Update: Renal cell carcinoma
Agenda

• clinical context
• what’s new?
• prognostic markers
RCC at diagnosis

extent of disease

- localized
- regional
- metastatic
- unstaged

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<tr>
<th>Stage</th>
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localized disease:
- partial/radical nephrectomy
- cryotherapy
- radiofrequency ablation
- active surveillance
- immunotherapy of no benefit

dystemic disease:
1st line
- high dose IL-2 (10% durable remissions)
- anti-angiogenic therapy or check-point inhibitor
2nd line
- VEGF-TKI, mTOR-I
- cytoreductive nephrectomy
- no role of chemotherapy, hormonal therapy, or radiation
Agenda

• clinical context
• what’s new?
  – Vancouver classification and beyond
  – new entities, names and codes
  – molecular characterization
• prognostic markers
ISUP conference Vancouver 2012

Vancouver classification of renal neoplasia, 2013

ISUP grading system for ccRCC and pRCC, 2013

best immunohistochemistry practice, 2014

TNM classification 2017

WHO classification 2016

ICCR dataset unpublished
• positive renal vein margin: tumor adherent to vessel wall at margin

• infiltration of renal sinus: if uncertain take ≥3 blocks
Urinary collecting system invasion

prognostic value (stage 1-2)


J Urol 182:854-859, 2009
Approach to histology

- child or adult?
- clear cell, papillary, eosinophilic, and/or high grade morphology?
- any unusual features?
- possibility of genetic syndrome?
RCC: histological types in adults

- clear cell (65-70%)
- papillary (~18%)
- chromophobe (5-7%)

→ other types: differential diagnosis of common types

other type:
- oncocytoma (5-9%)
- collecting duct carcinoma (1-2%)
- ...

non-RCC:
- urothelial cell carcinoma
- neuroendokrine tumours
- metastasis
**WHO 2016: new entities, names, and codes**

### Renal cell tumours
- Clear cell renal cell carcinoma
- Multilocular cystic renal neoplasm of low malignant potential
- Papillary renal cell carcinoma
- Hereditary leiomyomatosis and renal cell carcinoma--associated renal cell carcinoma
- Chromophobe renal cell carcinoma
- Collecting duct carcinoma
- Renal medullary carcinoma
- MiT family translocation renal cell carcinomas
- Succinate dehydrogenase-deficient renal carcinoma
- Mucinous tubular and spindle cell carcinoma
- Tubulocystic renal cell carcinoma
- Acquired cystic disease--associated renal cell carcinoma
- Clear cell papillary renal cell carcinoma
- Renal cell carcinoma, unclassified
- Papillary adenoma
- Oncocytoma

### Metanephric tumours
- Metanephric adenoma
- Metanephric adenofibroma
- Metanephric stromal tumour

### Nephroblastic and cystic tumours occurring mainly in children
- Nephrogenic rests
- Nephroblastoma
- Cystically differentiated nephroblastoma
- Paecicystic cystic nephroma

### Mesenchymal tumours occurring mainly in children
- Clear cell sarcoma
- Rhabdoid tumour
- Congenital mesoblastic nephroma
- Ossifying renal tumour of infancy

### Mesenchymal tumours occurring mainly in adults
- Leiomyosarcoma
- Angiosarcoma
- Rhabdomyosarcoma
- Osteosarcoma
- Synovial sarcoma
- Ewing sarcoma
- Angiomyolipoma
- Epithelioid angiomyolipoma
- Leiomyoma
- Haemangiompa
- Lymphangiompa
- Haemangioendothelioma
- Juxtaglomerular cell tumour
- Renomedullary interstitial cell tumour
- Schwannoma
- Solitary fibrous tumour

### Mixed epithelial and stromal tumour family
- Cystic nephroma
- Mixed epithelial and stromal tumour

### Neuroendocrine tumours
- Well-differentiated neuroendocrine tumour
- Large cell neuroendocrine carcinoma
- Small cell neuroendocrine carcinoma
- Phaeochromocytoma

### Miscellaneous tumours
- Renal haemangioendothelial neoplasms
- Germ cell tumours

### Metastatic tumours

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) (P7A). Behaviour is coded 10 for benign tumours; 1 for unspecified, borderline, or uncertain behaviour; 2 for carcinoma in situ and grade III intratubular neoplasia; and 3 for malignant tumours. The classification is modified from the previous WHO classification (756A), taking into account changes in our understanding of these lesions.

