Surgical Management of VHL-related Renal Cancers

Presentation to the VHL Family Alliance Annual Meeting,
Denver, CO
October 20, 2018

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Howard University Hospital
Director of Urologic Oncology
Howard University Cancer Center

Overview
- Background on VHL hereditary Renal Cancer Surgery
  - Define terms
  - Describe early history
  - Describe surgical principles for VHL renal surgery
- Technical Aspects of Partial Nephrectomy
  - Describe partial nephrectomy
  - Margins
  - Technical approaches
  - Renal functional outcomes
    - Impact of prolonged surgery on renal function
    - Rationale for Aggressive Renal Surgery

Disclosures
- none

Glossary
- VHL - Von Hippel Lindau
- ccRCC – clear cell renal cell carcinoma
- NSS - nephron sparing surgery
- PNx – partial nephrectomy
- RNx – radical nephrectomy
- BMF – bilateral multifocal
- SRM – Small Renal mass
Definitions

• Vast majority of RCC patients are unilateral, unifocal
  – 4-25% who initially present unifocal, unilateral go onto develop multiple renal masses

• Multifocal = >1 tumor in a single kidney
  – 90% of multifocal are also bilateral
  – 3-11% clinically detected; up to 25% on path
  – Papillary RCC seems to have highest incidence

• Bilateral = at least 1 tumor in both kidneys
  – >50% with bilateral tumors also multifocal

VHL Renal Surgical History

• Early papers report risk of ccRCC in VHL of >70%
• Onset of renal tumors occurs earlier than non-hereditary RCC (40 vs 64)
• Original treatment paradigm for bilateral renal tumors → bilateral RNx and transplant
• NSS surgery was pioneered as a reaction to this original treatment strategy
  – Began in late 1980s early 1990s

Hereditary Renal Cancer

• Despite controversy around partial nephrectomy, absolute indications exist
  – Hereditary renal cancer
  – Solitary kidney
  – Bilateral tumors
• Long-term studies show similar oncologic outcomes regardless of radical vs partial nephrectomy for small renal masses
• Hereditary renal cancers present unique challenges
Hereditary Renal Cancer Phenotypes

- **VHL** – mutation of VHL tumor suppressor gene on Chromosome 3, locus 3p25.1
  - Clear cell RCC (25-60% of affected patients)
  - Pheochromocytoma
  - Pancreatic cysts and neuroendocrine tumors
  - CNS hemangioblastomas
  - Cystadenomas (epididymis, mesosalpynx)
  - Autosomal dominant

VHL Surgical Principles

- Active surveillance
- 3cm rule
- enucleation
- “Reset the clock”

![3 cm Rule -- Update](image)

**Solid tumors: No patients developed metastatic disease when managed by the 3 cm guideline.**

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Unpublished data

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/3/2018
**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)

---Unpublished data

**Surgical Considerations**

**Surgical Margins in PNx**

- DOGMA: 2cm margin → 1cm margin
- Conclusion: width of resection margin after NSS does not correlate with long term disease progression.
- Fuhrman grade and TNM stage more important
- “a millimeter is a mile…”
Surgical Margins: do they matter?

- Literature review using nephron-sparing, partial nephrectomy, margin
- PSM = 0-7% in OPNx
- PSM = 0.7-4% in LPNx
- PSM = 3.9-5.7% in RPNx
- Complete tumor removal is the only factor
- PSM and high grade tumors increase risk of local recurrence
- Vast majority of patients will not recur despite PSM
- Frozen section offers little benefit over surgeons macroscopic assessment

-- Marszalek, M et al Eur Urol 2012 p757-763

Published Data

Feasibility and Outcomes of Repeat Partial Nephrectomy
Aaron Johnson,* Sunil Sudarshan,* Jack Liu, 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

- Repeat PNx—N=51,
  - 19.6% major complication or reoperation
  - mean Cr increased 1.16 to 1.35,
  - eGFR dropped from 95 to 85,
  - 4% long term HD,
  - median time to next surgery = 50mos, f/u=56mos

Published Data

Salvage Partial Nephrectomy for Hereditary Renal Cancer: Feasibility and Outcomes
Gennady Bratslavsky,* Jack J. Liu, Aaron D. Johnson, Sunil Sudarshan, Peter L. Choyke, W. Marston Linehan and Peter A. Pinto
From the Urologic Oncology Branch and Molecular Imaging Program (MIP), Center for Cancer Research, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland

- Salvage PNx—N=13,
  - 46% major complications,
  - 23% loss of kidney,
  - no HD in those whose kidneys were preserved
  - Creatinine : 1.2 → 1.4
  - eGFR: 95 → 79

