Renal Cell Carcinoma: An Overview

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Assistant Professor of Urology
Renal Cell Carcinoma – 2% of all malignancies

Heterogeneous disease:
- clear cell RCC
- papillary RCC
- chromophobe RCC
- oncocytoma
- angiomyolipoma
- unclassified RCC
Histologic Subtype Breakdown per Patient

N = 1120

- Clear Cell (743) 66%
- Chromophobe (88) 8%
- Oncocytoma (109) 10%
- Papillary (142) 13%
- Other (38) 3%
Background

- Prognosis determined by stage, grade and histologic subtype, clinical presentation

- 30% of all cases are metastatic (12 mos life expectancy)

- 30% of “localized” cases relapse after surgery
Median Tumor Size by Year

Year


Size (cm)

0 1 2 3 4 5 6 7 8

p < 0.01
DFS Survival by Tumor Size

Months from first diagnostic operation

<table>
<thead>
<tr>
<th>Group</th>
<th>Size (cm)</th>
<th>N</th>
<th>3Yr DFS</th>
<th>5Yr DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt; 4.0</td>
<td>393</td>
<td>96%</td>
<td>95%</td>
</tr>
<tr>
<td>2</td>
<td>4.1 - 7.0</td>
<td>372</td>
<td>86%</td>
<td>83%</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 7.0</td>
<td>302</td>
<td>63%</td>
<td>55%</td>
</tr>
</tbody>
</table>

1 v 2    p = 0.17
2 v 3    p < 0.001
DFS by Histologic Subtype

DFS by Histologic Subtype

DFS

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0

ONC v PAP/CHR  \( p = 0.06 \)

PAP v CHR  \( p = 0.80 \)

CLR v PAP/CHR  \( p < 0.001 \)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>N</th>
<th>3Yr DFS</th>
<th>5Yr DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONC</td>
<td>109</td>
<td>97%</td>
<td>97%</td>
</tr>
<tr>
<td>CHR</td>
<td>88</td>
<td>92%</td>
<td>86%</td>
</tr>
<tr>
<td>PAP</td>
<td>142</td>
<td>89%</td>
<td>89%</td>
</tr>
<tr>
<td>CLR</td>
<td>743</td>
<td>78%</td>
<td>73%</td>
</tr>
</tbody>
</table>

Months from first diagnostic operation
### DFS by Presentation

<table>
<thead>
<tr>
<th>Indications</th>
<th>N</th>
<th>3Yr DFS</th>
<th>5Yr DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidental</td>
<td>718</td>
<td>92%</td>
<td>88%</td>
</tr>
<tr>
<td>Local Symptoms</td>
<td>325</td>
<td>66%</td>
<td>63%</td>
</tr>
<tr>
<td>Systemic Symptoms</td>
<td>41</td>
<td>35%</td>
<td>10%</td>
</tr>
</tbody>
</table>

OS

<table>
<thead>
<tr>
<th>Months from first diagnostic operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1.0</td>
</tr>
</tbody>
</table>

- INC v LOC  \( p < 0.001 \)
- LOC v SYS  \( p < 0.001 \)
A Postoperative Prognostic Nomogram for RCC

**Points**

**Symptoms**
- I (incidental)
- L (local)
- S (systemic)

**Histology**
- Chromophobe
- Papillary
- Conventional

**Tumor Size**

**1997 P Stage**
- P1
- P2
- P3a
- P3b/c

**Total Points**

**60 Mo. Recurrence Free Surv.**
- 0.2
- 0.3
- 0.4
- 0.5
- 0.6
- 0.7
- 0.8
- 0.85
- 0.9
- 0.94
- 0.96
- 0.98

**Instructions for Physician:** Locate the patient’s symptoms (I=incidental, L=local, S=systemic) on the Symptoms axis. Draw a line straight upwards to the Points axis to determine how many points towards recurrence the patient receives for his symptoms. Repeat this process for the other axes, each time drawing straight upward to the Points axis. Sum the points achieved for each predictor and locate this sum on the Total Points axis. Draw a line straight down to find the patient’s probability of remaining recurrence free for 5 years assuming he or she does not die of another cause first.

