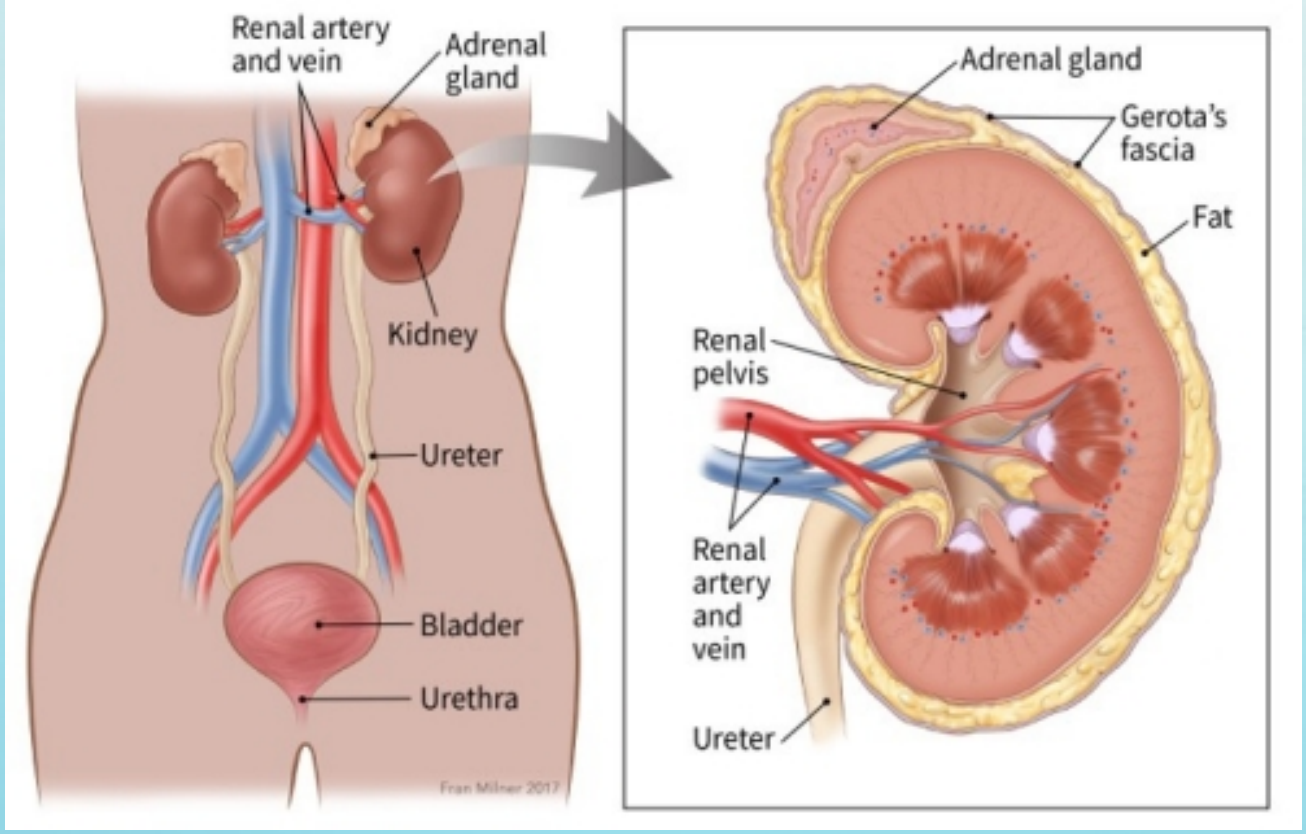
Angiomyolipomas in Tuberous Sclerosis (AML in TSC)

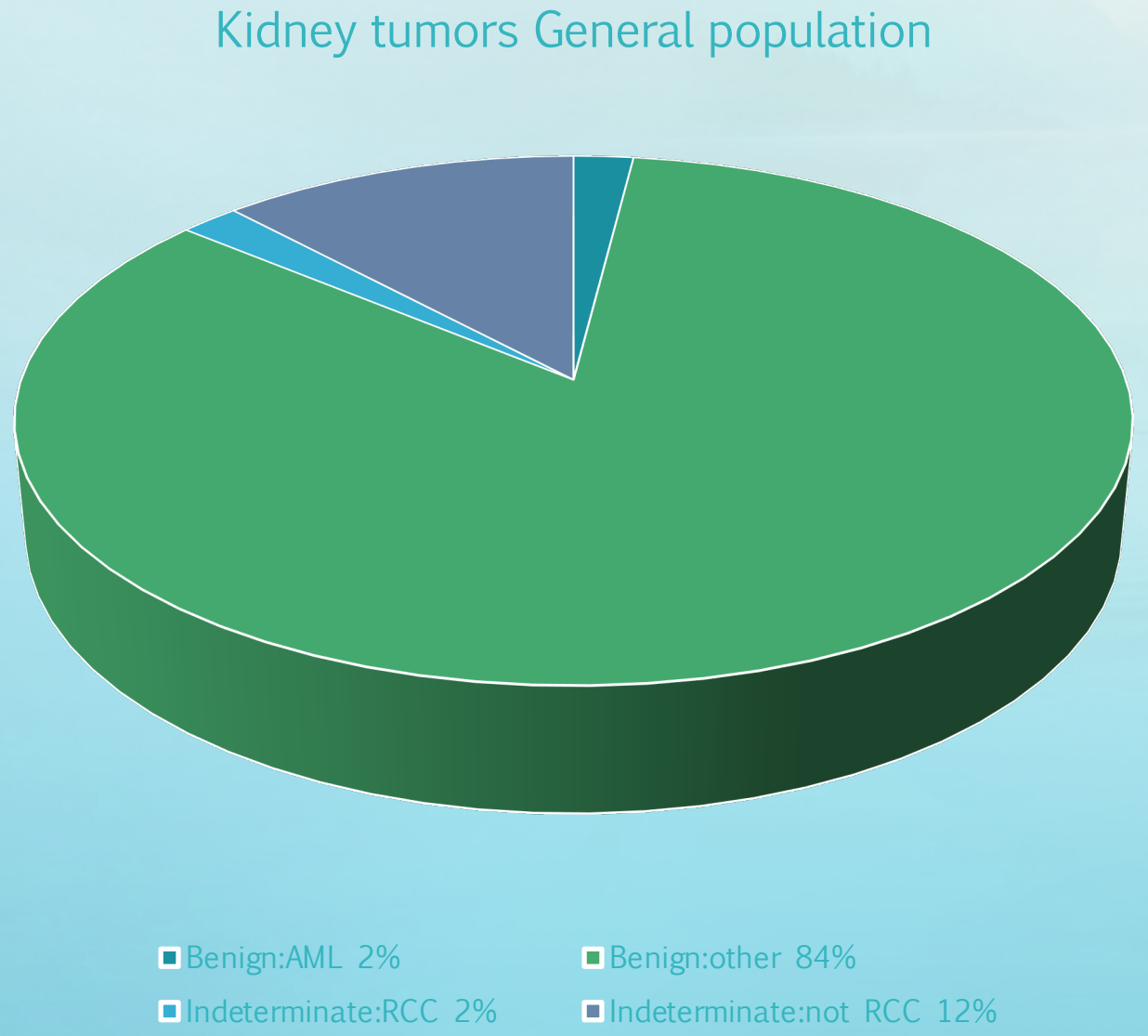
Carl E Schulze MD
UCLA Nephrology



Anatomy of the kidneys
-gross
-transverse (most common on CT and MRI)
-coronal (shown on Rt)
-sagittal

