

Approach to patients with European Network for the Study of Adrenal Tumor stages I and II adrenocortical carcinomas

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Source / Izvornik: **Current Opinion in Endocrinology, Diabetes & Obesity, 2021, 28, 265 - 270**

Journal article, Accepted version

Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

<https://doi.org/10.1097/MED.0000000000000626>

Permanent link / Trajna poveznica: <https://urn.nsk.hr/urn:nbn:hr:105:366291>

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Download date / Datum preuzimanja: **2024-09-14**



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Title: Approach to patients with ENSAT stage I-II adrenocortical carcinomas

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Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ABSTRACT

Purpose of review

Adrenocortical carcinoma (ACC) is a rare tumor with variable prognosis depending mostly on the disease stage and tumor grade. The staging system proposed by the European Network for the Study of Adrenal Tumors (ENSAT) has a reliable prognostic potential and defines ACC stages I-IV. Due to the absence of extraadrenal tissue invasion, patients with stage I-II have a lower recurrence rate and better prognosis. This article elaborates on the current understanding of the clinical approach to this group of patients.

Recent findings

Concerning the treatment, complete surgical resection of the tumor provides the only chance for cure. However, even after tumor removal, the risk of recurrence remains high and the main predictors of recurrence include tumor stage, grade (measured by Ki-67 proliferative index) and the tumor resection status. Adjuvant mitotane and/or adjuvant radiotherapy should be considered in patients with high risk of recurrence taking into account potential harmful effects of such treatment. Accordingly, careful selection of patients who may benefit from adjuvant treatment is of the utmost importance both for improving disease outcome and for avoiding potential overtreatment in patients who are at low risk of disease recurrence.

Summary

Many aspects of the management of patients with ACC stage I-II are not entirely evidence-based, and treatment decisions rely mostly on expert opinions and data from retrospective studies. Therefore, the treatment of these patients should be restricted to specialized centers with high expertise in ACC.

Keywords: adrenocortical carcinoma, ENSAT stage, adrenal surgery, adjuvant mitotane, adjuvant radiotherapy

INTRODUCTION

Adrenocortical carcinoma (ACC) is a rare tumor with an incidence of 0.7-2.0 cases per million/year (1). The prognosis of ACC is variable; some tumors are curable by complete surgery while others are unresectable, fast growing and disseminating in the early phase (2).

The staging system for ACC (Table 1) proposed by the European Network for the Study of Adrenal Tumors (ENSAT) has a reliable prognostic potential (3) and defines stages I and II as localized tumors with a size of ≤ 5 cm and ≥ 5 cm, respectively. Stage III is defined by infiltration of the surrounding tissue or local lymph nodes or by the presence of a tumor thrombus in the vena cava and/or renal vein, whereas stage IV is characterized by distant metastases (4). The five-year survival is found to be 66-82% for stage I, 58-64% for stage II, 24-50% for stage III, and 0-17% for stage IV (5).

ENSAT stage I and II as well as part of the stage III tumors are localized to the adrenal gland. However, due to the absence of extraadrenal tissue invasion, patients with ACC stage I-II have a lower recurrence rate after surgery and therefore a better prognosis. Accordingly, the decision on the optimal postoperative management of these patients should be weighed between the risk of adverse outcome on the one side and the risk of overtreatment on the other.

This article focuses on the ACC ENSAT stage I-II and it elaborates on the current understanding of the clinical approach to that group of patients.

Clinical presentation and hormonal work-up

The clinical presentation of ACC could be rather variable. Most patients present with symptoms of adrenal hormone excess and mass effects whereas in about 20% of them ACC is diagnosed incidentally. Autonomous glucocorticoid secretion, with or without androgen excess, is the most

common presentation among hormonally active ACCs, while autonomous estrogen and mineralocorticoid secretion occur less frequently (6, 7). Therefore, hormonal work-up should include measurements of cortisol in 1-mg dexamethasone test, basal ACTH, DHEAs, androstenedione, 17-hydroxyprogesterone, testosterone (in women), 17-beta-estradiol (in men and postmenopausal women), 11-deoxycortisol and aldosterone/renin ratio (in patients with hypertension and/or hypokalemia) (2). In addition, some hormonally active ACCs do not secrete end products of steroidogenesis, but only steroid precursors which can be identified and quantified by urine steroid profiling (8**, 9**).

