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Management of sporadic renal angiomyolipomas. A systematic review of available evidence to guide recommendations from the EAU RCC Guidelines panel.

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Abstract.

Context: Little is known about the natural history of sporadic angiomyolipomas**;** there is uncertainty regarding the indications of treatment and treatment options.

Objective: To evaluate the indications, effectiveness, harms and follow-up of different management modalities for sporadic AML to provide guidance for clinical practice.

Evidence acquisition: A systematic review of the literature was undertaken incorporating Medline, Embase and the Cochrane Library (from 1st January 1990 to 30th June 2017) in accordance with PRISMA guidelines. No restriction on study design was imposed. Patients with sporadic AML were included. The main interventions included active surveillance, surgery (nephron-sparing surgery and radical nephrectomy), selective arterial embolization, and percutaneous or laparoscopic thermal ablations (radiofrequency, microwaves or cryoablation). The outcomes included: indications for active treatment, AML growth rate, AML recurrence rate, risk of bleeding, post treatment renal function, adverse events of treatments and modalities of follow-up. Risk of bias assessment was performed using standard Cochrane methods.

Evidence synthesis: Among 2704 articles identified, 43 studies were eligible for inclusion (0 RCT, 9 non-randomized comparative retrospective studies and 34 single arm case series). Most studies were retrospective and uncontrolled, and had a moderate to high risk of bias.

Conclusions: In active surveillance series, the spontaneous bleeding was 2% and active treatment was undertaken in 5% of patients. Active surveillance is the most chosen option in 48% of the cases, followed by surgery in 31% and selective arterial embolization in 17% of the cases. Selective arterial embolization appeared to reduce AML volume but required secondary treatment in 30% of the cases. Surgery (particularly nephron sparing surgery) was the most effective treatment in terms of recurrence and need for secondary procedures. Thermal ablation was an infrequent option. The association between AML size and the risk of bleeding remained unclear; as such the traditional 4 cm cut-off should not *per se* trigger active treatment. In spite of the limitations and uncertainties relating to the evidence base, the findings may be used to guide and inform clinical practice, until more robust data emerge.

Patient summary: Sporadic AML is a benign tumour of the kidney consisting of a mixture of blood vessels, fat and muscle. Large tumours may have a risk of spontaneous bleed. However, the size beyond which needs to be treated remains unclear. Most small AMLs can be monitored without any active treatment. For those who need treatment, options include surgical removal or stopping its blood supply (selective embolization). Surgery has a lower recurrence rate and lower need for a repeat surgical procedure.

1. Introduction

Renal angiomyolipoma (AML) is a benign mesenchymal tumour composed of fat, smooth muscle and blood vessels. AMLs belong to the group of perivascular epithelioid cell tumours [1]. Most AMLs are sporadic but they can also be diagnosed in patients with tuberous sclerosis (TS) in 20% of the cases [2]. There are differences regarding the clinical presentation and management of sporadic and TS AMLs. TS AMLs occur at a younger age, can grow fast, and are often bilateral and multilocular. Sporadic AMLs occur between 50 and 60 years, are more common in women, are frequently unilateral and have a slow growth rate [3, 4]. AMLs can be diagnosed on imaging studies when there is evidence of fatty tissue inside the tumour. Biopsy is rarely needed. However imaging techniques cannot differentiate benign fat-poor AMLs from potentially malignant epithelioid AMLs [5, 6].

The main complication of AMLs is spontaneous bleeding in the retroperitoneum or into the collecting system, which can be life-threatening [7]. The risk of bleeding is related to the angiogenic component of the tumour that includes irregular blood vessels [7]. Little is known about the risk factors of bleeding, but it is believed to increase with tumour size [8].

There are several options for AML management: 1) Active surveillance (AS) based on regular imaging; 2) Selective arterial embolization (SAE) can be used to devascularize AMLs, which may minimize further risk of bleeding [9, 10]; 3) Surgical removal, preferably by nephron sparing surgery (NSS) [11], although total nephrectomy may be necessary for large tumours [8]; and 4) Thermal ablations, which are less frequently used [6, 7, 12] but can be offered in selected patients.

There is uncertainty regarding how best to manage patients with AML, and how the different treatment options compare to each other in terms of clinical effectiveness and harms. Also, very little is known about the natural evolution of AMLs and the risk of bleeding. A 4 cm cut-off has traditionally been proposed to trigger active treatment. This 4 cm cut-off is nevertheless quite arbitrary and was based on the results of a literature review in 1986 [13]; however, some recent series suggest that the risk of bleeding is increased only in much larger tumours [14, 15].

This systematic review (SR) was undertaken by the European Association of Urology (EAU) Renal Cell Carcinoma (RCC) Guidelines Panel to clarify the evidence available on the natural evolution, the risk of complications and management options of sporadic AMLs The findings will be used to formulate guideline recommendations regarding the management of sporadic AML in our 2019 guidelines, ***Supplement 1***.

2. Evidence acquisition

2.1 Search strategy and Screening of Studies.

The review was undertaken by the EAU RCC guideline panel that includes urologists, oncologists, pathologists, radiologists and patient representatives. The review was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [16]. The search was conducted in accordance with the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions [17]. Studies were identified by searching electronic databases and relevant websites. Highly sensitive electronic searches were conducted to identify published and ongoing comparative studies of AML treatment. Searches were limited to studies published between 1st January 1990 and 30th June 2017 with no language restriction. The search was complemented by additional sources, including relevant systematic reviews and the reference lists of included studies which were hand searched to identify additional relevant studies.

The searched databases were MEDLINE (1946 to Present), MEDLINE In-Process (1946 to Present), EMBASE (1974 to 2017 May 11), EBM Reviews -

Cochrane Central Register of Controlled Trials (April 2017), EBM Reviews - Cochrane Database of Systematic Reviews (2005 to May 10, 2017). Systematic reviews and other background information were identified by searching the Cochrane Database of Systematic Reviews (The Cochrane Library, 2015). Additionally, clinicaltrials.gov and the World Health Organization (WHO) International Clinical Trials Registry were searched to identify ongoing trials.

