What’s new in renal tumor pathology – what’s important and why

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Prognostic factors in RCC

1. Pathologic stage
2. Tumor WHO/ISUP grade
3. Morphologic type
4. Sarcomatoid-rhabdoid differentiation
5. Tumor necrosis
   (lymphovascular invasion)
The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasms

Nuclear grade (Fuhrman)

Grade heterogeneity

Grade based on worst area
Nuclear grading issues

<table>
<thead>
<tr>
<th>Size of worst area?</th>
<th>Clear cell type vs. other types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination of nuclear size, shape and nucleolar size</td>
<td>Nucleolar grading system (nucleolar size)</td>
</tr>
</tbody>
</table>

WHO/ISUP grading system (1-4)

1. absent or inconspicuous nuclei at x400
2. nuclei distinct visible at x400 (not at x100)
3. nuclei distinctly visible at x100
4. extreme nuclear pleomorphism, multinuclear giant cells, and/or rhabdoid and/or sarcomatoid differentiation

Note: validated for clear cell RCC and papillary RCC only!

Sarcomatoid dedifferentiation = WHO/ISUP grade 4

In any histologic type or unclassified (if pure) – poor prognosis [report %]

Rhabdoid (rhabdoid-like) differentiation = WHO/ISUP grade 4

Tumor necrosis

Microscopic and microscopic necrosis should be recorded

Except with presurgical embolization

Tumor necrosis (-) rerec %

Independent prognostic Fe in Clear cell and Chromophobe RCC

Controversial in Papillary RCC
ISUP Grading + Tumor necrosis (Clear cell RCC)

Prognostic factors in RCC

1. Tumor WHO/ISUP grade
2. Sarcomatoid/rhabdoid differentiation
3. Tumor necrosis
4. Morphologic type
5. Pathologic stage
Use as a guideline, not a gospel!

<table>
<thead>
<tr>
<th>Type</th>
<th>PAX8</th>
<th>CCA</th>
<th>CKB</th>
<th>C3</th>
<th>CAM5</th>
<th>C1CD7</th>
<th>CD10</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>Ch RCC</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Am J Surg Pathol 2014; 38: e35–e49

Immunohistochemistry should be used in conjunction with morphology for kidney tumor diagnosis.
ISUP Consensus Meeting on Adult Renal Tumors
Vancouver 2012 / WHO 2016

New epithelial tumors
- Focal hyperplasia, renal cell carcinoma
- Acquired cystic disease associated renal cell carcinoma
- Clear cell (tubulocystic), renal cell carcinoma
- NKF (not otherwise specified) renal cell carcinoma (including III B) (adult cell carcinoma)
- Renal lobar hyperplasia, renal cell carcinoma
- Urothelial-proximal entities
- Transitional cell carcinoma
- Acquired cystic disease associated renal cell carcinoma
- Clear cell (tubulocystic), renal cell carcinoma
- NKF (not otherwise specified) renal cell carcinoma
- Renal cell carcinoma, unclassified

TABLE 1. Proposed New Renal Epithelial Tumors and Emerging/Provisional Tumor Entities

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<td>Renal cell carcinoma, unclassified</td>
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</table>
ISUP Vancouver Classification of Renal Neoplasia
Proposed new entities

- Tubulocystic RCC
- Acquired cystic disease RCC
- Clear cell (tubulopapillary) RCC
- Translocation RCC (MT family)
- Hereditary leiomyomatosis associated RCC

Tubulocystic RCC

Tubulocystic carcinoma (note prominent nucleoli)
**Tubulocystic RCC**

- Low gc collecting duct RCC
  - (“Bellinian epithelioma”)
- Rare (<100)
- M:F > 7:1
  - **Low stage (indolent)**
- Similarities with Papillary RCC:
  - IHC
  - Array CGH
  - Cytogenetics

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**Acquired cystic disease associated RCC**
Acquired cystic disease associated RCC

- Dialysis or renal failure
- ACD (25% with tumors)
- ACD-RCC (papillary, clear cell)
- Some aggressive
- 10-20% with MS

IHC:
- CK7(-), AMACR (+)

Cytogenetics:
- Gains of chr 1, 2, 3, 6, 7, 16 and Y
- Array CGH with papillary RCC

Clear cell (tubulo)papillary RCC
Clear cell (tubulo)papillary RCC

IHC:
- CK7 (+), AMACR (-), CD10 (-)
- CAIX (cup shaped +)

Cytogenetics:
Different from Clear cell and Papillary RCC

End-stage kidney or sporadic
Incidence ~1%
Benign or indolent
Translocation type RCC (Xp11)

FISH for TFE3 or TFE3 necessary for diagnosis!

t(6;11) and Xp11 RCC similar MiT family translocation RCC

Ap(11):
- 55% MS or DOD (>25 years old)
- 1(11):
  - 21% with MS or DOD

IHC:
- Cytokeratin poor
- Some hMB45/Melan A (+)
- Cathepsin K (+); TFE3 ~60%

Wide age range (10 mean)
Hereditary leiomyomatosis associated RCC (HLRCC)