The purpose of the detailed hormonal evaluation is not only to define tumor phenotype but also to determine potential hormonal tumor markers that can be used during postoperative follow-up for early detection of ACC recurrence (9**). Furthermore, ACC phenotype can also serve as a prognostic factor since a recent systematic review showed that autonomous glucocorticoid secretion was associated with worse overall survival (10).

Pathology and molecular markers

Histopathology is key for diagnosing ACC. It begins with the immunohistochemical determination of the steroidogenic factor-1, the most valid histological marker of the adrenocortical tissue. Distinction between benign and malignant adrenocortical tumors is mostly done using the Weiss scoring system that evaluates nine histological characteristics of the tumor (Table 2) (11). Tumor proliferation rate, an important prognostic factor for ACC, is assessed by the Ki-67 index (3). For prognostic purposes, in addition to Ki-67 index, each ACC pathological report should also contain the information on the resection status and tumor invasion of the lymph nodes. Complete resection

(R0) correlates with better prognosis, in contrast to incomplete microscopic resection (R1), incomplete macroscopic resection (R2) or unknown resection (Rx) (12).

However, despite the prognostic value of the staging and grading systems for ACC, tumors at the same stage and with the same proliferation index might have a significantly different prognosis which prompted the molecular research of ACC. Recent pan-genomic studies showed that targeted molecular markers based on chromosome and gene alterations as well as on gene expression and methylation, have a prognostic value, especially in patients with stage I to III disease after complete surgical resection (13*, 14).

Surgical treatment

Given the lack of effective medical treatment, complete surgical resection of the tumor provides the only chance for potential cure. Performing this procedure in a referral center by an expert surgeon with expertise in oncologic and adrenal surgery (>20 adrenal procedures per year) is of utmost importance to assure an optimal outcome (2).

Although minimally invasive adrenalectomy (laparoscopic, robotic) has been increasingly used for the treatment of patients with adrenal tumors, the rationale for using the same approach in the treatment of ACC is debatable. On the positive side, minimally invasive surgery is associated with a shorter postoperative recovery, which allows early administration of adjuvant treatment, but on the negative side, there is a concern that these patients are at higher risk of disease recurrence. The literature data on the surgical approach in patients with ACC are mostly restricted to retrospective studies involving a limited number of patients and the results are equivocal. In addition, the validity of most of the studies is compromised by selection bias. Nevertheless, a recent systematic review, which included 1.171 patients with localized ACC, showed no differences between the open and

laparoscopic approach with regard to the postoperative recurrence free survival (RFS) and overall survival (OS) (15). On the other hand, a meta-analysis of 15 studies with 2,207 patients revealed a shorter time to ACC recurrence and more peritoneal recurrence in patients who underwent a minimally invasive surgery, although there were no differences in OS and disease specific survival (16*). In our series of ACC patients, both RFS and OS were comparable between the open and laparoscopic approach (17).

However, in the absence of prospective studies with a large number of patients there is no definitive answer to the question about the optimal surgical approach in patients with ACC. Therefore, it seems reasonable to consider an open surgery as a preferred method in the surgical management of localized ACC, whereas the laparoscopic approach should be limited to selected patients with smaller tumors who are operated in specialized centers with large experience, both in laparoscopic surgery and in the management of patients with ACC.

Notably, regional lymphadenectomy is still not a part of the standard surgical management in tumors with radiological suspicion of ACC. However, recent studies showed that regional lymphadenectomy might improve patients' outcome (18, 19). We therefore suggest considering regional lymphadenectomy in all adrenal tumors without clearly benign radiological features.

