Original Article

Natural History and Management of Ultrasound-detected Small Renal Angiomyolipoma

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Abstract

Background: Recent advances in imaging methods increased the incidental detection of small renal angiomyolipoma (AML). However, guidelines for managing small AML are lacking, and decisions about imaging frequency and timing of intervention are made on an individual basis. This study aims to investigate the clinical behavior of small sporadic AML and propose an optimal follow-up strategy. **Methods:** The study is a retrospective analysis of 168 individuals who had hyperechoic lesions, suggestive of AML detected during abdominal ultrasound as a part of their health checkup. The clinical information of the individuals, including tumor characteristics and renal function, was reviewed. Statistical analysis was performed to identify factors associated with tumor growth and renal function. **Results:** Most AMLs were small (≤20 mm) and did not exhibit malignant characteristics. The tumors showed a slow growth rate, with a mean growth rate of 0.24 mm/year. Only a small proportion of cases (1.2%) required intervention due to significant enlargement. Factors such as tumor size and gender were not significantly associated with tumor growth rate or renal function. However, younger patients showed a higher tumor growth rate and a more pronounced decline in renal function. **Conclusion:** Small sporadic AMLs have a slow growth rate and little risk of malignancy. Neither tumor size nor gender was predictive factors for tumor growth or renal function. Nevertheless, close monitoring of tumor growth and renal function is advised, particularly in younger patients. This study highlights the need for further research and guidelines to establish an optimal surveillance protocol for small AMLs.

Keywords: Growth rate, natural history, renal angiomyolipoma, ultrasonography

Introduction

Renal angiomyolipoma (AML) represents the most prevalent benign neoplasm affecting the kidney, constituting approximately 0.3%–3% of all renal tumors.[1] The majority of cases (around 80%) occur sporadically, while the remaining cases are associated with pulmonary lymphangioleiomyomatosis or tuberous sclerosis complex (TSC).[2,3] Imaging modalities play a pivotal role in both the diagnosis and management of AMLs.[4] These tumors comprise variable proportions of three distinct components, namely, vascular, muscular, and adipose tissues, which manifest as distinct imaging characteristics. The cardinal diagnostic criterion for the classic presentation of AML involves the identification of a substantial adipose tissue content through radiological imaging techniques. A characteristic manifestation of a fat-rich AML is the presence of hyperechoic lesions exhibiting comparable brightness to the renal sinus, accompanied by posterior acoustic shadowing.[5] Due to such distinctive features and the increasing availability of imaging methodologies, the incidental detection of small AMLs during imaging examinations for unrelated conditions or routine health checkups has risen. The motivation behind subsequent monitoring and further investigation of incidentally detected AMLs stems from the concern of potential malignancy, as a noteworthy proportion (up to 30%) of small renal cell carcinomas can also appear hyperechoic on ultrasound examination (USG).[6] Conversely, studies have revealed that a substantial portion of AMLs identified through USG exhibit no growth or malignant characteristics.[7,8] Despite the abundance of literature concerning the treatment of larger AMLs,[9-11] there is a lack of definitive guidelines for managing

Received: 15-06-2023 **Revised:** 08-07-2023 **Accepted:** 18-07-2023 **Available Online:** 10-01-2024

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jmut

DOI: 10.4103/jmu.jmu_73_23

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How to cite this article: Kobayashi M, Yokoyama M, Yuki H, Kamai T. Natural history and management of ultrasound-detected small renal angiomyolipoma. J Med Ultrasound 2024;32:154-60.

sporadic AMLs with regard to the frequency of imaging assessments or the preferred imaging modality. Consequently, decisions regarding these aspects should be based on the individual clinical scenario and patient history. Thus, our investigation aims to explore the clinical behavior of small hyperechoic lesions suggestive of sporadic AMLs detected during health checkups, with the intention of proposing an optimal follow-up strategy.

