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A suggestion for pathological grossing and reporting based on prognostic indicators of malignancies from a pooled analysis of renal epithelioid angiomyolipoma

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Abstract
Purpose Epithelioid angiomyolipoma (EAML) is a rare entity of the kidney. The guideline for grossing and reporting of renal EAML has not been established for Chinese patients. We planned this study to provide some preliminary indicators for draft guidelines of pathological diagnosis among Chinese people.
Methods The histopathological characteristics of 11 EAML cases from Cancer Hospital, Chinese Academy of Medical Sciences, were reviewed, and a pooled analysis based on our cases and cases from published articles was performed on the histopathological characteristics and prognosis of 56 Chinese patients with EAML. All the cases met the criteria of the 2004 World Health Organization classification of renal tumors.
Results The ratio of female to male was 1.2:1 with the mean age of 43.4 in the 11 cases. All the 11 cases were sampled following the guideline of renal cell carcinoma. The mean tumor size was 6.5 cm. Four (36.4 %) cases showed necrosis. Six (54.5 %) cases showed invasive borders. Only one case showed metastases. In pooled analysis of the total 56 cases with EAML, 10 cases (17.9 %) showed adverse prognosis. Tumor size, necrosis and invasive edge showed significant difference between favorite and adverse prognostic groups ($P < 0.05$).
Conclusion The majority of EAML is benign, and true malignant EAML is rare. The sample of EAML should follow the sample guidelines of renal cell carcinoma with some modifications, emphasizing the presence of necrosis and invading edge. The information of tumor size, necrosis and invasive edge should be included in the diagnostic report of each EAML case.

Keywords Kidney · Epithelioid · Angiomyolipoma · Prognosis · Pooled analysis

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Introduction

Renal angiomyolipoma (AML), a mesenchymal neoplasm, is composed of various proportions of dysmorphic blood vessels, smooth muscle and adipose tissue [1]. Since many studies indicated that AML is related to perivascular epithelioid cell (PEC) differentiation, it belongs to the PEComa tumor family [2]. Immunohistochemically, PEC expresses melanocytic and myogenic markers such as HMB45,

HMSA-1, MelanA/Mart1, microphthalmia transcription factor (Mitf), actin and less commonly desmin [3]. Epithelioid angiomyolipoma (EAML) of the kidney is a rare subtype of angiomyolipoma (AML), which was first reported by Mai [4]. EAML is characterized by polygonal cells with clear to eosinophilic cytoplasm, round to oval nuclei that may show various degrees of nuclear atypia, and the same immunoreactivity as AML [1, 5–8]. AMLs, including EAML, are strongly associated with tuberous sclerosis (TSC) [1, 5–8]. In contrast to the classic AML which is benign, local recurrence and distant metastases have been reported in EAML [5–8]. Approximately one-third of EAMLs have been reported to have metastasis to lymph nodes, liver, lungs or spine [9]. However, no prognostic histopathological features have been established.

Faraji et al. [10] studied the pathologic features of six EAML cases and conducted a meta-analytic study. They indicated that male patient and larger tumor size may be two potential predictive factors of adverse clinical course in EAML. Brimo et al. [11] purposed the clinicopathologic prognostic indicators of malignant EAML. Their study focused on adult patients (age $\geq$ 17) with EAML, which have no less than moderate atypia and the proportion of the epithelioid cells was no less than 5 %. In their study, the proportion of atypical epithelioid cells ($\geq$70 %), the number of mitotic figures ($\geq$2/10), atypical mitotic figures and necrosis were the four prognostic factors. Nese et al. [12] also proposed the risk stratification for pure renal EAML. They mainly focused patients (age $\geq$ 14) with pure EAML of different atypia. Their study indicated that TSC and/or concurrent AML, tumor size (>7 cm), carcinoma-like growth pattern, extrarenal extension and/or involvement of renal vein and necrosis were the five prognostic factors in the risk stratification. Yang et al. [13] indicated that atypical mitotic figures, blood vessel invasion and tumor embolus may be predicting malignant behavior of EAML focused on 27 Chinese patients with EAML from kidney and liver. Overall, these studies revealed: (1) EAML may have uncertain malignant potential; (2) the clinic courses of EAMLs were partially different based on the clinicopathologic factors; (3) the application of clinicopathologic features of EAML to predict its clinical course may be feasible. Today, a lot of genitourinary pathologists agreed that the EAMLs should be divided into low, intermediate and high risk of malignant behavior based on published criteria [14].

