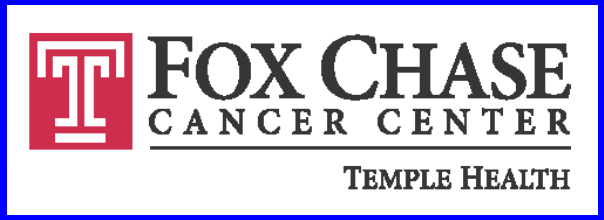
Surgical Considerations (Impediments) for Adjuvant Therapy Trials:

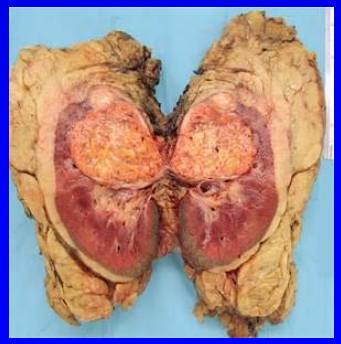
Robert G. Uzzo, M.D.

Willing G. Pepper Chairman of Surgery
Fox Chase Cancer Center
Temple University School of Medicine
Chair, Department of Urology
Urological Institute at Einstein Healthcare Network
Philadelphia, PA USA



We are all managers of health care risk

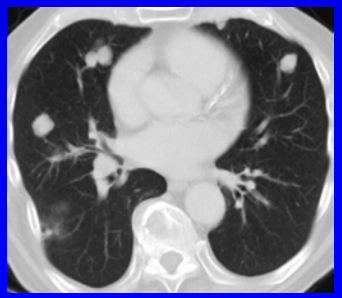
We seek to understand, predict and prevent future health care events



Adjuvant

→

Biomarkers
Clinical Models



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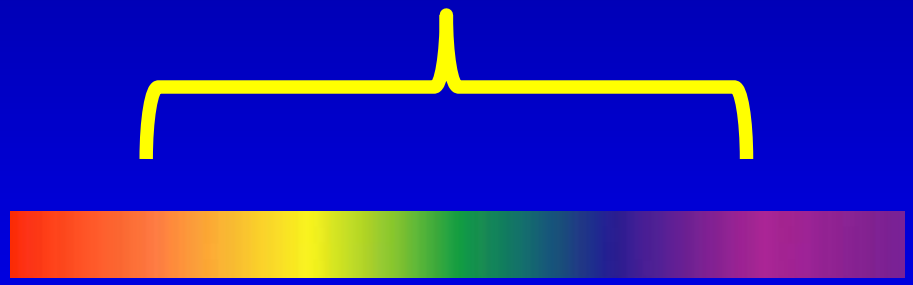
Adjuvant Rx space in solid tumors



Incompletely effective (high quality) surgery

Completely effective systemic Rx

WHO??

Prognostic Biomarkers in ccRCC

	HR (95% CI)	P
Clinicopathologic factors		
ECOG PS	4.610 (2.077-10.23)	<0.001
T classification	2.889 (1.918-4.352)	<0.001
Tumor size	1.234 (1.147-1.329)	<0.001
Fuhrman grade	2.073 (1.215-3.537)	0.008
UISS group	5.032 (2.856-8.865)	<0.001
Molecular markers		
p53	1.042 (1.020-1.065)	<0.001
VEGF-D (epithelial)	0.980 (0.968-0.992)	0.002
VEGFR-1 (endothelial)	1.038 (1.014-1.063)	0.002
VEGFR-1 (epithelial)	1.017 (1.004-1.029)	0.008
Ki-67	1.041 (1.004-1.079)	0.028
p21 (nuclear)	0.980 (0.962-0.999)	0.037
p27 (nuclear)	0.984 (0.966-1.002)	0.079
pS6	1.009 (0.999-1.019)	0.087
CAXII	0.990 (0.978-1.002)	0.099
VEGF-A (epithelial)	1.009 (0.997-1.020)	0.158
EpCAM	0.987 (0.969-1.006)	0.173
p21 (cytoplasmic)	0.979 (0.942-1.016)	0.263
VEGF-D (endothelial)	0.835 (0.600-1.162)	0.286
Gelsolin	1.005 (0.996-1.014)	0.312
pAkt (nuclear)	0.990 (0.969-1.011)	0.340
VEGF-A (endothelial)	1.007 (0.993-1.021)	0.350
VEGF-C (epithelial)	1.007 (0.993-1.021)	0.351
Vimentin	1.006 (0.993-1.019)	0.358
CXCR3	0.996 (0.984-1.008)	0.497
pAkt (cytoplasmic)	1.004 (0.992-1.016)	0.535
VEGFR-3 (endothelial)	1.003 (0.991-1.016)	0.612
VEGFR-2 (epithelial)	1.003 (0.992-1.014)	0.613
CAIX	1.003 (0.991-1.015)	0.651
PTEN	1.003 (0.990-1.016)	0.653
VEGF-C (endothelial)	1.006 (0.977-1.036)	0.702
p27 (cytoplasmic)	0.995 (0.966-1.024)	0.723
VEGFR-3 (epithelial)	1.005 (0.973-1.037)	0.778
VEGFR-2 (endothelial)	1.004 (0.971-1.038)	0.816
HIF-1α	0.999 (0.985-1.013)	0.909

