TSC related Angiomyolipoma - Management Strategies and Case Studies

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Disclosures

Anil Kapoor, MD, FRCSC

	Company/ Organization
I am a member of an **Advisory Board** or equivalent with a commercial or non-commercial organization	Pfizer, Novartis, BMS, Ipsen, Roche, Janssen, Bayer, Amgen

Learning Objectives

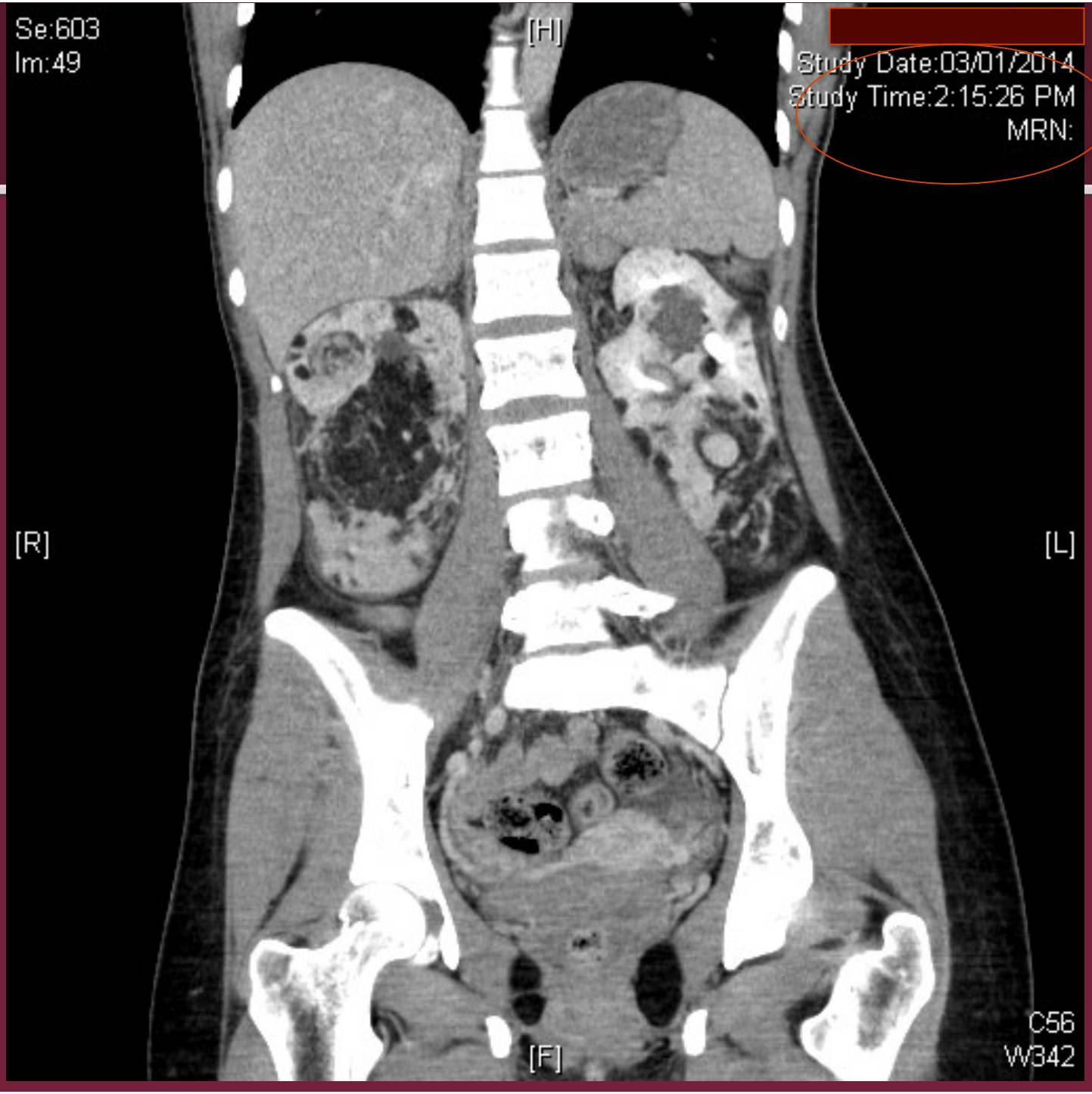
By the end of this program, participants will:

- Understand the diagnosis of TSC
- Determine the diagnosis of TSC-associated AML vs. Sporatic AML
- Understand the role of mTOR inhibitors in the management of AML
- Understand the dosing and monitoring of everolimus in AMLs
- Discuss the role of the TS clinic in patient care and referral as needed

