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The evolving role of surgery for renal cell carcinoma

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Disclosure of Conflicts of Interests

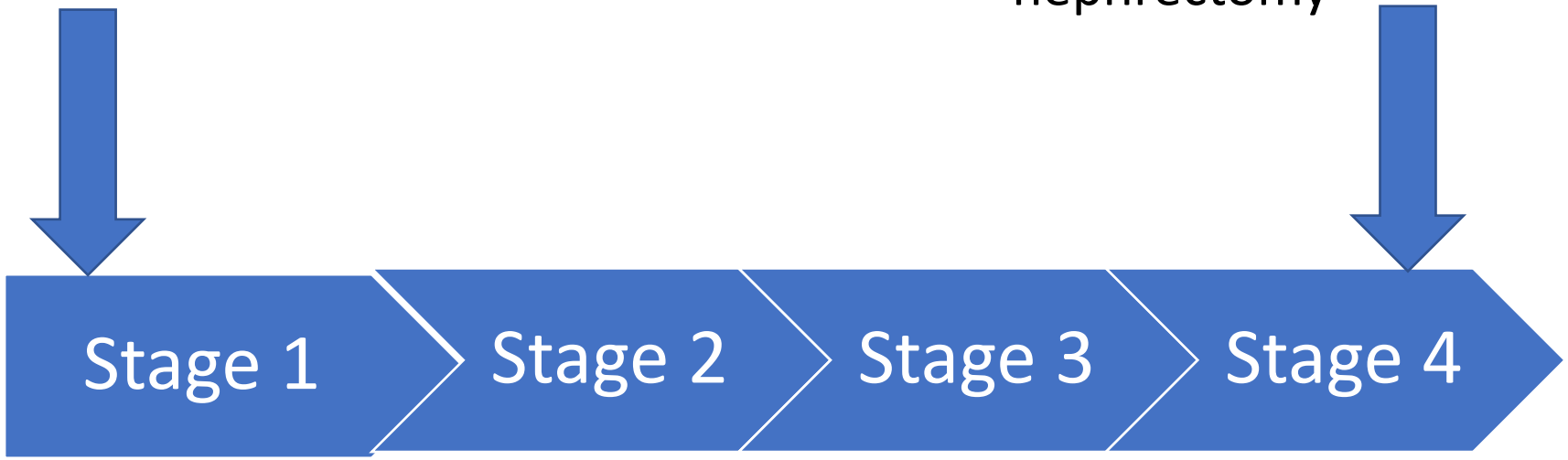
Surena F. Matin, MD, has the following financial relationships to disclose:

- Consulting
  - Merck
  - Johnson and Johnson
- Clinical trials: QED/Helsinn
- Journal editor: Elsevier

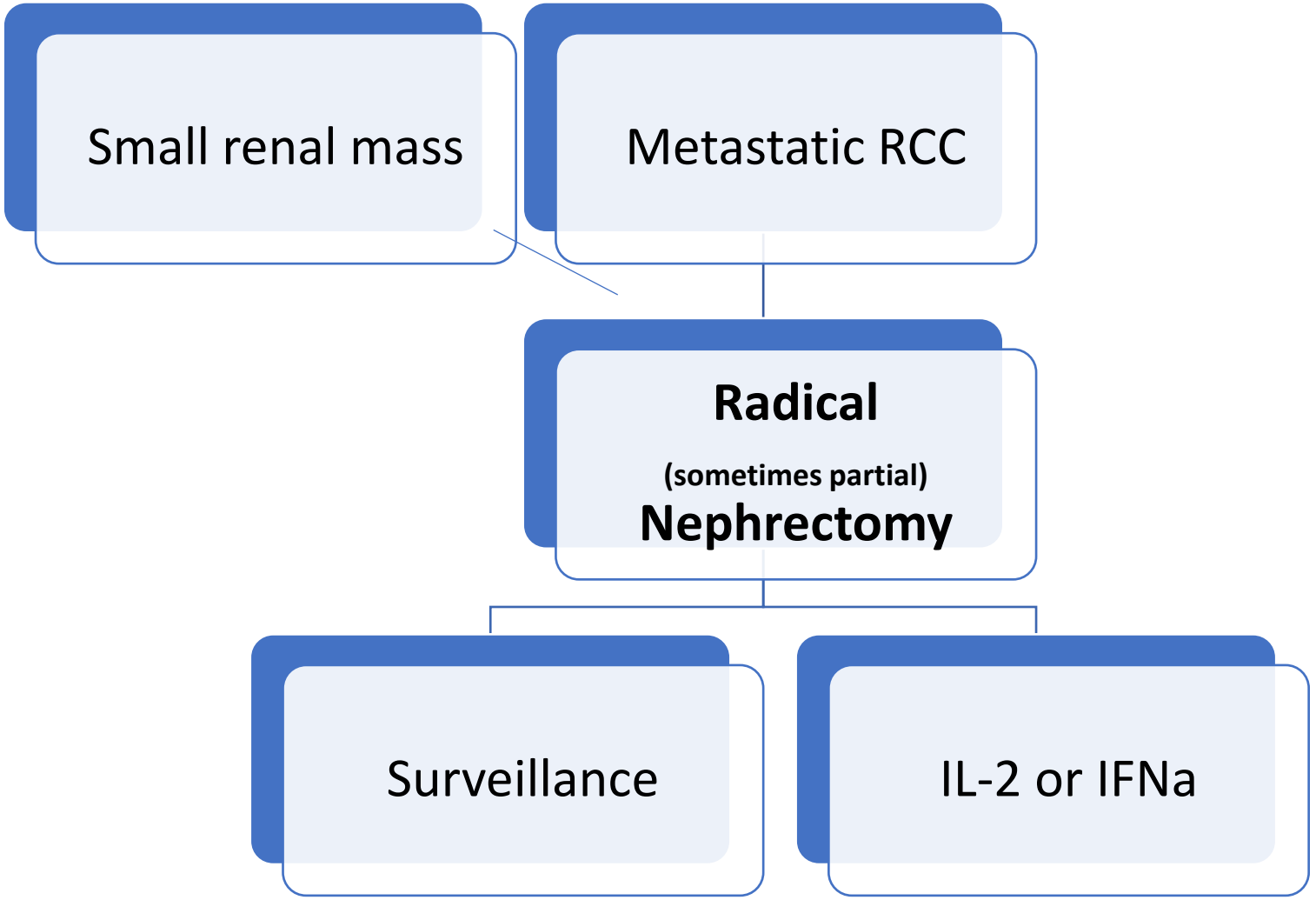
Outline: Evolving role of surgery for renal cell carcinoma (RCC)

- Historical context
- Role of kidney function
- Competing risks

- Small renal tumors/RCC
  - Role of active surveillance
- Metastatic RCC
  - Role of cytoreductive nephrectomy

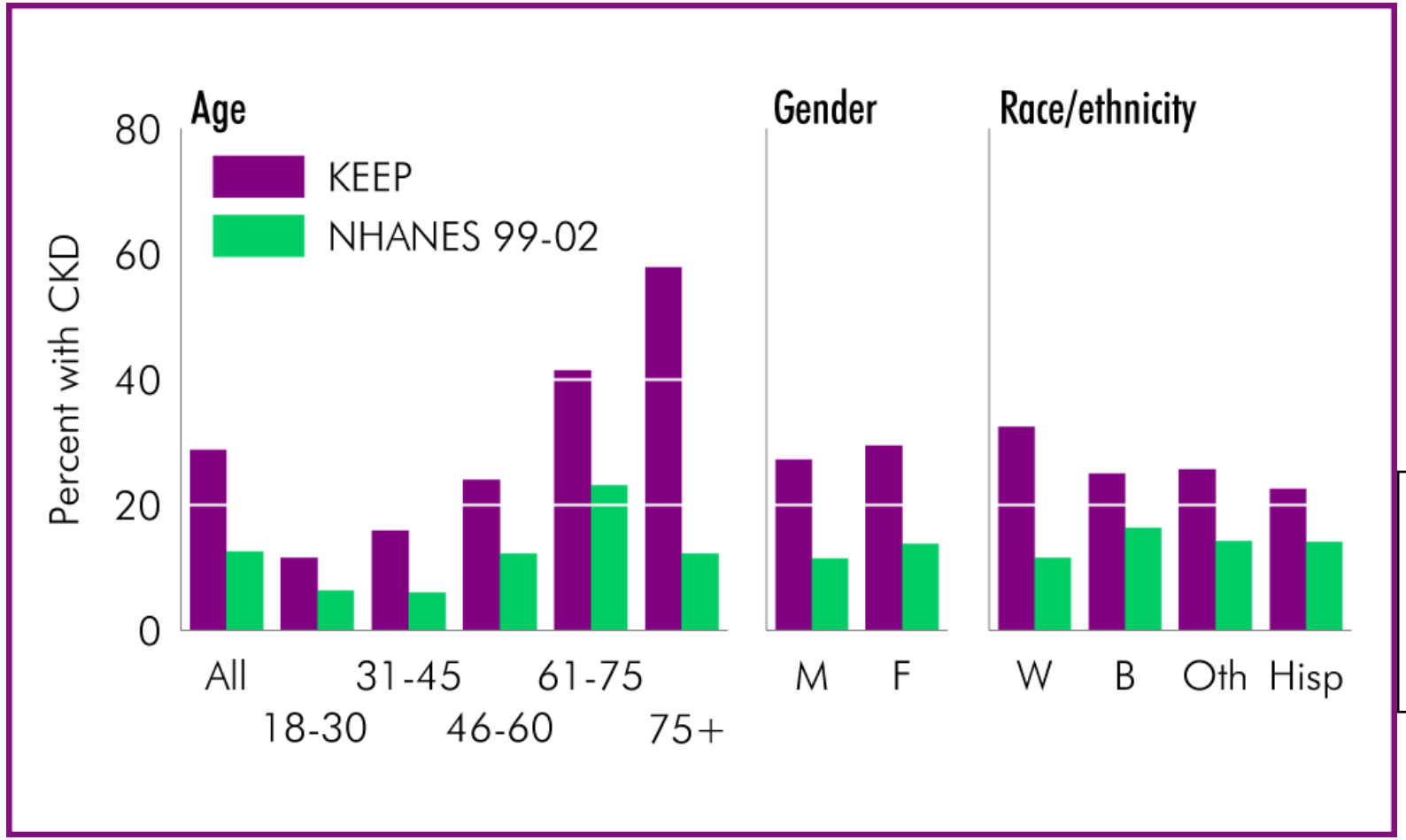


A historical context…..The state of kidney cancer treatment until early 2000s



Background: We Lose Kidney Function As We Age

-HTN, DM Accelerate That Loss-

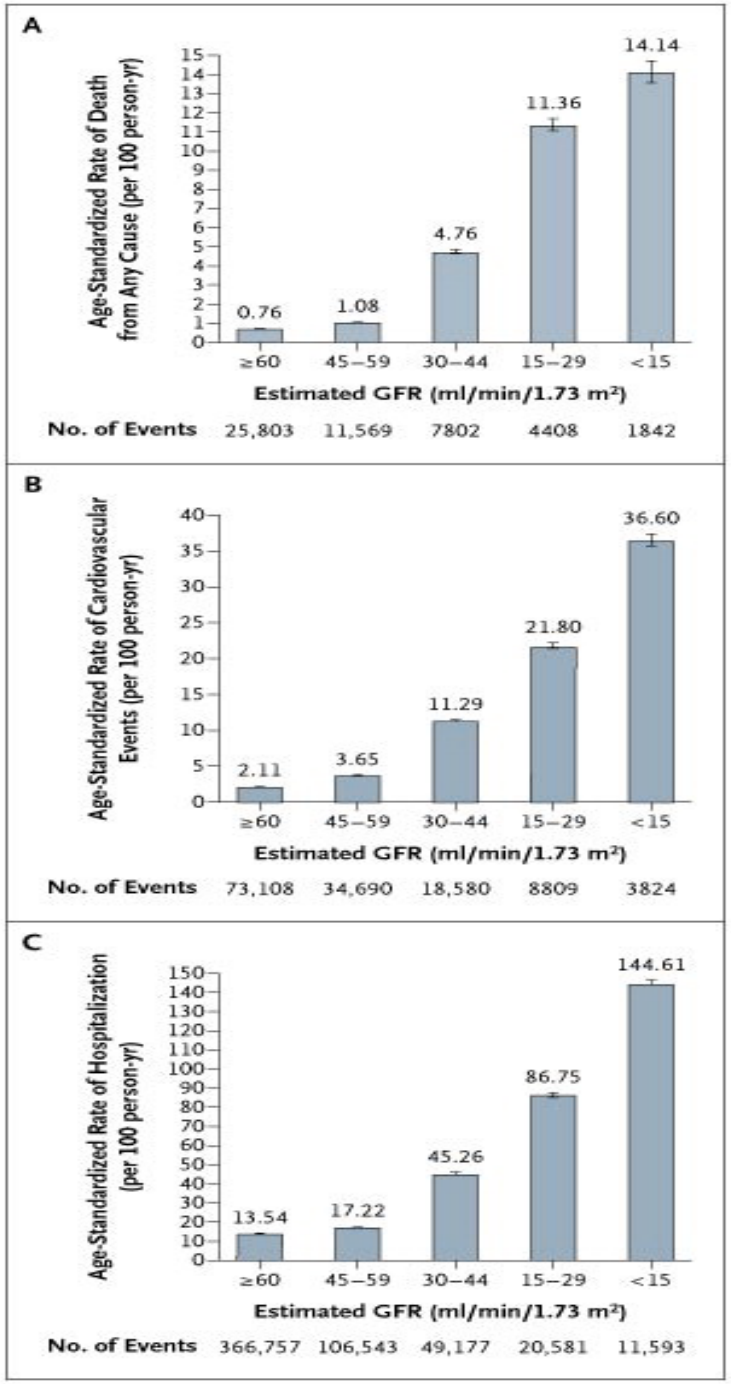


CKD Definition
If eGFR by K/DOQI MDRD <60 ml/min/1.73 m^2 or;
If eGFR by K/DOQI MDRD ≥ 60 ml/min/1.73 m^2 abnormal albumin/creatinine ratio (ACR ≥30 mg/g)

KEEP N = 45,311. NHANES N = 9,718.