https://www.cancer.org/cancer/kidney-cancer/about/what-is-kidney-cancer.html

Accessed 20191028

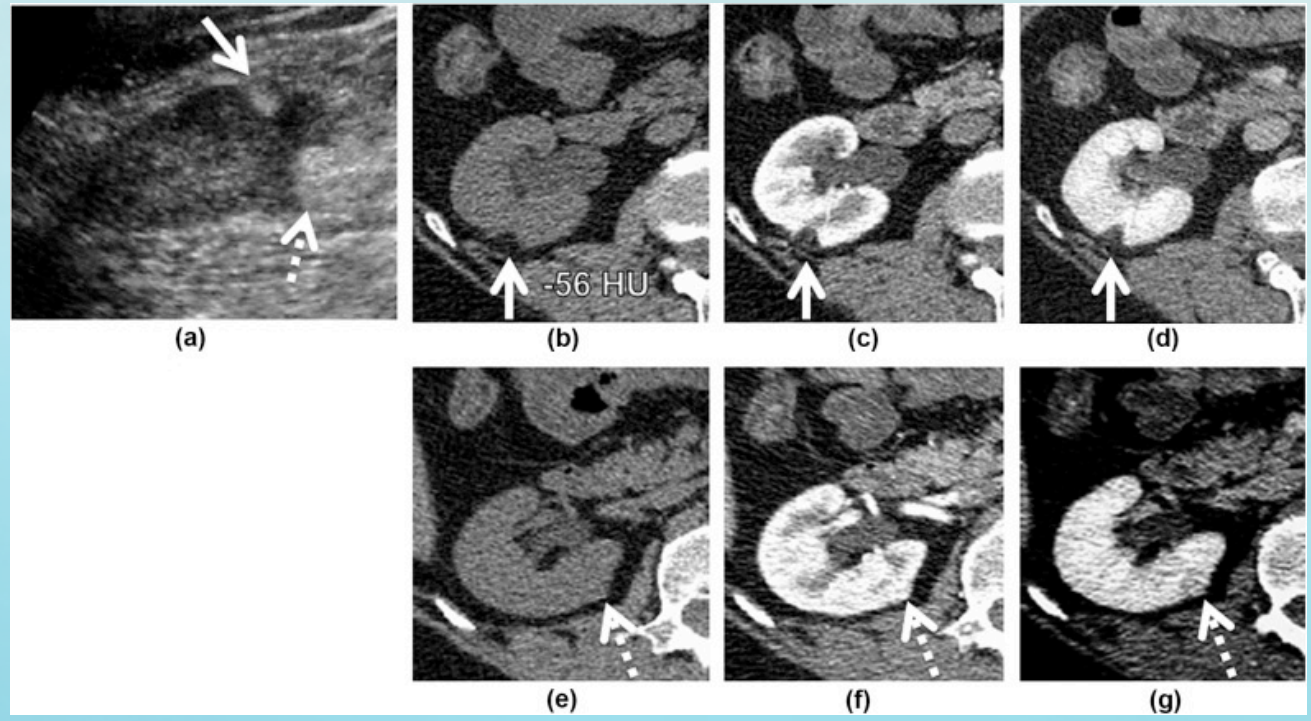


Types of kidney tumors found incidentally in a US population undergoing CT-colonography and kidney donor preop evaluation

AJR 2011;197(1):139

AJKD 2012;59(5):611

Angiomyolipoma (AML)



Cross sectional pictures of a kidney on ultrasound (a) and CT (b-g); b shows a tumor with fat density (low density) typical of a "classic" solitary AML

Clin Radiol 2017 Sep;72(9):708-721

AJR 2011;197(1)139

Eur Urol 1995;27(2):124

AJKD 2012;59(5):611

AMLs (Greek word roots) are defined as tumors with variable amount of blood vessels, smooth muscle, and fat cells

-usually are diagnosed based on ultrasound, CT, or MRI findings of fat-density tissue within renal tumors

-Radiology criteria for diagnosis: "fat-rich", "fat-poor", "fat-invisible"

- occasionally cannot be differentiated from RCC, requiring biopsy or ablation

-Prevalence of kidney tumors (gen US pop) 14.4%

-Prevalence of AMLs: 0.2-2.2%

-Female:male 2:1 (solitary AMLs)

AML in general population are different than in TSC

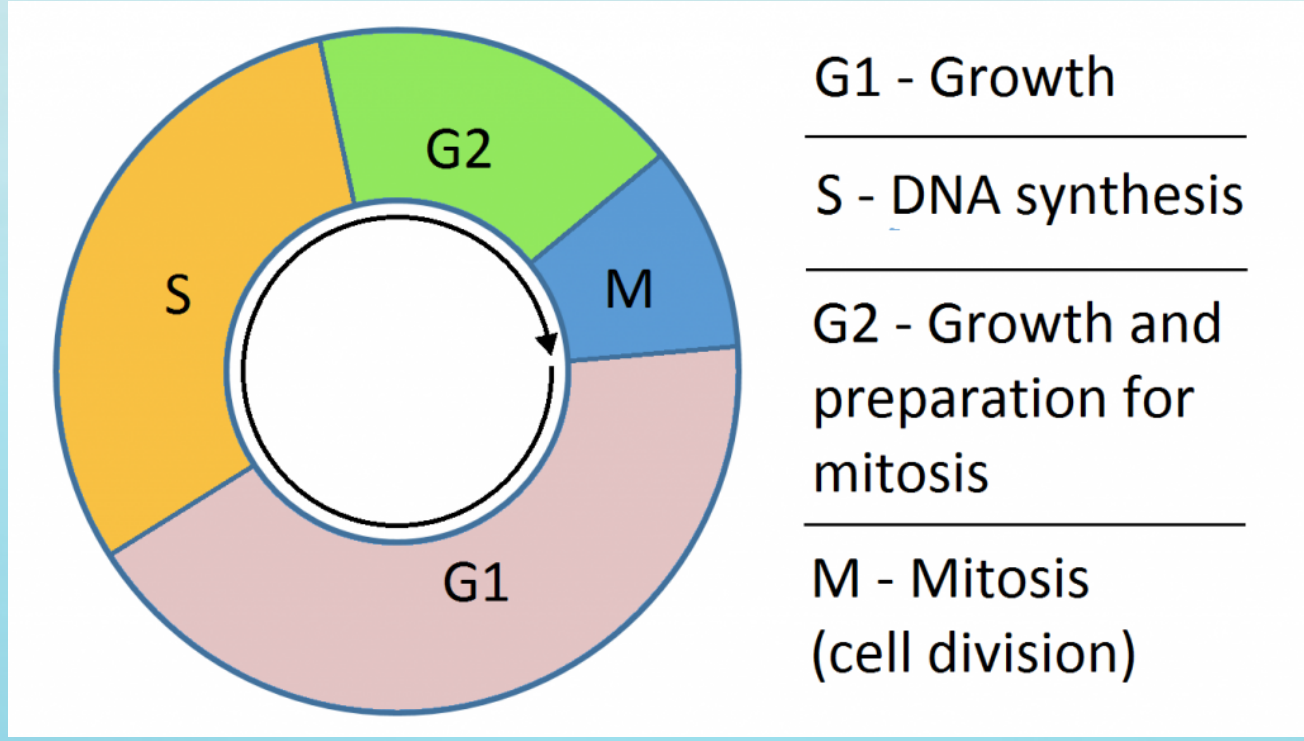
- AML 80% sporadic, 20% assoc with TSC
- AML tend to be bilateral in TSC
- AML more aggressive (larger, more prone to rupture) in TSC

Characteristic	General Pop	TSC
Prevalence	0.2-2%	75%
Age on onset	4-5th decades	1-2nd decade
Bilateral	Rare	Most
Gender differential	Female>>male	Female=male
Risk of RCC	1-2%	2-4% (increased)

J Belg Soc Radiol 2018;102(1):41, pp1-9
Eur Urol 1995;27(2):124
AJKD 2012;59(5):611
Eur Urol 2019;75:74-84
Am J Surg Pathol 2014;38(7):895-909

Regulations: Necessary for reliable function

CELL CYCLE



Eukaryotic cells (IE human cells) go through a set cycle from G1 to S to G2 to M to C (cytokinesis – cell splits in 2)

This cycle is strictly regulated by many enzymes, proteins, and messenger chemicals

Some cells stop dividing either temporarily or permanently (generally arrested in G1)