The search terms included: *kidney/renal hemangiomyolipoma*, *angiomyolipoma* or *angiomyo adj2 lipoma* or *angio adj2 myolipoma* or *hemangiomyolipoma*. Full details of the protocol, search strategies and websites consulted are described in ***Appendix 1***.

Two reviewers (SFP and RT) screened all abstracts and full-text articles independently. Abstract screening disagreement was resolved by discussion, and when no agreement was reached, the manuscript was considered as 'doubtful' and subsequently included for full text screening. In case of ambiguous studies at full text screening, decision on final study inclusion was made by reviewers with help of final input by an arbitrator (KB and MH).

2.2 Types of studies

Randomized controlled trials (RCTs), quasi-RCTs and non-randomized comparative studies (NRCS) were eligible for inclusion with a minimum of 10 patients and no language restrictions. Studies with no comparative elements (i.e. single arm case series) with ≥ 10 patients were also included. Studies with mixed populations (i.e. sporadic and TS AMLs) were included if the results were reported separately for the sporadic AML subgroup. In studies whereby subgroups were not reported separately, they would still be included if the sporadic AML subgroup represented ≥ 70% of the cohort.

2.3 Types of participants included

The study population consisted of patients diagnosed with sporadic AML with available follow-up after any treatment, including surveillance. In an effort to improve homogeneity, we considered exclusively series comprising only sporadic AMLs or with a minimum of 70% of sporadic AMLs.

2.4 Types of interventions included

The interventions included were the following: surgery (NSS and radical nephrectomy), SAE, percutaneous or laparoscopic thermal ablations (radiofrequency, microwaves or cryoablation) and AS.

2.5 Types of outcome measures included

The outcomes were:

- Duration and frequency of AS
- Indications for active treatment
- Incidence of hemorrhage and active treatment during AS
- Success rate of active treatments
- Incidence of re-treatment after active treatment
- Renal function outcome after treatment when available
- Adverse events of treatments

2.6 Data extraction

A data extraction form was developed *a priori* to collect information on study design, participants, interventions, outcome measures and risk of bias or confounders. Two reviewers (SFP and RT) independently extracted data related to pre-specified outcomes.

2.7 Assessment of risk of bias (RoB) and confounders

RoB in non-randomized comparative studies was assessed using a modified Cochrane tool. This is a pragmatic approach from the methodological literature designed to report RoB in non-randomized studies [18, 19, 20]. A list of four potential confounders was defined *a priori* by the panel group: AML size, emergency cases, TS syndrome and AML-related symptoms. Overall judgement regarding each confounder was based on whether it was measured or not, balanced across groups, and if any statistical adjustment was made.

RoB in case series was assessed using a pragmatic approach based on external validity (whether study participants were selected consecutively, application of an *a priori* protocol, how attrition bias was dealt with and if outcomes were properly addressed and measured) [21, 22].

2.8 Data analysis

Descriptive statistics were used to summarize baseline characteristics. Due to the anticipated clinical heterogeneity and majority of studies being non-randomized in design, a narrative (qualitative) synthesis was planned. A quantitative synthesis (i.e. meta-analysis) could not be performed because of the low level of evidence of the reported results.

3. Evidence synthesis

3.1 Quantity of evidence identified

2704 articles were identified by the literature search. Of these, 186 studies were eligible for full text screening and after removing duplicates, 163 full texts were reviewed. Forty-three studies including 2377 patients met the inclusion criteria and were evaluated for evidence synthesis. No RCT were included. There were no direct comparative studies, only unbalanced comparative results of different treatments in the same series. **Figure 1** represents the PRISMA flow diagram outlining the study selection process.

3.2 Characteristics of included studies

The synthesis of the evidence and the description of the results were as follows:

- One arm **surveillance**: n=4 studies, 899 patients
- One arm **ablation**: n=5 studies, 68 patients
- One arm **surgery**: surgery with or without previous SAE: n=13 studies, 583 patients)
- One arm **SAE:** n=12 studies, 321 patients
- Two arms **comparative**: surgery vs. surveillance: n=3 studies, 111 patients
- Two arms **comparative**: surgery vs. SAE: n=4 studies, 248 patients
- **Three arms**: surgery, surveillance, and SAE: n=2 studies, 147 patients

The length of follow-up was not equally reported across studies, but when available median follow-up varied from 4.5 to 96 months (37 months on average). The vast majority of studies were monocentric. Twelve studies exclusively contained sporadic AMLs, twelve studies had > 90% sporadic

AMLs, twelve studies reported 70 to 90% of sporadic AMLs whilst seven studies did not clearly mention the proportions but met the inclusion criteria.

3.3 Risk of bias assessment of the included studies

Overall, the RoB across studies was moderate to high. All studies had a retrospective and non-randomized design, excepting two prospective studies.

Figure 2 presents the RoB summary and confounders. All studies had a high risk of selection, performance and detection biases. The risks of attrition and reporting bias were low, and confounders were reported in the majority of studies with a trend towards bigger size, emergency situations and AML-related symptoms.

Figure 3 represents the RoB summary for the 33 case series. In general, these studies were at high RoB regarding the selection and detection of patients, and they were at low RoB in terms of follow-up/change of treatment reporting and selective or proper outcomes measurement reporting.

3.4 Comparison of intervention results

The summary of demographic findings of all included studies based on different treatment modalities are outlined in ***Table 1***. Patients were mostly in their 4th and 5th decades, and there was a clear predominance of female gender (ratio of 4:1). AML size was reported in an inconsistent way, and there was a trend towards choosing AS for small-asymptomatic AMLs and active treatment for larger-symptomatic AMLs. Many studies relied on the 4 cm cut-off to trigger active treatment.

3.4.1 Duration and frequency of AML follow-up.

The follow-up results of different treatment modalities are summarized in ***Table 2***.

In AS patients, the length of follow-up varied from 21 to 49 months. Imaging modalities were mostly ultrasound (US) and abdominal computed tomography (CT). There was no standardized follow-up protocol throughout the studies. One

based its follow-up on AML size [23]. All the others relied on an annual schedule except the first year where patients were controlled twice.

The mean FU after surgical treatment varied from 8 to 96 months. Likewise the imaging FU was mostly based on US and CT. The frequency was increased during the first year and then patients were followed annually.

