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Surgical Aspects in the Treatment of Adrenocortical Carcinomas in Children: Data of the GPOH-MET 97 Trial

Die Behandlung von Nebennierenrindenkarzinomen bei Kindern aus onkochirurgischer Sicht: Ergebnisse des GPOH-MET-97-Protokolls

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Key words
- adrenocortical carcinoma
- children
- surgery
- tumor biopsy
- tumor rupture

Schlüsselwörter
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- Kinder
- Chirurgie
- Tumorbiopsie
- Tumorruptur

Abstract

Background: Adrenocortical carcinomas (ACCs) are a rare entity, with an incidence of 1.5 per million population per year. The prognosis of ACC is poor. Complete surgical resection is essential for a curative approach and significantly determines overall prognosis. Tumor resection is sophisticated and complicated by the vulnerability of the tumor and its invasive growth. Chemotherapy and Mitotane are additional therapeutic approaches that are combined with surgery in an interdisciplinary strategy.

Patients and methods: In this study, 59 patients between 2 months and 18 years of age with histologically verified ACC were analyzed retrospectively with respect to oncosurgical aspects. Patients were registered in the GPOH-MET 97 trial of the Society of Pediatric Oncology and Haematology. Preoperative management, factors influencing surgical severity, and operative complications were assessed.

Results: The gender ratio was 1:2 (m:f). A total of 58 patients showed increased hormonal activity and associated clinical signs of hormonal excess. Tumor volume was ≥ 300 mL in 25 patients. These patients showed an increased rate of operative complications and a poorer overall survival (OS) rate ($p < 0.01$). A total of 14 patients showed metastatic spread, particularly to the lungs and lymph nodes. Biopsy of the tumor was performed in 12 patients. Tumor rupture occurred in 11 patients. Preoperative biopsy and/or experienced tumor rupture were associated with poorer OS rate. R2 resection only was achievable in 5 patients, and surgery was not feasible in 3 patients.

Conclusions: In conclusion, since most of the pediatric ACC are hormone active and can be diagnosed clinically, the need of a tumor biopsy has to be discussed critically. Thorough pre- and perioperative management is essential for oncosurgical success.

Zusammenfassung

Hintergrund: Das Nebennierenrindenkarzinom (ACC) ist eine seltene maligne Erkrankung mit einer Inzidenz von 1,5/1 000 000 Einwohner/Jahr und hat eine sehr ungünstige Prognose. Ein kurativer Ansatz ist nur durch die vollständige Resektion zu erreichen. Die Tumoren sind sehr vulnerabel und wachsen infiltrativ, so dass die Tumorresektion sehr anspruchsvoll ist. Chemotherapie und Mitotane sind weitere Bestandteile eines interdisziplinären Therapieansatzes.

Patienten und Methoden: 59 Patienten der GPOH-MET-97-Studie im Alter von 2 Monaten bis 18 Jahren mit histologisch gesichertem ACC wurden unter onkochirurgischen Aspekten retrospektiv analysiert. Besonderes Augenmerk lag auf dem präoperativen Management, Faktoren, die die Radikalität der Operation beeinflussten, und operativen Komplikationen.

Ergebnisse: Das Geschlechtsverhältnis war 1:2 (m:w). Fast alle Patienten hatten eine gesteigerte hormonelle Aktivität und klinische Zeichen des Hormonexzeses. Bei 25 Patienten betrug die Tumorgröße ≥ 300 ml. Diese Patienten hatten ein schlechteres Gesamtüberleben (OS). Insgesamt 14 Patienten zeigten eine Metastasierung vor allem in die Lunge und Lymphknoten. Bei 12 Patienten wurde eine Tumorbiopsie durchgeführt, bei 11 Patienten kam es intraoperativ zu einer Tumorruptur. Beides war assoziiert mit einem schlechteren OS. Bei 5 Patienten konnte lediglich eine R2-Resektion erreicht werden, und in 3 Fällen war eine Operation nicht möglich.

