The WHO Classification of Renal Tumors and Common Issues in TNM Staging for Renal Cell Carcinoma

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Weill Medical College of Cornell University,
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Outline

- Introduction
- WHO 2004 classification
- “Cystic” RCC
- “Granular” RCC
- “Spindle/sarcomatoid” RCC
- Staging issues
Increasing of Cancers of Kidney and Renal Pelvis in USA (1995-2008)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Kidney</td>
<td>51</td>
<td>56</td>
<td>66</td>
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<tr>
<td>Bladder</td>
<td>74</td>
<td>78</td>
<td>81</td>
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<td>Prostate</td>
<td>69</td>
<td>76</td>
<td>99</td>
</tr>
<tr>
<td>Testis</td>
<td>83</td>
<td>94</td>
<td>97</td>
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</tbody>
</table>

RCC Molecular Targeted Therapy

- PDGF
- Bevacizumab®
- VHL
- HIF
- Temsirolimus®
- Everolimus®

- Sorafenib®
- Sunitinib®
- Erlotinib®

VEGF

TGFα

mTOR
RCC “Molecular Targeted” Therapy

- All drugs are active in cytokine refractory patients
  - Tumor shrinkage observed in 50%-80% patients

- Sunitinib or bevacizumab + IFN produce more responses to prolong progression free survival relative to IFN in previously untreated patients

- Temsirolimus prolongs overall survival relative to IFN in patients with poor prognostic features

Surgical Treatment of Renal Tumor

- More smaller tumors are detected
- More incidental tumors
- More benign tumors
- More partial nephrectomy
- More use of laparoscopic approaches
Neoplasms and Partial Nephrectomy

Data from The Methodist Hospital, Houston (n=1280)

<table>
<thead>
<tr>
<th>Period</th>
<th>Benign Neoplasms (%)</th>
<th>Partial Nephrectomy (%)</th>
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<tr>
<td>1990-1998</td>
<td>4.7</td>
<td>12.2</td>
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<tr>
<td>1999-2003</td>
<td>8.6</td>
<td>20.8</td>
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<tr>
<td>2004-2007</td>
<td>14.1</td>
<td>28.2</td>
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Renal Cell Tumor Classification

**UICC/AJCC Consensus (1997)**

**BENIGN**
- Oncocytoma
- Papillary adenoma
- Metanephric adenoma

**MALIGNANT**
- Clear cell RCC
- Papillary RCC
- Chromophobe RCC
- Collecting duct carcinoma
- RCC, unclassified
Renal Cell Tumors Classification
(\textit{WHO 2004})

- Clear cell RCC
  - Multilocular cystic RCC
- Papillary RCC
- Chromophobe RCC
- Carcinoma of the collecting ducts of Bellini
- Renal medullary carcinoma
- Xp11 translocation carcinomas
- Carcinoma associated with neuroblastoma
- Mucinous tubular and spindle cell carcinoma
- RCC, unclassified
- Papillary adenoma
- Oncocytoma
Renal Cell Tumors Classification (WHO 2004)

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- Oncocytoma
Newly Defined RCC Entities

Xp11 translocation carcinoma
Mucinous tubular spindle cell carcinoma
Multilocular cystic clear cell RCC
Carcinoma associated with neuroblastoma
Proximal tubules

Clear cell RCC (3p-)

Papillary RCC (+7, +17, -Y, others)

Chromophobe RCC (-1, -Y) (others -2, -10, -13 etc)

Oncocytoma (-1, -Y) (Translocations chr 11)

Collecting ducts (medulla)

Collecting duct carcinoma (-1, -6, -14, -15, -22) LOH 8p and 13q
# Histology and Incidence

*(Selective large series since 1997)*

<table>
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<tbody>
<tr>
<td>Clear cell</td>
<td>78%</td>
<td>83%</td>
<td>68%</td>
<td>83.2%</td>
<td>86.3%</td>
<td>77.2%</td>
</tr>
<tr>
<td>Papillary</td>
<td>13.4%</td>
<td>11%</td>
<td>19.8%</td>
<td>11.3%</td>
<td>7.3%</td>
<td>15.2%</td>
</tr>
<tr>
<td>Chromophobe</td>
<td>6.5%</td>
<td>5%</td>
<td>6.4%</td>
<td>4.3%</td>
<td>6.2%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Collecting duct</td>
<td>0</td>
<td>1%</td>
<td>0</td>
<td>0.3%</td>
<td>0.3%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Unclassified</td>
<td>2.1%</td>
<td>?</td>
<td>6.1%</td>
<td>1%</td>
<td>0%</td>
<td>1.4%</td>
</tr>
</tbody>
</table>
Histology and Prognosis

(My simplistic view)

