Original Article

Clinical Presentation and Treatment outcomes of Benign Renal Tumor: Angiomyolipoma

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Background: Angiomyolipoma (AML) is a benign renal neoplasm composed of abnormal blood vessels, smooth muscle cells, and adipose tissue. About 40% of AMLs present with acute severe hemorrhage and is a potentially life-threatening condition. The risk of bleeding is proportional to tumor size and increasing significantly with size above 4 cm. Therefore, the patients with AMLs of 4 cm or more or spontaneous rupture of AMLs need interventional or surgical treatment.

Objective: To evaluate the clinical presentation and treatment outcomes of the AMLs.

Materials and Methods: The present report was a retrospective analytic study of the medical records and imaging studies in Phramongkutklao Hospital between January 2002 and December 2019.

Results: Sixty-three patients, with a female:male ratio of 47:6, and a median age of 54.76 years with a range of 8 to 84 years, were included in the present analysis. Seven (11.1%) had tuberous sclerosis complex (TSC) and 56 (88.9%) had sporadic. Fifty-four had a solitary lesion, whereas nine had bilateral lesions. Asymptomatic AMLs were 50 (79.4%) and symptomatic AMLs were 13 (20.7%). There were 46 (73.0%) AMLs smaller than 4 cm and 17 (27.0%) AMLs of 4 cm or larger. AMLs smaller than 4 cm were incidentally discovered (n=40, 87%) and revealed due to symptoms such as flank pain (n=3, 6.5%) and hematuria (n=3, 6.5%). AMLs of 4 cm or larger were incidentally discovered (n=10, 58.8%) and revealed due to symptoms such as flank pain (n=7, 41.2%) and not presented with hematuria. AMLs smaller than 4 cm were mostly treated by follow up (n=39, 84.78%) or surgery (n=7, 15.22). AMLs of 4 cm or larger were treated by follow-up (n=11, 64.7%) then converted to arterial embolization (n=4, 23.5%) and converted to surgery (n=8, 47.1%). Two AMLs of 4 cm or larger died (11.8%).

Conclusion: Significant differences in clinical manifestations and treatment outcomes were noted in respect to tumor characteristics, association with TSC, and treatment modality. Considering the benign nature of AML, size, and association with TSC ought to be considered when deciding upon active surveillance or prophylactic intervention.

Keywords: Angiomyolipoma; Tuberous sclerosis complex; Embolization; Nephrectomy

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Renal angiomyolipoma (AML) is a benign renal neoplasm composed of thick-walled poorly organized blood vessels, smooth muscle, and varying levels of mature adipose tissue, which often has characteristic imaging appearances on ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI)[1,2]. It is a rare condition and constitutes only 1% to 2% of all renal tumors. However, it is the most common benign mesenchymal tumor in the kidney. Most AMLs are isolated and occur sporadically (80%) and are typically identified in adults with mean age at symptomatic presentation of about 40 years with a strong female predilection with a female to male of 4 to 1[3]. Up to 20% of the AMLs occur in association with tuberous sclerosis complex (TSC), and approximately 50% of patients with TSC develop AMLs[4].

About 40% of AMLs are presented with acute severe hemorrhage and may cause hematuria, flank pain, acute abdomen, shock, and be a potentially life-threatening condition. The risk of bleeding is said to be proportional to the size of the tumor and increases significantly with size above 4 cm[3-5]. Based on an extensive literature review, it was reported that 82% of patients with AMLs larger than 4 cm in diameter were symptomatic, with 9% in hemorrhagic shock at the time of presentation. In contrast, the patients with smaller tumors were symptomatic only 23% of the time[4]. Therefore, the patients with AMLs larger than 4 cm or spontaneous rupture of AMLs need

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interventional selective arterial embolization (SAE) as the treatment of choice[6]. If SAE failed or AMLs have a large size, surgery may be performed, and some cases need for partial nephrectomy or radical nephrectomy[7].

Although clinically-insignificant, AMLs can be safely observed. Intervention is recommended for intractable pain, large size, suspicion of malignancy, and risk of life-threatening hemorrhage. Given the benign nature of AML, renal preserving treatment modalities such as nephron-sparing surgery (NSS) or selective renal artery angioembolization are preferred. To set a strategy for AML management, clinical prognosis according to tumor size, association with TSC, multiplicity, radiologic finding, and treatment modality were investigated[8].

