

Renal function, complications, and outcomes of a reduction in tumor size after transarterial embolization for renal angiomyolipomas: a meta-analysis

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Abstract

Objective: The present study aimed to evaluate renal function, complications, and changes in tumor size after transarterial embolization for patients with renal angiomyolipomas.

Methods: We performed a meta-analysis of transarterial embolization in patients with renal angiomyolipomas from January 1994 to April 2018. Endpoints of interest were the estimated glomerular filtration rate, serum creatinine levels, blood urea nitrogen levels, complications, and reduction of tumors.

Results: A total of 30 studies comprising 653 patients were included. A total of 32.0% of patients were treated by urgent transarterial embolization for spontaneous ruptured renal angiomyolipomas. Other patients sought to relieve symptoms or received embolism prophylactically. The estimated glomerular filtration rate showed no significant difference between before and after embolization. In 363 patients with data on complications, post-embolization syndrome occurred most frequently (54.0%). Only 16 (4.4%) patients had major complications. The diameter of sporadic angiomyolipomas was reduced by a mean of 2.09 cm (95% confidence interval [CI], 0.73–3.45 cm; $I^2 = 29.3%$) and they were reduced in size by 30.0% (95% CI, 16.0%–44.0%; $I^2 = 27.9%$).

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Conclusions: Transarterial embolization of renal angiomyolipomas affects renal function preservation, with a low complication rate. Transarterial embolization is useful for sporadic and tuberous sclerosis complex-related angiomyolipomas.

Keywords

Angiomyolipoma, transarterial embolization, creatinine, renal function, meta-analysis, estimated glomerular filtration rate

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Introduction

Renal angiomyolipoma (AML) is a benign renal tumor with a low incidence of 0.3% to 5.0%.^{1,2} Because of development and increasing use of imaging technology, the amount of AMLs that are discovered accidentally is increasing. AMLs can occur sporadically or in combination with tuberous sclerosis complex (TSC). The prevalence of sporadic AMLs is 0.44% (0.30% in females and 0.14% in males),³ and up to 80% patients with TSC suffer from AMLs.⁴ AMLs have three components, including abnormal blood vessels, smooth muscle, and fatty tissue.⁵ Although benign, AMLs have the potential to cause a variety of problems, including flank pain, hemorrhage, hematuria, renal dysfunction, and venous thrombosis. Acute rupture of tumors is even life-threatening, with an occurrence of up to 15% and shock in approximately 10% of tumors.⁶ Therefore, prophylactic treatment is necessary for patients with AMLs in high-risk groups. In recent years, transarterial embolization has become increasingly available. Transarterial embolization may provide an appropriate alternative to partial nephrectomy in patients who are not suitable candidates as a result of comorbidities or are unwilling to undergo surgery. Management recommendations are based on TSC status, tumor size, and symptoms. For TSCs with acute hemorrhage or symptoms, or a

diameter larger than 3 cm, transarterial embolization is recommended as an alternative therapy.⁷ However, a guideline for patients without TSC is still unclear. To date, most previous studies had a small sample, and case reports or analysis have accounted for many of the studies.^{6,8} Additionally, results on transarterial embolization therapy of AMLs are inconsistent. Therefore, we performed a meta-analysis on transarterial embolization for AMLs. We aimed to search and analyze the available literature to evaluate renal function, complications, and tumor sizes of AMLs after transarterial embolization.

Materials and methods

Search methods

According to the Meta-analysis of Observational Studies in Epidemiology criteria, a meta-analysis of transarterial embolization of AMLs was performed. We comprehensively searched the major databases (PubMed, Embase, Ovid, clinicaltrials.gov, and the Cochrane Library) from January 1994 to April 2018. Articles that related to renal AMLs were assessed. Mesh keywords included renal angiomyolipoma, treatment, intervention, and transarterial embolization. To identify any additional relevant studies, the reference lists of related articles were also screened.

Inclusion criteria were studies in which patients with AMLs were treated by transarterial embolization. Reviews, case reports, published abstracts without full text, animal studies, and reports from meetings were excluded.

