RECOMMENDATIONS / Genito-urinary imaging

Kidney damage due to tuberous sclerosis complex: Management recommendations

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KEYWORDS
Tuberous sclerosis complex;
Kidney;
Angiomyolipoma;
Embolisation;
mTOR

Abstract
Objective: To deduce recommendations from the literature on the management of kidney damage caused by tuberous sclerosis complex (TSC).

Material and methods: Five practitioners have written up recommendations after reviewing the literature. They were evaluated by 14 experts using a 9 level scale (1: complete disagreement; 9: complete agreement), then reworded until each item received a median score of greater than or equal to 8.

Results: Forty-eight to 80% of patients with TSC have kidney disease with the presence of angiomyolipomas (AML), cysts, cancers and/or progression towards renal insufficiency. An abdominal ultrasound (and serum creatinine level if there is an abnormality) is recommended as soon as the TSC is diagnosed. The evaluation should be repeated every 3 to 5 years if it is normal. Numerous and voluminous cysts are suggestive of associated polycystosis. After 20 years of age, the monitoring should be based on CT scan or MRI, which are more precise in the monitoring of AML. The biopsy of a renal mass should be discussed if there are calcifications, central necrosis

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Tuberous sclerosis complex (TSC) is a autosomal dominant phakomatosis affecting approximately one in 6000 births, with a prevalence of one in 11,000 to 14,000 after the age of 10 years [1,2]. It is caused by damage to the TSC1 (9q34) or TSC2 (16p13) genes coding respectively for hamartin and tuberin, which regulate cell proliferation and the mTOR route. TSC is characterised by the growth of multiple hamartomatous lesions (brain, skin, kidneys, heart, lungs, retina, etc.). The neurological signs are predominant with epilepsy, mental retardation and/or behavioural disorders such as autism [1,3].

Kidney damage is the second cause of mortality/morbidity all ages combined and the first cause of mortality after 30 years of age [4–7]. It affects 48 to 80% of patients [5,8–11], and is dominated by the onset of angiomylipomas (AMLs), cortical cysts, malignant lesions or lesions with malignant potential (renal cell carcinomas, epithelioid angiomylipomas [EAMLs]) and/or chronic renal insufficiency (CRI).

Renal AMLs affect 34 to 80% of patients [8–10,12,13]. They are numerous, bilateral and voluminous [14–17], especially if there is mutation of TSC2 [10,13] or intellectual retardation [13,18]. Patients with TSC appear to have more common retinal hamartomas, cardiac rhabdomyomas and cutaneous lesions [4]. The main complication of AML is spontaneous haemorrhagic rupture, which can require a nephrectomy or emergency embolisation. AMLs can also destroy the renal parenchyma and create CRI [16,19].

Renal cysts affect 14 to 45% of adults with TSC and 10 to 20% of children [5,8,10,12,20]. Small and rarely symptomatic [10,21], their number is less than 5 in 45 to 64% of cases. They are bilateral in 22 to 60% of cases [10,20].

The progression towards CRI, which is a cause of death in adulthood [7], concerns less than 2 to 5% of patients [21–23]. It can be iatrogenic (nephrectomy, embolisations, drug toxicity), or caused by AMLs or renal polycystosis (RPC) [9,19,20,24]. The TSC2 gene is the neighbour of the PKD1 gene (16p13.3) involved in adult dominant RPC. A deletion that simultaneously affects both genes can give rise to RPC that can be detected starting in childhood and causes terminal CRI in the second or third decade of life ("TSC2/PKD1 contiguous gene syndrome"). [3,5,25].

The association between TSC and malignant kidney tumours remains a subject of debate [26], with a cancer rate of 0.5 to 4.2% [5,8,10]. Paediatric cases and multiple tumours [27,28] have given rise to the hypothesis that TSC could be a risk factor, but this remains controversial [26]. Certain cancers described could also correspond to EAMLs, a potentially malignant variant of AMLs [6,29–34].

The management of renal damage caused by TSC, which is potentially serious, is still not very standardised. The objective of this work is to summarise this renal damage and deduce recommendations for management from the literature.

