European Society of Endocrinology Clinical Practice Guidelines on the Management of Adrenocortical Carcinoma in Adults, in collaboration with the European Network for the Study of Adrenal Tumors

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Abstract

Adrenocortical carcinoma (ACC) is a rare and in most cases steroid hormone producing tumor with heterogeneous prognosis. The purpose of these guidelines is to provide clinicians with best possible evidence-based recommendations for clinical management of patients with ACC based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system. We predefined four main clinical questions, which we judged as particularly important for the management of ACC patients and performed systematic literature searches: (A) What is needed to diagnose an ACC by histopathology? (B) Which are the best prognostic markers in ACC? (C) Is adjuvant therapy able to prevent recurrent disease or reduce mortality after radical resection? (D) What is the best treatment option for macroscopically incompletely resected, recurrent or metastatic disease? Other relevant questions were discussed within the group. SELECTED RECOMMENDATIONS: (i) We recommend that all patients with suspected and proven ACC are discussed in a multidisciplinary expert team meeting (ii) We recommend that every patient with (suspected) ACC should undergo careful clinical assessment, detailed endocrine work-up to identify autonomous hormone excess, and adrenal-focused imaging. (iii) We recommend that adrenal surgery for (suspected) ACC should be performed only by surgeons experienced in adrenal and oncological surgery aiming at a complete en bloc resection. (iv) We suggest that all suspected ACC should be reviewed by an expert adrenal pathologist using the Weiss score and providing Ki67 index. (v) We suggest adjuvant mitotane treatment in patients after radical surgery that have a perceived high risk of recurrence (ENSAT stage III, or R1 resection, or Ki67 >10%). (vi) For advanced ACC not amenable to complete surgical resection, local therapeutic measures (e.g. radiation therapy, radiofrequency ablation, chemo-embolization) are of particular value. However, we suggest against the routine use of adrenal surgery in case of widespread metastatic disease. In these patients we recommend either mitotane monotherapy or mitotane, etoposide, doxorubicin, and cisplatin depending on prognostic parameters. (vii) In patients with recurrent disease and a disease-free interval of at least 12 months, in whom a complete resection/ablation seems feasible, we recommend surgery or alternatively other local therapies. Furthermore, we offer detailed recommendations about the management of mitotane treatment and other supportive therapies. Finally, we suggest directions for future research.

1. Summary of recommendations

After the review process all Recommendations without Rational will be provided here as summary.

2. Adrenocortical Carcinoma – epidemiology, pathogenesis, clinical presentation, and general prognosis

Epidemiology and pathogenesis

The estimated incidence of adult adrenocortical carcinoma (ACC) is between 0.7 – 2.0 per million per year (1, 2). ACC can occur at any age with a peak incidence between 40 and 60 years, and with women being more often affected (55-60%). In adults, the vast majority of ACCs are sporadic. Occasionally, however, they occur as part of hereditary syndromes such as Li-Fraumeni syndrome, Lynch syndrome, multiple endocrine neoplasia (MEN) 1 and familial adenomatous polyposis (3, 4). In recent years several multi-center studies have shed light on the pathogenesis of ACC (5-7)(8), but 'multi-omic' studies (9-11) reveal that only a minority of ACC cases have pathogenic driver mutations. For details on this topic we refer to recent reviews (12-14).

Clinical presentation (Table 1)

ACC may present with autonomous adrenal hormone excess or with symptoms caused by an abdominal mass. An increasing number of cases are diagnosed within the group of incidentally discovered adrenal masses (incidentalomas) (≈ 10-15%). However, the likelihood of an adrenal incidentaloma being an ACC is low (15-17). About 50-60% of patients with ACC have clinical hormone excess. Hypercortisolism (Cushing's syndrome), or mixed Cushing's and virilizing syndromes are observed in the majority of these patients. Pure androgen excess is less frequent while estrogen or mineralocorticoid excess are very rare (13, 18-22). Non-specific symptoms from an abdominal mass include abdominal discomfort (nausea, vomiting, abdominal fullness) or back pain. Classical malignancy-associated symptoms such as weight loss, night sweats, fatigue or fever are rarely present.

Table 1: Clinical presentation of ACC[#]

Autonomous adrenal hormone excess	50-60 %
Hypercortisolism (Cushing's syndrome)*	50-70 %
Androgen excess (virilization) in female patients*	20-30 %
Estrogen excess (feminization) in male patients*	5 %
Mineralocorticoid excess*	2-3 %
Non-specific symptoms from an abdominal mass	30-40 %
Incidentally detected by imaging for other purpose	10-15 %

[#] *number derived from: (20, 23, 24), and the ENSAT ACC registry*

* *frequently combined*

General prognosis

The median overall survival of all ACC patients is about 3-4 years. The prognosis is, however, heterogeneous. Complete surgical resection provides the only means of cure. In

addition to radical surgery, disease stage, proliferative activity, and cortisol excess are independent prognostic parameters (see also section 4.2. and 5.5.). Five-year survival is 60-80% for tumors confined to the adrenal space, 35-50% for locally advanced disease, and much lower in case of metastatic disease with reported percentages ranging from 0% to 28% (19, 21, 25-30).

3. Methods

3.1. Guideline working group

This guideline was developed by The European Society of Endocrinology (ESE) in collaboration with the European Network for the Study of Adrenal Tumours (ENSAT). The chairs of the working group Martin Fassnacht and Massimo Terzolo as well as the methodological expert Olaf Dekkers were appointed by the ESE Clinical Committee. Tobias Else served as representative of The Endocrine Society, USA, and Radu Mihai as representative of the European Society of Endocrine Surgeons. The other members were suggested by the chairs and approved by the Clinical Committee of ESE. The multidisciplinary team consisted of the following experts: endocrinologists (Guillaume Assie (France), Olaf Dekkers (The Netherlands), Tobias Else (USA), Martin Fassnacht (Germany), Harm Haak (The Netherlands), Massimo Terzolo (Italy), oncologists (Eric Baudin (France), Alfredo Berruti (Italy), a pathologist Ronald de Krijger (The Netherlands), and an endocrine surgeon Radu Mihai (UK). The working group had three in-person meetings (November 2016, September 2017, and March 2018) and communicated by phone and email. Consensus was reached upon discussion; minority positions were taken into account in the rationale behind recommendations. Prior to the process, all participants completed conflict of interest forms.

3.2 Target group

This guideline was developed for healthcare providers involved in the care of patients with adrenocortical carcinoma *i.e.,* endocrinologists, oncologists, surgeons, radiologists, nuclear medicine physicians, radio-oncologists, pathologists, and specialists in general internal medicine. However, general practitioners might also find the guideline useful, as might our patients. In addition, the guideline document can serve as a source document for the preparation of patient information leaflets.

3.3 Aims

The overall purpose of this guideline is to provide clinicians with practical guidance for the management of patients with adrenocortical carcinoma. In clinical practice, treatment decisions should take into account the recommendations but also the clinical judgment of the treating physician. Recommendations are thus never meant to replace clinical judgment.

3.4 Summary of methods used for guideline development

The methods used have been described in more detail previously (31). In short, the guideline used GRADE (Grading of Recommendations Assessment, Development and Evaluation) as a methodological base. The first step was to define clinical question(s) (see section 3.5), the second being a systematic literature search (see Section 3.6). After including all relevant articles, we 1), rated the quality of the evidence, and 2) estimated an average effect for

specific outcomes (if possible). The quality of evidence behind the recommendations is classified as very low (+OOO), low (++OO), moderate (+++O) and strong (++++).
For the recommendations we took into account: 1) quality of the evidence, 2) balance of desirable and undesirable outcomes, 3) values and preferences (patient preferences, goals for health, costs, management inconvenience, feasibility of implementation, etc) (32, 33). The recommendations are worded as recommend (strong recommendation) and suggest (weak recommendation). The meaning of a strong recommendation can be stated as follows: reasonably informed persons (clinicians, politicians and patients) would want the management in accordance with the recommendation. For a weak recommendation, most persons would still act in accordance with the guideline, but a substantial number would not (33). Formal evidence syntheses were performed and graded only for recommendations addressing our initial four questions. Recommendations based on good practice and experience of the panelists were not graded (34). Recommendations were derived from majority consensus of the guideline development committee, but if members had substantial disagreements, this is acknowledged in the manuscript. For transparency, all recommendations are accompanied by text explaining why specific recommendations were made.

3.5. Clinical question, eligibility criteria and endpoint definition

At the beginning of the guideline development process, the panel agreed on 30 clinical questions in the management of patients with ACC that should be addressed in the guidelines. In a next step, we agreed on four most relevant clinical questions (Table 2), for which a detailed literature search and review was subsequently performed.

3.6 Description of search and selection of literature

A literature search of electronic medical databases was performed for all four clinical questions. As we expected that single publications could contribute to different questions (for example 2 and 4) we decided to perform one overarching search using broad search terms. The search revealed 5988 papers, of which 615 were duplicates. In summary, we included 18 publications for clinical question 1 (diagnostics for ACC), 35 studies for clinical question 2 (prognosis), 10 publications for clinical question 3 (adjuvant therapy) and 48 publications for clinical question 4 (recurrent/advanced disease). The review of hormonal overproduction as prognostic factor was published as stand-alone paper (35). For question 3, we included one study after having been provided with baseline characteristics and adjusted estimates for mitotane therapy not reported in the original publication (36).

3.7. Review process and endorsement of other societies

A draft of the guideline was reviewed by four experts in the field (see “Acknowledgment’ section) and has been submitted for comments by ESE and ENSAT members. In addition, the following societies and networks were asked for review and finally endorsed the guidelines: XXX. Furthermore, patient groups were approached to review the guidelines.

163 **Table 2: Overview of the key clinical questions and predefined outcome parameters**

Clinical Question	Predefined selection criteria and key outcome parameters	Metrics of the literature search
Question 1: Pathology - what is needed to diagnose an ACC? **Sub-question 1A:** How to make a distinction between adrenocortical/non-adrenocortical tumor? **Sub-question 1B** How to make a distinction between benign or malignant or indeterminate behavior in adrenocortical tumors	**Population** • Adrenal masses **Restriction** • Minimum 25 ACC patients • Each marker has to be reported in at least 2 independent cohorts **Outcome** • Diagnostic accuracy (Sensitivity/specificity/NPV/PPV) **Diagnostic marker:** • (Weiss Score), Ki67, reticulin, Helsinki, SF-1, melan A, inhibin, calretinin, chromogranin, SRC1 **Reference standard**: • Weiss-Score[1] • Recurrence	Number of papers included: 1a: n=4 1b: n=15 (2 papers contributed to both)
Question 2: Which are the best prognostic markers in ACC?	**Population** (minimum 100 ACC patients): 1) Patients after radically resected ACC 2) Patients with advanced ACC **Restriction:** • Prognostic marker has to be reported in at least 2 independent cohorts **Prognostic markers to be considered**: • Tumor stage (different systems: Sullivan, Lee, UICC, ENSAT, etc.), sex, age, Ki67, hormone section, Weiss score, mitotic index, R status, molecular/immunohistological markers **Outcome** • Overall survival, disease-free and progression-free survival, prognostic ability	Number of papers included: 35
Question 3: Is adjuvant therapy able to prevent recurrent disease or reduce mortality after radical resection?	**Population:** • Diagnosis of ACC with macroscopic radical resection (R0, R1, Rx) **Restriction:** • Studies with > 10 patients in the intervention group • Only studies providing baseline data per treatment group, and providing age and stage adjusted estimates • In case of >25% overlap only inclusion of the largest study	Number of papers included: Mitotane n=6 Radiation therapy n=4

	Intervention: • Adjuvant treatment with either mitotane, radiation therapy or cytotoxic chemotherapy **Control group:** • Without therapy or other treatment **Outcomes:** • Disease-free survival, overall survival, quality of life, adverse events	
<u>Question 4:</u> What is the best treatment option for macroscopically incompletely resected, recurrent or metastatic disease?	**Population:** • Macroscopically incompletely resected, recurrent or metastatic ACC **Restriction:** • Studies > 10 patients in the intervention group**.** Only studies providing baseline data per treatment group **Interventions** • Cytotoxic drugs including mitotane, surgery, radiation therapy, radiofrequency ablation, chemoembolization **Control** • Not mandatory (single arm cohort studies eligible) **Outcome** • Overall survival, progression-free survival, tumor response, quality of life, adverse events	Number of papers included: cytotoxic drugs including mitotane: n=27 surgery: n= 16 radiation therapy: n=1 radiofrequency ablation: n=1 radionuclide therapy: n=1

NPV negative predictive value, PPV positive predictive value, SF-1 steroidogenic factor 1, SRC1 steroid receptor coactivator 1, R status Resection status, R0 microscopically complete resection, R1 microscopically incomplete resection, Rx uncertain resection status

[1] we are aware that the Weiss score was never properly validated, but we decided that there is no other "gold standard")

4. Summary and conclusions from systematic literature reviews

4.1. Clinical question 1: Pathology

We included 17 publications (37-53) that contributed data to either the diagnosis of ACC in the context of adrenal vs. non-adrenal distinction (4 studies), or in the context of benign vs. malignant adrenocortical tumor distinction (15 studies) (two of them contributing to both subquestions (40, 45)). Details of studies are shown in Appendix 1. Melan-A and inhibin-alpha were studied in three publications; all other markers were studied in one or 2 publications only. In total data for twenty-seven diagnostic markers were reported. Since many publications included patients who did not reflect the target population in question for this guideline (i.e. patients with a suspicion for ACC), positive or negative predictive values were not provided. A formal meta-analysis was not performed given the low number of studies per marker. Importantly, no study reported on the combined diagnostic ability of a set of markers, which actually may reflect the approach in clinical practice.

4.2. Clinical question 2: Prognostic factors

Thirty-five studies reporting on risk factors for recurrence and/or mortality, and that included more than 100 patients with histologically proven ACC, were analyzed (1, 8, 20, 25, 26, 29, 54-82)(see Appendix 2 for details of studies included, and Appendix 3 for an overview of all prognostic factors studied). The threshold of 100 cases was defined upfront as with n=100 and an expected number of deaths of 50, statistical power was considered sufficient. Almost all studies reported age, sex and tumor stage as prognostic factors, although several different staging systems were used. A formal comparison of the studies was difficult due to heterogeneity regarding clinical characteristics, use of varying definitions of characteristics (e.g. stage) and different cut-offs (e.g. tumor size, age). Furthermore, the multivariable models presented include adjustment for different additional variables. We acknowledge a concern over the number of variables included in models relative to the number of events, and that this may have the potential to lead to false positive results.

The association between staging and prognosis was robust (+++O), despite different systems being used (29, 55, 70, 83-89). In a formal comparison, the ENSAT staging (29) was slightly superior to the UICC staging (88). Additionally, the association between hypercortisolism and mortality was consistent, and remained with a positive hazard ratio after adjustments for tumor stage HR 1.71, 95% CI 1.18-2.47 (35). Ki67 was studied in five publications, showing worse prognosis with increasing Ki67 in all studies. Other molecular markers have been studied in single cohorts only (Appendix 2+3).