In China, some case reports and small series of EAML were published since 2000 [15]. Although the diagnosis of EAML is not an issue when following the criteria of the 2004 World Health Organization classification of renal tumors [9], there are no guidelines on how to sample and what standard information should be reported in the pathological report in China. The purpose of this retrospective study was to: (1) investigate the clinicopathologic features of EAML cases in Cancer Hospital, Chinese Academy of Medical Sciences, to find some histopathological features, which may be related to prognosis and (2) perform pooled analysis of histopathological features and prognosis in Chinese patients with renal sporadic EAML. The results may provide useful information for the establishing guideline of properly sampling and reporting EAML.

Materials and methods

The summary of clinicopathologic features in the 11 cases with renal EAML in Cancer Hospital, Chinese Academy of Medical Sciences, was a part of a series of researches that was approved by NCC Ethics Committee/IRB. In this part, patient consent was not required as there were no risks anticipated to the participants. All the information of patient's identification was de-identified.

Clinical data and postoperative pathological evaluation on EAML cases from Cancer Hospital, Chinese Academy of Medical Sciences, in China

The EAML cases from 2005 to 2011 at our hospital were reviewed. All cases were sampled following the guideline of handling renal cell carcinoma, which was according to the tumor size as well as the relationship between tumor and perinephric fat or renal sinus fat.

The inclusion criteria were listed as follows: (1) Chinese adult (age $\geq$ 19); (2) radical nephrectomy or partial nephrectomy; (3) located in kidney only; (4) a minimum of 5 % of epithelioid component in tumor [11]; and (5) diagnosed according to the histological and immunohistochemical criteria of EAML in the current World Health Organization classification of renal tumors (2004) [9], including: (1) polygonal larger cells with abundant granular cytoplasm; (2) enlarged vesicular nuclei, prominent nucleoli, multinucleated or enlarged ganglion-like cells; (3) nuclear anaplasia or atypical mitotic figure; (4) expression of one or more melanocytic markers (HMB-45, Mart-1/MelanA, etc); (5) positive or negative for myoid markers (actin, smooth muscle actin, etc); and (6) a negative immunoreaction for one or more epithelial markers, pan-cytokeratin, CK8, CK18 and/or epithelial membrane antigen (Fig. 1).

Clinical data including sex, age and mode of surgery were collected from medical records. Follow-up information was obtained from medical records or telephone, including local recurrence (Rec), metastasis (Mets), death of disease (DOD) or no evidence of disease (NED) during the follow-up period. An adverse clinical course was defined as local Rec, Mets and DOD at different intervals after surgical excision [16, 17]. The pathological features including tumor size, degree of atypia, growth pattern, mitotic figures, necrosis,