Schlussfolgerung: Die meisten ACC im Kindesalter sind hormonaktiv, so dass die Diagnose praktisch immer klinisch gestellt werden kann. Somit muss die Notwendigkeit einer Tumorbiopsie kritisch hinterfragt werden. Ein sorgfältiges prä- und perioperatives Management ist entscheidend für den chirurgischen Erfolg.

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Introduction

Adrenocortical carcinomas (ACCs) are a rare heterogeneous entity, with an incidence of 1.5 per million population per year [10]. The first disease peak occurs in early childhood, with the second peak observed between 40 and 50 years of age [22]. In all age groups, predominantly females are affected (m:f ratio = 1:1.5) [8].

Although the pathogenesis of ACC has not been clarified, several different mechanisms have been proposed [3]. Furthermore, it has been suggested that different mechanisms of tumorigenesis are involved in infants and adults. Especially, a germline mutation of the TP53 gene is detectable in up to 80% of sporadic infantile ACC, but only in 30% of adults [5,8,28]. Molecular diagnostic markers also have a different prognostic impact in children compared to adult patients [5].

The leading ACC symptoms in childhood are marked virilization and/or Cushing syndrome. These symptoms are more frequent in childhood than in adults. Other signs include hypertension, hypokalemia, and hypoglycemia, which are caused by an excess of adrenal steroid hormones [8]. Nonfunctioning ACC usually presents with abdominal distress or back pain, but these symptoms are fairly uncommon in childhood.

Thorough initial laboratory testing and visualization of the ACC and its potential metastatic spread are mandatory to choose an appropriate therapeutic strategy. The aim of the endocrine assessment is to differentiate ACC from neuroblastomas and pheochromocytomas, and to exclude hypercortisolism [1]. Further useful diagnostic tests include the dexamethasone suppression test, analysis of the potassium level and aldosterone/renin ratio, and analysis of sex steroids and steroid precursors. However, the most important diagnostic test for ACC is the analysis of the urinary steroid profile [1,8,20,30].

Imaging is another keystone of the diagnostic work-up for ACC. The primary tumor can be visualized by ultrasound, enhanced computed tomography (CT), and/or magnetic resonance imaging (MRI). Prediction of the dignity of the tumor in children is uncertain at present, but can be achieved using these methods in adults [13,15,20,27]. CT under anesthesia and with well-ventilated lungs is the gold standard for detecting tumor metastases in the lungs. Further diagnostic tools include positron emission tomography [11] and single photon emission CT [12,27]. The need for a biopsy as a diagnostic tool in adults is controversial [2,6,8,17] and will be critically analyzed in children in this work.

The prognosis of ACC remains poor, due to the prolonged latency until definitive diagnosis, early metastatic spread, and high rate of recurrence. The 5-year overall survival rate in adults and children is less than 10%, depending on disease stage [7,14]. In addition, most chemotherapeutic drugs and radiation treatments have limited effects on the tumor. Mitotane (dichlorodiphenyldichloroethane) is the only adrenal-specific agent currently available for the treatment of ACC. Its effects are specific to the cell cycle of adrenocortical cells. The use of mitotane in high-grade tumors is limited by its serious side effects; however, if serum levels are monitored carefully, mitotane can be used safely. Mitotane seems to have a positive impact as an adjuvant treatment option after resection to prevent recurrence [8,26]. In general, a curative approach is only feasible after complete resection of the ACC. However, resection is complicated by the vulnerability of the tumor and its invasion into surrounding structures. Operative rupture of the tumor is associated with tumor recurrence and progress, resulting in a worse prognosis.