**Instruction to Patient:** “Mr. X, if we had 100 men or women exactly like you, we would expect between <predicted percentage from nomogram – 10%> and <predicted percentage + 10%> to remain free of their disease at 5 years following surgery, though recurrence after 5 years is still possible.”
## Genetic Findings in RCC Subtypes

<table>
<thead>
<tr>
<th>Histological Subtype</th>
<th>% MSKCC</th>
<th>Early Genetic/ Molecular Defects</th>
<th>Late Genetic/ Molecular Defects</th>
<th>Associated Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td>64.5</td>
<td>LOH 3p Mutation of 3p25 (VHL)</td>
<td>+5q -8p,-9p,-14q p53 mutation C-erB-1 Oncogene Expression</td>
<td>Von Hippel-Lindau Sporadic RCC Hereditary RCC</td>
</tr>
<tr>
<td>Papillary</td>
<td>14.2</td>
<td>+7, +17 -Y Met Gene mutation</td>
<td>+12, +16, +20 -9p, -11q, -14q, -17p, -21q PRCC-TFE3 Gene fusion</td>
<td>Hereditary Papillary (HPRC) Sporadic Pap</td>
</tr>
<tr>
<td>Chromophobe</td>
<td>8.2</td>
<td>-1</td>
<td>-1p, -2p, -6p, -13q, -21q, -Y p53 Mutation</td>
<td></td>
</tr>
<tr>
<td>Collecting Duct</td>
<td>0.4</td>
<td>-18, -Y</td>
<td>-1q, -6p, -8p, -11, -13q, -21q C-erB-1 Oncogene expression</td>
<td>Renal Medullary Carcinoma</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>9.7</td>
<td>1 -Y 11q Rearrangement</td>
<td></td>
<td>Familial Oncocytoma</td>
</tr>
</tbody>
</table>

*Zambrano N., Histopathology and Molecular Genetics of Renal Tumors J. Urol, Oct 1999*
Renal Cortical Tumors: Determination of Histological Subtype

• CT, MRI, and Ultrasound are non-specific.

• Percutaneous or open tumor biopsy currently inaccurate in 40% of cases.

• Possible effects of preoperative knowledge of histologic subtype on surgical management:
  – Extend indications for kidney-sparing surgery
  – Allow expectant management of small tumors
  – Inspire use of non-surgical alternative therapies
Mortality and Cancer

• Kidney cancer mortality has increased in spite of earlier detection of smaller renal masses

• Prostate cancer has noted a 6.7% decrease in mortality in the last decade

• Age adjusted mortality has risen in kidney cancer (SEER Data)
  1975 – 3/100,000
  1995 – 3.5/100,000

**Rate of distant disease has steadily increased as well**
The Kidney Cancer Paradox

Stage Migration > Rise in advanced disease + Early intervention = decline in mortality

Re-evaluate aggressive surgical treatment of all small renal lesions

Do tumors metastasize early, prior to intervention

Do biologic markers exist to predict the propensity to metastasize early?
Histology

- Historically, only 40% accuracy rate
- Modern series have been more accurate in interpretation of renal biopsies, but not necessarily in histology
Immunohistochemistry

- **Conventional (clear) cell RCC**: G-250, vimentin
- **Papillary RCC**: c-met proto-oncogene
- **Chromophobe RCC**: Hale’s colloidal iron, anti-mitochondrial antibody (113-1), parvalbumin
- **Oncocytoma**: parvalbumin
- **Collecting Duct Carcinoma**: CEA, PNA, UEA, Cytokeratins (34BE12 and CK7)
Cytogenetics

- **Clear Cell RCC**: 3p deletion (VHL), LOH distal portion 3p, gain 5q, loss 9p/14q, p53 mutation, c-erB-1 expression

- **Papillary RCC**: trisomy 7, 16, 17, loss of chromosome Y, translocation of X and 1, gain 12,16,20, loss 14,17,21, PRCC-TFE3 gene fusion protein

- **Chromophobe RCC**: Loss 1 and Y, combined chromosomal losses of 1,6,10,13,17,21, hyperdiploid tumor cells, p53 mutation

- **Oncocytoma**: Loss of chromosome 1 and Y most common, chromosome 9/11 and 5/11 translocations, c-erB-1 expression

- **Collecting Duct Carcinoma**: monosomy of chromosomes 1,6,14,15,22, LOH of chromosomal arm 1q
Molecular/Genetic Profiling

• Need 1ug RNA: is core biopsy enough tissue for cDNA array analysis.

