# Renal Cell Cancer Past, Present and the Future

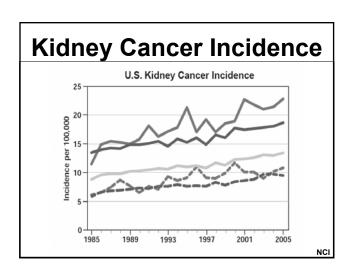
Ahmad Shabsigh, MD
David Sharp, MD
Assistant Professors of Urology
Urologic Oncology

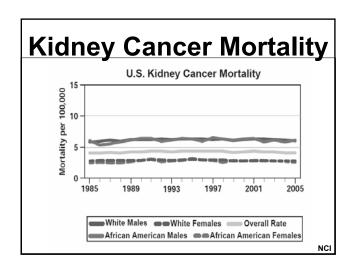
# **Presentation By Stage**

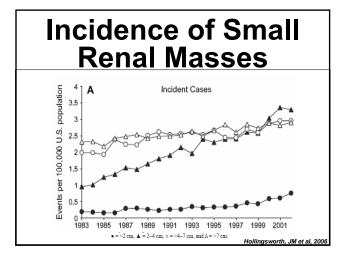
- 58% localized to kidney
- 18% locally advanced or to regional LNs
- 19% with metastatic disease

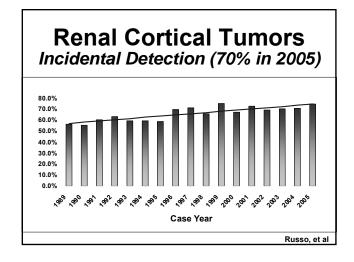
# Renal Cell Carcinoma Epidemiology

- Incidence (2009)
  - ✓ Estimated >49,000 new cases
  - √ >11,000 deaths
  - √ 2% of all cancers in US each year
  - ✓ Almost 300,000 alive with a history of disease
- Median age of diagnosis is 64 years, median age at death is 71 years









# **Etiology**

- More than 100 chemicals were investigated in animal models such as aromatic hydrocarbons, no specific agent has been definitively established as causative in human RCC
- Smoking
- Slightly increased relative risks for workers in the metal, chemical, rubber, and printing industries
- Obesity, low socioeconomic status, and urban background
- Thorotrast (which was used as a contrast agent in the past), radiation therapy, and antihypertensive medications

# Sporadic and Hereditary RCC

Sporadic R	enal-Cell Ca	rcinomas	Renal-Cell Carcinomas	in an Inherited Syndrome
Histologic Appearance			Rare Syndrome†	Gene
Conventional	75	VHL, 60	VHL disease FCRC Hereditary paraganglioma	VHL Chromosome 3p translocation SDHB
Papillary	12	MET, 13 TFE 3, <1	HPRC HLRCC	MET FH
Chromophobe	4		Birt-Hogg-Dubé syndrome	BHD
Oncocytoma	4		Birt-Hogg-Dubé syndrome	BHD
Collecting duct	<1			
Unclassified	3-5			
				Cohen HT et al, 2005

## Renal Masses Classified by Pathologic Features

Malignant	Benign	Inflammatory
Renal cell carcinoma Conventional Chromophilic Chromophilic Chromophobic Collecting duct Urothellum based Transitional cell carcinoma Squamous cell carcinoma Adenocarcinoma Sarcoma: Leiomyosarcoma, Liposarcoma, Angiosarcoma, Liposarcoma, Melmangiopericytoma Malignant fibrous histilocytoma, Synovial sarcoma, Cateogenic sarcoma, Ciear cell cateogenic proma Wilms' tumor Primitive neuroectodermal tumor Carcinoid Lymphoma Leukemia Metastases	Simple cyst Anglomyolipoma Oncocytoma Renal adenoma Cystic nephroma Mixed epithelial-stromal tumor Reninoma (JG cell tumor) Lelomyoma Fibroma Hemangioma Vascular Renal artery aneurysm Arteriovenous malformation Pseudotumor	Abscess Focal pyelonephritis Xanthogranulomatous pyelonephritis Infected renal cyst Tuberculosis Rheumatic granuloma

