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The challenge to differentiate between sarcoma or adrenal carcinoma—an observational study

Eva M Dobrindt[1], Wolfgang Saeger[2], Hendrik Bläker[3], Martina T Mogl[1], Marcus Bahra[1], Johann Pratschke[1] and Nada Rayes[1,4]

Abstract

Background: Adrenal sarcomas are rare malignant tumors with structural and clinical similarities to sarcomatoid adrenocortical carcinoma. Preoperative diagnosis of tumors of the adrenal gland can be challenging and often misleading thus detaining patients from appropriate oncological strategies.

Objective: This analysis of a case series evaluated the predictive capability of the primary clinical diagnosis in case of malignancies of the adrenal gland.

Methods: Thirty two patients were treated from 2009 to 2015 at our clinic and analyzed retrospectively. All patients had computed tomography and/or magnet resonance imaging and a primary histopathological examination at our institution after surgery. Ten questionable cases were surveyed by a reference pathologist.

Results: Twelve out of 32 diagnoses had to be revised (37.5%). Only 15 out of 24 tumors primarily classified as adrenocortical carcinoma were finally described as primary adrenal cancer. We found two leiomyosarcomas, one liposarcoma, one sarcomatoid adrenocortical carcinoma, and one epitheloid angiosarcoma among 12 misleading diagnoses. Other tumors turned out to be metastases of lung, hepatocellular, and neuroendocrine tumors. Larger tumors were significantly more often correctly diagnosed compared to smaller tumors. Four patients of the group of revised diagnoses died whereas all patients with confirmed diagnoses survived during the follow-up.

Conclusion: Preoperative assessment of tumors of the adrenal gland is still challenging. In case of wrong primary diagnosis, the prognosis could be impaired due to inadequate surgical procedures or insufficient preoperative oncological treatment.

Keywords

adrenal carcinoma, sarcoma, pheochromozytoma, adrenalectomy, background

Background

Cancer of the adrenal gland is an extremely rare malignancy, with an incidence of 0.5–2 cases per million per year in the general population. The sarcomatoid adrenocortical carcinoma was first mentioned in 1987[1]. Irrespective of this specific type, adrenocortical carcinomas mixed with sarcoma or sarcoma-like components have been reported until now[2,3]. These tumors are poorly differentiated and badly aggressive with a high risk for loco-regional recurrence, rapidly growing metastases

[1]Department of Surgery, Berlin Institute of Health, Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin, Germany
[2]Institute of Pathology, University of Hamburg, Hamburg, Germany
[3]Institute of Pathology, University of Leipzig, Leipzig, Germany
[4]Department of General, Visceral, Thoracic and Transplant Surgery, University of Leipzig, Leipzig, Germany

Corresponding author:
Eva M Dobrindt, Department of Surgery, Charité—Universitätsmedizin Berlin, Charitéplatz 1, Berlin 10117, Germay
Email: eva-maria.dobrindt@charite.de

and death occurring within a short period of time[3]. According to the World Health Organization (WHO), variants of adrenocortical carcinomas (ACC) include oncocytic ACCs, myxoid ACCs, and ACCs with sarcomatous areas[4–6]. Tumors showing both, carcinomatous and sarcomatous characteristics (so-called carcinosarcomas) are generally uncommon[7]. Due to the current WHO classification (2017), these neoplasms have been categorized as "sarcomatoid carcinomas" covering all carcinomas with "pleomorphic, sarcomatoid, or sarcomatous elements"[3,7,8]. Apparently, the sarcomatous part develops out of carcinoma by dedifferentiation[3]. Sarcomas of spindle cell type may develop from pheochromocytoma[9,10]. Others show a myofibroblastic type[11]. Some adrenal sarcomas, the epitheloid angiosarcoma, histologically resemble adrenal cancers and have to be distinguished from carcinomas by immunostainings[12,13]. Other primary adrenal sarcomas like leiomyosarcoma or liposarcoma are very rare[3,9,14–17]. Anaplastic and sclerosing Kaposi'ssarcomas can develop in the adrenals with or without immunodeficiency[18–21]. Alveolar sarcomas of the adrenals appear in children whereas adrenal Ewing sarcomas can be found in patients of any age[22–25]. Finally, synovial sarcomas of the adrenal have been described[26]. Sarcomatoid adrenocortical carcinomas should strictly be separated from sarcomas of the adrenal gland, as they require different treatment.