Kidney cells have some capacity to reenter the cell cycle which enables the organ to recover from injury

When the normal processes which regulate the cell cycle are disturbed, problems ensue

Teachmephysiology.com
Raven P and Johnson G. *How Cells Divide* in *Biology, 4th Ed.* Wm.C. Brown Publishers. 1996: Dubuque IA

Loss of Cell Cycle regulation in TSC causes AMLs

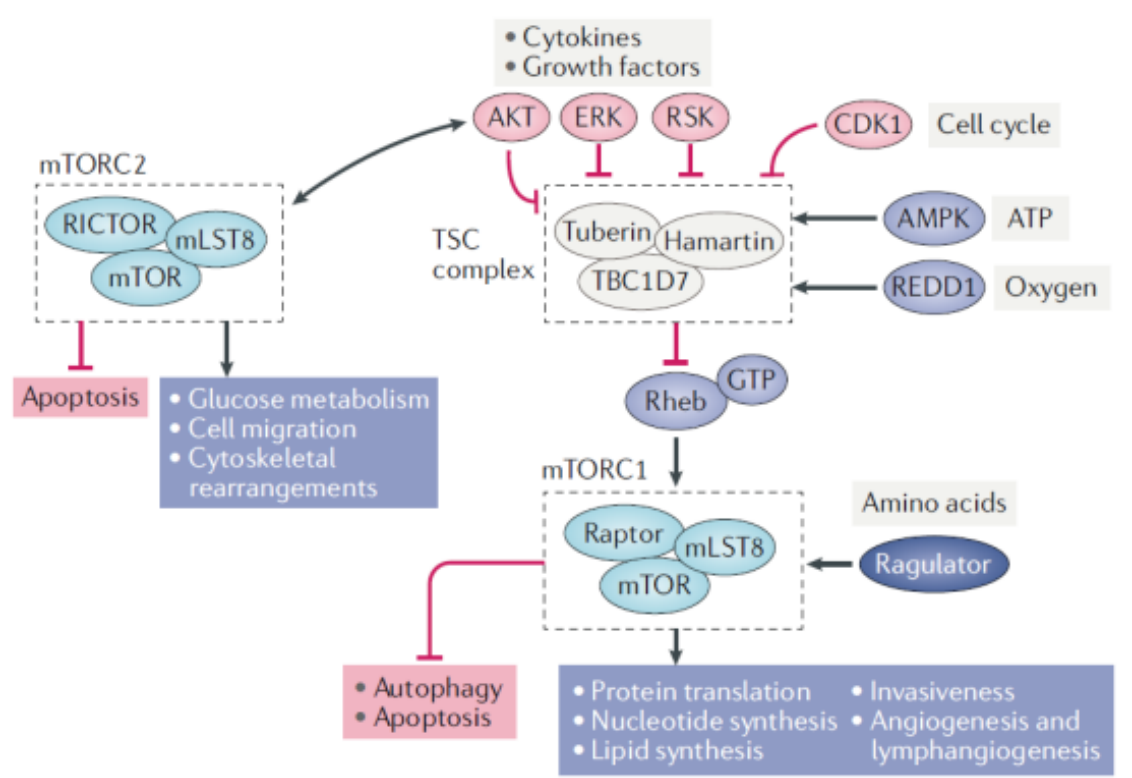


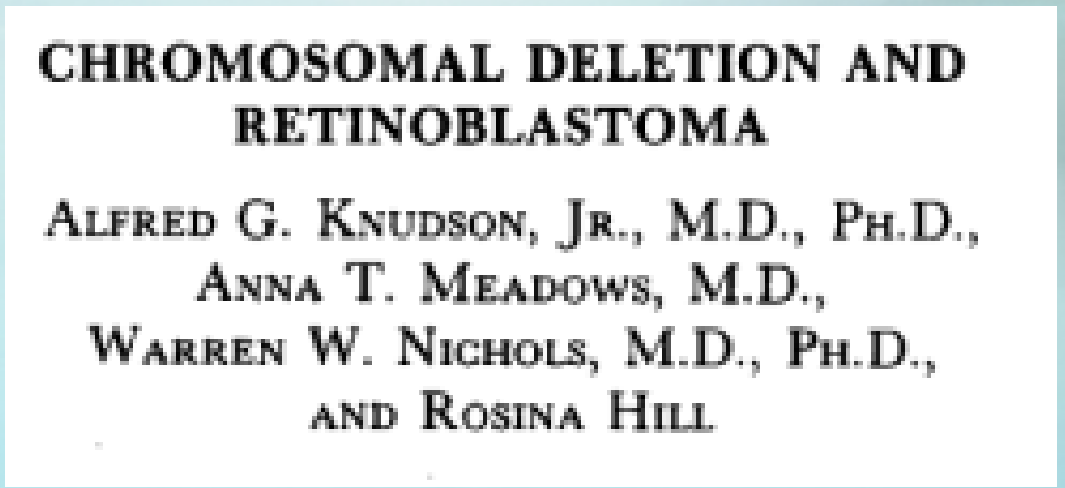
Fig. 1 | **The hamartin–tuberin complex regulates mTORC1 signalling by integrating extracellular and intracellular signals that promote metabolic homeostasis.**

- TSC mutations lead to loss of function of the Tuberin-Hamartin complex
- This complex is supposed to regulate mTORC1
- The loss of function of T-H leads to overactivity of mTORC1
- Overactivity ensues in the purple boxes, which leads to loss of cell cycle regulation, unregulated cell growth, and tumor formation

Nat Rev Nephrol 2018;14(11):704-716

Mechanism of T-H loss of function: 2 hit hypothesis

- Some tumors (IE unregulated cell growth) require a second mutation to occur on top of a first mutation which had been clinically silent
- In case of inherited tumor syndromes, the first “hit” is the inherited mutation itself. A second “hit” (mutation) is required for a tumor to form
- This is why kidney tumors in TSC arise in the first few decades of life, and not right at birth



