [SZ] with mitotane). EDP-mitotane use resulted in complete response in about 1% of cases and

partial response in 23% of participants, with median progression-free survival of 5 months. Despite the only modest efficacy of EDP-mitotane, the response rate was higher compared to SZ-mitotane (response rate 9%, with median progression-free survival of 2 months) (79). In a retrospective multicenter study of 145 patients with advanced ACC, gemcitabine use alone or in combination with capecitabine resulted in median progression-free survival of less than 3 months, with a very low partial response rate of 5% (80).

2. Are there targeted therapies and clinical trials available for patients with ACC?

Clinical studies using targeted therapies in ACC have shown limited response thus far; however, clinical trials examining the hepatocyte growth factor/cMET pathway and immune checkpoint inhibitors are under-way.

Over the past decade, cancer therapy has changed with the introduction small-molecule tyrosine kinase inhibitors. The use of these drugs in ACC has been disappointing so far, and no significant responses were seen. Sorafenib in combination with paclitaxel did not yield any responses (81), and single-agent salvage therapy with sunitinib in 35 patients with ACC was associated with a median progression-free survival of 2.8 months and a response rate of 15%. It is important to note that in most patients with ACC who are treated with mitotane, efficacy of subsequent therapies might be hampered by increased drug metabolism by induction of the hepatic CYP3A4 system (82).

As the majority of ACCs express high levels of insulin-like growth factor 2, targeting insulin growth factor receptors has been attempted using a small-molecule kinase inhibitor (linsitinib) as part of the phase III GALACCTIC trial. Despite the overall lack of efficacy, there was a small subset of patients with true responses to therapy (83). The combined targeting of insulin-like growth factor receptor 1 via monoclonal antibody (cixutumumab) in combination with an mTOR inhibitor (temsirolimus) resulted in stable disease in almost 40% of participants at >6 months (duration range, 6 to 21 months) (84).

Activation of the the hepatocyte growth factor/cMET pathway has been reported as one of the mechanisms of resistance to therapy in ACC after the exposure to commonly used therapies (cisplatin, radiation, and mitotane). Targeting the cMET pathway appears to be promising, and there is an ongoing clinical trial to assess the safety and efficacy of cabozantinib in ACC (NCT03370718) (85).

Most recently, immunotherapy gained significant popularity in cancer treatment, and several phase II studies using immune checkpoint inhibitors in ACC have been completed (86–89). These clinical studies found modest efficacy of immunotherapy in ACC. It still remains unclear whether concomitant cortisol overproduction could antagonize the effects of immunotherapy (86–89). Early data suggests that combining other treatments such as mitotane may enhance the efficacy of immunotherapy (90). In conclusion, future studies are urgently needed to identify better treatment options for metastatic ACC.

CASE 3 (continued):

The patient was started on a chemotherapy regimen including EDP and continued mitotane. On subsequent follow-up, he had some decrease in size of the pulmonary lesions but then developed a new intra-abdominal lesion as well as metastatic bone lesions.

1. Is there a role for palliative radiation therapy in advanced ACC?

   Despite a less-defined role in ACC, palliative radiation therapy may be successfully used in patients with advanced ACC for the treatment of bone, brain, and other metastases, including symptomatic control of mass effect. In the view of new bone metastases and intra-abdominal lesions, the patient should be evaluated for palliative radiotherapy.

Palliative radiotherapy has been extensively used in patients with metastatic cancer, particularly in those with bone and brain metastases. Other indications may include mass effect, including vena cava obstruction and symptomatic recurrence. The role of radiotherapy is less defined in patients with ACC compared to a number of more common malignancies, but it is effective for pain relief and may improve neurologic symptoms. It may also be used in patients with unresectable abdominal recurrences that cause pain or vascular or intestinal obstruction. Radiation therapy may be offered in carefully selected patients with oligo-metastases who are not a good candidate or do not want to pursue surgery or systemic therapy (91). In a review of the role of radiotherapy in 90 patients with advanced ACC who received palliative radiotherapy, a response rate of 57% was observed. The study demonstrated that radiotherapy may play an important role in the care of patients with advanced metastatic ACC (92). With newer, state-of-the-art radiotherapy technologies, the short- and long-term toxicities are mostly mild to moderate. The decision to offer radiotherapy to a patient with widespread metastasis and a very limited life expectancy should be individualized (93). The use of palliative radiotherapy for asymptomatic masses, which are not resectable, is not well defined. Targeted radionuclide therapy may offer an additional option for selected patients with advanced metastatic ACC but requires further evaluation in clinical trials (94).

2. What approach is recommended for ACC bone metastasis?

   The available data demonstrates the palliative benefit of radiotherapy as well as antiresorptive agents in patients with bone metastasis.

Skeletal-related events (clinical bone fracture, spinal cord compression, or hypercalcemia) were reported in 47% of patients with ACC and bone metastasis in a large multicenter analysis (95). Bone was the only metastatic site in 9% of the patients, and the median overall survival from the diagnosis of bone metastasis was 11 months. Bone metastasis may be associated with significant pain, pathologic fractures, and spinal cord compression, resulting in poor quality of life. Hypercalcemia may rarely occur in patients with ACC. The available data demonstrates the effectiveness of palliative radiotherapy in the form of external beam radiation or stereotactic radiosurgery in symptom relief in up to 90% of patients with metastatic bone disease (96,97). The observed benefit is mainly in pain relief but may also be associated with reduction in paresthesia or paralysis (92). In addition to radiotherapy, surgical intervention may be needed for patients with symptomatic bone involvement, such

as limb-saving procedures and vertebrectomy with spinal stabilization, provided the patient is suitable for surgery (98).

Compared to other malignancies, evidence for or against the use of antiresorptive therapy to reduce skeletal-related events in patients with ACC and bone metastasis is lacking. However, the use of antiresorptive therapies with bisphosphonates or denosumab in oncologic doses for patients with bone metastases and anti-osteoporotic doses for those with hypercortisolism seems to be justified until further studies are available (91). In a recent study, the use of bisphosphonates or densosumab was associated with a significantly lower risk of death in patients with ACC and bone metastasis who achieved mitotane levels >14 mg/L but not in those with subtherapeutic mitotane levels (95). Possible cytotoxic activity, prevention of cancer colonization outside the bone microenvironment, and synergism with mitotane have been postulated as potential underlying mechanisms that need to be further evaluated in future studies.

