Contemporary Management: Small Renal Masses

Michael Maddox, MD

Ochsner Health System

Objectives

- Define SRM
- Biology/Genetics of SRM
- Management Options
- Role for renal mass biopsy
- Important Guideline Statements
- Topics of intrigue, future directions

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Disclosures

- No relevant disclosures

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Epidemiology

- RCC among 10 most common cancers
  - 4.4 cases/100,000
  - Lifetime risk 0.5%
- North America:
  - 12 cases/100,000
  - Lifetime risk 1.4%

Capitanio U et al. Eur Urol 2019.

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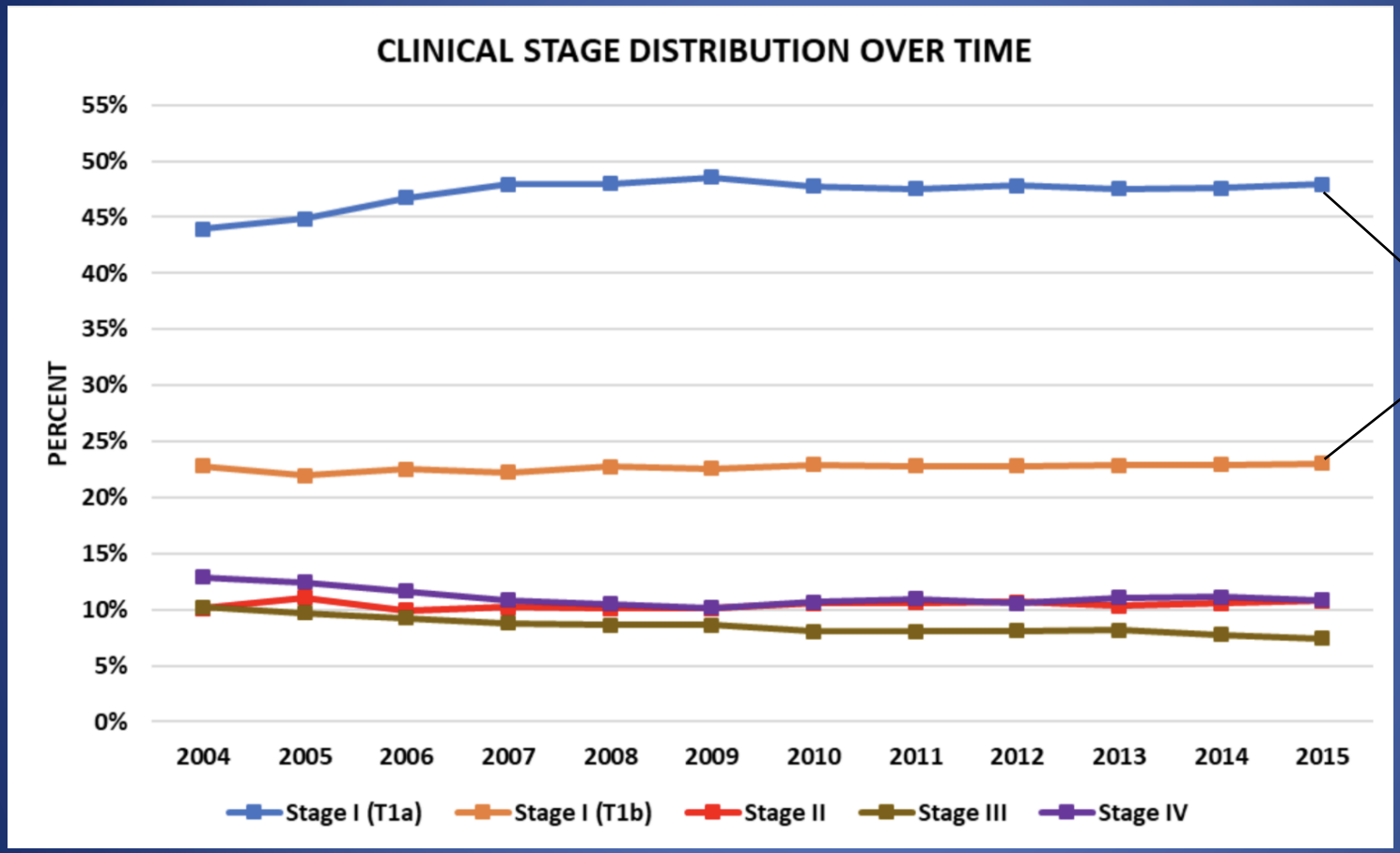
EPIDEMIOLOGY



70% OF NEW
RCC = STAGE 1

Patel et al. EU Oncology 2019.

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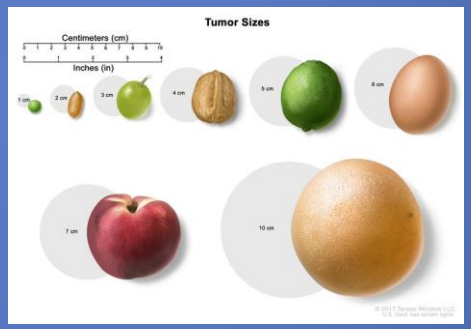
Small Renal Mass

- Solid

- < 4cm



- Solitary

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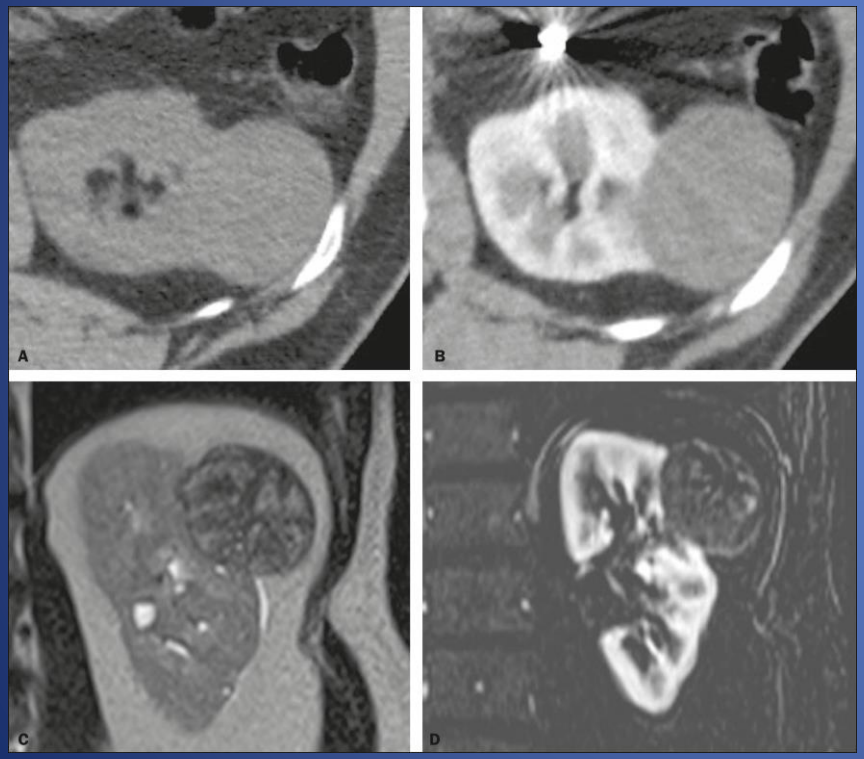
Small Renal Mass

CORTICAL LESIONS



UROTHELIAL, INFILTRATIVE

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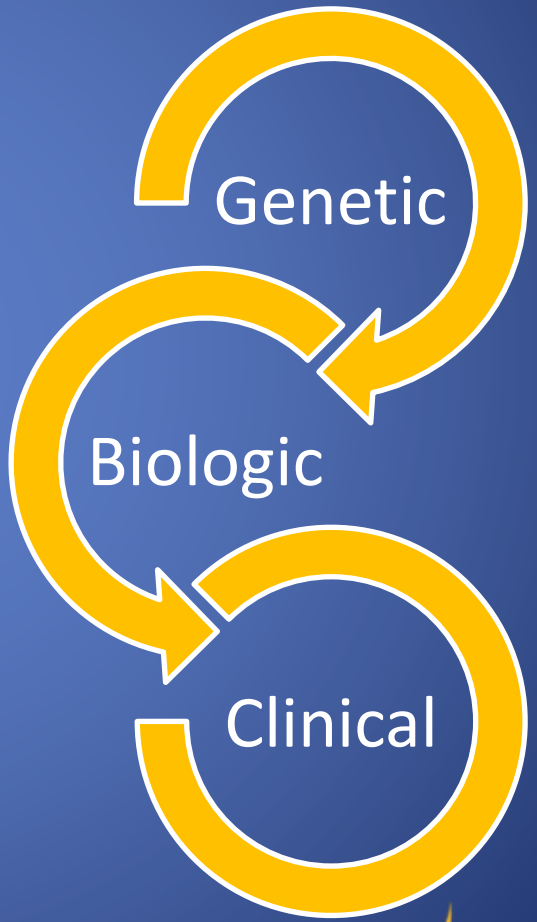
BIOLOGY & GENETICS:
HETEROGENEITY



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Importance of Size

- Pooled 19 studies: 8 US, 11 International
- SEER analysis: 2000-2009
  - **ESTIMATED US POPULATION BURDEN:** 2000→2009: ↑ 82% (3,098→ 5,624)

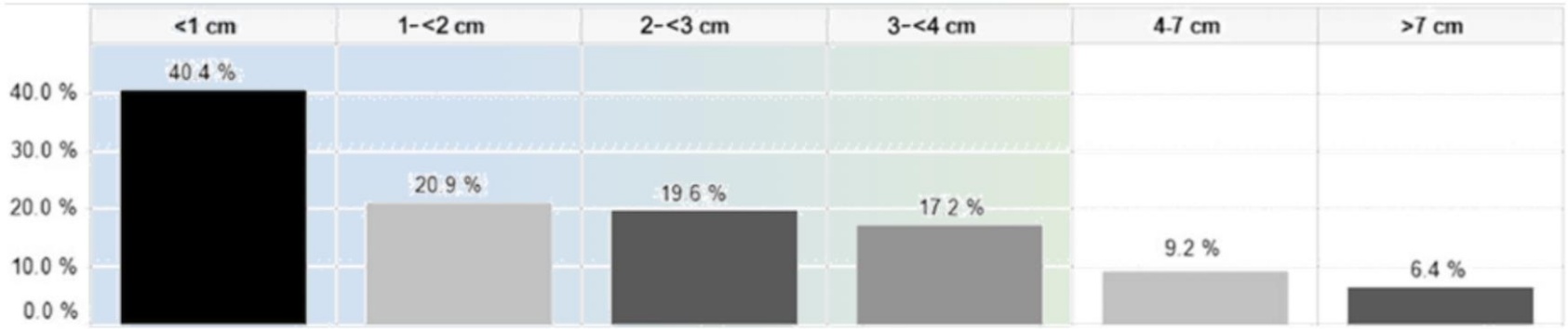

Figure 1. Estimated proportion of resected lesions with benign histology in American studies by 1 cm size strata (primary analysis).