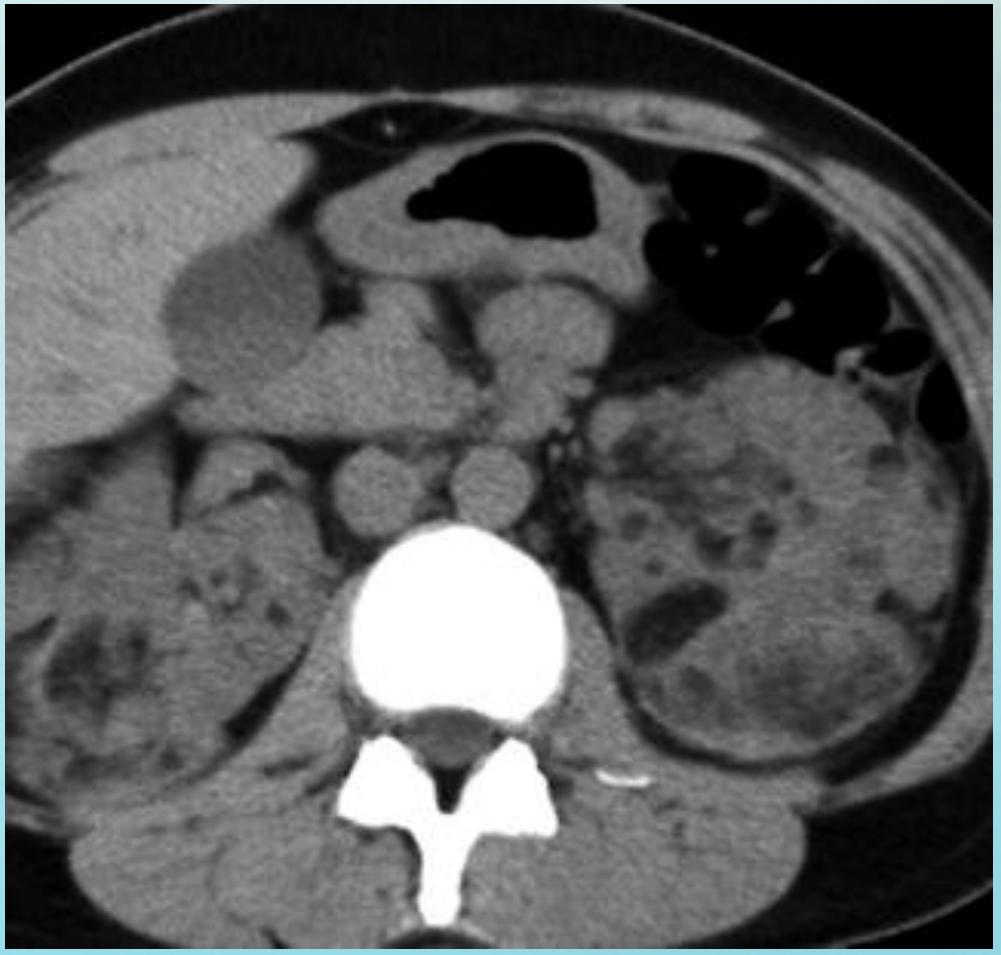
CHROMOSOMAL DELETION AND RETINOBLASTOMA

ALFRED G. KNUDSON, JR., M.D., PH.D.,
ANNA T. MEADOWS, M.D.,
WARREN W. NICHOLS, M.D., PH.D.,
AND ROSINA HILL

NEJM 1976 295 1120-3

“Two Hits” lead to multiple AMLs in most patients with TSC

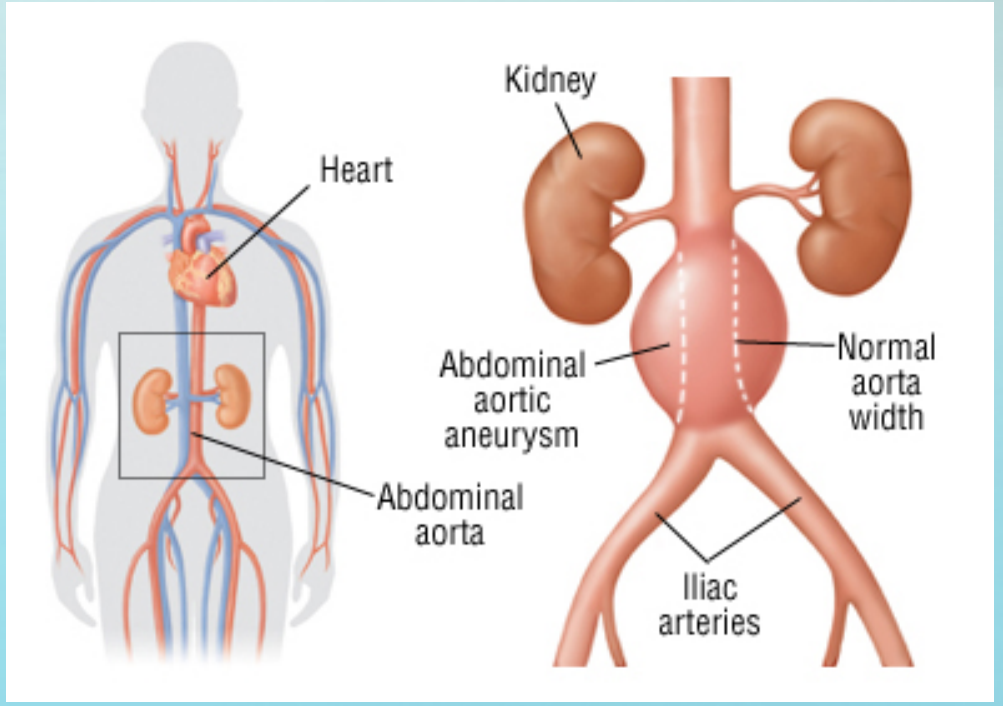
CT scan with cross sectional images of the kidneys in a patient with TSC. Both kidneys are affected by multiple AMLs which contain fat-density tissue.



Abdom Imaging 2014;39:588-604

Aneurism

- An aneurism is an abnormal dilation of an artery
- The picture at right is an abdominal aortic aneurism
- Aneurisms affect multiple organs including the brain and aorta (pictured)
- Aneurismal dilation leads to thinning and increased tension in the vessel wall
- Increased tension can lead to rupture
- Two main causes of aneurisms: atherosclerotic plaque in the vessel wall and genetic abnormalities of the vessel wall
- AMLs contain aneurismal blood vessels which are prone to rupture and bleeding



Picture downloaded from Google on Oct 30 2019

AMLs
Biggest risk is aneurismal rupture leading to bleeding

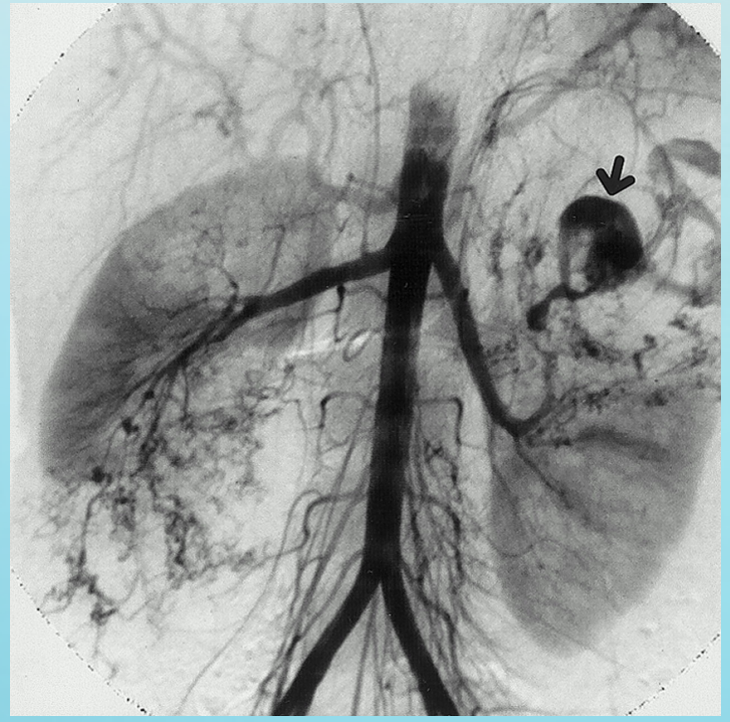


Figure 4a. Frontal aortogram demonstrates large angiomyolipomas in both kidneys. A large aneurysm (arrow) is seen in the ruptured lesion in the left kidney. Embolization was performed in the left kidney.