It is important to mention that relative risks, even if statistically significant, cannot inform clinical decision making unless translated into predictive values or incorporated in prediction models. Only one study presented a formal prediction model (including the variables tumor size, stage, mitotic index, venous invasion, and endocrine activity), showing a sensitivity of 0.91 and a specificity of 0.90 (63) Another study provided nomograms to facilitate prognosis in individual patients (68). None of these models, however, has been validated externally.

4.3. Clinical question 3: Adjuvant therapy

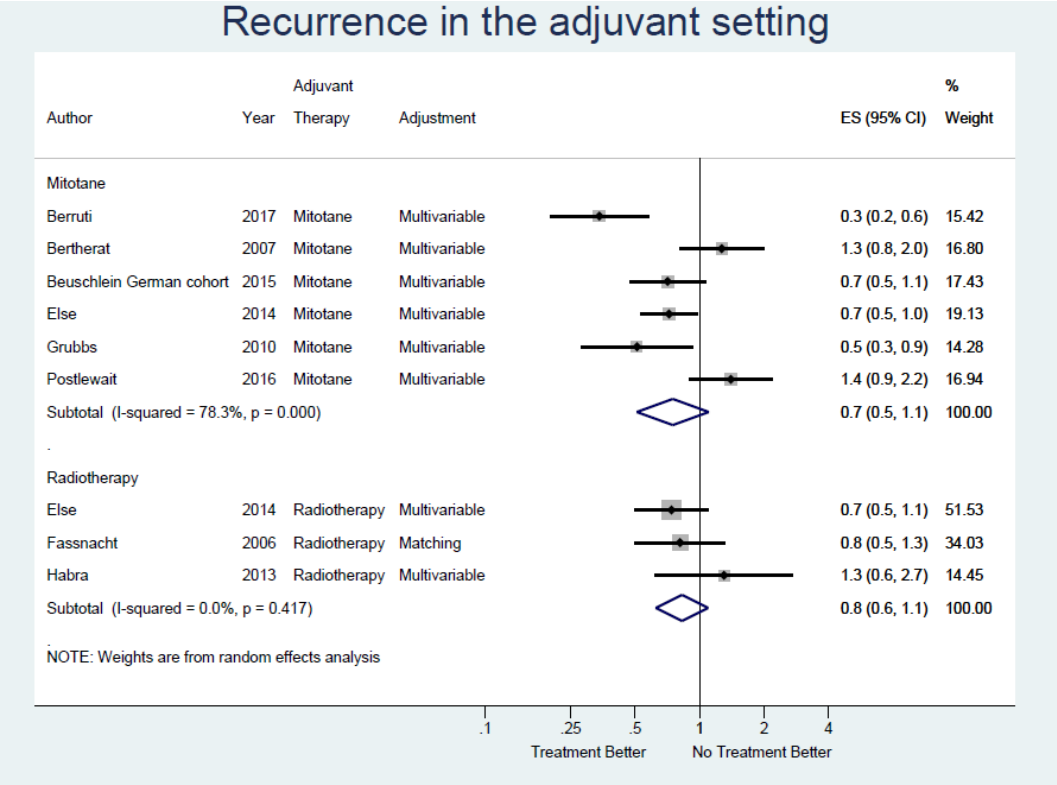
No randomized clinical trial has been published yet exploring adjuvant therapies; no studies comparing quality of life after different treatment modalities were found. We included six studies that assessed the effect of mitotane on recurrence and mortality (36, 58, 90-93). See Appendix 4 for details and Appendix 5 for risk of bias assessment. Due to an overlap of the study population of >25% between studies (36, 58, 90) only the German study cohort from

Beuschlein et al. was considered, but not the validation cohort (58). In one study, forty-seven patients were enrolled in 4 Italian centers where adjuvant mitotane was routinely recommended, 55 patients in 4 Italian centers where no adjuvant strategy was undertaken (control group 1), and 75 German patients left untreated after surgery (control group 2) (90, 94). However, only the most recent update of these series was included in the analysis (90). In order to avoid counting data twice only control group 1 was included.

In a meta-analysis the pooled hazard ratio for recurrence was 0.7, 95%CI 0.5-1.1; for mortality (5 studies) the pooled hazard ratio was 0.7, 95%CI 0.5-0.9 (Figure 1). All six studies were non-randomized with the potential of a (residual) confounding effect, meaning that treatment choices are based on prognosis (such as performance status of the patient, tumor stage etc.), which introduces imbalance in prognostic factors. It is known that when studying therapeutic effects this confounding effect is difficult to remedy statistically (95). One study (90) circumvented the confounding effect by comparing two treatment strategies applied in different settings; such comparison relies on other assumptions (96). A further bias in this context is immortal time bias, which can occur if treatment is initiated after follow-up time starts and this is not accounted for in the analysis. Such biases tend to overestimate treatment effects (97), and were not explicitly accounted for in most studies. Only one study applied a landmark analysis to address this bias (90). The overall quality rating was very low (+OOO).

Four studies assessed the impact of adjuvant radiation therapy (91, 98-100). See Appendix 4 for details and Appendix 5 for risk of bias assessment. The study by Sabolch et al. (100) was only considered for data on local recurrence, not for recurrence and mortality given the overlap with another study of the same group (91). All but one study (59 patients treated with adjuvant radiation therapy (91) were small. We found a pooled hazard ratio of 0.8 (95% CI 0.6-1.1) for recurrence and for mortality of 1.0 (95% CI 0.7-1.5)(Figure 1). The pooled hazard ratio for local recurrence (three studies) after treatment with radiotherapy was 0.3 (93% CI 0.1-1.9).

All studies were observational with the potential of (residual) confounding effects, immortal time bias was not explicitly accounted for in most studies, and the studies were small with imprecise effect estimates; the overall quality rating was therefore very low (+OOO).



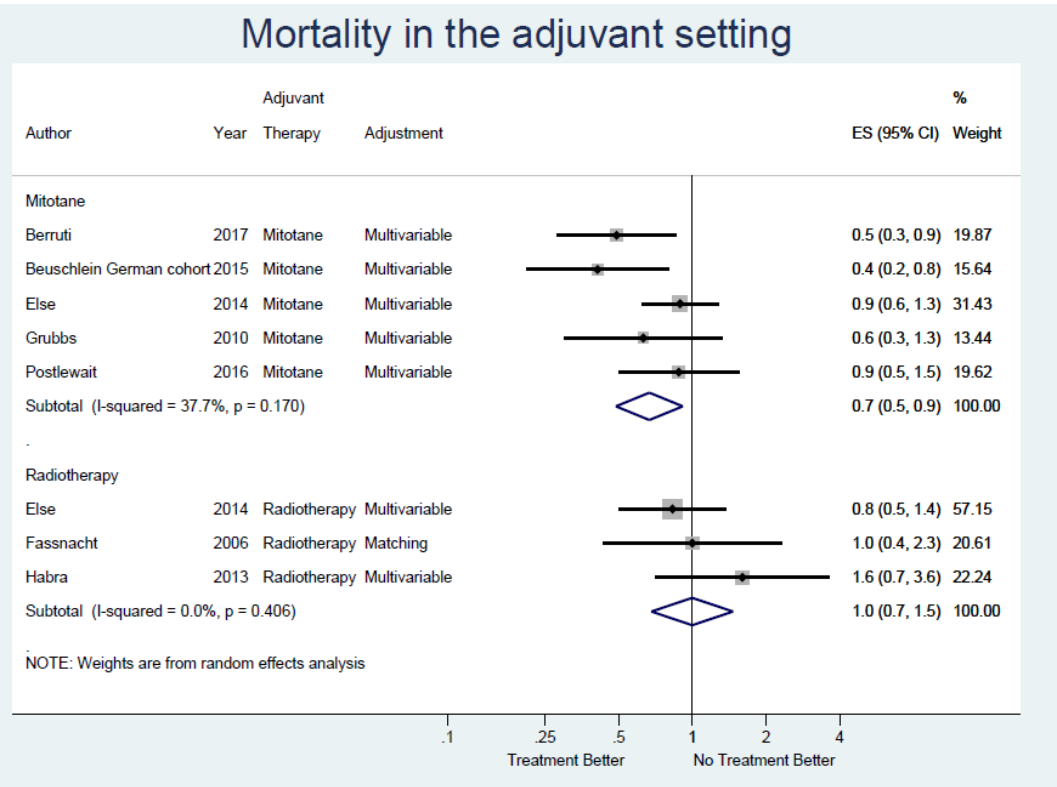


Figure 1 Meta-analysis of recurrence (A) and mortality (B) of included studies on adjuvant therapy after radical resection in ACC

4.4. Question 4: Therapy for advanced or recurrent disease.

A total of twenty-seven publications reported outcomes of 29 different systemic therapies for advanced or recurrent ACC (30, 66, 101-125); two were randomized controlled trials ((30,

102); see Appendix 6 for details of studies included). The first randomized trial compared mitotane plus a combination of etoposide, doxorubicin, and cisplatin (EDP-M) to mitotane plus streptozocin in 204 patients with advanced ACC (30). The trial showed a positive effect of EDP-M on progression-free survival HR 0.55 (95% CI, 0.43 to 0.69; P<0.001), but failed to show a significant effect on mortality (HR 0.79; 95% CI, 0.61 to 1.02; p=0.07); (+++O). The second randomized trial compared linsitinib to placebo (total 139 patients, 2:1 randomization to therapy) and did not show a clear effect on either progression free (HR 0.83, 95% CI 0.56–1.21; p=0.30) or overall survival (HR 0.94; 95%CI 0.61–1.44; p=0.77)(102); (+++O).

Many publications reported on single arm studies of different therapeutic regimens. These single arm studies have an inherent risk of selection bias, and direct comparison is not possible. Differences in patient characteristics, definition of response criteria and follow-up duration are a concern (+OOO). Given the uncontrolled design a final conclusion about the optimal treatment for advanced recurrent ACC cannot be given. Figure 2 shows response rates from all studies with data for at least one regimen. For most regimens at least some responses (partial or even complete) were reported; treatment merits in case of stable disease is more difficult to judge as this depends highly on duration of follow-up and biology of the disease. Adverse effects from chemotherapy, however, are common and diverse (see Appendix 6).

Study	Therapy	N
Henning, 2017 (124)	Gemcitabine and capecitabine	145
Fassnacht, 2012 A (30)	etoposide, doxorubicin, cisplatin, and mitotane	127
Fassnacht, 2012 B (30)	Streptozocin and mitotane	125
Hermsen, 2011 (103)	Mitotane and different cytotoxic drug	91
Fassnacht, 2015 (102)	Linsitinib	90
Berruti, 2005 (101)	Etoposide, doxorubicin, cisplatin, and mitotane	71
Gonzalez, 2007 (66)	Mitotane	67
Williamson, 2000 (122)	Cisplatin and etoposide	45
Bukowski, 1993 (110)	Cisplatin and mitotane	37
Decker, 1991 B (111)	Mitotane	36
Abraham, 2002 (105)	Doxorubicin, etoposide, vincristine, and mitotane	36
Sperone, 2010 (104)	Gemictabine + capecitabine/5-fluorouracil	28
Kroiss, 2012 (116)	Sunitinib	28
Naing, 2013 (117)	Cixutumumab and temsirolimus	26
Haak, 1994 (112)	Mitotane	23
Kroiss, 2016 (115)	Trofosfamide	21
Bonacci, 1998 (109)	Etoposide and cisplatin	18
Urup, 2013 (121)	Cisplatin and docetaxel	17
Decker, 1991 A (111)	Doxorubicin	16
Lerario, 2014 (125)	Cixutumumab and mitotane	15
Haluska, 2010 (113)	Figitumumab	14
Schlumberger, 1991 (120)	5-fluorouracil, doxorubicin, and cisplatin	13
O'Sullivan, 2014 (118)	Axitinib	13
Baudin, 2001 (107)	Mitotane	13
Baudin, 2002 (106)	Irinotecan	12
Kahn, 2004 (114)	Vincristine, teniposide, cisplatin, and cyclophosphamide	10
Wortmann, 2010 (123)	Bevacizumab and capecitabine	10
Quinkler, 2008 (119)	Erlotinib	9
Berruti, 2012 (108)	Sorafenib and metronomic paclitaxel	9

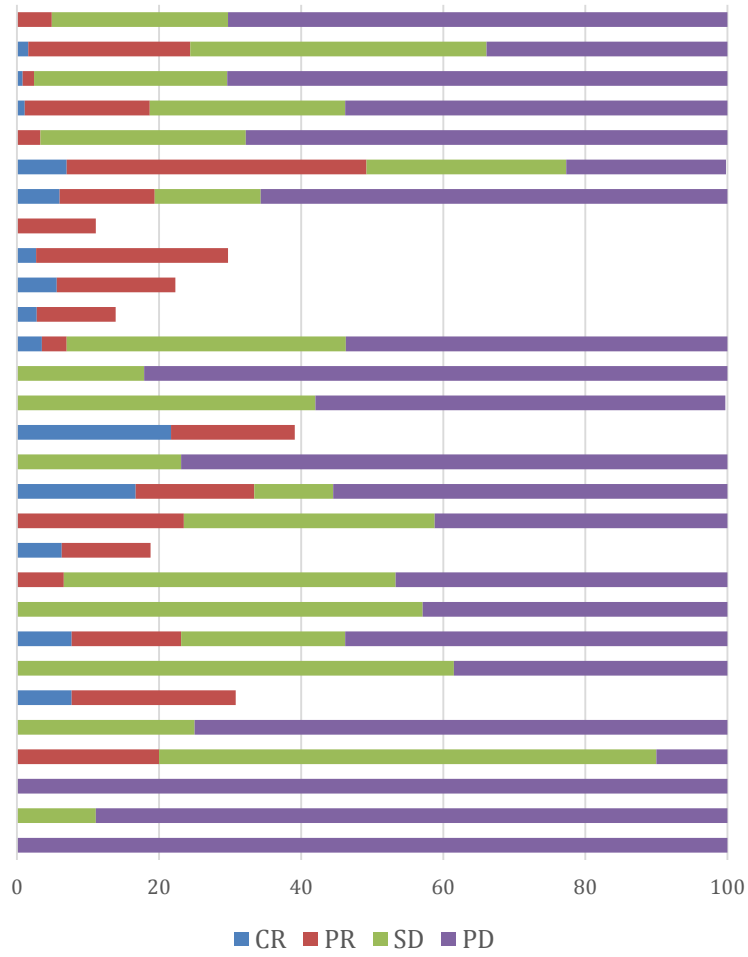


Figure 2: Overview of the objective response rates in studies with systemic therapies in ACC

The studies are ordered by number of included patients per regimen. This figure has to be interpreted very cautiously, because study protocols, patient cohorts and characteristics as well as outcome measurements are quite different precluding a direct comparison. CR: complete response; PR: partial response; SD: stable disease; PD: Progression of the Disease. Some of the older studies did not report stable disease or progression, thus these columns don't sum up to 100%

Sixteen studies focused on surgery in recurrent and advanced ACC; six publications reported on oligo-metastasectomy (lung, liver) (126-131), whereas 10 publications assessed the effect of surgery in local recurrent and/or metastatic disease (61, 66, 78, 132-138). In patients with metastasectomy 5-survival rates up to 40% were reported (126, 127), although control groups were lacking (+OOO). There were large differences regarding extent of disease, indication, and concurrent treatment in studies comparing a surgical approach to a non-surgical approach for recurrent or advanced disease. The reported benefit of surgery is confounded by differing indications for surgery, and this precludes firm conclusions from being drawn (+OOO). Therefore, the main conclusion is that in patients deemed radically operable by the surgeon/team operation is a treatment option. However, a key influencing factor in case of recurrence is the disease-free interval prior recurrence.
For radionuclide therapy (139), transcatheter arterial chemoembolization (140), radiofrequency ablation (141) and radiation (142) only one small study per procedure was found, and no conclusions can be drawn.