3. Is integration of palliative care (PC) an appropriate approach in this patient with ACC?

All patients with advanced metastatic ACC should be evaluated by the palliative care team as part of their standard of care.

PC, unlike hospice, can be utilized simultaneously with disease-modifying or curative therapies such as surgery. The goal of PC in patients with ACC is to improve the quality of life for patients and their families facing a life-threatening illness. It should include assessment and treatment of pain and address fears, worries, and end-of-life issues for patients. It can help guide treatment decisions to be in line with physical, psychological, and spiritual needs of the patients and result in less end-of-life treatment and decreased medical costs (99). Several oncology organizations have guidelines about PC, reflecting the need to integrate it into standard oncology care (100). All patients with advanced metastatic ACC should be evaluated by the palliative care team while being followed by their multidisciplinary team, including their endocrinologist and oncologist, recognizing that metastatic ACC is rarely a curable disease. The goal is to help patients have an active life as much as possible until death. After each disease progression, the team needs to discuss different options with the patient, including the best supportive care concept.

Paying particular attention to social and psychological aspects of therapy, including professional counseling, is important. These measures may be particularly useful in a subset of patients with a relatively long survival despite advanced disease. PC is best delivered at a location close to the patient’s home. New technologies such as telemedicine provide an opportunity for the care of patients with advanced metastatic ACC who prefer to have their care at home (101).

Medical therapy directed towards controlling hypercortisolism, hypertension, electrolyte disturbances, and hormonal deficiencies is necessary for achieving a better quality of life. There are several pharmacologic options to control effects of hypercortisolism, through enzyme inhibitors or direct antagonism on the glucocorticoid receptor (3). Mitotane has some antihormonal activity, likely due to its adrenolytic properties and the increase of hydrocortisone metabolism, but it only takes effect after some time (weeks). In order to

immediately control hypercortisolism, one can use ketoconazole or metyrapone (11β-hydroxylase inhibitor), with the latter being much more reliable and immediate in its effect (12). When using these medications, one can measure 24-hour urine cortisol to monitor for successful reduction in cortisol production. Metyrapone can be difficult to titrate, and an emerging approach is to 'block and replace'. For immediate control of hypercortisolism, etomidate, likewise a very potent 11β-hydroxylase inhibitor, can be used (roughly ~1/10 of anesthetic dose) (102). However, etomidate needs to be given intravenously, and administration is most often restricted to intensive care units.

Mifepristone is another alternative for controlling glucocorticoid effects. It binds and blocks the glucocorticoid receptor with very high affinity and efficacy. Due to the rise in cortisol following therapy with a glucocorticoid antagonist, cortisol levels cannot be used to monitor adequate drug effect. In addition, rising cortisol levels often overwhelm the 11β-hydroxysteroid dehydrogenase system in the kidney, causing hypertension and hypokalemia as cortisol activates renal mineralocorticoid receptors. This often necessitates the use of spironolactone and/or potassium replacement (103). Anti-androgenic therapy can be achieved with spironolactone or flutamide in women with significant hirsutism. Abiraterone might emerge as an alternative therapy for this purpose. Occasionally, therapy is necessary for male patients with gynecomastia due to tumor production of estradiol. This is best achieved with anti-estrogenic substances (e.g., tamoxifen) or aromatase inhibitors (12).

CASE 4:

The patient is a 50-year-old man with history of melanoma, which has been in remission on anti–programmed death 1 immunotherapy for 1 year. He presented for a surveillance CT-PET and was found to have an ^{18}FDG-positive left adrenal mass measuring 5 cm. He was then referred to an endocrinologist for work-up.

1. What is the role of imaging in patients with an incidental adrenal mass who have a history of extra-adrenal malignancy?

   The incidental adrenal mass in a patient with a history of extra-adrenal malignancy can represent a metastatic lesion, may also be a benign finding, and in very rare cases be an ACC. Imaging characteristics are helpful to determine likely benign versus malignant etiology.

The work-up of the incidentally discovered adrenal mass is generally focused on two aspects: ruling out malignancy and determining if there is hormonal hypersecretion. Available imaging techniques include CT, MRI, and ^{18}FDG-PET (5,6,104). Even in patients with high risk for adrenal malignancy (history of extra-adrenal malignancy) referred for adrenal biopsy, 0% of adrenal tumors with HU <10 were malignant or pheochromocytomas (104–106). However, imaging techniques such as CT and MRI demonstrate a high rate of false positives (many adrenal lesions with HU >10 or chemical shift on MRI still represent lipid-poor adenomas) and do not distinguish between various malignant etiologies or pheochromocytoma (all with absent chemical shift on MRI, majority with HU >20 or heterogeneous). ^{18}FDG-PET demonstrates false positives (for example functioning adenomas) and false negatives (such as a small metastasis) and cannot distinguish adrenal malignancy from pheochromocytoma. A recent report evaluating a cohort of patients with

history of extra-adrenal malignancy found that an incidental adrenal mass is more likely to be metastatic disease in patients with active malignancy than those with remote malignancy history (47% versus 26% of patients, respectively) (107).

2. Are there serum/urine markers to distinguish ACC from benign and/or extra-adrenal metastatic disease to the adrenal gland?

   Urine steroid metabolomics assays have recently been developed to distinguish ACC from benign disease or other malignant adrenal tumors.

Disorganized steroidogenesis with a buildup of adrenal steroid precursors is a hallmark of ACC (108). The absence of adrenal hormone excess does not exclude ACC, as not all ACCs exhibit hormonal excess leading to androgen excess, cortisol, and aldosterone excess. On the other hand, when present, in particular combined androgen and cortisol excess in an indeterminate adrenal mass, is strongly suggestive of ACC (104). Recently, novel assays using urine steroid metabolomics have been developed to distinguish benign adrenal tumors from ACC (15,16,42,43). This study found 11-deoxycortisol metabolite tetrahydro-11-deoxycortisol as the most differentiating biomarker, and in combination with several other metabolites, provided useful adrenal tumor classification. Urine steroid profiling for diagnosis of ACC is now commercially available. In addition to diagnosing ACC in a patient with indeterminate adrenal mass, urine steroid profiling was also shown to be useful in detecting ACC recurrence in patients with complete (R0) resection (17).

