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# Recommendations for imaging-based diagnosis and management of renal angiomyolipoma associated with tuberous sclerosis complex

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## Abstract

Renal angiomyolipomas are found in up to 80% of tuberous sclerosis complex (TSC) patients. Although these tumours are usually asymptomatic, lesions >3 cm in diameter are prone to bleeding and up to 10% of TSC patients may experience a massive and potentially fatal retroperitoneal haemorrhage. Diagnosis can be complicated because of the initial lack of symptoms and the fat-poor content of atypical renal angiomyolipomas. After diagnosis, tumour growth and the emergence of new tumours must be monitored. Treatment with mammalian target of rapamycin (mTOR) inhibitors can reduce tumour size and is indicated in patients with TSC-associated renal angiomyolipomas >3 cm in diameter. Imaging-based assessment of kidney disease is essential to the diagnosis and management of patients with TSC. The aims of imaging studies in this context are to detect and characterize tumours, assess and detect the risk of complications and evaluate the response to treatment, especially in patients treated with mTOR inhibitors. A multidisciplinary expert panel developed a series of recommendations based on current evidence and professional experience for imaging studies in adults and children with TSC-associated renal angiomyolipoma. The recommendations cover radiological diagnosis and follow-up of the classic and atypical or fat-poor TSC-associated renal angiomyolipomas, biopsy indications, minimal requirements for radiological requests and reports and recommended technical features and protocols for computed tomography and magnetic resonance imaging.

**Key words:** computerized tomography, magnetic resonance imaging, renal angiomyolipoma, tuberous sclerosis complex, ultrasonography

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## Introduction

Tuberous sclerosis complex (TSC) is a rare hereditary disease caused by mutations of the TSC1 or TSC2 genes [1] that are related to the PI3K/AKT/mTOR signalling pathway. These mutations induce overactivation of mammalian target of rapamycin (mTOR) protein, which in turn induces uncontrolled cell growth [2]. TSC is characterized by benign tumours that can develop in multiple organs, including the skin, brain, kidneys, liver, lungs and heart [3]. However, it is an extremely variable disease, with multiple and unspecific clinical manifestations that can differ in severity according to the patient's age and the stage of life at onset. Furthermore, TSC requires continued surveillance to monitor known manifestations and identify any potential new ones [1].

The most common renal manifestations of TSC are angiomyolipomas, which are found in up to 80% of TSC patients [4]; the presence of two or more renal angiomyolipomas is a major diagnostic criterion for a TSC diagnosis [5]. Another frequent kidney lesion in TSC is renal cysts, which are found in 14–32% of patients [6].

TSC-associated renal angiomyolipomas are usually multiple, bilateral and asymptomatic until there is irreversible renal damage or bleeding. They are more prone to bleeding and growth than sporadic angiomyolipomas, which are generally smaller and solitary [7, 8]. Diagnosis and follow-up of TSC-associated renal angiomyolipomas are based mainly on imaging studies. Although renal angiomyolipomas are still the main cause of morbidity and mortality in adults with TSC [4], mTOR inhibitors can reduce the size of angiomyolipomas and have become first-line therapy for tumours with diameters >3 cm [5]. There are no controlled trials comparing therapy with mTOR inhibitors and embolization to prevent bleeding and recurrence and preserve renal function [9]. However, mTOR inhibitors are recommended for pre-emptive treatment, while embolization should be reserved for acutely bleeding tumours [5] since this technique leads to loss of kidney parenchyma [10].

Radiological assessment of kidney disease in TSC patients is essential to the diagnosis and management of the disease in terms of both treatment and follow-up. Given the lack of imaging-based recommendations for the diagnosis and management of TSC-associated angiomyolipoma, a multidisciplinary expert panel developed a series of recommendations based on current evidence and their professional experience for imaging-based management of patients with TSC-associated renal angiomyolipoma.

## Imaging technologies in TSC-associated renal angiomyolipoma

The aims of imaging studies in TSC-associated renal angiomyolipomas are to detect and characterize tumours, to assess and detect the risk of complications (especially bleeding) and to evaluate the response to medical and surgical treatment.

The three currently available technologies for the study of TSC-associated renal tumours are ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI). See Supplementary data for technical features and recommended protocols.

### Ultrasound

Ultrasound is a useful initial approach to determine whether kidney lesions are present and whether these are cystic or solid. Contrast-enhanced ultrasound is not recommended, owing to its lack of reproducibility and the difficulty in analysing multiple

lesions in a single scan. In the case of simple cysts, ultrasound may be sufficient. However, if the content of the lesions is not completely anechoic or the lesions have thick septa or solid poles, further study with CT or MRI is needed [11–13]. MRI and CT can differentiate between infected or bleeding cysts and solid tumours [14]. Renal angiomyolipomas usually appear as hyper-echoic solid lesions, but their echogenicity may vary depending on the amounts of fat, muscle or vessels that constitute the lesion.