Material and methods

In September 2008, the French Reference Centre on TSC called on the Urology, Nephrology and Imaging Departments of French University Hospital Centres (UHCS) to establish recommendations on the treatment of renal damage caused by TSC. In May 2009, the physicians who were interested in nine UHCS wrote up 10 practical questions that should be the object of recommendations. Five practitioners (OR, HN, LZ, NG, ELC) wrote up, after reviewing the literature, a first version of the recommendations, which was evaluated by a panel of experts. The agreement of the experts for each item was estimated using a Likert scale with nine levels (1: complete disagreement; 9: complete agreement) and free comments. The recommendations were reworded until each item received a median score of greater than or equal to 8.

Clinical questions and recommendations

Should kidney damage caused by tuberous sclerosis complex be screened for?

The objective of screening for kidney damage caused by TSC is the prevention of the progressive risks (death, bleeding, CRI, cancer). Its benefit on the incidence of complications and morbidity/mortality has not been studied. However, a renal evaluation should be a part of the initial treatment of patients for most of the authors [1,4,9,20,24,35,36].

RECOMMENDATION 1: NEED FOR SCREENING FOR KIDNEY DAMAGE

Due to their frequency and severity, the screening and monitoring of renal lesions is indicated in all patients with TSC. The initial renal evaluation should make it possible to advise the family and the patient and to plan the follow-up and treatment (type of imaging, frequency, prophylactic treatment).
What type of monitoring should there be before the age of 20?

Kidney damage caused by TSC develops mainly before 20 years of age. In 41 patients, its prevalence was 19% before 7 years of age, 33% between 8 and 16 years of age and 62% after that [21]. In 60 children, the rate of kidney damage went from 55% at the beginning of monitoring (mean age, 6.9 years) to 80% at the end of the study (mean age, 10.5 years) [9]. The median age of detection for the first abnormality was 7.2 to 11.1 years [9,10,20,21]. Cysts can exist starting from birth, and AMLs can appear during the first 2 years of life [9,20]. The kidney damage appears to be constituted at the end of adolescence [9,21], with a few observations of abnormalities that appeared after 20 years of age [10,21]. In these cases, the kidney damage was detected by ultrasound, which is less sensitive than a CT scan. Certain patients could thus have moderate abnormalities that were not detected before 20 years of age.

AMLS grow in the second decade of life [9,10,20,21] with growth that can reach more than 4 cm per year [9,10]. Bleeding complications remain exceptional before 20 years of age [10,21].

The course of the cysts is variable: disappearance [9] or progression in size and in number [4,20]. Simple cysts that are not very numerous and not very progressive should be differentiated from RPC-related cysts, which are numerous, voluminous, bilateral and precocious [21].

The monitoring protocols in the literature are variable (Table 1). They prefer ultrasound (less expensive and non-radiating) in patients under 20 years of age, and they have relatively spaced-out follow-up (rareness of complications in this age bracket) [5,20,21,37,38].

RECOMMENDATION 2: SCREENING AND MONITORING DURING THE FIRST TWO DECADES OF LIFE

2a An abdominal ultrasound should be performed as soon as the TSC is diagnosed. It should be completed with an evaluation of kidney function (serum creatinine level) if the ultrasound is abnormal.

2b This evaluation should be repeated every 3 to 5 years if it is normal and every 2 to 3 years if the ultrasound only demonstrates a few cysts or AMLs of less than 4 cm.

2c If there are many voluminous bilateral cysts, associated polycystosis should be suspected. Due to the risk of rapid progression towards terminal renal insufficiency (second or third decade of life), renal function and blood pressure should be monitored every 12 months and the patient should be oriented towards a nephrology consultation.

2d The onset of symptoms that are compatible with a renal complication (pain in the side, abdominal heaviness, haematuria, state of shock), the rapid growth of an AML, AML size of greater than 4 cm or the development of a suspicious tissue mass seen on the ultrasound should result in a CT scan or MRI.

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Table 1  Patient monitoring suggestions in the literature.