Materials and Methods

We conducted a retrospective study encompassing individuals who exhibited hyperechoic lesions in the kidneys, suggestive of AML during abdominal ultrasound examination as a part of their health checkup at our medical facility, spanning the period from October 2008 to July 2022. Individuals demonstrating features indicative of an association with TSC were deliberately excluded from the analysis. The classical manifestation of AML on USG was characterized by the presence of hyperechoic lesions displaying similar echogenicity to the renal sinus, attributed to their adipose composition. Only individuals who were subject to a follow-up duration exceeding 6 months and underwent a minimum of 2 imaging assessments were included in our investigation. The index date was defined as the initial identification of the hyperechoic lesions. We meticulously reviewed the clinical information of the individuals, encompassing parameters such as the maximum length of the lesions and tumor burden (including the presence of multiple, bilateral, or multicentric tumors) at the index date. To determine the tumor growth rate, we employed a linear regression model, generating a line of best fit to represent the growth trajectory of each individual mass. The estimated glomerular filtration rate (eGFR) was calculated using the chronic kidney disease (CKD) epidemiology collaboration equation.[12] Furthermore, we determined the slope of eGFR change by considering the data available at the index date and the most recent value, adjusting for the duration of observations and interpolating to a 1-year interval, denoted as the eGFR slope. Ultrasound examinations were performed utilizing the Xario 200 system (Cannon Medical Systems, Tochigi, Japan) equipped with a convex probe (PVU-375BT, 2-5MHz). The study was approved by the Institutional Review Board (No: 2023-003) and conducted according to the Helsinki Declaration. All individuals were informed about the study, and written informed consent forms were collected.

Statistical analysis

Given that the acquired data did not adhere to a normal distribution, the principal method of data presentation involved reporting the median (interquartile range [IQR]), unless otherwise specified. To ascertain differences between the two groups, the Mann–Whitney *U*-test was employed. For comparisons among three or more groups, the Kruskal–Wallis test was utilized, with subsequent *post hoc* analysis conducted using the Mann–Whitney *U*-test and Bonferroni adjustment. The Fisher's exact test was employed to evaluate the relative proportions of cases. Linear regression analysis was performed to elucidate the relationship between the tumor growth rate or eGFR slope and clinical factors. $P < 0.05$ was deemed indicative of statistical significance. All statistical analyses were executed using the open-source R statistical software version 3.2.2, (R Foundation for Statistical Computing, Vienna, Austria).

Results

Table 1 presents the demographic characteristics of the study participants, comprising an initial cohort of 192 individuals with AML, of whom 168 met the eligibility criteria for analysis. The process of assessing eligible individuals and follow-up was shown in Figure 1. The majority of the patients were female (63.7%), with a median age of 50 (43.8–57.3) years. All patients remained asymptomatic throughout the study period. The median duration of follow-up was 35.5 (12.2–60.2) months. At the index date, the median size of the tumors was 9 (6–13) mm, with a corresponding median growth rate of 0.03 (−0.32–0.82) mm/year [Figure 2a]. Out of the 174 tumors subjected to analysis, 64 (37.2%), 20 (11.6%), and 88 (51.2%) exhibited negative, zero, and positive growth, respectively [Figure 2b]. Confirmatory computed tomography (CT) imaging was performed in 63 (37.5%) patients. However, ten tumors could not be visualized on repeat ultrasound examination during the follow-up period. Two patients (1.2%) underwent prophylactic selective embolization, with tumor sizes measuring 41 mm and 54 mm, after 7.4 years and 13.6 years of follow-up, respectively. Notably, no suspicious features indicative of malignancy were observed during the follow-up assessments.