Patient 2

23 yo female Tuberous Sclerosis

- recurrent gross hematuria - AML
- cortical tubers
- recurrent spontaneous pneumothoraces
- multiple ER visits
- HgB 60-70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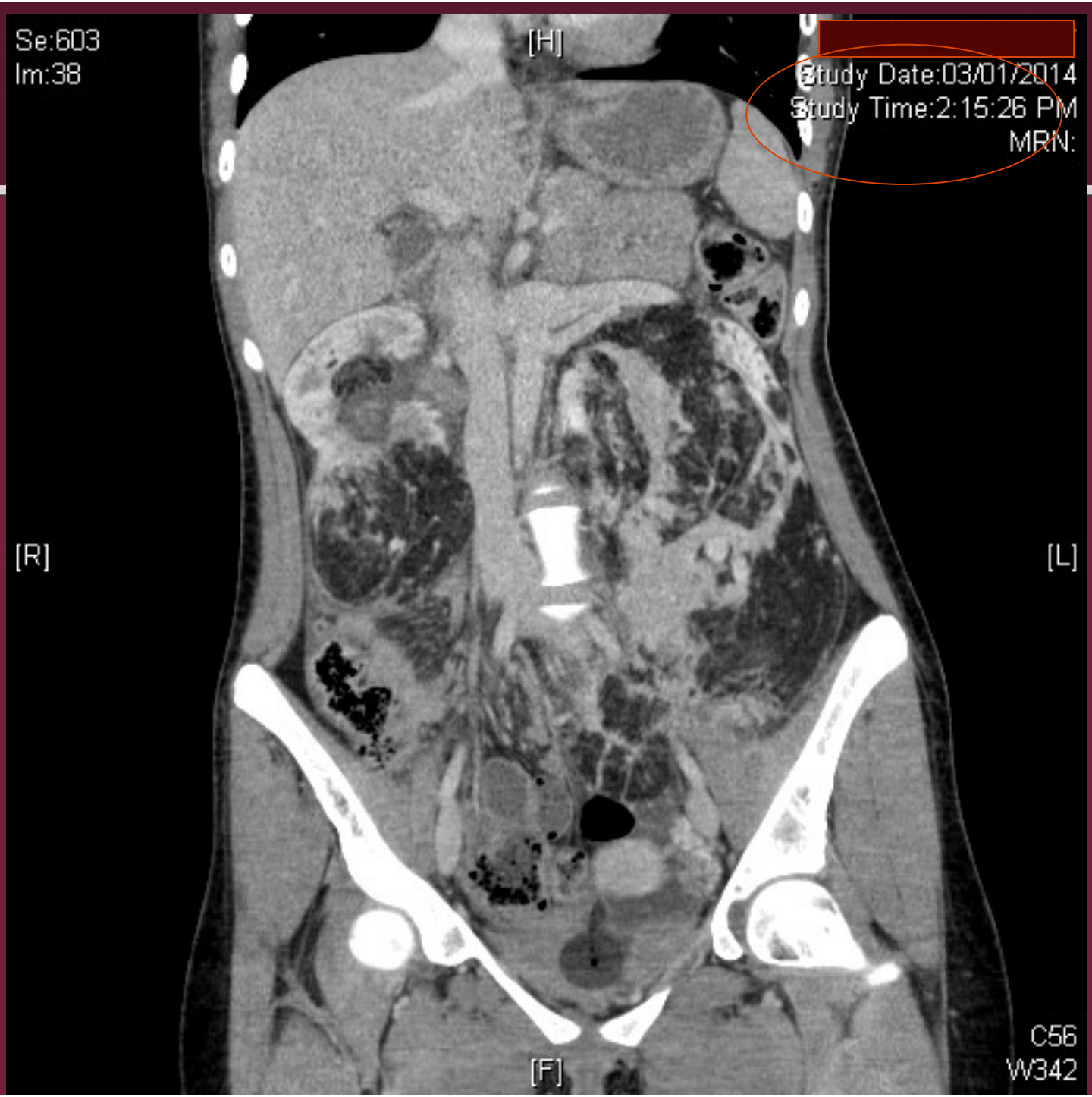
