Pathology of RCC: What do Clinicians Need to Know?

Holger Moch
Department Pathology
University Hospital Zurich
# Challenges for Pathologists

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<th>Renal Mass Biopsies</th>
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ISUP Consensus Conference

Vancouver (USCAP)
Working Group IV
(Biomarker: Diagnosis, Prognosis, Prediction)

Group Chair Holger Moch, Co-chair Liang Cheng,

Rapporteur Steven Shen,

Members: Victor Reuter, Nathalie Leclerq-Roux, Maria Merino, George Netto, Puay Hoon Tan
For distinguishing clear cell RCC from chromophobe RCC, do you use the following markers?

1. Both CD117 & CAIX
2. CAIX
3. CD117
4. CK7
5. Hale’s colloidal iron
Review – Kidney Cancer

Renal Tumor Biopsies for Evaluation of Small Renal Tumors: Why, in Whom, and How?

Mesut Remzi, Michael Marberger
Department of Urology, Medical University of Vienna, Vienna, Austria

Review Article

Renal mass sampling: An enlightened perspective

Mary K Samplaski, Ming Zhou, Brian R Lane, Brian Herts and Steve C Campbell
1Glickman Urological and Kidney Institute, 2Pathology and Laboratory Medicine Institute, and 3Imaging Institute, Cleveland Clinic, Cleveland, Ohio, and 4Division of Urology, Spectrum Health Hospital System, Grand Rapids, Michigan, USA

Review Articles

Renal Mass Biopsy—A Renaissance?

Brian R. Lane, Mary K. Samplaski, Brian R. Herts, Ming Zhou, Andrew C. Novick and Steven C. Campbell
From the Glickman Urological Institute (BRL, MKS, ACN, SCC) and Departments of Radiology (BRRH) and Anatomic Pathology (MZ), Cleveland Clinic, Cleveland, Ohio
Potential of Needle Biopsy

• Diagnostic accuracy increases
  – Before 2001: 82%
  – 2001-2006: 90%
  – 2010: >95%

• Non-informative biopsies: 10-20%

• „oncocytic neoplasm“: diagnostic dilemma?

• Metastases of RCC !!
Novel renal tumor types with clear cytoplasm

- Translocation carcinoma

- Renal Cancer in End Stage Renal Disease
  - ACD-related RCC
  - Clear cell and papillary RCC in ESRD

- Sporadic clear cell and papillary and cystic (!) renal cancer

- Leiomyomatous renal cancer

- Multilocular cystic renal cell carcinoma

- Angiomyolipoma / Epitheloid Angiomyolipoma
„Translocation“ Type of Renal Cancer in Children

no VHL-Mutations!
Clear cell-papillary RCC, sporadic (!)
Spectrum of Epithelial Neoplasms in End-Stage Renal Disease

An Experience From 66 Tumor-Bearing Kidneys With Emphasis on Histologic Patterns Distinct From Those in Sporadic Adult Renal Neoplasia

Satish K. Tickoo, MD,* Mariza N. dePeralta-Venturina, MD,†† Lara R. Harik, MD,* Heath D. Worcester, MD,§ Mohamed E. Salama, MD,‡ Andrew N. Young, MD,§ Holger Moch, MD,‖ and Mahul B. Amin, MD§
Differential Diagnosis of Cystic Renal Neoplasms

• Clear cell renal cell carcinoma with prominent cysts
• Clear cell renal cell carcinoma arising in a simple cysts
• Multilocular cystic renal cell carcinoma

• Cystic Nephroma/Mixed Epithelial and Stromal Tumor
• Synovial sarcoma ("Cystic embryonal sarcoma")
• Cystic partially differentiated nephroblastoma
• Tubulocystic carcinoma
• Renal cancer in end stage renal disease
smaller cysts with phyllodes glands pattern and stromal luteinization more common in MEST
large cysts, thin septae and low stromal to epithelial ratio more common in CN

"renal epithelial and stromal tumor" (REST)
Tubulocystic RCC
## Challenges for Pathologists

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Fuhrman Grading in RCC

Cancer-specific mortality-free rates

I (n = 20) II (n = 197) III (n = 162) IV (n = 52)

2-year 100.0% 95.9% 80.2% 38.5% II vs. I (log-rank P = 0.497)
5-year 95.0% 88.8% 60.5% 26.9% III vs. I (log-rank P = 0.010)
10-year 89.4% 83.3% 56.4% 11.5% IV vs. I (log-rank P < 0.001)

Duration of follow-up, months
Grading of Chromophobe RCC

Amin MA, Paner GP, Alvarado-Cabrero I, Young AN, Stricker HJ, Lyles R, Moch H:

Paner GP, Amin MA, Alvarado-Cabrero I, Young AN, Stricker HJ, Moch H, Lyles R:
Tumor Staging
Tumor Staging


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### Current Prognostic Parameters in ccRCC