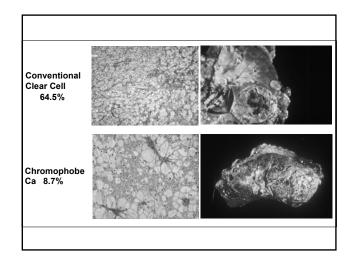
# **Clinical Presentations**

- 80% incidental
- Flank pain
- · Gross hematuria
- · Palpable mass
- Microhematuria
- Paraneoplastic syndromes (10-20%)

### 1997 Heidelberg Classification Renal Cortical Tumors

- · Benign Parenchymal Neoplasms
  - ✓ Metanephric Adenoma
  - √ Metanephric adenofibroma
  - ✓ Papillary renal cell adenoma
  - √ Renal Oncocytoma
- Malignant Parenchymal Neoplasms
  - √ Conventional renal cell carcinoma (Clear Cell)
  - ✓ Papillary renal cell carcinoma
  - √ Chromophobe renal cell carcinoma
  - ✓ Collecting duct carcinoma
    - · Medullary carcinoma of the kidney
  - ✓ Unclassified

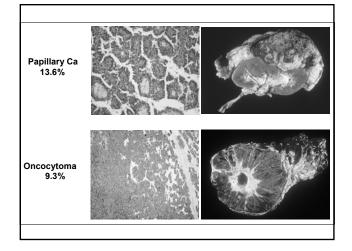
Kovacs, G., Akhtar, M., and Beckwith, B. J. J Pathol, 183: 131, 1997



# **Imaging: IVP**

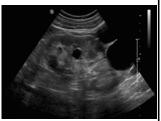
- Intravenous pyelography is rarely used
- Features suggestive of malignancy include
  - ✓ Calcification
  - ✓ Irregular margin
  - ✓ Increased tissue density
  - ✓ Distortion of the collecting system





# **Renal Ultrasound**

- Reliable for differentiation of solid mass from fluid and can establish the diagnosis of a simple renal cyst and complex renal cysts
- Helpful in suggesting the fat content of an angiomyolipoma (increased echogenicity)



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# **Renal Ultrasound**

- Reliable for differentiation of solid mass from fluid and can establish the diagnosis of a simple renal cyst and complex renal cysts
- Helpful in suggesting the fat content of an angio-myolipoma (increased echogenicity)
- Increased vascularity with doppler may indicate malignancy.
- Using microbubble contrast may be helpful (Wink et al2007)



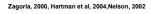
## **Renal Ultrasound**

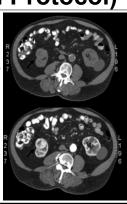
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- Increased vascularity with doppler may indicate malignancy.



# CT scan (Renal Protocol)

- Renal CT scan is the single most important radiographic test for defining the nature of a renal mass.
- Thin-slice CT scanning, with and without IV contrast
- Any renal mass that enhances by more than 15 Hounsfield units (HU) should be considered a renal cell carcinoma until proved otherwise
- Solid masses with areas of negative CT attenuation numbers (below -20 HU) indicative of fat are diagnostic of AMLs
- In approximately 10% of solid renal masses, CT findings are indeterminate, and additional testing or surgical exploration is needed





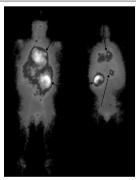
# **Magnetic Resonance Imaging**

- Should not be used routinely for evaluation of renal masses
- On T1 image Enhancement of renal mass with intravenous gadolinium-labeled diethylenetriamine-pentaacetic acid.
- This technique is most helpful in patients for whom iodinated contrast medium is contraindicated because of severe allergy.



### Cg250 Antibody For Pre-op Imaging

- Reacts only to clear cell renal carcinomas
- Antigen: Carbonic anhydrase-IX
- Normal tissue crossreactivity – bile duct – saturable

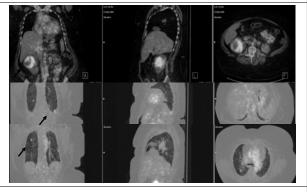


Ludwig Institute for Cancer Research

# **CT PET Scan**

- There is no role for CT PET-FDG in diagnosing primary lesion in the kidney
- Limited role for metastatic disease and local recurrence

# cG250 PET CT Scan



# cG250 PET CT Scan



# **Renal Mass Biopsy**

- Fine needle aspiration
- · Core biopsy
- · Complications:
  - √ 44% subcapsular hematoma on post biopsy CT scan.
  - ✓ Clinically significant bleeding is unusual and almost always self-limiting
  - ✓ Infections and pneumothorax are rare
  - √ Tumor Seeding