Unfortunately, the presurgical diagnosis of adrenocortical cancer (ACC) is difficult and that is why they are often detected in an advanced stage[7]. According to literature, 60–80% of ACC are functional and hypercortisolism can be found up to 60% of patients with ACC[7,27–30]. Radiologic differentiation of ACC from a sarcomatoid carcinoma or sarcoma remains difficult in patients without elevated corticosteroids[31]. Contrast-enhanced computed tomography (CT) indicates heterogeneous enhancement with areas of high- and low-attenuation (55–69 HU and 28–30 HU) within the tumor[31]. As a preoperative biopsy is obsolete in ACC, in most patients the correct diagnosis is made postoperatively.

Furthermore, even the postoperative pathological diagnosis of ACC is challenging[32]. The Weiss scoring system, which was introduced 27 years ago and represents the most popular scoring system today, is based on the verification of at least three out of nine morphological parameters by microscopy[6,32].

Due to the aggressive behavior, ACC has a poor prognosis, which underlines the importance of identifying diagnostic and prognostic markers to rule out other differential diagnosis especially a sarcoma[33]. As mentioned, a preoperative biopsy should be avoided in ACC, but could be useful in sarcomas to decide if neoadjuvant chemotherapy is indicated. Due to the lack of reliable diagnostic markers, the histopathological diagnosis after successful surgery may differ from the preoperative assumption causing a precious loss of time while the patient does not receive adequate therapy influencing outcome and survival.

The aim of the present study was an analysis of the frequency of misdiagnosis of adrenal tumors in preoperative imaging and its impact on outcome and tumor recurrence. Primary endpoint was the overall survival. Secondary endpoint was the time until tumor recurrence and evaluation of clinical risk factors.

Methods

We present retrospective data of a series of 32 patients who had an adrenalectomy at our clinic from September 2009 until the end of 2015. Inclusion criteria were a simple or multi-visceral adrenal resection due to preoperatively suspected malignancy. All patients underwent preoperative imaging and/or additional biopsy. We identified 10 questionable cases out of 32 patients and revised by a reference pathologist to especially identify sarcomatoid ACCs. We defined the clinical diagnosis as the radiomorphologic diagnosis only based on the preoperative imaging. The first histopathological diagnosis was defined and described in the first record of the institute of pathology of the Charité. The final diagnosis was derived from either the final report from the institute of pathology of the Charité or from the statement of the reference pathologist if this report was requested and. Other clinical parameters evaluated in this study were gender, age at diagnosis, size of tumor, site of tumor, hormonal activity, preoperative imaging (CT or magnet resonance imaging (MRI)), confirmed infiltration due to preoperative imaging, biopsy results, operating procedure (adrenalectomy only or multi-visceral resection), Weiss score, adrenal origin confirmed by pathology, metastases, locoregional recurrence, survival until recurrence, and overall survival. Patients (n = 32) were grouped to those, whose clinical diagnosis was finally confirmed (CONFIRMED, n = 20) and those whose diagnosis was ultimately revised (REVISED, n = 12). The data were retrospectively analyzed using our digital patient documentation system. Statistical analysis was performed by IBM SPSS Statistics® (Version 23, Armonk, NY, USA). Significances of nonparametric data were tested by Mann–Whitney-U-test. Variances of nominal data were tested by cross tables and Fisher's-exact-test. Kaplan–Meier-analyses were performed for survival analysis. Level of significance was defined as $p < 0.05$.

