The genetics of kidney cancer and the lessons learned from managing VHL

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Assistant Professor
Indiana University Department of Urology
VHL Alliance Family Meeting October 19th 2019
Overview of today’s discussion

• The emerging importance of the genetics of RCC

• Lessons learned from the care of VHL renal masses:
  - renal preservation and partial nephrectomy
  - the management of small renal masses
  - the role of tumor enucleation
Renal Cell Carcinoma

- In the United States over 54,000 patients are diagnosed with renal carcinoma annually.
- Over 13,000 die of this disease each year.
- There are over 200,000 alive with kidney cancer in the U.S.
- 7th most common cancer in men
- 9th most common cancer in women
- 8th leading cause of cancer death in the U.S.
### 2016 Cancer Statistics

#### Males
- Prostate: 186,320 (25%)
- Lung & bronchus: 114,690 (15%)
- Colon & rectum: 77,250 (10%)
- Urinary bladder: 51,230 (7%)
- Non-Hodgkin lymphoma: 35,450 (5%)
- Melanoma of the skin: 34,950 (5%)
- Kidney & renal pelvis: 33,130 (4%)
- Oral cavity & pharynx: 25,310 (3%)
- Leukemia: 25,180 (3%)
- Pancreas: 18,770 (3%)
- All Sites: 745,180 (100%)

#### Females
- Breast: 182,460 (26%)
- Lung & bronchus: 100,330 (14%)
- Colon & rectum: 71,560 (10%)
- Uterine corpus: 40,100 (6%)
- Non-Hodgkin lymphoma: 30,670 (4%)
- Thyroid: 28,410 (4%)
- Melanoma of the skin: 27,530 (4%)
- Ovary: 21,650 (3%)
- Kidney & renal pelvis: 21,260 (3%)
- Leukemia: 19,090 (3%)
- All Sites: 692,000 (100%)

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Jemal, et al. CA Cancer J Clin
### Human Renal Epithelial Neoplasms

<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>

*Image credits: Indiana University Health*
Demographics and Tumor Subtypes

**Racial disparities in renal cell carcinoma: a single-payer healthcare experience**

Abiodun Mafolasire¹, Xiaopan Yao², Cayce Nawaf³, Alfredo Suarez-Sarmiento¹, Wong-Ho Chow³, Wei Zhao⁴, Douglas Corley⁴, Jonathan N. Hofmann⁵, Mark Purdue⁵, Adebowale J. Adeniran⁶ & Brian Shuch¹

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²Yale Center for Analytical Sciences, Yale School of Medicine, New Haven, Connecticut
³Department of Epidemiology, Anderson Cancer Center, Houston, Texas
⁴Kaiser Permanente Division of Research, Kaiser Permanente San Francisco Medical Center, San Francisco, California
⁵Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland
⁶Department of Pathology, Yale School of Medicine, Yale University, New Haven, Connecticut

Relative to white patients African Americans with RCC had roughly:

1. 10X higher risk of CKD
2. 3X higher risk of **papillary** RCC (15 vs 5% overall cohort)
3. 2X higher risk of **chromophobe** RCC (4 vs 2%)
4. Similar outcomes regarding grade and stage and death rates from disease

**Chromophobe Renal Cell Carcinoma is the Most Common Nonclear Renal Cell Carcinoma in Young Women: Results from the SEER Database**

Michael Daugherty, Stephen Blakely, Oleg Shapiro, Srinivas Vourganti, Mehdi Mollapour and Gennady Bratslavsky*

From the Department of Urology, State University of New York Upstate Medical University, Syracuse, New York

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**Nonclear cell histological tumor distribution.** A, younger males. B, younger females. C, older males. D, older females. Blue areas indicate papillary RCC. Red areas indicate chromophobe RCC. Green areas indicate collecting duct RCC.
Genomics of Papillary, Chromophobe, and, Sarcomatoid RCC are very different!!

Not all kidney cancer is the same: Histology Matters!