In SAE series, the mean FU varied from 15 to 85 months. The imaging also relied on US and CT. Two studies alternated CT and magnetic resonance imaging (MRI). The frequency was similar to surgery groups with imaging control every 3-6 months during the first year and then annually.

The ablative series had a mean FU ranging from 6 to 25 months. The initial FU was more frequent with imaging at three days, one month, six months and yearly thereafter.

3.4.2 Indications for active treatment

The summary of indications for active treatment is shown in ***Table 3***. Indications for active treatment in the majority of the studies were: bleeding (spontaneous rupture or hematuria), larger size (generally ≥ 4 cm) and the presence of symptoms (most commonly pain). In AS studies, the growth of AML was constantly considered as a criterion for active treatment. On the contrary, AML growth was not considered to trigger active treatment, not even in two and three arms comparative series. Cancer suspicion on imaging and patient's preference were also considered as an indication for active treatment in the majority of the studies.

The 4 cm cut-off was considered to trigger active treatment in 21%, 41% and 82% of AS, surgery, and SAE patients, respectively. In AS series the 4 cm cut-off was retained only in one study (187 out of 899 patients). In surgical series the 4 cm cut-off was taken into account in 6 of 13 studies, and concerned 238/583 patients. In SAE series the 4 cm of cut-off was applied in 8 of 9 studies (264/321 patients).

3.4.3 Outcomes in active treatment groups

Summary of outcomes in active treatment groups are outlined in ***Table 4.***

In all surgical series (except two without treatment modality specifications), there was a clear predominance of NSS. Two NSS series reported the use of SAE before surgery. In the majority of the series there was no recurrence, but three publications reported a recurrence rate comprised between 4 and 15%. Improvement or complete remission of symptoms was seen in all five series that reported it. Secondary treatment after surgery was rare (5/583, 0.85%). Renal function measurement and reporting was inconsistent (the results are summarized in ***Table 4)***.

In SAE series, there was a predominant use of polyvinyl alcohol and coil particles to perform the procedures. The recurrence rate varied from 4 to 39%. Two series reported neither recurrence nor tumour growth. Symptoms outcomes were reported in eight series including 273 patients and improvement varied from 41 to 100%. Eighty-four patients (30.7%) required secondary AML treatment: 39 for unspecified reasons, 18 for hemorrhage, 24 for AML growth and three because of symptoms. When a secondary treatment was required, SAE was used in 69 procedures and surgery in 18 procedures. Renal function changes were reported in four studies with various measurements, but renal function alteration did not seem clinically relevant (***Table 4***).

Ablative series comprised patients treated by microwave, radiofrequency and cryotherapy. There was no reported recurrence. The resolution of symptoms was complete in the single study that reported it. Secondary treatments were inconsistently reported and only one patient required another thermal ablation for a reason that was not specified. There was no change in renal function after treatment (***Table 4***).

3.4.4 Outcomes in active surveillance groups

The findings regarding the outcomes are summarized in ***table 5***.

In one-arm AS series, there was a total of 97 patients (11%) with growing AMLs. The growth rate ranged from 3 to 20%. Two studies reported an annual growth rate of 0.02 and 0.01 cm/year. Other studies reported growth according

to AML size: AMLs < 2 cm had a growth rate of 0.07 cm/year, 2 cm < AMLs < 4 cm had a growth rate of 0.1 cm/year and AMLs > 4 cm had a growth rate of 0.92 cm/year. Twenty patients (2.2%) had spontaneous bleeding or hematuria and 51 patients (5.7%) required active treatment (77% SAE, 19% surgery and 4% RFA).

3.4.5 Adverse events in active treatment groups

Adverse events of active treatment according to the Clavien-Dindo classification are highlighted in ***Table 6***.

In surgical series there were no Clavien 4-5 complications. Minor complications occurred in 19% of the cases. The hospital stay was inconsistently reported but on average varied between 2 and 9 days.

In SAE series there was only one grade 5 complication. Minor complications occurred in 179 (56%) patients. The majority of the complications were SAE syndromes. Sixteen patients required surgery or secondary embolization because of hemorrhage. Hospital stay was inconsistently reported and varied between 1.5 and 8.5 days.

No major complication was reported in ablative series (68 patients). Grade 1, 2 and 3 minor complications occurred in 12 (17.64%), 3 (4.41%) and 1 (1.47%) patients, respectively. There was no reported data regarding the length of hospital stay.

3.5 Discussion

3.5.1 Principal findings

The main indications for active treatment of AML were: 1) Increased tumour size; 2) Presence of symptoms (bleeding and pain); and 3) Suspicion of cancer on imaging. The 4 cm cut-off to trigger active treatment has been followed for decades [13], mainly based on the assumption that larger tumors have an increased risk of bleeding. However, there is very little evidence to support the 4 cm threshold. In our SR, the 4 cm cut-off was followed in 18 out of 43 studies which involved 1016 patients representing 44% of the total AML population.

Some studies considered a larger size cut-off ranging from 5 to 10 cm [27, 28, 29]. In view of the results of AS series, where a 4 cm cut-off was considered in only 187 of 899 patients (21%), there is a valid argument that active treatment should not be decided solely on the 4 cm cut-off [14, 15]. The average size of the actively treated AMLs (that did not bleed) in the largest AS series was 8 cm ranging from 0.8 to 29 cm [3]. The AML size does seem to matter but the limit upon which active treatment should be proposed cannot be well defined based on the available evidence. Other factors such as AML growth and patient's preference should be taken into account [3, 13].

One of the most relevant findings in AS series was the rate of AML growth and risk of spontaneous bleeding. In AS studies, AML size was smaller (only 13.6% of AMLs were > 4 cm) than the size reported in treated patients. We found that 11% of the patients experienced AML growth and only 2% a spontaneous rupture or hematuria. The relationship between AML size and the probability of rupture remains unclear based on our findings. However, the probability of spontaneous rupture in small AML appears to be very low [27]. Active treatment in AS series was decided in 6% of the patients. Patients were most frequently treated by SAE (77%) rather than surgery (19%). As such AS of small AMLs appears to be a safe option. More data is needed regarding AS in larger AMLs (>4 cm) as they accounted for 14% of AS patients [3].

