Histologic Subtyping of Renal Tumors on Core Biopsy

Steven Shen, MD, PhD
Department of Pathology & Genomic Medicine
Houston Methodist Hospital and
Weill Medical College of Cornell University
Houston, Texas, USA
Outline – Renal Mass Biopsy

- Introduction
- Get adequate material
- Know the tumor entities
- Pattern-based diagnostic approach
- Use of immunohistochemistry
- Case examples
Introduction – Renal Mass

- Increased incidence
- Increased partial nephrectomy
- Increased treatment modalities
- Decreased biopsy morbidity

Increased Renal Mass Biopsy (RMB)
<table>
<thead>
<tr>
<th>Indications for RMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Biopsy in the setting of ablation</td>
</tr>
<tr>
<td>• Guidance for management options</td>
</tr>
<tr>
<td>• Patient with other primary</td>
</tr>
<tr>
<td>• Patient with prior renal lesion</td>
</tr>
<tr>
<td>• Patient with synchronous tumors</td>
</tr>
<tr>
<td>• Candidates for active surveillance</td>
</tr>
</tbody>
</table>
Objective of RMB

To establish the following:

- Neoplasm or not
- Histologic type
- Tumor grade
- Other features
Diagnostic Accuracy of RMB

86-100% Differentiating malignant from benign

~100% Specificity

86-98% Accuracy histol. subtyping

46-76% Accuracy in grading
Getting adequate material
RMB Technical Recommendation

• Image guidance (CT/MRI/US)
• At least 2 cores
• 18G or larger needle
• Sampling peripheral & central
• Challenging: cystic, anatomical location

Tsivian M et al. BJUI. 2014
Insufficient Material

- Not uncommon (0-47%)*
- More frequent in small, cystic or hemorrhagic, and necrotic lesion
- Communicate with radiologist
- Correlate with cytology
- Request deeper cut

Know the tumor entities
Renal Cell Neoplasm (1)
ISUP 2013 Vancouver Modified WHO Classification

- Papillary adenoma
- Oncocytoma
- Clear cell RCC
  - Multilocular cystic clear cell neoplasm of LMP*
- Papillary RCC
- Chromophobe
  - Hybrid oncocytiic chromophobe tumor*
- Carcinoma of the collecting ducts of Bellini
- Renal medullary carcinoma
- Unclassified RCC

Srigley JR et al. AJSP 2013:37: 1469-89
Renal Cell Neoplasm (2)
ISUP 2013 Vancouver Modified WHO Classification

- MiT family translocation RCC*
  - Xp11 translocation RCC
  - t(6,11) RCC*
- Carcinoma associated with neuroblastoma
- Mucinous tubular spindle cell RCC
- Tubulocystic RCC*
- Acquired cystic disease associated RCC*
- Clear cell papillary RCC*
- Hereditary leiomyomatosis associated RCC*
Emerging/Provisional Tumor Entities

- Thyroid-like follicular RCC
- Succinic dehydrogenase B deficiency associated RCC
- ALK-translocation RCC

Srigley JR et al. AJSP 2013:37: 1469-89
<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell RCC</td>
<td>~65%</td>
</tr>
<tr>
<td>Papillary RCC</td>
<td>~15%</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>~10%</td>
</tr>
<tr>
<td>Chromophobe RCC</td>
<td>~5%</td>
</tr>
<tr>
<td>Clear cell papillary RCC</td>
<td>~3%</td>
</tr>
<tr>
<td>Others</td>
<td>...</td>
</tr>
</tbody>
</table>
Pattern-based diagnostic approach
<table>
<thead>
<tr>
<th>Diagnostic Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clear cell</td>
</tr>
<tr>
<td>• Papillary</td>
</tr>
<tr>
<td>• Oncocytic</td>
</tr>
<tr>
<td>• Cystic</td>
</tr>
<tr>
<td>• Spindle cell</td>
</tr>
<tr>
<td>• High grade</td>
</tr>
</tbody>
</table>
CLEAR CELL

- Clear cell RCC
- Chromophobe RCC
- Clear cell papillary RCC
- Xp11 translocation RCC
- Papillary RCC with clear cells
- Renal urothelial carcinoma
Heterogeneous Nature of Tumor

