Original Article

Management of Adrenocortical Carcinoma

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Key Words

Adrenocortical cancer, adrenal carcinoma, Cushing's syndrome, mitotane

Abstract

Adrenocortical carcinomas (ACCs) are rare tumors that arise from the cortex of the adrenal gland with an incidence 1 to 2 per million. The rarity of this tumor translates into a paucity of experience in managing patients in most medical centers. Because clinical series are small and prospective evaluation of treatment strategies is limited, the current state of knowledge is strongly influenced by expert consensus opinion from a few medical centers specializing in ACCs. This article describes the basic diagnostic and prognostic issues in adrenal cancer management, and presents detailed rationales for therapeutic management. (*JNCCN* 2009;7:752–759)

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Describe the incidence of adrenocortical carcinoma (ACC)
- Identify the most common clinical presentations of ACC
- Describe the most useful diagnostic tests for ACC
- Describe a pathologic assessment for ACC to distinguish it from benign conditions
- Describe surgical approaches to the treatment of ACC

Epidemiology

Adrenocortical carcinomas (ACCs) are rare tumors that arise from the cortex of the adrenal gland with an incidence 1 to 2 per million.[1–3] This extremely low incidence translates into minimal experience with diagnosing and treating the disease in most medical centers. Moreover,

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series are small and prospective evaluation of strategies has been limited. Thus, the current state of knowledge is strongly affected by expert consensus opinion from a few centers with dedicated ACC programs.[4]

A bimodal age distribution shows peak incidences in early childhood and in the fourth to fifth decades of life with a female to male ratio of approximately 1.5 to 1.[5,6] Most cases are sporadic; however, ACCs have been observed in association with several hereditary syndromes, including Li-Fraumeni syndrome, Beck-with-Wiedemann syndrome, familial adenomatous polyposis, and multiple endocrine neoplasia type 1.[7–11] Although the underlying mechanisms of carcinogenesis in sporadic ACCs have not been fully elucidated, similar to familial ACC, inactivating mutations of the *p53* tumor suppressor gene (chromosome 17p13)[12,13] and activating mutations in the Wnt signaling pathway and alterations at the 11p15 locus (site of the *IGF-2* gene)[14,15] occur with high frequency.[16]

Clinical Presentation

Patients typically present either asymptomatically or with symptoms caused by hormone excess or mass effect of the tumor. Nonfunctional masses are discovered because of symptoms of local invasion or unrelated symptoms that lead to abdominal imaging. Approximately 60% of patients present with evidence of adrenal steroid hormone excess. Cushing's syndrome, with or without virilization, is the most common presentation.[2,3,17,18] Signs and symptoms associated with hypersecretion of cortisol include weight gain, weakness (primarily in proximal muscles), hypertension, hyperglycemia, and hypokalemia. Patients with rare aldosterone-secreting tumors may present with hypertension and pronounced hypokalemia. Androgen-secreting tumors in women may induce hirsutism, deepening of the voice, and oligo- or amenorrhea.[3] For men, estrogen-secreting tumors may induce gynecomastia and testicular atrophy. Patients whose tumors secrete multiple hormones causing mixed hormonal syndromes almost always have malignant tumors.

Hormonally inactive ACCs can produce symptoms related to tumor burden, including abdominal pain, back pain, early satiety, and weight loss, leading to abdominal imaging.[3,19] Some smaller ACCs are sometimes discovered during imaging for other indications. The challenge with these patients is distinguishing small ACCs from the many benign incidentally discovered adrenal tumors. Most ACCs discovered through imaging do not present a diagnostic challenge because they are large (mean tumor size is 10 cm and 95% are larger than 5 cm at diagnosis) and heterogeneous in internal appearance (Figure 1). However, because all large tumors were initially small tumors, distinguishing small malignant tumors from the multitude of small benign adenomas, although difficult, is of paramount importance.

Incidental Adrenal Masses

Full evaluation of incidental adrenal masses requires investigation for functional syndromes of medullary or cortical origin and risk for malignancy. Simple blood and urine testing together with standard CT scans are usually sufficient to distinguish a functional from a nonfunctional adrenal tumor, and a benign from a malignant mass.

