Surveillance imaging for sporadic renal angiomyolipoma less than 40 mm: lessons learnt and recommendations from the experience of a large district general hospital

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ABSTRACT

INTRODUCTION Sporadic renal angiomyolipomas, although benign in nature can cause life-threatening spontaneous haemorrhage. Surveillance of smaller lesions is recommended but there is no guidance on the surveillance interval or modality. Our aim was to study our sporadic angiomyolipoma population to determine the growth rate, factors that were associated with a higher growth rate and design a surveillance programme.

MATERIALS AND METHODS All sporadic renal angiomyolipomas diagnosed between September 2009 and March 2015 were included. Patients with a diagnosis of tuberous sclerosis were excluded.

RESULTS A total of 217 sporadic renal angiomyolipomas were diagnosed. The median follow-up was 24 months (range 10–118 months). The median size at diagnosis was 9.00 mm with a mean growth rate of 0.13 mm/year (standard deviation 0.88). One hundred and fifty angiomyolipomas (69%) were shown to have negative or zero growth. In the remaining 67, 59 had a growth rate of less than 2.00 mm/year. Size of angiomyolipoma, tumour burden and age were not associated with a higher growth rate on multivariate analysis.

CONCLUSION The majority of sporadic angiomyolipomas are small and do not grow. Our practice is to perform surveillance for those greater than 20 mm, with five-yearly ultrasound scans for 21–29 mm, and two-yearly surveillance for 30–39 mm tumours.

KEYWORDS

Angiomyolipoma – Surveillance – AML – Sporadic – Growth rate

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Introduction

Angiomyolipomas are benign mesenchymal tumours. The majority arise sporadically but a small proportion are hereditary and are associated with tuberous sclerosis (TSC-AML). Although these tumours are benign in nature, they can grow and have a risk of spontaneous haemorrhage. The current European Association of Urology guidelines recommend active surveillance for small angiomyolipomas with intervention for women of childbearing age, those who have poor access to emergency services and those with large tumours.¹ Historical data suggest that angiomyolipomas greater than 40 mm were associated with an increased risk of symptoms and spontaneous haemorrhage, and were more likely to require surgical intervention.^{2–9} More recently this, size cut-off point has been disputed.^{4,5,10–12}

Interventions for angiomyolipoma include partial nephrectomy or nephrectomy, mechanistic targeting of rapamycin (mTOR) inhibitors and selective arterial embolisation. The majority of studies investigating angiomyolipomas have included tuberous sclerosis patients in their analysis. Angiomyolipomas in these patients have a tendency for more aggressive behaviour, with higher rates of spontaneous haemorrhage, a faster growth rate and a higher incidence of intervention.^{2,13,14} They are also more likely to recur following intervention.¹⁵

The incidence of sporadic angiomyolipoma is estimated at 0.44% of the population, with the majority diagnosed incidentally in asymptomatic patients.^{16,17} The incidence is rising due to the increased use of diagnostic imaging. Although surveillance of angiomyolipoma is recommended, there is no consensus on the ideal modality for scanning or

time interval between scans. To tailor our surveillance programme to our local population, we evaluated patients with sporadic angiomyolipoma in our hospital trust to determine the growth rate of sporadic angiomyolipoma and factors associated with a higher growth rate to devise an optimal surveillance schedule.

Patients and methods

All patients with sporadic angiomyolipoma diagnosed between September 2009 and March 2015 were entered into a prospectively maintained database. Patients with a follow-up of less than 10 months were removed from the study to enable calculation of meaningful growth rate data. In addition, any patient with angiomyolipoma who underwent selective arterial embolisation within 10 months of diagnosis was also excluded. Lesions in which there was diagnostic uncertainty were not included. Any other patient with angiomyolipoma who underwent selective arterial embolisation after a period of 10 months was included in the study until the point of embolisation.

Data were collected for maximum measured size of angiomyolipoma, tumour burden (multiple or bilateral tumours), imaging modality and date, patient demographics and selective arterial embolisation where this had occurred. Rationale for terminating surveillance was also recorded. Diagnostic imaging was either by ultrasound or computed tomography (CT).

Statistical analysis

Growth rate was calculated by subtracting diagnosis size from the last recorded size and dividing by the number of years. Linear regression analysis was used to determine if there was an association between growth rate and overall size or age. The Mann-Whitney U test was used to calculate if there was an association between growth rate and gender or tumour characteristics (e.g. multiple tumours vs single tumours vs bilateral tumours).