Adjuvant mitotane therapy

The risk of ACC recurrence is high even after radical surgery with microscopically free margins, which provides a strong rationale for adjuvant treatment following tumor resection. Due to its adrenolytic effect, mitotane is the only medication specifically approved for the treatment of advanced ACC, but it is also considered in an adjuvant setting after tumor removal. However, recommendations for adjuvant mitotane therapy are based on a low level of evidence as they rely

only on data from retrospective, non-randomized studies of remarkable heterogeneity regarding the mitotane dosing regimen, mitotane plasma concentrations and duration of treatment.

The use of adjuvant mitotane therapy increased (20) after a large retrospective study involving 177 patients demonstrated the beneficial effect of adjuvant mitotane on RFS (21) and in many centers it today represents a standard treatment in patients with high risk of tumor recurrence (2). In addition, an update analysis in the same patient cohort with additional nine years of follow-up confirmed that adjuvant mitotane is associated with prolonged RFS (22). Furthermore, a recent meta-analysis of five retrospective studies with 1,249 patients reported improved RFS and OS in patients receiving adjuvant mitotane (23*). Finally, the most recent retrospective, single-center, study including 152 patients with localized ACC observed that adjuvant mitotane has favorable effect in patients with high risk of ACC recurrence (24**). It is important to note that none of these studies enrolled exclusively patients with stage I-II, but those with stage III disease were also involved. However, available data strongly support adjuvant mitotane treatment in stage I-II patients with Ki-67 >10% and/or R1/Rx resection (Figure 1). In contrast, administration of adjuvant mitotane in patients who are at low/intermediate risk of recurrence (R0 resection and Ki-67 \leq 10%) is still controversial and decision should be made on an individual basis (ESE guidelines). Results of the multicentric, randomized phase III clinical trial (ADIUVO; ClinicalTrials.gov NCT00777244) which has evaluated the efficacy of adjuvant mitotane in patients with low/intermediate risk of recurrence are expected in the year 2021.

Owing to the limited data available, there is still some uncertainty regarding the mitotane dosing regimen, target therapeutic concentration and duration of adjuvant mitotane treatment. It is recommended to start mitotane treatment shortly after the surgery aiming to reach the therapeutic mitotane level as soon as possible. The goal is to reach the mitotane concentration of \geq 14 mg/L

(2) even though the evidence supporting the association of the target mitotane concentration and patients' outcome when mitotane is used in an adjuvant setting is rather limited. However, a recent study by Puglisi et al. demonstrated that time in target range, defined as the number of months in which mitotane concentrations were ≥ 14 mg/L, was associated with a lower risk of ACC recurrence (25**).

Two different mitotane dosing regimens have been proposed. The high-dose regimen (start with 1.5 g/day and in the next 4-6 days increase to 6 g/day) may reduce the time required to reach the therapeutic concentration whereas the low-dose regimen (start with 1 g/day and in the next two weeks increase to 3-4 g/day) may be better tolerated by patients, resulting in a better compliance and a lower rate of treatment discontinuation due to side effects (26, 27).

In addition to liver toxicity and other side effects related to the gastrointestinal (anorexia, nausea, vomiting) and central nervous system (somnolence, lethargy, dizziness), mitotane treatment also affects the endocrine system and lipid metabolism (28). Due to the mitotane adrenolytic effect and enhanced metabolic clearance of glucocorticoids, all patients need steroid replacement in doses that are higher than in other types of adrenocortical insufficiency (26). It is noteworthy that even after mitotane cessation, it takes time to achieve the complete recovery of the hypothalamus-pituitary-adrenal axis (29). In contrast, zona glomerulosa is less frequently affected, so mineralocorticoid replacement is required only in some patients (28, 29). Lastly, mitotane administration could also affect thyroid and gonadal function resulting in the need for thyroxine and testosterone replacement (28).

The optimal duration of adjuvant mitotane treatment is unknown. Most ACC recurrences occur within the first two years after adrenal surgery, whereas the rate of recurrence more than five years after the surgery is quite low. Consequently, the guidelines suggest administering adjuvant

mitotane for at least two years, but not longer than five years (2). In addition, treatment duration also depends on patient compliance, drug tolerability and prognostic factors associated with tumor characteristics. Ki-67 index represents the single most powerful predictor of ACC recurrence and threshold levels of 10% and 20% have been suggested to define tumor grading into three different categories (3). With respect to the proposed grading system, our practice in patients with ACC stage I-II after R0 tumor resection is to administer adjuvant mitotane for two years if the Ki-67 index ranges from 11% to 20%, and for three years when Ki-67 is >20%. In our recent study, this treatment approach resulted in a rather low rate of disease recurrence (17%) after the median duration of follow-up of 52 months (17).

