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ORIGINAL ARTICLE

# Surgery for adrenal angiomyelolipoma: an individualized concept

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## Abstract

**Background** Because adrenal angiomyelolipoma (AAML) is rare and uniformly benign, the indications for surgery are ill defined.

**Methods** Among a series of 156 patients with adrenal pathologies surgically treated between 2013 and 2018, 12 patients were operated with the diagnosis of an AAML. The clinical as well as imaging parameters forming the individual indications for surgery were analyzed.

**Results** Preoperative diagnosis consistent with AAML was made in all 12 patients. The mean size of surgically removed AAML was 82.3 mm (45–150 mm). Gender and affected side were evenly distributed. Local symptoms but lack of radiological signs suspicious for malignancy or size increase were observed in 4 of 12 patients (group 1, 33%). In contrast, 4 of 12 patients (group 2, 33%) showed radiological signs suspicious for malignancy but lacked local symptoms. Additional 4 of 12 patients (group 3, 33%) showed both local symptoms and radiological signs suspicious for malignancy. Patients with local symptoms harbored significantly larger tumors compared to those patients that lacked local symptoms (93.9 mm ± 32.8 vs. 59.3 mm ± 2.7, $p = 0.021$). Patients with radiologically suspicious signs were older (60 years ± 9.9 vs. 53 years ± 5.4, $p > 0.05$), and time to surgery was shorter (4.4 months ± 3 vs. 6.0 months ± 3.0, $p > 0.05$). Importantly, surgical approach was not influenced by tumor size ($p = 0.65$). However, patients with suspicious imaging were more likely to be operated by conventional open approach (4 of 8 vs. 0 of 4, $p = 0.08$). The minimal invasive approach was associated with shorter hospital stay (7 days, ± 1.3 vs. 14.2 days, ± 8.8, $p = 0.038$). All lesions that showed radiological signs suspicious for malignancy proved benign in final histology.

**Conclusion** Large AAML present a clinical challenge. The presence of local symptoms and/or radiological signs suspicious for malignancy identifies three groups of patients that define the concept of an individualized indication for surgery in AAML. A minimal invasive approach can be advocated even for large AAML with radiological signs suspicious for malignancy.

**Keywords** Adrenal incidentaloma · Adrenal angiomyelolipoma · Laparoscopic adrenalectomy · Surgery

## Introduction

Due to the increased utilization of abdominal imaging, adrenal incidentalomas are identified more and more frequent. It is estimated that adrenal angiomyelolipoma (AAML) is found in about 5% of all CT scans. However, depending on inclusion criteria, the estimated incidence of AAML varies. For instance, based on a retrospective chart review of 62.279 CT scans, Campbell et al. identified only 150 patients (0.24%) with angiomyelolipoma [1]. Among 16.579 abdominal CT/MRI conducted in 2018 at our institute, an automated full-text report search identified AAML in only 0.04% of patients. In contrast, in surgical series, about 10% of resected tumors account for AAML [2].

AAML belong to the group of stromal tumors and are composed of fatty and myeloid tissue and are generally of benign nature. However, they can cause local symptoms due to their size [3]. The clinical importance arises from the challenge to differentiate AAML from other adrenal neoplasia especially adrenocortical carcinoma. On imaging, AAML appear as well-circumscribed tumors. However, as they are composed of adipose tissue and myeloid tissue, these tumors are often of heterogeneous appearance (Fig. 1). The presence of fatty tissue in adrenal lesions results in a low attenuation on

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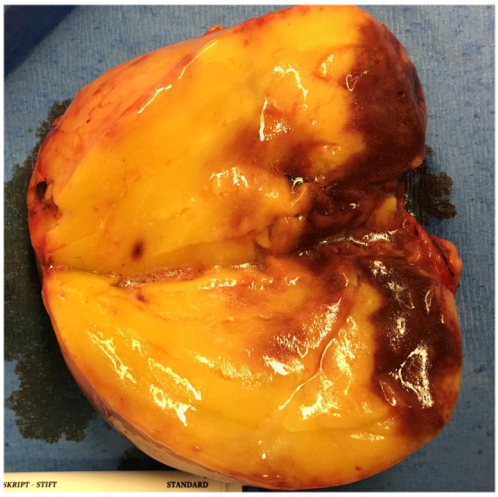

