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(Article begins on next page)

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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1 **Abstract**

2
3 Adrenocortical carcinoma (ACC) is a rare and in most cases steroid hormone producing
4 tumor with variable prognosis. The purpose of these guidelines is to provide clinicians with
5 best possible evidence-based recommendations for clinical management of patients with
6 ACC based on the GRADE (Grading of Recommendations Assessment, Development and
7 Evaluation) system. We predefined four main clinical questions, which we judged as
8 particularly important for the management of ACC patients and performed systematic
9 literature searches: (A) What is needed to diagnose an ACC by histopathology? (B) Which
10 are the best prognostic markers in ACC? (C) Is adjuvant therapy able to prevent recurrent
11 disease or reduce mortality after radical resection? (D) What is the best treatment option for
12 macroscopically incompletely resected, recurrent or metastatic disease? Other relevant
13 questions were discussed within the group. **SELECTED RECOMMENDATIONS:** (i) We
14 recommend that all patients with suspected and proven ACC are discussed in a
15 multidisciplinary expert team meeting (ii) We recommend that every patient with (suspected)
16 ACC should undergo careful clinical assessment, detailed endocrine work-up to identify
17 autonomous hormone excess, and adrenal-focused imaging. (iii) We recommend that
18 adrenal surgery for (suspected) ACC should be performed only by surgeons experienced in
19 adrenal and oncological surgery aiming at a complete en-bloc resection (including resection
20 of oligo-metastatic disease). (iv) We suggest that all suspected ACC should be reviewed by
21 an expert adrenal pathologist using the Weiss score and providing Ki67 index. (v) We
22 suggest adjuvant mitotane treatment in patients after radical surgery that have a perceived
23 high risk of recurrence (ENSAT stage III, or R1 resection, or Ki67 >10%). (vi) For advanced
24 ACC not amenable to complete surgical resection, local therapeutic measures (e.g. radiation
25 therapy, radiofrequency ablation, chemo-embolization) are of particular value. However, we
26 suggest against the routine use of adrenal surgery in case of widespread metastatic disease.
27 In these patients we recommend either mitotane monotherapy or mitotane, etoposide,
28 doxorubicin, and cisplatin depending on prognostic parameters. In selected patients with a
29 good response, surgery may be subsequently considered. (vii) In patients with recurrent
30 disease and a disease-free interval of at least 12 months, in whom a complete
31 resection/ablation seems feasible, we recommend surgery or alternatively other local
32 therapies. Furthermore, we offer detailed recommendations about the management of
33 mitotane treatment and other supportive therapies. Finally, we suggest directions for future
34 research.

35 **1. Summary of recommendations**

36
37 *After the review process all Recommendations without Rational will be provided here as*
38 *summary.*

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40
41 **2. Adrenocortical Carcinoma – epidemiology, pathogenesis, clinical**
42 **presentation, and general prognosis**

43 *Epidemiology and pathogenesis*

44
45 The estimated incidence of adult adrenocortical carcinoma (ACC) is between 0.7 – 2.0 per
46 million per year {Kebebew, 2006 #3;Kerkhofs, 2013 #2}. ACC can occur at any age with a
47 peak incidence between 40 and 60 years, and with women being more often affected (55-
48 60%). In adults, the vast majority of ACCs are sporadic. Occasionally, however, they occur
49 as part of hereditary syndromes such as Li-Fraumeni syndrome, Lynch syndrome, multiple
50 endocrine neoplasia (MEN) 1 and familial adenomatous polyposis {Berruti, 2012 #20;Petr,
51 2016 #34}. In recent years several multi-center studies have shed light on the pathogenesis
52 of ACC {de Reynies, 2009 #14;Fragoso, 2012 #18;Ronchi, 2013 #324}{Jouinot, 2017 #17},
53 but ‘multi-omic’ studies {Assie, 2014 #12;Juhlin, 2015 #19;Zheng, 2016 #16} reveal that only
54 a minority of ACC cases have pathogenic driver mutations. For details on this topic we refer
55 to recent reviews {Assie, 2014 #11;Else, 2014 #135;Faillot, 2016 #277}.

56
57 *Clinical presentation (Table 1)*

58 ACC may present with autonomous adrenal hormone excess or with symptoms caused by
59 an abdominal mass. An increasing number of cases are diagnosed within the group of
60 incidentally discovered adrenal masses (incidentalomas) (\approx 10-15%). However, the likelihood
61 of an adrenal incidentaloma being an ACC is low {Terzolo, 1997 #359;Cawood, 2009
62 #326;Fassnacht, 2016 #46}. About 50-60% of patients with ACC have clinical hormone
63 excess. Hypercortisolism (Cushing’s syndrome), or mixed Cushing’s and virilizing syndromes
64 are observed in the majority of these patients. Pure androgen excess is less frequent while
65 estrogen or mineralocorticoid excess are very rare {Seccia, 2005 #360;Fassnacht, 2011
66 #61;Else, 2014 #135;Berruti, 2014 #35;Kerkhofs, 2015 #78;Fassnacht, 2013 #60}. Non-
67 specific symptoms from an abdominal mass include abdominal discomfort (nausea, vomiting,
68 abdominal fullness) or back pain. Classical malignancy-associated symptoms such as weight
69 loss, night sweats, fatigue or fever are rarely present.

70
71 **Table 1: Clinical presentation of ACC#**

72

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 %

73 # number derived from: {Berruti, 2014 #35;Fassnacht, 2009 #56;Johanssen, 2010 #69}, and the
74 ENSAT ACC registry

75 * frequently combined

76

77 *General prognosis*

78 The median overall survival of all ACC patients is about 3-4 years. The prognosis is,
79 however, heterogeneous. Complete surgical resection provides the only means of cure. In
80 addition to radical surgery, disease stage, proliferative activity/tumor grade, and cortisol
81 excess are independent prognostic parameters (see also section 4.2. and 5.5.). Five-year
82 survival is 60-80% for tumors confined to the adrenal space, 35-50% for locally advanced
83 disease, and much lower in case of metastatic disease with reported percentages ranging
84 from 0% to 28% {Icard, 2001 #79; Bilimoria, 2008 #80; Sturgeon, 2006 #81; Fassnacht, 2010
85 #57; Fassnacht, 2009 #58; Fassnacht, 2011 #61; Fassnacht, 2012 #28; Kerkhofs, 2015 #78}.

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89 **3. Methods**

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91 **3.1. Guideline working group**

92 This guideline was developed by The European Society of Endocrinology (ESE) in
93 collaboration with the European Network for the Study of Adrenal Tumours (ENSAT). The
94 chairs of the working group Martin Fassnacht and Massimo Terzolo as well as the
95 methodological expert Olaf Dekkers were appointed by the ESE Clinical Committee. Tobias
96 Else served as representative of The Endocrine Society, USA, and Radu Mihai as
97 representative of the European Society of Endocrine Surgeons. The other members were
98 suggested by the chairs and approved by the Clinical Committee of ESE. The
99 multidisciplinary team consisted of the following experts: endocrinologists (Guillaume Assie
100 (France), Olaf Dekkers (The Netherlands), Tobias Else (USA), Martin Fassnacht (Germany),
101 Harm Haak (The Netherlands), Massimo Terzolo (Italy), oncologists (Eric Baudin (France),
102 Alfredo Berruti (Italy), a pathologist Ronald de Krijger (The Netherlands), and an endocrine
103 surgeon Radu Mihai (UK). The working group had three in-person meetings (November
104 2016, September 2017, and March 2018) and communicated by phone and email.
105 Consensus was reached upon discussion; minority positions were taken into account in the
106 rationale behind recommendations. Prior to the process, all participants completed conflict of
107 interest forms.

108

109 **3.2 Target group**

110 This guideline was developed for healthcare providers involved in the care of patients with
111 adrenocortical carcinoma *i.e.*, endocrinologists, oncologists, surgeons, radiologists, nuclear
112 medicine physicians, radio-oncologists, pathologists, specialists in general internal medicine,
113 and nurse specialists. However, general practitioners or gynecologists or dermatologists
114 (who are involved in the diagnostic of androgen excess) might also find the guideline useful,
115 as might our patients. In addition, the guideline document can serve as a source document
116 for the preparation of patient information leaflets.

117

118 **3.3 Aims**

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

123 some countries not all recommended tests and treatments, or both, might be available. Thus,
124 the recommendations have certainly be interpreted in the context of available
125 resources/treatment in the community, in which the patient is being seen.

126
127

128 **3.4 Summary of methods used for guideline development**

129 The methods used have been described in more detail previously {Bollerslev, 2015 #1}. In
130 short, the guideline used GRADE (Grading of Recommendations Assessment, Development
131 and Evaluation) as a methodological base. The first step was to define clinical question(s)
132 (see section 3.5), the second being a systematic literature search (see Section 3.6). After
133 including all relevant articles, we 1), rated the quality of the evidence, and 2) estimated an
134 average effect for specific outcomes (if possible). The quality of evidence behind the
135 recommendations is classified as very low (+OOO), low (++OO), moderate (+++O) and
136 strong (++++).

137 For the recommendations we took into account: 1) quality of the evidence, 2) balance of
138 desirable and undesirable outcomes, 3) values and preferences (patient preferences, goals
139 for health, costs, management inconvenience, feasibility of implementation, etc) {Andrews,
140 2013 #137;Andrews, 2013 #138}. The recommendations are worded as recommend (strong
141 recommendation) and suggest (weak recommendation). The meaning of a strong
142 recommendation can be stated as follows: reasonably informed persons (clinicians,
143 politicians and patients) would want the management in accordance with the
144 recommendation. For a weak recommendation, most persons would still act in accordance
145 with the guideline, but a substantial number would not {Andrews, 2013 #138}. Formal
146 evidence syntheses were performed and graded only for recommendations addressing our
147 initial four questions. Recommendations based on good practice and experience of the
148 panelists were not graded {Guyatt, 2015 #139}. Recommendations were derived from
149 majority consensus of the guideline development committee, but if at least one member had
150 substantial disagreements, this is acknowledged in the manuscript. If two or more panelists
151 did not agree with a recommendation, this was considered as not consensus. For
152 transparency, all recommendations are accompanied by text explaining why specific
153 recommendations were made.

154

155 **3.5. Clinical question, eligibility criteria and endpoint definition**

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

160

161 **3.6 Description of search and selection of literature**

162 A literature search of electronic medical databases was performed for all four clinical
163 questions. As we expected that single publications could contribute to different questions (for
164 example 2 and 4) we decided to perform one overarching search using broad search terms.
165 The search revealed 5988 papers, of which 615 were duplicates. In summary, we included
166 18 publications for clinical question 1 (diagnostics for ACC), 35 studies for clinical question 2
167 (prognosis), 10 publications for clinical question 3 (adjuvant therapy) and 48 publications for
168 clinical question 4 (recurrent/advanced disease). The review of hormonal overproduction as
169 prognostic factor was published as stand-alone paper {Vanbrabant, 2018 #140}. For question
170 3, we included one study after having been provided with baseline characteristics and

171 adjusted estimates for mitotane therapy not reported in the original publication {Bertherat,
172 2007 #82}.

173

174

175 **3.7. Review process and endorsement of other societies**

176 A draft of the guideline was reviewed by four experts in the field (see “Acknowledgment’
177 section) and has been submitted for comments by ESE and ENSAT members. In addition,
178 the following societies and networks were asked for review and finally endorsed the
179 guidelines: the European Society of Endocrine Surgeons, the Endocrine Society, USA, the
180 European Society of Pathology, the American-Australian-Asian Adrenal Alliance (A5), the
181 European Reference Network on Rare Endocrine Conditions (Endo-ERN), the European
182 Reference Network on Rare Adult Solid Cancers (ERN EURACAN). Furthermore, patient
183 groups were approached to review the guidelines. All comments and suggestions were then
184 discussed and implemented as appropriate by the panel (all comments and responses are
185 provided in Appendix 8).

186

187 **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
<p>Question 1:</p> <p>Pathology - what is needed to diagnose an ACC?</p> <p>Sub-question 1A: How to make a distinction between adrenocortical/non-adrenocortical tumor?</p> <p>Sub-question 1B How to make a distinction between benign or malignant or indeterminate behavior in adrenocortical tumors</p>	<p>Population</p> <ul style="list-style-type: none"> • Adrenal masses <p>Restriction</p> <ul style="list-style-type: none"> • Minimum 25 ACC patients • Each marker has to be reported in at least 2 independent cohorts <p>Outcome</p> <ul style="list-style-type: none"> • Diagnostic accuracy (Sensitivity/specificity/NPV/PPV) <p>Diagnostic marker:</p> <ul style="list-style-type: none"> • (Weiss Score), Ki67, reticulin, Helsinki, SF-1, melan A, inhibin, calretinin, chromogranin, SRC1 <p>Reference standard:</p> <ul style="list-style-type: none"> • Weiss-Score¹ • Recurrence 	<p>Number of papers included:</p> <p>1a: n=4</p> <p>1b: n=15</p> <p>(2 papers contributed to both)</p>
<p>Question 2:</p> <p>Which are the best prognostic markers in ACC?</p>	<p>Population (minimum 100 ACC patients):</p> <ol style="list-style-type: none"> 1) Patients after radically resected ACC 2) Patients with advanced ACC <p>Restriction:</p> <ul style="list-style-type: none"> • Prognostic marker has to be reported in at least 2 independent cohorts <p>Prognostic markers to be considered:</p> <ul style="list-style-type: none"> • Tumor stage (different systems: Sullivan, Lee, UICC, ENSAT, etc.), sex, age, Ki67, hormone section, Weiss score, mitotic index, R status, molecular/immunohistological markers <p>Outcome</p> <ul style="list-style-type: none"> • Overall survival, disease-free and progression-free survival, prognostic ability 	<p>Number of papers included: 35</p>
<p>Question 3:</p> <p>Is adjuvant therapy able to prevent recurrent disease or reduce mortality after radical resection?</p>	<p>Population:</p> <ul style="list-style-type: none"> • Diagnosis of ACC with macroscopic radical resection (R0, R1, Rx) <p>Restriction:</p> <ul style="list-style-type: none"> • 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 	<p>Number of papers included:</p> <p>Mitotane n=6</p> <p>Radiation therapy n=4</p>

	<p>Intervention:</p> <ul style="list-style-type: none"> • Adjuvant treatment with either mitotane, radiation therapy or cytotoxic chemotherapy <p>Control group:</p> <ul style="list-style-type: none"> • Without therapy or other treatment <p>Outcomes:</p> <ul style="list-style-type: none"> • Disease-free survival, overall survival, quality of life, adverse events 	
<p>Question 4:</p> <p>What is the best treatment option for macroscopically incompletely resected, recurrent or metastatic disease?</p>	<p>Population:</p> <ul style="list-style-type: none"> • Macroscopically incompletely resected, recurrent or metastatic ACC <p>Restriction:</p> <ul style="list-style-type: none"> • Studies > 10 patients in the intervention group. Only studies providing baseline data per treatment group <p>Interventions</p> <ul style="list-style-type: none"> • Cytotoxic drugs including mitotane, surgery, radiation therapy, radiofrequency ablation, chemoembolization <p>Control</p> <ul style="list-style-type: none"> • Not mandatory (single arm cohort studies eligible) <p>Outcome</p> <ul style="list-style-type: none"> • Overall survival, progression-free survival, tumor response, quality of life, adverse events 	<p>Number of papers included:</p> <p>cytotoxic drugs including mitotane: n=27</p> <p>surgery: n= 16</p> <p>radiation therapy: n=1</p> <p>radiofrequency ablation: n=1</p> <p>radionuclide therapy: n=1</p>

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189 *NPV negative predictive value, PPV positive predictive value, SF-1 steroidogenic factor 1, SRC1 steroid receptor coactivator 1, R status Resection status, R0*

190 *microscopically complete resection, R1 microscopically incomplete resection, Rx uncertain resection status*

191 *¹ we are aware that the Weiss score was never properly validated, but we decided that there is no other “gold standard”*

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4. Summary and conclusions from systematic literature reviews

4.1. Clinical question 1: Pathology

We included 17 publications {Blanes, 2007 #141;Creemers, 2016 #142;Erickson, 2001 #143;Arola, 2000 #144;Aubert, 2002 #108;Busam, 1998 #146;Kamio, 1990 #148;Komminoth, 1995 #149;Pan, 2005 #150;Rubin, 2016 #151;Sbiera, 2010 #15;Stojadinovic, 2003 #152;Volante, 2006 #153;Wajchenberg, 2000 #154;Wang, 2014 #155;Zhang, 2008 #156;Kovach, 2015 #353} 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 {Arola, 2000 #144;Pan, 2005 #150}). Details of studies are shown in Appendix 1 (in all samples, diagnosis based on histological examination). 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 {Amini, 2016 #157;Asare, 2014 #158;Assie, 2007 #114;Ayala-Ramirez, 2013 #160;Berruti, 2014 #35;Beuschlein, 2015 #50;Bilimoria, 2008 #80;Canter, 2013 #164;Duregon, 2017 #110;Erdogan, 2013 #55;Ettaieb, 2016 #117;Fassnacht, 2009 #58;Freire, 2013 #169;Gicquel, 2001 #170;Glover, 2015 #171;Gonzalez, 2007 #172;Icard, 2001 #79;Jouinot, 2017 #17;Kebebew, 2006 #3;Kendrick, 2002 #176;Kim, 2016 #177;Kim, 2017 #178;Libe, 2015 #29;Livhits, 2014 #180;Lucon, 2002 #181;Margonis, 2016 #182;Margonis, 2016 #183;Millis, 2015 #184;Paton, 2006 #185;Pennanen, 2015 #109;Schulick, 1999 #187;Tran, 2016 #188;Xiao, 2015 #189;Zini, 2009 #190;Ronchi, 2012 #321}(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 {Macfarlane, 1958 #281;Sullivan, 1978 #282;Lee, 1995 #283;DeLellis, 2004 #284;Asare, 2014 #158;Miller, 2010 #90;Lughezzani, 2010 #92;Fassnacht, 2009 #58;Libe, 2015 #29;Lam, 2017 #285}. In a formal comparison, the ENSAT staging {Fassnacht, 2009 #58} was slightly superior to the UICC staging {Lughezzani, 2010 #92}. 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

241 1.18-2.47 {Vanbrabant, 2018 #140}. Ki67 was studied in five publications, showing worse
242 prognosis with increasing Ki67 in all studies. Other molecular markers have been studied in
243 single cohorts only (Appendix 2+3).