Volpe, et al 2006

# **Renal Mass Biopsy**

- · Routine renal mass biopsy is not indicated.
- · US or CT scan guidance
  - ✓ Advantages of US: portability, multiplanar and real-time imaging, and lower cost
  - ✓ Advantages of CT:
    - Gas and other structures do not obscure visibility
    - · Excellent spatial resolution
    - Better needle visualization
    - · Easier to avoid necrotic areas
    - Rapid skill acquisition

# Renal Mass Biopsy

References	No. Tumors Biopsied	Imaging Guidance	Needle Size (gauge)	% Nondiagnostic Biopsies	No. Malignant Biopsies/No. Pathologically Confirmed	% Outcomes
Wood et al <sup>8</sup>	79*	CT/US	22 (FNA), 17-20 (cores)	6.3	49/41	Sensitivity 93, accuracy 95
Lechevallier et al <sup>15</sup>	73	CT	18	21	48/26	Concordance biopsy + surgica diagnosis 89
Hara et al <sup>13</sup>	33	CT/US	18	0	21/15	Concordance biopsy + surgica diagnosis 86.7
Caoili et al <sup>24</sup>	26	US	18	0	19/4	Sensitivity + specificity 100
Harisinghani et al <sup>39</sup>	28*,†	CT	22(FNA), 18(cores)	0	17/16	Concordance biopsy + surgica diagnosis 100
Neuzillet et al <sup>9</sup>	88	CT	18	9.1	66/62	Accuracy 92
Eshed et al <sup>14</sup>	22	CT	18	4.5	15/14	Sensitivity 93, specificity 100
Shah et al <sup>29</sup>	66	CT/US	18	21	37/15	Accuracy 98

Volpe, et al 2006

# **Renal Mass Biopsy**

		TABLE 3. Accure	acy of renal mass	FNA in recent series		
References	No. Biopsies	Imaging Guidance	Needle Size (gauge)	% Nondiagnostic Biopsies	No. Malignant Biopsies/No. Pathologically Confirmed	% Accuracy
Cristallini et al <sup>31</sup>	72	CT/US	21-22	7.1	34/22	Sensitivity 89.2, specificity 97.1
Niceforo and Coughlin <sup>32</sup>	23	CT	22	0	12/6	Sensitivity 80, specificity 100, accuracy 87
Campbell et al <sup>34</sup>	25	CT	22	24	19/19	Sensitivity 76
Truong et al <sup>7</sup>	108	CT/US	23-25	16	46/46	Sensitivity 97, specificity 100

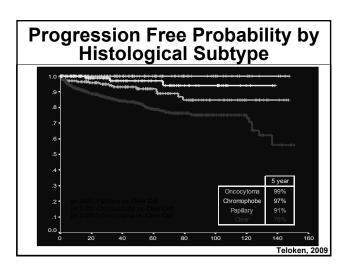
Volpe, et al 2006

# **Prognostic Factors**

- Stage TNM
- Histological type
- · Fuhrman grade
- · Performance status
- MSKCC Criteria
- Molecular markers

# Indications for Renal Mass Biopsy

- Rule out nonrenal cell primary tumors (mets or lymphoma)
- Rule out benign lesions
- Confirm the diagnosis and the histological subtype of a renal primary lesion in patients with metastases or unresectable masses
- Confirm diagnosis prior to ablations
- Confirm diagnosis for patient considering observation or when surgery is high risk



# **Therapeutic Modalities**

David Sharp, MD

# Chronic Kidney Disease (2000-present)

Independent Risk Factor for CVD

Kidney Disease as a Risk Factor for Development of Cardiovascular Disease tatement From the American Heart Association Councils on Kidney Cardiovascular Disease, High Biodo Pressure Research, Clinical Cardiology, and Epidemiology and Prevention

# **Treatment of Small Renal Tumors**

- · A plethora of options
  - ✓ Surveillance
  - √ Radical nephrectomy (open/ lap/ robotic)
  - ✓ Partial nephrectomy (open/ lap/ robotic)
  - √ Ablative
    - Cryoablation
    - · Radiofrequency ablation

Chronic Kidney Disease
(2000-present)
Independent Risk Factor for CVD

#### AHA Scientific Statement

h Chronic Kidney Disease as a Risk Factor for Cardiovascular A Stat Disease and All-Cause Mortality: A Pooled Analysis of Community-Based Studies