Renal arterial embolization (RAE) is the treatment of choice for acute hemorrhage from AML. It is also the first-line prophylactic treatment for AML at risk of bleeding[6]. Nephrectomy may be performed if the patients had refractory symptoms, complex renal artery anatomy, or in the rare instance of diagnostic uncertainty[9]. If surgery was performed, a nephron sparing approach may be performed. Radiofrequency ablation, cryoablation, and microwave ablation are other alternative treatment options that may be used to reduce the size of AML greater than 30 mm. Everolimus has been assessed in study among TSC- and LAM-associated AML[10].

As compared to surgical nephrectomy, renal artery embolization has less renal parenchymal volume loss, a shorter recovery time, and generally fewer complications. However, up to 5% of initial embolization may require a repeat embolization. In less than 7% of the cases, there is subsequent nephrectomy after Renal artery embolization. Lesions with a higher rate for subsequent re-embolization and potentially nephrectomy include larger lesions, hypervascular lesions, multiple lesions, bilateral lesions, and patients with tuberous sclerosis, which have a higher tumor recurrence[11].

The assessment of clinical factors and different management of renal AMLs such as arterial embolization and partial or radical nephrectomy are useful in reducing complications and mortality rate.

Objective

The present study aimed to evaluate the clinical presentation and treatment outcomes of the renal AMLs in Phramongkutklao Hospital.

Materials and Methods

Research design

The present research was conducted as a retrospective analytic study.

Study population

All consecutive patients with a diagnosis of renal AMLs that attended the department of urological surgery and department of interventional radiology at Phramongkutklao Hospital between January 2002 and December 2019 were included in this study.

Inclusion criteria

All consecutive patients with a diagnosis of renal AMLs during the study period at Phramongkutklao Hospital.

Exclusion criteria

Patients with renal cell carcinoma (RCC) and transitional cell carcinoma.

Sample size estimation

All patients who met the inclusion criteria were included in the analysis. No sample size calculation was made.

Data collection

- The research proposal was approved by the Institutional Review Board Royal Thai Army Medical Department.
- Permission to access the medical records was allowed by the Director of Phramongkutklao Hospital.
- Data of the patients with diagnosis of renal AML between January 2002 and December 2019 was collected from electronic search at the Department of information technology (IT) and the radiological information system (RIS), and the picture archiving and communication system (PACS). AML can be diagnosed with identifying the well-circumscribed hyperechoic mass on ultrasound or the negatively attenuating intra-tumor macroscopic fat component (–20 HU or less) on non-enhanced CT.
- Demographic data such as age and gender, presenting symptoms, tumor size and numbers, type of AMLs such as sporadic or TSC-related, management surveillance, intervention type such as RAE or nephrectomy, and complications of intervention were recorded. Underlying TSC was diagnosed with genetic testing. Case-record form is demonstrated in appendix.
- The data were processed using a statistical program.

Statistical analysis

The data would be re-evaluated for correctness and recorded in data files, then statistically analyzed as followed:

- Demographic data of the patients was described as range, mean, median, standard deviation and frequency in percentage.
- Correlation between the tumor size and presentation symptoms or management was determined using chi-square test and independent t-test.
- A p-value of less than 0.05 was considered statistical significance.
- Analysis was performed using STATA/MP 12 (StataCorp LP, College Station, TX, USA).

Ethical consideration

The study was performed in a retrospective basis. No patients were requested to receive any intervention. The analyses of the data were performed without recording the patients' names or any personal information.

The study was carried out in accordance with the Declaration of Helsinki (2000) guidelines. Written informed consent was obtained from all participants. All procedures were approved by the Ethics Committee of the Institution Review Board of Royal Thai Army Medical Department [Certificated of Approval number: IRBRA 572/2563 (R072h/63_Exp)].

Results

Demographic data

During the study period, 63 patients were diagnosed as renal AML and found in 47 females (74.6%) and 16 males (25.4%) with a median age of 54.54±18.16 and a range of 8 to 84 years as shown in Table 1.

