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Renal Angiomyolipoma: Beyond Size Criteria for Predicting Rupture

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ABSTRACT

Background: Renal Angiomyolipoma (AML) are vascular tumors that while histologically benign, carry a risk of potentially life threatening haemorrhage. Selective Arterial Embolization (SAE) has been demonstrated as effective treatment, however given most tumours are asymptomatic the challenge facing clinicians is in selection of which AML should undergo treatment. Historically size criteria have been used, but other factors such as tumour vascularity may help guide treatment choices.

Methods: Retrospective cohort analysis of all SAE treated AML at our quaternary level institution in the last ten years, evaluating tumour size, presence of intratumoral aneurysm and aneurysm size as a predictor of spontaneous haemorrhage.

Results: Twenty-seven renal AML underwent SAE. Five tumours had presented with spontaneous haemorrhage. Mean tumour size was 75.4 mm; there was no statistically significant size difference between ruptured and unruptured AML in our study population. 80% of ruptured AML contained at least one intratumoral aneurysm, 27% of unruptured contained an aneurysm (p-value <0.05). Mean aneurysm size in ruptured AMLs was 5.4 mm, unruptured 4.6 mm (p-value>0.05).

Conclusion: The presence of intratumoral aneurysm is a useful predictor for AML that are at risk of spontaneous haemorrhage, and should therefore be considered when selecting patients to undergo SAE.

Keywords: Renal Angiomyolipoma; Intratumoral aneurysm; Vascularity; Selective arterial embolization; Haemorrhage

INTRODUCTION

Angiomyolipoma (AML) are neoplasms consisting of vessels smooth muscle and fat originating from perivascular epitheloid cells. AML occur most commonly in the kidneys, but can also occur in other organ systems such as the liver, spleen and rarely in the skin or as isolated lesions in the retro peritoneum. While a rare malignant form, epitheloid angiomyolipoma does exist, renal AML are by convention considered a benign entity, without malignant or metastatic potential. AML are however hyper vascular, with fine feeding arteries accompanied by micro aneurysm. These tumours are

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therefore at risk of intratumoral haemorrhage, rupture and massive retroperitoneal or intraperitoneal haemorrhage. In the general population, the prevalence of renal AML is estimated between 0.3%-3% on autopsy series. Most AML occur sporadically, with approximately 10% associated with hereditary conditions, the most common (75%) being Tuberous Sclerosis Complex (TSC).

Tuberous sclerosis is a disease caused my loss of function mutations in TSC_1 or TSC_2 tumour suppressor genes, resulting in multiorgan hematoma formation. Renal AML are present in 25%-50% of patients with TSC. Other associated conditions include Von Hippel Lindau syndrome, neurofibromatosis type I and lymphagioleiomyomatosis. Given most AML are asymptomatic, tumours are predominantly (80%) found as incidental lesions on imaging. The presence of macroscopic faton computerized tomography is the hallmark imaging finding of AML. Approximately 5% of AML contain minimal or no fat visible on CT and are classified as lipid-poor. Other imaging modalities, namely magnetic resonance imaging with chemical shift artefactcan be utilized for confident diagnosis in the absence of tissue biopsy to differentiate from other renal masses such as renal cell carcinoma. Patients with TSC may undergo screening ultrasound for renal AML and renal cell carcinoma, with AML on ultrasound classically appearing as a well-defined, hyper echoic mass relative to normal renal parenchyma with acoustic shadowing. Due to the common prevalence of the renal AMLs, and that most are asymptomatic, it is difficult to accurately quantify the incidence of spontaneous haemorrhage. In prior studies reviewing active surveillance of known AMLs, the risk of spontaneous haemorrhage has been estimated at 2%. Oesterling, et al., published a management algorithm based on current evidence at time of publication in 1986 and their institutional experience with a case series of thirteen patients. A 4 cm cut-off was suggested for lesion size requiring management, with this size cutoff still incorporated into contemporary treatment decision making nearly four decades later. Numerous recent studies and guidelines have attempted to advance the decision around when to intervene on AMLs past this traditional 'rule of four', including considerations such as; lesion imaging characteristics, change over time and patient symptoms. Yamakado, et al., evaluated the relationship between tumour size, intratumoral aneurysm formation and spontaneous rupture in renal AML. From their analysis of 29 tumours in 23 patients they concluded that aneurysm size had greater specificity for AML rupture than tumour size. In their case series, as predictor of rupture, tumour size of 4 cm had a sensitivity of 100%, specificity 38%. Intratumoral aneurysm had a sensitivity of 100%, specificity 86%. Treatment options for AML include active surveillance, selective arterial embolization, surgical (nephron sparing surgery, nephrectomy) and pharmacological (mTOR inhibitors) [1-6].

