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CASE REPORT

Extremely long survival in six patients despite recurrent and metastatic adrenal carcinoma

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Abstract

Objective: Adrenal cortical carcinoma (ACC) is an aggressive tumour with a high mortality. We describe six patients living 12–28 years despite recurrent and/or metastatic ACC.

Patients: The first patient presented in 1979 with an ACC of 8 cm. After resection, she developed seven recurrences for which she was treated with resection and/or mitotane (*o*,*p*′-DDD) treatment. The patient is still alive 28 years after diagnosis. The second patient presented with an ACC of 9 cm. After resection, the patient developed liver metastases, which were treated with *o*,*p*′-DDD. The patient is still alive 25 years after diagnosis. The third patient presented with an ACC of 12 cm. The tumour was resected followed by *o*,*p*′-DDD treatment. She had a local recurrence that was completely resected. She is still alive 18 years after diagnosis. The fourth patient presented with an ACC of 14 cm. After resection, adjuvant *o*,*p*′-DDD was started. Subsequently, the patient developed two recurrences, which were resected. He is still alive 17 years after the initial diagnosis. The fifth patient presented with an ACC of 10 cm. After diagnosis, she developed lung metastasis, which were treated with *o*,*p*′-DDD and chemotherapy. The patient is still alive with slowly progressive disease 12 years after diagnosis. The sixth patient presented with an ACC of 7 cm. After resection, she developed four recurrences, which were resected. The patient is still alive 28 years after diagnosis.

Conclusion: Some patients can have an extremely long survival of ACC, despite recurrent disease and metastases. The mainstay of therapy in our patients was repeated surgery and *o*,*p*′-DDD.

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Introduction

Adrenal cortical carcinoma (ACC) is a rare and aggressive tumour. The first report of survival dates from 1958 and indicates that survival in untreated patients is only ∼3 months (1). In the past decades, diagnostic and surgical approaches have been improved. In addition, mitotane (*o*,*p*′-DDD) and chemotherapy were introduced in the adjuvant and metastatic settings (2–5).

Despite these treatments, adrenal carcinoma still carries an unfavourable prognosis. The median 5-year survival rates reported in several studies range between 16 and 38%, with early stages having better prognosis (5–12). Nonetheless, the long-term prognosis cannot be easily predicted from the initial presentation and may vary considerably between patients with similar tumour stages. Stage and radical resection is the only fully approved prognostic marker, but even after radical resection some patients die very shortly after being diagnosed, whereas others survive for several years. Only six case reports have been described with long-term survival of 15–18 years with recurrent and metastatic ACC (Table 1). In this paper, we describe six additional patients who were alive 12–28 years after the initial diagnosis despite recurrent and metastatic adrenal carcinoma.

Patients

The sequence of the events in each of the six patients is summarized in Table 1 and detailed below.

Patient A

In 1979, patient A presented at the age of 22 years with clinical and biochemical manifestations of Cushing's syndrome and hirsutism. She was diagnosed with a tumour arising from the left adrenal gland, with a diameter of 8 cm, which was surgically removed with free margins. Pathological examination revealed an ACC with a weight of 98 g. At that time, there was no evidence of local invasion or metastases. After surgery, the clinical symptoms and the laboratory abnormalities disappeared.

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Table 1 Overview of medical history with recurrences of adrenal cortical carcinoma (ACC) in patients A–F.

