RENAL CELL CARCINOMA CLASSIFICATION: The Histologic, Clinical and Molecular basis of the 2016 WHO system and beyond...

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WHO CLASSIFICATION OF RENAL TUMORS 2004

• Clear cell RCC
• Multilocular cystic RCC
• Papillary RCC
• Chromophobe RCC
• Carcinoma of the collecting ducts of Bellini
• Renal medullary carcinoma
• Renal carcinoma associated with Xp11.2 translocations/TFE3 gene fusions
• RCC associated with neuroblastoma
• Mucinous tubular and spindle cell carcinoma
• RCC unclassified
WHO CLASSIFICATION OF RENAL TUMORS 2016

- Clear cell RCC
- Multilocular cystic LMP
- Papillary adenoma and Papillary RCC
- Clear cell-papillary RCC
- Chromophobe RCC
  - Hybrid Oncocytic Chromophobe tumor
- Carcinoma of the collecting ducts
- Renal medullary carcinoma
- MITF family associated RCC
- Mucinous tubular and spindle cell carcinoma
- Acquired cystic disease-associated RCC
- Tubulocystic carcinoma
- Hereditary leiomyomatosis & RCC – associated RCC
- SDHβ mutation-associated RCC
- RCC unclassified

WHO Classification of Renal Neoplasia

- Emerging provisional entities
  - Thyroid-like follicular RCC
  - ALK-translocation RCC
- Entities moved in miscellaneous carcinoma group (less data than previously expected on clinicopathologic distinctiveness)
  - Post-neuroblastoma associated RCC

Beyond WHO 20016

- Eosinophilic, solid and cystic RCC
- TCEB-1 mutated RCC
- Fumarate hydratase deficiency associated RCC
ADULT RENAL EPITHELIAL TUMORS

Clinico-pathologic entities:
• Specific histologic, immunohistochemical profile
• Distinctive chromosomal and molecular abnormalities
• Patterns of Metastasis: distinct for subtypes of RCC
  - Clear cell, CDC, FH def & Sarcomatoid: Systemic
  - Papillary: Regional LNs
  - Chromophobe: Liver and then systemic

Organ confined disease: Prognostically distinctive - Clear cell-papillary, Chromophobe, Papillary, Clear Cell, Unclassified HG, CDC and FH deficient

Metastatic disease: Targeted therapies. Clear cell vs. non clear cell

Marker for Familial/Genetic Disorders: VHL, tuberous sclerosis, Birt Hogg Dube, HLRCC-RCC

Accurate subtyping of renal epithelial tumors is a clinically important exercise!!

APPROACH: MORPHOLOGY

Have easy access to a complete list of all renal tumors

The vast majority of renal tumors are still common subtypes: clear, papillary, chromophobe, clear cell-papillary
• Classic “traditional” approach: Clinical, gross, microscopic, ancillary studies
• Pattern based-approach: Clear cell, Eosinophilic, Papillary, HG unclassified, predominantly cystic, with prominent smooth muscle stroma
• Clinical: Age, Familial Setting and End Stage renal disease

**Approach to dx of renal epithelial tumors**

- Virtually any tumor:
  - clear
  - granular cells
  - papillary
  - spindle cell features or sarcomatoid growth
  - cystic architecture

Careful attention to:
- Gross appearance
- Microscopy: architecture
  - Nuclear
  - cytoplasmic features
  - adjunctive features
- Ancillary diagnostic studies
  - IHC
  - FISH
  - EM

Hence: “clear cell”, “granular cell”, “papillary”, “sarcomatoid”, “cystic” RCC are not a diagnoses based on a single feature
RENAL TUMORS WITH CLEAR CYTOPLASM

- Clear cell RCC
- Clear cell-papillary RCC
- Chromophobe RCC
- Translocation associated (typically xp11.2 translocation associated)
- TCEB mutated RCC
- Virtually any renal tumor incl. papillary RCC, epitheloid PEComa etc. can have clear cell features
RENAL TUMORS WITH EOSINOPHILIC CYTOPLASM