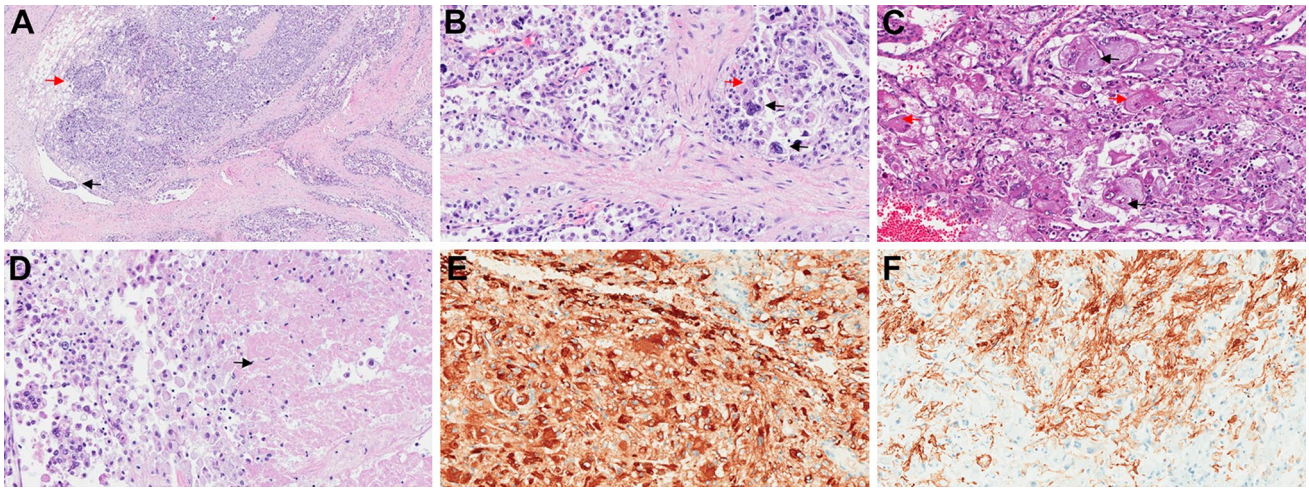

Fig. 1 Representative histopathological features of epithelioid angiomyolipoma. **a** Invasive edge (*red arrow*) and tumor embolus (*black arrow*). **b** Polygonal larger cells with abundant granular cytoplasm (*red arrow*) and multinucleated cells (*black arrow*). **c** Abundant granular cytoplasm (*red arrow*) and nuclear anaplasia with prominent nucleoli (*black arrow*). **d** Extensive necrosis (*black arrow*). **e** Immunohistochemistry for HMB45 showing diffuse strong reactivity. **f** Immunohistochemistry of SMA showing partly strong reactivity

multinucleate giant cells, extrarenal extension, invasive edge and/or involvement of renal vein are evaluated. Tumor size was obtained according to the gross description of the specimen after formalin fixation. All slides were reviewed by three pathologists (S. Z, Z.Y. and H. T. Z.).

Pooled analysis of histopathological characteristics and prognosis of renal EAML in published Chinese cases

We reviewed the literature to retrieve reported Chinese patients with EAML. Literatures of EAML were obtained from databases of PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and Wanfang (http://www.wanfangdata.com.cn/) from January 1, 2000, to December 31, 2014. Search terms were listed as follows: "renal or kidney" and "epithelioid AML or PEComa" and "pathology or pathological" and "prognosis" and "Language = English or Chinese". As very few reports of Chinese patients with EAML were associated with TSC [18, 19], only EAML without TSC was selected in this study. Papers published in English and Chinese core journals [20] were selected in this study.

Inclusion criteria

The inclusion criteria were the same as the cases in our cases (see in "Clinical data and postoperative pathological evaluation on EAML cases from Cancer Hospital, Chinese Academy of Medical Sciences, in China" section). Only case reports with available prognostic information were collected in this pooled analysis.

Approaches in assessing the methodological quality of the studies

Each study was evaluated independently by three investigators (S.Z., X.G. B. and Q. K. S.). We used the Oxman and Guyatt index to evaluate the research quality [21]. H. T. Z. and J. H. M. may be consulted when necessary. The data quality from each paper was valued by the integrity of information: age, sex, mode of surgery, tumor size, necrosis and invasive edge. According the previous researches mainly [10–13], we gave each factor different scores: (1) age and type of surgery scored 1; (2) sex and invasive edge scored 2; and (3) tumor size and necrosis scored 3. After scoring them separately, we met and compared the scores of each case report or article. When necessary, we read the contents of the study to identify the sources of disagreement and discussed them until an agreed score for each study. We add each score as the total score.

Data extraction and strategy

After this assessment was completed, the following information was extracted by S. Z.: name of first author; journal; date of publication; language; age; sex; type of surgery; tumor size; necrosis; invasive edge; and follow-up. Necrosis and invasive edge were divided into two groups of "+" and "−." All the patients were divided into two groups based on the information of follow-up—favorable group (patients of NED) or adverse group (patients of Rec, Mets and DOD) [16, 17].

