Clinical Management of Hereditary Kidney Cancer

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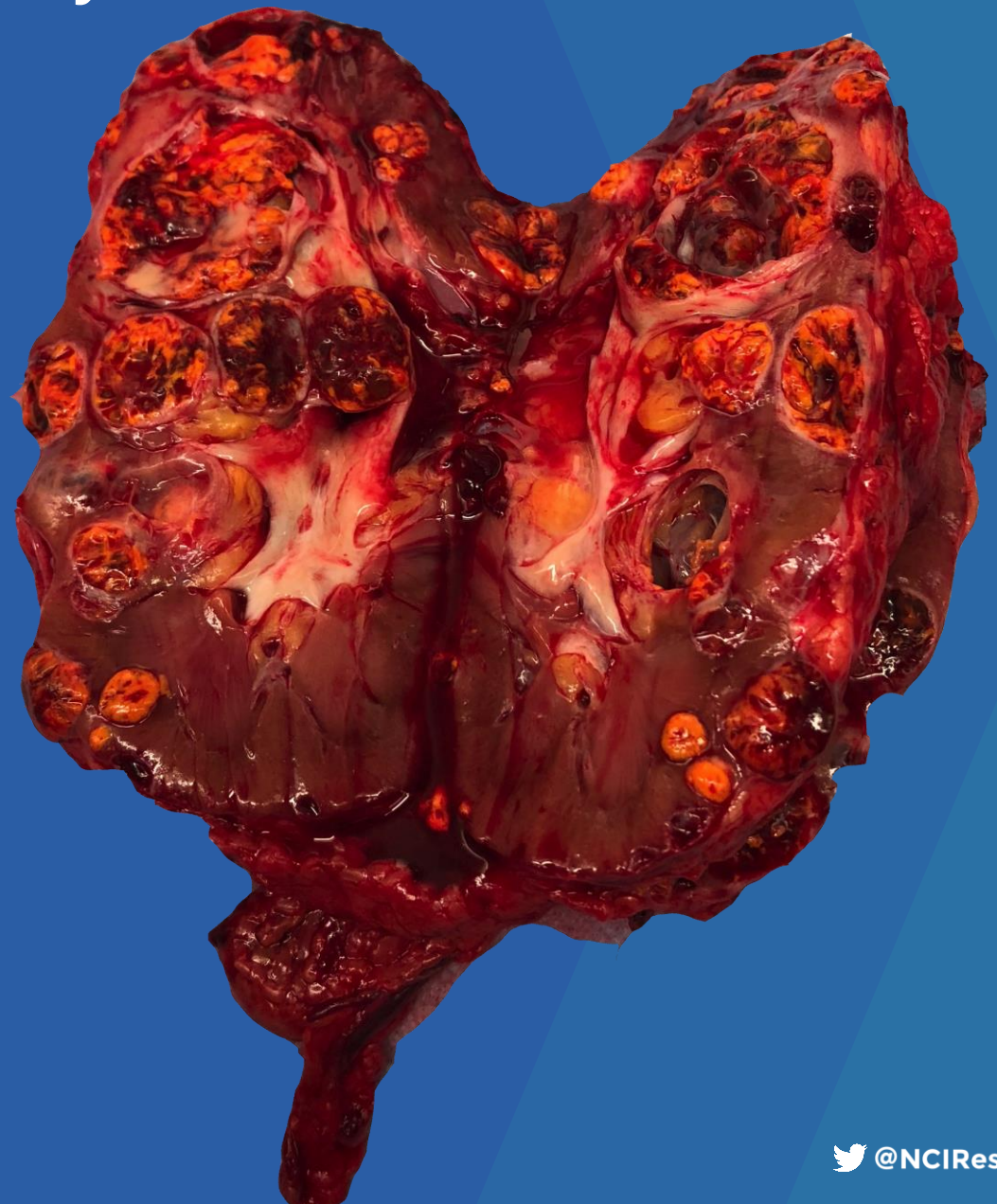
No disclosures.

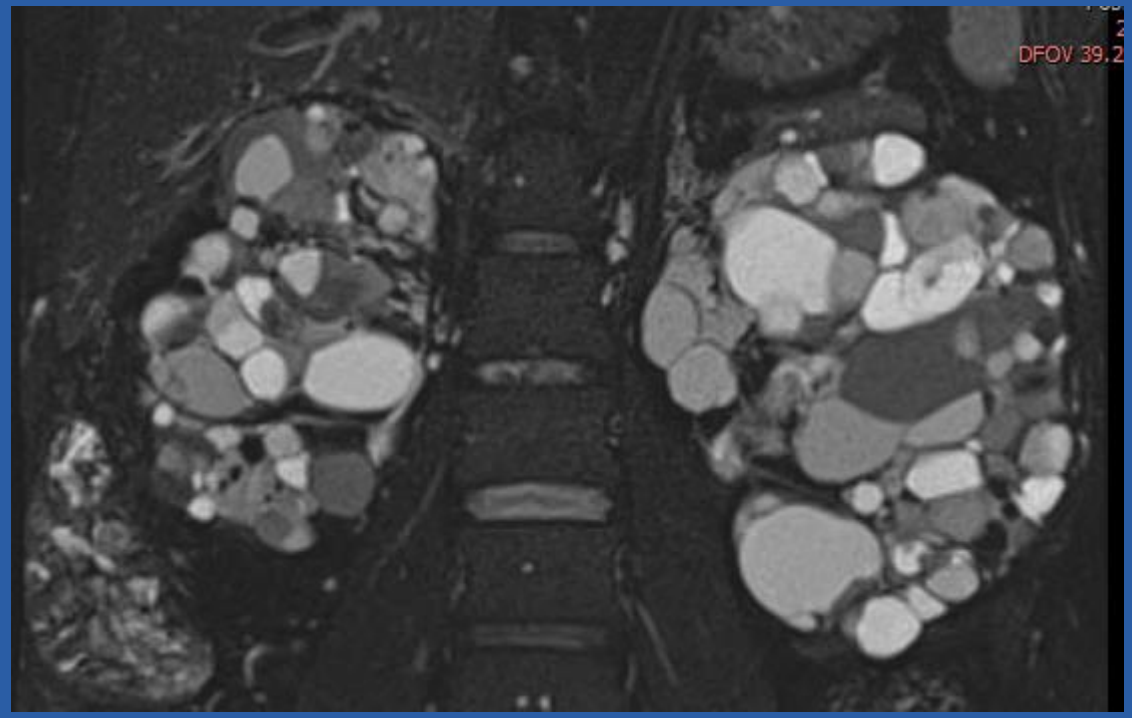
Objectives

- Discuss treatment strategies for patients with hereditary kidney cancer syndromes:
  - Active Surveillance
  - Surgery
  - Ablative therapy
  - Systemic therapy

Challenges in Hereditary Kidney Cancer

- Multiple kidney tumors
- Multiple operations
- When and how to intervene to:
  - Prevent metastasis
  - Preserve kidney function
  - Maintain quality of life

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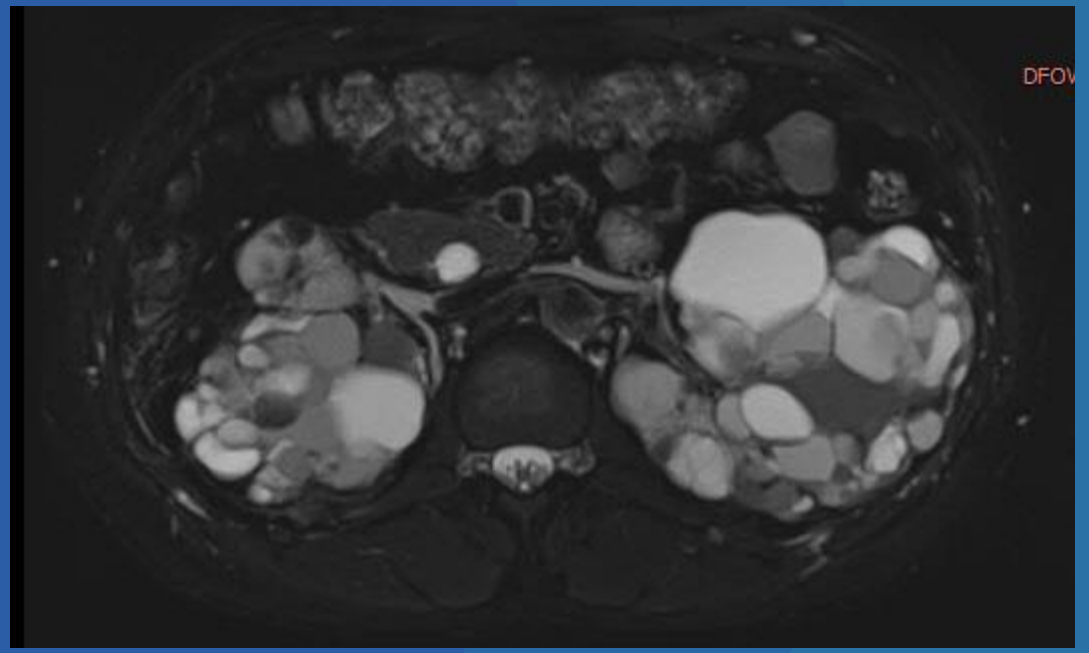
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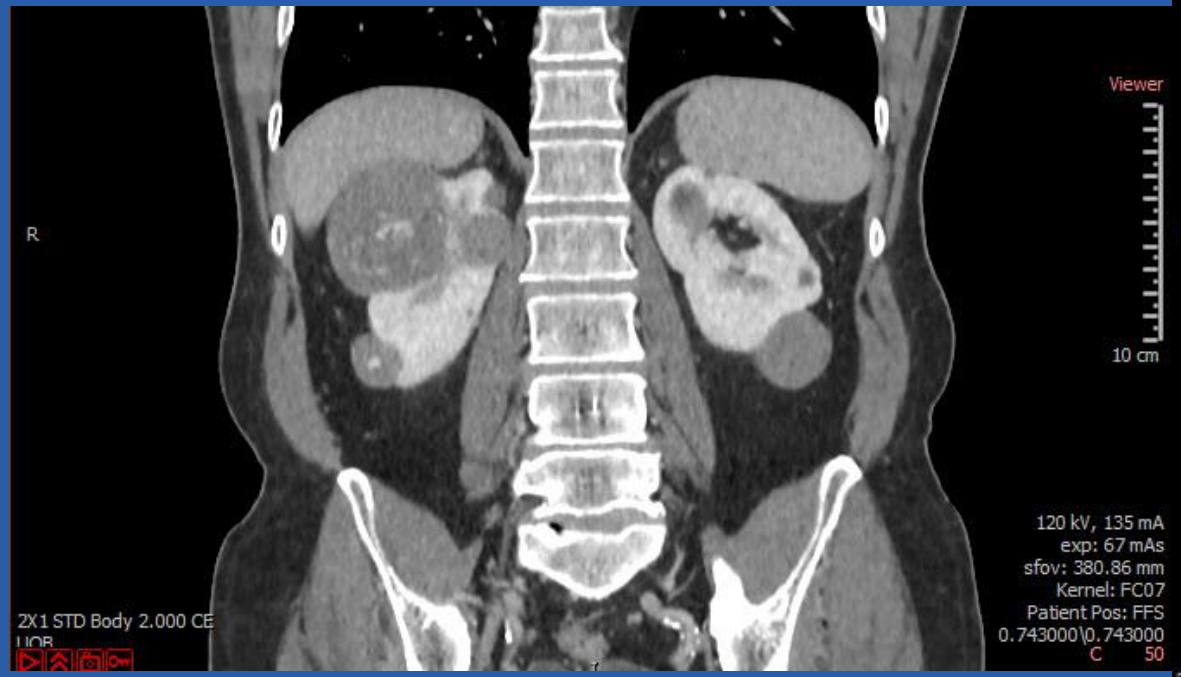
Viewer
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Patient Pos: FFS
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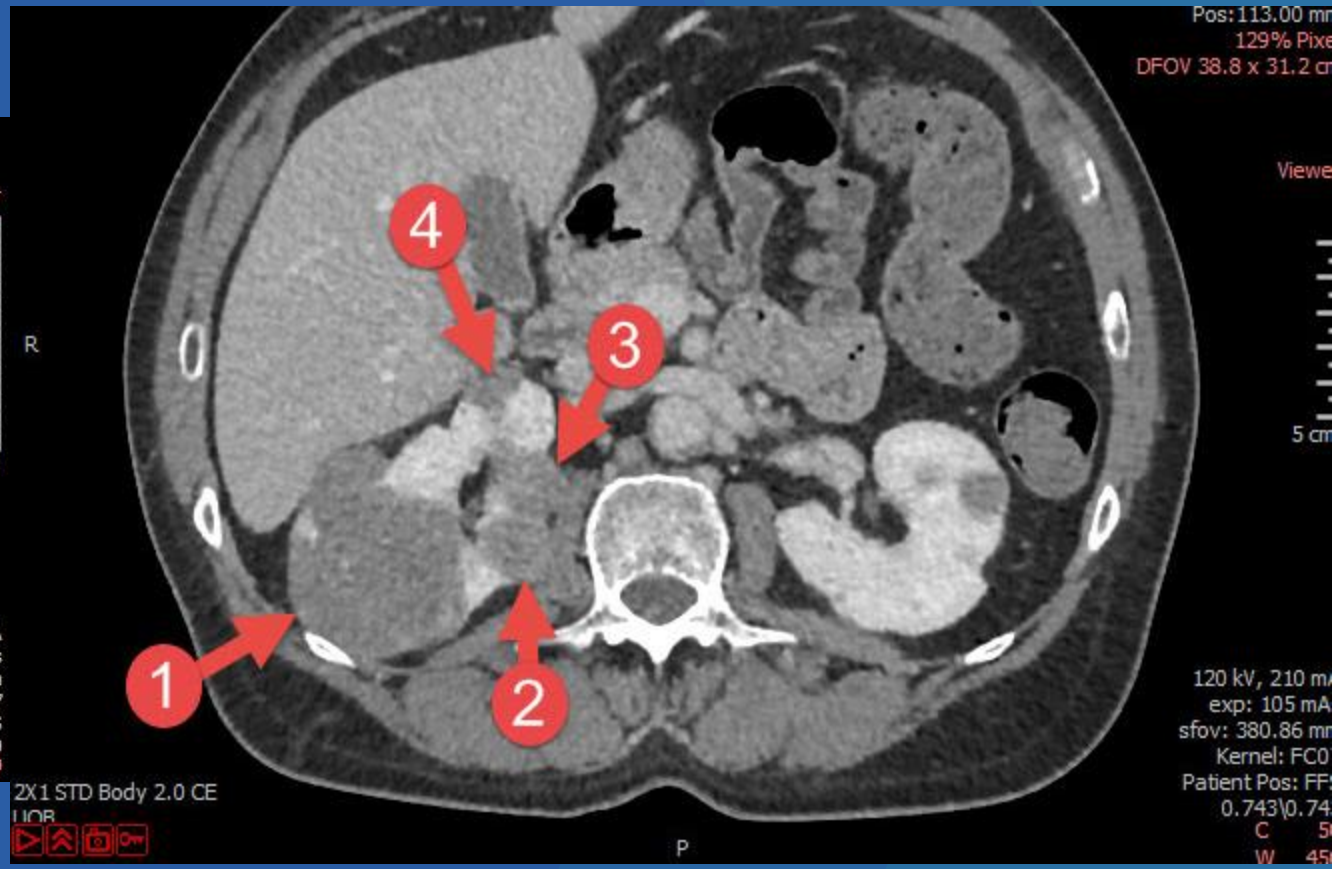
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2X1 STD Body 2.0 CE
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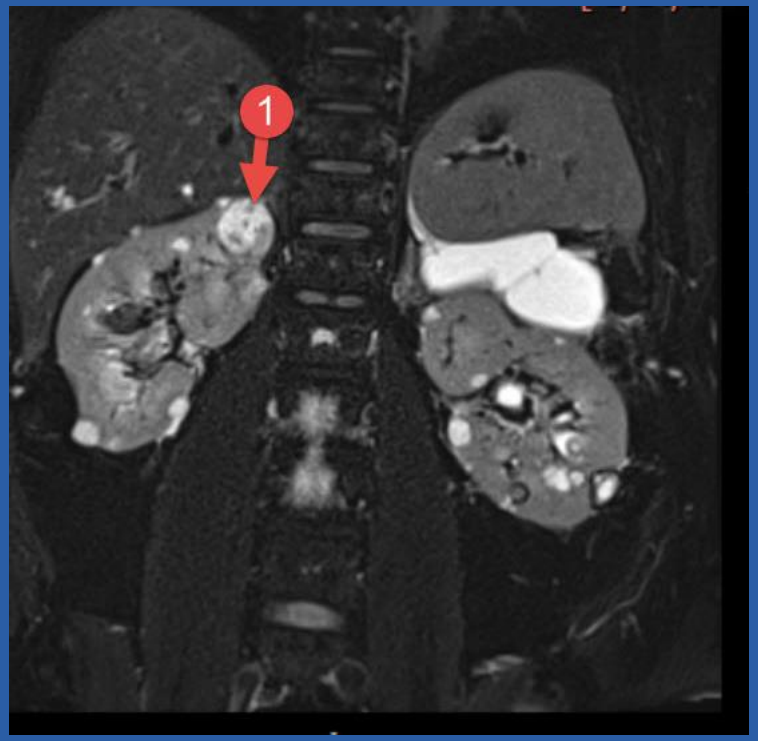
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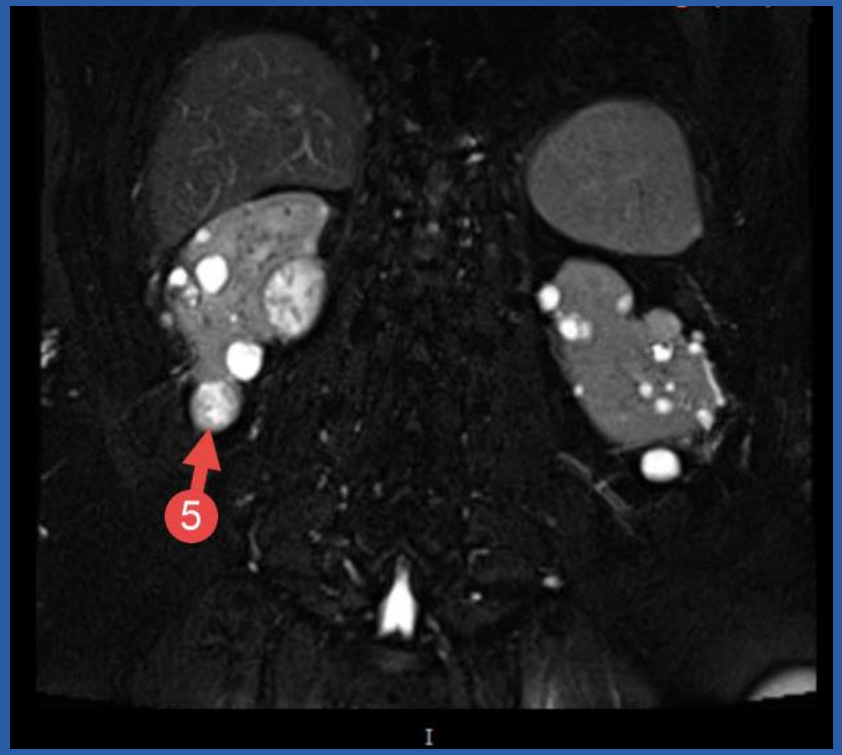
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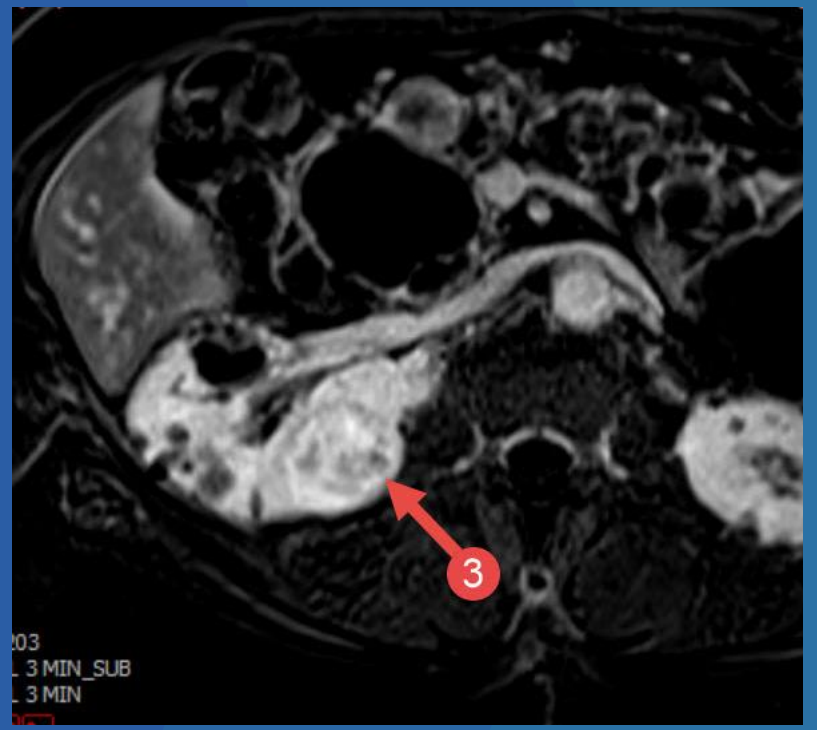
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Finding a favorable balance