244 It is important to mention that relative risks, even if statistically significant, cannot inform
245 clinical decision making unless translated into predictive values or incorporated in prediction
246 models. Only one study presented a formal prediction model (including the variables tumor
247 size, stage, mitotic index, venous invasion, and endocrine activity), showing a sensitivity of
248 0.91 and a specificity of 0.90 {Freire, 2013 #169} Another study provided nomograms to
249 facilitate prognosis in individual patients {Kim, 2016 #177}. None of these models, however,
250 has been validated externally.

251

252 **4.3. Clinical question 3: Adjuvant therapy**

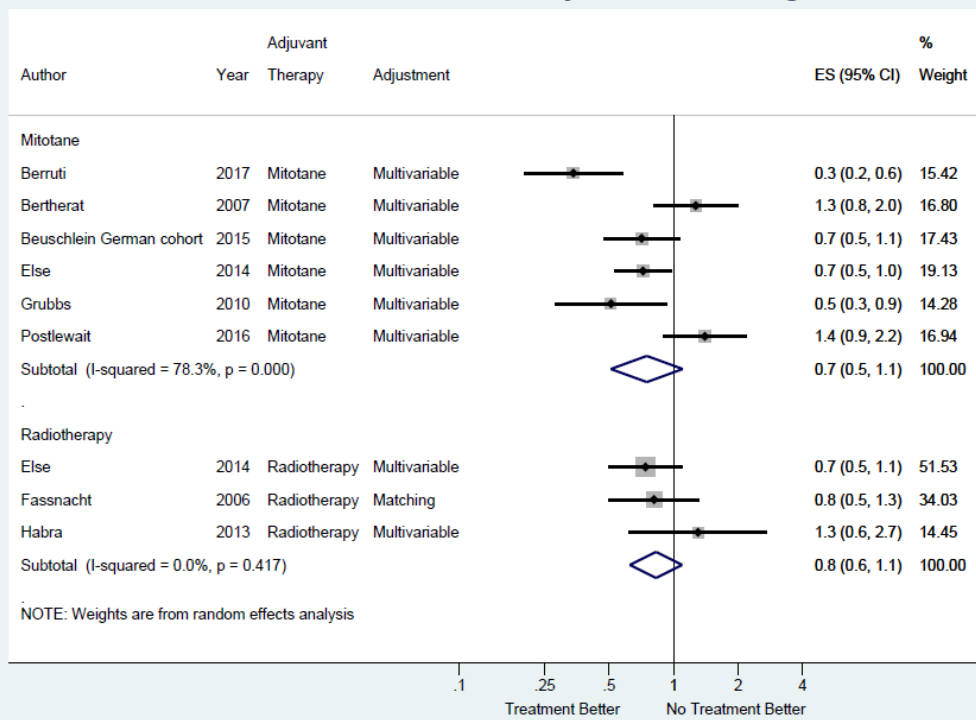
253 No randomized clinical trial has been published yet exploring adjuvant therapies; no studies
254 comparing quality of life after different treatment modalities were found. We included six
255 studies that assessed the effect of mitotane on recurrence and mortality {Berruti, 2017
256 #22;Bertherat, 2007 #82;Beuschlein, 2015 #50;Else, 2014 #125;Grubbs, 2010
257 #191;Postlewait, 2016 #192}. See Appendix 4 for details and Appendix 5 for risk of bias
258 assessment. Due to an overlap of the study population of >25% between studies {Berruti,
259 2017 #22;Bertherat, 2007 #82;Beuschlein, 2015 #50} only the German study cohort from
260 Beuschlein et al. was considered, but not the validation cohort {Beuschlein, 2015 #50}. In
261 one study, forty-seven patients were enrolled in 4 Italian centers where adjuvant mitotane
262 was routinely recommended, 55 patients in 4 Italian centers where no adjuvant strategy was
263 undertaken (control group 1), and 75 German patients left untreated after surgery (control
264 group 2) {Berruti, 2017 #22;Terzolo, 2007 #33}. However, only the most recent update of
265 these series was included in the analysis {Berruti, 2017 #22}. In order to avoid counting data
266 twice only control group 1 was included.

267 In a meta-analysis the pooled hazard ratio for recurrence was 0.7, 95%CI 0.5-1.1; for
268 mortality (5 studies) the pooled hazard ratio was 0.7, 95%CI 0.5-0.9 (Figure 1). All six studies
269 were non-randomized with the potential of a (residual) confounding effect, meaning that
270 treatment choices are based on prognosis (such as performance status of the patient, tumor
271 stage etc.), which introduces imbalance in prognostic factors. It is known that when studying
272 therapeutic effects this confounding effect is difficult to remedy statistically {Bosco, 2010
273 #193}. One study {Berruti, 2017 #22} circumvented the confounding effect by comparing two
274 treatment strategies applied in different settings; such comparison relies on other
275 assumptions {Hernan, 2006 #354}. A further bias in this context is immortal time bias, which
276 can occur if treatment is initiated after follow-up time starts and this is not accounted for in
277 the analysis. Such biases tend to overestimate treatment effects {Suissa, 2008 #194}, and
278 were not explicitly accounted for in most studies. Only one study applied a landmark analysis
279 to address this bias {Berruti, 2017 #22}. The overall quality rating was very low (+OOO).

280 Four studies assessed the impact of adjuvant radiation therapy {Fassnacht, 2006
281 #126;Habra, 2012 #123;Else, 2014 #125;Sabolch, 2015 #127}. See Appendix 4 for details
282 and Appendix 5 for risk of bias assessment. The study by Sabolch et al. {Sabolch, 2015
283 #127} was only considered for data on local recurrence, not for recurrence and mortality
284 given the overlap with another study of the same group {Else, 2014 #125}. All but one study
285 (59 patients treated with adjuvant radiation therapy {Else, 2014 #125} were small. We found
286 a pooled hazard ratio of 0.8 (95% CI 0.6-1.1) for recurrence and for mortality of 1.0 (95% CI
287 0.7-1.5)(Figure 1). The pooled hazard ratio for local recurrence (three studies) after treatment
288 with radiotherapy was 0.3 (93% CI 0.1-1.9).

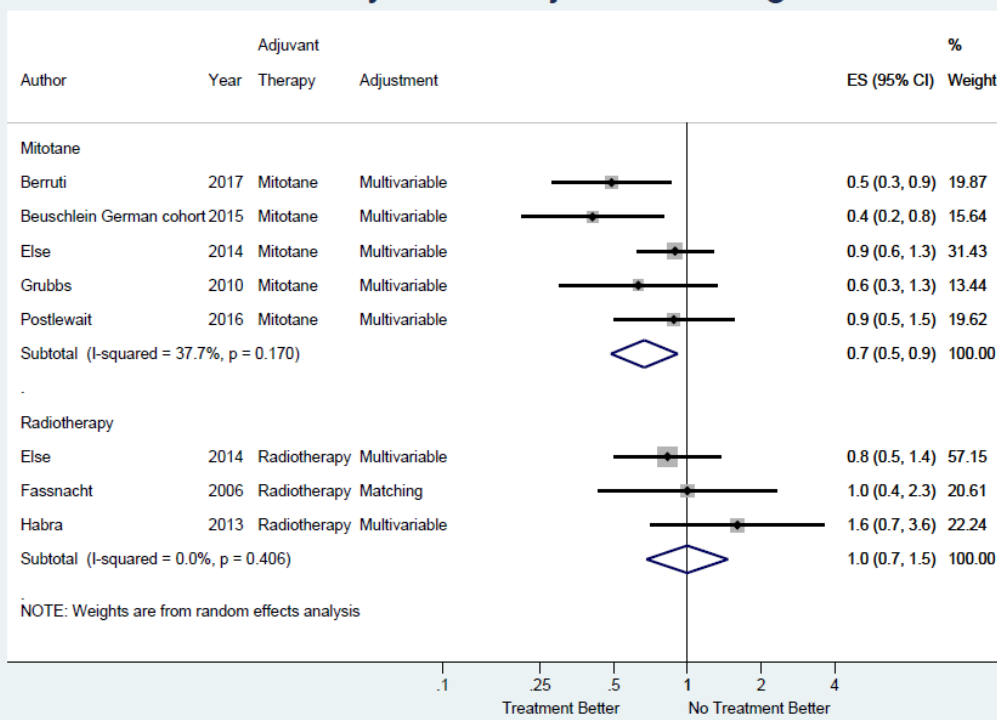
289 All studies were observational with the potential of (residual) confounding effects, immortal
 290 time bias was not explicitly accounted for in most studies, and the studies were small with
 291 imprecise effect estimates; the overall quality rating was therefore very low (+000).

Recurrence in the adjuvant setting



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Mortality in the adjuvant setting



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

300 **4.4. Question 4: Therapy for advanced or recurrent disease.**

301 A total of twenty-seven publications reported outcomes of 29 different systemic therapies for
302 advanced or recurrent ACC {Berruti, 2005 #24; Fassnacht, 2015 #27; Fassnacht, 2012
303 #28; Gonzalez, 2007 #172; Hermsen, 2011 #68; Sperone, 2010 #32; Abraham, 2002
304 #195; Baudin, 2002 #196; Baudin, 2001 #197; Berruti, 2012 #23; Bonacci, 1998
305 #199; Bukowski, 1993 #200; Decker, 1991 #201; Haak, 1994 #202; Haluska, 2010 #204; Khan,
306 2004 #205; Kroiss, 2016 #206; Kroiss, 2012 #207; Naing, 2013 #208; O'Sullivan, 2014
307 #209; Quinkler, 2008 #74; Schlumberger, 1991 #211; Urup, 2013 #212; Williamson, 2000
308 #213; Wortmann, 2010 #214; Henning, 2017 #215; Lerario, 2014 #216}; two were randomized
309 controlled trials ({Fassnacht, 2015 #27; Fassnacht, 2012 #28}; see Appendix 6 for details of
310 studies included). The first randomized trial compared mitotane plus a combination of
311 etoposide, doxorubicin, and cisplatin (EDP-M) to mitotane plus streptozocin in 204 patients
312 with advanced ACC {Fassnacht, 2012 #28}. The trial showed a positive effect of EPD-M on
313 progression-free survival HR 0.55 (95% CI, 0.43 to 0.69; P<0.001), but failed to show a
314 significant effect on mortality (HR 0.79; 95% CI, 0.61 to 1.02; p=0.07); (+++O). The second
315 randomized trial compared linsitinib to placebo (total 139 patients, 2:1 randomization to
316 therapy) and did not show a clear effect on either progression free (HR 0.83, 95% CI 0.56–
317 1.21; p=0.30) or overall survival (HR 0.94; 95%CI 0.61–1.44; p=0.77){Fassnacht, 2015 #27};
318 (+++O).

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

329

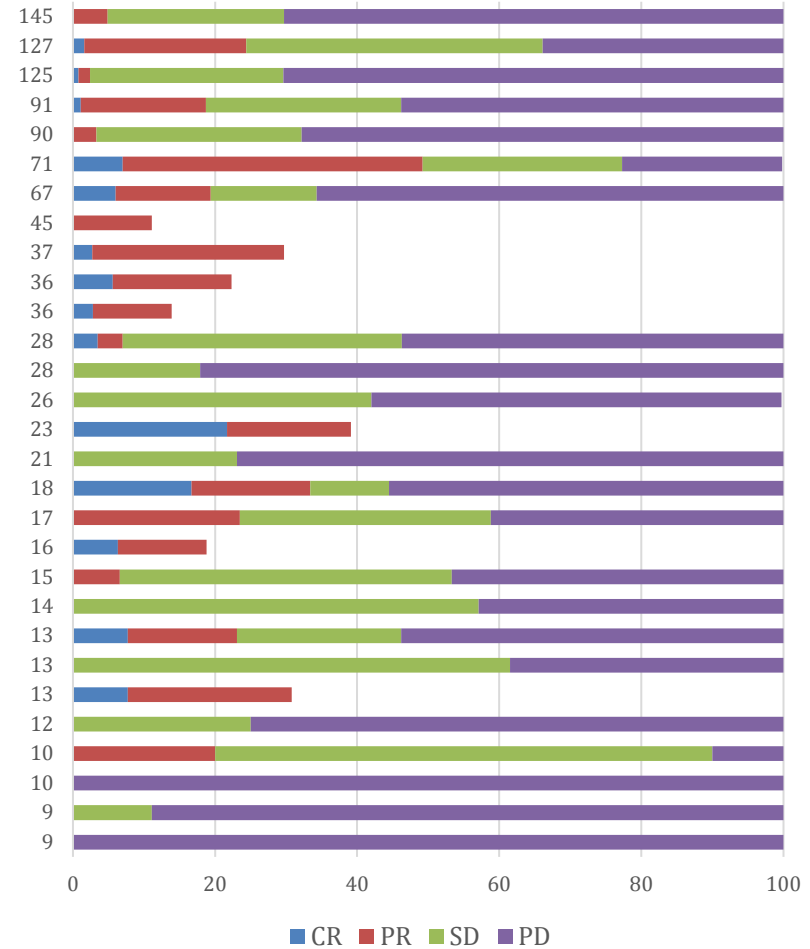
Study

Henning, 2017 {Henning, 2017 #215}
 Fasnacht, 2012 A {Fasnacht, 2012 #28}
 Fasnacht, 2012 B {Fasnacht, 2012 #28}
 Hermsen, 2011 {Hermsen, 2011 #68}
 Fasnacht, 2015 {Fasnacht, 2015 #27}
 Berruti, 2005 {Berruti, 2005 #24}
 Gonzalez, 2007 {Gonzalez, 2007 #172}
 Williamson, 2000 {Williamson, 2000 #213}
 Bukowski, 1993 {Bukowski, 1993 #200}
 Decker, 1991 B {Decker, 1991 #201}
 Abraham, 2002 {Abraham, 2002 #195}
 Sperone, 2010 {Sperone, 2010 #32}
 Kroiss, 2012 {Kroiss, 2012 #207}
 Naing, 2013 {Naing, 2013 #208}
 Haak, 1994 {Haak, 1994 #202}
 Kroiss, 2016 {Kroiss, 2016 #206}
 Bonacci, 1998 {Bonacci, 1998 #199}
 Urup, 2013 {Urup, 2013 #212}
 Decker, 1991 A {Decker, 1991 #201}

