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This is a pre print version of the following article:

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1833017> since 2022-02-14T11:02:00Z

Published version:

DOI:10.1038/s41416-021-01513-8

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Adjuvant platinum-based chemotherapy in radically resected adrenocortical carcinoma: a cohort study

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1 **Abstract**

2 **Background:**

3 After radical resection, patients with adrenocortical carcinoma (ACC) frequently experience
4 recurrence and, therefore, effective adjuvant treatment is urgently needed. The aim of the
5 study was to investigate the role of an adjuvant platinum-based therapy.

6 **Methods:**

7 In this retrospective multicentre cohort study, we identified patients treated with adjuvant
8 platinum-based chemotherapy after radical resection and compared them with patients
9 without adjuvant chemotherapy. Recurrence-free and overall survival (RFS/OS) were
10 investigated in a matched group analysis and by applying a propensity score matching using
11 the full control cohort (n=268). For both approaches, we accounted for immortal time bias.

12 **Results:**

13 Of the 31 patients in the platinum cohort (R0 n=25, RX n=4, R1 n=2; ENSAT stage II n=11,
14 III n=16, IV n=4, median Ki67 30%, mitotane n=28), 14 experienced recurrence compared to
15 29 of 31 matched controls (median RFS after the landmark at 3 months 17.3 vs. 7.3 months;
16 adjusted HR 0.19 (95% CI 0.09-0.42; p<0.001). Using propensity score matching, the HR for
17 RFS was 0.45 (0.29-0.89, p=0.021) and for OS 0.25 (0.09-0.69; p=0.007).

18 **Conclusions:**

19 Our study provides first evidence that adjuvant platinum-based chemotherapy may be
20 associated with prolonged recurrence-free and overall survival in patients with ACC and very
21 high risk for recurrence.

22

23

24 **Key words: adrenal cancer, adjuvant therapy, platinum-based chemotherapy**

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27

28 **Background**

29 Adrenocortical carcinoma (ACC) is a rare and aggressive disease with limited therapeutic
30 options and a high rate of recurrence even after complete resection (1-5). Therefore,
31 effective adjuvant treatments are critically needed (6). Until now, mitotane is the only drug
32 approved for the treatment of advanced ACC and is used also as adjuvant therapy (1, 7-11).
33 Adjuvant mitotane is not undisputed and some argue that mitotane while acting as
34 adrenolytic agent has low cure rates (12). There is also uncertainty about the target plasma
35 concentrations of mitotane required to prevent recurrence in this setting (13-15).
36 Furthermore, all published data on adjuvant mitotane are retrospectively collected, and
37 randomized trials are lacking. The recruitment of the prospective randomized ADIUVO trial
38 (NCT00777244), investigating the efficacy of adjuvant mitotane versus observation only in
39 patients with low-intermediate risk of recurrence is stopped, but the results are still pending.
40 Awaiting the results of the ADIUVO trial, both the comprehensive ESE-ENSAT guidelines
41 2018 and the new ESMO-EURACAN guidelines 2020 recommend an adjuvant treatment
42 with mitotane in patients who have a high risk of recurrence (i.e., stage III or IV, R1 or RX
43 resection, or Ki-67>10%) (1, 9). Nevertheless, the recurrence rate is still about 50% even
44 after mitotane treatment (7).

45 The available evidence for adjuvant radiotherapy is even more limited compared to mitotane
46 use. Most published reports indicate a reduced risk of local recurrences by an adjuvant
47 radiotherapy, but only few studies suggest that it is also helpful in prolonging overall
48 recurrence-free and overall survival (16-19). All of these studies are retrospective and hence
49 confer significant selection bias. Therefore, the ESE and ESMO guidelines suggest its use
50 only on an individual basis in patients with R1 or RX resection or in stage III.