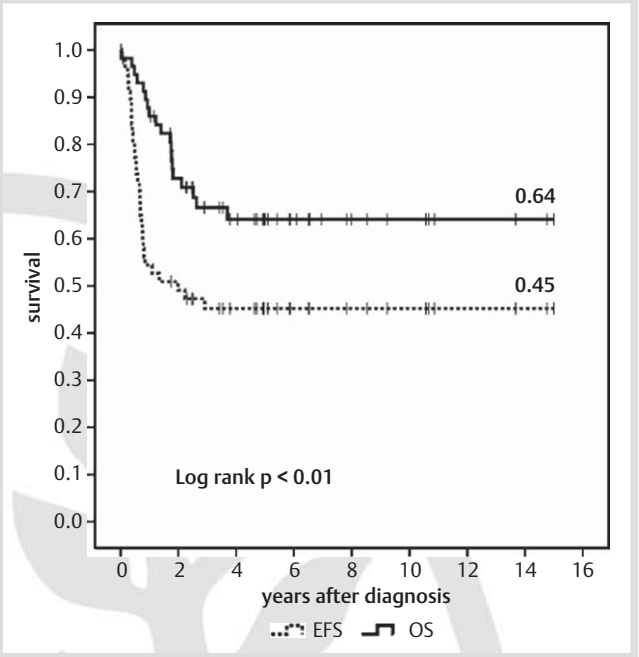

Fig. 1 Survival of the 59 patients with ACC from the GPOH-MET 97 trial. There is a significant difference between overall (OS) and event free survival (EFS).

The aim of this study was to identify factors influencing outcomes in pediatric patients with ACC, with special emphasis on surgical and preoperative management.

Patients and methods

In Germany, children and adolescents with ACC are registered and treated according to the GPOH-MET 97 protocol [21]. The treatment of children with malignancies in Germany in a national trial or registry is, whenever possible, highly recommended [9, 16]. Almost all children with ACC (97.1%) in Germany are registered in the German Childhood Cancer Registry [31] and treated according to the GPOH-MET 97 protocol. Until 2009 children with adrenocortical adenomas (ACA) are registered only sporadically, they are not part of the present analysis.

The study protocol suggested in complete resected tumors of stage I and II as well as in complete resected stage III tumors without lymph node involvement (T3, N0, M0) no additional chemotherapy. Stage III tumors with lymph node involvement (T1-2, N1, M0) were alternately treated with 4 cycle's chemotherapy (NN-I: Vincristin, Ifosphamid, Adriamycin or NN-II: Carboplatin, VP-16 respectively) in combination with mitotane over 9 month. All higher stages were alternately treated with 8 cycle's NN chemotherapy in combination with mitotane over 18 month. For primary unresectable tumors 2–4 cycle's chemotherapy and mitotane were suggested to enable a subsequent operation. The study protocol was approved by the ethical board of the University Kiel, Germany (97-125) and informed consent was obtained from all patients.

Since 1997, 86 patients between 2 months and 18 years of age (median 5.8 years) with adrenocortical tumors have been registered; 59 of these patients had histologically verified ACC and

were included in the present study. Patients with adrenocortical adenoma were excluded from the analysis. The present analysis focused on patient age, preoperative tumor size, diagnostic biopsies, invasive tumor growth and tumor rupture or spillage during operation. These factors were correlated with event free (EFS) and overall survival (OS) rate. The impact of chemotherapy and mitotane treatment on the survival rates has to be always considered, but will be thoroughly evaluated and presented in a different analysis.

Preoperative tumor sizes were estimated based on MRI and ultrasound images. The extent of resection and criteria such as invasive growth of the tumor were judged by the surgeon.

Statistical analyses were performed using SPSS® v19.0. Explorative analysis was performed without correction of p-values for multiple testing. The Mann-Whitney U-test was used for comparison of different statistical groups. OS and EFS were calculated by Kaplan-Meier estimation and compared using the log rank test. P-values of <0.05 were considered to be statistically significant.

Results

The gender ratio was 1:2 (m:f). A total of 59 patients met the inclusion criteria; 19 of these patients have died to date. The 5-years OS rate was 64%, and the EFS rate was 45% (**Fig. 1**).