Architectural patterns (n=40):
- Papillary 25 (63%)
- Tubulo-papillary 8 (20%)
- Tubular 2 (5%)
- Solid 1 (5%)
- Mixed 4 (10%)

Hereditary leiomyomatosis RCC

Autosomal Dominant

- Cutaneous and uterine leiomyomas
- (M > F)
- 50% hysterectomy (< 35y)
- Resemble PRCC "type 2"
or "collecting duct-like" RCC

Fumarate hydratase
germline mutations (1q42)

Abnormal succination
\[ = \text{ZGC} \]

Aggressive
up to 50% MS at Dx
FH deficient RCC
previously labelled as Unclassified, high grade

- Papillary type 2
- Tubulocystic with dedifferentiated foci
- Collecting duct carcinoma (CDC)

FH deficient RCC

Histomolecular entity
FH and 2SC IHC done on:
- 128 RCC whole slide sections (multiple institutions):
  - "unclassified, high grade" or "unclassified with papillary pattern"
  - at least focal prominent nucleoli
- In addition, 3 TMA with 796 renal neoplasms evaluated:

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>No. Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell RCC</td>
<td>213</td>
</tr>
<tr>
<td>Papillary RCC</td>
<td>181</td>
</tr>
<tr>
<td>Chromophobe RCC</td>
<td>21</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>26</td>
</tr>
<tr>
<td>Other RCCs</td>
<td>39</td>
</tr>
<tr>
<td>Urolithiasis Ca</td>
<td>78</td>
</tr>
</tbody>
</table>
IHC Screening of "Unclassified RCC" detects FH deficient tumors

Papillary (74%) + other patterns!

Tubulocystic (41%) and tubular (26%)
Tubulocystic Carcinoma of the Kidney With Poorly Differentiated Focus
A Frequent Morphologic Pattern of Fumarate Hydratase-deficient Renal Cell Carcinoma

25% (13/51) cases previously diagnosed as CDC reclassified as FH-deficient RCC upon review and IHC for FH and 2SC.
Data

“FH d efficie nt
RCC”
Summary
Negative FH on IHC strongly correlates with:
- FH gene alterations and morphology compatible with H/RCC.
- Aggressive behaviour (but often without the stigmata)
Negative FH IHC - screening for additional genetic testing
Negative FH - more specific and equally sensitive compared with ZSC

Prognostic factors in RCC
1. Tumor WHO/ISUP grade
2. Sarcomatoid/rhabdoid differentiation
3. Tumor necrosis
4. Morphologic type
5. Pathologic stage
Stage pT3a

- **pT2**
  - Tumor extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia

- **pT3a**
  - Tumor extends into the renal vein or its segmental branches, or involves the psoas or pararenal space, but not the perirenal and/or renal sinus fat but not beyond Gerota's fascia

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Renal tumor stage summary of changes - AJCC/TNM 8th edition

Definition of Primary Tumor (pT): T3a disease
Word "grossly" was eliminated from the description of renal vein involvement
"Muscle containing" - omitted as descriptor for "segmental veins" invasion of the pelvicalyceal system was added

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Renal tumor stage

Key prognostic parameter
Used in prognostic nomograms
7th edition (2009)
8th edition (2017)
Handling of renal tumors

Goals:
- Thorough gross examination
- Adequate sampling
- Reporting of stage and other important prognostic parameters

Specimen received in the lab

Identify and sample:
- Adrenal gland
- Vascular margins
- Ureter

Ureteral stump opened and examined
Ureteral invasion

Initial section of specimen along long axis (lateral or medial)

Probes in collecting system or in largest hilar veins

Initial section of specimen along long axis (lateral or medial)

Consider additional parallel sections
Radical and partial nephrectomies should be inked

Radical
Partial

Localised
Selective
(Incision margin)

Renal tumor measurement
(greatest dimension)

Measure any tumor invading into extrarenal tissue
Do not measure tumor invading into renal/renal vein

Stage T1 and T2
Tumor limited to kidney!
TNM 2009 (7th edition) same as AJCC/TNM 2017 (8th edition)

T2a (≤ 4 cm but > 2 cm) (CTB 46)
T2b (> 4 cm)
TNM Descriptors

“m” - multiple tumors in a single site - pT(m)NM

“y” - during or following initial multimodal therapy - ypTNM

“r” - recurrent tumor after a disease-free interval - rxTNM

“a” - stage determined at autopsy - apTNM

Residual tumor (R) - residual tumor after curative therapy

X - can’t be assessed; 0 - no; 1 - microscopic; 2 - macroscopic

How many blocks should you submit for examination?

Important to assess tumor relationship with:
- Renal capsule [peripheral fist]
- Renal sinus
- Adrenal gland
- Renal pelvis

Areas of different appearance or consistency!
- Sarcosomatoid differentiation, necrosis etc.

