Experience with surgical treatment of malignant primary adrenal tumors

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Background. *Adrenal tumors occur in 3–10 % of the population and are mostly benign adrenal cortical tumors. Adrenocortical carcinoma is a very rare tumor and has an annual incidence of 1–2 cases per million people. The U.S. National Cancer Data Base registered 4275 patients with adrenocortical carcinoma in 1985 to 2007. It is extremely difficult to assess Russia's epidemiological data, as reports on adrenocortical carcinoma are not presented separately.*

Materials and methods. *A total of 133 patients (49 men and 84 women (1:1.7)) with adrenal tumors were operated on at the clinics of the Siberian State Medical University in the period December 1998 to March 2015. The patients' mean age was 51.3 (16–80) years (median age 51.0 years). The right and left adrenal glands were affected in 49 (36.9 %) and 77 (57.9 %) patients, respectively; both adrenal glands were involved in 7 (5.3 %). A group of 21 (15.8 %) people with primary malignant adrenal tumors was identified among all the patients. The clinical manifestations of the disease were evaluated from the presence of hormonal activity, gastrointestinal symptoms, pain syndrome, and hypertension. All the patients were operated on under endotracheal anesthesia. The data were statistically processed using the program package Statistica 6.0. Survival rates were analyzed by the Kaplan–Meier method. The Gehan–Wilcoxon test was used to compare the groups.*

Results. *The investigation analyzed treatment results in 21 (15.8 %) patients with primary malignant adrenal lesions (Group 1). The most common morphological form was adrenocortical carcinoma in 15 (11.3 %) patients (5 men and 10 women (1:2)); their mean age was 48.1 years. The right, left, and both adrenal glands were affected in 4, 9, and 2 cases, respectively. In Group 2, other malignant adrenal involvements were identified from 1 case of rare malignant adrenal tumors: malignant pheochromocytoma, sarcoma, melanoma, squamous cell carcinoma, Castleman's disease, and oncocytic carcinoma. According to the tumor stage, the patients with adrenocortical carcinoma were divided as follows: Stage T1 (n = 3), Stage T2 (n = 3), Stage T3 (n = 4), and Stage T4 (n = 5). In the patients with adrenocortical carcinoma, the size of an adrenal tumor was 8.7 ± 4.9 cm; hypertension as a main clinical manifestation occurred in 5 patients; pain syndrome was observed in 10; hormonal activity was noted in 8, blood electrolyte disorders were seen in 3, and gastrointestinal manifestations were in 9 patients. In Group 1, 8 (38.1 %) patients were survivors and 13 (61.9 %) patients died. Moreover, the overall 5-year survival was 37.9 %. Five-year survival in patients with adrenocortical carcinoma was 42.4 % (6 (53.3 %) survivors and 9 (46.7 %)) dead persons); that in patients with other malignant adrenal tumors was 33.3 % (2 (33.3 %) survivors and 4 (66.7 %) dead persons).*

Conclusion. *Surgical removal of an adrenocortical tumor is the only treatment option that can cure a patient or considerably prolong life particularly if the disease is detected at stage I or II.*

Key words: *adrenocortical carcinoma, adrenalectomy, hormone hyperproduction of adrenocortical carcinoma, prognosis*

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Introduction

Adrenal tumors are very common, affecting 3 % to 10 % of the human population, and the majority of them are benign adrenocortical adenomas. Adrenocortical carcinoma (ACC) is an extremely rare malignancy with an estimated annual incidence of about 1–2 patients per million individuals. In the USA, the National Cancer Database recorded 4275 patients with ACC from 1985 to 2007. The Netherlands Cancer Registry included 359 patients between 1993 and 2010. The German ACC registry comprised 492 patients diagnosed between 1986 and 2007. Left-sided tumors seem to be more common. This malignancy accounts for about 0,2 % of all cancer deaths [1–4]. Epidemiological data in Russia is difficult to estimate as the oncology reports on ACC are not separately formed [5].

