# Adrenocortical Cancer Update

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**KEYWORDS**

• Adrenocortical cancer • Endocrinopathy • Adrenal imaging • Adrenalectomy
• Mitotane

**KEY POINTS**

- Adrenocortical cancer is a rare neoplasm with a poor prognosis. Patients can present with a nonfunctional or functional adrenal mass, either sporadically or as part of a hereditary endocrinopathy.
- Preoperative suspicion of malignancy based on clinical, biochemical, and radiologic criteria is essential in guiding an appropriate approach to surgical management.
- En bloc surgical resection with microscopically negative margins is the standard of care for locoregional disease, given the paramount prognostic importance of margin status.
- The high locoregional and systemic recurrence rates after initial resection have led to the development of a variety of adjuvant therapies, including surgical reintervention, mitotane-based combination chemotherapy, radioablative techniques, and targeted systemic agents.

## INTRODUCTION

Adrenocortical carcinoma (ACC) is a rare neoplasm, with an annual incidence of approximately 1–2/million people worldwide.[1] Although the clinical and biochemical features as well as the stage at initial presentation of these cancers can vary based on their functionality and association with various hereditary endocrinopathies, prognosis has remained unchanged over the past 20 years, with a median survival of 2 years for all patients and an unadjusted 5-year overall survival of approximately 40% for those individuals with surgically resectable disease.[2,3] Despite these unfavorable outcomes, recent strides have been made in terms of our understanding of the pathogenesis of this aggressive cancer, resulting in the introduction of novel multimodality therapies, as well as refinements to surgical techniques, which may lead to improved outcomes for these patients.

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## CLINICAL PRESENTATION

Most ACC's present in the fifth and sixth decades of life, with a median age of ~55 years, although there is a bimodal age distribution, with a second peak in incidence at less than 5 years of age, which is likely representative of ACCs associated with underlying germline mutations.[3,4] Although most ACCs are sporadic, there is increasing evidence of an association with various hereditary syndromes, including, Li-Fraumeni, Beckwith-Wideman, multiple endocrine neoplasia type 1, congenital adrenal hyperplasia, familial adenomatous polyposis, Lynch syndrome, and Carney complex.[5–7] In children from southern Brazil, for example, the incidence of ACC is ~10 to 15 times higher than that observed worldwide, given the increased prevalence of a germline p53 mutation.[8,9]

Whether sporadic or familial, ACCs can present either as a functional endocrinopathy, or as a nonfunctional adrenal mass, with the latter usually being incidentally discovered on cross-sectional imaging. Approximately 60% of patients present with functional tumors, with more than half of these manifesting as a non-ACTH dependent Cushing syndrome.[10] Virilizing symptoms in females secondary to androgen-only secreting tumors, and feminizing symptoms in males secondary to estrogen-only secretion, are observed in approximately 20% and 10% of functional ACCs, respectively. Isolated hyperaldosteronism is more uncommon, comprising only ~5% of functional ACCs. Up to 10% of functional ACCs show multihormone hypersecretion (eg, corticosteroids and androgens). Although these endocrinopathies can also be associated with benign adrenocortical adenomas, there are several clinical and biochemical factors on presentation that should raise the suspicion of malignancy, including the presence of constitutional symptoms, young age, feminization or virilization, increased urinary 17-ketosteroids, or evidence of multihormonal secretion. More novel biochemical profiling using a panel of urinary adrenal steroids may also be of benefit in assessing risk of malignancy. Using a metabolomics approach, Arlt and colleagues[11] identified a profile of 8 urinary steroids that could distinguish between an adrenocortical adenoma and an ACC, with both a sensitivity and specificity of 88%.

A complete hormonal workup is therefore required for all suspected ACCs, not only to rule out the presence of cortical hyperfunctionality in the form of subclinical Cushing syndrome, hyperaldosteronism, or hyperandrogenism but also to exclude evidence of catecholamine excess, which may suggest the presence of a pheochromocytoma or extra-adrenal paraganglioma.

## IMAGING EVALUATION

### *Computed Tomography*

Most patients with ACCs present with large adrenal masses (mean size of 11.5 cm) and evidence of extra-adrenal extension on cross-sectional imaging.[2,3] Although large tumor size has traditionally been one of the diagnostic hallmarks of ACC, this feature is not perfectly sensitive or specific, with approximately 5% to 10% of ACCs being smaller than 4 cm, and only 25% of adrenal incidentalomas greater than 6 cm harboring malignancy.[3,12–14] Various attempts to define an ideal cutoff size have been made, with variable results. In 1 retrospective study of 210 incidentalomas, a cutoff size of 5 cm yielded a sensitivity of 93% and a specificity of 64% for determining malignancy.[15] Hence, in addition to an absolute tumor size greater than 4 to 6 cm, any increase in tumor growth over a 6-month period should also raise the suspicion of malignancy.[16]

Additional morphologic features on computed tomography (CT) that suggest malignancy include tumor heterogeneity, regions of internal hemorrhage or necrosis,