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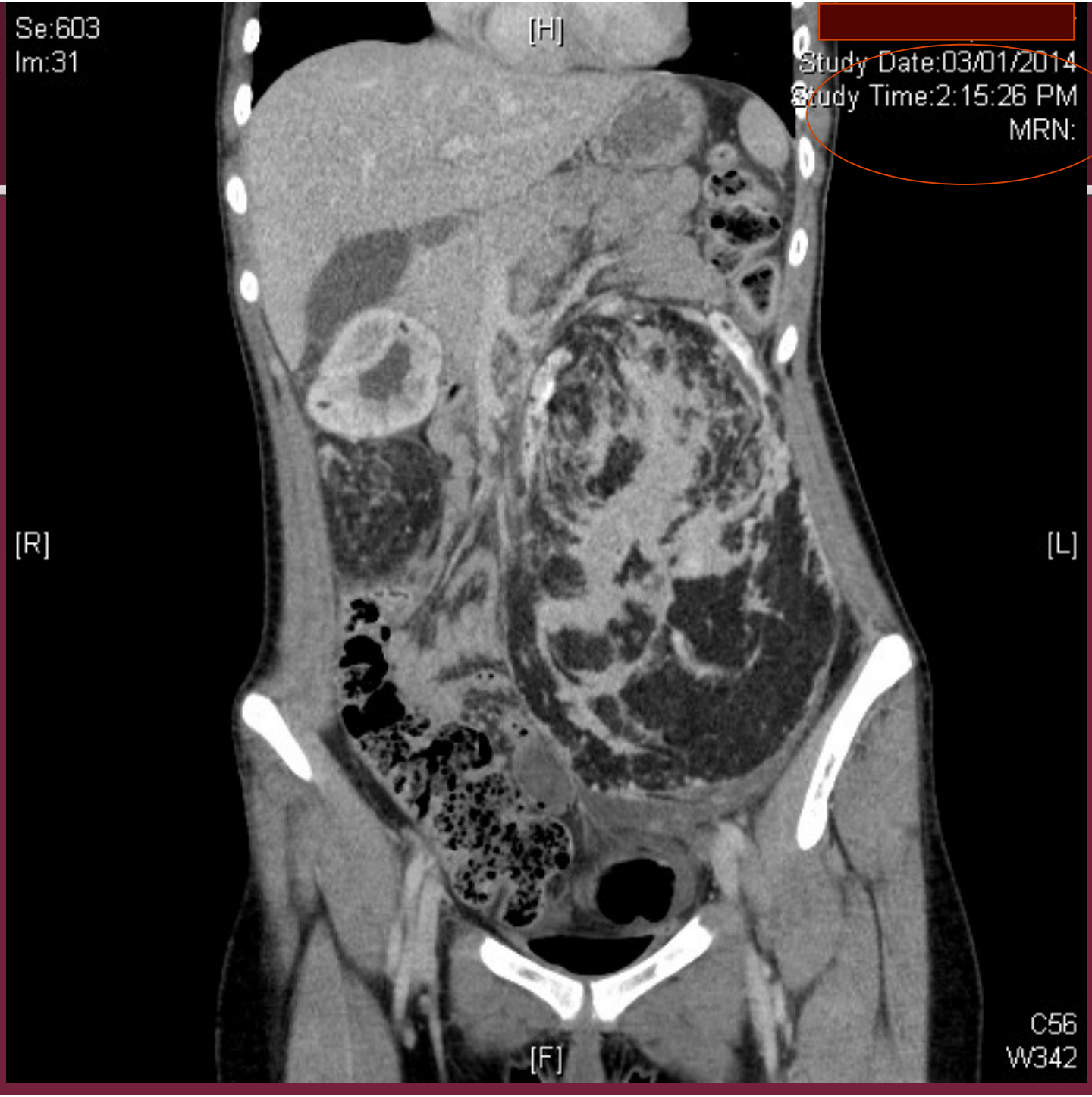
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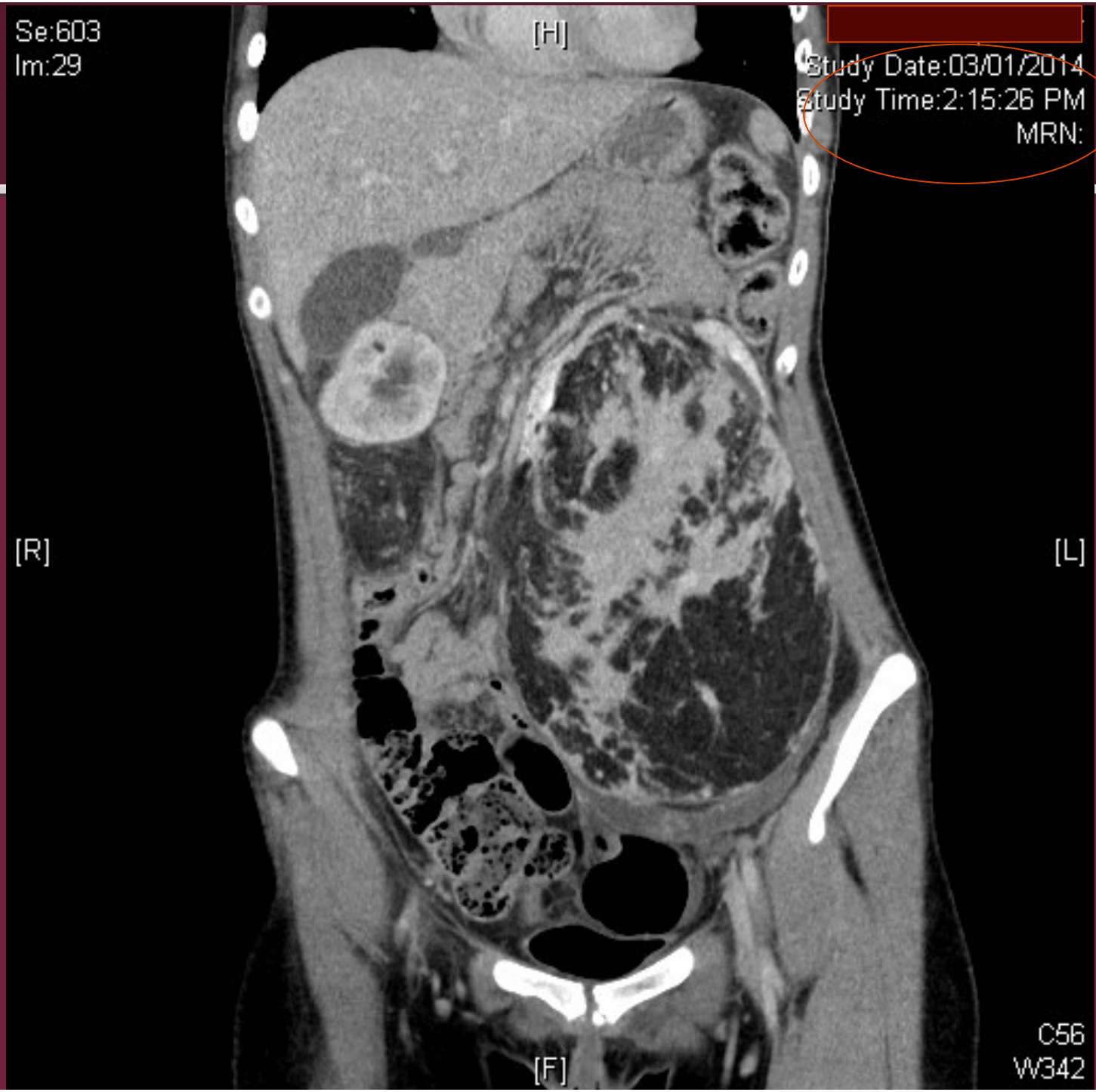
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OPTIONS ?