Johnson et al. J Urol 2015; 193(1): 30-35.

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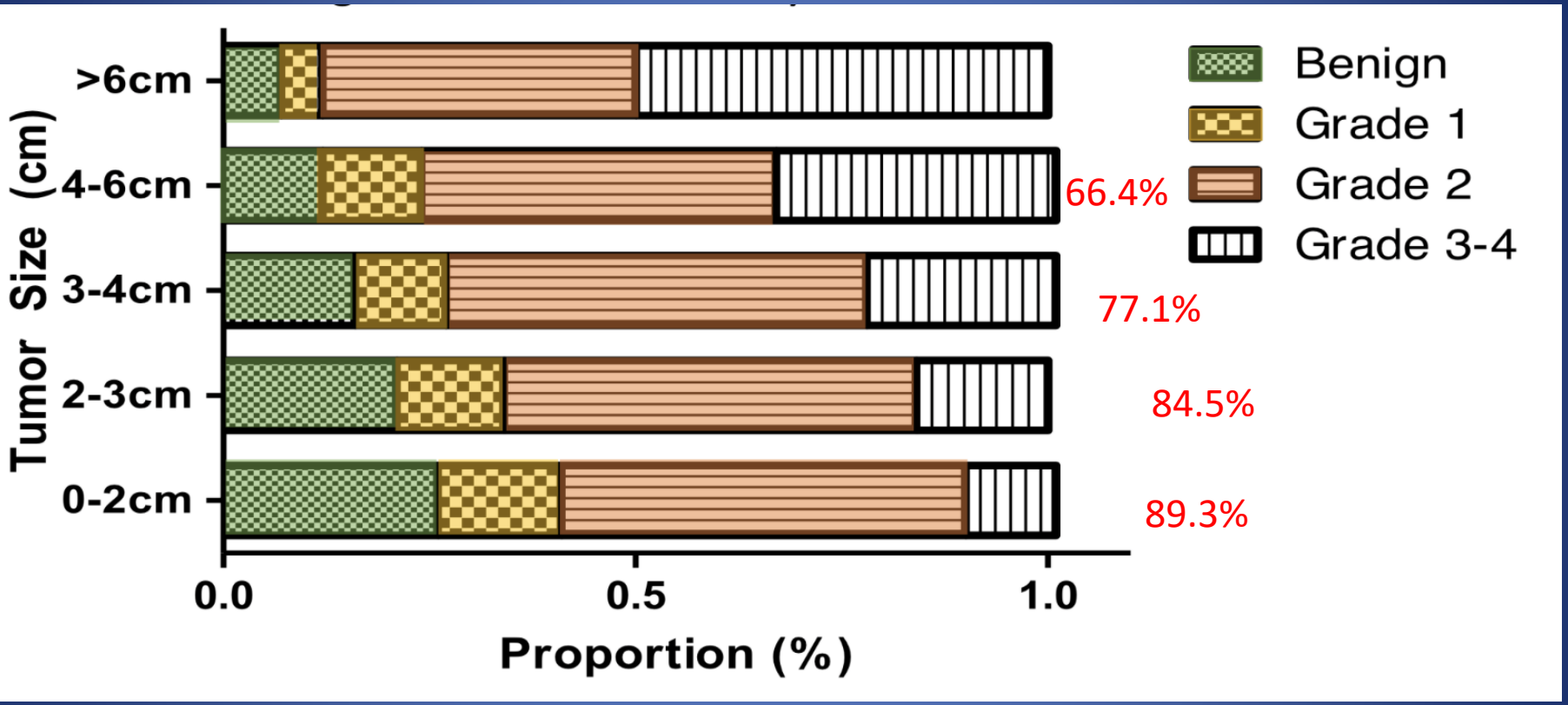
Size: Pathologic Risk



Patel H et al. Urologic Oncology 2019; 37: 519-524.

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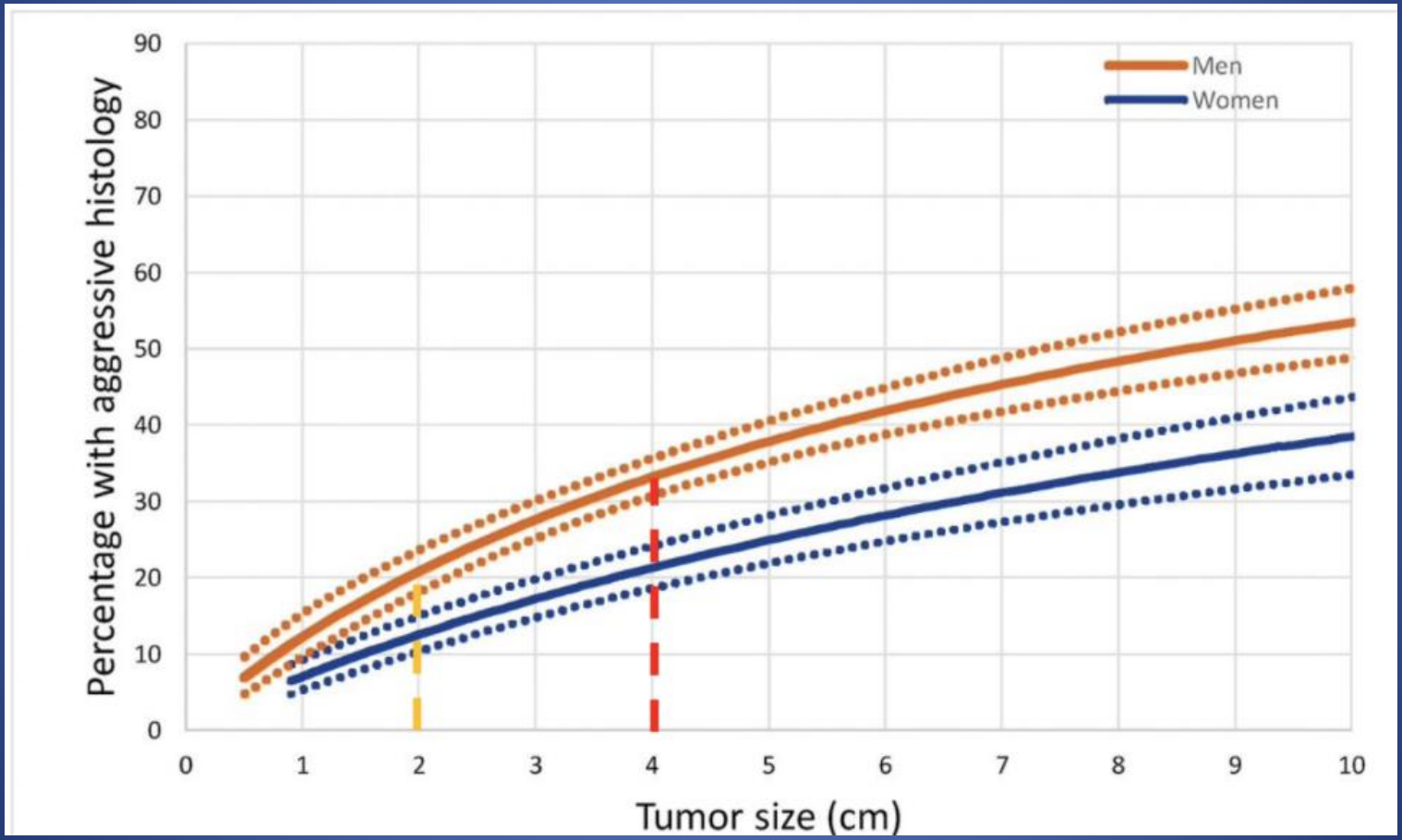
Aggressive Pathology: Size and Sex



Bhindi B et al. Eur Urol 2018; 74: 489-497.

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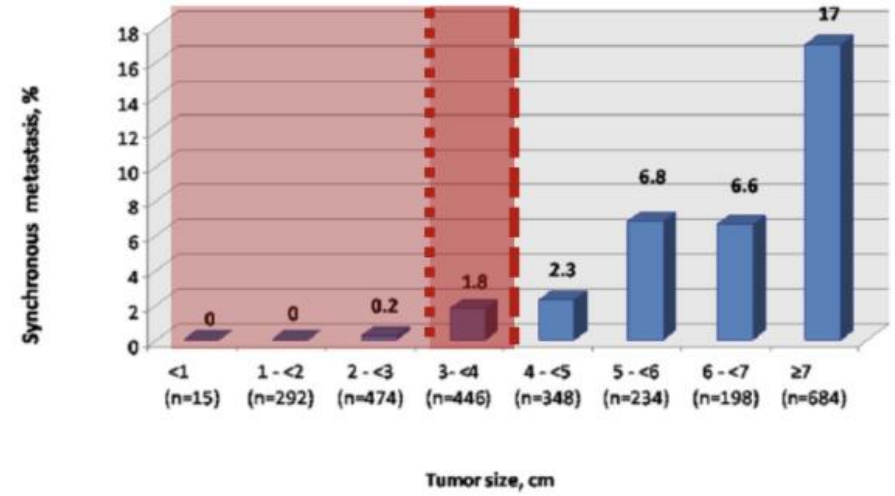
Size: Metastasis



Tumor Size (cm)	No. Pts	No. Metastasis at Followup	% 3-Yr Metastasis Probability (95% CI)
Less than 1	13	0	0
1–Less than 2	273	0	0
2–Less than 3	434	1	0
3–Less than 4	413	10	2 (1–4)
4–Less than 5	323	5	2 (1–5)
5–Less than 6	202	11	3 (1–7)
6–Less than 7	172	23	12 (7–19)
7+	537	121	20 (17–25)

- **SYNCHRONOUS METS:**
  - **<3CM---> <<1%**
  - **4CM ---> 2%**
- **ASYNCHRONOUS METS:**
  - **Only 1 patient < 3cm**

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THE RELATIONSHIP BETWEEN RENAL TUMOR SIZE AND METASTASES IN PATIENTS WITH VON HIPPEL-LINDAU DISEASE

BRANDEN G. DUFFEY, PETER L. CHOYKE, GLADYS GLENN, ROBERT L. GRUBB, DAVID VENZON, W. MARSTON LINEHAN AND MCCLELLAN M. WALTHER*

J Urol 2004; 172: 63-65.