51

52 In other solid malignancies, the use of adjuvant cytotoxic chemotherapy is known to reduce
53 recurrence risk. However, the role of adjuvant chemotherapy in ACC has not been
54 established, and the available evidence is extremely limited (20). Hovi et al. explored the
55 combination of cisplatin and etoposide in the adjuvant setting in a small series of five ACC
56 patients aged 1 to 21 years (21). Chemotherapy was given shortly after surgical resection,
57 and all patients remained in complete remission 29 to 109 months later (21). Another study
58 from Khan et al. tested the combination of streptozotocin plus mitotane as adjuvant therapy
59 in a phase II trial of 17 patients after complete tumor resection. This study suggests a longer
60 disease-free survival compared with a control cohort of 11 patients, who received no
61 adjuvant therapy (49 vs. 12 months) (22). However, confounding is likely an issue and it is
62 also not clear if the presumed advantage of adjuvant treatment can be attributed to mitotane,
63 streptozotocin or the combination of both. In line with the limited evidence, ESE and ESMO
64 guideline panelists could not reach a consensus on the use of adjuvant cytotoxic

65 chemotherapy (1, 9). Both guidelines suggest to consider treatment with an adjuvant
66 platinum-based chemotherapy in selected patients with very high risk for recurrence on an
67 individual basis (e.g. Ki67 >30%. large tumor thrombus in the vena cava, stage IV, or R1
68 resection). In patients with locally advanced or metastatic ACC, the randomized FIRM-ACT
69 trial demonstrated that the combination of etoposide, doxorubicin, cisplatin, and mitotane
70 (EDP-M) was superior to streptozotocin and mitotane (23). Although the primary endpoint,
71 overall survival, failed (potentially due to the crossover design), EDP-M led to a higher
72 objective response rate (23% vs. 9%) and improved progressive-free survival (5.0 vs. 2.1
73 months) (23). So far, no other regimen tested in larger studies could reach similar results (24,
74 25).

75

76 Here, we present the first retrospective study to explore the efficacy and safety of adjuvant
77 platinum-based chemotherapy in adult patients with macroscopically radical resected ACC.

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81 **Subjects and Methods**

82 **Study population**

83 This cohort study was part of the ENSAT registry study (www.ensat.org/registry) in four
84 European reference centers for ACC (Würzburg, Germany; Brescia, Italy; Berlin, Germany;
85 and Orbassano, Italy) and the MD Anderson Cancer Center in Houston, US. It was approved
86 by the ethics committees/institutional review boards at all participating institutions and all
87 patients provided written informed consent.

88 Only patients who had undergone radical surgery between 2002 and February 2020 were
89 included. Follow-up for this study was closed in August 2020. Histological and clinical
90 parameters (sex, age at diagnosis, tumor size, evidence of hormonal excess, tumor stage
91 according to ENSAT (26) classification, date of surgery, Weiss score, Ki67 index, size and
92 number of tumoral lesions, date of starting mitotane, date of starting chemotherapy, mitotane
93 plasma concentration and follow up information) were retrieved from the ENSAT ACC
94 registry, patients' histories and medical records. All histological diagnoses were confirmed by
95 experienced pathologists. Tumor staging at diagnosis was based on imaging studies and by
96 the findings during surgery. Patients with macroscopically incomplete resection (either R2
97 resection or distant metastases that were not removed), lack of relevant information on
98 primary diagnosis or follow-up, concomitant anti-tumor treatment apart from mitotane (e.g.
99 radiotherapy or other drugs than platinum-based therapies), or start of adjuvant
100 chemotherapy later than 3 months after surgery were excluded.

101 Medical records were reviewed for adverse events associated with adjuvant platinum-based
102 chemotherapy. All adverse events were scored according to the National Cancer Institute
103 Common Terminology Criteria Adverse Events (NCI-CTCAE) classification version 5.0 (27).