We proceeded to explore potential factors that could influence the tumor growth rate and renal function. The tumor growth rate, eGFR, and eGFR slope were compared across groups dichotomized by gender or median values for age or tumor size at the index date. The tumor growth rate did not exhibit significant differences based on gender or tumor size; however, it was notably higher among younger patients [Table 2 and Figure 3a]. To further investigate the relationship between tumor size and growth rate, the tumor size was subdivided into intervals of 5 mm, but no discernible differences in growth

Table 1: Patient demographics and tumor characteristics

Demographic or characteristic	Value	
Age (years)	50	(43.8-57.3)
Male (*n*)	62	
Female (*n*)	106	
Follow-up (months)	35.5	(12.2-60.2)
Size at index date (mm)	9	(6-13)
Growth rate (mm/year)	0.03	(-0.32-0.82)
mean (SD)	0.24	1.83
eGFR (mi/min/1.73m^2)	81	(73.8-90.9)
Tumor burden		
Bilateral (*n*)	2	
Multiple (*n*)	2	
Multicentric (*n*)	2	

Data were expressed as the median value (interquartile range).

Table 2: Comparison of tumor growth rate or renal function between the groups dichotomized by clinical factors

Clinical factor	No. cases	Tumor growth rate (mm/year)		*P*	eGFR (ml/min/1.73m²)		*P*	eGFR slope (ml/min/1.73m²/year)		*P*
Age*										
Younger	91	0.12	(-0.16-0.98)	0.016	85.2	(76.2-94.2)	0.004	-1.30	(-3.88-0.24)	0.057
Older	77	0	(-0.59-0.42)		79.0	(68.8-85.5)		-0.59	(-2.07-2.51)	
Gender										
Male	62	0	(-0.57-0.80)	0.598	75.9	(51.7-81.0)	0.620	-1.08	(-3.87-1.21)	0.278
Female	106	0.046	(-0.32-0.85)		70.6	(43.1-82.7)		-0.73	(-1.99-1.49)	
Tumor size*										
Smaller	104	0.05	(-0.17-0.55)	0.391	82.9	(74.7-91.9)	0.550	-0.99	(-3.35-1.20)	0.771
Larger	64	0	(-0.81-1.02)		79.2	(71.0-88.9)		-0.70	(-2.35-1.73)	

P-values were determined by the Mann-Whitney *U*-test. Data were expressed as the median value (interquartile range). *Patients were dichotomized by the median values for age (50) or tumor size (9mm).

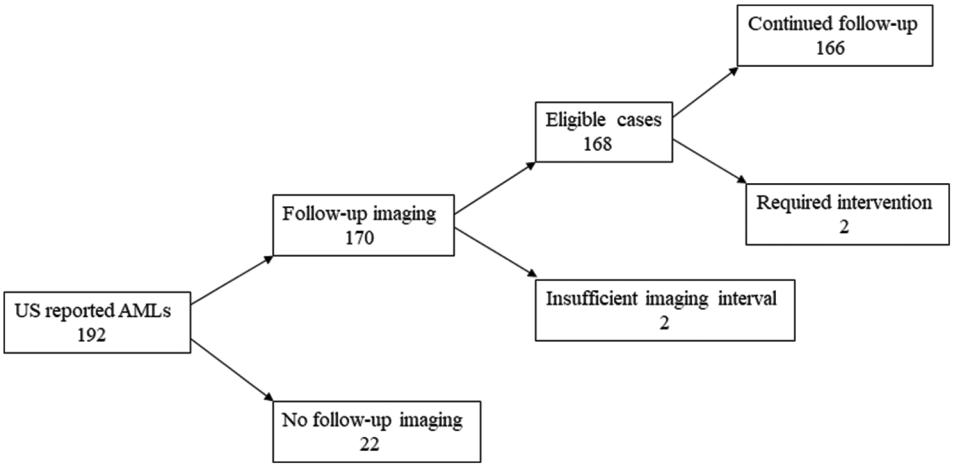

Figure 1: The flow of study entry for subjects and follow-up.