Radiology 2002;225:78-82

Aneurism size, tumor size, and rupture are directly related in AMLs

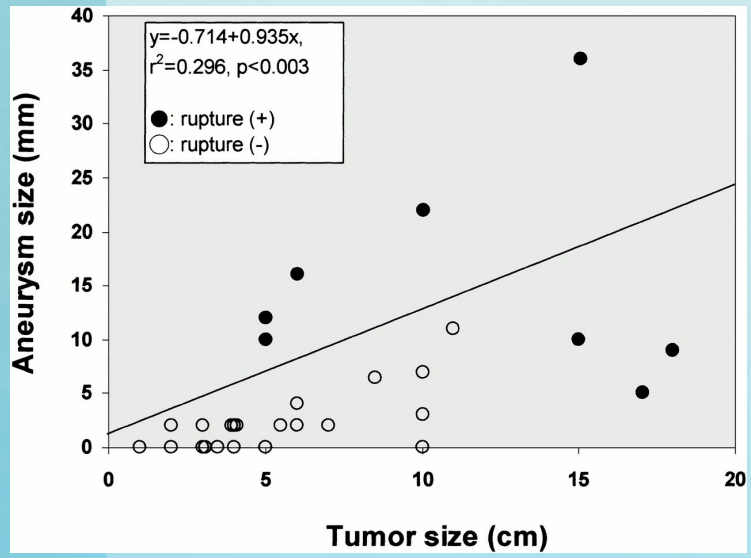


Figure 1: relationship between tumor size and aneurism size

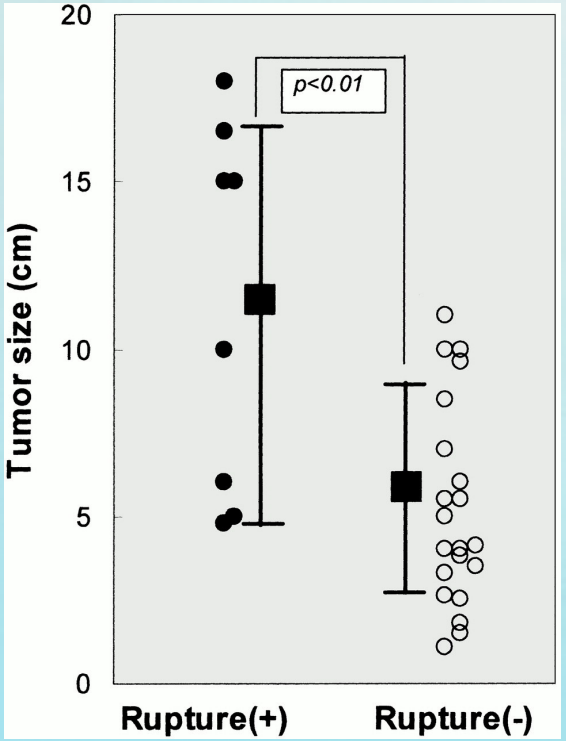


Figure 2: relationship between risk of rupture and tumor size

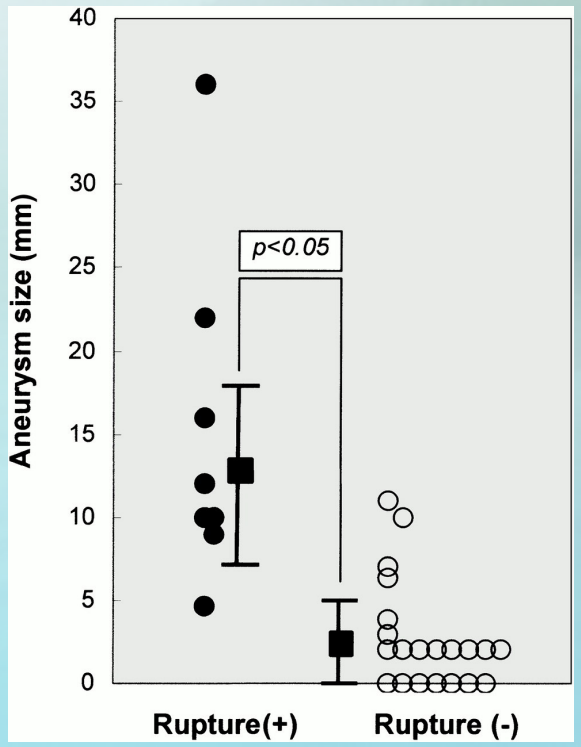


Figure 3: relationship between risk of rupture and aneurism size

The risk of rupture directly correlates with the tumor size and aneurism size.
In this series, no bleeding occurred in tumors < 4cm and aneurisms < 5mm.
Aneurism size was a more specific predictor of bleeding risk than tumor size
Radiology 2002;225:78-82

AML risk of rupture: modifications and other factors

- Some large tumors remain stable, though some tumors < 4 cm can rupture (in other words, tumor size alone is not that specific for rupture risk)
- Contact sports, pregnancy, horse chestnut seed extract, and a hard abdominal physical exam (!!) have all been reported to lead to rupture of AMLs.
- AMLs contain estrogen receptors (100% ERβ)
- They grow during pregnancy and also with use of birth control pills

Medicine 2018;97:16
Urology 2008 Oct;72(4):927-932
Obstet Gynecol 2006 Sept;108(3 Pt 2):734-6

Other adverse outcomes seen in AML+TSC

AML status	HTN	Anemia	CKD	Dialysis	Transplant	Death from Renal cause
None	11%	39%	5%	1%	1%	1%
Present	26%	61%	16%	2%	2%	2.6%
AML severity	Yes	Yes	Yes	Trend NS	Trend NS	Yes

- Patients with TSC and Renal AMLs have reduced survival compared to the general population
- Most common cause of death is renal cause
- Embolizations did not have a significant effect on above outcomes (IE presence of AMLs themselves are main driver, not complications from procedures)

Am J Kidney Dis 2015;66(4):638-645

Embolization for AMLs

- Embolization: when the flow in blood vessel is blocked off by an object, which typically breaks off one location and travels with the blood flow until becoming lodged in a spot where the blood vessel narrows or branches
- The object can be a clot, foreign body, fat, air
- Embolizations are the cause of many diseases including stroke, heart attack, and pulmonary embolism
- A foreign body can be placed in a bleeding artery to stop the bleeding – this is a therapeutic embolization
- This procedure is usually done by an interventional radiologist, who uses contrast to find which artery is supplying the site of bleeding

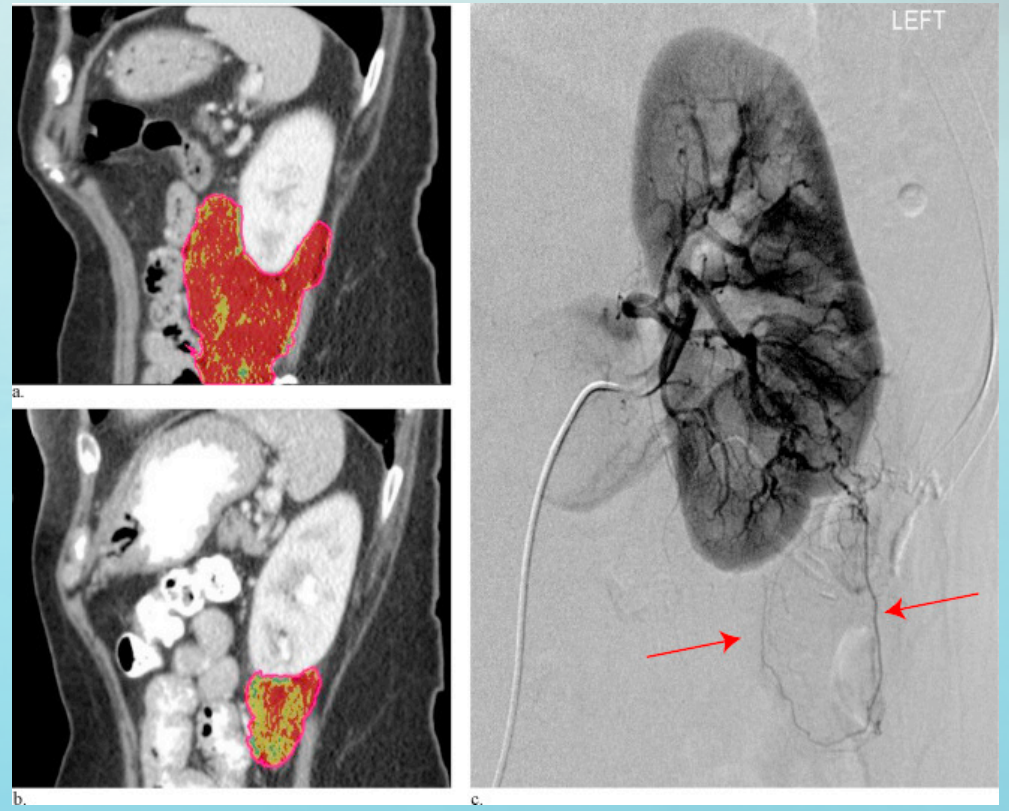
Embolization for AMLs

- More commonly needed for TSC-assoc than sporadic AMLs
- typical indications: tumor > 4cm, aneurism > 5mm, pain, active bleeding, abd mass
- Complications: post embolization syndrome 12-40%; regrowth; groin hematoma, hematuria, abscess, ongoing bleeding from AML also reported but uncommon
- Prevent and treat: bleeding, mass, pain
- Do not prevent: CKD, anemia, HTN
- With increased use of mTORi's (upcoming slides), embolization is becoming less common