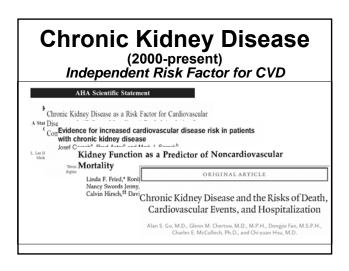
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PAUL C. STARK,\* BONNE MACLEOD,\* JOHN L. GRIFFITH,\* DEED N. SALEM,\*
ANDER W. S. LEVY,\* and JAMEN, S. ASANIAN,\*
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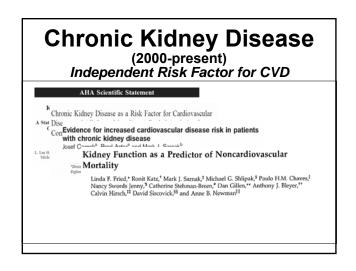
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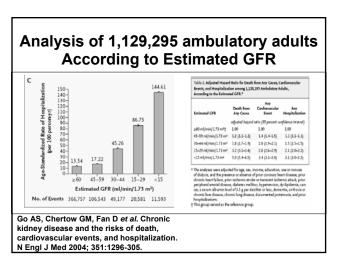
\*\*The Company of Cardinings\*\*

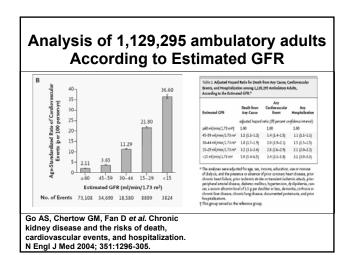
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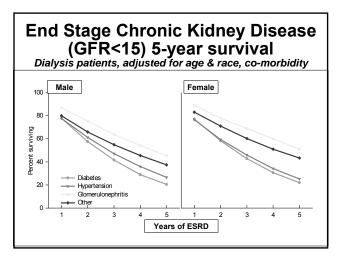
# Chronic Kidney Disease (2000-present) Independent Risk Factor for CVD AHA Scientific Statement Confevidence for increased cardiovascular disease risk in patients with chronic kidney disease Josef Coresh\*, Brad Astor\* and Mark J. Sarnak\* 1 Les II 1 Mich 1 Sprinning, Deprense of Circuit Care Bossech, and Disease of Careling, Top-Nov Process of Single-Deprense of Circuit Care Bossech, and Disease of Careling, Top-Nov





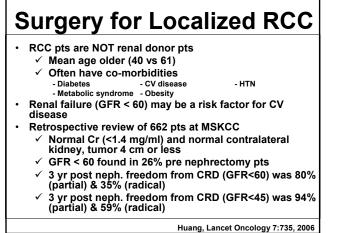


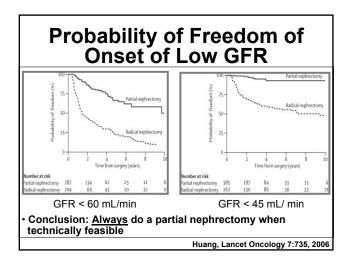




## 

N Engl J Med 2004; 351:1296-305.





# Partial nephrectomy with negative surgical margins = Radical nephrectomy For Local Recurrence and Overall Survival

Licht MR, Novick AC, J Urol 1993.

# **Under-utilized Kidney Sparing Centers vs. National Trends**

- MSKCC, Mayo Clinic, Cleveland Clinic, OSU: > 60% of kidney tumor operations are partial nephrectomy.
- U of Michigan Study: Nationwide Inpatient Sample of 54,069 patients undergoing kidney tumor surgery, only 9% were partial nephrectomy.
- PN more likely in recent years, major teaching centers, with high nephrectomy volumes (>28/yr).
- In 2009, partial nephrectomy rates up to 34% of tumors <4cm</li>

(Miller et al: J. Urol. 175:853, 2006)

# Who's a Candidate?

- Fesential
  - √ Tumor in solitary kidney (functional or anatomical)
  - ✓ CRF
  - ✓ AODM
  - ✓ Urolithiasis
  - ✓ Multifocal
  - ✓ Bilateral tumors (sporadic, familial, hereditary)

