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Refractory and relapsed paediatric ACC in the MET studies – A challenging situation necessitating novel diagnostic and therapeutic concepts

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ABSTRACT

Background: Paediatric adrenocortical carcinomas (ACC) are highly aggressive malignancies with a dismal prognosis in advanced and metastatic diseases. Little is known about outcome of patients with refractory and relapsed (r/r) disease.

Procedure: National retrospective multicentre study including r/r ACC diagnosed in patients aged < 18 years registered in the MET studies between January 1997 and December 2021

Results: A total of 16 patients (5 male; median age 12.9 years) with refractory disease were included. Median time to progression was 0.6 years [0.0–1.3]. Site of progression was locoregional (n = 1), distant (n = 3), and combined (n = 12). 3-year overall (OS) and progression-free (PFS) survival were both 0%. Thirty patients with relapse (11 male; median age 7.3 years) were identified. Median time to relapse was 0.7 years [0.1–3.2]. Site of relapse was locoregional (n = 8), distant (n = 15), and combined (n = 7). At last follow-up, 20 patients had died of disease or complications or were alive with disease, 10 patients were in second complete remission (median follow-up: 6.8 years [0–10.5]). 3-year OS and PFS following relapse were 39.1% and 31.9%. Survival was superior in patients with distant relapse (59.6%) compared to locoregional (28.6%) and combined (14.3%) (p = 0.028) and in patients with complete surgical resection of all sites of recurrence (70.0%) compared to incomplete (21.4%) and no surgery (0%) (p = 0.003).

Conclusions: For patients nonresponsive to first-line therapy or who experience relapse, prognosis is dismal and options are scarce. Site of relapse and resectability define prognosis. Novel therapeutic concepts are needed to improve the outcome of paediatric patients with r/r ACC.

Abbreviations: ACC, Adrenocortical carcinoma; CR, Complete remission; EFS, Event-free survival; EXPeRT, European Cooperative Study Group for Paediatric Rare Tumours; GPOH, German Society for Paediatric Oncology and Haematology; MET, Malignant Endocrine Tumour; OS, Overall survival; PARTNER, Paediatric Rare Tumours Network – European Registry

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1. Introduction

Adrenocortical carcinoma (ACC) is a highly aggressive endocrine neoplasm arising from the cortex of the adrenal gland. In children and adolescents with advanced and metastatic ACC outcome is poor with an overall survival of less than 20% [1,2].

In the hitherto largest prospective clinical trial in paediatric ACC (NCT00304070), patients with advanced and metastatic tumours were treated with the combination of chemotherapy, mitotane, and surgery of the primary tumour and metastases [3]. With this regimen, the 5-year event-free survival (EFS) was 81% in stage III but only 7.1% in stage IV patients. In stage II patients who only received surgery and retroperitoneal lymph node dissection, EFS was 53.3%. A high recurrence rate even after complete surgical resection was previously reported and disease recurrences in up to 50% of patients with large, localised tumours [1,4–6].

After failure of first-line therapy, salvage options in children and adolescents with ACC are scarce and not evaluated in clinical trials. Some new second- and third-line therapies have been developed in adults [7,8]. Indeed, paediatric ACC are biologically and molecularly distinct from their adult counterparts, including a high proportion of Li-Fraumeni syndromes [9,10].

Despite a substantial proportion of children and adolescents with refractory disease or relapse, data on outcome and second-line therapies are mostly lacking. Picard reported on 14 patients with refractory/relapsed ACC in the French cohort. They demonstrated a poor prognosis - almost 80% of these patients died of disease or were alive with severe disease progression.

To overcome these shortcomings, as a first step, we will explore outcome and salvage strategies in patients with refractory/relapsed disease registered with the MET studies. We aim at contributing to the improvement of individual treatment decisions in refractory/relapsed ACC and discuss the implications of our findings for future clinical strategies.

2. Patients and methods

This national retrospective multicentre study included all refractory and relapsed ACC diagnosed in patients aged 0- < 18 years registered in the MET studies between January 1997 and December 2021.

The GPOH-MET 97 protocol and registry were approved by the ethics committees of the University of Luebeck (Approval number 97125) and Otto-von-Guericke-University Magdeburg (Approval number 174/12), Germany. Informed consent was obtained from patients, parents, and legal guardians, as appropriate.

2.1. The MET studies

Patients were treated according to the GPOH-MET 97 study protocol and registry recommendation. Details on treatment and data collection are provided elsewhere [2,11]. Briefly, chemotherapy with mitotane was advised for patients with stage III (T1–2, N1, M0; AJCC 7th staging system) and stage IV tumours. For patients with primary unresectable tumours, neoadjuvant chemotherapy with mitotane was recommended. No recommendation was fixed for patients with refractory/relapsed disease.