<table>
<thead>
<tr>
<th>Author</th>
<th>Institution</th>
<th>Proposed monitoring</th>
</tr>
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<tbody>
<tr>
<td>Cook, 1996 [5]</td>
<td>Saint-James University Hospital, Leeds, UK</td>
<td>Abdominal ultrasound upon diagnosis of TSC</td>
</tr>
<tr>
<td></td>
<td>University Hospital of Wales, UK</td>
<td>Abdominal ultrasound every 5 years if negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abdominal ultrasound ever 1 to 2 years if AML</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT scan or MRI if there is a doubt about a malignant lesion</td>
</tr>
<tr>
<td>Ewalt, 1998 [9]</td>
<td>University of Texas, USA</td>
<td>Ultrasound every 2 to 3 years before puberty</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Annual ultrasound after this</td>
</tr>
<tr>
<td>Bradshaw, 1998 [38]</td>
<td>Scottish collaborative project</td>
<td>Ultrasound at 5 years of age</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ultrasound every 5 years if negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ultrasound and serum creatinine level every 2 to 3 years if renal abnormalities of &lt; 4 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ultrasound every year if renal abnormalities &gt; 4 years</td>
</tr>
<tr>
<td>Casper, 2002 [20]</td>
<td>Children’s Hospital Medical Centre, Cincinnati, Ohio, USA</td>
<td>No monitoring via imaging during the first decade of life</td>
</tr>
<tr>
<td>Castagnetti, 2007 [21]</td>
<td>University of Padua, Italy</td>
<td>Ultrasound every 2 years if negative or if lesions are small</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ultrasound every 6 to 12 months if lesions are voluminous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT scan or MRI only if there are symptoms</td>
</tr>
</tbody>
</table>

TSC: tuberous sclerosis complex; AML: angiomyolipomas.
What kind of monitoring in adulthood?

After the age of 20, the growth of AMLs slows down. We do not know if there is an age beyond which growth is zero [10]. Long-term monitoring of renal abnormalities has not been studied. Adults with kidney damage have three major risks: haemorrhagic rupture of an AML (most often after 20 years of age), CRI due to progressive destruction of the kidneys by AMLs (RPC is generally diagnosed before 20 years of age) or a malignant tumour.

These risks justify, in some cases, the need for monitoring using imaging [10,16]. The ultrasound is not ideal, as it does not assess the size of the AMLs well, especially if they are coalescent. CT scan and MRI have better precision [39,40]. CT scan, thanks to its short acquisition time, can make it possible to avoid general anaesthesia, but repeated use exposes the patient to high doses of radiation [40,41]. Non-radiating MRI is an alternative for monitoring, but its duration can make general anaesthesia necessary.

**RECOMMENDATION 3: MONITORING MODALITIES IN ADULTS**

3a Long-term monitoring of kidney damage is recommended to follow-up the progression of AMLs and to make sure that malignant tumours and renal insufficiency do not occur. The imaging monitoring in adults should be based on CT scans or MRIs (preferably MRIs to reduce patient exposure to radiation) rather than ultrasounds.

3b In asymptomatic patients with at least one AML of more than 4 cm, assay of serum creatinine and a CT scan or MRI examination should be carried out every 2 years. This frequency should be adjusted based on the progression of the AMLs.

3c In asymptomatic patients who do not have renal abnormalities or AMLs of less than 4 cm, the morphological monitoring (CT scan or MRI) and kidney function monitoring can be gradually spaced-out, especially if the results are stable.

3d The onset of symptoms that are compatible with a renal complication (pain in the side, abdominal heaviness, haematuria, state of shock) should result in a CT scan or MRI examination immediately.

How to distinguish between an angiomyolipoma and a malignant tumour. Are there indications for percutaneous biopsy of kidney masses?

On ultrasounds, AMLs are homogeneous and hyperechogenic [42–45] with a non-pathognomonic appearance, since up to 8% of kidney cancers are hyperechogenic [45]. AML is, with a few rare exceptions [46–49], the only kidney tumour that contains a fatty contingent. CT scan thus confirms the diagnosis by showing the presence of fat in the tumour (areas of negative density) [43,50,51]. MRI is not used very commonly in the positive diagnosis of renal AMLs.