### CT

CT has higher precision and reproducibility than ultrasound, minimizing inter- and intra-observer variability, therefore CT is the recommended technique in most cases. Moreover, it is the preferred technique for pre-surgical mapping prior to embolization or resection. However, its use in the diagnosis and follow-up of young patients is limited by the accumulation of radiation [15].

Intravenous administration of contrast media is necessary to achieve good definition of the lesions, to differentiate angiomyolipomas from other tumours and to perform CT angiogram and vascular mapping that may be useful in patient management. A glomerular filtration rate (GFR) <45 mL/min/1.73 m<sup>2</sup> is a relative contraindication to the use of intravenous iodinated contrast media; however, if necessary, prophylaxis against contrast-induced nephropathy can be administered [16].

An additional basal non-enhanced CT (NECT) will be helpful in cases of haemorrhage. By itself, NECT is of limited usefulness because it only distinguishes between fat and non-fat components (which include tumour as well as renal cortex). It will be used only in patients in which intravenous contrast cannot be administered and MRI cannot be performed. CT-induced adverse events and contrast reactions are more frequent than in MRI, as is nephrotoxicity [16].

### MRI

A minimum of 1.5 T is required for MRI scanners. MRI does not radiate and thus enables good characterization of lesions. Its spatial resolution is lower than that of CT, whose fast speed avoids artefacts caused by abdominal movements that blur lesions and organ contours on the MRI, even with higher-strength fields. However, MRI is sufficient to assess the size of angiomyolipomas and other renal lesions associated with TSC, even without contrast.

Sometimes contrast is needed for better definition of angiomyolipomas and the differential diagnosis between fat-poor angiomyolipomas and other renal tumours. Enhanced MRI has worse spatial resolution of the abdomen than CT, but it is useful for measuring microaneurysms, especially in patients with allergy to iodinated contrast or with a GFR between 30 and 45 mL/min/1.73 m<sup>2</sup>. Enhanced MRI is also useful in routine controls or treatment follow-up. If the GFR is <30 mL/min/1.73 m<sup>2</sup>, gadolinium is contraindicated due to an increased risk of nephrogenic systemic fibrosis [17]. Table 1 summarizes the advantages and disadvantages of the different imaging technologies.

## Diagnosis of angiomyolipoma

### Imaging-based diagnosis of angiomyolipoma

Angiomyolipoma is a triphasic tumour composed of fat, smooth muscle and blood vessels in variable proportions [18] (Figure 1).

Table 1. Advantages and disadvantages of imaging technologies in TSC-associated angiomyolipoma

Technology	Advantages	Disadvantages
Ultrasonography	No radiation Very accessible Fast Convenient for patients	Low precision Poor intra- and interobserver reproducibility
CT	High precision High reproducibility	Radiation Adverse events and reactions to iodinated contrast media
MRI	High resolution for differentiating tissues No radiation	Adverse events and reactions to gadolinium Less spatial resolution than CT



Fig. 1. Contrast-enhanced CT scan of a right-kidney angiomyolipoma composed mainly of adipose tissue ( $< -10$  HU).

Renal angiomyolipomas are classified into classic and atypical types according to their imaging features.

#### Classic renal angiomyolipomas

Classic renal angiomyolipomas can be found in up to 80% of TSC patients and are more frequent with increasing age. Fat is one of their major components and macroscopic adipose tissue can be seen in most cases (Figure 1).

Ultrasound shows them to be hyperechoic and usually homogeneous. Exophytic renal angiomyolipomas may be hidden by perirenal fat. The whole kidney should be scanned in the axial and coronal planes to visualize areas potentially hidden by rib shadows or colonic gas.

On CT, they are seen as assorted morphological masses. They can be numerous with diffuse margins. However, macroscopic fat with negative densitometric values (attenuations  $< -10$  HU) is always seen, as are non-fat components with enhancement in the early arterial phase and other smooth muscular components that are solid with lower enhancement.

The standard recommended study protocol with sections of 3 mm and reconstruction of 1.5 mm provides well-defined images of the abdomen and pelvis, making it possible to detect small amounts of fat that would not be seen in thicker sections. Very small regions of interest or even voxel values may be required to avoid the partial volume effect [18].

Measurement of size is important because of the increased risk of bleeding in angiomyolipomas  $>3$  cm and in microaneurysms  $>5$  mm [19].

On MRI, a hyperintense fat component is observed on T1- and T2-weighted images, as is a hypointense component on T2-weighted images with fat saturation (spectral saturation is preferable). On the dual sequence, the India ink sign, which highlights the lesion in the out-of-phase (opposed phase) sequence, is highly suggestive of angiomyolipoma [20].