KEEP Annual Data Report, 2006

National Kidney Foundation KEEP KIDNEY EARLY EVALUATION PROGRAM



Age-Standardized Rates of Death from Any Cause (Panel A),

Cardiovascular Events (Panel B), and

Hospitalization (Panel C), According to the Estimated GFR among 1,120,295 Ambulatory Adults.

CKD associated with worsening OS, CV events, and hospitalization

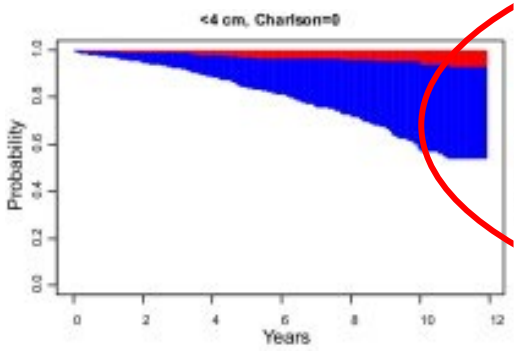
Go AS et al. N Engl J Med 2004;351:1296-1305.

Predicted competing risks of mortality by tumor size and comorbidity status

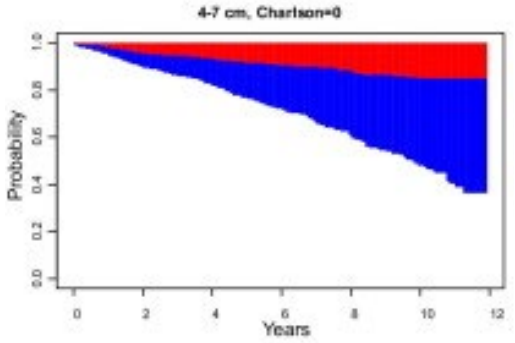
Red areas indicate probability of kidney cancer death. Blue areas indicate chance of death from another cause.

Charlson=0

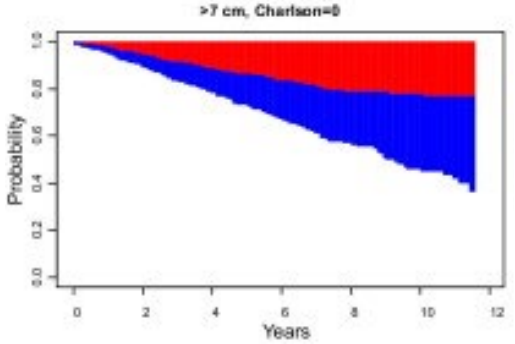
<4cm



4-7cm

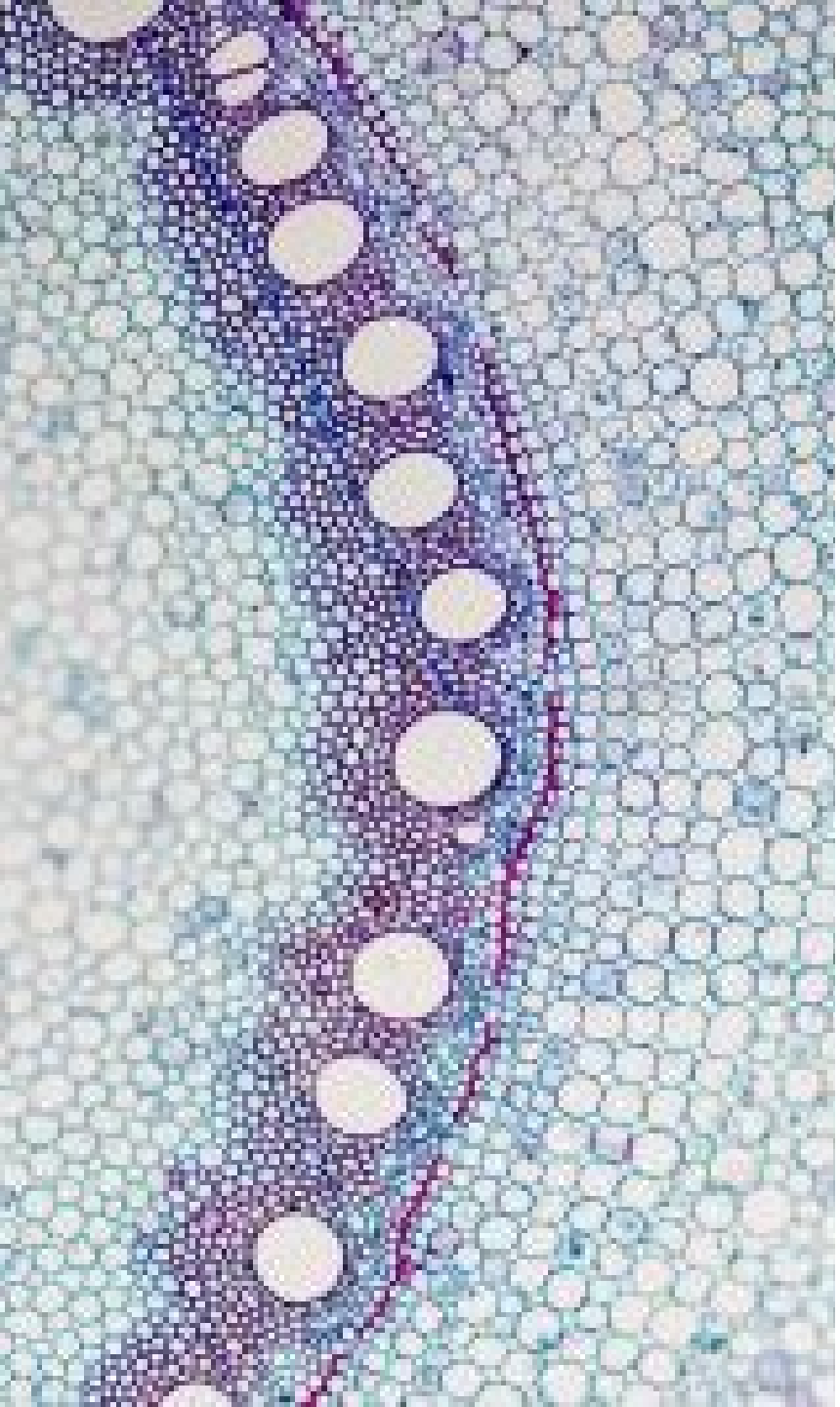


>7cm



Kutikov A J Urol 2012

Evolving role of surgery for small renal tumors



Small Renal Masses

- Solid renal cortical neoplasms <3-4cm, suspicious for cT1a RCC[1,2]

- Half of new RCC diagnoses [3,4]
- Metastatic disease
  - <1% for <3cm
  - <2% for <4cm
- 20-40% are benign
  - 5624 unnecessarily resected benign tumors/year[5]

1. Volpe, Nat Rev Urol, 2005
2. Youssif, Cur Oncol, 2009
3. Nguyen, J Urol, 2006
4. Hollingsworth, JNCI, 2006
5. Johnson, J Urol, 2015

EUO Priority Article – EUO Collaborative Review – Kidney Cancer

Role of Active Surveillance for Localized Small Renal Masses

Maria Carmen Mir[a,*], *Umberto Capitanio*[b,c], *Riccardo Bertolo*[d], *Idir Ouzaid*[e], *Maciej Salagierski*[f], *Maximilian Kriegmair*[g], *Alessandro Volpe*[h], *Michael A.S. Jewett*[i], *Alexander Kutikov*[j], *Phillip M. Pierorazio*[k],

on behalf of the Young Academic Urologists Kidney Cancer working group of the European Urological Association

- 28 studies
  - Clinically localized renal mass: cT1 or cT2 (16)
  - cT1a only (10)
  - cT1b-cT2 only (2)
- Primary outcome: 2 & 5 year OS
- Secondary outcome: 2&5 year CSS, growth kinetics, delayed intervention rate, progression to metastatic disease

Linear Growth Rate, Intervention, Progression

CLRM: clinically localized renal mass

Subgroup	Linear Growth Rate cm/yr
CLRM	0.37 (0.15-0.7)
cT1a (<4cm)	0.22 (0.11 – 0.27)
cT1-2 (≥4cm)	0.45 (0.34-0.57)

Subgroup	Delayed Surgery Rate
CLRM	0-30%
cT1a	1-26%
cT1-2	8-17%

Subgroup	Metastatic Progression
CLRM	0-6%
cT1a	0-5%
cT1-2	0-5%

Survival Outcomes

Subgroup	Cancer Specific Mortality
Clinically localized renal mass (CLRM)	1-18%
cT1a	1%
cT1-2	0

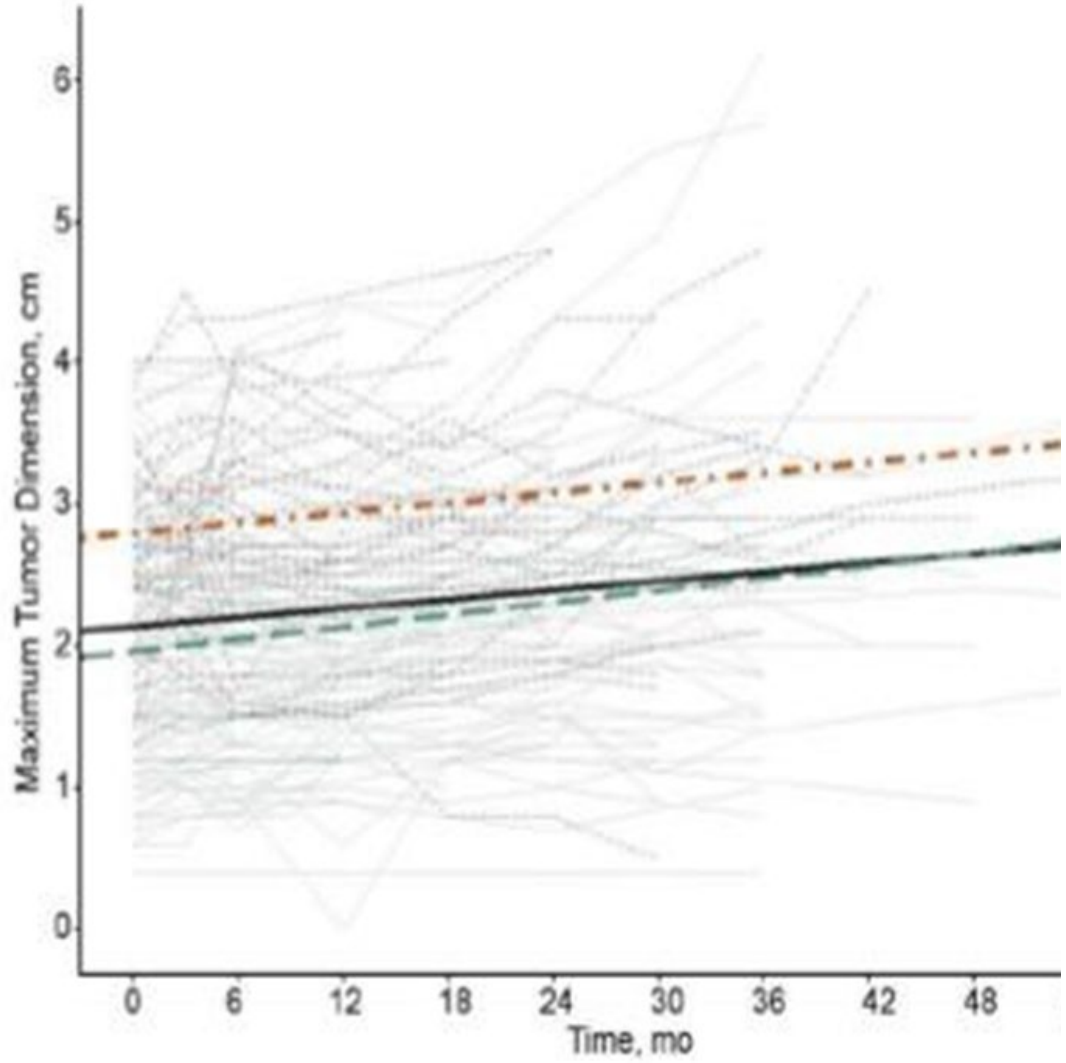
Subgroup	Other Cause Mortality
CLRM	0-45%
cT1a	1-45%
cT1-2	11-13%

Mir MC Eur Urol

Tumor Growth Rate on Active Surveillance

Growth does not differentiate benign from malignant or indolent vs aggressive RCC