Embolization ? Bilateral ?
(Right side painful side)

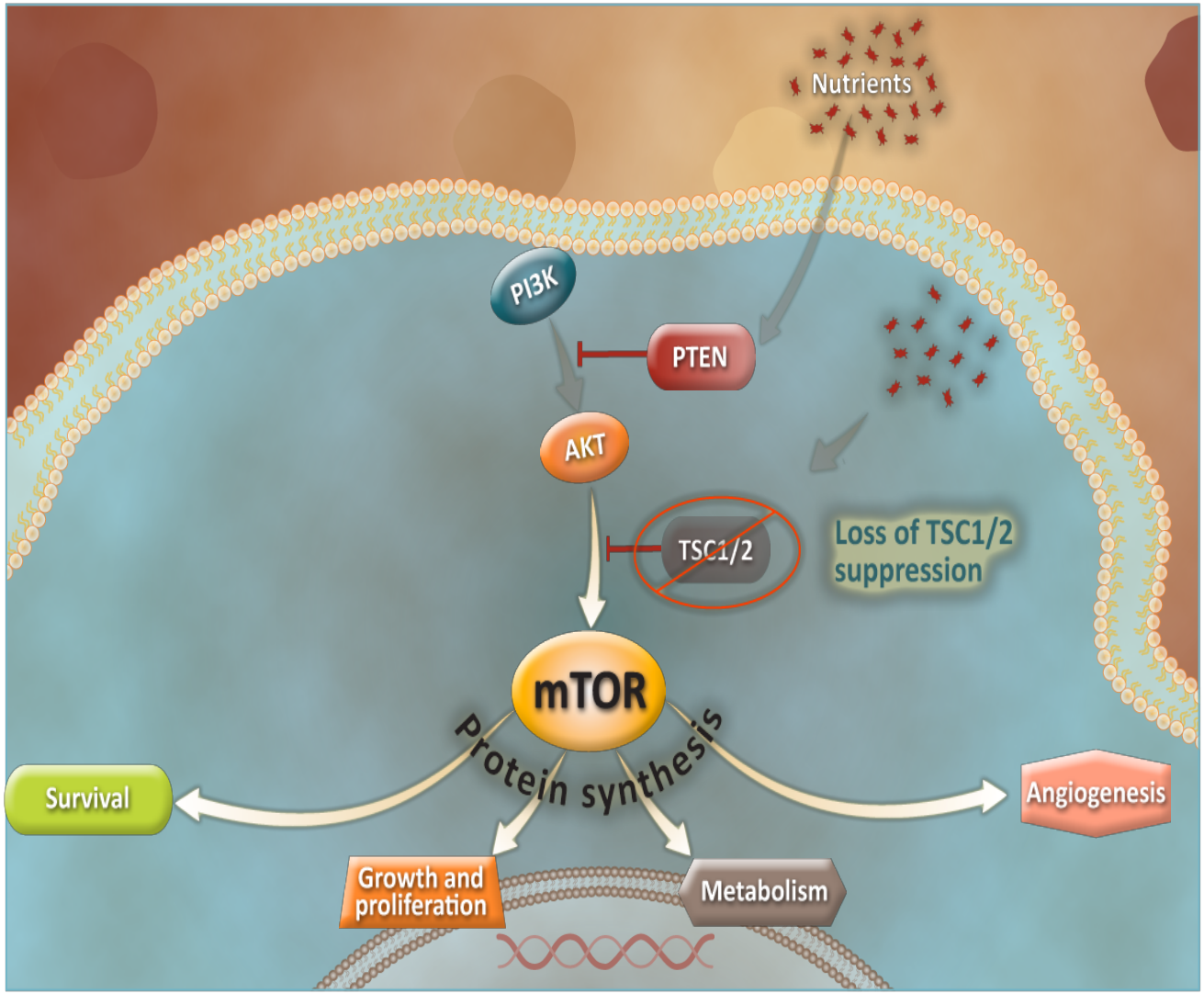
Left Nephrectomy; Right Partial Nephrectomy ?
Bilateral Nephrectomy ?

Tuberous Sclerosis Complex (TSC)

- Incidence 1:6000
- Affects 1-2 million people worldwide
  - Approximately 5,000 in Canada
- Genetic disorder
  - mutations in genes TSC1 and TSC2
- Multi-organ benign tumors throughout the body

Franz, et al. *Neuropediatrics 2010; 41:199-208*

The Role of the mTOR Pathway in TSC



- Loss of TSC1/ TSC2 in the mTOR pathway defines TSC
- The tuberous sclerosis complex (TSC1/TSC2) are tumor suppressor proteins
- Inactivation of TSC1 or TSC2 leads to increased mTOR activity

Crino PB et al. N Engl J Med. 2006;355:1345-1356; Paul E et al. N Engl J Med. 2008;358:190-192

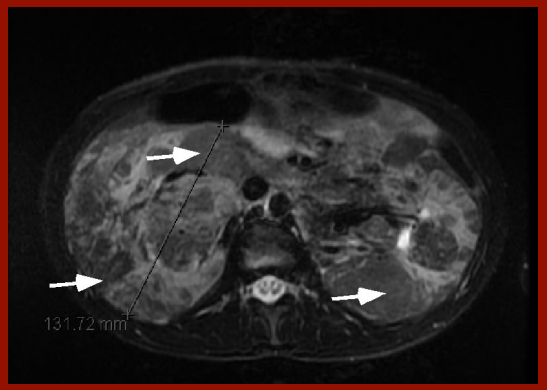
TSC Affects Multiple Organ Systems[1,2]

- **Neurologic**
  - **Epilepsy / Infantile Spasms**
  - **Brain tumors**
    - SENs
    - SEGAs
    - Cortical Tubers
- **Renal**
  - **Angiomyolipomas**
- **Cardiopulmonary**
  - **Cardiac rhabdomyomas**
  - **Lymphangioleiomyomatosis**
- **Ocular**
  - **Retinal lesions**
- **Skin**
  - Facial angiofibromas
  - Ash leaf spots
  - Shagreen patches
  - Ungual fibromas
- **Developmental/ Behavioral Problems**
  - Cognitive dysfunctional
  - Autism spectrum disorder
  - ADHD
  - Anxiety

SEGA, subependymal giant-cell astrocytoma; SEN, subependymal nodule; TSC, tuberous sclerosis complex.

1. Chho. *N Engl J Med* 2006;355:1345-1356; 2. Leung. *J Pediatr Health Care.* 2007; 21:108-114.

TSC Affects Multiple Organ Systems[1,2]



Angiomyolipoma

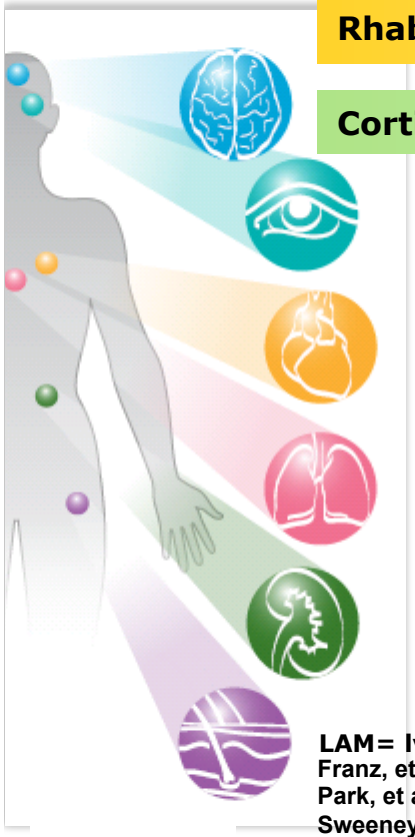
- Slow growing, bilateral kidney tumors
- Complications due to mass effect: hemorrage or rupture of blood vessels feeding the lestion, destruction of adjacent renal tissue, risk of hypertension/renal failure