No structural and functional evidence of disease was considered as complete remission (CR). Refractory disease was defined as an increase of tumour volume > 20% of existing lesions and/or evidence of new lesions without a period of CR. Relapse was defined as new tumour evolution (locoregional and/or distant) following any period of CR.

Data were included from 1997 until 31st of December 2022.

2.2. Statistical analyses

Overall survival (OS) and progression-free survival (PFS) were determined according to Kaplan–Meier estimates. OS was defined as the time from diagnosis to death of disease or other causes. PFS was defined as the time from diagnosis to first event, defined as progression, relapse, or death of disease, whichever occurred first. PFS-R was defined from first event following complete remission to second event, defined as progression, second relapse, or death of disease. Survivors were censored at the date of last follow-up.

Groups were compared using the log-rank or chi-squared test. For numerical data, the independent t-test or Mann-Whitney U test was used.

Statistical analyses were performed using SPSS version 26. Data visualisation and graphs were created using SPSS, R version 4.0.5, RStudio 2022.07.2 using the `survival´ and the `survminer´ packages.

3. Results

A total of 46 children and adolescents with refractory disease (n = 16) or tumour relapse following 1st CR (n = 30) were included (Table 1).

Table 1
Baseline characteristics at initial diagnosis of 46 children and adolescents with refractory (n = 16) and relapsed (n = 30) adrenocortical carcinoma.

	Refractory disease	Relapse
	n = 16	n = 30
Sex, n (%)		
Male	5 (31.3%)	11 (36.7%)
Female	11 (68.8%)	19 (63.3%)
Age at diagnosis, years		
Median (range)	12.9 (0.2–16.8)	7.3 (0.4–17.8)
Lymph node metastases		
No	10 (62.5%)	25 (83.3%)
Yes	6 (37.5%)	5 (16.7%)
Distant metastases		
No	1 (6.3%)	27 (90.0%)
Yes	15 (93.8%)	3 (10.0%)
Pathogenic *TP53* variant		
No	2 (50.0%)	2 (22.2%)
Yes	2 (50.0%)	7 (77.8%)
Not done/unknown	12	21
Endocrine phenotype		
Virilization	4 (25.0%)	14 (46.7%)
Cushing	1 (6.3%)	3 (10.0%)
Combined	5 (31.3%)	8 (26.7%)
Silent	6 (37.5%)	5 (16.7%)
Initial biopsy		
No	6 (37.5%)	26 (86.7%)
Yes	10 (62.5%)	4 (13.3%)
Tumour volume, ml		
Median (range)	542 (18–2907)	382 (15–3645)
Resection of the primary tumour		
No	4 (25.0%)	0
Yes	12	30
R_0	5 (31.3%)	23 (76.7%)
R_1	3 (18.8%)	3 (10.0%)
R_2	4 (25.0%)	2 (6.7%)
R_x	0	2 (6.7%)
Spillage	3 (18.8%)	9 (30.0%)
Ki67 index		
≤ 15%	3 (30.0%)	5 (19.2%)
> 15%	7 (70.0%)	21 (80.8%)
Not available/done	6	4
Stage according to AJCC 7th		
Stage I	0	1 (3.3%)
Stage II	0	17 (56.7%)
Stage III	0	5 (16.7%)
Stage IV	16 (100%)	7 (23.3%)

Table 2
Details on events, second-line therapy, and outcome in 16 patients with refractory disease.

Patient	Time to event (years)	Type of event	Second-line therapy					Outcome	Time to death (years)
			Surgery	Chemotherapy	Mitotane therapy	Radiotherapy	Best response		
1	0.10	Progression of disease	Mets	1) Trofosfamide/Idarubicin/Etoposide; 2) Temozolomide/ Cabozantinib	cont.	-	PD	alive	n.a.[a]
2	0.77	Progression of disease	-	1) Trofosfamide/Idarubicin; 2) Cisplatin/Paclitaxel	-	-	PD	DOD	1.40
3	0.35	Progression of disease	-	1) Pembrolizumab	-	-	unkn.	DOD	0.82
4	0.81	Progression of disease	unkn.	unknown	unkn.	unkn.	unkn.	DOD	1.76
5	0.00	Progression of disease	-	-	-	-	n.a.	DOD	0.04
6	0.34	Progression of disease	-	-	-	-	n.a.	DOD	0.48
7	1.28	Progression of disease	-	-	-	-	n.a.	DOD	1.99
8	0.6	Progression of metastases	-	1) Streptozocin; 2) Topotecan	cont.	-	PD	DOD	1.57
9	0.85	Progression of metastases	-	1) Docetaxel/Gemcitabine; 2) Trofosfamide/ Idarubicin	-	-	SD	DOD	1.76
10	0.84	Progression of metastases	-	1) Interferon alpha	+	Tumour	PD	DOD	2.57
11	0.76	Progression of metastases	-	-	cont.	-	PD	DOD	1.22
12	0.25	Local relapse & progression of metastases	-	1) MET	+	-	PR	DOD	0.58
13	0.39	Local relapse & progression of metastases	-	1) MET cont.	cont.	-	PD	DOD	0.99
14	0.5	Local relapse & progression of metastases	-	1) Cisplatin/Etoposide/Ifosfamide; 2) TECC with autologous SCT	-	-	PD	DOD	0.87
15	0.55	Local relapse & progression of metastases	-	1) Trofosfamide/Etoposide; 2) Vincristin/ Carboplatin/Etoposide/CSA	-	-	PD	DOD	0.79
16	1.01	Local relapse & progression of metastases	Mets	1) modified RIST[b]	cont.	Liver	PD	DOD	2.47