Certain AMLs have a very minority fatty contingent (< 10% [52]), which is undetectable on the CT scan. These "fat poor AMLs" account for 2.5 to 6.9% of operated kidney tumours [53–55]. Ultrasound is not informative, as fat poor AMLs are generally iso- or hypoechogenic [56–58]. Up to 39% of AMLs associated with TSC appear not to have a fatty component that can be visualised using CT scan [59]. Therefore, we cannot suggest biopsy for all renal masses that do not contain fat of patients with TSC. The main criteria for suspecting a cancer are rapid growth, calcifications, or central necrosis [60]. The interpretation of the speed of growth must take into account the circumstances where the AMLs progress: adolescence, pregnancy or oestro-progestin treatment [9,10,14,20,61–63]. In 12 patients (206 renal masses) monitored for a duration of 2 to 8 years (median, 4 years), three fast-growing masses (> 0.5 cm/year) were reported, including a renal cell carcinoma confirmed by biopsy [59]. As the AMLs associated with TSC are generally multiple and bilateral, the discovery of a single renal mass without a fatty contingent can also be a cause for biopsy.

**RECOMMENDATION 4: INDICATIONS FOR THE BIOPSY OF RENAL MASSES**

4a Given the high proportion of fat poor AMLs associated with TSC, the absence of fat in a renal mass is not a sufficient criterion for proposing a biopsy.

4b A biopsy can be considered to rule out a malignant tumour if there are calcifications, central necrosis or rapid growth of a mass without a fatty contingent, or if there is a single renal mass without a fatty contingent.

Should pulmonary lymphangioleiomyomatosis systematically be screened for in patients with renal damage caused by tuberous sclerosis complex?

Pulmonary lymphangioleiomyomatosis (LAM) is a rare disease that can be isolated or associated with TSC. It concerns almost exclusively adult women and combines pneumothorax, chylothorax and dyspnoea that can lead to terminal respiratory insufficiency. Chylous ascites and lymphangiomas can also be encountered [64,65].

In 388 patients (of both sexes) with TSC, 9 (2.3%, all women) had symptomatic LAM [66]. Three studies have researched the existence of LAM using chest CT scans in patients with TSC: 26 to 39% of these patients had pulmonary cysts that were compatible with asymptomatic LAM [67–69]. LAM is commonly associated with renal AMLs (32 to 53%) [65,70]. The incidence of LAM in patients with bilateral AMLs has been estimated to be between 6.4% and 24.8% [64]. The European Respiratory Society has recommended systematic screening for LAM using a chest CT scan in all women with TSC at 18 years of age, then, if this first CT scan is negative, at 30 to 40 years of age. The chest CT scan is only indicated in men if they have respiratory symptoms [64].
RECOMMENDATION 5: CHEST CT SCAN TO SCREEN FOR RELATED LAM

5a A chest CT scan without injection to screen for pulmonary LAM should be systematically carried out in all women with TSC without respiratory symptoms (with or without kidney damage) at 18 years of age, then, if negative, at 30 to 40 years of age.

5b Systematic screening for LAM is not necessary in men with TSC (even with kidney damage) without respiratory symptoms.

5c The onset of respiratory symptoms (unexplained dyspnoea, pneumothorax) should result in a chest CT scan regardless of the sex of the patient.

What therapeutic strategy should be adopted in case of spontaneous rupture of an angiomyolipomas?

Spontaneous rupture of an AML ranges from a limited and resolving perirenal haematoma to fatal bleeding. Conservative treatment (intensive care and transfusions) can prevent renal procedures in the long-term [71], but in principle, a spontaneous rupture requires treatment to avoid putting the patient’s life in danger and to prevent a relapse [5,14,33,72–82].

Conservative surgery, which is difficult in an emergency situation, often ends up in a haemostasis nephrectomy. Percutaneous embolisation can treat the origin of the bleeding with a low complication rate (Table 2). Bleeding relapses after emergency embolisation can occur (0 to 60% of cases) in a time period of up to 3 years. They are generally treated with success via a second embolisation [72–74,78,83]. Use of surgery is rare when embolisation is used as first-line treatment (Table 2).