3. Is a biopsy of the adrenal lesion indicated?

   In a patient with indeterminate adrenal mass (HU >10), after excluding pheochromocytoma and ACC with hormonal work-up, biopsy of adrenal mass may be considered in patients with a history of an extra-adrenal malignancy or high suspicion for adrenal metastasis (bilateral enlarging indeterminate lesions), if it is necessary for treatment decisions.

Biopsy of an adrenal lesion suspicious for ACC is not recommended. Neither fine-needle aspiration (FNA) nor core biopsy can reliably distinguish adrenal adenoma from ACC, as there are well-known challenges in differentiating adrenal cortical adenoma and carcinoma even when the entire tumor specimen is available (109). However, CT-guided FNA is a useful tool in patients in whom the detection of an infectious or metastatic lesion would modify therapy or prognosis (110). Needle-track metastases have been reported from ACC as well as from adrenal metastasis from other tumors (3,109,111). However, there is no evidence supporting the common misconception that biopsies of ACCs are more prone to cause needle-track metastasis than biopsies of other cancers. Prior to any FNA, pheochromocytoma should be ruled out with biochemical testing, because the procedure could induce hypertensive crisis or sudden death (112).

CASE 4 (continued):

The patient’s hormonal work-up was negative for cortisol, aldosterone, androgen, and catecholamine excess. Urine steroid profiling was not performed. He was referred to surgical resection of the left adrenal mass considering his history of melanoma. The pathology was consistent with oncocytic neoplasm and Ki67 of 5%.

1. Are oncocytic adrenal neoplasms always malignant?

   Oncocytic adrenal neoplasms can be benign or malignant. The Lin-Weiss-Bisceglia score is used to estimate malignant potential of this tumor.

Oncocytic neoplasms are distinguished by large, polygonal cells with a prominent granular eosinophilic cytoplasm owing to abundant cytoplasmic mitochondria (113,114). Adrenocortical oncocytic neoplasms can be either benign or malignant and frequently contain high-grade nuclear features. As they usually present as an incidental, large, lipid-poor adrenal mass, CT and MRI findings cannot be used to differentiate benign and malignant oncocytic neoplasms. Oncocytic adrenocortical carcinoma (OAC) is a rare subset of oncocytic neoplasms. The Weiss score, which is utilized to distinguish nononcocytic adrenal adenomas from carcinomas, overestimates the potential for malignancy in oncocytic neoplasms owing to parameters that are intrinsic to oncocytic cells. The Lin-Weiss-Bisceglia score was specifically developed for this type of tumor (113). Available literature suggests that OAC behaves in a more indolent fashion than ACC (115).

2. What is the treatment of OAC?

   Compared to most ACCs, OAC usually presents with a less-aggressive course. The treatment and monitoring plan is similar to other ACCs.

Two recent large, retrospective studies confirmed that, despite their frequent large and aggressive appearance on pre-operative imaging, OACs rarely invade adjacent organs, tend to be of lower stage, and have improved overall survival when compared to most other ACCs (116,117). The Helsinki score, which incorporates the Ki67 proliferation index, is the best prognostic score for this subset of ACCs. Guidelines for adjuvant therapy, follow-up, and surveillance of patients with OACs generally follow recommendations for other ACCs, although these recommendations are based on limited, largely retrospective data. It is notable that in one of the studies, patients with OAC treated with mitotane (presumably for higher-stage disease) also had improved survival compared to patients with other ACCs on the same treatment (117).

CONCLUSION

Coupled with the recent advances in the molecular underpinning of the disease, the standardization and multidisciplinary approach to clinical care of patients with ACC provide an opportunity towards personalized management and improved outcomes. While centralization and expert-based care for patients with rare disease, such as ACC, is an essential requirement towards progress, the scarcity of the expert programs and long travel distances in many cases preclude patients from seeking care in medical institutions with ACC expertise. In the era of the expanding informational technology and development of telemedicine practice, efforts should be placed towards expert-guided local care where local medical providers partner with the multidisciplinary expert teams to provide excellent and up-to date-care for patients with ACC.

DISCLOSURE

I.B. serves on the advisory board for Corcept and HRA Pharma, as well as serving as a consultant for HRA Pharma. A.H. serves on the advisory board for HRA Pharma. M.A.H. receives honoraria from Corcept and HRA Pharma, as well as research support from Exelixis. A.V. receives consulting fees from Corcept and HRA Pharma. T.E. serves on the advisory boards for Corcept and HRA Pharma. He also serves as PI on pharmaceutical institutional contracted studies for Corcept, Merck, and Strongbridge. The other authors have no multiplicity of interest to disclose.

Abbreviations:

ACC	adrenocortical carcinoma
ACTH	adrenocorticotropic hormone
BRACC	borderline resectable adrenocortical carcinoma
CT	computed tomography
DHEAS	dehydroepiandrosterone sulfate
EDP	etoposide, doxorubicin, cisplatin
FDG	^{18}F-fluorodeoxyglucose
FNA	fine-needle aspiration
HU	Hounsfield units
IVC	inferior vena cava
LFS	Li-Fraumeni syndrome
MEN1	multiple endocrine neoplasia type 1
MRI	magnetic resonance imaging
OAC	oncocytic adrenocortical carcinoma
PC	palliative care
PET	positron emission tomography

REFERENCES

1. Sharma E, Dahal S, Sharma P, et al. The characteristics and trends in adrenocortical carcinoma: a United States population based study. J Clin Med Res. 2018;10:636–640. [PubMed: 29977421]
2. Zheng S, Cherniack AD, Dewal N, et al. Comprehensive pan-genomic characterization of adrenocortical carcinoma. Cancer Cell. 2016;29:723–736. [PubMed: 27165744]
3. Fassnacht M, Dekkers OM, Else T, et al. European Society of Endocrinology clinical practice guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2018;179:G1–G46. [PubMed: 30299884]
4. Zeiger MA, Thompson GB, Duh QY, et al. The American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons medical guidelines for the management of adrenal incidentalomas. Endocr Pract. 2009;15(suppl 1): 1–20.