Oncocytoma

Chromophobe RCC

Adenoma  Type 1  Type 2  Papillary RCC

Clear cell RCC

Collecting duct Ca

Low  Malignant potential  High

Histology and Prognosis

(My simplistic view)
Clear cell (conventional) RCC

**Growth Pattern**
- Classic (solid/acinar)
- Tubular
- Cystic
- Pseudopapillary
- Hemorrhagic
- Hyalinized

**Cytomorphology**
- Classic clear cell
- Granular
- Epithelioid
- Rhabdoid
- Spindly/sarcomatoid
Clear Cell RCC

Differential Diagnosis

- Morphologic variation of clear cell RCC
- Chromophobe RCC
- Papillary type 2 RCC
- Cellular or epithelioid angiomyolipoma
- Adrenal cortical carcinoma
Papillary RCC

- The second most common type RCC
- Cytogenetic changes: +7, +17, -Y
- Met protooncogen
- More frequent regional nodal metastasis
- Prognosis variable
PRCC, type 1 vs. type 2

Type 1 (n=102)
Type 2 (n=48)

5-yr survival
65% vs. 47%

p=0.017

Shen SS et al. Presented at USCAP 2008, Denver, Colorado
Issues of Papillary RCC

- Mixed type 1 and type 2
- Clear cell RCC, particularly higher grade can have pseudopapillary pattern
- Mixed with clear cell
Papillary RCC with Clear Cell Features: A Clinicopathologic Study of 59 Cases

Steven S Shen, Soo-Jing Jung, Luan D Truong, Qin Yang, Max Lingamfelter, Federico A Monzon, Alberto G Ayala and Jae Y Ro

Presented at USCAP 2008, Denver, Colorado
PRCC with or without clear cells

5-yr survival
67% vs. 45%
p=0.001

Without clear cell
(n=99)

With clear cell
(n=51)
<table>
<thead>
<tr>
<th></th>
<th>Univariate Analysis</th>
<th></th>
<th>Multivariate Analysis</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>p value</td>
<td>HR</td>
</tr>
<tr>
<td>Patient age</td>
<td>1.038</td>
<td>1.008-1.068</td>
<td>0.011</td>
<td>1.024</td>
</tr>
<tr>
<td>Patient gender</td>
<td>1.413</td>
<td>0.757-2.636</td>
<td>0.277</td>
<td>1.802</td>
</tr>
<tr>
<td>TNM stage group</td>
<td>1.908</td>
<td>1.393-2.613</td>
<td>0.000</td>
<td>1.333</td>
</tr>
<tr>
<td>Nuclear grade</td>
<td>4.248</td>
<td>2.039-8.850</td>
<td>0.000</td>
<td>1.863</td>
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<tr>
<td>Lymphovascular Inv.</td>
<td>5.853</td>
<td>2.985-11.478</td>
<td>0.000</td>
<td>2.392</td>
</tr>
<tr>
<td>Necrosis</td>
<td>1.134</td>
<td>0.614-2.092</td>
<td>0.688</td>
<td>0.845</td>
</tr>
<tr>
<td>Macrophage</td>
<td>0.622</td>
<td>0.331-1.168</td>
<td>0.140</td>
<td>1.061</td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>8.506</td>
<td>3.855-18.769</td>
<td>0.000</td>
<td>3.796</td>
</tr>
<tr>
<td>Mucin</td>
<td>0.494</td>
<td>0.195-1.254</td>
<td>0.138</td>
<td>0.919</td>
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<tr>
<td>RCC Type (1 vs. 2)</td>
<td>1.997</td>
<td>1.116-3.571</td>
<td>0.020</td>
<td>1.449</td>
</tr>
<tr>
<td>Procedure (partial vs. radical)</td>
<td>4.462</td>
<td>1.382-14.409</td>
<td>0.012</td>
<td>2.282</td>
</tr>
<tr>
<td>PRCC with clear cell (with vs. without)</td>
<td>2.518</td>
<td>1.405-4.512</td>
<td>0.002</td>
<td>2.038</td>
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</tbody>
</table>
Papillary RCC with clear cell features

- Is not uncommon (33%)
- Often higher grade, associated with larger size tumor, more frequent LVI and nodal metastasis
- A strong poor prognostic feature
- Await further study for an unique subtype
Chromophobe RCC

- Two types in 1988
- Better prognostic group
- Association with oncocytoma?
Chromophobe RCC

Key Diagnostic Features

- **Growth patterns**
  - Solid sheets, broad alveoli, tubular
  - Broad fibrotic septae, thick-walled and hyalinized vessels, linear or parallel

- **Cytologic features**
  - Cell types (mixed)
  - Cytoplasmic quality (halo)
  - Nuclear features (wrinkling, binucleation)
  - Cytoplasmic membrane (prominent)
Chromophobe RCC