**Fig. 1** Macroscopic appearance of a 120-mm AAML with homogenous fatty tissue and hemorrhage at the lower aspect (patient 02, group 1). Resection was performed minimal invasively by a transabdominal approach

CT scan that is measured in Hounsfield units (HU). Commonly, a threshold value of 10 HU is used in clinical practice to differentiate benign adrenal adenoma with a sensitivity of 88% and specificity of 84% [4].

While there are over 400 case reports published on AAML, there is no systematic evaluation of the clinical and imaging features that lead to the indication for surgery. While the European Society of Endocrinology (ESE)/European network for the study of adrenal tumors (ENSAT) clinical practice guidelines are designed to provide a corridor for diagnosis and management of patients with adrenal incidentalomas, in some respects, they might not reflect the challenge of AAML [5]. It has to be questioned if tumor size is the driving parameter for the recommendation to perform surgery. This is important, as radiologic series reporting on the incidence of AAML show in average a smaller tumor size (i.e., around 2 cm) as compared to surgical series [1]. Furthermore, size increase over years might lead to local symptoms and thus follow-up might be indicated even for small AAML.

Because adrenal angiomyelolipoma (AAML) is rare and uniformly benign, the indication for surgery outside the setting of acute tumor rupture is ill defined.

The aim of this study was to outline the individualized indication for elective surgery for AAML.

## Material and methods

Between January 2013 and January 2018, 12 patients with AAML have been operated at our division. In the same time, an additional of 144 patients have been surgically treated for other adrenal neoplasia (Table 1).

**Table 1** Demographics of all 156 patients with adrenal neoplasia

| | | $n = 156$ |
|---|---|---|
| Age (mean) | 55 years | |
| Gender | Male | 87 |
| | Female | 69 |
| Adrenal adenoma | Hormonally active | 38 |
| | Hormonally inactive | 22 |
| Adrenal malignancy | Metastases | 64 |
| | Adrenocortical carcinoma | 12 |
| | Malignant pheochromocytoma | 3 |
| Angiomyelolipoma | | 12 |
| Other* | | 5 |

*Primary adrenal GIST, acute bleeding from ruptured cyst, bilateral adrenalectomy b/o ectopic ACTH production (2×), adrenal lymphangioma

For all 12 patients with AAML, the preoperative diagnosis was based on CT or MRI imaging. In addition, for all these 12 patients, the diagnosis was confirmed by final histology. All patients with AAML received native and contrast-enhanced CT scan or MRI prior to surgery. Furthermore, a complete hormone work-up was conducted for all patients to rule out hormone active adrenal tumor (Table 2). The clinical charts were screened for concomitant disease including hypertension, diabetes, history of malignant disease, immunodeficiency, and medication (Table 2).

We recommend surgery in three clinical scenarios: group 1: presence of local symptoms such as abdominal or flank pain or abdominal discomfort and absence of radiologically suspicious signs or size increase; group 2: absence of local symptoms as outlined above but presence of radiologically suspicious signs; radiological signs comprise elevated HU, necrosis, and suspicion for capsule penetrating tumor or size increase; group 3: the presence of local symptoms and radiological signs as outlined above (Table 2). The stratification based the clinical symptoms on the patient's self-assessment and was not further defined by utilizing a validated tool, such as a visual analog scale. None of these patients required a preoperative continuous analgesic medication.

Clinical and imaging variables have been compared by Student's $T$ test for unpaired samples, and statistical significances were assumed at a $p$ value $< 0.05$.