5. Recommendations

5.1. General remarks

The main part of this guideline addresses the management of adult patients with ACC. We divided the 62 recommendations in 12 sections. In addition, we provide two flow-charts on the management of patients with ACC amenable to radical resection (Figure 3) and on the management of patients with advanced ACC not amenable to radical resection (Figure 4) to give an efficient overview. However, we would like to emphasize once more that none of these flow-charts nor the entire recommendations can replace clinical judgment of the treating physician and joint decision-making with the patient.

5.1. Overarching recommendations

R.1.1. We recommend that all patients with suspected and proven adrenocortical carcinoma (ACC) are discussed in a multidisciplinary expert team meeting (including health care providers experienced in care of adrenal tumors, including at least the following disciplines: endocrinology, oncology, pathology, radiology, surgery) at least at the time of initial diagnosis. In addition, this team should have access to adrenal-specific expertise in interventional radiology, radiation therapy, nuclear medicine, and genetics as well as to palliative care teams.

Reasoning:
Despite the lack of studies, the panel was convinced that patients with ACC benefit from multidisciplinary management by a team of experts with experience in care for patients with this rare disease. Ideally, all patients would be managed by such a team throughout the course of their disease, but in many health care settings this is yet an unrealistic expectation. Therefore, we envision that in the future at least one reference center, that fulfills the above-mentioned criteria, will be established in every country. We believe that it is crucial that every case of suspected ACC is discussed in detail with a panel of experts for this disease at the

time of the initial diagnosis. Additionally, this expert team should be ideally requested every time progress is documented (or suspected) and new treatment options might be required. If there is no accessible center with all the required expertise in all disciplines, or the patient is not able to travel to such a center, telemedicine approaches should be encouraged to compensate for these limitations.

R.1.2. We suggest that at any time of decision-making regarding therapy, enrollment in a clinical trial (if available) should be considered. Furthermore, we encourage patients' participation in registries and the collection of biological material as part of structured research programs aimed at defining biomarkers of diagnosis, prognosis and treatment response.

Reasoning:

As described above, the evidence for almost all therapeutic strategies for ACC is very low. Furthermore, the efficacy of systemic therapies is limited, including the most commonly used treatments - mitotane and platinum-based chemotherapies, with response rates clearly less than 30% (3, 13, 30, 103, 107, 143). Thus, improved treatment paradigms are needed urgently. Clinical trials are the best way to improve our knowledge and patient care.

Because of the rarity of the disease, it is crucial to include as many patients as possible in research programs for multicenter therapeutic trials, as well as studies for diagnostic, prognostic and predictive markers. A list of ongoing trials is accessible on https://www.clinicaltrials.gov/. Biological material may include tumor samples, ideally frozen and paraffin-embedded, blood-derived and urine samples. National and international research networks such as ENSAT (www.ensat.org)(144) and the recently founded A5 (https://adrenal-a5.org/) play instrumental roles in coordinating research programs. Centers providing care to patients with ACC should register as investigators with ongoing trials and also facilitate the collection a of biological material and ensure appropriate consent.

5.2. Diagnostic procedures in suspected ACC

R.2.1. The diagnosis of ACC is not always obvious. We recommend establishing as soon as possible whether an adrenal mass is malignant, using all required diagnostic tools in a timely fashion.

Reasoning

Due to the potentially poor prognosis of ACC, it is critical to know as early as possible if an adrenal mass is malignant or not. Therefore, even if there is only a small likelihood that an adrenal mass is an ACC, this diagnosis should be rapidly excluded with the highest possible certainty. A particular suspicion for an ACC might arise from clinical aspects (e.g. rapidly developed features of adrenocortical hormone excess, see R.2.2), or results from hormonal work-up (see R.2.3), or indeterminate or suspicious imaging (see R.2.4). An adrenal biopsy should only be considered in those selected cases in which an adrenal metastasis of an extra-adrenal malignancy is suspected or when the tumor is considered as inoperable (17) (see also R.2.7). The proposed diagnostic work-up is summarized in Table 3.

Table 3: Diagnostic work-up in patients with suspected or proven ACC

Hormonal work up		
	• Glucocorticoid excess	- 1mg dexamethasone suppression test or free cortisol in 24-h urine[1]
		- basal ACTH (plasma)[2]
	• Sex steroids and steroid precursors[3]	- DHEA-S
		- 17-OH-progesterone
		- androstenedione
		- testosterone (only in women)
		- 17-beta-estradiol (only in men and postmenopausal women)
		- 11-deoxycortisol
	• Mineralocorticoid excess	- potassium
		- aldosterone/renin ratio (only in patients with arterial hypertension and/or hypokalemia)
	• Exclusion of a pheochromocytoma	- Fractionated metanephrines in 24h urine or free plasma-metanephrines
Imaging		- CT or MRI of abdomen and pelvis,
		- Chest CT
		- FDG-PET/CT[4]
		- Bone or brain imaging (when skeletal or cerebral metastases are suspected)

[1] The 1-mg dexamethasone test is the preferred method to exclude relevant hypercortisolism. However, if overt Cushing syndrome is evident, then cortisol in 24-h urine might be at least as good to quantify the cortisol excess. Alternatively, salivary or serum bedtime cortisol can be used.
[2] ACTH can be skipped if hypercortisolism is excluded.
[3] The most suitable set of precursors and sex hormones has not yet been established and local availability might be taken into account.
[4] The panel did not agree on the systematic use of FDG-PET/CT (see R.2.4).

R.2.2. We recommend that every patient with (suspected) ACC should undergo careful assessment including case history, clinical examination for symptoms and signs of adrenal hormone excess.

Reasoning

All patients should undergo a careful evaluation with detailed history and physical examination. In particular, patients should be evaluated for rapidly developing Cushing's syndrome (which frequently presents not as 'full blown' Cushing, but rather predominantly with muscle weakness, hypokalemia, wasting and constitutional symptoms), and symptoms and signs of a large abdominal mass. Clinical evaluation should additionally focus on symptoms and signs of androgen excess, hirsutism or virilization in women or recent onset of gynecomastia in men, because these might be clinical indicators for a cortisol-, androgen- or estrogen-producing ACC, respectively (13, 23, 145-148). Any evidence of co-secretion of different steroids raises the suspicion of an ACC (especially if sex-hormones are involved). In contrast, mild, long standing hirsutism is usually not caused by an ACC, but rather due to (among other diagnoses) polycystic ovary syndrome and non-classical congenital adrenal hyperplasia (149). Primary aldosteronism is rare in ACC and usually accompanied by severe hypokalemia (150). However, hypokalemia in ACC is more frequently caused by massive cortisol excess overwhelming the renal 11-β hydroxysteroid dehydrogenase type 2 system.

R.2.3. We recommend that all patients with suspected ACC undergo a detailed hormonal work-up to identify potential autonomous excess of glucocorticoids, sex-hormones, mineralocorticoids and adrenocortical steroid hormone precursors (see Table 3). In addition, a pheochromocytoma must be excluded.

Reasoning

A comprehensive endocrine work-up is helpful for various reasons. (i) The diagnosis of steroid excess is frequently able to establish the adrenocortical origin of the tumor. (ii) The steroid pattern may indicate whether an adrenal lesion is an ACC. For example, autonomous co-secretion of androgens and cortisol in any patient and secretion of steroid precursors or estradiol in males are highly suspicious for ACC (145). Furthermore, hormonal evaluation is of prognostic value as cortisol-secreting tumors generally have a worse prognosis (35). (iii) If undiagnosed, autonomous cortisol secretion may be followed by life-threatening adrenal insufficiency after complete resection of the primary tumor. The best test to diagnose autonomous cortisol secretion is the 1-mg overnight dexamethasone suppression test (147). If hypercortisolism is present, it is crucial to prove ACTH-independency, because an adrenal metastasis of an ectopic ACTH-secreting tumor (e.g. lung cancer) can mimic an ACC. (iv) Elevated hormones prior to surgery may serve as tumor markers during follow-up. Finally, conventional imaging cannot discriminate an ACC from a pheochromocytoma. However, undiagnosed pheochromocytoma may lead to dangerous hypertensive crises (especially during invasive procedures). Therefore, a pheochromocytoma has to be ruled out in any case of an adrenal tumor whenever no obvious autonomous steroid excess is present (17). It is important to note, however, that slightly elevated metanephrines levels (< 2-fold), particularly when inconsistent with a large tumor size, might be non-specific and can be observed in ACC.

R.2.4. We recommend adrenal-focused imaging in all patients with suspected ACC.

Reasoning

Imaging tools for adrenal tumors were carefully reviewed during the development of the ESE-ENSAT guidelines for adrenal incidentalomas (17, 151). Thus, we refer to these documents for details. Briefly, there are currently three main imaging techniques available for the differentiation of malignant and benign adrenal tumors: computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography with ^{18}F-2-deoxy-D-glucose (mostly combined with CT; FDG-PET/CT). CT and MRI are techniques mainly optimised to identify benign lesions, providing a tool for the exclusion of adrenal malignancy (152-155). Conversely, FDG-PET/CT is mainly used for the detection of malignant disease (156-158). A recently performed meta-analysis indicated that the level of evidence is low to very low for all these imaging methods (151). In the last 2 years some additional studies have been published (159-172). However, the panel still considers that of the available imaging modalities, only non-contrast CT is sufficiently reliable to rule-out an ACC when the adrenal lesion is homogenous and has low CT density ≤ 10 HU. In contrast, ACCs are usually large and of inhomogeneous appearance, and characterized by low fat content (and hence higher HU density)(173). Recently, FDG-PET has been proposed as possibly the best second-line test to assess indeterminate masses by unenhanced CT (159, 165, 166). However, the experience shows that sensitivity and negative predictive value are much better than specificity or positive predictive value. Therefore, no consensus could be reached

for a general recommendation on FDG-PET in all patients. Additional reasons in favor of systematic FDG-PET are: whole body imaging (beyond thorax and abdomen, particularly for distant bone metastasis) and in advanced disease, a reference uptake value for all metastases can be established, which can help judging the future evolution of disease. Evidence against FDG-PET includes cost, additional radiation exposure, false-positive findings, and difficult access in some countries.
If adrenal imaging indicates an indeterminate mass, other parameters should be considered: For instance, in such a situation a tumor size > 4 cm, combined adrenocortical hormone excess (see also R.2.3), rapidly developing symptoms or young age (e.g. < 40 years) might point to an ACC. However, it is important to note that no single imaging method can definitively prove the diagnosis of ACC.

R.2.5. We recommend in any case where there is high suspicion for ACC performing a chest CT, in addition to an abdominal-pelvic cross-sectional imaging (CT or MRI), because the results might influence therapeutic decision-making.

Reasoning:
Since decisions for treatment strategy, particularly decisions for surgery, and prognostication rely on tumor stage, it is mandatory to systematically and rapidly evaluate for metastases, before initiation of any anti-tumor treatment. Thoraco-abdomino-pelvic imaging will cover the vast majority of metastatic locations, which most often are lung and liver, and will assess locoregional tumor extent. Imaging should include contrast-enhanced imaging. For abdominal imaging there are advantages and disadvantages for both CT and MRI, but for thoracic imaging CT is the method of choice, because it outperforms all other methods in detecting small pulmonary lesions.
Additional imaging may be required to better characterize tumor vascularization, or specific tumor extent such as a vena cava thrombus.

R.2.6. We suggest performing additional imaging (e.g. bone and brain imaging) only in case of clinical suspicion of metastatic lesions.

Reasoning:
Bone and brain metastases are rare events (especially in patients without other metastatic lesions). Therefore, additional imaging focusing on these sites is only warranted when there is increased clinical suspicion or other imaging is suggestive for bone metastases. It should be noted, however, that the basis for this advice has never been studied systematically.

R.2.7. We recommend against the use of an adrenal biopsy in the diagnostic work-up of patients with suspected ACC unless there is evidence of metastatic disease that precludes surgery and histopathologic proof is required to inform oncological management.

Reasoning:
Differentiating benign from malignant adrenocortical tumors is very challenging on a biopsy only and may lead to misdiagnosis (17, 174). Furthermore, the biopsy comes with significant

risks such as hemorrhage (175). The risk of tumor dissemination precluding a R0 resection is very low (175). However, a biopsy might be indicated in an adrenal mass without any hormone excess in patients with a history of extra-adrenal cancers to exclude or prove an adrenal metastasis of an extra-adrenal malignancy. For details see the adrenal incidentaloma guidelines (17).

5.3. Surgery for suspected localized ACC

R.3.1. We recommend that adrenal surgery for suspected/confirmed ACC should be performed only by surgeons experienced in adrenal and oncological surgery.

Reasoning

ACC surgery requires expertise in both adrenal and oncological surgery due to the specific anatomy, the malignant character of the disease and the potential need for multi-organ en-bloc resection to optimize the probability of a R0 resection and minimize the risk of complications.

Data comparing outcome between 'high-volume' and 'low-volume' centers for ACC are limited. Published reports from the UK, USA and Spain show an unacceptable low annual workload for the majority of surgeons involved in any adrenal surgery, with a median 1 case/year (176-179). This situation is likely to have a negative impact on patient care and contrasts significantly with the current status in other surgical specialties.

Based on the upper quartile distribution of workload of surgeons in USA, a volume of 4 adrenalectomies/year was used to define a ‘high-volume’ surgeon (177) but this threshold might be too low to inspire confidence. Several studies showed that those doing more than 6-7 cases per year have shorter length of stay and less complications (176, 177, 180). Despite the perceived benefit of being operated in a high-volume center, published data from Italy and USA showed no significant association between overall survival / disease-free survival and workload even though patients operated in high-volume centers had more radical surgery, more lymph node assessment and more use of chemotherapy (181, 182). In contrast, the creation of national centers for adrenal surgery in The Netherlands led to significantly improved disease-free survival (1y: 93% vs. 78%, 5y: 63% vs. 42 %) (183, 184). Therefore, the panel believes that a minimal annual workload of 6 adrenalectomies/year seems to be required to ensure sufficient experience in adrenal surgery, but > 20 adrenalectomies/year are desirable for those involved in surgery for ACC. Furthermore, due to the complexity of some operations, it is essential to involve surgeons with different expertise (e.g. vascular, liver, and cardiac surgeons) for pre-surgical planning and during these complex operations.

