

Innovative Thinking for Locally Advanced Kidney Cancer

(for Patients)

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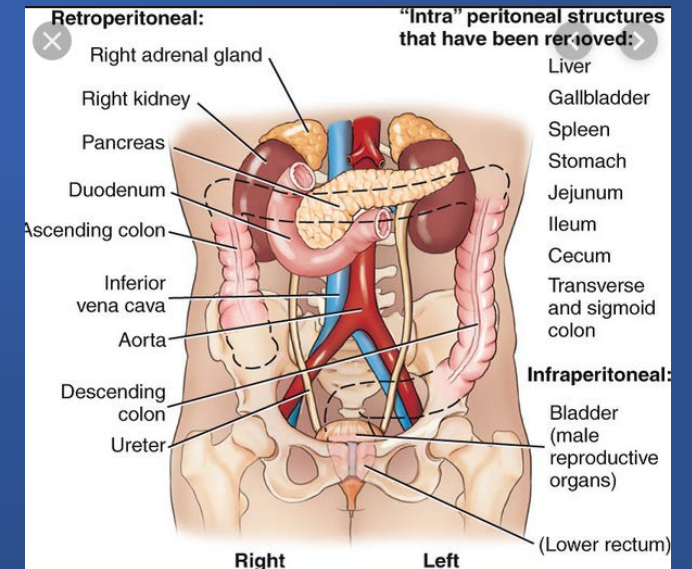
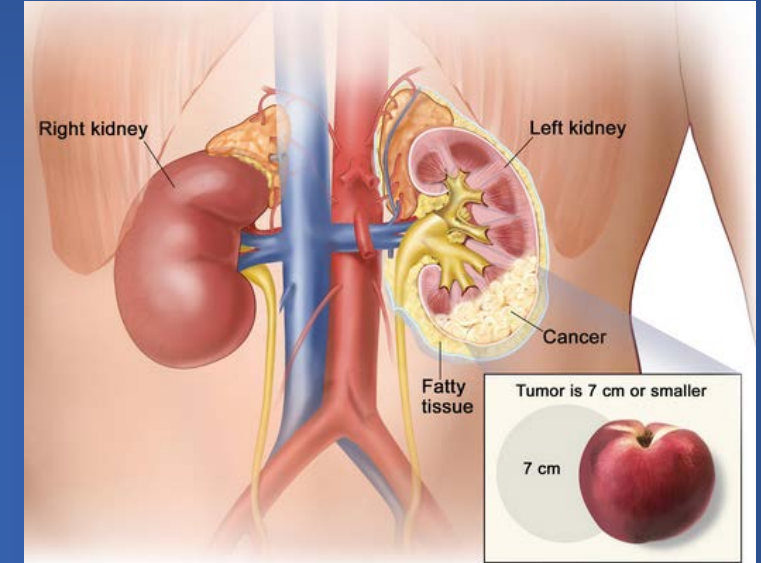
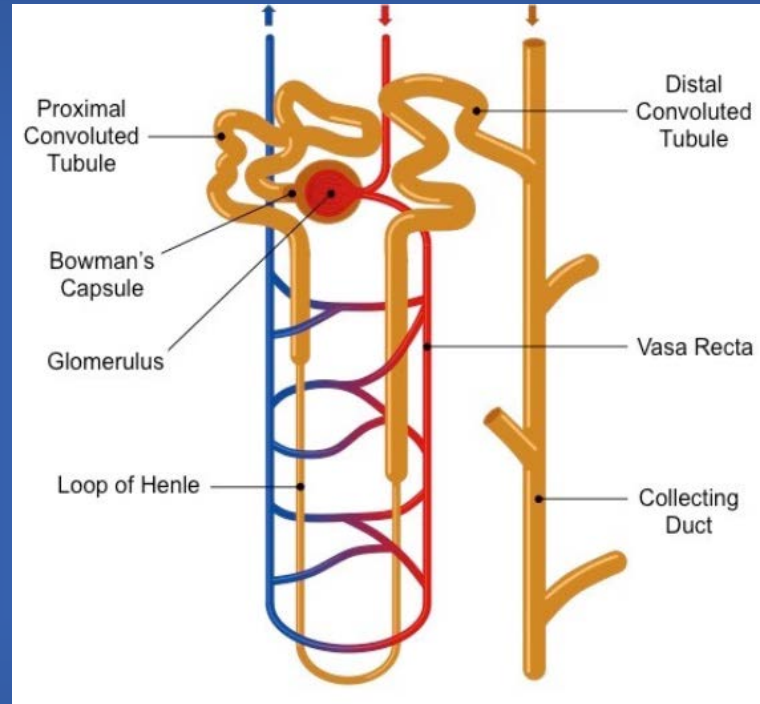
Disclosure

Type	Company
Consultant / Ad Board	Pfizer, GSK, Argos, Janssen, Urogen
Research, Data Monitor	Novartis, J & J

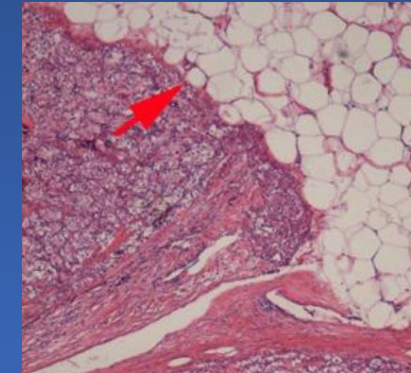
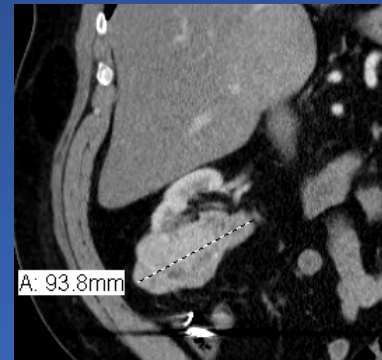
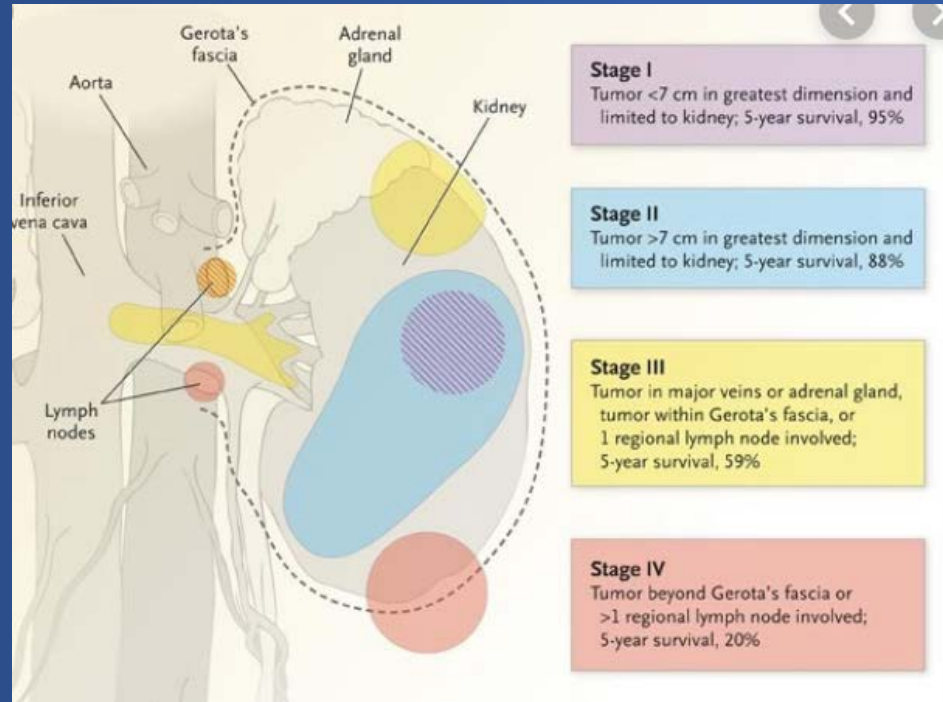
What is Locally Advanced RCC?

- Tumor involving the:

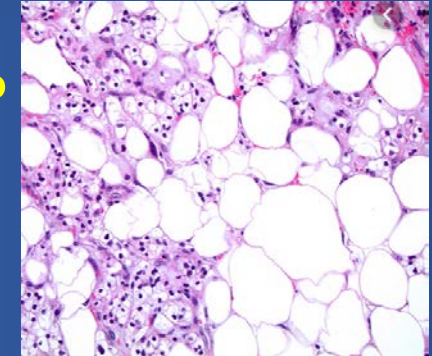
- Perinephric fat
- Renal Sinus Fat
- Renal Vein
- Inferior Vena Cava
- Nearby lymph Nodes
- Adjacent organs
 - Adrenal, pancreas, colon, spleen or musculature on the left
 - Adrenal, liver, colon or musculature on the right



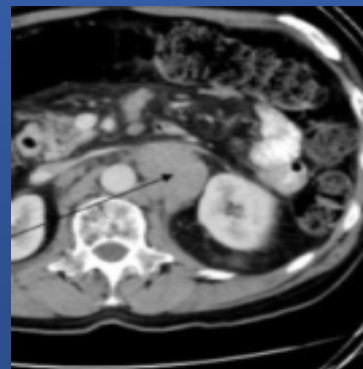
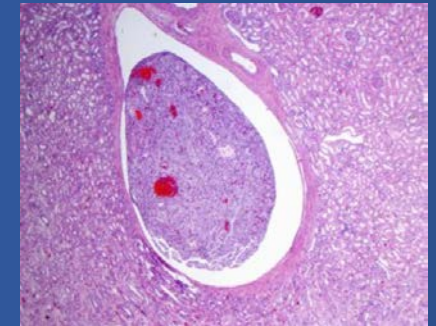
Clinical vs Pathological Staging: cTNM vs pTNM



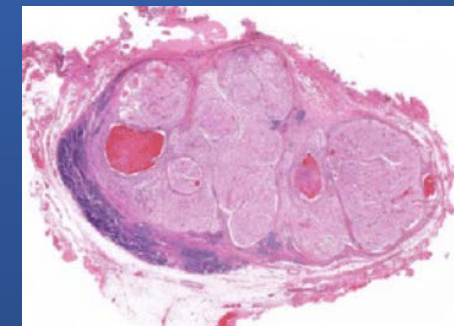
???