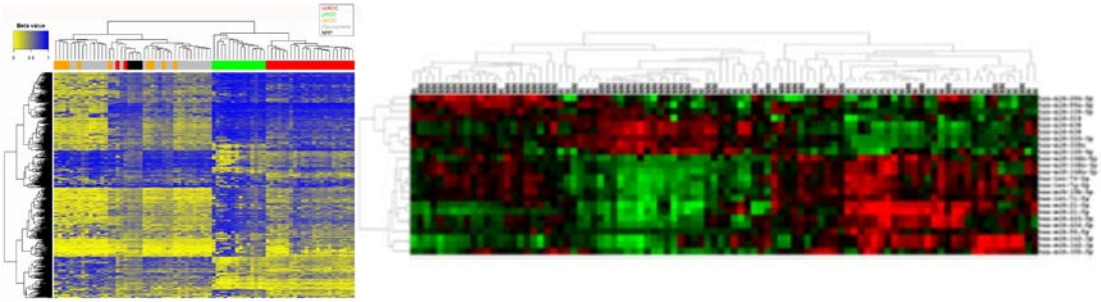
Cancer Epidemiol Biomarkers Prev 2009;18(3). March 2009

Stage
Grade
Histology

Genome-Wide Promoter Methylome of Small Renal Masses

PLOS ONE | www.plosone.org October 2013 | Volume 8 | Issue 10

Ilsiya Ibragimova[1], Michael J. Slifker[2], Marie E. Maradeo[1], Gowrishankar Banumathy[1], Essel Dulaimi[3], Robert G. Uzzo[4], Paul Cairns[1]*



MicroRNA expression signatures of stage, grade, and progression in clear cell RCC.
Cancer Biol Ther, 15 (3): 2014
Gowrishankar, Ibragimova, Zhou, Slifker, Devaraian, Al-Saleem, Uzzo and Cairns

Risk Models for "Localized" RCC

Model	Presentation	Reported/Externally validated C-index
UISS N=814	KM estimates	0.73/0.64-0.86
MSKCC* N=701	Nomogram	0.82/0.79-0.82
SSIGN N=1801	Points based algorithm	0.84/0.76-0.88
Leibovich* N=1671	Points based algorithm	0.82/0.7-0.86
Karakiewicz N=2474/2530	Nomogram	0.89/0.75-0.91
Yaycioglu	Formula	0.65/0.63-0.70
Condolo	Formula	0.67/0.63-0.75

1. *TNM stage*
2. *Nuclear Grade*
3. *Tumor Size*
4. *Performance Status*
5. *Presentation (symptoms)*
6. *Age*
7. *Gender*
8. *Coagulative necrosis*

All models retrospective

* Localized pts only

Risk Models for “Localized” RCC

Model	1° outcome	# events in NoMo patients
MSKCC*	RFS	72
Leibovich*	MFS	479
Karakiewicz	RCC specific survival	?
SSIGN	CSS	?
UISS	OS	14

565 “events” in NoMo patients predicted by these models

Eligibility for most recent adjuvant RCC RCT based on these predictive tools

n ± 10,000 pts accrued

Surgical Considerations for (neo)adjuvant Therapy Trials in RCC

1. Timing (and clonality)

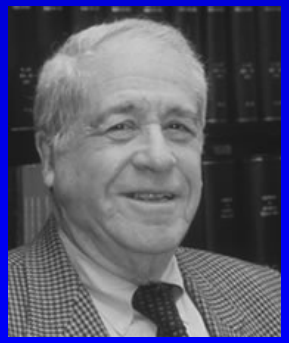
2. Technique
   a. Node dissection
   b. Margin status

3. Toxicity

4. Tenacity

TIMING
(and clonality)

OR



Timing of Adjuvant Rx

Micrometastases (CTCs) (Halstedian)

Subclinical Stage IV/ Clinical Stage IV

Clinical Stage 3

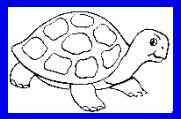
Clinical Stage 2

Clinical Stage 1

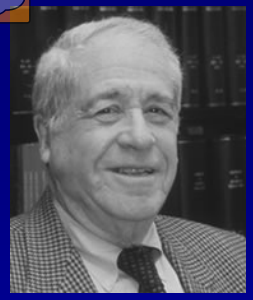
0

Adjuvant Rx

1 x $10^9/cm^3$



CTCs



Timing of Adjuvant Rx

Micrometastases (CTCs) (Fisheresque – NSABP)

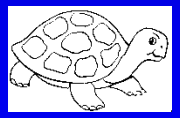
Sub clinical Stage IV / Clinical Stage IV