J Vasc Intervent Radiol 2016;27(10):1542-1549
Curr Med Res Opin 2017;33(5):821-827
Eur Urol 2009;55(5):1155-1161

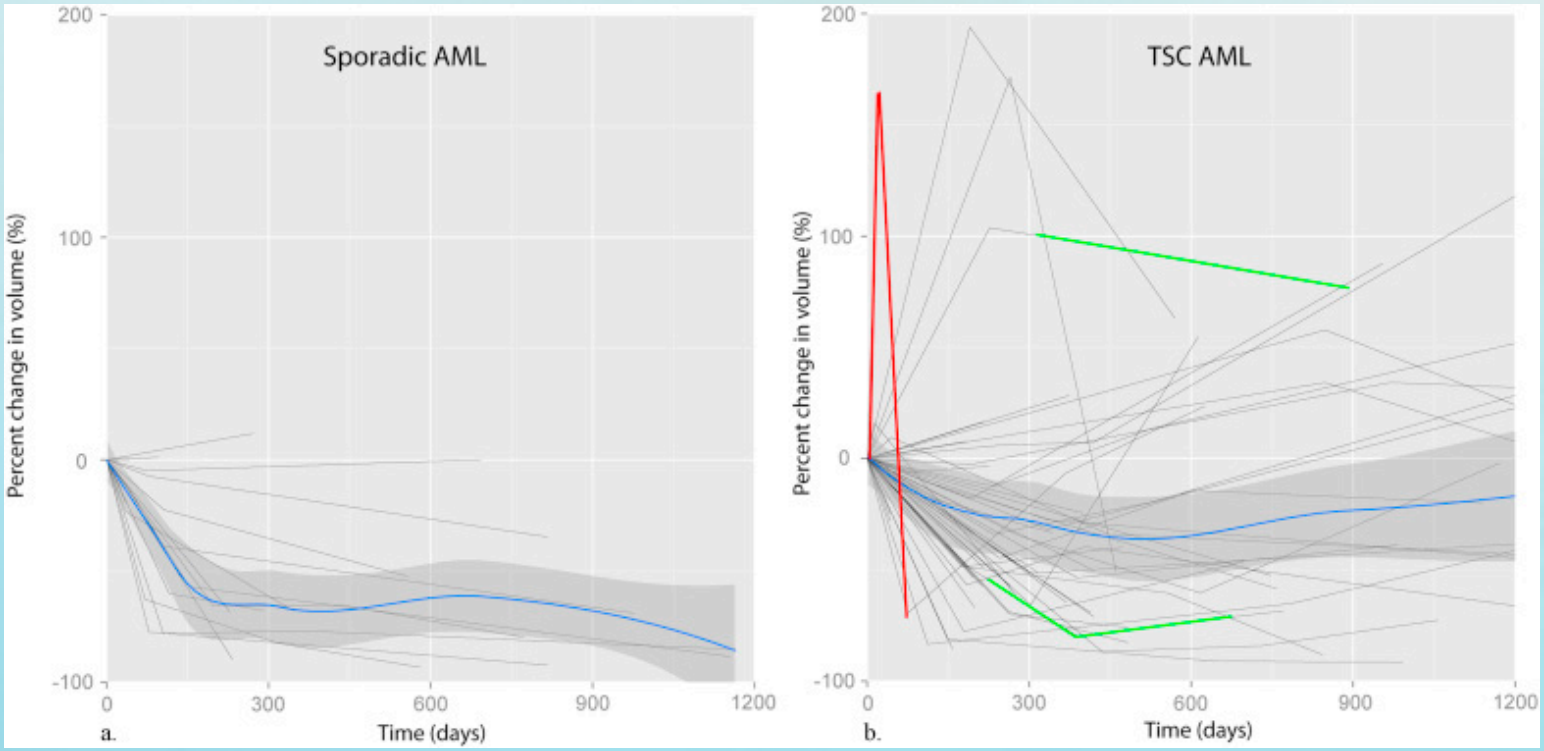
Radiographs of an Embolization

- CT with contrast (sagittal cuts) on the left with before and after images. The red color is demonstrating the fat-density on CT (usually would appear black)
- Angiogram pre embolization (contrast into the renal artery) on the right, showing the main artery supplying the aML which was then embolized



J Vasc Intervent Radiol 2016;27(10):1542-9

AMLs tend to regrow TSC in certain situations



- Age > 18
- Larger tumor size (400-500mL)

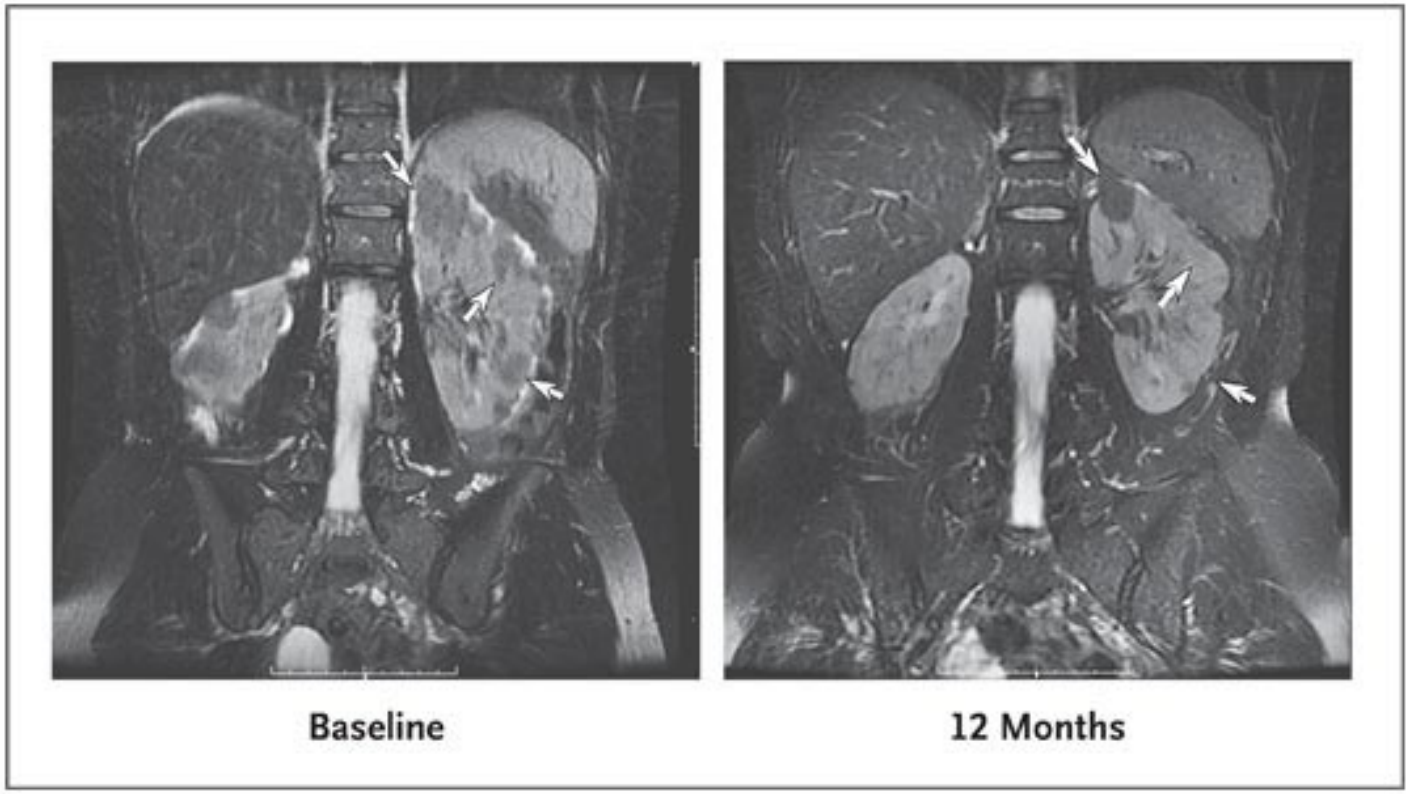
Figure: percent change in tumor volume as a function of time after embolization in a single-center series. TSC-assoc AMLs showed regrowth after ~1-2 years while sporadic AMLs did not regrow
From J Vasc Intervent Radiol 2016;27(10):1542-9