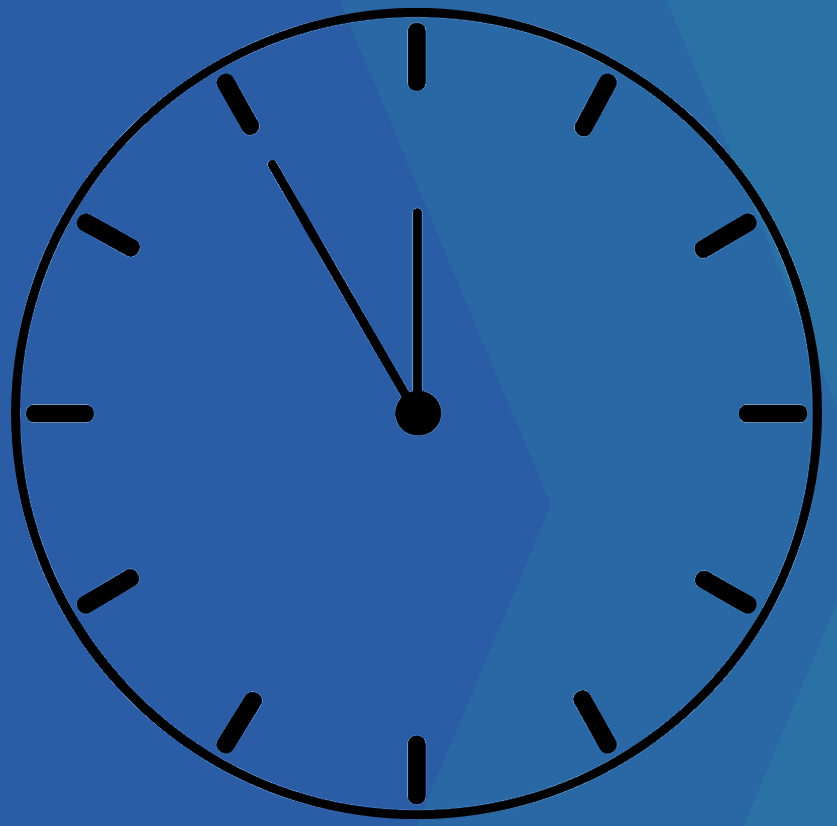
- Upfront bilateral radical nephrectomy + HD
- Historic approach
- Protect from metastasis
- Obviate the need for repeat surgeries

- Intervene for every observable renal tumor
- Would require dozens of renal interventions, each with increased complications

When are tumors safe to watch?

Goals of treatment

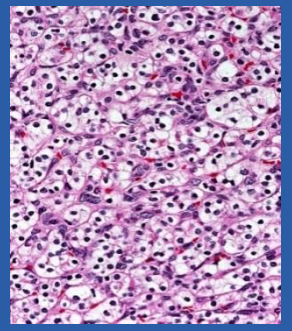
- In general, the over-arching goal of the surgeon is to “reset the clock” meaning removed as many lesions as possible in one surgery in an attempt to prolong the interval between ipsilateral renal surgeries.



Active Surveillance

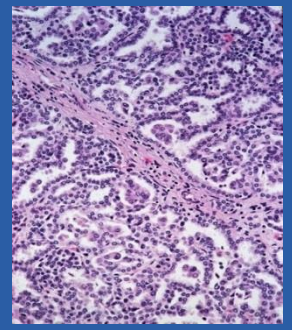
- Initial observations were consistent with the sporadic population:
  - Increasing size associated with increasing metastatic potential
- A threshold of 3 cm was developed at our institution

Hereditary Cancer as a Model



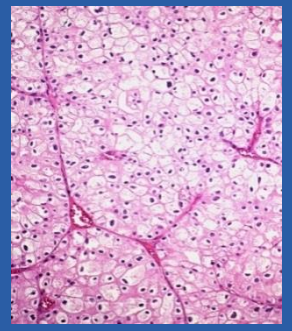
Clear Cell
VHL,TCEB1,BAP1

Von-Hippel Lindau Syndrome



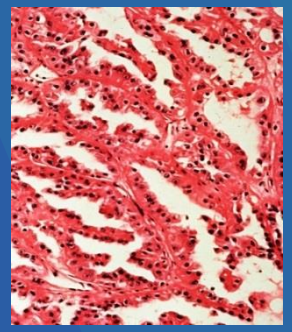
Papillary Type 1
MET

Hereditary Papillary Renal Cancer



Chromophobe
FLCN

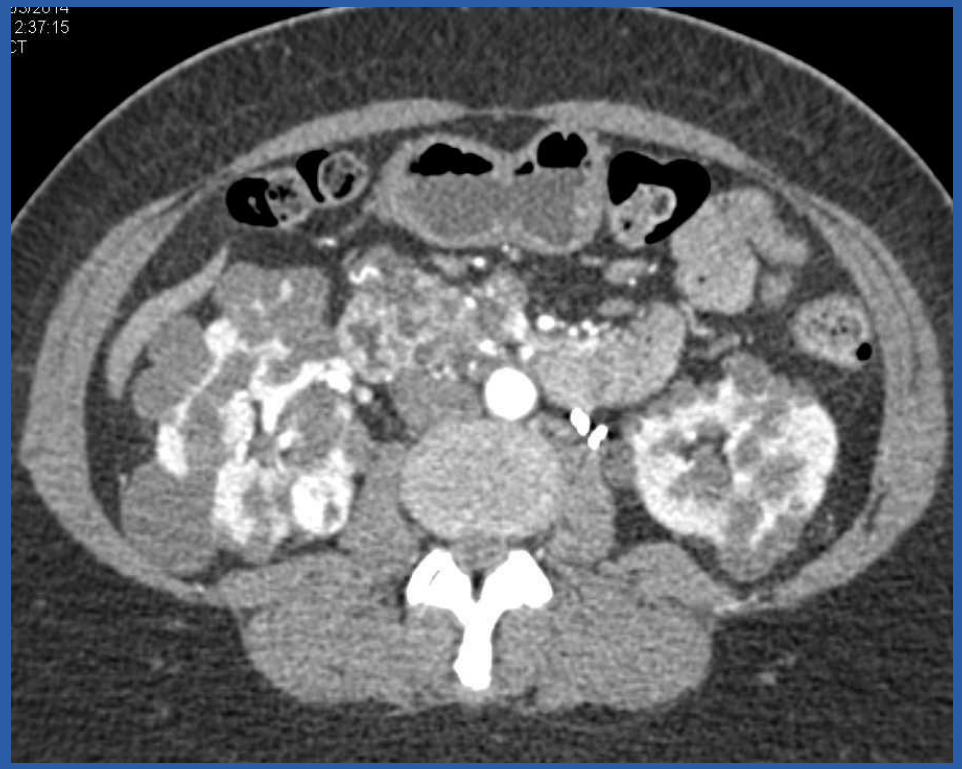
Birt-Hogg-Dubé



Papillary Type 2
FH

Hereditary Leiomyomatosis and RCC

Active Surveillance



Managed by 3 cm guideline

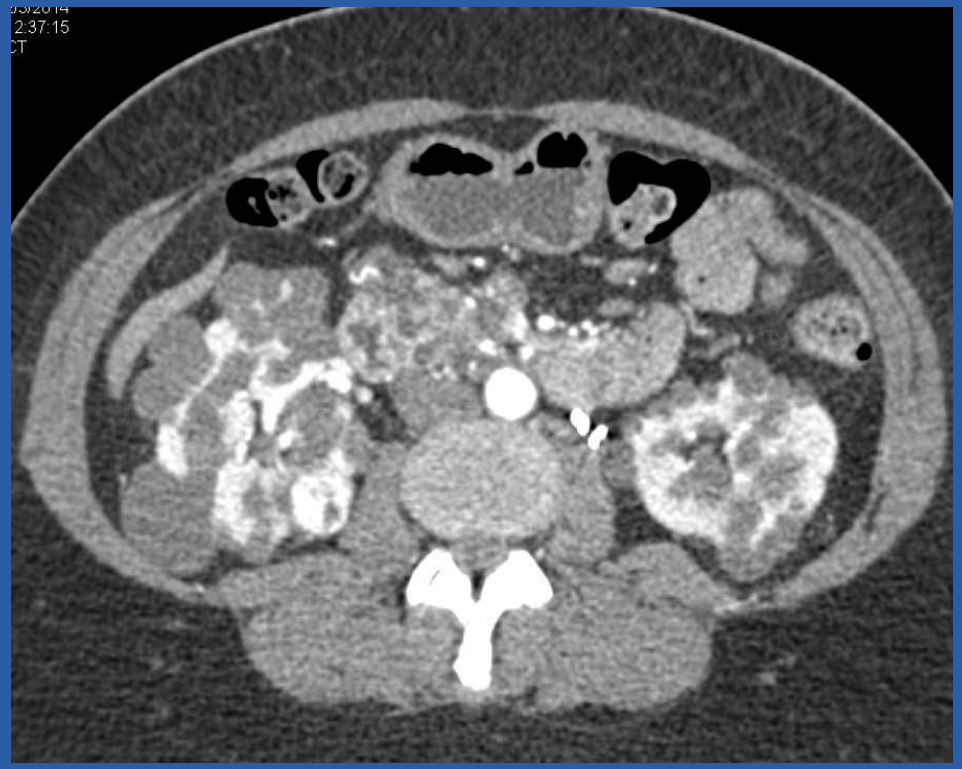
<u>Genetically defined:</u>

VHL (clear cell)
Hereditary Papillary Renal Carcinoma (*MET,* papillary)
Birt-Hogg-Dubé (Folliculin, Chromophobe)

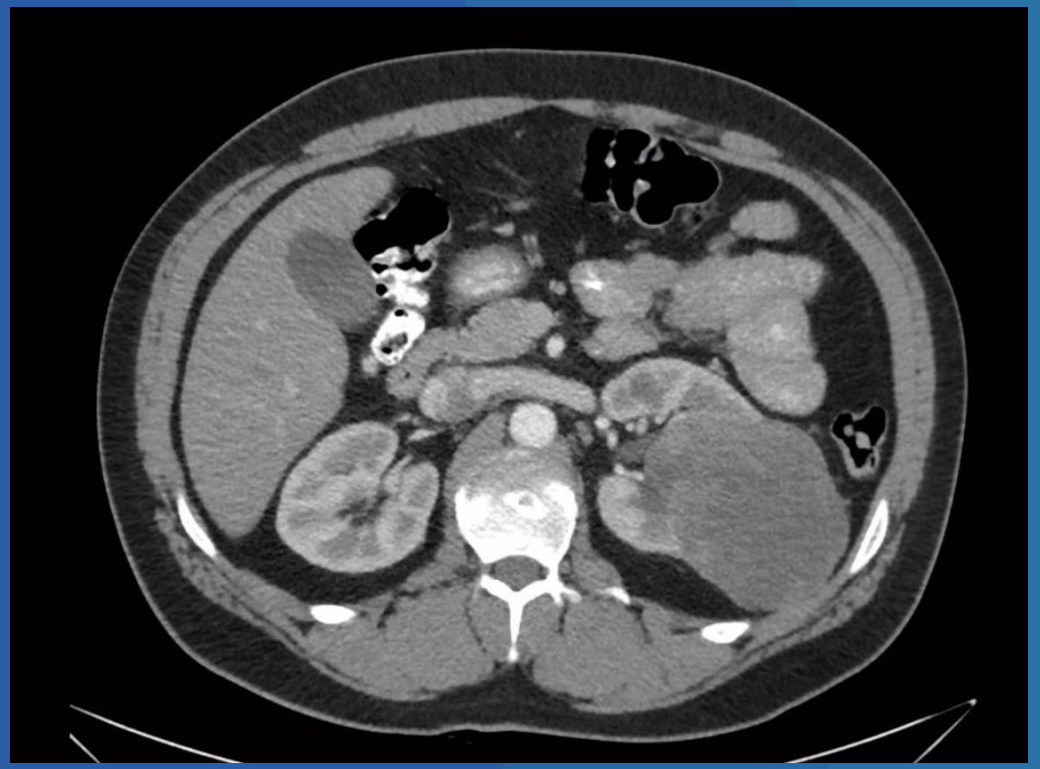
AS until largest tumor 3 cm → all tumors resected

Active Surveillance

Compare rates of Metastases



Managed by 3 cm guideline



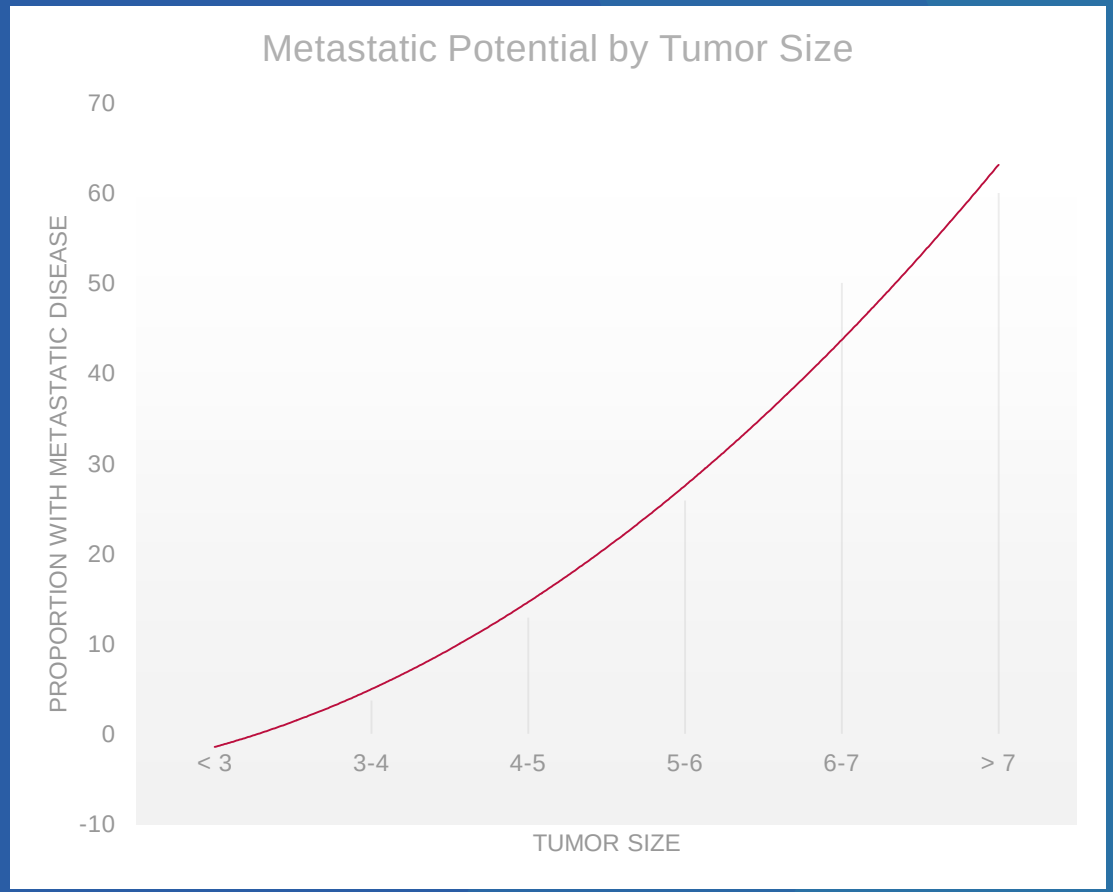
Not managed by 3 cm guideline
(new dx, referral, lost to fu)

Results

- From a total of 764 screened patients, 440 patients (57.5%) developed solid kidney tumors.
- Median follow-up was 8.6 years (IQR 2-14 year, max 27 years)
- 178 patients (42.7%) never had a tumor ≥ 3 cm
- Metastatic disease developed in 42 patients (10.1%).

No patients developed metastatic disease when managed by the 3 cm guideline.