Foretinib in PRCC (n=74)

- Germline mutations
- MET aberration (MET amplification, gain of chromosome 7 or somatic mutation; excluding germline mutations)
- No germline mutation; testing for MET aberration profile incomplete
- Confirmed PR

Inherited Forms of Renal Carcinoma

1. **Von Hippel Lindau**
   - Clear Cell RCC, renal cysts, eye, brain, spine, pancreas, adrenal

2. **Hereditary Papillary Renal Carcinoma**
   - Papillary Type 1 renal tumors (renal only)

3. **Hereditary Leiomyomatosis RCC (HLRCC)**
   - Papillary Type 2, uterine leiomyoma, skin lesions

4. **Birt Hogg Dubé**
   - Chromophobe/Oncocytoma/hybrid renal tumors, lung cysts, skin

5. **Succinate Dehydrogenase Deficiency**
   - Clear cell/possibly oncocytic renal tumors, adrenal/extraadrenal paragangliomas

6. **Tuberous Sclerosis**
   - AML known/Probably Clear/pap variant renal, brain, skin, poss MR

7. **Familial Renal Oncocytoma** (renal only)

8. **Lynch Syndrome** - urothelial upper tract tumors, colon, ovarian ca, breast
Hereditary Syndromes and their Histology

Human Renal Epithelial Neoplasms

<table>
<thead>
<tr>
<th>Histologic Type:</th>
<th>Clear Cell</th>
<th>Papillary Type 1</th>
<th>Papillary Type 2</th>
<th>Chromophobe</th>
<th>Oncocytoma</th>
<th>Angiomyolipoma</th>
<th>TFE3</th>
<th>Oncocytic</th>
<th>Clear/Chromophobe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary Gene:</td>
<td>VHL</td>
<td>Met</td>
<td>FH</td>
<td>FLCN</td>
<td>TSC1, TSC2</td>
<td>MITF</td>
<td>SDHB, SDHD</td>
<td>PTEN</td>
<td>VHL (89%)</td>
</tr>
<tr>
<td>Sporadic Gene:</td>
<td>VHL (89%)</td>
<td>Met (13%)</td>
<td>TBD*</td>
<td>TBD*</td>
<td>TSC1, TSC2</td>
<td>TFE3, TFEB</td>
<td>TBD*</td>
<td>TBD*</td>
<td>VHL (89%)</td>
</tr>
</tbody>
</table>

Figure 1.
Kidney cancer is not a single disease; it is made up of a number of different and specific types of cancers that can occur within the kidney. Each of these different types of kidney cancer can be characterized by differing histologies, different clinical courses, differing responses to a number of varied therapies and association with alterations to different genes. (TBD*: to be determined.)
How “heritable” is RCC

• Hereditary RCC may account for 2-8%

• Gudbjartsson et al in a nationwide study of Iceland suggested hereditary may play a role in up to 60% of patients

• Swedish Family Cancer Database (all swedes born after 1931) found that patients having a parent (2.8X) and sibling (9.9X) were at significantly increased risk of developing RCC

• Probably this disparity reflects lack of directed screening for at risk patient populations as well as lack of categories for all HRS patients
Who to screen for hereditary RCC?

1. Known patients with hereditary RCC (syndromes are expanding)
2. Patients with a family history of RCC (Swedish, Icelandic databases)
3. Patients with bilateral multifocal disease
4. Early onset kidney cancer patients
Reviewed 106,000 SEER kidney cancer pts

Compared this to over 600 NIH established hereditary kidney Ca patients

Mean age of hereditary RCC pts was 37yrs

Mean age of SEER RCC pts was 63 yrs
• Hereditary RCC presents on average roughly 27 yrs younger than observed general population

• Useful threshold around 10th %tile would be 46 years of age to max sens/spec and limit NNT

• All patients ≤46 yrs get genetic counseling

• Oversimplification since sex, race, histology were not considered in models
Currently no definitive screening guidelines exists for patients and family members at risk for hereditary kidney cancer and its related syndromes

Recent panel has been constructed to develop and create these guidelines and recommendations in the near future

Goal will be to have objective strategies and suggestions for care providers to assist with these often confusing and unsettling occurrences

Team comprised of primarily of medical oncologists, urologists, and geneticists is due to meet again later this year
VHL is an autosomal dominant syndrome associated (from a urology perspective) multifocal ccRCC, renal cysts, and pheochromocytoma of the adrenal gland.

VHL is located on 3p and encodes for the VHL protein, an essential component of the VHL complex.

The VHL complex targets hypoxia-inducible factors (HIFs) for proteasomal degradation. VHL patients lose the remaining allele, usually thru LOH, which inactivates VHL and allows accumulation of HIF-1 and HIF-2 and their targets which leads to the development of RCC.