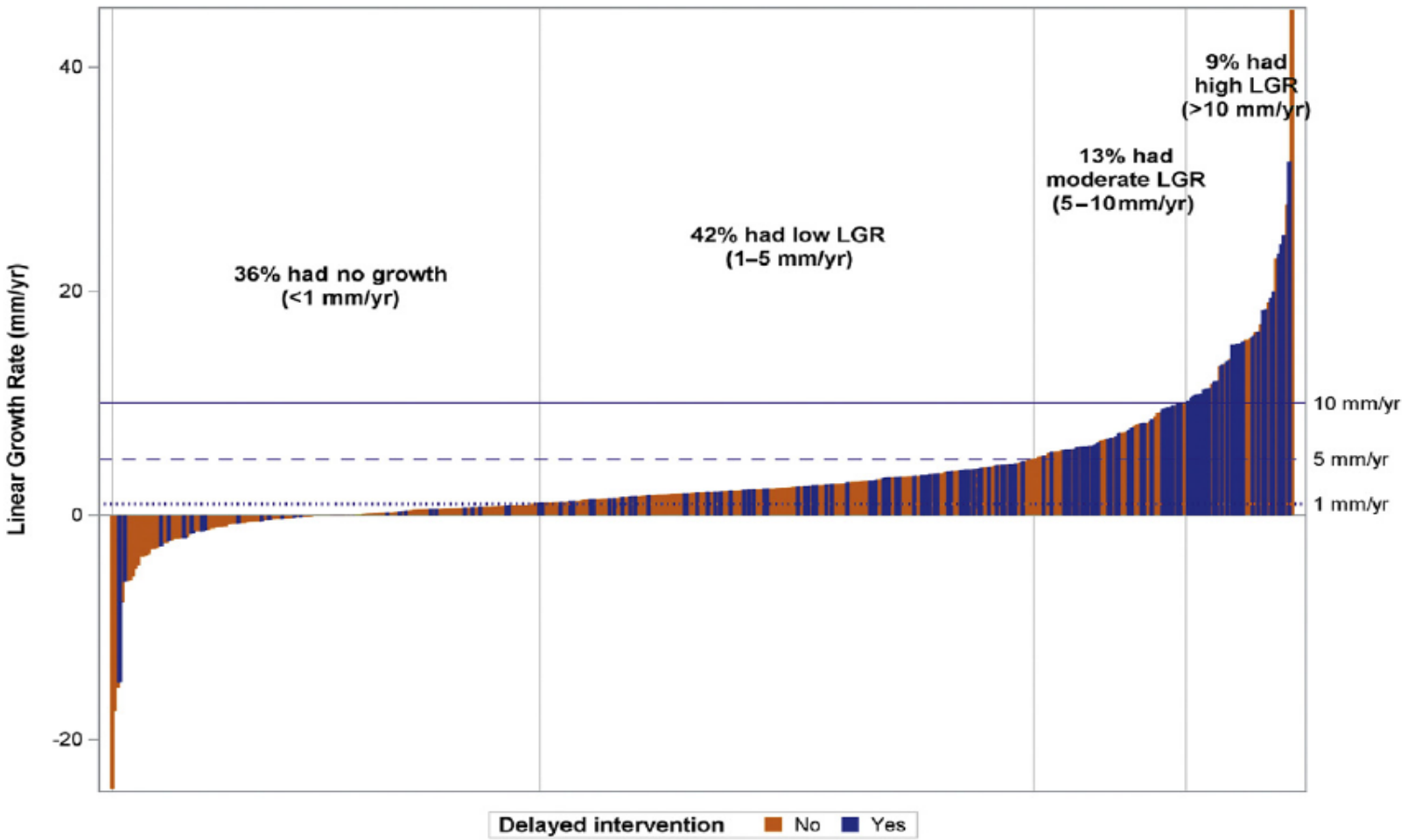
- RCC: 0.14cm/year
- Benign: 0.17cm/ year



Jewett, Eur Urol, 2011

Active Surveillance for Localized Renal Masses: Tumor Growth, Delayed Intervention Rates, and >5-yr Clinical Outcomes

Andrew G. McIntosh [a,b,*], *Benjamin T. Ristau* [b,c], *Karen Ruth* [b], *Rachel Jennings* [d], *Eric Ross* [b], *Marc C. Smaldone* [b], *David Y.T. Chen* [b], *Rosalia Viterbo* [b], *Richard E. Greenberg* [b], *Alexander Kutikov* [b], *Robert G. Uzzo* [b]



AS is not synonymous with “observation” or “watch and wait,” but instead entails a highly individualized follow-up strategy involving serial imaging evaluating growth of masses

Pierorazio, Rev. Urol, 2020

AUA Guidelines: For patients with small (especially <2 cm) solid, or Bosniak 3-4 complex cystic, masses:

- AS is an option for initial management. *(Conditional Recommendation; Evidence Level: Grade C)*
  - repeat imaging in 3-6 months
  - consider biopsy for additional risk stratification. (Expert Opinion)
- *Risk of intervention* or competing risks of death outweigh the potential oncologic *benefits* of active treatment
- AS w/ potential for delayed intervention only if the patient understands and is willing to accept the associated oncologic risk. (*Moderate Recommendation; Evidence Level: Grade C*)

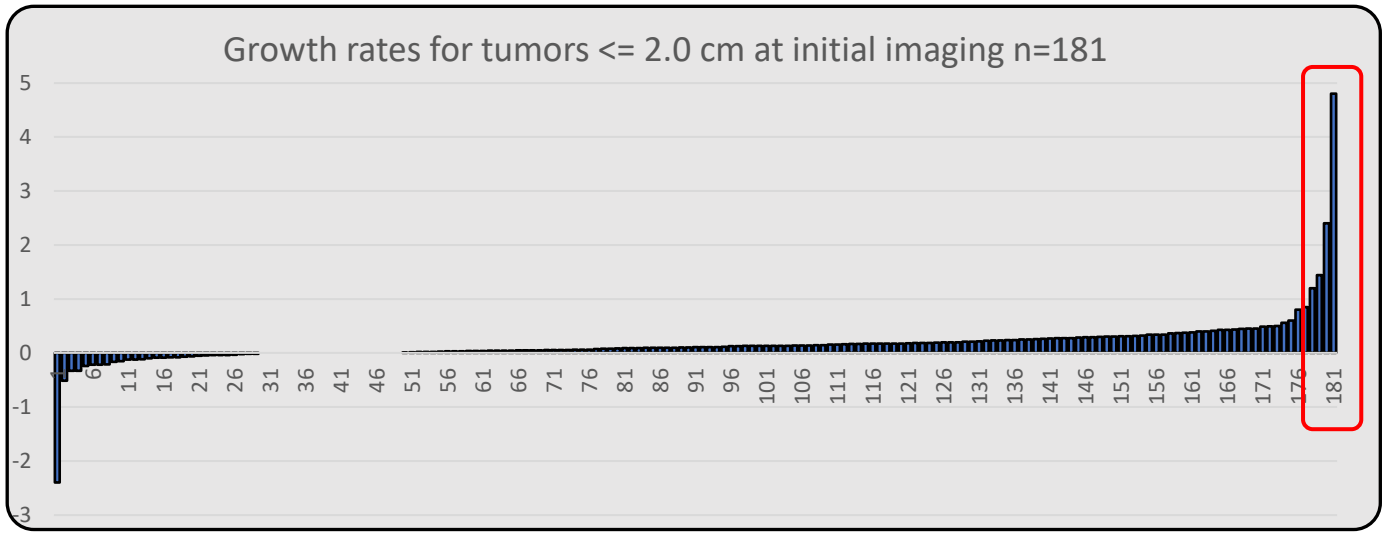
Campbell, *J. Urol*, 2017

AUA Guidelines: Selection based on patient- and tumor-related factors

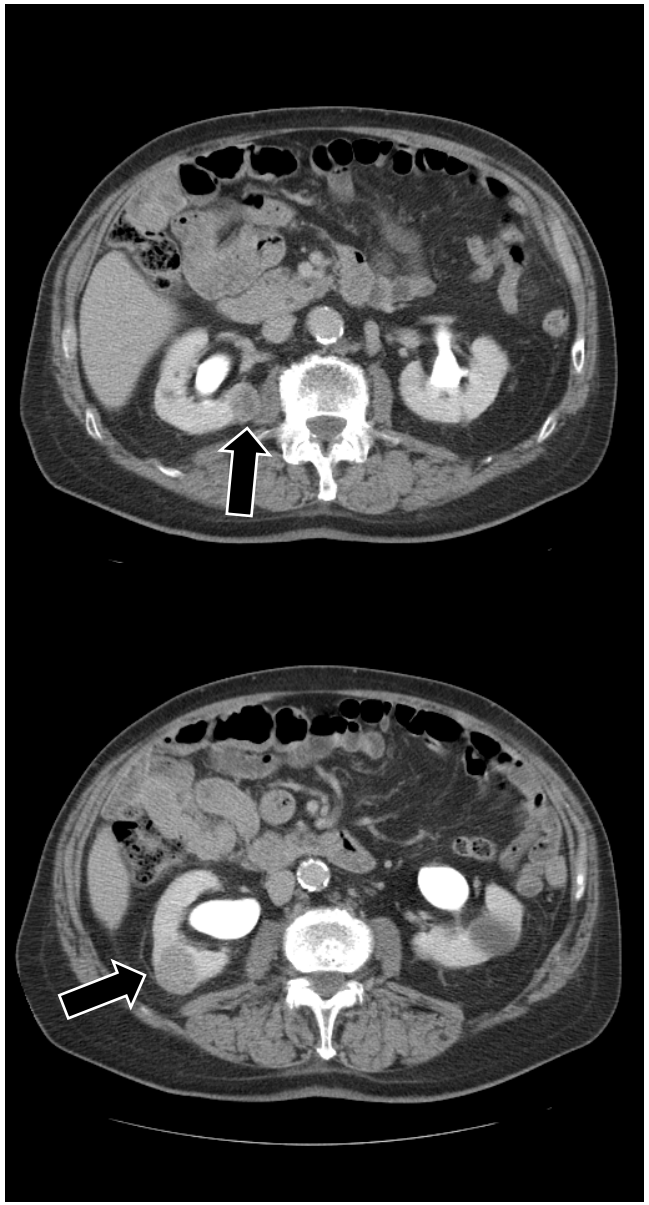
Factors Favoring AS/Expectant Management	
Patient-related	**Tumor-related**
Elderly	Tumor size <3 cm
Life expectancy <5 years	Tumor growth <5mm/year
High comorbidities	Non-infiltrative
Excessive perioperative risk	Low complexity
Frailty (poor functional status)	Favorable histology
Patient preference for AS	
Marginal renal function	

Imaging types and frequency

- **Contrast enhanced CT or MRI**
  - Renal mass protocol (WO/W contrast) is only needed one time to characterize it
  - After that can be contrast-only
- Get **1st follow up scan** within 3-4 months to make sure it is not an unusual rapidly growing tumor
  - I will skip this if patient comes in with 2 or more scans, >3mos apart, establishing indolent behavior
- **Ultrasound** alternating with CT/MR is reasonable after indolence and tumor characteristics are well-established→ CT or MRI if major change seen on US
- **Subsequent imaging** every 6 months
  - If tumor stays <2cm after 1-2 years→ annual imaging.



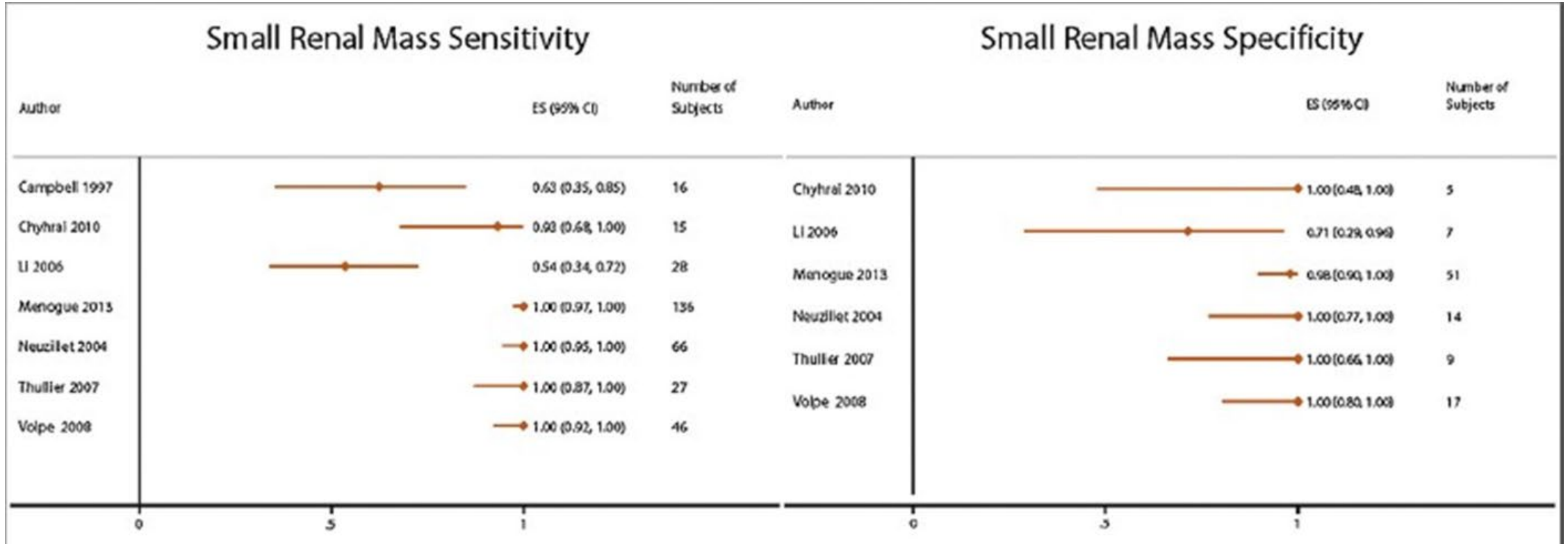
Role of biopsy



<u>83 yo referred with 2 growing renal masses</u>

- 3.1cm and 2.3cm
- CKD 3: eGFR 47
- Moderate comorbidities, well compensated
- Elects for active surveillance
- Biopsy or not?

