Conventional RCC

- Most common subtype of RCC (60-65%)
- Genetic abnormalities involve short arm chromosome 3
  - Deletion: 3p-
  - Mutations of VHL tumour suppressor gene in chromosome 3p
  - DNA methylation of VHL tumour suppressor gene

Conventional RCC (2)

- Characteristic feature is regular arborising network of thin walled blood vessels
  - Clear cytoplasm is more common in low-grade tumours; eosinophilic granular cytoplasm in higher grade
- Variant patterns
  - Acinar
  - Pseudopapillary
  - Microcystic

Conventional RCC (3)

- Immunoprofile
  - Positive for CA9 (diffuse membranous), CD10, vimentin, RCC marker, EMA, AE1/A3, CAM5.2, PAX2, PAX8
  - Negative for CK7, HMWCK

Conventional RCC Differential Diagnosis

- Chromophobe RCC (eosinophilic variant)
  - DD of granular cell conventional RCC and oncocytoma
  - Lacks vascular pattern of conventional RCC
  - CK7+, c-kit+, CA9-, CD10-
    - Pitfall: eosinophilic variant of chromophobe more often CK7- (oncocytoma mimic)

Conventional RCC Differential Diagnosis (2)

- Papillary carcinoma
  - Papillary carcinoma may have areas with clear cytoplasm (histiocytes in stalks, CK7+, CA9-)
    - Clear cell papillary RCC: distinct entity (CK7+, CA9+)
  - Conventional RCC may have pseudopapillary areas (CA9+, CK7-)
### Conventional RCC

**Differential Diagnosis (3)**

- **Angiomyoepithelioma with clear cells**
  - CK-, EMA-, CA9-, CD10-, HMB45+, SMA+
- **Adrenocortical tumours**
  - CK-, EMA-, inhibin+

### Multilocular Cystic RCC

**Differential Diagnosis**

- Numerous cysts containing groups of clear cells with grade 1 nuclei in septae
- Excellent prognosis
  - No risk of recurrence or metastasis
- ISUP Vancouver consensus meeting 2012 suggests re-naming it “multilocular cystic renal cell neoplasm of low-malignant potential”
  - Also suggested that grade 2 nuclei acceptable

### Multilocular Cystic RCC (MLCRCC)

**Differential Diagnosis**

- Conventional RCC with extensive cystic change
  - Expansile solid nodules not acceptable in MLCRCC
  - Grade 3-4 nuclei not acceptable in MLCRCC
- RCC with extensive cystic necrosis
  - MLCRCC: Thin septae, contains clear, serous or gelatinous fluid
  - Necrotic RCC: Thick irregular shaggy walls, contains haemorrhagic necrotic debris
- Translocation RCC (TRCC)
  - Young patient, psammoma bodies suggest TRCC

### Papillary RCC

**2 Subtypes**

- **Type 1**
  - More often multifocal
  - Single layer of small cells with scant cytoplasm
  - Psammoma bodies, histiocytes more frequent
  - CK7, vimentin, MUC1 positivity more frequent
  - Gains in chromosome 7p and 17p
  - Pseudostratified epithelium with abundant eosinophilic cytoplasm and high nuclear grade
  - Only 20% CK7+ (87% type 1 CK7+)
  - CK20, E-cadherin more often positive
  - Abnormalities in several chromosomes
    - No chromosome 7 or 17 abnormality
**Type 2 Papillary RCC**

**Differential Diagnosis**

- **Hereditary leiomyomatosis and RCC syndrome**
  - Previously included as type 2 PRCC
  - More aggressive than type 2 PRCC

- **Acquired cystic disease associated RCC**
  - Type 2 PRCC like cytology with variable proportion of papillary architecture

- **Tubulocystic RCC**
  - Some type 2 PRCCs have tubulocystic RCC like areas

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**RCC with Papillary Architecture and Clear Cell Cytology**

- **Clear cell papillary RCC**
  - Variable degree of papillary architecture
  - Clear cells of low nuclear grade
  - Nuclei aligned away from base of cells
  - CK7+, CA9+, HMWCK+, AMACR-, CD10-

- **Translocation-associated RCC**
  - Young patient, psammoma bodies
  - Underexpress cytokeratins and EMA

- **Acquired cystic disease associated RCC**

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**Chromophobe RCC (ChRCC)**

- About 5% of RCCs
- ISUP recommends not grading ChRCC
- Generally low-stage at presentation: 86% pT1/pT2

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**Chromophobe RCC**

- **Better prognosis than conventional or papillary**
  - Most studies: no significant difference stage for stage
  - Recent study from Mayo Clinic: ChRCC better prognosis after controlling for stage and grade
  - Some studies suggest that chromophobe metastasis progress more slowly than conventional

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**Chromophobe vs conventional**

When is it important?