The median age of patients with ACC varies from 40 to 50 years, in Germany this pathology is usually diagnosed at the age of 46 years. The disease appears to be relatively more common in children (1,3 %) than adults (0,2 %). In the adult as well as in the pediatric population, there is a predilection for the female gender (the ratio of female to male ranges from 1,5–2,5:1). In 2–10 % of cases, the tumors are bilateral. It is extremely uncommon to define hemangioma, angiosarcoma, lymphangioma, leiomioma, leiomiosarcoma, lymphoma, primary melanoma of the adrenal glands [6]. Aside from genetic predisposition, no risk factors for ACC have been firmly established.

The adrenal glands are the fourth most common site in the body for cancer cells to metastasize to, after the lungs, liver, and bone. Its incidence is up to 9–27 %, whereas

bilateral tumors occur in no more than 41 %. Possibility of developing adrenal glands metastases from renal cell carcinoma depends on the disease stage as well as tumor localization in the upper part of the kidney [2, 6].

There are 3 main clinical scenarios in which ACC patients present. The major presenting complaints are symptoms and signs of hormone excess. Rarely they present with nonspecific symptoms due to local tumor growth, such as abdominal or flank pain, abdominal fullness, early satiety, nausea, vomiting and others. Patients with ACC only rarely present with classical tumor symptoms, such as cachexia, night sweats or paraneoplastic syndromes.

Materials and methods

We conducted a study using data of 133 patients who»d been diagnosed with adrenal tumors and operated in SSMU clinic in the period between December, 1998 and March, 2015. Among them were 49 males and 84 females (1:1,7). Medium age was 51,3 (16–80) years, median – 51,0 years, males – 51,7 years, females – 51,1 years. Among the included patients 59 (44,4 %) were younger than 50 years and 74 (55,6 %) were older that age. Benign adrenal tumors were diagnosed in 101 (75,9 %) patients and malignant in 32 (24,1 %) patients. Tumor was located in the right adrenal gland in 49 (36,9 %) patients and in the left adrenal gland in 77 (57,9 %) patients, whereas bilateral tumors occurred in 7 (5,3 %) patients. In our study we analyzed the treatment results of 21 (15,8 %) patients with malignant primary adrenal tumors. All patients with radiologically-confirmed diagnosis including ultrasound imaging (USI), magnetic resonance imaging (MRI), spiral computed tomography (SCT) as well as after being consulted and examined by endocrinologist were hospitalized. After that surgical treatment was done at the urology department of SSMU clinic. In case the malignancy of the adrenal tumor had been confirmed, the patient was observed by the oncologist of the regional oncology dispensary. In case the primary adrenal insufficiency occurred after surgical removal of the adrenal glands, treatment plan was carried out by surgeon, oncologist and endocrinologist.

Hormonally active tumors were defined by endocrinological investigation which was done in addition to common laboratory tests. To investigate them serum or urinary cortisol, adrenocorticotropic hormone, testosterone, aldosterone, potassium, natrium and metanephrine levels were measured in all patients. Tumor growth was defined by the presence of such gastrointestinal (GI) signs and symptoms as nausea, feeling of fullness, bloating, constipation and others. We also evaluated pain syndrome (PS) and assessed arterial hypertension (AH) as one of the possible manifestations of hormone production. To assess the spread of the disease we did USI, MRI and SCT. Cancer staging was based on TNM-classification. Statistical processing of the data was performed by using Statistica 6.0 software package. We used the Kaplan-Meier method to describe survival.

Results

In our study we included 21 (15,8 %) patients with malignant primary adrenal tumors. The most common histologic type of adrenal cancer was ACC (1-st group) which was diagnosed in 15 (11,3 %) patients (5 males and 10 females (1:2)). Medium age was 48,1 years. Tumor was located in the right adrenal gland in 4 patients and in the left adrenal gland in 9 patients. Bilateral tumors occurred in 2 patients (table 1).