Accuracy of Biopsy in SRM



7 studies, 334 patients

99.7% sensitivity, and 98.2% specificity

Role of renal mass biopsy

AUA Guidelines

Renal Mass Biopsy (RMB)

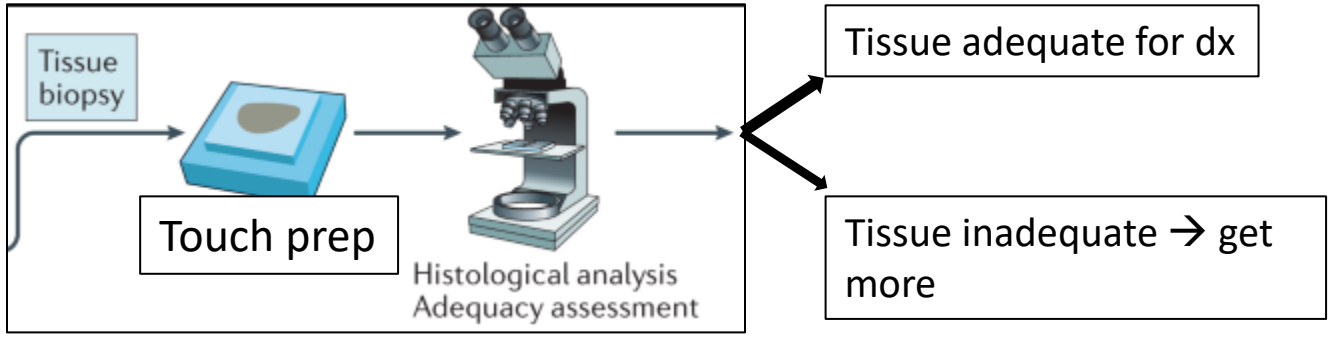
1. RMB should be considered when a mass is suspected to be hematologic, metastatic, inflammatory, or infectious.
2. RMB is not required for young/healthy patients who are not willing to accept the uncertainties associated with RMB or for older/frail patients who will be managed conservatively independent of RMB.
3. Counsel regarding rationale, positive/negative predictive values, potential risks and non-diagnostic rates of RMB.
4. Multiple core biopsies are preferred over FNA.

- Non-diagnostic rate 8-14.1% (historically was 30%)
- False positive rate <4%
- Diagnosis with Core biopsy:
  - Sensitivity: 97.5%, (CI 96.5,98.5)
  - Specificity: 96.2%, (CI 90.7-100)
- If biopsy was non-diagnostic, Repeat Biopsy led to diagnosis in 80% of patients.

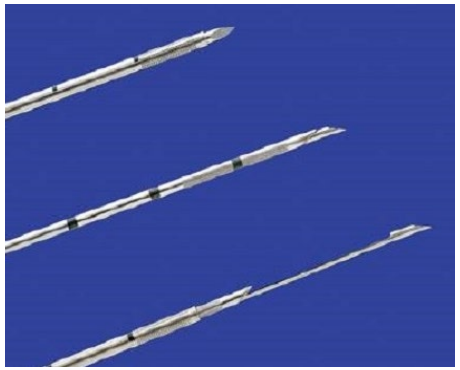
Patel HD J Urol 2016; Marconi L Eur Urol 2016

What has changed in the modern era to make biopsies better and safer?

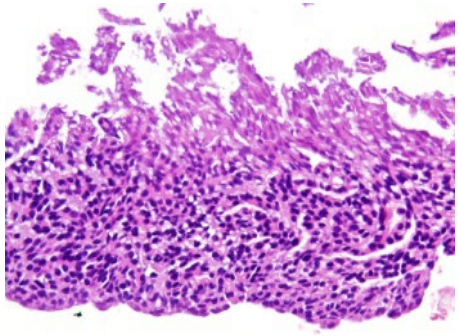
- Coaxial needles and improved techniques, image guidance
- **<u>Core biopsies + FNA</u>** >>> **Core bx** >>> FNA
- <u>Core bx enables immunohistochemical and genomic profiling</u>: improved diagnosis (CK7, CD10, S100, AMACR, CAIX, etc)
- Real-time assessment of tissue adequacy



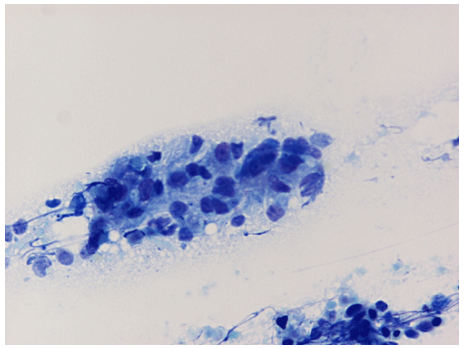
Coaxial needles



Core biopsy

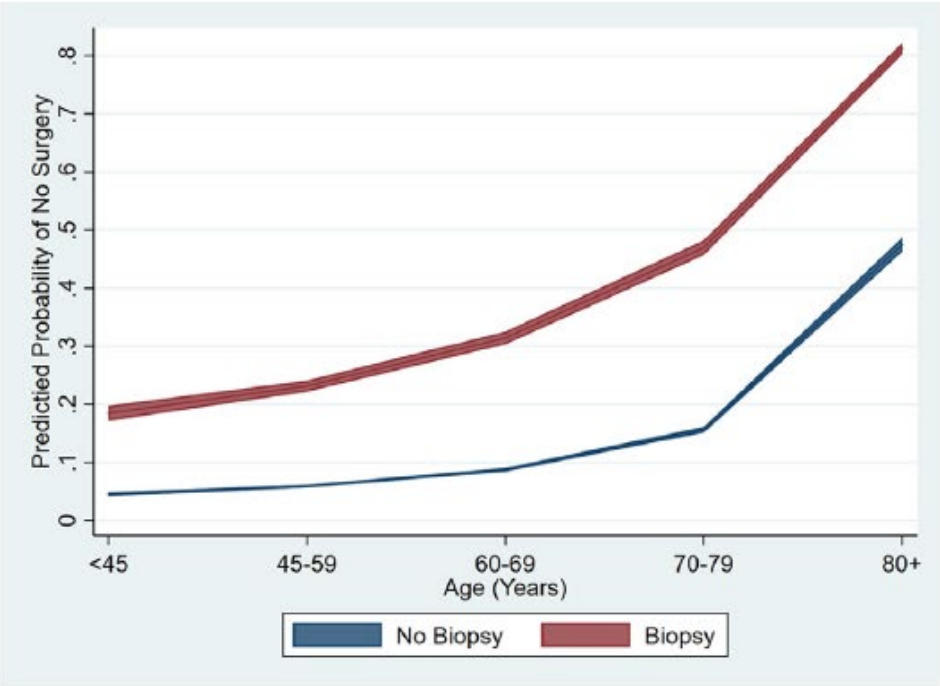


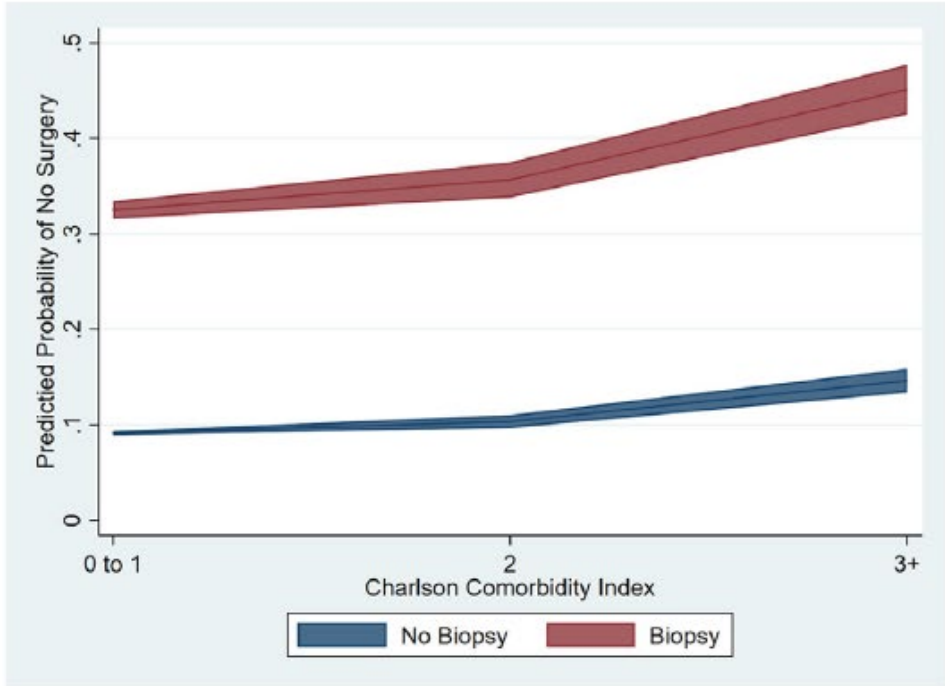
FNA



Renal Mass Biopsy is Associated with Reduction in Surgery for Early-Stage Kidney Cancer

Hiten D. Patel, Paige E. Nichols, Zhuo Tony Su, Mohit Gupta, Joseph G. Cheaib, Mohamad E. Allaf, and Phillip M. Pierorazio





Urology 2020

FNA and Biopsy was done

- FNA noncontributory;
- Core Bx: Renal oncocytic neoplasm; focally positive CD10 and cytokeratin 7 and diffusely positive for CD117. **Oncocytoma favored.**

Summary: Role of surgery in patients with a small renal mass

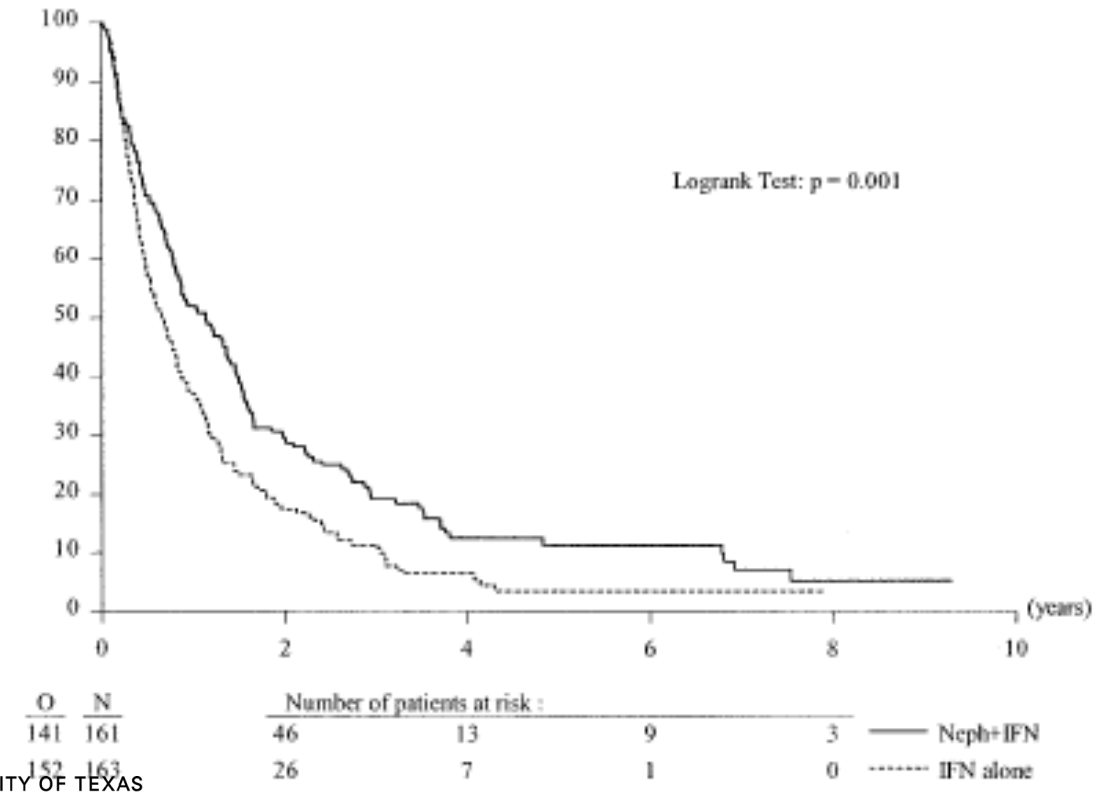
- Preponderance of data does not support aggressive or rush to surgery for most patients with SRM
- For the younger, healthier patient who may want to avoid long-term surveillance, intervention at some point in future is reasonable ("no-rush" intervention, or AS with planned delayed intervention)
- For the older or sicker patient, AS is indicated with delayed intervention only if growth >3cm. Unnecessary surgery is avoided for many of them who die of other causes.
- Biopsy is safe, diagnostic in >90%, and can be considered if it changes management or patient wants to know

Role of surgery for metastatic RCC

The evolving role of cytoreductive nephrectomy

Cytoreductive Nephrectomy in "Previous" Immunotherapy Era

Combined Results (SWOG 8949 + EORTC 30947)



Overall Survival

- Nephrectomy + IFNα → 13.6 months
- IFNα alone → 7.8 months

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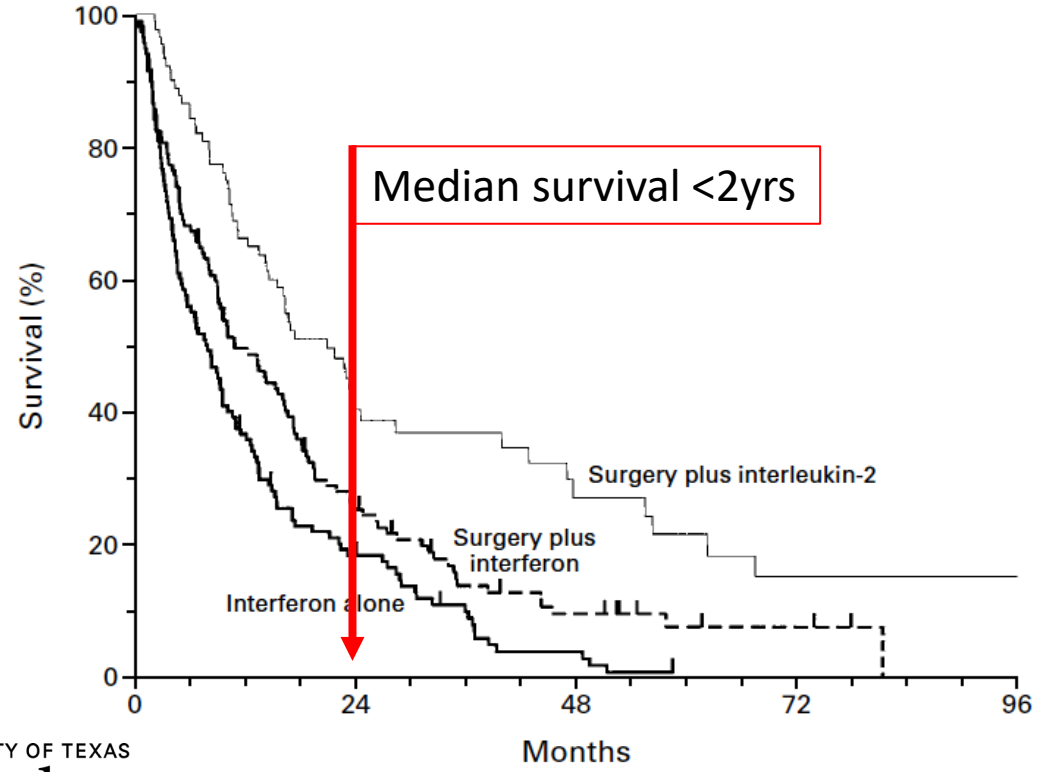
Flanigan RC. J Urol. 2004