Adjuvant radiotherapy

While the use of adjuvant radiotherapy (RT) in patients with stage I-II is still controversial, a few recent studies suggest its potential benefit in terms of local tumor recurrence, particularly in patients with R1/Rx tumor resection. In this regard, a population-based study with 1,184 non-metastatic ACC patients, of which 171 (14.4%) received adjuvant RT, observed improved survival following adjuvant RT in patients with positive tumor margins after surgical resection (30). Furthermore, a recent meta-analysis of four cohort studies and eight case series showed that adjuvant RT reduced the risk of local recurrence, but it had no effect on disease recurrence or overall mortality (31).

Based on the available literature data, our standpoint is that adjuvant RT should not be used routinely in patients with ACC stage I-II. However, we support the view that adjuvant RT should be considered after R1/Rx tumor resection. The absence of a definitive answer regarding the use

of adjuvant RT points out the need for prospective well-designed studies aiming to determine the true benefit of adjuvant RT, especially in patients with earlier stages of ACC.

CONCLUSION

Many aspects of the management of patients with ACC stage I-II are not entirely evidence-based, and treatment decisions rely mostly on expert opinions and data from retrospective studies. Therefore, the treatment of these patients should be restricted to specialized centers with high expertise in ACC.

While radical tumor resection represents a cornerstone of the treatment and provides the only realistic chance for cure, patients' long-term outcome still remains uncertain due to the high risk of tumor recurrence. Consequently, careful selection of patients who may benefit from adjuvant mitotane treatment, or adjuvant RT, is of the utmost importance to improve disease outcome in high-risk patients and avoid potential overtreatment in those who are at low risk of disease recurrence. In this respect, results from recent genomic studies, showing distinct patterns of molecular alterations associated with various clinical outcomes, will hopefully drive further progress towards a more personalized approach to ACC treatment.

Keypoints

1. ACC stage I-II tumors are localized to the adrenal gland, and therefore have lower risk of tumor recurrence and better prognosis compared to stages III and IV.
2. Complete surgical tumor resection is the cornerstone of ACC treatment and provides the only chance for cure.
3. In addition to disease stage, tumor proliferation rate (Ki-67 index) and tumor resection status are the most important prognostic factors.
4. Adjuvant mitotane should be considered in patients with stage I-II who are at high risk of disease recurrence (Ki-67 >10% and/or R1/Rx resection).
5. Adjuvant radiotherapy should not be used routinely but should be considered in patients after R1/Rx resection.

Acknowledgements: none.

Financial support and sponsorship: none.

Conflicts of interest

DK served on the HRA pharma advisory board.

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Table 1. European Network for the Study of Adrenal Tumors (ENSAT) staging classification

(4)

ENSAT stage	Definition
I	T1, N0, M0
II	T2, N0, M0
III	T1–T2, N1, M0 T3–T4, N0–N1, M0
IV	T1–T4, N0–N1, M1

T1: tumor ≤ 5 cm; T2: tumor > 5 cm; T3: infiltration into surrounding tissue; T4: tumor invasion into adjacent organs or venous tumor thrombus in vena cava or renal vein; N0: no positive lymph node; N1: positive lymph node(s); M0: no distant metastases; M1: presence of distant metastases.

Table 2. Histopathologic criteria by Weiss (11)

Presence of three or more criteria correlates with malignant behaviour

- High nuclear grade
- >5 mitoses per 50 high power field
- Atypical mitotic figures
- <25% of tumor cells are clear cells
- Diffuse architecture (>33% of tumor)
- Necrosis
- Venous invasion (smooth muscle in wall)
- Sinusoidal invasion (no smooth muscle in wall)
- Capsular invasion

Figure 1. Management of patients with ACC ENSAT stage I-II

