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

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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 19871. Irrespective of this specific type, adrenocortical carcinomas mixed with sarcoma or sarcomalike components have been reported until now2,3. These tumors are poorly differentiated and badly aggressive with a high risk for loco-regional recurrence, rapidly growing metastases
and death occurring within a short period of time. According to the World Health Organization (WHO), variants of adrenocortical carcinomas (ACC) include oncocytic ACCs, myxoid ACCs, and ACCs with sarcomatous areas. Tumors showing both, carcinomatous and sarcomatous characteristics (so-called carcinosarcomas) are generally uncommon. Due to the current WHO classification (2017), these neoplasms have been categorized as “sarcomatoid carcinomas” covering all carcinomas with “pleomorphic, sarcomatoid, or sarcomatous elements.” Apparently, the sarcomatous part develops out of carcinoma by dedifferentiation. Review of the literature found up to 60% of patients with ACC have concluded that sarcomatoid ACCs and ACCs with minimal sarcomatoid elements represent a distinct clinicopathologic entity.

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 derived 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 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 non-parametric 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
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 epitheloid 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 classified as a benign borderline tumor of the adrenal gland. 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

| 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 adenoma    | Borderline adrenocortical tumor |
| Adrenal carcinoma        | Adrenal tumor      | Epitheloid angiosarcoma  |
| Adrenal carcinoma        | Renal cancer       | Sarcomatoid adrenal cancer   |
| Neuroblastoma            | Adrenal carcinoma  | Adrenal adenoma       |
| Adrenal carcinoma        | Pheochromocytoma   | Metastasis of lung tumor  |
| Adrenal carcinoma        | Leimyosarcoma      | Leimyosarcoma          |
| Adrenal carcinoma        | Leimyosarcoma      | Leimyosarcoma          |
| Adrenal carcinoma        | Metastasis of neuroendocrine tumor | Metastasis of neuroendocrine tumor  |
| Adrenal carcinoma        | Oncotic 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            |

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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. The median age of onset of ACCs and liposarcomas is in the fifth and sixth decade whereas leiomyosarcomas normally appear in elderly patients. 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. 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. Sarcoma do not occur hereditarily but can be associated with immunodeficiency. 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. 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. Adrenal androgens are the second most secreted hormones by ACCs leading to hirsutism, virilization, and menstrual irregularities. However, 20–40% of ACCs are non-functional aggravating the differentiation from other retroperitoneal lesions which all cause similar unspecific symptoms. 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. In this study, a third of all revised cases and a quarter of the confirmed cases 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

| 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           | 12 (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.
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. 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. In contrast, adrenal adenomas are smaller (<4 cm), homogenous (≤10 HU) without calcification, necrosis or hemorrhage showing a greater wash-out than ACCs. The parenchyma of ACCs appears isointense to hypointense on T1-weighted MRI images and hyperintense on T2-weighted MRI images compared to the liver. If the imaging shows intralesional fat signs, that might be suspicious for liposarcomas, extramedullary hematopoiesis, and teratoma as differential diagnosis. 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. Nevertheless, necrosis might appear in nearly all dedifferentiated, primary, or secondary malignancies. 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. 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. 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. Therefore, physicians must rely on preoperative clinical presentation and radiological imaging. 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).
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\%\textsuperscript{44}–\textsuperscript{47}. ACCs have a variable tumor size, and a small tumor size does not exclude malignancy\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{6}. Especially in case of strong dedifferentiation a retroperitoneal tumor impedes the diagnosis of adrenocortical origin\textsuperscript{28}. There might be a mix of sarcomatoid and more mature parts requiring numerous immunostainings and molecular tests for exact differentiation\textsuperscript{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\textsuperscript{52}. However, myxoid or sarcomatoid histological features or an increased Ki-67 index are associated with a worse outcome\textsuperscript{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\textsuperscript{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\textsuperscript{19,55–57}. 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\textsuperscript{19,50,54}. Ipsilateral nephrectomy

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### 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.
by routine did not deliver a significant benefit\textsuperscript{57}. Twenty-five percent of patients present with tumor thrombus in the adrenal or renal vein or vena cava requiring thrombectomy or vascular replacement\textsuperscript{55–58}. The role of a consequent lymphadenectomy remains unclear but should be performed in stage III tumors\textsuperscript{59–64}. Depending 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\textsuperscript{65–66}.

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\textsuperscript{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\textsuperscript{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\textsuperscript{66,67}. Despite complete initial resection, more than 50\% of patients with a retroperitoneal sarcoma will relapse and adjuvant chemotherapy might be necessary\textsuperscript{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\textsuperscript{3,6,7}. They should be designated carcinosarcoma or sarcomatoid carcinoma as they show forms of mesenchymal malignancy\textsuperscript{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\textsuperscript{66}. 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\textsuperscript{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.
References

1. Okazumi S, Asano T, Ryu M, et al. [Surgical resection of adrenal carcinoma extending into the vena cava, right atrium and ventricle: case report and review of the literature]. Nihon Geka Gakkai Zasshi 1987; 88: 231–8.