NCI: Tenet of VHL
SRM management

TABLE 2. *Comparison of tumor size and metastases*

No. metastases/No. Pts (%)	Tumor size (cm)
0/108	3.0 or Less
1/27 (4)	3.2–4.0
4/19 (21)	4.1–5.5
10/20 (50)	6.0–10.0
5/7 (71)	10.1 or Greater

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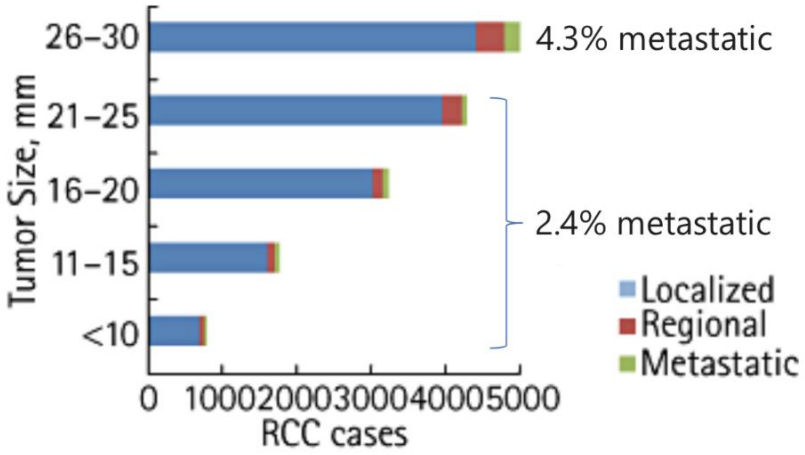
SEER DATA:



14,962 patients with RCC ≤3cm (1988-2007)
938 (6.3%) locally advanced disease
450 (3.0%) distant metastasis

METS

- **Age (65.9 vs 59.5 yrs)**

ADVANCED Dz

- **Age (>70)**
- **Male Sex**
- **Tumor Size (>2.5cm)**

Kates M et al. BJUi 2011; 109(10)1463-1467.

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Bad SRM:
Born or Developed

- SRM's can be associated with:
  - Advanced dz (6.3%)
  - Metastatic dz (3%)

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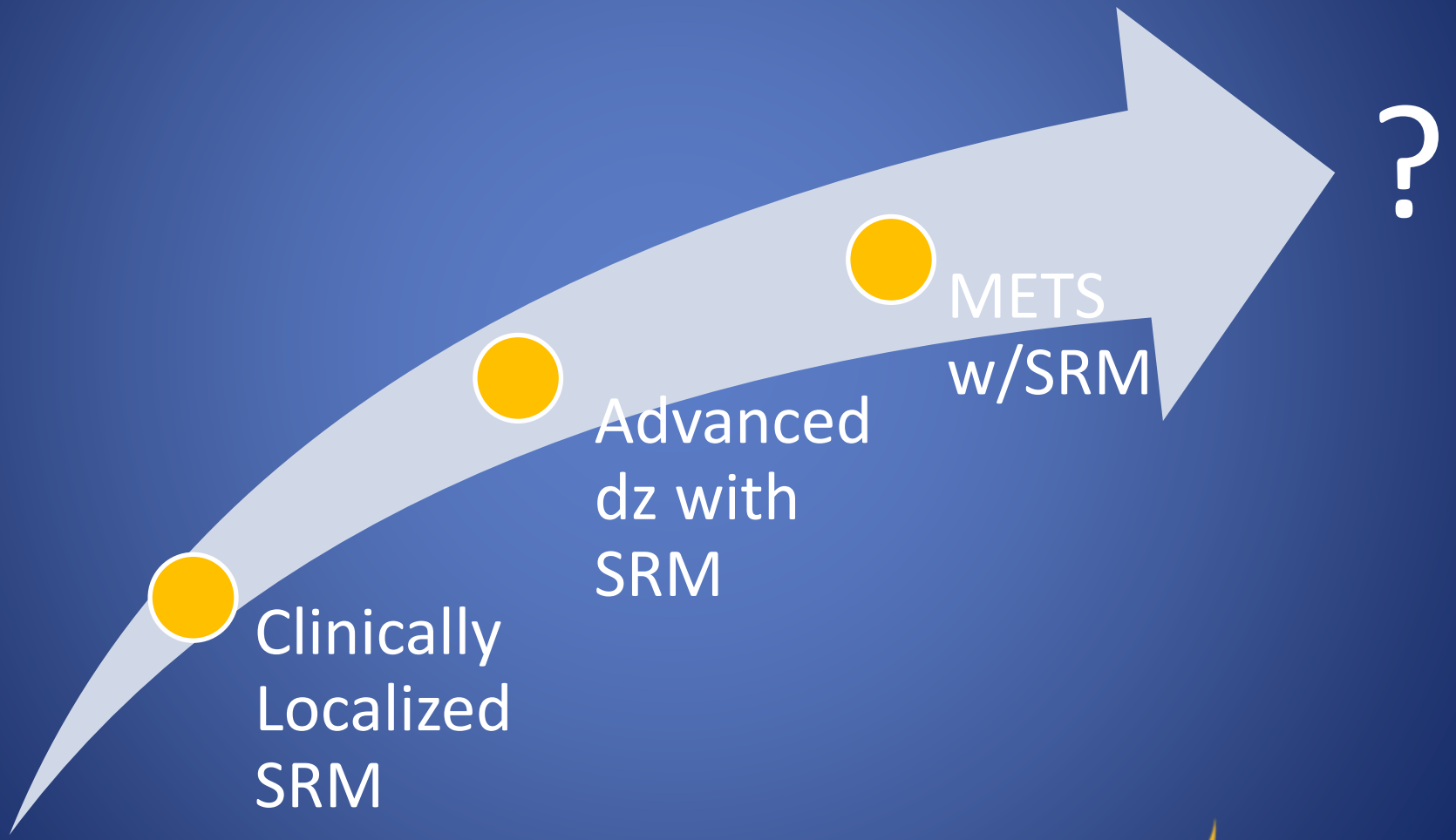
Bad SRM: Born or Developed



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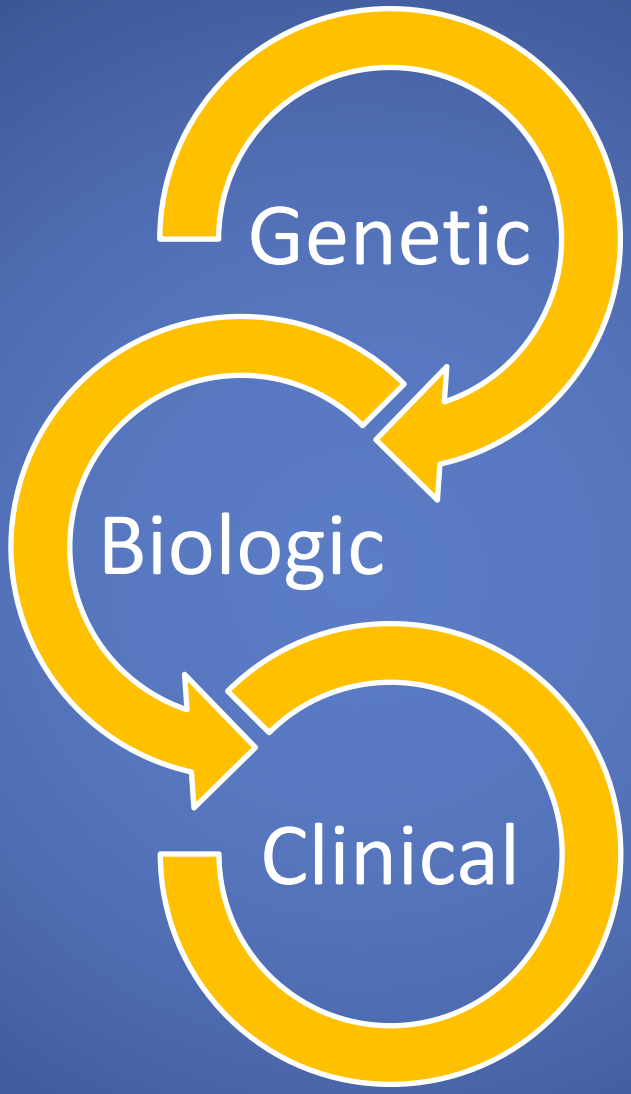

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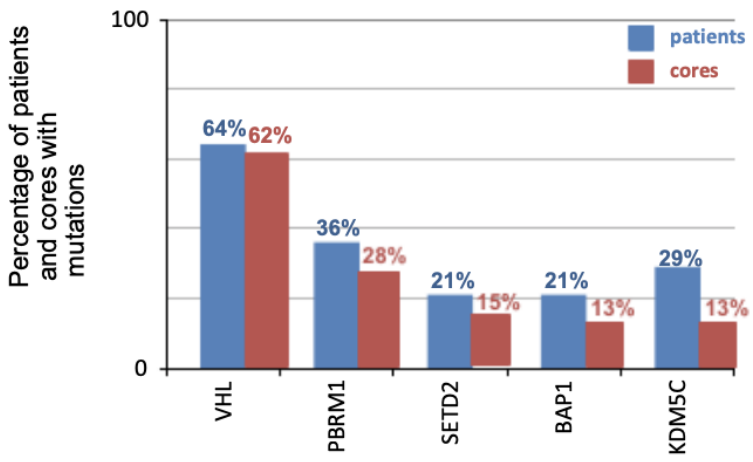
Genetic Heterogeneity



TCGA (*n* = 385)	52%	33%	12%	10%	7%
Sato et al (*n* = 106)	40%	26%	11%	8%	4%
Guo et al (*n* = 98)	28%	20%	4%	8%	0%

Figure 1. Overall mutation rate by patient (in blue, *n* = 14) and by core (in red, *n* = 47). Comparison cohort frequencies are shown in gray.

- **Chromosome 3p (VHL)→ tumorigenesis for ccRCC**
  - **Not prognostic**

- **PBRM1**
- **SETD2**
- **BAP1**
- **KDM5c**

Associated with ccRCC prognosis

Sankin et al. Cancer Med 2014; 3(6): 1485-1492.

