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REVIEW

Surgical treatment of adrenal carcinoma

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KEYWORDS
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Summary Adrenocortical carcinoma (ACC) is a rare disease with a poor prognosis. The presence of a mass syndrome or signs of hormonal hypersecretion often lead to its discovery, but more and more frequently, adrenocortical malignancy is fortuitously discovered as an incidentaloma. Cross-sectional imaging (CT and MRI) often points to the malignant character of the adrenal mass. Needle biopsy is contraindicated. Laboratory testing showing combined hypersecretion of cortisol, androgens or inactive corticosteroid precursors is highly suggestive of ACC. An 18F-fluoro-deoxyglucose Positron Emission Tomography (PET scan) should be performed to evaluate the malignancy of an adrenal mass and to detect regional or distant metastases. Although the majority of ACC are diagnosed at a locally advanced or metastatic stage, radical resection offers the only hope of cure. The peri-operative management of patients with ACC is not yet standardized. The aim of this review is to summarize the actual knowledge of the surgical management of ACC.

Introduction

Although the incidental discovery of adrenal masses by cross-sectional imaging now occurs frequently, adrenocortical carcinoma (ACC) remains a rare tumor, with an estimated annual incidence in Europe and North America of 0.5 to 2 cases per one million inhabitants [1]; ACC accounts for 0.04—0.2% of cancer deaths. ACC is one of the most dangerous malignant endocrine tumors with metastatic disease found in 20—40% of patients at the time of diagnosis, mostly involving liver, lung or bone [2]. Radical resection offers the only hope of cure, but overall survival at five years varies between 30 and 40% [3] and depends mainly on tumor stage. Stage is now evaluated according to the European Network for the Study of Adrenal Tumors classification (ENSAT) [4].

Despite recent recommendations from the European Society of Endocrine Surgeons (ESES) and ENSAT [5], several questions concerning the surgical management of ACC remain unanswered including:

- the need for lymph node dissection and its extent;
- the place of the laparoscopic approach;
- the indications for resection of loco-regional recurrences and resectable metastases;
- the place of adjuvant mitotane treatment.

This review is devoted to the surgical management of sporadic ACC in adults, which is generally associated with a worse prognosis than ACC occurring in children [6].

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Key points

- Adrenocortical carcinoma (ACC) is a rare tumor with poor prognosis; metastatic disease (hepatic, pulmonary or bone) is present in 20—40% at diagnosis.
- Clinical or subclinical hormonal hypersecretion is present in 75% of cases, which makes it possible to orient the diagnosis.
- Approximately 10% of ACC are discovered fortuitously (incidentaloma).
- The only indication for adrenal biopsy (pheochromocytoma must first be ruled out) is to eliminate the diagnosis of secondary adrenal metastasis, if necessary.
- The surgical treatment of ACC is wide *en-bloc* resection. Nephrectomy is not necessary in all cases.
- Lymphadenectomy must include peri-adrenal and peri-renal fat nodes of the renal hilum (although this approach is disputed).
- The laparoscopic approach is conceivable only for lesions smaller than 6 cm, stage I or II, and performed by highly experienced teams.

Epidemiology and clinical presentation

There are two frequency peaks, the first in childhood, the second between the fourth and fifth decades; there is a slight female predominance (sex ratio 1.5) [2,7]. There are no proven environmental risk factors. Although tobacco and oral contraceptive medications have been suggested as risk factors, their roles appear to be negligible. ACC's are sporadic in more than 95% of cases, although some hereditary diseases such as Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome and Lynch syndrome [8] are associated with an increased risk of ACC development. Cases have also been reported in patients with Multiple Endocrine Neoplasia Type I or familial adenomatous polyposis [9], but no certain causation can be imputed.