Due to the heterogeneity of the data, surgical and SAE series were hardly comparable. The results of ablative therapies were scarcely reported in terms of recurrence, secondary treatments and complications. Tumour growth or recurrence occurred in 4-15% in patients treated by surgery and in 6-39% in patients treated by SAE. However the definition of recurrence was different throughout SAE studies. Secondary treatment rate was 1% after surgery and 31% after SAE. The preferred modality for re-treatment was SAE (60% after surgery vs. 80% after SAE) [28, 29]. Based on these data, surgical treatment seems to perform better in terms of recurrence and requirement for secondary treatment. Both surgery and SAE were comparable in terms of major complications. There was no well-defined follow-up scheme. In most series, follow-up relied on US and CT.

3.5.2 Implications for clinical practice

Despite clinical heterogeneity and uncertainty in the evidence base, the following are potentially important findings that might be highlighted.

- The growth rate of sporadic AMLs is low
- The probability of spontaneous rupture is low
- The need for active treatment is infrequent
- There is no evidence to suggest any cut-off size for active treatment, and the 4 cm cut-off should be reconsidered
- Nephron sparing surgery seems to be the most effective treatment option in order to avoid recurrence and secondary treatments

3.5.6 Strengths and limitations of the review

The review was undertaken undertaken in a rigorous manner in accordance with recognized standards by a multidisciplinary panel of clinical, methodological and patient experts (EAU RCC Guidelines Panel) according to PRISMA guidance. Overall, the certainty of the evidence obtained from this SR is low, due to the nature of available studies which were retrospective, mostly non-comparative, had high clinical heterogeneity and had moderate to high risk of bias. This nature of the available evidence made a metaanalysis inappropriate.

4 Conclusions

The systematic review found that AML is mostly managed by AS, with relatively good outcomes. The data showed that most AMLs grow very slowly, that bleeding is a rare event and that there is no clear relationship between AML size and the occurrence of bleeding, although larger AMLs do seem to have an increased risk of bleeding. Nevertheless, the 4cm cut-off which has traditionally been used as an indication for active treatment may have to be reconsidered and should not be used in isolation to trigger active treatment; other factors such as patient age, rate of growth and patient preference should also be taken into account. The most frequently reported active treatment is NSS followed by SAE, both have similar morbidity but in SAE groups there are more recurrences

and need for secondary treatment. In spite of the limitations of the evidence base, the findings of this systematic review may be of clinical importance and can be used to guide and inform clinical practice, until more robust data emerge.

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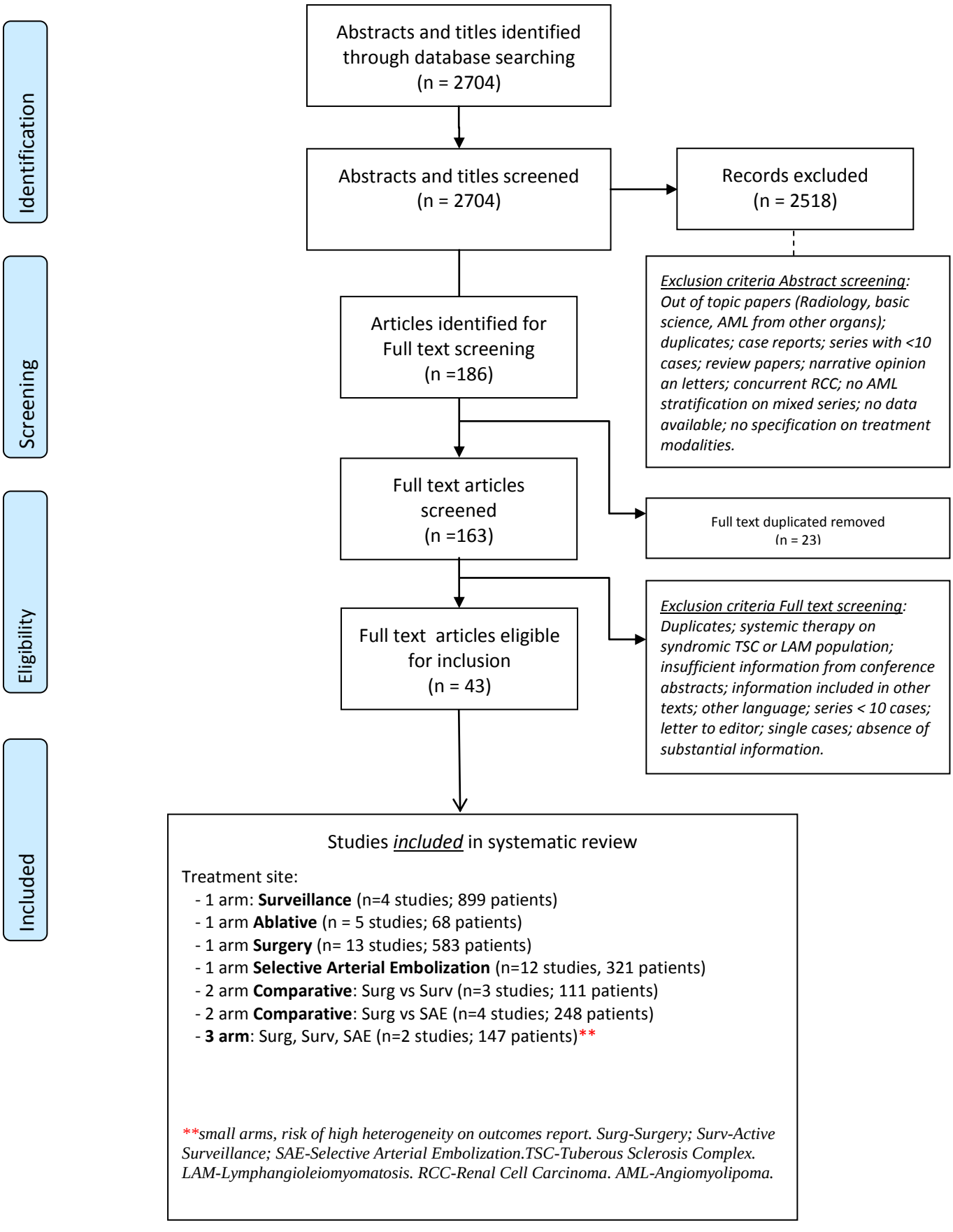
***Take Home Message**

The size beyond an AML needs to be treated remains unclear. Most small AMLs can be monitored without any active treatment. For those who need treatment, options include surgical removal or selective embolization. Surgery has a lower recurrence rate and lower need for a repeat surgical procedure.