ACC	Date	Clinical findings	Laboratory findings	Therapy	Response	Toxicity
A						
Primary ACC	1979	Cushing's syndrome	Hypercortisolism and hyperandrogenism	Surgery	X	
Recurrence 1	1981	Cushing's syndrome	Hypercortisolism and hyperandrogenism	Surgery	X	
Recurrence 2	1983	Cushing's syndrome	Hypercortisolism and hyperandrogenism	*o,p′*-DDD (2 years)	CR	CNS, severe
Recurrence 3	1990	Cushing's syndrome	Hypercortisolism and hyperandrogenism	Surgery	X	
Recurrence 4	1993	Cushing's syndrome	Hypercortisolism and hyperandrogenism	Surgery	X	
Recurrence 5	1994	Cushing's syndrome	Hypercortisolism and hyperandrogenism	*o,p′*-DDD (2 years)	CR	CNS, mild
Recurrence 6	2001	No signs of recurrence	No signs of recurrence	Surgery	X	
Recurrence 7	2003	No signs of recurrence	No signs of recurrence	Surgery	X	
B						
Primary ACC	1982	Conn's syndrome	Hypokalaemia	Surgery	X	
Recurrence 1	1986	Conn's syndrome	Hypokalaemia	*o,p′*-DDD (2 years)	CR	GI, mild
C						
Primary ACC	1988	Cushing's syndrome	Hypercortisolism	Surgery + adjuvant *o,p′*-DDD (2 years)	X	CNS, severe
Recurrence 1	1995	Abdominal pain	No signs of recurrence	Surgery	X	
D						
Primary ACC	1990	Abdominal pain	No biochemical signs of hormonal excess	Surgery	X	
Recurrence 1	1992	No signs of recurrence	No biochemical signs of hormonal excess	Surgery and *o,p′*-DDD	PR	GI and CNS, mild
Recurrence 2	1999	No signs of recurrence	No biochemical signs of hormonal excess	Surgery	X	
E						
Primary ACC	1996	Cushing's syndrome	Hypercortisolism and hyperandrogenism	Surgery	X	
Recurrence 1	2003	No signs of recurrence	Hypercortisolism and hyperandrogenism	*o,p′*-DDD (5 years)	PR	GI and CNS, mild
	2005	Progression lung metastasis	Hypercortisolism and hyperandrogenism	Sz	PD	
	2006	Progression lung metastasis	Hypercortisolism and hyperandrogenism	EDP	PR	
	2007	Progression lung metastasis	Hypercortisolism and hyperandrogenism	Radiotherapy	SD	
F						
Primary ACC	1990	Abdominal pain	No biochemical signs of hormonal excess	Surgery	X	
Recurrence 1	1999	No signs of recurrence	No biochemical signs of hormonal excess	Surgery	X	
Recurrence 2	2002	No signs of recurrence	No biochemical signs of hormonal excess	Surgery	X	
Recurrence 3	2007	Pain in the right hip	No biochemical signs of hormonal excess	Surgery + intra-operative	X	

Sz, streptozotocin; EDP, etoposide, doxorubicin and cisplatin; CR, complete remission; PR, partial remission; SD, stabil disease; GI, gastrointestinal side effects, CNS, central nervous system side effects.

In 1981, the patient again developed Cushing's syndrome. An abdominal computed tomography (CT) scan showed a local recurrence of the tumour with a diameter of 11 cm, with invasion of the left kidney and diaphragm. A complete resection of the tumour with left-sided nephrectomy and hemidiaphragmectomy was performed in January 1982. Pathological examination confirmed recurrence of the ACC. She was considered tumour free for that moment and a wait and see policy was decided for.

In 1983, there was a second recurrence of the clinical and biochemical features of Cushing's syndrome. A CT scan showed a local recurrence of the tumour behind the spleen of 2.0 cm. It was decided that a third laparotomy was not desirable, and *o*,*p*′-DDD treatment was started for 2 years. The levels of *o*,*p*′-DDD ranged between 20 and 30 mg/l with severe neurological side effects, consisting of ataxia, and difficult speech. After 1 year of *o*,*p*′-DDD treatment, the tumour had disappeared radiologically. The *o*,*p*′-DDD treatment was discontinued after 2 years as originally planned. Subsequently, the adverse effects completely resolved within 3 months and she had a tumour-free interval of 5 years.

In 1990, she developed a third recurrence with clinical and biochemical features of Cushing's syndrome with a tumour of 3 cm located between spleen and diaphragm. The tumour was surgically resected completely. The diagnosis of recurrent ACC was confirmed by pathological examination.

In 1993, the patient developed a fourth recurrence of Cushing's syndrome and hirsutism. An abdominal CT scan showed a small recurrent tumour behind the spleen. A laparotomy was performed and the tumour with a diameter of 2 cm was removed with free margins.