[a] follow-up 2.07 years.
[b] Rapamycin/Dasatinib/Irinotecan/Temozolomide; cont., continued; DOD, death of disease; n.a., not applicable; PD, progressive disease; PR, partial remission; SCT, stem cell transplantation; SD, stable disease; unkn, unknown.

3.1. Patients with refractory disease

Sixteen patients (5 male, 11 female) showed tumour progression before any remission. Median age at diagnosis was 12.9 years (range, 0.2–16.8). One patient was diagnosed with locally advanced disease, 15 patients presented with distant metastases [lung (n = 14), liver (n = 3), bone (n = 2), distant lymph nodes (n = 3), CNS (n = 1)]. In 6 patients, no histological diagnosis was performed prior to therapy. In 5 of those, ACC was histologically confirmed after tumour resection. Details on initial diagnosis are given in Supplementary Table 1.

Median time to tumour progression was 0.6 years (range, 0.0–1.3). Site of progression was locoregional (n = 1), distant (n = 3), and combined (n = 12). In 2 patients the present therapy was continued, in 3 salvage therapy was added to concomitant mitotane therapy, in 6 salvage therapy was administered, 4 did not receive any salvage therapy, and management following progression was unknown in 1 patient. Salvage therapy included various types of chemotherapy (n = 8), mitotane (n = 2), and other individual therapies (n = 6; kinase inhibitors, n = 2; taxane, n = 2; streptozocin, n = 1; interferon alpha, n = 1; mTOR inhibitor, n = 1; PD1 inhibitor, n = 1). In 2 patients each, resection of metastases and radiotherapy, respectively, were performed. For details on second-line therapy please refer to Table 2.

One patient with extensive metastatic disease died shortly after diagnosis (14 days) at start of neoadjuvant therapy. Fourteen patients showed progression before any remission and died at a median time of 1.3 years (range, 0.5–2.6) after diagnosis. One patient with lung metastases showed disease progression 0.1 years after diagnosis, was switch to second-line therapy with trofosfamide, idarubicin, and etoposide and subsequently once more switch to third-line therapy including temozolamide and cabozantinib while mitotane was continued from first-line therapy. The patient underwent re-resection of lung metastases and was still alive 2.1 years later. Three-year OS and PFS of patients with refractory disease were both 0% (Fig. 1).

3.2. Patients with tumour relapse following complete remission

Thirty patients (11 male, 19 female) showed tumour relapse following first remission. Median age at initial diagnosis was 7.3 years (range, 0.4–17.8). One patient was initially diagnosed with stage I, 17 patients were diagnosed with stage II, 5 with stage III, and 7 with stage IV. Details on initial diagnosis are given in Supplementary Table 2.

Relapse occurred at a median of 0.7 years (range, 0.1–3.2) after diagnosis. Sites of relapse were locoregional recurrences in 8 patients, distant metastases in 15, and combined relapses in 7. $R_{1/2}$ resection and spillage were more frequently reported in patients with locoregional relapses compared to patients with distant and combined relapses, whereas biopsy was no predictor of the site of relapse. Non-secreting tumours and Cushing syndrome were only determined in patients with distant metastases and combined relapses.

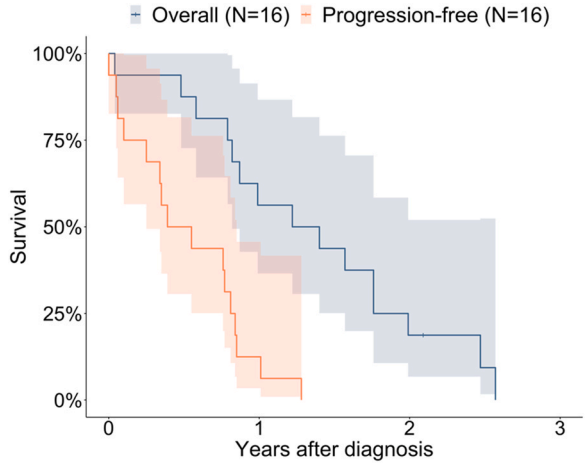

Fig. 1. 3-year overall (OS 0%) and progression-free survival (PFS 0%) of patients with refractory disease. For PFS analysis, the patient still alive was censored at last follow-up.