Statistical analysis

Analyses of two parts were performed in this study. In the first part, a descriptive statistical analysis was provided for the cases from our hospital. All target variables were described using the descriptive statistics. Counting data frequency and proportion were reported. For continuous data, mean, standard deviation (SD), minimum and maximum were reported. The second part is a pooled summary in which data from the eligible studies and our cases were pooled. For age, sex, mode of surgery and tumor size, only the data from our patients and the individual data from the selected papers were used. The aggregated data in the selected papers were not included in the analyses. For showing necrosis and invasive edge, the data from aggregated data can be used as the number of "+" (or "−") cases was provided in these papers. Therefore, the sample size for each variable might be different. Final sample size for each variable was included in the summary tables. Wilcoxon test was provided for continuous variables. Similarly, for categorical variables, Fisher's exact test was used. All of the tests were two-tailed with the p value to indicate the strength of the evidence of the difference between two classified groups. Data were analyzed by SAS 9.2 version (SAS institute Inc., Cary, NC).

Results

Clinicopathologic features of EAML cases from Cancer Hospital, Chinese Academy of Medical Sciences, in China

According to the inclusion criteria, 11 patients with EAML from our hospital were selected. No case was associated with TSC. There were 5 (45.5 %) males and 6 (54.5 %) females. The mean age of the patients was 43.4 years old (23–58). Radical nephrectomy was performed in 8 (72.7 %) patients, while partial nephrectomy was performed in the other 3 (27.3 %) patients. The mean tumor size was 6.5 cm (2.0–17.5 cm). Four (36.4 %) cases showed necrosis. Six (54.5 %) cases showed invasive edge (Fig. 1). Other pathologic characters, including degree of atypia, growth pattern, mitotic figures, multinucleate giant cells, extrarenal extension and/or involvement of renal vein, will be described in detail in a separate paper (unpublished data). Information on prognosis was retrieved for 10 patients, while 1 patient was lost during follow-up (Table 1, case number 47–57).

Pooled analysis of histopathological characteristics and prognosis of renal EAML in Chinese cases

There were 104 reports of Chinese patients with EAML during 2000–2014. Thirteen papers were published in Scientific Citation Index in English language, and 91 papers were published in Chinese journals. Eighteen papers were selected according to the inclusion criteria [15, 22–38] (Fig. 2). The Oxman and Guyatt index of each study was no less than three. The data quality score was no less than six.

Twelve papers are case series report, while others six papers are case reports [15, 22–38] (Table 1). All the eligible studies had intact information of age and sex, while the information of mode of surgery, tumor size, necrosis and invasive edge was not reported in 3, 1, 5 and 6 cases individually [23, 33, 34, 38]. The intact rate of each information was from 87.0 to 100.0 % (40/46–46/46), while the rate of intact information case/total case was 84.8 % (39/46) [15, 22–38]. All the pathologic diagnoses were confirmed by immunohistochemistry. The range of number of cases in case series articles was 2–10.

There were 56 cases included in the pooled analysis of histopathological features and prognosis of renal EAML in Chinese population (Table 2). Tumor size, necrosis and invasive edge showed statistically significant difference between favorable and adverse clinical course groups ($P < 0.05$).

Discussion

As EAML is one of the malignant potential tumors [9], possible predictive pathologic features should be identified and included in the pathologic report by the pathologist. As we known, some important features can only be recorded correctly when performing the grossing at the appropriate level. In the practice, grossing relevant features may be neglected due to no standard grossing and reporting protocol. Currently, there is no guideline on grossing and reporting of EAML in China. We believe that data from Chinese population should be more helpful in clinical practice in China. In this study, we reviewed the clinicopathologic characters of our own hospital's EAML patients to get some potential pathologic characters related to malignancy, which were gotten from grossing. Based on the results from our patients and published articles, we explored the possibility of using histopathological features for prognosis of renal EAML malignancy from pooled Chinese patients without TSC. Our findings may be useful for establishing the guideline of grossing and reporting EAML in China and may also help the clinical practices in this disease in other countries.