Hormonal Evaluation

A hormonal workup of hypercortisolism and catecholamine excess has been considered standard care for all symptomatic and asymptomatic patients because of the morbidity of subclinical Cushing's syndrome and the potential for hypertensive emergency in a patient with subclinical pheochromocytoma. Only asymptomatic patients with definitive imaging evidence of myelolipoma or an adrenal cyst have been considered by some to be exempt from this evaluation. Historically, the workup of primary hyperaldosteronism was only considered to have diagnostic efficacy in hypertensive patients. Because recent data indicate subclinical hyperaldosteronism in as high as 10% of patients with clinically silent incidentally discovered adrenal masses, all patients in this cohort are screened for primary hyperaldosteronism.

Plasma or urine free metanephrines are the preferred tests for excluding or confirming the diagnosis of pheochromocytoma. Because of a 99% sensitivity, testing of plasma levels is reserved for patients with a high index of suspicion (i.e., incidental adrenal mass), wherein any value above the normal range is considered diagnostic of a pheochromocytoma; 24-hour urine free metanephrines are usually reserved for patients with a low index of suspicion. Levels 2 to 3 times the upper end of the normal range are consistent with a pheochromocytoma.

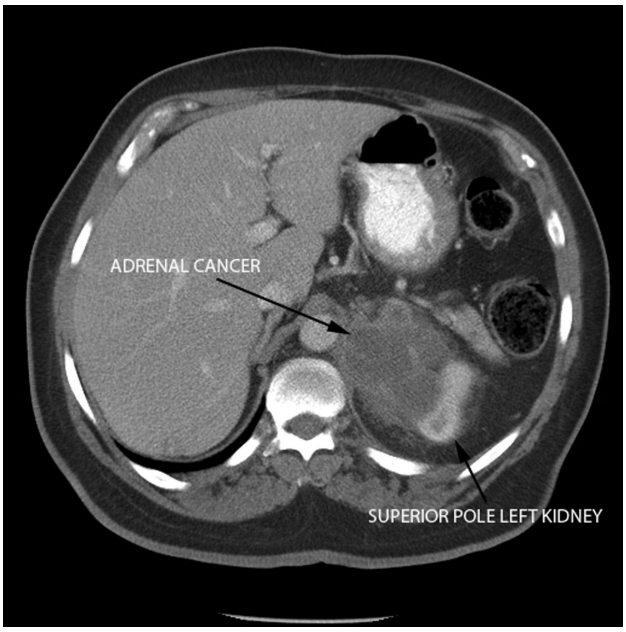

Figure 1 A typical left adrenal carcinoma showing its large size, irregular borders, and vascular periphery with central necrosis.

Cushing's syndrome is evaluated using 1 of 3 screening tests: an overnight (1 mg) dexamethasone suppression test, 24-hour urine free cortisol, or midnight salivary cortisol. After the administration of 1-mg dexamethasone at bedtime, most normal people suppress serum cortisol to less than 2 µg/dL. Lack of suppression is indicative of autonomous production of cortisol. An adrenocorticotropin (ACTH) that is undetectable is consistent with the presumed adrenal (vs. pituitary) autonomy. An elevated 24-hour urinary free cortisol measurement is equally diagnostic and can help confirm Cushing's syndrome in a borderline suppression test. Similarly, a plasma aldosterone concentration of greater than 15 ng/dL with a concomitant aldosterone:renin ratio greater than 20 support autonomous aldosterone production. The measurement of sex steroids can be limited to patients who present with masculinization or feminization, because sex steroid excess is rarely an incidental finding. Measurements include follicle stimulating hormone, leuteinizing hormone, dehydroepiandrosterone sulfate, testosterone, and estradiol.[3]

Radiographic Studies

In surgical series of adrenal incidentalomas, ACCs comprise approximately 2% of tumors smaller than 4 cm, 6% of tumors 4 to 6 cm, and 25% of tumors with a diameter greater than 6 cm. For this reason, radiologic studies include size as a risk factor for malignancy. A high lipid content has proven to be one of the most useful lesion characteristics to confirm the presence of a benign adrenocortical adenoma. For this reason, standard radiologic evaluation now involves a non–contrast CT to determine size and homogenous lipid content of the adrenal mass.