Study selection

Two reviewers participated in the study selection procedure. When the reviewers had disagreements, discussion and consensus were conducted. Titles and abstracts of the articles were initially screened for inclusion. Finally, a full-text review was performed on the articles that met the inclusion criteria. For this type of study, ethical approval was not required. Informed consent was obtained from all individual participants in each included study.

Data extraction

The same two reviewers extracted and evaluated the outcome data and study characteristics. When more than one report describing the same population was published, the most current or complete report was used. Data representing renal function, complications, and tumor sizes were extracted. With regard to these data, changes in renal function included the estimated glomerular filtration rate (eGFR), creatinine levels, and blood urea nitrogen (BUN) levels. Complications were divided into major and minor. Major complications included embolization-related renal abscess, femoral arterial injury, and acute respiratory distress. Minor complications consisted of postoperative pain, retroperitoneal hematoma, and post-embolization syndrome (PES). PES manifested as low-grade fever, pain, and vomiting 3 to 7 days after transarterial embolization. Computed tomography, magnetic resonance imaging, or ultrasound was used to measure tumor sizes. All of the indices depended on reports in original articles.

We also extracted baseline characteristics of the patients. The data were entered into a data extraction sheet that had been previously designed and approved by all reviewers.

Data synthesis and statistical analysis

Statistical analysis was performed using Stata 14.0 (StataCorp, College Station, TX, USA). All of the extracted data were pooled in a random effects model, and the mean with 95% confidence interval (95% CI) are presented. Additionally, I^2 was calculated to assess the heterogeneity between the studies, which ranged from 0% to 100% (25%, 50%, and 75% represents low, medium, and high heterogeneity, respectively). When the median with range, instead of mean with standard deviation (SD), was available in the original articles, data were transformed according to the methods described by Hozo et al.⁹

Quality assessment

We referred to the 11-item checklist recommended by the Agency for Healthcare Research and Quality to assess the quality of each study. Among the 11 items in the checklist system, 'yes' scored "1", while "no" or "unclear" scored "0". Quality was assessed as follows: low quality, 0–3; moderate quality, 4–7; and high quality, 8–11.¹⁰ Data organization was completed in Revman 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Results

Literature review

A flow chart of the article search is shown in Figure 1. The initial screening identified 1521 articles, of which 40 were eligible for full-text review and 30 matched our criteria. These studies included a total of 653 patients. All of the articles were observational cohorts

