Cystic Renal Cell “Carcinoma” in Pathology Practice

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Definition of “Cystic” Renal Mass?

• Imaging (Clinical)
  – Composed of <25% non-enhancing tissue (Bosniak, version 2019).
  – Some studies showed >75% cystic component to correlate with improved prognosis.
  – Management based on Bosniak class. (I to IV).

• Pathology
  – Older studies with threshold of >75% cystic to define cystic RCC.
  – Assessment of % cystic not commonly practiced.
  – Use descriptors, e.g. “cystic” or “purely”, “extensively”, “predominantly”, “partially” cystic.

Pathology of Resected (Atypical) Renal Cysts by Imaging (French Research Network for Kidney Cancer, UroCCR)

- Atypical – Bosniak II, III and IV

<table>
<thead>
<tr>
<th>Malignant or LMP (n=175)</th>
<th>%</th>
<th>Benign (n=41)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell RCC*</td>
<td>60</td>
<td>Cystic nephroma</td>
<td>29.3</td>
</tr>
<tr>
<td>Type 1 papillary RCC</td>
<td>18.3</td>
<td>Simple cyst</td>
<td>22</td>
</tr>
<tr>
<td>MCRNLMP*</td>
<td>6.9</td>
<td>MEST</td>
<td>17.1</td>
</tr>
<tr>
<td>Type 2 papillary RCC</td>
<td>5.7</td>
<td>Inflammatory pseudocystic</td>
<td>14.6</td>
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<tr>
<td>Chromophobe RCC</td>
<td>2.3</td>
<td>Hemorrhagic cyst</td>
<td>4.9</td>
</tr>
<tr>
<td>Clear cell papillary RCC*</td>
<td>2.3</td>
<td>Other</td>
<td>12.2</td>
</tr>
<tr>
<td>Tubulocystic RCC*</td>
<td>1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACD-associated RCC*</td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# 2016 WHO Classification of Kidney Tumors

## Renal cell tumours
- Clear cell renal cell carcinoma: 8310/3
- Multilocular cystic renal neoplasm of low malignant potential: 8316/1
- Papillary renal cell carcinoma: 8255/1
- Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated renal cell carcinoma: 8311/3
- Chromophobe renal cell carcinoma: 8317/3
- Collecting duct carcinoma: 8319/3
- Renal medullary carcinoma: 8510/3
- MIT Family translocation carcinomas: 8311/3
- Succinate dehydrogenase (SDH)-deficient renal carcinoma: 8312/3
- Mucinous tubular and spindle cell carcinoma: 8480/3
- Tubulocystic renal cell carcinoma: 8316/3
- Acquired cystic disease associated renal cell carcinoma: 8316/3
- Clear cell papillary renal cell carcinoma: 8323/1
- Renal cell carcinoma, unclassified: 8312/3
- Papillary adenoma: 8260/0
- Oncocytoma: 8290/0

## Metanephrine tumours
- Metanephrine adenoma: 8325/0
- Metanephrine adenofibroma: 9013/0
- Metanephrine stromal tumour: 8935/1

## Nephroblastic tumours
- Nephrogenic rests: 8960/3
- Nephroblastoma: 8960/3
- Cystic partially differentiated nephroblastoma: 8959/1
- Paediatric cystic nephroma: 8959/0

## Mesenchymal tumours

### Mesenchymal tumours occurring mainly in children
- Clear cell sarcoma: 8964/3
- Rhabdoid tumour: 8963/3

### Mesenchymal tumours occurring mainly in adults
- Congenital mesoblastic nephroma: 8960/1
- Ossifying renal tumour of infants: 8967/0

## Mesenchymal tumours
- Leiomyosarcoma: 8990/3
- Angiosarcoma: 9120/3
- Rhabdomyosarcoma: 8900/3
- Osteosarcoma: 9160/3
- Synovial sarcoma: 9040/3
- Ewing sarcoma / Peripheral neuroectodermal tumour: 9260/3
- Angiomyolipoma: 8860/0
- Epithelioid angiomyolipoma: 8860/1
- Leiomyoma: 8890/0
- Haemangioma: 9120/0
- Lymphangioma: 9170/0
- Haemangioblastoma: 9161/1
- Juxtaglomerular cell tumour: 8361/0
- Renomedullary interstitial cell tumour: 8966/0
- Schwannoma: 9560/0
- Solitary fibrous tumour: 8815/1

## Mixed epithelial and mesenchymal tumours
- Cystic nephroma: 8959/0
- Mixed epithelial and stromal tumour: 8959/0

## Neuroendocrine tumours
- Well-differentiated neuroendocrine tumour: 8240/3
- Large cell neuroendocrine carcinoma: 8013/3
- Small cell neuroendocrine carcinoma: 8041/3
- Paragangioma: 8693/1
- Phaeochromocytoma: 8700/0

