Histopathology and prognosis in renal cancer
Luca Mazzucchelli
Istituto cantonale di patologia, Locarno

Targeted therapy and renal cancer: sharing clinical experience,
November 2009

Granular cell carcinoma

Renal Cancer

Clear cell carcinoma
Granular cell carcinoma

Unusual and new renal tumor entities

Renal cancer unclassified

Collecting duct carcinoma
Papillary carcinoma Type 1
Type 2

metanephric adenoma, adenofibroma

Clear cell carcinoma

Chromophobe cell carcinoma

Papillary carcinoma Type 2

Oncocytoma

WHO classification of tumors of the kidney
(2004)

- Clear cell renal carcinoma
- Multilocular clear cell renal carcinoma
- Papillary renal cell carcinoma (Type 1 and Type 2)
- Chromophobe renal cell carcinoma
- Carcinoma of the collecting ducts of Bellini
- Renal medullary carcinoma
- Xp11 translocation carcinomas
- Carcinoma associated with medulloblastoma
- Mucinous tubular and spindle cell carcinoma
- Renal cell carcinoma, unclassified
- Papillary adenoma
- Oncocytoma

New and emerging tumors of the kidney

- Tubulocystic carcinoma
- Carcinoma associated with end stage renal disease
- Follicular renal carcinoma
- Clear cell papillary and cystic renal cell carcinoma
- Oncocytic papillary renal cell carcinoma
- Leiomyomatous renal carcinoma

Siegler JR, Dehnhart B. Modern Pathol 2009; 22:S2-S23
Incidence of renal cell tumors according to histological type

- Clear cell carcinoma 70-75%
- Papillary renal cell carcinoma 10-15%
- Chromophobe renal cell carcinoma 3-5%
- Oncocytoma 3-5%
- Others 1%

Clear cell renal carcinoma

- 70-75% of all renal cancer cases
- Originates from the proximal tubule of the nephron
- Architecturally diverse (solid, alveolar, acinar)
- Well vascularized
- Cytoplasm clear (lipids and glycogen) and eosinophil
- Nuclei irregular depending upon the grade
- Sarcomatoid changes in 5% of the tumors
- Nuclear grade after stage is the most important prognostic factor

Papillary renal cell carcinoma

- 10-15% of renal cancer cases
- Bilateral and multifocal tumors are more common
- Varying proportions of papillae and tubuli
- Type 1: small cell with scanty cytoplasm
- Type 2: higher nuclear grade with eosinophilic cytoplasm
- Sarcomatoid changes in 5% of the tumors
- There is no specific grading system

Chromophobe renal cell carcinoma

- 5% of all renal cancers
- Solid, cut surface brown, less necrosis than other carcinomas
- Large polygonal cells with prominent membrane
- Amphophilic cytoplasm (eosinophilic variant)
- Perinuclear halo
- Calcifications
- Thick walled vessels
- CD117 positive

Oncocytoma

- 5% at all renal neoplasms
- Benign
- Well-circumscribed, non-encapsulated neoplasms, brown
- Central scar in up to 40%
- Solid compact nests of eosinophilic cells
- Nuclear pleomorphism
- Mitotic figures rare to absent
- CD117 positive

Familial renal cell carcinoma

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Chr</th>
<th>Kidney</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Hippel-Lindau</td>
<td>VHL</td>
<td>3p25</td>
<td>Multiple bilateral RCC, renal cysts</td>
<td>Hemangioblastoma, phaeochromocytoma, ecc</td>
</tr>
<tr>
<td>Hereditary papillary renal cancer</td>
<td>C-MET</td>
<td>7q31</td>
<td>Multiple bilateral RCC, renal cysts</td>
<td></td>
</tr>
<tr>
<td>Hereditary leiomyomatosis and RCC</td>
<td>FH</td>
<td>1q42-43</td>
<td>PRCC Type 1</td>
<td>Skin and uterine leiomyomas and leiomyosarcomas</td>
</tr>
<tr>
<td>Birt-Hogg-Dubé</td>
<td>BHD</td>
<td>17p11.2</td>
<td>Multiple chromophobe RCC, hybrid oncocytoma, oncocytoma</td>
<td>Facial fibrofolliculoma, lung cysts</td>
</tr>
</tbody>
</table>
Mutations in sporadic renal cell carcinoma

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell</td>
<td>75%</td>
</tr>
<tr>
<td>Papillary type 1</td>
<td>5%</td>
</tr>
<tr>
<td>Papillary type 2</td>
<td>10%</td>
</tr>
<tr>
<td>Chromophobe</td>
<td>5%</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>5%</td>
</tr>
</tbody>
</table>

VHL associated carcinogenesis

Normal VHL → VHL Ubiquitin Ligase → HIF-α → HIF-Degradation

Mutated VHL → No HIF-Degradation → Upregulation of HIF down-stream genes

VEGF, PDGF, TGFr, EGFR, IGF, GLUC1, EPO, CXCR4
Neovascularisation, Proliferation, Energy supply, Metastasis

Targeting the VHL pathway

HIF-α → VHL Ubiquitin Ligase → HIF-Degradation

Bevacizumab → Upregulation of HIF down-stream genes

VEGF, PDGF, TGFr, EGFR, IGF, GLUC1, EPO, CXCR4
Neovascularisation, Proliferation, Energy supply, Metastasis

MET associated carcinogenesis

Truncated forms of HGF act as antagonists of HGF
Anti-HGF antibodies present in several cancers (juxtamembrane domain)
Activating mutations in the TK domain is characteristic for HPRC
Duplication of chromosome 7 is common in HPRC

TKI inhibitors
MET-pathway inhibitors

Evidence-based algorithm for metastatic renal cancer therapy

- Sunitinib or IFN + bevacizumab as front line therapy in patients with good or intermediate prognosis
- Temsirolimus for patients with poor prognostic features
- Sorafenib for patients with progression after immunotherapy
- Everolimus for patients with progression after VEGF-receptor inhibition

The ultimate goal is to be able to chose treatment strategies that take into consideration the pathologic, molecular and/or biological features of the tumor.
**Histological type**

![Histological type graph](image)

- Stage I and II
- Stage III and IV


**Immunotherapy**

- Responses to immunotherapy are most frequently seen with RCC of the clear cell histologic type.
- Carbonic anhydrase IX (CAIX) has been associated with higher objective response rate in IL-2 treated patients.
- Genetic studies suggest that complete responders to IL-2 have a signature gene and protein expression pattern that includes CAIX, PTEN, and CXCR4, or losses in sections of chromosome 9p.

**mTOR inhibitors**

- Temsirolimus has a preferential activity in non-clear cell RC (sorafenib and sunitinib have only limited activity in non-clear cell RC).
- High expression of phospho-AKT or phospho-S6 ribosomal protein is associated with objective response.
- No correlation with PTEN and CAIX.

**VEGF pathway targeted therapy**

- VEGF in serum is not a predictive factor.
- sVGRF2 may predict better response.
- HIF2-alpha expression detected by IHC may predict better response.
- VHL gene mutations are not predictive of response...
- ...but loss of function mutations may have a predictive role.

**Conclusions and summary**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response predictor</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>Histology, expression factors (CAIX, PTEN, CXCR4)</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>Nonclear cell, high phospho-Akt, phospho S6</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>High CAIX, VHL -/-</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>High HIF-2a, VHL-WT</td>
</tr>
</tbody>
</table>

Functional imaging studies?