In 1993, the patient was also diagnosed with papillary thyroid carcinoma, tumour stage T2N0M0, for which she was treated by total thyroidectomy and postoperative ablation with radioactive iodine. Subsequently, there have been no clinical, biochemical and radiological indications of recurrence of this thyroid carcinoma.

In 1994, a follow-up CT scan showed nodular lesions in the right lung. There were clinical and biochemical signs of recurrent Cushing's syndrome. Because one of the lesions, situated in the right hilus of the lung, was considered irresectable, *o*,*p*′-DDD was resumed for a period of 2 years with serum levels ranging between 14 and 20 mg/l. After a period of 4 months, the tumour lesions in the lungs completely regressed.

In 2001, two new lesions were diagnosed on a follow-up CT scan. By means of a video-assisted transthoracal endoscopic procedure, the lung metastases were completely resected in February 2002.

In 2003, a new lesion (seventh recurrence of the disease) behind the spleen was seen on a CT scan. There were no clinical or biochemical signs of Cushing's disease. The lesion was completely resected by a thoracolumbotomy. Because of the relative benign course of the disease, the serious side effects that the patient had experienced during *o*,*p*′-DDD and the fact that *o*,*p*′-DDD had not prevented any recurrence of lesions in this patient, a decision was made to perform follow-up without additional treatment.

In 2007, this patient with metastatic adrenocortical carcinoma is in good condition and considered tumour-free 28 years after primary diagnosis.

Patient B

In 1982, patient B presented at the age of 31 years with Conn's syndrome. Blood pressure was 180/100 mmHg, potassium concentration 2.6 mmol/l, sodium 144 mmol/l and creatinine 108 μmol/l. An abdominal CT scan showed a large mass arising from the right adrenal gland. The tumour was completely resected. Pathological examination revealed a diameter of 9 cm, a weight of 110 g and histological evidence of ACC.

In 1986, the patient developed recurrent Conn's syndrome, evidenced by hypertension and hypokalaemia. She had a local recurrence and metastases in the right kidney and liver, which could not be curatively resected. After the removal of the local recurrence and the right kidney, she started palliative treatment with *o*,*p*′-DDD treatment for 2 years The levels of *o*,*p*′-DDD ranged between 25 and 30 mg/l. As a result of *o*,*p*′-DDD, she developed severe neurological side effects, mild gastrointestinal side effects and endometrial hyperplasia. During treatment with *o*,*p*′-DDD, the clinical and biochemical symptoms of Conn's syndrome, the local recurrence of the tumour and the metastases completely disappeared. After discontinuation of *o*,*p*′-DDD, the patient remained in complete remission.

In 2007, a CT scan did not show any signs of tumour recurrence. This patient is still alive 25 years after being diagnosed with adrenal carcinoma and 21 years after first occurrence of metastases.

Patient C

In 1988, patient C at the age of 34 years presented with clinical and biochemical features of Cushing's syndrome. On abdominal CT scan, a large mass arising from the right adrenal gland was seen without any signs of local infiltration or metastases. The tumour with a diameter of 12 cm and a weight of 300 g was completely resected. Histological examination revealed an ACC with tumour-negative margins. After surgery, adjuvant treatment with *o*,*p*′-DDD was started for 2 years. The patient experienced severe neurological side effects as a result of *o*,*p*′-DDD use. The levels of *o*,*p*′-DDD were between 25 and 30 mg/l.

In 1995, the patient presented with right-sided abdominal pain without further clinical or biological

signs of a recurrence. However, on CT scan, a local recurrence with a diameter of 3 cm was seen again without signs of local invasion or distant metastases. The recurrent ACC was resected radically. No adjuvant treatment with *o*,*p*′-DDD was started because of the previous severe toxicity of *o*,*p*′-DDD. She was tumour free in the following years.

In 2007, a follow-up CT scan of the thorax and abdomen did not show any tumour recurrence. The patient is still alive 18 years after the initial diagnosis with ACC due to sequential surgical treatment for recurrent disease.