*New code approved by the IARC/WHO Committee for ICD-O.*

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**names:**
- multilocular cystic renal neoplasm of low malignant potential
- MiT family translocation RCC
- paediatric/adult cystic nephroma/mixed epithelial and stromal tumour
- neuroendocrine tumours

**entities:**
- hereditary leiomyomatosis and renal cell carcinoma--associated RCC
- succinat dehydrogenase-deficient RCC
- tubulocystic RCC
- aquired cystic disease-associated RCC
- clear cell papillary RCC
Hereditary leiomyomatosis and renal cell carcinoma-associated RCC

- **DD: papillary RCC type 2**
- germline mutation of fumarate hydrogenase
- leiomyomas of the skin and uterus (85%), adrenal nodular hyperplasia in a subset
- papillary histology with large cells, abundant eosinophilic cytoplasm, large nuclei with prominent inclusion-like eosinophilic nucleoli
- IHC: FH-, 2SC+ (cytoplasm and nucleus)
Succinat dehydrogenase-deficient RCC

- DD: oncocytoma, eosinophilic variant of chRCC
- germ line mutations of SDH genes
- pheochromocytoma, paraganglioma, GIST (all more common than RCC)
- usually nested or solid growth with low grade nuclei, eosinophilic granular cytoplasm, characteristic cytoplasmic inclusions (giant mitochondria)
- IHC: SDHB-, CK7-, CD117-
Tubulocystic RCC

- well circumscribed („sponge-like“) multi-cystic renal mass
- tubules admixed with larger cysts, single layer of epithelium (flat to columnar, hobnail), eosinophilic cytoplasm, high grade nuclei
- IHC: CK7+, AMACR+, CD10+
Aquired cystic disease-associated RCC

- **DD:** papRCC type 2, ccRCC
- most common tumour in end-stage renal disease (long-term hemodialysis, frequently bilateral and multifocal
- variable growth patterns, presence of cribriform/microcystic/sieve-like areas, oxalate crystals common, abundant eosinophilic cytoplasm, prominent nucleoli
- **IHC:** AMACR+, CD10+, CK7-, CA9-
Clear cell papillary RCC

- DD: ccRCC, papRCC
- often cystic, frequently found in end-stage renal disease
- prominent papillary architecture, clear cystoplasm, low grade nuclei, nuclear arrangement in linear alignment away from the basal aspect
- characteristic IHC: CK7+, CA9+ (cup-like), 34bE12+, AMACR-
Emerging entities

- oncocytic RCC occurring after neuroblasiaoma
- thyroid-like follicular RCC
- ALK rearrangement-associated RCC
- RCC with (angio) leiomyomatous stroma

→ remember: there is a category of unclassified RCC
Molecular characterization

Comprehensive molecular characterization of clear cell renal cell carcinoma


Comprehensive Molecular Characterization of Papillary Renal-Cell Carcinoma


The Somatic Genomic Landscape of Chromophobe Renal Cell Carcinoma

Cancer Cell 26:319-330, 2014
Molecular characterization

- type 1, 2, and unclassified
- difference between type 1 and 2
- type 2 further classified into 3 groups
- distinct subgroup of type 2 with CpG island methylator phenotype, mutations of fumarate hydratase, and poor survival

**Comprehensive molecular characterization of clear cell renal cell carcinoma**


**Comprehensive Molecular Characterization of Papillary Renal-Cell Carcinoma**


**The Somatic Genomic Landscape of Chromophobe Renal Cell Carcinoma**

*Cancer Cell* 26:319-330, 2014
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- clinical context
- what’s new?
- prognostic markers
Prognostic factors

- anatomic extent (TNM staging)
- tumor type? (ccRCC does worse than papRCC or chRCC)
- tumor grade (ISUP grading)
- sarcomatoid component, rhabdoid component (%)
- tumor necrosis (%; generally >10% relevant, in stage I and II >20%)

UpToDate.com: Prognostic factors in patients with renal cell carcinoma
International Collaboration on Cancer Reporting: upcoming dataset for kidney carcinoma
single high-power field showing greatest nuclear pleomorphism

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<td>1</td>
<td>nucleoli absent or inconspicuous at x400</td>
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<td>2</td>
<td>nucleoli are conspicuous and eosinophilic at x400 and visible but not prominent at x100</td>
</tr>
<tr>
<td>3</td>
<td>nucleoli are conspicuous and eosinophilic at x100</td>
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<tr>
<td>4</td>
<td>extreme nuclear pleomorphism, ultinucleate giant cells, and/or rhabdoid and/or sarcomatoid differentiation</td>
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Cancer-specific survival by the ISUP grading system for 3017 patients with ccRCC

- grade ccRCC and pRCC
- do not grade chrRCC

Diagnose nach ICCR

Niere rechts (radikale Nephrektomie):
Keine sarkomatoide oder rhabdoide Morphologie. Tumornekrosen (20%). Keine enthaltene Nebenniere, Lymphknoten oder andere Organe.
Tumorfreie Resektionsränder.
G3, pT3a, pNX, L0, V1, Pn0, lokal R0

Nicht neoplastisches Nierengewebe mit Arteriolosklerose, interstitieller Fibrose und Tubulusatrophie (10%).