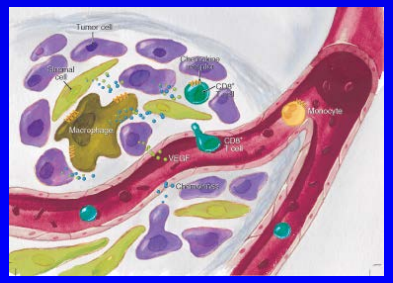
Clinical Stage 3

Clinical Stage 2

Clinical Stage 1

0 Adjuvant Rx $1 \times 10^9/cm^3$





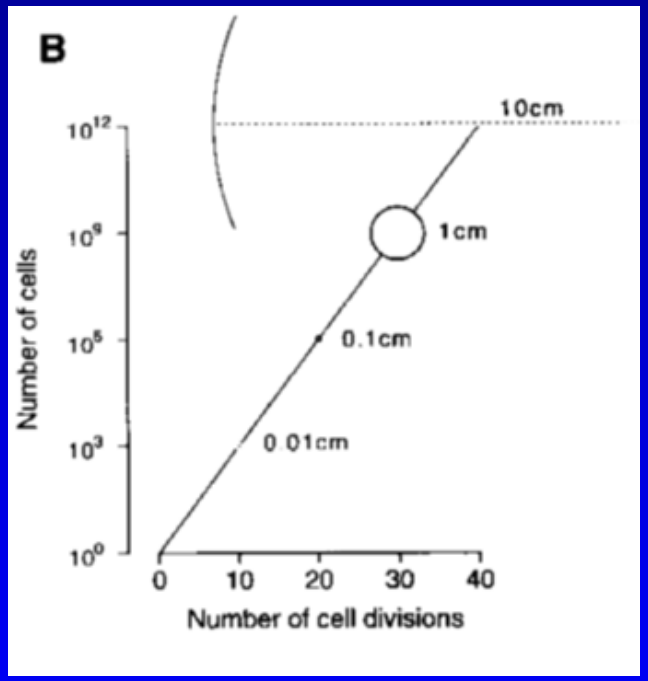
CTCs

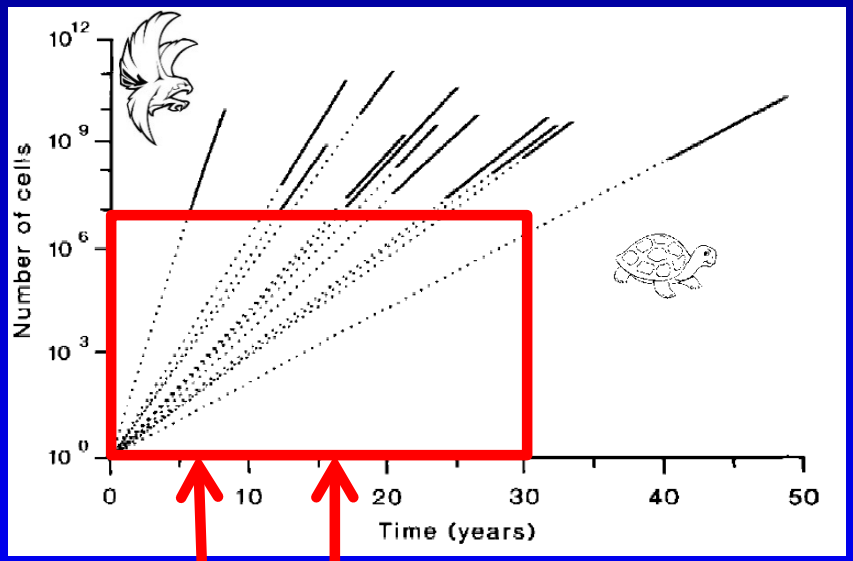
How long is the process of micromets in RCC?

Exceptionally variable!

On the Growth Rates of Human Malignant Tumors: Implications for Medical Decision Making

Journal of Surgical Oncology 1997;65:284–297





A 1 cm tumor = 10^9 cells (billion)
+/- 40 tumor doublings

Primary	TVDT[a] (days)	Number of cases	References
Kidney	66	5	Chahinian and Israel [66]
"	89	12	Fujimoto et al. [46]
"	132	8	Brenner et al. [24]

Full Spectrum “omic” Heterogeneity

DNA RNA Proteins Metabolytes

Courtesy of Jonathan Chernoff, MD, PhD.

Surgical Issues in Timing/eligibility for Adjuvant Trials

Is this patient surgically eligible for an adjuvant trial?

- **Patient with partial nephrectomy 3 yrs prior**

- **Tumor recurrence in residual kidney with local LN metastasis and soft tissue metastasis (fat tissue)**

Does the renal recurrence represent:
Local persistence?
Primary recurrence?
Persistent multifocal?
New event?

Which is the N+ metastasis from? What about the soft tissue clone?

Who's call is it??

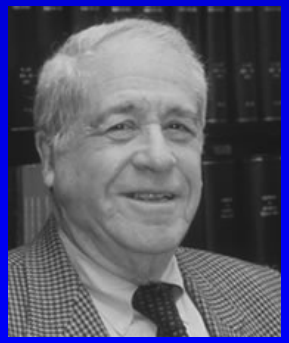
Surgical Implications

- The Role of lymphadenectomy?
- The Role of cytoreduction or metastasctomy?
- The Role of neoadjuvant or adjuvant Rx????