#### Atypical or fat-poor angiomyolipomas

Around 5% of angiomyolipomas are atypical or fat poor, yet they affect up to 33% of TSC patients [21]. Fat cannot be detected with unenhanced CT where fat-poor angiomyolipomas have a density  $> -10$  HU [18]. On MRI, there is no fat suppression on fat saturation sequences, although it is observed in the dual out-of-phase sequence. Even though CT and MRI are useful for diagnosing atypical angiomyolipomas [22–26], biopsy may be necessary to complete the analysis.

There are three subtypes of atypical or fat-poor angiomyolipomas: hyperattenuating, isoattenuating and angiomyolipoma with epithelial cysts. A fourth and very rare subtype is epithelioid angiomyolipoma.

The ‘hyperattenuating subtype’ is the most common fat-poor angiomyolipoma (4–5%). It is composed predominantly of smooth muscle cells and its fat content is low ( $\leq 4\%$ ). Its mean diameter is 3 cm. Ultrasound images are unspecific with a solid, homogeneous and muscle-isoechoic nodule. Hence diagnosis requires CT and/or MRI [27].

Isoattenuating angiomyolipoma is very rare and its fat content is dispersed. On CT, it is isodense to muscle and has early enhancement and fast washout (ratio arterial/late HU  $>1.5$ ). On MRI, it is hypointense on T2-weighted images. It does not always suppress fat on fat saturation sequences, although it typically does so on the dual out-of-phase sequence. The possibility of an isoattenuating angiomyolipoma must be considered in the presence of a renal mass that is suppressed on the out-of-phase sequence [27].

Angiomyolipoma with epithelial cysts is also very rare, although more common in women. It is composed of smooth muscle and cysts, with little or no fat content. Its radiological features are not well known [27].

Epithelioid angiomyolipoma is a singularly rare subtype of atypical angiomyolipoma. It is usually larger than the other fat-poor angiomyolipomas, with a mean diameter of 7 cm [28]. It may bleed like a classic angiomyolipoma, but its import lies in its potential malignancy with local recurrence and distant metastasis [29]. Histologically, it can mimic other renal tumours, such as clear cell renal carcinoma (CCRC) [30]. It has little or no fat content and, accordingly, can be hyperattenuating on unenhanced CT and hypointense on an MRI T2 sequence. Small fat masses can be detected in some cases. It can also present as a solid mass with homogeneous or heterogeneous

Table 2. Types of angiomyolipoma according to their imaging features<sup>a</sup>

Type of angiomyolipoma	Ultrasound	CT	MRI
Classic	Hyperechoic	< -10 HU	T2 hypointense on FS T1 hypointense ring on OOP (in some cases)
Atypical			
Fat poor			
Hyperattenuating	Isoechoic	≥45 HU on unenhanced CT	Hypointense on unenhanced T1 and T2 sequences ± T1 suppression on OOP
Isoattenuating	Slightly hyperechoic	< -10 to ≥45 HU	T2 hypointense + signal loss on FS
With epithelial cysts	Unknown	Hyperattenuating with cysts or multilocular cystic	Solid component in T2 hypointense ± signal loss on FS
Epithelioid	Unknown	Hyperattenuating (>45 HU) and heterogeneous	Signal loss on FS

<sup>a</sup>Based on Yamakado et al. [19], Jinzaki et al. [27], Rosser et al. [28], Israel et al. [20] and Froemming et al. [31]. FS, frequency-selective fat suppression; HU, Hounsfield units; OOP, out-of-phase sequence.

enhancement or as a multicystic mass [31]. Table 2 shows the main imaging features of angiomyolipomas.

### Differential diagnosis between angiomyolipomas and other entities

The diagnosis of angiomyolipoma can only be confirmed by means of a tumour biopsy. However, as aggressive procedures should be avoided in TSC patients, it is preferable to first attempt a differential diagnosis using imaging techniques.

The differential diagnosis aims to distinguish angiomyolipomas from retroperitoneal extrarenal tumours and malignant renal neoplasms. TSC-associated renal neoplasms are generally specific subtypes, which are not very aggressive, and are found in patients younger than the general population with renal tumours. Fat content in a renal tumour is highly suggestive of angiomyolipoma, especially in a patient with TSC [13, 32]. Moreover, TSC-associated renal neoplasms can mimic fat-poor angiomyolipomas; if this is the case and a reliable diagnosis cannot be made by imaging, a tumour biopsy is needed.

#### Classic angiomyolipoma

Classic angiomyolipoma should be differentiated from other solid tumours containing macroscopic fat, mainly CCRCs and liposarcomas, as well as other less common tumours such as Wilms tumours and teratomas. Fat-free tumours are sometimes embedded in fat from the renal sinus, which looks like part of the tumour. There are no imaging-based pathognomonic signs of angiomyolipoma, although some data highly increase the probability of angiomyolipoma and other types of tumour.