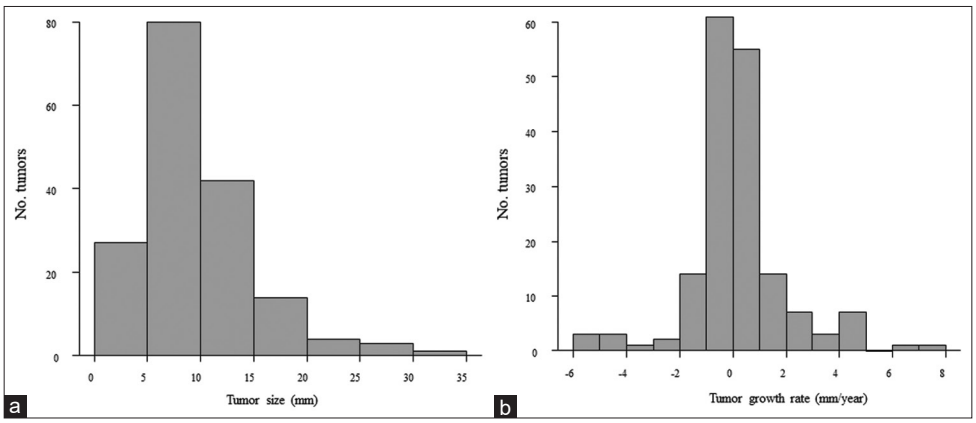

Figure 2: The histograms of tumor size (a) and tumor growth rate (b).

rate were observed among any of the size groups [Figure 4]. There were no significant differences in eGFR or eGFR slope based on gender or tumor size, although younger patients exhibited significantly higher eGFR levels and numerically greater eGFR decline [Table 2 and Figure 3b, c]. To identify clinical factors predictive of tumor growth, we compared them between groups categorized according to growth trends, namely, positive growth versus zero or negative growth. Half of the tumors (88/172, 51.2%) demonstrated either zero ($n = 23$) or negative ($n = 65$) growth in tumor size. Nevertheless, no discernible differences in these clinical factors were identified between the two groups [Table 3].

Discussion

Large AMLs possess a significant risk of hemorrhage and

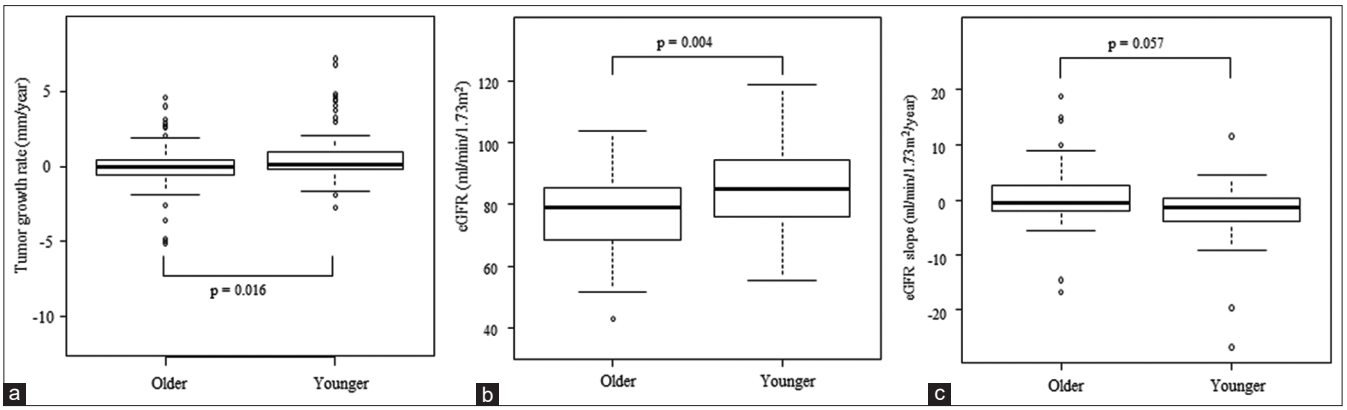

Figure 3: The Comparison of tumor growth rate (a), and renal function indicated by eGFR (b) and eGFR slope (c) between older and younger patients.