Science **357**, 55–60 (2017)

TIMING
(and clonality)

AND



Surgical Considerations for (neo)adjuvant Therapy Trials in RCC

Technique:

- Node dissection

- Margin status
  Venous margins/partials/other

Surgical Progress in Advanced RCC

- We have debated role of lymphadenectomy
  - Conclusions ….
    - We have defined how poor N+ disease is
    - We don't do enough LNDs (we think)
    - We refined "at risk" populations
    - We debate if lymphadenectomy is diagnostic or therapeutic (and have failed to answer the question)
    - ***We have not changed OS***

Radical Nephrectomy with and without Lymph-Node Dissection for T1 RCC

EORTC 30881

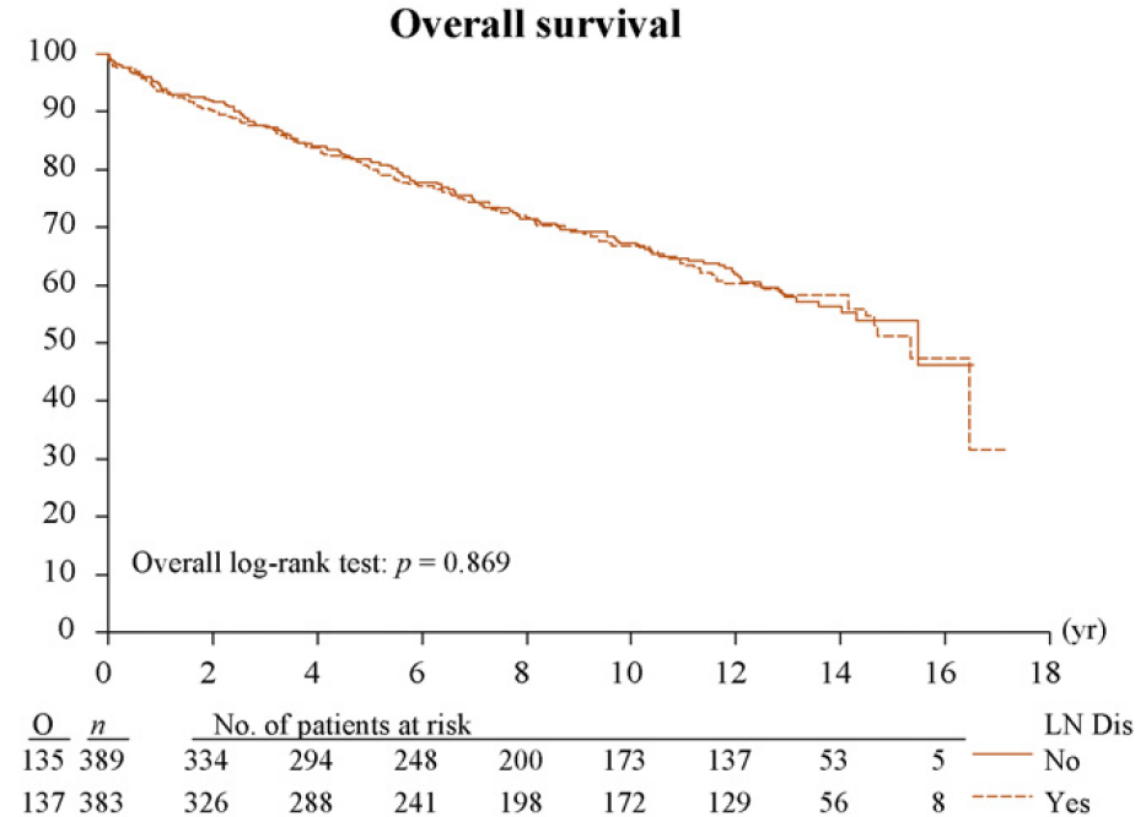


Fig. 1 – Overall duration of survival. O: number of deaths; *n*: total number of patients; LN Dis: lymph node dissection.

If cNo…

then <5% were pN1

implying you don't

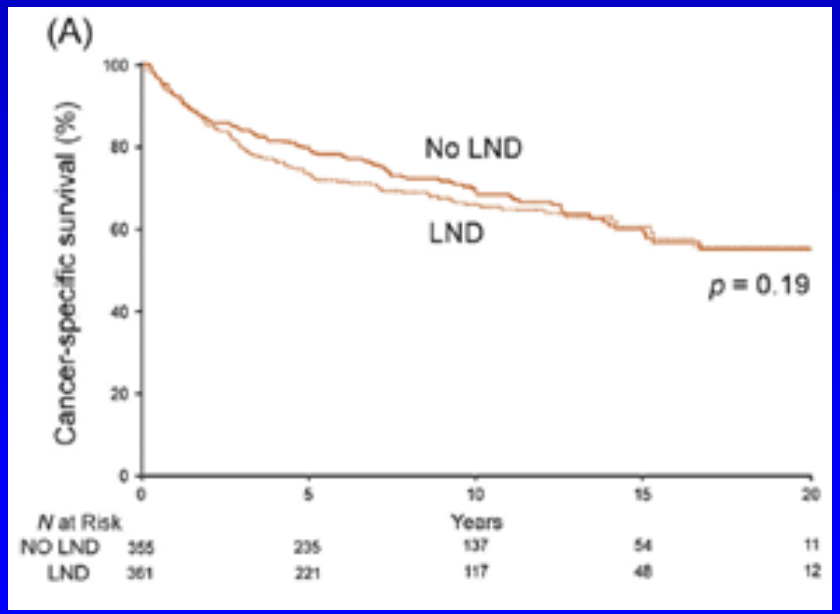
need to do LN dissection

J. H.M. Blom et al., Eur Urol., 55:28-34, 2009

Lymphadenectomy?...NO

High Risk No or N1 RCC Patients

- N=606/1797 (34%) RN for Mo RCC had LND at Mayo Clinic 1990 – 2010
- N=111 (6.2%) N+
- 1:1 Propensity matching – no difference in DSS, OS