Density measurement of 10 or less Hounsfield units (HU) is consistent with a benign adenoma. Lesions that are large, poorly circumscribed, more than 10 HU, or heterogeneous in signal are more worrisome. MRI can provide similar diagnostic value, with ACC usually isointense to liver on T1-weighted images but having increased intensity on T2 sequences. Lastly, fluorodeoxyglucose (FDG)-PET is emerging as a powerful adjuvant in the determination of benign versus malignant disease.[20–27] FDG-PET scans typically show FDG uptake in malignant tumors, especially high-grade tumors, but less frequently in benign adenomas.[28,29]

Because the lung and liver are the most common sites of metastatic spread, and pelvic metastatic deposits are not uncommon, thoracic, abdominal, and pelvic scans are integral to the staging workup of ACC. MRIs are particularly useful in assessing local invasion and involvement of the inferior vena cava.[30,31] Bone scans may be considered to evaluate bone pain.

Pathologic Assessment

Preoperative pathologic assessment of an adrenal mass is almost never indicated. Image-guided biopsy is only considered useful in patients with a known extra-adrenal primary cancer to determine whether the adrenal mass is a primary adrenal neoplasm versus metastatic disease from the nonadrenal primary. This rationale is predicated on data that indicate that the procedure is dangerous for patients with medullary tumors, in whom biopsy can result in a hypertensive crisis. Moreover, a biopsy is likely to be uninformative for cortical lesions because of the cytologic overlap between normal, benign, and malignant adrenocortical tissue. Lastly, peritoneal seeding of the ACC after biopsy can impair the opportunity for subsequent curative resection.

In the absence of local invasion or distant metastases, the pathologic distinction between a malignant

and benign adrenal tumor can be difficult. The most commonly used diagnostic tool is the Weiss score.[32,33] This score (0–9) can be determined for each patient, based on the presence or absence of 1) high mitotic rate, 2) atypical mitoses, 3) high nuclear grade, 4) low percentage of clear cells, 5) necrosis, 6) diffuse architecture of tumor, 7) capsular invasion, 8) sinusoidal invasion, and 9) venous invasion. A Weiss score of 3 or more is considered consistent with a malignant adrenal tumor.

Staging and Tumor Grading

The WHO staging system for ACC, which is based on tumor size and invasion (T), regional nodal involvement (N), and distant metastases (M), is routinely used to compare disease status at presentation across patients and medical centers and to guide therapy (Table 1).[34] The TNM staging is similar to the MacFarlane classification originally proposed in 1958 and then modified.[35] However, individual prognostication to allow rational planning for therapy and follow-up monitoring requires integration of the information from the staging system and histologic grading. For example, patients whose carcinoma has a high mitotic rate (> 20 mitoses per 50 hpf) have a more limited disease-free interval.[36,37]

Prognosis largely depends on stage and grade. In one large study, the actuarial 5-year survival rates were 66% for patients with stage I tumors, 58% for stage II, 24% for stage III, and 0% for stage IV.[38]

Table 1 WHO Staging of Adrenocortical Carcinomas

Primary Tumor (T)	
T1	Tumor ≤ 5 cm in greatest dimension, local invasion absent
T2	Tumor > 5 cm in greatest dimension, local invasion absent
T3	Tumor outside adrenal, in fat
T4	Tumor invading adjacent organs
Regional Lymph Nodes (N)	
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Stage Grouping	
Stage I	T1, N0, M0
Stage II	T2, N0, M0
Stage III	T1 or T2, N1, M0 T3, N0, M0
Stage IV	T3 or T4, N1, M0 Any T, any N, M1

From DeLellis RA, Lloyd RV, Heitz PU, Eng C, eds. World Health Organization Classification of Tumours: Pathology & Genetics of Tumours of Endocrine Organs. Lyon: IARC Press; 2004; with permission.

Surgical Therapy

Definitive resection should be considered for patients with functional adenomas/carcinomas or apparently localized ACCs. For incidentally identified lesions that may be ACCs, careful surgical judgment must determine the operative approach (laparoscopic vs. open exploration).[39] Laparoscopic resection is reserved for patients believed to harbor small, benign, functional tumors or those with borderline risk for malignancy.