Results

Patient demographics are shown in Table 1. A total of 217 angiomyolipomas were diagnosed in 187 patients (23 multiple angiomyolipomas). Eighty per cent of the patients were female (151/187) and the median age was 61 years (range 20–89 years). The median follow-up was 24 months (range 10–118 months). The median size at diagnosis was 9.00 mm (range 3.00–86.00 mm) with a mean overall growth rate of 0.13 mm/year with a standard deviation of 0.88 (Fig 1). Of the 217 angiomyolipomas, 150 (69%) were shown to have a negative (17%) or zero growth (52%). In the remaining 67, 59 had a growth rate of less than 2.00 mm/year. Eight angiomyolipomas had a growth rate of greater than 2.00 mm/year to a maximum of 2.67 mm/year.

A total of six patients with angiomyolipoma underwent selective arterial embolisation. Half of these ($n = 3$) underwent selective arterial embolisation within 10 months of diagnosis and so were removed from the overall analysis.

Table 1 Patient demographics and angiomyolipoma characteristics

Demographic or characteristic	Value
Age (years) median (range)	61 years (20–89)
Male (n)	37
Female (n)	150
Follow up (months) median (range)	24 (10–118)
Size at diagnosis (mm) median (range)	9.00 (3–86)
Growth rate (mm/year) mean (SD)	0.13 (0.88)
Single (n)	164
Angiomyolipoma (n):	
Multiple (≥ 2 unilateral)	19
Bilateral (1 in both kidneys)	15
Bilateral and multiple (≥ 3 bilaterally)	19

The remaining three tumours were included until the point of selective arterial embolisation. One patient with two angiomyolipomas in one kidney is awaiting selective arterial embolisation because of size progression above 40 mm. No patients required surgery or mTOR inhibitors. No patient under surveillance experienced acute spontaneous haemorrhage.

Factors affecting growth rate

There were no significant differences in growth rate when single angiomyolipomas were compared with those with a greater tumour burden (multiple, bilateral or multiple and bilateral tumours). Gender, age and size at diagnosis did not have an impact on the growth rate.

Figure 1 Growth rate histogram

Imaging modality

Overall, there were 755 scans performed over the follow-up period. The majority of these (93%) were ultrasound (703). The remainder (52) were CT. The diagnosis was made by ultrasound in the majority of cases (90%). Of the 705 ultrasound scans performed, 52 of these were performed by radiologists. The remainder (653), were performed by trained radiographers. Ultrasound was not successful in visualising the angiomyolipoma in one patient (diagnosis made incidentally on CT) despite repeated attempts. There were five instances where ultrasound was not successful at visualising the tumour when it had been seen on previous or subsequent ultrasound scans.

Patient follow-up

During the surveillance period, 29 patients (31 angiomyolipomas) were lost to follow-up after minimum surveillance of 10 months. The mean follow-up for these patients was 24 months. Seven patients were diagnosed with a separate, palliative disease during surveillance and so surveillance was stopped. Five patients died from causes not related to their tumour. Thirty-Seven angiomyolipomas were discharged due to lack of size progression (Fig 2). The mean follow-up in patients discharged was 49 months.

Discussion

The uptake of widespread abdominal imaging has lead to an increase in the detection of sporadic renal angiomyolipomas, 80% of which are found incidentally. Although these are benign in nature, they can grow to large sizes and rarely can cause spontaneous haemorrhage. The natural history of sporadic angiomyolipoma is poorly understood and therefore, although the current guidelines recommend surveillance of smaller tumours, there is no guidance on the suitable timing or modality of follow-up. Sporadic angiomyolipomas have a significantly different behaviour to TSC-AMLs and many consider them to be a

different disease.¹² The majority of early studies, which formed the basis for the management of angiomyolipoma, included both these forms in their analyses. The gradual increase in prevalence of sporadic angiomyolipoma has resulted in a decrease in the reported growth rate in more recent literature 0.2–0.8 mm/year.^{10,11,16,18} The majority of angiomyolipomas in our series were small at diagnosis (median 9.00 mm) and 69% of lesions showed no growth (52%) or were smaller on subsequent imaging (17%). The diagnosis of an angiomyolipoma was made using ultrasound as the predominant imaging modality. This potential source of selection bias could explain why the tumours in our series were small in comparison with other studies. There was no association between size at diagnosis, gender, age or tumour burden and growth rate on multivariate analysis. This is in contrast to MacLean *et al.*,¹⁸ who found a higher growth rate with larger lesions, greater tumour burden and at a younger age. They included TSC-AMLs in their cohort, which are known to have a greater need for intervention with a higher tumour burden and this could explain the differences with our results.¹⁹