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

## Metastatic tumours
Bosniak Classification

Introduction in 1986

CT Imaging Features:
- Wall
- Septa
- High attenuation
- Calcifications
- Wall/septum enhancement

<table>
<thead>
<tr>
<th>Bosniak Category</th>
<th>Likelihood of malignancy</th>
<th>Recommended Management</th>
<th>Malignancy diagnosis in resections*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Highly unlikely</td>
<td>No follow-up</td>
<td>0%</td>
</tr>
<tr>
<td>II</td>
<td>Unlikely</td>
<td>No follow-up</td>
<td>9%</td>
</tr>
<tr>
<td>III</td>
<td>Equivocal</td>
<td>Follow-up</td>
<td>18%</td>
</tr>
<tr>
<td>IV</td>
<td>Likely</td>
<td>Surgery in most or strict follow-up</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td>Highly likely</td>
<td>Surgery</td>
<td>86%</td>
</tr>
</tbody>
</table>

Oncologic outcome of Bosniak IIF-IV Renal Cysts

- Excellent prognosis – discrepant to high % of malignant diagnosis.

- UroCCR-12 Study:
  - 216 patients (175 malignant or LMP) - **only 2 (0.9%) had recurrence** (Bosniak IV) and **no (0%) cancer-related deaths** (med 20 mos ff-up).

- Chandrasekhar et al. 2018.
  - 336 patients (≈45% Bosniak III or IV), **only 1 cancer-specific death** (VHL patient) or **99.7% CSS** (med 67 mos ff-up).

- Schoots et al. 2017 (systematic review).
  - 373 patients with malignant cysts (85% Bosniak III or IV, ≈2/3 clear cell RCC), **only 5 (1.3%) had recurrence and 1 (0.8%) metastasis** (ave 31 mos ff-up).

• Used radiological threshold of >50% for cystic.
• 138 cystic RCC:
  – 65.9% clear cell RCC, 77.5% Fuhrman grade 1-2 and 83.4% ≤pT2.
• No evidence of metastasis or recurrence (med ff-up >4 years).

Surgical Overtreatment of Cystic Renal Masses

- 140 Bosniak III cysts needed to treat to avoid 1 metastasis.
- 1.9 Bosniak III cysts needed to treat to have 1 malignant diagnosis.
- 40 Bosniak IV cysts needed to treat to avoid 1 metastasis.
- Current management recommendation for localized Bosniak III/IV and solid renal masses similar (AUA 2017).
- Overtreatment can lead to procedural morbidity, loss of renal function, higher costs.

- Is there pathologic over-diagnosis of malignancy in cystic renal masses?

Bosniak Classification, Version 2019

- To improve the classification’s ability to predict the likelihood of malignancy in cystic renal mass.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Suggested Terms and Phrases</th>
</tr>
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<tbody>
<tr>
<td>Bosniak I</td>
<td>“Benign simple renal cyst requiring no follow-up.”</td>
</tr>
</tbody>
</table>
| Bosniak II     | (Option 1) “Benign Bosniak II renal cyst requiring no follow-up.”*  
|                | (Option 2) “Likely benign Bosniak II renal mass requiring no follow-up.”† |
| Bosniak IIIF   | “Bosniak IIIF cystic renal mass. The large majority of Bosniak IIIF masses are benign. When malignant, nearly all are indolent. Generally, Bosniak IIIF masses are followed by imaging at 6 months and 12 months, then annually for a total of 5 years to assess for morphologic change.” |
| Bosniak III    | “Bosniak III cystic renal mass. Bosniak III masses have an intermediate probability of being malignant. If not already obtained, consider urology consultation.” |
| Bosniak IV     | “Bosniak IV cystic renal mass. The large majority of Bosniak IV masses are malignant. If not already obtained, consider urology consultation.” |

- To reduce interobserver variation.

Multilocular Cystic Renal Neoplasm of Low Malignant Potential

- WHO 2016: Change in name from multilocular cystic “RCC”.
- WHO 2016: Composed entirely of numerous cysts and septa containing individual or group of cells without expansile growth.
- Morphologically indistinguishable from low-grade clear cell RCC.
- VHL mutations in 25% and Ch 3p deletions in 74%.
- <1% of all renal tumors, affecting middle-aged adults, and mostly as incidental tumors.
- Meta-analysis of >200 published cases with >5 years follow-up identified no recurrence or metastasis.
Multilocular Cystic Renal Neoplasm of Low Malignant Potential

Multilocular cysts

Thin septa with 1 or few layers of cells
Multilocular Cystic Renal Neoplasm of Low Malignant Potential

Clear cells with low grade nuclei (WHO/ISUP 1-2)

Clear cells within septa (non-expansile)
DDX: Predominantly Cystic Clear Cell RCC

Solid area/Septa thickened by clear cells

Clear cells can be higher grade (≥WHO/ISUP 3)
DDX: Predominantly Cystic Clear Cell RCC

“Expansile growth” of clear cells – absolute cut-off or part of continuum?