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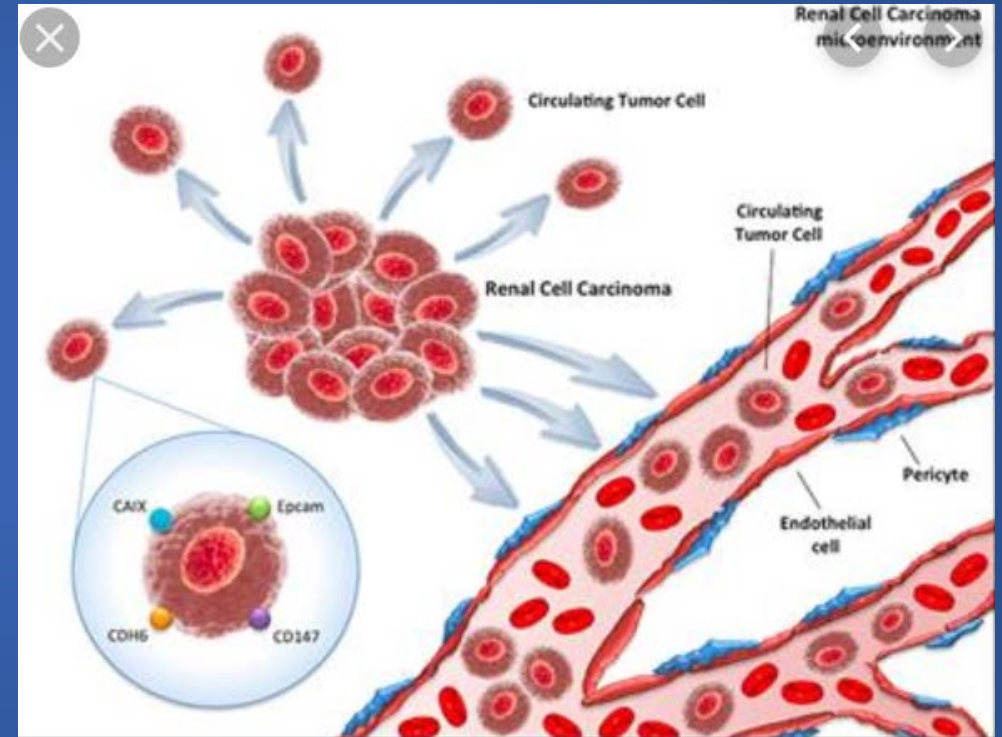


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Why is Locally Advanced RCC Concerning?

- Risk of Micrometastatic Disease:
 - Timing of microscopic spread unclear and not measureable
 - Implies that the tumor will recur at some time in the future
- Currently believe that all metastases evolve from prior micrometastases that have been present yet undetectable or “suppressed”

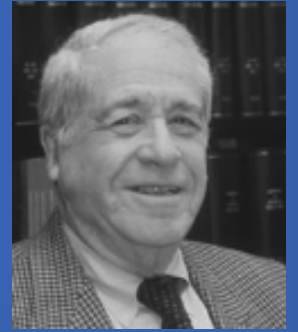


Tumor Progression Paradigms

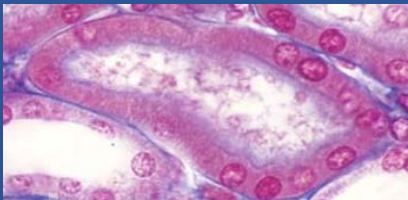
(evolution of micrometastases)



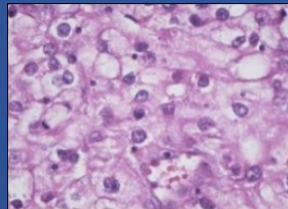
**Surgery
then systemic Rx**



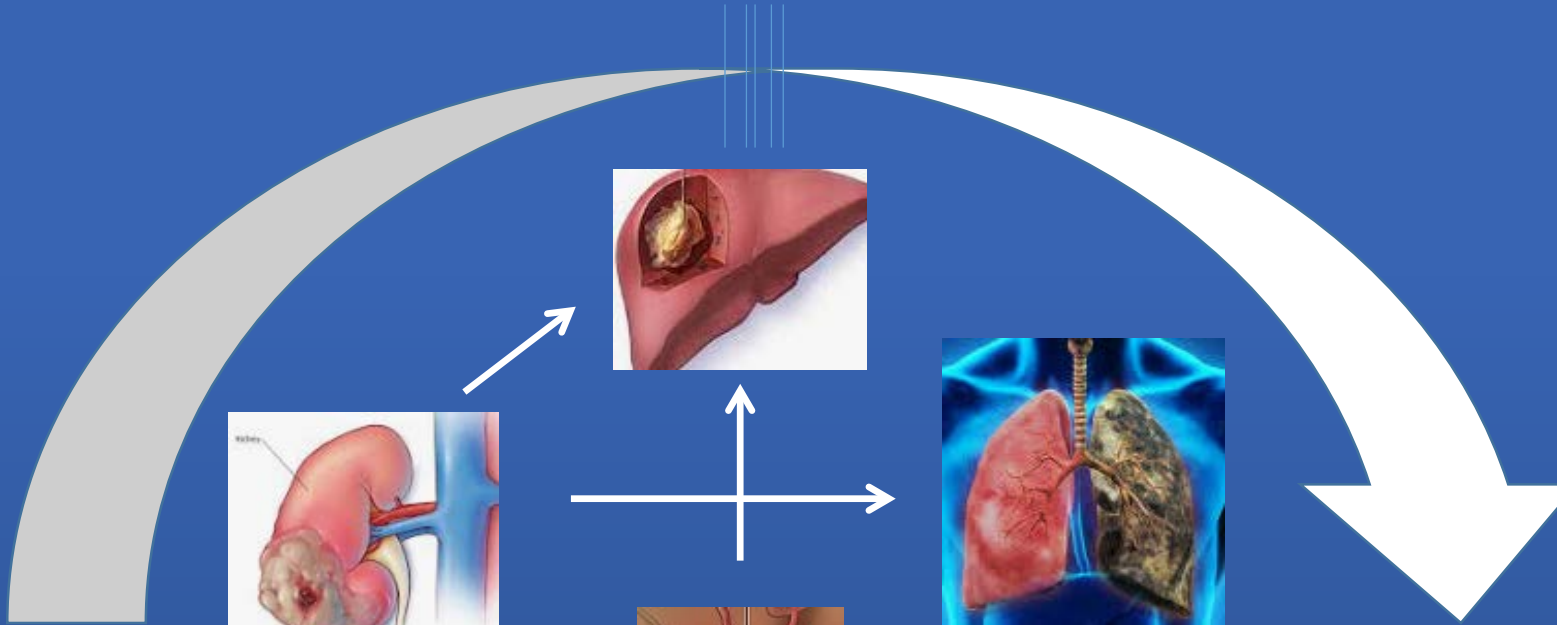
**Neoadjuvant Rx
± surgery**



n driver (truncal) mutations



Clones/subclones



Timing of Perioperative Systemic Rx

Micrometastases (CTCs) (Halstedian)



Subclinical Stage IV/ Clinical Stage IV

Clinical Stage 3

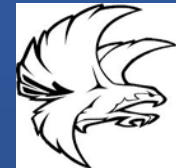
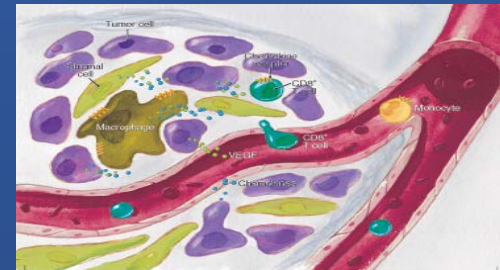
Clinical Stage 2

Clinical Stage 1

(Neo) Adjuvant Rx

$1 \times 10^9/\text{cm}^3$

0



CTCs

Timing of Perioperative Systemic Rx

Micrometastases (CTCs) (Fisheresque – NSABP)