CCRCs may contain fat, usually as a result of fat necrosis and, like angiomyolipomas, are hyperechoic. However, ultrasound images can help: if the tumour is <3 cm and an acoustic shadow is discernible, the most probable diagnosis is angiomyolipoma, while the presence of a hypoechoic halo and intratumoural cysts suggests CCRC [33]. Additionally, a tumour treated with radiofrequency or embolization will sometimes show a halo of fat necrosis. It is also worth noting that intratumoural calcifications are very suggestive of CCRC [34]. Moreover, bleeding angiomyolipomas can be mistaken for other types of tumours because fat can be hidden by blood; a comparison between current and older images can prove useful in these cases [35].

Finally, renal liposarcoma is extremely rare, but imaging studies can help to differentiate it from angiomyolipoma. Thus, if the feeding vessel and claw sign are present, angiomyolipoma is highly probable [36]. Intratumoural or perirenal bleeding and dilated or bridging intratumoural vessels are also suggestive of angiomyolipoma [37].

#### Atypical angiomyolipomas

Atypical or fat-poor angiomyolipomas show lower signal intensity (SI) on T2 sequences than the classic type owing to the predominance of the muscular component. Another useful finding is a tumour/kidney SI ratio >1.2 on T2-weighted images with fat saturation, which indicates 100% specificity for renal cell carcinoma [13].

If imaging features are highly suggestive of fat-poor angiomyolipoma (such as a renal mass ≤3 cm in diameter, hyperattenuating on unenhanced CT and homogeneously enhancing for hyperattenuating subtype or a T2 hypointense renal mass for isoattenuating subtype [18]) rather than another tumour with a worse prognosis, the panel recommends performing the same follow-up as for the classic type. Table 3 summarizes the differential diagnosis of this type of angiomyolipoma.

#### Recommendations for biopsy

There are no current statistics or solid indications to biopsy fat-poor angiomyolipomas. The most common indications are intratumoural calcifications, intratumoural cysts, solitary fat-poor angiomyolipomas or any uncertain image on MRI [13], as these features are not usually found in angiomyolipoma.

Although previously not favoured, the use of renal mass core biopsies is increasing because of a diagnosis efficacy of >92%, being able to differentiate between benign and malignant renal masses in most of them [38]. The reported complication rate is ~8%, with most of them having a Clavien–Dindo classification of <2 [39].

In patients with TSC, the coexistence of classic angiomyolipomas and atypical lesions is common. If MRI or the other techniques are not able to differentiate between benign and malignant masses, these atypical lesions should then be biopsied. If the pathology confirms a fat-poor angiomyolipoma, this result may be extrapolated to the others (Figure 2), but close

Table 3. Differential diagnosis of fat-poor angiomyolipomas<sup>a</sup>

Subtype	Differential diagnosis
Hyperattenuating	RCC (papillary type) Oncocytoma Metastases Other less frequent tumours (lymphoma, metanephric adenoma and leiomyoma)
Isoattenuating	Papillary tumour <sup>b</sup>
With epithelial cysts	Multilocular cystic RCC <sup>c</sup> Multilocular cyst Cystic nephroma MEST <sup>c</sup>

<sup>a</sup>Based on Siegel et al. [33], Silverman et al. [34], Schieda et al. [36], Ellingson et al. [37], Chung et al. [13] and Jinzaki et al. [18].

<sup>b</sup>Papillary tumour is T2 hypointense as an angiomyolipoma but usually shows late enhancement.

<sup>c</sup>Biopsy is needed. Angiomyolipoma and MEST may be positive for actin and desmin but multilocular cystic RCC is not.

RCC, renal cell carcinoma; MEST, mixed epithelial and stromal tumour.