- **Renal**
  - *Angiomyolipomas (AML)* — *55-75%*
  - *Renal cystic disease* — *50%*

1. Crino. *N Engl J Med* 2006;355:1345-1356; 2. Leung. *J Pediatr Health Care.* 2007; 21:108-114.

A Patient's Journey with TSC

Prenatal	< 1 year	1 – 5 yrs	5 – 18 yrs	> 18 yrs
Geneticists	Neurologist	Opthamologist	Nephrologist/	Pulmonologist
OB/GYN	Dermatologist		Urologist	
Cardiologist				



- Rhabdomyomas
- Cortical Tubers
- Subependymal nodules (SENs)
- Subependymal giant cell astrocytomas (SEGAs)
- Dermatologic manifestation
- Retinal hamartomas
- Angiomyolipomas (AML)
- LAM

LAM= lymphangioleiomyomatosis.

Franz, et al. *J Child Neurol* 2004;19:690-8.; Isaacs. *Am J Perinatol* 2009;26:755-60; Park, et al. *Acta Neuropathol* 1997;94:180-6; Adriaensen, et al. *Eur J Neurol* 2009;16:691-6; Sweeney, et al. *Adv Dermatol* 2004;20:117-35; Roach, et al. *J Child Neurol* 2004;19:643-9; Sparagana, et al. *Curr Opin Neurol* 2000;13:115-9.

Diagnosis of TSC

2012 Revised Guidelines Criteria

Clinical Diagnostic Criteria[1,2]

Major features		Minor features	
1	Hypomelanotic macules (≥3, at least 5 mm in diameter)	1	"Confetti" skin lesions
2	Angiofibromas (≥3) or fibrous cephalic plaque	2	Dental enamel pits (>3)
3	Ungual fibromas (≥2)	3	Intraoral fibromas (≥2)
4	Shagreen patch	4	Retinal achromic patch
5	Multiple retinal hamartomas	5	Multiple renal cysts
6	Cortical dysplasias*	6	Nonrenal hamartomas
7	Subependymal nodules		
8	Subependymal giant cell astrocytomas		
9	Cardiac rhabdomyoma		
10	Lymphangioleiomyomatosis (LAM)**		
11	Angiomyolipomas (≥2)**		

* Includes tubers and cerebral white matter radial migration lines.
**A combination of the two major features LAM and angiomyolipomas without other features does not meet criteria for a definite diagnosis

Definite Diagnosis:	Possible Diagnosis:
•2 major features or •1 major feature + ≥2 minor features	•1 major feature or •≥2 minor features

Northrup H, et al. *Pediatr Neurol* 2013;49:243-254.

2012 Genetic Diagnostic Criteria for TSC

Either a TSC1 or TSC2 pathogenic mutation is sufficient for a definite diagnosis of TSC.

A pathogenic mutation is a:

- mutation that clearly inactivates the function of TSC1 or TSC2 protein (e.g., out-of-frame indel or nonsense mutation)
- mutation that prevents protein synthesis (e.g., large genomic deletion)
- missense mutation whose effect on protein function has been established by functional assessment

Other TSC1 or TSC2 variants whose effect on function is less certain do not meet these criteria, and are not sufficient to make a definite diagnosis of TSC.

- Genetics-based diagnosis even in the absence of clinical signs would facilitate appropriate monitoring of the genetically diagnosed individual throughout his/her lifetime
- It is noteworthy that 10-25% of individuals with TSC have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC or have any effect on the use of Clinical Diagnostic Criteria to diagnose TSC

Surveillance and Management Recommendations

Already Diagnosed with Definite or Possible TSC – Renal Angiomyolipoma

Kidney:

- MRI of abdomen every 1-3 years
- Renal function (including GFR) and blood pressure at least annually
- *Acute hemorrhage*: embolization + corticosteroid, nephrectomy to be avoided
- *Asymptomatic, growing angiomyolipoma >3 cm:*
  - Treatment with mTOR recommended as first-line therapy
  - Embolization/kidney-sparing resection acceptable second-line options

Brain Tumors and Tubers, Neurocognition and Behavior, Epilepsy:

- Brain MRI,1-3 years in asymptomatic patients <25 yrs to monitor for new occurrence of SEGA
- Screen for TAND symptoms at least annually
- EEG with known/suspected seizure activity, as clinically needed; anticonvulsant therapy

Lung:

- Clinical screening for symptoms at each visit
- No lung cysts: HRCT every 5-10 years;
- Lung cysts: HRCT every 2-3 years, annual PFT tests

Eye/Skin/Teeth:

- Annual skin and eye exams
- Bi-annual dental exam, panoramic radiograph by 7 years

Angiomyolipomas may be TSC-Associated or Sporadic

- Although identified in patients with TSC, renal disorders are not specific to TSC pathophysiology
- Angiomyolipomas that occur in patients with no other clinical features of TSC are called sporadic
  - Account for 80% of all angiomyolipomas
  - Usually solitary and occur almost exclusively in women in their 40s
- Angiomyolipomas may be associated with retroperitoneal hemorrhage and impingement of the kidneys and other vital organs, impairing their function

Blute ML, et al. *J Urol* 1988;139:20-24; Nelson CP, et al. *J Urol* 2002;168:1315-25. El-Hashemite N, et al. *Lancet* 2003;361:1348-9; Smolarek TA, et al. *Am J Hum Genet* 1998;62:810-5; Avila NA, et al. *Radiology* 2007;242:277-85.