Sub clinical Stage IV

/

Clinical Stage IV

Clinical Stage 3

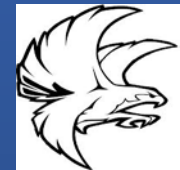
Clinical Stage 2

Clinical Stage 1

0

(Neo) Adjuvant Rx

$1 \times 10^9/\text{cm}^3$



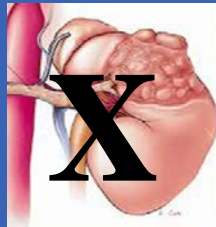
CTCs

Adjuvant/Neoadjuvant Therapy

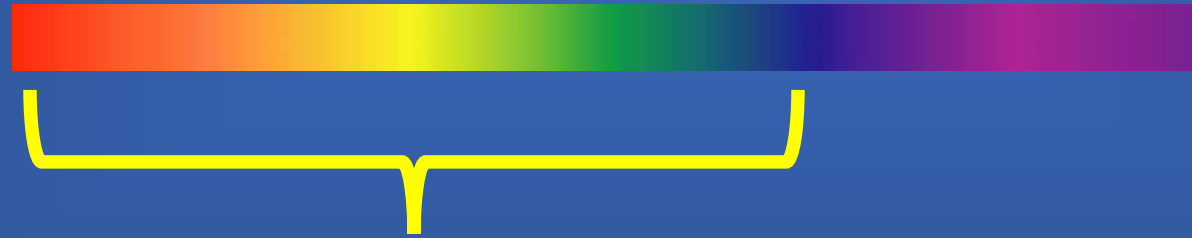
Elusive

^

The Holy Grail of Surgery



Incompletely
effective
(high quality)
surgery



Completely
effective
systemic Rx

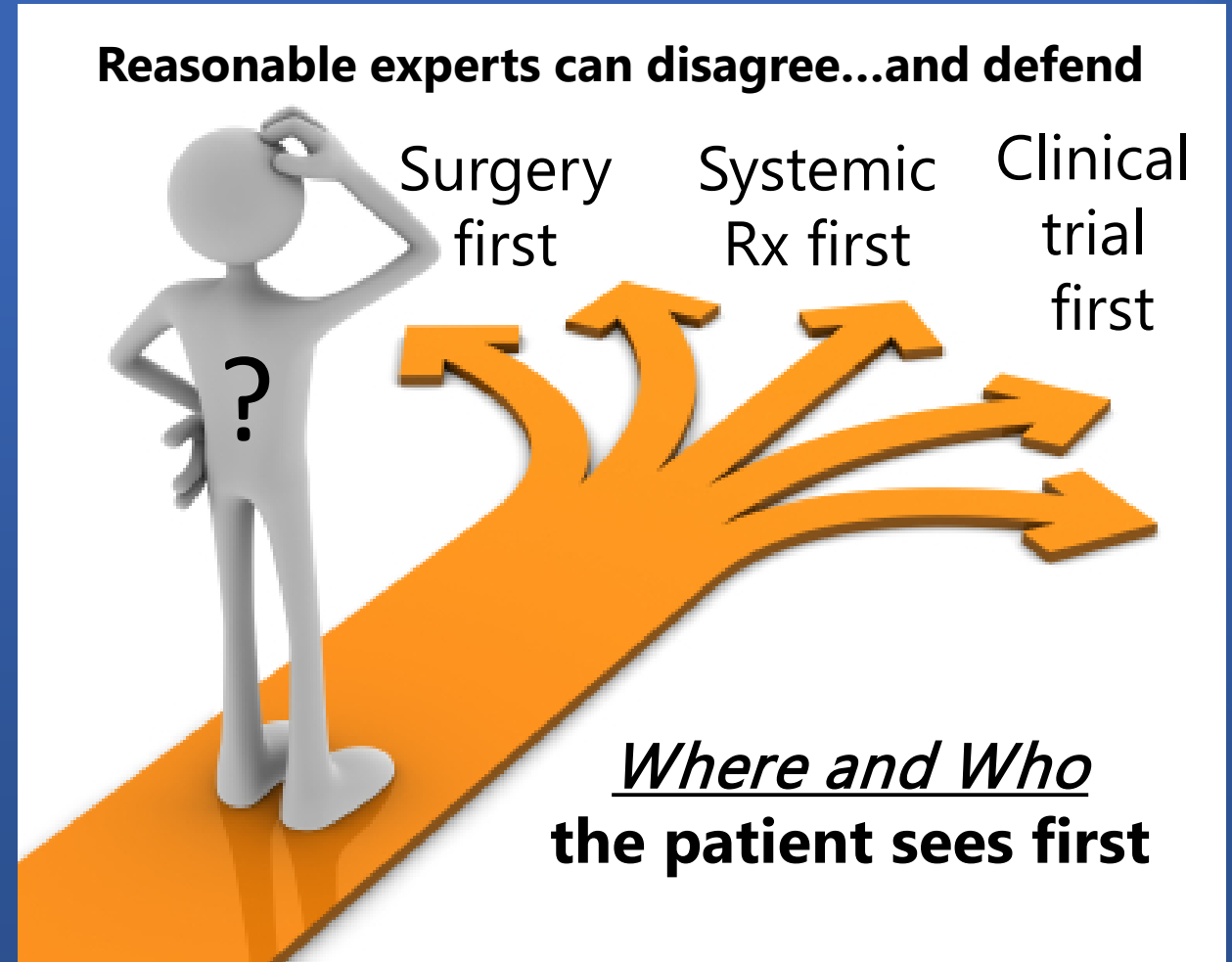
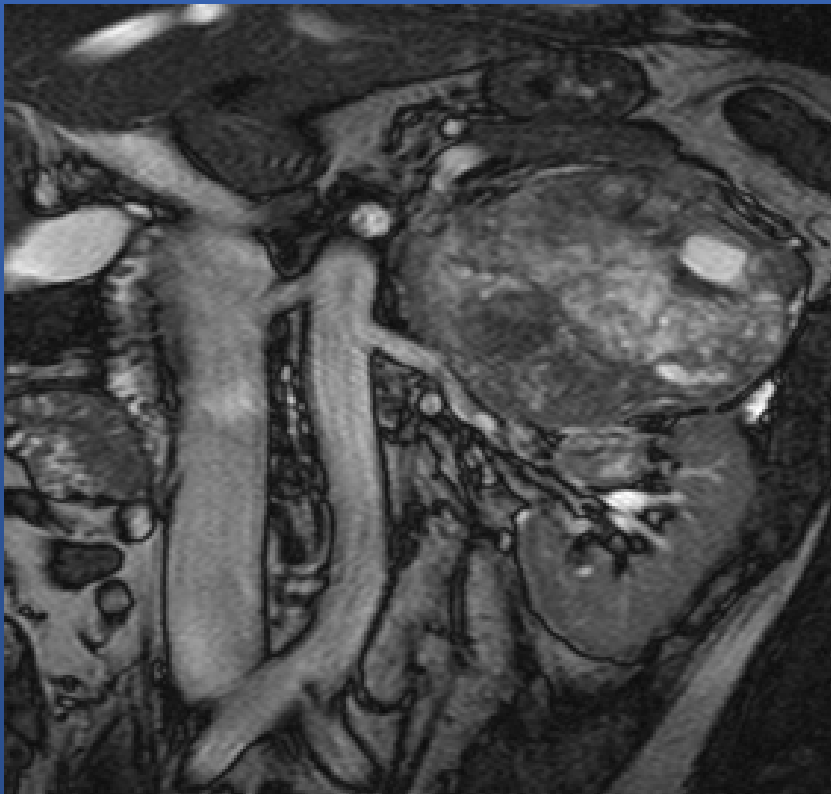
Incompletely
effective
systemic Rx