Protocols ensuring referral to regional or national centers should be established and patients should feel empowered to ask about the previous experience of individual surgeons.

R.3.2. We recommend complete *en bloc* resection of all adrenal tumors suspected to be ACC including the peritumoral/periadrenal retroperitoneal fat. We recommend against enucleation and partial adrenal resection for suspected ACC. If adjacent organs are suspected to be invaded, we recommend *en bloc* resection. However, we suggest against the routine resection of the ipsilateral kidney in the absence of direct renal invasion.

Reasoning

Complete resection is of utmost importance for all ACCs and successful surgery is a prerequisite for cure. As the diagnosis of ACC might only become apparent after histological analysis, it remains imperative for all adrenalectomies (laparoscopic or open) in patients with a reasonable suspicion for ACC to respect the principles of oncological surgery in order to ensure complete resection (R0 status) (185, 186).

To ensure that the pathologist can judge the completeness of surgery, any fragmentation of the tumor has to be avoided. Intraoperative tumour rupture or spillage and R2 resection are associated with very high recurrence rates and poor overall survival (26) (133).

Although there are no specific studies comparing outcome of surgery with and without resection of invaded adjacent organs, it is deemed to be 'good surgical practice' to resect adjacent tissues that are/could be invaded by tumor. This holds true for involvement of spleen, distal pancreas, stomach, kidney, right liver, colon, diaphragm, the wall of the IVC or left renal vein. A cohort study compared the oncological results of patients with stage II ACC treated by radical adrenalectomy alone or by *en-bloc* resection with kidney. The results did not support the hypothesis that nephrectomy improves the oncological outcome (187). Combined nephrectomy, however, offers a lower risk of capsular rupture and can include complete lymphadenectomy of the renal hilum, but impairs kidney function and this may limit further access to chemotherapy.

R.3.3. Open surgery is the standard surgical approach for confirmed or highly suspected ACC. Therefore, we recommend open surgery for all tumors with radiological findings suspicious of malignancy and evidence for local invasion. However, for tumors < 6 cm without any evidence of local invasion, laparoscopic adrenalectomy (respecting the principles of oncological surgery) is reasonable.

Reasoning

There is an ongoing debate if laparoscopic adrenalectomy is an acceptable alternative for adrenal tumors with suspicion of ACC. Based on the systematic review on this topic until July 2014 (17) and an additional literature search until December 2017 (188-195), we conclude that the quality of evidence from these observational studies is still very low. The main concerns with all these studies are differences of baseline characteristics between groups, and between important prognostic factors, such as tumor stage or size. The lack of any randomized trial prevents any final conclusions. However, in order to provide guidance for clinicians the panel concurs with two other recent European guidelines (17, 185) and agrees that all tumors with some radiological evidence of local invasion (including enlarged lymph nodes) should undergo surgery with an open approach. The likelihood of a benign adrenal tumor is higher in the group of adrenal incidentalomas ≤ 6 cm, for whom a laparoscopic approach is reasonable. However, this cut-off is arbitrary and the experience of the surgeon is the single most important factor. For detailed discussion we refer to the recent recommendations for the surgical management of ACC by ESES and ENSAT (185) and the guidelines on adrenal incidentaloma (17).

Although retroperitoneoscopic adrenalectomy is gaining popularity, only a small number of surgeons are likely to have completed the learning curve to reach sufficient expertise, which is estimated to be at least 20 cases (196, 197). This is a very significant issue in the context

of the overall minimal experience of most surgeons offering adrenalectomy (see above). Outside specialized centers with large volume practice, retroperitoneoscopic adrenalectomy should only be considered for benign tumors <4 cm.

R.3.4. We suggest that routine locoregional lymphadenectomy should be performed with adrenalectomy for highly suspected or proven ACC. It should include (as a minimum) the periadrenal and renal hilum nodes. All suspicious or enlarged lymph nodes identified on preoperative imaging or intraoperatively should be removed.

Reasoning

Reports from several databases indicated that patients with stage III tumors and positive lymph nodes can have a 10-year overall survival rate of up to 40 per cent after resection (29, 70, 88, 198, 199). However, the wide range of reported lymph node involvement in ACC (from 4 to 73%) (25, 26, 200) demonstrates that regional lymphadenectomy is neither formally performed by all surgeons nor accurately assessed or reported by all pathologists. According to large American and French series, approximately 10-30% of patients with ACC had formal lymphadenectomy as part of the tumor resection, reflecting the heterogeneity of operative management (25, 198). A minimum of four lymph nodes should be retrieved in order to declare lymph node negative cases (201) Furthermore, in an analysis of 120 cases identified from a multi-institutional database, the benefit of lymphadenectomy on overall survival persisted on multivariable analysis controlling for adverse preoperative and intraoperative factors associated with lymphadenectomy, such as tumor size, palpable mass, irregular tumor edges, suspicious nodes on imaging, and multivisceral resection (202). The largest series so far included 283 patients and the resection of more than five lymph nodes reduced also the risk of local recurrence and disease-related death in a multivariate analysis (203).

However, the panel is not in favor of a re-do operation if complete adrenalectomy was performed without lymphadenectomy (e.g. due to perceived benign tumor). The clinical benefit is uncertain and probably lower than the harm (e.g. delayed adjuvant therapy).

R.3.5. We recommend that individualized treatment decisions are made in case of tumors with extension into large vessels based on multidisciplinary surgical team. Such tumors should not be regarded 'unresectable' until reviewed in an expert center.

Reasoning

Extension of ACC into the adrenal vein, renal vein or inferior vena cava occurs in approximately 15-25% (29, 204, 205). Venous involvement consists mostly of intravenous tumor thrombus. Thrombectomy might require vena cava cross-clamping above or below the hepatic vein confluence or cardiopulmonary bypass, depending on the upper level of extent of the thrombus. The resection might include a complete thrombectomy, a flush manoeuvre and, occasionally, vascular cuff or prosthetic IVC replacement. A 3-year overall survival rate of about 25% in a large series (206) encourages the performance of a venous resection in the presence of vena cava or renal vein invasion but without distant metastases.

R.3.6. If the first surgery was suboptimal and macroscopically incomplete (R2 resection), we suggest to discuss re-do surgery in a multidisciplinary expert team.

Reasoning

There has been no prospective study assessing the benefits (or the lack thereof) of early reoperation in patients whose initial adrenalectomy was incomplete (R2 status). It is the panel's view that such patients should have intensive postoperative monitoring and if local recurrence is detected radiologically, in the absence of other metastases, they should undergo surgery with a curative intent at an expert center, if it is deemed likely to lead to an R0 resection.

R.3.7. We recommend perioperative hydrocortisone replacement in all patients with hypercortisolism that undergo surgery for ACC.

Reasoning:

Overt ACTH-independent Cushing's syndrome or biochemical autonomous cortisol secretion might lead to adrenal insufficiency after removal of the adrenal source of cortisol (even in patients with incompletely suppressed ACTH) (207). Therefore, the group unanimously sees a clear indication of intra- and postoperative glucocorticoid replacement, preferably with hydrocortisone, in all patients with evidence for '(possible) autonomous cortisol secretion' (post-dexamethasone cortisol >50 nmol/L (>1.8 µg/dL)). This should follow the suggestions for major stress dose replacement as per recent international guidelines (208). Postoperatively, the dose of glucocorticoid should be tapered on an individualized basis by a physician experienced with this clinical scenario.

5.4. Pathological work-up

R.4.1. We recommend that the diagnosis of ACC should be confirmed by histopathology (+++0).

Reasoning:

Histopathology is the gold-standard of diagnosing ACC and should in principle be obtained in all patients. For patients deemed operable this will be done on the basis of the resection specimen and for those patients that are inoperable, a biopsy will be taken in accordance with good oncological practice. However, the majority of panelists argued that in selected cases biopsy might be omitted when there is advanced disease with unequivocal ACTH-independent cortisol excess, androgen excess (testosterone, DHEAS) or estradiol excess. There is no role for biopsy in a patient who is considered suitable for surgery of the adrenal mass.

R.4.2. We suggest that all adrenal tumors, which cannot be readily classified, and all suspected ACC, should be reviewed by an expert adrenal pathologist (++OO).

Reasoning:

Diagnosing ACC can be challenging and misdiagnoses are relatively frequent events. In 21 of 161 of the patients (13%) registered with the German ACC Registry between 2006 and 2009, the diagnosis of ACC had to be revised by the reference pathologist (24). Similar results were found in a large series from Italy with a rate of misdiagnosis in 26 out of 300 cases (9%) (209).

R.4.3. We suggest the use of immunohistochemistry for steroidogenic factor-1 (SF1) for the distinction of primary adrenocortical tumors and non-adrenocortical tumors (+OOO).

Reasoning:

Generally, the distinction between adrenocortical and non-adrenocortical tumors is clear and can be made on the basis of hematoxylin and eosin-stained slides. In case of doubt, on the basis of histology only, whether a tumor originates from the adrenal cortex or not, immunohistochemistry with SF1 is the most sensitive and specific marker currently available to establish if the tumor in question is of adrenocortical origin, with a sensitivity of 98% and a specificity of 100% (47). If this marker is not available, we advise a combination of markers, which should include inhibin-alpha, melan-A, and calretinin (210, 211). Depending on the differential diagnosis, other immunohistochemistry markers used to make alternative diagnoses may be considered following local standard procedures.

R.4.4. We recommend the use of the Weiss system, based on a combination of 9 histological criteria that can be applied on hematoxylin and eosin-stained slides, for the distinction of benign and malignant adrenocortical tumors (++OO).

Reasoning:

There are many classification systems based on histology and/or a limited number of additional markers for the distinction of benign and malignant adrenocortical tumors. The Weiss system is the most widely used, and although it is not fully standardized (212, 213) the panel favors use of this score. It should be noted that all scoring systems have similar inherent problems. Using the Weiss system, a score of 3 or higher (on a total of 9 criteria, see Table 4) indicates ACC (214, 215). A score of 2 and 3 may be considered as borderline between benign and malignant tumors (tumors of uncertain malignant potential). In such instance, one of several other classification systems, including the van Slooten index (216), the modified Weiss score (41), the Helsinki classification (60, 77), and the addition of reticulin stain assessment (217) may be used.

Special attention should be paid to histological variants of adrenocortical tumors, mainly oncocytic tumors, which, because of their specific characteristics, will always have a Weiss score of least 3, whether they are benign or malignant. For these tumors, an adapted scoring system should be used (218-220).

Table 4 Histopathologic criteria by Weiss (214, 215)

The presence of three or more of the following criteria highly correlated with subsequent malignant behavior: • High nuclear grade (Fuhrman criteria (221)) • > 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

R.4.5. We recommend the use of Ki67 immunohistochemistry for every resection specimen of an adrenocortical tumor (++OO).

Ki67 immunohistochemistry has been proposed for prognostic purposes. Higher Ki67 levels are consistently associated with poor prognosis. Threshold levels of 10% and 20% have been considered for discriminating low from high Ki67 labeling index (58, 70). However it is not clear whether any single significant threshold can be determined (see R.5.2.).

Ki67 labeling has been shown to be unevenly distributed in tumors. Therefore, determination of the labeling index should be done on whole tumors, with specific attention to the area of highest Ki67 labeling, preferably by use of an image analysis system (222, 223). If only a biopsy is available a low Ki67 labeling may not be representative and therefore can be misleading.

If Ki67 immunohistochemistry is not available, mitotic count may help in prognostic stratification of ACC. Mitotic count has been proposed for grading of ACC, using >20 mitoses per 50 high-power field to define high-grade tumors (56, 87, 215). However, the precise correlation between mitotic count and Ki67 labeling is undetermined.

R.4.6. We recommend that the pathology report of a suspected ACC should at least contain the following information: Weiss score (including the exact mitotic count), exact Ki67 index, resection status, and pathological tumor stage (indicating invasion or not of the capsule and/or surrounding tissue and organs) and nodal status (+OOO).

Reasoning

The importance of Weiss score and Ki67 index has been discussed in R4.4 and R4.5, respectively. It is important that the exact values are given, because this is of prognostic relevance. Resection status is a major prognostic factor (see R 5.2.). Tumor stage, including nodal involvement, is discussed below (see R.5.1).

5.5. Staging classification and prognostic factors

R.5.1. At initial diagnosis, we recommend using the ENSAT staging classification (Table 5) (+++O).

Reasoning

Tumor staging is the most important prognostic factor. Specifically, the presence of metastases is by far the strongest indicator of poor prognosis. Several staging classifications have been proposed (29, 55, 70, 83-89). Among these, the ENSAT staging classification appears to be the most discriminant, but the differences between staging systems are minor (17)(see also section 4.2.). The panel felt strongly that a one unique staging classification should be adopted across centers in order to improve standardization and documentation of clinical data, and so improve patient care and enhance clinical research.

The ENSAT classification requires extensive imaging prior to surgery (see R.2.4.), systematic lymph node resection, a complete surgical report (see R.3.3.3.+4.), and a complete pathological report (see R.4.6.).

Table 5: ENSAT staging classification (17)

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 ≤ 5cm; T2: tumor > 5cm; 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; M0: no distant metastases; M1: presence of distant metastases.

R.5.2. At initial diagnosis, we recommend taking the following factors into account when assessing the prognosis and treatment options: tumor stage, resection status, Ki67 index (or mitotic count), autonomous cortisol secretion and the patient's general condition (++OO).

Reasoning

Of the many reported prognostic factors tumor stage is the most important, because it reflects tumor extent. Especially the presence of metastases is strongly pejorative (see R.5.1.). Resection status is also a strong prognostic factor (24, 26, 70), and should be carefully documented in the surgical and pathology reports. Furthermore, several studies have identified Ki67 immunostaining (or mitotic index) as major prognostic factors (58, 70, 87, 215, 224). As revealed by our systemic literature search, hypercortisolism was also one of the most consistent prognostic factors (see section 4.2; (20, 35, 225).

Finally, the patient's general condition is an obvious prognostic factor, especially at advanced age (55). It is, however, noticeable that ACC patients often do not show altered general condition despite advanced disease.

From a patient perspective, the panel felt it important to consider two distinct scenarios. First, the risk of recurrence of patients with a localized (stage I-III) disease. For these patients, tumor stage, resection status and Ki67 labeling index are currently the main prognostic

factors. This panel proposes to define two classes of localized ACC: low/moderate risk ACC includes stage I-II and R0 and Ki67 ≤10%, whereas high risk ACC includes stage III, R1, or Ki67 >10%. However, the panel is aware that the dichotomy is arbitrary.
Second, the prognosis of patients with advanced disease (stage IV or recurrent disease not amenable to complete resection or R2 resection). High tumor burden, high tumor grade, high Ki67 index, and uncontrolled symptoms are major factors associated with worse prognosis (56, 70). However, there is consensus that the kinetics of tumor growth might be also relevant, particularly when making the decision for initiation of cytotoxic chemotherapy. However, this parameter has not been formally assessed. Although a correlation of tumor growth and tumor grade exists, it is not true for all tumors.

R.5.3. During follow-up, we recommend re-assessing prognosis at each evaluation, to guide treatment strategy (++OO).