5. Vaidya A, Hamrahian A, Bancos I, Fleseriu M, Ghayee HK. The evaluation of incidentally discovered adrenal masses. Endocr Pract. 2019;25:178–192. [PubMed: 30817193]
6. Terzolo M, Stigliano A, Chiodini I, et al. AME position statement on adrenal incidentaloma. Eur J Endocrinol. 2011;164:851–870. [PubMed: 21471169]
7. Dinnes J, Bancos I, Ferrante di Ruffano L, et al. Management of endocrine disease: imaging for the diagnosis of malignancy in incidentally discovered adrenal masses: a systematic review and meta-analysis. Eur J Endocrinol. 2016;175:R51–R64. [PubMed: 27257145]
8. Takeuchi S, Balachandran A, Habra MA, et al. Impact of 18F-FDG PET/CT on the management of adrenocortical carcinoma: analysis of 106 patients. Eur J Nucl Med Mol Imaging. 2014;41:2066–2073. [PubMed: 24990404]
9. Ghander C, Tissier F, Tenenbaum F, et al. A concomitant false-negative 18F-FDG PET imaging in an adrenocortical carcinoma and a high uptake in a corresponding liver metastasis. J Clin Endocrinol Metab. 2012;97:1096–1097. [PubMed: 22319030]
10. Fassnacht M, Allolio B. Clinical management of adrenocortical carcinoma. Best Pract Res Clin Endocrinol Metab. 2009;23: 273–289. [PubMed: 19500769]
11. Luton JP, Cerdas S, Billaud L, et al. Clinical features of adrenocortical carcinoma, prognostic factors, and the effect of mitotane therapy. N Engl J Med. 1990;322:1195–1201. [PubMed: 2325710]
12. Else T, Kim AC, Sabolch A, et al. Adrenocortical carcinoma. Endocr Rev. 2014;35:282–326. [PubMed: 24423978]
13. Abiven G, Coste J, Groussin L, et al. Clinical and biological features in the prognosis of adrenocortical cancer: poor outcome of cortisol-secreting tumors in a series of 202 consecutive patients. J Clin Endocrinol Metab. 2006;91:2650–2655. [PubMed: 16670169]
14. Greene LW, Geer EB, Page-Wilson G, Findling JW, Raff H. Assay-specific spurious ACTH results lead to misdiagnosis, unnecessary testing, and surgical misadventure-a case series. J Endocr Soc. 2019;3:763–772. [PubMed: 30963134]
15. Arlt W, Biehl M, Taylor AE, et al. Urine steroid metabolomics as a biomarker tool for detecting malignancy in adrenal tumors. J Clin Endocrinol Metab. 2011;96:3775–3784. [PubMed: 21917861]
16. Bancos I, Taylor AE, Chortis V, et al. Urine steroid metabolomics for the differential diagnosis of adrenal incidentalomas in the EURINE-ACT study: a prospective test validation study. Lancet Diabetes Endocrinol. 2020;8:773–781. [PubMed: 32711725]
17. Chortis V, Bancos I, Nijman T, et al. Urine steroid metabolomics as a novel tool for detection of recurrent adrenocortical carcinoma. J Clin Endocrinol Metab. 2020;105:e307–e318.
18. Kerkhofs TM, Verhoeven RH, Bonjer HJ, et al. Surgery for adrenocortical carcinoma in The Netherlands: analysis of the national cancer registry data. Eur J Endocrinol. 2013;169:83–89. [PubMed: 23641018]
19. Leboulleux S, Deandreis D, Al Ghuzlan A, et al. Adrenocortical carcinoma: is the surgical approach a risk factor of peritoneal carcinomatosis? Eur J Endocrinol. 2010;162:1147–1153. [PubMed: 20348273]
20. Cooper AB, Habra MA, Grubbs EG, et al. Does laparoscopic adrenalectomy jeopardize oncologic outcomes for patients with adrenocortical carcinoma? Surg Endosc. 2013;27:4026–4032. [PubMed: 23765427]
21. Nilubol N, Patel D, Kebebew E. Does lymphadenectomy improve survival in patients with adrenocortical carcinoma? A population-based study. World J Surg. 2016;40:697–705. [PubMed: 26510563]
22. Saade N, Sadler C, Goldfarb M. Impact of regional lymph node dissection on disease specific survival in adrenal cortical carcinoma. Horm Metab Res. 2015;47:820–825. [PubMed: 25938888]
23. Weiss LM. Comparative histologic study of 43 metastasizing and nonmetastasizing adrenocortical tumors. Am J Surg Pathol. 1984;8:163–169. [PubMed: 6703192]
24. Fuhrman SA, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol. 1982;6:655–663. [PubMed: 7180965]