## Who's a Candidate?

- Elective
  - √ Renal tumor of 7cm or less, particularly if exophytic

## Who's a Candidate?

 Whoever has a tumor that is amenable to nephron-sparing approach

# Who's a Candidate?

- Extended
  - √ Renal hilar
  - √ Renal sinus
  - √ Large cystic tumors

# Robotic Partial Nephrectomy

- Minimally invasive-
  - ✓ Done through 4-5 small incisions
  - √ Less pain
  - √ Shorter recovery
- Easier, more precise intracorporeal suturing for renal reconstruction than traditional laparoscopic techniques
- Can assist for technically challenging cases, such as hilar and multiple renal tumors
- Difficulties-
  - ✓ Space limitations, ischemia time- requires warm ischemia, less precise reconstruction than open techniques, not all tumors amenable

# Robotic Partial Nephrectomy

- · Potential advantages
  - √ Smaller incisions
  - ✓ Quicker recovery
  - ✓ Less painful
- · Potential disadvantages
  - ✓ learning curve
  - ✓ Dependant on technical advances in instrumentation
  - ✓ Effective methods of cooling difficult
  - ✓ Precision of closure of collecting system and parenchyma



# **Case Presentation**

- 56 yo female, incidental finding of L renal mass
- L radical nephrectomy recommended, came for 2<sup>nd</sup> opinion
- PMHx sig for bilat LE lymphedema
- Preop GFR >60 mL/ min / 1.73 m<sup>2</sup>, SCr = 0.7 ng/mL



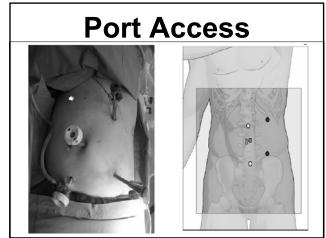












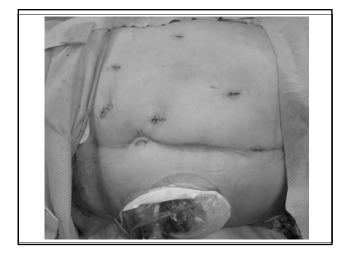


Dr. Sharp's Video

# Who's a candidate?

· Not just the skinny easy ones





# **Open vs Min Invasive Partial Nx**

Comparison of 1,800 Laparoscopic and Open Partial Nephrectomies for Single Renal Tumors

Inderbir S. Gill, Louis R. Kavoussi, Brian R. Lane, Michael L. Blute, Denise Babineau, J. Roberto Colombo, Jr., Igor Frank, Sompol Permpongkosol, Christopher J. Weight, Jihad H. Kaouk, Michael W. Kattan and Andrew C. Novick\*

Pron the Glichema Urelogical Institute 180, BBL, BBC, CIW, ACO, and Department of Quantitative Health Sciences (DB, MWK). Circuland Clinic, Circuland, Ohio, and Department of Virology, The Johns Hopkins Houpital (LBR, SP), Baltimere, Maryland, and Mayo Clinic (GLR, Do, Rochester, Manuscola).

0022-5347/07/1781-0041/0 The Journal of Unilogy® Copyright © 2007 by American Urological Association

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# Open vs Min Invasive Partial Nx

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LPN: ↓ EBL, LOS, O.R. time

LPN: ↑ ischemia, complications (post-op hemorrhage)

Cancer control same

Renal function same

The Journal of Uniocoy®

Vol. 178, 41-46, July 2007 Printed in U.S.A. DOI:10.1016/j.juro.2007.03.038

## What Technique When?

· What is important is:

Location, Location, Location.

Size Matters (but not that much)

Centrally-extending renal tumors require more complex reconstructions and are more likely to have post-op complications

- Robotic partial nephrectomy/ MIS for exophytic or when ischemia times comfortably less than 30 minutes
- Regardless of technique, goal is Nephron Sparing Surgery

# Robotic Partial Nephrectomy for Complex Renal Tumors: Surgical Technique

Table 2 - Summary of results after robotic partial nephrectomy for complex renal tumors

Mean warm ischemia time, min (range) Mean operative time, min (range) 192 (165-214) Mean blood loss, ml (range) Mean hospital stay, d (range) 2.6 (2.0-3.0) Mean increase in serum 0.03 (-0.2-0.2) creatinine at discharge, mg/dl (range) Mean decrease in eGFR, -5.6 (-3.4-15) ml/min/1.73 m2 (range) Complex tumor features (n) Endophytic Multiple eGFR = estimated glomerular filtration rate.