104

105 **Platinum-based chemotherapy and control group**

106 The platinum-based chemotherapy group included patients who met the following criteria:
107 macroscopically radical resected ACC (defined as no evidence of macroscopic residual
108 disease based on surgical reports, histopathological analysis, and postoperative imaging)
109 with resection status R0, Rx or R1, and start of an adjuvant platinum-based chemotherapy <
110 3 months after primary surgery. Adjuvant platinum-based chemotherapy was defined as
111 monotherapy with cisplatin or carboplatin or in combination with other cytotoxic drugs.

112 The inclusion criteria for the control group were identical except for the use of platinum-
113 based chemotherapy.

114 We performed two different methodological approaches for analysis. First, every patient was
115 matched with one control patient according to the following criteria: Ki67 index (+/- 5% in
116 tumors with Ki67 <20%, +/-15% in tumors with Ki67 20-49% and +/-20% in tumors with Ki67
117 ≥50%) resection status (R0, R1, Rx), tumor stage, concomitant treatment with mitotane
118 (yes/no) and presence of preoperative glucocorticoid excess (yes/no). Matching was
119 performed by an investigator who was not aware of patient outcome. This was done in a
120 hand-picked manner only with the above-mentioned clinical data available for all patients. To
121 reduce the impact of potential immortal time bias, we performed a landmark analysis
122 excluding all patients who experienced recurrent disease or died within 12 weeks after
123 radical resection. Second, we applied a propensity score approach; firstly, we calculated a
124 propensity score for every patient (see below). Subsequently, this propensity score was used
125 in a multivariable model (see below).

126

127 **Outcome assessment**

128 Upfront, we defined recurrence-free survival (RFS) as the most relevant outcome for the
129 present analysis. Disease recurrence was defined as unequivocal radiologic evidence of
130 local recurrence and/or distant metastasis during follow-up. Radiological evaluation was
131 performed according local standards every 2-5 months.

132

133 **Statistical analysis**

134 Recurrence-free survival (RFS) was defined as the time from the date of surgery to the first
135 evidence of recurrent disease or last follow-up or death whichever occurs first. Overall
136 survival (OS) was defined as the time from the date of surgery to the date of death or last
137 follow-up. Patients without recurrence or death were censored at the date of last follow up.

138 Survival analysis was performed using the Kaplan-Meier method, and differences between
139 groups were assessed by log-rank statistics.

140 In a multivariable approach using the Cox proportional hazards model, recurrence-free and
141 overall survival were adjusted for the following variables: resection status, tumor stage,
142 presence of glucocorticoid excess, Ki67 index, and adjuvant mitotane therapy

143 Secondly, we performed a propensity-matched analysis. Using logistic regression, we
144 estimated a propensity score for every patient based on the following prognostic variables:
145 age at diagnosis, sex, tumor size, ENSAT stage, Ki67category, glucocorticoid excess and
146 adjuvant mitotane. Subsequently, the multivariable Cox analysis included the propensity
147 score.

148 To avoid immortal time bias a time-dependent approach was chosen for both methods (28),
149 using chemotherapy as a time-dependent variable. Here, only the person-time at risk (not
150 including the time until start of chemotherapy) was counted.

151 Data were analyzed using SPSS v.26 (IBM SPSS Statistics) and STATA 16.0.

152

153

154

155 **Results**

156 **Patient characteristics**

157 The total cohort consisted of 299 patients and key patients' characteristics are given in Table
158 1. Thirty-one of them were treated with adjuvant platinum-based chemotherapy. In
159 comparison to the entire control group, median Ki67 index was higher (30% vs. 20%,
160 $p=0.008$), more patients had ENSAT tumor stage III and IV, and more patients were treated
161 with adjuvant mitotane in the platinum-based chemotherapy group. The control group
162 included more women, with higher age, less patients with glucocorticoid excess and R0
163 resection, and the median tumor diameter was slightly smaller (Table 1).

