Renal Cell Cancer
Past, Present and the Future

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Urologic Oncology

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

Presentation By Stage

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

Kidney Cancer Incidence

U.S. Kidney Cancer Incidence

**Incidence per 100,000**

- 0 5 10 15 20 25

NCI
Kidney Cancer Mortality

U.S. Kidney Cancer Mortality

Incidence of Small Renal Masses

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

Clinical Presentations

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

Renal Masses Classified by Pathologic Features

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

**Conventional**
- Clear Cell 64.5%
- Chromophobe Ca 8.7%

**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 angio-myolipoma (increased echogenicity)
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.

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 diethylene triamine-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 cross-reactivity – bile duct – saturable

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### 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

[Imagery of CT and PET scans demonstrating differentiation and detection capabilities.]
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

- 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

**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

### Prognostic Factors
- Stage TNM
- Histological type
- Fuhrman grade
- Performance status
- MSKCC Criteria
- Molecular markers

### Progression Free Probability by Histological Subtype

![Graph showing progression free probability by histological subtype.](image-url)

- Oncocytoma: 99%
- Chromophobe: 97%
- Papillary: 91%
- Clear Cell: 76%

Teloken, 2009
Therapeutic Modalities

David Sharp, MD

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

Analysis of 1,129,295 ambulatory adults
According to Estimated GFR

Analysis of 1,129,295 ambulatory adults according to Estimated GFR


End Stage Chronic Kidney Disease (GFR<15) 5-year survival
Dialysis patients, adjusted for age & race, co-morbidity


End Stage Chronic Kidney Disease (GFR<15) 5-year survival
Dialysis patients, adjusted for age & race, co-morbidity

Huang, Lancet Oncology 7:735, 2006

Surgery for Localized RCC

- RCC pts are NOT renal donor pts
  - Mean age older (40 vs 61)
  - Often have co-morbidities
    - Diabetes
    - CV disease
    - HTN
    - Metabolic syndrome
    - Obesity
    - Renal failure (GFR < 60) may be a risk factor for CV disease
- Retrospective review of 662 pts at MSKCC
  - Normal Cr (<1.4 mg/ml) and normal contralateral kidney, tumor 4 cm or less
  - GFR < 60 found in 26% pre nephrectomy pts
  - 3 yr post neph. freedom from CRD (GFR<60) was 80% (partial) & 35% (radical)
  - 3 yr post neph. freedom from CRD (GFR<45) was 94% (partial) & 99% (radical)

Huang, Lancet Oncology 7:735, 2006
Probability of Freedom of Onset of Low GFR

![Graph showing probability of freedom of onset of low GFR](image)

- Conclusion: Always do a partial nephrectomy when technically feasible

Huang, Lancet Oncology 7:735, 2006

Surgery for Localized RCC

- Partial nephrectomy with negative surgical margins = Radical nephrectomy

For Local Recurrence and Overall Survival


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


Who’s a Candidate?

- Essential
  - 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

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

## Who’s a Candidate?

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

## Robotic Partial Nephrectomy

### Minimally invasive-
- Done through 4-5 small incisions
- Less pain
- Shorter recovery

### 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
  - Dependent 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 2nd opinion
- PMHx sig for bilat LE lymphedema
- Preop GFR >60 mL/min / 1.73 m², SCr = 0.7 ng/mL
Port Access

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

Indrjeet K. Gill, Louis R. Kavoussi, Brian R. Lane, Michael L. Hitoe, Josanne Balsimis,
J. Roberto Colombo, Jr., Igor Frank, Supap Preechapong, Christopher J. Wright,
Ahmed H. Kavoussi, Michael W. Kottke and Andrew C. Novick

From the Cleveland Clinic Foundation, Urology, and Institute for Urological Health Sciences (IUHS); Minneapolis Clinic, Cleveland Clinic, Cleveland, Ohio; and Department of Surgery, Johns Hopkins Hospital, Baltimore, Maryland, and Mayo Clinic, Rochester, Minnesota.
Open vs Min Invasive Partial Nx

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

Indrieko S. Goff, Louis R. Karoumi, Brian R. Loso, Michael L. Blute, Denise Robinson, J. Roberts Columbus, Jr., Igor Frank, Rongping Peng, and Christopher A. Wright.

LPN: ↓ EBL, LOS, O.R. time
LPN: ↑ ischemia, complications (post-op hemorrhage)
Cancer control same
Renal function same

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>31 (24-48)</th>
<th>255 (153-258)</th>
<th>210 (165-483)</th>
<th>2.6 (2.0-0.5)</th>
<th>0.3 (0.2-0.3)</th>
<th>3.0 (2.3-4.0)</th>
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<th>5</th>
<th>4</th>
<th>3</th>
</tr>
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<tr>
<td>Mean ischemic time, min (range)</td>
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<td>Mean hospital stay, d (range)</td>
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<td>Mean increase in serum creatinine</td>
<td>31 (24-48)</td>
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<td>Median increase in eGFR, ml/min/1.73 m² (range)</td>
<td>5</td>
<td>4</td>
<td>3</td>
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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%

Loss of pVHL in Conventional Clear Cell Ca
Stimulation of tumor cell growth and vascularity

Targeted Approach to RCC Therapy
Drugs and Targets
Targeted Approach to RCC Therapy

**Drugs and Targets**

- bVHL
- Bevacizumab
- Sunitinib, Sorafenib
- VEGF, VEGFR
- PDGF, PDGFR
- TGF-α, EGFR
- Temsirolimus

HIF = Temsirolimus

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:
  - 
<table>
<thead>
<tr>
<th>Nephrectomy/IFNα</th>
<th>IFNα</th>
</tr>
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<tbody>
<tr>
<td>Pt number</td>
<td>161</td>
</tr>
</tbody>
</table>
  | 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
<table>
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<th>How does this apply to oral targeted therapies?</th>
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<td>We don’t know.....</td>
<td>Cytoreductive nephrectomy remains standard of care when surgically resectable</td>
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<th>Areas of Exploration</th>
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<tr>
<td>• Adjuvant therapy being explored in clinical trials</td>
</tr>
<tr>
<td>• In certain patients, neoadjuvant targeted therapy is a reasonable option</td>
</tr>
<tr>
<td>• Further research necessary to further delineate the role of targeted meds and surgery and in what order</td>
</tr>
<tr>
<td>• Multimodality treatment will be the mainstay of treatment for locally advanced and metastatic RCC</td>
</tr>
</tbody>
</table>
## 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 |