The second group consisted of 6 patients (4 males, 2 females) with other malignant adrenal tumors: 1 patient with malignant pheochromocytoma, sarcoma, melanoma, squamous cell carcinoma, Castleman disease and oncocytic carcinoma. Medium age was 60,8 years. Tumor was located in the right adrenal gland in 3 patients and in the left adrenal gland in 2 patients. Bilateral tumors occurred in 1 patient (table 1). Metastatic lesions in patients

Table 1. *Types of malignant primary adrenal tumors*

Histologic type	Number of patients	Gender		Tumor site		
		males	females	right	left	bilateral
Adrenocortical carcinoma	15	5	10	4	9	2
Malignant pheochromocytoma	1	1	–	–	1	–
Sarcoma	1	1	–	1	–	–
Melanoma	1	–	1	1	–	–
Squamous cell carcinoma	1	1	–	1	–	–
Castleman disease	1	–	1	–	1	–
Oncocytic carcinoma	1	1	–	–	–	1
Total	*21*	*9*	*12*	*7*	*11*	*3*

Table 2. *TNMcharacteristics of patients*

Histologic type	Tumor size, cm	T				N		M	
		1	2	3	4	0	1	0	1
Adrenocortical carcinoma (n = 15)	8,7 ± 4,9	3	3	4	5	14	1	12	3
Malignant pheochromocytoma (n = 1)	5,0	–	1	–	–	1	–	1	–
Sarcoma (n = 1)	2,5	1	–	–	–	1	–	–	1
Melanoma (n = 1)	5,5	–	–	1	–	1	–	1	–
Squamous cell carcinoma (n = 1)	11,1	–	–	–	1	1	–	1	–
Castleman disease (n = 1)	6,7	–	–	1	–	1	–	1	–
Oncocytic carcinoma (n = 1)	9,3	–	–	1	–	1	–		1
Total		*4*	*4*	*7*	*6*	*20*	*1*	*16*	*5*

with sarcoma and melanoma were not proved. The patient with adrenal sarcoma died of cerebral sarcoma which was regarded as a metastatic lesion. The patient with melanoma of the adrenal gland died due to disease progression.

The group 1 tumor stages were as follows: stage T1–2 in 3 patients, stage T3 in 4 patients and stage T4 in 5 patients. Signs of regional lymph node metastases (N1) were registered in 1 patient, whereas 3 patients in this group had distant metastases (M1). Median tumor size in ACC patients was 8,7 ± 4,9 cm. The group 2 tumor stages were as follows: stage T1 in 1 patient, stage T3 in 4 patients and stage T4 in 1 patient. No regional lymph node metastases in that group had been found. Distant metastases were registered in 2 patients. Median tumor size was 6,7 ± 3,1 cm (table 2).

In the 1st group AH as the main clinical symptom of tumor growth was found in 5 patients, PS in 10 patients, hormonally active tumor in 8 patients, abnormal values of blood electrolytes in 3 patients, GI signs in 9 patients. The lethal outcome was registered in 2 patients with AH, 7 patients with PS, 3 patients with hormonally active tumors. In the 2nd group AH was registered in 2 patients, PS in 2 patients, AH and PS in 1 patient, hormonally active tumor in 1 patient, abnormal values of blood electrolytes in 1 patient and GI signs in 1 patient (table 3).

In 11 cases adrenalectomy (AE) was performed from lumbotomic approach and in 10 cases laparotomy was done. Lymphadenectomy was done in all cases. Radical AE in combination with nephrectomy was performed in 7 patients, duodenum resection in 1 patient, pancreatic tail resection in 2 patients, liver resection in 2 patients, splenectomy in 1 patient, thrombectomy with inferior vena cava resection in 2 patients. No cases of operative mortality were observed, 1 patient died 1 moth after radical AE with nephrectomy, pancreatic tail resection (cause of death was acute pancreatitis and pancreatic necrosis in the postoperative period). Eight (38,1 %) patients remain alive and 13 (61,9 %) died during follow-up period. The overall 5-yr survival in all patients with malignant adrenal tumors was 37,9 %. The overall 5-yr survival in the 1st group was 42,4 % (among them 6 (53,3 %) patients were alive and 9 (46,7 %) patients died). The overall 5-yr survival in the 2nd group was not reached (2 patients were alive and 4 patients died, fig. 1). All patients died due to disease progression (except 1 patient whose cause of death was pancreatic necrosis). We did not define any signs of disease progression among patients who remained alive. These patients did not receive any other treatment options.