164

165 **Platinum-based chemotherapy**

166 The majority of patients was treated with a combination of either cisplatin or carboplatin plus
167 etoposide (for details see Table 2). In median, treatment had started 38.5 days (13-71) after
168 surgery and 4 cycles (2-8) chemotherapy have been administered. Twenty-eight of 31
169 patients have been treated concomitantly with adjuvant mitotane and plasma mitotane levels
170 were almost identical to the matched control group (Table 1). Using a multivariate analysis,
171 there was no significant difference in recurrence-free survival, although patients treated with
172 cisplatin ($n=21$) seemed to do better than with carboplatin ($n=10$) ($HR=0.26$, 95% CI 0.03-

173 2.43; p=0.24). Neither a significant difference in recurrence-free survival was detectable if 2
174 to 3 cycles (n=8) or 4 and more cycles (n=23) have been applied (HR=0.47, 95% CI 0.10-2.1;
175 p=32).

176

177 **Clinical outcomes using the matched control cohort**

178 Tumor response was assessed similarly between groups: thoracic and abdominal computed
179 tomography (n=17 in the platinum group vs. n=20 in the control group), thoracic computed
180 tomography and abdominal magnetic resonance imaging (n=5 vs. n=7 or FDG-PET/CT (n=9
181 vs. n=4). There was no significant difference in the time intervals for imaging between the
182 groups (platinum-based group 3.2±1.6 months vs. 3.7±2.2 months in the control group for the
183 first imaging and platinum-based group 6.0±2.0 months vs. 8.0±3.0 months in the control
184 group for the second imaging). Median time of follow-up in the platinum group was 27.1 (3.0-
185 182.0) months and in the control group 37.4 (3.1-133.1) months.

186 Fourteen of 31 patients with adjuvant platinum-based therapy experienced recurrence,
187 whereas this was the case in 29 of 31 matched controls. Patients with adjuvant platinum-
188 based therapy had a longer median RFS than matched controls (20.5 months vs. 9.1
189 months; p<0.001; figure 1A). In a multivariable analysis adjusted hazard ratio (HR) for RFS
190 was of 0.35 (95% CI 0.19-0.67; p=0.001). Applying a landmark approach, median RFS three
191 months after surgery was 17.7 vs. 7.3 months; p=0.002) leading to an adjusted HR of 0.19
192 (95% CI 0.09 - 0.42; p<0.001). Using a time-dependent exposure analysis, the 14
193 recurrences in the chemotherapy group occurred in 896.7 person months, whereas the 29
194 recurrences in the control group occurred in 573.7 person months yielding to a relative risk
195 reduction of 0.32.

196 Median overall survival after the landmark of 3 months was not reached in the adjuvant
197 chemotherapy group and was 43.1 months in the control group. At last follow-up, 5 patients
198 in the chemotherapy group and 19 patients in the control group had died; there were no
199 deaths unrelated to ACC. Overall survival was longer in the platinum-treated group (adjusted
200 HR 0.26; 95% CI 0.09-0.72; p=0.010; Figure 1B).

201 There was no difference regarding the pattern of recurrence in the platinum group and the
202 matched control group.

203

204 **Clinical outcome using propensity score matching**

205 In addition to the matched control analysis, we performed a second approach with a
206 propensity score matching. After adjustment for propensity scores and accounting for
207 immortal time bias, the HR for RFS was 0.45, 95% CI 0.29-0.89, p=0.021. The HR for OS
208 was 0.25 (95% CI 0.09-0.69; p=0.007), respectively.

209 **Adverse events in patients with platinum-based chemotherapy**

210 The documented adverse events associated with platinum-based chemotherapy were all
211 well-known and mostly mild or moderate (Table 4). Neither grade 4 nor grade 5 events
212 occurred. Only in 1 patient a grade 3 event with febrile neutropenia and oral mucositis was
213 recorded. All patients showed a decrease of neutrophil cells, but only in the above-mentioned
214 patient clinical sequels developed. Most of the patients suffered from vomiting, nausea and
215 fatigue grade 1 and 2. All patients experienced alopecia. No patient suffered from heart,
216 hepatic or renal failure or nervous system disorders.