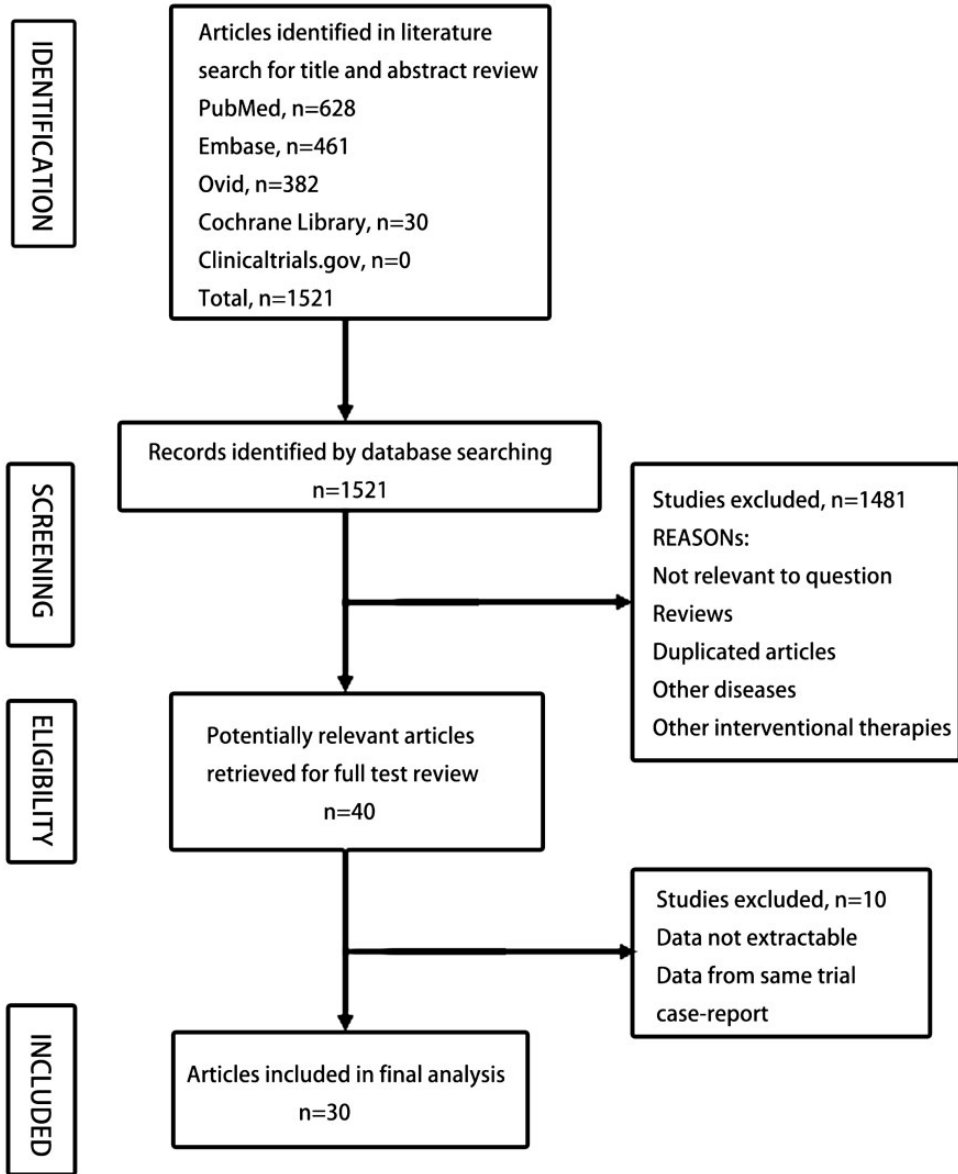


Figure 1. Flow chart of preferred reporting items for the meta-analysis with evidence synthesis.

without control groups. The 30 studies included studies that were published from 1994 to 2018, and 20 of them were published after 2010.

The quality of the articles included was high. Among the 30 studies, 18 studies

scored 11 points¹¹⁻²⁸ in the Agency for Healthcare Research and Quality Cross-Sectional/Prevalence Study Quality checklists, six studies scored 10 points,²⁹⁻³⁴ three studies scored 9 points,³⁵⁻³⁷ and the other three studies scored 8 points.³⁸⁻⁴⁰

Study population

Baseline characteristics are shown in Table 1. The mean age of the patients was 45.8 ± 8.7 years and most of the patients were women (79.9%). Among these patients, data of TSC status were available, and 200 (37.8%) had a history of TSC. With regard to treatment, 32.0% of patients were treated by urgent transarterial embolization for spontaneous ruptured renal AMLs, and the remaining patients sought to relieve symptoms or received embolism prophylactically. Additionally, the course of embolization described in studies was inconsistent, and embolization agents varied.

Renal function

No intraprocedural mortality occurred. Creatinine levels, eGFR, and BUN levels were used to assess renal function in the different studies (Figures 2 and 3). In the short term, mean serum creatinine levels increased from $71.25 \pm 8.49 \mu\text{mol/L}$ to

$78.08 \pm 13.55 \mu\text{mol/L}$, and mean BUN levels increased from $6.3 \pm 2.5 \text{ mmol/L}$ to $8.4 \pm 3.8 \text{ mmol/L}$ after 1 week of embolization (Figure 2). Mean serum creatinine and BUN levels were still slightly higher than baseline after 6 months (creatinine, $73.50 \pm 15.50 \mu\text{mol/L}$; BUN, $7.9 \pm 3.5 \text{ mmol/L}$). Similarly, the mean eGFR before transarterial embolization was $85.61 \pm 8.57 \text{ mL/min/1.73 m}^2$, and it decreased to $79.00 \pm 18.20 \text{ mL/min/1.73 m}^2$ 3 days after the intervention (Figure 3). The mean eGFR started to slowly increase during 2 months of follow-up ($80.80 \pm 11.30 \text{ mL/min/1.73 m}^2$). In the long term, mean serum creatinine levels were $67.04 \pm 12.41 \mu\text{mol/L}$ at 12 months and $61.40 \pm 18.60 \mu\text{mol/L}$ at

Table 1. Baseline characteristics of patients with angiomyolipomas.