Reasoning
After complete surgery, the major prognostic factor is whether there is any tumor recurrence. At the time of recurrence the main prognostic factors are time between initial surgery and recurrence, tumor burden and resectability (61, 62, 126, 136).
For patients with advanced disease, prognostic factors include Ki67 index, tumor burden, general patient condition, and kinetics of tumor growth, as well as response to treatment. Limited evidence is available, but these factors make clinical sense and are corroborated by this panel's experience.

5.6. Methods and time interval for imaging and hormonal assessment during follow-up

R.6.1. We recommend following patients with regular cross-sectional imaging of the abdomen, pelvis and chest for disease recurrence or progression.

Reasoning
A majority of disease recurrence and progression occurs either loco-regionally, or with metastases to lung or liver and therefore should be identified by thoraco-abdomino-pelvic imaging. Bone metastases are rare and brain involvement is exceptional (23, 70, 226). In general, 18-FDG-PET/CT might provide additional information (see R.2.4.) particularly prior to any surgical intervention (156, 227, 228). In addition, change in tracer uptake might inform about disease evolution.

R.6.2. After complete resection, we suggest radiological imaging every 3 months for 2 years, then every 3-6 months for a further 3 years. The majority of the panel suggests continuation of follow-up imaging beyond 5 years, but surveillance should then be adapted.

Reasoning
There are no published studies that address specifically this issue. Therefore, the suggested imaging interval is in accordance with the practice at many expert centers, and with

standards for other malignant tumors. In the experience of the panel few tumors with initial curative surgery will recur after more than five years and therefore a 5-yr surveillance is likely to include >90% of the ACC population that will experience disease recurrence. However, the majority of the panel felt uncomfortable with the notion of complete cessation of imaging after 5 years and preferred for instance an annual imaging for another 5 years. After stopping regular imaging, patients and primary care physicians should remain vigilant in terms of potential symptoms or signs of late recurrences.

R.6.3. For advanced ACC, we recommend surveillance based on prognostic factors, expected treatment efficacy and treatment-related toxicity, as well as the available alternative treatment options.

Reasoning

The imaging interval in advanced ACC depends on the ongoing treatment and the overall prognosis, but will usually be in 2-3 monthly intervals. For patients receiving mitotane alone, imaging intervals might be even more individualized (e.g. 2-5 months) based on tolerability and tumor kinetics. For patients undergoing loco-regional treatments, specific surveillance following procedures must be determined by the team performing these procedures, both to assess efficacy and adverse effects. For patients opting for entirely palliative management, without any anti-neoplastic therapy, no systematic imaging is advised.

R.6.4. In all patients, we recommend regular screening for hormone secretion.

Reasoning

Biochemical evaluation together with clinical evaluation fulfills two purposes: (i) it allows in few patients the early detection of recurrences and (ii) it also identifies patients that might benefit from early anti-hormonal therapy. Biochemical evaluation should focus on steroid hormones or metabolites that were present at the time of diagnosis of the initial tumor. However, some panelists favored a more complete hormonal evaluation, because some tumors might change their steroid secretion pattern over time.

5.7. Adjuvant therapy

R.7.1. For adrenal tumors with uncertain malignant potential, we recommend against adjuvant therapy (+OOO).

Reasoning:

In certain tumors it is difficult to define if the tumor is truly malignant (see R.4.4.). Since all adjuvant therapies are associated with potential toxicity, only patients with a definitive diagnosis of ACC should be considered for adjuvant treatment.

R.7.2. We suggest adjuvant mitotane treatment in those patients without macroscopic residual tumor after surgery that have a perceived high risk of recurrence (+OOO). However, we cannot suggest for or against adjuvant therapy for

patients at low/moderate risk of recurrence (stage I-II, R0 resection and Ki67 ≤ 10%) and adjuvant therapy options should be discussed on an individual basis.

Reasoning:

The panel is in favor of offering mitotane to patients with high risk of recurrence (stage III, or R1 resection, or Ki67 >10%; see R.5.2.) despite the absence of completely convincing evidence (see section 4.3). The panel decided to use of mitotane in the adjuvant setting based on three arguments: (i) the perceived effects (28, 36, 90-94, 229) (acknowledging this is based on low quality evidence), see Figures 1A + B; (ii) published data showing a tumor response in ~20% of patients with advanced disease treated with mitotane (13, 107, 143, 230); (iii) clinical experience of the panelists. For details on mitotane management see section 5.9.

Ki67 has emerged as the most powerful predictor of recurrence, and tumors with Ki67 ≤10% might represent a subset of patients with a good prognosis. For these patients mitotane might be considered overtreatment. For this subset of patients (<30% of all localized ACCs) the ongoing ADIUVO trial, a prospective study where patients are randomized to adjuvant mitotane vs. observation, will provide guidance in a few years.

There is no clinical, histopathological, or molecular marker that reliably predicts response to mitotane although few markers have been proposed (231, 232). A study showed that mitotane levels may influence patient outcome in adjuvant setting (233) as it has been reported in advanced ACC. The secretory status of the tumor has a negative prognostic value but does not seem to influence response to treatment (20, 90, 230).

In patients who undergo surgery for recurrence of ACC but who have not previously had medical therapy, the decision on adjuvant mitotane should follow the same lines of reasoning.

R.7.3. Once the decision for mitotane treatment is established, we recommend starting mitotane as soon as clinically possible after surgery (+OOO).

Reasoning:

The ideal timing to start adjuvant mitotane is unknown; however, by analogy with other oncological adjuvant treatments we are convinced that starting mitotane within six weeks is ideal, and would not initiate the treatment later than 3 months. This reasoning is sound with the biological concept of adjuvant therapy in general, and with the latency of mitotane to reach effective levels and anti-tumor activity. However, no published data are available to demonstrate the superiority of an early start of treatment or the lack of efficacy when started later than 3 months.

R.7.4. In patients without recurrence who tolerate mitotane in an acceptable manner, we suggest to administer adjuvant mitotane for at least 2 years, but not longer than 5 years (+OOO).

Reasoning:

The optimal duration of mitotane treatment is unknown and practice varies among different centers. Some members of the panel continue treatment for 3 to 5 years if tolerated (234), while others discontinue after 2 to 3 years (3, 13, 19). Prognostic factors at diagnosis, patient compliance with treatment and plasma mitotane levels reached during treatment are factors

that influence duration of treatment. Mitotane possibly acts as an oncostatic measure in those patients (235, 236). However, the rate of recurrence 5 years after surgery is potentially too low to advise continuation of therapy treatment beyond this time point. Treatment-related toxicity, lack of experience in long-term administration are additional factors portending against indefinite treatment.

R.7.5. The panel did not come to a definitive consensus on adjuvant radiation therapy. However, we suggest against the routine use of radiation therapy in patients with stage I-II and R0 resection (+OOO). The panel suggests considering radiation in addition to mitotane therapy on an individualized basis therapy in patients with R1 or Rx resection or in stage III.

Reasoning:

The systematic literature search indicated that radiation therapy is able to prevent local recurrence but does not significantly affect distant recurrences or overall survival (91, 98-100, 237, 238) (see section 4.3. and Figure 1). However, distant metastases account for about 40-60% of tumor relapses (54, 61, 90) and have large impact on the patient prognosis, and are more difficult to treat effectively. Conversely, prevention of the complications due to local recurrence argues in favor of radiation therapy. Adjuvant radiation therapy might be particularly reasonable in patients with R1 resection. This was already suggested by earlier studies, but also by a very recent study that was published after our meta-analysis (239).

Radiation therapy is not advised for patients who experienced widespread tumor spillage during surgery. The combination of radiation therapy and mitotane is biologically sound (240, 241) and possible but at the cost of greater toxicity (e.g. constitutional, gastrointestinal and liver toxicity). In addition, there is concern that radiation therapy may delay systemic therapy or prevent effective mitotane administration resulting in lower drug levels.

R.7.6. If adjuvant radiation therapy is administered, we recommend starting treatment as soon as clinically possible after surgery and to deliver radiation therapy at the dose of 50-60 Gy to the previous tumor bed in fractionated doses of approximately 2 Gy each (+OOO).

Reasoning:

Radiation therapy was delivered following this scheme in previous observational studies (91, 98-100, 238) and lower dosage seems to be less effective (237).

R.7.7. The panel did not come to a definitive consensus on adjuvant use of cytotoxic drugs. We suggest against the routine use of cytotoxic drugs in the adjuvant setting. However, the panel suggests considering adjuvant chemotherapy in selected patients with very high risk for recurrence.

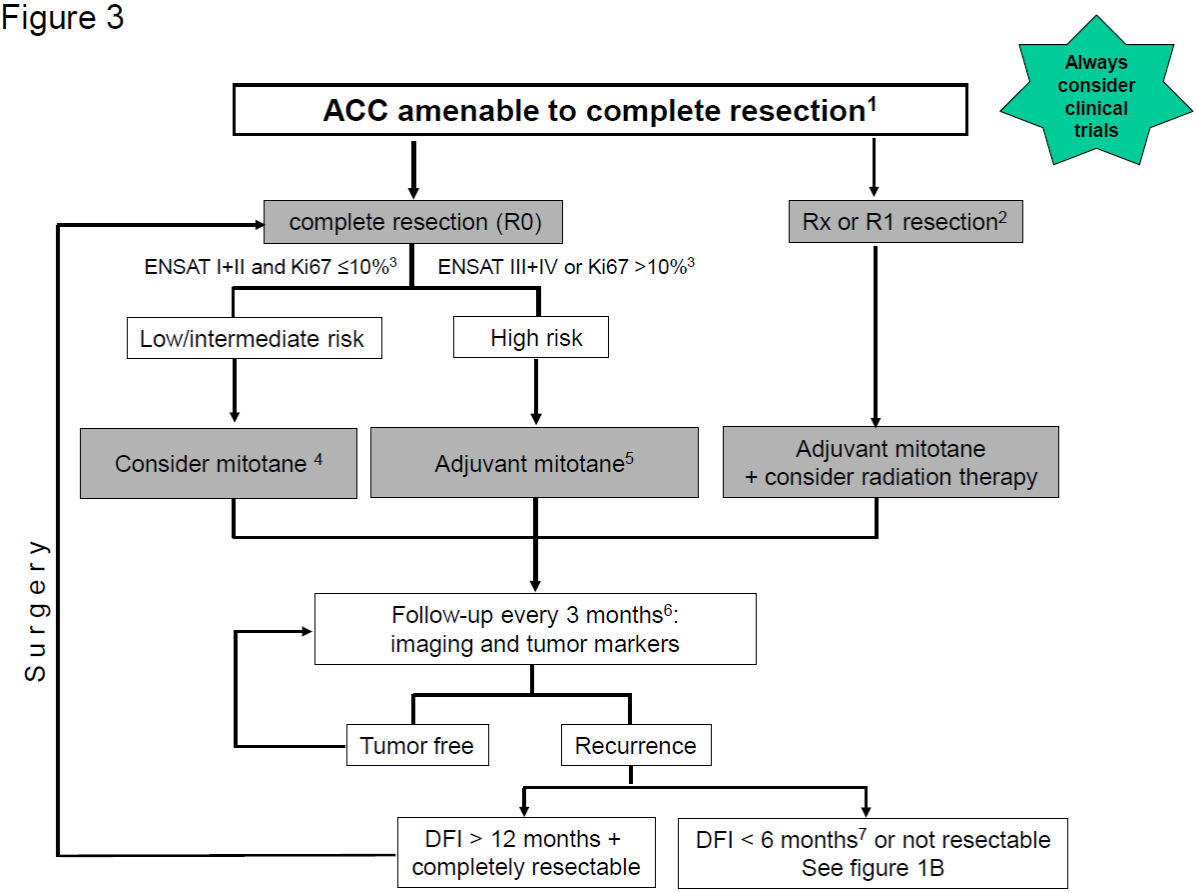
Reasoning:

Scant data are available on the use of cytotoxic drugs in an adjuvant setting and the studies did not control the results of treatment with a matched control group of untreated patients, or patients treated undergoing mitotane therapy (242). However, the majority of panelists favors

discussion of this option with patients with high risk of recurrence (ideally in the setting of clinical trials). Despite the lack of published data, some members of the panel are currently using cisplatin, with or without etoposide, in patients at perceived very high risk of recurrence (e.g. Ki67 >30%. large tumor thrombus in the vena cava, stage IV, or R1 resection).
In patients with R2 resection or tumor spillage, the same considerations for treatment of (locally) advanced disease should apply (see section 5.8.).

Figure 3: Treatment for ACC amenable to complete resection

Figure 3



DFI disease-free interval between complete resection and recurrence

[1] All patients with stage I+II and most patients with stage III should be amenable to radical resection. If complete resection is not feasible, consider neo-adjuvant treatment (e.g. cisplatin or EDP). In selected patients with single metastases complete resection might be possible as well.

[2] In patients with R2 resection, consider re-surgery by an expert surgeon (see R.3.6) or see Figure 1B

[3] If Ki67 staining is not available, a low (<20 mitoses / 50 high power fields) or a high mitotic rate (> 20 mitoses / 50 high power fields) may be used for risk stratification.

[4] Individual decision (see R.7.2.). If possible enroll in clinical trial like ADIUVO (www.adiuvo-trial.org).

[5] In some patients (e.g. Ki67 >30%. large tumor thrombus in the vena cava, stage IV, or R1 resection) consider additional cytotoxic therapy (e.g. 3-4 cycle of cisplatin + etoposide).

[6] After two years the time intervals are gradually extended.

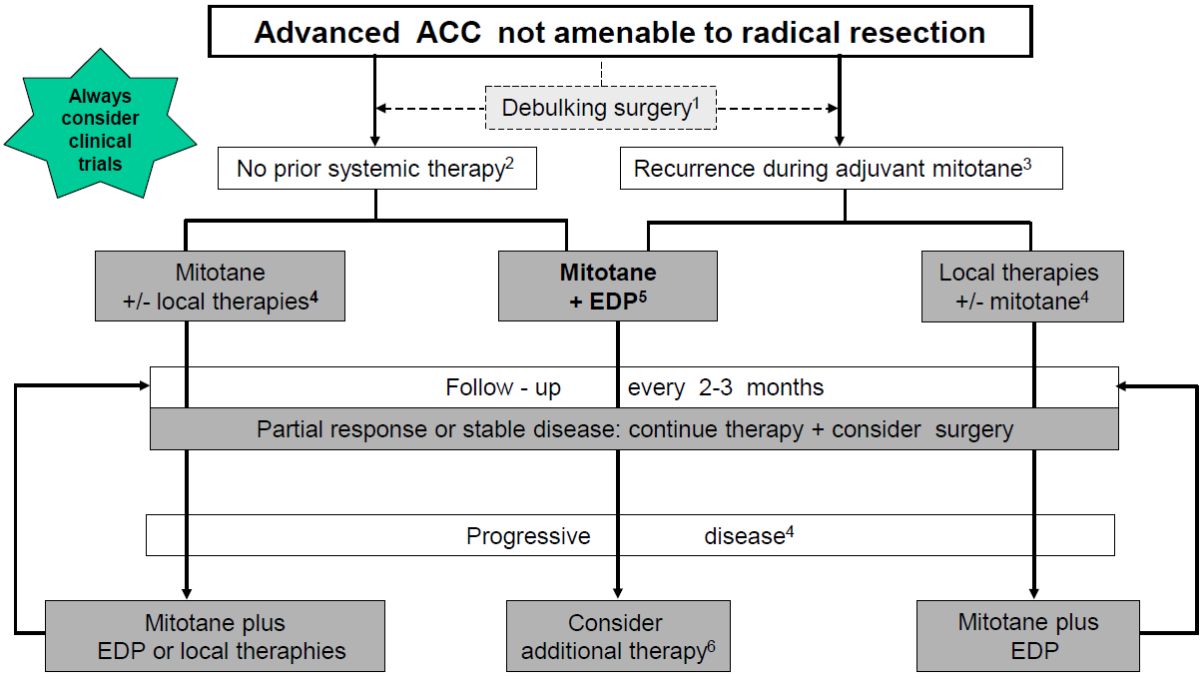
[7] If the disease-free interval is between 6 and 12 months or in patients with DFI > 12, in whom complete resection is not possible, an individual approach is required (see R.8.7.)