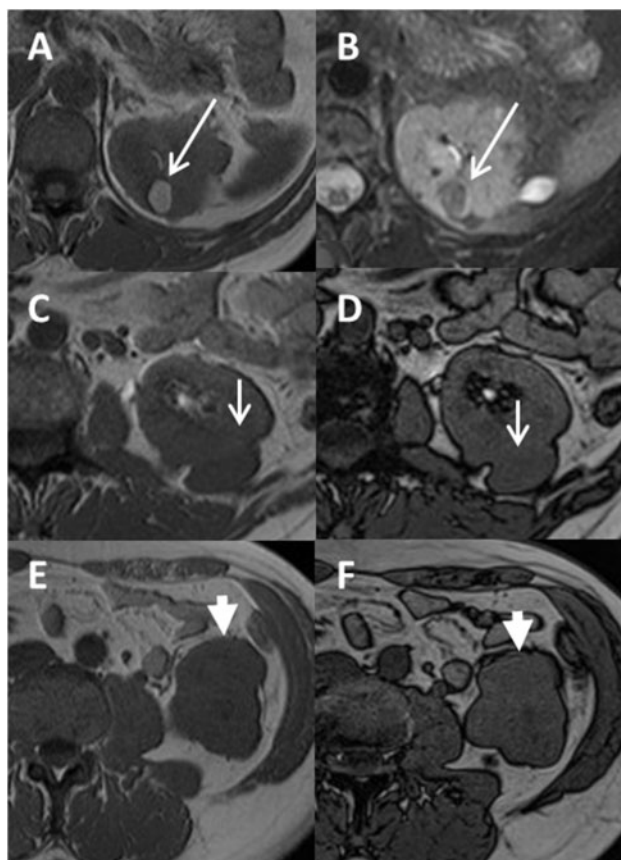


Fig. 2. Abdominal MRI of a female patient with TSC. Images (A) and (B) show an angiomyolipoma with its typical MRI features (arrows): hyperintense on a T1-weighted in-phase image (A) and marked signal loss on a T2-weighted fat-saturated sequence (B). T1-weighted in-phase images (C and E) and out-of-phase images (D and F) show undetermined lesions with the same SI as kidney without the India ink sign in out-of-phase sequences. (C and D) show a lesion in the posterior pole of the middle third of the left kidney (short arrow), (E and F) show a lesion hanging from the lower pole (flat arrows). There were more lesions with this atypical appearance in both kidneys (data not shown). The lesion in the lower pole was biopsied and diagnosed as angiomyolipoma with sclerosis and no visible fat. The other atypical lesions were also thought to be atypical angiomyolipomas.

surveillance is needed. The need for further biopsies should be assessed individually.

## Monitoring the progression of renal angiomyolipoma

Regular controls are needed because of the risk of haemorrhage associated with angiomyolipomas and the possibility of other types of tumours. When untreated, TSC-associated angiomyolipomas have a growth rate of 1.25 cm/year, which is higher than that of sporadic angiomyolipomas (0.19 cm/year) [40]. Lesions >3 cm are prone to bleeding and up to 10% of patients may experience a massive and potentially fatal retroperitoneal haemorrhage [41]. Moreover, the number and size of angiomyolipomas increases with age [42], thus exacerbating the risk of bleeding. Regular follow-up checks are also important in angiomyolipomas with no visible fat [43].

Imaging techniques enable the identification of TSC-associated renal angiomyolipomas with a diameter >3 cm. They are also useful for monitoring volume reduction and stabilization in treated patients.

## Surveillance of untreated patients

As organ involvement varies according to the age of patients with TSC, imaging follow-up protocols for children and adults should be different [5, 43]. We offer several recommendations for imaging-based surveillance of untreated TSC patients.

Recommendations for patients <18 years of age:

- Perform ultrasound and/or MRI at the diagnosis of TSC. If sedation is needed, the panel recommends taking advantage of the opportunity to perform brain and abdominal MRI in the same study. If renal lesions are detected, surveillance is mandatory.
- Tailor surveillance according to findings.
  - If an angiomyolipoma of <3 cm is detected, perform follow-up checks every 1 or 2 years. If MRI is not needed for neurological follow-up, ultrasound-based follow-up of renal lesions may be acceptable. If no variations are found, the interval between follow-up checks can be as long as 3 years.
  - If an asymptomatic angiomyolipoma of  $\geq 3$  cm is detected, assess microaneurysms with CT or MRI. A decision on treatment should be made and then assessment of the angiomyolipoma should be made every year.

Recommendations for adults:

- For asymptomatic patients with an angiomyolipoma of <3 cm, perform follow-up checks every 2 years using tomographic techniques, mainly MRI. If the disease is stable, increase the interval between follow-up checks.
- For asymptomatic patients with at least one angiomyolipoma >3 cm, assess possible intratumoural aneurysms using CT angiography or MRI angiography. Asymptomatic patients should be followed up annually with MRI.
- For asymptomatic patients with atypical tumours where no biopsy has been carried out, perform a yearly MRI follow-up check.
- Any emergency involving lower back pain, signs of peritoneal irritation, haematuria or hypovolemic shock denotes a complication of angiomyolipoma. Urgent cases should be



Fig. 3. Contrast-enhanced CT coronal reconstruction and axial images showing measurement of the three dimensions used to calculate angiomyolipoma volume based on the ellipsoid formula.

assessed using CT angiography to identify active bleeding points and obtain angiographic mapping.

### Follow-up of patients treated with mTOR inhibitors

mTOR inhibitors constitute a new approach to the management of TSC-associated angiomyolipoma [44, 45]. The only mTOR inhibitor approved for the treatment of renal angiomyolipoma is everolimus, which is indicated in the treatment of adult patients with TSC-associated angiomyolipoma who are at risk of complications but do not need immediate surgery [46]. Everolimus reduced tumour size in clinical trials [47, 48] and no kidney bleeding was observed during long-term therapy [48]. Guidelines recommend initiating mTOR inhibitor therapy in TSC patients who have at least one growing, asymptomatic angiomyolipoma >3 cm in diameter [5].