Likelihood of Malignant Behavior

Purely cystic → Solid component → Purely solid
Predominantly cystic clear cell renal cell carcinoma and multilocular
cystic renal neoplasm of low malignant potential form a low-grade
spectrum

Maria Tretiakova1 · Vikas Mehta2 · Masha Kocherginsky3 · Agata Minor4 · Steven S. Shen5 ·
Sahussapong Joseph Sirintrapun6 · Jorge L. Yao7 · Isabel Alvarado-Cabrero8 · Tatjana Antic4 · Scott E. Eggener9 ·
Maria M. Picken2 · Gladell P. Paner4,9

- 57 MCRNLMP, 69 predominantly cystic (≥50%) clear cell RCC and 46 non-cystic clear cell RCC.

<table>
<thead>
<tr>
<th>Group</th>
<th>N cases</th>
<th>ISUP grade (%)</th>
<th>Stage (%)</th>
<th>NED</th>
<th>Median F/U for surviving patients Months</th>
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<tr>
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<td></td>
<td>1 2 3 4</td>
<td>T1 T2 T3</td>
<td></td>
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<tr>
<td>MCRNLMP</td>
<td>57</td>
<td>72.7 27.3 0 0</td>
<td>91.2 8.8 0</td>
<td>100</td>
<td>40.9</td>
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<tr>
<td>Cystic CCRCC</td>
<td>69</td>
<td>31.3 59.7 9 0</td>
<td>92.5 1.5 6</td>
<td>97.1</td>
<td>35.8</td>
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<tr>
<td>Solid CCRCC</td>
<td>46</td>
<td>8.7 52.2 26.1 13</td>
<td>58.7 6.5 34.8</td>
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<td>38.9</td>
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<tr>
<td>p value</td>
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<td>&lt;0.001*</td>
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<td>&lt;0.001$</td>
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</table>

- PFS – time from surgery to develop relapse, metastasis or death from disease.
- Med ff-up 40.9 mos.

• 18 MCRNLMP, 95 cystic clear cell RCC (>75% cystic), and 32 cystic clear cell papillary RCC.
• Median follow-up for survivors 10.3 years.
• Recurrence rates:
  – 1/18 (5.5%) MCRNLMP.
  – 5/95 (5.2) cystic clear cell RCC (1 distant metastasis and death at 22 yrs).
  – 4/32 (12.5%) cystic clear cell papillary RCC.
• 10- and 20-year CCS across subtypes were 100%.

- Westerman et al. Urology 2019 (epub ahead of print)
From our study, we recommend that presence and extent (%) of cystic component in clear cell RCC should be documented in pathology report.

Questions needing answers:

1. Does focal “expansile nodule” or ≤5% solid in extensively cystic clear cell RCC warrants a diagnosis of carcinoma?
2. Does incremental increase in % cystic in clear cell RCC correlates with increasingly favorable outcome (ex. solid, <50%, 50-75%, >75 cystic)?

Current renal cancer pathology reporting protocols (CAP, ICCR) do NOT require reporting and quantifying of cystic component in clear cell RCC.
Cystic partially regressed clear cell renal cell carcinoma: a potential mimic of multilocular cystic renal cell carcinoma

Sean R Williamson, Gregory T MacLennan, Antonio Lopez-Beltran, Rodolfo Montironi, Puay Hoon Tan, Guido Martignoni, David J Grignon, John N Eble, Muhammad T Idrees, Marina Scarpelli & Liang Cheng

- With areas of fibrosis, hyalinization, vascular proliferation, hemosiderin deposits and calcifications.
- Cystic component 20-80% (med 65%).
- pT1 (89%).
- Fuhrman grade 2 (48%) and 1(33%).
- **No patients develop recurrence or metastasis (med 74.5 mos).**

- From Williamson et al. 2013;63:767
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§

Acquired Cystic Disease Associated RCC
Clear Cell Papillary RCC
Clear Cell RCC
Papillary RCC
Chromophobe RCC

Clear Cell Papillary RCC

- Usually partially cystic
- Predominantly cystic (Bosniak II-IV)
Clear Cell Papillary RCC

• WHO 2016: An indolent renal epithelial neoplasms composed of bland clear epithelial cells arranged in tubules and papillae, with at least a predominantly linear nuclear alignment away from the basement membrane and a distinctive immunophenotype.