Variables	Data
Number of patients	653
Mean age at presentation, years	45.8
Sex*, n (%)	
Male	126 (20.1)
Female	501 (79.9)
TSC status, n (%)	
Yes	200 (37.8)
No	329 (62.2)
Type of transarterial embolization, n (%)	
Prophylactic	251 (68.0)
Emergency	118 (32.0)
Symptoms, n (%)	
Flank pain	147 (34.5)
Bleeding	91 (21.4)
Hematuria	38 (8.9)
No symptoms	150 (35.2)

TSC: tuberous sclerosis complex; n: number of patients; *the sex of 26 patients was unknown.

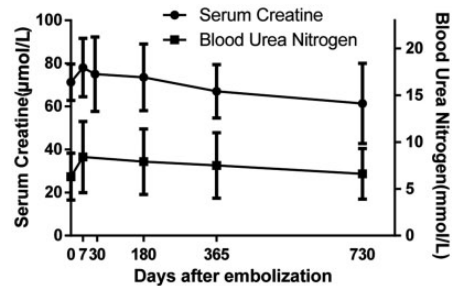


Figure 2. Variation in serum creatinine and blood urea nitrogen levels after embolization.

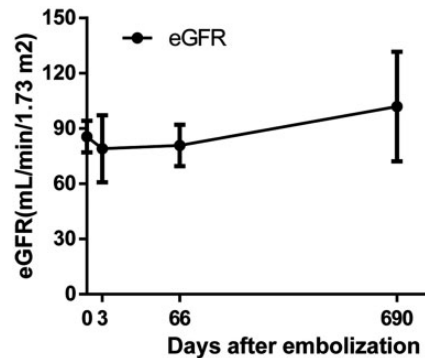


Figure 3. Variation in the eGFR after embolization. eGFR: estimated glomerular filtration rate.

24 months. Mean BUN levels were 7.5 ± 3.5 mmol/L at 12 months and 6.6 ± 2.7 mmol/L at 24 months. The mean eGFR was 101.97 ± 29.75 mL/min/1.73 m² at 23 months after embolization.

Complications

PES was reported in 16 (363 patients) studies,^{11-14,17,21,22,28-32,36,37,40} in which researchers adopted different approaches to PES. As a result, the rate of PES was 54.0% (95.0% CI, 36.6%-70.4%; $I^2=91.0\%$; $p < 0.001$) (Figure 4), with a significant difference between studies. The maximum rate of PES reported by Hitomi et al.¹¹ was 100%, while the minimum rate from Ramon et al.¹² was 12.2%. Additionally, only 16 (4.4%) patients

underwent major complications after embolization, including renal abscesses,¹²⁻¹⁴ femoral arterial pseudoaneurysms,^{13,15} urinary tract infection,¹⁶ renal insufficiency,¹⁶ acute respiratory distress,¹⁵ and pleural effusion.¹⁶ One patient with a femoral false aneurysm and renal abscess eventually died from hemodynamic failure.¹³ Another patient with an eGFR of 26 mL/min/1.73 m² died 17 months after treatment as a result of a stroke.²⁹ Other patients who had major complications recovered well after proper management.

Reduction in tumor size

Data of tumor sizes were available in 14 studies (364 cases). Five of these studies reported sporadic AML sizes and three of