Clinical presentation of renal AMLs

Underlying TSC was diagnosed with genetic testing in seven patients (11.1%) and 56 patients (88.9%) had sporadic renal AMLs. Fifty-four patients had a solitary lesion on imaging, whereas nine patients had bilateral lesions. In a solitary lesion group, 25 patients had lesion on the left kidney and 29 patients had lesion on the right kidney. The lesion was incidentally discovered in 50 patients (79.4%) and were revealed due to symptoms in 13 patients (20.7%). Chief complaints included flank pain (n=10, 15.9%) and hematuria (n=3, 4.8%). Forty-six patients (73.0%) had AMLs smaller than 4 cm and 17 patients (27.0%) had AMLs of 4 cm or larger (Table 1, 2).

Table 1. Patients' demographic and clinical data

Variables	Statistics data; n (%)
Presentation symptoms	
Incidental	50 (79.4)
Flank pain	10 (15.9)
Hematuria	3 (4.8)
Age (year); mean±SD	54.76±18.16
Sex	
Female	47 (74.6)
Male	16 (25.4)
TSC	
No	56 (88.9)
Yes	7 (11.1)
Number of AML	
1	54 (85.7)
2	9 (14.3)
Side	
Both	9 (14.3)
Left	25 (39.7)
Right	29 (46.0)
Size (cm)	
<4	46 (73.0)
≥4	17 (27.0)
Follow up	
No	14 (22.2)
Yes	49 (77.8)
Arterial embolization	
No	59 (93.7)
Yes	4 (6.3)
Surgery	
No	48 (76.2)
Yes	15 (23.8)
Reason for converting to surgery	
Equivocal CT finding	5 (7.9)
Fail embolization	3 (4.8)
Fail surgery due to bowel adhesion	1 (1.6)
Refuse embolization	1 (1.6)
Progressive symptom after follow up	5 (7.9)
Death	
No	61 (96.8)
Yes	2 (3.2)

SD=standard deviation; TSC=tuberous sclerosis complex; AML=angiomyolipoma; CT=computed tomography

TSC-related renal AMLs

Underlying TSC was found in seven patients (11.1%) and 56 patients (88.9%) had sporadic renal

Table 2. Clinical presentation

	Presentation symptoms; n (%)			p-value
	Incidental (n=50)	Flank pain (n=10)	Hematuria (n=3)	
Age (year); mean±SD	54.04±19.09	57.3±16.41	58.33±4.51	0.827
Sex				
Female	36 (72)	8 (80)	3 (100)	0.508
Male	14 (28)	2 (20)	0 (0)	
TSC				
No	45 (90)	9 (90)	2 (66.7)	0.455
Yes	5 (10)	1 (10)	1 (33.3)	
Number of AML				
1	43 (86)	8 (80)	3 (100)	0.680
2	7 (14)	2 (20)	0 (0)	
Side				
Both	7 (14)	2 (20)	0 (0)	0.170
Left	17 (34)	5 (50)	3 (100)	
Right	26 (52)	3 (30)	0 (0)	
Size (cm); mean±SD	2.36±2.2	11.68±10.69	1.97±0.93	<0.001*
<4	40 (80)	3 (30)	3 (100)	0.003
≥4	10 (20)	7 (70)	0 (0)	
Follow up				
No	7 (14)	4 (40)	3 (100)	0.001
Yes	43 (86)	6 (60)	0 (0)	
Arterial embolization				
No	50 (100)	6 (60)	3 (100)	<0.001*
Yes	0 (0)	4 (40)	0 (0)	
Surgery				
No	43 (86)	4 (40)	1 (33.3)	0.002
Yes	7 (14)	6 (60)	2 (66.7)	
Reason for converting to surgery				
Equivocal CT finding	5 (10)	0 (0)	0 (0)	<0.001*
Fail embolization	0 (0)	3 (30)	0 (0)	
Fail surgery due to bowel adhesion	1 (2)	0 (0)	0 (0)	
Refuse embolization	1 (2)	0 (0)	0 (0)	
Progressive symptom after follow up	0 (0)	3 (30)	2 (66.7)	
Death				
No	49 (98)	9 (90)	3 (100)	0.399
Yes	1 (2)	1 (10)	0 (0)	

SD=standard deviation; TSC=tuberous sclerosis complex; AML=angiomyolipoma; CT=computed tomography

Chi-square test, * p<0.05 is statistical significance

AMLs. TSC was found in six female patients (85.7%) and one male patient (14.3). Six patients (85.7%) had a solitary lesion on imaging, whereas one patient (14.3%) had bilateral lesions. In a solitary lesion group, three patients (42.9%) had lesion on the left kidney and three patients (42.9%) had lesion on the right kidney. These patients (42.9%) with AMLs smaller than 4 cm and four patients (57.1%) with AMLs of 4 cm or larger. TSC-related renal AMLs with incidental found in five patients, flank pain in one patient, and hematuria in one patient. In TSC group, there was no statistically significant analysis (Table 3).