Figure 1. AML systematic review PRISMA flow diagram



Illustration

Table 7. Risk of bias and confounder assessment for non-randomized comparative studies (n=9).

	Selection bias		Performance bias		Detection bias	Attrition bias	Reporting bias	Confounding bias 1, 2, 3 and 4			
	Random sequence generation	Allocation concealment	Blinding of patients	Blinding of personnel	Blinded outcome assessment	Incomplete outcome reporting	Selective outcome reporting	Size	Emergency	Pure Sporadic AML	symptoms
Amano 2002	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(?)	(?)	(-)
De Luca 1999	(-)	(-)	(-)	(-)	(-)	(+)	(+)	(-)	(-)	(+)	(-)
Delhorme 2017	(-)	(-)	(-)	(-)	(-)	(+)	(?)	(-)	(?)	(+)	(?)
Huyghe 2009	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(+)	(?)	(+)
Koo 2010	(-)	(-)	(-)	(-)	(-)	(+)	(+)	(?)	(?)	(+)	(?)
Faddegon 2001	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(?)	(-)
Lee 2009	(-)	(-)	(-)	(-)	(-)	(+)	(+)	(?)	(-)	(+)	(-)
Mues 2010	(-)	(-)	(-)	(-)	(-)	(+)	(+)	(-)	(-)	(+)	(-)
Seyam 2008	(-)	(-)	(-)	(-)	(-)	(+)	(+)	(-)	(-)	(+)	(-)

Green indicates low risk, red indicates high risk and yellow indicates unclear risk. Confounders:-Is the size equally distributed?-Is the emergently treated AML equally distributed?-Is the pure sporadic AML equally distributed?-Are the symptoms equally distributed?

*analyses SAE vs SAE+Surgery.

Illustration

Table 8. Risk of bias assessment for case series (n=33).

	Selection bias	Detection bias	Attrition bias	Reporting bias	
	Consecutive patients?	A priori protocol?	Loss of FU accounted for? Change of treatment accounted for?	Selective outcome reporting	Outcome appropriately measured?
Surveillance					
- Bhatt JR 2016	(+)	(+)	(+)	(+)	(+)
- Chan KE 2016	(+)	(-)	(+)	(-)	(?)
- Maclean DFW 2014	(+)	(+)	(-)	(+)	(+)
- Ouzaid I 2014	(-)	(+)	(+)	(+)	(-)
Ablative					
Zhi-yu Han 2015	(-)	(-)	(-)	(+)	(+)
Castle SM 2012	(-)	(-)	(-)	(-)	(-)
Guo H 2009	(?)	(?)	(-)	(-)	(-)
Makki A 2016	(+)	(?)	(-)	(+)	(+)
Swanson J 2012	(-)	(-)	(-)	(-)	(-)
Surgery					
Lane BR 2009	(?)	(-)	(-)	(?)	(-)
Boorjian SA 2007	(-)	(-)	(+)	(+)	(+)
Heidenreich A 2002	(-)	(-)	(+)	(+)	(+)
Minervini A 2007	(-)	(-)	(+)	(-)	(+)
Golan S 2017	(-)	(-)	(+)	(+)	(+)

Liu W 2016	(+)	(+)	(+)	(+)	(+)
Wang D 2017	(?)	(-)	(+)	(+)	(+)
Yip SKH 2000	(-)	(-)	(+)	(+)	(+)
Qin C 2017	(-)	(?)	(+)	(+)	(+)
Lin CY 2016	(+)	(-)	(+)	(+)	(+)
Ng WM 2016	(?)	(-)	(-)	(+)	(+)
Msezane L 2010	(?)	(-)	(+)	(+)	(+)
SAE					
Wang C 2017	(-)	(+)	(+)	(-)	(-)
Bardin F 2017	(?)	(+)	(+)	(+)	(+)
Chan CK 2011	(+)	(+)	(+)	(+)	(+)
Chick CM 2010	(+)	(+)	(+)	(+)	(+)
Duan XH 2016	(?)	(+)	(+)	(+)	(+)
Ramon J 2009	(?)	(?)	(+)	(+)	(+)
Sheth RA 2016	(-)	(-)	(-)	(?)	(?)
Takebayashi S 2009	(-)	(-)	(-)	(-)	(-)
Urbano J 2017	(-)	(+)	(+)	(+)	(?)
Tso WK 2005	(-)	(-)	(+)	(?)	(?)
Tillou X 2010	(-)	(-)	(-)	(?)	(-)
Chatziioannou A 2012	(-)	(-)	(+)	(-)	(-)

Green indicates low risk, red indicates high risk and yellow indicates unclear risk.

Table

Table 1. Demographic summary of included studies.

	Patients	Age - Average	Gender	% Sporadic AML	Size Average	Size Range	Size other reports	Asymptomatic	Symptomatic
Active Surveillance (1 arm)	899	[49.6-59]	155 M / 599 F	92-96.7%	1.124 cm Min NR Max NR	NR	615 < 4cm 97 > 4cm	498	69
Surgery (1 arm)	583	[40.75-57]	135 M / 448 F	85-100%	6.73 cm Min 2 cm Max 13.3 cm	[0.3-24.0]	33 < 4cm 108 >4cm	203	199
SAE (1 arm)	321	[37-59]	79 M / 251 F	75-100%	8.98 cm Min 6.68 cm Max 12.7 cm	[2.0-24.4]		112	176
Ablative (1 arm)	68	[49.2-67]	12 M / 33 F	100%	2.5 cm Min 1.5 cm Max 3.4cm	[1.0-5.5]		5	9
Active Surveillance (2 arms)	111	[46.7-56]	32 M / 79 F	90-97.14%	6.75 cm Min 1.5 cm Max 10	[0.3-30.0]	39 <5cm 14 >5cm	59	29
Surgery (2 arms)							7 <5cm 13 >5cm		
SAE (2 arms)	248	[45.2-53]	28 M / 111 F	86-90%	6.12 cm Min 3.70 cm Max 9.40 cm	[1.2-14.3]	5.5 cm SAE	122	55
Surgery (2 arms)							4.4 cm Surg		
3 arm AS	147	[35-59]	43 M / 134 F	73-75%	6.78 cm Min 1.70 cm Max 11.0 cm	[0.3-21.0]	3 cm AS	89	58
3 arm SAE							9.5 cm SAE		
3 arm Surg.							3.8 cm Surg		

NR not reported; Surg surgery; M male; F female.