Tumor Size	# mets/ # pts (%)
≤ 3 cm	0/178 (**0%**)
3-4 cm	4/109 (**3.7%**)
4-5 cm	8/62 (**12.9%**)
5-6 cm	7/27 (**25.9%**)
6-7 cm	6/12 (**50%**)
> 7 cm	17/28 (**60%**)



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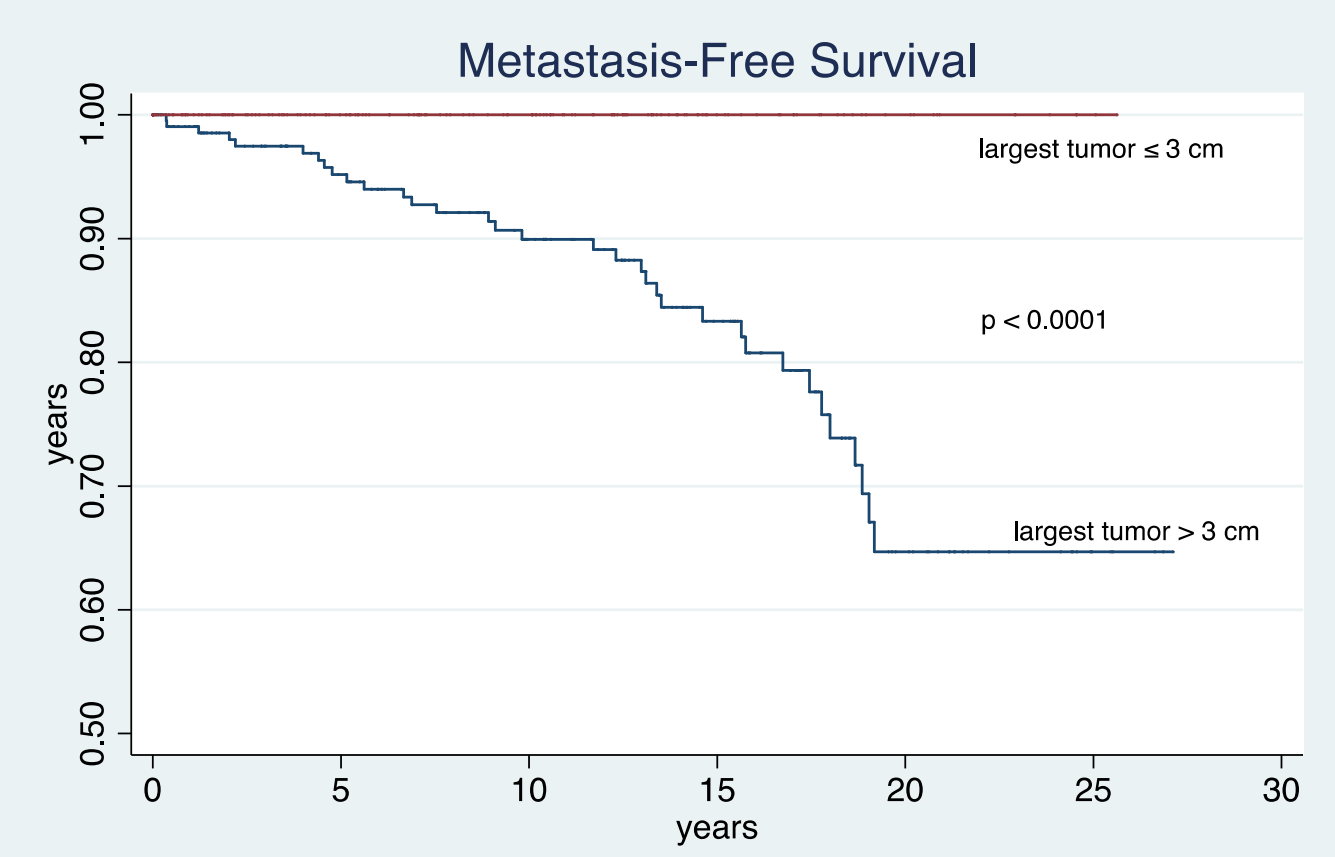
Metastasis-Free Survival



Interval	MFS
5 year	95.7%
10 year	91.1%
20 year	69.5%

Impact of size (per cm):
HR 1.6 (95%CI 1.5-1.8), p < 0.0001

Size-based Risk Stratification of Genetically-Defined Renal Tumors

Tumor Size	VHL # mets/# pts	BHD # mets/# pts	HPRC # mets/# pts	All # mets/# pts
< 3 cm	0/148 (0%)	0/61 (0%)	0/15 (0%)	0/224 (0%)
3-4 cm	4/139 (2.9%)	0/27 (0%)	0/5 (0%)	4/171 (2.3%)
4-5 cm	8/62 (12.9%)	1/18 (5.3%)	1/6 (16.7%)	10/86 (11.6%)
5-6 cm	7/27 (25.9%)	0/14 (0%)	0/5 (0%)	7/46 (15.2%)
6-7 cm	6/12 (50%)	0/7 (0%)	0 (0%)	6/19 (31.6%)
> 7 cm	11/28 (60%)	7/23 (30%)	5/12 (41.7%)	23/53 (43.4%)

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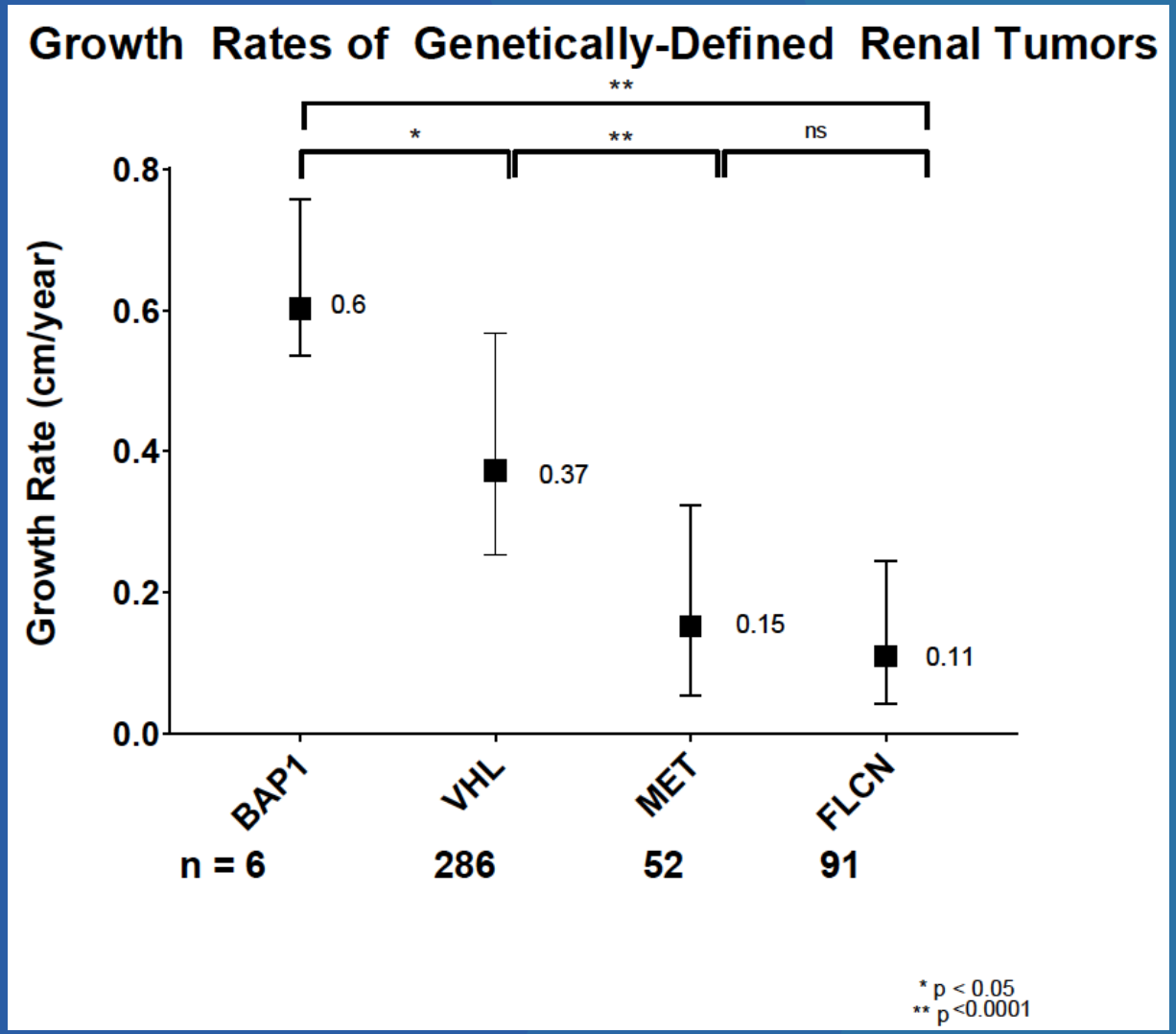
Surveillance Schedules

- AS follow-up intervals should be optimized so that patients are neither under- or over-imaged, which requires knowledge of tumor growth kinetics
- AS schedules are often proposed based on sporadic renal tumor cohorts, comprising both benign and malignant tumors of different histologic subtypes (e.g. q6-12 months).
- Less is known about the growth kinetics of hereditary -associated renal tumors

Tumor growth on AS

	VHL	FLCN	MET	BAP1	Total
Patients	182	81	27	2	292
Tumors	286	91	52	6	435
Tumor measurements	1474	443	268	28	2213



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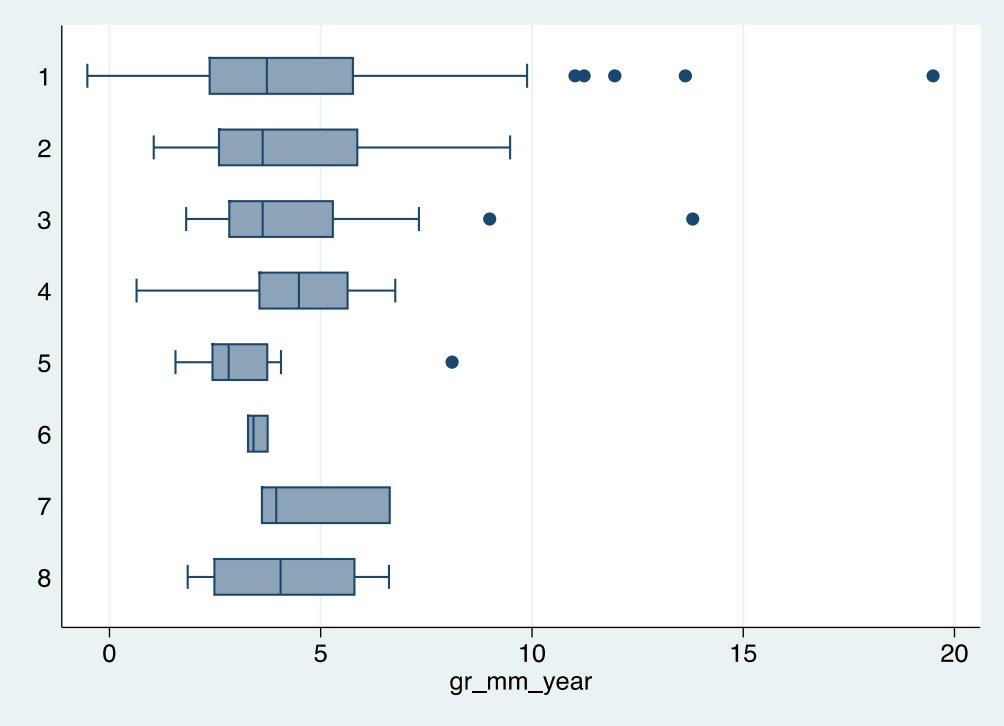
Growth on AS

Type of genetic alteration does not impact growth

Missense
Partial Deletion
Nonsense
Frameshift
Deletion
Splice Donor
AA Deletion
Spice acceptor



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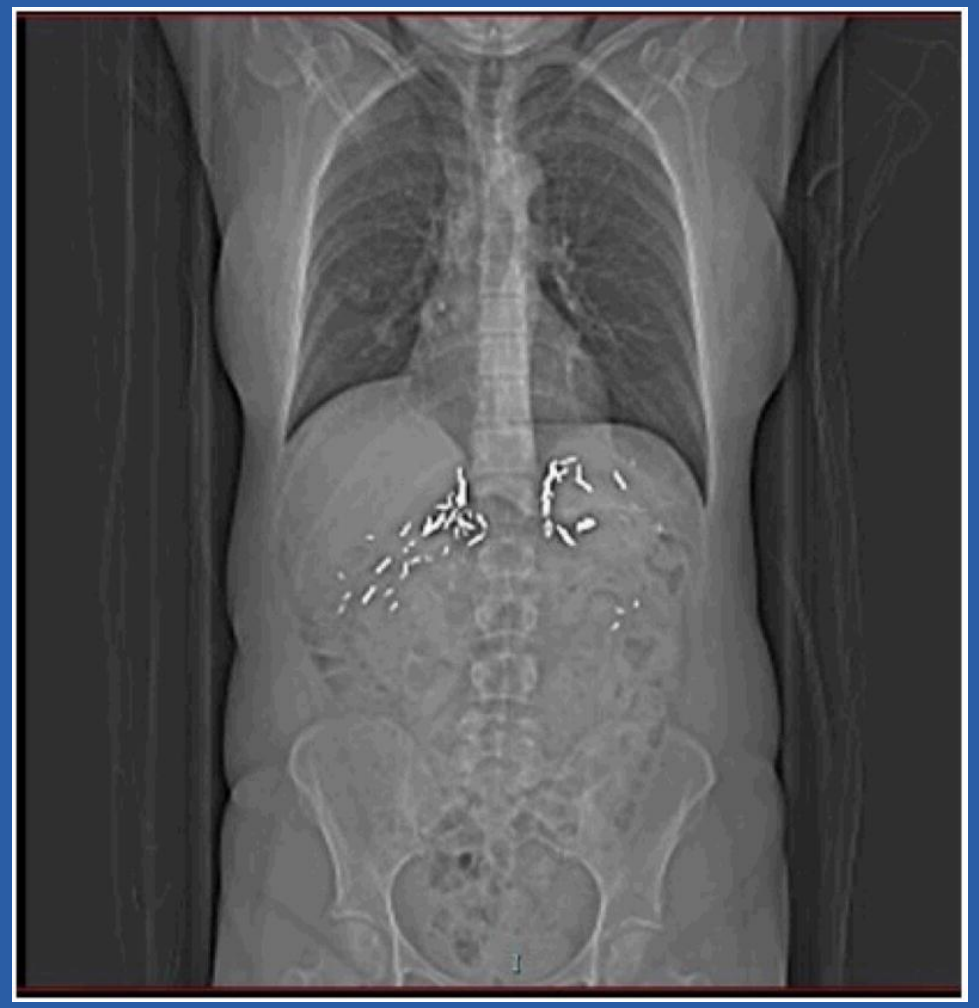
Surveillance Recommendations

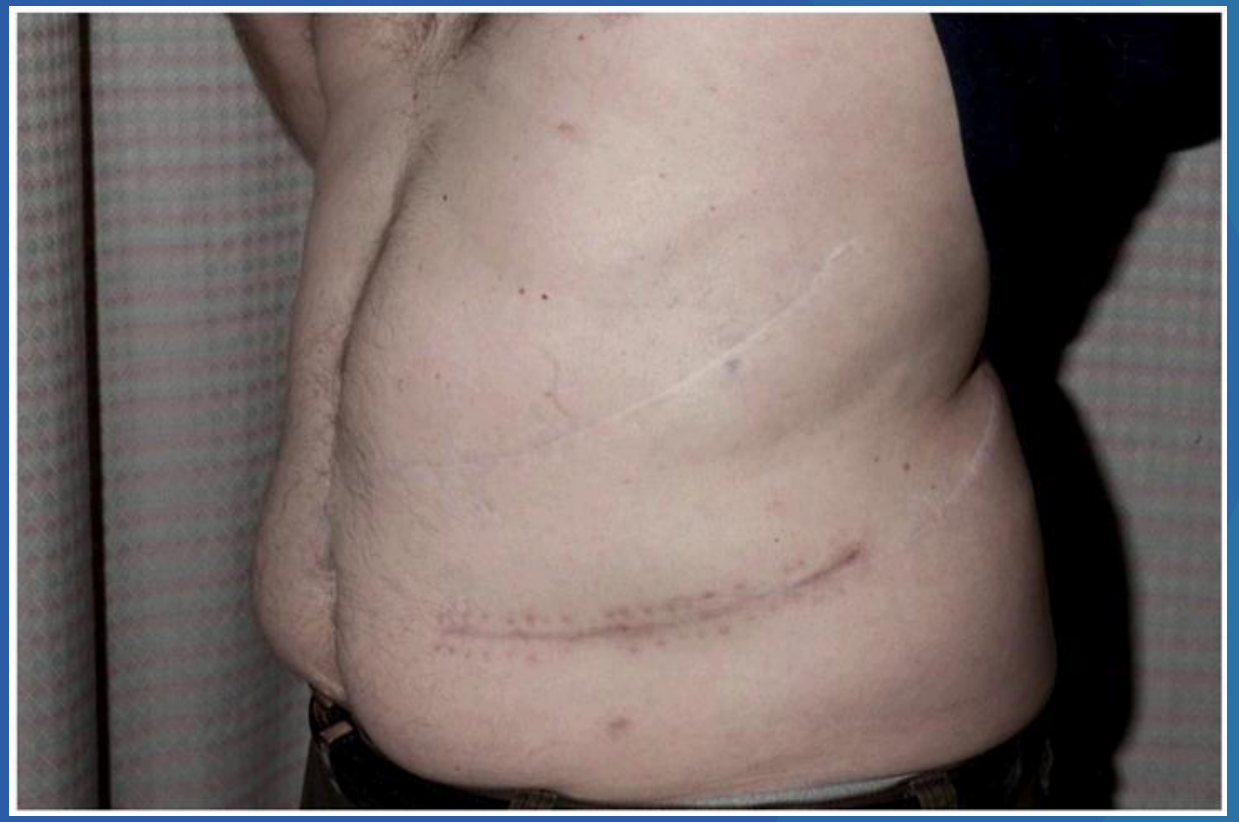
- Cross-sectional imaging
  - MRI preferred
- VHL, BHD, HPRC – every 1 -3 years depending on tumor burden
- HLRCC – annual imaging

Surgical Considerations

- Bilateral multifocal tumors
- Reoperative surgery
- Tumor enucleation – spare normal renal parenchyma.
- Selective ischemia – reserve for deep and/or hilar tumors, resect off clamp