The mean age of EAML in our 11 cases was 43.4 years, with slightly female predominance. All the 11 cases were sporadic. Only 10 % patients with EAML showed advanced clinical course, which is much lower than reported in the literature [9]. The possible reasons were as follows: (1) all

Table 1 Summary of cases of EAML for meta-analysis

Case no.	Age(years)/sex	Mode of surgery	Tumor size (cm)	Necrosis	Invasive edge	Follow-up
1 [22]	55/F	Radical nephrectomy	7.5	+	+	Mets to lung in 84 months and DOD in 180 months
2 [23]	62/F	Radical nephrectomy	8	+	NA	NED after 10 months
3 [23]	34/M	Radical nephrectomy	10.5	+	+	Mets to live and retroperitoneal after 11 months
4 [24]	39/M	Radical nephrectomy	15	+	+	Mets to liver and retroperitoneal after 20 months
5–14 [25]	35.6 (26–47)/M/F = 1.5:1	Radical nephrectomy (ten cases)	14 (5–28)	+ (one case)/− (nine cases)	+ (one case)/− (nine cases)	NED after 24–36 months
15 [26]	52/F	Radical nephrectomy	11.5	−	+	NED after 18 months
16 [26]	40/F	Radical nephrectomy	5	−	+	NED after 15 months
17 [27]	49/M	Radical nephrectomy	5.5	+	+	NED after 24 months
18 [28]	27/F	Radical nephrectomy	4	+	+	NED after 2 months
19–23 [30]	46 (26–64)/M/F = 1.5:1	Radical nephrectomy (one case)/partial nephrectomy (three cases)	2.9–10.1	+	+ (three cases)/− (two cases)	NED after 2 to 12 months
24 [31]	30/F	Radical nephrectomy	3	+	+	NED after 2 months
25 [31]	51/F	Radical nephrectomy	5	+	+	NED after 45 months
26 [32]	28/F	Radical nephrectomy	6	+	+	NED after 28 months
27 [32]	40/M	Radical nephrectomy	8	+	+	NED after 8 months
28 [32]	32/F	Radical nephrectomy	3	−	+	NED**
29 [33]	37/F	Radical nephrectomy	4	NA	NA	Rec after 72 months, mets to liver and retroperitoneal after 88 months
30 [33]	34/M	Radical nephrectomy	NA	+	+	Mets to liver and retroperitoneal
31 [34]	58/M	NA	37	NA	NA	DOD after 24 months
32 [34]	34/M	NA	6	NA	NA	NED after 12 months
33 [34]	27/M	NA	11	NA	NA	DOD after 24 months
34 [35]	30/F	Radical nephrectomy	8	−	−	NED after 24 months
35 [35]	40/F	Radical nephrectomy	13	+	−	NED after 6 months
36 [35]	41/F	Radical nephrectomy	8	+	−	NED after 3 months
37 [36]	78/F	Radical nephrectomy	12.5	+	+	Mets to bone after 4 months, DOD after 5 months
38 [37]	42/M	Radical nephrectomy	7	+	+	NED after 10 months
39 [37]	30/M	Radical nephrectomy	15	+	+	NED after 10 months
40 [38]	30/M	Radical nephrectomy	6	NA	NA	Rec after 12 months
41 [29]	39/M	Radical nephrectomy	13	+	+	NED after 8 months