2. Mark D, Boyd C and Eatock F. Adrenal sarcomatoid carcinoma: a case report and review of the literature. Ulster Med J 2014; 83: 89–92.

3. Sturm N, Moulai N, Laverrière MH, et al. Primary adrenocortical sarcomatoid carcinoma: case report and review of literature. Virchows Arch 2008; 452: 215–219.

4. Giordano TJ, Chrousovs GP, de Krijger RR, et al. Tumours of the adrenal cortex. In: Lloyd RV, Osamura RY, Klöppel G (eds) WHO classification of tumours of endocrine organs, 4th ed. Heidelberg-Berlin: Springer, 2017, pp. 161–178.

5. Tischler AS, de Krijger RR, Gill A, et al. Tumours of the adrenal medulla and extra-adrenal paraganglia. In: Lloyd RV, Osamura RY, Klöppel G (eds) WHO classification of tumours of endocrine organs. 4th ed. Heidelberg-Berlin: Springer, 2017, pp. 179–207.

6. de Krijger RR and Papathomas TG. Adrenocortical neoplasia: evolving concepts in tumorigenesis with an emphasis on adrenal cortical carcinoma variants. Virchows Arch 2012; 460: 9–18.

7. Coli A, Di Giorgio A, Castri F, et al. Sarcomatoid carcinoma of the adrenal gland: a case report and review of literature. Pathol Res Pract 2010; 206: 59–65.

8. Duregon E, Volante M, Rapa I, et al. Dissecting morphological and molecular heterogeneity in adrenocortical carcinoma. Turk Patoloji Derg 2015; 31 Suppl 1: 98–104.

9. Harach HR and Laidler P. Combined spindle cell sarcoma/phaeochromocytoma of the adrenal. Histopathology 1993; 23: 567–569.

10. Michal M and Havlicek F. Corticomediullary tumors of the adrenal glands. Pathol Res Pract 1996; 192: 1082–1089.

11. McLaughlin SA, Schmitt TM, Huguet KL, et al. Myofibrosarcoma of the adrenal gland. Am Surg 2005; 71: 191–193.

12. Hart J and Mandavilli S. Epithelioid angiosarcoma: a brief diagnostic review and differential diagnosis. Arch Pathol Lab Med 2011; 135: 268–272.

13. Hayashi T, Guer C and Mete O. A mimic of sarcomatoid adrenal cortical carcinoma: epithelioid angiosarcoma occurring in adrenal cortical adenoma. Endocr Pathol 2014; 25: 404–409.

14. Lack EE, Graham CW, Azumi N, et al. Primary leiomyosarcoma of adrenal gland. Am J Surg Pathol 1991; 15: 899–905.

15. Lam KY and Lo CY. Adrenal lipomatous tumours: a 30 year clinicopathological experience at a single institution. J Clin Pathol 2001; 54: 707–712.

16. Lee CW, Tsang YM and Liu KL. Primary adrenal leiomyosarcoma. Abdom Imaging 2006; 31: 123–124.

17. Wei J, Sun A, Tao J, et al. Primary adrenal leiomyosarcoma. Int J Surg Pathol 2014; 22: 722–726.

18. Bisciglia M, Minnena E, Altobella A, et al. Anaplastic kaposis’s sarcoma of the adrenal in an HIV-negative patient with literature review. Adv Anat Pathol 2019; 26: 133–149.

19. Bons J, Moreau L and Lefebvre H. Adrenal disorders in human immunodeficiency virus (HIV) infected patients. Ann Endocrinol 2013; 74: 508–514.

20. Castrejón N, Nicolau C, González-Cordón A, et al. Sclerosing Kaposi’s sarcoma of the adrenal gland in an HIV-infected patient under antiretroviral therapy. Ann Diagn Pathol 2019; 38: 123–125.

21. de Risi-Pugliese T, Genc S, Bertherat J, et al. Classic kaposi sarcoma: an exceptional cause of adrenal incidentaloma. J Endocrinol Soc 2017; 1: 737–741.

22. Fascetti-Leon F, Scotton G, Pio L, et al. Minimally invasive resection of adrenal masses in infants and children: results of a European multi-center survey. Surg Endosc 2017; 31: 4505–4512.

23. Guo H, Chen S, Liu S, et al. Rare adrenal gland incidentaloma: an unusual Ewing’s sarcoma family of tumor presentation and literature review. BMC Urol 2017; 17: 1: 24.