Reoperative Surgery

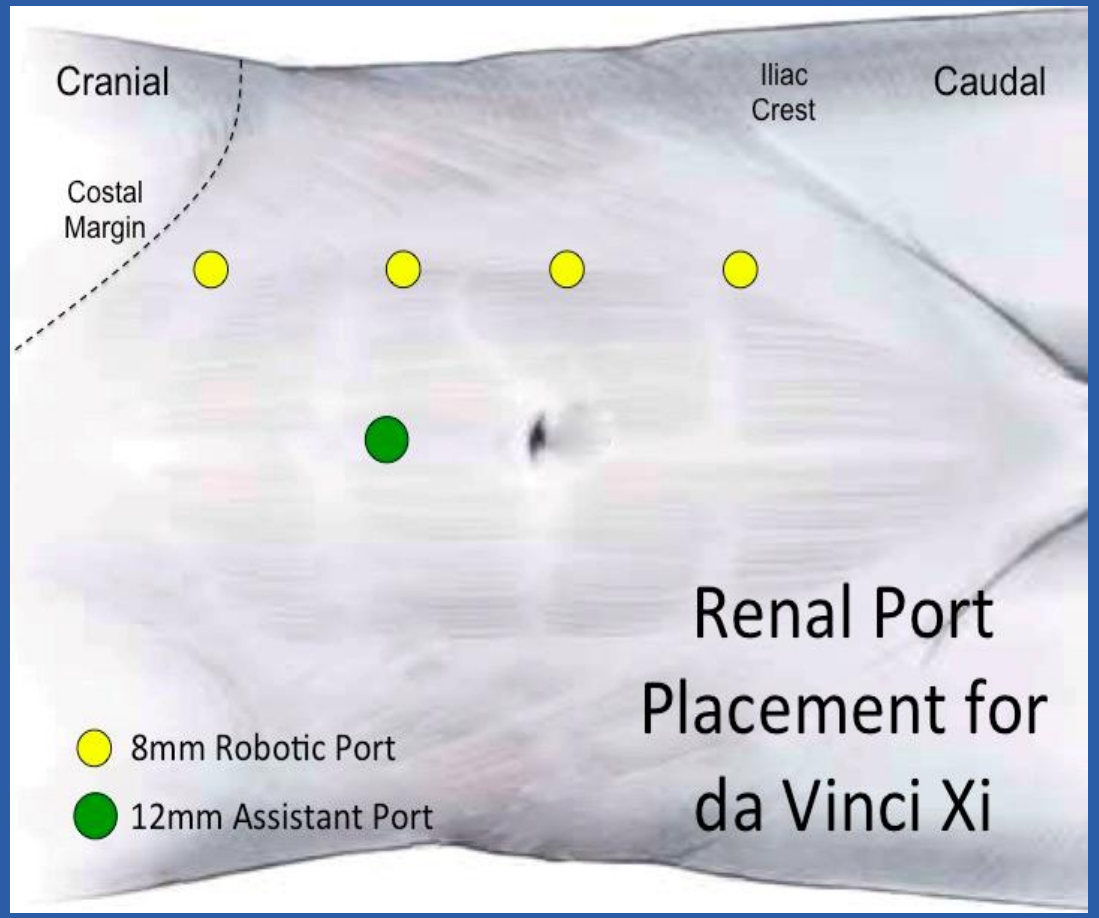


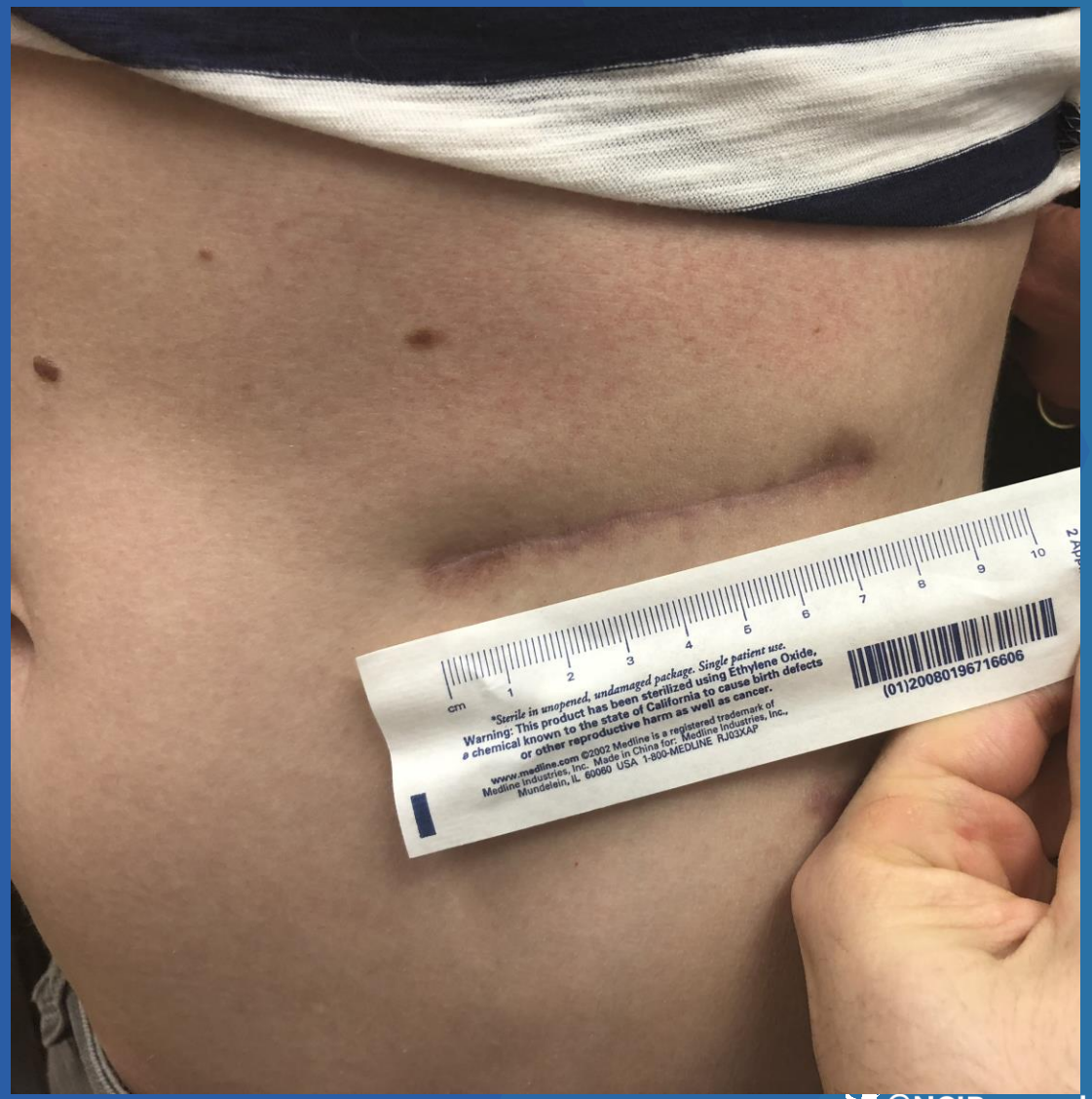


Principles

- Minimize surgical footprint
  - Preserve Gerota's fascia
  - Preserve psoas fascia
  - Minimize hilar dissection – perform many resections off clamp
  - Minimally invasive as possible
  - Preoperative MRI
  - Intraoperative Ultrasound