• Modern gene chips have 39,000 genes for analysis

• Precedent exists to re-classify RCC by genetic profiles
Molecular Profiling of RCC


Evaluated 4 clear cell, one chromophobe, 2 oncocytomas with cDNA microarrays

Large scale gene-expression patterns were able to distinguish clear cell from chromophobe/oncocytoma

**Chromophobe/oncocytomas:** overexpressed distal nephron genes and genes involved with oxidative phosphorylation

**Clear Cell RCC:** underexpressed mitochondrial and distal nephron genes, overexpressed vimentin, class II MHC-related genes
Molecular Profiling of RCC

- 29 clear cell tumors studied
- Distinction in genetic profiles of aggressive vs. non-aggressive forms of clear cell
- 40 genes were able to make distinction
- Breast cancer example - BRCA1 and 2 – two genetically distinct forms

Takahashi et al. PNAS 98(17): 9754-9759, 2001
Goals of Molecular Profiling

- Identify common alterations of varying histologic subtypes for diagnostic purposes

- Identify expression signatures within each subgroup for staging/prognostic purposes (use normal kidney as internal control) – hierarchical clustering utilized to look at variation in gene expression

- Correlate genetic profiles with outcome
Proteomics

• Can we utilize tissue/protein array to identify biomarkers for RCC

• Collection of serum samples?
Role of Nephrectomy in Metastatic Disease

The Cytoreductive Nephrectomy
CT Scan
Ultrasound Guided Biopsy

• Core biopsy: oncocytic renal neoplasm with focal papillary architecture, favor papillary renal cell carcinoma.
Left Radical Nephrectomy

- Embolization of 2 of 3 L renal arteries one day before surgery.
- Left radical nephrectomy performed via thoracoabdominal approach
- Significant hilar and retroperitoneal adenopathy was unresectable.
Pathology
(Left Kidney)

Papillary Ca

Collecting duct Ca
Pathology

Solid sheets; high nuclear grade
Pathology
(Retroperitoneal Mass)

Metastatic Ca involving LN
Pathology

• Renal Cell Carcinoma, Unclassified
  – Tumor 15cm in greatest dimension
  – Extensive tumor necrosis
  – Extracapsular extension into perinephric fat
  – Renal vein free of tumor
  – Inked margins free of tumor
  – RP mass (5.5 cm) metastatic carcinoma involving lymph node c/w renal primary
Postoperative Course

• Doing well 3 months month postoperatively

• Follow-up CT scan shows marked para-aortic, retro-aortic, retrocaval, and left common iliac LAD.

• CT/CXR of the chest shows no evidence of disease

• Enrolled in Atrogen and interferon clinical trial
Case #2: History

- 51 y.o. white male experiences new onset right sided focal seizures
- PMHx/PSHx: RIH repair
- No medications
- Social Etoh; 15 pk/yr smoker, quit 24 yrs ago
- FH: Both parents deceased due to MI (mother 80, father 61)
Case #2 History – ER Evaluation

- NI exam, except R sided weakness
- Laboratory: WNL
- CT/MRI Head: 3 x 1.5 cm L hemispheric mass
- CXR: R sided pulmonary nodules 3 x 1.5 cm
- CT: confirms nodules, lower cuts show L renal mass 5-6 cm
CT/ABD
Management

- Percutaneous Biopsy of renal lesion
- Pathology consistent with renal cell carcinoma
- Due to continuing seizures, patient undergoes L frontal craniotomy with sterotactic resection of tumor: RCC
Case #2: Management

- Recovers well from craniotomy; minimal R hand weakness; placed on dilantin
- Undergoes L laproscopic nephrtx
- Pathology: 9 cm Grade II clear cell RCC invading peri-renal fat: pT3aN0M1
Case #2: Management

• Recovering well

• Awaits start of immunotherapy
Nephrectomy Followed by Interferon α-2b Compared with Interferon α-2b Alone for Metastatic Renal-Cell Cancer

Robert C. Flanigan, M.D., Sydney E. Salmon, M.D., Brent A. Blumenstein, Ph.D., Scott I. Bearman, M.D., Vivek Roy, M.D., Patrick C. McGrath, M.D., John R. Caton, Jr., M.D., Nikhil Munshi, M.D., and E. David Crawford, M.D.
Radical nephrectomy plus IFN-α based immunotherapy compared with IFN-α alone in metastatic renal-cell carcinoma: a randomized trial

Similarities – SWOG/EORTC

• General Study Design:
  – Surgery + adjuvant IFN-α2b v. IFN-α2b alone
  – Intention to treat
  – Randomized