Results

We identified 32 patients, who underwent adrenal surgery due to suspected adrenal carcinoma at our clinic from September 2009 until December 2015. Histopathology confirmed the preoperative diagnosis in 17 patients (CONFIRMED, 53.1%), whereas the diagnosis had to be revised in 15 patients (REVISED, 46.9%). A reference pathologist (W.S.) retrospectively reviewed 10 questionable cases. Five

Table 1. Table shows the preoperative clinical diagnosis, the first histological result and the final histological diagnosis of group REV (n = 15). Each line replaces one case.

Clinical diagnosis	First histology	Final histology
Confirmed (n = 17)		
Adrenal carcinoma (n = 11)		
Sarcoma (n = 6)		
Revised (n = 15)		
Malignant pheochromocytoma	Adrenal adenoma	Adrenal carcinoma
Adrenal carcinoma	Adrenal tumor	Borderline adrenocortical tumor
Adrenal carcinoma	Adrenal carcinoma	Epitheloid angiosarcoma
Adrenal carcinoma	Renal cancer	Sarcomatoid adrenal cancer
Neuroblastoma	Adrenal carcinoma	Adrenal adenoma
Adrenal carcinoma	Pheochromocytoma	Metastasis of lung tumor
Adrenal carcinoma	Leimyosarcoma	Leiomyosarcoma
Adrenal carcinoma	Leiomyosarcoma	Leiomyosarcoma
Adrenal carcinoma	Metastasis of neuroendocrine tumor	Metastasis of neuroendocrine tumor
Adrenal carcinoma	Oncocytic tumor	Metastasis of hepatocellular cancer
Adrenal carcinoma	Pheochromocytoma	Metastasis of lung cancer
Adrenal carcinoma	Pheochromocytoma	Pheochromocytoma
Adrenal carcinoma	Pheochromocytoma	Pheochromocytoma
Adrenal carcinoma	Pheochromocytoma	Pheochromocytoma
Adrenal carcinoma	Liposarcoma	Liposarcoma

out of those 10 histological diagnoses (50.0%) were defined by the reference pathologist.

Table 1 shows an overview of the 12 diagnoses, which had to be adapted during postoperative work-up. Fourteen out of 23 patients, who were primarily diagnosed with ACC, retained their diagnosis of ACC. Six out of six primarily described sarcomas were confirmed as retroperitoneal sarcoma later. The remaining 12 clinically presumed ACCs turned out to be metastases of a hepatocellular tumor (n = 1), lung cancer (n = 1), neuroendocrine tumor (n = 1), retroperitoneal sarcoma (n = 4), and epitheloide angiosarcoma of the adrenal gland (n = 1). One tumor suspicious of ACC was finally classified as a benign borderline tumor of the adrenal gland. In contrast, one presumed malignant pheochromocytoma was finally defined as an ACC. One clinically assumed neuroblastoma turned out to be an adrenal adenoma and a tumor first classified as renal cancer was finally classified as a sarcomatoid ACC.

Demographic data are given in Table 2. The total cohort included more women (66%) than men (43%). The median age was 56.5 (5–82) years. Tumors were located on the left side in 17 cases (53%), on the right side in 13 cases (41%), and bilateral in two cases (6%). The median size was 128 mm (45–400 mm). Nine patients (29%) showed hormonal activity. Eighty-four percent had a CT-scan and 34% MRI for preoperative assessment. Imaging showed tumor infiltration to surrounding organs in 57%. A biopsy was performed in 22%. Simple adrenalectomy was performed in 41% of patients and 59% underwent multi-visceral resection. Pathology confirmed an adrenal origin in 69% of tumors. Fifty-two percent of patients developed metastases during follow up and 32% local recurrence.