<table>
<thead>
<tr>
<th>Oncocytoma</th>
<th>Mixed clear cell/Eosinophilic</th>
<th>Papillary</th>
<th>Tubulocystic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell RCC</td>
<td>PAPILLARY RCC</td>
<td>Papillary RCC</td>
<td></td>
</tr>
<tr>
<td>Chromophobe RCC</td>
<td>Translocation associated RCC</td>
<td>Type 2 - Oncocytic - Warthin like</td>
<td></td>
</tr>
<tr>
<td>HOC</td>
<td>TFE3 rearranged RCC</td>
<td>TFE3 rearranged RCC</td>
<td></td>
</tr>
<tr>
<td>Clear cell RCC</td>
<td>SDH def RCC</td>
<td>Unclassified papillary RCC</td>
<td></td>
</tr>
<tr>
<td>ESC-RCC</td>
<td>Collecting duct RCC</td>
<td>Thyroid like follicular RCC</td>
<td></td>
</tr>
<tr>
<td>Low grade FH Deficient RCC</td>
<td>Acquired cystic disease associated RCC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelioid PEComa</td>
<td>Unclassified RCC, oncocyotic</td>
<td></td>
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</tbody>
</table>

DIFFERENTIAL DIAGNOSIS OF HIGH GRADE ADENOCARCINOMA OF KIDNEY

- Collecting Duct Ca (CDC)
- Renal Medullary Ca (RMC) & related tumors
- HLRCC- associated RCC & FH deficient tumors
- Invasive Urothelial Ca of pelvicalyceal system involving renal parenchyma
- Metastatic carcinoma involving kidney
- Unclassified RCC

TUMORS OCCURRING IN YOUNGER AGE GROUP

- Translocation associated renal cell carcinoma (TFE3 and TFEB RCC)
- SDH deficient RCC
- HLRCC- RCC
- ESC-RCC
- Renal medullary
- Renal cell carcinomas of all subtypes can occur at any age (papillary, clear cell and chromophobe RCC)
Sporadic RCC
- Clear cell RCC
- Chromophobe RCC
- Papillary RCC
- Collecting Duct Ca

Familial RCC
- VHL
- Birt-Hogg-Dube
- HPRCC
- HLRCC-RCC
- Renal medullary

Post treatment RCC
- Post chemotherapy RCC
- Post neuroblastoma RCC

ESRD
- ACD-assoc RCC
- Clear-papillary RCC

Hereditary Renal Cell Carcinoma Syndromes

“More common or known”
- Von Hippel-Lindau (VHL) Syndrome
- Hereditary Papillary Renal Carcinoma (HPRC) Syndrome
- Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) Syndrome
- Birt-Hogg-Dubé (BHD) Syndrome
- Tuberous Sclerosis (TS) Syndrome
- Succinate Dehydrogenase B (SDHB) Mutation-Associated Renal Cell Carcinoma
- Lynch syndrome –HNPCC (Hereditary Nonpolyposis Colorectal Cancer syndrome)

CLEAR CELL CARCINOMA

Definition:
- Heterogenous group of tumors
- Clear or eosinophilic cytoplasm
- Typical vessel formation
- Molecular background of VHL inactivation & HIF1 upregulation

Recommendation:
- Use ISUP/WHO grading system – New proposed name
PAPILLARY ADENOMA

Definition:
• Unencapsulated
• Tubulopapillary
• Low ISUP/WHO nuclear grade
• 15 mm in diameter or smaller
• Extreme caution in making diagnosis in biopsy – I would not recommend making it
• Revised definition should see significant alteration of RCC statistics for incidence of papillary RCC

PAPILLARY RCC
RENAL ONCOCYTOMA

**Definition:**
- Benign epithelial tumor
- Solid, solid nested and rarely cystic
- Uniform eosinophilic cells packed with mitochondria
- Round regular nuclei
- Dx. of exclusion – extensive sampling