MATERIALS AND METHODS

A retrospective cohort analysis of patients undergoing Selective Arterial Embolization (SAE) at our institution was performed. Our study population was all patients undergoing SAE at Royal Prince Alfred hospital, Sydney, Australia with data obtained from an institutional database that was commenced in 2011. The identified data was used, with ethics approval for data collection obtained from the Royal Prince Alfred hospital research governance office (X21-0472 and 2021/ETH12306). Patient demographics and co-morbidities were obtained from electronic medical records. AML size and location, lesion multiplicity, presence and size of intratumoral aneurysm and haemorrhage were evaluated independently by two radiologists (DB eight years' experience, SM five years' experience). When discrepancy between radiologists was encountered, the imaging was reviewed with a consensus decision used for analysis. If a patient had more than one AML, the ruptured tumour or alternatively largest tumour was used in data analysis. Lesion size was measured from 3D reformatted pre-procedural CT, with imaging performed on Siemens. Force multi detector CT with 0.75 mm axial acquisition slice thickness, reformatted in three planes to 3 mm. The greatest dimension in any imaging plane was assigned to AML size. Tumours were evaluated for the presence of intratumoral aneurysmon CT and catheter angiographic imaging. Aneurysm was defined as a vessel saccular out pouching of 2 mm, or fusiform dilation of 150%. Aneurysm measurement was performed from measurement calibrated angiographic imaging. When measurement calibration had not been performed at the time of SAE, retrospective calibration was completed between the coronal plane catheter angiogram and CT measurement of the mid portion of the ipsilateral renal artery. In our institution SAE is performed by multiple consultant interventional radiologists. All tumours are treated under anesthetist administered IV sedation or general anesthesia. Arterial access is *via* femoral arterial access, with a 5 or 6 sheath and micro catheter. Embolization technique varies, depending operator preference and lesion characteristics. Embolization techniques include PVA particles, micro coils, lipoid, ethanol or a combination. The procedure is managed as an overnight admission, with follow up phone consultation at six weeks post procedure. All patients receive follow up imaging within the first year post embolization (**Tables 1-3** and **Figure 1**) [7-11].

Table 1: The (means) beyond size criteria for predicting rupture.

			Means				
Rupture	N Obs	Factor	N	Mean	Std dev	Minimum	Maximum

Rupture (-)	22	Tumour size (cm)	22	7.486364	3.805672	3.3	21.7
		Aneurysm size (mm)	6	4.633333	2.325224	1.1	8.4
Rupture (+)	5	Tumour size (cm)	5	7.8	2.460691	6.1	12
		Aneurysm size (mm)	4	5.375	3.435477	2	9.9

Table 2: The (Univariate Analysis) beyond size criteria for predicting rupture.

Univariate analysis				
Factor	**Coefficient (β)**	**Standard error**	**t-value**	**P-value**
Tumour size (cm)	0.00389	0.02225	0.17	0.8627
Aneurysm size (mm)	0.02792	0.06788	0.41	0.6917

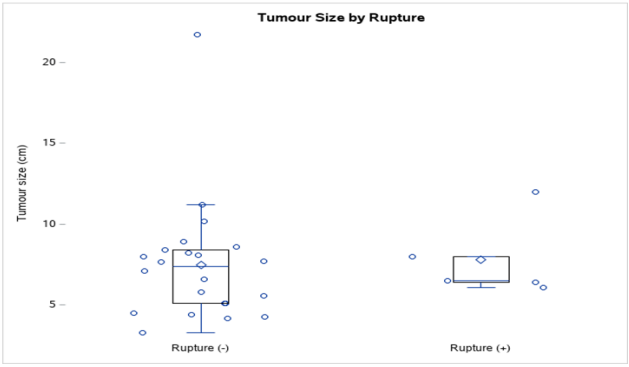

Figure 1: Tumar size by rupture.