Analysis was performed for the groups CONFIRMED and REVISED without any significant difference concerning demographic data, except for tumor size (Figure 1). There was a trend towards a longer recurrence-free survival in the group CONFIRMED (53.7 months, 95% CI: 29.5–77.9) compared to REVISED (35.1 months, 95% CI: 16.4–53.8), but without significance (p = 0.406, Figure 2). The estimated overall survival of CONFIRMED was 99 months (95% CI: 87.6–110.0) and 75.7 months within REVISED (95% CI: 52.5–98.9, p = 0.107, Figure 2). This difference was not statistically significant.

Furthermore, patients with ACC and retroperitoneal sarcoma (SARCOMA) were compared according to the demographic data (Table 3). There was no significant difference in gender, age, size, and localization and especially not in preoperative assessment, hormone activity, or surgical treatment. ACCs were less often misdiagnosed preoperatively compared to SARCOMA, but without significance. However, there were significantly more questionable reports which were revised by a reference pathologist (p = 0.000) among patients with sarcoma. Overall, survival of patients with ACC and retroperitoneal sarcomas was not statistically different but seems to be longer in the sarcoma patients (ACC: 51.6 months 95% CI: 43.3–59.9 vs. sarcoma: 81.9 months 95% CI: 53.7–109.6, p = 512). Among the patients with a retroperitoneal sarcoma, the overall survival was

Table 2. Demographic Data for the total cohort, and both groups CONFIRMED and REVISED.

	Total (n = 32)	Confirmed (n = 17)	Revised (n = 15)	p value
Gender (male/female), n/n (%/%)	11/21 (34/66)	3/14 (18/82)	8/7 (53/47)	0.062
Age at diagnosis	56.5 (5–82)	57.0 (19–78)	52.0 (5–82)	0.737
Side, n (%)				
Both	2 (6)	1 (6)	1 (7)	0.730
Left-sided	17 (53)	8 (47)	9 (60)	
Right-sided	13 (41)	8 (47)	5 (33)	
Size (mm)	127.5 (45–400)	155.0 (75–400)	100 (45–190)	0.023
Positive hormone activity, n (%)	9 (29)	4 (25)	5 (33)	0.704
Preoperative assessment, n (%)				
Staging CT	27 (84)	16 (94)	11 (73)	0.161
Staging MRI	11 (34)	4 (24)	7 (47)	0.266
Infiltration by imaging	16 (57)	10 (59)	6 (40)	0.497
Biopsy	7 (22)	5 (16)	2 (6)	0.402
Surgical procedure, n (%)				
Adrenalectomy	12 (41)	5 (29)	8 (53)	0.208
Multi-visceral resection	19 (59)	12 (71)	7 (47)	
Reference pathology	10 (31)	5 (29)	5 (33)	1.000
Adrenal origin	22 (69)	11 (6%)	11 (73)	0.712
Metachronal metastases	16 (52)	6 (38)	10 (67)	0.156
Local recurrence	10 (32)	6 (38)	4 (27)	0.704

(Absolute numbers and percentage, median, minimum and maximum).
N = 32.

similar in the patients who were initially diagnosed correctly and the patients whose diagnosis had to be revised (p = 0.228).

Discussion

Histopathology could not confirm preoperative diagnoses in 47% of patients with adrenal malignancy or malignancies involving the adrenal gland. Fifty percent of questionable pathological reports, which were seen by a reference pathologist were revised after reevaluation. Twelve out of 23 clinically diagnosed ACC were misdiagnosed and turned out to be sarcomas in four cases. One ACC was not detected before resection (Table 1). We must note, that even in specialized centers, large retroperitoneal tumors within or close to the adrenal gland might be misdiagnosed preoperatively. The discrimination of these tumors seems to be difficult, a fact, which may lead to delayed or inadequate oncological therapy.