Cytoreductive Nephrectomy in "Previous" Immunotherapy Era

Role of Cytoreductive Nephrectomy + *IL-2*



- Retrospective
- 89 patients (UCLA)
- Met criteria for SWOG 8949
- Treated with IL-2 (not IFNα)
- Overall survival → 16.7 months

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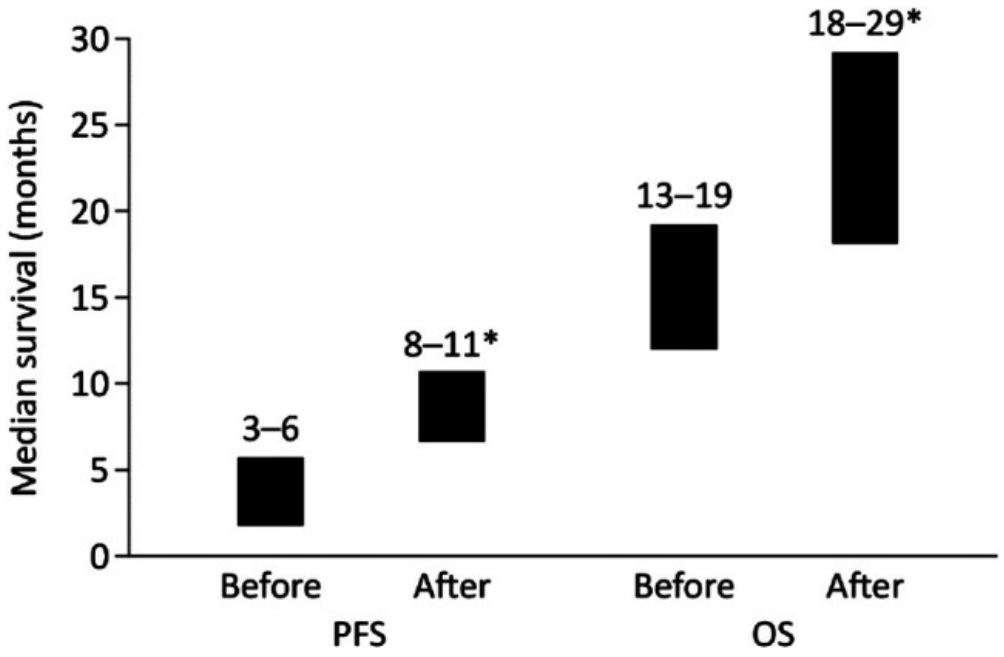
Pantuck AJ. NEJM. 2001

The era of targeted therapy created a paradigm shift in this approach

Sutent is first TKI approved in 2006

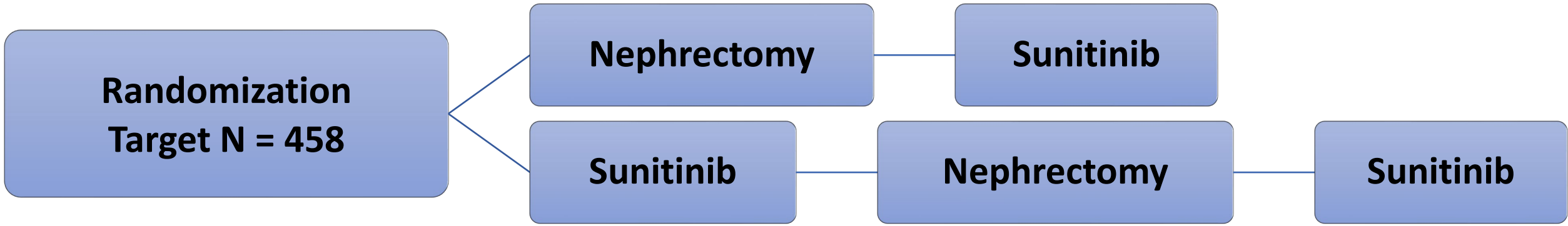
For the first time, survival for metastatic RCC extended beyond 2 years!

Initial cytoreductive nephrectomy came into question



Motzer R Oncologist 2017

SURTIME trial: Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients With Metastatic Kidney Cancer

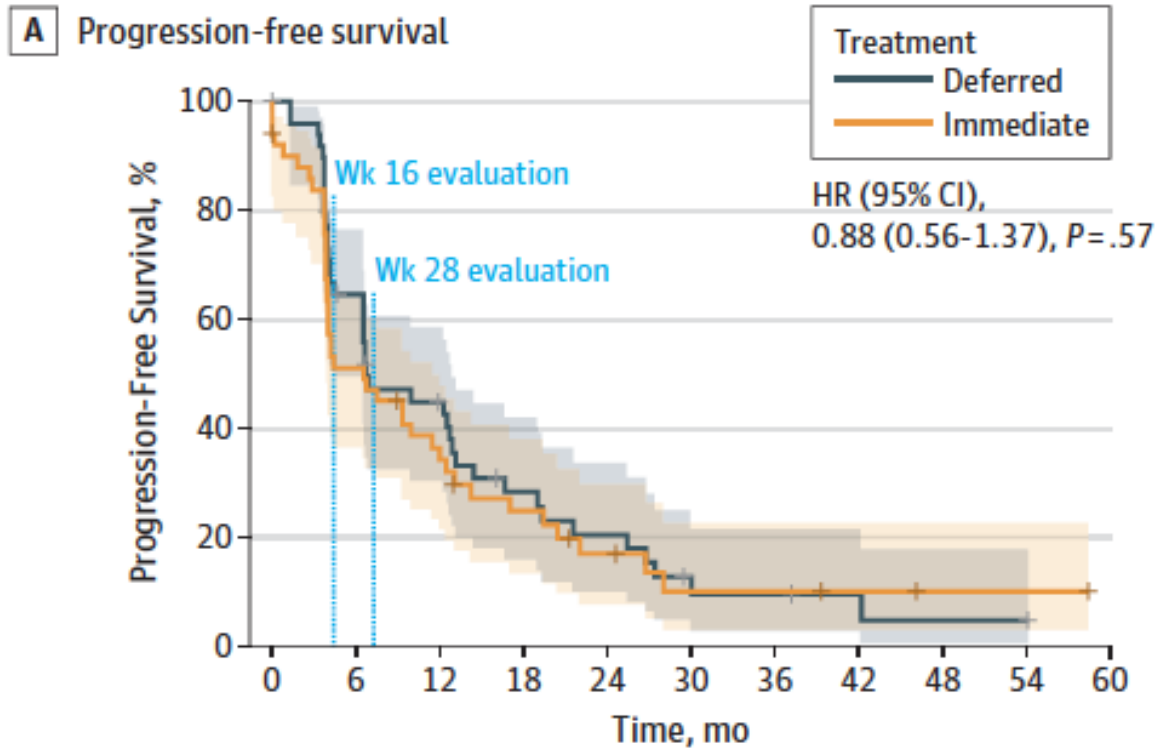


- **PI:** Dr. Axel Bex
- **Primary Endpoint:** PFS → 24-week PFR

ClinicalTrials.gov Identifier: NCT01099423

Progression-Free Survival

trial terminated early due to poor accrual

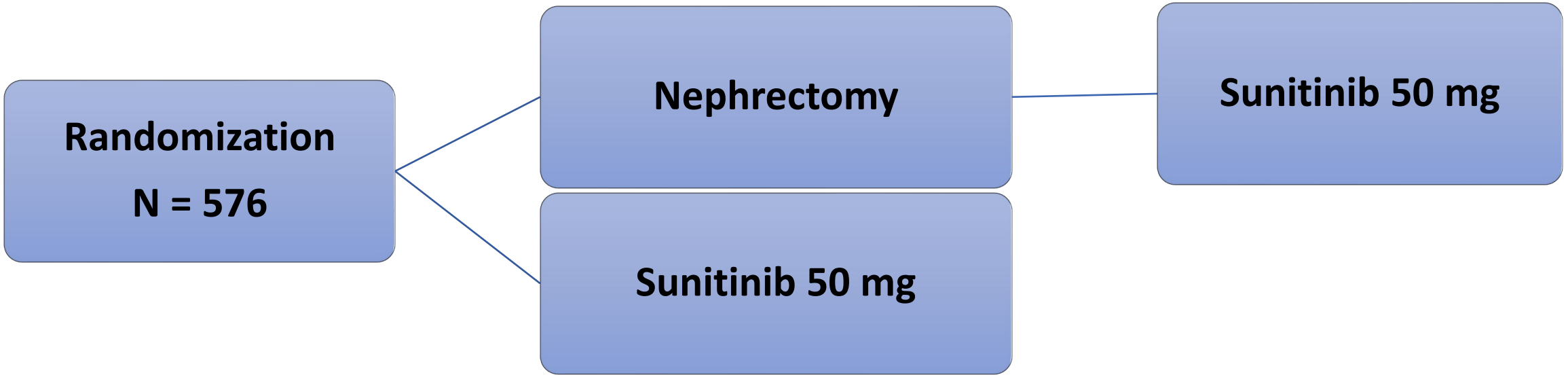


No. at risk

Treatment											
Deferred	49	30	19	11	8	3	3	2	1	1	0
Immediate	50	25	16	10	6	3	3	2	1	1	0

Bex A. JAMA Oncol. 2018

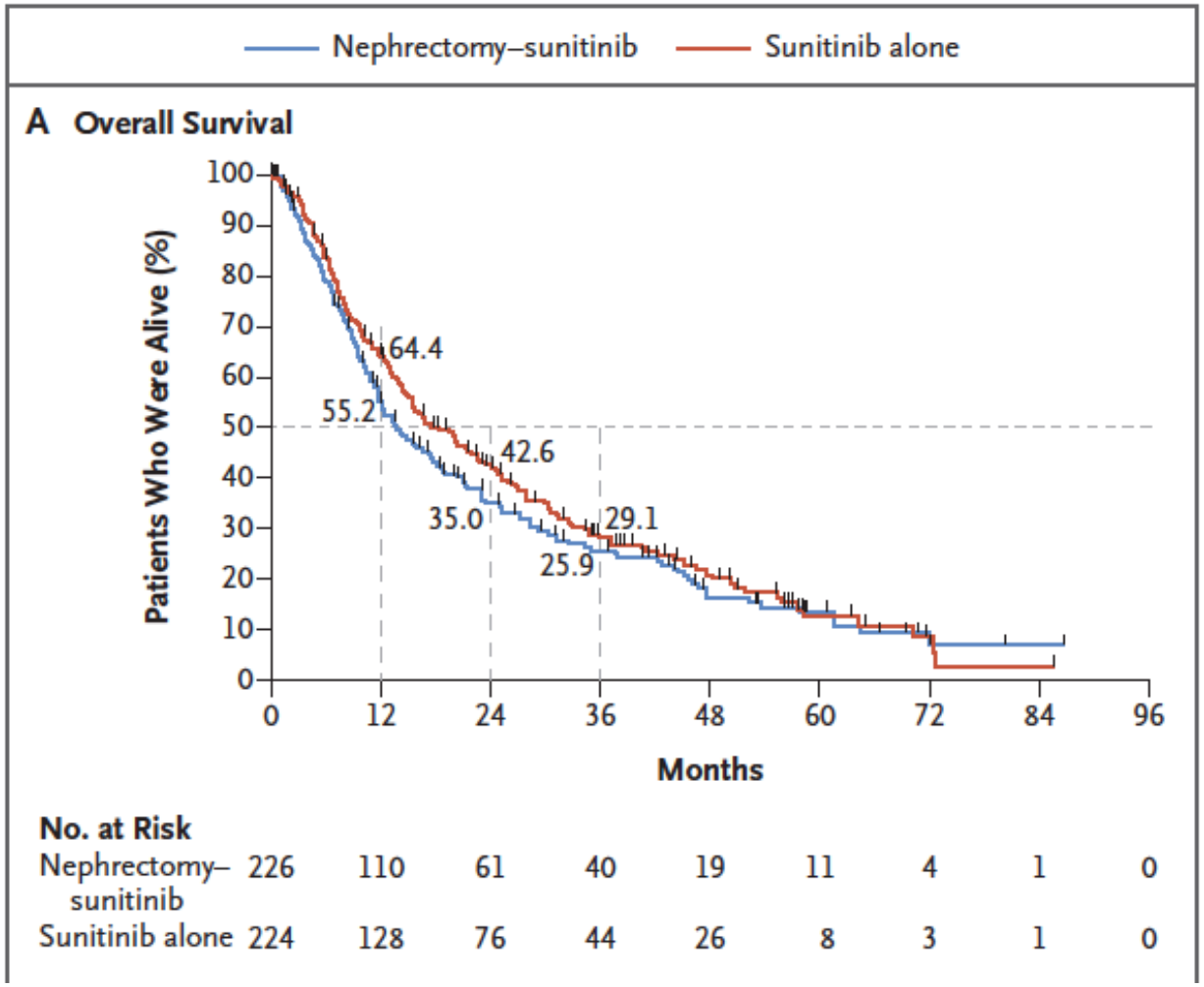
CARMENA trial: Phase 3 Randomized Study Comparing Nephrectomy plus Sunitinib versus Sunitinib without Nephrectomy in 1st line Metastatic RCC (noninferiority trial)