25. Sangoi AR, Fujiwara M, West RB, et al. Immunohistochemical distinction of primary adrenal cortical lesions from metastatic clear cell renal cell carcinoma: a study of 248 cases. Am J Surg Pathol. 2011;35:678–686. [PubMed: 21490444]
26. Weissferdt A, Phan A, Suster S, Moran CA. Adrenocortical carcinoma: a comprehensive immunohistochemical study of 40 cases. Appl Immunohistochem Mol Morphol. 2014;22:24–30. [PubMed: 23531850]
27. Sbiera S, Schmull S, Assie G, et al. High diagnostic and prognostic value of steroidogenic factor-1 expression in adrenal tumors. J Clin Endocrinol Metab. 2010;95:E161–E171. [PubMed: 20660055]
28. Beuschlein F, Weigel J, Saeger W, et al. Major prognostic role of Ki67 in localized adrenocortical carcinoma after complete resection. J Clin Endocrinol Metab. 2015;100:841–849. [PubMed: 25559399]
29. Libé R, Borget I, Ronchi CL, et al. Prognostic factors in stage III-IV adrenocortical carcinomas (ACC): an European Network for the Study of Adrenal Tumor (ENSAT) study. Ann Oncol. 2015;26:2119–2125. [PubMed: 26392430]
30. Papathomas TG, Pucci E, Giordano TJ, et al. An international Ki67 reproducibility study in adrenal cortical carcinoma. Am J Surg Pathol. 2016;40:569–576. [PubMed: 26685085]
31. Yamazaki Y, Nakamura Y, Shibahara Y, et al. Comparison of the methods for measuring the Ki-67 labeling index in adrenocortical carcinoma: manual versus digital image analysis. Hum Pathol. 2016;53:41–50. [PubMed: 26980031]
32. Phan AT, Grogan RH, Rohren E. Adrenal cortical carcinoma. In: AJCC Cancer Staging Manual. Eighth edn. Switzerland: Springer; 2017.
33. Fassnacht M, Arlt W, Bancos I, et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016;175: G1–G34. [PubMed: 27390021]
34. Fassnacht M, Libé R, Kroiss M, Allolio B. Adrenocortical carcinoma: a clinician's update. Nat Rev Endocrinol. 2011;7:323–335. [PubMed: 21386792]
35. Bilimoria KY, Shen WT, Elaraj D, et al. Adrenocortical carcinoma in the United States: treatment utilization and prognostic factors. Cancer. 2008;113:3130–3136. [PubMed: 18973179]
36. Icard P, Goudet P, Charpenay C, et al. Adrenocortical carcinomas: surgical trends and results of a 253-patient series from the French Association of Endocrine Surgeons study group. World J Surg. 2001;25:891–897. [PubMed: 11572030]
37. Fassnacht M, Johanssen S, Fenske W, et al. Improved survival in patients with stage II adrenocortical carcinoma followed up prospectively by specialized centers. J Clin Endocrinol Metab. 2010;95:4925–4932. [PubMed: 20668036]
38. Berruti A, Grisanti S, Pulzer A, et al. Long-term outcomes of adjuvant mitotane therapy in patients with radically resected adrenocortical carcinoma. J Clin Endocrinol Metab. 2017;102: 1358–1365. [PubMed: 28324035]
39. Else T, Williams AR, Sabolch A, Jolly S, Miller BS, Hammer GD. Adjuvant therapies and patient and tumor characteristics associated with survival of adult patients with adrenocortical carcinoma. J Clin Endocrinol Metab. 2014;99:455–461. [PubMed: 24302750]
40. Grubbs EG, Callender GG, Xing Y, et al. Recurrence of adrenal cortical carcinoma following resection: surgery alone can achieve results equal to surgery plus mitotane. Ann Surg Oncol. 2010;17:263–270.
41. Postlewait LM, Ethun CG, Tran TB, et al. Outcomes of adjuvant mitotane after resection of adrenocortical carcinoma: a 13-institution study by the U.S. Adrenocortical Carcinoma Group. J Am Coll Surg. 2016;222:480–490. [PubMed: 26775162]
42. Hines JM, Bancos I, Bancos C, et al. High-resolution, accurate-mass (HRAM) mass spectrometry urine steroid profiling in the diagnosis of adrenal disorders. Clin Chem. 2017;63:1824–1835. [PubMed: 28814383]
43. Bancos I, Arlt W. Diagnosis of a malignant adrenal mass: the role of urinary steroid metabolite profiling. Curr Opin Endocrinol Diabetes Obes. 2017;24:200–207. [PubMed: 28234802]
44. Chompret A, Abel A, Stoppa-Lyonnet D, et al. Sensitivity and predictive value of criteria for p53 germline mutation screening. J Med Genet. 2001;38:43–47. [PubMed: 11332399]

45. Chompret A, Brugières L, Ronsin M, et al. P53 germline mutations in childhood cancers and cancer risk for carrier individuals. Br J Cancer. 2000;82:1932–1937. [PubMed: 10864200]
46. Abiven-Lepage G, Coste J, Tissier F, et al. Adrenocortical carcinoma and pregnancy: clinical and biological features and prognosis. Eur J Endocrinol. 2010;163:793–800. [PubMed: 20699382]
47. de Corbière P, Ritzel K, Cazabat L, et al. Pregnancy in women previously treated for an adrenocortical carcinoma. J Clin Endocrinol Metab. 2015;100:4604–4611. [PubMed: 26461265]
48. Baszko-Blaszyk D, Ochmańska K, Waśko R, Sowiński J. Pregnancy in a patient with adrenocortical carcinoma during treatment with Mitotane - a case report. Endokrynol Pol. 2011;62: 186–188. [PubMed: 21528483]
49. Tripto-Shkolnik L, Blumenfeld Z, Bronshtein M, Salmon A, Jaffe A. Pregnancy in a patient with adrenal carcinoma treated with mitotane: a case report and review of literature. J Clin Endocrinol Metab. 2013;98:443–447. [PubMed: 23275528]
50. Sirianni R, Zolea F, Chimento A, et al. Targeting estrogen receptor-alpha reduces adrenocortical cancer (ACC) cell growth in vitro and in vivo: potential therapeutic role of selective estrogen receptor modulators (SERMs) for ACC treatment. J Clin Endocrinol Metab. 2012;97:E2238–E2250. [PubMed: 23074235]
51. Schteingart DE. Adjuvant mitotane therapy of adrenal cancer - use and controversy. N Engl J Med. 2007;356:2415–2418. [PubMed: 17554125]
52. Sbiera S, Leich E, Liebisch G, et al. Mitotane inhibits sterol-O-acyl transferase 1 triggering lipid-mediated endoplasmic reticulum stress and apoptosis in adrenocortical carcinoma cells. Endocrinology. 2015;156:3895–3908. [PubMed: 26305886]
53. Terzolo M, Angeli A, Fassnacht M, et al. Adjuvant mitotane treatment for adrenocortical carcinoma. N Engl J Med. 2007;356: 2372–2380. [PubMed: 17554118]
54. El Ghorayeb N, Rondeau G, Latour M, et al. Rapid and complete remission of metastatic adrenocortical carcinoma persisting 10 years after treatment with mitotane monotherapy: case report and review of the literature. Medicine (Baltimore). 2016;95: e3180. [PubMed: 27043680]
55. Megerle F, Herrmann W, Schloetelburg W, et al. Mitotane monotherapy in patients with advanced adrenocortical carcinoma. J Clin Endocrinol Metab. 2018;103:1686–1695. [PubMed: 29452402]
56. Kerkhofs TM, Baudin E, Terzolo M, et al. Comparison of two mitotane starting dose regimens in patients with advanced adrenocortical carcinoma. J Clin Endocrinol Metab. 2013;98:4759–4767. [PubMed: 24057287]
57. Chortis V, Taylor AE, Schneider P, et al. Mitotane therapy in adrenocortical cancer induces CYP3A4 and inhibits 5alpha-reductase, explaining the need for personalized glucocorticoid and androgen replacement. J Clin Endocrinol Metab. 2013;98: 161–171. [PubMed: 23162091]
58. Tessonnier L, Ansquer C, Bournaud C, et al. (18)F-FDG uptake at initial staging of the adrenocortical cancers: a diagnostic tool but not of prognostic value. World J Surg. 2013;37:107–112. [PubMed: 23001287]
59. Datta J, Roses RE. Surgical management of adrenocortical carcinoma: an evidence-based approach. Surg Oncol Clin North Am. 2016;25:153–170.
60. Dy BM, Wise KB, Richards ML, et al. Operative intervention for recurrent adrenocortical cancer. Surgery. 2013;154:1292–1299; discussion 1299. [PubMed: 24238048]
61. Erdogan I, Deutschbein T, Jurowich C, et al. The role of surgery in the management of recurrent adrenocortical carcinoma. J Clin Endocrinol Metab. 2013;98:181–191. [PubMed: 23150691]
62. Glenn JA, Else T, Hughes DT, et al. Longitudinal patterns of recurrence in patients with adrenocortical carcinoma. Surgery. 2019;165:186–195. [PubMed: 30343951]
63. Gaujoux S, Al-Ahmadie H, Allen PJ, et al. Resection of adrenocortical carcinoma liver metastasis: is it justified? Ann Surg Oncol. 2012;19:2643–2651. [PubMed: 22526905]
64. Datrice NM, Langan RC, Ripley RT, et al. Operative management for recurrent and metastatic adrenocortical carcinoma. J Surg Oncol. 2012;105:709–713. [PubMed: 22189845]
65. Baudin E, Leboulleux S, Al Ghuzlan A, et al. Therapeutic management of advanced adrenocortical carcinoma: what do we know in 2011? Horm Cancer. 2011;2:363–371. [PubMed: 22161625]
66. Miller BS. 5th International ACC Symposium: surgical considerations in the treatment of adrenocortical carcinoma: 5th International ACC Symposium Session: Who, When and What Combination? Horm Cancer. 2016;7:24–28. [PubMed: 26728469]