Carlo et al, Eur Uro, 2019
• Among patients with VHL disease the lifetime risk of RCC is about 70% with an average age of 40-45 years, roughly 2 decades earlier than most sporadic RCC

• Kidneys of VHL patients typically have numerous cystic and solid lesions, ranging from simple to complex and the majority being low grade

• Cystic masses are measured by the solid component of renal cysts

• The ccRCC in VHL patients usually exhibits low grade and stage as they are usually closely monitored and removed when they are no greater than 3 cm

• Partial nephrectomy remains the mainstay of surgical treatment and in order to maximize renal preservation tumor enucleation is usually the technique of choice

• Robotic kidney surgery has been successfully implemented in patients with VHL both for initial partial nephrectomy and recently described even for repeat, redo partial nephrectomy amongst hereditary kidney patients

Carlo et al, Eur Uro, 2019
Let's consider the impact of VHL kidney treatment on sporadic RCC…

- Does tumor size matter?
- Should partial nephrectomy be performed at all costs?
- Does tumor enucleation make a difference?
Surgical Management of Renal Carcinoma
In VHL, HPRC and BHD

Surgery = nephron sparing

“3 cm rule”
Delay surgery until diameter of largest renal tumor = 3 cm

**TABLE 1.** Comparison of groups 1 and 2

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size (cm.)</td>
<td>3 or Less</td>
<td>3.2–26.0</td>
</tr>
<tr>
<td>No. pts.</td>
<td>52</td>
<td>44</td>
</tr>
<tr>
<td>No. renal surgery</td>
<td>26</td>
<td>39</td>
</tr>
<tr>
<td>No. operations:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrectomy</td>
<td>2</td>
<td>27</td>
</tr>
<tr>
<td>Partial nephrectomy</td>
<td>46</td>
<td>45</td>
</tr>
<tr>
<td>Median mos. followup</td>
<td>60</td>
<td>66.5</td>
</tr>
<tr>
<td>No. with metastases (Fisher’s exact test p &lt;0.0001)</td>
<td>0</td>
<td>11</td>
</tr>
</tbody>
</table>

**TABLE 2.** Comparison of tumor size and metastases

<table>
<thead>
<tr>
<th>No. Metastases/No. Pts. (%)</th>
<th>Tumor Size (cm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/52</td>
<td>3.0 or Less</td>
</tr>
<tr>
<td>1/17 (6)</td>
<td>3.2–4.0</td>
</tr>
<tr>
<td>2/10 (20)</td>
<td>4.1–5.5</td>
</tr>
<tr>
<td>4/12 (33)</td>
<td>6.0–10.0</td>
</tr>
<tr>
<td>4/5 (80)</td>
<td>10.0 or Greater</td>
</tr>
</tbody>
</table>

Walther et al. J Urol 1999
**Solid tumors: No patients developed metastatic disease when managed by the 3 cm guideline.**

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th># mets/ # pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 3 cm</td>
<td>0/178 (0%)</td>
</tr>
<tr>
<td>3-4 cm</td>
<td>4/109 (3.7%)</td>
</tr>
<tr>
<td>4-5 cm</td>
<td>8/62 (12.9%)</td>
</tr>
<tr>
<td>5-6 cm</td>
<td>7/27 (25.9%)</td>
</tr>
<tr>
<td>6-7 cm</td>
<td>6/12 (50%)</td>
</tr>
<tr>
<td>&gt; 7 cm</td>
<td>17/28 (60%)</td>
</tr>
</tbody>
</table>

Ball et al AUA 2018

![Graph showing metastatic potential by tumor size](image)
VHL Growth Rate

- 240 tumors followed in 152 patients
- 1301 measurements made
- Median Growth rate was 3.7mm/yr
- Faster growth rate → Male, youth
- No association between germline mutation or starting tumor size
- Higher risk of mets with higher diameter growth rate (7mm/yr vs 3.7mm/yr, p=0.01)
The metastatic potential of renal tumors: Influence of histologic subtypes on definition of small renal masses, risk stratification, and future active surveillance protocols

Michael Daugherty, M.D., Dillon Sedaghatpour, B.S., Oleg Shapiro, M.D., Srinivas Vourganti, M.D., Alexander Kutikov, M.D., Gennady Bratslavsky, M.D.

a Department of Urology, SUNY Upstate Medical University, Syracuse, NY
b Department of Surgical Oncology, Fox Chase Cancer Center-Temple University Health System, Philadelphia, PA

Received 8 August 2016; received in revised form 6 November 2016; accepted 13 November 2016