RECOMMENDATION 6: TREATMENT OF A SPONTANEOUS HAEMORRHAGIC RUPTURE OF AN AML

6a Patients should be informed of the risk and clinical signs of a haemorrhagic rupture of an AML (acute pain in the side, state of shock) and the hospital centres that are able to treat these acute ruptures that are near their homes should be identified.

6b Embolisation should be proposed as first-line treatment in case of spontaneous haemorrhagic rupture of an AML.

6c Surgery should only be used in cases where embolisation is not available in an emergency context or not technically possible. It should be as conservative as possible.

Should angiomyolipomas associated with tuberous sclerosis complex be treated preventively? If yes, based on what criteria and using what technique?

Sporadic AMLs of more than 40 mm have more risks of complications. Preventive treatment with embolisation or surgery is recommended [14,76,84–86].

AMLs associated with TSC progress more quickly [15] and appear to become complicated more frequently [15,72,74,87]. A threshold of 35 mm has thus been suggested for their prophylactic treatment [88]. However, the frequency of their complications could simply be due to their larger mean diameter and their larger number per patient.

In two studies, the mean size of the AMLs (sporadic or associated with TSC) embolised for bleeding was 85 mm (35 to 200 mm) and 78 mm (45 to 180 mm) [75,89] and the individual bleeding risk remains moderate, even in patients with TSC (approximately 6%) [10]. Some have thus suggested a threshold of 80 to 100 mm for the prophylactic treatment of AMLs associated with TSC [33,85].

The size alone, however, does not appreciate the risk of bleeding very well. The relative importance of the vascular and fatty contingents and the existence of intra-tumoural micro-aneurisms of greater than 5 mm could also be risk factors [90,91]. Unfortunately, the detection of micro-aneurisms requires arteriography.

Surgery or embolisation can be used for the preventive treatment of AMLs.

Surgical removal of sporadic AMLs has a low risk of complications and relapse (Table 3) [92–96]. However, partial surgery is clearly more complicated in TSC due to the multiplicity of AMLs.