## Results

A total of 156 patients have been treated for adrenal neoplasia between January 2013 and January 2018 in our division (Table 1). The mean age was 55 years (1 to 86 years), and there were 69 female and 87 male patients. Of these 156 patients, 60 patients harbored an adenoma of which 38 (63.3%) were hormonally active. Seventy-nine patients (50.6%) were

**Table 2** Clinical, radiological findings, and outcome after surgery

| Patient | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 |
| Gender | Female | Female | Male | Male | Female | Male | Male | Male | Female | Male | Female | Female |
| Age (years) | 53 | 47 | 52 | 60 | 43 | 68 | 73 | 51 | 60 | 62 | 68 | 55 |
| Adrenal | Right | Right | Left | Right | Right | Left | Left | Right | Right | Left | Left | Left |
| Clinical symptoms | Right flank and abdominal discomfort | Right flank and back pain | Left flank and abdominal pain | Diffuse abdominal discomfort | No | No | No | No | Right flank and back pain | Diffuse abdominal pain and left flank | Epigastric discomfort and back pain | Left flank and back pain |
| Hypertension | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | No | No |
| Diabetes | No | Yes | Yes | No | Yes | No | Yes | No | No | No | No | No |
| Metanephrine | 27 ng/l | 38 ng/l | 18 pg/ml | 12 pg/ml | 15 ng/l | 41 pg/ml | 53 pg/ml | 25 pg/ml | 10 pg/ml | 31 pg/ml | wnl | 17 pg/ml |
| Normetanephrine | 46 ng/l | 61 pg/ml | 74 pg/ml | 109 pg/ml | 25 ng/l | 52 pg/ml | 153 pg/ml | 61 pg/ml | 40 pg/ml | 83 pg/ml | wnl | 61 pg/ml |
| Aldosterone | 70 ng/l | 44 nmol/ml | 60 nmol/l | 69 ng/l | 34 ng/ml | 54 ng/l | 37 ng/ml | 355 ng/l | 25 ng/l | 42 nmol/l | wnl | 37 ng/ml |
| Cortisol | 21 nmol/l | 19 μg/24 h | 250 nmol/l | 355 nmol/l | 14 μg/24 h | 27 nmol/l | 32 μg/24 h | 293 nmol/l | 13 nmol/l | 21 μg/24 h | wnl | 22 nmol/l |
| Radiologically suspicious/size increase | No | No | No | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Time diagnosis to surgery (months) | 1 | 12 | 1 | 10 | 1 | 8[§] | 4 | 3[#] | 1* | 3 | 6 | 9[§] |
| Surgery | MI | MI | MI | MI | MI | MI | Open | Open[a] | MI | Open | Open | MI |
| Days in hospital | 10 | 7 | 6 | 6 | 7 | 7 | 7 | 13 | 7 | 27 | 10 | 6 |
| Dindo–Clavien | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | IVa[b] | 0 | 0 |
| Follow-up (months) | 57 | 28 | 13 | 12 | 67 | 26 | 26 | 23 | 68 | 63 | 18 | 15 |

*wnl* within normal limits, *MI* minimal invasive surgery, *Open* open adrenalectomy

*Thirty years since the initial finding of an incidentaloma (45 mm)

[#] Ten years since the initial finding of an incidentaloma (24 mm)

[§] Tumor progress within 6 months follow-up

[a] Open approach due to history of CAPD induced peritonitis

[b] Deep vein thrombosis with pulmonary embolism

treated because of a malignancy (64 patients had metastatic disease, 12 patients harbored an ACC, and 3 patients had a malignant pheochromocytoma). One hundred and five patients (67.3%) were operated by minimal invasive approach (transabdominal laparoscopic or retroperitoneoscopic), and 51 patients were operated with an open laparotomy (Table 1).

This series of 156 patients included 12 patients with the diagnosis of AAML (7.7%).