- SEER review of 55,000 cases of kidney cancer
- Clear cell, papillary, and chromophobe RCC were followed
- Size of tumor was identified at the time of metastasis
- Using a cutoff of no more than 3% metastatic rates would make CLEAR CELL and PAPILLARY small renal masses up to 4cm and CHROMOPHOBEB a SRM up to 7cm
Concept of “active surveillance” for small renal masses is now being considered across all patient types

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (SRMs), n</th>
<th>Mean tumour size, cm</th>
<th>Available histology, n (%)</th>
<th>Histologically proven RCC, n (%)</th>
<th>Mean follow-up, mo</th>
<th>Growth rate, cm/yr</th>
<th>Progression to metastasis, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosniak et al [134]</td>
<td>37 (40)</td>
<td>1.73</td>
<td>26 (70.3)</td>
<td>22 (85)</td>
<td>39</td>
<td>0.36</td>
<td>0</td>
</tr>
<tr>
<td>Volpe et al [102]</td>
<td>29 (32)</td>
<td>2.48</td>
<td>9 (31)</td>
<td>8 (89)</td>
<td>27.9</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>Chawla et al [107]</td>
<td>49 (61)</td>
<td>2.97</td>
<td>21 (42.9)</td>
<td>17 (81)</td>
<td>36</td>
<td>0.2</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Abou Youssif et al [108]</td>
<td>35 (44)</td>
<td>2.2</td>
<td>8 (23)</td>
<td>6 (75)</td>
<td>47.6</td>
<td>0.21</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Abouassaly et al [104]</td>
<td>110 (-)</td>
<td>2.5</td>
<td>9 (8)</td>
<td>3 (33)</td>
<td>24</td>
<td>0.26</td>
<td>0</td>
</tr>
<tr>
<td>Crispen et al [106]</td>
<td>154 (172)</td>
<td>2.5</td>
<td>68 (44.2)</td>
<td>57 (84)</td>
<td>31</td>
<td>0.28</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Rosales et al [105]</td>
<td>212 (223)</td>
<td>2.8</td>
<td>40 (18.9)</td>
<td>37 (92.5)</td>
<td>35</td>
<td>0.34</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>

SRM = small renal mass; RCC = renal cell carcinoma.
Growth Kinetics and Short-Term Outcomes of cT1b and cT2 Renal Masses under Active Surveillance


Division of Urologic Oncology, Department of Surgical Oncology, Fox Chase Cancer Center-Temple University Health System, Philadelphia, Pennsylvania

Entire AS cohort: 461 patients

68 Patients with Renal Mass ≥4 cm

# Patients Remained Under Active Surveillance 45

# Patients Progressed to Surgical Intervention 23

# Patients Progressed to Metastatic Disease 0

RCC Specific Mortality 0/5 Deaths

# Patients Progressed to Metastatic Disease 0

RCC Specific Mortality 0/4 Deaths

Patients with T1b/T2 masses under AS
What have been the historical tenets of hereditary renal tumor surgery?

• Kidneys may possess up to 500 tumors and complete eradication of disease may not always be possible

• Partial nephrectomy is attempted in the majority of cases unless renal salvage not feasible

• Goal is to “reset the clock” by removing as many tumors as possible, preserving as much renal tissue as possible, and repeating this process for as long as the kidney is “worth fighting for” or preventing a patient from requiring renal replacement treatment
Figure 4. Representative MRI images pre and postoperatively. A. T1 weighted gadolinium-enhanced coronal MRI abdomen of right kidney pre-operatively on showing numerous multifocal renal tumors throughout the kidney. B. Right kidney post-operatively on T1 weighted gadolinium-enhanced MRI showing no renal tumors and post-operative changes.

Note: RMxPNx performed on 8/22/2014: 31 tumors excised, 2500cc EBL, 0min ischemia
Feasibility and Outcomes of Partial Nephrectomy for Resection of at Least 20 Tumors in a Single Renal Unit

Amaka T. Fadahunsi, Thomas Sanford, W. Marston Linehan, Peter A. Pinto and Gennady Bratslavsky*

From the Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland

- N=30pts & 34 operations
- 1 lost kidney
- median 26.5 tumors removed
- eBL=3500mL
- OR time =9hrs
- >50% complication rate,
- eGFR=67→57
- subsequent intervention at median of 52 months

Alternative to these heroic surgeries would mean living with minimally functioning or non functioning renal units for years or decades….
Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization

Alan S. Go, M.D., Glenn M. Chertow, M.D., M.P.H., Dongjie Fan, M.S.P.H., Charles E. McCulloch, Ph.D., and Chi-yuan Hsu, M.D.
Renal insufficiency and mortality

Rate of Death

Age-Standardized Rate of Death from Any Cause (per 100 person-yr)

Estimated GFR (ml/min/1.73 m²)

No. of Events

≥ 60  45–59  30–44  15–29  <15
25,803  11,569  7802  4408  1842

Go, et al. NEJM 2004
Is partial nephrectomy beneficial?