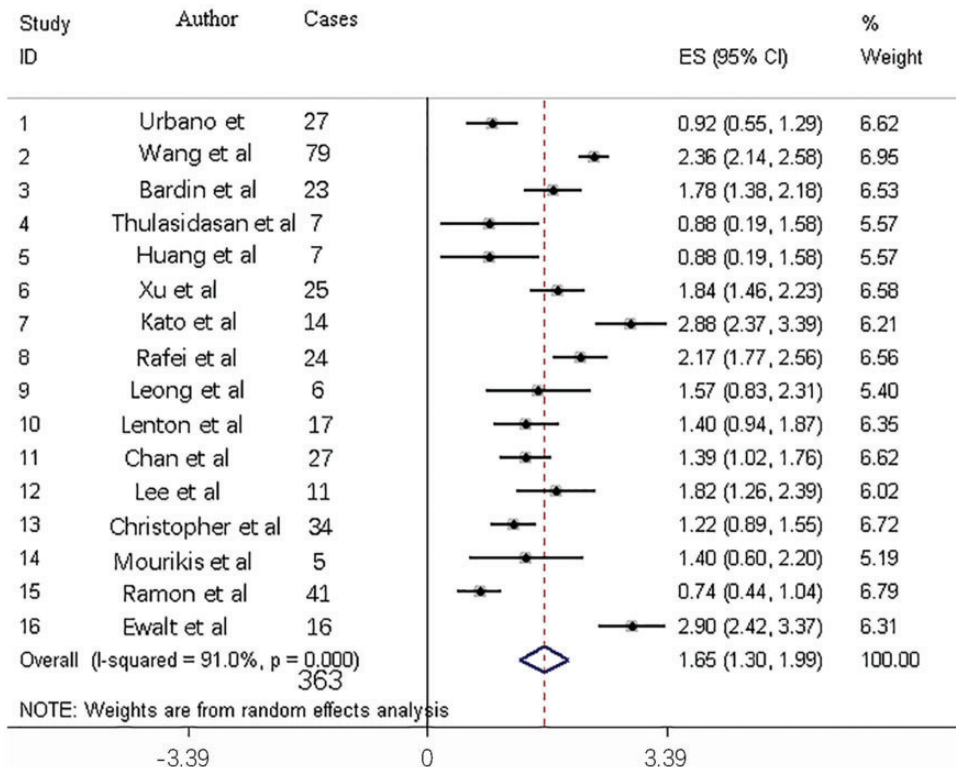


Figure 4. Pooled estimates of the rate of post-embolization syndrome. ES: effect size; CI: confidence interval.

them reported TSC-related AMLs in detail. The mean diameter of tumors before transarterial embolization was 7.73 cm (95.0% CI, 6.09–9.36 cm; $I^2 = 0.0\%$; $p = 0.970$), the maximum mean diameter was 15.6 cm,³⁰ and the minimum mean diameter was 4.2 cm.³⁵ Tumor shrinkage was observed in sporadic and TSC-related AMLs after embolization. Based on a mean reduction in diameter of 2.96 cm (32.0%) in general, the diameter of sporadic AMLs was reduced by a mean of 2.09 cm (95.0% CI, 0.73–3.45 cm; $I^2 = 29.3\%$; $p = 0.226$) and the percentage of the reduction in size was 30.0% (95.0% CI, 16.0%–44.0%; $I^2 = 27.9\%$; $p = 0.236$) (Figure 5). The diameter of TSC-related AMLs was reduced by a mean of 2.12 cm (95.0% CI, 1.48–2.75 cm; $I^2 = 0.0\%$; $p = 0.904$) and the percentage of the reduction in size was 20.0% (95.0% CI, 9.0%–31.0%; $I^2 = 0.0\%$; $p = 0.739$) at the

final follow-up. However, the size of AMLs in 11.4% (95.0% CI, 6.8%–17.0%) of patients was not different or continued to enlarge during the follow-up.

Discussion

In the present study, we performed a meta-analysis to evaluate renal function, complications, and tumor size in renal AMLs after embolization. We found a 7.83- $\mu\text{mol/L}$ decrease in serum creatinine levels overall, with no change in the eGFR. There was a mean reduction in size of 2.09 cm (30.0%) in sporadic AMLs and 2.12 cm (20.0%) in TSC-related AMLs, and the rate of PES occurrence of 54.0%. These results suggested that transarterial embolization could preserve renal function and had a therapeutic effect on sporadic AMLs, with a low complication rate.