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Genetic Heterogeneity

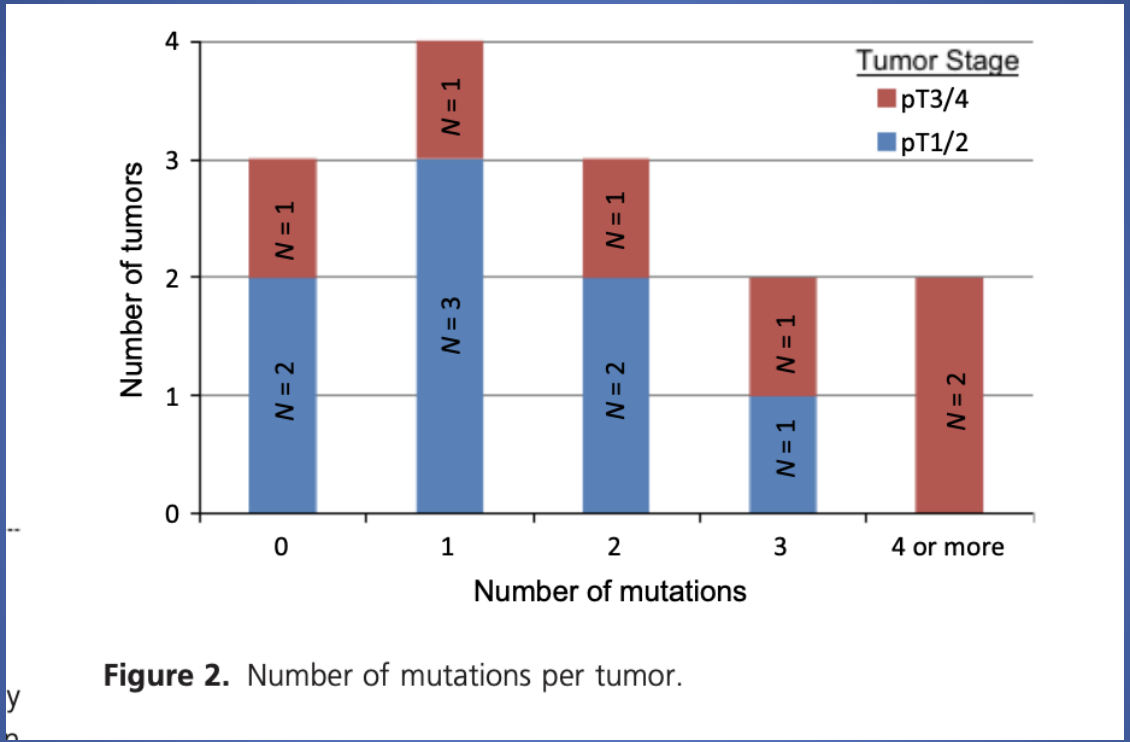

Figure 2. Number of mutations per tumor.

- **↑Genetic complexity, ↑ stage**

Sankin et al. Cancer Med 2014; 3(6): 1485-1492.

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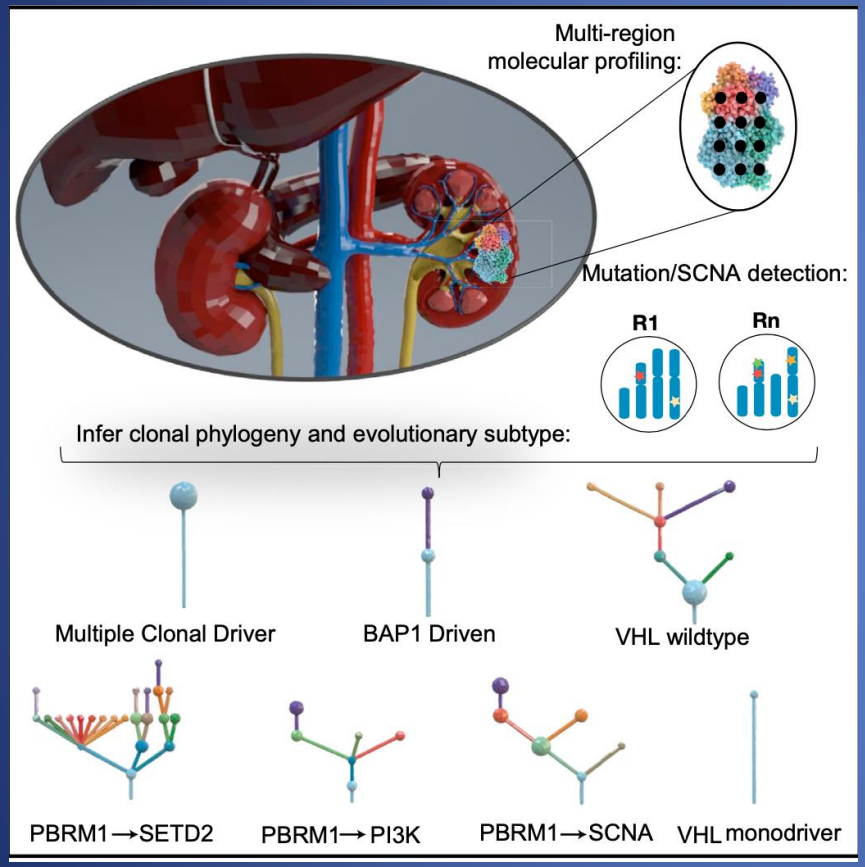
Deterministic Evolutionary Trajectories Influence Primary Tumor Growth: TRACERx Renal



Highlights

- ccRCC evolutionary subtypes correlate with clinical phenotypes
- Genetic diversity and chromosome complexity contribute to patient outcomes
- Early fixation of multiple driver events leads to rapid growth and metastases
- Subclonal diversification is linked with slower growth and attenuated metastases

Turajlic S et al. Cell 2018; 173: 595-610.

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Deterministic Evolutionary Trajectories Influence Primary Tumor Growth: TRACERx Renal

Lower Stage,
Lower genetic complexity

Higher stage,
Higher genetic complexity

Turajlic S et al. Cell 2018; 173: 595-610.

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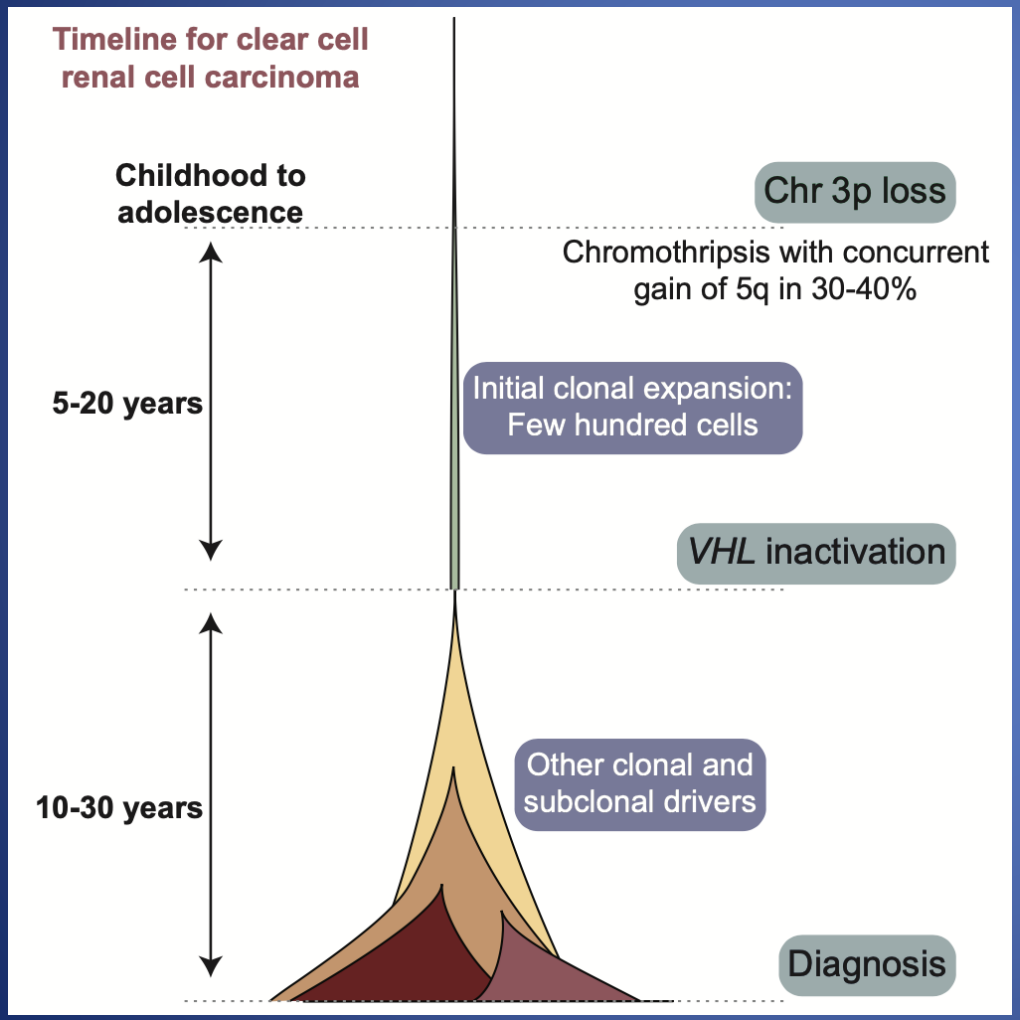
Deterministic Evolutionary Trajectories Influence Primary Tumor Growth: TRACERx Renal



SRM is ”born” decades before diagnosis.

Mitchell TJ et al. Cell 2018; 173:611-623.

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Management Options

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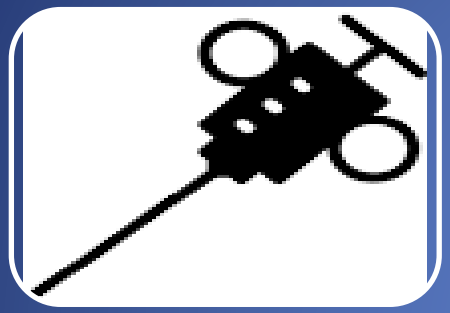
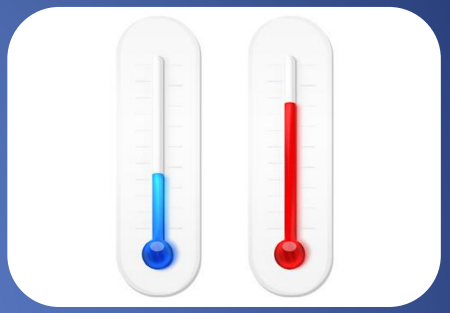
Management Options