Therapy

Gemcitabine and capecitabine
 etoposide, doxorubicin, cisplatin, and mitotane
 Streptozocin and mitotane
 Mitotane and different cytotoxic drug
 Linsitinib
 Etoposide, doxorubicin, cisplatin, and mitotane
 Mitotane
 Cisplatin and etoposide
 Cisplatin and mitotane
 Mitotane
 Doxorubicin, etoposide, vincristine, and mitotane
 Gemcitabine and capecitabine/5-fluorouracil
 Sunitinib
 Cixutumumab and temsirolimus
 Mitotane
 Trofosfamide
 Etoposide and cisplatin
 Cisplatin and docetaxel
 Doxorubicin

N



Lerario, 2014 {Lerario, 2014 #216}	Cixutumumab and mitotane
Haluska, 2010 {Haluska, 2010 #204}	Figitumumab
Schlumberger, 1991 {Schlumberger, 1991 #211}	5-fluorouracil, doxorubicin, and cisplatin
O'Sullivan, 2014 {O'Sullivan, 2014 #209}	Axitinib
Baudin, 2001 {Baudin, 2001 #197}	Mitotane
Baudin, 2002 {Baudin, 2002 #196}	Irinotecan
Kahn, 2004 {Khan, 2004 #205}	Vincristine, teniposide, cisplatin, and cyclophosphamide
Wortmann, 2010 {Wortmann, 2010 #214}	Bevacizumab and capecitabine
Quinkler, 2008 {Quinkler, 2008 #74}	Erlotinib and gemcitabine
Berruti, 2012 {Berruti, 2012 #23}	Sorafenib and metronomic paclitaxel

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

331 *The studies are ordered by number of included patients per regimen. This figure has to be interpreted very cautiously, because study protocols, patient cohorts*
332 *and characteristics as well as outcome measurements are quite different precluding a direct comparison. CR: complete response; PR: partial response; SD:*
333 *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%*

334 Sixteen studies focused on surgery in recurrent and advanced ACC; six publications reported
335 on oligo-metastasectomy (lung, liver) {Datrice, 2012 #118;Gaujoux, 2012 #218;Kemp, 2011
336 #219;Kwauk, 1993 #220;op den Winkel, 2011 #221;Ripley, 2011 #222}, whereas 10
337 publications assessed the effect of surgery in local recurrent and/or metastatic disease
338 {Bellantone, 1997 #223;Crucitti, 1996 #83;Dy, 2013 #225;Erdogan, 2013 #55;Gonzalez,
339 2007 #172;Jensen, 1991 #228;Schulick, 1999 #187;Simon, 2017 #136;Tran, 2013 #231;Dy,
340 2015 #232}. In patients with metastasectomy 5-survival rates up to 40% were reported
341 {Datrice, 2012 #118;Gaujoux, 2012 #218}, although control groups were lacking (+OOO).
342 There were large differences regarding extent of disease, indication, and concurrent
343 treatment in studies comparing a surgical approach to a non-surgical approach for recurrent
344 or advanced disease. The reported benefit of surgery is confounded by differing indications
345 for surgery, and this precludes firm conclusions from being drawn (+OOO). Therefore, the
346 main conclusion is that in patients deemed radically operable by the surgeon/team operation
347 is a treatment option. However, beside prognostic factors like Ki67 a key influencing factor in
348 case of recurrence is the disease-free interval prior to recurrence.
349 For radionuclide therapy {Hahner, 2012 #373}, transcatheter arterial chemoembolization
350 {Cazejust, 2010 #233}, radiofrequency ablation {Wood, 2003 #235} and radiation {Ho, 2013
351 #234} only one small study per procedure was found, and no conclusions can be drawn.

352
353
354

355 **5. Recommendations**

356

357 **5.1. General remarks**

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

365
366

367 **5.1. Overarching recommendations**

368

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

377

378 **Reasoning:**

379 Despite the lack of studies, the panel was convinced that patients with ACC benefit from
380 multidisciplinary management by a team of experts with experience in care for patients with
381 this rare disease. Ideally, all patients would be managed by such a team throughout the

382 course of their disease, because during the follow-up considerations of multiple diagnostic
383 and treatment modalities might be required. However, in many health care settings this is yet
384 an unrealistic expectation. Therefore, we envision that in the future at least one reference
385 center, that fulfills the above-mentioned criteria, will be established in every country. We
386 believe that it is crucial that every case of suspected ACC is discussed in detail with a panel
387 of experts for this disease at the time of the initial diagnosis. Additionally, this expert team
388 should be ideally requested every time progress is documented (or suspected) and new
389 treatment options might be required. If there is no accessible center with all the required
390 expertise in all disciplines, or the patient is not able to travel to such a center, telemedicine
391 approaches should be encouraged to compensate for these limitations.

392
393

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

399
400

Reasoning:

401 As described above, the evidence for almost all therapeutic strategies for ACC is very low.
402 Furthermore, the efficacy of systemic therapies is limited, including the most commonly used
403 treatments - mitotane and platinum-based chemotherapies, with response rates clearly less
404 than 30% {Baudin, 2001 #197;Berruti, 2012 #20;Else, 2014 #135;Fassnacht, 2012
405 #28;Hermsen, 2011 #68;Hahner, 2005 #64}. Thus, improved treatment paradigms are
406 needed urgently. Clinical trials are the best way to improve our knowledge and patient care.
407 However, the benefits and risk for the individual patient have to be weighed against available
408 data of agents with known or predicted efficacy in ACC.

409 Because of the rarity of the disease, it is crucial to include as many patients as possible in
410 research programs for multicenter therapeutic trials, as well as studies for diagnostic,
411 prognostic and predictive markers. A list of ongoing trials is accessible on
412 <https://www.clinicaltrials.gov/>. Biological material may include tumor samples, ideally frozen
413 and paraffin-embedded, blood-derived and urine samples. National and international
414 research networks such as ENSAT (www.ensat.org){Stell, 2012 #91} and the recently
415 founded A5 (<https://adrenal-a5.org/>) play instrumental roles in coordinating research
416 programs. Centers providing care to patients with ACC should register as investigators with
417 ongoing trials and also facilitate the collection a of biological material and ensure appropriate
418 consent.

419
420
421

422 **5.2. Diagnostic procedures in suspected ACC**

423

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

427
428

Reasoning

429 Due to the potentially poor prognosis of ACC, it is critical to know as early as possible if an
430 adrenal mass is malignant or not. Therefore, even if there is only a small likelihood that an
431 adrenal mass is an ACC, this diagnosis should be rapidly excluded with the highest possible
432 certainty. A particular suspicion for an ACC might arise from clinical aspects (e.g. rapidly
433 developed features of adrenocortical hormone excess, see R.2.2), or results from hormonal
434 work-up (see R.2.3), or indeterminate or suspicious imaging (see R.2.4). An adrenal biopsy
435 should only be considered in those selected cases in which an adrenal metastasis of an
436 extra-adrenal malignancy is suspected or when the tumor is considered as inoperable
437 {Fassnacht, 2016 #46} (for details and explanation see R.2.7). The proposed diagnostic
438 work-up is summarized in Table 3.
439

440
441

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
	- CT or MRI of abdomen and pelvis,
	- Chest CT
	- FDG-PET/CT ⁴
	- Bone or brain imaging (when skeletal or cerebral metastases are suspected)

Imaging

442

¹ The 1-mg dexamethasone test is the preferred method to exclude relevant hypercortisolism.

443

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.

444

445

² ACTH can be skipped if hypercortisolism is excluded.

446

447

³ The most suitable set of precursors and sex hormones has not yet been established and local availability might be taken into account.

448

449

⁴ The panel did not agree on the systematic use of FDG-PET/CT (see R.2.4).

450

451

452

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.

453

454

455

456

Reasoning

457

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 an androgen- or estrogen-producing ACC, respectively {Fassnacht, 2004 #59;Allolio, 2006 #236;Else, 2014 #135;Fassnacht, 2009 #56;Nieman, 2008 #134;Libe, 2007 #237}. 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 {Legro, 2013 #238}. Primary aldosteronism is rare in ACC and usually accompanied by severe hypokalemia {Funder, 2016 #239}. However, hypokalemia in ACC is more frequently caused by massive cortisol excess overwhelming the renal 11-β hydroxysteroid dehydrogenase type 2 system.

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

479

480 Reasoning

481 A comprehensive endocrine work-up is helpful for various reasons. (i) The diagnosis of
482 steroid excess is frequently able to establish the adrenocortical origin of the tumor. (ii) The
483 steroid pattern may indicate whether an adrenal lesion is an ACC. For example, autonomous
484 co-secretion of androgens and cortisol in any patient and secretion of steroid precursors or
485 estradiol in males are highly suspicious for ACC {Fassnacht, 2004 #59}. Furthermore,
486 hormonal evaluation is of prognostic value as cortisol-secreting tumors generally have a
487 worse prognosis {Vanbrabant, 2018 #140}. (iii) If undiagnosed, autonomous cortisol
488 secretion may be followed by life-threatening adrenal insufficiency after complete resection of
489 the primary tumor. The best test to diagnose autonomous cortisol secretion is the 1-mg
490 overnight dexamethasone suppression test {Nieman, 2008 #134}. If hypercortisolism is
491 present, it is crucial to prove ACTH-independency, because an adrenal metastasis of an
492 ectopic ACTH-secreting tumor (e.g. lung cancer) can mimic an ACC. (iv) Elevated hormones
493 prior to surgery may serve as tumor markers during follow-up. Finally, conventional imaging
494 cannot discriminate an ACC from a pheochromocytoma. However, undiagnosed
495 pheochromocytoma may lead to dangerous hypertensive crises (especially during invasive
496 procedures). Therefore, a pheochromocytoma has to be ruled out in any case of an adrenal
497 tumor whenever no obvious autonomous steroid excess is present {Fassnacht, 2016 #46}. It
498 is important to note, however, that slightly elevated metanephrines levels (< 2-fold),
499 particularly when inconsistent with a large tumor size, might be non-specific and can be
500 observed in ACC.

501

502

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

504

505 Reasoning

506 Imaging tools for adrenal tumors were carefully reviewed during the development of the ESE-
507 ENSAT guidelines for adrenal incidentalomas {Dinnes, 2016 #54;Fassnacht, 2016 #46}.
508 Thus, we refer to these documents for details. Briefly, there are currently three main imaging
509 techniques available for the differentiation of malignant and benign adrenal tumors:
510 computed tomography (CT), magnetic resonance imaging (MRI), and positron emission
511 tomography with ¹⁸F-2-deoxy-D-glucose (mostly combined with CT; FDG-PET/CT). CT and
512 MRI are techniques mainly optimised to identify benign lesions, providing a tool for the
513 exclusion of adrenal malignancy {Peppercorn, 1998 #244;Caoili, 2002 #243;Blake, 2006
514 #242;Ilias, 2007 #245}. Conversely, FDG-PET/CT is mainly used for the detection of
515 malignant disease {Mackie, 2006 #121;Groussin, 2009 #247;Deandreis, 2011 #246}. A
516 recently performed meta-analysis indicated that the level of evidence is low to very low for all
517 these imaging methods {Dinnes, 2016 #54}. In the last 2 years some additional studies have
518 been published {Cistaro, 2015 #362;Altinmakas, 2017 #254;Ciftci, 2017 #255;Bluemel, 2017
519 #250;Werner, 2016 #248;Wu, 2016 #249;Nakajo, 2017 #257;Guerin, 2017 #256;Marty, 2018
520 #251;Kim, 2018 #252;Delivanis, 2018 #253;Romeo, 2018 #258;Thomas, 2018 #259;Ng,
521 2018 #260;Kim, 2018 #252}. However, the panel still considers that of the available imaging

522 modalities, only non-contrast CT is sufficiently reliable to rule-out an ACC when the adrenal
523 lesion is homogenous and has low CT density ≤ 10 HU. In contrast, ACCs are usually large
524 and of inhomogeneous appearance, and characterized by low fat content (and hence higher
525 HU density){Petersenn, 2015 #323}. Recently, FDG-PET has been proposed as possibly the
526 best second-line test to assess indeterminate masses by unenhanced CT {Cistaro, 2015
527 #362;Guerin, 2017 #256;Nakajo, 2017 #257}. However, the experience shows that sensitivity
528 and negative predictive value are much better than specificity or positive predictive value.
529 Therefore, no consensus could be reached for a general recommendation on FDG-PET in all
530 patients. Additional reasons in favor of systematic FDG-PET are: whole body imaging
531 (beyond thorax and abdomen, particularly for distant bone metastasis) and in advanced
532 disease, a reference uptake value for all metastases can be established, which can help
533 judging the future evolution of disease. Evidence against FDG-PET includes cost, additional
534 radiation exposure, false-positive findings, and difficult access in some countries.
535 If adrenal imaging indicates an indeterminate mass, other parameters should be considered:
536 For instance, in such a situation a tumor size > 4 cm, combined adrenocortical hormone
537 excess (see also R.2.3), rapidly developing symptoms or young age (e.g. < 40 years) might
538 point to an ACC. However, it is important to note that no single imaging method can
539 definitively prove the diagnosis of ACC.

540
541

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

545
546

Reasoning:

547 Since decisions for treatment strategy, particularly decisions for surgery, and prognostication
548 rely on tumor stage, it is mandatory to systematically and rapidly evaluate for metastases,
549 before initiation of any anti-tumor treatment. Thoraco-abdomino-pelvic imaging will cover the
550 vast majority of metastatic locations, which most often are lung and liver, and will assess
551 locoregional tumor extent. Imaging should include contrast-enhanced imaging. For
552 abdominal imaging there are advantages and disadvantages for both CT and MRI, but for
553 thoracic imaging CT is the method of choice, because it outperforms all other methods in
554 detecting small pulmonary lesions.

555 Additional imaging may be required to better characterize tumor vascularization, or specific
556 tumor extent such as a vena cava thrombus.

557
558

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

561
562

Reasoning:

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

567
568

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

573

574 Reasoning:

575 Differentiating benign from malignant adrenocortical tumors is very challenging on a biopsy
576 only and may lead to misdiagnosis {Bancos, 2016 #49; Fassnacht, 2016 #46}. Furthermore,
577 the biopsy comes with significant risks such as hemorrhage {Williams, 2014 #262}. The risk
578 of tumor dissemination precluding a R0 resection is very low {Williams, 2014 #262}.
579 However, a biopsy might be indicated in an adrenal mass without any hormone excess in
580 patients with a history of extra-adrenal cancers to exclude or prove an adrenal metastasis of
581 an extra-adrenal malignancy. For details see the adrenal incidentaloma guidelines
582 {Fassnacht, 2016 #46}.

583

584

585

586 **5.3. Surgery for suspected localized ACC**

587

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

590

591 Reasoning

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

596 Data comparing outcome between 'high-volume' and 'low-volume' centers for ACC are
597 limited. Published reports from the UK, USA and Spain show an unacceptable low annual
598 workload for the majority of surgeons involved in any adrenal surgery, with a median 1
599 case/year {Palazzo, 2016 #7; Park, 2009 #9; Lindeman, 2018 #264; Villar, 2010 #263}. This
600 situation is likely to have a negative impact on patient care and contrasts significantly with
601 the current status in other surgical specialties.