Characteristics of TSC-Associated vs. Sporadic Angiomyolipomas

	TSC-associated Angiomyolipoma	Sporadic Angiomyolipoma	*P*-value (Chi-square test)
Mean age (years)	30.3	52.1	—
Tumour diameter (cm)	8.9	5.4	—
% multiple tumours	97	13	<0.0001
% at presentation:			
Symptomatic	64	72	0.2584
Acute hemorrhage	44	14	<0.0001

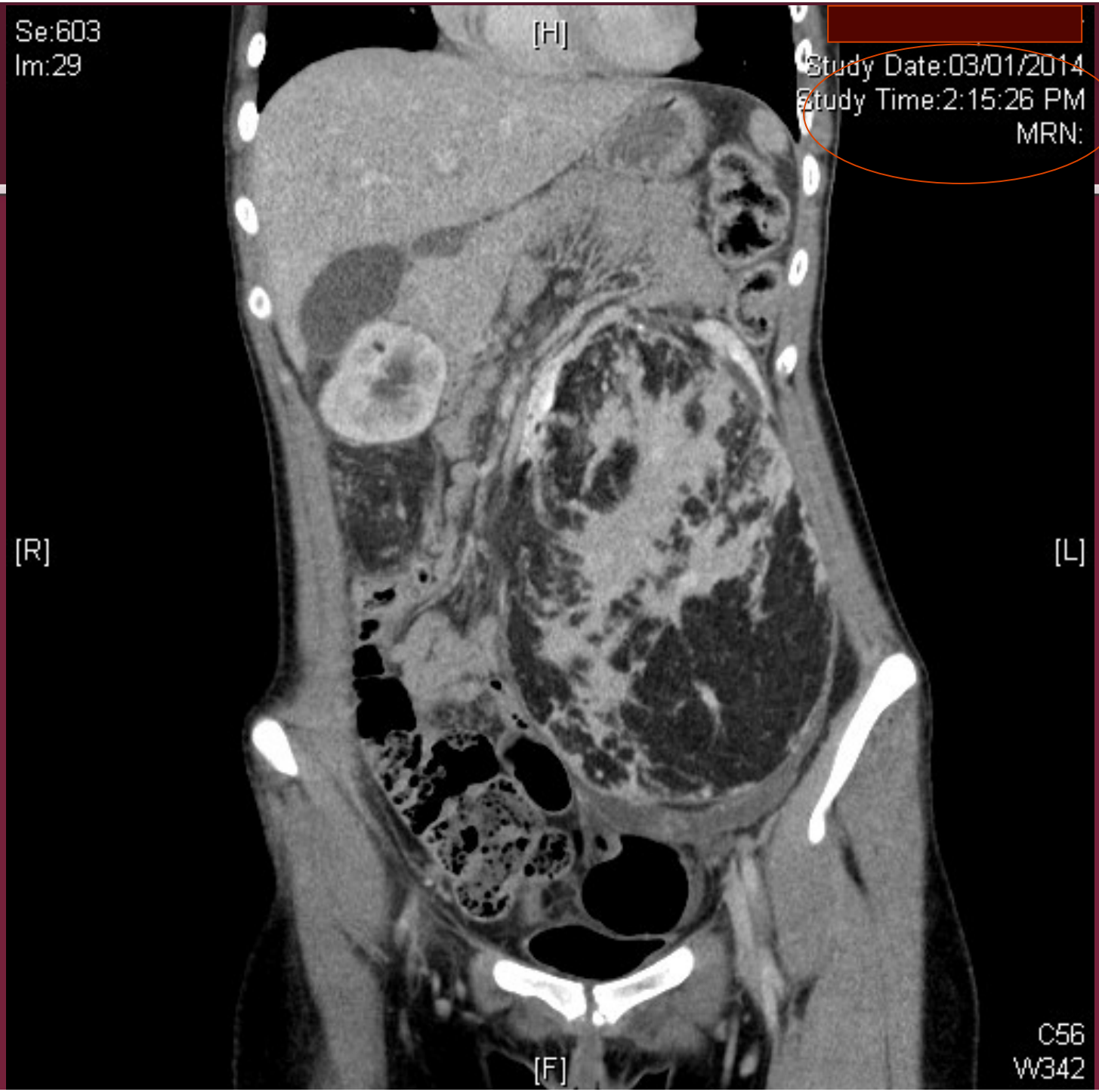
Nelson CP, et al. *J Urol* 2002;168:1315-25.

Management of Angiomyolipomas in TSC

- **Surveillance**
- **First-line therapy:**
  - mTOR inhibitor for asymptomatic, growing angiomyolipoma > 3 cm
  - Embolization followed by corticosteroids for hemorrhage
    - Nephrectomy to be avoided
- **Second-line therapy:**
  - Selective embolization or kidney-sparing resection

Remember Surveillance:

- **MRI of abdomen every 1-3 years**
  - **Attention to vascularity and presence of aneurysm**
- **BP and renal function (including GFR) at least annually**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Patient 2