5.8. Treatment of recurrent and/or advanced ACC

Clinical scenarios of patients with recurrent and/or advanced ACC are highly variable. Therefore, we try to provide recommendations for at least the most frequent presentations (see also Figure 4). Although a (small) proportion of patients experience a relatively long survival (13, 29, 70, 243), the prognosis of advanced/metastatic is generally limited. The goal of any therapy is to palliate symptoms and prolong survival. In this situation it is even more important than in other scenarios to tailor treatment on an individual basis taking into account the disease extent, the patient performance status and particularly the preference of the patient.

Figure 4: Treatment of advanced ACC

Figure 4



EDP Etoposide, Doxorubicin, cisPlatin

[1] only in selected patients (e.g. with severe hormone excess)

[2] The following factors might guide the decision: site of disease involvement, tumor burden, symptoms, tumor grade/Ki67 index

[3] The following factors might guide the decision: site of disease involvement, tumor burden, symptoms, tumor grade/Ki67 index, and importantly kinetics of tumor growth

[4] radiotherapy, radiofrequency ablation, cryo ablation, microwave ablation, (chemo-)embolization

[5] Few panelist favored cisplatin + etoposide

[6] For the currently available cytotoxic regimens see Table 6 and contact specialized center.

R.8.1. For patients presenting at time of initial diagnosis with limited intra-abdominal metastases we suggest surgical therapy if complete resection of all lesions seems feasible (+OOO). In case of limited extra-abdominal lesions, we suggest adrenal tumor resection in conjunction with therapy aiming at long-term tumor

control of the other lesions (+OOO). In all patients, we recommend to start mitotane therapy as soon as clinically possible (+OOO).

Reasoning:

Complete surgery is the best chance to reach long-term disease control although the likelihood of complete tumor removal in advanced ACC is low. If clinically possible, a single surgical approach should be planned. If a one-time surgical approach is impossible (e.g. due extra-abdominal metastases), other loco-regional approaches (see R.8.2) should be discussed on an individual basis. Local expertise and preference of the patient should be taken into account. Any initial treatment (surgery, local and/or medical therapy) should be initiated in a timely fashion (≤ 4-6 weeks following initial diagnosis).

In general, prognostic parameters (see R.5.2 + 5.3) should influence the overall treatment strategy. If the disease has an aggressive behavior (i.e. increase in tumor burden [e.g. increasing size of existing tumors or new metastasis] observed in subsequent imaging performed within few weeks) systemic options (chemotherapy plus mitotane) may be favored. If partial responses or prolonged stabilization are then observed, surgery and/or additional loco-regional options might be particularly useful (“neo-adjuvant approach", see also R.8.3). This strategy could also be potentially advantageous in patients for whom tumor shrinkage might allow a more conservative surgical approach (i.e. patients in whom radical surgery would imply the complete or partial removal of neighboring organs such as kidney, spleen and part of the pancreas)(244).

These patients are at high risk for recurrence and therefore adjuvant mitotane seems to be justified (245). Addition of cytotoxic drugs might be a possible option (although data are lacking; see also R.7.7.).

R.8.2. The panel is convinced that in addition to surgery other local therapeutic measures (e.g. radiation therapy, radiofrequency ablation, cryoablation, microwave ablation, chemo-embolization) are of value for therapy of advanced ACC. We suggest individualization of the decision on the method of choice based on the localization of the tumor lesion(s), local expertise, prognostic factors, and patient's preference (+OOO).

Reasoning:

Published data on local therapies in advanced ACC are very limited (140-142, 237) and summarized in Appendix 6. However, the experience of many panelists provides additional evidence of efficacy of these local measures. Nevertheless, it is impossible to indicate which method is superior. Most important, the expertise of the local team in applying these methods should be taken into account when discussing this issue with patients in a shared decision-making process.

R.8.3. We suggest against the routine use of adrenal surgery in case of widespread metastatic disease at the time of first diagnosis (+OOO).

Reasoning: Despite the lack of large studies addressing this particular question, a majority of the panel agreed that patients with widespread and unresectable disease will usually not

benefit from surgery. However, few panelists favored adrenalectomy in all patients, in whom this approach is technically possible.
In patients who respond very well to systemic therapy, surgery should be considered at an appropriate time point; especially if complete resection becomes feasible ("neo-adjuvant approach"). However, the published evidence for such an approach is scant (244, 246).
In selected cases (e.g. patients with severe hormone excess) debulking surgery might be an option, although anti-hormonal drugs (see R.10.1) should be considered here. In these cases, surgery might be especially reasonable if > 80% of the tumor burden can be removed safely. In patients with a poor clinical condition and significant localized metastatic burden, additional localized therapies (see R.8.2) may be considered as an alternative.

R.8.4. In patients with advanced ACC at the time of diagnosis not qualifying for local treatment, we recommend either mitotane monotherapy or mitotane + EDP depending on prognostic parameters (+++O).

Reasoning:
Mitotane is the treatment of choice for patients with advanced ACC (for details about the management of mitotane see section 5.9). However, a very recent cohort study suggests that patients with metastastic disease at the time of primary diagnosis might not be the ideal candidates for mitotane monotherapy (230). Furthermore, unfavorable prognostic parameters (e.g. high tumor burden, uncontrolled symptoms, high proliferative index, clinical evidence of a fast growing tumor) are important factors favoring a more aggressive/more rapidly active therapeutic approach. If more aggressive therapy is indicated, then the combination of EDP in addition to mitotane (EDP-M) is the most validated regimen (30). EDP-M is the only treatment approach in ACC that is successfully evaluated in a randomized trial, the FIRM-ACT study. It has to be highlighted, however, that only progression-free survival was significantly improved in comparison to the alternative therapy (in this case streptozotocin plus mitotane; 5.0 vs. 2.1 months; HR 0.55; 95% CI 0.43 to 0.69; P<0.001)), whereas for overall survival the crossover design might have diluted the results (14.8 vs 12.0 months, HR 0.79; 95% CI, 0.61 to 1.02; P=0.07).
The administration of EDP-M comes with risk of adverse events and the risks might outweigh the benefits (especially in patients with reduced performance status). If there are concerns about the use of doxorubicin, cisplatin/carboplatin with or without etoposide (EP or P) might be an alternative option. Carboplatin may be an alternative to cisplatin, particularly when cardiac or renal function is compromised. Again, in this cohort, loco-regional treatment options may be particularly applicable.
Several studies have tried to find biomarkers that predict response to cytotoxic therapy in ACC (247-250). However, no reliable marker could be identified yet.
Few centers prefer the combination of etoposide and cisplatin (EP), because there is no single study proving that EDP is truly superior to EP. In patients with poor overall health cisplatin with mitotane may be an option. However, the evidence for etoposide + cisplatin or cisplatin alone is based only on small phase II studies (109, 110, 122).
There is limited evidence that standard chemotherapeutic agents may be more active in presence of elevated mitotane concentrations (30, 104, 251), but the panel is not in favor in delaying cytotoxic therapy for this reason for more than 14 days.

R.8.5. In patients with recurrent disease and a disease-free interval of at least 12 months, in whom a complete resection/ablation seems feasible, we recommend surgery or alternatively other local therapies (+OOO). We recommend starting mitotane as soon as possible after the intervention.

R.8.6. We recommend EDP-M as first line treatment if the time interval between last surgery/loco-regional therapy and recurrence is less than 6 months (++OO), rather than repeat loco-regional measures.

R.8.7. For all other patients with recurrent disease an individualized approach is needed.

Reasoning:

It has been suggested that patients with disease-free interval of 12 months or more have a significantly better prognosis and long-term disease control is achievable, if loco-regional measures are successful (61, 126). The choice of different loco-regional therapies depends again on benefit/risk ratio, local availability and expertise, and the clinical scenario in a given individual patient. Most panelists favor surgery (if complete resection is feasible) followed by mitotane therapy.

If the recurrence occurs during adjuvant mitotane therapy, additional measures could be considered. In patients with local recurrence, adjuvant radiation therapy after surgery should be discussed. In other scenarios, additional administration of cytotoxic drugs should be discussed with the patient, particularly when mitotane blood levels were in the recommended range > 14 mg/l.

Patients with early recurrence usually suffer from a very aggressive tumor, which most likely cannot be controlled by surgery or localized therapies. Decision-making should incorporate the concern that any local measure will only delay the administration of systemic therapy. Similar to the discussion to R.9.3, the FIRM-ACT data indicate EDP-M as the most effective form of therapy. An exception might be patients in whom incomplete initial surgery is the most likely cause for early progression. In these selected patients repeat surgery at an expert center might be an appropriate alternative (see R.3.6).

Patients with recurrence between 6 and 12 months after primary surgery usually have a poor prognosis and would, therefore, benefit from a more aggressive therapeutic approach (e.g. EDP-M). However, this decision should be discussed with the patient taking into account prognostic parameters (see section 5.5.), the feasibility of a R0 resection and patient's general condition. Patients with a disease-free interval > 12 months, in whom complete resection or loco-regional therapy is not feasible and who are currently not treated with mitotane, might be good candidates for mitotane monotherapy (230).

R.8.8. In patients who progress under mitotane monotherapy, we recommend to add EDP (+++O).

Reasoning:

Mitotane is a slow-acting drug and in patients with rapidly progressing tumor, it might be too slow or not effective enough. In these patients, based on the FIRM-ACT data (30), additional administration of EDP is the first choice (for alternatives see Reasoning R.8.4.). However, if the tumor burden is limited despite obvious progression, another 2-3 months mitotane monotherapy could also be justified, particularly if adequate mitotane levels have not been achieved. In these cases, additional loco-regional options should be considered.

R.8.9. In patients who respond to medical therapy (including achievement of long-term stable disease), we suggest re-considering local measures aiming at long-term tumor control. Such an approach could be also considered in patients attaining a generally good control of the disease, in which a limited number of lesions are progressing.

Reasoning:

In some patients, in whom long-term disease control could be achieved, loco-regional measures (in addition to ongoing medical therapy) might be able to reach complete remission or at least significantly reduce tumor burden (101). In patients with "mixed responses"; e.g. progressive disease limited to few lesions, loco-regional options might be reasonable to add to the ongoing medical therapy.

R.8.10. In patients who progress under EDP-M we suggest considering additional therapies including clinical trials on an individual basis (+OOO).

Reasoning:

Several drugs and drug combinations have been tested in advanced ACC. However, except EDP-M none of them has been successfully evaluated in large randomized trials. Figure 2 outlines the outcomes of the different approaches. However, this figure has to be interpreted with great caution, because differences in the characteristics of the patients included in the different cohorts preclude direct comparison between studies. Therefore, it is not possible to draw definitive conclusions. Due to the limited treatment options, the panel clearly favors enrollment of patients with progressing tumors in clinical trials investigating experimental therapies including phase I trials. However, the panel felt that despite the lack of convincing data, some guidance might be helpful for patients that cannot be enrolled in clinical trials (Table 6). Beyond cisplatin-based therapies, the two reasonably well-studied second-line cytotoxic regimens are gemcitabine + capecitabine (+/- mitotane) (104, 124) and streptozotocin + mitotane (30, 242). However, objective response rates are clearly below 10% and median progression-free survival (PFS) is generally <4 months, but a few patients with long-term disease control and even complete responses in single patients are described. Nevertheless, few panelists argued against the use of streptozotocin, because median PFS in the FIRM-ACT trial was only two months (30).

Loco-regional measures can be particularly useful when progression is limited, or only affects limited areas (e.g. single organs). In these cases, such localized therapies (see R.8.2) might be able to provide higher response rates for these specific organ/tissue areas than second line systemic options.

Several tyrosine kinase inhibitors have been investigated in advanced ACC (102, 108, 116, 118), but the results were largely disappointing. However, in retrospect, drug efficacy could have been hampered by increased metabolism of the TKI due to mitotane-induced CYP3A4 activity. Nevertheless, currently no specific TKI can be suggested for the treatment of advanced ACC. Targeting the IGF2/IGF receptor signaling pathway was pathophysiologically a very promising approach and initial small studies suggested some efficacy (113, 117, 125, 252-258). However, the large placebo-controlled phase III GALACCTIC trial demonstrated that the IGF1R inhibitor linsitinib did not improve progression-free or overall survival (102).

Therefore, monotherapy with drugs targeting this pathway are not reasonable for therapy in an unselected patient population.

Table 6: Systemic therapies for recurrent / advanced ACC

First-line therapies (see text for details)

- **Surgery +/- other local measures (see R.8.1 and R.8.4)**

- **Mitotane monotherapy**
  - details on the management see section 5.9.

- **Etoposide, Doxorubicin and Cisplatin (EDP) plus Mitotane (EDP/M)** (30)
  every 28 days:
  day 1 40mg/m^2 doxorubicin (D)
  day 2 100mg/m^2 etoposide (E)
  day 3+4 100mg/m^2 etoposide (E) + 40mg/m^2 cisplatin (P)
  plus oral mitotane aiming at a blood level between 14-20mg/l.

  In patients unfit for the EDP-M regimen, (E)P-M may constitute a reasonable alternative.
  Every 28 days
  day 1 100mg/m^2 etoposide (E)
  day 2+3 100mg/m^2 etoposide (E) + 40mg/m^2 cisplatin (P)

Additional therapeutic options

- **Consider enrollment of patients in clinical trials (www.clinicaltrial.gov)**

- **Consider loco-regional therapies**

- **Gemcitabine plus capecitabine** (104, 124)
  800 mg/m^2 gemcitabine on day 1 and 8 (repeated every 3 weeks)
  1,500 mg capecitabine orally per day in a continuous fashion
  Mitotane can be continued (individualized decision)

- **Streptozotocin plus Mitotane (Sz/M) (30)**
  induction: day 1-5: 1g Sz/d
  afterwards 2g/d Sz every 21 days
  plus oral mitotane aiming at a blood level between 14-20mg/l

R.8.11. The optimal timing of mitotane discontinuation is currently unknown and the panel could not come to a specific recommendation on this issue.