602 Based on the upper quartile distribution of workload of surgeons in the USA, a volume of 4
603 adrenalectomies/year was used to define a 'high-volume' surgeon {Park, 2009 #9} but this
604 threshold might be too low to inspire confidence. Several studies showed that those doing
605 more than 6-7 cases per year have shorter length of stay and fewer complications {Palazzo,
606 2016 #7; Park, 2009 #9; Gallagher, 2007 #265}. Despite the perceived benefit of being
607 operated in a high-volume center, published data from Italy and the USA showed no
608 significant association between overall survival / disease-free survival and workload even
609 though patients operated in high-volume centers had more radical surgery, more lymph node
610 assessment and more use of chemotherapy {Lombardi, 2012 #266; Gratian, 2014 #268}. In
611 contrast, the creation of national centers for adrenal surgery in The Netherlands led to
612 significantly improved disease-free survival (1y: 93% vs. 78%, 5y: 63% vs. 42 %) {Hermsen,
613 2012 #36; Kerkhofs, 2013 #41}. Therefore, the panel believes that a minimal annual workload
614 of 6 adrenalectomies/year seems to be required to ensure sufficient experience in adrenal
615 surgery, but > 20 adrenalectomies/year are desirable for those involved in surgery for ACC.
616 Furthermore, due to the complexity of some operations, it is essential to involve surgeons

617 with different expertise (e.g. vascular, liver, and cardiac surgeons) for pre-surgical planning
618 and during these complex operations.
619 Protocols ensuring referral to regional or national centers should be established and patients
620 should feel empowered to ask about the previous experience of individual surgeons.

621
622

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

629

630 Reasoning

631 Complete resection is of utmost importance for all ACCs and successful surgery is a
632 prerequisite for cure. As the diagnosis of ACC might only become apparent after histological
633 analysis, it remains imperative for all adrenalectomies (laparoscopic or open) in patients with
634 a reasonable suspicion for ACC to respect the principles of oncological surgery in order to
635 ensure complete resection (R0 status) {Gaujoux, 2017 #87;Gaujoux, 2012 #86}.

636 To ensure that the pathologist can judge the completeness of surgery, any fragmentation of
637 the tumor has to be avoided. Intraoperative tumour rupture or spillage and R2 resection are
638 associated with very high recurrence rates and poor overall survival {Bilimoria, 2008 #80}
639 {Crucitti, 1996 #83}.

640 Although there are no specific studies comparing outcome of surgery with and without
641 resection of invaded adjacent organs, it is deemed to be 'good surgical practice' to resect
642 adjacent tissues that are/could be invaded by tumor. This holds true for involvement of
643 spleen, distal pancreas, stomach, kidney, right liver, colon, diaphragm, the wall of the IVC or
644 left renal vein. A cohort study compared the oncological results of patients with stage II ACC
645 treated by radical adrenalectomy alone or by *en-bloc* resection with kidney. The results did
646 not support the hypothesis that nephrectomy improves the oncological outcome {Porpiglia,
647 2016 #31}. Combined nephrectomy, however, offers a lower risk of capsular rupture and can
648 include complete lymphadenectomy of the renal hilum, but impairs kidney function and this
649 may limit further access to chemotherapy. Thus, in case of possible invasion in the kidney,
650 partial nephrectomy should be considered on an individual basis.

651

652

653 **R.3.3. Open surgery is the standard surgical approach for confirmed or highly**
654 **suspected ACC. Therefore, we recommend open surgery for all tumors with**
655 **radiological findings suspicious of malignancy and evidence for local invasion.**
656 **However, for tumors < 6 cm without any evidence of local invasion,**
657 **laparoscopic adrenalectomy (respecting the principles of oncological surgery)**
658 **is reasonable if the surgeon has sufficient experience in these types of surgery.**

659

660 Reasoning

661 There is an ongoing debate if laparoscopic adrenalectomy is an acceptable alternative for
662 adrenal tumors with suspicion of ACC. Based on the systematic review on this topic until July
663 2014 {Fassnacht, 2016 #46} and an additional literature search until December 2017
664 {Donatini, 2014 #274;Sgourakis, 2015 #273;Autorino, 2016 #272;Langenhuijsen, 2016

665 #271;Lee, 2017 #6;Zheng, 2018 #269;Mpaili, 2018 #270;Huynh, 2016 #333}, we conclude
666 that the quality of evidence from these observational studies is still very low. The main
667 concerns with all these studies are differences of baseline characteristics between groups,
668 and between important prognostic factors, such as tumor stage or size. The lack of any
669 randomized trial prevents any final conclusions. However, in order to provide guidance for
670 clinicians the panel concurs with two other recent European guidelines {Fassnacht, 2016
671 #46;Gaujoux, 2017 #87} and agrees that all tumors with some radiological evidence of local
672 invasion (including enlarged lymph nodes) should undergo surgery with an open approach.
673 The likelihood of a benign adrenal tumor is higher in the group of adrenal incidentalomas ≤ 6
674 cm, for whom a laparoscopic approach is reasonable. However, this cut-off is arbitrary and
675 the experience of the surgeon is the single most important factor. Furthermore, it is advised
676 to convert to an open procedure when obvious signs of invasion are encountered during
677 laparoscopic surgery that would prevent complete resection. For detailed discussion we refer
678 to the recent recommendations for the surgical management of ACC by ESES and ENSAT
679 {Gaujoux, 2017 #87} and the guidelines on adrenal incidentaloma {Fassnacht, 2016 #46}.
680 Although retroperitoneoscopic adrenalectomy is gaining popularity, only a small number of
681 surgeons are likely to have completed the learning curve to reach sufficient expertise, which
682 is estimated to be at least 20 cases {Barczynski, 2007 #275;Schreinemakers, 2010 #276}.
683 This is a very significant issue in the context of the overall minimal experience of most
684 surgeons offering adrenalectomy (see above). Outside specialized centers with large volume
685 practice, retroperitoneoscopic adrenalectomy should only be considered for benign tumors
686 <4 cm.

687
688

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

694
695

Reasoning

696 Reports from several databases indicated that patients with stage III tumors and positive
697 lymph nodes can have a 10-year overall survival rate of up to 40% after resection
698 {Fassnacht, 2009 #58;Lughezzani, 2010 #92;Libe, 2015 #29;Nilubol, 2016 #8;Saade, 2015
699 #93}. However, the wide range of reported lymph node involvement in ACC (from 4 to 73%)
700 {Icard, 2001 #79;Bilimoria, 2008 #80;Harrison, 1999 #88} demonstrates that regional
701 lymphadenectomy is neither formally performed by all surgeons nor accurately assessed or
702 reported by all pathologists. According to large American and French series, approximately
703 10-30% of patients with ACC had formal lymphadenectomy as part of the tumor resection,
704 reflecting the heterogeneity of operative management {Icard, 2001 #79;Nilubol, 2016 #8}. A
705 minimum of four lymph nodes should be retrieved in order to declare lymph node negative
706 cases {Panjwani, #89} Furthermore, in an analysis of 120 cases identified from a multi-
707 institutional database, the benefit of lymphadenectomy on overall survival persisted on
708 multivariable analysis controlling for adverse preoperative and intraoperative factors
709 associated with lymphadenectomy, such as tumor size, palpable mass, irregular tumor
710 edges, suspicious nodes on imaging, and multivisceral resection {Gerry, 2016 #94}. The
711 largest series so far included 283 patients and the resection of more than five lymph nodes
712 reduced also the risk of local recurrence and disease-related death in a multivariate analysis

713 {Reibetanz, 2012 #75}.

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

717

718

719 **R.3.5. We recommend that individualized treatment decisions are made in cases of**
720 **tumors with extension into large vessels based on multidisciplinary surgical**
721 **team. Such tumors should not be regarded ‘unresectable’ until reviewed in an**
722 **expert center.**

723

724 Reasoning

725 Extension of ACC into the adrenal vein, renal vein or inferior vena cava occurs in
726 approximately 15-25% {Chiche, 2006 #96;Turbendian, 2010 #95;Fassnacht, 2009 #58}.
727 Venous involvement consists mostly of intravenous tumor thrombus. Thrombectomy might
728 require vena cava cross-clamping above or below the hepatic vein confluence or
729 cardiopulmonary bypass, depending on the upper level of extent of the thrombus. The
730 resection might include a complete thrombectomy, a flush manoeuvre and, occasionally,
731 vascular cuff or prosthetic IVC replacement. A 3-year overall survival rate of about 25% in a
732 large series {Mihai, 2012 #97} encourages the performance of a venous resection in the
733 presence of vena cava or renal vein invasion but without distant metastases.

734

735

736 **R.3.6. If the first surgery was suboptimal and macroscopically incomplete (R2**
737 **resection), we suggest to discuss repeat surgery in a multidisciplinary expert**
738 **team.**

739

740 Reasoning

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

747

748

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

751

752 Reasoning:

753 Overt ACTH-independent Cushing's syndrome or biochemical autonomous cortisol secretion
754 might lead to adrenal insufficiency after removal of the adrenal source of cortisol (even in
755 patients with incompletely suppressed ACTH) {Eller-Vainicher, 2010 #4}. Therefore, the
756 group unanimously sees a clear indication of intra- and postoperative glucocorticoid
757 replacement, preferably with hydrocortisone, in all patients with evidence for ‘(possible)
758 autonomous cortisol secretion’ (post-dexamethasone cortisol >50 nmol/L (>1.8 µg/dL)). This
759 should follow the suggestions for major stress dose replacement as per recent international

760 guidelines {Bornstein, 2016 #314}. Postoperatively, the dose of glucocorticoid should be
761 tapered on an individualized basis by a physician experienced with this clinical scenario.

762
763
764

765 **5.4. Pathological work-up**

766

767 **R.4.1. We recommend that the diagnosis of ACC should be confirmed by** 768 **histopathology (+++0).**

769

770 Reasoning:

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

779

780

781 **R.4.2. We suggest that all adrenal tumors, which cannot be readily classified, and all** 782 **suspected ACC, should be reviewed by an expert adrenal pathologist (++OO).**

783

784 Reasoning:

785 Diagnosing ACC can be challenging and misdiagnoses are relatively frequent events. In 21
786 of 161 of the patients (13%) registered with the German ACC Registry between 2006 and
787 2009, the diagnosis of ACC had to be revised by the reference pathologist {Johanssen, 2010
788 #69}. Similar results were found in a large series from Italy with a rate of misdiagnosis in 26
789 out of 300 cases (9%) {Duregon, 2015 #98}.

790

791

792 **R.4.3. We suggest the use of immunohistochemistry for steroidogenic factor-1 (SF1)** 793 **for the distinction of primary adrenocortical tumors and non-adrenocortical** 794 **tumors (+OOO).**

795

796 Reasoning:

797 Generally, the distinction between adrenocortical and non-adrenocortical tumors is clear and
798 can be made on the basis of hematoxylin and eosin-stained slides. In case of doubt, on the
799 basis of histology only, whether a tumor originates from the adrenal cortex or not,
800 immunohistochemistry with SF1 is the most sensitive and specific marker currently available
801 to establish if the tumor in question is of adrenocortical origin, with a sensitivity of 98% and a
802 specificity of 100% {Sbiera, 2010 #15}. If this marker is not available, we advise a
803 combination of markers, which should include inhibin-alpha, melan-A, and calretinin {Sangoi,
804 2011 #99;Weissferdt, 2014 #100}. Depending on the differential diagnosis, other
805 immunohistochemistry markers used to make alternative diagnoses may be considered
806 following local standard procedures.

807

808

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

813

814 Reasoning:

815 There are many classification systems based on histology and/or a limited number of
816 additional markers for the distinction of benign and malignant adrenocortical tumors. The
817 Weiss system is the most widely used, and although it is not fully standardized {Tissier, 2010
818 #102;Tissier, 2012 #101} the panel favors use of this score. It should be noted that all
819 scoring systems have similar inherent problems. Using the Weiss system, a score of 3 or
820 higher (on a total of 9 criteria, see Table 4) indicates ACC {Weiss, 1984 #104;Weiss, 1989
821 #103}. A score of 2 and 3 may be considered as borderline between benign and malignant
822 tumors (tumors of uncertain malignant potential). In such instance, one of several other
823 classification systems, including the van Slooten index {van Slooten, 1985 #107}, the
824 modified Weiss score {Aubert, 2002 #108}, the Helsinki classification {Pennanen, 2015
825 #109;Duregon, 2017 #110}, and the addition of reticulin stain assessment {Duregon, 2013
826 #26} may be used.

827

828 Special attention should be paid to histological variants of adrenocortical tumors, mainly
829 oncocytic tumors, which, because of their specific characteristics, will always have a Weiss
830 score of least 3, whether they are benign or malignant. For these tumors, an adapted scoring
831 system should be used, the Lin-Weiss-Bisceglia system {Bisceglia, 2004 #111;Duregon,
832 2011 #112;Wong, 2011 #113}.

833 **Table 4 Histopathologic criteria by Weiss {Weiss, 1984 #104;Weiss, 1989 #103}**

The presence of three or more of the following criteria highly correlated with subsequent malignant behavior:

- High nuclear grade (Fuhrman criteria {Fuhrman, 1982 #357})
- > 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

834

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836

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

839 Ki67 immunohistochemistry has been proposed for prognostic purposes. Higher Ki67 levels
840 are consistently associated with poor prognosis. Threshold levels of 10% and 20% have
841 been considered for discriminating low from high Ki67 labeling index {Beuschlein, 2015
842 #50;Libe, 2015 #29}. However it is not clear whether any single significant threshold can be
843 determined (see R.5.2.).

844 Ki67 labeling has been shown to be unevenly distributed in tumors. Therefore, determination
845 of the labeling index should be done on whole tumors, with specific attention to the area of
846 highest Ki67 labeling, preferably by use of an image analysis system {Lu, 2014
847 #115;Papathomas, 2016 #116}. If only a biopsy is available a low Ki67 labeling may not be
848 representative and therefore can be misleading.

849 If Ki67 immunohistochemistry is not available, mitotic count may help in prognostic
850 stratification of ACC. Mitotic count has been proposed for grading of ACC, using >20 mitoses
851 per 50 high-power field to define high-grade tumors {Weiss, 1989 #103;Assie, 2007
852 #114;Miller, 2010 #90}. However, the precise correlation between mitotic count and Ki67
853 labeling is undetermined.

854

855

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

861

862 Reasoning

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

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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 {Macfarlane, 1958 #281;Sullivan, 1978 #282;Lee, 1995 #283;DeLellis, 2004 #284;Asare, 2014 #158;Miller, 2010 #90;Lughezzani, 2010 #92;Fassnacht, 2009 #58;Libe, 2015 #29;Lam, 2017 #285}. Among these, the ENSAT staging classification appears to be the most discriminant, but the differences between staging systems are minor {Fassnacht, 2016 #46}(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 and R.3.4.), and a complete pathological report (see R.4.6.).

Table 5: ENSAT staging classification {Fassnacht, 2016 #46}

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

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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 {Bilimoria, 2008 #80;Johanssen, 2010 #69;Libe, 2015 #29}, 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 {Morimoto, 2008 #278;Weiss, 1989 #103;Miller, 2010 #90;Beuschlein, 2015 #50;Libe, 2015 #29}. As revealed by our systemic literature search,

912 hypercortisolism was also one of the most consistent prognostic factors (see section 4.2;
913 {Abiven, 2006 #279;Berruti, 2014 #35;Vanbrabant, 2018 #140}).

914 Finally, the patient's general condition is an obvious prognostic factor, especially at advanced
915 age {Asare, 2014 #158}. It is, however, noticeable that ACC patients often do not show
916 altered general condition despite advanced disease.

917 From a patient perspective, the panel felt it important to consider two distinct scenarios. First,
918 the risk of recurrence of patients with a localized (stage I-III) disease. For these patients,
919 tumor stage, resection status and Ki67 labeling index are currently the main prognostic
920 factors. This panel proposes to define two classes of localized ACC: low/moderate risk ACC
921 includes stage I-II and R0 and Ki67 $\leq 10\%$, whereas high risk ACC includes stage III, R1, or
922 Ki67 $>10\%$. However, the panel is aware that the dichotomy is arbitrary.

923 The second scenario to consider deals with the prognosis of patients with advanced disease
924 (stage IV or recurrent disease not amenable to complete resection or R2 resection). In this
925 situation, high tumor burden, high tumor grade, high Ki67 index, and uncontrolled symptoms
926 are major factors associated with worse prognosis {Assie, 2007 #114;Libe, 2015 #29}.
927 However, there is consensus that the kinetics of tumor growth might be also relevant,
928 particularly when making the decision for initiation of cytotoxic chemotherapy. However, this
929 parameter has not been formally assessed. Although a correlation of tumor growth and tumor
930 grade exists, it is not true for all tumors.