### Measurement of angiomyolipoma volume

Measurement of renal angiomyolipoma volume is useful for follow-up and for assessing the effect of treatment on an individual angiomyolipoma. Different methods can be used to calculate angiomyolipoma volume. The borders of lesions can sometimes be difficult to define because angiomyolipomas tend to be convergent, heterogeneous and disorganized and their fat component can be confused with perirenal and/or sinusal adipose tissue.

The use of specialized volumetric software enables angiomyolipoma volume to be calculated using various three-dimensional (3D) techniques [49, 50]. However, these methods are not suitable for routine examinations in daily practice because image processing is time-consuming.

An easier alternative for estimating angiomyolipoma volume is the ellipsoid formula:  $\pi/6 \times D1 \times D2 \times D3$ , where D1, D2 and D3 are the maximum diameters measured in 3D (Figure 3). The panel recommends always using the same method and keeping a register of the diameters obtained to compare with future measurements.

Furthermore, TSC patients may have giant angiomyolipomas and/or multiple convergent tumours that replace renal parenchyma, thus preventing exact determinations of volume. In such cases, response to therapy can be assessed by determining total kidney volume (Figure 4).

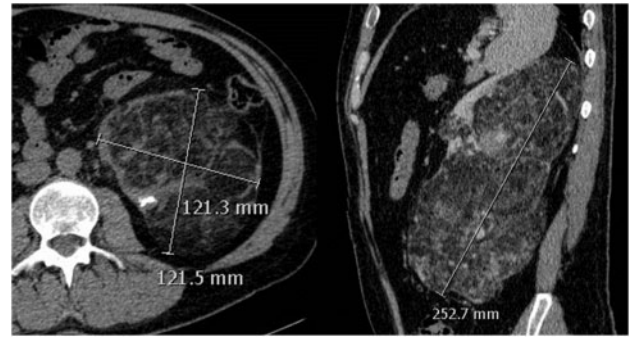


Fig. 4. Unenhanced CT images in the axial plane and sagittal reconstruction show voluminous left-kidney angiomyolipomas that converge and virtually replace renal parenchyma: measurement of total kidney volume is then the best option since it is impossible to delimit individual lesions.

Table 4. Essential points in radiology requests and reports

Diagnosis	Disease (TSC)
	Signs and symptoms
	Suspected diagnosis (angiomyolipoma)
	Size of bigger angiomyolipomas or total kidney volume
Follow-up	Presence of microaneurysms, especially those >5 mm
	Disease (TSC)
	Reason for request: routine or new sign or symptom
	Current therapy
	Measurement of diameter of bigger angiomyolipomas or extent of marked growth of any other angiomyolipoma

### Radiology requests and reports

Due to the complexity of angiomyolipoma images, expert radiologists should be in charge of radiology reports. However, when there is a possibility of reports being made by non-specialist radiologists, radiology requests should be as detailed as possible.

Physicians should indicate why they are requesting a CT or MRI examination. If the request is because the patient is experiencing pain, haematuria or any other specific reason, then searching for bleeding is important. If CT or MRI is performed as a routine examination, its main purpose is to measure the larger angiomyolipomas (or the total kidney volume in some cases) to evaluate either the impact of mTOR inhibitor therapy or the course of the disease in untreated patients. When possible, previous images and radiology reports will help to assess this.

Based on their experience, the panel proposes a series of essential points to be covered in radiology requests and reports (Table 4).

### Recommendations for first diagnosis (CT or MRI)

Radiology reports should include the following:

- Presence or absence of angiomyolipomas and any solid lesion other than classic TSC-associated angiomyolipoma.
- Number and size of any angiomyolipomas with a diameter >3 cm. If the angiomyolipomas are so numerous that they cannot be assessed, the total kidney volume should be indicated. An appropriate approximation is to calculate the ellipsoid volume (see section above “Follow-up of patients treated with mTOR inhibitors”).

Table 5. Recommendations for imaging assessment of renal angiomyolipomas associated with TSC

**Diagnosis**

- Ultrasonography is useful as an initial approach to determine the presence of kidney lesions and to determine whether these are solid or cystic.
- The finding of macroscopic fat tissue usually confirms the radiological diagnosis of angiomyolipoma.
- Protocols for CT and MRI examinations are available.
- A hypointense renal mass on T2 that suppresses fat on the out-of-phase sequence is suggestive of isoattenuating fat-poor angiomyolipoma.
- If the diagnosis of angiomyolipoma is uncertain on CT or MRI, a percutaneous biopsy should be performed before surgery. If this biopsy is not performed or all the tumours are thought to be angiomyolipomas, radiological surveillance is essential.

**Monitoring**

- MRI does not radiate and is preferred to CT for the surveillance of patients with known angiomyolipomas.
- Regular radiological monitoring is recommended to assess the risk of bleeding and the presence of tumours other than angiomyolipomas.
- In children, surveillance must be tailored to the radiological findings.
- In untreated adults, the frequency of follow-up examinations depends on the tumour size.