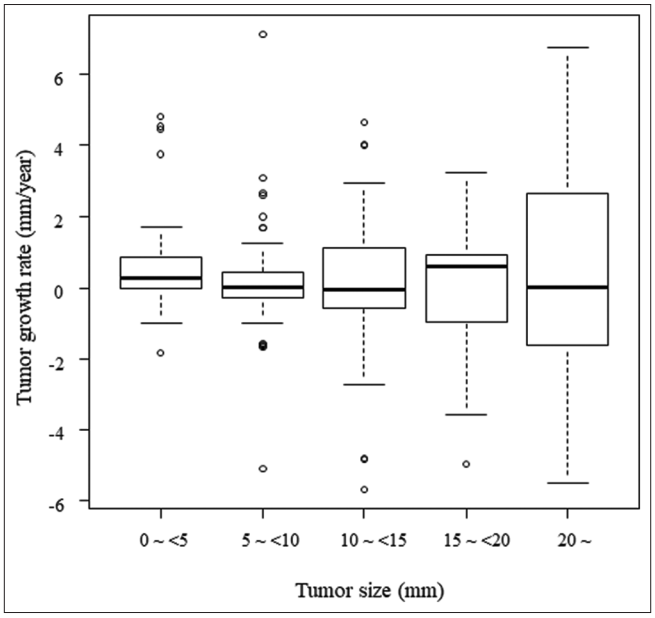

Figure 4: Comparison of tumor growth rate among the groups stratified by tumor size

there have been a large number of recommendations on how to deal with these tumors.[9-11] However, little is known about the natural history of small sporadic AMLs, some of which could eventually develop larger lesions. The specific size threshold for defining small renal AMLs may vary slightly depending on the context or guidelines being followed. In general, small renal AMLs are often considered to be those that measure 4 cm or less in diameter, similar to the definition of small renal tumors.[15] Typically, active surveillance is employed for small asymptomatic cases under the rationale to oversee their growth and preemptively identify those at risk of becoming symptomatic. Currently, there is a dearth of consensus concerning the surveillance of minute lesions that have not yet attained clinical significance. On the other hand, the prevalence of screening examinations using cutting-edge ultrasound equipment has played a role in detecting such incidentalomas. This accentuates the necessity for a contemporary inquiry into the natural course of small AML, upon which to establish guidelines for its surveillance.

Nevertheless, the factors prognosticating augmented tumor growth that predispose to future hemorrhagic events remain inadequately elucidated, especially for sporadic cases. To address this issue, we conducted a retrospective analysis of patients diagnosed with sporadic AML within our health-care system, to ascertain the rate of its growth and identify variables that correlated with accelerated growth, thereby facilitating the development of an optimal surveillance protocol.

Our findings demonstrated that a considerable number and proportion (163/174, 94.8%) of AML, initially detected by USG in a health checkup, measured ≤20 mm, and these diminutive lesions did not exhibit malignant characteristics and exhibited a rare incidence (1.2%) of clinically significant enlargement necessitating intervention. The mean growth rate of these tumors (0.24 ± 1.83 mm/year) was consistent with data from prior retrospective studies [Table 4]. These lesions tend to progress slowly, with a mean growth rate of 0.1–1 mm/year, implying that it may take more than a decade to attain a size of 1 cm. Despite their sluggish pace of growth, a minuscule fraction of cases mandates intervention, thereby underscoring the criticality of prognostication for the early identification of high-risk factors associated with augmented tumor growth. According to several studies, there is evidence to suggest that the presence of multiple and bilateral AMLs is associated with a more accelerated disease progression.[2,18] However, this feature appears to be distinctive to individuals with TSC and may not always be applicable to sporadic cases.[9,15] Indeed, no discernible difference in the tumor growth rate was detected in the present study between individuals afflicted with single and multiple tumors ($n = 4$ cases, data not shown). Tumor size seems predictive of the tumor growth rate and hemorrhage as a consequence of expanded tumor growth. Maclean *et al*. reported that there was a significant risk of growth in larger AML than its small counterpart (0.7 vs. 9.2 mm/year).[9] Lee *et al*. reported that 16% of 513 patients with sporadic AML experienced spontaneous hemorrhage, and the tumor size was significantly greater in cases of hemorrhage as compared to those without (median of 8 cm vs. 4.1 cm).[19] Similarly, other studies have indicated that a significant tumor size is a risk factor for hemorrhage.[20,21] On the other hand, several

