Histologic Subtypes of Renal Cell Carcinoma

~ M. Scott Lucia, MD

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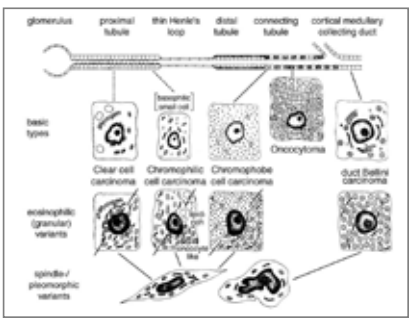
History of Classification of Renal Cell Neoplasms

- First case in literature reported by G. Miriel in 1810
- First classification in 1826, proposed by König, on basis of *gross* morphologic appearance into four types: Fungoid, Medullary, Scirrhous, Steatomatous
- Many subsequent classifications – many based upon descriptive histologic features of tumors (archetectural and cytologic)
- Mainz classification proposed by Thoenes 1986
  - based upon cytologic features of tumors
  - first to correlate the subtypes of tumors with cell of origin in nephron

Delahunt B. Eble JN. History of the development of the classification of renal cell neoplasia. Clinics in Laboratory Medicine. 2005;25:231-46.

The Mainz Classification 1986



From: Delahunt B. Eble JN. Clinics in Laboratory Medicine. 2005;25:231-46. © 2005 Elsevier Inc.

Studies have confirmed cytogenetic differences between major tumor subtypes in Mainz classification

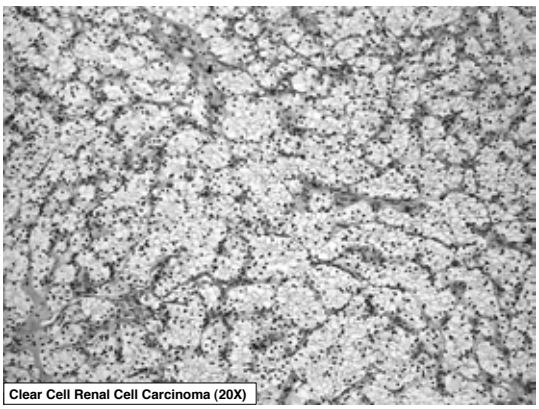
Tumor type	Freq	Histopathology	Cytogenetics
Clear cell RCC	70%	-Clear cytoplasm -Alveolar, tubular and cystic architecture -Vascular stroma	-3p, +5q, -6q, -8p, -14q
Chromophil RCC	15%	-Papillary architecture -basophilic, low N:C (type I) -eosinophilic, high N:C (type II)	Trisomy 7, 17, -Y, +3q
Chromophobe RCC	5%	-Solid architecture -Pale or granular cytoplasm -Prominent cell membranes -Occ. Bizarre nuclei	-1, -2, -6, -10, -13, -17, -21
Collecting duct Carcinoma	1-2%	-Medullary location -Tubuloglandular architecture -Hobnail cells -Desmoplastic stroma	-1q, -6p, -8p, -13q, -21q

Heidelberg Classification 1997[1]

Expanded on Mainz classification; based upon cytogenetics

- Clear cell – "conventional RCC"
- Papillary RCC – to replace "Chromophil"
- Chromophobe RCC
- Collecting duct carcinoma
  - Medullary carcinoma – associated with sickle cell trait

1. Kovacs et al. J Pathol 1997;183:131-3.

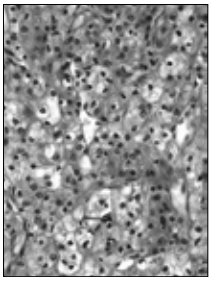


Clear Cell Renal Cell Carcinoma (20X)

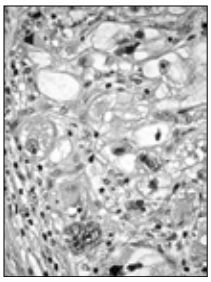
Clear Cell Renal Cell Carcinoma with necrosis

Fuhrman grading predictive of outcome

Fuhrman grade II



Fuhrman grade IV



Clear Cell RCC - Cytogenetics

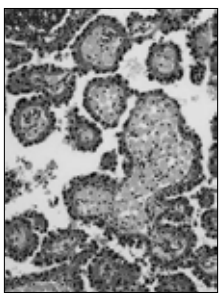
- Abnormalities involving VHL gene (3p25.3) (tumor-suppressor gene):
  - Deletion (3p-)
  - Translocation (3;6, 3;8, 3;11)
  - Somatic mutation or hypermethylation (80% RCC)
  - In both sporadic (95%) and familial (4%) RCC
- Familial, associated with VHL (Von Hippel-Lindau) syndrome:
  - Hemangioblastomas of the cerebellum and retina
  - Bilateral renal cysts
  - Multiple RCCs (nearly all, if they survive older age)

VHL Gene

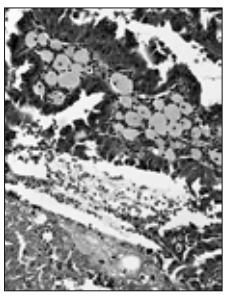
- VHL protein part of ubiquitin ligase complex
  - Degrades hypoxia-inducible factor (HIF-1)
  - Degrades insulin-like growth factor-1 (IGF-1)
- Loss/ mutation results in:
  - High levels of HIF-1 (stimulates angiogenesis via VEGF and TGF-b)
  - Upregulation of IGF-1 (stimulates cells growth)