For GFR < 60


For GFR < 45
Tumor enucleation is typical surgical approach to VHL and other hereditary renal syndromes
1. A tumor pseudocapsule of separates most renal tumors from adjacent parenchyma (Figure 1)
2. A perfectly executed tumor enucleation looks like the tumor on the right (Figure 2)
3. Volume of submitted tissue for tumor enucleation will universally be less than in traditional partial nephrectomy (Figure 3)
4. Terms for this technique (tumor enucleation, simple enucleation, enucleo-resection, minimal margin) ARE CONFUSING
Safety and Feasibility of Tumor Enucleation for Hereditary Syndromes

Enucleation in the hereditary arena has been well documented as safe and feasible for both open and robotic techniques.

Repeat “Re-do” multifocal enucleation, although challenging, has also been shown to be safe and effective in high volume institutions.
Safety and Feasibility of Tumor Enucleation for Sporadic Disease

- Operative time and blood loss were lower for TE in comparison to SPN
- No loss of renal units
- No difference in major medical and surgical complications between groups
- 3% urine leak rate and 1% bleed rate requiring selective embolization
- TE in complex renal tumors (PADUA score 10-13) grade III and IV complication rate were low (9%)
- Suggest that enucleation is not only safe but widens the indications for nephron sparing surgery
Functional Outcomes for Tumor Enucleation

- Calaway et al demonstrated avg. 5m clamp time and 50% zero-ischemia rate for enucleated renal masses in solitary kidneys (Canju, 15)

- Blackwell et al demonstrated a 56% zero-ischemia in TE compared to 2% for SPN with tumor enucleation serving as the only predictor of improved parenchymal preservation (Blackwell et al, Urol, 2016)

- Dong et al demonstrated a 49% zero-ischemia in TE compared to 0% for SPN with median eGFR preservation (100 vs 89%) and new onset CKD 3 or higher (2.8 vs 12%) significantly better in TE group (Eur Urol, 2017)
Oncologic Outcomes comparing TE to both RN and standard PN

- 332 TE vs 143 Radical Nx patients
- No difference in 5 and 10 year progression free survival between groups (95 and 93% for TE vs. 91 and 88% after RN)
- Technique did not predict progression-free or cancer-specific survival

- 537 TE vs 982 Standard PNx (SPN)
- 50 months average follow up
- No difference in 5 and 10 yr survival between groups (94 and 93% for TE vs 94 and 91% for SPN)
- Technique did not predict local recurrence or cancer-specific survival between groups
Let's recap what we’ve learned….

- The “genetics” of RCC is an emerging consideration for many patients presenting with renal masses and is being increasingly incorporated into care plans for patients.

- Understanding the behavior of VHL has greatly impacted how we treat and manage all forms of kidney cancer in both hereditary and non-hereditary patients.

- The “3cm rule” for the treatment of VHL has set the foundation for active surveillance of small renal masses in the sporadic patient population as well as the importance of PNx whenever possible.

- Tumor enucleation and the understanding of the tumor pseudocapsule is now being applied to many patients with sporadic RCC disease.

- Are we “Millennializing” the way we look at renal tumors….
Hypothesizing a new algorithm for managing, evaluating, and treating renal tumors?

- **Demographics**
  - Age
  - Race
  - Gender
  - Obvious Surgical Candidate (Single big tumor/reasonable health) >50%

- **Radiology Testing**
  - CT
  - MRI
  - PET

- **Histology/Grade**
  - Clear
  - Pap
  - chrom

- **Genomic Risk**
  - Inter
  - low
  - high

- **Germline Testing**
  - Early Onset
  - Hereditary
  - B/L/MF

- **Oncotype Test**

- **Treatment**

- All other tumors

- Immediate intervention
THANK YOU!!

To refer a patient:
Contact the Kidney Cancer Services Program at the IU Health Simon Cancer Center. Please call the Program Coordinator at 317.944.3539.

Renal Cancer:  
Hereditary, Multifocal and Early Onset

Cancer Centers