Table 3: Comparison of clinical variables between the groups dichotomized by the trends in tumor growth

	Positive growth	Zero/Negative growth	*P*
Tumor size (mm)	8 (6-12)	9 (7-13)	0.178*
Age	48 (42.5-55.5)	51 (46-58)	0.016*
eGFR (ml/min/1.73m^2)	84.8 (72.0-93.8)	79.4 (75.0-88.3)	0.178*
eGFR slope (ml/min/1.73m^2/year)	-0.88 (-2.14-1.25)	-0.87 (-3.43-1.71)	0.786*
Gender[†]			
Male	27	35	0.263**
Female	57	49	

[†]Number of tumors. Data were expressed as the median value (interquartile range). *P*-values were determined by the Mann-Whitney *U*-test* or Fisher's exact test.**

Table 4: Reports regarding tumor growth rate of sporadic angiomyolipoma on active surveillance

Author	*n*	Follow-up (months)	Tumor size (mm)	Growth rate (mm/year)	Intervention (%)
Mues[13]	45	median 55	mean 17	mean 0.9	6
Maclean[9]	125	median 22	75%: <2 cm, 17%: 2-4cm, 8%: >4 cm	mean 0.7 : ≤2 cm, 1: 2-4cm, 9.2 : ≥4 cm	2
Dorin[17]	25	NR	mean 16	mean 0.75	8
Bhatt[14]	447	median 43	median 10, 90%: ≤4cm	median 0.21	6
Chan[15]	187	median 24	median 9	mean 0.13	3
Hussan[8]	438	mean 15 <1cm, 11 ≥1cm	mean 7 <1cm, 14.3 ≥1cm	mean 0.26 <1cm, 0.006 ≥1cm	2
Nason[16]	458	median 65	median 10	median <2.5	7
Present study	168	median 36	median 9	mean 0.24	1

NR: not reported

studies including ours, showed no significant association between size at initial detection and the tumor growth rate or risk of hemorrhage. This incongruity could be attributed to variations in the targeted tumor size. The first two studies involved sizable tumors, measuring medians of 32 mm and 47 mm, respectively,[9,19] and the third investigation included larger tumors, of which 30% measured 4 cm or greater.[21] In contrast, other accounts, including our own, comprised tumors of lesser dimensions, mostly measuring less than the mean or median of 20 mm. Taken these together, although this study did not yield direct outcomes, it could be extrapolated that AMLs measuring < 20 mm generally do not exhibit conspicuous tumor growth and are rarely linked to the risk of hemorrhage.

We identified age as a potential factor linked to tumor growth, with younger patients demonstrating a greater rate of growth as compared to their older counterparts, which is consistent with the finding of Maclean *et al*.[9] A couple of researchers also demonstrated an increased risk of hemorrhage in younger patients.[14,19] Attention should be drawn to the difference in tumor growth and intervention requirements between genders. Research suggests that AML incidence is higher among females than males, plausibly due to the effects of estrogenic hormones.[22] Pregnant women, in particular, face an elevated rate of AML growth and an augmented risk of hemorrhagic complications.[23] Nevertheless, the present study demonstrated no discernible variation in the rate of tumor growth between males and females, particularly for small tumor sizes measuring predominantly <2 cm. Although data pertaining to this matter were unavailable for analysis in the present study, previous studies indicated that a greater body mass index represents a heightened susceptibility to hemorrhagic events.[19,21] Hence, it was deduced that age is the only factor implicated in the tumor growth rate and the likelihood of hemorrhagic events within tumors of small diameters.