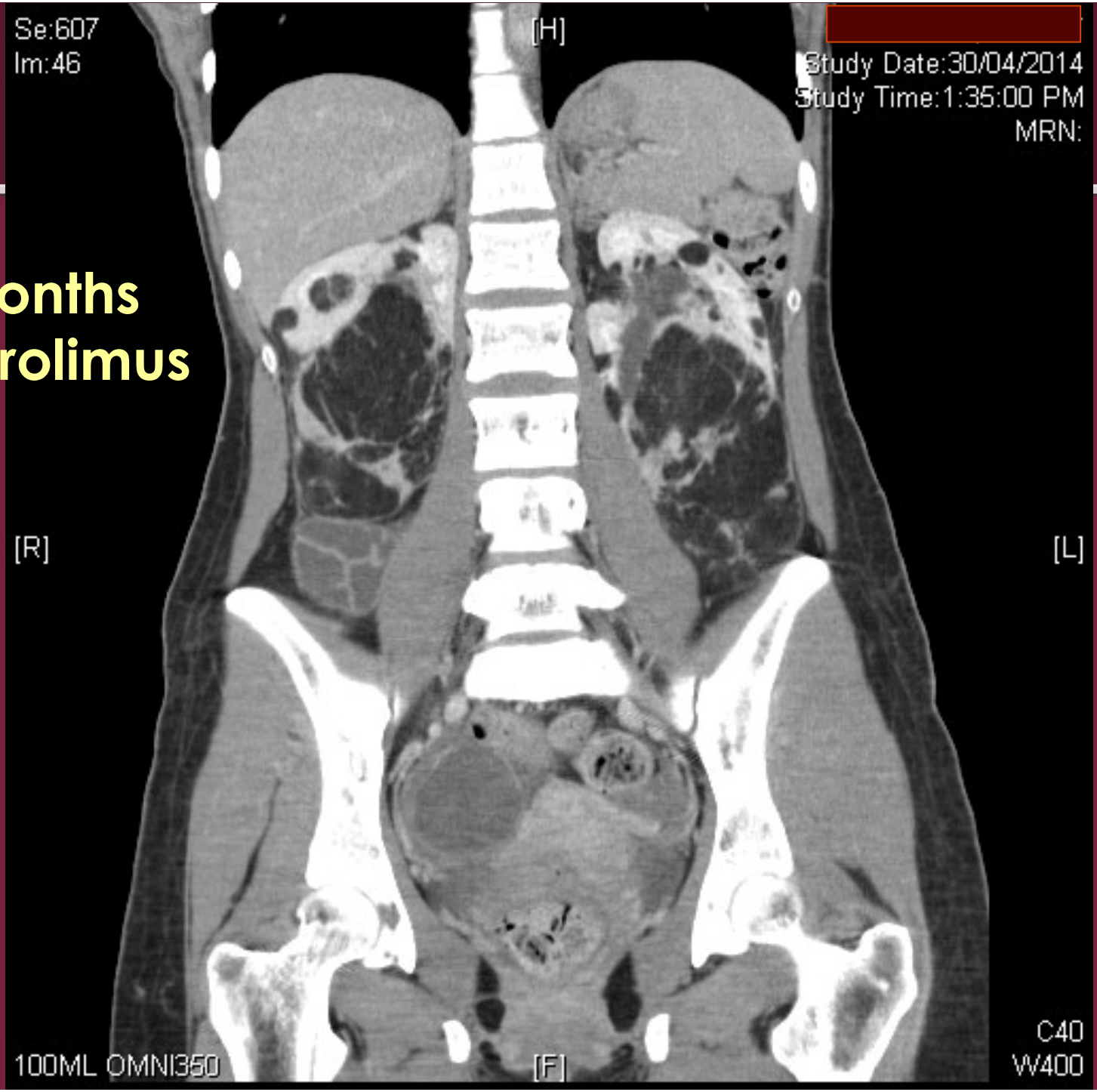
OPTIONS ?

Embolization ? Bilateral ?
(Right side painful side)

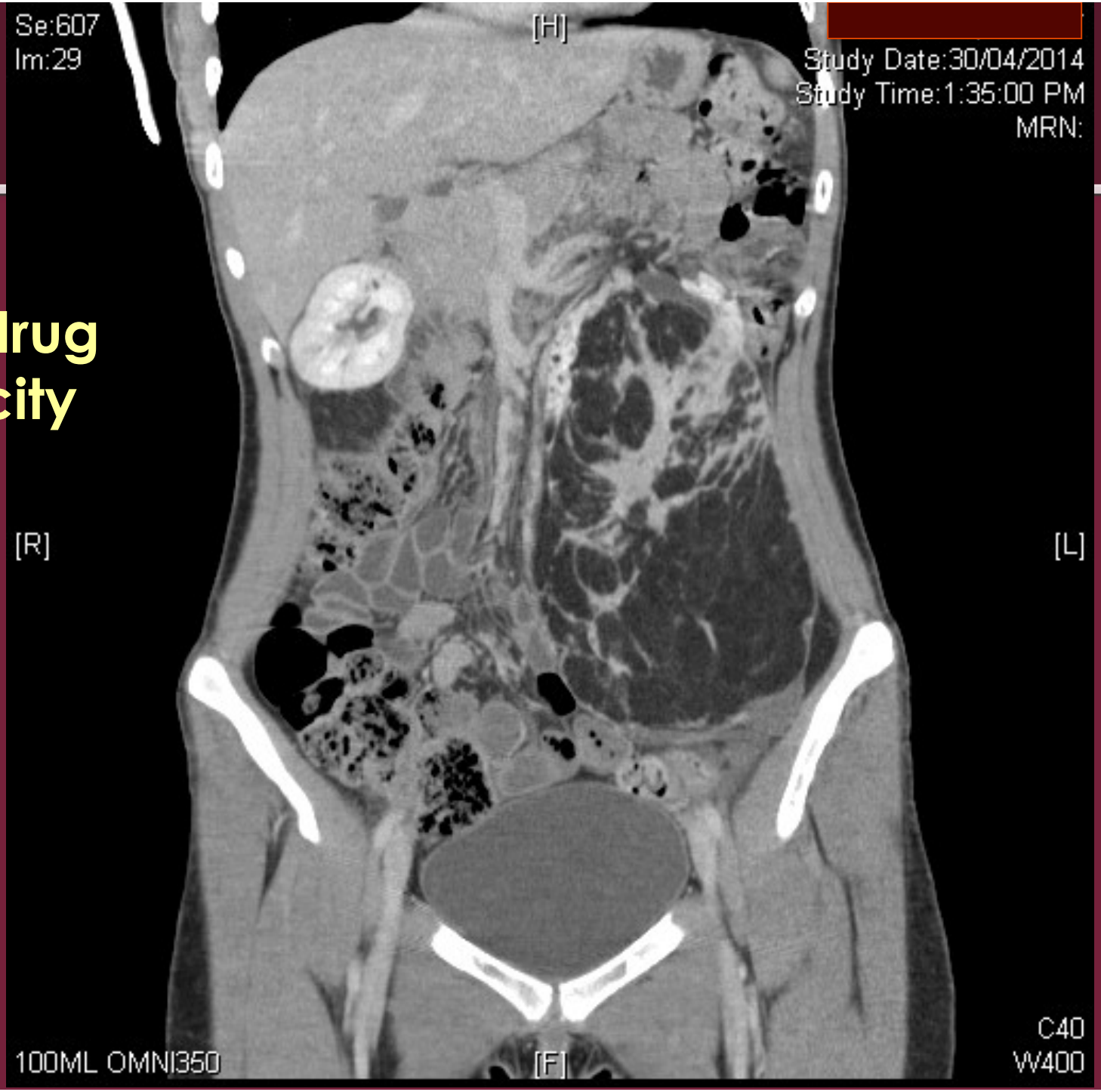
Left Nephrectomy; Right Partial ?

mTORi ?