Embolisation appears to be the easiest solution for AMLs in patients with TSC, with few complications [Table 2] [33,37,73–75,77,80–83,89,97,98]. Six to 100% of patients have a “post-embolisation syndrome” with lumbar pain and fever, which can be controlled with a non-steroidal anti-inflammatory treatment [73] or short-term corticosteroid treatment [99]. Embolisation causes a reduction in the diameter of the treated AML, the importance of which (20 to 70%) depends on the proportion of vascular and fatty contingents. The fatty part of the AML does not regress very much after embolisation [37,75,81,82,87,89,90,98] but there are however some exceptions [100]. The reduction in size is accentuated over time: in the Takemayashi et al. series, it was 29.4%, 45.7% and 59.3% at 3, 6 and 12 months, respectively [101]. Embolisation can be repeated during monitoring in 6 to 50% of patients (Table 2). In a series of 44 treated kidneys, survival without re-embolisation was 71% at 5 years and 37% at 10 years, and survival without surgery was 94% at 5 and 10 years [73]. Embolisation, therefore, appears to avoid surgery, but at the price of repeated sessions. The percentage of spontaneous bleeding after embolisation is low (0 to 5.3%, Table 2).
<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Pts</th>
<th>% Pts TSC</th>
<th>Embolic agent</th>
<th>% acute bleed.</th>
<th>Mean size (mm)</th>
<th>% failure</th>
<th>Post-embol. syndrome (%)</th>
<th>Major complications (%)</th>
<th>% Re-embol.</th>
<th>% post-embol. bleed.</th>
<th>Post-embol. surgery</th>
<th>Mean follow-up (months)</th>
</tr>
</thead>
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<tr>
<td>Han, 1997 [98]</td>
<td>14</td>
<td>7.1</td>
<td>Alcohol + lipiodol, alcohol alone, coils + microparticles + gel foam</td>
<td>0</td>
<td>110 (40–350)</td>
<td>0</td>
<td>100</td>
<td>Abscess (drainage, n = 1)</td>
<td>14.3</td>
<td>0</td>
<td>7.1</td>
<td>&gt; 12 months in 12 pts</td>
</tr>
<tr>
<td>Harabayashi, 2004 [33]</td>
<td>12</td>
<td>100</td>
<td>Alcohol + coils</td>
<td>0</td>
<td>ND</td>
<td>0</td>
<td>ND</td>
<td>Renal atrophy (n = 1)</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>60 (12–170)</td>
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<td>Ewalt, 2005 [37]</td>
<td>16</td>
<td>100</td>
<td>Microparticles</td>
<td>18.8</td>
<td>ND (40–210)</td>
<td>0</td>
<td>68.8</td>
<td>Pneumonia (n = 1)</td>
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<td>ND</td>
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<td>Khotary, 2005 [74]</td>
<td>19</td>
<td>52.6</td>
<td>Alcohol + lipiodol</td>
<td>36.8</td>
<td>ND</td>
<td>0</td>
<td>100</td>
<td>31.6a</td>
<td>5.3</td>
<td>0</td>
<td>1</td>
<td>51.5 (6–132)</td>
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<td>William, 2006 [82]</td>
<td>16</td>
<td>100</td>
<td>Microparticles ± coils</td>
<td>37.5</td>
<td>NDb</td>
<td>0</td>
<td>6.2</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>40 (6–62)</td>
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<tr>
<td>Dabbeche, 2006 [75]</td>
<td>37</td>
<td>10.8c</td>
<td>Microparticles ± coils ± Alcohol</td>
<td>43.2</td>
<td>78 (45–180)/53 (40–110)d</td>
<td>8.1</td>
<td>16.2</td>
<td>Arterial breach (nephrectomy, n = 1), arterial dissection (stent, n = 1)</td>
<td>10.8</td>
<td>2.7e</td>
<td>32.4 (50/21.1)d</td>
<td>21</td>
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<td>Lenton, 2008 [80]</td>
<td>17</td>
<td>70</td>
<td>Microparticles (350–500 μm) ± coils</td>
<td>43.5</td>
<td>ND</td>
<td>0</td>
<td>30.4</td>
<td>0%</td>
<td>17.6</td>
<td>4.4</td>
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<td>Chick, 2009 [97]</td>
<td>34</td>
<td>26</td>
<td>Alcohol + lipiodol</td>
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<td>119 (29–244)</td>
<td>0</td>
<td>32.4</td>
<td>Renal infarction (n = 1)</td>
<td>5.9</td>
<td>0</td>
<td>8.8</td>
<td>44 (12–116)</td>
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<td>Sooriakumaran, 2009 [83]</td>
<td>19</td>
<td>26.3</td>
<td>ND</td>
<td>31.6</td>
<td>ND</td>
<td>0</td>
<td>15.8</td>
<td>Abscess (n = 1), renal atrophy (n = 1), refractory hypertension (n = 1)</td>
<td>36.8</td>
<td>0</td>
<td>5.3</td>
<td>ND</td>
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<td>Lee, 2009 [81]</td>
<td>11</td>
<td>36.4</td>
<td>Gel foam ± coils, alcohol + lipiodol</td>
<td>36.4</td>
<td>85 (45–128)</td>
<td>18.2</td>
<td>63.7</td>
<td>Abscess (drainage, n = 1)</td>
<td>9.1</td>
<td>0</td>
<td>9.1</td>
<td>28.2 (8.8–84.5)</td>
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<tr>
<td>Author</td>
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<td>% Pts</td>
<td>Embolic agent</td>
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<td>Post-embol. surgery</td>
<td>Mean follow-up (months)</td>
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<tr>
<td>Ramon, 2009</td>
<td>41</td>
<td>19.5</td>
<td>Alcohol + microparticles (45–50 µ) ± coils Coils, alcohol + lipiodol, microparticles (150–250 µ) Microparticles (40–1200 µ)</td>
<td>24.4</td>
<td>103 (25–200)</td>
<td>0</td>
<td>12.5</td>
<td>0</td>
<td>36.6</td>
<td>0</td>
<td>7.3</td>
<td>57</td>
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<tr>
<td>Chan, 2011</td>
<td>27</td>
<td>3.7</td>
<td>Alcohol + microparticles (45–50 µ) ± coils Coils, alcohol + lipiodol, microparticles (150–250 µ) Microparticles (40–1200 µ)</td>
<td>53.6</td>
<td>109 (4–30)</td>
<td>7.1</td>
<td>40.7</td>
<td>0</td>
<td>14.8</td>
<td>0</td>
<td>14.8</td>
<td>85 (15–242)</td>
</tr>
<tr>
<td>Villalta, 2011</td>
<td>48</td>
<td>34.8</td>
<td>Alcohol + microparticles (45–50 µ) ± coils Coils, alcohol + lipiodol, microparticles (150–250 µ) Microparticles (40–1200 µ)</td>
<td>44.7/7.1f</td>
<td>78 (35–320)/85 (35–200)f</td>
<td>ND</td>
<td>6.2</td>
<td>Acute dyspnoea (n = 3), abscess (nephrectomy, n = 1), common femoral lesion (n = 1)</td>
<td>29.2</td>
<td>0</td>
<td>2.1</td>
<td>20/21f</td>
</tr>
</tbody>
</table>