Table 1 continued

Case no.	Age(years)/sex	Mode of surgery	Tumor size (cm)	Necrosis	Invasive edge	Follow-up
42 [29]	31/M	Radical nephrectomy	3	+	+	NED after 10 months
43–46 [15]	46.8 (24–73)/M:F = 3:1	Radical nephrectomy (four cases)	5.0 (one case), >12.0 (in other three cases)	+ (three cases)/− (in one case)	−	NED after 19.5 (6–36) months
47	40/F	Partial nephrectomy	5.5	−	+	NED after 21 months
48	41/F	Radical nephrectomy	6	+	+	NED after 21 months
49	49/M	Radical nephrectomy	4	+	−	NED after 30 months
50	23/M	Radical nephrectomy	3.5	−	+	NED after 24 months
51	41/M	Partial nephrectomy	2	−	−	NED after 24 months
52	46/M	Radical nephrectomy	8.5	−	−	NED after 44 months
53	25/F	Radical nephrectomy	12.5	+	+	Mets to liver after 12 months, mets to iliac fossa after 20 months, Rec in Pelvic after 27 months
54	51/F	Radical nephrectomy	4.5	+	−	NED after 16 months
55	56/F	Partial nephrectomy	6	−	+	NED after 68 months
56	58/F	Radical nephrectomy	17.5	−	+	NED after 7 months
57	47/M	Radical nephrectomy	2	−	−	NA

DOD dead of disease, *EAML* epithelioid angiomyolipoma, *Mets* metastasis, *NA* not available, *NED* no evidence of disease, *Rec* recurrence

* The two cases were reported by the same author. Only one case showed frequent mitosis figure without detail illustration in the corresponding paper

** The follow-up time was not available in the corresponding paper

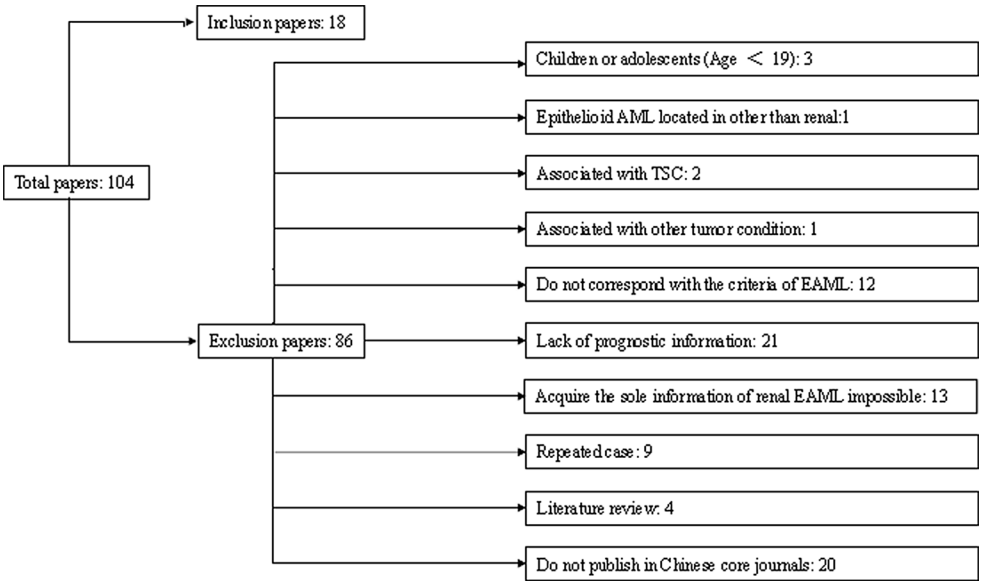

Fig. 2 Summary of literature selection

Table 2 Summary of clinicopathologic features [15, 22–38]

	Outcome [*n* (%)]		*P*
	Favorable clinical course group	Adverse clinical course group	
Mean age (*n*)	40.9 (27)	41.7 (10)	0.599
Sex			0.234
Male	23 (50.0)	6 (60.0)	
Female	23 (50.0)	4 (40.0)	
Mode of surgery			1.000
Radical nephrectomy	39 (86.7)	8 (100)	
Partial nephrectomy	6 (13.3)	0	
Mean tumor size (cm, *n*)	7.0 (29)	12.9 (7)	<0.05
Necrosis			<0.05
+	25 (55.6)	6 (100)	
−	20 (44.4)	0	
Invasive edge			<0.05
+	22 (50.0)	6 (100)	
−	22 (50.0)	0	

The relationship between age/size and outcome was analyzed by Wilcoxon test, while others were analyzed by Fisher's exact test

* Only the cases in which the corresponding information was acquired were analyzed

of our cases were sporadic and none of them was associated with TSC; (2) the follow-up time in some cases was short (only 7 months), while it may need more time to confirm the clinical course in the corresponding case; (3) there may be some selection bias in the literatures as benign EAML may not be reported. Based on our reviews of 11 cases with EAML in our hospital, large tumor size, tumor necrosis and invasive tumor edge may be three grossing relevant pathologic characters related to malignant potential.