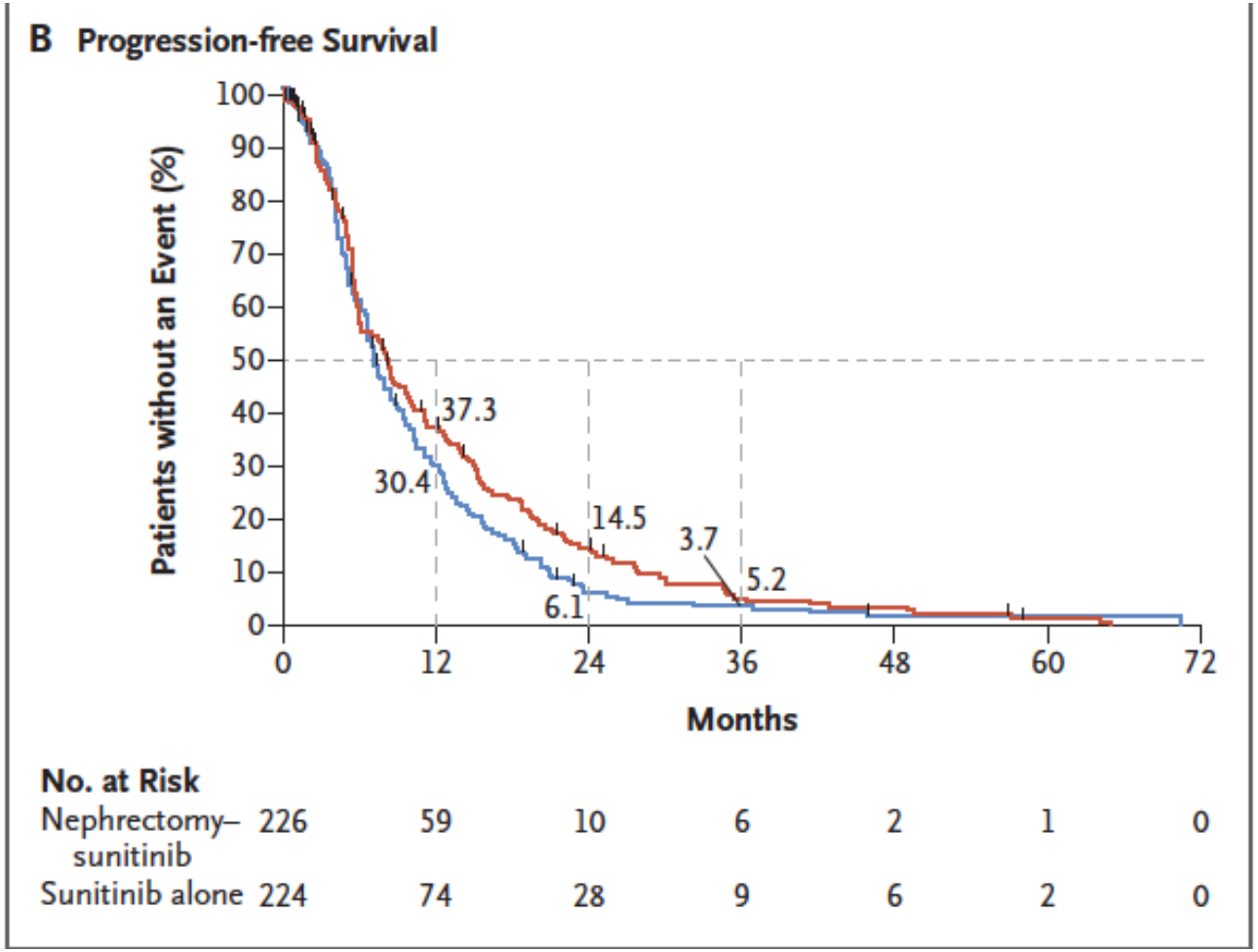


- **PI:** Dr. Arnaud Mejean
- **Primary Endpoint:** Overall Survival
- **Start Date:** September 2009

ClinicalTrials.gov Identifier: NCT00930033

CARMENA trial: Phase 3 Randomized Study Comparing Nephrectomy plus Sunitinib versus Sunitinib without Nephrectomy in 1st line Metastatic RCC





Mejean A. NEJM. 2018

CARMENA-Issues

- All patients were MSKCC intermediate or poor risk (by definition)
- Tumor bulk in enrolled patients
- Crossover between study arms
- Who are the patients who did **not** enter CARMENA?
  - 450 patients-8 years, ~80 centers !

CARMENA-*posthoc* Analysis

- Reclassified patients based on IMDC risk groups
- Analyzed patients with:
  - One metastatic site vs more than one
  - Secondary nephrectomy in arm B (sunitinib only)
- Updated median follow-up of 61.5 months
  - Number of metastatic sites is not helpful
  - Only one IMDC risk factor? → CN might be beneficial
  - **Patients with secondary nephrectomy → very long OS (median 4 years)**

IMDC: International Metastatic RCC Database Consortium

Mejean A. J Clin Oncol 37, 2019 (abstract 4508)

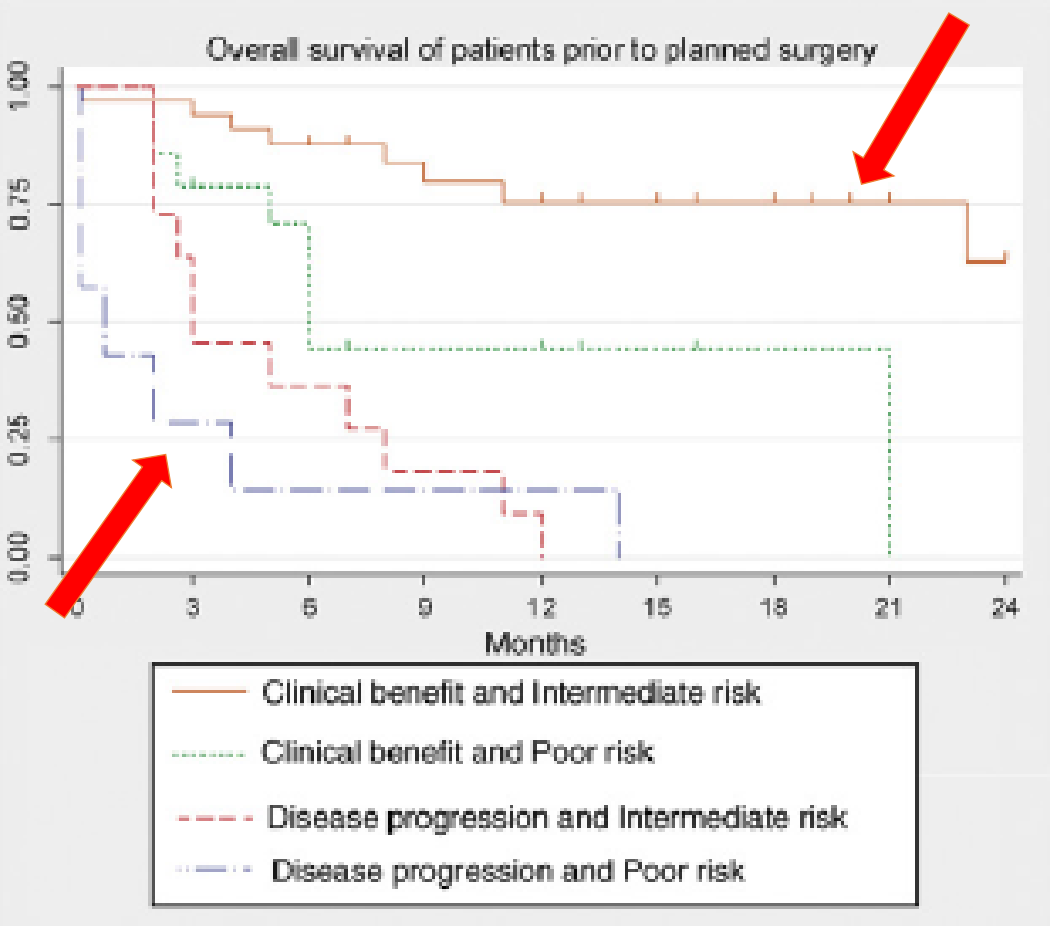
Despite its limitations, CARMENA further changed the paradigm of metastatic RCC

- Initial systemic therapy for all but the few with very favorable features
- Response to therapy determines need for delayed cytoreductive nephrectomy

The Outcome of Patients Treated with Sunitinib Prior to Planned Nephrectomy in Metastatic Clear Cell Renal Cancer

Thomas Powles[a], Christian Blank[b], Simon Chowdhury[c], Simon Horenblas[b], John Peters[d], Jonathan Shamash[a], Naveed Sarwar[a], Ekaterini Boleti[e], Anju Sahdev[a], Tim O'Brien[c], Dan Berney[a], Luis Beltran[d], Paul Nathan[f], John Haanen[b], Axel Bex[b,]*

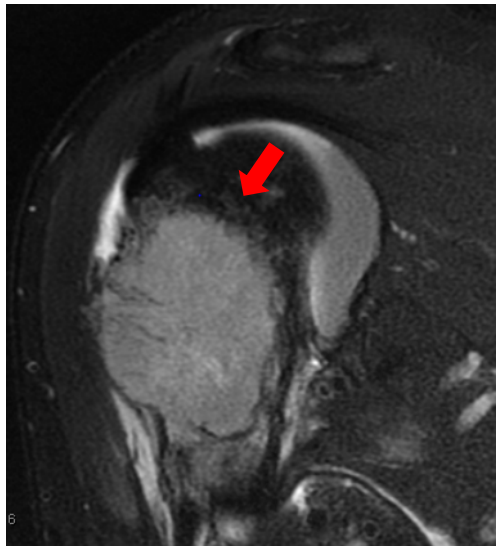
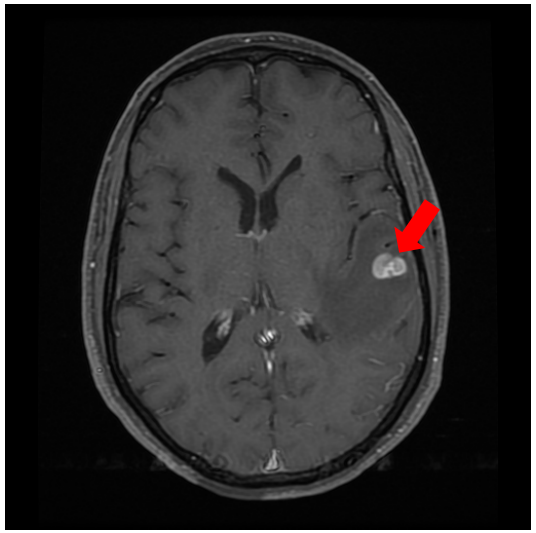
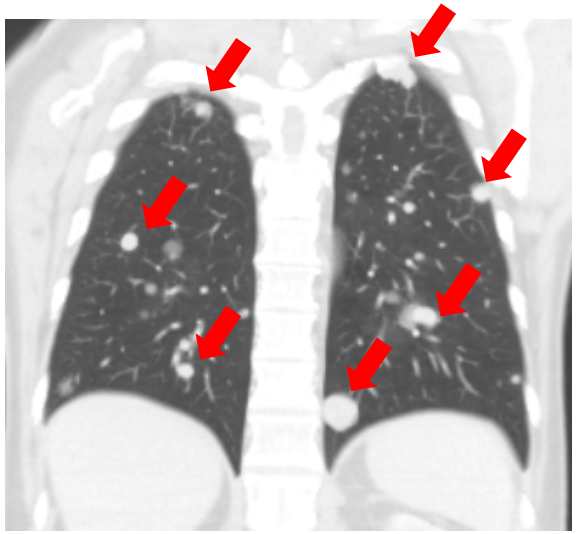
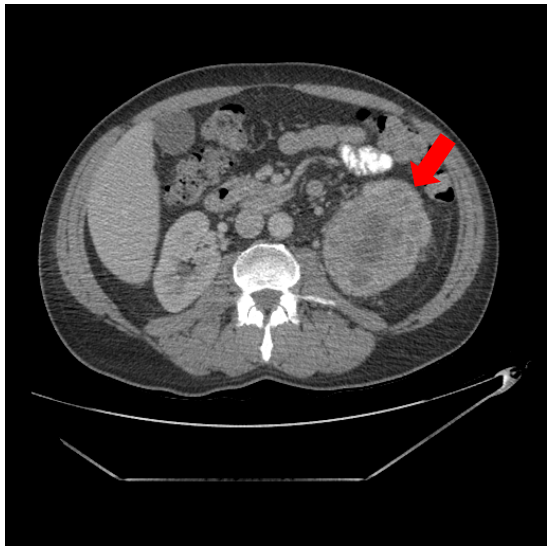
Overall Survival



- 2 single-arm Phase II studies
- 66 patients, ccRCC
- 2-3 cycles of Sunitinib
- 47 patients had surgery
- 17 pts (26%) with Progressive Disease in metastatic sites while on therapy

Powles T. Eur Urol. 2011

53 year old with left RCC, pathologic fracture humerus, brain mets, lung mets, hypercalcemia, anemia, PS 1