Only the series of more than 10 patients were taken into account. Bleed.: bleeding; Pts: patients; embol.: embolisation; TSC: tuberous sclerosis complex.

- Only in TSC patients.
- Mean volume: 315 cc (27.8 to 814.4 cc).
- Plus two patients with pure LAM.
- Emergency embolisation/planned embolisations.
- Twice.
- TSC patients/non TSC patients.
RECOMMENDATION 7: PREVENTIVE TREATMENT OF AMLs

7a Any preventive treatment of an AML must be validated in a multidisciplinary manner and discussed with the patient and his or her family, who must be informed of the potential complications of treatment and the uncertainties with regard to the prediction of the bleeding risk.

7b A preventive treatment is recommended for asymptomatic AMLs cumulating bleeding risk factors: size greater than 80 mm, predominant vascular contingent, presence of micro-aneurisms.

7c A preventive treatment can be considered for AMLs that are greater than 40 mm after informed consent of the patient and his or her family, especially if there are other risk factors (risks of lumbar trauma, intention to become pregnant, anti-coagulant treatment, distance from a healthcare centre, etc.). It must be validated in a multidisciplinary manner (7a).

7d When preventive treatment of an asymptomatic AML is decided, embolisation must be suggested as first-line treatment.

7e Embolised AMLs must be checked by CT scan (or MRI) at 1 and 2 years. If the result is good, monitoring every 2 years is sufficient from that point on (3b).

7f When there is an indication for preventive treatment, surgery can be an option if there is failure of embolisation or in certain particular cases (isolated AML, exo-renal location, predictable difficulties for post-embolisation follow-up, etc.).

RECOMMENDATION 8: EMBOLISATION TECHNIQUE

8a Embolisation must concern both the tumour bed and the proximal trunks upstream of the micro-aneurysms.

8b If microparticles are used, their size must be greater than 500 µ to reduce the risk of intrapulmonary passage.

8c Ethanol is effective but must only be used by teams that have been trained in its endovascular use.

What advice should be given to a woman with angiomyolipomas who would like to become pregnant or who would like a contraceptive treatment?

Pregnant patients should know that the child has a 50% risk of being a carrier of the disease.

Pregnancy and oestro-progestin contraception are risk factors for the progression and/or spontaneous rupture of AMLs [61,62,106–112].

Patients with a related LAM have an increased risk of pneumothorax and chylothorax in case of pregnancy and administration of oestrogen can accelerate the degeneration of their respiratory function [64].

RECOMMENDATION 9: ADVICE FOR PATIENTS WHO WOULD LIKE TO BECOME PREGNANT OR WHO WOULD LIKE AN OESTRO-PROGESTIN TREATMENT

9a Patients with TSC who would like to become pregnant must have a genetic consultation before any conception.

9b Patients with TSC who would like to become pregnant must be informed of the risks inherent to a possible pregnancy: AML rupture and (in case of related pulmonary LAM) risks of pneumothorax, chylothorax and progression of respiratory insufficiency.

9c Patients with TSC who have renal AMLs (and/or pulmonary LAM) should avoid oestrogenic treatments (oestro-progestin pill, oestrogen replacement treatment) due to the risk of rupture of renal AMLs and progression of the pulmonary LAM.