Reasoning:

A recent cohort study reported that discontinuation of mitotane should be considered in patients who experienced progressive disease after one year of mitotane therapy (259). Part of the panel considers mitotane discontinuation when there is progressive disease despite mitotane blood levels above 14 mg/L while others often continue mitotane indefinitely in their practice. Tolerability of treatment is an important issue to consider in this decision. Moreover, it has to be considered that CYP3A4 induction by mitotane can greatly enhance metabolism of many drugs (260), including a number of experimental anti-ACC compounds, and so potentially limit their effectiveness.

5.9. Special considerations on mitotane

If mitotane therapy is started (independent of the clinical scenario) the following issues have to be considered.

R.9.1. We recommend starting therapy with mitotane in an escalating regimen depending on the performance status of the patient as well as the tolerability in the first weeks.

Reasoning

There are different regimens to administer mitotane, but none of them has been proven to be superior. In patients with good performance status some panelists use a high starting dose approach: mitotane is administered at a starting dose of 1.5 g/day and if well-tolerated from a gastrointestinal perspective the dose is increased on day two to 3 g/day, on day three to 4.5 g/day, and on day four to 6 g/day (261, 262). This dosage will be administered until first mitotane blood level is assessed. In this high dose regimen, it is strongly recommended to measure mitotane blood levels 2-3 weeks after initiation of therapy. Afterwards dosage will be adjusted according to blood concentrations and tolerability. Other panelists prefer a low starting dose approach. With this approach, mitotane is administered at a starting dose of 1 g/day and increased when there is good gastrointestinal tolerance every 3 days by 0.5 g up to a total dose of 3.0 - 4.0 g/day and then adjusted according to blood concentrations and tolerability (234, 263, 264).

In a formal comparative pharmacokinetic study, the high-dose starting regimen led to slightly higher mitotane plasma levels within 12 weeks of treatment, and more patients reached the target level of 14 mg/L (265). However, these results were not statistically significant due to lack of power. Beyond these two regimens, there is a variety of other possibilities and choice depends on personal practice, clinical scenario and patient conditions.

R.9.2. We recommend monitoring of blood concentration of mitotane. The general aim is to reach a mitotane blood level above 14 mg/L (+OOO).

Reasoning

As long as mitotane plasma levels are increasing and have not yet reached a plateau at >14mg/L, mitotane plasma levels will be assessed every 3-4 weeks. Mitotane plasma level determination is best done as morning trough sampling, at least 12 hours after the last dose, preventing false high levels (266). When mitotane plasma levels have reached a plateau, it is usually sufficient to measure blood levels every 6-12 weeks.

Usually it takes several weeks (sometimes months) to reach mitotane levels > 14 mg/L. As long as the concentration is < 14 mg/L it is reasonable to continue to increase the dosage if this is tolerated by the patient. Due to slow pharmacokinetic characteristics, the dose of mitotane can be reduced in most patients as soon as a plasma level of > 14mg/L is reached. Over time, mitotane dosage will be titrated to the best tolerable dose while maintaining a plasma level >14mg/L. Most patients experience adverse effects to a certain extent and these usually correlate with the plasma mitotane level (although there is major inter-individual variability). However, some gastrointestinal adverse effects (like diarrhea) seem to correlate more with the oral dosage than with the plasma level and occur more frequently in the first phase of treatment (146, 234, 263, 264, 267). Several studies (107, 112, 268) have shown

that CNS-related adverse events in particular occur more frequently when the plasma mitotane is > 20 mg/L. Therefore, many experts recommend aiming to keep plasma concentrations below 20 mg/L. However, it can be speculated that higher plasma levels may also be associated with better clinical efficacy. Furthermore, some patients do not experience relevant adverse events even at plasma levels well above 20 mg/L. Regarding the lower limit it has to be acknowledged that in at least a few patients objective responses are seen even though plasma levels of >14 mg/l were not achieved (230). Therefore, some panelists favored a target range of plasma mitotane of 8-30 mg/L, whereas others aim at an individualized target level of mitotane.

Most studies addressing plasma mitotane levels analyze patients with advanced disease. However, there is one study suggesting that the same target level is also reasonable for the adjuvant setting (233). Therefore, the panel is in favor to use the same approach for both patient groups.

R.9.3. We recommend glucocorticoid replacement in all patients treated with mitotane (except those with ongoing cortisol excess). We suggest to using hydrocortisone/cortisone acetate for this purpose. Due to increased steroid clearance and increase cortisol-binding globulin at least twice the standard replacement dose is usually required.

Reasoning

A possible strategy is to start concomitant treatment on day one of mitotane treatment with hydrocortisone 20 mg/d. Alternatively, patients can be instructed to start hydrocortisone later (e.g. after 2-3 weeks or in case they experience adrenal insufficiency), because impairment of glucocorticoid effectiveness is rarely observed within the first few weeks. Due to the increased clearance and increased cortisol-binding globulin (267, 269-271) with increasing mitotane plasma levels and based on clinical symptoms, the total hydrocortisone replacement dose will usually increased to a typical total daily dose of 50 mg in two or three divided doses. However, some patients require daily dosages up to 100 mg. There is no reliable laboratory marker to guide the optimal dosage of hydrocortisone (270, 272), which has to be based on clinical judgment similar to the management of patients with adrenal insufficiency (208). Mitotane-induced increase in cortisol binding globulin may confound interpretation of serum cortisol measurement. Some panelists measure plasma ACTH and use ACTH levels more than 2-fold of the upper limit of normal as evidence for insufficient glucocorticoid replacement.

In case of acute adverse events and/or hospital admission, patients should be treated intravenously with high-dose hydrocortisone (e.g. 100 mg TID) until resolution of symptoms.

Some patients experience symptoms and signs of insufficient mineralocorticoid activity (hyperkalemia, hyponatremia, hypotension, decreased wellbeing) despite full-dose substitution with hydrocortisone. In these patients, addition of fludrocortisone should be considered. Clinical judgment, electrolytes, and plasma renin concentration can be used for decision making whether to start fludrocortisone (146, 234, 264, 267).

R.9.4. We recommend regular monitoring of mitotane-induced adverse effects (Table 7) and to treat them appropriately (Table 8). To increase tolerability of mitotane, we suggest starting supportive therapy ideally before severe toxicity occurs.

Reasoning

In addition to adrenal insufficiency (see R.9.3.) mitotane treatment comes with a plethora of potential adverse events (267)(Table 2). Therefore, it is important to evaluate the patients regularly (e.g. in the first 6 months every 3-4 weeks, thereafter every 6-12 weeks).

Gastrointestinal adverse effects are frequent, particularly in the first months of therapy. Supportive therapy should include antiemetic and ant-diarrheal medication, as needed. Some centers even start supportive therapy at initiation of mitotane therapy. However, one has to be aware that nausea may also be a sign of adrenal insufficiency that needs recognition and appropriate treatment. Nevertheless, it should be emphasized that despite optimization of dosing schedules, the key factor influencing build-up of appropriate mitotane plasma levels is patient tolerability, so efforts should be made in order to optimize this.

In case of central nervous system (CNS) adverse effects grade 2 (moderate) and/or gastro-intestinal adverse effects grade 3 (severe, but not life-threatening), mitotane dose should be reduced by 1-1.5 gram/day. In case of CNS adverse effects grade 3 or any relevant grade 4 toxicity (life-threatening), and/or increase of liver enzymes >5 times baseline (except GGT), mitotane should be interrupted until significant improvement of symptoms occurs and be restarted at 50–75% of the last dose.

Assessment of thyroid hormone status (TSH, FT4, every 3 months) is advised as mitotane may induce a clinical picture similar to central hypothyroidism (267, 273), possibly through a direct effect on the pituitary gland or induction of thyroid hormone metabolism. Replacement therapy with levothyroxine can be considered for these patients.

In men with signs of hypogonadism, assessment of testosterone and sex hormone-binding globulin levels is warranted, as hypogonadism is common (267). Mitotane-induced increase in SHBG may confound interpretation of testosterone measurement. Testosterone supplementation may be considered in patients with low testosterone and symptoms of hypogonadism, but inhibition of 5-α reductase might prevent full activity of testosterone (269). Ovarian steroid synthesis is less affected but women in childbearing age treated with mitotane may develop multiple, and sometimes huge, ovarian cysts that may be painful and sometimes require treatment.

Cholesterol levels very frequently increase during mitotane treatment (274). Hypercholesterolemia can be treated with statin therapy using agents not metabolized by CYP3A4 (e.g. rosuvastatine or pravastatine). However, in most patients the risk of dying from ACC progression outweighs the risk of death from cardiovascular events. Thus, statin therapy might only be beneficial in patients with a good prognosis and who are treated in an adjuvant setting.

Psychological and social aspects of treatment should not be neglected, i.e., professional counseling may be warranted. Follow-up on patient's well-being may be performed by questionnaire-based assessment of toxicity upon the start of the treatment and by repeating this assessment every 3 months.

R.9.5. We recommend being aware of significant drug interactions of mitotane (e.g. due to strong induction of CYP3A4). All concomitant medication should be checked for CYP3A4 interactions and substituted for an alternative if necessary

and available. Other care-providers should be advised not to initiate other drug therapies without consultation.

Reasoning

A comprehensive (but not exhaustive) summary of relevant drug interactions with mitotane is provided in Kroiss et al. (260) and in the Appendix 7.

Table 7: Adverse effects during mitotane treatment*

Adverse Effect	Frequency
• Gastrointestinal: nausea, vomiting, diarrhea, anorexia	very common
• Adrenal insufficiency	very common
• CNS: lethargy, somnolence, vertigo, ataxia	very common
Confusion, depression, dizziness, decreased memory	common
• Increase of hepatic enzymes (in particular gamma-GT)	very common
• Liver failure	rare
• Hepatic microsomal enzyme induction with	
increased metabolism of glucocorticoids and other steroids	very common
and barbiturates, phenytoin, warfarin, and many other drugs (see Appendix 7)	common
• Increase in hormone binding globulins (CBG, SHBG, TBG, etc.)	very common
• Disturbance of thyroid parameters (interference with binding of T4 to TBG, total T4↓, free T4↓, TSH↓)	very common
• Hypercholesterolemia, hypertriglyceridemia	very common
• Primary hypogonadism in men	common
• Gynaecomastia	common
• Skin rash	common
• Prolonged bleeding time	common
• Leucopenia	common
• Thrombocytopenia, anemia	rare
• Autoimmune hepatitis	rare
• Cardiovascular: hypertension	very rare
• Ocular: blurred or double vision, toxic retinopathy, cataract, macular edema	very rare
• Hemorrhagic cystitis	very rare

**modified by the authors based on information published by the European Medicine Agency (EMEA): http://www.emea.eu.int and clinical experience*

Table 8: Monitoring during mitotane treatment

Parameter	Interval	Comment
Recommended monitoring		
Mitotane blood level	Every 3-4 weeks, as soon as plateau of blood level is reached every 2-3 months	Target blood level > 14 mg/L (details see R.9.2)
GOT, GPT, bilirubin, (gGT)	Initially every 3-4 weeks, after 6 months every 2-3 months	GGT is invariably elevated without clinical consequences. If other liver enzymes are rapidly increasing (> 5-fold of baseline), there is risk of liver failure: interrupt mitotane
Blood count	Initially after 3-4 weeks, then every 3-4 months	Check for rare and in most cases not significant leucopenia, thrombocytopenia, and anemia
Suggested monitoring		
ACTH	Suspected glucocorticoid deficiency or excess	Glucocorticoid status is difficult to determine Target: ACTH in the normal range or slightly above
TSH, fT4	Every 3 – 4 months	Disturbance of thyroid hormones is frequent. Thyroid hormone replacement is only recommended in patients with clinical symptoms of hypothyroidism
Renin	Every 6 months	If renin ↑ and clinical symptoms of hypoaldosteronism are present, add fludrocortisone
Cholesterol (HDL, LDL)	Every 3-4 months (in adjuvant setting)	If LDL / HDL cholesterol ↑↑ consider treatment with statins in selected cases.
Testosterone and SHBG in men	Every 3-4 months (in adjuvant setting)	If testosterone is low and clinical symptoms of hypogonadism are present add testosterone

5.10. Other supportive therapies

R.10.1. We recommend medical therapy to control hormone excess in all patients with clinically relevant hormone-producing ACC.

Reasoning

Overt glucocorticoid excess causes significant morbidity, such as diabetes, osteoporosis, muscle weakness and immunosuppression, conditions that can impact quality of life and increase mortality. Mitotane is effective in controlling adrenocortical hormone excess syndromes, but its efficacy is delayed by several weeks. In general, mild hormone secretion can be effectively managed by mitotane alone. However, severe Cushing syndrome needs a more rapid control. Furthermore, these patients should receive appropriate anticoagulation and also pneumocystis directed antibiotic prophylaxis until cortisol levels are safely controlled (275).

Available steroidogenic enzyme inhibitors and steroid receptor antagonists are able to attain quick reduction of cortisol effects. Anti-hormonal agents can be initiated together with mitotane. Once therapeutic mitotane levels are established, anti-steroidogenic action is also maximized, and other anti-hormonal drugs can be reduced guided by tolerability, symptoms and biochemical measurements. If possible doses should be titrated to normalization of hormone levels, or in the case of receptor antagonists to improved well-being, accepting that assessment of this can be challenging in cancer patients.

Despite the lack of comparative studies, the majority of panel members considers that metyrapone is the first therapeutic choice for the management advanced ACC patients with severe Cushing syndrome. The drug is well tolerated and can be safely administered in association with mitotane and cytotoxic chemotherapy (276). Moreover, its metabolism and elimination are not altered by concomitant mitotane. Ketoconazole an inhibitor of several key cytochrome P450 (CYP) enzymes involved in multiple steps of steroidogenesis in the adrenal

cortex, is another alternative, but often less effective than metyrapone and requires regular monitoring of liver function tests. Its advantage is that it also inhibits androgen production. Ketoconazole should be avoided at initiation of mitotane therapy because both substances are potentially hepatotoxic and it will be difficult to attribute the hepatotoxicity to one or the other drug. Hypercortisolemia can also be treated with mifepristone, a glucocorticoid antagonist, but dosing is based on clinical judgement as cortisol levels remain elevated or rise further on therapy (277). Moreover, the high circulating cortisol levels when on mifepristone may cause mineralocorticoid effects, including hypertension and hypokalemia that necessitate treatment with high doses of spironolactone. Patients treated with enzyme inhibitors or receptor antagonists need to be educated about symptoms and signs of adrenal insufficiency. All patients at risk for adrenal insufficiency need to be supplied with emergency medication and instructions. Intravenous etomidate can be used for seriously ill patients with severe hypercortisolemia who cannot take oral medication.

In the management of severe Cushing's syndrome, locoregional options (see R.8.2.) should also be discussed, in selected cases.

Androgen excess in women can impact quality of life due to hirsutism and virilization. It can be treated with androgen receptor antagonists, such as bicalutamide, flutamide, or spironolactone.