Table 3. TSC-related renal AML

	Size; n (%)		p-value	TSC; n (%)		p-value
	<4 cm (n=46)	≥4 cm (n=17)		No (n=56)	Yes (n=7)	
Presentation symptoms						
Incidental	40 (87.0)	10 (58.8)	0.003*	45 (80.4)	5 (71.4)	0.455
Flank pain	3 (6.5)	7 (41.2)		9 (16.1)	1 (14.3)	
Hematuria	3 (6.5)	0 (0)		2 (3.6)	1 (14.3)	
Age (year); mean±SD	55.78±18.17	52±18.39	0.468	55.52±17.12	48.71±25.95	0.354
Sex						
Female	33 (71.7)	14 (82.4)	0.39	41 (73.2)	6 (85.7)	0.474
Male	13 (28.3)	3 (17.6)		15 (26.8)	1 (14.3)	
TSC						
No	43 (93.5)	13 (76.5)	0.057	56 (100)	0 (0.0)	N/A
Yes	3 (6.5)	4 (23.5)		0 (0.0)	7 (100)	
Number of AML						
1	40 (87.0)	14 (82.4)	0.643	48 (85.7)	6 (85.7)	1
2	6 (13.0)	3 (17.6)		8 (14.3)	1 (14.3)	
Side						
Both	6 (13.0)	3 (17.6)	0.860	8 (14.3)	1 (14.3)	0.982
Left	19 (41.3)	6 (35.3)		22 (39.3)	3 (42.9)	
Right	21 (45.7)	8 (47.1)		26 (46.4)	3 (42.9)	
Size (cm)						
<4	46 (100)	0 (0.0)	N/A	43 (76.8)	3 (42.9)	0.057
≥4	0 (0.0)	17 (100)		13 (23.2)	4 (57.1)	
Follow up						
No	8 (17.4)	6 (35.3)	0.129	11 (19.6)	3 (42.9)	0.164
Yes	38 (82.6)	11 (64.7)		45 (80.4)	4 (57.1)	
Arterial embolization						
No	46 (100)	13 (76.5)	0.001*	52 (92.9)	7 (100)	0.465
Yes	0 (0.0)	4 (23.5)		4 (7.1)	0 (0.0)	
Surgery						
No	39 (84.8)	9 (52.9)	0.008*	43 (76.8)	5 (71.4)	0.754
Yes	7 (15.2)	8 (47.1)		13 (23.2)	2 (28.6)	
Reason for converting to surgery						
Equivocal CT finding	4 (8.7)	1 (5.9)	0.008*	5 (8.9)	0 (0.0)	0.089
Fail embolization	0 (0.0)	3 (17.6)		3 (5.4)	0 (0.0)	
Fail surgery due to bowel adhesion	0 (0.0)	1 (5.9)		0 (0.0)	1 (14.3)	
Refuse embolization	0 (0.0)	1 (5.9)		1 (1.8)	0 (0.0)	
Progressive symptom after follow up	3 (6.5)	2 (11.8)		4 (7.1)	1 (14.3)	
Death						
No	46 (100)	15 (88.2)	0.018*	55 (98.2)	6 (85.7)	0.075
Yes	0 (0.0)	2 (11.8)		1 (1.8)	1 (14.3)	

SD=standard deviation; TSC=tuberous sclerosis complex; AML=angiomyolipoma; CT=computed tomography

Chi-square test and independent t-test, * $p<0.05$ is statistical significance

Size of renal AMLs

To determine the potential difference in clinical outcomes according to tumor size, the subsets were analyzed by a cut off size of 4 cm. Patients with