931

932

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

935

936 Reasoning

937 After complete surgery, the major prognostic factor is whether there is any tumor recurrence.
938 At the time of recurrence the main prognostic factors are time between initial surgery and
939 recurrence, tumor burden and resectability {Datrice, 2012 #118;Erdogan, 2013 #55;Ettaieb,
940 2016 #117;Simon, 2017 #136}.

941 For patients with advanced disease, prognostic factors include Ki67 index, tumor burden,
942 general patient condition, and kinetics of tumor growth, as well as response to treatment.
943 Limited evidence is available, but these factors make clinical sense and are corroborated by
944 this panel's experience.

945

946

947 **5.6. Methods and time interval for imaging and hormonal assessment during**
948 **follow-up**

949

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

952

953 Reasoning

954 A majority of disease recurrence and progression occurs either loco-regionally, or with
955 metastases to lung or liver and therefore should be identified by thoraco-abdomino-pelvic
956 imaging. Bone metastases are infrequent and brain involvement is exceptional {Fassnacht,
957 2009 #56;Libe, 2015 #29;Burotto, 2015 #119}. In general, 18-FDG-PET/CT might provide
958 additional information (see R.2.4.) particularly prior to any surgical intervention {Leboulleux,

959 2006 #120;Mackie, 2006 #121;Ardito, 2015 #122}. In addition, change in tracer uptake might
960 inform about disease evolution.

961

962

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

967

968 Reasoning

969 There are no published studies that address specifically this issue. Therefore, the suggested
970 imaging interval is in accordance with the practice at many expert centers, and with
971 standards for other malignant tumors. In the experience of the panel few tumors with initial
972 curative surgery will recur after more than five years and therefore a 5-yr surveillance is likely
973 to include >90% of the ACC population that will experience disease recurrence. However, the
974 majority of the panel felt uncomfortable with the notion of complete cessation of imaging after
975 5 years and preferred for instance an annual imaging for another 5 years. After stopping
976 regular imaging, patients and primary care physicians should remain vigilant in terms of
977 potential symptoms or signs of late recurrences (see also R.6.4.).

978

979

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

983

984 Reasoning

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

992

993

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

995

996 Reasoning

997 Biochemical evaluation together with clinical evaluation fulfills two purposes: (i) it allows in a
998 few patients the early detection of recurrences and (ii) it also identifies patients that might
999 benefit from early anti-hormonal therapy. Biochemical evaluation should focus on steroid
1000 hormones or metabolites that were present at the time of diagnosis of the initial tumor.
1001 However, some panelists favored a more complete hormonal evaluation, because some
1002 tumors might change their steroid secretion pattern over time.

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1006 **5.7. Adjuvant therapy**

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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 but who 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 on the use of mitotane in the adjuvant setting based on three arguments: (i) the perceived effects {Terzolo, 2007 #33;Berruti, 2010 #21;Berruti, 2017 #22;Bertherat, 2007 #82;Else, 2014 #125;Fassnacht, 2010 #57;Grubbs, 2010 #191;Postlewait, 2016 #192} (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 {Baudin, 2001 #197;Else, 2014 #135;Hahner, 2005 #64;Megerle, 2018 #294}; (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 several markers have been proposed {Volante, 2012 #327;Ronchi, 2014 #322}. A study showed that mitotane levels may influence patient outcome in adjuvant setting {Terzolo, 2013 #313} 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 {Berruti, 2014 #35;Berruti, 2017 #22;Megerle, 2018 #294}.

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

1055 reach effective levels and anti-tumor activity. However, no published data are available to
1056 demonstrate the superiority of an early start of treatment or the lack of efficacy when started
1057 later than 3 months.

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1059

1060 **R.7.4. In patients without recurrence who tolerate mitotane in an acceptable manner,**
1061 **we suggest to administer adjuvant mitotane for at least 2 years, but not longer**
1062 **than 5 years (+OOO).**

1063
1064

Reasoning:

1065 The optimal duration of mitotane treatment is unknown and practice varies among different
1066 centers. Some members of the panel continue treatment for 3 to 5 years if tolerated {Terzolo,
1067 2014 #363}, while others discontinue after 2 to 3 years {Fassnacht, 2011 #61;Berruti, 2012
1068 #20;Else, 2014 #135}. Prognostic factors at diagnosis, patient compliance with treatment and
1069 plasma mitotane levels reached during treatment are factors that influence duration of
1070 treatment. Mitotane may possibly act as an oncostatic measure in those patients {Huang,
1071 2008 #350;Terzolo, 2009 #328}. However, the rate of recurrence 5 years after surgery is
1072 potentially too low to advise continuation of therapy treatment beyond this time point.
1073 Treatment-related toxicity, lack of experience in long-term administration are additional
1074 factors portending against indefinite treatment.

1075
1076

1077 **R.7.5. The panel did not come to a definitive consensus on adjuvant radiation therapy.**
1078 **However, we suggest against the routine use of radiation therapy in patients**
1079 **with stage I-II and R0 resection (+OOO). The panel suggests considering**
1080 **radiation in addition to mitotane therapy on an individualized basis therapy in**
1081 **patients with R1 or Rx resection or in stage III.**

1082
1083

Reasoning:

1084 The systematic literature search indicated that radiation therapy is able to prevent local
1085 recurrence but does not significantly affect distant recurrences or overall survival {Else, 2014
1086 #125;Fassnacht, 2006 #126;Habra, 2012 #123;Polat, 2009 #73;Sabolch, 2015
1087 #127;Sabolch, 2013 #124} (see section 4.3. and Figure 1). However, distant metastases
1088 account for about 40-60% of tumor relapses {Berruti, 2017 #22;Amini, 2016 #157;Erdogan,
1089 2013 #55} and have large impact on the patient prognosis, and are more difficult to treat
1090 effectively. Conversely, prevention of the complications due to local recurrence argues in
1091 favor of radiation therapy. Adjuvant radiation therapy might be particularly reasonable in
1092 patients with R1 resection. This was already suggested by earlier studies, but also by a very
1093 recent study that was published after the meta-analysis associated with this report {Nelson,
1094 2018 #358}.

1095

1096 Radiation therapy is not advised for patients who experienced widespread tumor spillage
1097 during surgery. The combination of radiation therapy and mitotane is biologically sound
1098 {Cerquetti, 2008 #330;Cerquetti, 2010 #329} and possible but at the cost of greater toxicity
1099 (e.g. constitutional, gastrointestinal and liver toxicity). In addition, there is concern that
1100 radiation therapy may delay systemic therapy or prevent effective mitotane administration
1101 resulting in lower drug levels.

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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 (+000).

Reasoning:

Radiation therapy was delivered following this scheme in previous observational studies {Fassnacht, 2006 #126;Habra, 2012 #123;Sabolch, 2013 #124;Else, 2014 #125;Sabolch, 2015 #127} and lower dosage seems to be less effective {Polat, 2009 #73}.

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.

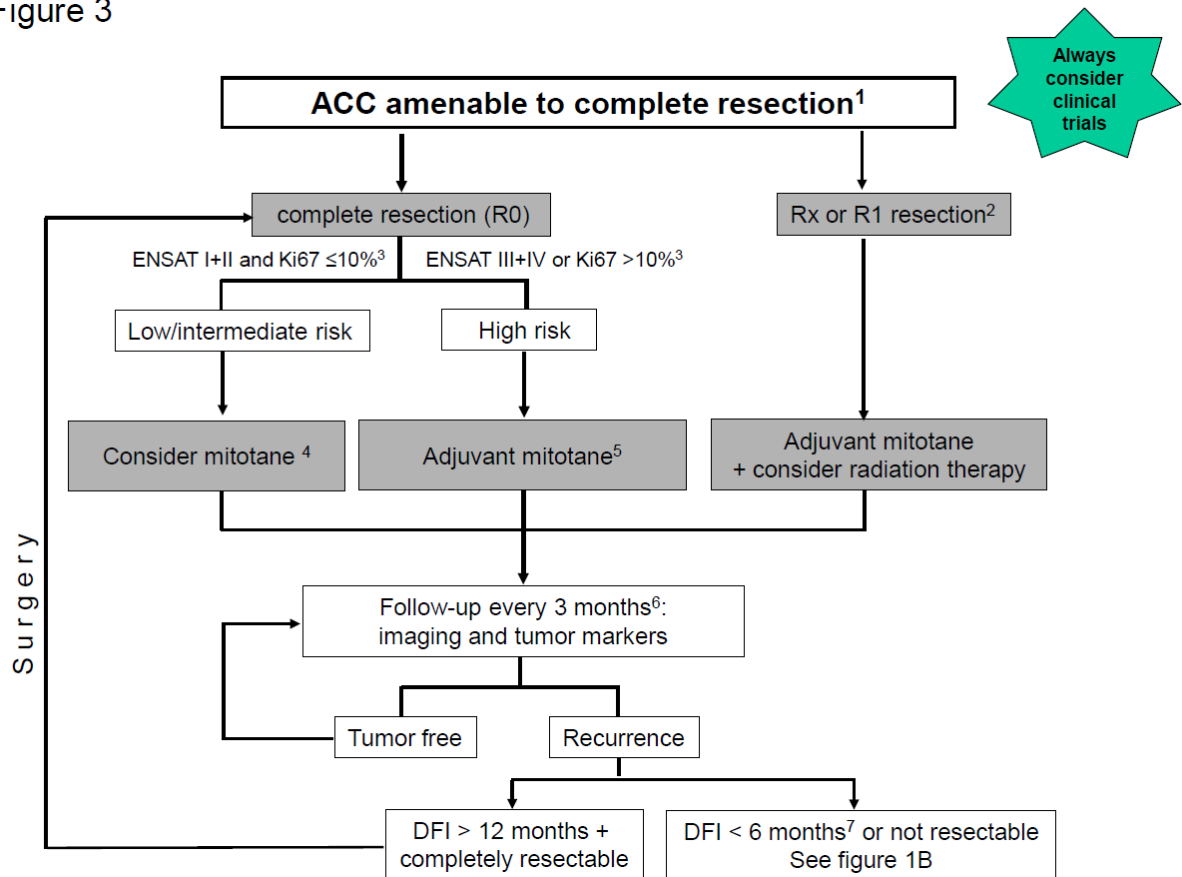
Reasoning:

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 {Khan, 2000 #296}. 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



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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 stage IV and oligo-metastatic disease complete resection might be possible as well and should be aimed at.

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.)

1150 **5.8. Treatment of recurrent and/or advanced ACC**

1151
1152 Clinical scenarios of patients with recurrent and/or advanced ACC are highly variable.
1153 Therefore, we try to provide recommendations for at least the most frequent presentations
1154 (see also Figure 4). Although a (small) proportion of patients experience a relatively long
1155 survival {Hermesen, 2008 #128; Fassnacht, 2009 #58; Libe, 2015 #29; Else, 2014 #135}, the
1156 prognosis of advanced/metastatic ACC is generally limited. The goal of any therapy is to
1157 palliate symptoms and prolong survival. In this situation it is even more important than in
1158 other scenarios to tailor treatment on an individual basis taking into account the disease
1159 extent, the patient performance status and particularly the preference of the patient.

1160
1161
1162 **R.8.1. For patients presenting at time of initial diagnosis with limited intra-abdominal**
1163 **metastases we suggest surgical therapy if complete resection of all lesions**
1164 **seems feasible (+OOO). In case of limited extra-abdominal lesions, we suggest**
1165 **adrenal tumor resection in conjunction with therapy aiming at long-term tumor**
1166 **control of the other lesions (+OOO). In all patients, we recommend to start**
1167 **mitotane therapy as soon as clinically possible (+OOO).**

1168 Reasoning:

1169
1170 Complete surgery is the best chance to reach long-term disease control although the
1171 likelihood of complete tumor removal in advanced ACC is low. If clinically possible, a single
1172 surgical approach should be planned. If a one-time surgical approach is impossible (e.g. due
1173 to extra-abdominal metastases), other loco-regional approaches (see R.8.2) should be
1174 discussed within a multidisciplinary expert team and the patient on an individual basis. Local
1175 expertise and preference of the patient should be taken into account. Any initial treatment
1176 (surgery, local and/or medical therapy) should be initiated in a timely fashion (\leq 4-6 weeks
1177 following initial diagnosis).

1178 In general, prognostic parameters (see R.5.2 + 5.3) should influence the overall treatment
1179 strategy. If the disease has an aggressive behavior (i.e. increase in tumor burden [e.g.
1180 increasing size of existing tumors or new metastasis] observed in subsequent imaging
1181 performed within a few weeks) systemic options (chemotherapy plus mitotane) may be
1182 favored. If partial responses or prolonged stabilization are then observed, surgery and/or
1183 additional loco-regional options might be particularly useful ("neo-adjuvant approach", see
1184 also R.8.3). This strategy could also be potentially advantageous in patients for whom tumor
1185 shrinkage might allow a more conservative surgical approach (i.e. patients in whom radical
1186 surgery would imply the complete or partial removal of neighboring organs such as kidney,
1187 spleen and part of the pancreas){Bednarski, 2014 #334}.

1188 These patients are at high risk for recurrence and therefore adjuvant mitotane seems to be
1189 justified {Wangberg, 2010 #361}. Addition of cytotoxic drugs might be a possible option
1190 (although data are lacking; see also R.7.7.).

1191
1192
1193 **R.8.2. The panel is convinced that in addition to surgery other local therapeutic**
1194 **measures (e.g. radiation therapy, radiofrequency ablation, cryoablation,**
1195 **microwave ablation, chemo-embolization) are of value for therapy of advanced**
1196 **ACC. We suggest individualization of the decision on the method of choice**

1197 **based on the localization of the tumor lesion(s), local expertise, prognostic**
1198 **factors, and patient's preference (+OOO).**

1199

1200 Reasoning:

1201 Published data on local therapies in advanced ACC are very limited {Cazejust, 2010
1202 #233;Ho, 2013 #234;Polat, 2009 #73;Wood, 2003 #235} and summarized in Appendix 6.
1203 However, the experience of many panelists provides additional support of efficacy of these
1204 local measures. Nevertheless, it is impossible to indicate which method is superior. Most
1205 important, the expertise of the local team in applying these methods should be taken into
1206 account when discussing this issue with patients in a shared decision-making process.

1207

1208

1209 **R.8.3. We suggest against the routine use of adrenal surgery in case of widespread**
1210 **metastatic disease at the time of first diagnosis (+OOO).**

1211

1212 Reasoning: Despite the lack of large studies addressing this particular question, a majority of
1213 the panel agreed that patients with widespread and unresectable disease will usually not
1214 benefit from surgery. However, a few panelists suggested that adrenalectomy could be an
1215 option if technically possible.

1216 In patients who respond very well to systemic therapy, surgery should be considered at an
1217 appropriate time point; especially if complete resection becomes feasible ("neo-adjuvant
1218 approach"). However, the published evidence for such an approach is scant {Rangel, 2013
1219 #331;Bednarski, 2014 #334}.

1220 In selected cases (e.g. patients with severe hormone excess) debulking surgery might be an
1221 option, although anti-hormonal drugs (see R.10.1) should be considered here. In these
1222 cases, surgery might be especially reasonable if > 80% of the tumor burden can be removed
1223 safely. In patients with a poor clinical condition and significant localized metastatic burden,
1224 additional localized therapies (see R.8.2) may be considered as an alternative.

1225

1226

1227 **R.8.4. In patients with advanced ACC at the time of diagnosis not qualifying for local**
1228 **treatment, we recommend either mitotane monotherapy or mitotane + EDP**
1229 **depending on prognostic parameters (+++O).**

1230

1231 Reasoning:

1232 Mitotane is the treatment of choice for patients with advanced ACC (for details about the
1233 management of mitotane see section 5.9). However, a very recent cohort study suggests that
1234 patients with metastatic disease at the time of primary diagnosis might not be the ideal
1235 candidates for mitotane monotherapy {Megerle, 2018 #294}. Furthermore, unfavorable
1236 prognostic parameters (e.g. high tumor burden, uncontrolled symptoms, high proliferative
1237 index, clinical evidence of a fast growing tumor) are important factors favoring a more
1238 aggressive/more rapidly active therapeutic approach. If more aggressive therapy is indicated,
1239 then the combination of EDP in addition to mitotane (EDP-M) is the most validated regimen
1240 {Fassnacht, 2012 #28}. EDP-M is the only treatment approach in ACC that is successfully
1241 evaluated in a randomized trial, the FIRM-ACT study. It has to be highlighted, however, that
1242 only progression-free survival was significantly improved in comparison to the alternative
1243 therapy (in this case streptozotocin plus mitotane; 5.0 vs. 2.1 months; HR 0.55; 95% CI 0.43

1244 to 0.69; $P < 0.001$)), whereas for overall survival the crossover design might have diluted the
1245 results (14.8 vs 12.0 months, HR 0.79; 95% CI, 0.61 to 1.02; $P = 0.07$).