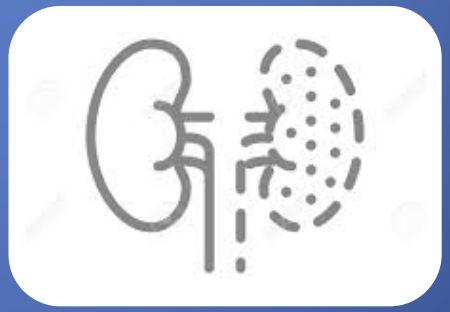
Biopsy

Surveillance



Ablation

Partial Nx



Radical Nx

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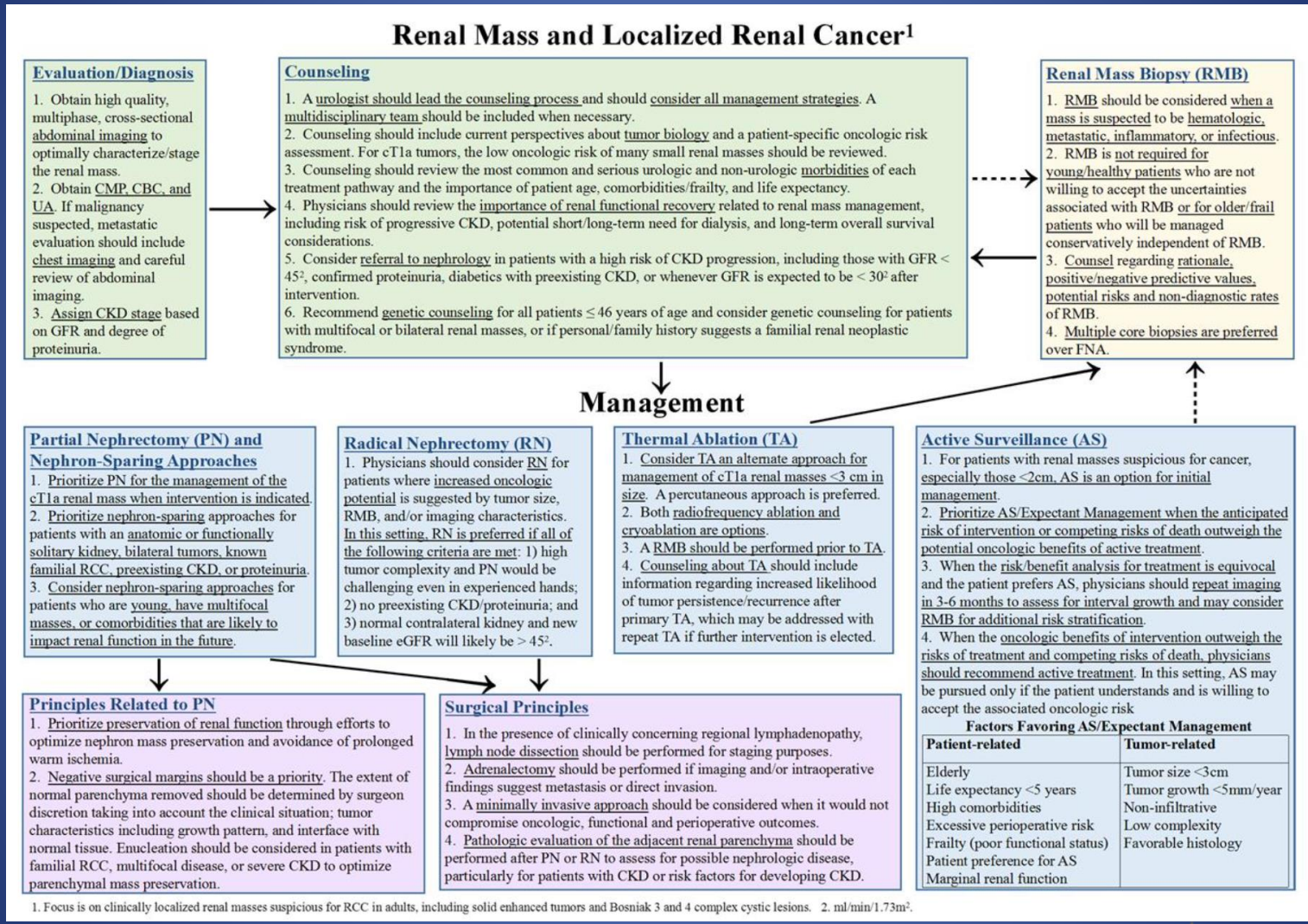
AUA Guidelines



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AUA Guidelines

- #7. Physicians should review the importance of renal functional recovery related to renal mass management, including the risk of progressive CKD, potential short- or long-term need for renal replacement therapy, and long-term overall survival considerations.

- #8. Physicians should consider referral to nephrology in patients with a high risk of CKD progression. Such patients may include those with eGFR less than 45 ml/min/1.73m^2, confirmed proteinuria, diabetics with preexisting CKD, or whenever eGFR is expected to be less than 30 ml/min/1.73m^{2}after intervention.

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AUA Guidelines

- #14-18:
- Prioritize PN for cT1a SRM.
  - Minimizes risk of CKD / CKD Progression
  - Excellent oncologic outcomes
- Prioritize Nephron Sparing when...:
  - Solitary kidney
  - Bilateral tumors
  - Known familial RCC
  - Pre-existing CKD
  - Proteinuria

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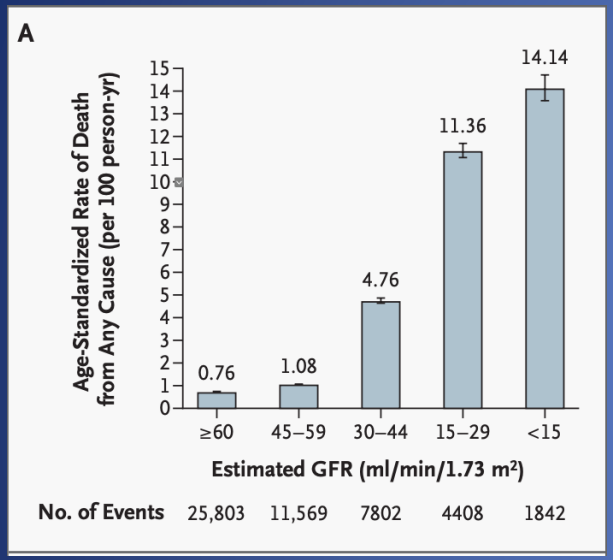
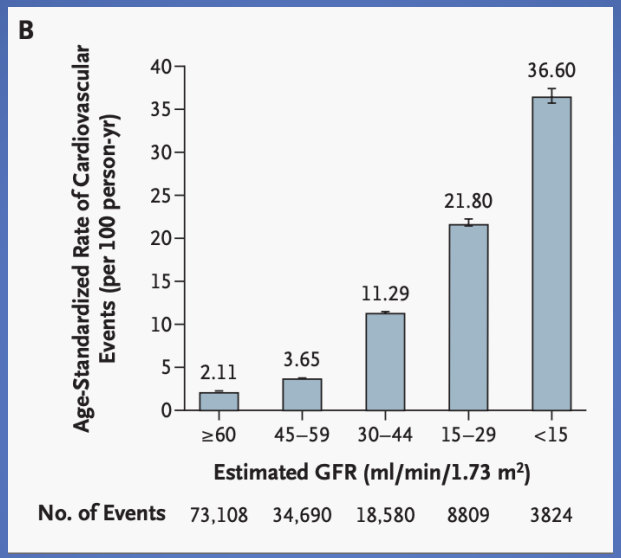
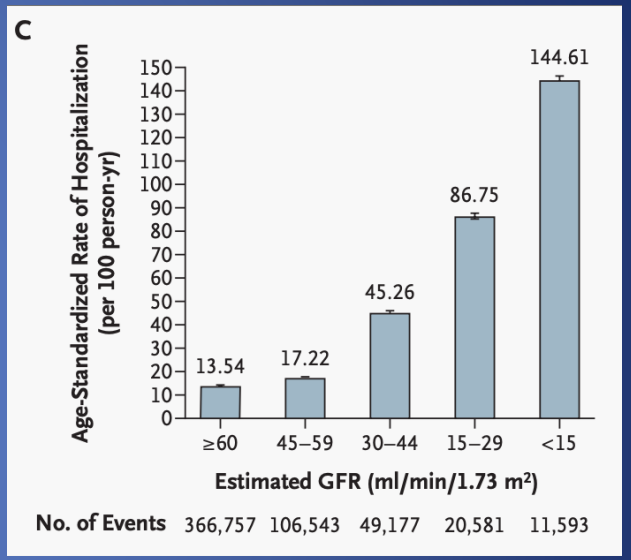
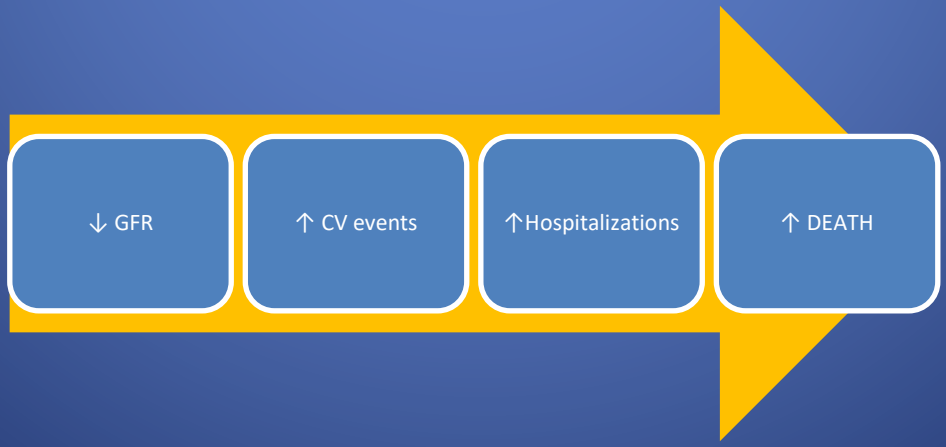
Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization

Alan S. Go, M.D., Glenn M. Chertow, M.D., M.P.H., Dongjie Fan, M.S.P.H., Charles E. McCulloch, Ph.D., and Chi-yuan Hsu, M.D.









NEJM 2004; 351: 1296-1305.

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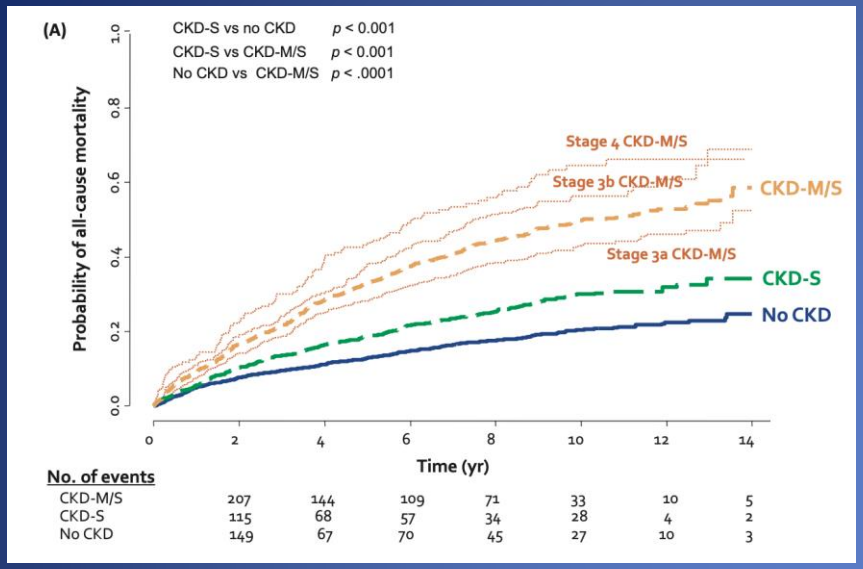
Medical vs Surgical CKD