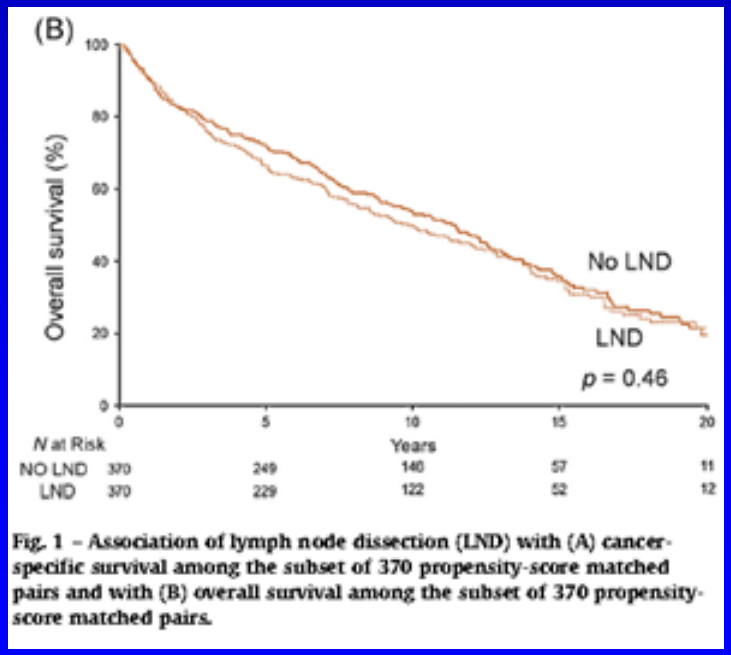


Fig. 1 – Association of lymph node dissection (LND) with (A) cancer-specific survival among the subset of 370 propensity-score matched pairs and with (B) overall survival among the subset of 370 propensity-score matched pairs.

Gershman et al: Euro Urol, 2016

AUA Guidelines 2017

Surgical Principles

20. For patients who are undergoing surgical excision of a renal mass with clinically concerning regional lymphadenopathy, physicians should perform a lymph node dissection for staging purposes. (Expert Opinion)

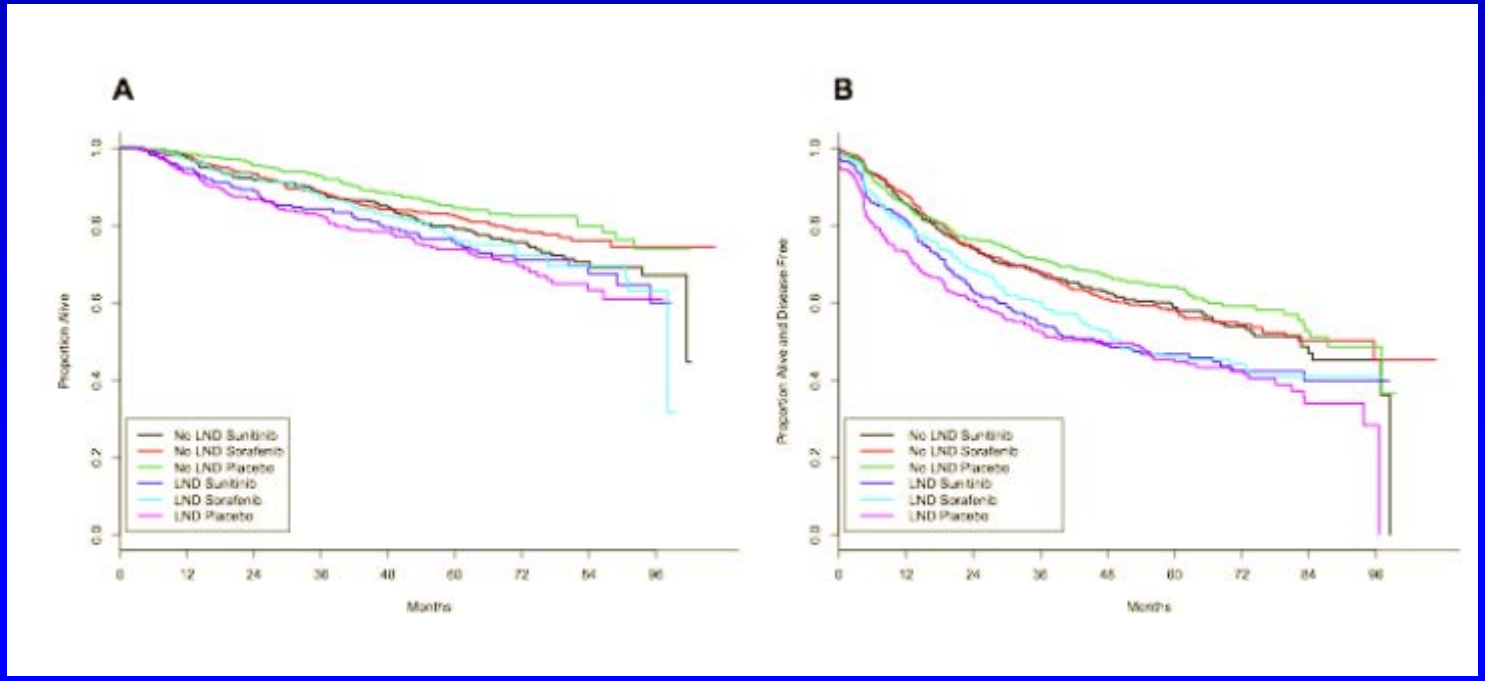
If suspicious lymphadenopathy is identified on imaging or during surgical exploration, a lymph node dissection (LND) should be performed primarily for staging and prognostic purposes.[34] Selective performance of LND for patients who may have locally advanced disease can also be considered for staging purposes.[34] Recent studies have been unable to confirm a survival benefit for LND for RCC.[35] If lymph node involvement is confirmed on final pathology, medical oncology consultation should be considered. Level-1 evidence has contributed to strong consensus that LND need not be performed in patients with localized kidney cancer and clinically negative nodes.[36]