Sampling of renal tumor for examination

One block per cm, minimum of 3 blocks
(subject to modification)
Multiple renal tumors

<table>
<thead>
<tr>
<th>Hereditary</th>
<th>Sporadic: about 5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Hippel Lindau disease</td>
<td>Papillary RCC - more common bilateral</td>
</tr>
<tr>
<td>Birt-Hogg Dubé Sy</td>
<td>Index and satellite tumors mostly identical</td>
</tr>
<tr>
<td>Hereditary papillary carcinoma</td>
<td>Discordant TU 17-26% (clear cell + papillary)</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>Likely local recurrence if nephron-sparing surgery</td>
</tr>
<tr>
<td>Oncocytosis</td>
<td></td>
</tr>
</tbody>
</table>

Measurement of multiple tumors

Measure and report tumor dimensions for all tumors, up to a maximum of 5

Sampling and staging of multiple tumors

Minimum of 5 largest tumors (if smaller look similar)
If uncertain about histologic type or adverse findings in remaining tumors, do additional sampling
Largest T used – label with [m] pT[m]
Different subtype – separate stage
Stage pT3a

- **pT2**
  - Tumor extends into major veins or perinephric tissues, but not into the perirenal adipose gland and not beyond Gerota's fascia.

- **pT3a**
  - Tumor extends into the renal vein or its segmental branches, or involves the perinephric fat or involves perirenal and/or renal sinus fat but not beyond Gerota's fascia.

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**Assessment of perinephric fat invasion (pT3a)**

- Pushing borders, even if beyond normal kidney, **NOT** diagnostic of fat invasion.
- Invasion: the smooth interface, or irregular, red edges protruding into fat.

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**Assessment of perinephric fat invasion (pT3a)**

- Multiple perpendicular sections of tumor fat interface.
**Perinephric fat invasion (pT3a) - micro**

- Tumor touching fat
- Tumor extending as irregular tongues into fat (with or without desmoplasia)

**Problematic perinephric fat invasion (pT3a)**

- Description of problematic invasion
- Microscopic features

**Renal sinus**

- Central perinephric fat compartment
- No fibrous capsule
- Between pelvicalyceal system and renal parenchyma
- Main lymphovascular supply of kidney
Principle route for extrarenal extension:
- Clear cell RCC, but also other types
- >90% of clear cell RCCs ≥7 cm invaded renal sinus
- Invasion into sinus – worse prognosis than into perinephric fat

Renal sinus invasion - sampling

If sinus invasion graphically evident, or obviously absent (e.g., small peripheral tumor):
Sample only 1 block to confirm sinus invasion present or absent

When uncertain if sinus invasion present:
Sample at least 3 blocks of tumor - sinus interface

Renal sinus invasion present on micro if tumor seen in:
- Direct contact with sinus
- Invade connective tissue beyond renal periphery
- Any endothelial linings space within sinus, regardless of size
Renal vein invasion – AJCC 8th edition

Renal vein invasion (pT3a):
“tumor extends into renal vein or segmental branches”

Renal vein invasion

Tumor attached to the vessel wall or

Tumor fills and distends vessel lumen

Vein invasion in the renal sinus = pT3a
Vein invasion in the perinephric tissues = pT3a

Renal vein and margin sampling
Submit actual margin + Additional sections of tumor thrombus, if grossly suspected to be adherent to vein wall

Renal vein margin positivity
Renal margin positive only if tumor adherent at actual margin, confirmed microscopically
Invasion into pelvicalyceal system = pT3a (new in AJCC 8th edition)

Vena cava invasion

Vena cava invasion – pT3c
Specimen submitted as “caval thrombus”

Include 2 or more sections to search for adherent caval wall tissue and possible invasion

Adrenal gland involvement

Contiguous spread (pT4)
Metastasis (pM1)
Prognostic significance!

Direct adrenal gland involvement - pT4

Direct invasion into adrenal – pT4 disease
Associated with significantly worse prognosis than perinephric fat invasion
Matches pT4 tumors (invasion into adjacent organs)
Metastatic adrenal gland involvement – M1

Assessment of hilar lymph nodes

restrict evaluation to palpation and dissection of hilar fat only

nodes found in less than 10% of cases

nodes rarely identifiable!

Assessment of hilar lymph nodes

Grossly visible hilar nodes positive in 40% of cases

Microscopic nodes found in only 25% of cases

all benign!

Searching for occult nodes not practical!
Regional lymph nodes – N1

- Single or multiple regional nodes involved
- Examine all submitted separately
  - Renal hilar
  - Cava (pre-, para-, retro-, interaortocava)
  - Aortic (pre-, para-, retro-)

Sampling uninvolved renal parenchyma

- Adjacent to tumor, as well as distant from tumor
- Routine assessment for concurrent glomerular, tubulointerstitial and vascular kidney disease

Non-neoplastic kidney pathology (~5 mm parenchyma)

- Diabetic nephropathy/WW nodules
- Hypertensive vascular disease
It is expected that AJCC 8th edition staging for renal cancer will perform (at least) as well as the 7th AJCC/TNM edition.

Take home messages

- Utilize the new WHO/UPL grading system (and educate clinicians!)
- Recognize the expanding spectrum of novel renal tumors
- AJCC 8th edition introduces some (minor) staging changes and refines some definitions, but retains most of the 7th edition parameters
- Stage remains key to prognostication of renal cancer patients
Hope you don't feel like this now!

Questions?

Thank you