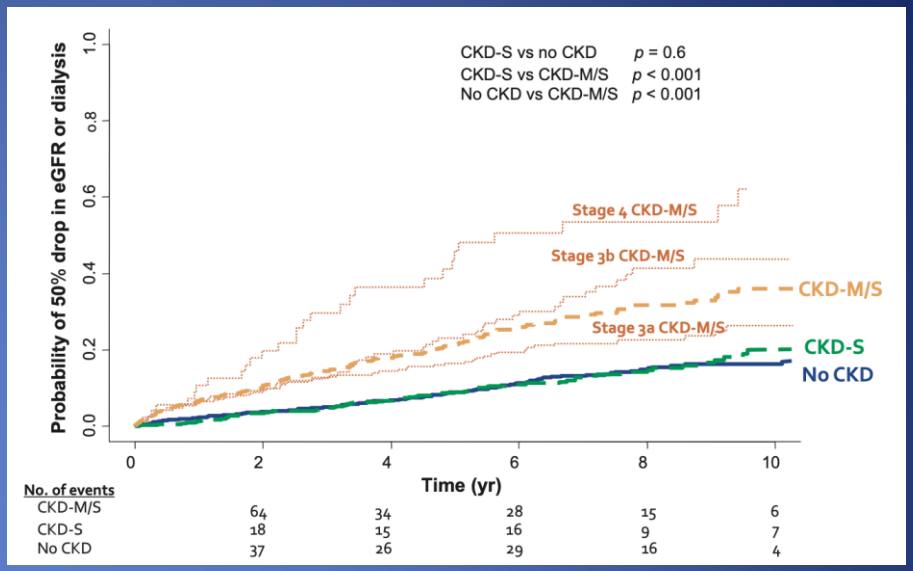


Table 3 – Multivariable analysis of renal function stability and survival

	Hazard ratio (95% confidence interval) [a]					
	50% GFR decline or dialysis	*p* value	All-cause mortality	*p* value	Non–renal cancer mortality	*p* value
CKD-S vs no CKD	1.10 (0.82–1.49)	0.5	1.19 (1.02–1.40)	0.030	1.07 (0.86–1.32)	0.5
CKD-M/S vs no CKD	2.33 (1.76–3.10)	<0.001	2.01 (1.73–2.33)	<0.001	1.97 (1.63–2.38)	<0.001
CKD-M/S vs CKD-S	2.13 (1.59–2.86)	<0.001	1.69 (1.45–1.96)	<0.001	1.85 (1.53–2.22)	<0.001

CKD = chronic kidney disease; CKD-S = CKD due to surgical removal of nephrons; CKD-M/S = CKD due to medical and surgical causes; GFR = glomerular filtration rate.

[a] Adjusted for age, gender, race, hypertension, diabetes mellitus, and cardiac disease.

Lane B et al. Eur Urol 2015; 68: 996-1003.

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Nephron Sparing or Partial Nx

- **Excision vs Enucleation**
  - Enucleation associated with renal preservation by volume
  - No consistent functional benefit
- **Cold vs Warm ischemia**
  - Literature mixed
  - Consider cold ischemia IF:
    - Solitary kidney
    - Complex Mass/Prolonged Ischemia anticipated

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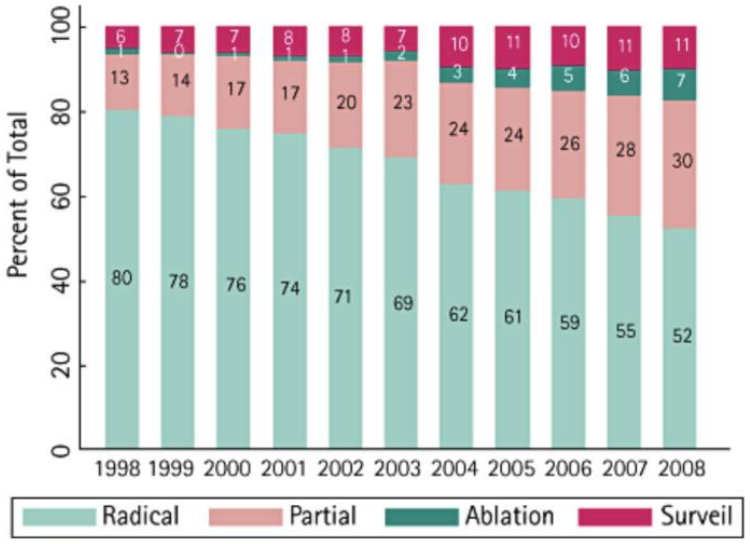
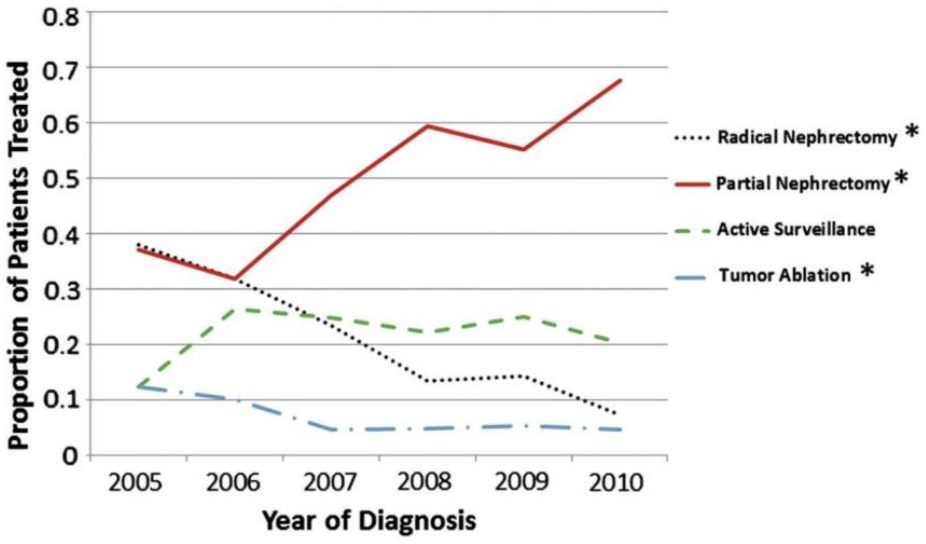
Management Trends





- ↓RN, ↑ PN
- ? Underutilization of AS

Yang et al. BJUi 2012.
Smaldone et al. Urology 2013.

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Management of Renal Masses and Localized Renal Cancer: Systematic Review and Meta-Analysis

Phillip M. Pierorazio, Michael H. Johnson, Hiten D. Patel,* Stephen M. Sozio, Ritu Sharma, Emmanuel Iyoha, Eric B. Bass and Mohamad E. Allaf

5-year outcomes	Radical Nephrectomy	Partial Nephrectomy	Thermal Ablation	Active Surveillance
Cancer-specific survival	**95.5-99%** (IQR 91-100%)	**97.8-100%** (IQR 94.4-100%)	**95.4-96%** (IQR 92-98%)	**98-100%** FU 12-36 months

Pierorazio PM et al. J Urol 2016; 196(4): 989-999.

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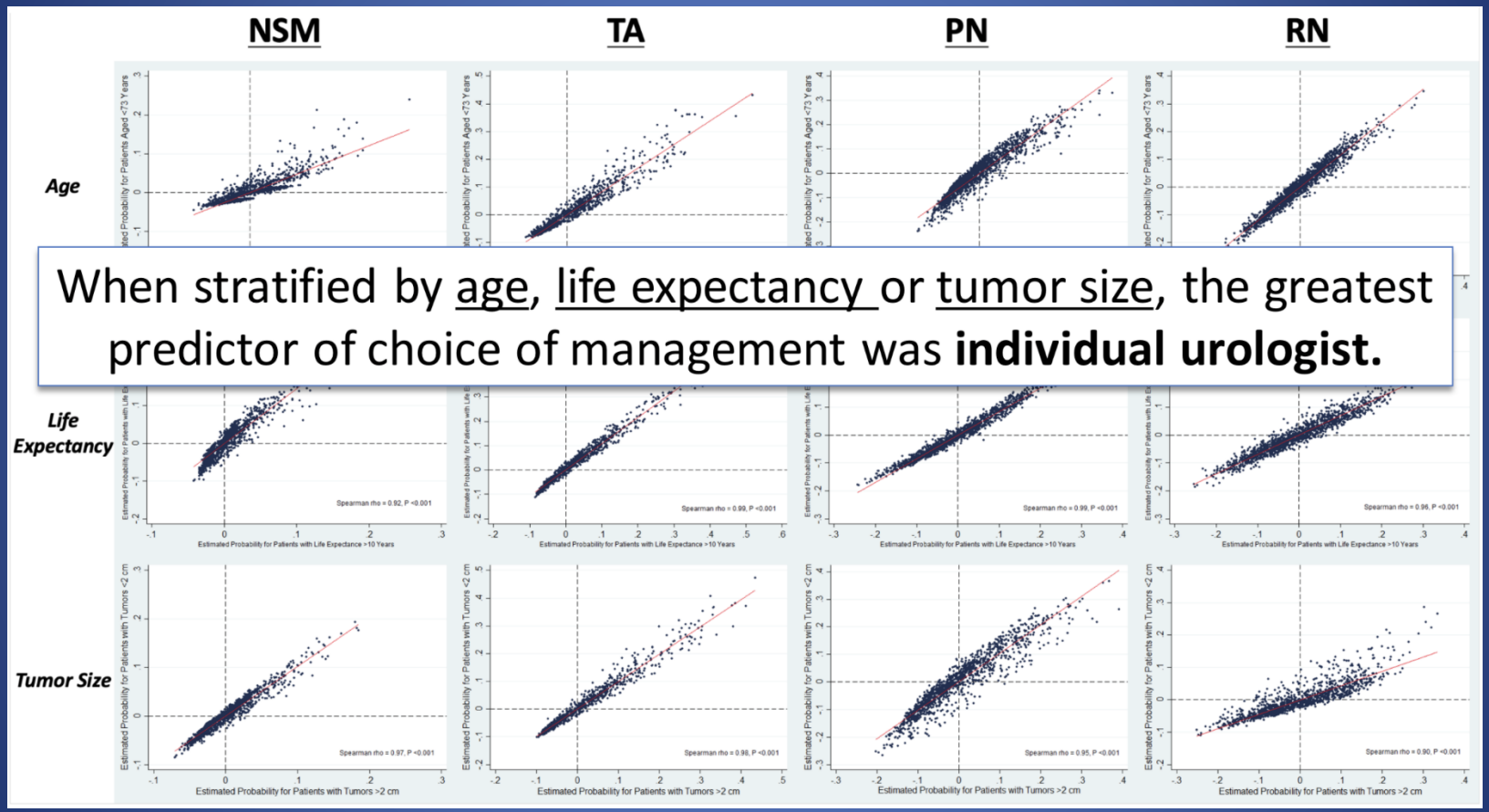
Management Drivers



When stratified by age, life expectancy or tumor size, the greatest predictor of choice of management was **individual urologist.**

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What Do We Do?