Stastical Analysis

Normally distributed continuous variables (tumour size, aneurysm size) were analyzed using students t-test. Categorical variables (presence of aneurysm) was analyzed with Fishers exact test. Unitarian and multivariate logistical regression analysis was performed to identify significant predictors of spontaneous haemorrhage. A p-value <0.05 was considered significant (**Table 3** and **Figure 2**).

Table 3: Multiple Regression of the differential values.

Multiple regression				
Factor	**Coefficient (β)**	**Standard error**	**t value**	**P value**
Intercept	0.32853	1.6729	0.2	0.8569
Age	0.000345	0.02763	0.01	0.9908
Tumour size (cm)	-0.01824	0.1112	-0.16	0.8801
Sex	-0.07856	0.81807	-0.1	0.9296
Multiplicity	0.10384	0.91777	0.11	0.9171
Aneurysm size (mm)	0.03038	0.1994	0.15	0.8886

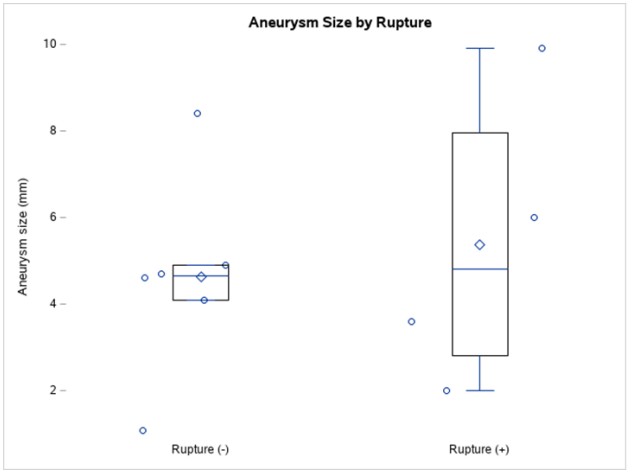

Figure 2: Aneurysm size by rupture.

RESULTS

Twenty-seven patients were included in the study. Mean patient age was 46.3 years (range 31-74). Twenty-one patients were female (78%), six male (22%). Seven patients had known TSC (26%). Eleven patients (40.7%) were symptomatic prior to selective arterial embolization. If present, the most common symptom was pain, followed by haemorrhage and hematuria. Sixteen patients (59.3%) were asymptomatic. In the study population, tumour size ranged from 23 mm to 217 mm (mean 75.4 mm). Ten tumours (37.0%) contained vascular aneurysms on review of CT and catheter angiographic imaging. Five patients (18.5%) presented with acutetumour associated spontaneous haemorrhage. Mean tumour size for this cohort of patients was 7.8 cm (range 6.1 cm-12.0 cm). The remaining twenty two patients in the study did not have associated haemorrhage, with mean tumour size 7.5 cm (range 3.3 cm-21.7 cm). Univar ate analysis of tumour size as a predictor of rupture did not produce statistically significant result (p-value 0.87) in our study population of the five AMLs that had ruptured; four contained at least one intratumoral aneurysm. In the twenty two patients in the study without tumour associated spontaneous haemorrhage mean, six (27.3%) contained intratumoral aneurysm. Fishers exact test statistical value for this observed difference is 0.0473 ($p < 0.05$), a statistically significant result. Assessing aneurysm size, within the ruptured AML cohort aneurysm size ranged from 2.0 mm to 9.9 mm (mean 5.4 mm). In non-ruptured AML, aneurysm size ranged from 1.1 mm to 8.4 mm (mean 4.6 mm). Intratumoral aneurysm size was also not a statistically significant predictor of tumour rupture (p-value 0.69). Multiple regression analysis was used to control for variables such as patient age, sex and the presence of multiple tumours in a single patient however tumour size and intratumoral aneurysm size remained statistically insignificant predictors of tumour rupture. Two of the ruptured aneurysms required further management after initial SAE. One requiring re-embolization and one nephrectomy. Two non-ruptured AMLs required further or repeated treatment following initial SAE. There was no significant change in serum creatinine for any patient post SAE (**Figures 3-5**) [12-14].