Three Types of Cells

Type 1: Eosinophilic cell with no perinuclear halo

Type 2: Eosinophilic cell with perinuclear halo

Type 3: Largest polygonal cells with voluminous, reticulated cytoplasm
Chromophobe RCC
Morphologic Spectrum

❖ **Typical:**  
Type 3 cells mixed with type 1 and type 2 cells easy to diagnose, ddx from clear cell RCC

❖ **Eosinophilic:**  
Predominant type 1 or type 2 cells; difficult to differentiated from oncocytoma
RCC, Unclassified

Definition: tumor that does not fit into any known types by **morphology** or **genetics**

- RCC with mucin production?
- Composites of recognizable types?
- Unrecognizable cell types
- RCC with sarcomatoid change in which the epithelial elements cannot be assigned to one of the known categories
RCC with Mucin Production

- Unclassified RCC

- Papillary RCC (20%~30%)
- Collecting duct carcinoma
- Invasive urothelial carcinoma
- Mucinous tubular and spindle cell carcinoma
Composite Recognizable Types = Unclassfied?

- If low grade, better to diagnose as mixed subtypes
- If high grade, ? RCC, unclassified
“Cystic” Renal Neoplasms

- Cystic nephroma/mixed epithelial and stromal tumor of kidney (MESTK)
- Renal cell carcinoma with cystic change
  - Papillary RCC
  - Clear cell RCC
- Multilocular cystic clear cell RCC
- Tubulocystic RCC
Cystic Nephroma/Mixed Epithelial and Stromal Tumor of Kidney (MESTK)

Lack of nodules or nests of clear cells

Cystic lining – single layers of cells

Variable amount of stroma
Multilocular Cystic Clear Cell RCC

- Composed of entirely cystic components
- Lined by layers of clear cells
- Low nuclear grade (G1 or G2)
- Lack of nodules of solid area of clear cells
- Excellent prognosis
"Granular Cell" RCC

- Granular cell RCC is not a specific entity
- Differential diagnoses include:
  - Clear cell RCC
  - Chromophobe RCC, eosinophilic variant
  - Papillary RCC type 2
  - Oncocytoma
  - Epithelioid angiomyolipoma
<table>
<thead>
<tr>
<th>Description</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>All clear cells</td>
<td>12.3%</td>
</tr>
<tr>
<td>Mixed clear /granular cell</td>
<td>67.1%</td>
</tr>
<tr>
<td>All granular cell</td>
<td>20.6%</td>
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</tbody>
</table>

Data modified from Victor Reuter’s USCAP Long Course 2008
Clear Cell RCC with Granular Cells

- Often mixed with clear cells
- Granular cell component often have higher nuclear grades
- Keys to the diagnosis of clear cell RCC
  - Component of classic clear cell
  - Typical vascular pattern
  - Exclude other histologic types
“Granular” RCC

- Not a specific entity
- Think about clear cell RCC first
- Be familiar with chromophobe RCC
- Keep “angiomyolipoma” in mind
Issues of “Sarcomatoid” RCC
Sarcomatoid Changes Occur in All Histologic Types of RCC

<table>
<thead>
<tr>
<th></th>
<th># Cases</th>
<th># Sarcomatoid (%)</th>
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</thead>
<tbody>
<tr>
<td>Clear cell</td>
<td>818</td>
<td>44 (5.4)</td>
</tr>
<tr>
<td>Papillary</td>
<td>149</td>
<td>7 (4.5)</td>
</tr>
<tr>
<td>Chromophobe</td>
<td>60</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Collecting duct</td>
<td>6</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td>Unclassified</td>
<td>15</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Total</td>
<td>1048</td>
<td>62 (6)</td>
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</table>

(TMH Unpublished Data)
Proximal tubules

- Clear cell RCC (3p-)
- Papillary RCC (+7, +17, -Y, others)

Intercalated cells (cortex)

- Chromophobe RCC (-1, -Y) (others -2, -10, -13 etc)
- Oncocytoma (-1, -Y) (Translocations chr 11)

Collecting ducts (medulla)

- Collecting duct carcinoma (-1, -6, -14, -15, -22) LOH 8p and 13q

Collecting Ducts

SARCOMATOID TRANSFORMATION
Sarcomatoid (Spindle Cell) Changes

- **Histology** of spindle cell
  - Fibrosarcoma (54%)
  - Malignant fibrous histiocytyoma (44%)
  - Undifferentiated sarcoma (NOS) (3%)
  - Rhabdomyosarcomatous component (2%)

- **Amount** of spindle cell
  - Average 45% (range 1% to 99%)

- **Grade** of the spindled elements
  - Low grade (9%)
  - Intermediate to high grade (91%)

De Peralta-Venturina et al. AJSP 2001 25:275-84
Diagnostic Issues of Spindle Cell-Sarcomatoid