24. Maity K, Agrawal A, Datta C, et al. Primary Ewing’s sarcoma of adrenal gland: a rare case. J Clin Diagn Res 2019; 13: D01–D02.

25. Saboo SS, Krajewski KM, Jagannathan JP, et al. IVC tumor thrombus: an advanced case of rare extraaortic ewing sarcoma of the adrenal gland. Urology 2012; 79: e77–8.

26. Just PA, Tissier F, Silvera S, et al. Unexpected diagnosis for an adrenal tumor: synovial sarcoma. Ann Diagn Pathol 2010; 14: 56–59.

27. Feng YC, Yang ZG, Chen TW, et al. Adrenal sarcomatoid carcinoma: a rare case depicted on multi-detector row computed tomography. Indian J Med Sci 2010; 64: 37–40.

28. Else T, Kim AC, Sabolch A, et al. Adrenocortical carcinoma. Endocr Rev 2014; 35(2): 282–326.

29. Allolio B and Fassnacht M. Adrenocortical carcinoma: clinical update. J Clin Endocrinol Metab 2006; 91: 2027–2037.

30. Luton JP, Cerdas S, Billaud L, et al. Clinical features of adrenocortical carcinoma, prognostic factors, and the effect of mitotane therapy. New Engl J Med 1990; 322: 1195–1201.

31. Matta M, Bongard V, Grunenwald S, et al. Clinical and metabolic characteristics of acromegalic patients with high IGF1/normal GH levels during somatostatin analog treatment. Eur J Endocrinol 2011; 164: 885–889.

32. Papotti M, Libè R, Duregon E, et al. The weiss score and beyond-histopathology for adrenocortical carcinoma. Adv Anat Pathol 2019; 26: 272–276.

33. Wanis KN and Kanthan R. Diagnostic and prognostic features in adrenocortical carcinoma: a single institution case series and review of the literature. World J Surg Oncol 2015; 13: 117.