Patient D

In 1990, Patient D at the age of 38 years presented with abdominal pain and a large mass in the left upper quadrant of the abdomen. There were no clinical or biochemical signs of hormonal excess. Ultrasound examination showed a large tumour arising from the left adrenal gland. A CT scan also revealed a pulmonary lesion with a diameter of 2 cm in the upper lobe of the right lung. The patient underwent a left-sided adrenalectomy. The removed tumour had a diameter of 14 cm and weighed 725 g. Histological examination documented the presence of ACC. Immediately after surgery, treatment with *o*,*p*′-DDD was started for 2 years with plasma levels between 20 and 28 mg/l, with neurological side effects such as concentration and balance disorders. The treatment with *o*,*p*′-DDD resulted in a reduction of tumour size of 50%. Because of the favourable response, it was decided to resect the pulmonary lesion in February 1991. During this procedure, two tumours (5 and 8 mm) were resected from the right lung. Pathological examination confirmed the presence of metastases of the ACC. The lesions were completely removed. In September 1992, *o*,*p*′-DDD was discontinued after 2 years of treatment.

In November 1992, a follow-up CT scan showed a new lesion in the left lung, which was removed by a second thoracotomy. Histological examination again revealed a metastasis of the ACC.

In 1999, after a disease-free period of 6 years, a biopsy proven metastasis in the liver was observed during follow-up. Subsequently, a partial liver resection was performed. The resected tumour had a diameter of 2.2 cm. Since then, there have not been signs of tumour recurrence. The patient is still alive 17 years after a diagnosis of metastasized ACC.

Patient E

In 1996, patient E at the age of 53 years presented with Cushing's syndrome, hypertension and hirsutism. On CT scan, a tumour of the left adrenal gland was seen. Adrenalectomy was performed and pathological examination revealed an adrenocortical carcinoma with a diameter of 10 cm, without signs of metastasis. In the subsequent 4 years, the patient had no complaints and the follow-up clinical, laboratory and radiological examinations showed no signs of recurrence.

From 2001, the blood pressure increased, associated with a gradual biochemical recurrence of Cushing's syndrome. Finally, in 2003, a CT scan showed multiple metastases in both the lungs. Therefore, *o*,*p*′-DDD was initiated in October 2003. The *o*,*p*′-DDD resulted in a partial remission (25–50%) of the pulmonary lesions seen on a CT scan performed in February 2004. The serum levels of *o*,*p*′-DDD during this period ranged between 14 and 26 mg/l.

In April 2005, progression of the lung metastases was documented on a CT scan. The *o*,*p*′-DDD was continued in combination with chemotherapy according to the first international randomised trial in locally and metastatic adrenocortical carcinoma treatment (FIRM-ACT) protocol (ISRCTN94256573). The patient was randomized to the streptozotocin (Sz) regimen that started in May 2005. After a total of four courses of Sz, progressive disease, after an initial stabile situation, was observed. Therefore, the treatment switched according to the protocol to the etoposide, doxorubicin and cisplatin (EDP) regimen in September 2005.

In February 2006, after six courses of EDP, a partial response was observed. After this initial partial response, progression under chemotherapy EDP was observed in September 2006. It was decided to stop with EDP chemotherapy and *o*,*p*′-DDD was continued. From the end of 2006, the disease slowly progressed and one pulmonary became so large that it was radiated. The radiotherapy resulted in stabilization of tumour growth.

At present, the patient is still alive but with slowly progressing disease, 12 years after the initial diagnosis.

Patient F

In 1990, patient F at the age of 49 years presented with abdominal discomfort. The patient showed no clinical signs of hormonal excess. A mass of the left adrenal gland of 7 cm in diameter was found on CT examination. The laboratory investigations did not find any evidence of hormonal overproduction. After radical resection, the histological examination revealed an ACC with tumour-negative margins without signs of metastases.

In 1999, after 9 years without recurrence, a CT examination showed two enlarged mesenteric lymph nodes that were removed in February 1999. Pathological examination documented lymph node metastases of adrenocortical carcinoma.