Lymphadenectomy during Surgery for high risk RCC: Results from ASSURE Trial

36% of pts (701/1943) underwent LND in ASSURE

- All with cN+ and 30% of those with cNo
- 23% pN+
- Average LN yield n=3 (IQR 1-8) without an agreed upon template
- No increase in complications
- No improvement in OS/DFS observed in placebo vs adjuvant arms of cNo, pNo or pN+

Overall Survival (A) and Disease-free Survival (B) by Adjuvant Arm and LND Category



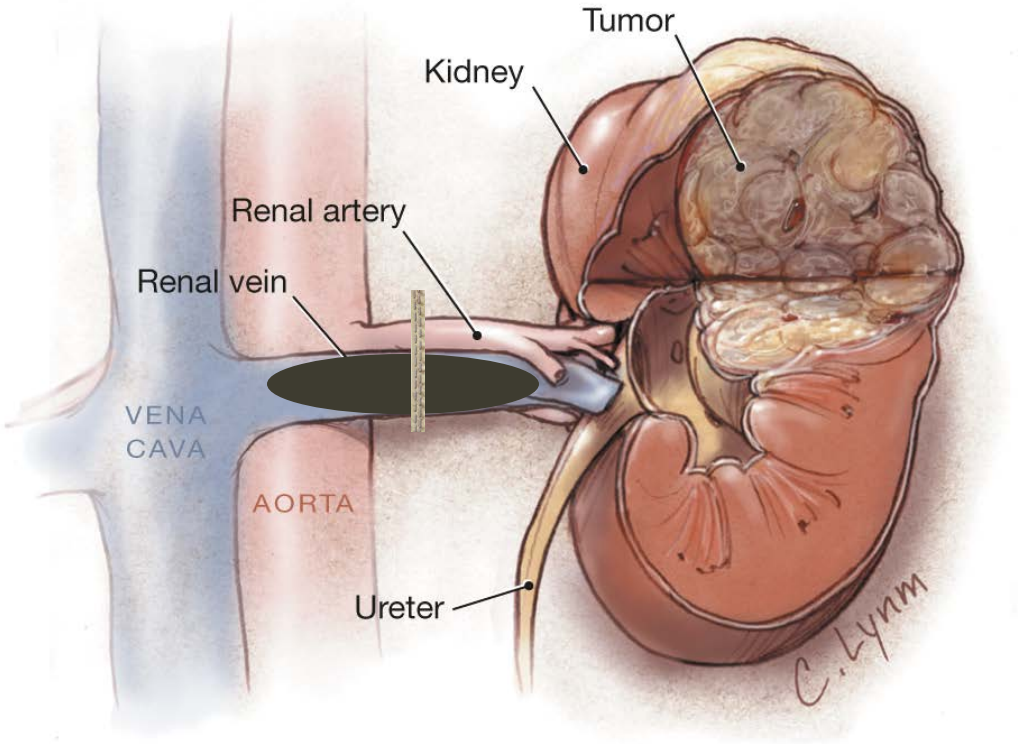
Ristau, Haas and Uzzo et al., J Urol July 2017

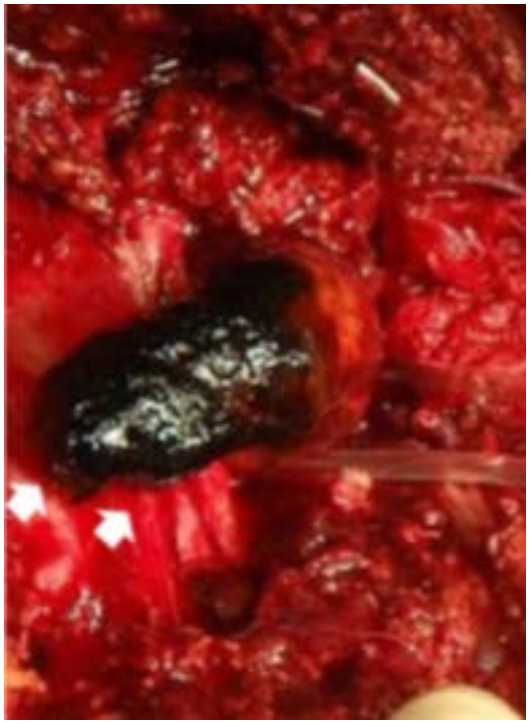
Margin Status…R0 vs R1

(R2 less of a concern)

- **A combination of what the surgeon "sees" and what the pathologist "sees"**
  - **Lack of standardization re:**
    - **role of frozen section**
    - **inking process**
    - **Intraoperative communication**
    - **Extent of margin sampling (surgical AND pathological)**
- **Lack of evidence that microfocal margins "matter" for low risk disease**
  - **Implications for high risk disease??**
- **Biologically relevant margins??**
  - **Does fat = parenchymal = vascular??**
- **Reporting venous margin**

Science **357**, 55–60 (2017)


Tumor
Kidney
Renal artery
Renal vein
VENA CAVA
AORTA
Ureter
C. Lynn



Surgical Considerations for (neo)adjuvant Therapy Trials in RCC

Toxicity:

The surgical bar is high!!