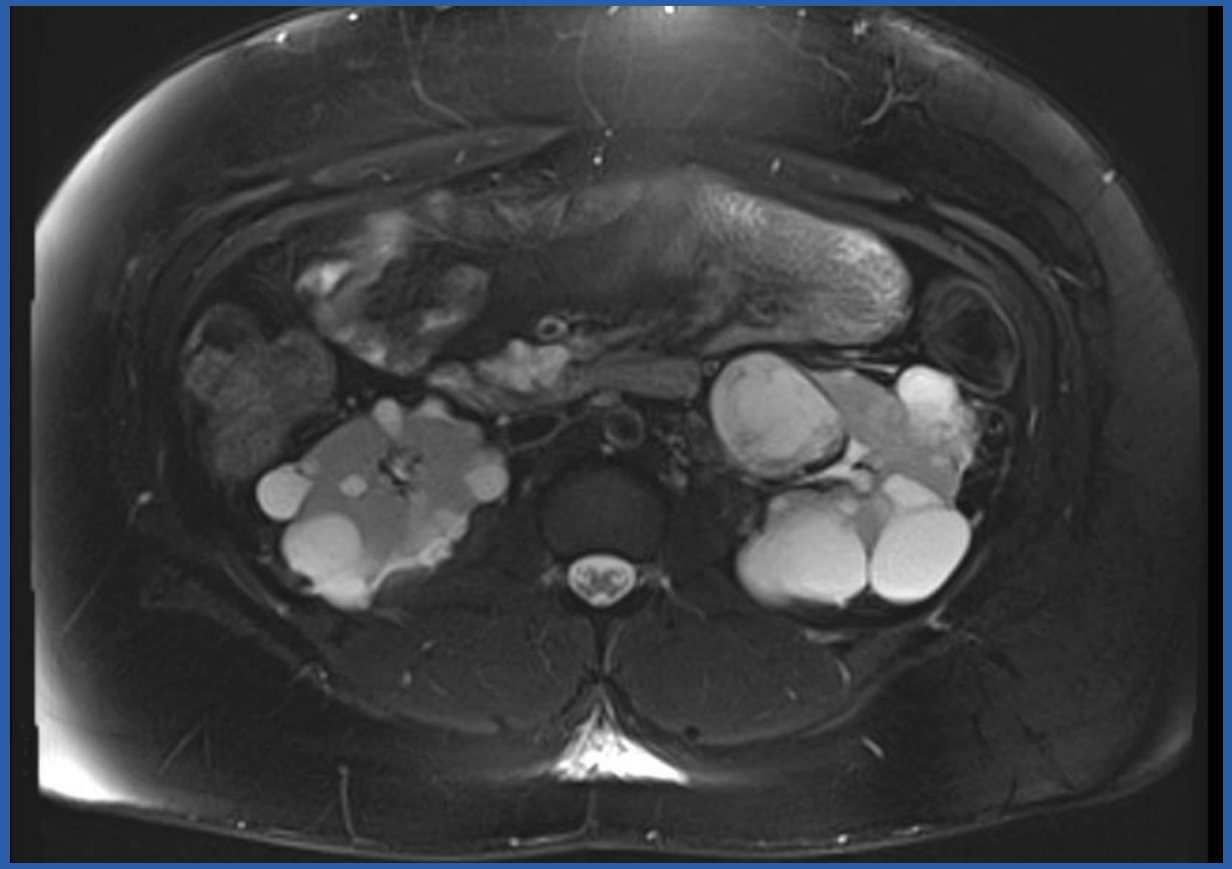
Operative Approach

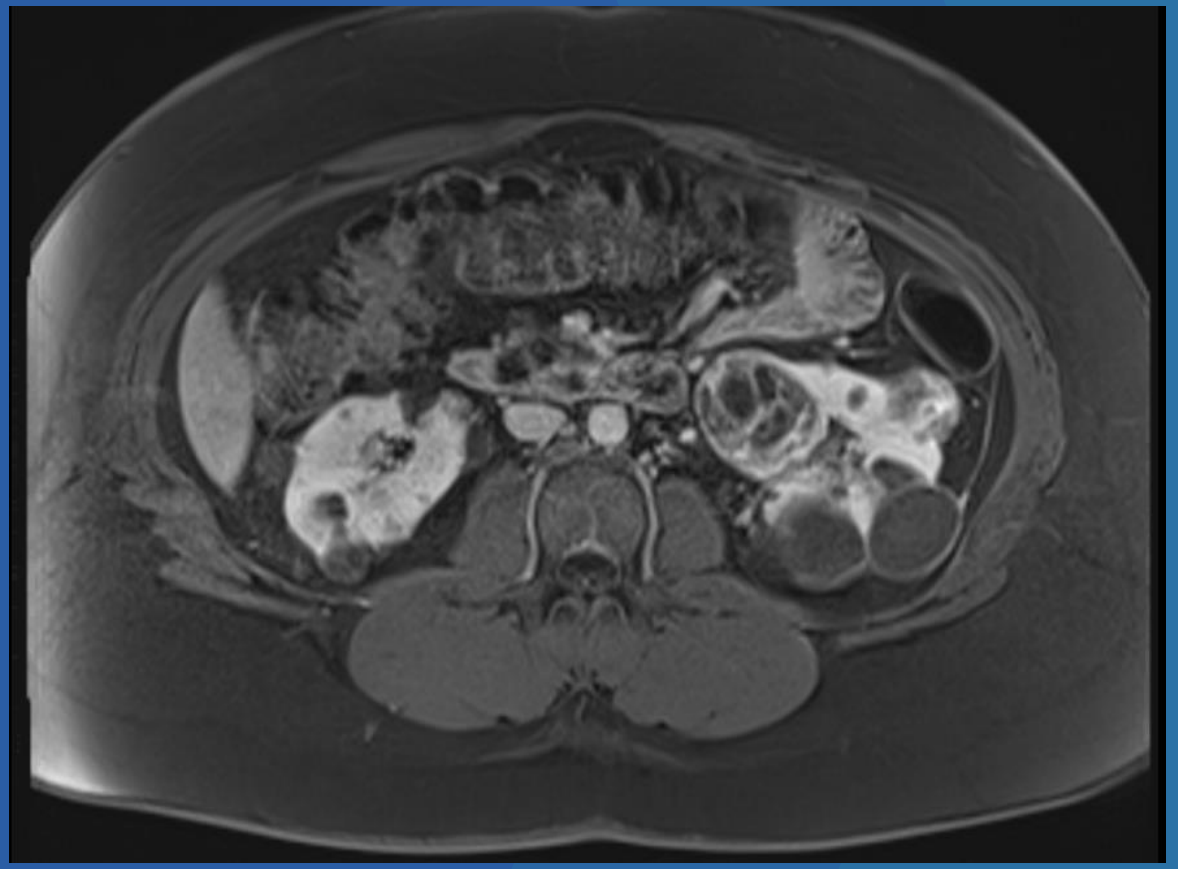




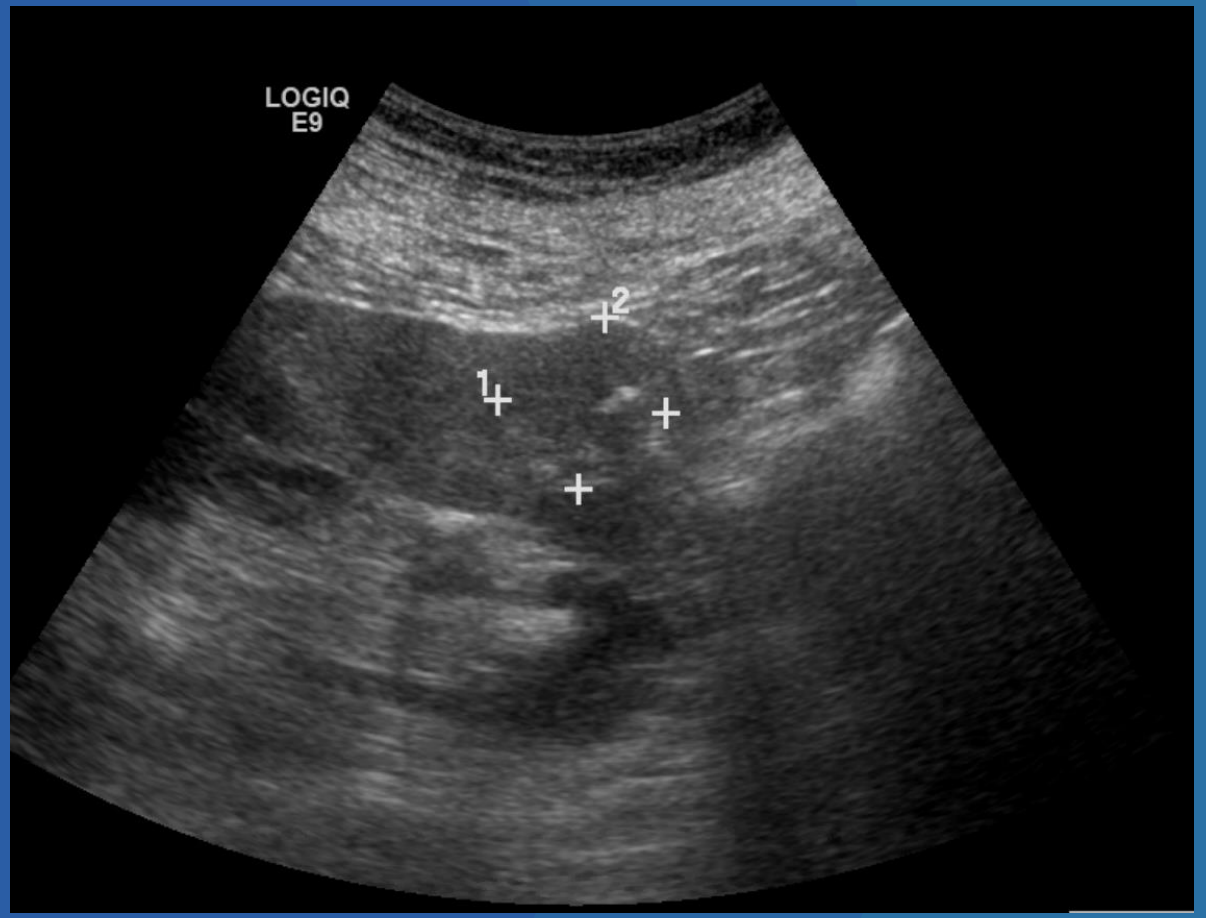
MRI

- Both T2 and T1 contrast enhanced phases are useful

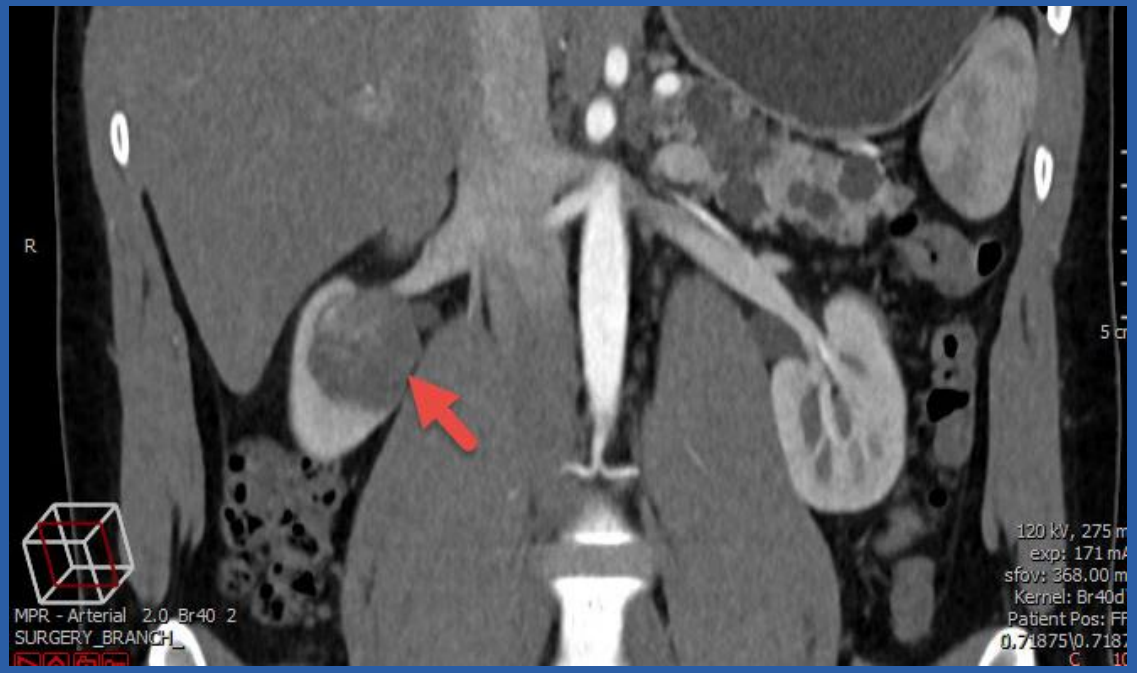


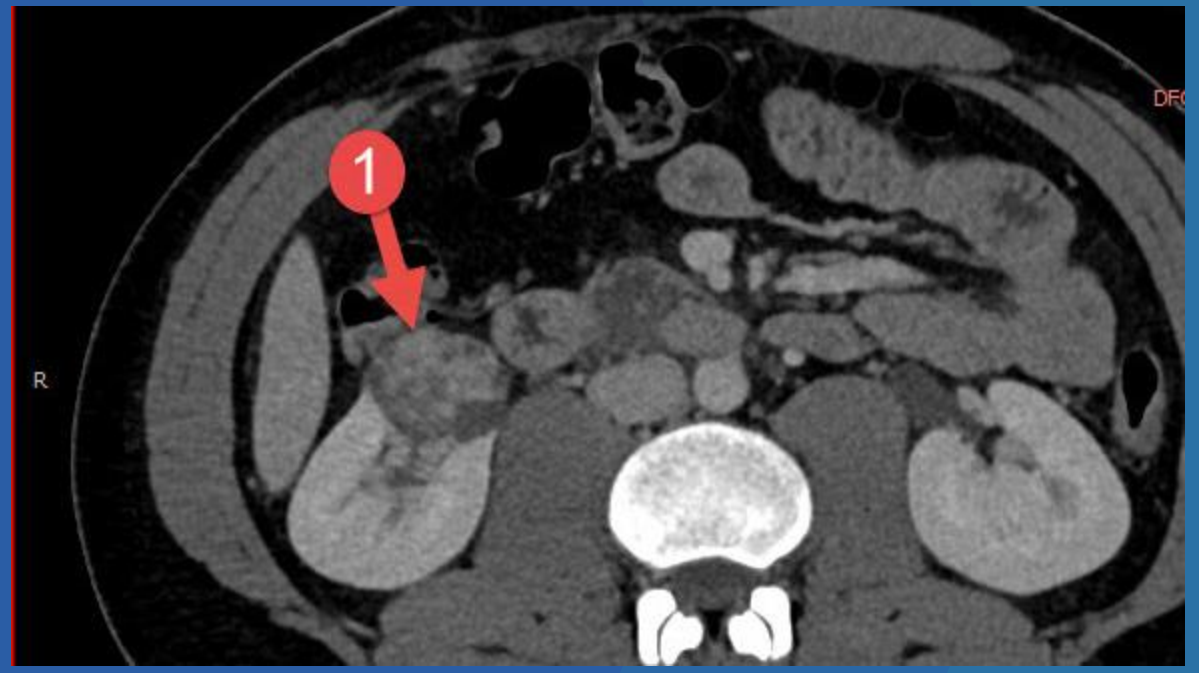


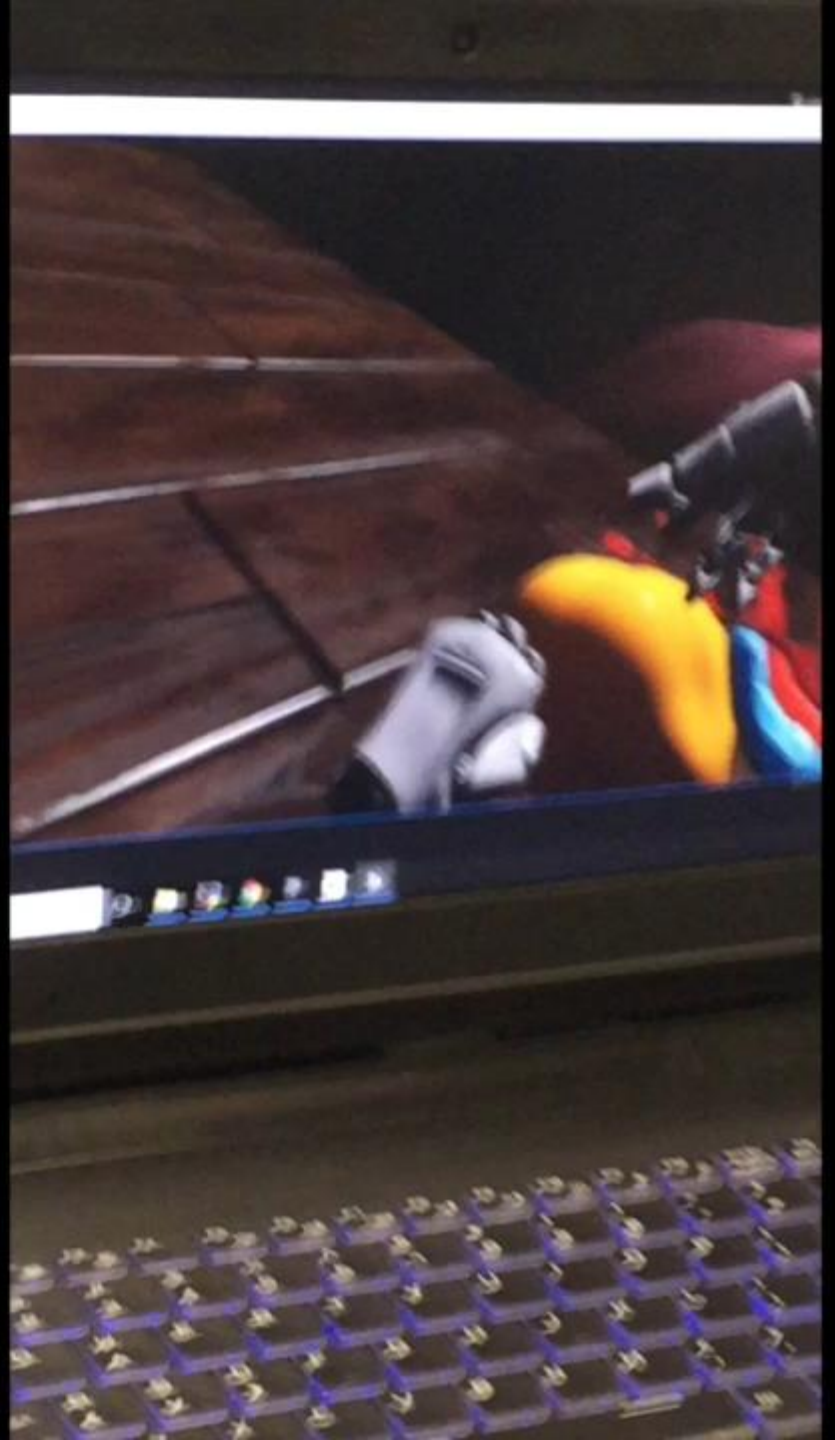
Clinic-Based Ultrasound



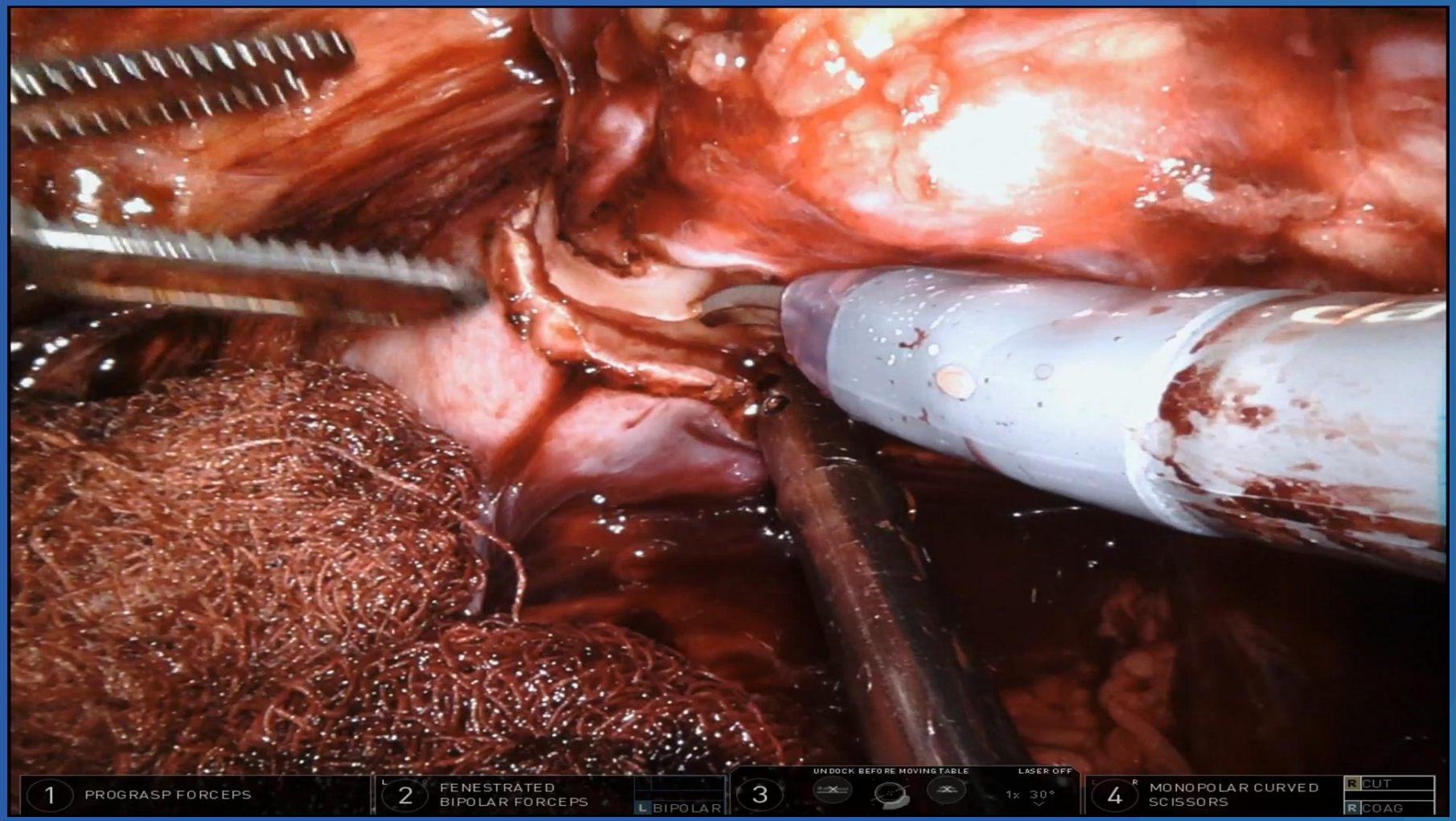
Preoperative Planning



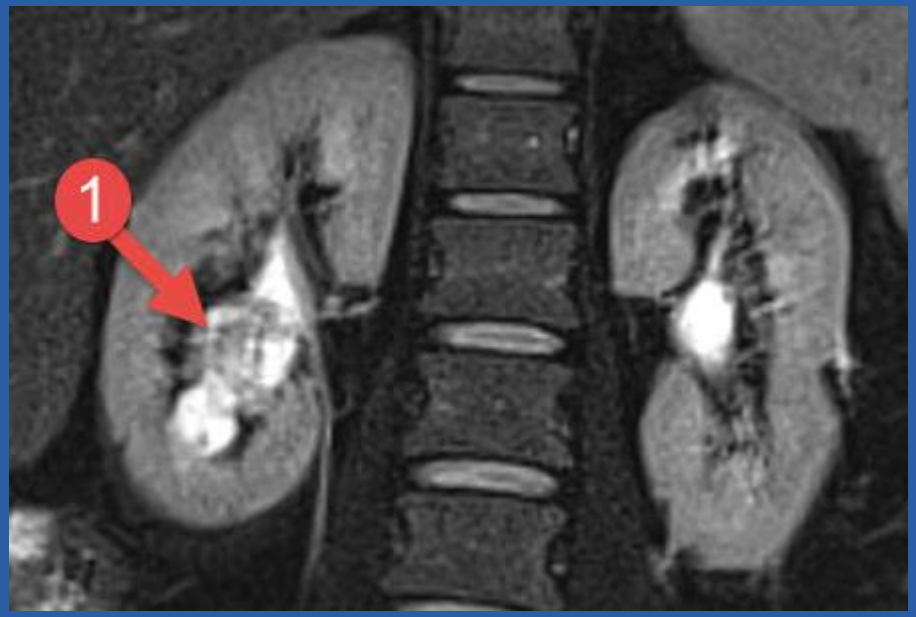


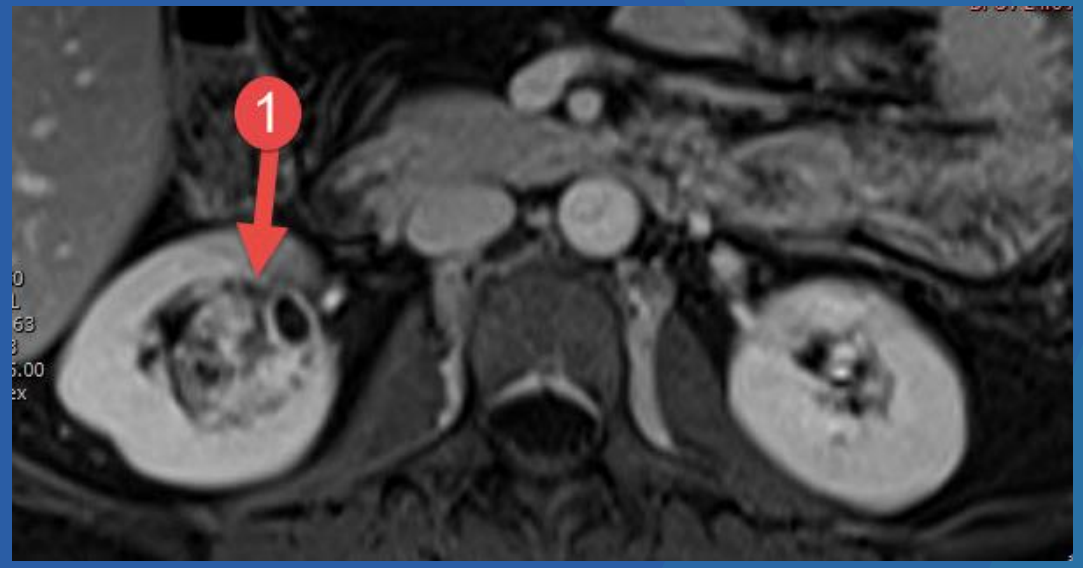


Enucleation

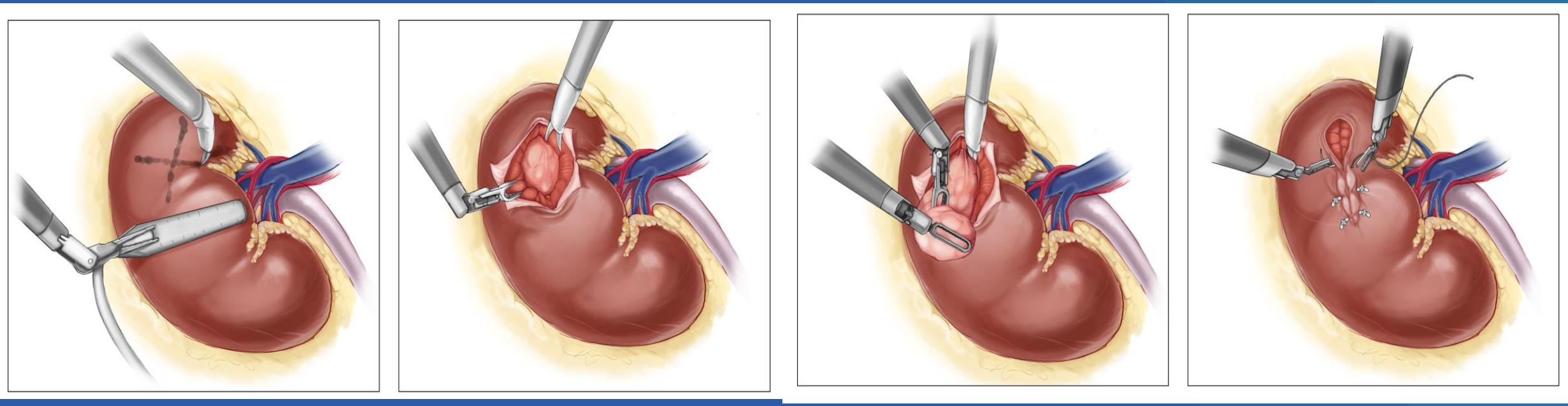


Endophytic Tumors





Endophytic Tumors



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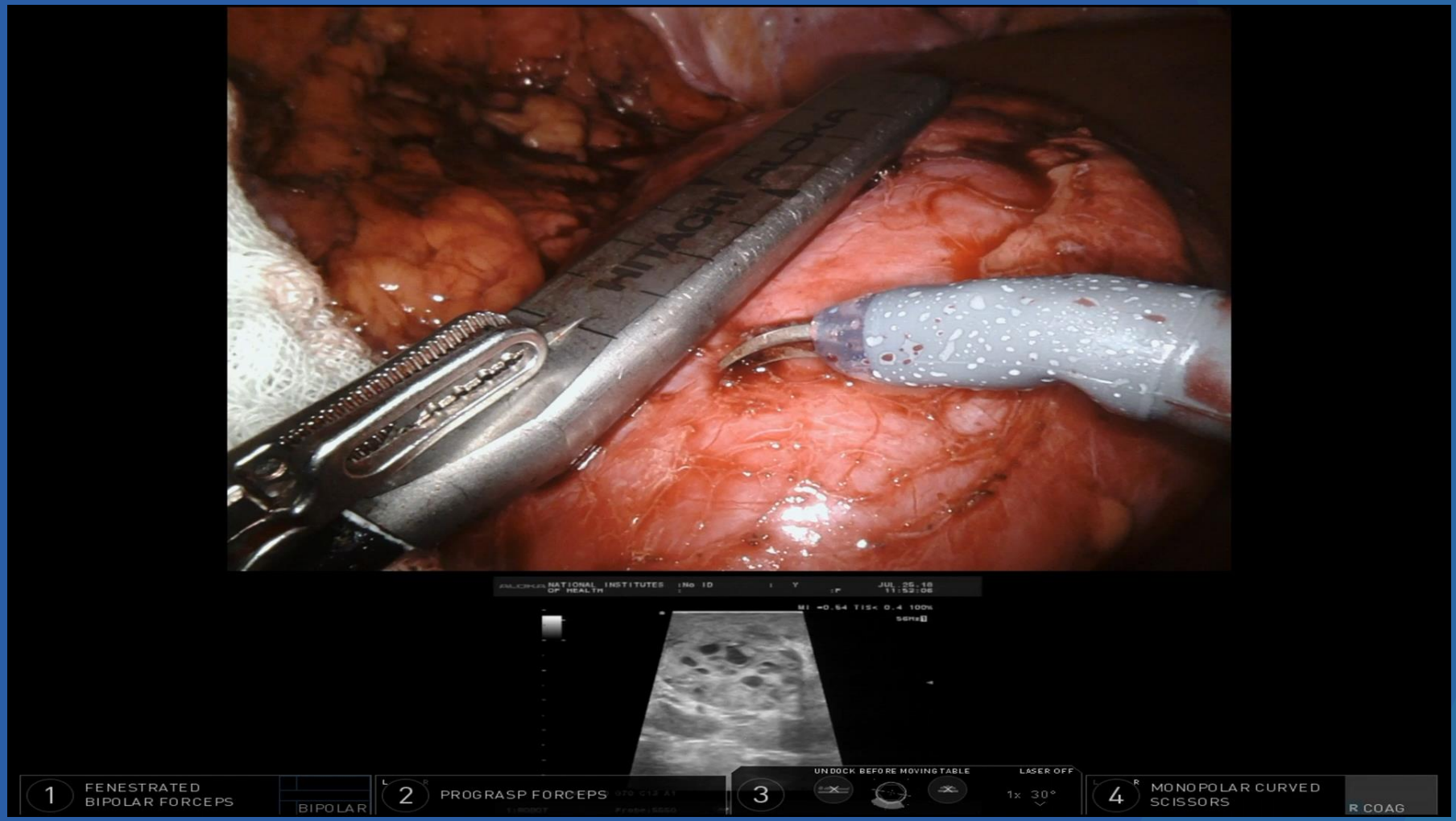
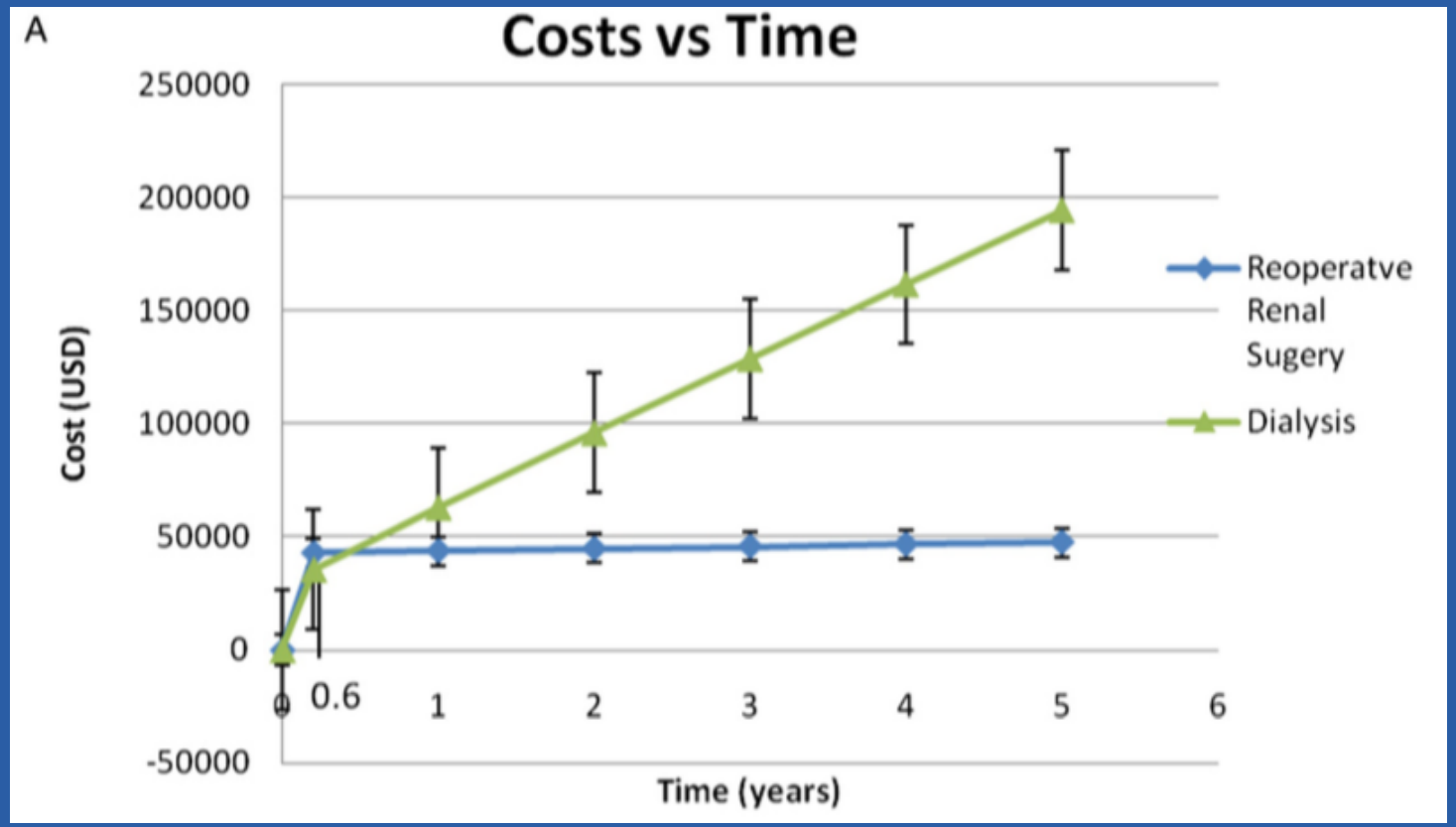