Clinical and differential diagnoses of retroperitoneal tumors are challenging as the retroperitoneum hosts a wide range of heterogeneous lesions[34]. The median age of onset of ACCs and liposarcomas is in the fifth and sixth decade whereas leiomyosarcomas normally appear in elderly patients[28,34,35]. ACC's have a genetic predisposition in seldom cases and are associated with the germline mutation of TP53 and therefore the Li Fraumeni syndrome as well as the Beckwith–Wiedemann syndrome in pediatric patients[28]. In adult patients, the Multiple Endocrine Neoplasia I, Lynch syndrome, familial adenomatous polyposis, neurofibromatosis type I and the Carney complex bare a higher risk for ACCs[28]. Sarcoma do not occur hereditarily but can be associated with immunodeficiency[35]. In general, the clinical presentation of retroperitoneal tumors besides functional ACCs is uncharacteristic, depends on its localization and may occur after a certain latency period, in which its size had grown enough to provoke severe sight effects by compression, displacement, or invasion of the surrounding structures[34,36]. Functional ACCs show the clinical image of hypercortisolism in up to 80% with a glucocorticoid-mediated mineralocorticoid receptor activation followed by hypokalemia, hypertension, and clinically severe muscle weakness and a Cushing's syndrome[28,29]. Adrenal androgens are the second most secreted hormones by ACCs leading to hirsutism, virilization, and menstrual irregularities[28,29]. However, 20–40% of ACCs are non-functional aggravating the differentiation from other retroperitoneal lesions which all cause similar unspecific symptoms[28–30]. Those complaints might be discomfort, abdominal pain, weight loss, the palpation of the tumor mass, and in case of a close localization to the aorta an unspecific abdominal pulsing[27,28,36]. In this study, a third of all revised cases and a quarter of the confirmed cased were functional active tumors (Table 2). Nevertheless, hormone diagnostic among the revised can be misleading especially as values were not strongly elevated and even three pheochromocytomas were not clearly detecting. Furthermore, the

clinical presentation of this questionable cases was also unspecific.

Therefore, a detailed hormone work-up, CT, and MRI are mostly able to differentiate between adrenal adenomas, non-adenomas, or a further retroperitoneal entity[34,36–40]. ACCs are normally large tumors (>4 cm), occur in 2 to 10% bilaterally and show a heterogeneous enhancement in CT-scan (>10 HU) because of internal hemorrhage, necrosis, and calcifications[28,41–43]. In contrast, adrenal adenomas are smaller (<4 cm), homogenous (≤10 HU) without calcification, necrosis or hemorrhage showing a greater wash-out than ACCs[28]. The parenchyma of ACCs appears isointense to hypointense on T1-weighted MRI images and hyperintense on T2-weighted MRI images compared to the liver[28,42]. If the imaging shows intralesional fat signs, that might be suspicious for liposarcomas, extramedullary hematopoiesis, and teratoma as differential diagnosis[34]. Calcifications are associated with leiomyosarcomas, teratomas, undifferentiated pleomorphic sarcoma, or neurogenic tumors and a hyperintense signal in T2-weighted MRI sequences with delayed contrast enhancement characterizes a myxoid stroma which is related to neurogenic tumors, myxofibrosarcomas, and myxoid liposarcomas[34]. Nevertheless, necrosis might appear in nearly all dedifferentiated, primary, or secondary malignancies[34]. Therefore, a well-differentiated liposarcomas might show a typical picture with larger size (>10 cm), septa and nodular enhancement, and can be easily distinguished from an ACC. However, low-differentiated sarcomas with necrosis and calcification might much harder be delimited from a malignant adrenal lesion[34]. In our series, imaging was not significant in sarcomas, metastases, and ACCs probably due to low differentiation of the tumors showing an unclear image of inhomogeneous mass with calcifications and necrosis. In the three cases of pheochromocytomas, the smaller size of the lesions might have played a role. If a tumor does not clearly arise from a solid organ, it can be defined as a primary retroperitoneal lesion. Those lesions are suspicious for sarcoma and patients should be referred to a qualified center for percutaneous biopsy, which represents the gold standard for preoperative diagnosis in retroperitoneal sarcomas[34,37]. In contrary, a preoperative biopsy is not recommended in case of an ACC because of the risk of tumor spilling unless there is evidence of metastatic disease requiring a histopathologic proof[39]. Therefore, physicians must rely on preoperative clinical presentation and radiological imaging[38]. If the tumor is located inside the adrenal gland, the differentiation between sarcoma and adrenal tumors seems easy. However, in case of unclear relation, which is more likely in large tumors, the discrimination between ACC, metastases, a rare primary sarcoma of the