34. Mota MMDS, Bezerra ROF and Garcia MRT. Practical approach to primary retroperitoneal masses in adults. Radiol Bras 2018; 51(6): 391–400.
35. Zhou Y, Tang Y, Tang J, et al. Primary adrenal leiomyosarcoma: a case report and review of literature. Int J Clin Exp Pathol 2015; 8(4): 4258–63.
36. Gáitia CE, Georgescu I and Nemes R. Difficulties in diagnosis of primitive retroperitoneal tumors. Curr Health Sci J 2010; 36: 132–135.
37. Marin D, Soher BJ, Dale BM, et al. Characterization of adrenal lesions: comparison of 2D and 3D dual gradient-echo MR imaging at 3 T-preliminary results. Radiology 2010; 254(1): 179–187.
38. Messiou C, Moskovic E, Vanel D, et al. Primary retroperitoneal soft tissue sarcoma: Imaging appearances, pitfalls and diagnostic algorithm. Eur J Surg Oncol 2017; 43(7): 1191–1198.
39. Fassnacht M, Arlt W, Bancos I, et al. Management of adrenal incidentalomas: european society of endocrinology clinical practice guideline in collaboration with the European network for the study of adrenal tumors. Eur J Endocrinol 2016; 175: G1–G34.
40. Inan N, Arslan A, Akansel G, et al. Dynamic contrast enhanced MRI in the differential diagnosis of adrenal adenomas and malignant adrenal masses. Eur J Radiol 2008; 65(1): 154–162.
41. Johnson PT, Horton KM and Fishman EK. Adrenal mass imaging with multidetector CT: pathologic conditions, pearls, and pitfalls. Radiographics 2009; 29: 1333–1351.
42. Bharwani N, Rockall AG, Sahdev A, et al. Adrenocortical carcinoma: the range of appearances on CT and MRI. AJR Am J Roentgenol 2011; 196: W706–W714.
43. Dun nick NR, Heastdon D, Halvorsen R, et al. CT appearance of adrenal cortical carcinoma. J Comput Assist Tomogr 1982; 6: 978–982.
44. Dackiw AP, Lee JE, Gagel RF, et al. Adrenal cortical carcinoma. World J Surg 2001; 25: 914–926.
45. Johanssen S, Hahner S, Saeger W, et al. Deficits in the management of patients with adrenocortical carcinoma in Germany. Dtsch Arztebl Int 2010; 107: 885–891.
46. Kostia nien I, Hakaste L, Kejo P, et al. Adrenocortical carcinoma: presentation and outcome of a contemporary patient series. Endocrine 2019; 65(1): 166–174.
47. Fassnacht M, Terzolo M, Allolio B, et al. Combination chemotherapy in advanced adrenocortical carcinoma. N Engl J Med 2012; 366: 2189–2197.
48. Saeger W, Mohren W, Behrend M, et al. Sarcomatoid adrenal carcinoma: case report with contribution to pathogenesis. Endocr Pathol 2017; 28: 139–145.
49. Weiss LM. Comparative histologic study of 43 metastasizing and nonmetastasizing adrenocortical tumors. Am J Surg Pathol 1984; 8: 163–170.
50. Abdel-Aziz TE, Rajeev P, Sadler G, et al. Risk of adrenocortical carcinoma in adrenal tumours greater than 8 cm. World J Surg 2015; 39(5): 1268–1273.
51. Fischler DF, Nunez C, Levin HS, et al. Adrenal carcinosarcoma presenting in a woman with clinical signs of virilization. A case report with immunohistochemical and ultrastructural findings. Am J Surg Pathol 1992; 16: 626–631.
52. Khan MS, Ali A, Tariq I, et al. A clinical study and treatment results of adrenocortical carcinoma patients presented in Shaukat Khanum memorial cancer hospital and research center, Lahore. J Pak Med Assoc 2019; 69(5): 717–719.
53. Sung TY, Choi YM, Kim WG, et al. Myxoid and Sarcomatoid variants of adrenocortical carcinoma: analysis of rare variants in single tertiary care center. J Korean Med Sci 2017; 32(5): 764–771.
54. Icard P, Goudet P, Charpenay C, et al. Adrenocortical carcinomas: surgical trends and results of a 253-patient series from the French association of endocrine surgeons study group. World J Surg 2001; 25: 891–897.
55. Lorenz K, Langer P, Niederle B, et al. Surgical therapy of adrenal tumors: guidelines from the German association of endocrine surgeons (CAEK). Langenbecks Arch Surg 2019; 404(4): 385–401.
56. Gajoux S, Mihai R and Joint working group of ESES and ENSAT. European society of endocrine surgeons and European network for the study of adrenal tumours recommendation for the surgical management of adrenocortical carcinoma. Br J Surg 2017; 04: 358–376.
57. Berruti A, Baudin E, Gelderblom H, et al. Adrenal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; 23(Suppl. 7): vii131–viii138.
58. Fiori C, Daffara F, Defrancia S, et al. Does nephrectomy during adrenalectomy for adrenal cancer improve oncological results? Eur Urol Suppl 2012; 11: e1105–e1105a.
59. Mihai R, Iacobone M, Makay O, et al. Outcome of operation in patients with adrenocortical cancer invading the inferior vena cava—a European Society of Endocrine Surgeons (ESES) survey. Langenbecks Arch Surg 2012; 397: 225–231.
60. Reibetanz, Jurowich C, Erdogan I, et al. Impact of lymphadenectomy on the oncologic outcome of patients with adrenocortical carcinoma. Ann Surg 2012; 255: 363–369.
61. Saade N, Sadler C and Goldfarb M. Impact of regional lymph node dissection on disease specific survival in adrenal cortical carcinoma. Horm Metab Res 2015; 47: 820–825.
62. Nibulol N, Patel D and Kebebew E. Does lymphadenectomy improve survival in patients with adrenocortical carcinoma? A population-based study. World J Surg 2016; 40: 697–705.
63. Megerle F, Herrmann W, Schloetelburg W, et al. Mitotane monotherapy in patients with advanced adrenocortical carcinoma. J Clin Endocrinol Metab 2018; 103: 1686–1695.
64. Terzolo M, Zaggia B, Allasono B, et al. Practical treatment using mitotane for adrenocortical carcinoma. Curr Opin Endocrinol Diabetes Obes 2014; 21(3): 159–165.
65. Berruti A, Grisanti S, Pulzer A, et al. Long-term outcomes of adjuvant mitotane therapy in patients with radically resected adrenocortical carcinoma. J Clin Endocrinol Metab 2017; 102: 1358–1365.
66. Casali PG and Blay JY. Soft tissue sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncology* 2010; 21(21 Suppl 5): v198–v203.
67. van Houdt WJ, Zaidi S, Messiou C, et al. Treatment of retroperitoneal sarcoma: current standards and new developments. *Curr Opin Oncol* 2017; 29(4): 260–267.
68. Toulmonde M, Bonvalot S, Ray-Coquard I, et al. Retroperitoneal sarcomas: patterns of care in advanced stages, prognostic factors and focus on main histological subtypes: a multicenter analysis of the French Sarcoma Group. *Ann Oncol* 2014; 25(3): 730–734.
69. Thiery JP, Acloque H, Huang RY, et al. Epithelial-mesenchymal transitions in development and disease. *Cell* 2009; 139: 871–890.
70. Liu J and Brown RE. Immunohistochemical detection of epithelial-mesenchymal transition associated with stemness phenotype in anaplastic thyroid carcinoma. *Int J Clin Exp Pathol* 2010; 3: 755–62.