The decrease in size seen in 17% of angiomyolipomas was an unexpected finding. This may be due to genuine fluctuation in tumour size or, more likely, is a reflection on the limitations of ultrasound in the measurement of very small lesions, which have a margin of error of between 1 mm and 7 mm when compared with CT.^{18,20} In the angiomyolipomas that did demonstrate an increase in growth, 59/67 (88%) of these patients had a mean growth of less than 2.00 mm/year. The remaining 8/67 (12%) had a growth rate up to a maximum of 2.67 mm/year. This represents only 3.70% of our overall cohort. Based on our findings, we agree with MacLean *et al.* that angiomyolipomas of less than 20 mm do not need to continue routine surveillance. Our local surveillance policy is to perform five-yearly ultrasound scans for patients with tumours between 21 mm and 29 mm and two-yearly those with tumours of 30–39 mm (Fig 3). Surveillance is stopped if the

Figure 2 Patient follow-up flowchart (FU = follow-up)

angiomyolipoma remains the same size or is smaller on follow-up imaging. Although the evidence surrounding intervention for angiomyolipomas of greater than 40 mm is still disputed, we discuss the rationale for intervention or continued surveillance with our patients who have angiomyolipomas greater than 40 mm.

Several studies have reported an increased incidence of spontaneous haemorrhage in patients who have lesions greater than 40 mm.^{5,6,9,21} Increased need for intervention is also noted at larger sizes and with symptomatic lesions; however, the reasons for intervention are multifactorial (increased size, suspicion of malignancy and continuing symptoms, e.g. visible haematuria) and do not necessarily reflect an increased risk of spontaneous haemorrhage.^{2,5,7,8,22} Spontaneous haemorrhage is also not restricted to a size greater than 40 mm⁴ with lesions as small as 20 mm leading to haemorrhage⁸ and it is recognised that, although size is important, it is not the only factor contributing to risk of haemorrhage.¹² Angiographic studies have identified microaneurysms in 80% of angiomyolipomas where there was spontaneous haemorrhage. These were also more common with larger tumours, with none seen in those less than 40 mm in comparison with 50% of those greater than 40 mm.²⁵ Likewise, Yamakado *et al.* also showed larger aneurysm sizes in ruptured angiomyolipomas compared with those without rupture and this was more sensitive than overall size at predicting risk of haemorrhage.⁹ It would appear that both size and vascularity are important factors in determining risk of spontaneous haemorrhage and an assessment of vascularity may

become increasingly useful in determining which patients would be best suited for prophylactic treatment to prevent spontaneous haemorrhage.

Conclusion

Interpretation of the research into angiomyolipoma is challenging because of the small cohort sizes, lack of distinction between TSC-AMLs and sporadic angiomyolipomas, and the lack of clarity in decisions behind intervention. Size and vascularity appear to be the important factors in predicting the risk of spontaneous haemorrhage. There is a belief that large angiomyolipomas began as smaller tumours which have grown over time. Although this is a sensible assumption, the natural history of these large angiomyolipomas is not clear and they are rare when compared with the large number of very small angiomyolipomas that are detected. This suggests that perhaps these are two distinct groups of patients; those that grow and those that do not. Our study presents the experience of a large district general hospital in the management of sporadic renal angiomyolipoma. The majority of angiomyolipomas are small and do not grow and therefore we only recommend surveillance for angiomyolipomas greater than 20 mm, with five-yearly surveillance for 21–29 mm lesions and two-yearly surveillance for 30–39 mm lesions. The aim of our recommendation is to identify angiomyolipomas with a higher growth rate while also minimising unnecessary investigations in patients with angiomyolipoma where growth is negligible. We welcome further research into the

vascularity of angiomyolipomas, which may help to better understand the natural history of these lesions.