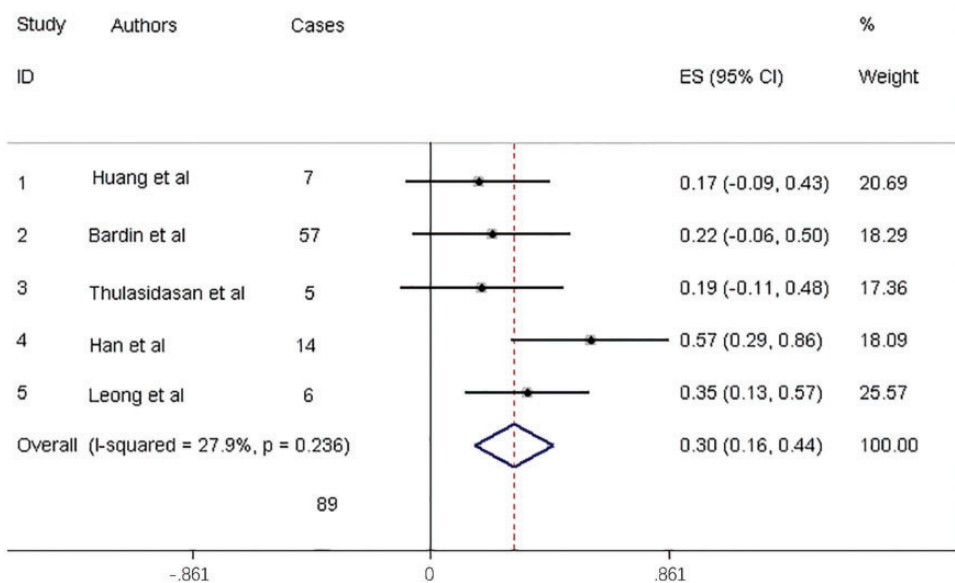


Figure 5. Forest plot and meta-analysis showing the percentage of reduction in tumor size of sporadic angiomyolipomas after embolization. ES: effect size; CI: confidence interval.

The percentages of 0% or 100% appeared among the evaluation indices in the included articles and could not be pooled in the meta-analysis. Therefore, we adopted the sinusoidal conversion method to continue analysis. The results shown in the figure were transferred by sinusoidal conversion and the formula of inverse conversion was as follows: $\text{disp}(\sin(\frac{\text{average}}{2}))^2 \left(\sin(\frac{95\% \text{ lower limit}}{2}) \right)^2 \left(\sin(\frac{95\% \text{ upper limit}}{2}) \right)^2$.

During the past decade, for patients with renal AMLs in whom intervention was indicated, surgery was the most well characterized.⁴¹ With development of mini-invasive therapy, transarterial embolization is increasingly being used to treat renal AMLs. In 2015, Murray et al.⁴² published a systematic review of transarterial embolization for AMLs. They included a total of 524 cases. On the basis of a mean follow-up of 39 months, Murray et al.⁴² reported a high technical success of 93.3%, with a mean reduction in size of 3.4 cm. Sun et al.⁴³ performed a real-world study in 2017, and examined outcomes of embolization (4280 patients) and nephrectomy (3842 patients) for renal AMLs associated with TSC. They reported that embolization had a reduction in gross hematuria (−27.7%), retroperitoneal hemorrhage (−8.4%), and abdominal mass (−6.9%). In recent years, only these two articles aggregated available data to examine outcomes of transarterial embolization for AMLs. Except for the effect of transarterial embolization on TSC-related AMLs, these two articles did not focus on the change in renal function after management. Additionally, treatment for sporadic AMLs still remains unclear. Therefore, we performed this meta-analysis, with the aim of discussing advantages (e.g., renal function reservation, low incidence of complications) of transarterial embolization and efficacy for sporadic AMLs.

Our findings of a decrease in creatinine levels and almost unchanged eGFR showed an advantage in terms of preservation of renal function. A previous study showed that, without treatment, renal function tended to decline more rapidly in patients with sporadic AMLs than in the general population (eGFR, −1.1 vs. −0.8 mL/min/1.73 m²/year; $p=0.081$), which increased the risks of cardiovascular comorbidity and mortality.⁴⁴ In patients with TSC, renal function declines more rapidly than in those with sporadic AMLs.⁴⁵ Although

renal function deteriorated temporarily in the short term after embolization, it did not decline in the long term in our study. This is most likely due to the use of contrast agents during the procedure.⁴⁶ Therefore, for ensuring the therapeutic effect of AMLs and benefiting renal function, transarterial embolization could be considered as an alternative management to surgery, especially for older people and patients with a poor renal function or physical condition.