Table 4. Management of renal AML

	Size (cm); n (%)		p-value
	Size ≥4 (n=17)	Size <4 (n=46)	
Follow up	11 (64.7)	38 (82.6)	0.129
Arterial embolization	4 (23.5)	0 (0.0)	0.001*
Surgery	8 (47.1)	7 (15.2)	0.008*
Presentation symptoms			
Incidental finding	10 (58.8)	40 (87.0)	0.014*
Flank pain	7 (41.2)	3 (6.5)	0.001*
Hematuria	0 (0.0)	3 (6.5)	0.281

SD=standard deviation; TSC=tuberous sclerosis complex; AML=angiomyolipoma; CT=computed tomography

Chi-square test, * p<0.05 is statistical significance

AMLs smaller than 4 cm were incidentally discovered (n=40, 87%) and were revealed due to symptoms such as flank pain (n=3, 6.5%), and hematuria (n=3, 6.5%). Patients with AMLs of 4 cm or larger were incidentally discovered (n=10, 58.8%) and were revealed due to symptoms such as flank pain (n=7, 41.2%), but not presented with hematuria (Table 3).

Management of renal AMLs

To determine the potential difference in clinical outcomes according to tumor size, the subsets were analyzed by a cut off size of 4 cm. Patients with AMLs smaller than 4 cm were mostly treated by follow up (n=39, 84.78%), and converted to surgery (n=7, 15.22) because equivocal CT findings (n=4, 8.7%) and symptomatic (n=3, 6.5%). Patients with AMLs of 4 cm or larger were treated by follow-up (n=11, 64.7%) then converted to arterial embolization (n=4, 23.5%) and converted to surgery (n=8, 47.1%) due to equivocal CT findings (n=1, 5.9%) and fail RAE (n=3, 17.6%) and refuse RAE (n=1, 5.9%) and progressive symptom after follow up (n=2, 11.8%) (Table 4).

A prophylactic procedure with renal AMLs size larger than 4 cm was found in four patients (23.5%) that underwent RAE. Fifteen patients underwent surgery due to equivocal CT finding (n=5, 7.9%), failed RAE (n=3, 4.8%), refused RAE (n=1, 1.6%), and symptomatic (n=5, 7.9%) such as flank pain (n=3) and hematuria (n=2) (Table 4).

Two patients with AMLs of 4 cm or larger died (11.8%). The patient with 36 cm AML that underwent RAE using coil and gelfoam followed by nephrectomy and died of postoperative complication. Another patient with 9.1 cm AML related TSC refused RAE and the tumor was slightly progress and underwent nephrectomy due to her concern, but the surgery failed due to bowel adhesion and death from AML at the postoperative period. The other patients with renal AMLs were still doing well (Figure 4).

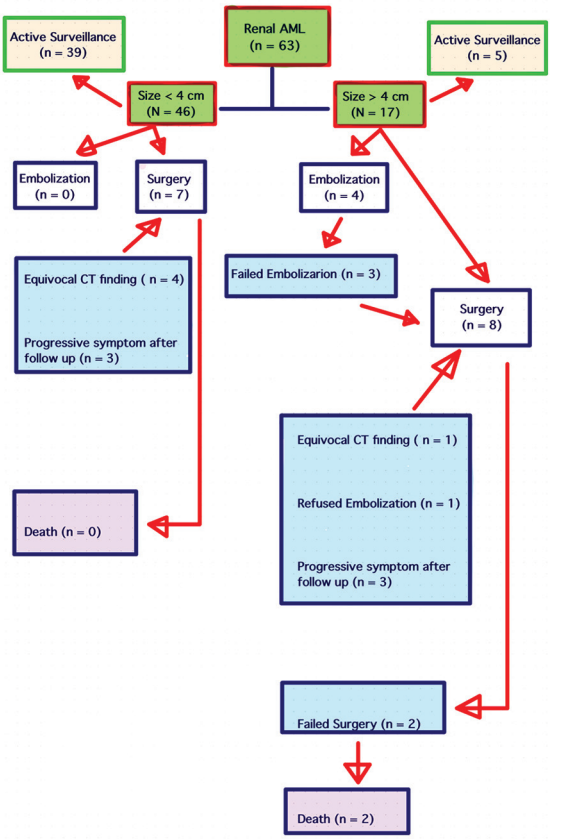

Figure 1. Management of renal AML.