Discussion

Most types of adrenal cancer are large, hormonally active tumors that produce excessive amounts of cortisol or adrenal androgens, including dehydroepiandrosterone and its sulfate. Generally, ACC have several defective steroid biosynthesis enzymes, causing elevated levels of steroid precursors typical of enzymatic blocks. Therefore, patients with ACC have elevated plasma levels of steroid precursors [7]. Biochemically or clinically apparent adrenocortical hormone production is evident in up to 40 % to 70 % of ACC patients [2, 8]. Hypercortisolism is the most common presentation of patients presenting with hormone excess (50 % – 80 % of hormone-secreting ACCs), causing classic symptoms including plethora, diabetes mellitus, muscle weakness/atrophy, and osteoporosis. However, in the study published by Loncar Z. and colleagues, most of the tumors (73,6 %) were not hormonally active [9]. Clinical and biological features of ACC patients with overt hypercortisolism are discussed in the article published by Abiven G. and colleagues and the review written by Berruti A. and colleagues [10, 11]. It has been noticed that cortisol excess is more typical for young ACC patients. No difference according to initial staging, gender and tumor grade was observed. Another study [11] included 524 ACC patients with completely resected tumors and no signs of

Table 3. *Clinical characteristics of patients with malignant primary adrenal tumors*

Gender	Age, years	Tumor site	Histologic type	Tumor size, cm	Tumor signs			
					arterial hypertension/pain syndrome	prognosis	hormones*	electrolytes*
M	50	Right	Adrenocortical carcinoma	7	+/–	Dead	Norm	Norm
F	45	Left	Adrenocortical carcinoma	4,2	+/–	Alive	Norm	Norm
M	35	Left	Adrenocortical carcinoma	8	–/+	Dead	Norm	Norm
F	47	Right	Adrenocortical carcinoma	4,6	–/+	Alive	Cortisol	Norm
F	50	Left	Adrenocortical carcinoma	6	+/–	Dead	Norm	Norm
F	45	Bilateral	Adrenocortical carcinoma	5	–/+	Dead	Adrenocorticotropic hormone	Norm
F	48	Left	Adrenocortical carcinoma	2	+/–	Alive	Metanephrine	Potassium
F	17	Right	Adrenocortical carcinoma	17	–/+	Dead	Testosterone	Norm
M	70	Left	Adrenocortical carcinoma	8	–/+	Dead	Norm	Norm
F	57	Left	Adrenocortical carcinoma	7	–/+	Dead	Adrenocorticotropic hormone	Potassium
F	74	Right	Adrenocortical carcinoma	15	+/–	Alive	Aldosterone	Potassium
F	36	Bilateral	Adrenocortical carcinoma	19,4	–/+	Dead	Norm	Norm
M	80	Left	Malignant pheochromocytoma	5	+/–	Dead	Metanephrine	Norm
M	61	Right	Sarcoma	2,5	+/–	Alive	Norm	Norm
F	53	Right	Melanoma	5,5	–/–	Dead	Norm	Norm
M	58	Right	Squamous cell carcinoma	11,1	–/+	Dead	Norm	Norm
F	48	Left	Adrenocortical carcinoma	8,8	–/+	Alive	Cortisol, testosterone	Norm
F	55	Left	Castleman disease	6,7	–/+	Alive	Norm	Potassium
M	58	Bilateral	Oncocytic carcinoma	9,3	+/+	Dead	Norm	Norm
M	35	Left	Adrenocortical carcinoma	10,6	–/+	Dead	Norm	Norm
M	64	Left	Adrenocortical carcinoma	8,2	–/+	Alive	Follicle-stimulating hormone, luteinizing hormone	Norm