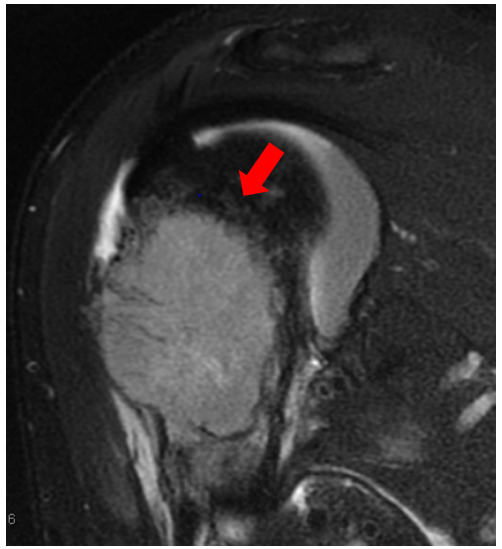
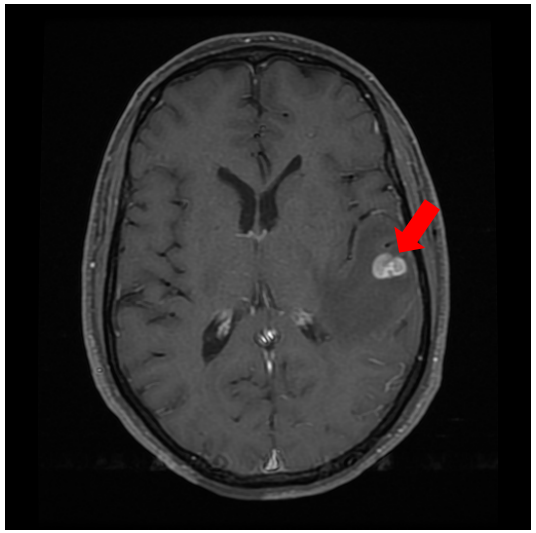
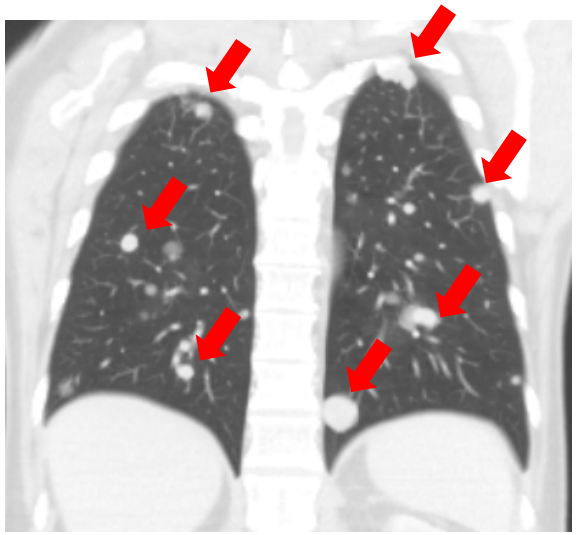
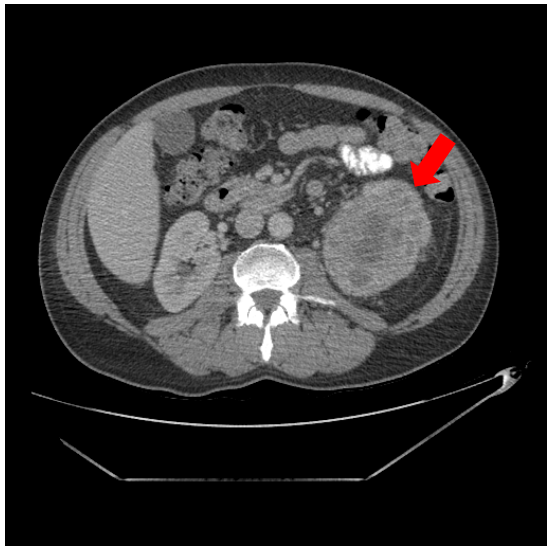
Resection/XRT humerus

XRT/Gamma knife brain

Next options in 2010-2018:

TKI, IL-2, CN

53 year old with left RCC, pathologic fracture humerus, brain mets, lung mets, hypercalcemia, anemia, PS 1

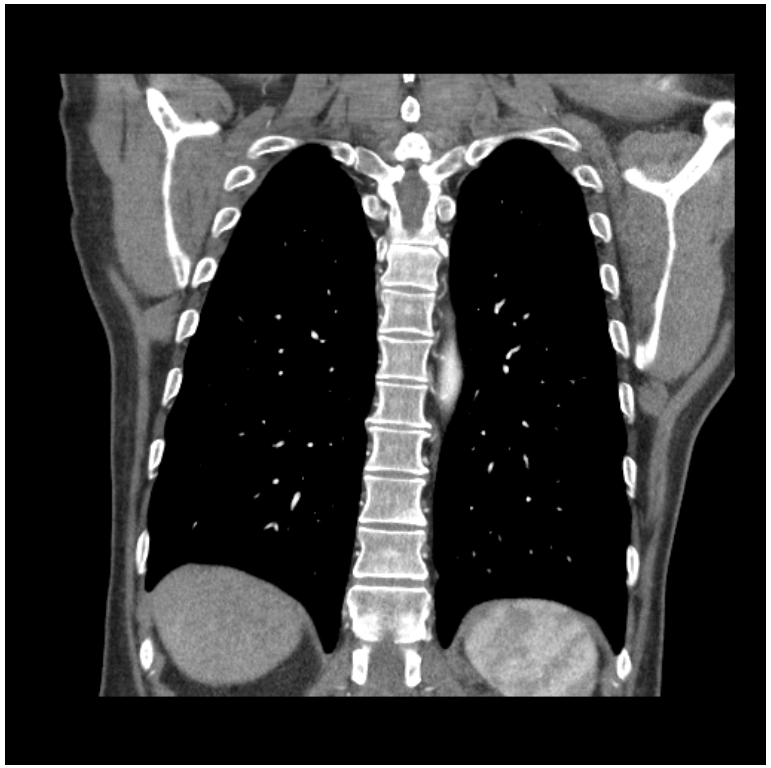






Resection/XRT humerus → XRT/Gamma knife brain → **After 2019** **Nivolumab/ Ipilimumab**

Develops immune-related pancreatitis. Nivo/ipi stopped permanently.

Restaging: near CR in all but primary tumor (7→3cm)
PS is much improved (0, excellent)

Patient is referred for delayed cytoreductive nephrectomy. Should we do it?



The era of checkpoint blockade (aka IO: anti-CTLA4, anti-PD-1, anti-PD-L1) has further shifted the role of cytoreductive nephrectomy

- Combinations of IO or IO+TKI show dramatically better responses than seen with TKIs, often with better side effect profiles

- As the shift is now toward initial systemic therapy for most patients, the question becomes when is delayed cytoreductive nephrectomy appropriate, if ever?

Combination IO and IO+TKI vs Sutent

Intervention	Year	No. pts	Adverse Events	Endpoint	Hazard Ratios
Ipilimumab+Nivolumab v Sutent	2018	1096	Grade 3-4: -Nivo/Ipi: 46% -Sutent: 63%	Median OS: **-Nivo/Ipi: NR** -Sutent: 26m	**HR for death, 0.63; P<0.001.**
Pembrolizumab+Axitinib v Sutent	2019	861	Grade 3+: -Pembro/Ax: 75.8 -Sutent 70.6	Median PFS: **-Pembro/Ax: 15.1m** - Sutent: 11.1m	**HR for progression or death, 0.69; P<0.001.**
Nivolumab+Cabozantinib v Sutent	2021	651	Grade 3+ -Niv/Cab: 75.3 -Sutent: 70.6	OS 12 months **- Niv/Cab: 85.7** -Sutent: 75.6	**HR for death, 0.60; P = 0.001**
Pembrolizumab+Lenvatinib v Pembro+Everolimus v Sutent	2021	1069	Grade 3+: -Pem/Len: 82.4 -Pem/Ev: 83.1 -Sutent 71.8	OS at 24 months: -**Pem/Len: 79.2** -Pem/Eve: 66.1 - Sutent 70.4	**HR for death, 0.66; P=0.005 (Pem/Len vs sutent only)**

Cytoreductive Nephrectomy is evolving away from initial to a deferred treatment in some patients

- Preponderance of data now supports initial systemic therapy for most patients, driven initially in TKI-based clinical trials, now furthered by results of IO combinations in metRCC.
  - Deferred nephrectomy considered in some patients

- We do not yet fully know impact of cytoreductive nephrectomy in IO era.
  - Will resection of the Primary remove potential sources of neoantigens, ending continued response?
  - Or does it remove a source of potentially resistant clones?
  - Could evaluation of the resected primary tumor inform future therapies?

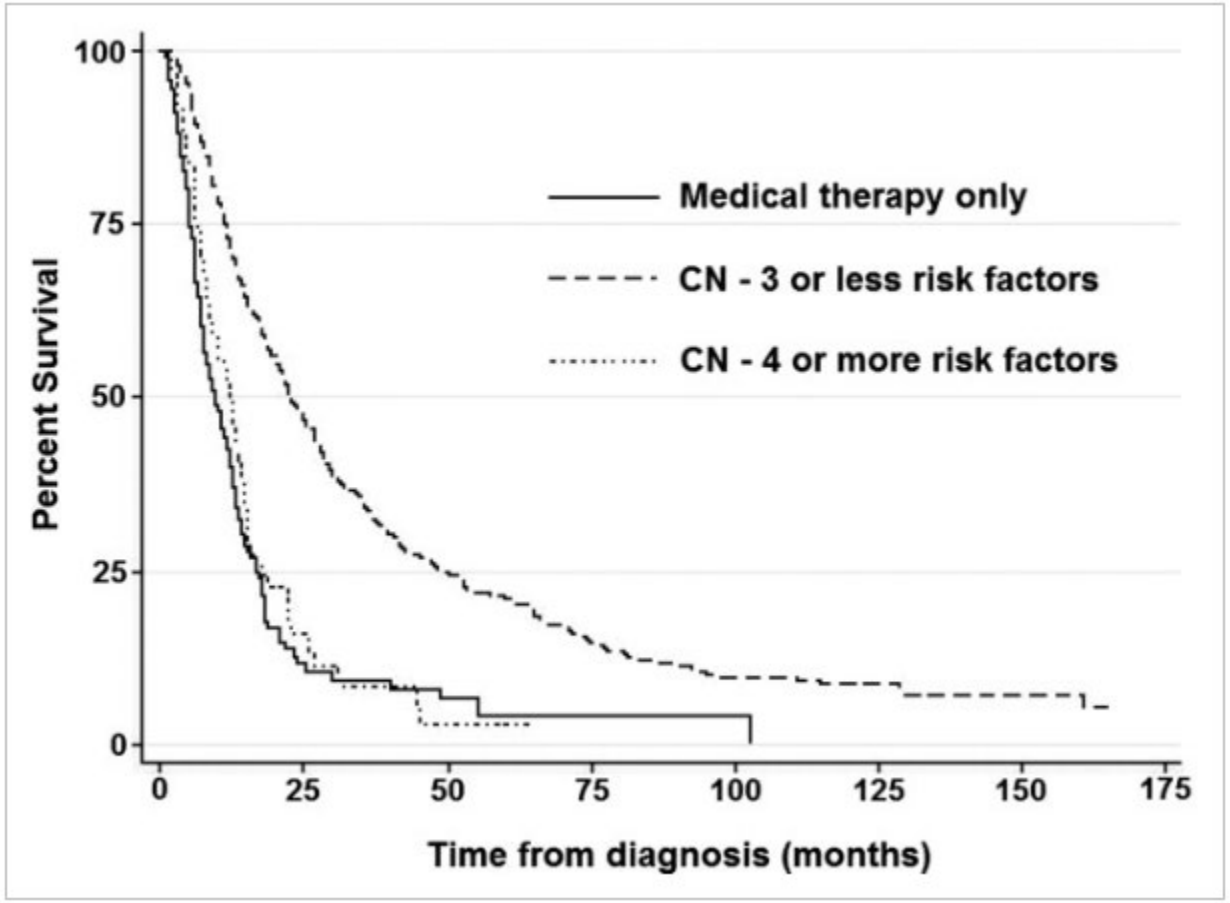
We will need new criteria for delayed cytoreductive nephrectomy alongside determination of its benefit

- Objective selection process is needed
  - Improving PS
  - Response of metastatic sites vs primary
  - Anticipated residual (post nephrectomy) renal function all should play a role in the evaluation

Can we better select patients with metastatic renal cell carcinoma for cytoreductive nephrectomy?

7 negative predictors of survival:

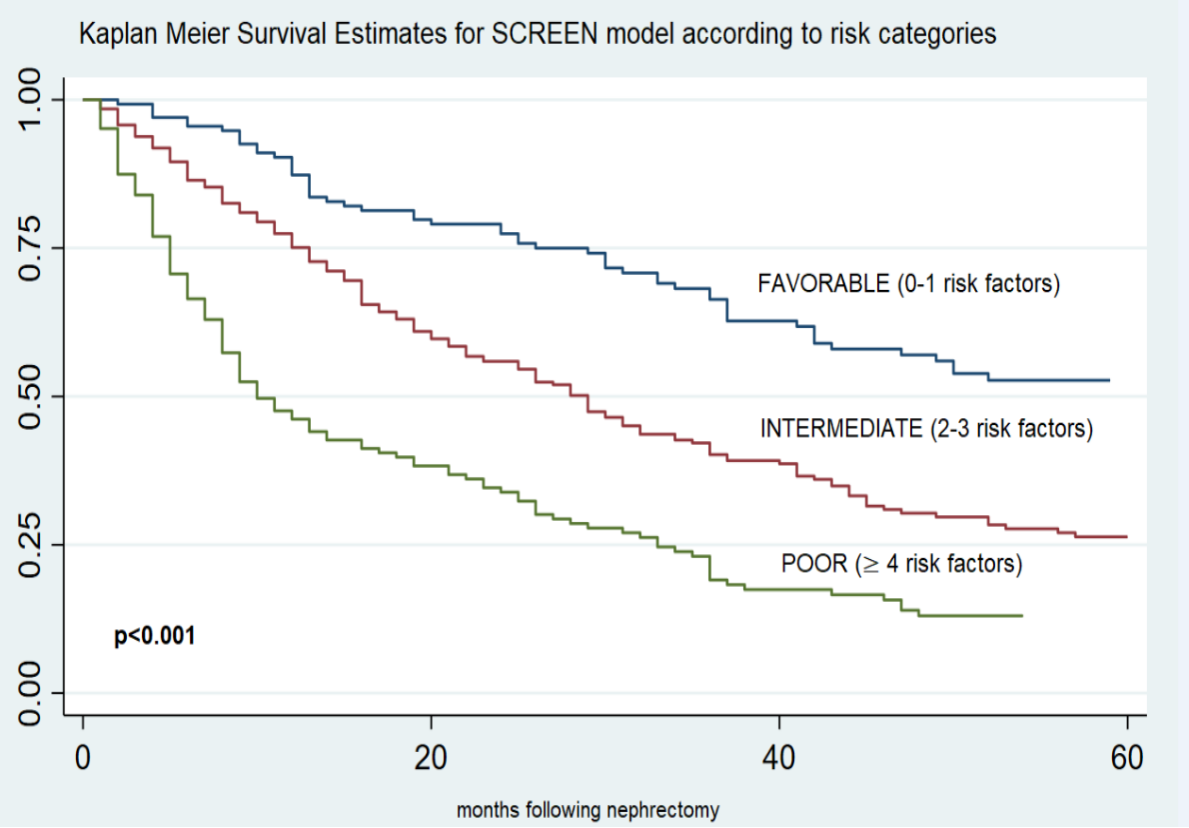
- Serum albumin < LLN
- Serum LDH > ULN
- cT3 or T4
- Symptoms from mets at presentation
- Liver metastasis
- Retroperitoneal or supradiaphragmatic LNs >1cm