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References

1. Ljungberg B, Bensalah K, Canfield S *et al*. EAU guidelines on renal cell carcinoma: 2014 update. *Eur Urol* 2015; **67**(5): 913–924.
2. Steiner MS, Goldman SM, Fishman EK, Marshall FF. The natural history of renal angiomyolipoma. *J Urol* 1993; **150**(6): 1,782–1,786.
3. Chen SS, Lin AT, Chen KK, Chang LS. Renal angiomyolipoma: experience of 20 years in Taiwan. *Eur Urol* 1997; **32**(2): 175–178.
4. Kessler OJ, Gillon G, Neuman M *et al*. Management of renal angiomyolipoma: analysis of 15 cases. *Eur Urol* 1998; **33**(6): 572–575.
5. Dickinson M, Ruckle H, Beagler M, Hadley HR. Renal angiomyolipoma: optimal treatment based on size and symptoms. *Clin Nephrol* 1998; **49**(5): 281–286.
6. De Luca S, Terrone C, Rossetti SR. Management of renal angiomyolipoma: a report of 53 cases. *BJU Int* 1999; **83**(3): 215–218.
7. Tsai HN, Chou YH, Shen JT *et al*. The management strategy of renal angiomyolipoma. *Kaohsiung J Med Sci* 2002; **18**(7): 340–346.
8. Seyam RM, Bissada NK, Kattan SA *et al*. Changing trends in presentation, diagnosis and management of renal angiomyolipoma: comparison of sporadic and tuberous sclerosis complex-associated forms. *Urology* 2008; **72**(5): 1,077–1,082.
9. Yamakado K, Tanaka N, Nakagawa T *et al*. Renal angiomyolipoma: relationships between tumor size, aneurysm formation, and rupture. *Radiology* 2002; **225**(1): 78–82.
10. Mues AC, Palacios JM, Haramis G *et al*. Contemporary experience in the management of angiomyolipoma. *J Endourol* 2010; **24**(11): 1,883–1,886.
11. Bhatt JR, Richard PO, Kim NS *et al*. Natural history of renal angiomyolipoma (AML): most patients with large AMLs >4cm can be offered active surveillance as an initial management strategy. *Eur Urol* 2016; **70**(1): 85–90.
12. Ribal MJ. Challenging already established statements on the therapy of renal angiomyolipoma. *Eur Urol* 2016; **70**(1): 91–92.
13. Sooriakumaran P, Gibbs P, Coughlin G *et al*. Angiomyolipomata: challenges, solutions, and future prospects based on over 100 cases treated. *BJU Int* 2010; **105**(1): 101–106.
14. Bissler J, Cappell K, Charles H *et al*. Rates of interventional procedures in patients with tuberous sclerosis complex-related renal angiomyolipoma. *Curr Med Res Opin* 2015; **31**(8): 1,501–1,507.
15. Kothary N, Soulen MC, Clark TW *et al*. Renal angiomyolipoma: long-term results after arterial embolization. *J Vasc Interv Radiol* 2005; **16**(1): 45–50.
16. Fittschen A, Wendlik I, Oeztuerk S *et al*. Prevalence of sporadic renal angiomyolipoma: a retrospective analysis of 61,389 in- and out-patients. *Abdom Imaging* 2014; **39**(5): 1,009–1,013.
17. Al-Thani H, El-Menyar A, Al-Sulaiti M *et al*. Clinical presentation, management, and outcome of patients with incidental renal angiomyolipoma in qatar. *Oman Med J* 2014; **29**(6): 419–424.
18. Maclean DF, Sultana R, Radwan R *et al*. Is the follow-up of small renal angiomyolipomas a necessary precaution? *Clin Radiol* 2014; **69**(8): 822–826.
19. Eijkemans MJ, van der Wal W, Reijnders LJ *et al*. Long-term follow-up assessing renal angiomyolipoma treatment patterns, morbidity, and mortality: an observational study in tuberous sclerosis complex patients in the Netherlands. *Am J Kidney Dis* 2015; **66**(4): 638–645.
20. Ray AA, Ghiculete D, Pace KT, Honey RJ. Limitations to ultrasound in the detection and measurement of urinary tract calculi. *Urology* 2010; **76**(2): 295–300.
21. Ouzaid I, Autorino R, Fatica R *et al*. Active surveillance for renal angiomyolipoma: outcomes and factors predictive of delayed intervention. *BJU Int* 2014; **114**(3): 412–417.
22. Kuusk T, Biancari F, Lane B *et al*. Treatment of renal angiomyolipoma: pooled analysis of individual patient data. *BMC Urol* 2015; **15**: 123.
23. Champagnac J, Melodelima C, Martinelli T *et al*. Microaneurysms in renal angiomyolipomas: Can clinical and computed tomography features predict their presence and size? *Diagn Interv Imaging* 2016; **97**(3): 321–326.
24. Ramon J, Rimon U, Garniek A *et al*. Renal angiomyolipoma: long-term results following selective arterial embolization. *Eur Urol* 2009; **55**(5): 1,155–1,161.
25. Takebayashi S, Horikawa A, Arai M *et al*. Transarterial ethanol ablation for sporadic and non-hemorrhaging angiomyolipoma in the kidney. *Eur J Radiol* 2009; **72**(1): 139–145.
26. Patatas K, Robinson GJ, Ettles DF, Lakshminarayan R. Patterns of renal angiomyolipoma regression post embolisation on medium- to long-term follow-up. *Br J Radiol* 2013; **86**(1024): 20120633.