**Therapy**

- Imaging-based assessment of renal angiomyolipomas is mandatory to identify patients who can be treated with mTOR inhibitors and to monitor the decrease and stabilization of these tumours in treated patients.
- CT is the test of choice for pre-surgical mapping or before embolization or resection.
- If an angiomyolipoma bleeds, urgent CT angiography is required and embolization may be needed.
- Radiologic interventional procedures with selective embolization should only be used in exceptional cases, such as in acute bleeding.

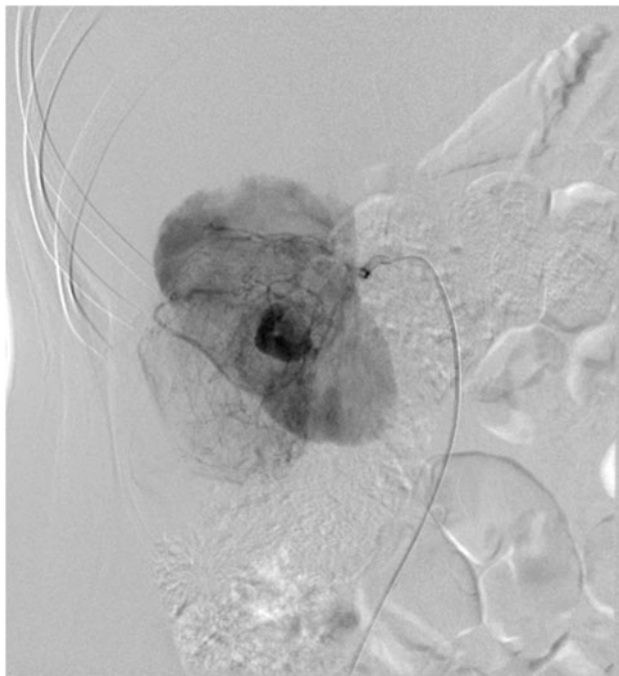


Fig. 5. Arteriography of an angiomyolipoma in the middle part of the right kidney before selective embolization. The darker image corresponds to an intratumoural aneurysm.

- Presence or absence of microaneurysms within the angiomyolipoma. Instances larger than 5 mm should be indicated.
- Presence or absence of acute or chronic intratumoural, perirenal and retroperitoneal bleeding. In the case of an emergency radiology request resulting from a bleeding angiomyolipoma, CT should be performed with multiplanar reconstructions in the arterial and portal phases separately if bleeding is to be treated with either embolization or surgery.

- Presence or absence of cysts. Complicated cysts should be assessed with enhanced or unenhanced CT or with MRI and their size and location should then be described for further monitoring.
- Presence or absence of fat-poor angiomyolipomas. If they are indistinguishable from renal carcinomas or other potentially malignant tumours, biopsy should be recommended to confirm the diagnosis.
- When liver and/or spleen are included in the CT or MRI examination, the presence or absence of hamartomas in these organs must be assessed.
- When the lungs are partially visible in the CT or MRI examination, possible lung cysts should be assessed, especially in women  $\geq 18$  years of age, because they are at risk for lymphangioleiomyomatosis.

**Interventional radiology**

Embolization used to be the classic first-line therapy for preventing spontaneous bleeding of angiomyolipomas and for symptomatic angiomyolipomas [5]. Selective embolization was preferred to nephrectomy because it preserves more of the renal parenchyma. It reduces angiomyolipoma volume and helps control symptoms [51] but causes loss of healthy renal tissue. Arteriography may be useful prior to embolization of actively bleeding angiomyolipomas (Figure 5). Selective embolization is not recommended as the first approach to management of TSC-associated renal angiomyolipoma, mainly because these tumours are usually bilateral and multifocal. Embolization procedures should only be used in exceptional circumstances, such as in acute bleeding [5].

**Summary of panel recommendations**

Table 5 shows the recommendations of the panel for diagnosis and follow-up of TSC-associated renal angiomyolipoma. Moreover, algorithms for the diagnosis of renal lesions in TSC (Figure 6) and follow-up of untreated patients (Figures 7 and 8) are provided.