Any difficulty in the laparoscopic approach demands conversion to open resection. Resection includes gross total removal of the tumor and adrenal gland without capsular breach. For patients with stage II or III disease, concomitant resection of adjacent structures can include the kidney, liver, spleen, pancreas, stomach, colon, or vena cava if needed to completely remove direct tumor extension to those structures. En bloc resection of the kidney should be planned for any patient with apparent involvement of the renal capsule or vasculature.

Resection should be considered for recurrent tumors in selected patients with excellent performance status and locoregional recurrence, or isolated distant metastases, if complete resection can be achieved. For some patients, a symptomatic recurrence (e.g., from local effects or hormone hypersecretion) can be palliated through operative resection; however, surgical resection is rarely indicated if incomplete resection can be achieved or for patients with unresectable, distant, metastatic disease.[2–4,38]

Adjuvant Treatment

Because ACC is so rare, no randomized, prospective trials of adjuvant therapy have been published. Most retrospective reports have examined the use of adjuvant mitotane, an oral adrenocorticolytic agent.[40–42] The largest study retrospectively analyzed 177 pa-

tients with resected ACC (stages I–III) treated in Italy and Germany.[43,44] Adjuvant mitotane at doses ranging from 1 to 5 g/d was administered to almost half of patients (47 of 102 patients) in the Italian cohort, compared with none in the German cohort (75 patients). The median duration of treatment was 29 months. In follow-up, the treatment cohort had significantly longer disease-free and overall survival than the control cohorts, suggesting that adjuvant mitotane may be an effective postoperative strategy.

A recommended protocol for mitotane use is as follows:[4]

- The usual tolerated dose is 3.0 to 4.0 g/d; however, serum levels and patient tolerance should determine optimal dose.
- Adjuvant therapy duration goal is 2 years, but patients should be treated longer if they are doing well.
- Treatment should begin with 2 g/d and advance to achieve serum levels of 14 to 20 mg/dL.[45] The therapeutic window of mitotane is low and toxicities increase sharply with blood levels exceeding 20 mg/L. Side effects are mainly gastrointestinal and neurologic, including nausea, dizziness, and somnolence.[46] The target blood level may be unattainable because of side effects, and therefore the dose should be adjusted to tolerance.
- Patients should be monitored clinically and by measuring ACTH, urinary free cortisol, and electrolytes.
- The dose of cortisol replacement should be adjusted to assure adequate glucocorticoid replacement. All patients with ACC receiving mitotane require cortisol replacement because mitotane will also destroy any normal adrenocortical tissue. Because mitotane stimulates the catabolism of cortisol, patients require supraphysiologic doses of hydrocortisone (30–40 mg/d in divided doses) while on mitotane. Mineralocorticoid replacement is rarely indicated because glomerulosa function is often maintained on mitotane.
- Thyroid function, serum testosterone, and lipids should be monitored and corrected as needed.
- Vigorous antiemetics and other symptomatic support should be provided.

Data regarding the efficacy of adjuvant radiotherapy for ACC are limited.[47–49] However, evidence suggests that radiotherapy is probably as effective in ACC as it is for other solid tumors. Although in other solid tumors radiotherapy is routinely recommended as a supplemental treatment for local control after marginal resection, its use to limit ACC local recurrence is not specifically proven. The risk:benefit ratio should be individually assessed and account for the grade of the tumor, margins of resection, and likelihood of recurrence.

Treatment of Metastatic Disease

For more than 50 years, the only registered FDA-approved drug for ACC was the adrenolytic drug mitotane, a derivative of the pesticide DDT. The efficacy of mitotane has been evaluated in multiple small, single-arm studies and retrospective series. Although whether treatment with mitotane alone is associated with a survival benefit remains unclear in the absence of randomized prospective studies, objective radiographic response rates have been observed in approximately 25% of patients.[17,50–52] Mitotane also palliates symptoms of excess corticosteroids in the majority of patients by the inhibition of steroidogenic enzymes.