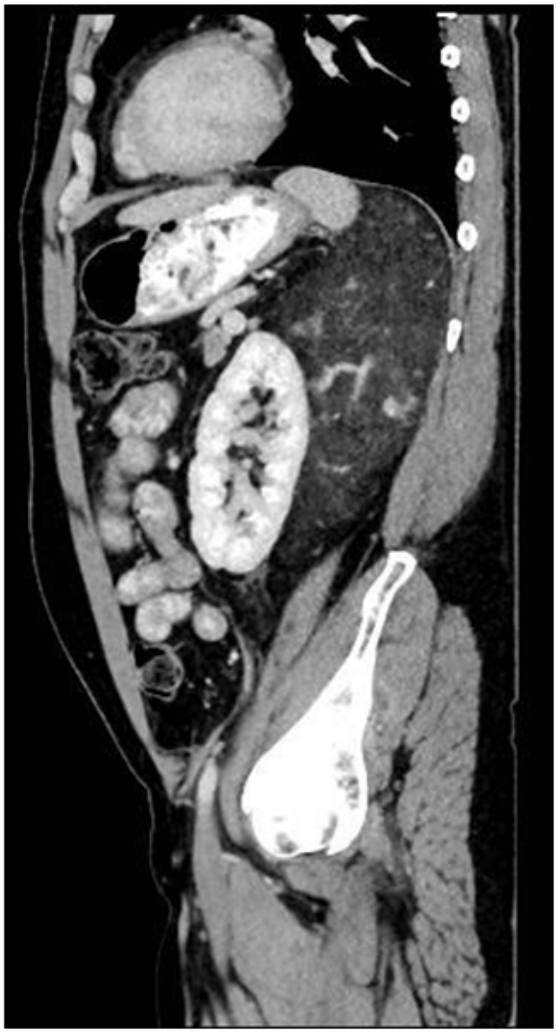

Figure 3: Arising from the left kidney, a predominately fat containing angiomyolipoma, with tortuous and dilated intratumoral vessels. There are multiple small saccular aneurysms within the tumor.

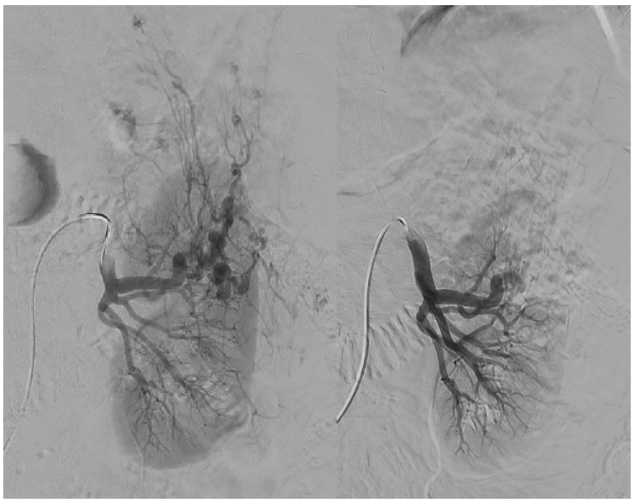

Figure 4: Catheter angiogram of the left renal artery in the same patient redemonstrates the presence of multiple small aneurysms within the AML. Post embolidaiton demonstrates exclusion of tumour supply vessels with maintained arterial supply to the upper pole cortex.