** Deviation at least once above the normal values*

metastases. Postoperative recurrence was documented in 339 patients (64,7 %). Death occurred in 204 patients (38,9 %). Clinical signs of cortisol plus or minus other hormone excess were observed in 197 patients (37,6 %) and clinical hyperandrogenism in 58 patients (11,1 %). Seven patients (1,3 %) had symptoms and signs of pure mineralocorticoid excess, 9 patients (1,8 %) had clinical evidences of estrogen excess. In this study the authors demonstrate that hormone-secreting ACC tumors most frequently produce cortisol. The presence of clinical signs of cortisol excess in completely operated ACC patients is prognostically relevant in terms of survival. The mechanism underlying this relationship, however, is not clear. Although in patients with metastatic disease, hypercortisolism leads to increased mortality [11]. In 2012 Peppa M. and colleagues reported the case of a 59 year-old woman with a large right ACC (6,1 × 6,5 × 5,5 cm) hypersecreting cortisol, testosterone and aldosterone [12].

The second most commonly produced hormones in patients with ACC are adrenal androgens (40 % – 60 % of

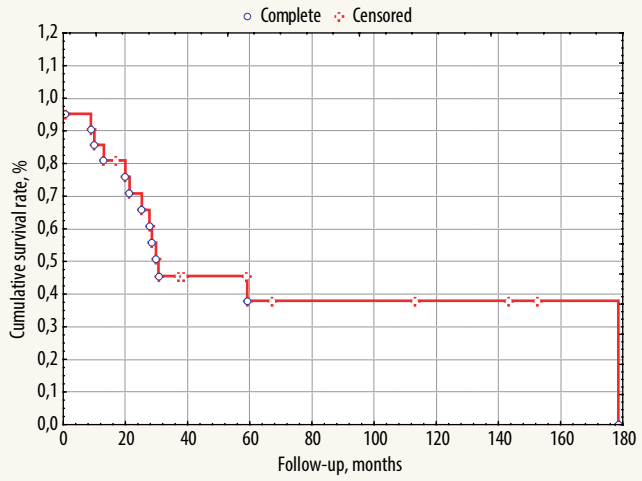

Fig. 1. Overall survival of patients with malignant adrenal tumors (Kaplan-Meier method)

hormone-secreting ACCs), causing rapid-onset male pattern baldness, hirsutism, virilization, and menstrual irregularities in women. Concurrent androgen and cortisol overproduction is evident in roughly half of all ACC patients with hormone excess. However, isolated hyperandrogenism in male patients is often unrecognized due to the paucity of significant symptoms. Instead, it is the cosecretion of estrogen from the ACC that induces significant symptoms. Estrogen production occurs in 1 % to 3 % of male ACC patients, causing gynecomastia and testicular atrophy. In the evaluation of adrenal tumors, regardless of size, androgen or estrogen production should always raise the suspicion of a malignant tumor [2].

In 2013 Galketiya KP and colleagues reported the case of a 47 year-old woman with androgen-secreting right ACC (tumor size was 10 cm). She presented with clinical signs of androgen-secreting tumor and had the increased testosterone serum concentrations [13]. Similar case was described by Varma T. and colleagues [14].

Rarely, patients present with aldosterone excess or a pure hormonal syndrome of hyperaldosteronism which occur in 2,5 % of ACC patients. The main typical features of patients with aldosterone-producing ACC include the average age of patients more than 40 years, a trend towards a preference for women and left localization of the tumor. In most cases the clinical picture features such classical signs as hypertension, hypocalemia (associated with weakness, diffuse muscle pain, muscle spasms), fever, weight loss. These tumors are generally large, however sometimes they can be less than 3 cm [15, 16].