We all struggle

**to advise the right treatment for locally
advanced and mRCC
in the right patient
at the right time**

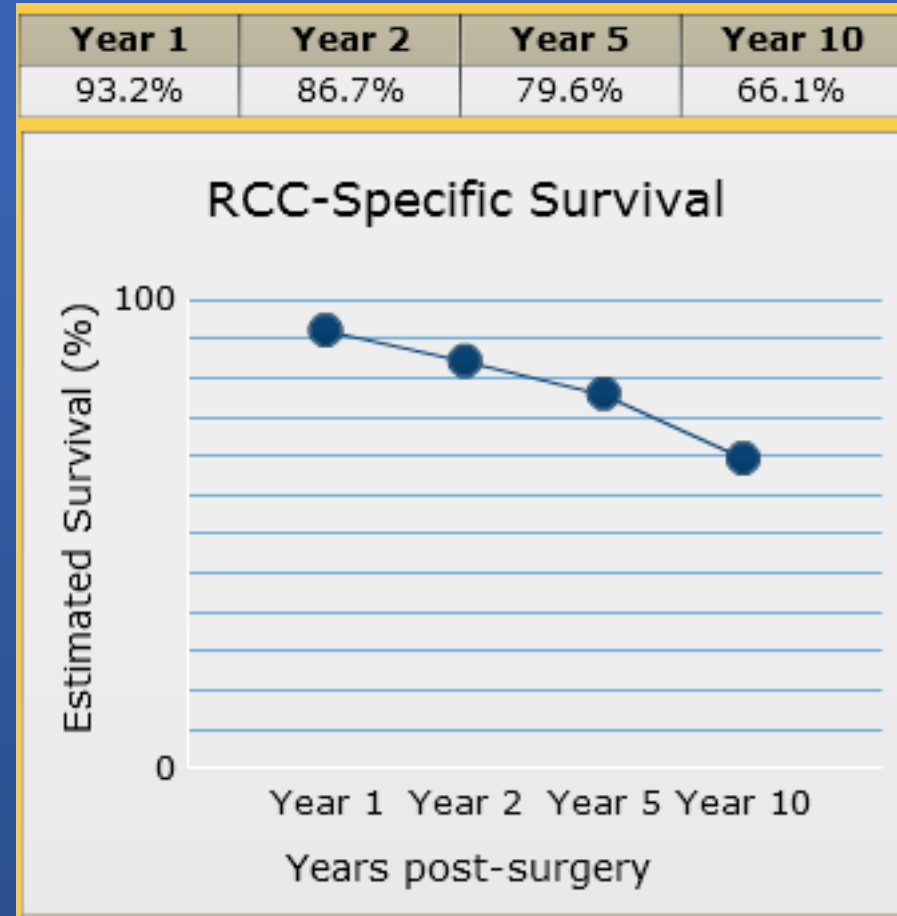
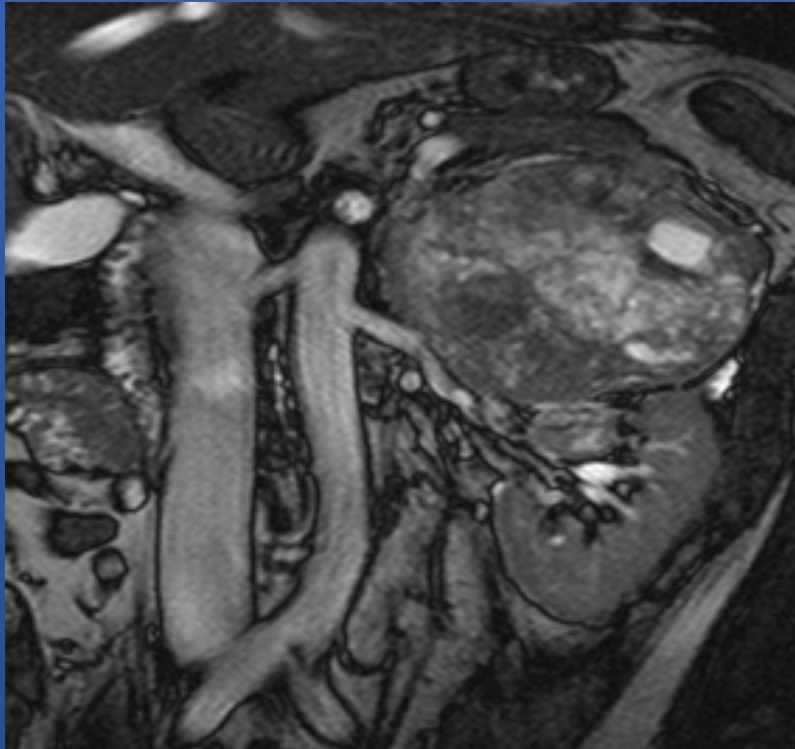
Locally Advanced or mRCC...

- 71 yo and very healthy
- Good Renal Function



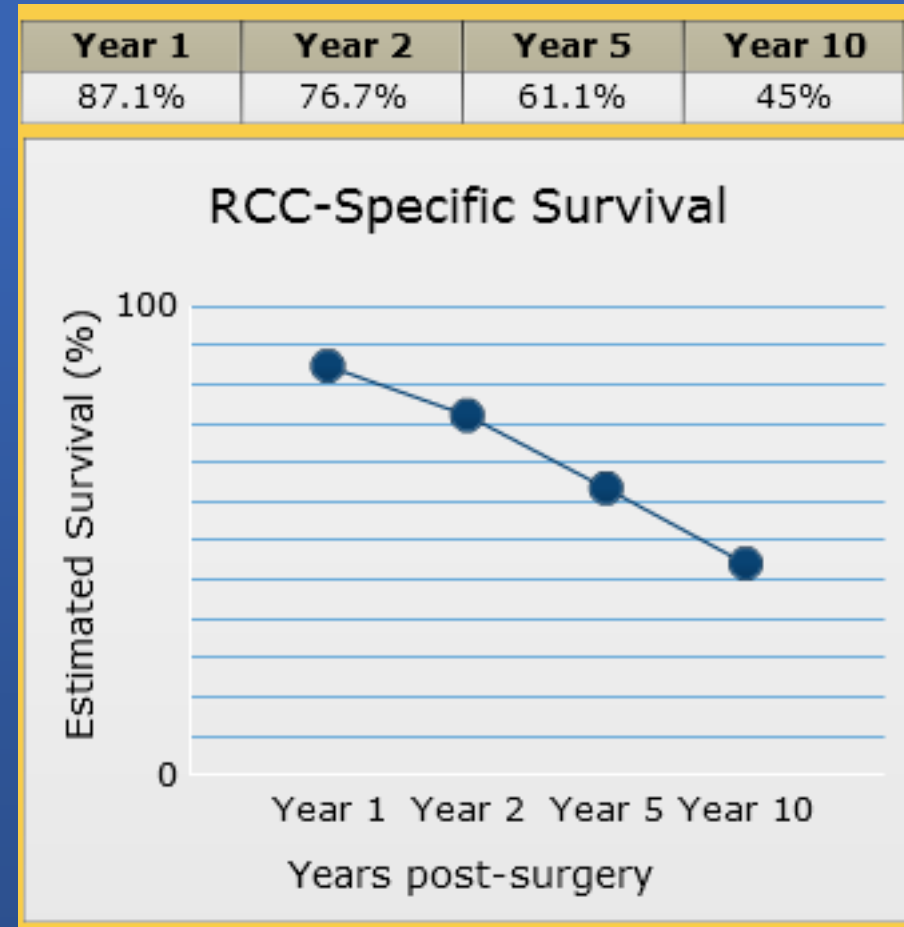
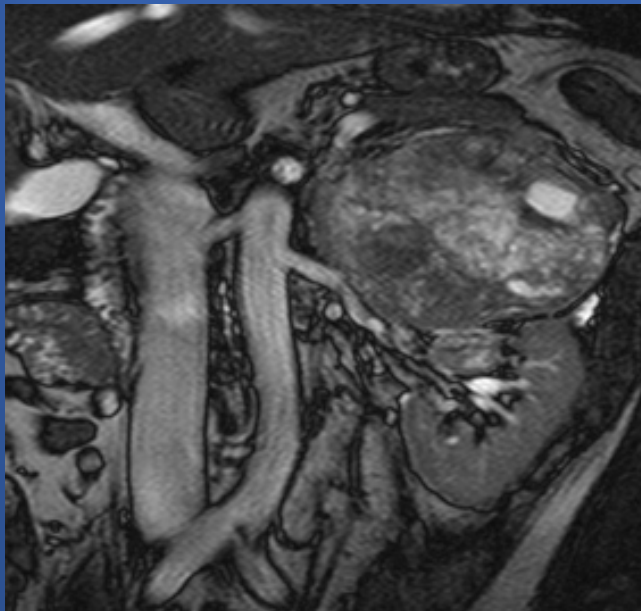
Surgical Outcomes – pT3aNoMo ccRCC

- 71 yo and very healthy
- Good Renal Function



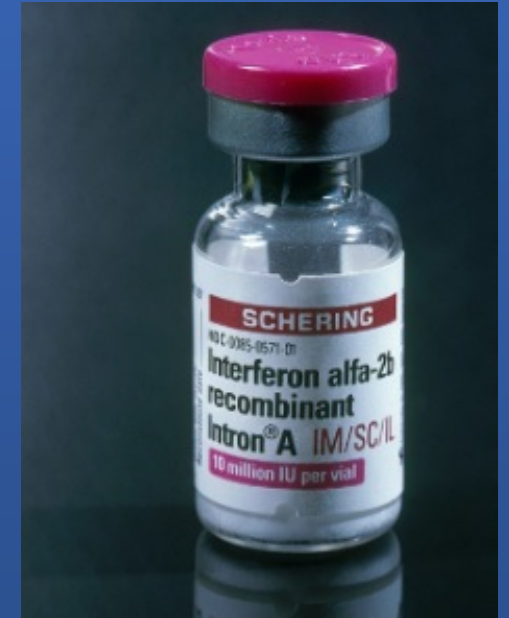
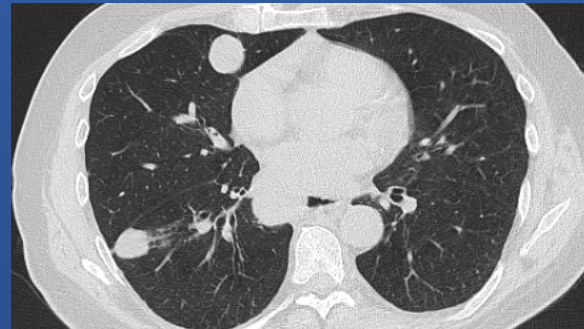
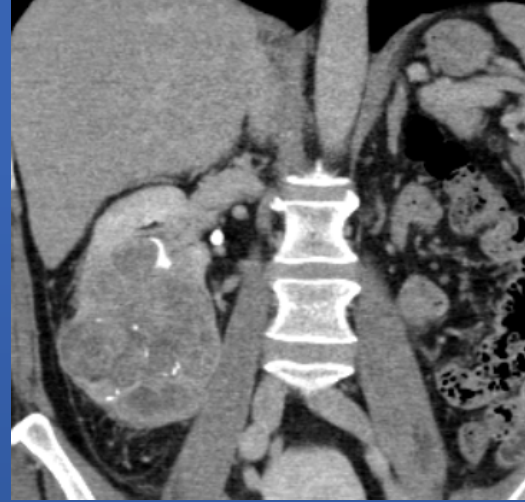
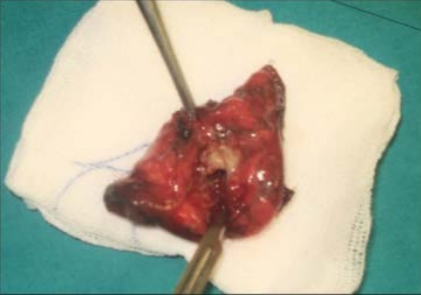
Surgical Outcomes – pT3aN1Mo ccRCC