There was an even gender distribution with six female and six male patients. The mean age was 57.7 years (43 to 73 years). In addition, there was an even distribution of the affected adrenal gland (six left side and six right side). Hormone secretion was ruled out for all 12 patients (Table 2). The average tumor size was 82.3 mm (45–150 mm). In three patients (25%), the AAML exceeded the 100 mm range considered for giant angiomyelolipoma (Table 3). Preoperative imaging identified all lesions consistent with AAML and final histology proved AAML for all patients. Among the remaining hormonally inactive adrenal tumors ($n = 103$), there were two patients with a diagnosis of AAML on preoperative imaging. Both were diagnosed as adrenal adenoma on final histology. Thus, in this series, the sensitivity and specificity to identify AAML preoperatively was 100% and 98%, respectively. However, the latter will decline to 90.9% (20 of 22) if we only consider the non-metastatic, hormonally inactive adrenal tumors (Table 1).

There was no malignancy identified. There was no mortality and one grade IVa complication (pulmonary embolism) that required intensive care management (Table 2).

Four of 12 patients belonged to group 1, defined by the presence of local symptoms. None of these patients showed radiologically suspicious findings such as calcification or high HU, but imaging was consistent with AAML (Fig. 1). Gender and affected side did not differ between group 1 and the other two groups.

Patients with local symptoms but lesions considered radiologically unsuspicious (i.e., group 1) were more likely to be treated by minimal invasive surgery (4 out of 4, 100%) compared to those belonging to group 2 and 3 (4 out of 8, 50%). However, this difference did not meet statistical significance ($p = 0.08$). Furthermore, group 1 patients were of younger age (53.0 years ± 2.7) compared to group 2 (58.7 years ± 7.1) and group 3 (61.3 years ± 2.7) (Table 2). Interestingly, the mean time to surgery in group 1 patients was longer compared to the other patients (6.0 months ± 2.9 vs. 4.1 months ± 1.5) (Table 2). However, these differences were not statistically significant. One patient in this group (patient 03) received follow-up after 6 months during which the tumor did not show signs of progression, but surgery was indicated due to the abdominal pain the patient developed (Table 2).

In total, abdominal pain and/or discomfort that was reported by 8 of 12 patients (66.7%) (group 1 and group 3) (Table 2). Importantly, tumor size was considerable larger in these patients reporting local pain or discomfort compared to those (group 2) that lack local symptoms (93.9 mm ± 32.8 vs. 59.3 ± 2.7, $p = 0.021$) (Table 3). Neither gender, surgical approach, nor affected side was different between those patients that presented with abdominal pain/discomfort (group 1 and 3) and those that did not (group 2).

Eight of the 12 adrenal lesions were radiologically consistent with AAML but showed radiological signs suspicious for malignancy or showed an increase in tumor size (group 2 and group 3). Radiological signs suspicious of malignancy include features such as HU, calcification, necrosis, or potential penetration beyond the tumor capsule (Fig. 2). Interestingly, two of the eight patients (06 and 12) belonging to groups 2 and 3 showed a tumor progress within 6-month follow-up (55 to 60 mm and 60 to 65 mm). Furthermore, one patient (09, group 3) showed a tumor size increase from 45 to 92 mm after 30 years of follow-up. In addition, this patient also

**Table 3** Radiological findings

| Patient | Group | HU > 10 | Chemical shift on MRI | Lipid rich | Size (mm) | Inhomogeneous | Calcification |
|---|---|---|---|---|---|---|---|
| 01 | 1 | No | | Yes | 110 | Yes | No |
| 02 | 1 | | Yes | Yes | 120 | Yes | No |
| 03 | 1 | | Yes | Yes | 90 | Yes | No |
| 04 | 1 | | Yes | Yes | 45 | Yes | No |
| 05 | 2 | No | | Yes | 52 | Yes | No |
| 06 | 2 | | Yes | Yes | 60 | Yes | Yes |
| 07 | 2 | Yes | | Yes | 65 | Yes | No |
| 08 | 2 | No | | Yes | 60 | Yes | No |
| 09 | 3 | No | | Yes | 92 | Yes | No |
| 10 | 3 | No | | Yes | 150 | Yes | Yes |
| 11 | 3 | Yes | | Yes | 79 | Yes | Yes |
| 12 | 3 | | Yes | Yes | 65 | Yes | No |