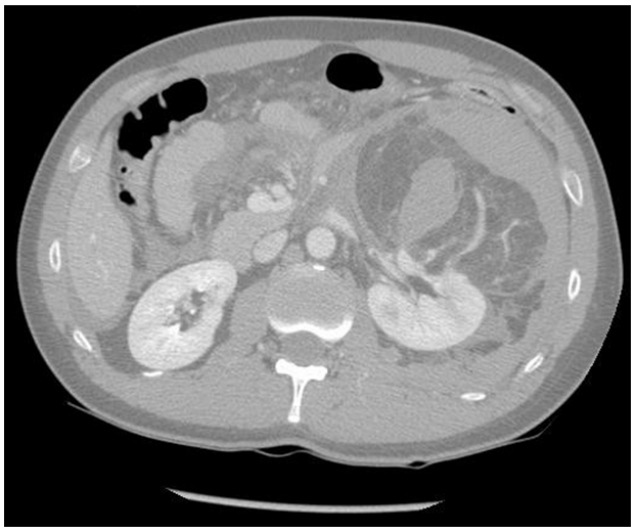

Figure 5: Axial CT slice from separate patient demonstrates a large left renal angiomyolipoma with spontaneous intratumoral haemorrhage. Haemorrhage has ruptured to the retroperitoneal space.

DISCUSSION

Our study population and results demonstrate a statistically significant difference in the presence of intratumoral AML aneurysm in patients with spontaneous haemorrhage and those without spontaneous haemorrhage. There was however, no difference in AML tumour size in these two groups, and aneurysm size was also not a predictor of spontaneous haemorrhage. This outcome is of benefit to the interventional radiologists in selecting patients to undergo selective arterial embolization. Since its description in the 1970's, SAE of renal Angiomyolipoma has offered a treatment modality that can be effective and well tolerated by patients. SAE has been demonstrated to decrease tumour volume, decrease risk of haemorrhage and successfully manage acute haemorrhage. As previously discussed, one of the main challenges facing the interventional radiologist as part of a clinical management team is selecting which tumours to treat. Historically the main imaging factor utilized for predicting AML rupture, and therefore selecting tumours for treatment, has been tumour size. Since publications by Oesterling, other studies have confirmed the correlation between tumour size and risk of haemorrhage. In the pursuit of advancing clinical decision making past the 'rule of four' Yamakado, et al., demonstrated a significant relationship between tumour size, aneurysm size, and spontaneous rupture in their series of 23 patients. Our study of 27 treated AML contributes to extending the body of evidence for management of AML. While there is discrepancy with other studies around the role of tumour size as predictor of tumour spontaneous haemorrhage, the differences in our results with previous studies such as Yamakado, et al., is not necessarily a contradiction of evidence. Our study population shared some similar characteristics to the Japanese cohort; including mean age (46 years, 43 years), and sex (78% female, 74% female). However, the overall prevalence of spontaneous haemorrhage between the two studies was disparate; Yama ado eight of twenty-three patients (35%), our study population five of twenty-seven (19%). The Yamakado patient population was collected between 1990 and 2001, twenty years before our study population. In the intervening two decades the increased detection of asymptomatic AMLs though the increased utility of diagnostic CT and MRI may explain why patient parameters are equivocal between studies but with a discrepancies between rate of spontaneous haemorrhage. This relatively low rate of spontaneous haemorrhage in our small contemporary study population likely meant our study was underpowered to re-establish the findings of Yamakado et al for tumour and aneurysm size. Our study serves to highlight the importance of recognizing intratumoral imaging characteristics of renal. AML when selecting which to undergo treatment or conservative management, beyond historical size criteria. A major limitation of our study results with respect to the presence of intratumoral aneurysm as a predictor of haemorrhage is that aneurysms within AML are more readily detected on catheter angiography than CT.

CONCLUSION

Our study demonstrates that in patient selection for selective arterial embolization of renal angiomyolipoma, interventional radiologists and indeed all clinicians must continue to look beyond simple tumour size criteria. We believe than any patient with detected intratumoral AML aneurysm should be strongly considered for SAE.

DISCLOSURE

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