• Initially described in ESRD; occur sporadically and in VHL patients.
• 95% are pT1 tumors, typically detected incidentally.
• Molecular profiles distinct from clear cell RCC and papillary RCC.
• No recurrence or metastasis of pure form reported.
• Proposal to rename as “Clear cell papillary renal neoplasm of low malignant potential”.

Clear Cell Papillary RCC

- Papillae lined by clear cells
- Low grade nuclei in linear arrangement
Clear Cell Papillary RCC

- Solid area or collapsed acini
- Low grade luminally aligned nuclei
Clear Cell Papillary RCC

- CA-IX cup like +
- CK7+ (unlike clear cell RCC)
- AMACR- (unlike papillary RCC)
Extensively Cystic Clear Cell Papillary RCC

- Can mimic MCRNLMP.
- Benign cysts with clear cell papillary features - putative precursor of CCP RCC?

- Hosseini et al. Hum Pathol 2014;45:1406
Acquired Cystic Disease-Associated RCC
Acquired Cystic Disease-Associated RCC

• WHO 2016: Most common tumor in kidneys of patients with ESRD and ACD characterized by variable morphological patterns, microcystic (sieve-like) architecture, and abundant intratumoral oxalate crystals.

• Occurs exclusively in patients with ACD, more commonly in patients undergoing long-term hemodialysis.

• May have intracystic growth and forms cysts extending into fat.

• Shows gains in Ch 3, 7, 16, 17 and Y.

• Favorable clinical behavior, likely because of early detection of tumors in patients with periodic follow-up imaging for CRF.
  – Metastasis reported in tumors with sarcomatoid or usual features.
  – In series of 36 patients, 1 had visceral metastasis resulting to death and 1 had metastasis to regional LNs.

Acquired Cystic Disease-Associated RCC

Solid & cystic, intracystic growth

Sieve-like appearance
Acquired Cystic Disease-Associated RCC

Calcium oxalate crystals

Polarized light
Acquired Cystic Disease-Associated RCC

Cystic foci

Cystic foci
Tubulocystic Carcinoma

• **WHO 2016:** *Uncommon cystic renal epithelial malignancy with pure tubulocystic architecture.*

• Radiologic findings broad, but may present as Bosniak II to IV renal cyst.

• Strong male predominance (M:F = 7:1).

• ~60% incidentally discovered.

• Some shows gains of ch 7 and 17 and loss of Y, suggesting close relationship with papillary RCC.

• **Potentially low malignant behavior.**
  – Of 70 reported cases, only 1 case recurred and 4 metastasized.

Tubulocystic Carcinoma

“Bubble-wrap” appearance

More cystic
Tubulocystic Carcinoma

Purely tubulocystic

Small tubules to large cysts
Tubulocystic Carcinoma

Single layer, flattened, cuboidal or hobnail

Usually WHO/ISUP grade 3
Fumarate Hydratase (FH)-Deficient RCC

- Tubulocytic w/ PD foci or intracystic papillae – **Beware of an aggressive tumor!**


High-grade with inclusion-like nucleoli surrounded by halo
• **FH-deficient RCC** - suggestive morphology and FH- and 2SC+ immunophenotype but hereditary leiomyomatosis and renal cell carcinoma (HLRCC) stigmata/history cannot be reliably ascertained and germline confirmation is not available.

• ~33-66% FH-deficient RCCs contain tubulocystic pattern.

• Highly aggressive, with metastasis in up to 86% of cases.

Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC) Syndrome-Associated RCC

• WHO 2016: RCCs associated with HLRCC and can be exclusively papillary or can have an infiltrative growth pattern, and have nuclei with inclusion-like nucleoli and perinuclear clearing.

• Morphologic overlap with type 2 PRCC, collecting duct carcinoma, medullary carcinoma, and tubulocystic RCC.

• Diagnosis confirmed by germline mutation in FH at Ch1q42.

• Younger patients (ave. 36-46 yo) and may present with cutaneous or uterine smooth muscle tumors.

• Prognosis poor with tendency for early widespread dissemination; metastasis reported in small tumors.

HLRCC-Associated RCC

Papillae, intracystic (previously diagnosed as papillary RCC or CDC)

High-grade with inclusion-like nucleoli surrounded by halo
HLRCC-Associated RCC

Tubulocystic

High-grade with inclusion-like nucleoli surrounded by halo
HLRCC-Associated RCC

Fumarate Hydratase (FH) -

S-(2-succino)cysteine (2SC) +

Eosinophilic Solid and Cystic RCC

- Gross: “Mixed solid and cystic (~75%), some with macrocysts and can be markedly cystic”.
- Associated with \textit{TSC} mutations with or without tuberous sclerosis.

- Mehra et al, Eur Urol 2018;74:483
Thank you!