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218

219

220 **Discussion**

221 In this report, we present the first cohort study of adult patients with ACC treated with
222 adjuvant platinum-based therapy. The aim of our analysis was to provide exploratory
223 evidence for or against the use of this potentially toxic therapy in patients with very high risk
224 of recurrence. The results of this study were clearly in favor of adjuvant platinum therapy. To
225 ascertain the efficacy of adjuvant chemotherapy, we performed two statistical approaches.
226 First, we used well-matched controls (accounting for the key prognostic factors like ENSAT
227 stage, resection status, Ki67 index, cortisol excess, but also the use of concomitant mitotane
228 treatment). Second, we performed a propensity score matching using the entire cohort of 299
229 patients. Both approaches clearly suggest that patients treated with an adjuvant platinum-
230 based chemotherapy have a significantly decreased risk of recurrence. Twenty-nine of 31
231 patients (94%) in the matched control group experienced recurrence, whereas this was the
232 case in only 14 of 31 (45%) of the platinum-based therapy group. Furthermore, these results
233 were confirmed when we applied two different analyses to account for an immortal time bias,
234 namely a landmark approach and a time-dependent exposure analysis. The very high
235 recurrence rate in the control group - despite the fact that more than 90% of patients were
236 treated with adjuvant mitotane - confirmed the very high-risk constellation identified by the
237 above-mentioned prognostic factors. Overall, adjuvant platinum-based therapy was
238 associated with a risk reduction in recurrence of ~ 65%. Furthermore, this effect seems to
239 translate also to a significantly improved overall survival with a risk reduction for mortality of
240 ~70%, respectively.

241

242 Our study has obvious limitations including the retrospective nature and lack of
243 randomization in addition to the relatively small sample size. However, due to the virtually
244 absent evidence for the application of cytotoxic chemotherapy in an adjuvant setting in ACC

245 and the consecutive lack of a clear recommendation for its use, it is unlikely that a larger
246 cohort will be recruited in the near future. Furthermore, to each patient in the 'platinum group'
247 only one control patient could be matched. Another limitation are the various platinum-based
248 chemotherapy regimens and the different combination of drugs and number of cycles and the
249 non-standardized treatment with mitotane. As expected for a group of high-risk for
250 recurrence patients, almost all patients in the 'platinum group' have been treated with
251 mitotane. However, the same number of patients were treated with mitotane in the matched
252 controls and the documented mitotane plasma level were similar.

253 In addition, we have to acknowledge that the decision for (or against) adjuvant platinum-
254 based chemotherapy was made by local staff and was not based on any defined criteria.
255 However, it is obvious that these patients had a perceived very high risk of recurrence.
256 Nevertheless, the results cannot be generalized.

257 We are well aware that our study only provides first evidence supporting the use of adjuvant
258 platinum-based therapy in ACC. However, it clearly underlines the need for a randomized
259 trial on this topic to eliminate the uncertainties and limitations of retrospective cohort studies.
260 Recently, an international consortium initiated such a trial which reflects an excellent
261 opportunity to include ACC patients with very high risk of recurrence (NCT03583710,
262 NCT03723941). We certainly have to acknowledge that there is no universally accepted
263 definition of presumably very high-risk patients. However, our study provides some hint that
264 the suggestion by the ESE-ENSAT guidelines in this context seems to be reasonable. In
265 these guidelines, the panelists propose with caution that in patients with one of the following
266 risk factors Ki67 >30%, large tumor thrombus in the vena cava, stage IV, or R1 resection,
267 adjuvant chemotherapy should be considered (9). Furthermore, in some selected patients
268 (e.g. after R1 resection) even a combination of mitotane plus etoposide and cisplatin with
269 local radiotherapy could be considered. However, data on this combination are completely
270 lacking.