- 71 yo and very healthy
- Good Renal Function



Past State (prior to 2006)

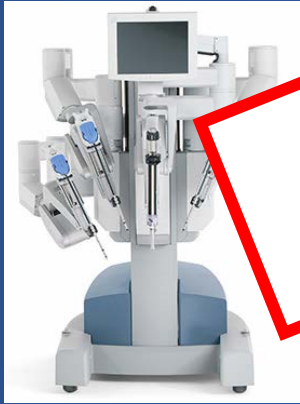
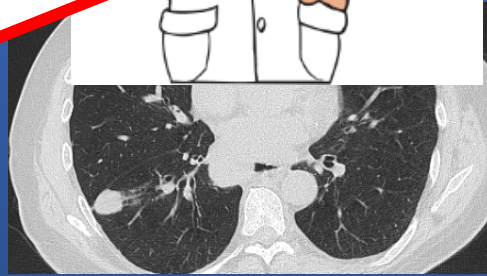
Incompletely effective surgery vs incompletely effective systemic Rx



Present State

Incompletely effective surgery vs more effective systemic Rx

Surgery perceived as playing offense
Systemic therapy perceived as playing defense



Hypotheses (Rationale) of RNx

(for locally advanced or mRCC)

- Clonal Deletion

- Potential for curative resection (Ro) in locally advanced disease
- Decrease source of new metastases from primary tumor

- Improved pharmacodynamics

- Drugs don't get into tumor

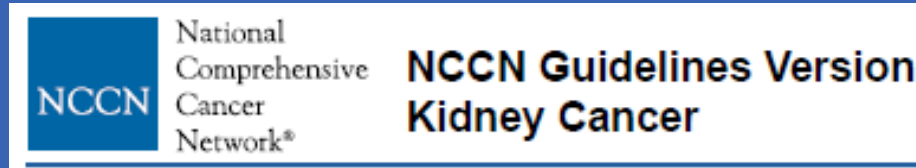
- Primary tumor suppressive and pro-angiogenic

- Reduced tumor regressions

- Symptomatic relief

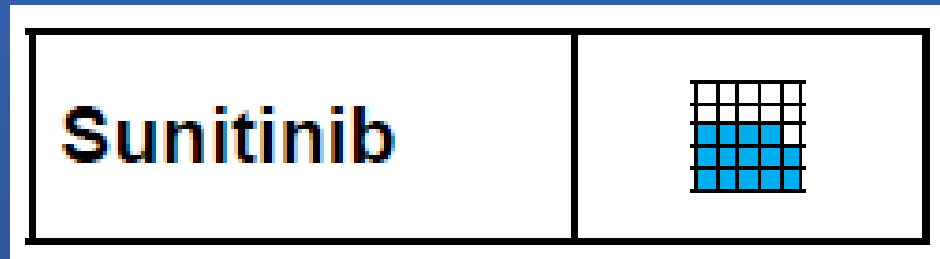
**It's "aggressive therapy" ...
(and that is perceived as better)**

Guidelines for Perioperative Systemic Rx in RCC:



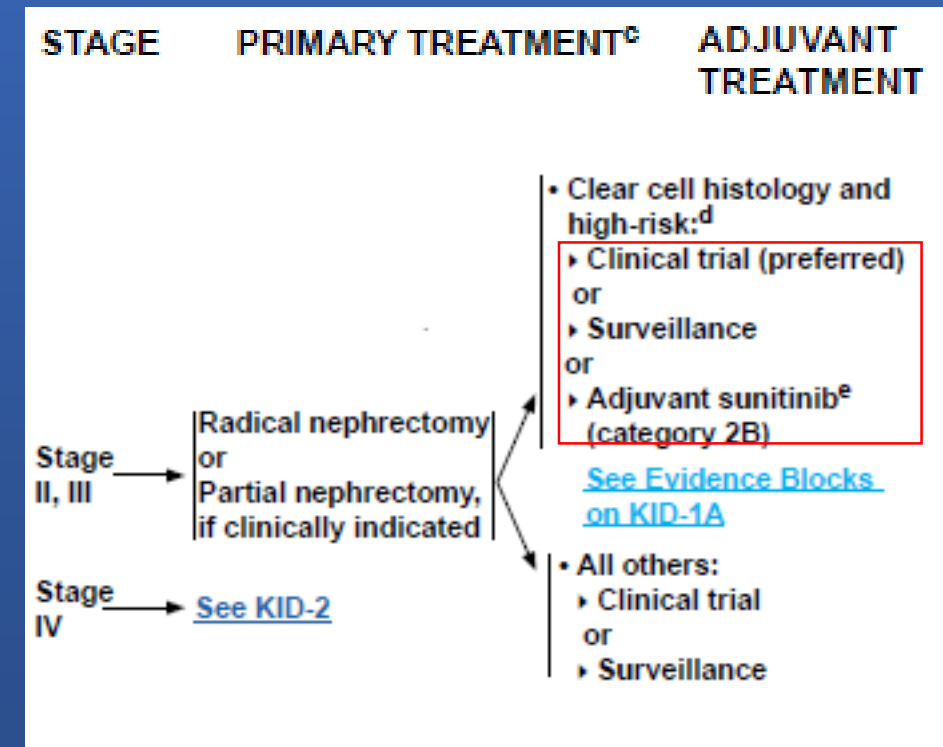
- Adjuvant Space (n=8076)

- Reported Level 1 data from ASSURE, S-TRAC, PROTECT, ATLAS
- Fully accrued trials SORCE and EVEREST



- Neoadjuvant Space

- No mention in guidelines



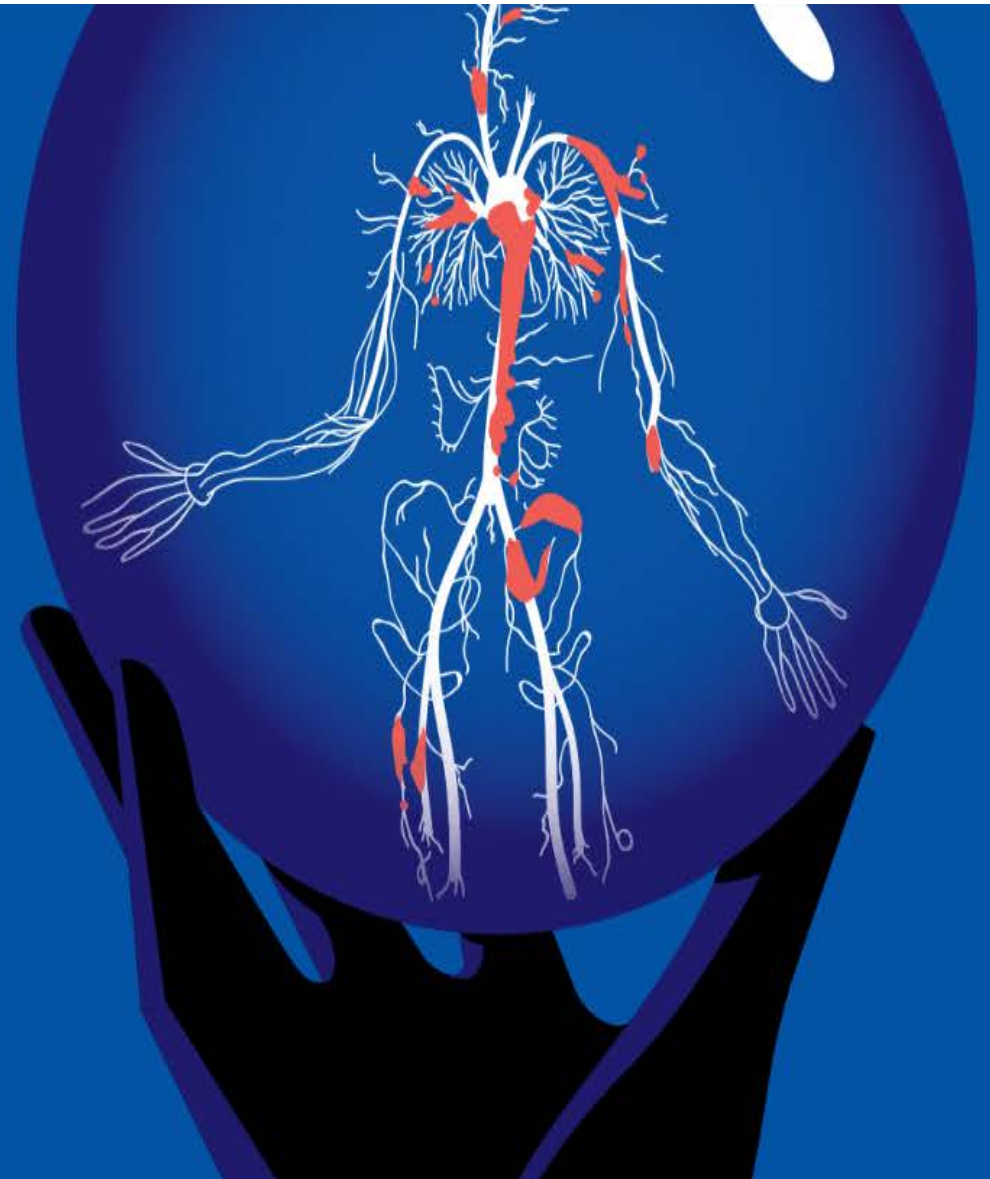
ANNALS OF MEDICINE SEPTEMBER 11, 2017 ISSUE