Looking at patients relapsing after initial stage I and II in more detail, no established risk factor was present in the single patient with stage I. Of note, Ki67 index was not determined. In this patient, lung metastases were diagnosed 2.5 years after diagnosis of ACC. Details on risk factors in patients relapsing after stage II are depicted in Supplementary Fig. 1. Relapse pattern and outcome in patients with localised disease at initial diagnosis are depicted in Supplementary Fig. 2.

Of 30 patients, 29 patients underwent salvage therapy including surgery (n = 28; local relapse, n = 11; metastases, n = 17), chemotherapy (n = 19; according to MET, n = 15; other chemotherapy, n = 5; chemotherapy combined with regional hyperthermia, n = 1; multikinase inhibitors, n = 2; inhibitor of the insulin receptor and of the insulin-like growth factor 1 receptor, n = 1; details unknown, n = 4); mitotane (n = 22, in 3 of those mitotane was continued since first-line therapy), and radiotherapy (n = 2). One patient did not receive any salvage therapy. For details on second-line therapy please refer to Table 3 and Fig. 2.

Median follow-up of relapsed patients was 2.37 years (range, 0.39–11.25). Of 30 patients, 15 died of disease (locoregional relapse, n = 5; distant metastases, n = 5; combined relapse, n = 5) and 1 patient died of complications (combined relapse). Median time to death after relapse was 1.16 years (range, 0.12–3.29). Four patients were alive with disease (locoregional, n = 1; distant metastases, n = 2; combined, n = 1), whereas 10 patients were alive without evidence of disease at last follow-up (locoregional, n = 2; distant metastases, n = 8). Median follow-up of patients alive after relapse was 6.78 years (range, 0–10.52). Three-year OS and PFS-R were 39.1% and 31.9% (Fig. 3A).

Second-line therapy in those 10 relapsed patients surviving without evidence of disease included surgery (n = 10), chemotherapy analogous to the MET protocol (n = 6), mitotane therapy (n = 6, thereof continued in one patient), and radiotherapy (n = 2). In 4 of those 10 patients, resection of metastases was performed only. Five of the 6 patients undergoing MET chemotherapy had not received chemotherapy during first-line treatment. In one of those patients, maintenance therapy with trofosfamide, idarubicin, and etoposide was additionally administered. One patient (no. 27) sustained a second relapse following resection of metastases and chemotherapy. The patient again underwent chemotherapy (analogous to the ARAR0332 protocol) and re-resection of metastases and was in third complete remission 3.2 years later.

Survival was superior in patients with distant relapse compared to locoregional and combined relapse ($p = 0.028$; Fig. 3B), in patients with complete surgical resection of all sites of recurrence compared to patients with incomplete and no surgery ($p = 0.003$; Fig. 3C), and in patients relapsing after achieving 1st CR compared to patients with refractory disease ($p < 0.001$; Fig. 3D).

4. Discussion

To our knowledge, this is the largest series of 46 paediatric patients with refractory and relapsed ACC. We confirmed the dismal prognosis of patients with refractory disease with the 3-year PFS and OS both being 0%. However, outcome of relapsed disease was better than could be expected. Of 30 patients, 10 achieved a second CR corresponding to a 3-year PFS-R of 31.9%. Strikingly, survival was 59.6% in patients with distant relapse.

Although disease recurrence in paediatric patients with ACC is a common event affecting up to 50% of patients [1,4], published data are sparse. In the ARAR0332 study, 24 of 77 patients sustained a relapse

Table 3
Details on events, relapse therapy, and outcome in 30 patients with tumour relapse.

