Renal Cell Carcinoma: *Traditional subtypes*

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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

- 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

- More often multifocal and bilateral
- Architectural patterns: papillary, tubulopapillary, solid and glomeruloid
- Cytology: eosinophilic, amphophilic or focally clear
- Use of Fuhrman grading system controversial
  - ISUP recommends grading based on nucleolar prominence alone

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

Papillary RCC:
2 Subtypes

- **Type 2**
  - 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

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**

Chromophobe RCC (ChRCC)

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

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

Chromophobe RCC

- **Architecture: Generally solid sheets**
  - May have nested or glandular patterns
  - Lacks complex fine vasculature of conventional
  - Broad fibrotic septae with thick walled vessels
- **Cytology: clear cells and eosinophilic cells**
  - Clear cells have reticulated rather than optically clear cytoplasm
  - Typical cytology: Koilocyte-like with wrinkled nuclei and perinuclear halos (unlike round nuclei of oncocytoma)

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 oncocytoma architecture may be present in chromophobe RCC
- **Cytology: Uniform round nuclei without perinuclear halos**
  - Foci of degenerative atypia acceptable in oncocytoma
- **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 oncocytoma
    - 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

Antibody	Clear Cell	Papillary	Chromophobe	Oncocytoma
CD10	+ (membranous)	+ (lumenal)	-/+	-
AMACR	-	+	-	-
CK7	-	+	+ (diffuse)	-/+ (patchy)
Vimentin	+	+	-*	-/+ (focal)
C-KIT	-	-	+	+
Carbonic Anhydrase IX**	++	-/+	-/+	-

*: Eosinophilic 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

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