CANCER'S INVASION EQUATION

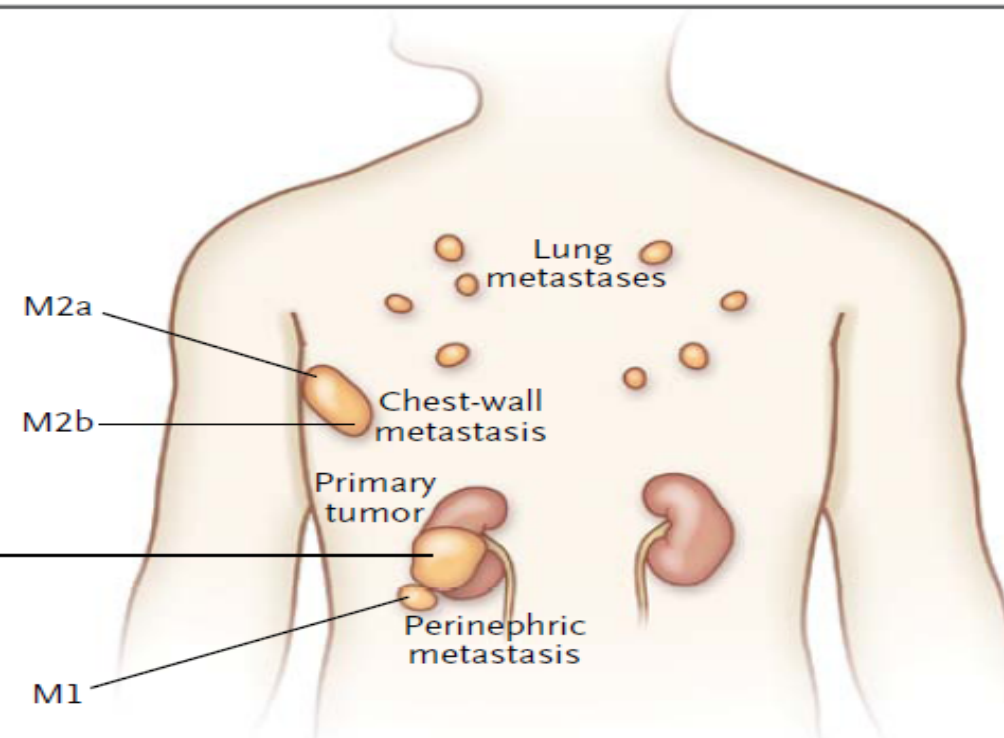
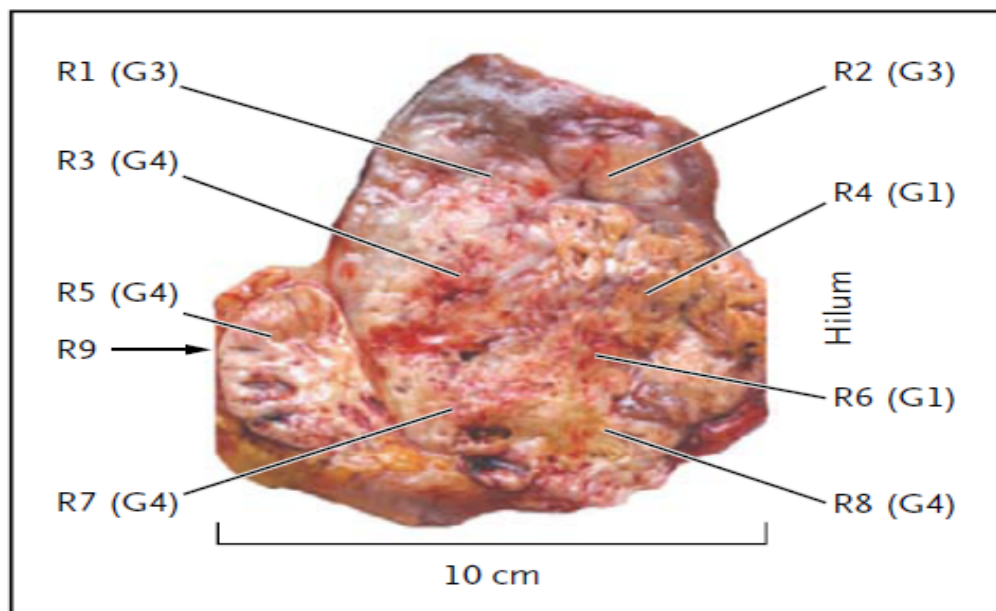
*We can detect tumors earlier than ever before. Can
we predict whether they're going to be dangerous?*

By Siddhartha Mukherjee

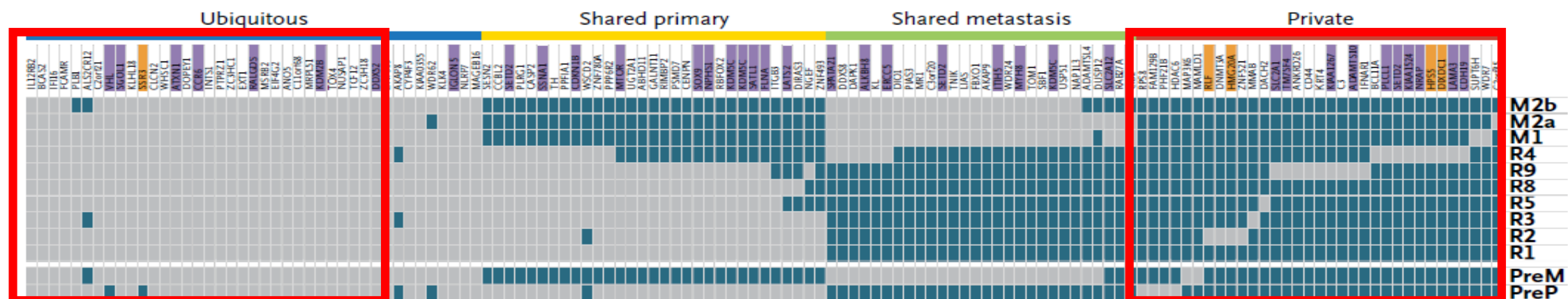
Cancer is an evolving ecosystem



A Biopsy Sites



B Regional Distribution of Mutations



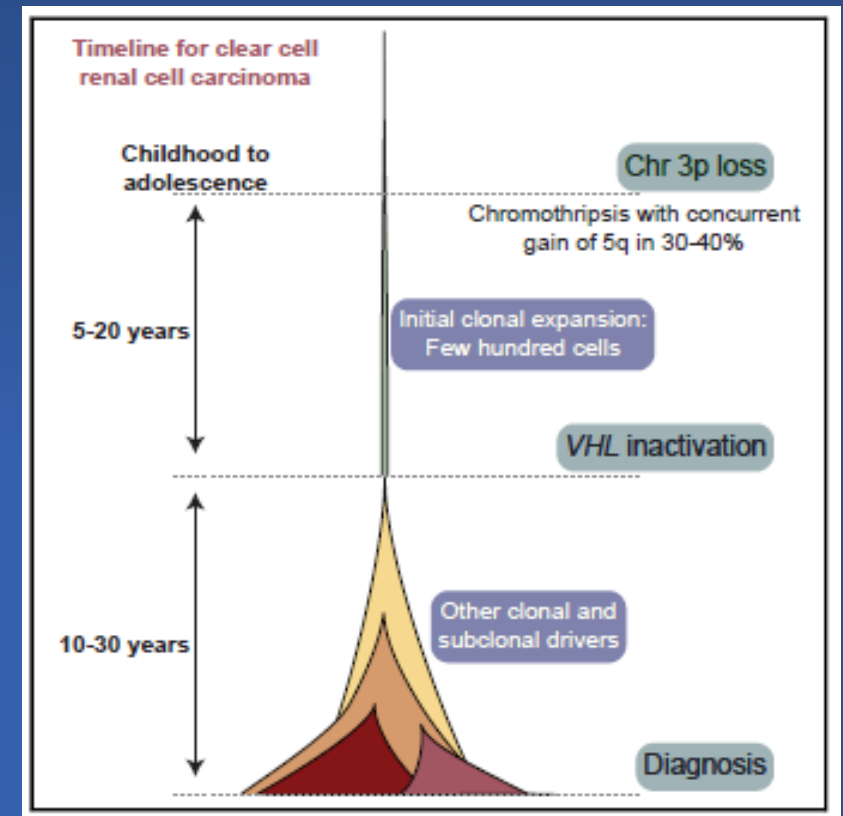
Timing the Landmark Events in the Evolution of Clear Cell Renal Cell Cancer: TRACERx Renal

Authors

Thomas J. Mitchell, Samra Turajlic,
Andrew Rowan, ..., Charles Swanton,
Peter J. Campbell, the TRACERx Renal
Consortium

TRACKing renal cell Cancer Evolution through Therapy (Rx)

- 95 cancer biopsies from 33 pts with ccRCC
 - Average of 7,680 unique somatic substitutions and 1,193 indels per patient
- Driver event is loss of 3p loss (40Mb segment) occurs decades before diagnosis
 - Loss of 4 tumor suppressors = *VHL* (70-80%), *PBRM1* (40%), *BAP1* (10%), *SETD2* (10%)
 - Simultaneous 5q gain through chromothripsis where 40% resulted in t(3;5)
 - Initial clonal expansion of only a few hundred cells with long latency
- Inactivation of second *VHL* allele leads to clonal evolution down multiple pathways