1246 The administration of EDP-M comes with risk of adverse events and it is important that the
1247 treatment will be administered by physicians with sufficient experience in oncology
1248 treatments. All cytotoxic drugs induce asthenia, nausea, vomiting and reversible
1249 myelotoxicity. In addition, etoposide might lead (among other adverse effects) to liver toxicity
1250 and reversible alopecia, doxorubicin to congestive heart failure and reversible alopecia;
1251 cisplatin to renal toxicity, ototoxicity, peripheral neuropathy. In some patients, the risks might
1252 even outweigh the benefits (especially in patients with reduced performance status). If there
1253 are concerns about the use of doxorubicin, cisplatin/carboplatin with or without etoposide
1254 (EP or P) might be an alternative option. Carboplatin may be an alternative to cisplatin,
1255 particularly when cardiac or renal function is compromised. Again, in this cohort, loco-
1256 regional treatment options may be particularly applicable.

1257 Several studies have tried to find biomarkers that predict response to cytotoxic therapy in
1258 ACC {Ronchi, 2009 #320; Malandrino, 2010 #335; Roca, 2017 #319; Laufs, 2018 #336}.
1259 However, no reliable marker could be identified yet.

1260 A few centers prefer the combination of etoposide and cisplatin (EP), because there is no
1261 single study proving that EDP is truly superior to EP. In patients with poor overall health
1262 cisplatin with mitotane may be an option. However, the evidence for etoposide + cisplatin or
1263 cisplatin alone is based only on small phase II studies {Bonacci, 1998 #199; Bukowski, 1993
1264 #200; Williamson, 2000 #213}.

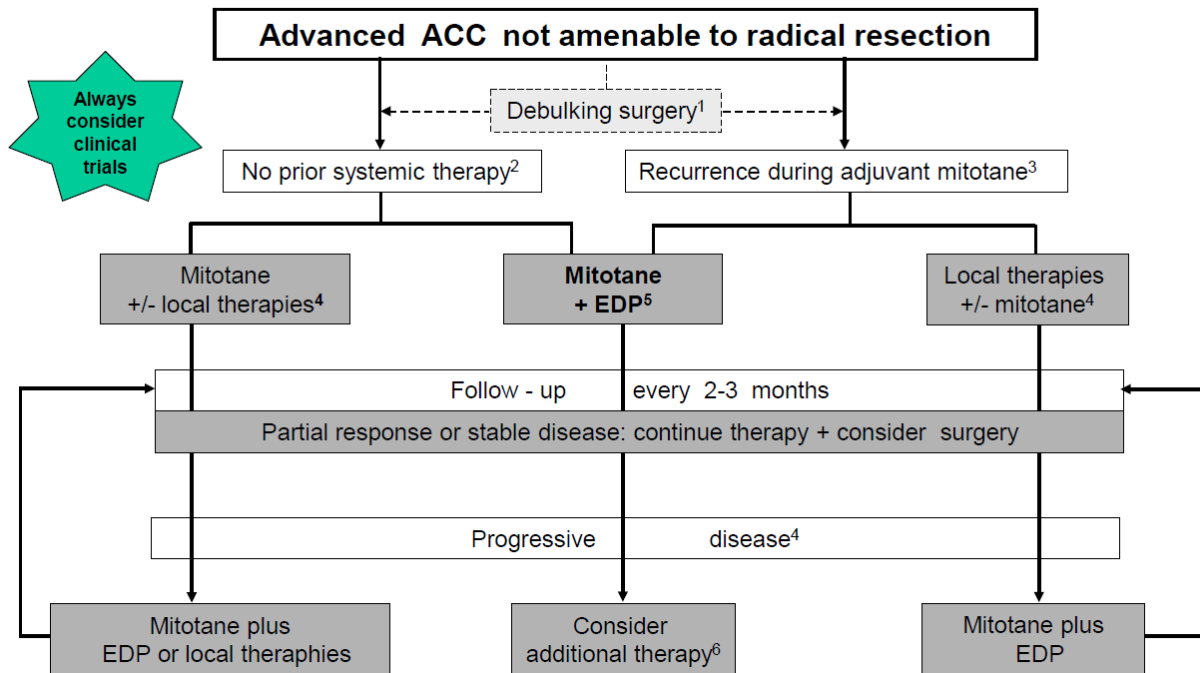
1265 There is limited evidence that standard chemotherapeutic agents may be more active in the
1266 presence of elevated mitotane concentrations {Bates, 1991 #295; Fassnacht, 2012
1267 #28; Sperone, 2010 #32}, but the panel is not in favor in delaying cytotoxic therapy for this
1268 reason for more than 14 days. Several centers start mitotane and cytotoxic therapy in
1269 parallel.

1270

1271 **Figure 4: Treatment of advanced ACC**

1272

Figure 4



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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.

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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.

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Reasoning:

It has been suggested that patients with a 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 {Datrice, 2012 #118;Erdogan, 2013 #55}. 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.

1304 If the recurrence occurs during adjuvant mitotane therapy, additional measures could be
1305 considered. In patients with local recurrence, adjuvant radiation therapy after surgery should
1306 be discussed. In other scenarios, additional administration of cytotoxic drugs should be
1307 discussed with the patient, particularly when mitotane blood levels were in the recommended
1308 range > 14 mg/l.

1309 Patients with early recurrence usually suffer from a very aggressive tumor, which most likely
1310 cannot be controlled by surgery or localized therapies. Decision-making should incorporate
1311 the concern that any local measure will only delay the administration of systemic therapy.
1312 Similar to the discussion to R.9.3, the FIRM-ACT data indicate EDP-M as the most effective
1313 form of therapy. An exception might be patients in whom incomplete initial surgery is the
1314 most likely cause for early progression. In these selected patients repeat surgery at an expert
1315 center might be an appropriate alternative (see R.3.6).

1316 Patients with recurrence between 6 and 12 months after primary surgery usually have a poor
1317 prognosis and would, therefore, benefit from a more aggressive therapeutic approach (e.g.
1318 EDP-M). However, this decision should be discussed with the patient taking into account
1319 prognostic parameters (see section 5.5.), the feasibility of a R0 resection and patient's
1320 general condition. Patients with a disease-free interval > 12 months, in whom complete
1321 resection or loco-regional therapy is not feasible and who are currently not treated with
1322 mitotane, might be good candidates for mitotane monotherapy {Megerle, 2018 #294}.

1323
1324

1325 **R.8.8. In patients who progress under mitotane monotherapy, we recommend to add**
1326 **EDP (+++O).**

1327

1328 Reasoning:

1329 Mitotane is a slow-acting drug and in patients with rapidly progressing tumor, it might be too
1330 slow or not effective enough. In these patients, based on the FIRM-ACT data {Fassnacht,
1331 2012 #28}, additional administration of EDP is the first choice (for alternatives see Reasoning
1332 R.8.4.). However, if the tumor burden is limited despite obvious progression, another 2-3
1333 months mitotane monotherapy could also be justified, particularly if adequate mitotane levels
1334 have not been achieved. In these cases, additional loco-regional options should be
1335 considered.

1336
1337

1338 **R.8.9. In patients who respond to medical therapy (including achievement of long-**
1339 **term stable disease), we suggest re-considering local measures aiming at long-**
1340 **term tumor control. Such an approach could be also considered in patients**
1341 **attaining a generally good control of the disease, in which a limited number of**
1342 **lesions are progressing.**

1343

1344 Reasoning:

1345 In some patients, in whom long-term disease control could be achieved, loco-regional
1346 measures (in addition to ongoing medical therapy) might be able to reach complete
1347 remission or at least significantly reduce tumor burden {Berruti, 2005 #24}. In patients with
1348 "mixed responses"; e.g. progressive disease limited to few lesions, loco-regional options
1349 might be reasonable to add to the ongoing medical therapy.

1350
1351

1352 **R.8.10. In patients who progress under EDP-M we suggest considering additional**
1353 **therapies including clinical trials on an individual basis (+OOO).**
1354

1355 Reasoning:

1356 Several drugs and drug combinations have been tested in advanced ACC. However, except
1357 EDP-M none of them has been successfully evaluated in large randomized trials. Figure 2
1358 outlines the outcomes of the different approaches. However, this figure has to be interpreted
1359 with great caution, because differences in the characteristics of the patients included in the
1360 different cohorts preclude direct comparison between studies. Therefore, it is not possible to
1361 draw definitive conclusions. Due to the limited treatment options, the panel clearly favors
1362 enrollment of patients with progressing tumors in clinical trials investigating experimental
1363 therapies including phase I trials. However, the panel felt that despite the lack of convincing
1364 data, some guidance might be helpful for patients that cannot be enrolled in clinical trials
1365 (Table 6). Beyond cisplatin-based therapies, the two reasonably well-studied second-line
1366 cytotoxic regimens are gemcitabine + capecitabine (+/- mitotane) {Henning, 2017
1367 #215;Sperone, 2010 #32} and streptozotocin + mitotane {Khan, 2000 #296;Fassnacht, 2012
1368 #28}. However, objective response rates are clearly below 10% and median progression-free
1369 survival (PFS) is generally <4 months, but a few patients with long-term disease control and
1370 even complete responses in single patients are described. Nevertheless, a few panelists
1371 argued against the use of streptozotocin, because median PFS in the FIRM-ACT trial was
1372 only two months {Fassnacht, 2012 #28}. As for EDP, these cytotoxic drugs should be
1373 administered only by physicians experienced with chemotherapy. Typical adverse effects of
1374 streptozotocin are nausea, vomiting, diarrhea, renal and liver toxicity and of the association
1375 gemcitabine and capecitabine nausea, vomiting and reversible myelotoxicity.
1376 Loco-regional measures can be particularly useful when progression is limited, or only
1377 affects limited areas (e.g. single organs). In these cases, such localized therapies (see
1378 R.8.2) might be able to provide higher response rates for these specific organ/tissue areas
1379 than second line systemic options.

1380 Several tyrosine kinase inhibitors have been investigated in advanced ACC {Berruti, 2012
1381 #23;Fassnacht, 2015 #27;Kroiss, 2012 #207;O'Sullivan, 2014 #209}, but the results were
1382 largely disappointing. However, in retrospect, drug efficacy could have been hampered by
1383 increased metabolism of the TKI due to mitotane-induced CYP3A4 activity. Nevertheless,
1384 currently no specific TKI can be suggested for the treatment of advanced ACC. Targeting the
1385 IGF2/IGF receptor signaling pathway was pathophysiologically a very promising approach
1386 and initial small studies suggested some efficacy {Almeida, 2008 #303;Boulle, 1998
1387 #304;Gicquel, 1994 #305;Giordano, 2003 #306;Weber, 2000 #307;Haluska, 2010
1388 #204;Jones, 2015 #299;Lerario, 2014 #216;Naing, 2011 #301;Naing, 2013 #208}. However,
1389 the large placebo-controlled phase III GALACCTIC trial demonstrated that the IGF1R
1390 inhibitor linsitinib did not improve progression-free or overall survival {Fassnacht, 2015 #27}.
1391 Therefore, monotherapy with drugs targeting this pathway are not reasonable for therapy in
1392 an unselected patient population.

1393
1394
1395 **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)** {Fassnacht, 2012 #28}
every 28 days:
 - day 1 40mg/m² doxorubicin (D)
 - day 2 100mg/m² etoposide (E)
 - day 3+4 100mg/m² etoposide (E) + 40mg/m² 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/m² etoposide (E)
 - day 2+3 100mg/m² etoposide (E) + 40mg/m² cisplatin (P)

Additional therapeutic options

- **Consider enrollment of patients in clinical trials (www.clinicaltrial.gov)**
- **Consider loco-regional therapies**
- **Gemcitabine plus capecitabine** {Henning, 2017 #215; Sperone, 2010 #32}
800 mg/m² 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)** {Fassnacht, 2012 #28}
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

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1397

1398

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.

1399

1400

1401 Reasoning:

1402

A recent cohort study reported that discontinuation of mitotane should be considered in patients who experienced progressive disease after one year of mitotane therapy {Vezzosi, 2018 #308}. 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 {Kroiss, 2011 #72}, including a number of experimental anti-ACC compounds, and so potentially limit their effectiveness.

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1410 **5.9. Special considerations on mitotane**

1411
1412 If mitotane therapy is started (independent of the clinical scenario) the following issues have
1413 to be considered.

1414
1415 **R.9.1. We recommend starting therapy with mitotane in an escalating regimen**
1416 **depending on the performance status of the patient as well as the tolerability in**
1417 **the first weeks.**

1418
1419 Reasoning

1420 There are different regimens to administer mitotane, but none of them has been proven to be
1421 superior. In patients with good performance status some panelists use a high starting dose
1422 approach: mitotane is administered at a starting dose of 1.5 g/day and if well-tolerated from a
1423 gastrointestinal perspective the dose is increased on day two to 3 g/day, on day three to 4.5
1424 g/day, and on day four to 6 g/day {Faggiano, 2006 #309;Mauclere-Denost, 2011 #310}. This
1425 dosage will be administered until first mitotane blood level is assessed. In this high dose
1426 regimen, it is strongly recommended to measure mitotane blood levels 2-3 weeks after
1427 initiation of therapy. Afterwards dosage will be adjusted according to blood concentrations
1428 and tolerability. Other panelists prefer a low starting dose approach. With this approach,
1429 mitotane is administered at a starting dose of 1 g/day and increased when there is good
1430 gastrointestinal tolerance every 3 days by 0.5 g up to a total dose of 3.0 - 4.0 g/day and then
1431 adjusted according to blood concentrations and tolerability {Terzolo, 2000 #311;Terzolo,
1432 2008 #364;Terzolo, 2014 #363}.

1433 In a formal comparative pharmacokinetic study, the high-dose starting regimen led to slightly
1434 higher mitotane plasma levels within 12 weeks of treatment, and more patients reached the
1435 target level of 14 mg/L {Kerkhofs, 2013 #38}. However, these results were not statistically
1436 significant due to lack of power. Beyond these two regimens, there is a variety of other
1437 possibilities and choice depends on personal practice, clinical scenario and patient
1438 conditions.

1439 Mitotane is a lipophilic drug and is supposed to be better absorbed from the gut with a high
1440 fat content of the diet, e.g. with milk or chocolate. {Moolenaar, 1981 #374}. In case of limited
1441 gastrointestinal tolerance, symptomatic treatments of nausea and or diarrhea may be
1442 proposed.

1443
1444 **R.9.2. We recommend monitoring of blood concentration of mitotane. The general aim**
1445 **is to reach a mitotane blood level above 14 mg/L (+OOO).**

1446
1447 Reasoning

1448 As long as mitotane plasma levels are increasing and have not yet reached a plateau at
1449 >14mg/L, mitotane plasma levels will be assessed every 3-4 weeks. Mitotane plasma level
1450 determination is best done as morning trough sampling, at least 12 hours after the last dose,
1451 preventing false high levels {Kerkhofs, 2014 #351}. When mitotane plasma levels have
1452 reached a plateau, it is usually sufficient to measure blood levels every 6-12 weeks.