Most patients (n=46) had clinical signs of hormonal excess or increased hormonal activity with positive laboratory tests (n=52). The predominant clinical sign was virilization (80% of cases), followed by Cushing syndrome (26%). Indications of symptomatic somatomegaly in the medical reports from the referring doctors were found in 24% of patients. 8 patients suffered from abdominal pain, and the ACC was an incidental finding in 10 patients.

Tumor staging was performed according to the international TNM classification [7,25]. Stage II (n=26) and stage IV (n=24) tumors were predominant. Disease stage correlated with OS rate ($p<0.001$). Patients with stage I disease had an OS rate of 100%, but the OS rate decreased to 49% for those patients with stage IV tumors (**Fig. 2**). Except for stage I disease, the EFS rate was equally poor for all disease stages. The lung was the most affected organ for metastases (n=12), followed by the liver (n=4), bone marrow (n=3), and central nervous system (n=1). ACC-positive lymph nodes were seen in 9 patients. Vascular invasion was present in almost 20% (n=11).

The median tumor volume was 189 mL, ranging from 9 mL to 3 645 mL. Tumor volume correlated with patient age, indicating that older patients had larger tumors ($p<0.001$). Furthermore, tumor volume correlated negatively with OS rate ($p<0.01$). Choosing the optimal cutoff value of 300 mL by receiver operating characteristic (ROC) curve analysis showed that patients with a tumor volume <300 mL (n=34) had a significantly better OS rate (80%) than patients with tumors ≥300 mL (42%).

A total of 44 patients were operated on by pediatric surgeons, 3 patients in a urology department and 3 in a general surgery department. Nearly all tumors were resected by laparotomy. In 1 patient, the operation was initiated laparoscopically and then converted due to operative tumor rupture. Biopsy of the tumor was performed in 12 patients (3 fine needle biopsies [FNBs], 9 laparotomies). There was an interesting association between OS and preoperative biopsy status. The OS rate in patients who did not undergo biopsy was 69% in contrast to 42% in patients who underwent biopsy (**Fig. 3**). Patients who underwent FNB appeared to have a more favorable OS rate, at 67%, versus 32% for those underwent open biopsy; however, statistical analysis was

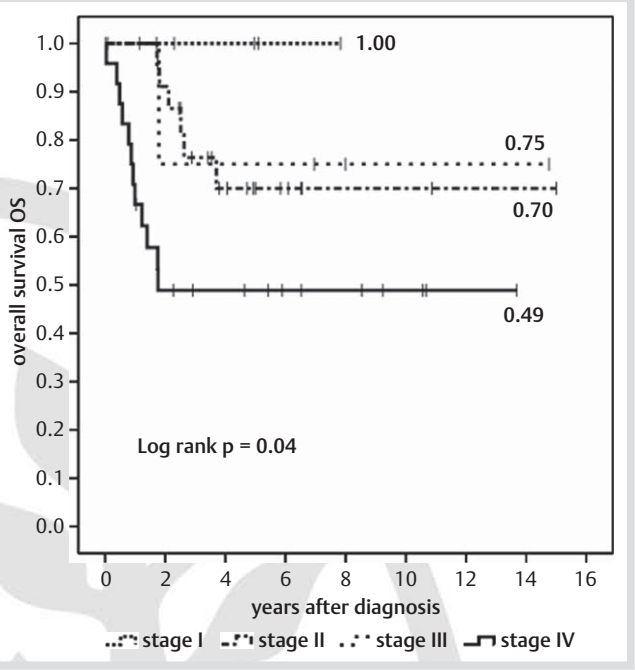

Fig. 2 Stage dependent overall survival (OS) of patients with ACC of the GPOH-MET 97 trial. Stage I: N=5; mean age=5.0 years; mean tumor volume=17.9 ml. Stage II: N=26; mean age=5.7 years; mean tumor volume=401.5 ml. Stage III: N=4; mean age=6.9 years; mean tumor volume=361.6 ml. Stage IV: N=24 mean age=9.2 years; mean tumor volume=679.9 ml.