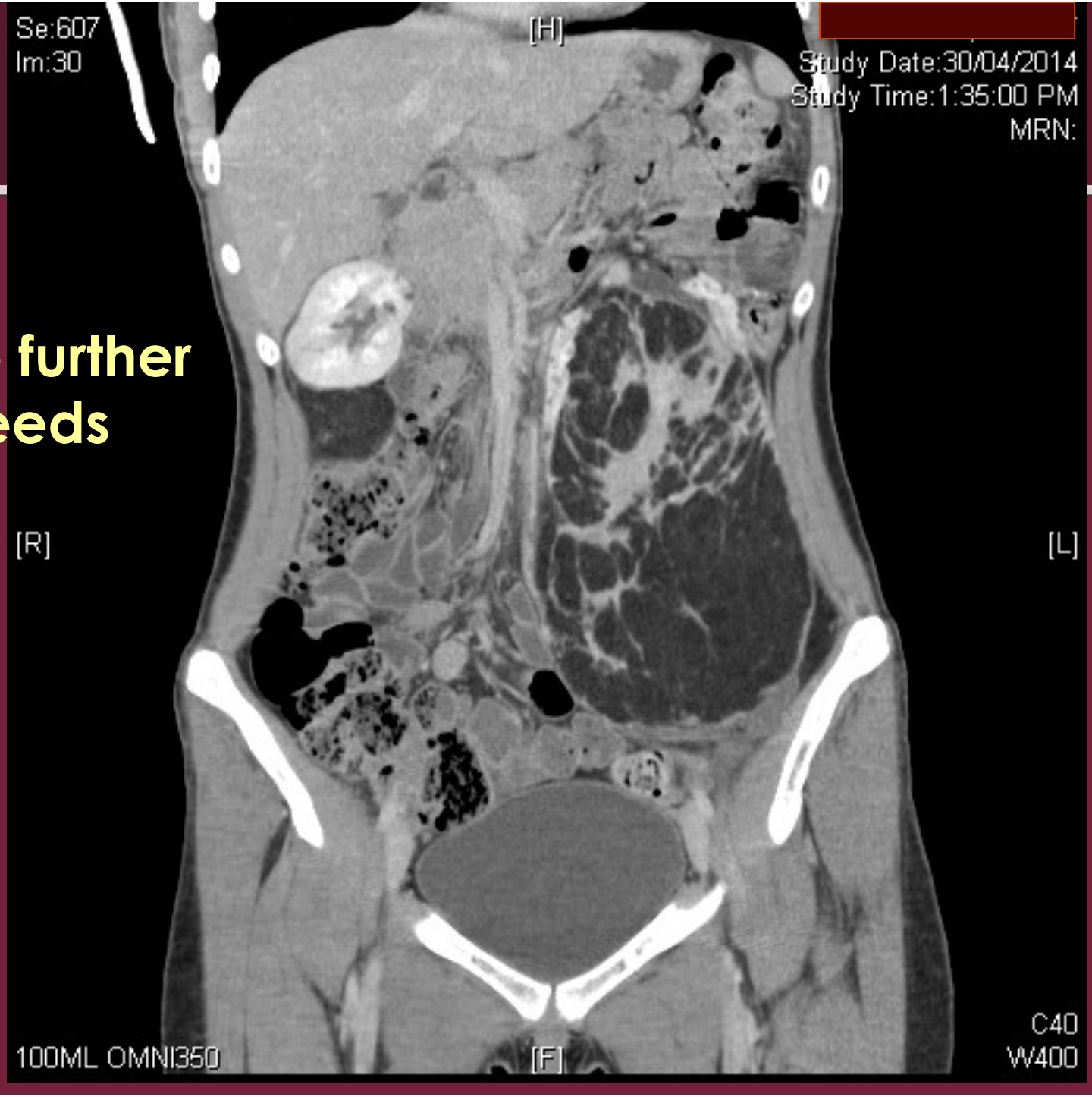
3 months everolimus



No drug toxicity



No further bleeds



Conclusions

- TSC – AML can be treated with mTORi (Everolimus) before embolization or surgery
- Toxicity is manageable
- Ideally, Multidisciplinary team of Urology, Neurology, Nephrology, Nursing, Pulmonary, Dermatology

Questions ?

UROLOGY

Evolving Strategies in the Treatment of Tuberous Sclerosis Complex-associated Angiomyolipomas (TSC-AML)

Anil Kapoor, Louis Girard, Jean-Baptiste Lattouf, York Pei, Ricardo Rendon, Paul Card, and Alan So

Tuberous sclerosis complex (TSC) is a rare autosomal dominant genetic disorder characterized by the development of numerous benign tumors that occur in multiple organ systems throughout the lifetime of the affected individuals. Renal angiomyolipomas occur in up to 80% of TSC patients, and chronic kidney disease from increasing tumor burden is the primary cause of TSC-related mortality. Our review evaluates evidence for localized and systemic therapy in the management of TSC-angiomyolipomas. Urologists or nephrologists experienced in TSC disease should coordinate the care of TSC patients with renal involvement to improve care and reduce costs. UROLOGY 89: 19–26, 2016.