The rate of complications was low in our study. The most common complication after embolization was PES (54.0%) and different medical institutions adopted different approaches to this complication. Preventive medications were provided before embolization in some studies, while others did not have preventive medications. Although PES had a high occurrence rate, patients with PES recovered well after they were treated properly. The high rate of PES suggested prophylaxis before embolization. Additionally, the rate of other complications was lower than partial nephrectomy (PN; 4.4% vs. 17.6%).

Because of a deficient guideline of sporadic AMLs, another aim of the present study was to evaluate the change in sporadic AML size. We found a similar change in sporadic AML size compared with the overall reduction in size. With regard to tumor size, those >4 cm are a high-risk factor for onset of symptoms and tumor rupture, and transarterial embolization of tumors that are >4 cm can reduce this risk.⁸ Therefore, a reduction in size could be regarded as an index for evaluating the efficacy of transarterial embolization. Researchers have measured a reduction in tumor size using various follow-up times. Villalta et al.¹⁵ reported a 31.0% reduction in tumor size with 29 months of follow-up and Chan et al.²¹ reported 32.0% with 85.2 months. Neither of these studies showed a significant difference in a reduction in

tumor size. Based on a mean follow-up of 33.3 months, we believe that a reduction in tumor size in the present study could represent final shrinkage after embolization. A 30.0% reduction helps reduce the risk of symptoms and prevents the possibility of tumor rupture for sporadic AMLs. However, we found that 11.4% of embolized AMLs continued to enlarge. The main reason for this finding may be the low angiomyogenic component of AMLs.⁴⁷ Lin et al.⁴⁷ showed that AMLs did not significantly decrease in size after embolization if the lesions had little blood supply.

We also compared transarterial embolization with historical surgery and with everolimus, although all of the relevant studies lacked a control group. One of the largest series of nephron-sparing surgery for AMLs showed an 8.84- $\mu\text{mol/L}$ increase in creatinine levels and a 12.1% complication rate at a median follow-up of 96.0 months.⁴⁹ Similar results were demonstrated in several other studies.^{50,51} Rivero et al.⁵² reported a greater decrease in the eGFR after PN ($-13.09 \text{ mL/min/1.73 m}^2$). Furthermore, use of everolimus in TSC-related AMLs resulted in a >40% to 50% reduction in volume, with continued volume reduction and stable renal function according to the EXIST-2 study.⁵³ Currently, the effect of everolimus on sporadic AMLs is unclear. Therefore, the recommended management for sporadic AMLs is surgery and embolization. Transarterial embolization has a similar therapeutic outcome as surgery and is more beneficial for protection of renal function.

Our study has some limitations. First, a fundamental limitation is the lack of prospective, comparative studies for inclusion in our meta-analysis. All studies that were included were performed retrospectively, and most of the studies had small sample sizes. Therefore, these studies may have been prone to bias. Second, we were unable to divide tumor sizes into

subgroups and did not perform further analysis because of unavailable original data. Therefore, we could not evaluate the therapeutic effects of transarterial embolization on different tumor sizes. Third, there were diverse types of embolization materials in the studies, including ethanol, polyvinyl alcohol, coils, microspheres, and micro-balloons, which could be used alone or in combination. To date, no study has shown the superiority of any embolic agent over another regarding actively treating patients with hemorrhaging AMLs, preventing hemorrhage, or treating symptoms.⁶ Finally, the different studies that were included in our analysis showed different rates of PES. Because of unavailable information about the precaution of PES in some studies, articles could not be divided into a PES prevention group and non-prevention group for further analysis. Despite these limitations, the present study suggests that a well-designed, randomized, controlled trial and further investigation are required to prove these potential benefits in the future.

Conclusions

This present study provides evidence that transarterial embolization affects preservation of renal function, and there is a low complication rate. Furthermore, transarterial embolization is useful for sporadic and TSC-related AMLs. These results highlight that, in patients whose AMLs require intervention (AML size >4 cm, continuous enlargement of tumors, and symptomatic AMLs of any size), transarterial embolization can be considered to retain renal function with a low complication rate for sporadic and TSC-related AMLs.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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