Histology grade
(Necrosis, cellularity, mitotic count)

Amount of spindle cell component

Histologic type
Sarcomatoid Changes

- Sampling is important
- Histologic types
- Spindle cell area with at least moderate cytologic atypia
- Report the percentages of sarcomatoid and tumor necrosis
RCC Staging Issues

- Tumor size
- T2 tumors
- T3a
  - Perirenal fat invasion
  - Sinus fat invasion
  - Extent of fat invasion
  - Adrenal invasion
<table>
<thead>
<tr>
<th>Staging</th>
<th>1997 AJCC</th>
<th>2002 AJCC</th>
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<tbody>
<tr>
<td>T1</td>
<td>Tumors ≤7 cm, limited to kidney</td>
<td>NA</td>
</tr>
<tr>
<td>T1a</td>
<td>NA</td>
<td>Tumors 4 cm, limited to kidney</td>
</tr>
<tr>
<td>T1b</td>
<td>NA</td>
<td>Tumor &gt;4 cm and ≤ 7 cm, limited to kidney</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt;7 cm, limited to kidney</td>
<td>Tumor &gt;7 cm, limited to kidney</td>
</tr>
<tr>
<td>T3</td>
<td>Tumors extends into major veins or invades adrenal or perinephric tissue, but not beyond Gerota's fascia</td>
<td>Tumors extends into major veins or invades adrenal or perinephric tissue, but not beyond Gerota's fascia</td>
</tr>
<tr>
<td>T3a</td>
<td>Perinephric or adrenal extension</td>
<td>perinephric or sinus fat or adrenal extension</td>
</tr>
<tr>
<td>T3b</td>
<td>Renal-vein or vena-cava involvement below diaphragm</td>
<td>Renal-vein or vena-cava involvement below diaphragm</td>
</tr>
<tr>
<td>T3c</td>
<td>Vena-cava involvement above diaphragm</td>
<td>Vena-cava involvement above diaphragm</td>
</tr>
<tr>
<td>T4</td>
<td>Outside Gerota's fascia</td>
<td>Outside Gerota's fascia</td>
</tr>
</tbody>
</table>
Size Matters

- Largest dimension
- Multiple tumors
- Cut-off criteria for staging
- T1a vs. T1b (4 cm T1 substage)
- T2 (10 cm substage?)
### T2 Tumors Are Uncommon

<table>
<thead>
<tr>
<th>T Stage</th>
<th># Cases</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>T1</td>
<td>628</td>
<td>60%</td>
</tr>
<tr>
<td>T2</td>
<td>107</td>
<td>10%</td>
</tr>
<tr>
<td>T3</td>
<td>295</td>
<td>28%</td>
</tr>
<tr>
<td>T4</td>
<td>18</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1048</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

Form TMH RCC database (1990-2006)
T3a Issues

- Perinephric and sinus fat invasion
- Extend of fat invasion
- Ipsilateral adrenal invasion (T4?)
Renal Sinus Invasion

- Tumor exceeded 4 cm, statistically significant increase in incidence of sinus invasion ($p < .001$)
- Sinus invasion correlated with Fuhrman grade, tumor size, tumor type
- pT1b, pT2 is actually T3 in most clear cell RCC

<table>
<thead>
<tr>
<th>TNM Formulation</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>42</td>
<td>4</td>
<td>28</td>
</tr>
<tr>
<td>2002</td>
<td>32</td>
<td>1*</td>
<td>41</td>
</tr>
</tbody>
</table>

*8 cm multilocular cystic renal cell carcinoma.

(Bonsib SM AJSP 2004 174:1594-1600)
Renal Sinus Fat Invasion

- pT3a: directly invades perinephric tissue including sinus fat, direct adrenal invasion

(Bonsib et al. AJSP 2000)
Renal Sinus vs. Perirenal Fat Invasion

Worse

5 yr survival

Perirenal fat inv. 51%
Sinus fat inv. 26%

No difference

SF = Sinus fat inv.
PF = Perirenal fat inv.

Thompson RH et al. J of Urol 2005

Margulis V. et al. J of Urol 2007
Extent of perirenal fat invasion (focal vs. extensive)

Extent of Perirenal Fat Invasion

RCC Adrenal Invasion

- Direct invasion (pT3a)
- Metastasis (M1)
Adrenal Invasion

- Direct adrenal invasion: pT3a
- More aggressive behavior than fat invasion

(Han et al. J Urol 2003)
Adrenal Invasion

(Thompson et al. Cancer 2005)
Ipsilateral adrenal invasion may be reclassified as pT4 tumor?

RCC Staging Summary

- Cut-off size in localized lesion
- T2 tumors are uncommon
- Many >4 cm tumors may have sinus invasion
- Ipsilateral adrenal invasion may be reclassified as pT4?