Patient	Time to event (years)	Type of event	Relapse therapy					Outcome		
			Surgery	Chemotherapy	Mitotane therapy	Radiotherapy	Best response	Subsequent events	Status at last follow-up	Time to death or last follow-up (years)
17	0.73	Local relapse incl. LN	+	1) MET	+	+	CR	-	2nd CR	11.3
18	0.49	Local relapse incl. LN	+	1) MET	+	-	CR	-	2nd CR	9.2
19	1.09	Local relapse incl. LN	+	1) MET[a]	+	-	PD	Lung mets	DOD	2.20
20	0.41	Local relapse	+	1) MET	+	-	CR	Local rel	DOD	3.70
21	1.21	Local relapse	+	1) Hyper-PEI; 2) Sorafenib	-	-	SD	Abdominal rel, mets	DOD	2.12
22	0.86	Local relapse	+	unknown	cont.	-	unkn.	PD	alive with disease	0.9
23	1.34	Local relapse	+	-	-	-	PD	Local rel, mets	DOD	2.52
24	0.38	Local relapse	+	-	cont.	-	PD	Local rel	DOD	2.11
25	2.47	Metastases: Lung	+	1) MET	+	-	-	-	2nd CR	3.5
26	0.68	Metastases: Lung	+	1) MET reused; 2) Trofo/Ida	+	-	PD	PD	DOD	1.81
27	1.99	Metastases: Lung	+	1) MET; 2nd relapse: CED	+	-	PR	Lung mets	3nd CR	6.3
28	0.84	Metastases: Lung	+	yes, details unknown	+	-	unkn.	PD	alive with disease	1.4
29	0.78	Metastases: Lung	+	1) Linsitinib	cont.	-	PD	Bone, liver, LN mets	DOD	2.45
30	2.92	Metastases: Lung	+	-	-	-	n.a.	-	2nd CR	10.1
31	0.68	Metastases: Lung	+	-	-	-	n.a.	-	2nd CR	10.7
32	3.16	Metastases: Lung, CNS	-	-	-	-	-	PD	alive with disease	3.2
33	0.54	Metastases: Lung, liver	+	1) MET; 2) Trofo/Ida/Eto	+	-	CR	-	2nd CR	9.9
34	0.59	Metastases: Liver	-	1) MET	+	-	unkn.	PD	DOD	1.00
35	0.26	Metastases: Liver	+	1) MET reused	+	-	-	PD	DOD	1.67
36	0.67	Metastases: Liver	+	-	-	-	n.a.	-	2nd CR	9.1
37	2.83	Metastases: CNS	+	1) MET reused	+	CNS	CR	-	2nd CR	11.2
38	0.08	Metastases: LN	+	-	-	-	CR	-	2nd CR	6.4
39	0.29	Metastases: LN, liver, CNS	+	1) Regorafenib	+	-	PD	PD	DOD	0.30
40	0.28	Combined relapse incl. LN, lung liver	Loc	1) MET; 2) Trofo/Ida/Eto	+	-	PD	Abdominal rel	DOD	1.73
41	0.39	Combined relapse incl. LN, lung	Loc	1) MET	+	-	CR	Abdominal rel, mets	DOD	2.00
42	0.65	Combined relapse incl. lung	Loc	-	+	-	PD	PD	DOD	0.93
43	0.43	Combined relapse incl. liver	Mets	1) MET	+	-	unkn.	Abdominal rel, mets	DOD	2.29
44	2.05	Combined relapse incl. liver	Mets	1) MET	+	-	unkn.	Abdominal rel	alive with disease	7.1
45	0.27	Combined relapse incl. liver, bone	Mets	-	-	-	PR	n.a.	Death of complications	0.39
46	0.80	Combined relapse incl. LN, bone	Mets	-	+	-	PD	PD	DOD	1.40

[a] previously treated with CED chemotherapy; CED, Cisplatin/Etoposide/Doxorubicin; PEI, Cisplatin/Etoposide/Ifosfamide; Trofo/Ida/Eto; Trofosfamide/Idarubicin/Etoposide; CR, complete remission; DOD, death of disease; loc, local relapse; mets, metastases; n.a., not applicable; PD, progressive disease; PR, partial remission; SD, stable disease; rel, relapse; unkn, unknown.