67. Long SE, Miller BS. Adrenocortical cancer treatment. Surg Clin North Am. 2019;99:759–771. [PubMed: 31255205]
68. Mayo-Smith WW, Dupuy DE. Adrenal neoplasms: CT-guided radiofrequency ablation--preliminary results. Radiology. 2004;231:225–230. [PubMed: 14990812]
69. Wood BJ, Abraham J, Hvizda JL, Alexander HR, Fojo T. Radiofrequency ablation of adrenal tumors and adrenocortical carcinoma metastases. Cancer. 2003;97:554–560. [PubMed: 12548596]
70. Ripley RT, Kemp CD, Davis JL, et al. Liver resection and ablation for metastatic adrenocortical carcinoma. Ann Surg Oncol. 2011;18:1972–1979. [PubMed: 21301973]
71. Soga H, Takenaka A, Ooba T, et al. A twelve-year experience with adrenal cortical carcinoma in a single institution: long-term survival after surgical treatment and transcatheter arterial embolization. Urol Int. 2009;82:222–226. [PubMed: 19322014]
72. Megerle F, Kroiss M, Hahner S, Fassnacht M. Advanced adrenocortical carcinoma - what to do when first-line therapy fails? Exp Clin Endocrinol Diabetes. 2019;127:109–116. [PubMed: 30469158]
73. Gaujoux S, Weinandt M, Bonnet S, Reslinger V, Bertherat J, Dousset B. Surgical treatment of adrenal carcinoma. J Visc Surg. 2017;154:335–343. [PubMed: 28754418]
74. Ayala-Ramirez M, Jasim S, Feng L, et al. Adrenocortical carcinoma: clinical outcomes and prognosis of 330 patients at a tertiary care center. Eur J Endocrinol. 2013;169:891–899. [PubMed: 24086089]
75. Bednarski BK, Habra MA, Phan A, et al. Borderline resectable adrenal cortical carcinoma: a potential role for preoperative chemotherapy. World J Surg. 2014;38:1318–1327. [PubMed: 24615603]
76. Hughes MS, Lo WM, Beresnev T, et al. A phase II trial of cytoreduction and hyperthermic intraperitoneal chemotherapy for recurrent adrenocortical carcinoma. J Surg Res. 2018;232:383–388. [PubMed: 30463745]
77. Brix D, Allolio B, Fenske W, et al. Laparoscopic versus open adrenalectomy for adrenocortical carcinoma: surgical and oncologic outcome in 152 patients. Eur Urol. 2010;58:609–615. [PubMed: 20580485]
78. Miller BS, Ammori JB, Gauger PG, Broome JT, Hammer GD, Doherty GM. Laparoscopic resection is inappropriate in patients with known or suspected adrenocortical carcinoma. World J Surg. 2010;34:1380–1385. [PubMed: 20372905]
79. Fassnacht M, Terzolo M, Allolio B, et al. Combination chemotherapy in advanced adrenocortical carcinoma. N Engl J Med. 2012;366:2189–2197. [PubMed: 22551107]
80. Henning JEK, Deutschbein T, Altieri B, et al. Gemcitabine-based chemotherapy in adrenocortical carcinoma: a multicenter study of efficacy and predictive factors. J Clin Endocrinol Metab. 2017;102:4323–4332. [PubMed: 29092062]
81. Berruti A, Sperone P, Ferrero A, et al. Phase II study of weekly paclitaxel and sorafenib as second/third-line therapy in patients with adrenocortical carcinoma. Eur J Endocrinol. 2012;166: 451–458. [PubMed: 22189997]
82. Kroiss M, Quinkler M, Johanssen S, et al. Sunitinib in refractory adrenocortical carcinoma: a phase II, single-arm, open-label trial. J Clin Endocrinol Metab. 2012;97:3495–3503. [PubMed: 22837187]
83. Fassnacht M, Berruti A, Baudin E, et al. Linsitinib (OSI-906) versus placebo for patients with locally advanced or metastatic adrenocortical carcinoma: a double-blind, randomised, phase 3 study. Lancet Oncol. 2015;16:426–435. [PubMed: 25795408]
84. Naing A, Lorusso P, Fu S, et al. Insulin growth factor receptor (IGF-1R) antibody cixutumumab combined with the mTOR inhibitor temsirolimus in patients with metastatic adrenocortical carcinoma. Br J Cancer. 2013;108:826–830. [PubMed: 23412108]
85. Phan LM, Fuentes-Mattei E, Wu W, et al. Hepatocyte growth factor/cMET pathway activation enhances cancer hallmarks in adrenocortical carcinoma. Cancer Res. 2015;75:4131–4142. [PubMed: 26282167]
86. Le Tourneau C, Hoimes C, Zarwan C, et al. Avelumab in patients with previously treated metastatic adrenocortical carcinoma: phase 1b results from the JAVELIN solid tumor trial. J Immunother Cancer. 2018;6:111. [PubMed: 30348224]