Papillary RCC

Basophilic (Type I)



Eosinophilic (Type II)

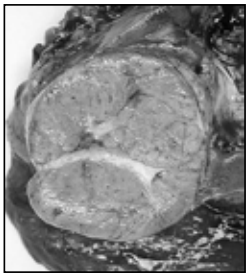


Papillary RCC

- Hereditary and sporadic forms
  - Hereditary usually multifocal and bilateral
- Most common cytogenetic abnormalities:
  - Trisomy 7, 17 (hereditary and sporadic forms)
  - Loss of Y in male patients (sporadic form)
- Protooncogene locus on chromosome 7 (cMET):
  - Tyrosine kinase receptor for HGF
  - Mutated in some sporadic cases

Chromophobe renal cell carcinoma

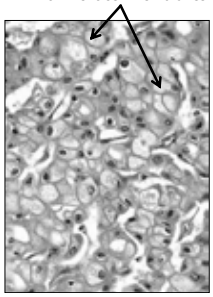
- 5% of RCC
- Gross appearance:
  - Solid tumor
  - Mimics oncocytoma
- Derived from intercalated cell of collecting duct
- Numerous mitochondria and mitochronria-derived cytoplasmic vesicles



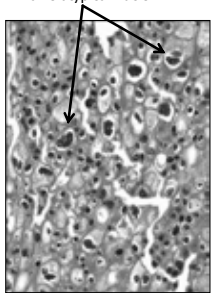
Chromophobe renal cell carcinoma

Fuhrman grading not reliable

Prominent cell membranes

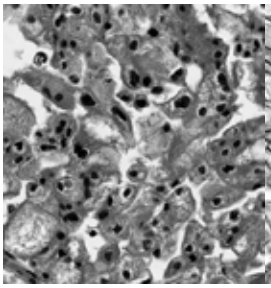


Bizarre atypical nuclei

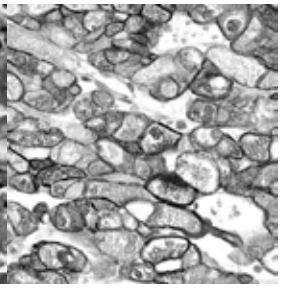


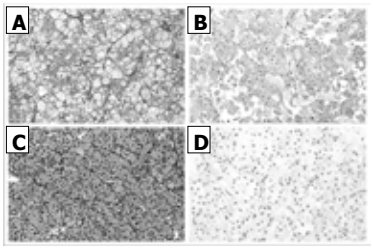
Chromophobe RCC

Eosinophilic variant



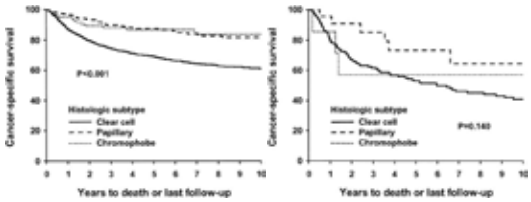
CD117 Expression





A. Chromophobe RCC
B. Chromophobe RCC Colloidal iron
C. Oncocytoma
D. Oncocytoma Colloidal iron

Cancer-specific survival among clear cell, papillary and chromophobe RCC

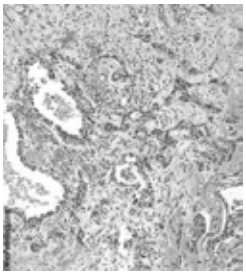


Overall Stage pT3

Cheville, J. et al. Amer J Surg Pathol 2003;27:612-624

Carcinoma of the Collecting Ducts of Bellini (Collecting Duct Carcinoma)

- Centrally located
  - Medullary origin
- Derived from principal cell of collecting duct
- Usually present in advanced stage and higher grade
- Medullary carcinoma
  - Aggressive variant of CDC that occurs in young black males with sickle cell trait



2004 World Health Organization Classification of Renal Cell Tumors

Expanded on Mainz and Heidelberg classifications to account for cytogenetics, behavior, and associated conditions

- Clear cell RCC
- Multi-locular clear cell RCC (VHL gene mutation, good prognosis)
- Papillary RCC (Type I=basophilic, good prognosis; type II=eosinophilic, worse prognosis)
- Chromophobe RCC
- Carcinoma of the collecting ducts of Bellini
- Renal medullary carcinoma
- Xp11 translocation carcinoma
- Carcinoma associated with neuroblastoma
- Mucinous, tubular, and spindle cell carcinoma
- Renal cell carcinoma, unclassified

- Papillary adenoma
- Oncocytoma

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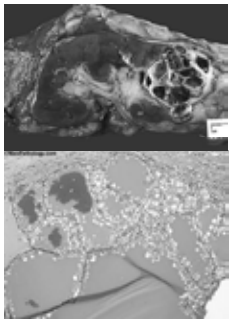
Multilocular cystic renal cell carcinoma

- Good prognosis
- Most low grade (Fuhrman I or II)
- Usually stage I or II
- Mets not reported
- VHL mutations



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- Renal cell carcinoma, unclassified (5% of RCC)

- Papillary adenoma
- Oncocytoma

Conclusions

- The classification of renal cell carcinomas is expanding
- Classification has morphological and cytogenetic basis
- Proper classification important for prognosis