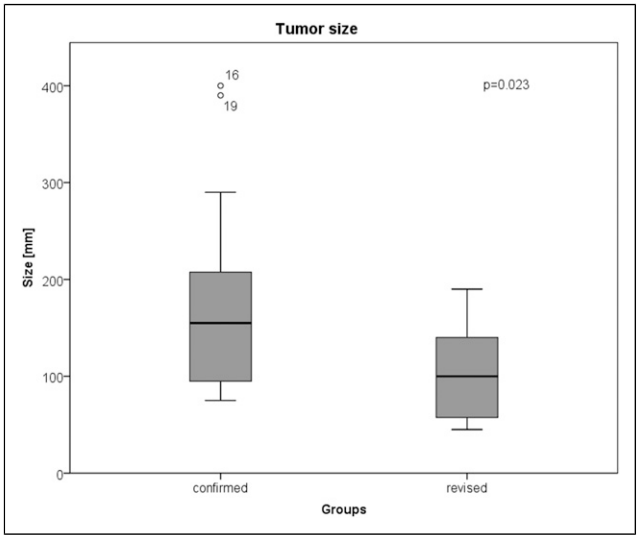

Figure 1. Boxplots. Tumor Size in (mm) according to the groups.

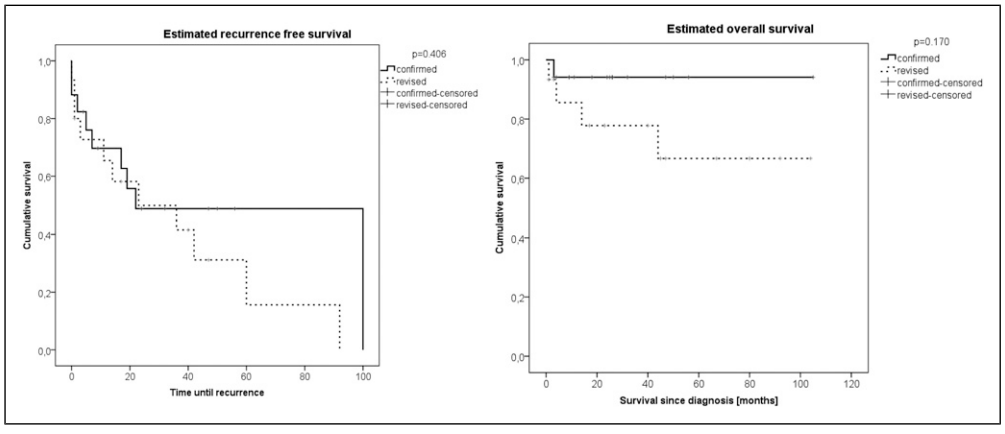

Figure 2. Left: Kaplan–Meier-Analysis. Estimated recurrence-free survival in the patients, whose primary clinical diagnosis was confirmed, and the patients with revision of the diagnosis (n = 32). Right: Kaplan–Meier-Analysis. Estimated overall survival grouped to those patients, whose primary clinical diagnoses was confirmed, and those, whose primary diagnosis changed during histopathological work-up (n = 32).

Table 3. Demographic Data of patients with adrenocortical carcinoma and with retroperitoneal sarcoma (SARCOMA).