Preferences

- **Biases**

Patient health

Tumor characteristics

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Active Surveillance

- DISSRM: (Delayed intervention and surveillance for small renal masses)
- RCCC (Renal cell carcinoma consortium of Canada)
- FCCC AS cohort

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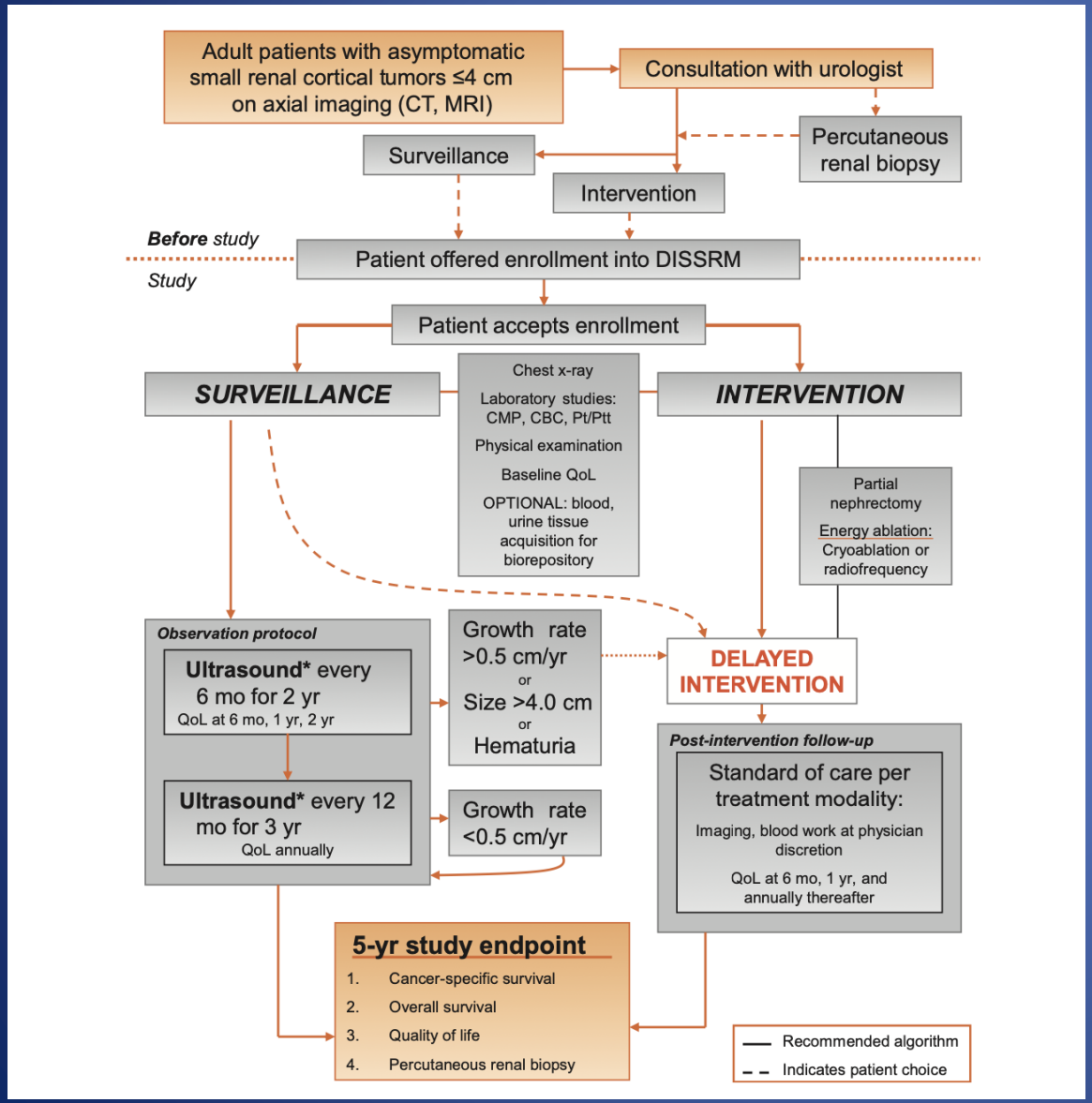
DISSRM



Pierorazio P et al. Eur Urol 2015; 68: 408-415.

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DISSRM

Table 1 – Definitions of progression and recurrence for the active surveillance and intervention cohorts, respectively

Parameter	Patients
Progression (active surveillance patients only; $n = 36$, 49 events) [a]	
Growth rate >0.5 cm/yr	34
Greatest tumor diameter >4.0 cm	2
Development of distant metastases	0
Crossover to delayed intervention	21
Recurrence (intervention patients only; $n = 11$)	
Local: at the resection site for partial nephrectomy	0
Metachronous: a new lesion within either kidney at a site distant to the original tumor	5
Distant: recurrence outside the kidney	2
Persistence: persistent enhancement following ablative treatment	2

[a] A patient can experience multiple progressions while on active surveillance. For instance, a single patient may progress by growth rate, exceed a tumor diameter of 4 cm, and undergo delayed intervention at a single time point. Alternatively, a patient's tumor may grow at >0.5 cm/yr on three separate occasions and also be considered as having three events during follow-up.

- 21 crossover patients
  - 15 "elective"
  - 6 had GR > 0.5cm/yr or GTD > 4cm
- 5 yr CSS:
  - AS 100%
  - PI 99%
- 5 yr OS:
  - AS 75%
  - PI 92%

Pierorazio P et al. Eur Urol 2015; 68: 408-415.

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BIOPSY

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BIOPSY

- Suspect:
  - Hematologic
  - Metastatic
  - Inflammatory
  - Infectious
- ”Utility based approach”
- When Ablation pursued

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Biopsy: Accuracy

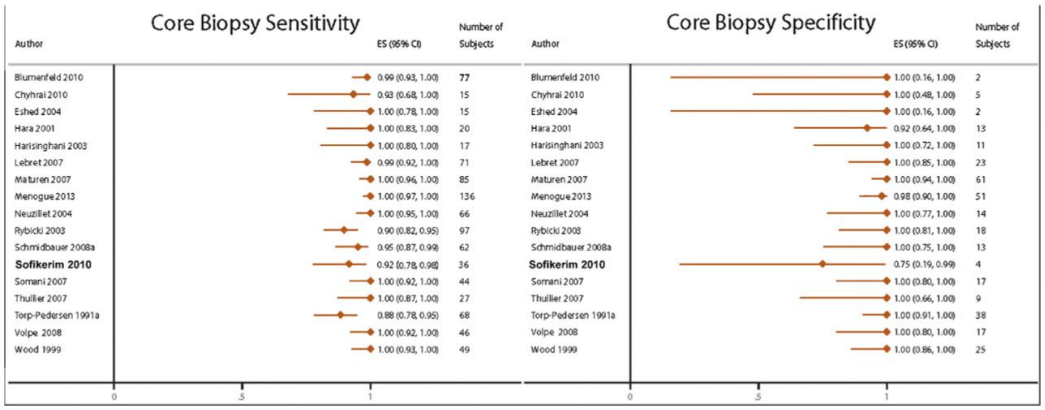
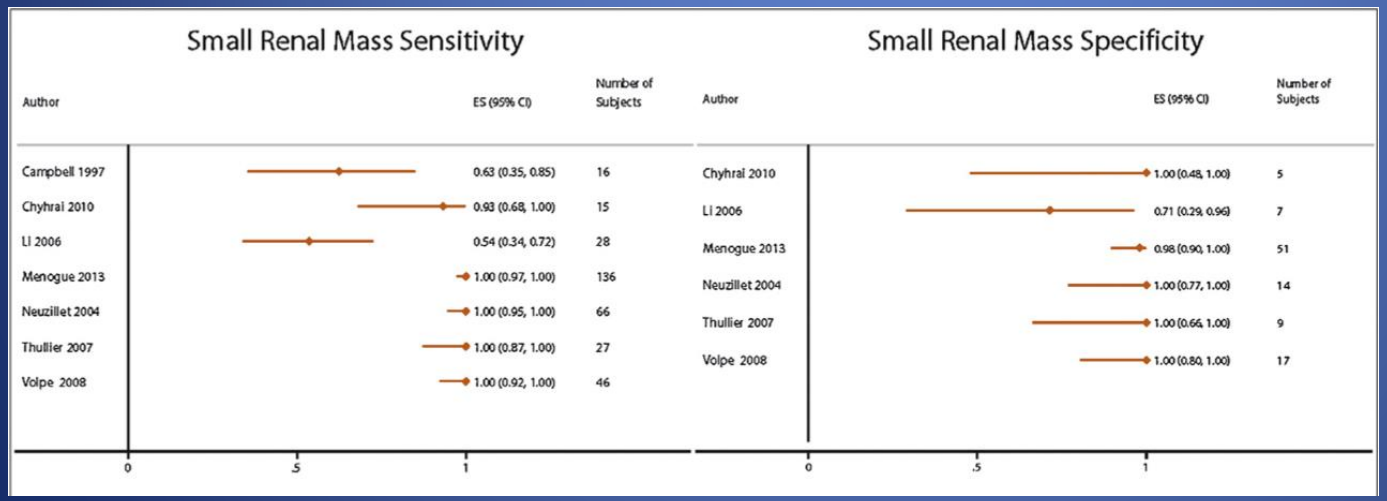


Fig. 3 – Forest plot of estimates of sensitivity and specificity of percutaneous core biopsy for the diagnosis of tumour malignancy (univariate analysis). CI = confidence interval; ES = estimate.

TAKE AWAYS:

1. Median diagnostic rate = 92%
2. Core biopsy > FNA
3. Sens: 99.1%, Spec: 99.7%
4. Histology agreement: good (k=0.683)
5. Fuhrman grade agreement: fair (k=0.34)
6. Complication >CG 2 n=3



Marconi L et al. Eur Urol 2016; 69(4): 660-673.