Three main clinical pictures may be seen at presentation:

- nearly half of ACC's are associated with clinical signs of hormonal hypersecretion, which entails, by decreasing frequency, a mixed hypersecretion of cortisol and androgens, an isolated hypersecretion of cortisol, virilization due to androgenic hypersecretion, or other varied associations of steroidal hypersecretion [2]. ACC's that secrete aldosterone, estradiol or corticosteroid precursors alone are more rare. Overall, complete testing for adrenal hormones is likely to reveal clinical or subclinical hypersecretion in 75% of the cases, which makes it possible to orient the diagnosis [2];
- presentation with a palpable mass is frequent in non-secreting ACC. Palpable ACC's have an average weight of > 500 grams and a diameter of 12—15 cm on pathological exam [2,10]. Symptoms may include abdominal or lumbar pain, palpable mass, weight loss, tumor fever, or signs of inferior vena cava (IVC) compression. It should be noted that ACC patients maintain a good general clinical condition for a long time, explaining the frequency of late diagnosis of these tumors;
- more rarely, the diagnosis of ACC is made during the investigation of an incidentaloma, that is to say, following the fortuitous discovery of an adrenal tumor on an imaging study carried out for another indication. Currently, about 10% of ACC's are discovered incidentally, and these are most often in early stages [2]. It is important to note that the probability of malignancy increases with the size of the adrenal mass [11]: malignancy is extremely rare for lesions < 4 cm and about 15—20% for lesions > 6 cm. The frequency of incidental diagnosis seems to be increasing [3], although this observation is not always confirmed, particularly in the United States [12]. The discovery of malignant lesions at an early stage is a major challenge in the management of incidentalomas. Finally, it is not uncommon for ACC to be discovered in the context of the assessment of its metastatic lesions.

Confirmation of malignancy when faced with an adrenal mass suspicious for ACC

Above all, every adrenal mass must be subjected to specific clinical, laboratory and radiological assessment, the details of which are beyond the scope of this review.

Clinical and laboratory criteria

Presentation with a voluminous palpable adrenal mass causing pain and signs of caval compression, while not specifically diagnostic, is highly suspicious of malignancy. Laboratory findings of a combined hypersecretion of cortisol and androgens, the presence of androgens with virilization, or estrogens with feminization, or the hypersecretion of inactive steroid precursors (17-hydroxy-progesterone, Deoxy cortisone, compound S) are very suggestive of the diagnosis of ACC [2].

Radiological criteria

On CT, the typical aspect of ACC is that of a large adrenal mass, > 6 cm in diameter, with poorly-defined borders, containing areas of intra-lesional necrosis, with heterogeneous contrast uptake after injection, and possibly containing calcifications due to intra-tumoral hemorrhages. The presence of aorto-caval or para-aortic lymphadenopathy, invasion of adjacent organs, thrombus within the IVC or left renal vein, or hepatic and/or pulmonary metastases strongly suggest the diagnosis of ACC. For intermediate-sized lesions between 3 and 6 cm, well-established radiological CT criteria suggest malignancy. For this purpose, millimeter-thin slice CT should be performed, with measurement of the non-injected density and the density at one minute and 10 minutes after contrast injection. The density ratio allows calculation of the wash-out percentage. Several concordant studies have established that the vast majority of malignant lesions have a spontaneous density greater than 20 Hounsfield units (HU) with relative or absolute washout less than 40% or 60% at 10 minutes [13], respectively. CT can exclude the diagnosis of benign adenoma with a sensitivity and specificity greater than 90% [14].

On MRI, ACC appears as a hypo- or iso-intense tumor on the T1 sequences with heterogeneous contrast enhancement after gadolinium injection [13], and an iso- or hyper-intense signal on T2 sequences. Morphologic findings on MRI that favor the diagnosis of malignancy are similar to those observed on CT scan [15]. Benign adrenal adenomas, unlike ACC's, have high lipid content. With in-phase sequences and out-of-phase sequences (fat subtraction), MRI can differentiate adenomas from suspected malignant lesions with excellent sensitivity (85—100%) and specificity (92—100%) according to reported series [13,14]. For adenomas, there

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