• Among different tumor

• Within same tumor
  – Different growth pattern
  – Different cell types
  – Different nuclear grade
Clear Cell RCC
Morphologic Spectrum

Growth Patterns
- Solid/acinar (classic)
- Tubular/Cystic
- Pseudopapillary
- Hemorrhagic
- Hyalinized

Cytomorphology
- Clear cell
- Granular
- Epithelioid
- Rhabdoid
- Spindly/sarcomatoid
Clear Cell RCC: Growth Patterns

- Solid/acinar
- Sinusoid
- Tubular
- Vascular
- Hyalinized
- Hemorrhagic
- Pseudopapillary
- Sclerotic
Clear Cell RCC: Cytologic and Nuclear Features
Non-clear Cell RCC: Has Clear Cells

- Papillary RCC
- Chromophobe RCC
- Clear cell papillary RCC
- Renal urothelial carcinoma
## PAPILLARY

- Papillary RCC
- Clear cell papillary RCC
- Clear cell RCC with pseudopapillary
- Chromphobe RCC (rarely)
- Mucinous tubular spindle cell RCC
- Metanephric adenoma
- Collecting duct carcinoma
- Metastatic
Papillary RCC: Patterns and Cells

• Has other growth patterns:
  – Solid
  – Tubular
  – Cystic

• Has different cell types:
  – Basophilic
  – Eosinophilic
  – Clear
Papillary RCC: Patterns
- Oncocytoma
- Chromophobe RCC
- Hybrid oncocytic tumor
- Clear cell RCC with granular cells
- Oncocytic papillary or type 2 papillary
- Acquired cystic renal disease associated RCC
- Epithelioid angiomyolipoma
- Carcinoid
Oncocytic Tumor

Chromophobe RCC

Oncocytoma

Angiomyolipoma

Clear cell RCC
<table>
<thead>
<tr>
<th>CYSTIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clear cell RCC</td>
</tr>
<tr>
<td>• Papillary RCC</td>
</tr>
<tr>
<td>• Clear cell papillary RCC</td>
</tr>
<tr>
<td>• Oncocytic RCC</td>
</tr>
<tr>
<td>• Cystic nephroma/mixed epithelial and stromal tumor of kidney</td>
</tr>
<tr>
<td>• Benign cystic renal disease</td>
</tr>
</tbody>
</table>
SPINDLE CELL

- RCC with sarcomatoid
- Mucinous tubular spindle cell RCC
- Myoid-rich angiomyolipoma
- Leiomyoma/leiomyosarcoma
- Other renal sarcoma
HIGH GRADE

• RCC
  – Clear cell
  – Papillary
  – Collecting duct/medullary
  – Unclassified
• Urothelial
• Metastatic
## General Diagnostic Approach

- Cytologic evaluation
- Multiple H&E levels (3x)
- Differential diagnosis based on growth pattern and cytology
- IHC work up
- Report & communication
Biopsy Cytology Evaluation

- Clear cell RCC
- Papillary RCC
- Renal oncocytoma
- Chromophobe RCC
Use of IHC – Renal Mass Biopsy

Role of Immunohistochemistry in Diagnosing Renal Neoplasms
When Is It Really Useful?

Steven S. Shen, MD, PhD; Luan D. Truong, MD; Marina Scarpelli, MD; Antonio Lopez-Beltran, MD, PhD

Arch Pathol Lab Med 2012;136: 410-417
Renal Tumors
Diagnostic and Prognostic Biomarkers

Puay Hoon Tan, MD, FRCPA,* Liang Cheng, MD,† Nathalie Rioux-Leclercq, MD,‡ Maria J. Merino, MD,§ George Netto, MD,∥ Victor E. Reuter, MD,¶ Steven S. Shen, MD,# David J. Grignon, MD,† Rodolfo Montironi, MD, FRCPath,** Lars Egevad, MD,†† John R. Srigley, MD, FRCPC,‡‡ Brett Delahunt, MD, FRCPA,§§ Holger Moch, MD,|| and The ISUP Renal Tumor Panel

Best Practices Recommendations in the Application of Immunohistochemistry in the Kidney Tumors
Report From the International Society of Urologic Pathology Consensus Conference