1453 Usually it takes several weeks (sometimes months) to reach mitotane levels > 14 mg/L. As
1454 long as the concentration is < 14 mg/L it is reasonable to continue to increase the dosage if
1455 this is tolerated by the patient. Due to slow pharmacokinetic characteristics, the dose of
1456 mitotane can be reduced in most patients as soon as a plasma level of > 14mg/L is reached.
1457 Over time, mitotane dosage will be titrated to the best tolerable dose while maintaining a

1458 plasma level >14mg/L. Most patients experience adverse effects to a certain extent and
1459 these usually correlate with the plasma mitotane level (although there is major inter-individual
1460 variability) (see Table 7). However, some gastrointestinal adverse effects (like diarrhea)
1461 seem to correlate more with the oral dosage than with the plasma level and occur more
1462 frequently in the first phase of treatment {Terzolo, 2000 #311;Allolio, 2006 #236;Daffara,
1463 2008 #25;Terzolo, 2008 #364;Terzolo, 2014 #363}. Several studies {van Slooten, 1984
1464 #312;Baudin, 2001 #197;Haak, 1994 #202} have shown that CNS-related adverse events in
1465 particular occur more frequently when the plasma mitotane is > 20 mg/L. Therefore, many
1466 experts recommend aiming to keep plasma concentrations below 20 mg/L. However, it can
1467 be speculated that higher plasma levels may also be associated with better clinical efficacy.
1468 Furthermore, some patients do not experience relevant adverse events even at plasma
1469 levels well above 20 mg/L. Regarding the lower limit it has to be acknowledged that in at
1470 least a few patients objective responses are seen even though plasma levels of >14 mg/l
1471 were not achieved {Megerle, 2018 #294}. Therefore, some panelists favored a target range
1472 of plasma mitotane of 8-30 mg/L, whereas others aim at an individualized target level of
1473 mitotane.

1474
1475 Most studies addressing plasma mitotane levels analyze patients with advanced disease.
1476 However, there is one study suggesting that the same target level is also reasonable for the
1477 adjuvant setting {Terzolo, 2013 #313}. Therefore, the panel is in favor to use the same
1478 approach for both patient groups.

1479
1480
1481 **R.9.3. We recommend glucocorticoid replacement in all patients treated with mitotane**
1482 **(except those with ongoing cortisol excess). We suggest to using**
1483 **hydrocortisone/cortisone acetate for this purpose. Due to increased steroid**
1484 **clearance and increase cortisol-binding globulin at least twice the standard**
1485 **replacement dose is usually required.**

1486
1487 Reasoning
1488 A possible strategy is to start concomitant treatment on day one of mitotane treatment with
1489 hydrocortisone 20 mg/d. Alternatively, patients can be instructed to start hydrocortisone later
1490 (e.g. after 2-3 weeks or in case they experience adrenal insufficiency), because impairment
1491 of glucocorticoid effectiveness is rarely observed within the first few weeks. Due to the
1492 increased clearance and increased cortisol-binding globulin {Daffara, 2008 #25;Chortis, 2013
1493 #52;Reimondo, 2017 #349;Kerkhofs, 2015 #39} with increasing mitotane plasma levels and
1494 based on clinical symptoms, the total hydrocortisone replacement dose will usually increased
1495 to a typical total daily dose of 50 mg in two or three divided doses. However, some patients
1496 require daily dosages up to 100 mg. There is no reliable laboratory marker to guide the
1497 optimal dosage of hydrocortisone {Reimondo, 2017 #349}, which has to be based on clinical
1498 judgment similar to the management of patients with adrenal insufficiency {Bornstein, 2016
1499 #314}. Mitotane-induced increase in cortisol-binding globulin may confound interpretation of
1500 serum cortisol measurement. The measurement of free cortisol may offer additional
1501 information, but more studies are required to clarify the value of this method {Alexandraki,
1502 2010 #325}. Some panelists measure plasma ACTH and use ACTH levels more than 2-fold
1503 of the upper limit of normal as evidence for insufficient glucocorticoid replacement. Other
1504 centers prefer a combined measurement of plasma ACTH and 24-hour urine free cortisol
1505 levels to assess adequacy of and optimize glucocorticoid replacement for patients receiving

1506 mitotane. However, when urinary cortisol is measured by immunoassays, interference by
1507 cortisol metabolites induced by mitotane might occur.

1508 In case of acute adverse events and/or hospital admission, patients should be treated
1509 intravenously with high-dose hydrocortisone (e.g. 100 mg TID) until resolution of symptoms.

1510 Some patients experience symptoms and signs of insufficient mineralocorticoid activity
1511 (hyperkalemia, hyponatremia, hypotension, decreased wellbeing) despite full-dose
1512 substitution with hydrocortisone. In these patients, addition of fludrocortisone should be
1513 considered. Clinical judgment, electrolytes, and plasma renin concentration can be used for
1514 decision making whether to start fludrocortisone {Allolio, 2006 #236;Daffara, 2008
1515 #25;Terzolo, 2008 #364;Terzolo, 2014 #363}.

1516
1517

1518 **R.9.4. We recommend regular monitoring of mitotane-induced adverse effects (Table**
1519 **7) and to treat them appropriately (Table 8). To increase tolerability of mitotane,**
1520 **we suggest starting supportive therapy ideally before severe toxicity occurs.**

1521
1522

Reasoning

1523 In addition to adrenal insufficiency (see R.9.3.) mitotane treatment comes with a plethora of
1524 potential adverse events {Daffara, 2008 #25}(Table 2). Therefore, it is important to evaluate
1525 the patients regularly (e.g. in the first 6 months every 3-4 weeks, thereafter every 6-12
1526 weeks).

1527 Gastrointestinal adverse effects are frequent, particularly in the first months of therapy.
1528 Supportive therapy should include antiemetic and anti-diarrheal medication, as needed.
1529 Some centers even start supportive therapy at initiation of mitotane therapy. However, one
1530 has to be aware that nausea may also be a sign of adrenal insufficiency that needs
1531 recognition and appropriate treatment. Nevertheless, it should be emphasized that despite
1532 optimization of dosing schedules, the key factor influencing build-up of appropriate mitotane
1533 plasma levels is patient tolerability, so efforts should be made in order to optimize this.

1534 In case of central nervous system (CNS) adverse effects grade 2 (moderate) and/or gastro-
1535 intestinal adverse effects grade 3 (severe, but not life-threatening), mitotane dose should be
1536 reduced by 1-1.5 gram/day. In case of CNS severe, but not life-threatening (grade 3) adverse
1537 effects or any relevant grade 4 toxicity (life-threatening), and/or increase of liver enzymes >5
1538 times baseline (except GGT), mitotane should be interrupted until significant improvement of
1539 symptoms occurs and be restarted at 50–75% of the last dose.

1540 Assessment of thyroid hormone status (TSH, FT4, every 3 months) is advised as mitotane
1541 may induce a clinical picture similar to central hypothyroidism {Daffara, 2008 #25;Russo,
1542 2016 #365}, possibly through a direct effect on the pituitary gland or induction of thyroid
1543 hormone metabolism. Replacement therapy with levothyroxine can be considered for these
1544 patients.

1545 In men with signs of hypogonadism, assessment of testosterone and sex hormone-binding
1546 globulin levels is warranted, as hypogonadism is common {Daffara, 2008 #25}. Mitotane-
1547 induced increase in SHBG may confound interpretation of testosterone measurement.
1548 Testosterone supplementation may be considered in patients with low testosterone and
1549 symptoms of hypogonadism, but inhibition of 5- α reductase might prevent full activity of
1550 testosterone {Chortis, 2013 #52}.

1551 Ovarian steroid synthesis is less affected but women in childbearing age treated with
1552 mitotane may develop multiple, and sometimes huge, ovarian cysts that may be painful and
1553 sometimes require treatment.

1554 Cholesterol levels very frequently increase during mitotane treatment {Tada, 2014 #332}.
 1555 Hypercholesterolemia can be treated with statin therapy using agents not metabolized by
 1556 CYP3A4 (e.g. rosuvastatine or pravastatine). However, HDL cholesterol is usually also
 1557 elevated significantly and this should be taken in consideration. Thus, statin therapy might
 1558 only be beneficial in selected patients (e.g. with good prognosis in an adjuvant setting, high
 1559 LDL cholesterol and additional high cardiovascular risk factors). Therefore, an individual
 1560 decision making regarding the benefits of any lipid lowering therapy is necessary.
 1561 Psychological and social aspects of treatment should not be neglected, i.e., professional
 1562 counseling may be warranted. Follow-up on patient's well-being may be performed by
 1563 questionnaire-based assessment of toxicity upon the start of the treatment and by repeating
 1564 this assessment every 3 months.

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 1567 **R.9.5. We recommend being aware of significant drug interactions of mitotane (e.g.
 1568 due to strong induction of CYP3A4). All concomitant medication should be
 1569 checked for CYP3A4 interactions and substituted for an alternative if necessary
 1570 and available. Other care-providers should be advised not to initiate other drug
 1571 therapies without consultation.**

1572
 1573 Reasoning
 1574 A comprehensive (but not exhaustive) summary of relevant drug interactions with mitotane is
 1575 provided in Kroiss et al. {Kroiss, 2011 #72} and in the Appendix 7.

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1579 **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	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 and barbiturates, phenytoin, warfarin, and many other drugs (see Appendix 7)	very common 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
• Gynecomastia	very common
• Skin rash	common
• Primary hypogonadism in men	common
• Prolonged bleeding time	common
• Leucopenia	common
• Thrombocytopenia, anemia	rare
• Autoimmune hepatitis	rare
• Cardiovascular: hypertension	not known
• Ocular: blurred or double vision, toxic retinopathy, cataract, macular edema	not known
• Hemorrhagic cystitis	not known

1581 **modified by the authors based on information published by the European Medicine Agency*
 1582 *(EMA):*
 1583 [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000521/human](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000521/human_med_000895.jsp&mid=WC0b01ac058001d124)
 1584 [_med_000895.jsp&mid=WC0b01ac058001d124](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000521/human_med_000895.jsp&mid=WC0b01ac058001d124) *and clinical experience*

1585 *Frequency is defined according to the following convention: very common ($\geq 1/10$), common*
1586 *($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare*
1587 *(< $1/10,000$), Not known (cannot be estimated from the available data)*
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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

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5.10. Other supportive therapies

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

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Reasoning

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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 {Nieman, 2015 #133}. In selected patients, surgery might even be postponed for few weeks until Cushing's syndrome is partly under control with the use of rapid agents inhibiting steroidogenesis (i.e. metyrapone). However, some panelists argued that surgery might be the fastest way to control severe hypercortisolism.

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

1623 association with mitotane and cytotoxic chemotherapy {Claps, 2017 #131}. Moreover, its
1624 metabolism and elimination are not altered by concomitant mitotane. Ketoconazole an
1625 inhibitor of several key cytochrome P450 (CYP) enzymes involved in multiple steps of
1626 steroidogenesis in the adrenal cortex, is another alternative, but often less effective than
1627 metyrapone and requires regular monitoring of liver function tests. Its advantage is that it
1628 also inhibits androgen production. Ketoconazole should be avoided at initiation of mitotane
1629 therapy because both substances are potentially hepatotoxic and it will be difficult to attribute
1630 the hepatotoxicity to one or the other drug. Hypercortisolemia can also be treated with
1631 mifepristone, a glucocorticoid antagonist, but dosing is based on clinical judgement as
1632 cortisol levels remain elevated or rise further on therapy {Castinetti, 2009 #132}. Moreover,
1633 the high circulating cortisol levels when on mifepristone may cause mineralocorticoid effects,
1634 including hypertension and hypokalemia that necessitate treatment with high doses of
1635 spironolactone. Patients treated with enzyme inhibitors or receptor antagonists need to be
1636 educated about symptoms and signs of adrenal insufficiency. All patients at risk for adrenal
1637 insufficiency need to be supplied with emergency medication and instructions. Intravenous
1638 etomidate can be used for seriously ill patients with severe hypercortisolemia who cannot
1639 take oral medication.

1640 In the management of severe Cushing's syndrome, locoregional options (see R.8.2.) should
1641 also be discussed, in selected cases.

1642 Androgen excess in women can impact quality of life due to hirsutism and virilization. It can
1643 be treated with androgen receptor antagonists, such as bicalutamide, flutamide, or
1644 spironolactone.

1645 Only a small fraction of all tumors produce aldosterone, leading to hypertension and
1646 hypokalemia. Mineralocorticoid excess is best treated with mineralocorticoid receptor
1647 antagonists, such as spironolactone or eplerenone. However, patients with severe Cushing's
1648 syndrome may also experience hypokalemia, related to mineralocorticoid receptor activation.
1649 In case of severe hypokalemia, spironolactone and epithelial sodium channel inhibitors such
1650 as amiloride can be used, potentially at high doses, along with potassium supplementation.
1651 In such cases, frequent serum electrolyte measurement, initially several times a week, are
1652 mandatory, as there is a risk of rapid occurrences of hyperkalemia and hyponatremia.

1653 In the rare situation of estradiol production by tumors in male patients, therapy with estrogen
1654 receptor antagonists or aromatase inhibitors could be considered.

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1657 **R.10.2. We recommend therapy with anti-resorptive treatment in patients with bone**
1658 **metastasis.**

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1660

Reasoning

1661 Bone metastasis in cancer patients are associated with poor quality of life due to bone pain
1662 and increased risk of adverse skeletal-related events (SREs) such as pathological fractures,
1663 spinal cord compression and hypercalcemia. Several randomized phase III trials have
1664 demonstrated that bone resorption inhibitors such as bisphosphonates and denosumab are
1665 efficacious in the prevention of skeletal-related events in patients with bone metastasis from
1666 breast, prostate, lung and others primary malignancies. No data are available for ACC
1667 patients. However, based on these results, it has become general practice to treat patients
1668 with any kind of bone metastasis with anti-resorptive therapies. The administration of
1669 denosumab or bisphosphonates in 'oncological doses' in association with calcium intake and
1670 vitamin D supplementation are therefore advisable in ACC patients with metastatic bone

1671 disease, with the aim to prevent adverse skeletal-related events and improve control of bone
1672 pain.

1673 In patients with ACC with Cushing's syndrome that cannot be otherwise controlled anti-
1674 resorptive treatment, using 'anti-osteoporotic doses', should be considered, because it is well
1675 established that glucocorticoid-excess increases the risk of osteoporotic fractures. Since
1676 fracture risk declines rapidly after lowering excess cortisol, or antagonizing its effects, anti-
1677 osteoporotic therapies are usually not required once cortisol secretion is controlled (either by
1678 surgery or medical therapy).

1679

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1681 **R.10.3. We recommend palliative radiation for symptom palliation in**
1682 **advanced/metastatic ACC patients**

1683

1684 Reasoning

1685 Palliative radiation therapy is a commonly utilized intervention for symptom relief among
1686 patients with metastatic cancer. Two schedules of irradiation are commonly used, which
1687 include 8 Gy in a single fraction or 30 Gy in ten fractions. This treatment modality is highly
1688 effective in achieving relief of symptoms arising from bone metastases, with positive
1689 responses in up to 50% - 90% of cancer patients {Chow, 2012 #355;Pin, 2018 #356}. Painful
1690 bone metastases are, therefore, the main indication of palliative radiation in metastatic ACC
1691 patients {Polat, 2009 #73}. Other indications are symptomatic recurrences, severe mass
1692 effect and the rare case of brain metastases.

1693

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1695 **R.10.4. We recommend integrating palliative care into standard oncology care for all**
1696 **patients with advanced ACC**

1697

1698 Reasoning

1699 According to the WHO palliative care is defined as 'an approach that improves the quality of
1700 life of patients and their families facing the problems associated with life-threatening illness,
1701 through the prevention and relief of suffering by means of early identification and impeccable
1702 assessment and treatment of pain and other problems, physical, psychosocial and spiritual'
1703 (WHO: WHO definition of palliative care. <http://www.who.int/cancer/palliative/definition/en/>).

1704 As previously stated, the goal of care for metastasized ACC is to obtain long-term disease
1705 control and prolong patient survival. Although prognosis of patients with advanced ACC is
1706 often poor, there is a patient subset destined to obtain a relatively long survival, while treated
1707 with antineoplastic therapies. The needs of patients with cancer and their families have
1708 changed over time. According to the ASCO guidelines the best model to manage metastatic
1709 patients is to integrate palliative care early in the course of the disease and throughout the
1710 trajectory of care, extending to long-term survivorship as well as end-of-life (hospice) care. In
1711 this integrated approach the primary endocrinologists and oncologists focus on the primary
1712 oncologic disease, and the palliative care team addresses the majority of the patient's
1713 physical and psychological concerns. The team plans all therapy aiming to integrate patient
1714 wishes and employ treatment options balancing quality of life and increased survival with
1715 therapy associated risks and complications {Ferrell, 2017 #316}.