In the past decade, a lot of published cases indicated that the potential pathologic features (such as male patient, larger tumor size and tumor necrosis) may be associated with malignant EAML, although definitive pathologic indictors were not affirmed [10–13]. Patients with tumors showing one or more such features may have a worse outcome. In order to have a relative large sample size, data from the eligible studies and our cases were pooled. Based on the indication from our patients and the findings from published articles, we selected tumor size, tumor necrosis and invasive tumor edge, as the possible pathologic features relevant to grossing in the pooled data analysis. The age, sex and mode of surgery were investigated as well.

In our study, we did not find that sex was related to the outcome of EAML. Compared with other studies, we only chose adult patients with sporadic EAML, while others included all patients with EAML in all age groups irrespective of sporadic or associated with TSC [10–12]. The difference in case selection may lead to the different results. In this study, we found for the first time that invasive tumor edge may also have potential for predicting malignant EAML. As shown in our series, invasive tumor edge was a relatively frequent finding, compared with extrarenal extension and involvement of renal vein (unpublished data). In our series, all cases were sampled according to the guideline of renal cell carcinoma grossing, i.e., sampling 1 block/cm of tumor. All the tumors were sampled no less than 4 blocks and tumors no more than 2 cm were entirely submitted, since all cases were suspicious of renal cell carcinoma before operation. Based on the findings in this study, we suggested that when renal EAML is confirmed, the tumor interface with adjacent structures and areas of tumors suspicious for necrosis should be carefully re-sampled to offer enough information if necessary. For the reporting, the information of tumor size, the presence of tumor necrosis and invasive tumor edge should be reported as well.

As far, there were no guidelines concerning follow-up management, adjuvant treatment, treatment types or response. The length of follow-up will affect the grouping. To overcome those limits in maximum degree, we used strict inclusion criteria, methodological quality control to guarantee the maximum of clinical and methodological homogeneity in each selected study. This is the first paper that focused on the potential pathological features for malignant sporadic EAML in Chinese. As EAML is a rare disease, we believe that it is necessary to initiate a multicenter clinical research of EAML in China in the future. Not only the grossing protocol but also the microscopic features will be included in that clinical research. A larger sample size study makes the results more reliable.

In conclusion, the majority of EAML is benign, and true malignant EAML is rare. Detailed clinical information, sufficient sampling and necessary test of immunophenotype were three key points for accurate diagnosis. For grossing, we suggested that the sampling of EAML should follow the guidelines of renal cell carcinoma with some modifications [39], emphasizing the presence of necrosis and invading tumor edge. Larger tumor size, the presence of tumor necrosis and invasive tumor edge may be the potential indicators for malignant EAML and should be reported in each case. When such characters are present, we should emphasize them in the pathologic diagnosis and communicate with clinicians for attention and provide better clinical management for these patients.

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Author contributions S.Z. and X.G.B. helped to interpret the data and drafted the initial manuscript. Q.K.S. helped to analyze the data. H.T.Z. and J.H.M. helped to design the study. S.Z., Z.Y. and H.T.Z. helped to review the slides of all the 11 cases from the participating Cancer Hospital, Chinese Academy of Medical Sciences, in China. X.G.B. and J.H.M. helped to review all the clinical information and follow up all the 11 cases from the participating Cancer Hospital, Chinese Academy of Medical Sciences, in China. G.L. helped the data management. H.T.Z. and J.H.M. both did critical revisions of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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