Outcomes

- MIPN after prior open (J Endourol. 2013 Feb; 27(2): 196–201)
  - 40% conversion rate to open
- > 20 tumors in 1 surgery (J Urol. 2011 Jan; 185(1): 49–53.)
  - Mean OR times 9 hours
  - 60% off clamp
  - Mean EBL 3500
  - Complications >50%

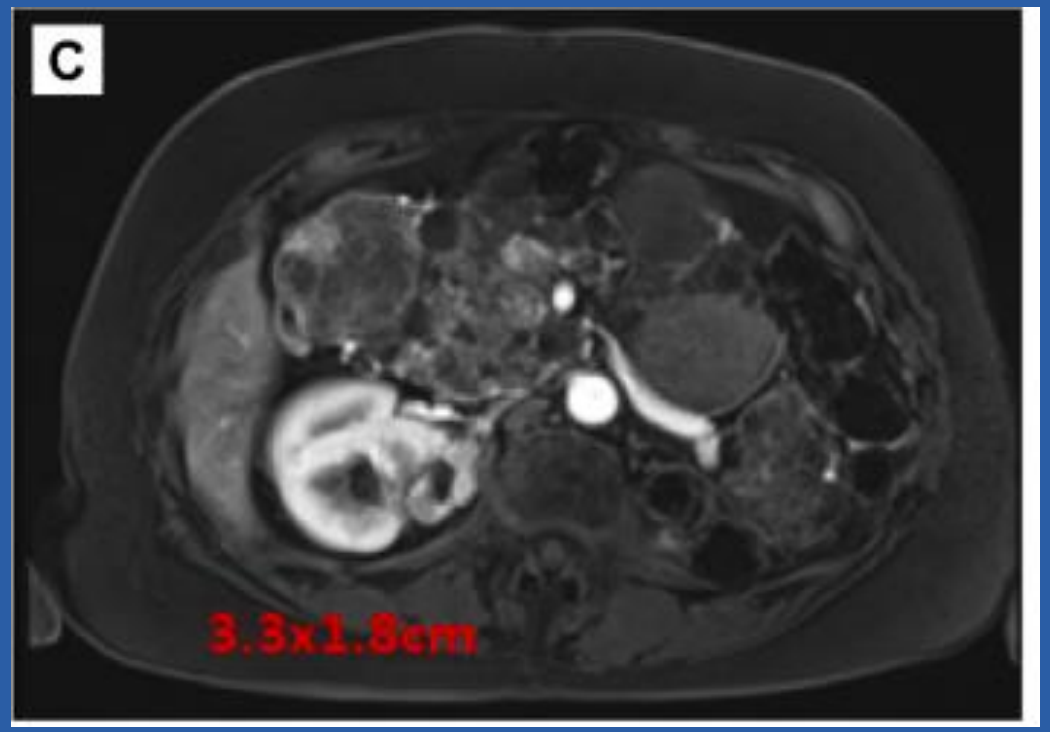
Economic Burden of Repeat Renal Surgery on Solitary Kidney—Do the Ends Justify the Means? A Cost Analysis

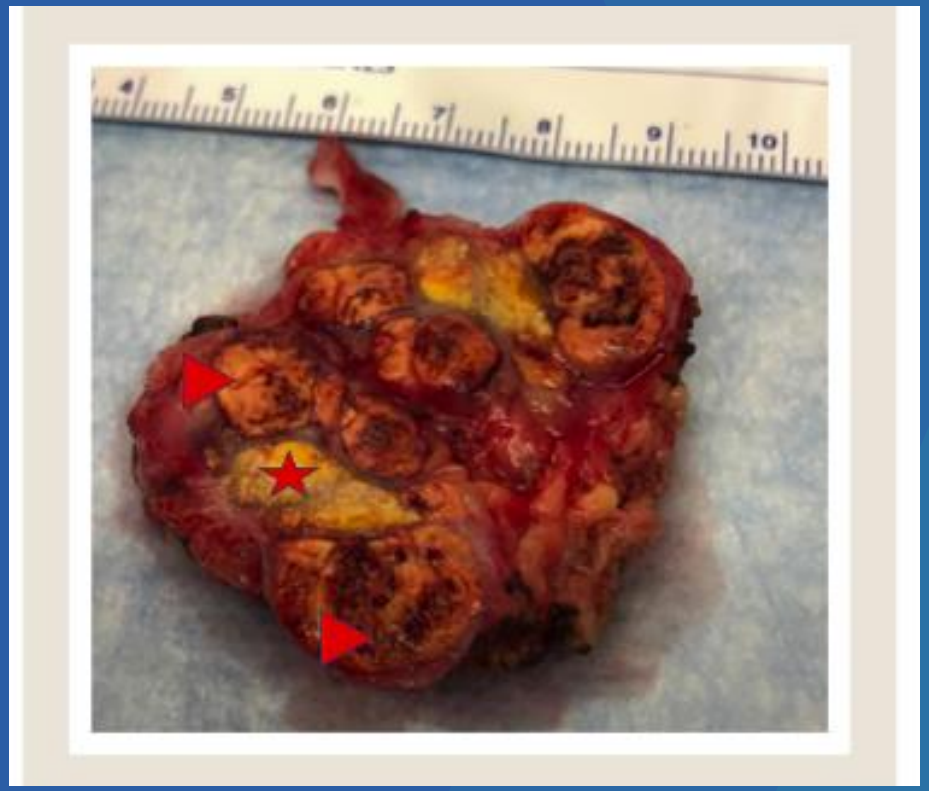
Nnenaya Q. Agochukwu, Adam R. Metwalli, Alexander Kutikov, Peter A. Pinto, W. Marston Linehan and Gennady Bratslavsky*



Salvage Surgery After Percutaneous Ablation of Renal Mass in Solitary Kidney in a Patient With Von Hippel-Lindau

Patrick T. Gomella, W. Marston Linehan, Mark W. Ball



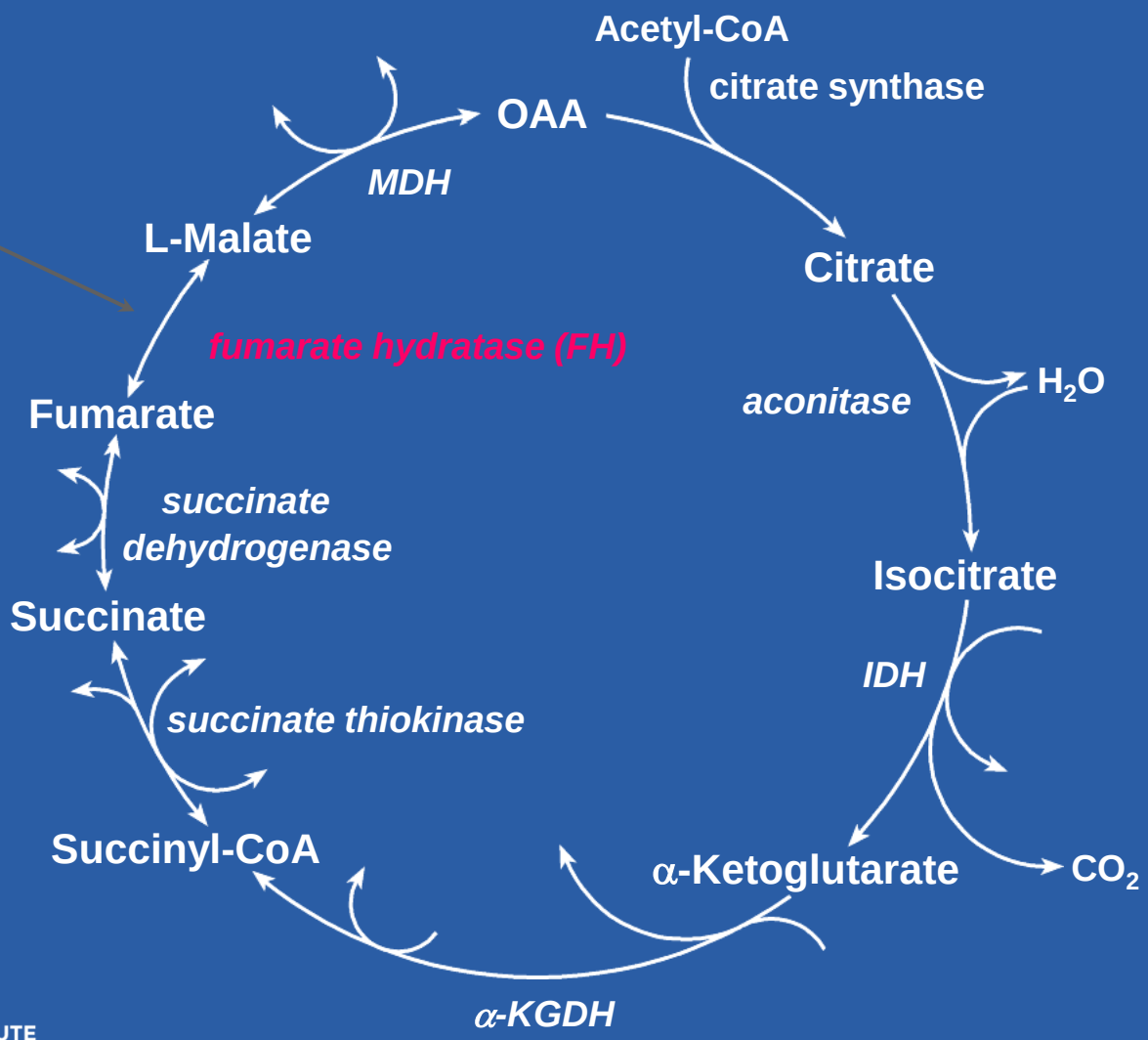


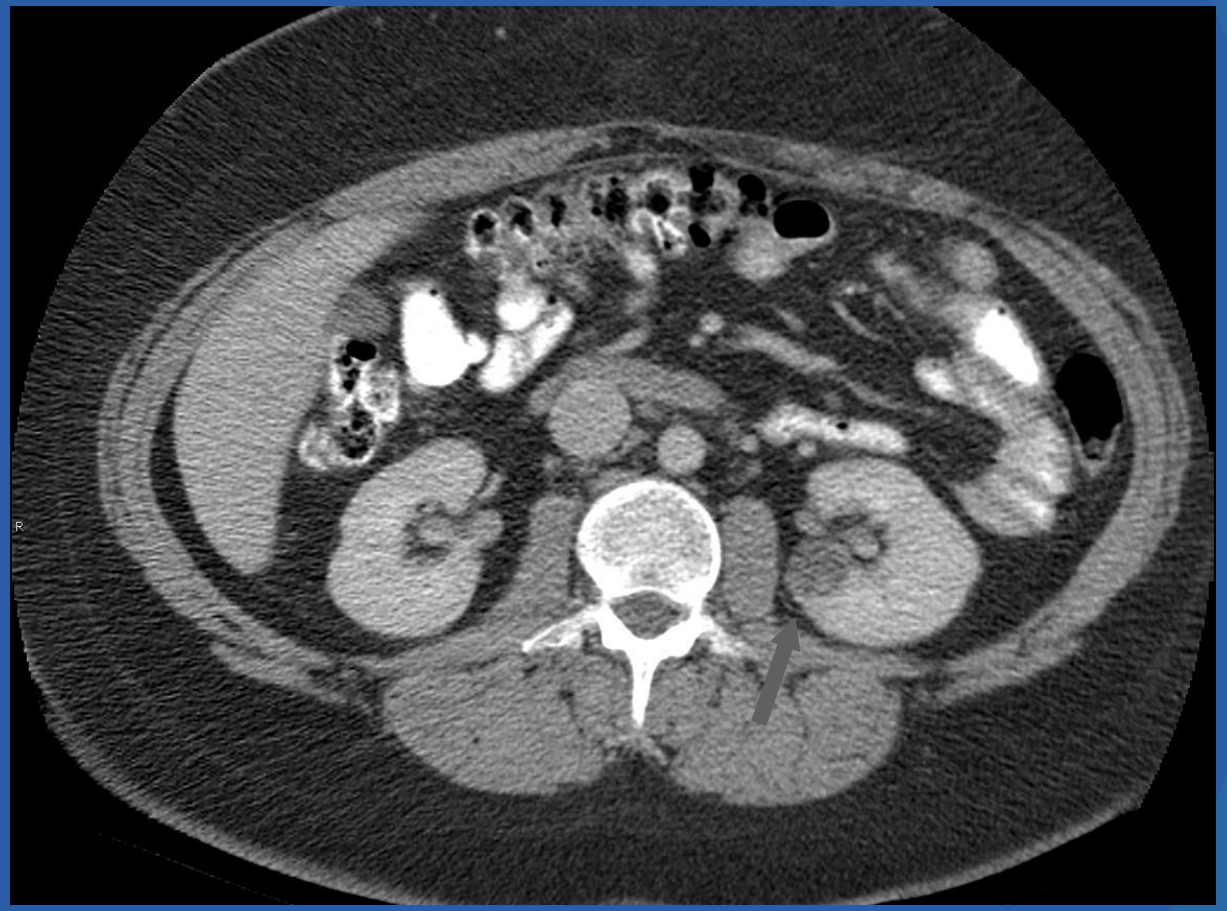
Hereditary Leiomyomatosis Renal Cell Carcinoma