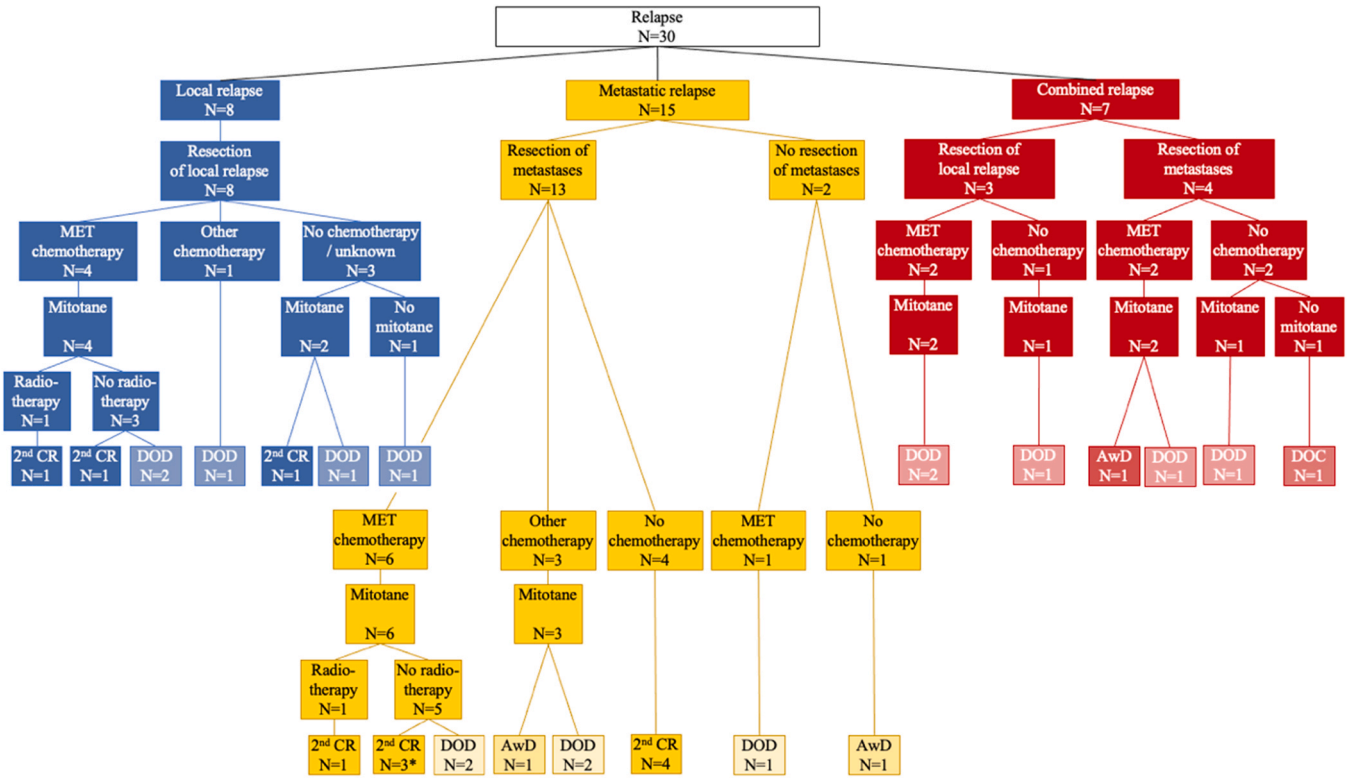

Fig. 2. Details on outcome depending on site of relapse and treatment in 30 patients relapsing following first complete remission. *including one patient in 3rd CR, 2nd CR, second complete remission; AwD, alive with disease; DoC, death of complications; DoD, death of disease.

and 2 patients died of disease as first event [12]. No details on outcome were provided. Picard and colleagues reported on 10 patients with refractory and 4 with relapsed disease among 95 patients in the French study [13]. Three of 14 patients were alive in second CR corresponding to a 5-year OS and PFS of 33% and 15%. In the Italian study, 2 of 58 patients died resulting from local recurrence [14]. The International Paediatric Adrenocortical Tumour Registry reported on 92 of 259 patients dying of disease progression (including relapse) or being alive with active disease at last follow-up [15].

Most events in paediatric ACC occur within 2 years following diagnosis [13,16,17]. In our study, progression occurred at a median time of 0.6 years. Site of progression was combined in 12 of 16 patients in our cohort and metastatic in 7 of 10 patients in the French study [13]. In both studies, patients underwent a variety of treatment including surgery, chemotherapy, mitotane, radiotherapy, and other therapies. All but one patient in our study died of disease within 1.3 years. This patient received cabozantinib combined with temozolamide as third-line therapy, while mitotane was continued from first-line therapy [18]. In poorly responding advanced tumours, the EXPeRT/PARTNER recommendations suggest discussion of mutilating large resections and second-line chemotherapy used in adults [7,19]. Alternatively, enrolment in a prospective trial testing new regimens or targeted therapies should be taken into consideration [20–22]. However, a prospective trial eligible for patients aged < 18 years with ACC is yet not within sight (clinicaltrials.gov, accessed 01.03.2023).

Most events in our study occurred as relapse following 1st CR. A variety of salvage therapies was administered resulting in an OS of 42.5%. Picard and colleagues reported an OS of 33% including patients with refractory disease [13].

We showed a superior survival in patients with metastatic relapse (59.6%) compared to locoregional (28.6%) and combined relapse (14.3%). Four of the metastatic patients presented with localised resectable metastases to the lungs, liver, and/or lymph node. In these patients, R_0 resection of all sites of recurrence was achieved by surgery alone without any systemic therapy.