Table

Table 2. Duration, frequency and imaging modalities performed throughout the different studies.

	FU Available	Frequency	Modality	Duration Month [range]
Active Surv. 1 arm				
-Bhatt 2016	Yes	Not reported	Not reported	43 [14-144]
-Chan 2016	Yes	<2cm: no FU; 2-3cm: US 5y; 3-4cm: US 2y; >4cm: consider Surgery	US	30 [8.66-51.34]
-MacLean 2014	Yes	12 mo	US and CT	21.8 [6-85.3]
-Ouzaid 2014	Yes	6 mo, 6 mo, yearly	CT	49 [9-89]
Surgery 1 arm				
-Lane 2009	Yes	Not reported	CT	40.8 [0-288]
-Boorjian 2007	Yes	Not reported	Not reported	96 [1-372]
-Heidenreich 2002	Yes	3 mo after surgery	CT	58 [3-114]
-Minervini 2007	Yes	3 mo after surgery, 6m, 6m, 6m, 6m, yearly	CT / US alternative	56 [10-120]
-Golan 2017	Yes	Not reported	Not reported	8 [1-15]
-Lui 2016	Yes	3 mo after surgery	Not reported	23.1 [17.7-18.5]
-Wang 2017 *	Yes	3 mo, 6 mo	CT	8.2 [4-20.5]
-Yip 2000	Yes	Not reported	CT	26 [1-80]
-Qin 2017 *	Yes	3m,3m,3m,3m,yearly	CT	Not reported
-Lin 2016	Yes	3m, 6m, 1y, yearly	US, if abnormality CT	40 [30.5-61.5]
-Ng 2016	Not reported	-	-	-
-Msezane 2010	Yes	Not reported	Not reported	29 (SD 20)
-Zhang 2016	Yes	Not reported	Not reported	19.5
SAE 1 arm				
-Wang 2017	Yes	Not reported	Not reported	35.9
-Bardin 2017	Yes	3 mo after SAE, yearly	CT / MRI	20.5 [0.5-56]
-Chan 2017	Yes	3 mo after SAE, 3 mo, yearly	CT	85.2 [15.6-242.4]
-Chick 2010	Yes	Not reported	CT / US	44.2 [12-116]
-Duan 2016	Yes	1 weak after SAE, 6 mo, 12 mo, 24 mo	CT	50.2 [24-72]
-Ramon 2009	Yes	3 mo after SAE, 3 mo, yearly	CT	58 [3-148]
-Sheth 2016	Yes	Not reported	CT	54 [2-266]
-Takebayashi 2009	Yes	3 mo after SAE, 6 mo, 12 mo, yearly	CT	26.4 [14.64-38.6]
-Urbano 2017	Yes	6 mo, 12 mo, 24 mo	CT / MRI	36.7 [5-124]
-Tso 2005	Yes	Not reported	CT	48 [2-84]
-Tillou 2010	Yes	Not reported	Not reported	53.2 [5-101]
-Chatziioannou 2012	Yes	Not reported	CT / US	15 [6-15]

Ablative 1 arm				
-Han 2015	Yes	3d, 3d, 1m, 3m, 3m, 3m, 3m, 6m, each 6 m	CT / CE-US / MRI	10 [6-36]
-Castle 2012	Yes	1mo after Ablation, 6mo,12mo, yearly	CT	21.2 [1.3-71.7]
-Guo 2009	Yes	1 mo after Ablation, 6 mo	CT / CE-US	14.6 [6-23]
-Makki 2016	Yes	Not reported	CT / MRI	25 [12-33]
-Swanson 2012	Yes	Not reported	MRI	6 [3-46]
Surg. vs AS 2 arm				
- Amano 2002	Not reported	-	-	-
- de Luca 1999	Yes	2 y	US	[22-164]
- Delhorme 2017	Yes	6-12 mo first 5 years, then yearly	CT	43 [1-205]
Surg. vs SAE 2 arm				
- Huyghe 2009	Not reported	-	MRI	-
- Koo 2010	Not reported	-	-	64.8 [11-97]
- Faddegon 2001	Not reported	6 mo after Surgery	-	-
- Lee 2009	Not reported	-	-	21,53 (SD22,58)
Surg., AS, SAE 3 arm				
- Mues 2010	Yes	12 mo	CT / MRI	54.8[0.2-211.7]
- Seyam	Yes	-	-	39.3 [33.9-44.7]

*includes a SAE group in addition to surgery.

Surg surgery; AS Active Surveillance; SAE Selective Arterial Embolization; CT Computed Tomography; US ultrasounds; CEUS contrast enhanced ultrasounds; MRI Magnetic resonance

Table

Table 3. Indication analysis for active treatment and size cut-off.