In 2000, she developed two pulmonary lesions in the right lung, diagnosed on a follow-up CT scan. Therefore, a lobectomy of the right lower quadrant of the lung was

performed. Histological examination showed metastases of adrenocortical carcinoma.

In 2002, she developed a third recurrence in the left lung with two new pulmonary metastases. The lesions were resected by lobectomy of the left lower quadrant. The pathologic examination revealed the presence of two metastases of an ACC.

In 2007, after a disease-free period of 5 years, the patient presented with pain of the right hip. During physical examination, a large tumour was felt. Magnetic resonance imaging of the hip showed a tumour of 10 cm in diameter. This fourth recurrence was treated with radiotherapy and subsequent surgical resection.

This patient is still alive with metastatic disease 18 years after the initial diagnosis with ACC, treated by sequential surgical treatment for recurrent disease.

Discussion

This report documents the long-term survival of six patients despite recurrent and metastatic ACC. These patients are alive 12–28 years after the initial diagnosis of ACC. Because of the aggressive nature of the disease, few patients survive as long as described in this report. At Leiden University Medical Centre, 120 patients with ACC were treated in the past 28 years. Four patients of this group are living more than 15 years despite recurrent and metastatic disease. Therefore, the prevalence of these patients with extremely long survival despite recurrent disease is very low ($\sim$3–4%).

In the literature, only six reports have been published on long-term survival of individual patients with ACC (13–19; Table 2). This low number of reports is in accordance with the low prevalence of such patients. All describe patients with recurrent and/or metastatic disease treated with *o*,*p*′-DDD and (recurrent) surgery.

A few prognostic factors have been investigated that might elucidate why some patients survive this long. Whereas the influence of gender, age and functionality of the tumour on prognosis is subject to debate (19–21) and the prognosis was influenced by tumour stage at diagnosis and the possibility to perform a complete resection (19, 22). Recently, Assié *et al.* discussed the prognostic parameters of metastatic adrenocortical carcinoma. They conclude that the number of tumoral organs at time of first metastasis and high mitotic rate influences the prognosis in patient with stage 4 disease (23). In general, a good response to *o*,*p*′-DDD is associated with a better prognosis (24). Accordingly, the first four patients responded well to *o*,*p*′-DDD monotherapy.

Several studies have been published on the different treatment options of ACC (Table 3). The most commonly used treatment options for ACC are (recurrent) surgery, *o*,*p*′-DDD and cytotoxic chemotherapy. The patients described in this article were treated by surgery and/or *o*,*p*′-DDD. Patient F did not receive *o*,*p*′-DDD treatment. The follow-up of this patient was provided by an oncological surgeon who did not consider treatment with *o*,*p*′-DDD at that time. The *o*,*p*′-DDD is a drug widely used for the treatment of recurrent and metastatic ACC. It remains the treatment of choice for patients who are not emendable by surgery. The efficacy of *o*,*p*′-DDD has been investigated in several trials. However, the interpretation of their results is difficult because of the use of different response criteria. Overall, the response to *o*,*p*′-DDD treatment in terms of tumour regression ranges from 13 to 35%. This tumour response is influenced by the serum concentrations of *o*,*p*′-DDD (7, 12, 28, 31). The *o*,*p*′-DDD levels between 14 and 20 mg/l proved to be most effective in achieving tumour response, whereas the levels >20 mg/l are associated with serious adverse effects (12, 31, 46). All patients described earlier, who received *o*,*p*′-DDD treatment, were treated with high doses of *o*,*p*′-DDD. At Leiden University Medical Centre, it was common before 1994, to reach levels up to 30 mg/l, provided that the patient did not have severe side effects. Since 1994, the aim was to reach therapeutic levels of *o*,*p*′-DDD between 14 and 20 mg/l, since the side effect correlated with serum levels >20 mg/l (12). In addition to effects on tumour regression, *o*,*p*′-DDD also controls hormonal hypersecretion (30).