The observed reduction in size noted in 38% of the tumors was an unexpected finding. This result could be attributed to genuine fluctuation in tumor size or, more likely, could be ascribed to the inherent limitations of ultrasound in assessing very small lesions, which have a range of measurement errors ranging from 1 mm to 7 mm compared to CT scans.[24] Furthermore, an additional contributing factor to lower growth rates could potentially be ascribed to the utilization of regression analysis as opposed to simple arithmetic calculations when determining growth patterns. Previous investigations employing regression analysis have indicated considerably decelerated growth rates (approximately 1 mm/year) in contrast to the approximate rate of 3 mm/year yielded by arithmetic methodologies.[25] We feel that regression analysis offers a more precise prediction of renal mass growth over extended periods, as it effectively controls for aberrant measurements that may distort growth curves constructed from relatively short-term follow-up intervals.

Previous studies have elucidated that the patient affected with TSC manifests noteworthy compromised renal function and increased mortality rates predominantly attributable to renal-associated complications, notably renal insufficiency.[26,27] However, certain subsequent investigations have posited the notion that a substantial proportion of patients manage to sustain normal renal function despite the implementation of myriad interventions to prevent or control hemorrhagic incidents.[28,29] Conversely, scant literature exists regarding the association

between sporadic AML and renal function. Ruud Bosch *et al*. provided evidence of conspicuous renal impairment, specifically among young adults affected with larger AMLs measuring ≥3.5 cm. This subgroup, in comparison to their counterparts with smaller AMLs, underwent interventions at a higher frequency, potentially exerting an adverse influence on renal function. Furthermore, it was observed that patients with sporadic AML exhibited an earlier onset of Stage 2 CKD on average at a younger age, in contrast to the general population of the Netherlands.[30] These findings allude to the possible effect of sporadic AML on renal function. Thus, we examined the impact of tumor on renal function and found no substantial differences in renal function, as denoted by the eGFR and eGFR slope, irrespective of tumor size or tumor growth. However, associations between the age group and the tumor growth rate or eGFR slope were revealed. Specifically, younger patients exhibited a considerably higher tumor growth rate and a more pronounced decline in eGFR slope, the former and the latter of which corresponded coherently with the conclusions reached by Maclean *et al*. and Ruud Bosch *et al*., respectively.[9,30] This implies that not only tumor growth but also renal function should be monitored more closely in younger patients with sporadic AML.

The present study has several limitations. First, our patient collection is not representative of the general population, but it is based on incidental AML detected by ultrasound examination in health checkup, in which none of the patients had symptoms or complications. Second, since most tumors were <1 cm, confirmatory CT or magnetic resonance imaging was not performed in all patients due to the limited capability of qualitative diagnosis and the unlikelihood of malignancy for such small lesions. Third, the follow-up ultrasound examination was not always performed by the same examiner, although the old images were available for appropriate comparison during the examinations.

Conclusion

AMLs exhibit a range of sizes and manifestations; nevertheless, the prevalence of asymptomatic AMLs surpasses that of larger symptomatic counterparts. There exists a belief that large AMLs originate from smaller tumors that have gradually expanded over time. Although this assumption is logical, the precise course of development for these sizable tumors remains unclear, especially considering their rarity compared to the vast number of small tumors that are incidentally detected. This observation suggests the possibility of two distinct cohorts of patients: Those whose tumors grow and those whose tumors do not. The present study did not isolate any clinical variables, other than age, that could proficiently prognosticate the rate of tumor growth. Nevertheless, our findings corroborate that the majority of AMLs are diminutive in size and exhibit no growth. Conversely, we observed a heightened propensity for tumor growth and a more pronounced decline in renal function among younger patients. Consequently, we propose a surveillance strategy for AMLs exceeding 20 mm in size, as these are more likely to belong to the former of the aforementioned cohort and exhibit substantial growth. In addition, we emphasize the importance of monitoring both tumor size and renal function in younger patients with AML even smaller than 20 mm. We eagerly await further research exploring the vascularity of AML, which may relate to increased tumor growth, as such investigations may enhance our comprehension of the natural progression of these lesions.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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