Type 2 Papillary RCC

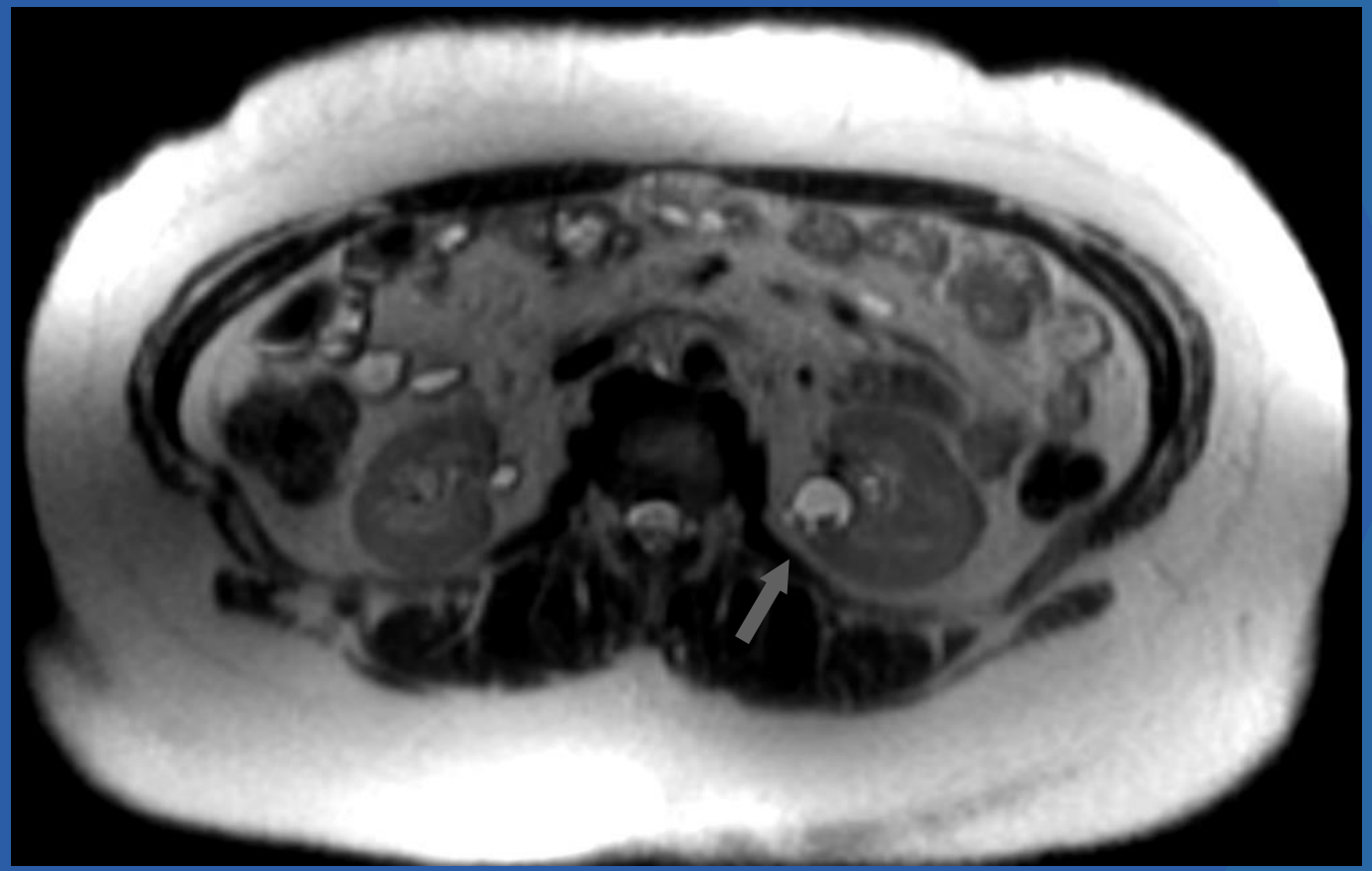
Fumarate Hydratase (FH): HLRCC Gene

FH catalyzes the conversion of fumarate to malate





24 Year Old Female



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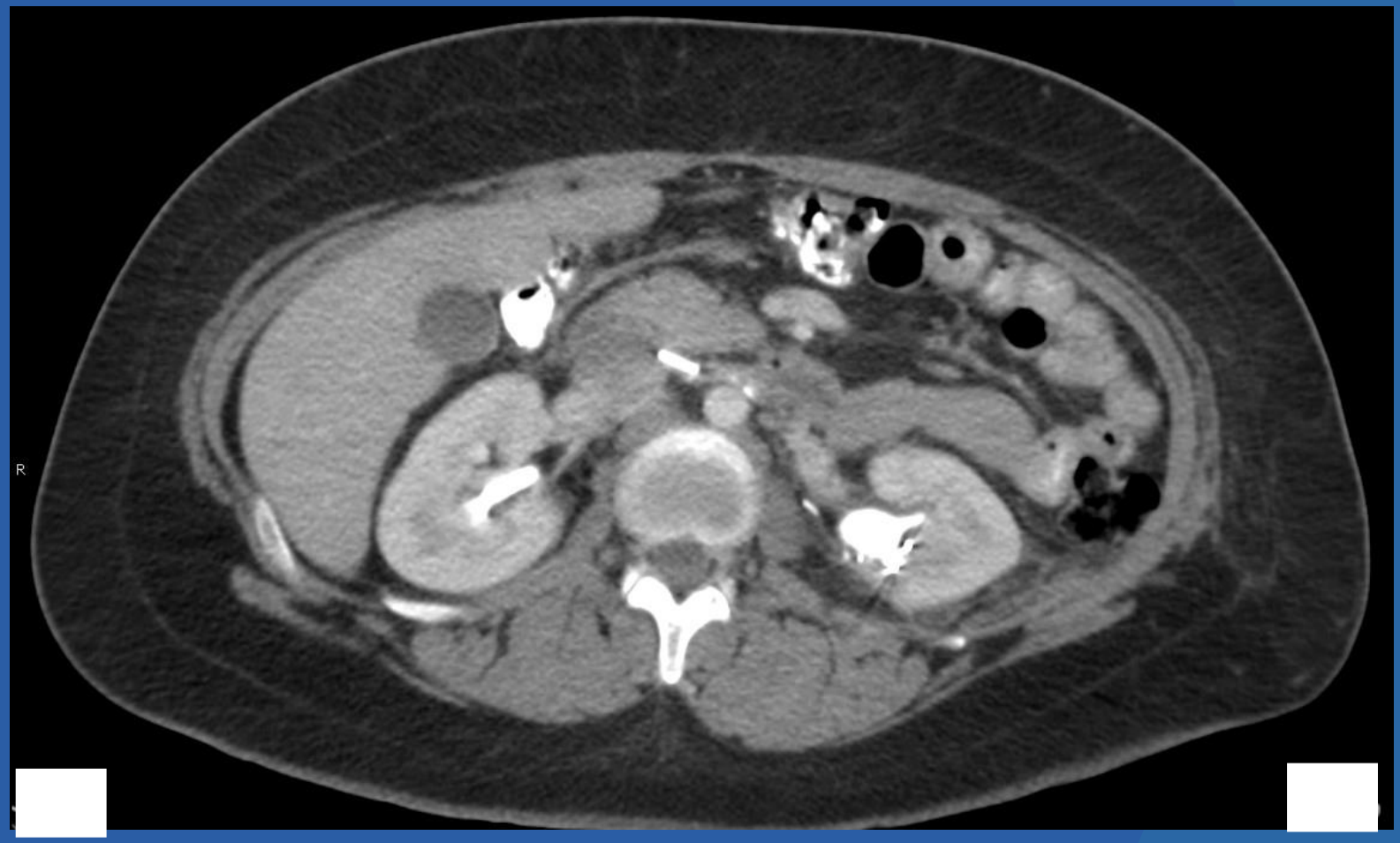
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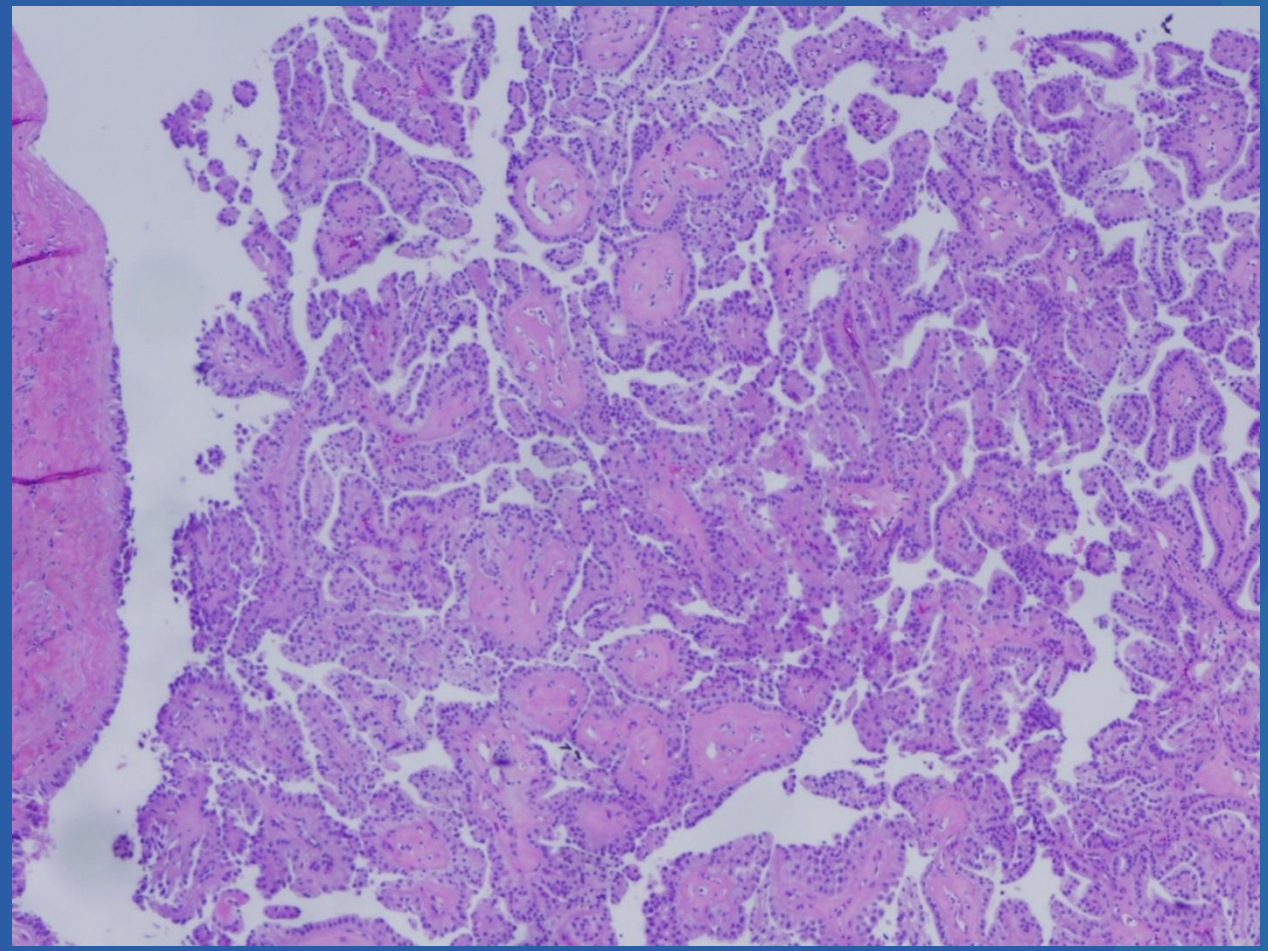
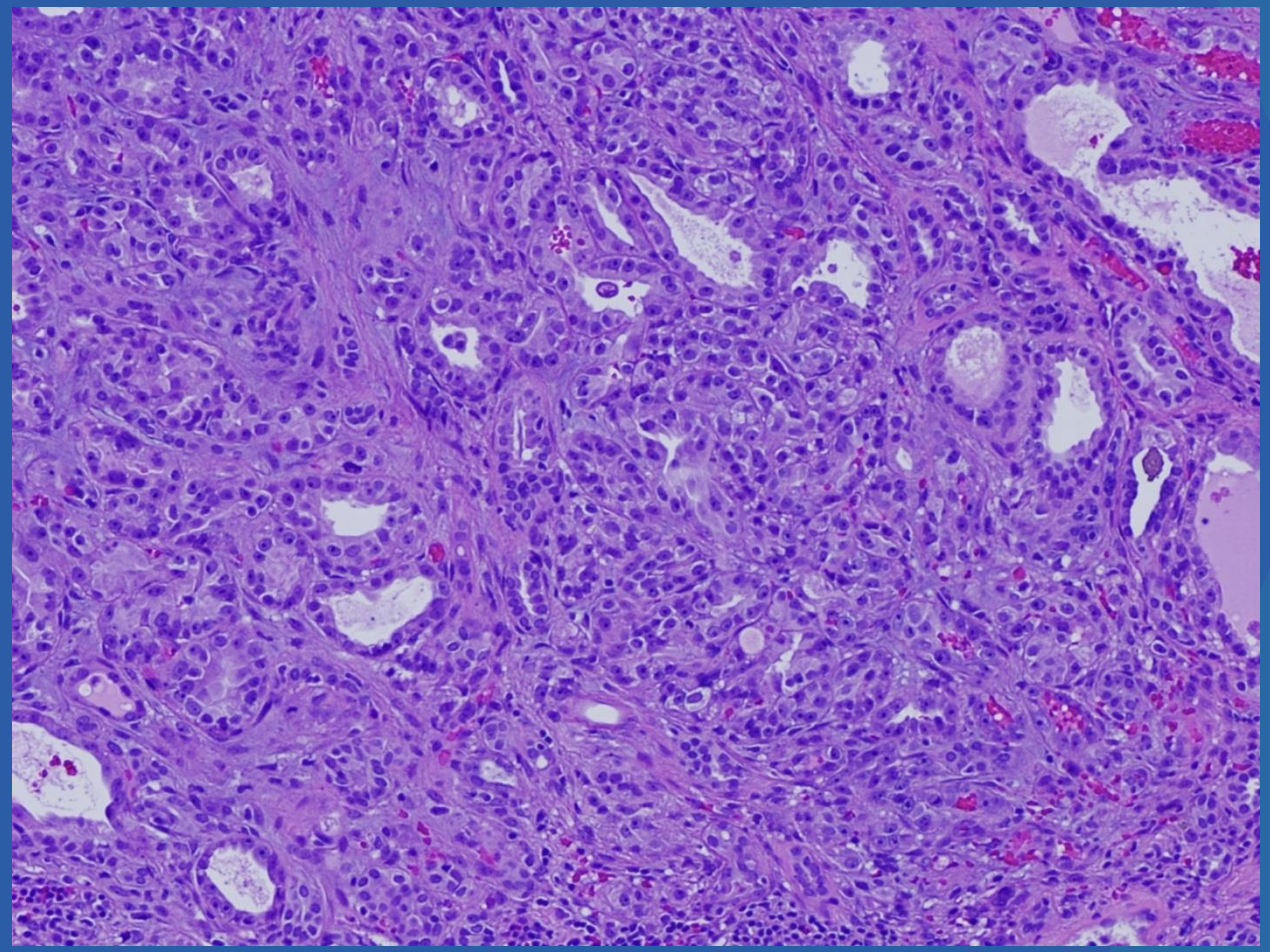
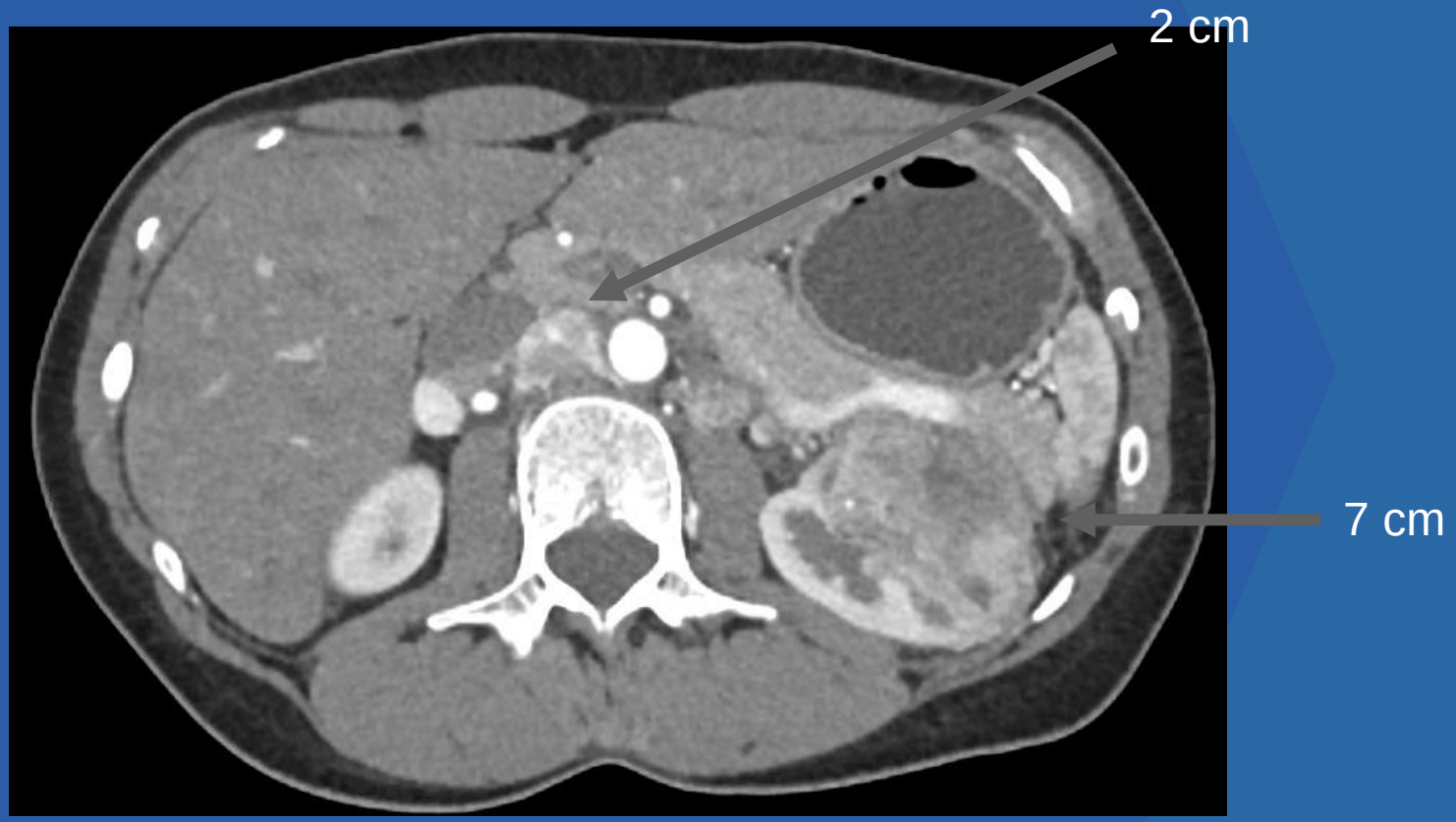
Tumor Inside Cyst

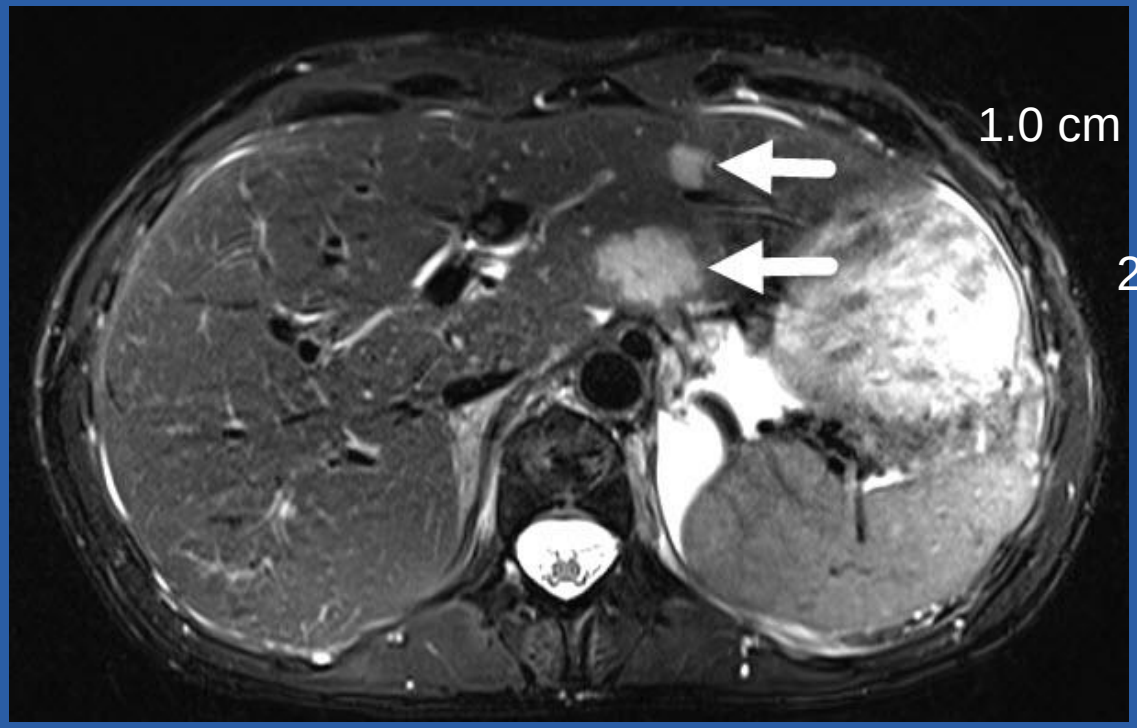


Tumor Invading Renal Parenchyma

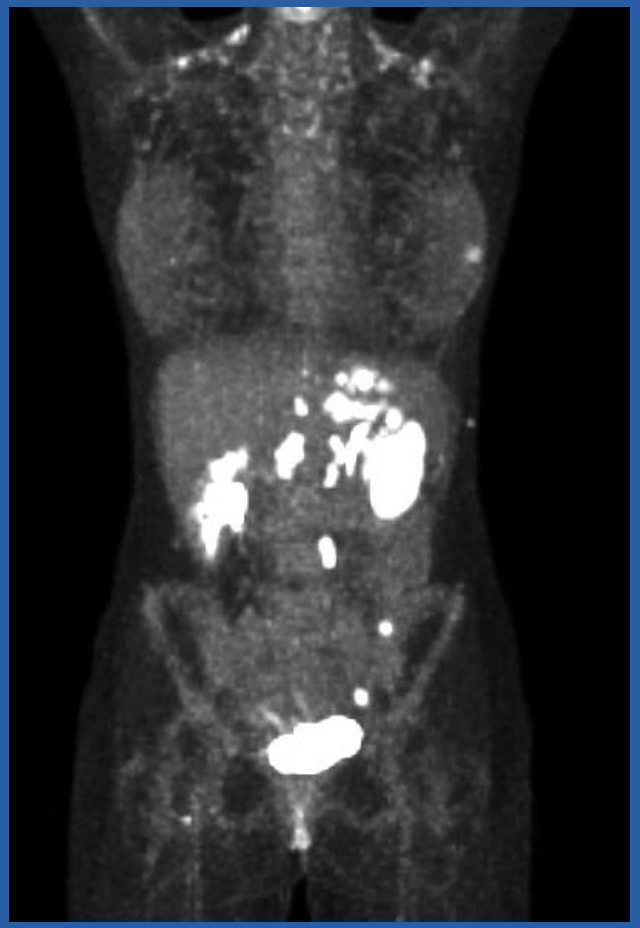




43-year-old woman



43-year-old woman



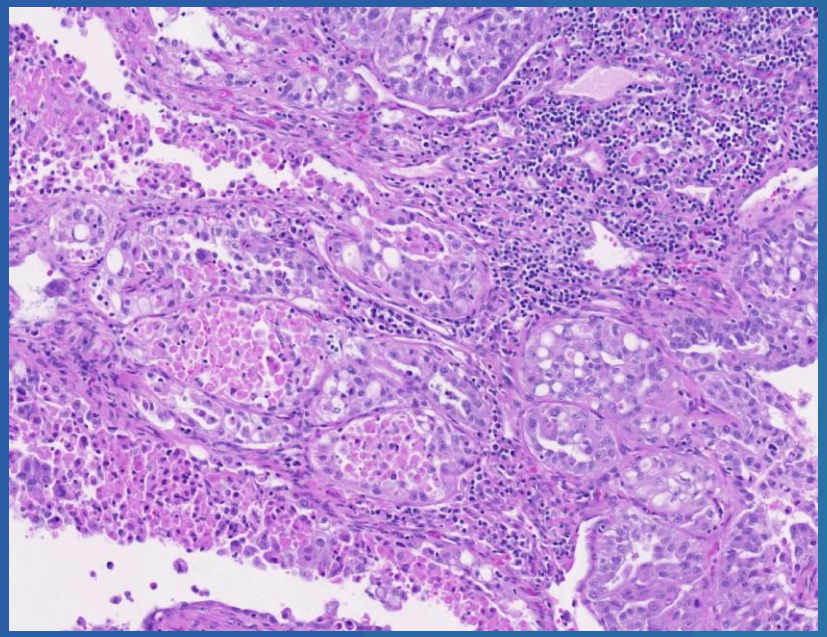
PET

HLRCC Case 2

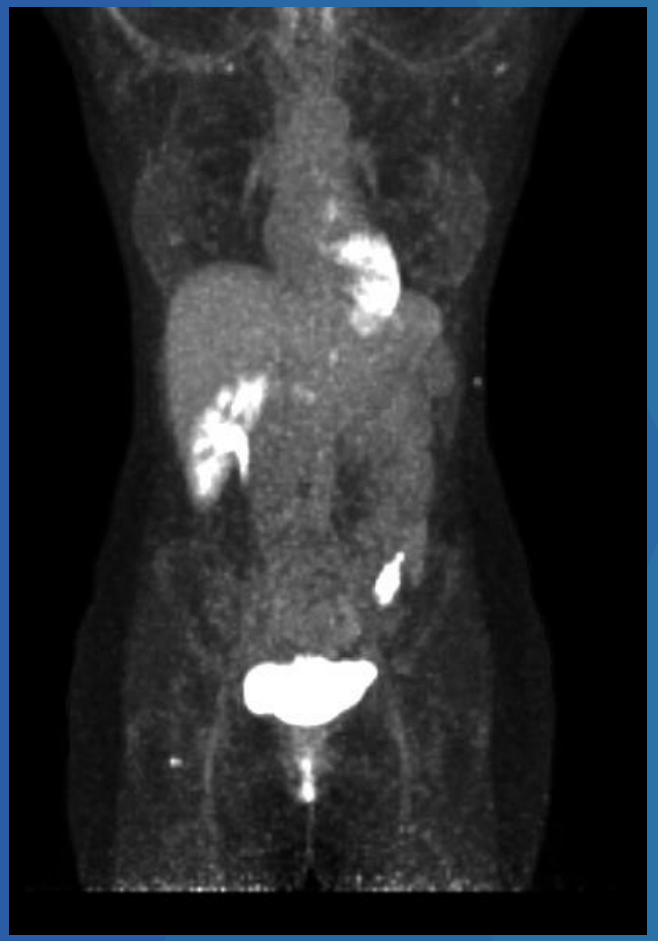
Surgery: left robotic radical nephrectomy & RPLND