Culp S Cancer 2015

Selection for **C**yto**RE**ductiv**E** **N**ephrectomy (SCREEN) Score: Improving Surgical Risk Stratification by Integrating Common Radiographic Features

- Systemic symptoms
- Number of metastatic sites ≥ 3
- Total cm of metastatic tumor burden ≥ 5 cm
- Bone metastasis
- Low serum albumin
- Neutrophil to lymphocyte ratio >4



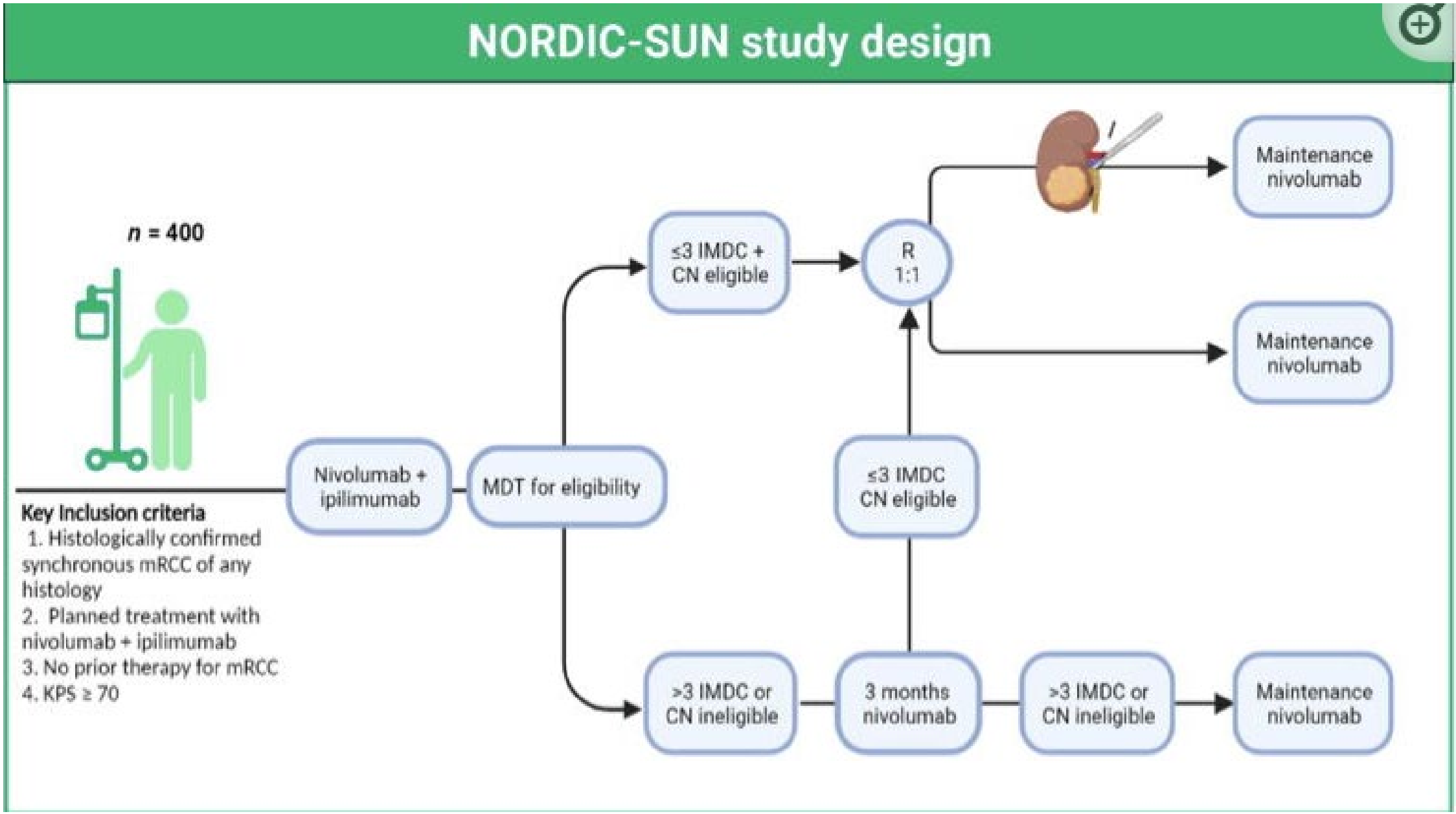
Abel J in preparation

Patient case: After extensive discussion, patient underwent uneventful laparoscopic nephrectomy

- Hilar dissection quite difficult/desmoplastic
- Pathology: Largely necrotic tumor with microscopic areas of viable tumor

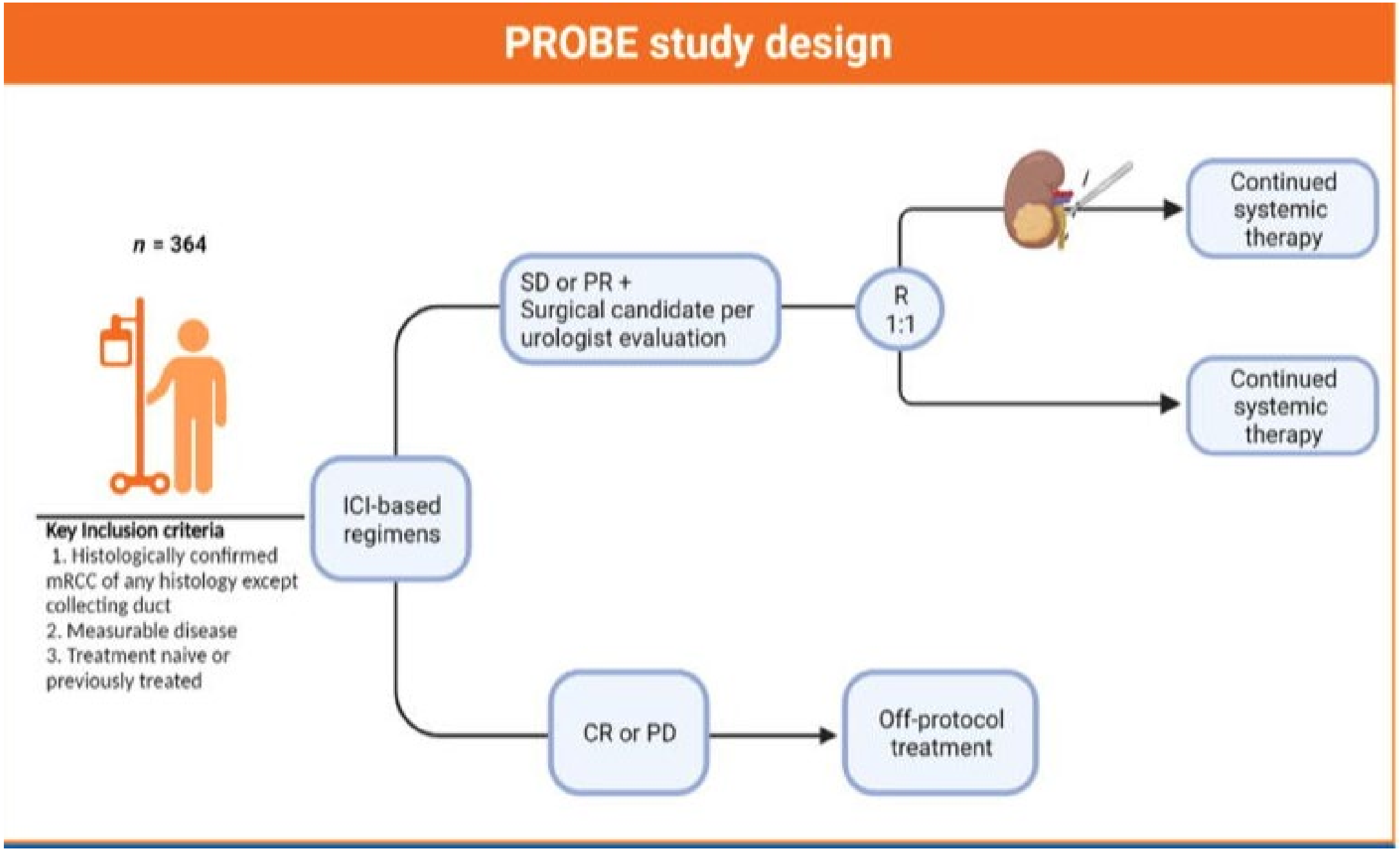
- Has received no additional systemic therapy
- Follow up at 12 months: stable disease/no progression
- Gratifying, but did we actually make a difference?

Denmark



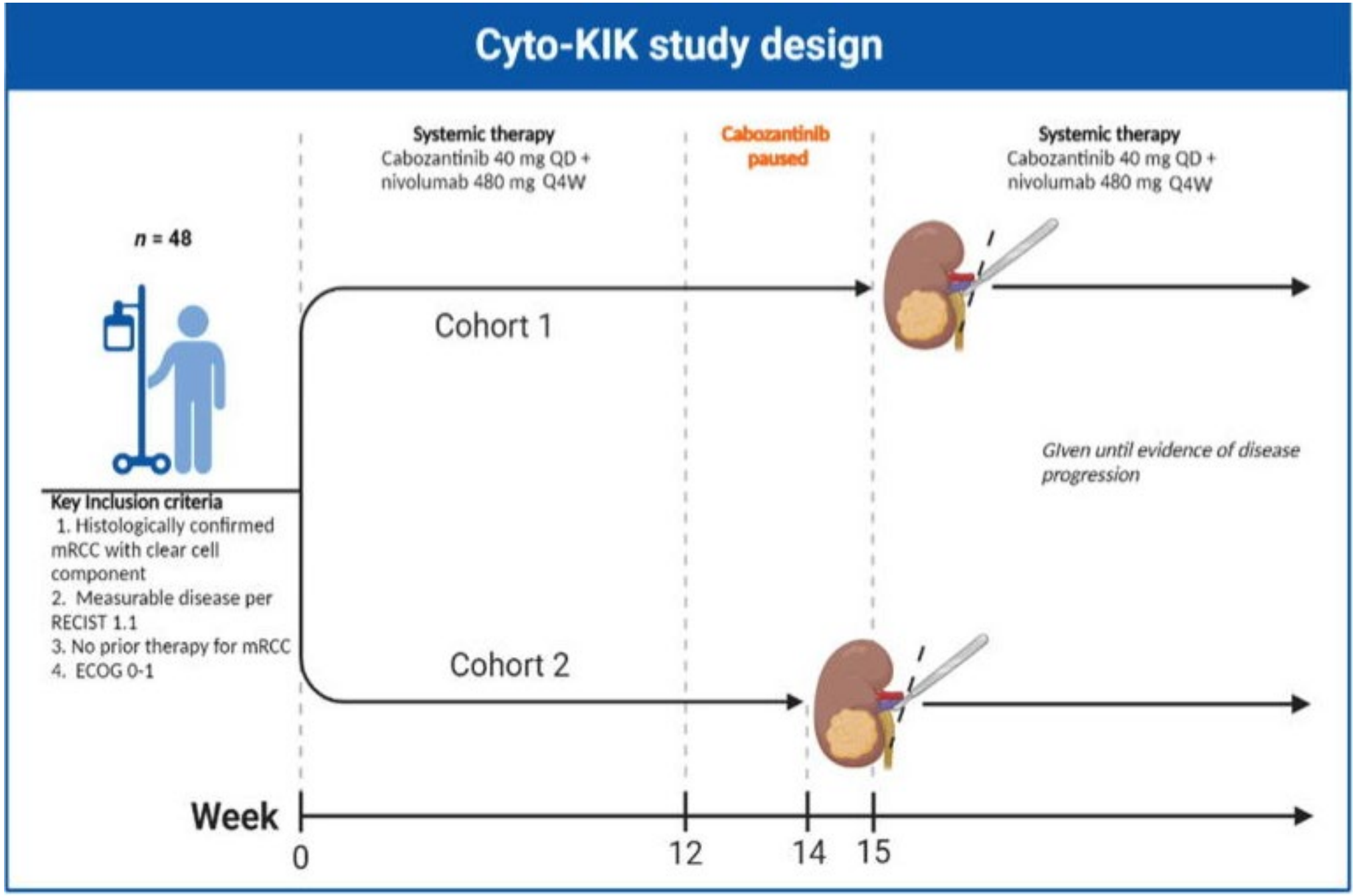
https://clinicaltrials.gov/ct2/show/NCT03977571; Mesa L Eur Urol Open Sci. 2022

SWOG



https://clinicaltrials.gov/ct2/show/NCT04510597; Mesa L Eur Urol Open Sci. 2022

Rutgers, Columbia, Cleveland Clinic



https://clinicaltrials.gov/ct2/show/NCT04322955; Mesa L Eur Urol Open Sci. 2022

Summary: role of nephrectomy for metastatic RCC

- Prospective studies show no benefit of initial surgery in the era of targeted (TKI) therapy
- Probably less so with new-generation immunotherapy
- Current paradigm consists of upfront systemic therapy for most patients, with possible delayed cytoreductive nephrectomy for select patients

Thank you