- **High-grade tumour**
  - “high-grade” chromophobe less aggressive than high-grade conventional

- **Distinction between small low-grade conventional and chromophobe less important**
  - Both have excellent prognosis
  - Same follow-up protocol
**Oncocytoma**

- 5-10% of renal neoplasms
- Benign neoplasm, do not Fuhrman grade
- Architecture: nested, sheets, tubular, microcystic
  - Foci with oncocytooma architecture may be present in chromophobe RCC
- Cytology: Uniform round nuclei without perinuclear halos
  - Foci of degenerative atypia acceptable in oncocytooma
- C-kit+, CK7- (may have scattered CK7+ cells)
  - Chromophobe typically diffusely CK7+

**Chromophobe vs Oncocytoma: When is it important?**

- **Small tumour**
  - Both have excellent prognosis
  - In borderline cases err on the side of oncocytooma
    - Avoids unnecessary anxiety and follow-up
- **Large tumour**
  - Chromophobe has distinct metastatic potential
    - Low threshold for second opinion
  - In borderline cases err on the side of chromophobe

**Why do we follow-up cancer patients?**

- To pick up recurrence/metastasis early
- Early Rx (low tumour bulk) better prognosis?
- RCCs not rarely present with late solitary metastasis
  - Good prognosis after excision of metastasis

**Metastasis: early vs late**

- Patients presenting with late metastasis have better prognosis
- Intrinsically more indolent tumours
- All metastasis occur before tumour resection
  - Patients presenting with mets after 20 years had actually developed mets 20 years earlier!

**Immunohistochemistry**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Clear Cell</th>
<th>Papillary</th>
<th>Chromophobe</th>
<th>Oncocytoma</th>
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<td>CD10</td>
<td>+ (membranous)</td>
<td>+ (lumenal)</td>
<td>-/+</td>
<td>-</td>
</tr>
<tr>
<td>AMACR</td>
<td>-</td>
<td>+</td>
<td>-</td>
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</tr>
<tr>
<td>C-kit</td>
<td>-</td>
<td>+</td>
<td>+ (diffuse)</td>
<td>-/+ (patchy)</td>
</tr>
<tr>
<td>Vimentin</td>
<td>+</td>
<td>+</td>
<td>-*</td>
<td>-/+ (focal)</td>
</tr>
<tr>
<td>Carbonic Anhydrase</td>
<td>++</td>
<td>-/+</td>
<td>-/+</td>
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</tbody>
</table>

*: Eosinophillic variant of chromophobe more often CK7-
**: Ignore positivity in ischaemic areas

**Collecting Duct Carcinoma**

- Rare, 1% of renal epithelial tumours
- Aggressive tumour generally presents with metastasis
- Very high mortality
- Renal medullary carcinoma is related to collecting duct carcinoma
  - Young patients with sickle cell trait
  - Dismal outcome
**Collecting Duct Carcinoma**

- Infiltrative tumour centred in medulla
- High-grade adenocarcinoma associated with desmoplastic stroma
- Variable growth patterns
  - Tubular, papillary, solid, microcystic
- Differential diagnosis
  - Papillary RCC
  - Urothelial carcinoma
  - ISUP consensus: Diagnose as urothelial carcinoma if even focal urothelial differentiation

**Renal Adenoma**

- Only low-grade papillary tumours up to 5mm diameter are designated as adenoma in the kidney
  - Tumours with clear cells, irrespective of size are designated as RCC

**Angiomyolipoma**

- Common in tuberous sclerosis (80%) but most AMLs are sporadic
- Classical AML easily diagnosed by radiology so not excised unless large or equivocal
- Excised AMLs often fat poor or show fat predominance
- Immunoprofile: Positive for melanocytic markers (HMB45, A103) and cathepsin-K

**Epithelioid AML**

- Polygonal cells with intense eosinophilic cytoplasm
- May show marked nuclear atypia
- May show focal to extensive clear cell change mimicking conventional RCC
- Immunoprofile: HMB45+, A103+

**Epithelioid AML: Prognosis**

- Earlier studies
  - Case reports and small series
  - Tertiary referral centres
  - Poor prognosis
- Recent studies
  - Larger series
  - Non-consult cases
  - Better prognosis
  - Less aggressive than high-grade RCC

**References**