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1719 **R.10.5. We suggest counseling for fertility protection in female patients in**
1720 **reproductive age. Fertility counseling should not only be restricted to patients**
1721 **undergoing cytotoxic chemotherapy, but also given to patients who plan to**
1722 **embark on mitotane therapy.**

1723

1724 Reasoning

1725 A considerable proportion of patients are diagnosed with ACC during their reproductive
1726 years. Several drugs used to treat ACC harbor significant risk for impairment of fertility or the
1727 exact risks are unknown (e.g. mitotane). On the other hand, in recent years several treatment
1728 options for preservation of fertility have been introduced. However, none of them has gained
1729 general acceptance. Therefore, we just advise to discuss this topic with every patient. This
1730 discussion should include the consideration given in section 5.12. on pregnancy and ACC in
1731 general.

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1735 **5.11. Genetic counseling**

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1737 **R.11.1. For adults with ACC, we recommend at least a basic clinical genetic**
1738 **evaluation, exploring personal and family history for evidence of a hereditary**
1739 **predisposition syndrome.**

1740

1741 Reasoning

1742 The detection of germline mutations impacts on the clinical care and surveillance of index
1743 patients and offers the possibility to identify at risk family members. Probably, up to 5% of
1744 adult ACC arise in patients with germline *TP53* mutations {Herrmann, 2012 #287;Raymond,
1745 2013 #289;Waldmann, 2012 #77} and about 3% of all ACC patients have an underlying
1746 diagnosis of Lynch syndrome {Raymond, 2013 #288;Zheng, 2016 #16}. Special attention
1747 should be given to these two hereditary syndromes, because for them there are well-
1748 established screening guidelines available {Stoffel, 2015 #367;Daly, 2017 #368;Kratz, 2017
1749 #370;Ballinger, 2017 #369;Gupta, 2017 #366}. Up to 13% of all adrenal lesions in patients
1750 with MEN1 represent adrenal cancer (22084155). Cases of ACC have been reported in
1751 patients with Beckwith-Wiedemann syndrome (children), Familial Adenomatous Polyposis
1752 (APC) and Carney Complex {Petr, 2016 #34}.

1753 Germline genetic testing for ACC patients should primarily be considered for the genes
1754 related to Li-Fraumeni syndrome and Lynch syndrome. ACC is an integral part of Li-
1755 Fraumeni syndrome and when considering germline genetic testing, it is important to keep in
1756 mind that at least 20% of germline *TP53* pathogenic variants occur as de novo mutations in
1757 the absence of any family history. Lynch syndrome is present in the same fraction of ACC
1758 patients as in colorectal cancer patients (3-5%), where general screening for Lynch
1759 syndrome is recommended {Stoffel, 2015 #367;Stoffel, 2015 #372}. Both, Li-Fraumeni
1760 syndrome and Lynch syndrome have well established surveillance guidelines for carriers of
1761 pathogenic variants {Stoffel, 2015 #367;Daly, 2017 #368;Kratz, 2017 #370;Ballinger, 2017
1762 #369;Gupta, 2017 #366}. Evaluation for Lynch syndrome can be initiated by
1763 immunohistochemistry for MSH2, MLH1, PMS2, MSH6 and microsatellite instability testing,
1764 or direct genetic germline analysis of *MSH2*, *MLH1*, *PMS2*, *MSH6* and *EPCAM*. Genetic
1765 diagnosis of Li-Fraumeni syndrome is usually done by germline analysis for variants in *TP53*.

1766 For other syndromes (depending on family history and clinical suspicion) we refer to other
1767 sources {Petr, 2016 #34;Else, 2012 #290}.

1768 Although not the topic of this guideline, all children with a diagnosis of ACC should undergo a
1769 systematic search of germline *TP53* pathogenic variants, because 50-90% of ACC in
1770 children are related to germline pathogenic *TP53* variants {McDonnell, 2003 #291;Custodio,
1771 2013 #293;Wasserman, 2015 #292}

1772

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1774 **R.11.2. The panel does not recommend for or against genetic tumor testing for**
1775 **somatic alterations.**

1776

1777 Reasoning

1778 While the panel recognizes that there is great hope that testing for somatic mutations and
1779 other markers in cancers general may allow tailoring of therapy and personalized
1780 approaches for therapy, for ACCs this approach is not yet established in routine clinical
1781 practice. Therefore, molecular testing should be offered within the framework of structured
1782 and systematic research projects.

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1786 **5.12. Pregnancy and ACC**

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1789 **R.12.1. When an adrenal mass suspected to be an ACC is diagnosed during**
1790 **pregnancy, we recommend prompt surgical resection regardless of pregnancy**
1791 **trimester.**

1792

1793 Reasoning

1794 Considering the poor prognosis of ACC and the importance of a prompt and complete
1795 surgical removal for prognosis, adrenal surgery should be pursued independent of the term
1796 of the pregnancy {Eschler, 2015 #129}. Preterm delivery (especially in the third trimester)
1797 and pregnancy loss are obvious risks when surgery is performed. Therefore, the patient and
1798 their family, obstetric providers and the ACC care team must engage in an informed
1799 discussion considering disease prognosis and the risk to the mother and fetus as related to
1800 the underlying disease and interventional procedures. A shared decision-making after
1801 discussion of all options is imperative.

1802

1803

1804 **R.12.2. Patients should be informed on pregnancy-related concerns specific to the**
1805 **current or past diagnosis of ACC.**

1806

1807 Reasoning

1808 No evidence is available regarding how long patients should wait after the treatment of an
1809 ACC before they can safely consider pregnancy.

1810 Importantly, the main concern is the poor prognosis of the malignant tumor and the potential
1811 that pregnancy could be a negative prognostic factor, possibly increasing the risk of
1812 recurrence. There is limited evidence that ACC occurring during pregnancy or in the
1813 postpartum period is associated with a worse prognosis than in non-pregnant women

1814 {Abiven-Lepage, 2010 #315}. The hypothesis that pregnancy could favor the development of
1815 a more aggressive variant of ACC was raised.

1816 Due to the extreme paucity of information about this issue, it seems prudent to relay the
1817 information to the patient that there is a substantial risk of disease recurrence in the first
1818 years following the diagnosis of ACC.

1819 Since ACC may express estrogen receptors and there are preclinical data showing that
1820 estrogen may facilitate tumor development and progression through cross-talk with the IGF
1821 pathway {Sirianni, 2012 #317}, contraceptive measures other than estrogen-containing
1822 preparations are preferred.

1823

1824

1825 **R.12.3. We recommend avoiding pregnancy while being on mitotane treatment.**

1826

1827 Reasoning

1828 The main concern with mitotane therapy is the potential of teratogenic effects, due to the
1829 suspicion that the drug may cross the placenta and cause adrenolytic activity on the human
1830 fetus. However, there are only few case reports of pregnancies when on mitotane therapy
1831 {Tripto-Shkolnik, 2013 #130}. Therefore, it is impossible to draw definitive conclusions about
1832 the safety of mitotane treatment or its associated risks. Woman treated with mitotane should
1833 be informed about these risks, and ensure effective contraception to avoid pregnancy.
1834 Moreover, when mitotane treatment is discontinued, it seems wise to ensure undetectable
1835 mitotane plasma levels before considering pregnancy {de Corbiere, 2015 #318}, which might
1836 take 3-12 months. In case a patient becomes pregnant while on mitotane therapy, the
1837 uncertainty regarding risks of mitotane for the fetus should be discussed. In case the patient
1838 wishes to continue pregnancy mitotane therapy should be withheld.

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1843 **6. Future directions and recommended research**

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1845 Due to the fact that the evidence for most of the recommendations provided in these
1846 guidelines is weak or even very weak, there are no doubts that major efforts are needed to
1847 improve diagnosis, treatment, and quality of life for patients with ACC.

1848 Among many important research questions, we selected ten topics as particularly important.
1849 All of them can only be addressed in an international collaborative interdisciplinary manner.

1850 1) Clinical response to the best available therapy (i.e. EDP + mitotane) for advanced ACC is
1851 very limited with an objective response rate of less than 25%. Therefore, we undeniably
1852 lack efficient drugs for treating this disease. Thus, identifying new therapeutic targets and
1853 options is a high priority. Here is a comprehensive but by far not complete list of
1854 emerging therapies: internal radionuclide therapy, such as metomidate-based therapies;
1855 drugs targeting the following pathways or targets: Wnt/beta-catenin; CDKN2A / TP53 /
1856 RB; IGF2 / mTOR; telomeres; drugs targeting histone modifications. In general, a
1857 combined approach seems to be reasonable. There is a growing notion that individual
1858 patients and individual tumors might respond better to certain therapies, depending on
1859 their molecular landscape. Therefore, studies focusing on subgroup classification and
1860 identification are important. Due to the mitotane-associated pharmacological issues (e.g.

1861 CYP3A4 induction), it might be reasonable to test experimental drugs in mitotane-naïve
1862 patients within clinical studies.

1863 2) Immunotherapy is the latest revolution in cancer therapy, however preliminary data with
1864 single immune check point inhibitors showed a modest activity in ACC patients. Molecular
1865 and oncogenic pathways either in tumor cells or tumor microenvironment that can impair
1866 induction or execution of a local antitumor immune response should be carefully studied in
1867 ACC.

1868 3) Since currently available systemic therapies have limited efficacy, but a subgroup of
1869 patient is destined to obtain a consistent benefit from them, the identification of predictive
1870 markers of efficacy (either clinical or molecular) of standard treatments is of paramount
1871 importance in order to spare toxic regimens to patients not destined to obtain a disease
1872 response.

1873 4) With regards to improvement of surgery for ACC, standardization of procedures (e.g.
1874 laparoscopic vs. open surgery, lymph node dissection) should be promoted and tested in
1875 clinical trials.

1876 5) The high recurrence rate in the majority of patients even after complete resection calls for
1877 improvement of adjuvant therapy. There are significant gaps in our understanding, which
1878 patients might truly benefit from the different adjuvant therapies and prospective trials are
1879 urgently needed. The ongoing ADIUVO trial will hopefully provide important information for
1880 low/intermediate risk patients, but a trial in high-risk patients (e.g. mitotane vs. mitotane +
1881 cisplatin + etoposide) is equally important.

1882 6) Despite extensive efforts, the mechanism of action and pharmacodynamics of mitotane
1883 remain poorly understood {Hescot, 2015 #338;Hescot, 2013 #339;Sbiera, 2015
1884 #337;Hescot, 2017 #340}. In addition, mitotane is a strong inducer of xenobiotics
1885 metabolism, probably negatively impacting subsequent and parallel therapies. Therefore,
1886 further understanding and improving the pharmacology and mechanism of action of
1887 mitotane with the goal of development of mitotane related drugs that do not share the
1888 negative adverse-effects would be a significant goal.

1889 7) Translational research with the goal of rational treatment stratification should be promoted.
1890 Recent molecular classifications, identifying distinct molecular subtypes with different
1891 outcomes, should be tested prospectively. These markers could provide a cornerstone for
1892 stratifying treatment strategies. This would mean that some patients of the 'better
1893 outcome' molecular group might benefit from forgoing any adjuvant therapy. Reversely,
1894 patients in the "poor outcome" molecular group could be included in a randomized trial
1895 testing mitotane + cytotoxic drugs as an adjuvant therapy. In addition, it will be important
1896 to define differences in pharmacogenomics or tumor genomics that define exceptional
1897 responders to mitotane and/or EDP. This data can fuel further sub-stratification of ACC
1898 patients for certain therapies.

1899 8) In addition to improving treatment, other future research directions may include the use of
1900 artificial intelligence in diagnostic work-up of adrenal tumors and the improvement of
1901 screening and follow-up procedures using non-invasive techniques such as urine or
1902 serum steroid metabolomics {Arlt, 2011 #48;Kerkhofs, 2015 #40;Taylor, 2017 #341;Hines,
1903 2017 #342} or 'liquid biopsies' with circulating tumor cells {Pinzani, 2013 #343}, circulating
1904 miRNAs {Chabre, 2013 #344;Szabo, 2014 #345;Perge, 2017 #346}, or circulating cell-free
1905 tumor DNA {Creemers, 2017 #347;Garinet, 2018 #348} for early diagnosis or detection of
1906 recurrence.

1907 9) In the long term, a better understanding of the pathogenesis of ACC is needed to pave the
1908 way for future progress. Therefore, basic research efforts have to continue. Preclinical

1909 models are needed, to test new treatments, including additional new cell lines, tumor
1910 organoids, and new animal models. Mechanisms of tumorigenesis, tumor evolution
1911 (genetic heterogeneity, clonal evolution) and further definition of known and future
1912 therapeutic targets should be encouraged.

1913 10) No studies so far have revealed the wishes and experiences of patients. Given the poor
1914 prognosis and the toxic therapies, there is a definite need for 'Patient Related Outcomes'.
1915 PRO's should be measured (PROM's) and incorporated in our strategy for value based
1916 cure and care.

1917
1918 In general, it is our common task to overcome the major limitation in ACC research – the
1919 rarity of this disease. Therefore, beyond proofs of concept requiring few patients, clinical
1920 trials can only be performed if a large number of centers gather multicenter studies. This
1921 underscores the critical role of adrenal research networks, such as ENSAT or A5, to
1922 coordinate these efforts. Ideally a limited number of large prospective trials should
1923 continuously be ongoing, in order to allow for sufficient patient recruitment. In the same
1924 context we envision that at least one reference center in every country will be established to
1925 provide multidisciplinary expertise for this rare disease to all patients.

1926
1927 Altogether, owing to its rarity and its severity, ACC should continue to mobilize researchers,
1928 physicians and patients in a coordinated engaged effort.

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Appendices

- 1934 • Appendix 1: Question 1: Pathology - what is needed to diagnose an ACC? Summary
1935 of included studies (1a: distinguishing adrenal from non-adrenal tumors; 1b:
1936 distinguishing benign from malignant behavior in adrenal tumors)
- 1937 • Appendix 2: Question 2: Which are the best prognostic markers in ACC? Summary of
1938 included studies
- 1939 • Appendix 3: Question 2: Prognostic factors in ACC - overview of studies markers
- 1940 • Appendix 4: Question 3: Is adjuvant therapy able to prevent recurrent disease or
1941 reduce mortality after radical resection? Summary of included studies (3a: Adjuvant
1942 mitotane after surgery; 3b: Adjuvant radiotherapy after surgical resection)
- 1943 • Appendix 5: Evidence tables Question 3 (adjuvant therapy)
- 1944 • Appendix 6: Question 4: What is the best treatment option for macroscopically
1945 incompletely resected, recurrent or metastatic disease? Summary of included studies
- 1946 • Appendix 7: Summary of relevant drug interactions with mitotane
- 1947 • Appendix 8: Comments to this Guidelines by invited reviewers and members of the
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1952

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1955
1956

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1960

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1967
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Declaration of potential conflict of interests (in the last 5 years)

1969

1970
1971 Guillaume Assié

- 1972 • Speakers fee / travel support for congresses from: HRA Pharma (2016); Ipsen
1973 Pharma (2013, 2014); Novartis (2012, 2013, 2014, 2015, 2016)

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- 1982 • Speakers fee / travel support for congresses from: Astellas, Sanofi, Janssen,
1983 Novartis, Ipsen
- 1984 • Research support by Janssen (Phase II trial of Abiraterone in the management of
1985 Cushing Syndrome induced by Adrenocortical Carcinoma; 2016); Sanofi: Phase II
1986 trial of Cabazitaxel as second line treatment in the treatment of patients with
1987 advanced Adrenocortical Carcinoma; 2014)

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1993 Pharma (2011, 2012)

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- 1999 • Advisory Board member of HRA Pharma (2013; not remunerated), Atterocor-Millendo
2000 (2013-2015)
- 2001 • Research support by HRA Pharma (2016)
- 2002 • Speaker fee/travel support from HRA Pharma (2014, 2015)

2003

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2005

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