Clinical case

A 74-year old patient Sh. *presented to her local hospital due to a tumor mass located in the right adrenal gland. She had AH. Endocrinological investigation revealed the following: aldosterone level – 460 pg/ml (reference values 35–350 pg/ml), metanephrine level – 11,9 pg/ml (normal value < 90,0 pg/ml), normetanephrine level – 34,8 pg/ml (normal value < 200,0 pg/ml), potassium – 2,7 mMol/l, natrium – 142 mMol/l, ionized calcium – 1,19 mMol/l. Abdominal SCT revealed large tumor-like heterogenous mass grown towards right liver lobe. It had clear irregular contours, was 11,8 × 9,2 × 9,4 cm in size, contained soft-tissue fat component and had zones of calcification. Its density was 33–39 HU in the central areas and 44–46 in peripheral zones. The patient underwent AE with preservation of the kidney (fig. 2) and resection of the right lobe of liver. Histopathological analysis: tumor is composed of cells with clear cytoplasm and a mild degree of nuclei polymorphism which form small and large cellules and wrong columns. There are zones of extensive hemorrhage and necrosis. Conclusion: adrenocortical carcinoma. The patient experienced postoperative acute renal failure. She was discharged home in satisfactory condition and at the moment the study was completed there has been no data of the recurrence.*

It is extremely rare for an ACC to present as an adrenal medullary tumor – catecholamine secreting tumor. Its clinical manifestations are typical for pheochromocytoma. Blood pressure numbers could rise at a very high level and be combined with tachycardia. In the literature only few cases have been reported so far making these tumors a rare entity [17, 18].

Among all patients with malignant adrenal tumors who were included in our study functional hormonally active tumors were found in 9 (42,9 %) patients. Hormonal overproduction was as follows: adrenaline in 1 patient, cortisol in 2 patients (1 patient had cortisol + testosterone overproduction), testosterone in 1 patient, metanephrine in 1 patient, adrenocorticotropic hormone in 1 patient, aldosterone in 1 patient.

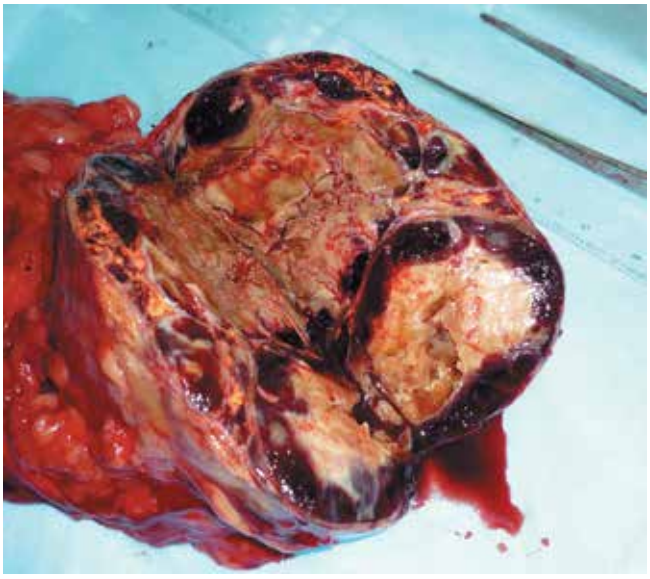

Fig. 2. Patient Sh.: right adrenal gland tumor

Approximately third of the patients present with nonspecific symptoms due to local tumor growth, such as abdominal or flank pain, abdominal fullness, or early satiety, nausea, vomiting. Roughly 20 % to 30 % of ACCs are incidentally diagnosed by imaging procedures for unrelated medical issues. In the study published by Loncar Z. and colleagues pain was the predominant symptom in 25 out of the 44 symptomatic patients. The 6-month overall survival in patients with ACC was 69,8 %. The 1-, 3-, 5-, and 10-yr survivals were 52,5 %, 48,2 %, 41,1 %, and 16,4 %, respectively [9].

In our study 6 out of 21 adrenal tumors were discovered accidentally (4 patients in the 1st group and 2 patients in the 2nd). Tumor size in patients with ACC were 4,6; 6,0; 19,4 and 8,8 cm. The major clinical signs (PS and AH) were presented in 13 (61,9 %) and 7 (33,3 %) analyzed patients, respectively. Patients with ACC only rarely present with classical tumor symptoms, such as cachexia or night sweats.