In line with this, in all patients surviving after relapse complete surgical resection was achieved either primarily or following salvage therapy including two patients with metastatic disease at initial diagnosis. Vice versa, complete resection of all sites of recurrence was only achieved in one patient with locoregional and no patient with metastatic or combined relapse subsequently dying of disease. This highlights the importance of complete surgical resection of all tumoral sites, emphasised by a superior survival of patients with complete surgical resection in our study. Even in an initially metastatic disease and/or in patients with a metastatic relapse, the surgical resection of all tumoral sites seems to be advantageous regarding survival [23–25]. It should not go unmentioned that radiotherapy to the tumour bed and CNS metastases, respectively, was administered in 2 of the surviving patients. The role of radiotherapy in the treatment of paediatric ACC, however, has yet not been determined [26].

In relapsed ACC, the EXPeRT/PARTNER recommendations do not advise for a specific therapy. In case of a local relapse, repeated surgeries and reuse of mitotane may prolong survival, but the use of second-line chemotherapy depending on the previous drugs used or enrolment in prospective trials is also advised [19]. A combination of chemotherapy and mitotane was administered in 16 relapsed patients, mitotane alone in 6. In 3 of those mitotane was continued from first-line therapy. We recently demonstrated that the reuse of mitotane is not beneficial in patients exposed to the drug during first-line therapy [17]. To what extent the same applies to the reuse of chemotherapy has yet not been evaluated. In our study, MET chemotherapy was reused in 3 of 15 patients, of those one was still alive in second CR.

Multiple second-line therapies were used in the French study, with a very low impact on survival [13]. In the GPOH-MET study protocol, no second-line or relapse therapy was fixed. Hence, treatment was decided on an individual basis by the treating physician. As a result, a large variety of therapies was used including MET chemotherapy in previously untreated patients, second-line chemotherapy regimens adopted from adult ACC therapy including gemcitabine-based regimens

