Surgical Management of Adrenocortical Carcinoma

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KEYWORDS

- Adrenocortical tumor • Adrenocortical carcinoma
- Metastatic adrenocortical carcinoma • Open adrenalectomy • Mitotane treatment
- Chemotherapy for adrenocortical carcinoma

KEY POINTS

- Adrenocortical carcinoma (ACC) is one of the most aggressive malignant endocrine tumors.
- ACC has a bimodal age distribution, with the first peak occurring at the age of 5 years and the second in the fourth to sixth decade of life.
- A comprehensive biochemical evaluation is required before surgical resection.
- Complete surgical resection is the first-line treatment of ACC.
- The definite diagnosis of ACC is made by the presence of preoperative locoregional invasion or distant metastases on imaging studies or the presence of capsular or vascular invasion on postoperative pathology specimens.

INTRODUCTION

Adrenocortical carcinoma (ACC) is one of the most malignant endocrine tumors.[1,2] ACC occurs infrequently, with an incidence of 2 cases per million persons per year.[1,3–9] In the United States, ACC accounts for 0.2% of cancer-related deaths.[1,2] ACC is one of the most aggressive cancers, generally carrying a poor prognosis because most patients present with large tumors and advanced disease.[2] Adrenocortical carcinoma has a bimodal age distribution, with the first peak occurring at the age of 5 years and the second in the fourth to sixth decade of life.[2,8] Adrenocortical carcinoma is most common in women, with an female/male ratio ranging from 1.5:1 to

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2.5:1.[2,7,10–12] These tumors are most often sporadic, but may occur in patients with hereditary syndromes such as multiple endocrine neoplasia type 1 (MEN1), Li-Fraumeni syndrome, and Beckwith-Wiedemann syndrome.[13–15] The incidence is 10-fold to 15-fold higher in children in southern Brazil, where some environmental factors and genetic changes have been identified in the pathogenesis of adrenocortical carcinoma.[16–18] These tumors may be hormone-secreting tumors (functional), leading to Cushing syndrome or virilization, or may be nonfunctional.

Because ACC can lead to the rapid development of locoregional invasion or distant metastasis, the 5-year survival rate varies from 32% to 50% for patients with resectable tumors. The median survival rate is less than 1 year for patients who present with metastatic disease.[19,20] Detection of tumors at an early clinical stage is imperative for curative resection. Surgical resection of ACC remains the first-line treatment and accomplishing an initial complete resection (R0) of the tumor is the most important factor for treatment success.[1,2,21,22] It is important to understand that patients with ACC require a comprehensive assessment and plan for the treatment of their disease in the preoperative, operative, and postoperative periods that should be performed by a multidisciplinary group of specialists ideally with representation from radiology, nuclear medicine, endocrinology, endocrine surgery, medical oncology, pathology, and genetics.

Surgical techniques for the treatment of ACC have evolved in the last 2 decades. The classic open transabdominal or lumbar approaches have slowly been replaced by the laparoscopic approach for removal of benign adrenocortical tumors.[23,24] However, although there is an ongoing debate on the role of the laparoscopic approach for the treatment of ACC, open techniques remain the approach of choice for treating most malignant primary adrenal disorders.

The main focus of this article is to provide comprehensive insight into the surgical management of ACC with an up-to-date review of surgical decision making.

MOLECULAR PATHOGENESIS

The molecular events involved in the development of sporadic ACC remain poorly understood.[24] As in colorectal cancer, a multistep tumor progression model has also been proposed for ACC.[19] Mutations of the TP53 gene (chromosome 17p13) are the most frequent mutations reported in human cancers.[25] The common finding of loss of heterozygosity (LOH) at the 17p13 locus in sporadic ACC suggests an important role of the TP53 tumor suppressor gene in the pathogenesis of sporadic ACC.[26,27] Specific germline mutations have been identified in some high-risk populations, such as a subset of children from a southern Brazilian population with one of highest incidences of ACC, occurring 10 to 15 times more frequently than the general population.[16–18] In this population, a distinct TP53 germline mutation (R337H) has been identified in up to 97% of children with adrenocortical tumors.[28–30] However, only a fraction of patients with ACC harbor a mutation of TP53, indicating that there are likely to be other molecular events responsible for the pathogenesis of ACC that have not been yet identified.[28–36]

Other chromosomal syndromes have been strongly implicated in the pathogenesis of ACC. Alterations of the DNA methylation of 11p15, the area of abnormality in Beckwith-Wiedemann syndrome, have been implicated in the pathogenesis of ACC.[37] The chromosomal locus 11p15 harbors the coding region for insulinlike growth factor (IGF)-2. Both the LOH at 11p15 and the overexpression of IGF-2 have been associated with the development of sporadic ACC.[26,38,39]

In contrast with the more commonly seen sporadic ACC, a subset of adrenocortical tumors are associated with hereditary cancer syndromes.[15] The Li-Fraumeni