*HU* Hounsfield units, *CT* computed tomography, *MRI* magnetic resonance imaging

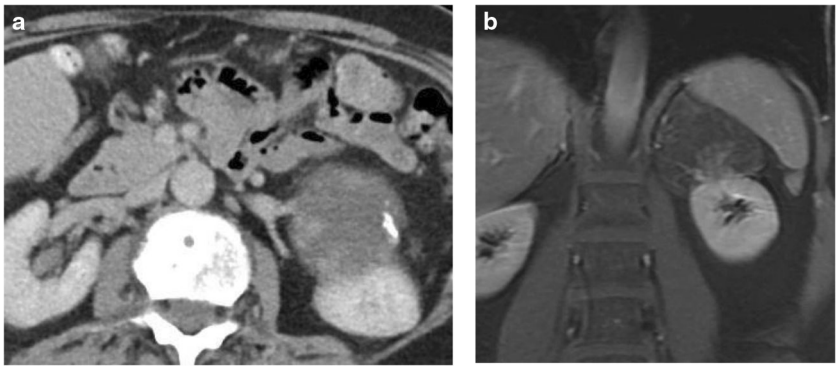


**Fig. 2** **a** Non-contrast enhanced CT of a patient 11 (group 3) with a 79-mm adrenal lesion. HU − 31 to 68, average 16.1. The lesion was considered inhomogeneous and suspicious, as the tumor appeared to penetrate into the left kidney. Open adrenalectomy was performed. Intra-operative tumor infiltration was not observed. **b** Chemical shift MRI showing a 65-mm hypointense lesion during in-phase and signal drop during out-phase (patient 12, group 3). The tumor was considered suspicious as an invasion into the left kidney was suspected. Transabdominal laparoscopic adrenalectomy was performed and completed. Intra-operatively a tumor infiltration was not observed

complained of strong abdominal pain. Patients in group 2 and 3 were in average older (60 years ± 9.9) compared to those of group 1 (53 years ± 5.4). However, this difference was not statistically significant ($p = 0.14$) (Table 2).

The concomitant presence of abdominal discomfort and suspicion for malignancy was observed in four patients (group 3). Tumor size in group 3 (96.5 mm ± 18.7) was considerably larger compared to group 2 patients (59.3 mm ± 2.7, $p = 0.09$) (Table 3), further indicating that tumor size is associated with the development of local symptoms.

Interestingly, the average hospital stay of patients belonging to group 3 was longer compared to all other patients (12.5 days vs. 8.5 days group 2 and 7.2 days group 1). However, this observation likely reflects the benefit of minimal invasive procedures utilized more frequently in group 1 and 2 patients (Table 2). The average hospital stay for the minimal invasive group was significantly shorter than for the conventional open approach group (7 days vs. 14.2 days, $p = 0.038$). Importantly, the choice of procedure was not related to tumor size. The average tumor size was 79.3 mm (± 27.7 mm) in the minimally invasive group compared to 88.5 mm (± 41.8 mm) in the open group. This difference was not significant ($p = 0.65$).

## Discussion

AAML is a rare and generally benign disease with only minor risk for clinical complications. However, rupture of large AAML that requires emergency adrenalectomy has been reported but must be considered a rare event [6]. In our series, AAML comprised about 7% of all adrenalectomies performed. This is consistent with other reviews that estimate the incidence of AAML among surgical series up to 10% [2].

Indication for elective surgery in AAML is ill defined. We recommend surgery in patients that either show radiologically suspicious findings and/or present with local abdominal symptoms (Figs. 1 and 2). In our setting, these local clinical symptoms (i.e., abdominal pain or discomfort) have been a main contributor to recommend surgery and are associated with increase in tumor size. Abdominal discomfort or abdominal pain was reported by two-thirds (67%) of our patients. Similarly, a systematic review of over 400 case reports conducted by Decmann et al. identified pain/discomfort in over 60% of all patients [3].