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Biopsy: Non-Diagnostic Rate

- More common in:
  - FNA (32%) vs Core biopsy (22%)
  - Cystic (25%) vs Solid (10.4%)
  - Skin to tumor distance >13cm (26.9%)
  - Tumor size < 2cm

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Looking Ahead

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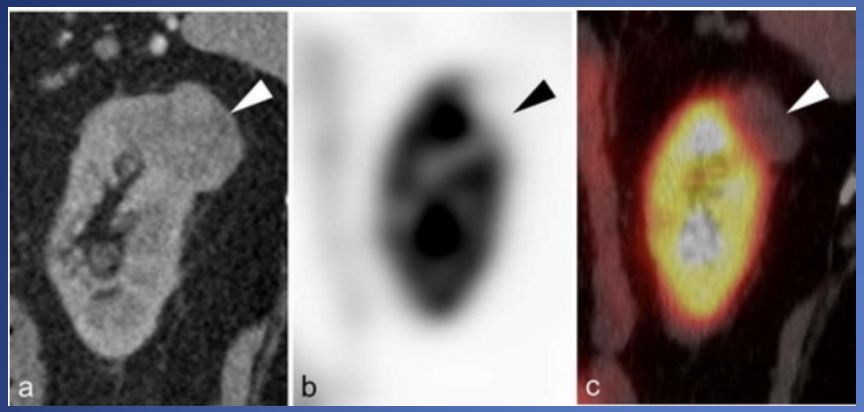
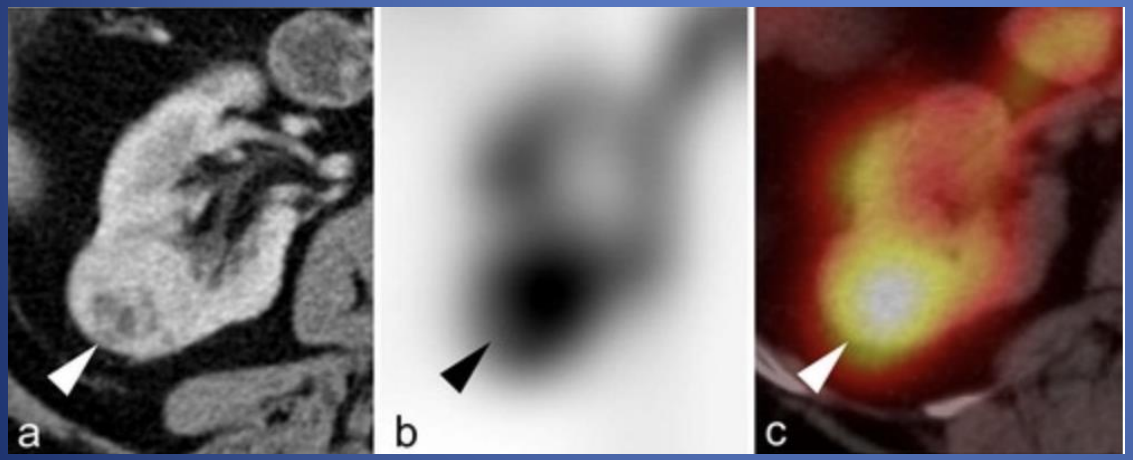
^{99m}Tc-sestamibi SPECT/CT for the characterization of renal masses: a pictorial guide

Scott P Campbell, Antonios Tzortzakakis, Mehrbod S Javadi, Mattias Karlsson, Lilja B Solnes, Rimma Axelsson, Mohamad E Allaf, Michael A Gorin and Steven P Rowe



"COLD LESION"
CONFIRMED CLEAR CELL RCC



"HOT LESION"
CONFIRMED ONCOCYTOMA

Br J Radiol 2018; 91: 1084.

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Diagnostic accuracy of 99mTc-sestamibi SPECT/CT for detecting renal oncocytomas and other benign renal lesions: a systematic review and meta-analysis

Mitchell P. Wilson[1] · Prayash Katlariwala[1] · Mohammad H. Murad[2] · Jonathan Abele[1] · Matthew D. F. McInnes[3] · Gavin Low[1]

	Sensitivity (95% CI)	Specificity (95% CI)
Oncocytoma versus other renal lesions	92% (72–98%)	88% (79–94%)
Oncocytoma versus ChrRCC	89%*	67%*
Oncocytoma-ChrRCC spectrum versus other renal lesions**	83% (66–92%)	96% (84–99%)
Benign versus malignant lesions	86% (66–95%)	90% (80–95%)

*Denotes insufficient sample size for confidence interval analysis

**Oncocytoma-ChrRCC spectrum is characterized as any of renal oncocytoma, hybrid oncocytic/chromophobe tumor, or chromophobe RCC (ChrRCC)

- Meta analysis: 4 studies, 117 renal lesions
- May help counsel on AS candidacy
- Unclear role in diagnostic algorithm

Abdom Radiol 2020; 45(8): 2532-2541.

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Contrast-Enhanced Ultrasound

- Sulphur hexafluoride microbubbles
- Eliminated via lungs and liver
- Insonated→bubbles collapse producing transient high-intensity signal

- No nephrotoxicity
- Contraindicated:
  - Known R→L shunt
  - Severe pulmonary HTN
  - Dobutamine use
  - Uncontrolled HTN

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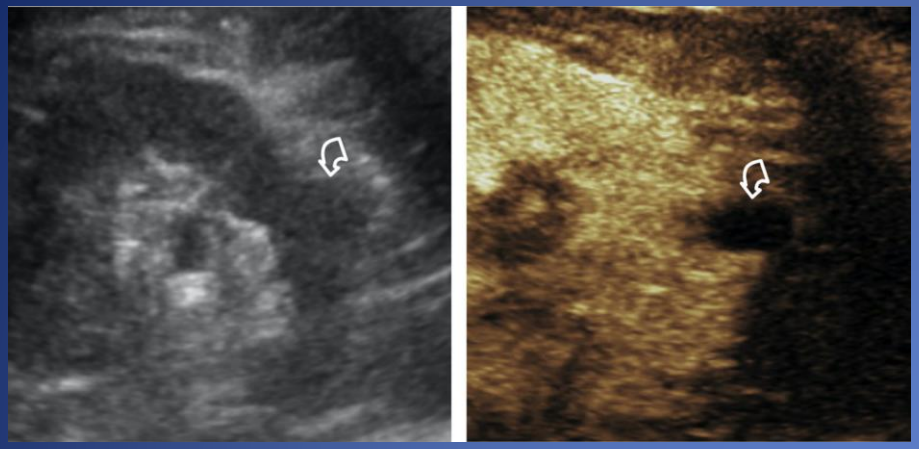
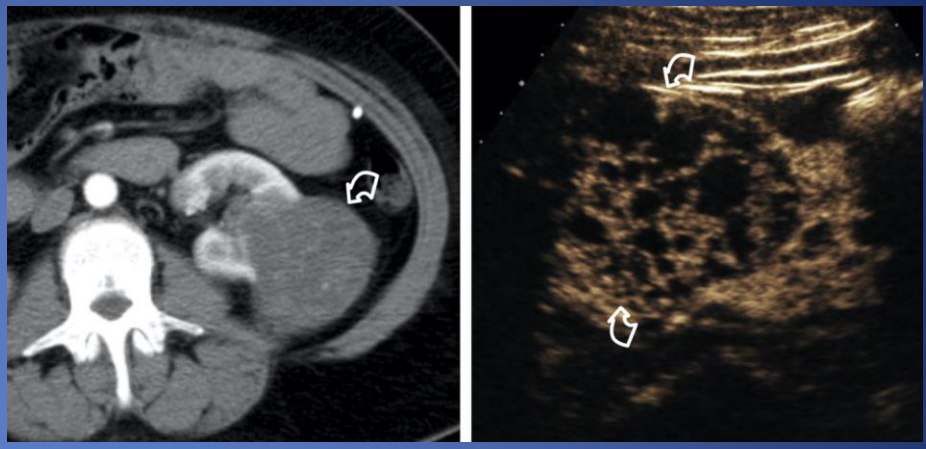
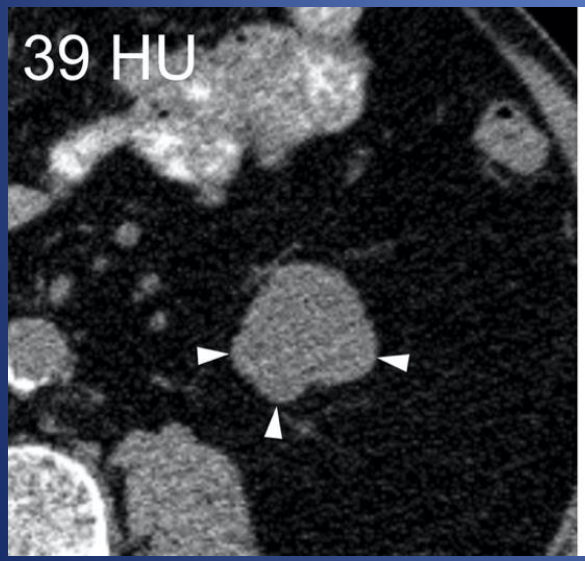
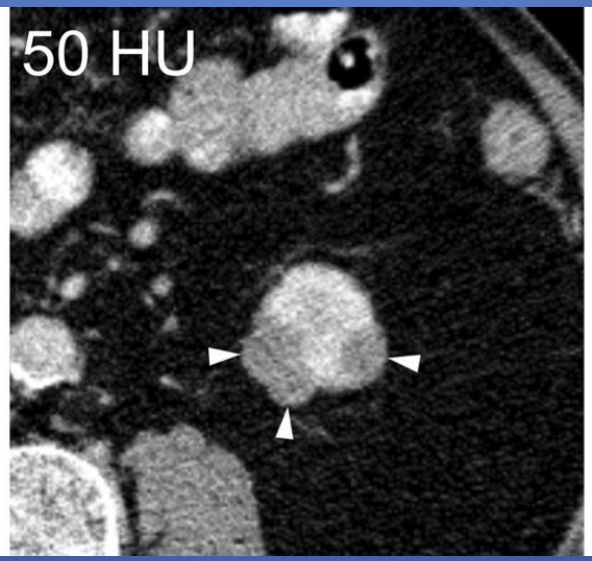
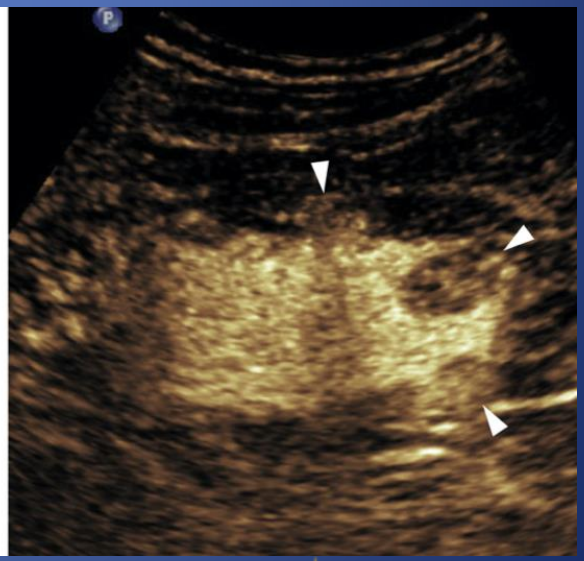
Contrast-Enhanced Ultrasound











Bertolotto M et al. Eur J Radiol 2018; 105: 41-48.

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