The use of *o*,*p*′-DDD as an adjuvant therapy remains controversial (7, 10–13, 24, 30, 47). Terzolo *et al.* recently questioned this adjuvant use (5). He retrospectively analysed 177 ACC patients. He compared a group who had *o*,*p*′-DDD treatment directly after surgery with two control groups. The group treated with

Table 2 Case reports on long-term survival in adrenal cortical carcinoma (ACC).

Author	Age	Tumour function	Tumour stage	Treatment	Survival
Aalderen (1992) (14)	50 years	Cushing's syndrome	Stage 2	Recurrent resection and *o*,*p*′-DDD, CR	22 years
Sakamoto (1995) (15)	40 years	Non-functioning	Stage 3	Recurrent resection	18 years
Ilias (2001) (16)	39 years	Cushing's syndrome +virilization	Stage 2	*o*,*p*′-DDD, PR	14 years
	21 years	Cushing's syndrome	Stage 4	Cisplatin and *o*,*p*′-DDD, PR	16 years
Meyer (2001) (17)	34 years	Non-functioning	Stage 2	Recurrent resection and *o*,*p*′-DDD	32 years
De Leon (2002) (18)	2 months	Cushing's syndrome	Stage 3	Recurrent resection, adjuvant *o*,*p*′-DDD	15 years
Orlando (2003) (19)	58 years	Non-functioning	Stage 2	Recurrent resection	15 years

Table 3 Overview of articles describing results of different treatment options for adrenal cortical carcinoma (ACC).

Study	Year	No. of patients	Treatment	Outcome
o,*p*′-DDD				
Venkatesh *et al.* (10)	1989	72	*o*,*p*′-DDD	29% overall response rate
Luton *et al.* (6)	1990	37	*o*,*p*′-DDD	22% overall response rate
Decker *et al.* (25)	1991	36	*o*,*p*′-DDD	21% overall response rate
Wooten *et al.* (26)	1993	8	*o*,*p*′-DDD	35% overall response rate
Haak *et al.* (12)	1994	55	*o*,*p*′-DDD	27% overall response rate
Barzon *et al.* (27)	1997	11	*o*,*p*′-DDD	18% overall response rate
Williamson *et al.* (28)	2000	16	*o*,*p*′-DDD	13% overall response rate
Heilmann *et al.* (29)	2001	6	*o*,*p*′-DDD	50% overall response rate
Vassilopoulou-Sellin *et al.* (30)	1993	8	Adjuvant *o*,*p*′-DDD	14 months survival, disease-free period 10 months
Haak *et al.* (12)	1994	11	Adjuvant *o*,*p*′-DDD	51 months survival
Baudin *et al.* (31)	2001	11	Adjuvant *o*,*p*′-DDD	24 months survival, disease-free period 7 months
Terzolo *et al.* (5)	2007	47	Adjuvant *o*,*p*′-DDD	110 months survival, disease-free period 42 months
Chemotherapy				
van Slooten *et al.* (32)	1983	11	CDP	18% overall response rate
Schlumberger *et al.* (33)	1991	13	5-FU, D,P	23% overall response rate
Decker *et al.* (25)	1991	16	D	19% overall response rate
Bukowski *et al.* (34)	1993	37	P/*o*,*p*′-DDD	30% overall response rate
Bonacci *et al.* (35)	1998	18	EP/*o*,*p*′-DDD	33% overall response rate
Williamson *et al.* (28)	2000	45	EP	11% overall response rate
Khan *et al.* (36)	2000	22	Sz	36% overall response rate
Baudin *et al.* (37)	2002	12	CPT-11	0% overall response rate
Abraham *et al.* (38)	2002	36	EDV	14% overall response rate
Khan *et al.* (39)	2004	11	VPTC	18% overall response rate
Berruti *et al.* (40)	2005	72	EDP/*o*,*p*′-DDD	48.6% overall response rate
Surgery				
Nader *et al.* (41)	1983	77	Surgery	30% overall 5-year survival rate
Pommier *et al.* (11)	1992	73	Surgery	35% overall 5-year survival rate, after CR 47%
Haak *et al.* (12)	1995	96	Surgery	27% overall 5-year survival rate, after CR 49%, IR 9%
Crucitti *et al.* (8)	1996	129	Surgery	35% overall 5-year survival, after CR 48%, IR 7%
Khorram-Manesh *et al.* (42)	1998	18	Surgery	58% overall 5-year survival rate
Harrison *et al.* (43)	1999	46	Surgery	36% overall 5-year survival rate
Schulick *et al.* (44)	1999	113	Surgery	37% overall 5-year survival rate, after CR 55%, IR 5%
Icard *et al.* (7)	2001	253	Surgery	38% overall 5-year survival rate
Kendrick *et al.* (45)	2001	58	Surgery	37% overall 5-year survival rate
Vassilopoulou-Sellin *et al.* (13)	2001	139	Surgery	45% overall 5-year survival rate