In addition, radiological signs on CT or MRI might be present that are suspicious for malignancy. The assessment of the risk of malignancy relies on tumor homogeneity and lipid content. Non-contrast-enhanced CT is recommended as imaging of choice. Based on the threshold values employed, the diagnostic sensitivity and specificity to identify lipid-rich, benign adrenal lesions ranges from 88% and 84% for a HU of 20 to 47% and 100% for a HU of 2 [4].

A threshold value of 10 HU is used in clinical practice to differentiate benign adrenal adenoma with a sensitivity of 71% and specificity of 98% [4]. Of the patients in our series that received non-contrast enhanced CT, two patients (28.6%) showed a HU above 10 (16HU and 21HU). When compared to a series of 13 patients with ACC treated by our division between 2016 and 2018, we noted that the average HU in this ACC series was 34.5 with a range between 15.8HU and 56HU. Thus, there is a gray zone in which an adrenal malignancy cannot be ruled out. Increasing the cutoff value to 20HU might result in an improved sensitivity (71 to 88%) but one will lose specificity (i.e., 98 to 84%) [4]. Importantly, additional radiological imaging characteristics such as inhomogeneity or calcification are found quite frequently in AAML. In our series, all lesions were inhomogeneous adrenal lesions and calcification was observed in 28% of patients. Others have also reported atypical imaging appearance as a main indication for elective surgery [2]. In addition, while Decmann et al. did not provide information on as

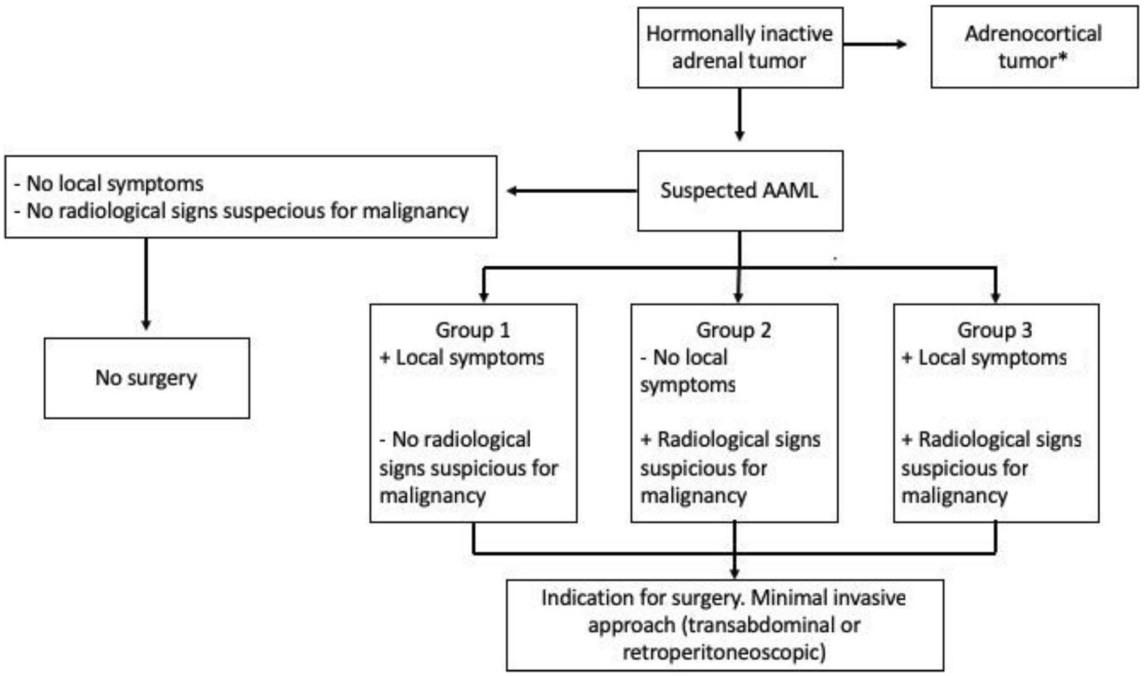


**Fig. 3** Flow chart outlining the management of AAML. See ESE/ENSAT clinical practice guidelines [5] (asterisk)

systematic evaluation of the imaging features observed, these authors state that calcification is observed frequently [3].