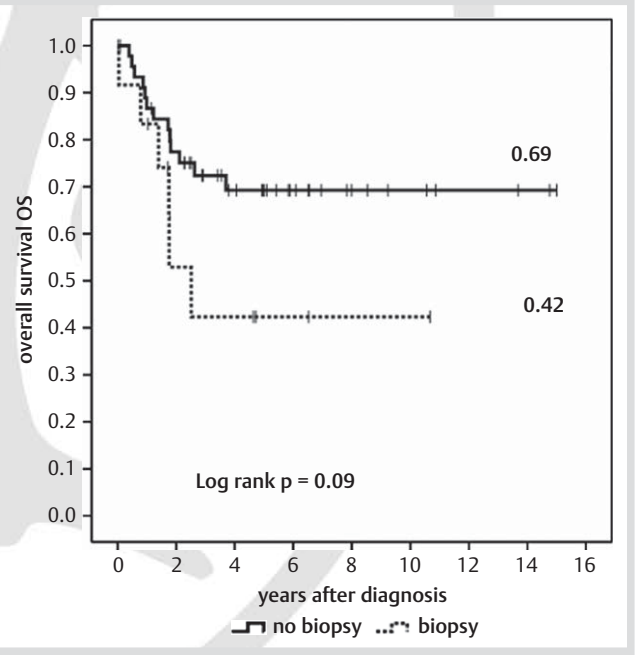

Fig. 3 Overall survival and preoperative biopsy status. The difference between both groups shows a statistical trend in the log rank test. Biopsies were performed either as fine needle biopsy N=3 or open surgical biopsy N=9. Patients without biopsies: N=47; mean age=6.8 years; mean tumor size=424.9 ml. Patients with biopsies: N=12; mean age=8.5 years; mean tumor size=693.5 ml. The differences in age and tumor size were statistically not significant.

not possible due to the small number of patients. In addition to open biopsy, operative rupture of the tumor had a negative impact on OS. Tumor rupture occurred in 11 patients and was negatively associated with OS. Tumor spillage in general (ruptures and biopsies) were associated with a dramatic reduction of OS rate (80% in patients without vs. 45% in patients with spillage P=0.017).

Based on operative reports, R0 resection was achieved in at least 31 patients. Tumor tissue remaining in situ (Rx resection) and/or tumor rupture occurred in another 25 patients. 3 tumors were inoperable. Whereas the OS rate of patients with R0 resection was 82%, OS rate decreased to 48% for patients with Rx resection. Thus the degree of the resection is assoiated with the OS rate (p=0.01). Comparable results were seen for patients with tumors with invasion of surrounding tissues. A total of 18 invasive tumors were observed. Patients with invasive tumors had an OS rate of 44%, versus 82% in patients with noninvasive tumors (p=0.01). However, there was no significant difference between groups regarding the probability of operative tumor rupture (p>0.05).

Discussion

Our data suggest that both the diagnosis and treatment of ACC have special characteristics in our pediatric pediatric population. We found that almost all of our pediatric patients showed clinical signs of hormonal excess (82.5%). The appearance of ACC as an incidentaloma is relatively rare (17.5%). In contrast to children, clinical signs of hormonal excess in adult ACC are seen only in about 50% of patients [8]. While Cushing syndrome is the predominant sign of ACC in adults, most pediatric patients examined in this study suffered from virilization (80%). Almost all studied children (89.7%) showed elevated hormonal levels in laboratory tests. Thus, in combination with radiologic findings, the diagnosis of an adrenocortical tumor could almost always be performed clinically. This is in line with the findings of others groups [19,23]. However, prediction of the dignity of the tumor is especially difficult in children [20,23,29]. This observation is particularly important for the preoperative management of adrenocortical tumors in children. Therefore, all suspected adrenal tumors must be managed as ACCs until the final diagnosis is made.