	ACC (*n* = 12)	SARCOMA (*n* = 11)	*p* value
Gender (male/female), *n/n* (%/%)	9/3 (75/25)	3/8 (27/73)	0.635
Age	52 (19–78)	62 (29–82)	1.000
Side, *n* (%)			
Bilateral	1 (8)	–	0.142
Left-sided	7 (58)	3 (27)	
Right-sided	4 (33)	8 (73)	
Size (mm)	120.0 (75–215)	14 (55–400)	0.426
Hormonal activity, *n* (%)	4 (33)	–	0.090
Preoperative assessment, *n* (%)			
Staging CT	11 (92)	9 (82)	0.590
Staging MRI	5 (42)	2 (18)	0.371
Infiltration by imaging	7 (58)	6 (55)	1.000
Biopsy	1 (8)	4 (36)	0.155
Surgical procedure, *n* (%)			
Adrenalectomy	6 (50)	3 (27)	0.400
Multi-visceral resection	6 (50)	8 (7)	
Reference pathology, *n* (%)	0	8 (73)	0.000
Revised diagnosis, *n* (%)	1 (8)	5 (46)	0.069
Metachrone metastases, *n* (%)	4 (36)	5 (46)	1.000
Local recurrence, *n* (%)	2 (18)	6 (55)	0.183

(Absolute numbers and percentage, median, minimum and maximum).
N = 32.

adrenal gland, or a retroperitoneal sarcoma remains difficult. Forty-seven percent of our patients were preoperatively misdiagnosed. The preoperative assessment did not differ between those, whose diagnosis was confirmed or revised (Table 2). Furthermore, patients with sarcoma or an ACC received nearly the same preoperative work-up and unfortunately, not all patients with sarcoma underwent preoperative biopsy mainly due to the suspicion of an ACC (Table 3). Ten to fifteen percent of ACCs present as incidentalomas. These asymptomatic adrenal tumors are more frequently detected with the increasing use of imaging, while the prevalence of ACC among adrenal incidentalomas varies between 1–11%[44–47]. ACCs have a variable tumor size, and a small tumor size does not exclude malignancy[46]. We found that especially smaller tumors were significantly more often misdiagnosed. In addition, there was no significant difference in the diameter of ACCs and sarcomas (Figure 1; Table 3). Gender, tumor side, and tumor infiltration of other organs were not significantly associated with the fact, that a preoperative clinical diagnosis was either confirmed or revised (Table 2, 3).

Furthermore, the histological diagnosis of ACC remains challenging in the absence of metastatic disease. Nine histological characteristics are usually assessed as part of the Weiss score[32,48,49]. The Weiss system comprises nine issues of invasive behavior, cell architecture and mitotic characteristics, but is limited in borderline tumors, pediatric patients and oncocytic and myxoid variants[6]. Sarcomatoid ACCs present histopathological features of a conventional ACC as well as sarcomatoid lesions of a sarcoma, which are not accounted in the Weiss system and may lead to confusion when dealing with these malignancies[6]. Especially in case of strong dedifferentiation a retroperitoneal tumor impedes the diagnosis of adrenocortical origin[28]. There might be a mix of sarcomatoid and more mature parts requiring numerous immunostainings and molecular tests for exact differentiation[3,7,50,51]. In our study we resected 23 tumors, which we clinically suspected to be ACCs, but only 11 of them were histologically classified as ACCs. ACC is a rare and aggressive malignancy with an incidence of 0.5–2 per million per year and its overall prognosis is already very poor[52]. However, myxoid or sarcomatoid histological features or an increased Ki-67 index are associated with a worse outcome[53]. Especially in tumors with a high proliferation rate, a rapid initiation of adequate therapy is essential.

The suggested treatment of stage I-III ACC is complete surgical resection. Negative resection margins and an intact tumor capsule are important prognostic factors[54]. Smaller tumors (<6 cm or stage I-II) without any evidence of local invasion can be resected by a minimally invasive approach with given expertise[39,55–57]. The recommended surgical strategy for large ACC implies an open procedure with complete tumor excision with en-bloc excision of perirenal fat and if necessary infiltrated adjacent organs to achieve negative resection margins[39,50,54]. Ipsilateral nephrectomy

by routine did not deliver a significant benefit[57]. Twenty-five percent of patients present with tumor thrombus in the adrenal or renal vein or vena cava requiring thrombectomy or vascular replacement[55–58]. The role of a consequent lymphadenectomy remains unclear but should be performed in stage III tumors[59–64]. Dependent on the Ki-67 index, adjuvant treatment with mitotane is indicated. Stage IV ACCs necessitate chemotherapy. Even after full surgical resection, the risk for recurrence is up to 85% and adjuvant mitotane is recommended in case of high risk of recurrence[63–65].