CHROMOPHobe RENAL CELL CARCINOMA

**Definition:**
- Tumors with cells containing prominent cell membranes, wrinkled nuclei with perinuclear halos
- Pale to eosinophilic cytoplasm

**Recommendation:**
- No major changes
- No formal grading system recommendations
- Hybrid oncocytic chromophobe tumors (HOCT) – tumors with overlapping histology between oncocytoma & chromophobe
- Seen in Birt-Hogg-Dube syndrome and sporadically

CHROMOPHobe RCC - Eosinophilic variant
CHROMOPHOBKE RCC
Classic type

- Autosomal dominant genodermatosis
- Cutaneous fibrofolliculomas, pulmonary cysts
- Bilateral, multifocal renal tumors (15-27%)
- Hybrid of chromophobe RCC and renal oncocytoma (50%), chromophobe RCC (34%)
- 17p11.2 (BHD gene) encodes follicullin

Birt-Hogg-Dube Syndrome

- Autosomal dominant genodermatosis
- Cutaneous fibrofolliculomas, pulmonary cysts
- Bilateral, multifocal renal tumors (15-27%)
- Hybrid of chromophobe RCC and renal oncocytoma (50%), chromophobe RCC (34%)
- 17p11.2 (BHD gene) encodes follicullin
Collecting Duct Carcinoma

Criteria:
- High-grade infiltrating adenocarcinoma
- Often gray white, smaller and ill-defined
- Epicenter in the renal medullary region
- Urothelial carcinoma, HLRCC and metastatic carcinoma must be ruled out
- May be mucin producing
MITF FAMILY TRANSLOCATION ASSOCIATED RCC

- RCC associated with Xp 11.2 translocation/TFE3 gene fusion
- RCC associated with t(6;11) (p21;q12) - TFB amplified associated RCC

*Both subtypes may be sporadic or associated with prior chemotherapy*

MITF FAMILY NEOPLASMS

<table>
<thead>
<tr>
<th>Gene</th>
<th>Translocation</th>
<th>IHC</th>
<th>Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>MITF</td>
<td>No</td>
<td>MITF</td>
<td>Angiomyolipoma (PECOMA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Malignant melanoma &amp; clear cell sarcoma</td>
</tr>
<tr>
<td>TFE3</td>
<td>Xp11.2</td>
<td>TFE3</td>
<td>ASP Sarcoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Xp11.2 translocation carcinoma</td>
</tr>
<tr>
<td>TFEB</td>
<td>t(6,11)</td>
<td>TFEB</td>
<td>t(6,11) renal carcinoma</td>
</tr>
<tr>
<td>TFEC</td>
<td>Unknown</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
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Xp11 Translocation RCC

- Results in *TFE3* transcription factor gene fusion
- Likely constitute 50% of childhood renal tumors
- 1-4% of adult renal tumors
- 15% have history of chemotherapy exposure
- >90% disease free (5 year follow up)
- Adults have worse prognosis, often presenting with metastatic disease
- Metastasis after 20-30 years is known
- Clinical trials with *mTOR* and *met* inhibitors
Older patients (median age 64.5 years) compared with unamplified t(6;11) RCC (median age 31 years)

Not entirely distinctive, nests of high grade epithelioid cells with eosinophilic cytoplasm associated with pseudopapillary formation and necrosis, or true papillary formations

These patterns raise the differential diagnosis of high grade clear cell and papillary RCC

Nucleoli are very prominent

Melan A is sensitive marker for this subtype of RCC

TFEB-amplified RCC were associated with a more aggressive clinical course
**Definition**
- Rare variant of AML
- At least 80% epithelioid cells
**EPITHELIOID ANGIOMYOLIPOMA**