AMLs: mTOR inhibitors

- Recall that in TS, loss of function of Tuberin-Hamartin leads to overactivity of mTOR
- Two commercially available mTOR inhibitors: sirolimus and everolimus
- Sirolimus (rapamycin) first isolated by investigators from the Canadian Medical Mission from soil in Easter Island in 1976
- Sirolimus originally FDA-approved in 1999 for prophylaxis against rejection in kidney transplantation
- Everolimus, an analogue of sirolimus, was first approved in 2009 for kidney cancer; in 2012 it received FDA approval for TSC-assoc AMLs
- Temsirolimus only approved for kidney cancer

NEJM 2008;358:140-151
Ther Drug Monit 2001;23:559-586
Everolimus package insert: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022334s036lbl.pdf

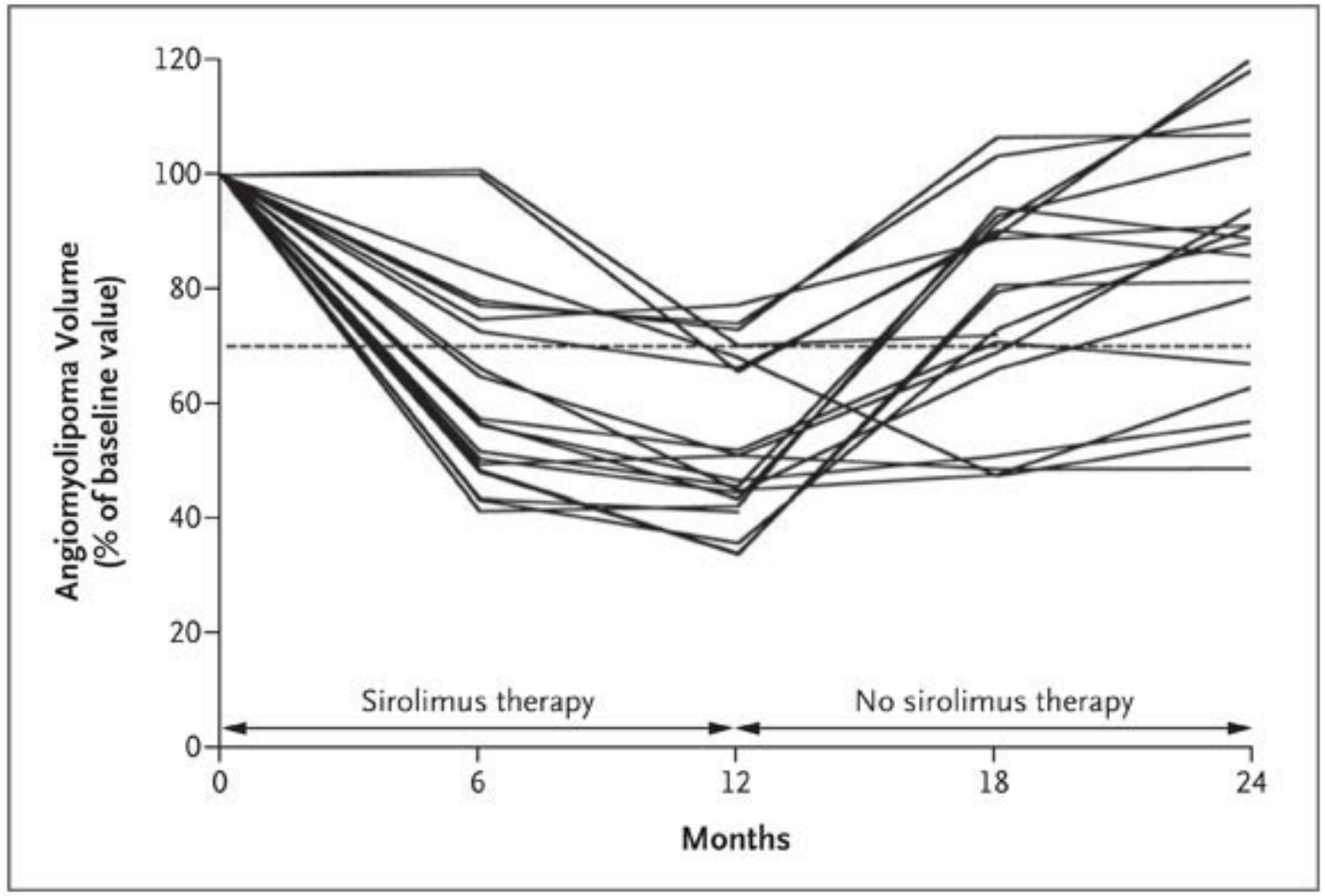
Sirolimus phase 2 trial in 2008



- Sirolimus has shrunk tumors in animal models of TSC
- Sirolimus was shown in 2008 to shrink renal AMLs in TSC (as well as pulmonary LAM)
- At left is an MRI with coronal cuts showing before and after kidney images in a patient with TSC

Bissler JJ et al. N Engl J Med 2008;358;140-151

AML Volume in the Patients with the TSC or LAM



- 25 patient received standard dose sirolimus for 12 months, then stopped
- Most patients had > 30% reduction in tumor volume, though most regrew after drug was stopped
- Side effects of mTORi are common

Bissler JJ et al. N Engl J Med 2008;358;140-151

Everolimus: EXIST trials

- EXIST1: used everolimus to treat SEGA (subependymal giant cell astrocytoma) with target trough 5-15
- Renal AMLs in the kidneys shrunk over the study period
- Subgroup analysis found that AML sum volume reduction was 57, 78, and 80 (%) at 12, 24, and 48 weeks compared to placebo

Nephrol Dial Transpl 2014;29:1203

- EXIST2: used everolimus to treat renal AMLs
- 118 patients with TSC or LAM, largest AML > 3cm, randomized in 2:1 fashion to receive EV 10mg/d or placebo and titrated to tolerability; median exposure was 38 weeks
- Sum volume reduction of > 50% at 24 weeks: 55%
- Sum volume reduction of > 30% at 24 weeks: 80%
- Reduction of > 50% was 42%
- Median time to response was 2.9 months
- AML progression: 4% (ev group), 21% (placebo group)