Discussion

AMLs are recognized as hamartomatous lesions composed of heterogenous tissue components including blood vessels, smooth muscles, and fat. Renal AMLs occupy 1% to 3% of renal tumors and occur in two clinical spectrums, sporadic and those associated with TSC. TSC is an autosomal disease with various characteristics such as mental retardation, adenoma sebaceum, seizure, renal manifestations, and loss of heterozygosity of TSC1 and TSC2 genes. Although AML is uncommon among the general population, previous studies has shown that 20% of patients with TSC are known to develop AML while on the other hand, more than 50% of AMLs are associated with TSC. In this rare setting, tumors tend to be larger, develop earlier in life, and are more often multiple or bilateral.

The present study demonstrated a relatively low prevalence rate for TSC-associated AMLs

(11.1%), compared with 20% reported by Lendvay and Marshall[12]. However, significant differences in the clinical spectrum of TSC-association according to age at presentation, tumor size, symptom, and multiplicity correlated with those of the previous studies. TSC-associated AMLs tended to be more symptomatic, multiple, and bilaterally. Therefore, active surveillance is strongly recommended for asymptomatic tumors smaller than 4 cm, while angioembolization or surgical interventions with maximal parenchymal preservation including partial nephrectomy, enucleation, or wedge resection should be an alternative option for symptomatic tumors of 4 cm or larger. The authors reported a relatively large average tumor size for TSC-associated AML patients at 7.35 cm with a range 2.7 to 23.0 cm, compared with 6.6 cm reported by Harabayashi et al[13]. The authors' experience of two TSC-associated patients with tumors of 4 cm or larger who finally ended up with receiving a radical nephrectomy demonstrated that, although angioembolization could be a primary option in controlling existing or impending hemorrhages in spontaneous ruptured AMLs, a prophylactic radical nephrectomy is relatively recommended for tumors of 4 cm or larger or those refractory to angioembolization.

Small or less than 4 cm AMLs found incidentally have traditionally been managed conservatively, but follow-up is recommended to assess for growth. Tumors of 4 cm or larger or those having symptoms can be selectively embolized or resected with partial or radical nephrectomy. SAE is a treatment option for renal AMLs in both the elective and emergency setting.

With the advancement of non-invasive radiological imaging techniques, the detection of fat poor AMLs has recently surged in line with increased detection of incidental and asymptomatic small sized renal tumors. Although the diagnosis of AML is typically based upon presence of fat component on CT scans, many AMLs with a scant fat component may evade radiographic diagnosis. Fergany et al[14] described that solid renal tumors ought to be primarily considered as RCCs and surgical intervention are performed, since solid tumors originating from renal parenchyma are mostly malignant and that 85% to 90% are RCCs. McCullough et al[15] also recommended surgical treatment for tumors that are undistinguishable from RCC or those that contain calcification, a feature implying malignancy. In addition, Lemaitre et al[16] stated that 14% of AMLs demonstrated low fat content on radiographic imaging. However, of 63 AMLs in the present series, five patients (7.9%) had equivocal radiographic features prompting surgical management based on clinical suspicion of RCC. All five patients were surgically managed based on the previously established principle. Three patients who failed embolization was successfully treated with salvage nephrectomy.

However, there were some limitations in the present study. First, the study was a retrospective study with small sample size. Many patients were excluded from the study because of lacking follow-up data and received a variety the treatment. In addition, the modality of imaging used to follow-up was varied between the groups of patients. Second, the number of patients with TSC-related AMLs was too small to trace for the difference in the course of disease comparing with the non-TSC cases. Lastly, the efficacy should not be evaluated only upon the single criteria of tumor size. It may be evaluated by the absence of a bleeding episode at the end of long follow-up period, as well as by the disappearance of the vascular component of tumor. Therefore, prospective studies are required to confirm these findings and better evaluate the characteristic of AMLs and its clinical outcomes.

Conclusion

Significant differences in clinical manifestations and treatment outcomes of renal AMLs were noted in respect to tumor characteristics, association with TSC, and treatment modality. Considering the benign nature of AMLs, size, and association with TSC ought to be considered when deciding upon active surveillance or prophylactic intervention.

What is already know on this topic?

AML is the benign renal tumor, but some AMLs are presented with acute severe hemorrhage and may cause hematuria, flank pain, acute abdomen, shock, and potentially life-threatening condition.

What this study adds?

This report describes current trends in treatment of renal AMLs larger than 4 cm.

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Conflicts of interest

The authors declare no conflict of interest.

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