**Prognosis**
- Tumors have malignant potential
- Frequency of malignancy varies from 5-66%
- Features associated with malignancy beyond those listed in the next slide include
  - Older age
  - Severe atypia
  - High mitotic count
  - Vascular lymphatic invasion
ADVERSE PROGNOSTIC PARAMETERS-BASED RISK STRATIFICATION MODEL

Based on frequency of 5 adverse parameters associated with disease progression

TSC or concurrent AML, size, necrosis, morphologic pattern, perirenal extension/renal vein involvement

<table>
<thead>
<tr>
<th>Low risk group</th>
<th>Intermediate risk group</th>
<th>High risk group</th>
</tr>
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<tbody>
<tr>
<td>0-1 parameters</td>
<td>2-3 parameters</td>
<td>4-5 parameters</td>
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</table>

Based on frequency of 5 adverse parameters associated with disease progression

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MUCINOUS TUBULAR & SPINDLE CELL CARCINOMA
MUCINOUS TUBULAR & SPINDLE CELL CARCINOMA

TUBULOCYSTIC CARCINOMA
LIVER METASTASIS
ESRD Kidney Neoplasms

- Acquired cystic disease-associated RCC (36%)
- Clear-cell papillary RCC of the end stage kidney (23%)
- Sporadic type renal tumors (41%)
  - Clear cell RCC (18%)
  - Papillary RCC (15%)
  - Chromophobe RCC (8%)

Clear cell-papillary RCC

- Unique morphology of tubules & papillae with clear cytoplasm
- Frequently small multifocal tumors

CLEAR CELL PAPILLARY-RENAL CELL CARCINOMA
Acquired Cystic Disease-Associated RCC

- Most common subtype of RCC occurring in ESRD
- > 10 years stronger association with RCC
- Multifocality (50%) and bilaterality (20%)
- Relatively favorable prognosis as patients with ESRD under clinical surveillance
- Rhabdoid or sarcomatoid morphology, pT3 disease associated with progression
RCC with smooth muscle stroma

Spectrum of tumors still evolving:
clear cell tumors +/- papillary areas, voluminous cytoplasm

- Clear cell RCC with smooth muscle or angioleiomyomatous stroma
- Clear cell-papillary RCC with prominent smooth muscle stroma
- TCEB 1 mutated RCC
- TSC associated RCC with smooth muscle stroma

Tumors have clear cell RCC, clear cell-papillary RCC or TSC history

TCEB1-mutated renal cell carcinoma:
a distinct genomic and morphological subtype

Ari Hakimi 1, 2, 9, Satish K Tickoo 3, 9, Anders Jacobsen 4, 9, Judy Sarungbam, John P Stakianos, Yusuke Sato 5, Teppei Morikawa, Haruki Kuma, Masashi Fukayama, Yukio Homma, Ying Bei Chen, Alexander I Sankin, Roy Mano, Jonathan A Coleman, Paul Russo, Satish Ogawa, Chris Sander, James J Hsieh 2, 8, 9 and Victor E Reuter 3

1 Department of Surgery — Urology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA; 2 Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA; 3 Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; 4 Computational Biology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; 5 Department of Urology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan; 6 Department of Tumor Biology, Graduate School of Medicine, Kyoto University, Kyoto, Japan and 8 Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA


* TCEB1 (8q21.11) is a gene that contributes to the VHL complex to ubiquitinate HIF
Clinical and Genetic aspects
- Multiple cutaneous and uterine leiomyomas – well described since 1950s (Reeds syndrome)
- Autosomal dominant form of syndrome with RCC association in 2001
- Incidence unknown
- 20% of families develop HLRCC (36-39yrs)
- Uterine leiomyomas, 90%, early age and requiring hystrectomy
- Small subset develop leiomyosarcomas
- Adrenal cortical hyperplasia reported