o,*p*′-DDD, mitotane; 5-FU, 5-fluorouracil; D, doxorubicin; P, cisplatin; E, etoposide; V, vincristine, CPT-11, irinotecan; T, teniposide; C, cyclofosfamid; Sz, streptozotocin; CR, complete resection; IR, incomplete resection.

adjuvant *o,p′*-DDD showed a prolonged recurrence-free survival. In addition to the prolonged recurrence-free survival, overall survival seemed significantly better in the *o,p′*-DDD group after 5 years. The effects of *o,p′*-DDD treatment cannot be judged after 10 years because of the small number of patients who survive for a long period. Nevertheless, multivariate analysis indicated a significant improvement in the overall survival.

Surgical removal of the ACC is the best chance for cure in early stages, in the case of complete removal, the chance of survival is highest (8, 44). At presentation, however, most patients have advanced disease, because of late diagnosis and/or rapidly progressive disease, and the chances of curative resection are poor. After surgical removal of the tumour, the median survival reported in various studies is 27.6–74 months, after complete resection, and 7.6–15.9 months after incomplete resection (8, 44, 48, 49). Furthermore, local recurrence or metastases of ACC are common after surgical removal, the incidence rates ranging from 23 to 50% of the patients (7, 8, 45). When local recurrences appear and metastases are present, the 5-year survival rates are only 0–6.5% (7, 8, 50). By contrast, however, the patients described in this manuscript survived 5–22 years after the first appearance of distant metastasis, which is quite remarkable.

Several studies have investigated the use of chemotherapy in ACC (32–40). Several combinations of cytotoxic agents have been used. Like the studies on the efficacy of *o,p′*-DDD, the various chemotherapeutic regimens are difficult to compare, because the nature of these uncontrolled phase II studies or retrospectively analysed series. Consequently, there is at present no consensus on the optimal treatment of advanced ACC. The two most promising regimens are *o,p′*-DDD with EDP, and *o,p′*-DDD with Sz with response rates of 48.5 and 37% respectively (36, 40). Currently, the first randomized prospective therapeutic trial called FIRM-ACT is comparing the efficacy of these two regimens in combination with *o,p′*-DDD (www.firm-act.org).

Because of the high recurrence rates, even after complete resection, adjuvant treatment options are needed. Although considered ineffective in the past, radiotherapy seems to be a possible treatment option according to Fassnacht *et al.* (51). Another treatment option for patients with metastatic disease with tumours <5 cm might be radiofrequency thermal ablation. (52, 53). Further investigations are needed to verify the exact value and usefulness of both treatment options.

In conclusion, despite the aggressive nature of the disease, a few patients with ACC survive for many years, even despite metastatic and recurrent disease. The disease remains very unpredictable with some patients dying within months and some apparently living 12–28 years after diagnosis. A few prognostic factors have been described in the literature but none of them has to be found to explain the survival in the individual patients so far. The most commonly used treatment options for ACC are (recurrent) surgery, *o,p′*-DDD and cytotoxic chemotherapy. In our six patients, repeated surgery and *o,p′*-DDD were obviously of benefit. In agreement with the current literature, we suggest that *o,p′*-DDD should be given to all patients with ACC and surgery should be considered even after repeated recurrence.

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