- **Patient factors**
  - Age
  - Sex

- **Pathologic factors**
  - pTNM
  - Histologic type
  - Fuhrman grade
  - LVI
  - Tumor necrosis

- **Clinical factors**
  - ECOG performance status
  - Hgb level
  - Serum lactate dehydrogenase

### Emerging Potential Molecular Prognostic and Predictive Parameters in ccRCC

- Hypoxia-inducible:
  - HIF1
  - CAIX
  - CAXII
  - CXCRI
  - VEGF-165
  - ILGF1

- Cell adhesion markers:
  - EpCAM
  - E-cadherin
  - α-Catenin
  - Catenin-6

- Proliferation markers:
  - Ki-67
  - MCM2

- Cell cycle regulators:
  - Cyclin
  - p27

- Apoptosis regulators
  - p53
  - Bcl2
  - Smac/DIABLO

- RANKL pathway:
  - PTEN
  - Akt
  - Phos S6k

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**Abbreviations:** ECOG, Eastern Cooperative Oncology Group; Hgb, hemoglobin; LVI, lamina propria invasion.
Molecular Pathways and Targeted Therapies in Renal-Cell Carcinoma

von Hippel-Lindau Gene Status and Response to Vascular Endothelial Growth Factor Targeted Therapy for Metastatic Clear Cell Renal Cell Carcinoma

VHL-Mutation ↔ Gene expression

Banks, R.E.et al.; Cancer Res 2006: Correlation of VHL Mutation type with gene expression
VHL Mutation in clear cell renal cancer

Driver and Passenger VHL Mutations

3 different groups of missense mutations:

1) severe destabilization of pVHL

2) without destabilizing effects on pVHL but relevance for the interaction with HIFα, elongin B, and elongin C

3) pVHL functions comparable with wild type.

Rechsteiner et al., Cancer Res. 2011 Aug 15;71(16):5500-11
The future has arrived

"Here's my sequence..."

New Yorker
Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing
Marco Gerlinger, M.D., Andrew J. Rowan, B.Sc., Stuart Honnor, M.Math., James Larkin, M.D., Ph.D.,
David Endesfelder, Dip.Math., Eva Gronroos, Ph.D., Pierre Martinez, Ph.D., Nicholas Matthews, B.Sc.,

Single-Cell Exome Sequencing Reveals Single-Nucleotide Mutation Characteristics of a Kidney Tumor
Xun Xu,1,2,14 Yong Hou,1,3,4,14 Xuyang Yin,1,14 Li Bao,1,14 Aifa Tang,5,6,14 Luting Song,1 Fuqiang Li,1 Shirley Tsang,7
Kui Wu,1 Hanjie Wu,1,8 Weiming He,1 Liang Zeng,1 Manjie Xing,1 Renhua Wu,1 Hui Jiang,1 Xiao Liu,1 Dandan Cao,1
VHL and Deep Sequencing

- several low frequency single nucleotide variants
- different VHL mutations: 2 independent clonal expansions-parallel somatic evolution of primary-and mets (Gerstung M. et al.; Nature Comm; May 2012)
Exome sequencing identifies frequent mutation of the SWI/SNF complex gene PBRM1 in renal carcinoma

Ignacio Varela1, Patrick Tarpey1, Keiran Raine1, Daehwan Huang2, Choon Kiat Ong2, Philip Stephens1, Helen Davies1, David Jones1, Meng-Lay Lin1, Jon Teague1, Graham Bignell1, Adam Butler1, Jun Qi1, Gillian L. Daigleish1, Danushka Galappaththige1, Chris Greenman1, Claire Hardy1, Mingming He1, Calli Latimer1, King Wai Lau1, John Marshall1, Stuart McLaren1, Andrew Menzies1, Laura Mudie1, Lucy Stebbings1, David A. Largaespada1, L. F. A. Wessels1, Stephanie Richard1,4, Richard J. Kahnoski1, John Anema1, David A. Tuveson5, Pedro A. Perez-Mancera5, Ville Mustonen7, Andrey Fischer5,10, David J. Adams11, Alistair Rust11, Waraporn Chan-on7, Chutima Subimerb5, Karl Dykema7, Kyle Furgo7, Peter J. Campbell1, Bin Tean Teh2,13,14, Michael R. Stratton1,15 & P. Andrew Futreal7
Polybromo-1 (BAF180) in ccRCC

~40% ccRCC mutated in PBRM1!


Nucleosome/Histone/Chromatin Remodeling Complexes

Loss of PBRM1 expression is correlated with tumor stage, grade and survival

Rafal Pawłowski et al., Int J Cancer, 2012
Conclusions

• Renal mass biopsy - a renaissance!

• Subtype specific clinical trials!
• Current grading system useful?

• Predictive marker - Relevance of Driver Mutations
  • different groups of VHL mutations with/without PBRM1 alterations might have different predictive impact

• Multi-regional analyses required for therapeutic outcome prediction