Victor E. Reuter, MD,* Pedram Argani, MD,† Ming Zhou, MD, PhD,‡ Brett Delahunt, MD, FRCPA,§ and Members of the ISUP Immunohistochemistry in Diagnostic Urologic Pathology Group

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Positive Markers</th>
<th>Negative Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell RCC</td>
<td>Vim, <strong>CAIX</strong>, CK, EMA, CD10, <strong>RCCm</strong>, PAX8, PAX2</td>
<td><strong>CK7</strong>, Ksp-cadherin, Parvalbumin</td>
</tr>
<tr>
<td>Papillary RCC</td>
<td>CK, <strong>CK7</strong>, <strong>AMACR</strong>, RCCm</td>
<td>CD117, Ksp-cadherin, WT1</td>
</tr>
<tr>
<td>Chromophobe RCC</td>
<td>E-cad, <strong>Ksp-cad</strong>, <strong>CD117</strong>, CK, <strong>CK7</strong></td>
<td>Vim, <strong>CAIX</strong>, <strong>AMACR</strong></td>
</tr>
<tr>
<td>Collecting duct RCC</td>
<td>p63, HMCK, PAX8, IN1</td>
<td>CD10, RCCm, CK20, GATA3</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>P63, HMCK, OCT4, PAX8</td>
<td>IN1, RCCm, GATA3</td>
</tr>
<tr>
<td>Clear cell papillary RCC</td>
<td><strong>CK7</strong>, <strong>CAIX</strong>, PAX8</td>
<td><strong>AMACR</strong>, <strong>RCCm</strong></td>
</tr>
<tr>
<td>MiTF-TFE Translocation</td>
<td>Cathepsin-K, TFE3, TFEB, <strong>RCCm</strong></td>
<td>CK (or weak)</td>
</tr>
<tr>
<td>RCC with sarcomatoid</td>
<td>CK7, PAX8, CD10, vim, AMACR</td>
<td></td>
</tr>
<tr>
<td>Angiomyolipoma</td>
<td><strong>HMB45</strong>, <strong>Melan-A</strong>, SMA</td>
<td><strong>CK</strong>, CD10, RCCm, PAX8</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>Ksp-cad, <strong>CD117</strong>, Parvalbumin, S100A1</td>
<td><strong>CK7</strong>, MOC31, CD82</td>
</tr>
<tr>
<td>Metanephric adenoma</td>
<td><strong>WT1</strong>, <strong>CD57</strong>, S100</td>
<td><strong>AMACR</strong>, <strong>RCCm</strong></td>
</tr>
</tbody>
</table>

Establishing Renal Cell Origin

- **Recommended marker by ISUP:**
  - PAX-8

- **Potentially useful markers:**
  - CD10
  - RCC marker antigen
  - KSP-cadherin

Reuter V et al. AJSP 014; 38:e35-e49
IHC for Histologic Subtyping

Should be based on careful morphologic evaluation (growth patterns and cells) and well constructed differential diagnoses

Reuter V et al. AJSP 014; 38:e35-e49
### Renal Tumor with Clear Cell

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>CA IX</th>
<th>CK7</th>
<th>CD117</th>
<th>Cathepsin K</th>
<th>HMB45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Clear cell pRCC (cup-like)</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chromophobe</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AML</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Xp11</td>
<td>-/+</td>
<td>-</td>
<td>-/+</td>
<td>+(50%)</td>
<td>-</td>
</tr>
<tr>
<td>T(6;11)</td>
<td>-/+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+(focal)</td>
</tr>
</tbody>
</table>

*Reuter V et al. AJSP 2014; 38:e35-e49*
<table>
<thead>
<tr>
<th>Tumor type</th>
<th>CA IX</th>
<th>CK7</th>
<th>AMACR</th>
<th>Cathepsin K</th>
<th>TFE3/TFEB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell RCC</td>
<td>++</td>
<td>-</td>
<td>-/+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>pRCC, type 1</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>pRCC, type 2</td>
<td>-</td>
<td>-/+</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Clear cell pRCC</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(cup-like)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MiTF-TFE RCC</td>
<td>-/+</td>
<td>-</td>
<td>-</td>
<td>+(50%)</td>
<td>+</td>
</tr>
</tbody>
</table>