The ESE/ENSAT guidelines provide three options for the management of indeterminate lesions [5]: first, immediate re-evaluation and imaging with another technique. To this end, the utility of fluorodeoxyglucose (FDG) PET/CT in our hands does not provide for additional diagnostic accuracy. Usually, AAML is not FDG avid. Other studies have shown that lipid-rich adrenal tumors with increased FDG uptake are likely hormone-secreting adenomas [7]. Immediate imaging with MRI would be likely inconclusive as well, as all AAML diagnoses in our series by MRI showed the typical behavior on chemical shift imaging but also displayed inhomogeneity and even suggested tumor infiltration in adjacent organs (Fig. 2). While further quantitative analysis such as the signal intensity index provides advantages, in clinical practice, this quantitative analysis is frequently error prone and thus provides hardly an advancement beyond the determination of signal intensity loss [8].

Second, ESE/ENSAT guidelines advocate that interval imaging after 6–12 months should be employed. Four patients in our series received interval imaging after 6 months. Indication for surgery was issued because of increase in HU and/or increase in size > 5 mm in three of these patients.

Interestingly, one of our patients showed a size increase of 45 mm over a 30-year period (i.e., 0.15 cm per year), which is in line with the observation by Campbell et al. who showed based on a series of 150 radiological diagnosed AAML that the mean tumor growth rate per year is about 0.16 cm (0.08 to 0.71 cm) [1]. Importantly, this patient developed severe local symptoms.

Our findings suggest that there might be a correlation between tumor size increase and the presentation with local clinical symptoms. Thus, while the ESE/ENSAT do not recommend, it might be feasible to perform follow-up imaging even in patients with small, asymptomatic AAML in order to identify patients that are at risk to develop local symptoms. Importantly, Campbell et al. could not show a correlation between the initial tumor size and growth rate [1]. Thus, a measurable increase in growth within a 6-month time frame might be considered suspicious.

Endocrine and non-endocrine disorders are additional features that might be associated with AAML. To this end, the study by Su et al. suggested that AAML is associated with adrenal hormone excess [9]. Others have reported that congenital adrenal hyperplasia is observed in up to 10% of patients with angiomyelolipoma [3]. The study by Campbell et al. showed that of the 150 patients with AAML identified among 62,279 patients that received a CT scan, frequently observed clinical symptoms are considered to be part of the metabolic syndrome such as obesity, hypertension, diabetes, or hypokalemia [1]. However, only 20 of 150 patients received a hormone work-up and in which four of 20 patients showed signs for endocrine dysfunction. As all our patients received a full hormone evaluation, any form of hormone excess can be ruled out. Thus, based on our series, an association of AAML with subclinical hormone excess cannot be proposed. Furthermore, Peppa et al. reported a higher incidence of metabolic syndrome in patients with apparently hormone inactive adrenal lesions [10]. Based on our series, we cannot support this finding as 8 of 12 (67%) patients present

with arterial hypertension and only 4 of 12 patients (33%) were diagnosed with diabetes.

Large AAML can present a clinical challenge. Elective surgery in patients with radiologically finding consistent with AAML is indicated in the presence of clear local symptoms and/or radiological signs suspicious for malignancy (Fig. 3). Importantly, patients in our series showed preoperatively radiological finding consistent with AAML but displayed suspicious signs such as potential local invasion, the final histology proofed a benign disease in all cases. Therefore, we recommend minimal invasive approach even for these tumors irrespective of tumor size at the discretion of the surgeon's experience and preferences.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee (votum of the ethics committee Medical Faculty, University Duisburg-Essen: No.19-8597-BO) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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