87. Carneiro BA, Konda B, Costa RB, et al. Nivolumab in metastatic adrenocortical carcinoma: results of a phase 2 trial. J Clin Endocrinol Metab. 2019;104:6193–6200. [PubMed: 31276163]

88. Raj N, Zheng Y, Kelly V, et al. PD-1 blockade in advanced adrenocortical carcinoma. J Clin Oncol. 2020;38:71–80. [PubMed: 31644329]

89. Habra MA, Stephen B, Campbell M, et al. Phase II clinical trial of pembrolizumab efficacy and safety in advanced adrenocortical carcinoma. J Immunother Cancer. 2019;7:253. [PubMed: 31533818]

90. Head L, Kiseljak-Vassiliades K, Clark TJ, et al. Response to immunotherapy in combination with mitotane in patients with metastatic adrenocortical cancer. J Endocr Soc. 2019;3:2295–2304. [PubMed: 31745526]

91. Jasim S, Habra MA. Management of adrenocortical carcinoma. Curr Oncol Rep. 2019;21:20. [PubMed: 30798468]

92. Polat B, Fassnacht M, Pfreundner L, et al. Radiotherapy in adrenocortical carcinoma. Cancer. 2009;115:2816–2823. [PubMed: 19402169]

93. Fay AP, Elfiky A, Telo GH, et al. Adrenocortical carcinoma: the management of metastatic disease. Crit Rev Oncol Hematol. 2014;92:123–132. [PubMed: 24958272]

94. Hahner S, Kreissl MC, Fassnacht M, et al. [131I]iodometomidate for targeted radionuclide therapy of advanced adrenocortical carcinoma. J Clin Endocrinol Metab. 2012;97:914–922. [PubMed: 22170726]

95. Berruti A, Libè R, Lagana M, et al. Morbidity and mortality of bone metastases in advanced adrenocortical carcinoma: a multicenter retrospective study. Eur J Endocrinol. 2019;180:311–320. [PubMed: 30970324]

96. Janssen S, Bartscht T, Rades D. Prognosis of patients with metastatic spinal cord compression from adrenocortical carcinoma. In Vivo. 2016;30:717–719. [PubMed: 27566097]

97. Pin Y, Paix A, Le Fèvre C, Antoni D, Blondet C, Noël G. A systematic review of palliative bone radiotherapy based on pain relief and retreatment rates. Crit Rev Oncol Hematol. 2018;123:132–137. [PubMed: 29482774]

98. Lee D, Yanamadala V, Shankar GM, Shin JH. Metastatic adrenal cortical carcinoma to T12 vertebrae. J Clin Neurosci. 2016;27: 166–169. [PubMed: 26765762]

99. Schlick CJR, Bentrem DJ. Timing of palliative care: when to call for a palliative care consult. J Surg Oncol. 2019;120:30–34. [PubMed: 31102469]

100. Smith CB, Phillips T, Smith TJ. Using the new ASCO clinical practice guideline for palliative care concurrent with oncology care using the TEAM approach. Am Soc Clin Oncol Educ Book. 2017;37:714–723. [PubMed: 28561696]

101. Worster B, Swartz K. Telemedicine and palliative care: an increasing role in supportive oncology. Curr Oncol Rep. 2017;19:37. [PubMed: 28417310]

102. Schulte HM, Benker G, Reinwein D, Sippell WG, Allolio B. Infusion of low dose etomidate: correction of hypercortisolemia in patients with Cushing's syndrome and dose-response relationship in normal subjects. J Clin Endocrinol Metab. 1990;70:1426–1430. [PubMed: 2159485]

103. Fleseriu M, Biller BM, Findling JW, et al. Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome. J Clin Endocrinol Metab. 2012;97:2039–2049. [PubMed: 22466348]

104. Iñiguez-Ariza NM, Kohlenberg JD, Delivanis DA, et al. Clinical, biochemical, and radiological characteristics of a single-center retrospective cohort of 705 large adrenal tumors. Mayo Clin Proc Innov Qual Outcomes. 2017;2:30–39. [PubMed: 30225430]

105. Delivanis DA, Erickson D, Atwell TD, et al. Procedural and clinical outcomes of percutaneous adrenal biopsy in a high-risk population for adrenal malignancy. Clin Endocrinol (Oxf). 2016;85: 710–716. [PubMed: 27248805]

106. Canu L, Van Hemert JAW, Kerstens MN, et al. CT characteristics of pheochromocytoma: relevance for the evaluation of adrenal incidentaloma. J Clin Endocrinol Metab. 2019;104:312–318. [PubMed: 30383267]

107. Hammarstedt L, Muth A, Sigurjónsdóttir HA, et al. Adrenal lesions in patients with extra-adrenal malignancy - benign or malignant? Acta Oncol. 2012;51:215–221. [PubMed: 21879835]