Intervention Group	General Indications for Active Treatment	Size Cut-off	Size Cut-off (cm)
Active Surveillance (n=4 studies; 899 patients)	-Size Growth: yes. -Bleeding: spontaneous rupture or hematuria. -Size: > 4cm -Location: no. -Pain: yes. -Cancer Suspicion on imaging: yes. -Patient preference: yes.	1 study (187/899 pts)	4 cm: 1 study (187/899)
Surgery (n= 13 studies; 583 patients)	-Size Growth: no. -Bleeding: spontaneous rupture or hematuria. -Size: >4, >5, >7, >10 cm. -Location: no. -Pain: yes. -Cancer Suspicion on imaging: yes. -Patient preference: yes.	9 Studies (325/583 pts)	4 cm: 6 studies (238/583). 5 cm: 1 study (28/583). 7 cm: 1 study (36/583). 10 cm: 1 study (23/538).
SAE (n=12 studies, 321 patients)	-Size Growth: no. -Bleeding: spontaneous rupture or hematuria. -Size: > 4, >8 cm -Location: no. -Pain: no. -Cancer Suspicion on imaging: no. -Patient preference: no.	9 Studies (274/321 pts)	4 cm: 8 studies (264/321). 8 cm: 1 study (10/321).
Ablative Therapies (n=5 studies, 68 patients)	-Size Growth: not reported. -Bleeding: not reported. -Size: not reported. -Location: not reported. -Pain: yes (9 patients) -Cancer Suspicion on imaging: not reported. -Patient preference: not reported.	0 studies	-
Surgery vs AS (n=3 studies, 111 patients)	-Size Growth: no. -Bleeding: yes. -Size: yes, but not specified. -Location: no. -Pain: yes.	1 study (23/111 pts)	<2 cm, <4cm: AS >4 cm: surgery

	-Cancer Suspicion on imaging: yes. -Patient preference: no.		
Surgery vs SAE **(n=3 studies, 213 patients) ****	-Size Growth: no. -Bleeding: yes. -Size: 4 cm -Location: no. -Pain: yes. -Cancer Suspicion on imaging: yes. -Patient preference: yes.	1 study (129/213 pts)	4 cm: 1 study (129/213 pts)
3 arm AS vs Surgery vs SAE **(n=4 studies, 177 patients)**	-Size Growth: no. -Bleeding: yes. -Size: yes, but not specified. -Location: no. -Pain: yes. -Cancer Suspicion on imaging: yes. -Patient preference: no.	1 study (87/177 pts)	4 cm: 1 study (87/177)

** Only 3 of 5 studies in Surg vs SAE report data about ‘treatment indications’.

Table

Table 4. General outcomes in active treatment modalities.

	Active Treatment modality	Growth / Relapse	Pain / Symptom Resolution	2nd Treatment Requirement	2nd Treatment Modality	Renal function evolution
Surgery						
-Lane 2009 *	Not specified	0% relapse	Not reported	0, No 2nd Treatment	-	Not reported
-Boorjian 2007	Nss	4% relapse (2 pts)	100%	1, after haemorrhage	SAE	preop cr 1 and postop 1.1
-Heidenreich 2002	Not specified	0% relapse	100%	0, No 2nd Treatment	-	preop cr 0.9 and postop 1.2
-Minervini 2007	Nss	0% relapse	Not reported	0, No 2nd Treatment	-	preop cr 0.95 and postop 0.99
-Golan 2017	Nss	0% relapse	100%	1, after haemorrhage	SAE	preop cr 0.85 and postop NR
-Liu 2016	Nss	0% relapse	Not reported	0, No 2nd Treatment	-	preop eGFR 42,5/postop 33,5
-Wang 2017	Nss +/- SAE	0% relapse	Not reported	0, No 2nd Treatment	-	Nss: preop 69,8 /postop 84,2 Nss/SAE: preop 71,1/post 70,1
-Yip 2000	Nss, RN	4% relapse	100%	1, RCC suspicion on FU	Surgery	Not reported
-Qin 2017	Nss +/- SAE	0% relapse	100%	0, No 2nd Treatment	-	Nss: <33.05%eGFRpostop Nss/sae: <15.08%eGFRpostop
-Lin 2016	Nss	0% relapse	Not reported	0, No 2nd Treatment	-	preop eGFR 102,4/postop 99,8
-Ng 2016	Nss	15% relapse (3 pts)	Not reported	Not reported	-	<11% eGFRpostop
-Msezane 2010	Nss	0% relapse	Not reported	1, contralateral AML 1, after haemorrhage	Nss SAE	preop eGFR 99,2 /postop 84
-Zhang 2016	Nss	0% relapse	Not reported	0, No 2nd Treatment	-	preop cr 92/postop 92; preop eGFR 32 / postop 32
SAE						
-Wang 2017	PVO, coils	0%	94%	39 (34 'planned'; 5 'unplanned' for growth)	39 SAE	Not reported
-Bardin 2017	10 agents	13% (3 pts)	91%	5 (4 haemorrhage, 1 growth)	4 SAE 1 Surgery	preop eGFR 78 / postop 77
-Chan 2011	PVO, coils	6% (1 pts)	81%	8 (7 haemorrhage, 1 growth)	4 SAE 4 Surgery	Not reported
-Chick 2010	PVO	17% (6 pts)	83%	5 (2 symptoms, 3 growth)	2 SAE 3 Surgery	Not reported
-Duan 2016	PVO, coils	4% (1 pts)	96%	2 (1 haemorrhage, 1 SAE syndrome)	2 Surgery	preop eGFR 58,5 /postop 73,5
-Ramon 2009	PVO	39% (16 pts)	97.5%	17 (1 haemorrhage, 16 growth)	15 SAE 2 Surgery	preop cr 0.89 / postop 0.87

-Sheth 2016	Microspheres, coils, gelatin	0% relapse	Not reported	Not reported	-	Not reported
-Takebayashi 2009	Alcohol	Not reported	Not reported	Not reported	-	4 patients > Cr 0.1-0,2 mg/dl; 1 patient > Cr 1-2 mg/dl
-Urbano 2017	EVO	0% relapse	100%	2 (2 haemorrhage)	2 SAE	Not reported
-Tso 2005	Lipids and OH	23% (3 pts)	41%	3 (3 growth)	1 SAE 2 Surgery	Not reported
-Tillou 2010	Microspheres, coils	Not reported	100%	Not reported	3 Surgery	Not reported
-Chatziioannou 2002	4 agents	Not reported	Not reported	3 (3 haemorrhage)	2 SAE 1 Surgery	Not reported
Ablative						
-Han 2015	MWA	0	100%	0	-	Not reported
-Castle 2012	RFA	Not reported	Not reported	Not reported	-	Not reported
-Guo 2009	RFA	0	Not reported	Not reported	-	Not reported
-Makki 2016	Cryotherapy	Not reported	Not reported	Not reported	-	Not reported
-Swanson 2012	RFA, cryotherapy	0	Not reported	Not reported	1 Ablative	preop eGFR 77 / postop eGFR 75

Nss Nephron Sparing Surgery; RN Radical Nephrectomy; SAE Selective Arterial Embolization; cr serum creatinine; eGFR estimated glomerular filtration rate; preop preoperative; postop postoperative; PVO polyvinyl alcohol; EVO Ethilenvinyl alcohol; MWA microwave ablation; RFA radiofrequency ablation;

*no specification about the modality of surgery (radical or nephron sparing) or approach.