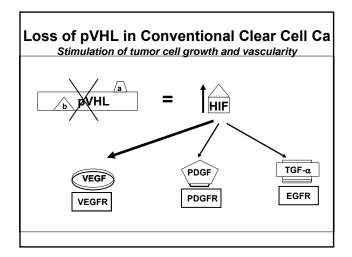
Craig G. Rogers\*\*, Amer Singh, Adam M. Blatt, W. Marston Linehan, Peter A. Pi

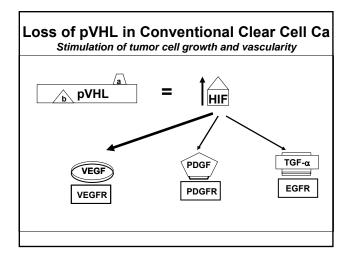
## **More Advanced Disease**

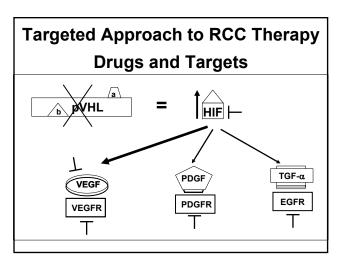
- Surgery remains a integral part of the management of patients with advanced disease
  - √ Metastatic disease
    - Cytoreductive nephrectomy (open or laparoscopic)
    - Excision of metastatic deposits
  - ✓ Tumor thrombus into IVC
  - ✓ Locoregional lymphadenopathy

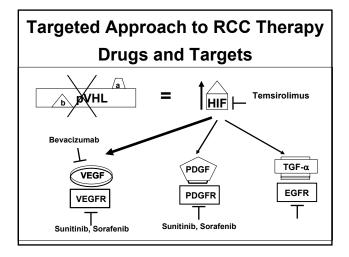
# Treatment of Metastatic RCC

- Until recently, options limited to immunotherapy regimens
  - √ IL-2 or IFN-α
  - √ Response rates low (10-15%)
  - √ Median survival 13 months at best
  - ✓ For those that failed first-line therapy, no effective treatment existed with response rates for second-line regimens <5%</p>









## **Cytoreductive Nephrectomy**

- Initially nephrectomy performed for palliation in patients with metastatic RCC
- Spontaneous regression noted in 0.8% of patients with metastatic disease
- Survival advantage of debulking radical nephrectomy followed by IFN-α in patients with metastatic RCC has been confirmed

# **Current Targeted Therapies**

- FDA approved:
  - √ Sunitinib (Sutent®, Pfizer)
  - ✓ Sorafenib (Nexavar®, Bayer/ Onyx)
  - ✓ Temsirolimus (*Torisel*™, *Wyeth*)
  - ✓ Everolimus (Afinitor™, asdf)
  - ✓ Pazopanib (Votrient™, GlaxoSmithKline)
  - ✓ Bevacizumab (Avastin®, Genentech) with IFN- α
  - √ IL-2

# SWOG 8949 and EORTC 30947

· Combined results:

<u>N</u>	ephrectomy/IFNα	<u>IFNα</u>
Pt number	161	163
Median OS (mos)	13.6	7.8 p=0.002
% Response	6.9	5.7 p=0.60

- Overall survival increased a median of 5.8 mos in pts who had a cytoreductive nephrectomy
- Healthier pts with less bulky disease did better than sick pts with kidney removal

Flanigan, J Urology 171:1071, 2004

How does this apply to oral targeted therapies?

# How does this apply to oral targeted therapies?

We don't know.....

Cytoreductive nephrectomy remains standard of care when surgically resectable

# How does this apply to oral targeted therapies?

We don't know.....

# **Areas of Exploration**

- Adjuvant therapy being explored in clinical trials
- In certain patients, neoadjuvant targeted therapy is a reasonable option
- Further research necessary to further delineate the role of targeted meds and surgery and in what order
- Multimodality treatment will be the mainstay of treatment for locally advanced and metastatic RCC

# **Conclusions**

- · Renal cell carcinoma is increasing in incidence
- · Imaging is increasingly precise and specific
- · Biopsy rarely indicated
- Nephron-sparing surgery is underutilized for the treatment of small renal masses
- The ability to offer NSS via minimally-invasive robotic surgery increases the acceptance
- Targeted therapies are leading to exciting advances in the treatment of advanced RCC
- Technological advances will continue to decrease morbidity while improving surgical outcomes and cancer cure