ACS Calculator – *Lap* RNx

75 yo male
ASA II
Healthy
71”
230 lb

Serious complication = 5%
Any complication = 6%
LOS = 2days

http://riskcalculator.facs.org

2017: AUA Guidelines/AHRQ: Complication Risks

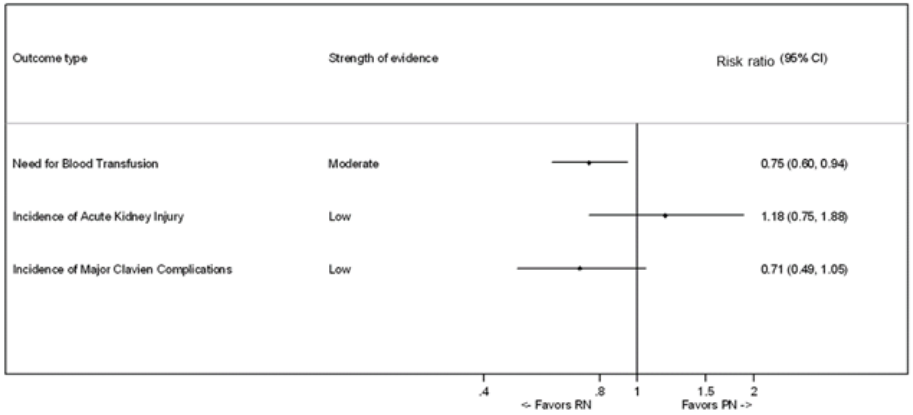
Perioperative outcomes and harms

N=38 studies,11,802 pts evaluated perioperative outcomes including:

- **EBL, transfusions, conversions and LOS**
- **N=24 studies compared RNx to PNx**

patients respectively.[17] When considering specific harms, partial nephrectomy had higher rates of urologic complications (including renal abscess, ureteral injury, urine leak and subsequent interventions) when compared to radical nephrectomy (low strength of evidence) and thermal ablation (low strength of evidence). However, rates of minor and major complications were similar among all three treatment modalities. Thermal ablation had the lowest reported rates of

Figure E. Pooled comparisons of perioperative outcomes and harms for radical nephrectomy (RN) versus partial nephrectomy (PN) from studies that presented effect estimates as risk ratios



CI: Confidence interval

Pierorazio et al: 2016 AHRQ report

Toxicities of Systemic Therapies in RCC

- **mAb against VEGF**
  - **Hypertension, proteinuria, poor wound healing**
- **Tyrosine Kinase Inhibitors**
  - **HTN, fatigue, hand foot syndrome, nausea, diarrhea**
  - **LV dysfunction, hypothyroid, stomatitis, hematopoietic**
- **mTOR inhibitors**
  - **Stomatitis, pneumonitis**
  - **Hyperlipidemia**
- **Checkpoint inhibitors**
  - **Autoimmune disorders**

RCTs and systemic therapy complicate the surgical "episode" of care
…and people are…
……..watching
…….measuring
……grading "surgical" care

Most autoimmune toxicities are reversible with immunosuppression (steroids) – *Implications for surgery*

VOLUME 30 · NUMBER 21 · JULY 20 2012
JOURNAL OF CLINICAL ONCOLOGY REVIEW ARTICLE

Management of Immune-Related Adverse Events and Kinetics of Response With Ipilimumab