Wide excision with negative margins also is the only curative modality for retroperitoneal sarcomas. It is defined as a retroperitoneal quasi-compartmental resection with en-bloc visceral resections of adjacent organs and tissues[66]. Even if the role of preoperative radiotherapy and chemotherapy is not completely established and still investigated, it should be considered when radical resection is technically uncertain or in case of higher grading. Therefore, the standard preoperative approach requires preoperative histopathological proof, different to the guidelines for ACC[66]. Delayed diagnosis or misdiagnosis of patients with retroperitoneal sarcoma may also result in increased tumor size or metastases which is associated with a worse prognosis. As the treatment of retroperitoneal sarcomas is complex, outcome improves when patients are treated in high-volume sarcoma centers[66,67]. Despite complete initial resection, more than 50% of patients with a retroperitoneal sarcoma will relapse and adjuvant chemotherapy might be necessary[67,68]. In our cohort, there was no difference regarding the surgical procedure despite misdiagnosing or depending on the entity (Table 2, 3). Preoperative misdiagnosing did not influence the overall survival (Figure 2).

We found one case of sarcomatoid adrenocortical cancer. According to WHO classification 2004, oncocytic ACCs, myxoid ACCs, and ACCs with sarcomatous areas are regarded as rare variants of ACC and only few cases of this unusual sarcomatous variant have been previously reported[3,6,7]. They should be designated carcinosarcoma or sarcomatoid carcinoma as they show forms of mesenchymal malignancy[6,51]. The limited number of reported cases does not allow any precise definition, but adrenocortical carcinosarcomas and sarcomatoid carcinomas have similar clinical outcome and a worse prognosis compared to ACC[6]. This aggressive behavior may be influenced by progressive biological dedifferentiation from a pre-existing better differentiated ACC, in analogy to the anaplastic carcinoma of the thyroid gland[6,69,70]. The one patient detected in our cohort showed poor survival and died within 14 months of follow up.

Conclusion

The limitation of this study is the small number of cases, the retrospective character, and the heterogeneity of presented patients. However, we wanted to outline that even in a high-volume center, the prevalence of retroperitoneal sarcomas and ACCs is low and the differentiation between both entities challenging by clinical and radiological methods as well as by histopathology. Biopsy of an ACC is not recommended but could be helpful in case of a sarcoma. Nevertheless, disease-free survival in both entities depends on radical resection and surgery should be performed in questionable cases. In case of an equivocal pathological report, a reference pathologist should be consulted as soon as possible to allow early initiation of adjuvant treatment.

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Conflicting interests

The authors declare that there is no conflict of interest.

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Ethical approval

The Ethics committee of Charité does not require approval for reporting case series. This study was completed in accordance with the Helsinki Declaration as revised 2013.

Informed consent

Verbal informed consent was generally obtained from all subjects for research projects. Written informed consent was partly given for research reasons and research register. Full written consent especially for this project could not be obtained as patients have already died or been lost for follow up as data comprises the period from 2009 till 2015.

Contributorship

E.M.D. and N.R. analyzed and interpreted the patient data. H.B. and W.S. performed the histological interpretation and evaluation; examination of the kidney, and was a major contributor in writing the manuscript. M.M. and M.B. participated in drafting the manuscript. JP had the supervision of the presented work. All authors read and approved the final manuscript.

ORCID iD

Eva M Dobrindt https://orcid.org/0000-0002-1616-9826

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