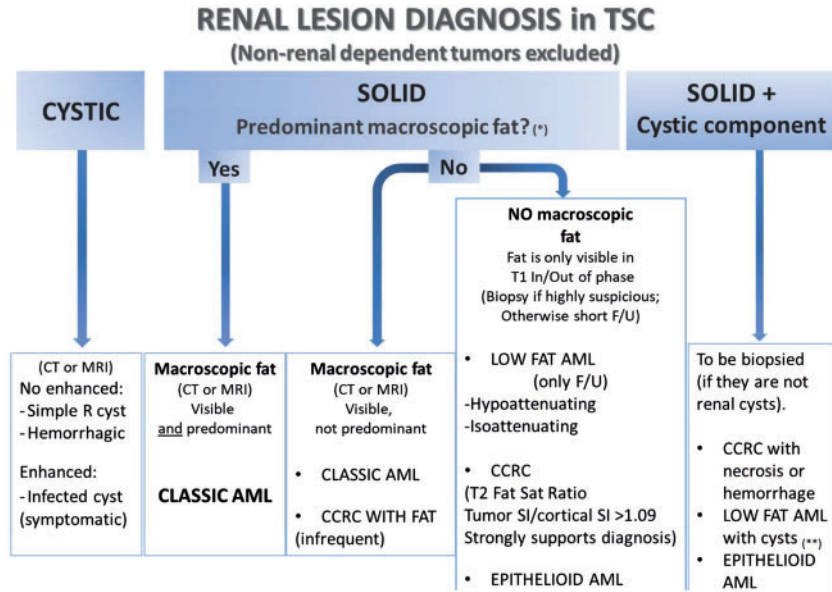


Fig. 6. Diagnosis of TSC-associated renal angiomyolipomas [13, 27, 52]. \*Denotes that predominant fat is equivalent to the pathologic concept of the >25% HPF (high power field) as in Milner et al. [52]. \*\*Has no special risk, but cannot be differentiated from the other two.

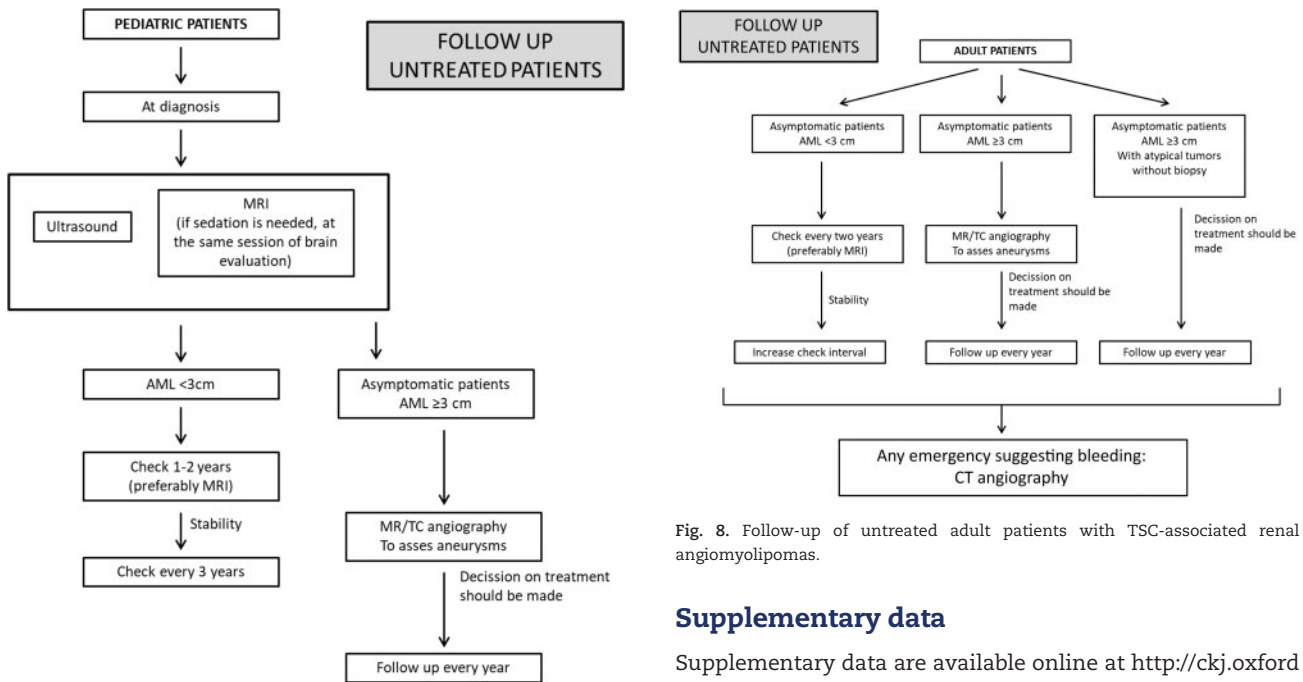


Fig. 7. Follow-up of untreated paediatric patients with TSC-associated renal angiomyolipomas.

Fig. 8. Follow-up of untreated adult patients with TSC-associated renal angiomyolipomas.

## Conclusion

CT and MRI and their specific protocols are essential components of imaging-based diagnosis and follow-up of TSC-associated renal angiomyolipomas. Biopsy of renal masses can be useful in exceptional cases. In addition, arteriography should be used only prior to embolization of actively bleeding angiomyolipomas. Our recommendations are intended as a tool for the specialist care of patients with TSC-associated renal angiomyolipomas.

## Supplementary data

Supplementary data are available online at <http://ckj.oxfordjournals.org>.

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## Conflict of interest statement

R.T. has acted as an advisor for Otsuka, Sanofi-Genzyme, Shire, Amicus, Novartis, Alexion and Orphan-Recordatti.



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