As almost all ACCs in children could be diagnosed clinically, the need for biopsy in the diagnostic follow-up has to discussed critically. Biopsies can delay the preoperative diagnosis, providing especially in large tumors often no reliable and representative histological information, but can also deteriorate the prognosis due to tumor spillage [23]. In the present study, preoperative tumor biopsy is associated with a reduction of the OS rate from 69% in patients who did not undergo biopsy to 42% in patients who did undergo biopsy. In the recent literature regarding adult ACC populations, diagnostic biopsies have been the subject of much debate [2,6,8]. Our data suggest that biopsies should be avoided, at least in children. According to Fassnacht et al. [8], there are only 2 indications for biopsy in adults. The first is advanced, incurable, stage IV ACC and the second is an inoperable primary tumor; in both cases, biopsy may be performed to achieve a histologic diagnosis.

To date, ACCs are only curable by complete resection of the tumor [8]. Therefore, all efforts must be made to achieve R0 resection of the primary tumor. ACC vulnerability, tumor size, and invasion of surrounding tissues are negative predictive factors and determine the success of primary tumor resection. The vulnerability of the ACC was found to be responsible for the high rate of operative tumor ruptures (19%) and was associated with poor outcome in this study. Because few studies have examined laparoscopic ACC resection in children, we recommend tumor resection via laparotomy. Many authors recommend a similar treatment approach for ACC in adults and children, namely, an open surgical resection, but discussion of the optimal therapeutic method is still ongoing [2,4,8,18,23].

We have also shown in this study that tumor size is associated with prognosis. The OS rate of patients with tumors ≥300 mL was only about 41%, with older children suffering from larger tumors. This is in accordance with the results from other pediatric groups, however, the suggested optimal cutoff varies between 200 and 400 mL tumor size [11,23].

Thorough preoperative visualization of the tumor by experienced radiologists can describe the relationship between the tumor and surrounding tissues and help the surgeon to plan the resection. In our study, at least 31% of tumors showed invasion of other organs, complicating the resection. Knowledge of such potential invasion can facilitate preoperative planning. In cases of huge tumor size and invasive tumor growth, neoadjuvant use of chemotherapy and mitotane should be considered for a volume reduction. If all these aspects are considered carefully, the chance of achieving complete surgical resection of the tumor may be increased.

Besides the pre- and intraoperative management analyzed in the present study, other factors like age, tumor size, histology, adjuvant chemotherapy and mitotane treatment can influence the EFS and OS. To draw attention to this problem, we always indicated age and tumor size in the figures.

If not standardized, diagnostic assessment and treatment of children with (very) rare tumors like ACC may lead to incomplete or to elaborate assessment on one hand as well as under- or overtreatment on the other. Diagnostic and therapeutic guidelines from national expert groups may provide a significant assistance to the treating physician that may increase the quality of care [24]. Therefore all children with ACC should be registered in the national trials or registries and treated according to the actual recommendations [9,16,23].

Conclusion

Pre- and perioperative management is important for long-term outcomes of children with ACC. A special challenge for the pediatric surgeon, which is crucial for the patient, is the complete resection of the primary tumor without tumor spillage. Since diagnosis of ACC in children can be made in most patients by clinical examination, the need for a diagnostic biopsy in children, which is associated with a poor outcome, is challenging. Laparoscopic tumor resection in childhood is not recommended due to the risk of tumor rupture. Precise imaging of the tumor, including accurate tumor size, local and vascular invasion pattern, and lymph node involvement, by ultrasound CT and MRI techniques, as well as steroid hormone measurements in serum and urine are obligate preoperative diagnostic procedures. All children should be treated in pediatric oncologic centers with experienced pediatric surgeries in a highly interdisciplinary setting.

Although an optimal pre- and perioperative management always influence the outcome of a surgical therapy, our study does not allow to draw conclusions about causal relationships between both.

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Conflict of Interest: The authors have no conflict of interest to disclose.

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