Pathology

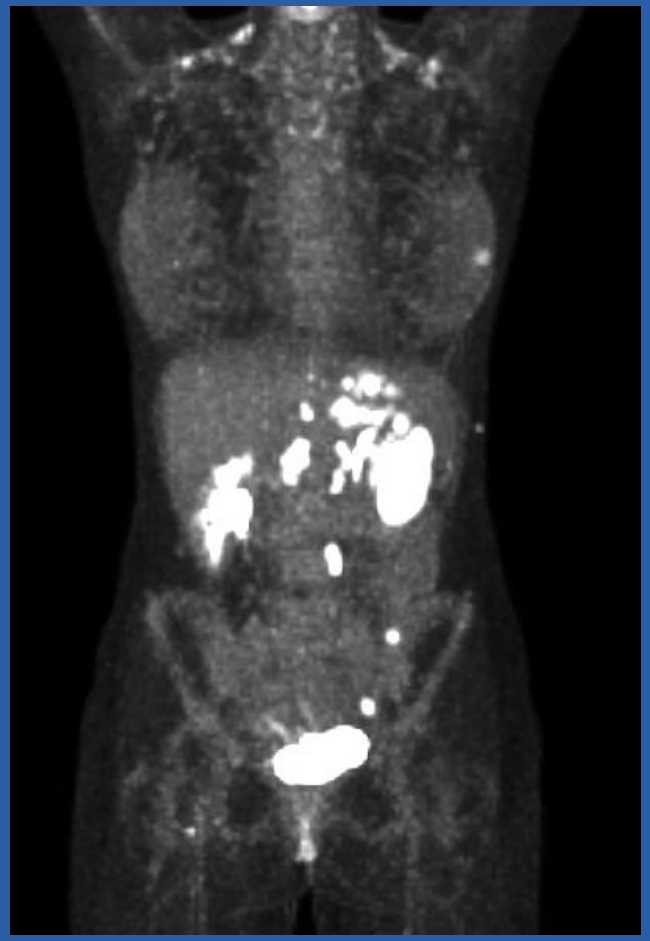
- Poorly differentiated
- Type 2 Papillary RCC
- pT3a
- 8/31 lymph nodes positive



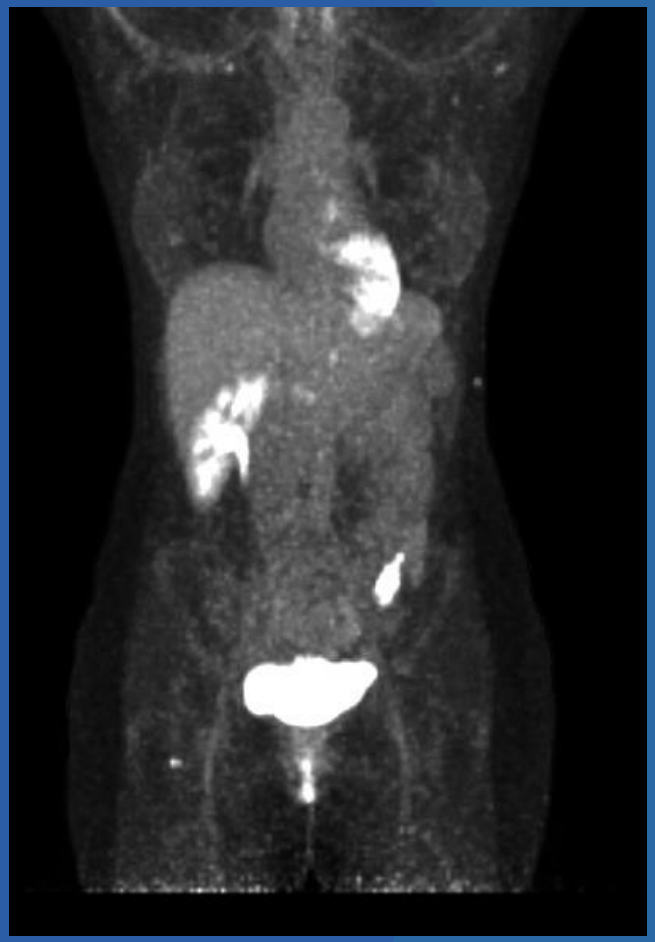
- Enrolled in phase II clinical trial:
  - Bevacizumab and erlotinib
    - Cycle 35
  - 3 years post-operatively
  - Ongoing partial response
  - Only site of metastasis is left iliac bone



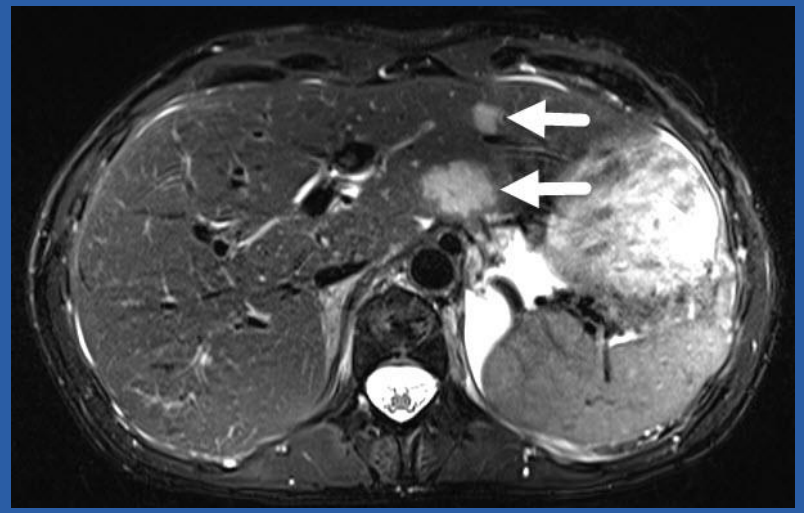
PET Post-treatment



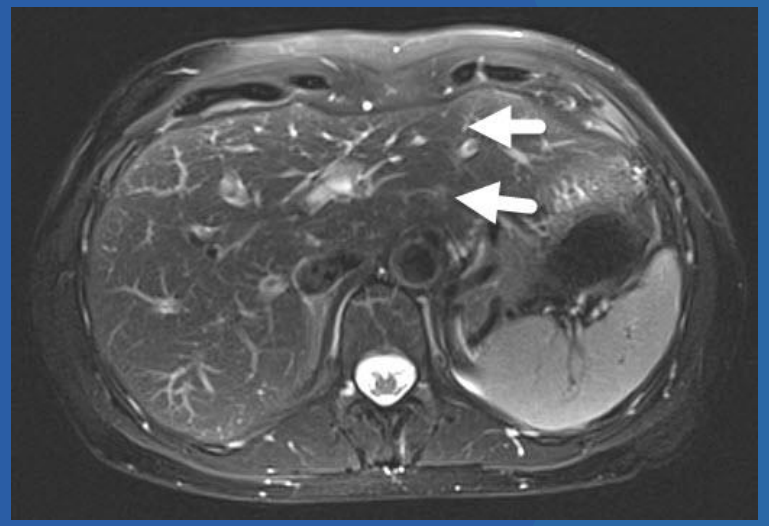
PET Pre-treatment



PET Post-treatment

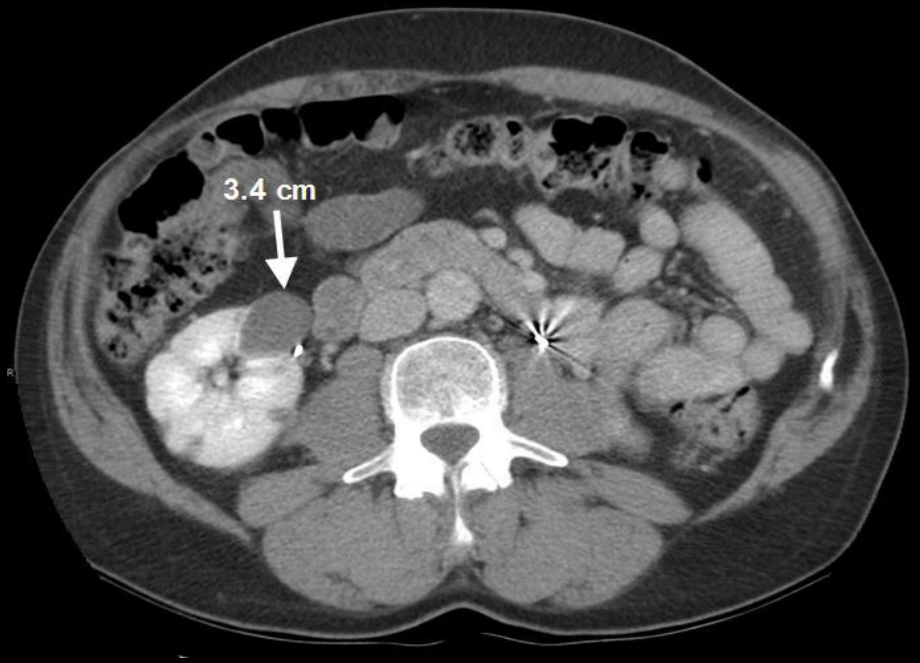


Hepatic Metastasis
Pre-treatment



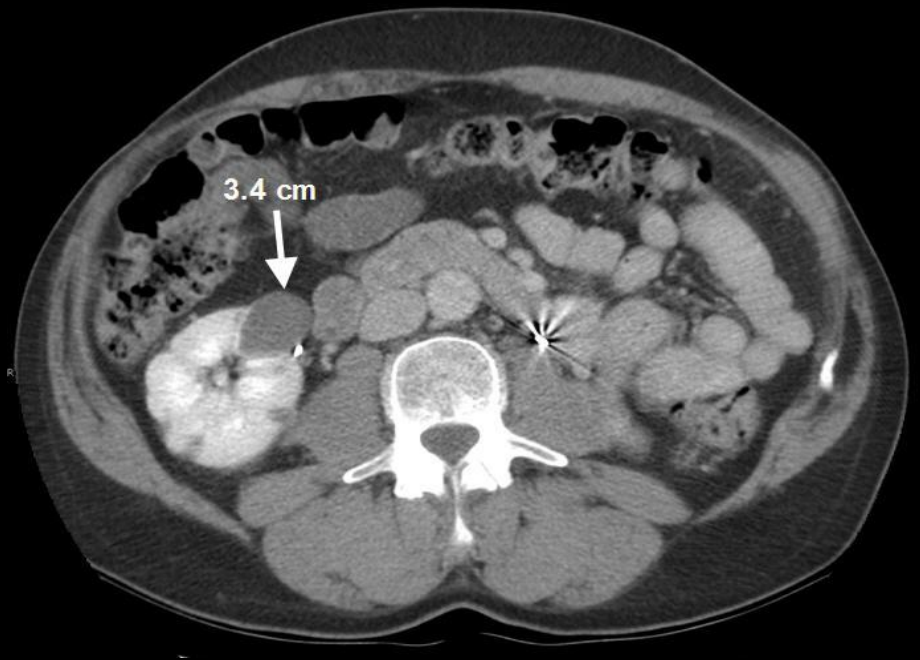
Hepatic Metastasis
Post-treatment

Regression of a renal tumor in a patient with HPRC treated with Foretinib

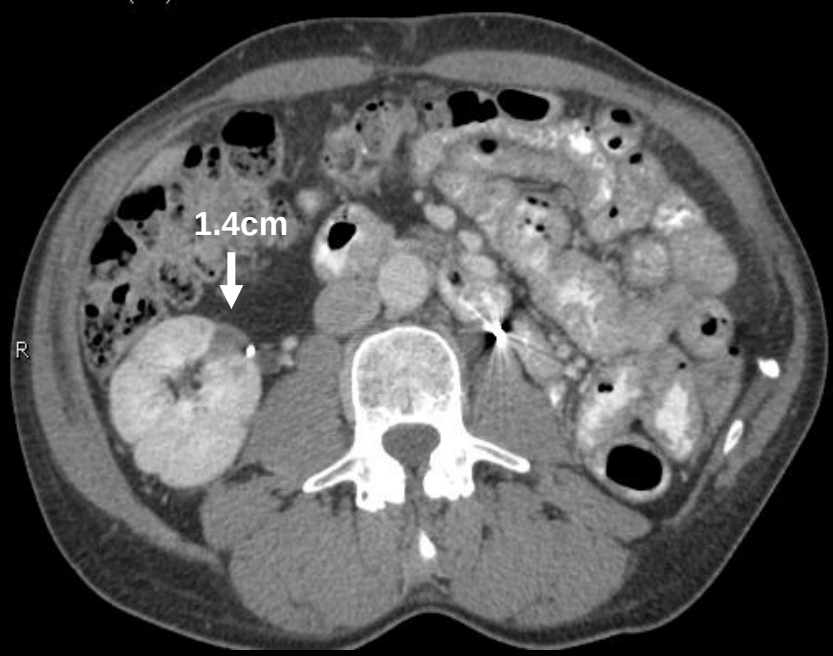


Pre-Treatment

Regression of a renal tumor in a patient with HPRC treated with Foretinib

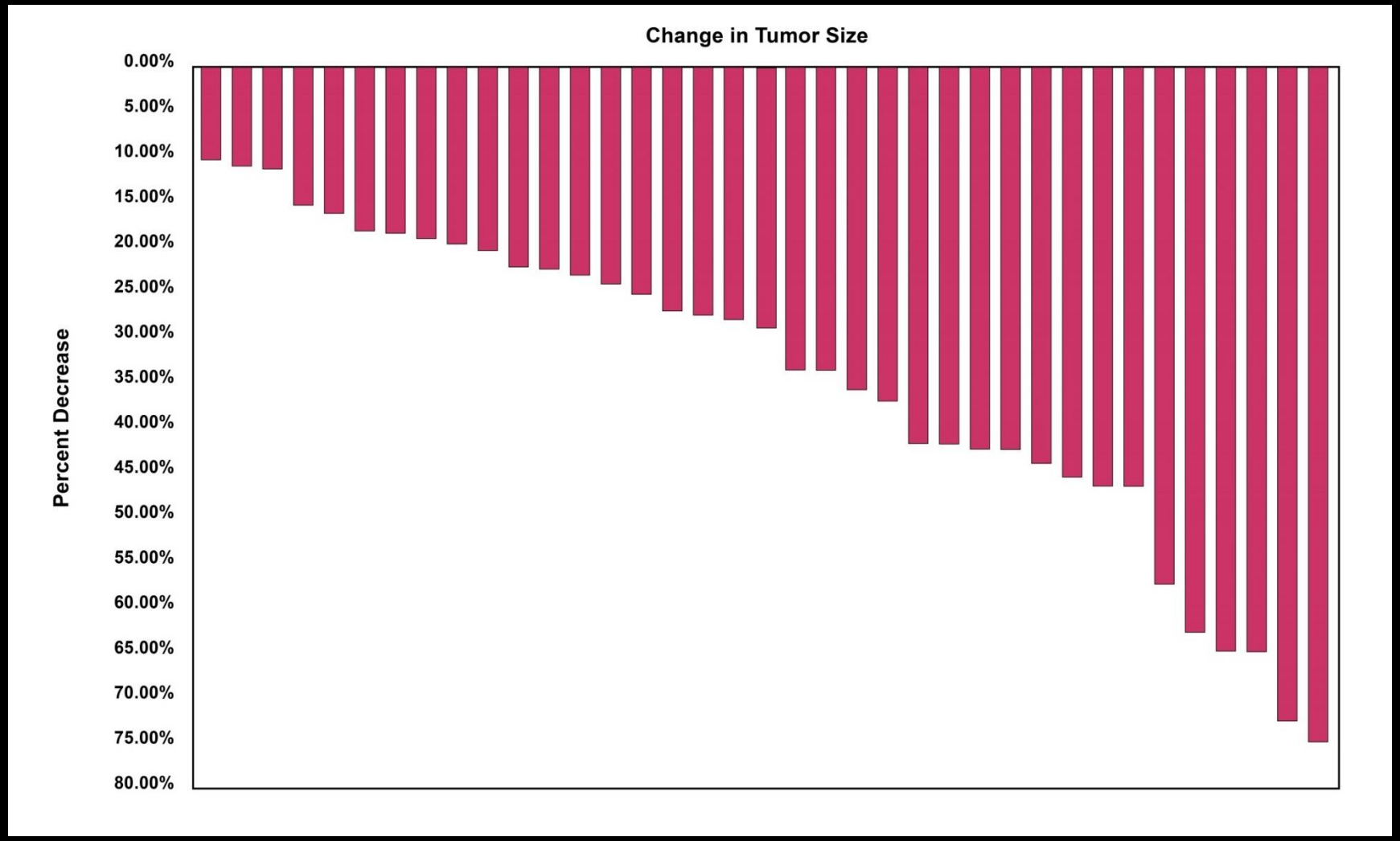


Pre-Treatment



Following 49 cycles of therapy

Foretinib 39 Target Lesions from 9 Patients With Known Gene Mutation (*MET*)



Conclusions

- Genes matter – different gene, different treatment paradigms
- Active surveillance is appropriate for most syndromes, and limits the number of renal interventions.
- HLRCC is the exception – recommend against surveillance, and wide resection for any solid tumor.

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