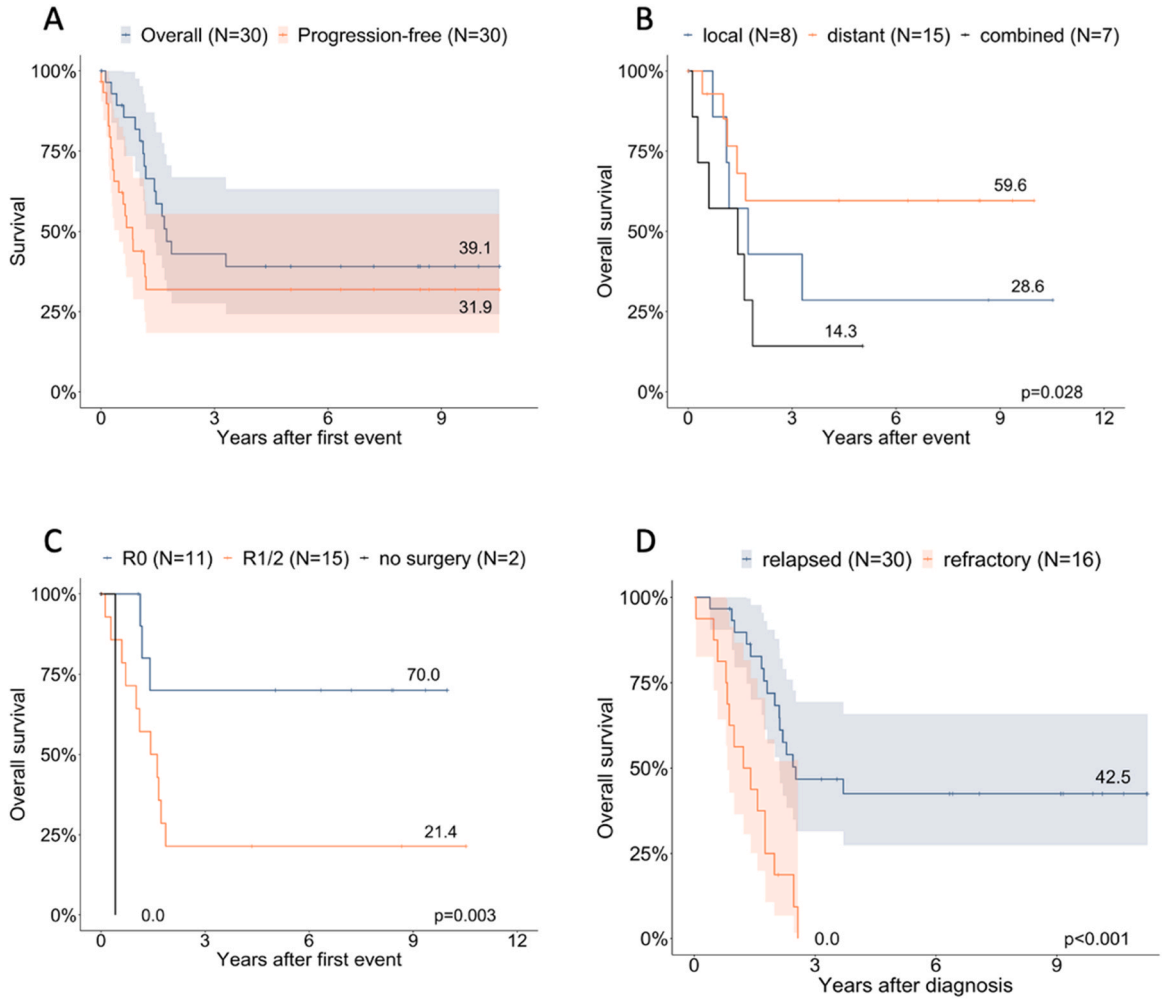

Fig. 3. (A) 4-year overall survival (OS 39.1%) and progression-free survival following relapse (PFS-R 31.9%). Overall survival following event in patients (B) with locoregional, distant and combined relapse, (C) with complete compared to incomplete/no surgical resection of all sites of recurrence (data missing in 2 patients), and (D) with refractory disease compared to relapse.

and streptozocin [23,27–29], other paediatric relapse protocols, and treatment strategies from early clinical trials or anecdotal responses, among others PD1, kinase, and IGF1 inhibitors [30,31]. Partial response to immunotherapy with pembrolizumab was reported in two of four paediatric patients with PD-L1-positive ACC, complete remission in one of two paediatric patients with advanced disease [31,32]. Clinical trials with multi-kinase inhibitors were so far negative, most likely because of drug interactions with mitotane. Only recently, partial response in 3 and stable disease in 5 of 16 adult patients with advanced ACC treated with cabozantinib monotherapy were reported [18]. In one patient with refractory disease, cabozantinib in combination with temozolomide and continued mitotane was administered in our cohort. The patient was still alive 2.1 years after disease progression. IGF1R overexpression was reported in paediatric ACC and preclinical studies have been promising [33]. However, results of clinical trials in adults were disappointing [34,35]. In our cohort, one patient with metastatic relapse underwent linsitinib treatment and died of progressive disease. It should not go unmentioned, that we did not systematically collect data on treatment rationales and response to individual therapies in our study.

We looked in more detail in those 17 (of 43) patients relapsing after initial AJCC stage II. Of those, only 4 patients were rescued by salvage therapy. In the ARAR0332 study, 46.7% of the COG stage II patients relapsed [3]. This is of particular importance for a number of reasons. First, the high relapse risk warrants adjuvant treatment at least in a subgroup of stage II patients. To allocate patients appropriately, molecular determinants that indicate high risk situations are urgently needed. Second, relapses occurred in 58.8% of patients as metastatic/combined relapse highlighting the need for systemic therapy in stage II patients. Third, outcome of relapsed patients was poor despite a variety of salvage therapies. Thus, novel therapeutic concepts in paediatric ACC based on molecular vulnerabilities are urgently needed. The EXPeRT/PARTNER recommendations advise for considering mitotane in stage II patients [19]. However, its effectiveness has still to be proven in prospective trials.

5. Conclusions

The outcome of children and adolescents with refractory ACC and combined relapses was very poor. It was best in patients with resectable metastatic recurrence. The site of relapse and its surgical resectability define prognosis.

A molecular-based classification of paediatric ACT is needed to identify tumours with high-risk features to facilitate sophisticated risk stratification for (early) clinical trials. In order to design international trials novel therapeutic concepts are desperately needed to ultimately improve the outcome of children and adolescents with ACT.

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CRediT authorship contribution statement

Michaela Kuhlen: Conceptualization, Methodology, Formal analysis, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Marina Kunstreich:** Investigation, Data curation, Writing – review & editing, Project administration. **Lienhard Lessel:** Investigation. **Stefan A. Wudy:** Investigation, Resources. **Paul-Martin Holterhus:** Investigation, Resources, Writing – review & editing. **Christian Vokuhl:** Investigation, Resources. **Eva Juettner:** Investigation, Resources. **Christoph Roecken:** Investigation, Resources. **Guido Seitz:** Investigation, Writing – review & editing. **Christoph Slavetinsky:** Investigation. **Jörg Fuchs:** Investigation, Resources, Writing – review & editing. **Denis M. Schewe:** Resources, Writing – review & editing. **Rainer Claus:** Writing – review & editing. **Pascal D. Johann:** Writing – review & editing. **Michael C. Frühwald:** Investigation. **Peter Vorwerk:** Methodology, Investigation, Resources, Funding acquisition. **Antje Redlich:** Methodology, Formal analysis, Resources, Data curation, Visualization, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejcped.2023.100015.

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