108. Levine AC, Mitty HA, Gabrilove JL. Steroid content of the peripheral and adrenal vein in Cushing's syndrome due to adrenocortical adenoma and carcinoma. J Urol. 1988;140:11–15. [PubMed: 2967899]
109. Williams AR, Hammer GD, Else T. Transcutaneous biopsy of adrenocortical carcinoma is rarely helpful in diagnosis, potentially harmful, but does not affect patient outcome. Eur J Endocrinol. 2014;170:829–835. [PubMed: 24836548]
110. Bancos I, Tamhane S, Shah M, et al. Diagnosis of endocrine disease: the diagnostic performance of adrenal biopsy: a systematic review and meta-analysis. Eur J Endocrinol. 2016;175: R65–R80. [PubMed: 27257146]
111. Mody MK, Kazerooni EA, Korobkin M. Percutaneous CT-guided biopsy of adrenal masses: immediate and delayed complications. J Comput Assist Tomogr. 1995;19:434–439. [PubMed: 7790554]
112. Ridho FE, Adam FM, Adam JM. Adrenal incidentaloma. Acta Med Indones. 2009;41:87–93. [PubMed: 19390128]
113. Bisceglia M, Ludovico O, Di Mattia A, et al. Adrenocortical oncocytic tumors: report of 10 cases and review of the literature. Int J Surg Pathol. 2004;12:231–243. [PubMed: 15306935]
114. Canberk S, LiVolsi VA, Baloch Z. Oncocytic lesions of the neuroendocrine system. Adv Anat Pathol. 2014;21:69–82. [PubMed: 24508690]
115. Wong DD, Spagnolo DV, Bisceglia M, Havlat M, McCallum D, Platten MA. Oncocytic adrenocortical neoplasms--a clinicopathologic study of 13 new cases emphasizing the importance of their recognition. Hum Pathol. 2011;42:489–499. [PubMed: 21237489]
116. Mills JK, Khalil M, Pasieka J, Kong S, Xu Y, Harvey A. Oncocytic subtypes of adrenal cortical carcinoma: aggressive in appearance yet more indolent in behavior? Surgery. 2019;166: 524–533. [PubMed: 31472975]
117. Renaudin K, Smati S, Wargny M, et al. Clinicopathological description of 43 oncocytic adrenocortical tumors: importance of Ki-67 in histoprognostic evaluation. Mod Pathol. 2018;31: 1708–1716. [PubMed: 29921900]

Table 1

Imaging Characteristics of Benign Versus Malignant Adrenal Mass

Characteristic	Likely benign	Suspicious for malignancy
Size	Small (<4 cm)	Large (>4 cm)
Shape	Round or oval	Irregular
Margins	Smooth	Irregular
Texture	Homogenous	Heterogenous
Calcifications/Necrosis/Hemorrhage	Rare	Common
Growth	Slow	Rapid
Density of non-contrast CT	<10 HU	>10 HU
Contrast washout on CT protocol at 10–15 minutes	Absolute > 60% Relative > 40%	Absolute < 60% Relative < 40%
MRI chemical shift	Yes	No
FDG-PET	Non-avid	Avid

Abbreviations: CT = computed tomography; FDG-PET = fluorodeoxyglucose positron emission tomography; HU = Hounsfield units; MRI = magnetic resonance imaging.

Modified from Vaidya A. Endocrine Practice. 2019; 25(2):178–192.

Table 2

Diagnostic Evaluation in Patients With Adrenal Mass Suspicions for ACC

Diagnostic Evaluation	Essential for Clinical Care	Non-Essential, but Potentially Informative
Evaluation for Autonomous Adrenal Cortical Hormone Excess	History and Physical Examination Blood Pressure Measurement Serum Potassium 1 mg dexamethasone suppression test and/or 24-h urinary free cortisol Morning ACTH level Aldosterone-to-renin ratio Total testosterone and DHEA-S	Plasma glucose Glycated hemoglobin 24-h urine steroid profiling Androstnedione 11-deoxycortisol 17-beta-estradiol 17-hydroxyprogesterone
Exclusion of Pheochromocytoma	Plasma metanephrines	24-hour urinary fractionated metanephrines
Diagnostic Imaging	Abdominal CT or MRI	FDG-PET
Staging Imaging	Chest CT	FDG-PET

Abbreviations: ACC = adrenocortical carcinoma; ACTH = adrenocorticotropic hormone; CT = computed tomography; DHEA-S = dehydroepiandrosterone sulfate; FDG-PET = fluorodeoxyglucose positron emission tomography; MRI = magnetic resonance imaging.

Table 3

Weiss Score (17) System to Evaluate Benign Versus Malignant Adrenal Neoplasm

Criteria	Present in adrenocortical carcinoma	Score
Nuclear Grade	High (grade 3 or 4)[a]	1
Mitotic rate	Greater than 5 per 50 HPF	1
Presence of atypical mitosis	Present	1
Clear cells	Present in 25% or less of the tumor	1
Diffuse architecture	Greater than 1/3 of the tumor	1
Necrosis	Present	1
Venous invasion	Present	1
Sinusoidal invasion	Present	1
Capsular invasion	Present	1
Total Weiss score > 3 is suggestive of adrenocortical carcinoma		

Abbreviation: HPF = high-power field.

[a]High-grade parameters as defined by Fuhrman et al (18) in renal cell carcinoma.

Table 4

Variables for Pathologic Evaluation of Tumor Suspicious for Adrenocortical Carcinoma

Weiss criteria variables
Tumor size (cm^3)
Tumor weight (gm)
Surgical margins
Lymph node status
Extra adrenal extension
Immunohistochemistry
Steroidogenic factor 1 (SF1)
Alpha-inhibin
Synaptophysin
MelanA
KI-67
P53
B-catenin
MMR stains (MLH1, PMS2, MSH2, MSH6)

Table 5

AJCC (24) and ENSAT (25) Staging System for ACC

Staging group	AJCC staging			ENSAT staging		
Stage I	T1	N0	M0	T1	N0	M0
Stage II	T2	N0	M0	T2	N0	M0
Stage III	T1–2	N1	M0	T1–2	N1	M0
	T3–4	N0–1, NX	M0	T3–4	N0–1	M0
Stage IV	T1–4	N0–1, NX	M1	T1–4	N0–1	M1

Abbreviations: AJCC = American Joint Committee on Cancer; ENSAT = European Network for the Study of Adrenal Tumors.

T1: 1:rope≤5 cm, no extra-adrenal invasion; T2: 2:m, no5 cm, no extra-adrenal invasion; T3: 3:m, no extra-adrenal invasion; f Adrenal Tumorswidth:410.2T4: 4:m, no extra-adrenal invasion; F Adrenal NX: X:m, no extra-adrenal invasion; N0: 0:m, no extra-adrenal invasion; f; N1: 1:m, no extra-adrenal invasion; f Adrenal 0: No distant metastasis; M: Distant metastasis.