9d A preventive treatment can be considered for AMLs greater than 40 mm after informed consent of the patient and of his or her family, and multidisciplinary discussion, if the patient would like to become pregnant (7c).

Is there a role for treatment with mTOR inhibitors?

Two prospective non-randomised studies used sirolimus [113,114]. One randomised study (everolimus versus placebo) is ongoing.
### Table 3  Results of the main series of surgery of angiomyolipomas.

<table>
<thead>
<tr>
<th></th>
<th>Number of Pts</th>
<th>TSC Pts (%)</th>
<th>Mean size (mm)</th>
<th>Nephrectomy type</th>
<th>Complications</th>
<th>Re-procedures (except ureteral stent placement)</th>
<th>Mean follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fazeli-Matin, 1998 [95]</td>
<td>27</td>
<td>7.4</td>
<td>74 (15—260)</td>
<td>Partial</td>
<td>Significant increase in serum creatinine levels (only if single kidney, n = 15)</td>
<td>0</td>
<td>39 (median) (2—177)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Urinary fistula (n = 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Postop. infections (n = 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adrenal insufficiency (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heidenreich, 2002 [96]</td>
<td>28</td>
<td>3.6</td>
<td>55 (median)</td>
<td>Partial</td>
<td>Urinary fistula (n = 3)</td>
<td>1 (closure of urinary fistula)</td>
<td>58 (median) (3—114)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(25—150)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yip, 2000 [92]</td>
<td>23</td>
<td>13</td>
<td>123 (15—300)</td>
<td>Partial (n = 16)</td>
<td>Minor stroke (n = 1)</td>
<td>0</td>
<td>26 (1—80)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total (n = 7)</td>
<td>Arteriovenous fistula (embolisation, n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boorijian, 2007 [93]</td>
<td>58</td>
<td>0</td>
<td>39 (median)</td>
<td>Partial</td>
<td>Urinary fistula (n = 3)</td>
<td>1 (embolisation of postop. bleeding)</td>
<td>72 (median) (12—372)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(8—125)</td>
<td></td>
<td>Postop. abscess (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Postop. ileus (n = 5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pneumothorax (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Postop. bleeding (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acute renal insufficiency (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Luca, 1999 [94]</td>
<td>20</td>
<td>10</td>
<td>81 (25—170)/20</td>
<td>Partial (n = 14)</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TSC: tuberous sclerosis complex; Pts: patients; Postop.: postoperative.

* Symptomatic/asymptomatic.
The studies with sirolimus showed a regression of the volume of the AMLs under treatment. In the first study, at 12 months, the volume of the AMLs was 53.2 ± 26.6% of the initial volume. But the size of the AMLs increased again after discontinuation of treatment and their volume after 12 months of discontinuation was 85.9 ± 28.5% of the initial volume [113]. In the second study, the response rate (RECIST criteria) was 80% for patients who remained in the study until the end (8 out of 10). It should be noted, however, that five AMLs grew during treatment in two patients who withdrew from the study early [114].

Serious complications under treatment (stomatitis, diarrhoea and various infections [particularly pulmonary infections]) are numerous: six out of 25 patients in the first study, seven out of 16 (including one death) in the second study and one case of retroperitoneal bleeding [113].

Treatment with mTOR inhibitors can have beneficial effects on the respiratory function of patients with LAM by improving [113] or slowing down its deterioration [114,115]. It may improve certain cognitive functions [114].

In all, treatments with mTOR inhibitors can significantly reduce the volume of most AMLs (but not all AMLs). Their effect is reversible upon treatment discontinuation. It has not yet been proven that the decrease in the size of the AMLs is accompanied by a decrease in the bleeding risk. The benefit/risk ratio of mTOR inhibitors is not sufficiently favorable to use them as first-line treatment.

**RECOMMENDATION 10: ROLE OF TREATMENT WITH mTOR INHIBITORS**

10a Due to their potential adverse effects, mTOR inhibitors should only be prescribed by specialised teams and if possible within the framework of clinical studies. The creation of a national registry listing patients treated outside of a protocol is encouraged.

10b mTOR inhibitors must not be used as first-line treatment in the treatment of renal AMLs.

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