Discussion

Tumor size. In 2014 Else T. and colleagues summarized their knowledge about therapy of ACC patients. They noticed that ACCs are generally large tumors, measuring on average 10 to 13 cm. Only a minority of tumors are <6 cm (9 % – 14 %), with only 3 % presenting as lesions <4 cm [2]. Mihai R. found tumor size to be the most important predictor of tumor malignancy. This conclusion was done on the results of the analysis of 457 patients with ACC. For tumors smaller than 4 cm, larger than 6 cm, larger than 8 cm and larger than 10 cm, the risk of malignancy increased from 52 % to 80, 95 and 98 %, respectively. This is the basis of recommending adrenalectomy for non-functional incidentalomas larger than 4 cm [3]. Loncar Z. and colleagues noticed that approximately 70 % out of 72 patients had a tumor ≤ 10 cm in diameter weighing ≤ 300 gram. At time of diagnosis, ACC distant metastases were present in 6 (12 %) patients (lung, n = 3; liver, n = 2; contralateral adrenal gland, n = 1). Local tumor invasion was present in ≥ 40 % of patients, which demonstrates the aggressive nature of the tumors. One patient presented with an inferior vena cava thrombosis. Two-thirds of patients were operated through a subcostal laparotomy approach and 22 % through a transdorsal approach [9].

In our study the median tumor size in a group of ACC patients (n=15) was 8,7 ± 4,9 cm. Tumors ≤ 5 cm were registered only in 3 cases, whereas of 5–8 cm and ≥ 8 см were found in 4 and 8 patients, respectively. The median tumor size in the 2nd group (n=6) was 6,7 ± 3,1 cm, while tumors ≥ 8 cm were found only in 2 patients.

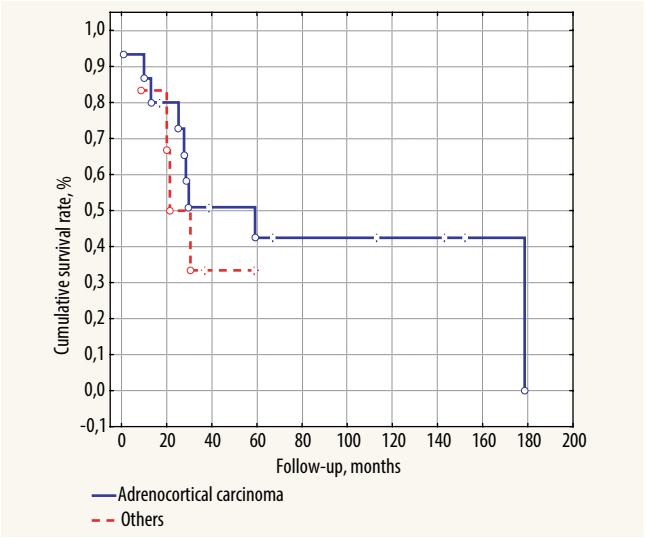

Fig. 3. Survival according to the histologic type

Survival. In a review published by Allolio B. and Fassnaht M. they noticed that prognosis of ACC patients depends largely on tumor stage. In a series from France including 253 patients, the 5-yr survival rates were 60 % for stage I, 58 % for stage II, 24 % for stage III, and 0 % for stage IV. The overall 5-yr survival in different series ranged between 16 and 38 %. Functionality, age, or sex seem to play no major role for survival. Large tumor size (diameter > 12 cm) has been associated with inferior survival after complete resection [8]. The overall 5-yr survival in all ACC patients is only 30 %. Most commonly ACC affects people above age of 50 (the oldest patient was 72 years, the youngest –17 years). In one of the trials [3] the median age was 50,4 years.

In our study the youngest patient was 17 years and the oldest was 80 years. The overall 5-yr survival in all patients with malignant adrenal tumors was 37,9 %. The overall 3-yr and 5-yr survival in the 1st group was 50,4 and 42,4 %, respectively. The overall 3-yr survival in the 2nd group was 33,3 % and median 5-yr overall survival was not reached (fig. 3)

The overall 5-yr survival of all patients with malignant adrenal tumors according to the tumor size was the following: 20 % for tumors ≥ 8 cm, 30 % and 51,3 % for tumors 5–8 cm and ≤ 5 cm, respectively.

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