271
272 In summary, our study indicates that adjuvant treatment with platinum-based chemotherapy
273 is associated with beneficial effects on clinical outcome in patients with adrenocortical
274 carcinoma with very high risk of recurrence. We believe that our retrospective analysis
275 should raise interest in adjuvant chemotherapy as treatment tool for this disease in selected
276 patients. In the future, prospective, randomized trials like ADIUVO-2 will finally define the role
277 of an adjuvant platinum-based chemotherapy in adrenocortical carcinoma.

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282 **Additional Information**

283

284 Acknowledgements

285 This study was made possible by the ACC database of the European Network for the Study
286 of Adrenal Tumors (ENSAT). We are thankful for continuous help in data documentation from
287 Michaela Haaf.

288

289 Author contribution

290 Otilia Kimpel: Conceptualization; Data curation; Formal analysis; Visualization; Roles/Writing
291 - original draft

292 Sara Bedrose: Data curation; Writing - review & editing

293 Felix Megerle: Data curation; Writing - review & editing

294 Alfredo Berruti: Data curation; Writing - review & editing

295 Massimo Terzolo: Data curation; Writing - review & editing

296 Matthias Kroiss: Data curation; Funding acquisition; Writing - review & editing

297 Knut Mai: Data curation; Writing - review & editing

298 Olaf M. Dekkers: Formal analysis; Methodology; Writing - review & editing

299 Mouhammed Amir Habra: Conceptualization; data curation; Writing - review & editing,
300 Supervision

301 Martin Fassnacht: Conceptualization; Data curation; Formal analysis; Data curation; Funding
302 acquisition ; Writing - review & editing, Supervision

303

304

305 Ethics approval and consent to participate

306 This cohort study was part of the ENSAT registry study (www.ensat.org/registry) in four
307 European reference centers for ACC (Würzburg, Germany; Brescia, Italy; Berlin, Germany;
308 and Orbassano, Italy) and the MD Anderson Cancer Center in Houston, US. It was approved
309 by the ethics committees/institutional review boards at all participating institutions and all
310 patients provided written informed consent. It was performed in accordance with the
311 Declaration of Helsinki.

312

313

314 Consent for publication

315 Not applicable

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319 Data availability:

320 The datasets generated and/or analysed during the current study are not publicly available
321 due privacy issues of the patients with a very rare disease, but are available in an
322 anonymized fashion from the corresponding author on reasonable request.

323

324

325 Competing interests:

326 MK received travel cost reimbursement, speaker honoraria, and research support from Ipsen
327 Pharma. AB received funds for research in adrenocortical carcinoma from Novartis, Janssen
328 Cilag and Sanofi. MT received speaker honoraria and research grants from HRA Pharma
329 that were paid to the University Department. MAH received honoraria from HRA Pharma for
330 advisory board. MF has served in an advisory board of HRA Pharma on the management of
331 adrenocortical carcinoma (2018 + 2021); remuneration was paid to his University Hospital.
332 OK, SB, FM, KM, OMD declare that they have no competing interests.

333

334

335 Funding

336 This study was supported by the German Research Foundation (Deutsche
337 Forschungsgemeinschaft; project numbers: 314061271 – CRC/TRR 205 to MF and MK and
338 641697 to MF and 641696 to MK.

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340

341

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419 **Figure legends:**

420

421 **Figure 1. Kaplan–Meier estimates of recurrence-free survival (A) and overall survival**
422 **(B) applying a landmark analysis 3 months after surgery in 31 patients with ACC**
423 **treated with platinum-based chemotherapy and 31 matched controls.**

424 Adjusted HR for PFS from Cox analysis is 0.19 (95% CI 0.09 - 0.42; $p < 0.001$) and for OS
425 0.26 (95% CI 0.09-0.72; $p = 0.010$).