Branched Evolution (Clone Chasers)

Heterogeneity as a Hallmark

****Cancer Specific Death****



Selective Intrinsic Pressures (stochastic)



Variable Latency



Clonal Evolution

- linear vs branched vs punctuated
- selective sweeps



Failure to recognize/repair/rescue

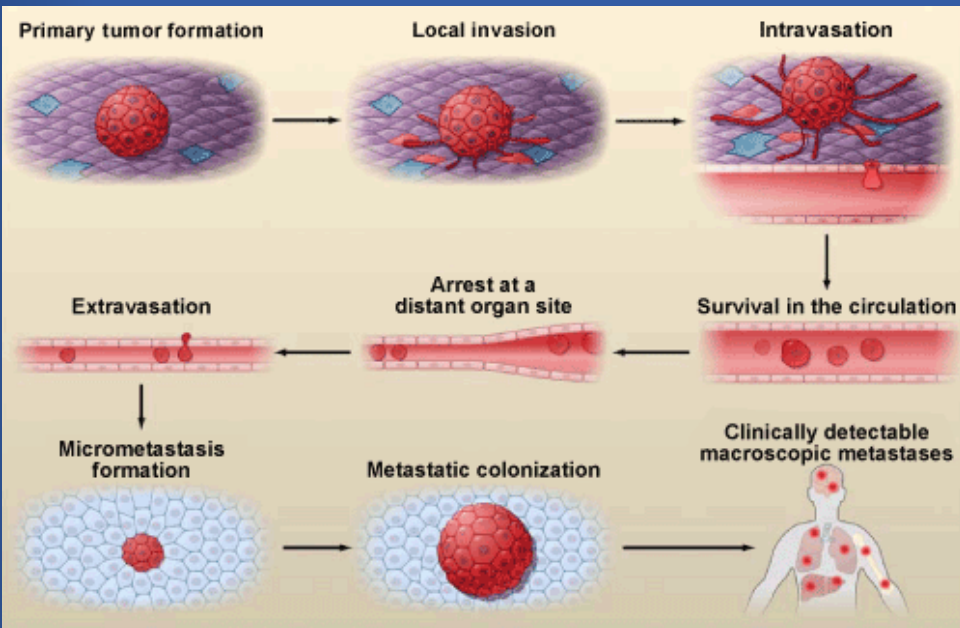


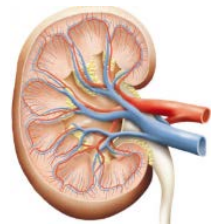
Metastatic Cascade

- migration/invasion
- intravasation/extravasation
- colonization/proliferation



Selective Extrinsic Pressures = Rx





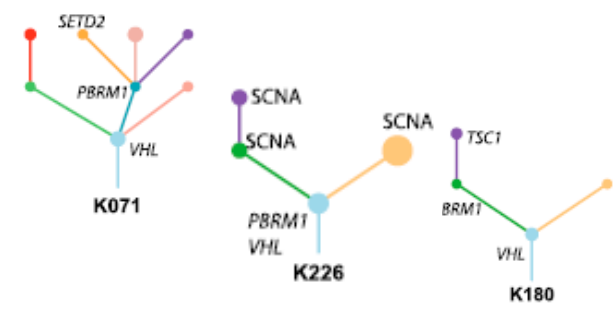
Example Trees

DRIVERS

VHL
Mono



PBRM1-->
SETD2
PBRM1-->
SCNA
PBRM1-->
PI3K



Multiple
Clonal



BAP1



VHL
Wild
Type



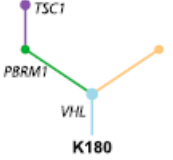
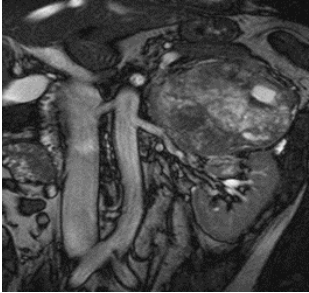
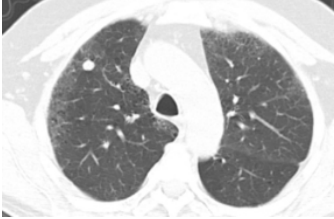

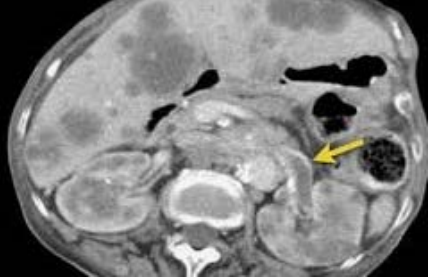




PFS

Intratumor heterogeneity

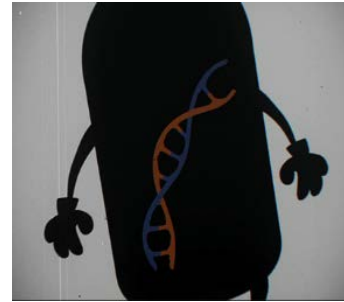
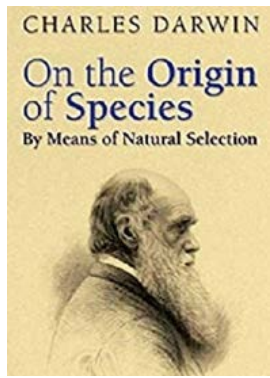
Genomic instability (SCNA)

Time

Intratumoral Heterogeneity

		High	Low
Genomic Instability (SCNA)	High	 <p>ATTENUATED PROGRESSION</p> <p>+++</p>  	<p>RAPID PROGRESSION</p> <p>+++++</p>  
	Low	<p>ATTENUATED PROGRESSION</p> <p>++</p>  	<p>LOW PROGRESSION</p> <p>+</p>  

On the Origin of Species





Intratumoral Heterogeneity



**Genomic
Instability
(SCNA)**

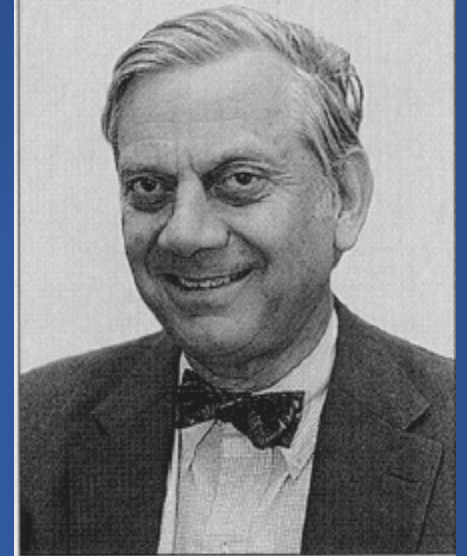
	High	Low
High		
Low		

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Basic Principles in Surgical Oncology

Blake Cady, MD

Presented at the 77th Annual Meeting of the New England Surgical Society, Dixville Notch, NH, September 27, 1996.



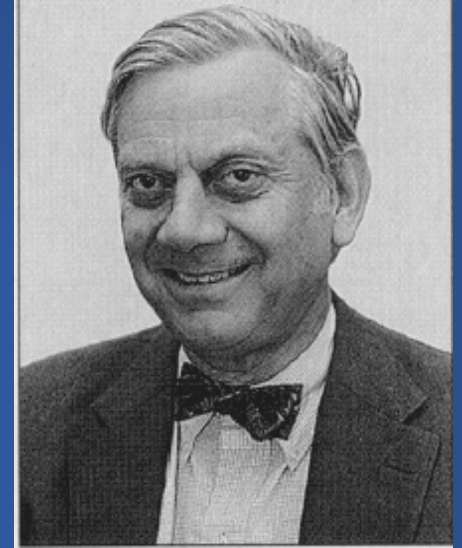
Tumor Biology is King

(but we don't fully understand it)