• Treatment
  – Continuous 3x/wk regimen while tolerable

• Surgery
  – Radical resection of primary tumor
Study Criteria: SWOG & ECOG

- Histologic dx of RCC
- Metastases extending beyond regional lymphatics
- Measurable disease in unresectable area by standard nephrectomy
- Primary RCC amenable to resection
- WBC ≥ 4, Cr < 3, nl plts, nl LFT’s
- Performance status 0 or 1
- no prior immunotherapy
- Brain metastases ineligible
<table>
<thead>
<tr>
<th>Metastatic sites</th>
<th>1st Group</th>
<th>2nd Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distant nodes</td>
<td>11 (26%)</td>
<td>18 (43%)</td>
</tr>
<tr>
<td>Lung or pleura</td>
<td>33 (79%)</td>
<td>34 (81%)</td>
</tr>
<tr>
<td>Liver</td>
<td>5 (12%)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Other abdominal</td>
<td>4 (10%)</td>
<td>5 (12%)</td>
</tr>
<tr>
<td>Skin or subcutaneous</td>
<td>2 (5%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Bone</td>
<td>9 (21%)</td>
<td>10 (24%)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>
Comparison of response rates: 19% vs 12%, P=0.38.

<table>
<thead>
<tr>
<th></th>
<th>Study group (n=42)</th>
<th>Control group (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Partial</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>No change</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Progression</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>CHARACTERISTIC</td>
<td>INTERFERON ALONE (N=121)</td>
<td>Nephrectomy plus Interferon (N=120)</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>--------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>59.0</td>
<td>58.8</td>
</tr>
<tr>
<td>Range</td>
<td>29–87</td>
<td>37–80</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>69.4</td>
<td>69.2</td>
</tr>
<tr>
<td>Measurable metastatic lesion (%)</td>
<td>75.2</td>
<td>81.7</td>
</tr>
<tr>
<td>Performance status 1 (%)*</td>
<td>58.1</td>
<td>45.0†</td>
</tr>
<tr>
<td>Only lung metastases (%)</td>
<td>66.9</td>
<td>65.8</td>
</tr>
</tbody>
</table>

*Performance was scored as 0 or 1, with 1 indicating decreased activity.

†P = 0.04 for the comparison with the interferon-only group.
TABLE 2. Survival in Subgroups Defined According to Stratification Factors.

<table>
<thead>
<tr>
<th>Category</th>
<th>Median Survival</th>
<th>1-Yr Survival</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Interferon alone</td>
<td>Nephrectomy plus interferon</td>
<td>Interferon alone</td>
</tr>
<tr>
<td></td>
<td>mo</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Not stratified</td>
<td>8.1</td>
<td>11.1</td>
<td>36.8</td>
</tr>
<tr>
<td>Stratification factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurable disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7.8</td>
<td>10.3</td>
<td>34.7</td>
</tr>
<tr>
<td>No</td>
<td>11.2</td>
<td>16.4</td>
<td>43.1</td>
</tr>
<tr>
<td>Performance status†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11.7</td>
<td>17.4</td>
<td>49.2</td>
</tr>
<tr>
<td>1</td>
<td>4.8</td>
<td>6.9</td>
<td>28.2</td>
</tr>
<tr>
<td>Type of metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung only</td>
<td>10.3</td>
<td>14.3</td>
<td>41.5</td>
</tr>
<tr>
<td>Other</td>
<td>6.3</td>
<td>10.2</td>
<td>34.6</td>
</tr>
</tbody>
</table>

*P values for the comparison of median survival between groups were derived with the log-rank test.
†Performance was scored as 0 or 1, with 1 indicating decreased activity.
Actuarial Survival - SWOG
<table>
<thead>
<tr>
<th>SWOG</th>
<th>EORTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>245 pts</td>
<td>85 pts</td>
</tr>
<tr>
<td>Nephrx v. IFN alone:</td>
<td>Nephrx v. IFN alone:</td>
</tr>
<tr>
<td>11.1 v 8.1 mo’s overall survival (P = 0.5)</td>
<td>17 v 7 mo’s overall survival (HR 0.54; 95% CI 0.31 – 0.94)</td>
</tr>
<tr>
<td>Time to progression not assessed</td>
<td>5 v. 3 mo’s time to progression (HR 0.6; 95% CI 0.36 v 0.97)</td>
</tr>
<tr>
<td>No differences in response rates</td>
<td>No differences in overall response rates (5 CR in nephrx group v. 1 in IFN alone)</td>
</tr>
</tbody>
</table>
SWOG and EORTC: Further Considerations

- 50 – 100% increase in duration of survival translates to 4 – 10 months
- smaller benefit to pt’s with poor performance status in SWOG trial
- decreased morbidity to nephrex with laproscopic techniques
- Nephrex beneficial to pt’s with good performance status
## ECOG PERFORMANCE STATUS

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>