Germline alternations and implications
- Activating mutations in Fumarate Hydratase (FH) gene
- FH an enzyme for Krebs cycle, catalyses conversion of fumarate to malate
- Mutation results in pseudohypoxic drive and dysregulation of HIF regulation
- Mapped to chr 1q42.3-q43
- Potential therapeutic targets: Bevacizumab and erlotinib
Clinical and Genetic aspects
- 20% of families develop HLRCC (36-39yrs)
- Uterine leiomyomas, 90%, early age and requiring hysterectomy
- Majority of patients have advanced disease & die
- Activating germ line mutations in Fumarate Hydratase (FH) gene (mapped to chr 1q42.3-q43)

Hereditary Leiomyomatosis and RCC Syndrome Associated RCC (HLRCC)

Benign smooth muscle tumor with prominent inclusions
TYPE 2 PRCC FEATURES

PROMINENT ‘CMV-LIKE’ EOSINOPHILIC INCLUSION

GROSS PATHOLOGY
• 2.3 to 20.0cm
• Mostly solid with a minor cystic component
• Most high stage (perinephric and renal vein or caval extension)
• May involve the perirenal fat, renal sinus fat, renal vein or have a contiguous extension/metastatic extension into the adrenal gland
• The metastatic potential of these tumors is not proportional to the size of the tumor as smaller tumors can metastasize
• Widespread metastases have been observed
Solitary & unilateral tumors

Morphology overlaps between a collecting duct carcinoma & papillary RCC with papillary, tubulocystic, cribriform and solid architecture:
Multiple patterns

Prominent macronucleoli with eosinophilic inclusions & viropathic like features

Findings can be confirmed by loss of FH and induction of 2SC immunohistochemistry

Cysts (42%) described in the background kidney-potentially premalignant
FH deficient/ HLRCC Associated RCC

Take home points

- Aggressive tumors; most reported cases die within 5 years – MOST LETHAL OF ALL HEREDITARY CANCERS
- Suspect when histology is of type 2 Pap RCC, CDC or mixed high grade patterns
- IHC helpful in dx, requires evaluation for stigmata of disease
- Definitive confirmation: test for germ line mutations
- Refer appropriately for genetic counseling

HLRCC Associated RCC

HG tumors, mixed tubulopap histology, CMV like inclusions, FH (-) and 2 SC(+)

- Family history of renal cancer
- Absent/ Unknown family history of renal cancer
- Stigmata of HLRCC syndrome
- Absent/ Unknown Stigmata of HLRCC syndrome
- Germ line FH mutations
- Absent/ Unknown Germ line FH mutations status

FH deficient RCC

Eosinophilic, Solid, and Cystic Renal Cell Carcinoma: Clinicopathologic Study of 16 Unique, Sporadic Neoplasms Occurring in Women

Trpkov, Kiril MD, FRCP(C); Hes, Ondrej MD, PhD†; Bonert, Michael MD”; Lopez, Jose I. MD, PhD”; Bonsib, Stephen M. MD; Neui, Gabriella MD; Comperat, Eva MD; Sibony, Mathilde MD†; Berney, Daniel M. MD‡; Martinnek, Petr MSc; Bulimbasic, Sulea MD; Suster, Saul MD”; Sango, Ankur MD; Yilmaz, Atili MD; Higgins, John F. MD; Zhou, Ming MD, PhD; Gill, Anthony J. MD, PhD”; Polyzynin, Christopher G. MD”; Magi-Galluzzi, Cristina MD, PhD”; McHenry, Jesse K. MD***


Mean age: 55 yrs.
Majority are females, only rare males
ESC-RCC

- Single tumors, no multifocality
- Tan, mixed solid and macrocystic
- Size: 50 mm (range 15 to 135 mm); majority < 50 mm

Eosinophilic, Solid and Cystic (macro- and micro-)

Hobnal cell lining, variable thickness of septae
Cytoplasmic ‘stippling’ (coarse granularity)!!