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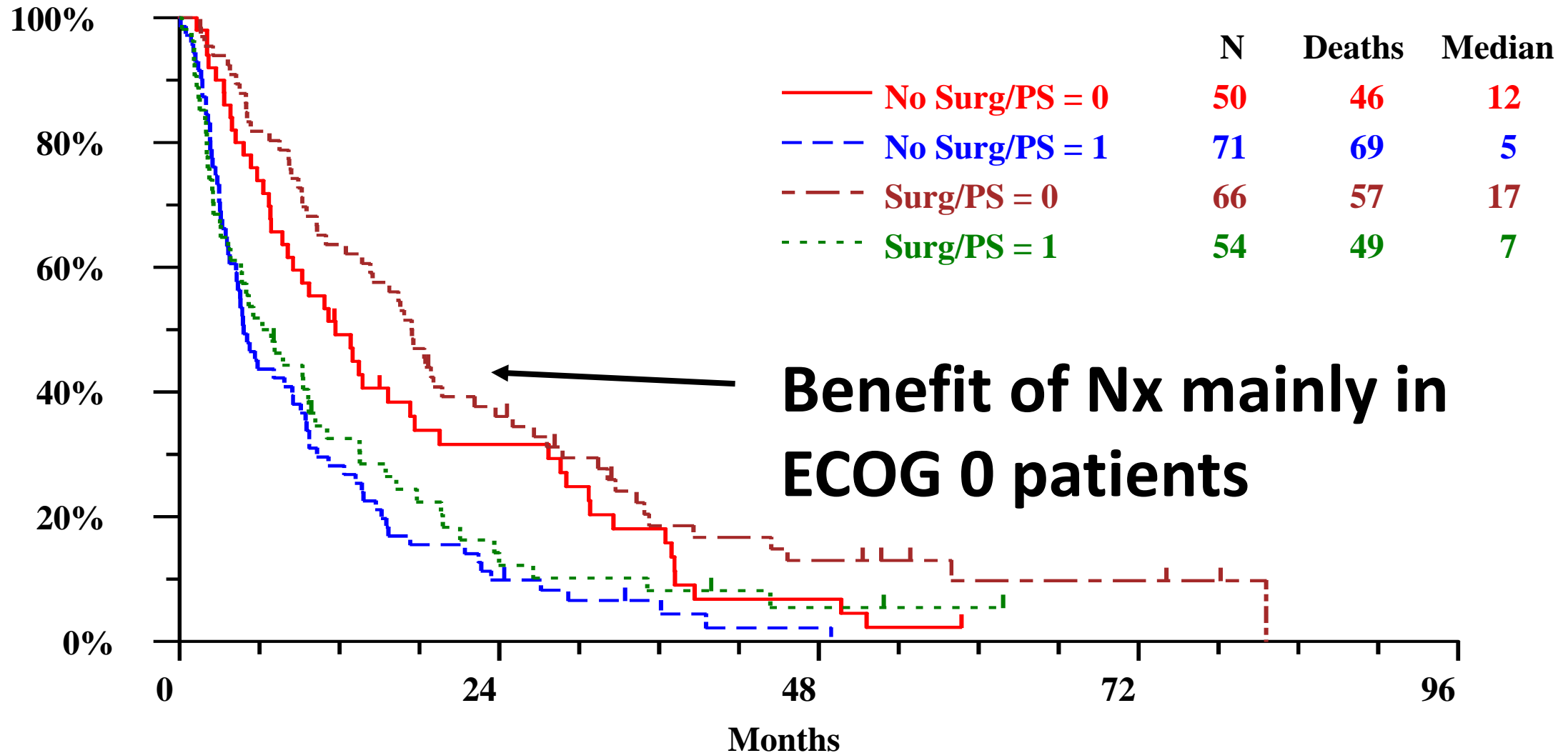
Basic Principles in Surgical Oncology

Blake Cady, MD *Presented at the 77th Annual Meeting of the New England
Surgical Society, Dixville Notch, NH, September 27, 1996.*



Case Selection is Queen

SWOG 8949: Cytoreductive Nephrectomy Improves Survival.....in patients with good performance status



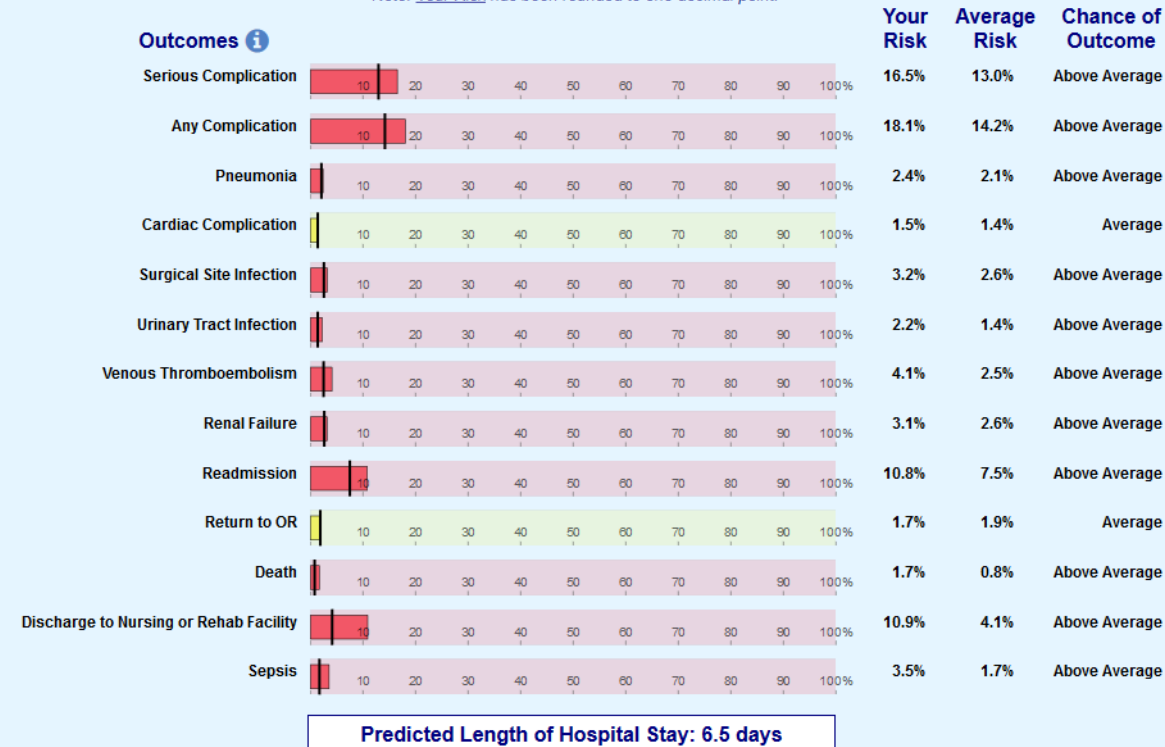
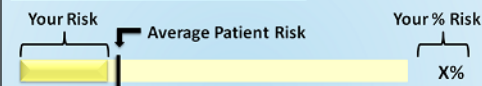
[Home](#)[About](#)[FAQ](#)[ACS Website](#)[ACS NSQIP Website](#)

Procedure: 50230 - Nephrectomy, including partial ureterectomy, any open approach including rib resection; radical, with regional lymphadenectomy and/or vena caval thrombectomy

Risk Factors: 65-74 years, Male, Partially dependent functional status, Mild systemic disease, Disseminated cancer, Diabetes (Oral), HTN, Class1 Obese

[Change Patient Risk Factors](#)

Note: Your Risk has been rounded to one decimal point.

**How to Interpret the Graph Above:****Surgeon Adjustment of Risks ⁱ**

This will need to be used infrequently, but surgeons may adjust the estimated risks if they feel the calculated risks are underestimated. This should only be done if the reason for the increased risks was NOT already entered into the risk calculator.

1 - No adjustment necessary

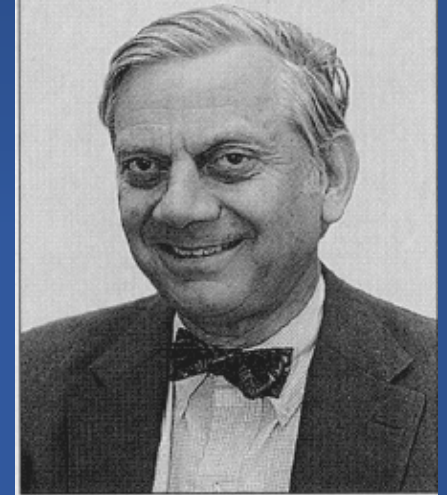
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Step 3 of 4

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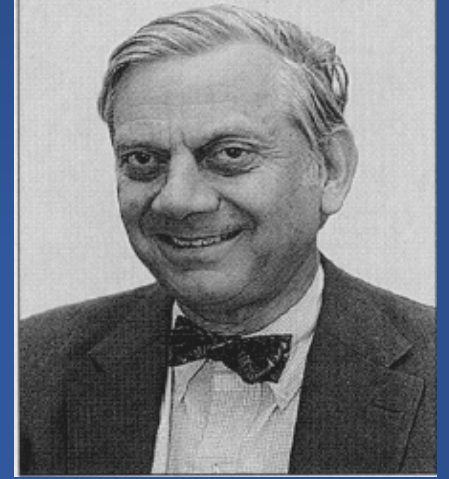
Blake Cady, MD *Presented at the 77th Annual Meeting of the New England Surgical Society, Dixville Notch, NH, September 27, 1996.*



**Therapies are the Prince and Princess
who occasionally try to usurp the
throne ...**

Basic Principles in Surgical Oncology

Blake Cady, MD *Presented at the 77th Annual Meeting of the New England Surgical Society, Dixville Notch, NH, September 27, 1996.*



**but current therapies often fail
to overcome the powerful forces
of the King and the Queen**

Clinical Trials

Improve Decision Making...

Can address the known knowns...

*...but cannot completely
remove uncertainty*

In the Absence of Certainty:

Prospect Theory

Philosophy and Perspective Matter


- 1. Simplify Choices*
- 2. Frame the Decision*
- 3. Estimate probability*



**Biases
and
cognitive
dissonance**

Verma AA, Razak F, Detsky AS: JAMA 311:6, 2014

Perspective Contextualizes and Validates Approach



Effective Systemic Therapy

Level 1 data




Validates pt/MD perspectives

Validates
pt/MD
perspectives



SOC and population based
data

Systemic Rx
not curative



**Carmena does put an end to
unnecessary**

Cytoreduction

**Biology is King
Selection is Queen**

Unbiased judgment and surgical excellence are Prince and Princess

so I struggle less....

**advise the right treatment for mRCC
in the right patient
at the right time**

(Cytoproactive Rx will cure more RC patients) – selection will become easier