Only a small fraction of all tumors produce aldosterone, leading to hypertension and hypokalemia. Mineralocorticoid excess is best treated with mineralocorticoid receptor antagonists, such as spironolactone or eplerenone. However, patients with severe Cushing's syndrome may also experience hypokalemia, related to mineralocorticoid receptor activation. In case of severe hypokalemia, spironolactone and epithelial sodium channel inhibitors such as amiloride can be used, potentially at high doses, along with potassium supplementation. In such cases, frequent serum electrolyte measurement, initially several times a week, are mandatory, as there is a risk of rapid occurrences of hyperkalemia and hyponatremia.

In the rare situation of estradiol production by tumors in male patients, therapy with estrogen receptor antagonists or aromatase inhibitors could be considered.

R.10.2. We recommend therapy with anti-resorptive treatment in patients with bone metastasis.

Reasoning

Bone metastasis in cancer patients are associated with poor quality of life due to bone pain and increased risk of adverse skeletal-related events (SREs) such as pathological fractures, spinal cord compression and hypercalcemia. Several randomized phase III trials have demonstrated that bone resorption inhibitors such as bisphosphonates and denosumab are efficacious in the prevention of skeletal-related events in patients with bone metastasis from breast, prostate, lung and others primary malignancies. No data are available for ACC patients. However, based on these results, it has become general practice to treat patients with any kind of bone metastasis with anti-resorptive therapies. The administration of denosumab or bisphosphonates in 'oncological doses' in association with calcium intake and vitamin D supplementation are therefore advisable in ACC patients with metastatic bone disease, with the aim to prevent adverse skeletal-related events and improve control of bone pain.

In patients with ACC with Cushing's syndrome that cannot be otherwise controlled anti-resorptive treatment, using anti-osteoporotic doses, should be considered, because it is well

established that glucocorticoid-excess increases the risk of osteoporotic fractures. Since fracture risk declines rapidly after lowering excess cortisol, or antagonizing its effects, anti-osteoporotic therapies are usually not required once cortisol secretion is controlled (either by surgery or medical therapy).

R.10.3. We recommend palliative radiation for symptom palliation in advanced/metastatic ACC patients

Reasoning

Palliative radiation therapy is a commonly utilized intervention for symptom relief among patients with metastatic cancer. Two schedules of irradiation are commonly used, which include 8 Gy in a single fraction or 30 Gy in ten fractions. This treatment modality is highly effective in achieving relief of symptoms arising from bone metastases, with positive responses in up to 50% - 90% of cancer patients (278, 279). Painful bone metastases are, therefore, the main indication of palliative radiation in metastatic ACC patients (237). Other indications are symptomatic recurrences, severe mass effect and the rare case of brain metastases.

R.10.4. We recommend integrating palliative care into standard oncology care for all patients with advanced ACC

Reasoning

According to the WHO palliative care is defined as ‘an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual’ (WHO: WHO definition of palliative care. http://www.who.int/cancer/palliative/definition/en/).
As previously stated, the goal of care for metastasized ACC is to obtain long-term disease control and prolong patient survival. Although prognosis of patients with advanced ACC is often poor, there is a patient subset destined to obtain a relatively long survival, while treated with antineoplastic therapies. The needs of patients with cancer and their families have changed over time. According to the ASCO guidelines the best model to manage metastatic patients is to integrate palliative care early in the course of the disease and throughout the trajectory of care, extending to long-term survivorship as well as end-of-life (hospice) care. In this integrated approach the primary endocrinologists and oncologists focus on the primary oncologic disease, and the palliative care team addresses the majority of the patient’s physical and psychological concerns. The team plans all therapy aiming to integrate patient wishes and employ treatment options balancing quality of life and increased survival with therapy associated risks and complications (280).

R.10.5. We suggest counseling for fertility protection in female patients in reproductive age. Fertility counseling should not only be restricted to patients undergoing cytotoxic chemotherapy, but also given to patients who plan to embark on mitotane therapy.

Reasoning

A considerable proportion of patients are diagnosed with ACC during their reproductive years. Several drugs used to treat ACC harbor significant risk for impairment of fertility or the exact risks are unknown (e.g. mitotane). On the other hand, in recent years several treatment options for preservation of fertility have been introduced. However, none of them has gained general acceptance. Therefore, we just advise to discuss this topic with every patient. This discussion should include the consideration given in section 5.12. on pregnancy and ACC in general.

5.11. Genetic counseling

R.11.1. For adults with ACC, we recommend at least a basic clinical genetic evaluation, exploring personal and family history for evidence of a hereditary predisposition syndrome.

Reasoning

The detection of germline mutations impacts on the clinical care and surveillance of index patients and offers the possibility to identify at risk family members. Probably, up to 5% of adult ACC arise in patients with germline *TP53* mutations (281-283) and about 3% of all ACC patients have an underlying diagnosis of Lynch syndrome (11, 284). Special attention should be given to these two hereditary syndromes, because for them there are well-established screening guidelines available (285-289). Up to 13% of all adrenal lesions in patients with MEN1 represent adrenal cancer (22084155). Cases of ACC have been reported in patients with Beckwith-Wiedemann syndrome (children), Familial Adenomatous Polyposis (APC) and Carney Complex (4).

Germline genetic testing for ACC patients should primarily be considered for the genes related to Li-Fraumeni syndrome and Lynch syndrome. ACC is an integral part of Li-Fraumeni syndrome and when considering germline genetic testing, it is important to keep in mind that at least 20% of germline *TP53* pathogenic variants occur as de novo mutations in the absence of any family history. Lynch syndrome is present in the same fraction of ACC patients as in colorectal cancer patients (3-5%), where general screening for Lynch syndrome is recommended (285, 290). Both, Li-Fraumeni syndrome and Lynch syndrome have well established surveillance guidelines for carriers of pathogenic variants (285-289). Evaluation for Lynch syndrome can be initiated by immunohistochemistry for MSH2, MLH1, PMS2, MSH6 and microsatellite instability testing, or direct genetic germline analysis of *MSH2, MLH1, PMS2, MSH6* and *EPCAM*. Genetic diagnosis of Li-Fraumeni syndrome is usually done by germline analysis for variants in *TP53*. For other syndromes (depending on family history and clinical suspicion) we refer to other sources (4, 291).

Although not the topic of this guideline, all children with a diagnosis of ACC should undergo a systematic search of germline *TP53* pathogenic variants, because 50-90% of ACC in children are related to germline pathogenic *TP53* variants (292-294)

R.11.2. The panel does not recommend for or against genetic tumor testing for somatic alterations.

Reasoning

While the panel recognizes that there is great hope that testing for somatic mutations and other markers in cancers general may allow tailoring of therapy and personalized approaches for therapy, for ACCs this approach is not yet established in routine clinical practice. Therefore, molecular testing should be offered within the framework of structured and systematic research projects.

5.12. Pregnancy and ACC

R.12.1. When an adrenal mass suspected to be an ACC is diagnosed during pregnancy, we recommend prompt surgical resection regardless of pregnancy trimester.

Reasoning

Considering the poor prognosis of ACC and the importance of a prompt and complete surgical removal for prognosis, adrenal surgery should be pursued independent of the term of the pregnancy (295). Preterm delivery (especially in the third trimester) and pregnancy loss are obvious risks when surgery is performed. Therefore, the patient and their family, obstetric providers and the ACC care team must engage in an informed discussion considering disease prognosis and the risk to the mother and fetus as related to the underlying disease and interventional procedures. A shared decision-making after discussion of all options is imperative.

R.12.2. Patients should be informed on pregnancy-related concerns specific to the current or past diagnosis of ACC.

Reasoning

No evidence is available regarding how long patients should wait after the treatment of an ACC before they can safely consider pregnancy.

Importantly, the main concern is the poor prognosis of the malignant tumor and the potential that pregnancy could be a negative prognostic factor, possibly increasing the risk of recurrence. There is limited evidence that ACC occurring during pregnancy or in the postpartum period is associated with a worse prognosis than in non-pregnant women (296). The hypothesis that pregnancy could favor the development of a more aggressive variant of ACC was raised.

Due to the extreme paucity of information about this issue, it seems prudent to relay the information to the patient that there is a substantial risk of disease recurrence in the first years following the diagnosis of ACC.

Since ACC may express estrogen receptors and there are preclinical data showing that estrogen may facilitate tumor development and progression through cross-talk with the IGF pathway (297), contraceptive measures other than estrogen-containing preparations are preferred.

R.12.3. We recommend avoiding pregnancy while being on mitotane treatment.

Reasoning

The main concern with mitotane therapy is the potential of teratogenic effects, due to the suspicion that the drug may cross the placenta and cause adrenolytic activity on the human fetus. However, there are only few case reports of pregnancies when on mitotane therapy (298). Therefore, it is impossible to draw definitive conclusions about the safety of mitotane treatment or its associated risks. Woman treated with mitotane should ensure effective contraception to avoid pregnancy. Moreover, when mitotane treatment is discontinued, it seems wise to ensure undetectable mitotane plasma levels before considering pregnancy (299), which might take 3-12 months. In case a patient becomes pregnant while on mitotane therapy, the uncertainty regarding risks of mitotane for the fetus should be discussed. In case the patient wishes to continue pregnancy mitotane therapy should be withheld.

6. Future directions and recommended research

Due to the fact that the evidence for most of the recommendations provided in these guidelines is weak or even very weak, there are no doubts that major efforts are needed to improve diagnosis, treatment, and quality of life for patients with ACC.

Among many important research questions, we selected ten topics as particularly important. All of them can only be addressed in an international collaborative interdisciplinary manner.

1) Clinical response to the best available therapy (i.e. EDP + mitotane) for advanced ACC is very limited with an objective response rate of less than 25%. Therefore, we undeniably lack efficient drugs for treating this disease. Thus, identifying new therapeutic targets and options is a high priority. Here is a comprehensive but by far not complete list of emerging therapies: internal radionuclide therapy, such as metomidate-based therapies; drugs targeting the following pathways or targets: Wnt/beta-catenin; CDKN2A / TP53 / RB; IGF2 / mTOR; telomeres; drugs targeting histone modifications. In general, a combined approach seems to be reasonable. There is a growing notion that individual patients and individual tumors might respond better to certain therapies, depending on their molecular landscape. Therefore, studies focusing on subgroup classification and identification is important. Due to the mitotane-associated pharmacological issues (e.g. CYP3A4 induction), it might be reasonable to test experimental drugs in mitotane-naïve patients within clinical studies.
2) Immunotherapy is the latest revolution in cancer therapy, however preliminary data with single immune check point inhibitors showed a modest activity in ACC patients. Molecular and oncogenic pathways either in tumor cells or tumor microenvironment that can impair induction or execution of a local antitumor immune response should be carefully studied in ACC.
3) Since currently available systemic therapies have limited efficacy, but a subgroup of patient is destined to obtain a consistent benefit from them, the identification of predictive markers of efficacy (either clinical or molecular) of standard treatments is of paramount importance in order to spare toxic regimens to patients not destined to obtain a disease response.

4) With regards to improvement of surgery for ACC, standardization of procedures (e.g. laparoscopic vs. open surgery, lymph node dissection) should be promoted and tested in clinical trials.
5) The high recurrence rate in the majority of patients even after complete resection calls for improvement of adjuvant therapy. There are significant gaps in our understanding, which patients might truly benefit from the different adjuvant therapies and prospective trials are urgently needed. The ongoing ADIUVO trial will hopefully provide important information for low/intermediate risk patients, but a trial in high-risk patients (e.g. mitotane vs. mitotane + cisplatin + etoposide) is equally important.
6) Despite extensive efforts, the mechanism of action and pharmacodynamics of mitotane remain poorly understood (300-303). In addition, mitotane is a strong inducer of xenobiotics metabolism, probably negatively impacting subsequent and parallel therapies. Therefore, further understanding and improving the pharmacology and mechanism of action of mitotane with the goal of development of mitotane related drugs that do not share the negative adverse-effects would be a significant goal.
7) Translational research with the goal of rational treatment stratification should be promoted. Recent molecular classifications, identifying distinct molecular subtypes with different outcomes, should be tested prospectively. These markers could provide a cornerstone for stratifying treatment strategies. This would mean that some patients of the 'better outcome' molecular group might benefit from forgoing any adjuvant therapy. Reversely, patients in the "poor outcome" molecular group could be included in a randomized trial testing mitotane + cytotoxic drugs as an adjuvant therapy. In addition, it will be important to define differences in pharmacogenomics or tumor genomics that define exceptional responders to mitotane and/or EDP. This data can fuel further sub-stratification of ACC patients for certain therapies.
8) In addition to improving treatment, other future research directions may include the use of artificial intelligence in diagnostic work-up of adrenal tumors and the improvement of screening and follow-up procedures using non-invasive techniques such as urine or serum steroid metabolomics (304-307) or 'liquid biopsies' with circulating tumor cells (308), circulating miRNAs (309-311), or circulating cell-free tumor DNA (312, 313) for early diagnosis or detection of recurrence.
9) In the long term, a better understanding of the pathogenesis of ACC is needed to pave the way for future progress. Therefore, basic research efforts have to continue. Preclinical models are needed, to test new treatments, including additional new cell lines, tumor organoids, and new animal models. Mechanisms of tumorigenesis, tumor evolution (genetic heterogeneity, clonal evolution) and further definition of known and future therapeutic targets should be encouraged.
10) No studies so far have revealed the wishes and experiences of patients. Given the poor prognosis and the toxic therapies, there is a definite need for 'Patient Related Outcomes'. PRO's should be measured (PROM's) and incorporated in our strategy for value based cure and care.

In general, it is our common task to overcome the major limitation in ACC research – the rarity of this disease. Therefore, beyond proofs of concept requiring few patients, clinical trials can only be performed if a large number of centers gather multicenter studies. This underscores the critical role of adrenal research networks, such as ENSAT or A5, to coordinate these efforts. Ideally a limited number of large prospective trials should continuously be ongoing, in order to allow for sufficient patient recruitment. In the same

context we envision that at least one reference center in every country will be established to provide multidisciplinary expertise for this rare disease to all patients.

Altogether, owing to its rarity and its severity, ACC should continue to mobilize researchers, physicians and patients in a coordinated engaged effort.

Appendices

- Appendix 1: Question 1: Pathology - what is needed to diagnose an ACC? Summary of included studies (1a: distinguishing adrenal from non-adrenal tumors; 1b: distinguishing benign from malignant behavior in adrenal tumors)
- Appendix 2: Question 2: Which are the best prognostic markers in ACC? Summary of included studies
- Appendix 3: Question 2: Prognostic factors in ACC - overview of studies markers
- Appendix 4: Question 3: Is adjuvant therapy able to prevent recurrent disease or reduce mortality after radical resection? Summary of included studies (3a: Adjuvant mitotane after surgery; 3b: Adjuvant radiotherapy after surgical resection)
- Appendix 5: Evidence tables Question 3 (adjuvant therapy)
- Appendix 6: Question 4: What is the best treatment option for macroscopically incompletely resected, recurrent or metastatic disease? Summary of included studies
- Appendix 7: Summary of relevant drug interactions with mitotane

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