Multinucleation and vacuolated cytoplasm
Succinate Dehydrogenase Deficient Renal Cell Carcinoma

New addition to the WHO classification of renal tumors

Succinate Dehydrogenase: Familial Renal Cancer

- Autosomal dominant germline mutations in 3 of the 4 succinate dehydrogenase genes (SDHB, SDHC, and SDHD) - associated with familial paraganglioma/pheochromocytoma (higher % clinically malignant)
- Gastric stromal tumors - early onset & regional lymph node mets
- Recently early onset renal tumors - individuals with germline SDHB mutations - 14% lifetime risk of renal neoplasia (rare tumors associated with SDHC & D germline)
- Pathway: Implicated in Krebs cycle, ↑ succinate inhibits HIF prolyl hydroxylase and affects HIF stability

Succinate Dehydrogenase Deficient RCC

Solid pattern

Entrapped non-neoplastic renal tubules
Cystic pattern

Eosinophilic cytoplasm contained cytoplasmic vacuoles

Hyaline Globules
SDH-deficient RCC
- Majority males (M:F = 1.4:1)
- Wide age range – 3 peaks: children, young adults, and older patients
- 5 ALK fusion partners; in some cases, none of these partner genes were found
- Majority have an indolent course; metastasis has been reported

ALK-translocation RCC
**ALK-translocation RCC**

- Discohesive epithelioid features ranging from polygonal, spindle, cuboidal to low columnar
- Abundant eosinophilic cytoplasm and intercytoplasmic mucin
- May show prominent stromal mucin
- May overlap with RMC – solid, reticular, tubular growth

**UNCLASSIFIED RCC**

**Definition:** A primary carcinoma of the kidney in which the histology does not conform to any of the known subtypes of renal epithelial neoplasms and in which urothelial carcinoma & metastasis is ruled out

**Work-up:**

- Renal vs Metastasis vs. Urothelial – TREATMENT DIFFERENCES

**Diagnosis:** Renal cell carcinoma [clinical correlation]

- **Diagnostic IHC:** PAX 8, RCC, S100A1: (+)
- **Supportive IHC:** CD10, vimentin
Prognostic Impact of Histologic Subtyping of Adult Renal Epithelial Neoplasms
An Experience of 405 Cases

[Diagram showing survival rates and histologic subtypes]
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### Targeted therapy in Renal Cell Carcinoma

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Known somatic alterations</th>
<th>Involved pathway</th>
<th>Targeted therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell</td>
<td>VHL, PMM12, SETD2, E4P1, mTOR, PD-1</td>
<td>VEGF pathway; mTOR pathway</td>
<td>Tyrosine kinase inhibitor; TKI (sorafenib, sunitinib); Newer TKI (pazopanib, axitinib); mTOR inhibitors (everolimus &amp; temsirolimus)</td>
</tr>
<tr>
<td>Papillary RCC</td>
<td>MET</td>
<td>MET-PGF pathway</td>
<td>TKI, mTOR inhibitors, dual MET; VEGFR inhibitor (foretinib)</td>
</tr>
<tr>
<td>Chromophobe RCC</td>
<td>TP53</td>
<td>Upregulation of the mTOR pathway</td>
<td>mTOR inhibitors ( everolimus &amp; temsirolimus)</td>
</tr>
<tr>
<td>Collecting duct Ca</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown (cytotoxic chemotherapy is common)</td>
</tr>
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</table>

For MiT family RCC:
- Xp11.2 and 16p11 translocations
- MET signals as a downstream consequence of aberrant TFE3 activity
- MET inhibitor (tivantinib) in small cohort
ADULT RENAL EPITHELIAL TUMORS

Clinico-pathologic entities:

- **Organ confined disease**: Prognostically distinctive - Clear cell-papillary, Chromophobe, Papillary, Clear Cell, Unclassified HG, CDC and FH deficient

- **Metastatic disease**: Targeted therapies. Clear cell vs. non clear cell

- **Marker for Familial/Genetic Disorders**: VHL, tuberous sclerosis, Birt Hogg Dube, HLRCC-RCC

*Accurate subtyping of renal epithelial tumors is a clinically important exercise!!*