Lancet 2013;381:817-824

EXIST2 trial: other findings

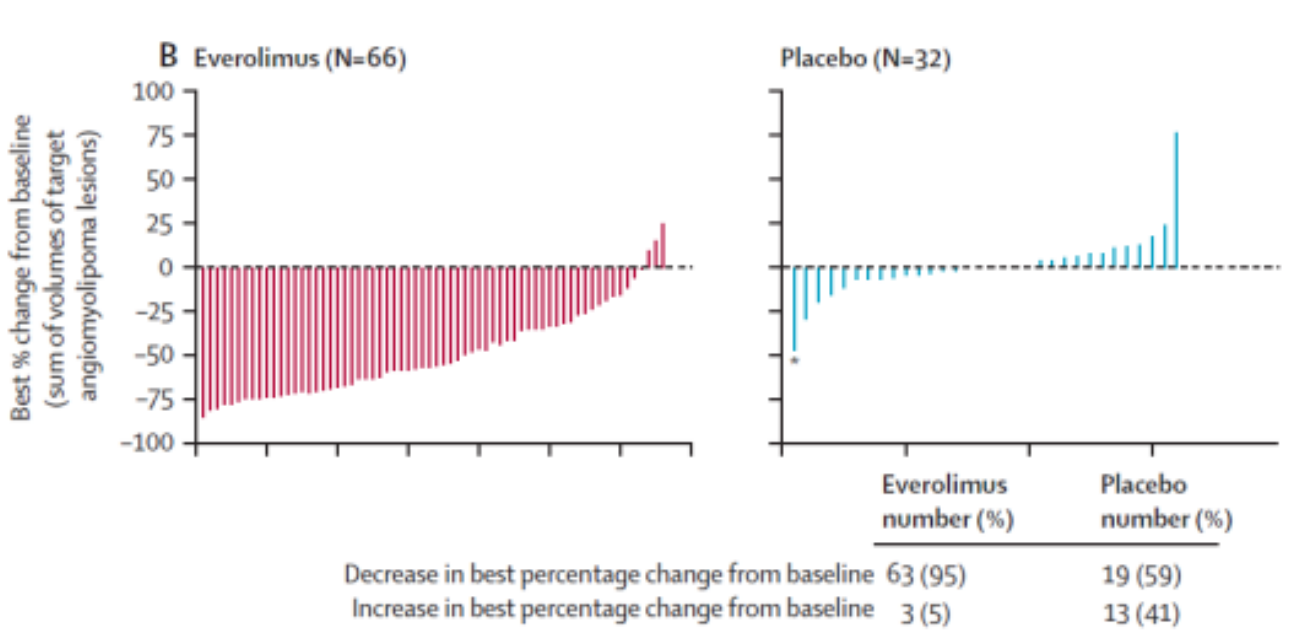


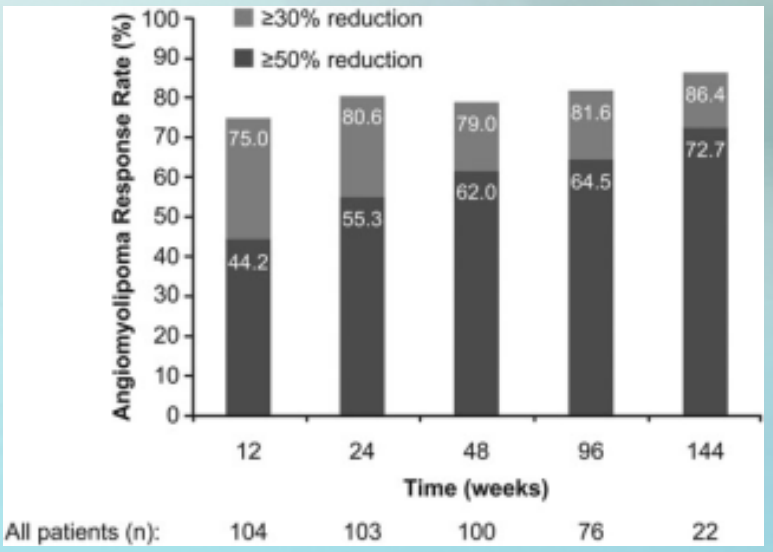
Figure showing variable amount of reduction in AML size among patients receiving EV, versus no reduction in size with placebo

- Higher skin lesion response rate in EV group
- Mean troughs highly variable (56-94%)
  - 7.6 at week 2
  - 9.4 at week 24
  - 5.1 in patients using enzyme-inducing AEDs v 10.4 in those who were not
- Large variation between trough levels and AML size changes
- VEGF and collagen-4 levels correlated with AML size changes (possibly can avoid MRI)

Lancet 2013;381:817-824

EXIST2 open label extension

- Extension of earlier trial with median EV exposure 28.9 months
- Same dosing scheme (10mg/d then titrated to tolerability)
- Response rate (>50% reduction in total lesions): increased from 42% to 54% and gradually increased with longer duration of exposure (figure to right)
- Progression rate was 5.6%
- Safety profile similar



Nephrol Dial Transpl 2016;31:111-119

Side effects

https://www.cartoonstock.com/directory/u/unintended_consequences.asp

	Everolimus (n=79)			Placebo (n=39)		
	All grades	Grade 3	Grade 4*	All grades	Grade 3	Grade 4*
Stomatitis	38 (48)	1 (1)	0	3 (8)	0	0
Nasopharyngitis	19 (24)	0	0	12 (31)	0	0
Acne-like skin lesions	17 (22)	0	0	2 (5)	0	0
Headache	17 (22)	0	0	7 (18)	1 (3)	0
Cough	16 (20)	0	0	5 (13)	0	0
Hypercholesterolaemia	16 (20)	0	0	1 (3)	0	0
Aphthous stomatitis	15 (19)	2 (3)	0	4 (10)	0	0
Fatigue	14 (18)	1 (1)	0	7 (18)	0	0
Mouth ulceration	13 (16)	2 (3)	0	2 (5)	0	0
Nausea	13 (16)	0	0	5 (13)	0	0
Urinary tract infection	12 (15)	0	0	6 (15)	0	0
Vomiting	12 (15)	0	0	2 (5)	0	0
Anaemia	10 (13)	0	0	1 (3)	0	0
Arthralgia	10 (13)	0	0	2 (5)	0	0
Diarrhoea	10 (13)	0	0	2 (5)	0	0
Abdominal pain	9 (11)	0	0	3 (8)	1 (3)	0
Blood lactate dehydrogenase increased	9 (11)	0	0	2 (5)	0	0
Hypophosphataemia	9 (11)	0	0	0	0	0
Eczema	8 (10)	0	0	3 (8)	0	0
Leucopenia	8 (10)	0	0	3 (8)	0	0
Oropharyngeal pain	8 (10)	0	0	4 (10)	0	0
Upper respiratory tract infection	8 (10)	0	0	2 (5)	0	0

Data are n (%). A patient with multiple occurrences of an adverse event is counted only once in that adverse event category. *Four grade 4 adverse events were reported in the everolimus group: two were laboratory abnormalities reported by the central laboratory (blood uric acid increased and neutropenia), one was a convulsion, and one was a hypertensive crisis. One grade 4 adverse event occurred in the placebo group (volvulus).

Table 2: **Adverse events of any cause experienced by 10% or more patients in the everolimus treatment group, by grade**

Side effects in EXIST2: similar to other indications and other data

- Amenorrhea in 13% of women
- Grade 2 pneumonitis in 1 patient in EV group

Lancet 2013;381:817-824

Management of side effects

Side effect	Management
Severe	Stop drug
Moderate	Consider 50% dose reduction
Mild	Often can treat through and reassure
PJP	Pneumocystis pneumonia – severe infection – stop drug and treat
Fungal infections	Usually stop drug and treat
milder infections	Usually ok to treat through (eg, cold, flu, bladder infection)
Stomatitis	Soft toothbrushes, sucralfate suspension, triamcinolone ointment, L-asparagine, gentle oral care
Rash	Benzoyl-peroxide/antibiotic, topical steroid, doxy or minocycline
Hypercholesterolemia	Consider modification of dose and or statin therapy
Bone marrow suppression (IE, low cell counts)	Reduce or stop drug depending on severity
Proteinuria	More often with sir than ev; dose reduce or stop depending on severity (> 1g/d)

Orph J Rare Dis 2017;12:35

Drug interactions

- Many drugs are metabolized by the liver cytochrome P450 enzyme system, and also affect the activity of this system
- MTORi's are metabolized by Cyp3A4 within this system
- Drugs which speed up these enzymes will increase metabolism of mTORi's and hence reduce their concentrations: Tegretol, phenytoin, babiturates, rifampin, St Johns Wort
- Drugs which slow down these enzymes will reduce the metabolism of mTORi's and increase their concentrations: azole antifungal drugs, clarithromycin, some HIV meds

Orph J Rare Dis 2017;12:35

Conclusions

- Renal angiomyolipomas are benign kidney tumors which are more common and more aggressive in people with tuberous sclerosis
- The arise due to mutations leading to loss of function of regulators of the cell cycle
- The can cause bleeding, pain, and loss of kidney function
- They develop by the 1-2 decade of life in most patient with TS
- They tend to regrow after treatment is stopped
- They can be treated with mechanical (embolization) or chemical (mTOR inhibitors) means
- mTORi’s are highly effective against renal AMLs but have side effects and the tumors regrow when the drug is stopped

Thank you!!!