Reuter V et al. AJSP 2014; 38:e35-e49
<table>
<thead>
<tr>
<th>Tumor type</th>
<th>CD117</th>
<th>CK7</th>
<th>Ksp-cad</th>
<th>HMB45</th>
<th>Cath_K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncocytoma</td>
<td>++</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chromophobe, eosinophilic</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>pRCC, oncocytic</td>
<td>-</td>
<td>+</td>
<td>N/A</td>
<td>-</td>
<td>N/A</td>
</tr>
<tr>
<td>AML, oncocytic</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Reuter V et al. AJSP 2014; 38:e35-e49
# Renal Tumor with Spindle Cells

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Vim</th>
<th>CAIX</th>
<th>Pax8</th>
<th>CK7</th>
<th>34βE12</th>
<th>GATA3</th>
<th>p63</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell RCC</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Papillary RCC</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chromophobe RCC</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MTSC RCC</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-/+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Urothelial Ca</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Reuter V et al. AJSP 2014; 38:e35-e49
For many tumors that have classic morphology, a histologic diagnosis can be made on H&E section alone.
Case 1: 73 yo female with 5.0 left renal mass
Case 1: Oncocytoma
Case 2: 82 yo man with large R renal mass and inferior vena cava extension
Case 2: Clear cell RCC
Case 3: 54M 5.5 cm R renal mass
Case 3: Papillary RCC, type 1
Case 4: 65 M with flank pain & was found to have a 5 cm R renal mass
Case 4: Necrotic tumor, most likely clear cell RCC
A week later...

Right kidney, radical nephrectomy:
- Papillary renal cell carcinoma
  - Fuhrman nuclear grade 3
  - Invades into renal sinus tissue
  - Multiple papillary adenomas
Most Common Situations That IHC May Be Helpful

- Clear cell RCC with granular cells vs. chromophoboe RCC
- Oncocytoma vs. chromophoboe RCC
- Clear cell pRCC vs. clear or pRCC
- Solid papillary RCC vs. clear cell
- Diagnosis of spindle, high grade Ca
- Confirm AML, urothelial Ca, etc.
Case 5: 66 M with 4 cm L renal mass
Case 5: Clear cell RCC

CK7

Vimentin
Case 6: 87F with 3.0 cm L renal mass
Case 6: Clear cell RCC

Pax 8

RCC marker
Case 7: 52M with 3.5 cm L renal mass
Case 7: Papillary RCC, type 1

AMACR

CD57

WT-1
Metanephric Adenoma vs Papillary RCC

- Metanephric Adenoma
- Papillary RCC

**RCCm**

**AMACR**

**WT-1**
Case 8: Clear cell papillary RCC
Clear cell papillary renal cell carcinoma is the fourth most common histologic type of renal cell carcinoma in 290 consecutive nephrectomies for renal cell carcinoma.

- A newly recognized RCC entity
- CK7+/RCCm-/-CD10-/AMACR-
- No specific chromosomal changes
- Benign indolent tumor
Case 9: 80M 6 cm R renal mass
Case 9: Oncocytoma
Case 10: Chromophobe RCC

CK7
Case 11: 70M 4.5 cm R renal mass
Case 11:
Clear cell RCC
Case 12: 48F 6.5 cm left renal mass
Case 12: Angiomyolipoma
Case 13: Another Angiomyolipoma
Case 14: Small Focus of Tumor
Case 14: RCC, most likely clear cell RCC
Case 15: 69 F with 6.5 cm right renal mass
Case 15: High grade unclassified RCC with spindle cells
Radical Nephrectomy

Additional IHC stain results:
– Negative: RCCm, AMACR
– Positive (focal): CK7, Vim, CD10

Diagnosis:
– Clear cell RCC with sarcomatoid changes
– T3aN1 (5/25)
Case 16: Invasive urothelial carcinoma

CK7

p63
Summary – Renal Mass Biopsy

- Obtain adequate material
- Get familiar with renal tumor entities
- Adopt a pattern-based histologic evaluation and diagnostic approach
- Use IHC in selective situations
- Recognize the limitations
Thank you