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427

428 **Table 1. Baseline characteristics of the patients.**

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	Adjuvant platin therapy (n=31)	Matched controls (n=31)	P value platin vs matched controls	Entire control cohort (n=268)	P value platin vs entire control group
Sex (F:M)	16:15	19:12	0.44	177:91	0.11
Median age yrs (range)	41 (4-59)	44 (18-67)	0.79	49 (4-79)	0.066
Median tumor size mm (range)	124 (25-300)	120 (38-220)	0.79	110 (25-260)	0.45
Autonomous hormone secretion					
Cortisol +/- androgens- n (%)	15 (48.4)	12 (38.7)	0.068	101 (37.7)	0.11
Androgens	5 (16.1)	3 (9.7)		22 (8.2)	
Aldosterone	0	1 (3.2)		6 (2.2)	
Estrogens	0	0		0	
Inactive	7 (22.6)	15 (48.4)		119 (44.4)	
Unknown	4 (12.9)	0		20 (7.5)	
ENSAT tumor stage					
I - n (%)	0	0	1.0	14 (5.3)	0.026
II - n (%)	11 (35.5)	11 (35.5)		138 (52.2)	
III - n (%)	16 (51.6)	16 (51.6)		101 (38.4)	
IV - n (%)	4 (12.9)	4 (12.9)		10 (3.8)	
Venous tumor thrombus ¹ - n (%)	10 (32.3)	10 (32.3)	1.0	16 (6.3)	<0.001
Resection status					
R0 - n (%)	25 (80.6)	25 (80.6)	1.0	183 (68.3)	0.56
RX - n (%)	4 (13)	4 (13)		54 (20.1)	
R1 - n (%)	2 (6.4)	2 (6.4)		30 (11.2)	
Ki67 index - median (range)	30 (10-80)	32.1 (8-80)	0.86	20 (1-90)	0.008
<20%	7 (25)	5 (17.9)	0.55	92 (44.7)	0.014
20-39%	10 (35.7)	14 (50)		79 (38.3)	
≥40%	11 (39.3)	9 (32.1)		35 (17.0)	
Number of patients with adjuvant mitotane (%)	28 (90.3)	28 (90.3)	1.0	120 (44.9)	<0.001
Highest mitotane plasma concentration (mg/L) - median (range)	12 (3-28)	10 (1-23)	0.87		
in the first 3 months	n=20	n=23			
No. of analyzed patients					
until progress/end of therapy	18 (3-34)	17 (1-27)	0.86		
No of analyzed pts.	n=24	n=24			
No. of pts with mitotane level >14mg/L during therapy (%)	17 (54.8)	17 (54.8)	1.0		

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431 ¹ in the inferior vena cava or renal vein

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433

434 **Table 2 Details on platinum-based chemotherapy and number of cycles administered.**
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 436

Chemotherapy regimen n (%)	Number of patients (%)	Median number of cycles (min-max)
Cisplatin/etoposide (d1-3 100mg/m ² E, d2-3 40mg/m ² P; every 3-4 weeks)	16 (51.6)	4 (2-8)
Carboplatin/etoposide (d1-3 100mg/m ² E, d3 P AUC 5; every 3-4 weeks)	8 (25.8)	4 (2-6)
Cisplatin/etoposide/doxorubicin (d1 40mg/m ² D, d2-4 100mg/m ² E, d3-4 40mg/m ² P; every 4 weeks)	5 (16.2)	4 (3-6)
Carboplatin/etoposide/doxorubicin (d1 40mg/m ² D, d2-4 100mg/m ² E, d4 P AUC 5; every 4 weeks)	1 (3.2)	4 (3-4)
Cisplatin	1 (3.2)	2

437
 438 d day, E etoposide, P cisplatin and carboplatin, respectively, D doxorubicin
 439
 440

441 **Table 3. Adverse events according to the NCI CTC criteria v5.0 (27).**

	442		
Adverse event	Grade 1	Grade 2	Grade 3
Anemia	8	0	0
Neutrophil count decreased	24	7	1
Febrile neutropenia			1
Ear and labyrinth disorders	1	0	0
Mucositis oral	0	0	1
Vomiting	5	3	0
Nausea	16	6	0
Fatigue	8	4	
Alopecia	0	31	
Weight loss	11	2	0
Peripheral neuropathy	0	0	0