Several small studies evaluating the combination of mitotane with other cytotoxic agents, including cisplatin and etoposide, have shown modest objective responses, albeit in small patient cohorts. A large recent study analyzed the combination of mitotane (4 g/d) with cisplatin, etoposide, and doxorubicin (the *Italian Protocol*), yielding an overall response rate of 49% (according to WHO criteria) and a complete hormonal response in 9 of 16 patients with functioning tumors.[53] In a separate study, the combination of mitotane with streptozotocin yielded a reported objective response rate of 36%.[54] Currently, one randomized international trial (FIRM-ACT) is comparing the effectiveness of mitotane/streptozotocin with mitotane/etoposide/doxorubicin/cisplatin for the treatment of ACC (http://www.firm-act.org/).[55]

Additional treatment strategies for isolated metastatic deposits may include surgery, radiation therapy, chemoembolization, cryotherapy, or other local therapeutic options that are routinely reserved for relieving signs or symptoms of hormone excess, pain, or impending organ damage caused by metastatic ACC.

Medical Treatment of Corticosteroid Excess

Palliative treatment may be required for patients who experience symptoms secondary to adrenocortical steroid secretion, such as hypertension, hyperglycemia, hypokalemia, and muscle atrophy. In addition to mitotane, other steroidogenic inhibitors include ketoconazole, metyrapone, aminoglutethimide, and etomidate. Ketoconazole is most commonly used at doses of 400 to 1200 mg/d because of its easy availability and relatively tolerable toxicity profile. Although ketoconazole has measurable benefits in lowering cortisol levels in benign adrenal disease, it does not effectively control the extreme cortisol excess in many patients with ACC. Therefore, current trials are examining the efficacy of glucocorticoid receptor blockade (mifepristone) in Cushing's syndrome associated with ACC.

Prognosis and Follow-up Strategy

Patients who have undergone complete tumor resection should be evaluated for endocrine markers of disease recurrence every 3 months based on the preoperative hormonal profile. Cross-sectional imaging should be performed at 3-month intervals to identify tumor recurrence and allow subsequent intervention for recurrence. CT scanning is convenient and sensitive for detecting disease recurrence in most patients, although MR and FDG-PET scans may be useful in patients with equivocal findings or occult recurrence detected through hormonal elevations.[4]

For patients with metastatic disease undergoing therapy, follow-up studies should be performed every 3 months or less to assess therapeutic efficacy.

Emerging Therapies

Because current therapeutic regimens have had modest results, at best, in treating metastatic ACC, new therapeutic modalities are clearly essential to significantly impact life expectancy in these patients. Genomic studies have begun to uncover a common set of genetic alterations in ACC. Similar to familial forms of ACC, sporadic ACCs frequently have activation mutations in the insulin-like growth factor and Wnt signaling pathway together with loss of function mutation in *p53*. Pre- and early clinical studies targeting these pathways have shown promise, and multi-institutional groups are beginning to enroll patients with ACC in phase II trials involving these and other potential pathways.

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Adrenocortical Carcinoma

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1. Which of the following best describes the peak incidence of adrenocortical carcinoma (ACC)?
   A. Fourth to fifth decades of life
   B. Childhood and young adulthood
   C. Over 50 years
   D. Early childhood and fourth to fifth decades of life
2. Which of the following is the most common clinical presentation of ACC?
   A. Incidental finding
   B. Weight loss
   C. Cushing's syndrome
   D. Abdominal pain
3. A 45-year-old man presents with early satiety, weight loss, and abdominal pain. Which of the following is least helpful as a diagnostic test to rule out ACC?
   A. Noncontrast CT scan
   B. Dexamethasone suppression test
   C. Image-guided adrenal biopsy
   D. Urine free cortisol
4. An adrenal specimen shows a high rate of atypical mitosis with a low percentage of clear cells and necrosis. Which of the following is the most likely Weiss score for the specimen?
   A. 2
   B. 3
   C. 4
   D. 5
5. In which of the following situations is surgery least likely to be recommended for patients with adrenal tumors?
   A. Metastatic disease
   B. Extension to renal capsule
   C. Benign functional tumor
   D. Localized ACC

Activity Evaluation

1. The activity supported the learning objectives.
   Strongly Disagree 1 2 3 4 5 Strongly Agree
2. The material was organized clearly for learning to occur.
   Strongly Disagree 1 2 3 4 5 Strongly Agree
3. The content learned from this activity will impact my practice.
   Strongly Disagree 1 2 3 4 5 Strongly Agree
4. The activity was presented objectively and free of commercial bias.
   Strongly Disagree 1 2 3 4 5 Strongly Agree

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