Table

Table 5. Success and Outcomes in active surveillance groups.

	Growth	Growth rate cm/y	Spontaneous bleeding / hematuria	Active Treatment (patients)	Active Treatment modality (treatments)
Surveillance 1 arm 4 studies=899pts					
- Bhatt 2016	9% (40 pts)	0,021	12 pts	5.59% (25)	SAE 22 (73.3%); Surgery 4 (13.3%); RFA 2 (6.7%); mtor 2 (6.7%)
- Chan 2016	19.78% (37 pts)	0,013	1 pts	3.2% (6)	SAE 6 (100%)
- Maclean 2014	11.85% (16 pts)	<2cm (0.07); 2-4cm(0.1); >4cm(0.92)	3 pts	2.22% (3)	SAE 2; Surgery 1
- Ouzaid 2014	3% (4 pts)	Not reported	4 pts	13.07% (17)	SAE 11 (64.7%); Partial neph 5 (29.4%); mtor 1 (5.9%)
	97/899		20/899	51/899	SAE 41, Surgery 10, RFA 2, mtor 3

mtor mammalian target of rapamycin

Table

Table 6. Adverse events in active treatment modalities according Clavien-Dindo (CD) system and hospital length stay.

	CD 1	CD1 explanation	CD 2	CD2 explanation	CD 3	CD3 explanation	CD 4	CD4 explanation	CD 5	CD5 explanation	Hosp Stay Day av. [range]
Surgery											
-Lane 2009	-	e	-		-		-		-		-
-Boorjian 2007	5	5-ileus	14	1-Infection 13-Transfusion	4	1-Hemorrh-SAE 3-Urinoma-Stent	-		-		6 [2-13]
-Heidenreich 2002	-		0		3	2-3a 1-3b	-		-		-
-Minervini 2007	-		2	1-Infection 1-Transfusion	1	1-Infection-drain	-		-		6 [5-11]
-Golan 2017	3	1-Urinoma 1-ileus 1-Atrial Fibr.	4	2-Infection 2-Transfusion	1	1- Hemorrh-SAE	-		-		2 [2-3]
-Liu 2016	-		1	1-Transfusion	-		-		-		-
-Wang 2017	1	1-Urinoma	4	1-Infection 2-Pain-SAE sd 1-Transfusion	-		-		-		-
-Yip 2000	-		1	1-CVAtransient	1	1-AV fistula-SAE	-		-		9 [6-21]
-Qin 2017	-		4	4-Transfusion	-		-		-		5 (+/-1,3)
-Lin 2016	1	1-ileus	4	1-ileus 3-transfusion	-		-		-		8 (+/-1,4)
-Ng 2016	-		3	1-infection 3-transfusion	-		-		-		3,3 [2-8]
-Msezane 2010	-		1	1-Transfusion	1	1-Pseudoan-SAE	-		-		2.3 (SD 2.6)
-Zhang 2016	NR		NR		NR		NR		NR		7 (SD2)
SAE											
-Wang 2017	-		69	68-SAE sd 1-Infection	-		-		-		NR

-Bardin 2017	-		15	1-Infection 14-SAE sd	6	2-Infection-drain 3-Hemorrh-SAE 1-Hemorrh-Surg	-		1	1-CVA brain	NR
- Chan 2011	-		11	11-SAE sd	6	3-Hemorrh-SAE 3-Hemorrh-Surg	-		-		5-7 [5-20]
- Chick 2010	-		12	1-Infection 11-SAE sd	-		-		-		NR
- Duan 2016	-		15	15-SAE sd	2	1-SAE sd-Surg 1-Hemorrh-Surg	-		-		NR
- Ramon 2009	-		5	5-SAE sd	1	1-Hemorrh-Surg	-		-		NR
-Sheth 2016	-		6	6-SAE sd	2	2-Infection-drain	-		-		NR
Takebayashi'09	NR		NR		NR		NR		NR		[2-4]
-Urbano 2017	0		5	5-SAE sd	0		0		0		1.5 [1-3]
- Tso 2005	0		6	6-SAE sd	0		0		0		NR
- Tillou 2010	NR		11	10-SAE sd 1-Infection	0		0		0		8.5 [1-28]
- Chatziioannou	-		4	4-SAE sd	3	2-Hemorrh-SAE 1-Hemorrh-Surg	-		-		6 [2-8]
Ablative											
-Han 2015	11	11-pain	1	1-Infection-AB	1	1-Colonic injury-Surg	-		-		NR
-Castle 2012	NR		NR		NR		NR		NR		NR
-Guo 2009	NR		NR		NR		NR		NR		NR
-Makki 2016	1		2		-		-		-		NR
-Swanson 2012	NR	1-skin enfisema	NR	2-transfusion	NR		NR		NR		NR
Surg vs Surv											

3 studies with inconsistent report of adverse events, except one which reports: C1+C2=15; C3+C4+C5=0.											
Surg vs SAE											
4 studies with inconsistent report of adverse events, except one with more blood loss for SAE and better hospital stay for SAE (16 vs 19 pts)											

CD 1 Clavien-Dindo grade 1; CD 2 Clavien-Dindo grade 2; CD 3 Clavien-Dindo grade 3; CD 4 Clavien-Dindo grade 4; CD 5 Clavien-Dindo grade 5; NR nor reported; SAE Selective arterial embolization; hemorrh hemorrhage; Surg surgery; sd syndrome; AB antibiotic;

Supplementary file

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