Jeffrey S. Weber, Katharina C. Kähler, and Axel Hauschild

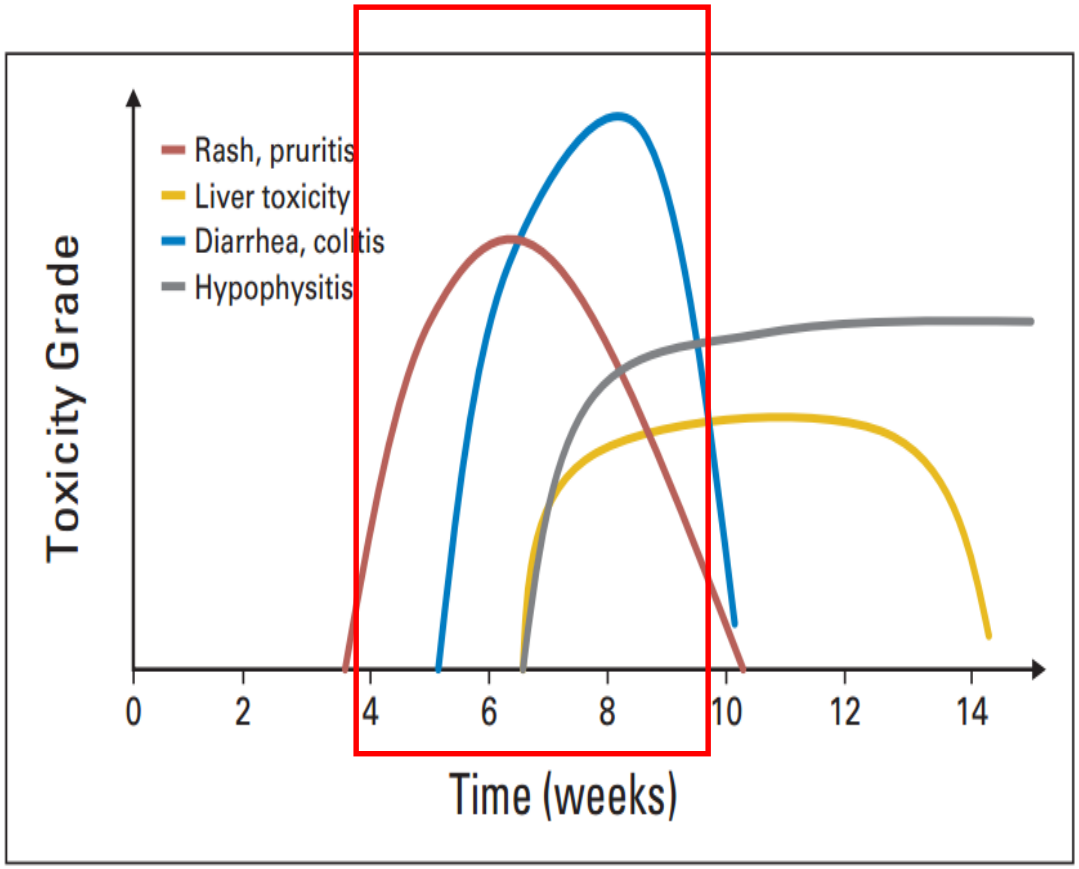
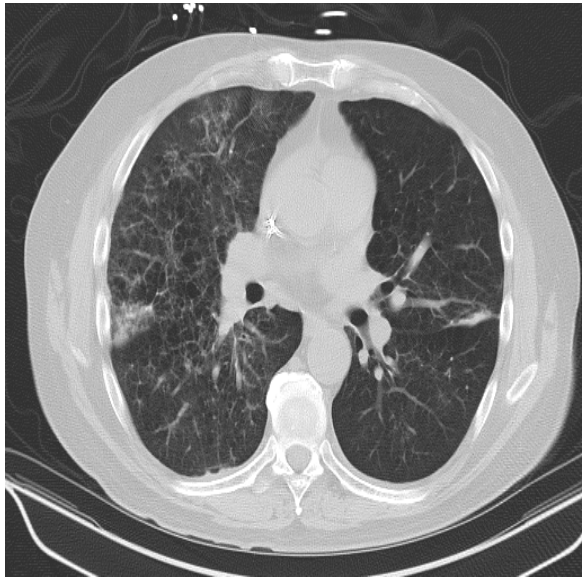
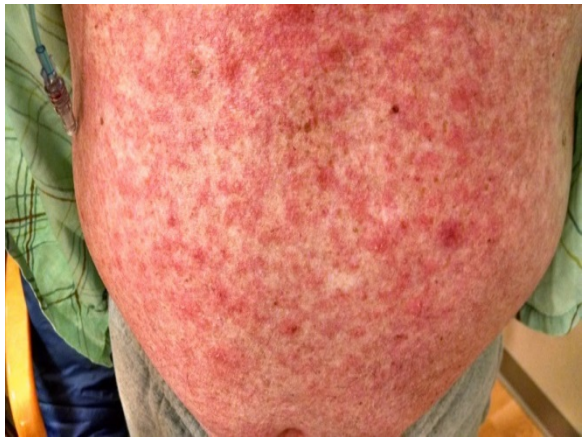


Fig 2. Kinetics of appearance of immune-related adverse event.

Autoimmune toxicities seen with checkpoint inhibitors

- Endocrinopathies
  - Hyper → Hypothyroid
  - Central adrenal insufficiency
- Pneumonitis
- Diarrhea / Colitis
- Rash
- Myositis
- Neurotoxicity
  - Guillain-Barré syndrome
  - Cranial Nerve Palsy





Surgical Considerations for (neo)adjuvant Therapy Trials in RCC

Tenacity

Getting surgeons into an RCT mindset

Examples of successes in RCC

- **ASSURE, STRAC, PROTECT, ATLAS, ARISER etc….**

- **"ADAPT Trial" *(AGS-007 - Argos Therapeutics)***

  - Phase 3 Open-Label Randomized Study

  - Cytoreductive NTX followed by Sunitinib vs Sunitinib + AGS-003

  - **Largest cytoreductive NTX trial ever performed to date**

  - **N= 1133 nephrectomies to randomize 462 patients to treatment**

  - **SUO-CTC performed 712 (62% of total) nephrectomies and randomized 284 (61% of randomized pts) patients to treatment**

7+ years to accrue n=246 patients in SWOG 8949 (1991 – 1998)
2.5 yrs to collect n = 1133 cytoreductive NTX specimens (Nov 2012 – July 2015)

Surgical Considerations (impediments) for (neo)adjuvant Therapy Trials in RCC

1. **Risk tools (models) are poor**

2. **Timing (and clonality) = undefined**
   - “a chance to cut is a chance to cure”

3. **Technique = non standardized**

4. **Toxicity = a concern**

5. **Tenacity = an evolving culture of RCTs**