Published Data

Repeat Partial Nephrectomy on the Solitary Kidney: Surgical, Functional and Oncological Outcomes
Nick W. Liu, Kiranpreet Khurana, Sunil Sudarshan, Peter A. Pinto, W. Marston Linehan and Gennady Bratslavsky†
From the Urologic Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, and Department of Urology, San Antonio Medical Center Hospital (US), San Antonio, Texas

- Repeat PNx solitary—N=25
  - # tumors = 4 median
  - EBL=2400,
  - OR time = 8.5hrs
  - 52% complications
  - no significant difference in eGFR at 1yr f/u
  - 8 required repeat surgery median 36mos
  - 95% metastasis free at 57mos
Post-RFA PNx—N=13
- median time from RFA to surgery was 2.75 yrs,
- # tumors=7 median
- EBL=1500
- OR time 7.8hrs
- 75% op notes reported “severe fibrosis,”
- higher reoperation rate compared to repeat PNx series
- Cr=1→1.1; eGFR= 91→81
- low rate of visceral injury but 31% rate of pleural entry

- 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

Long Story Short……..

Minimally Invasive Published Data for Multifocal Renal Tumors
Robotic Multiplex Partial Nephrectomy: Outcomes

Multiplex Partial Nephrectomy (MxPNx).
- Kidney with ≥3 masses in complex locations
- Most commonly seen with hereditary renal cancer syndromes.

Performed a retrospective analysis of patients that underwent Robotic partial nephrectomy at NIH from 2007-2013.
- Collected demographics, EBL, operative time, WIT, as well as perioperative creatinine and GFR.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (range)</td>
<td>46 (20-84)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female % (n)</td>
<td>33 % (18)</td>
</tr>
<tr>
<td>Male% (n)</td>
<td>66 % (36)</td>
</tr>
<tr>
<td>Race % (n)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>83%</td>
</tr>
<tr>
<td>AA</td>
<td>11%</td>
</tr>
<tr>
<td>Asian</td>
<td>4%</td>
</tr>
<tr>
<td>Latino</td>
<td>2%</td>
</tr>
<tr>
<td>Mean ASA score (range)</td>
<td>1.96 (2-3)</td>
</tr>
<tr>
<td>Mean BMI (range)</td>
<td>30.5 (22.5-41.6)</td>
</tr>
<tr>
<td>Estimated Preoperative GFR (SD)</td>
<td>85.4 (21.5)</td>
</tr>
</tbody>
</table>

VHL: 32
BMF: 11
BHD: 7
HPRCC: 2
UMF: 1
BMF - PAP1: 1

77.8% with hereditary disorder.
remainder have multifocal dz with an unknown germline genetic alteration

Table 2. Operative Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous Surgery (mean)</td>
<td>1.63 (0.8)</td>
</tr>
<tr>
<td>Operative side</td>
<td></td>
</tr>
<tr>
<td>Right (%)</td>
<td>54%</td>
</tr>
<tr>
<td>Left (%)</td>
<td>46%</td>
</tr>
<tr>
<td>Conversion R-&gt;O (n)</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>Partial--Radical (n)</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>Number of masses (mean)</td>
<td>8.63 (8.9)</td>
</tr>
<tr>
<td>EBL (SD)</td>
<td>1434mL (1475)</td>
</tr>
<tr>
<td>Surgery time (SD)</td>
<td>385min (124)</td>
</tr>
<tr>
<td>WIT (SD)</td>
<td>23.3min (6.4)</td>
</tr>
</tbody>
</table>

Mean: 8.63±8.9 masses
Minimum: 3.0
Maximum: 52

Robotic Functional Outcomes after Robotic Multiplex Partial Nephrectomy: The National Cancer Institute Experience with Robotic Partial Nephrectomy for 3 or more Tumors in a Single Kidney

Ryan A. Hankin, Annerlein Walten-Diaz, Hong Truong, Joanna Shih, Gennady Bratslavsky, Peter A. Pinto, W. Marston Linehan, and Adam R. Metwalli
Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute

--Int J Urol Nephrol Nov 2016 Vol 48(11) pp1817-21
Robotic MxPNx – Robotic to Open Conversion

<table>
<thead>
<tr>
<th>Conversion Type</th>
<th>Numbers</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total: 6/54 cases</td>
<td></td>
<td>11%</td>
</tr>
<tr>
<td>First 20: 6/20</td>
<td></td>
<td>30%</td>
</tr>
<tr>
<td>Last 34: 0/34</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>Conversions since 2010 1/36</td>
<td></td>
<td>2.7%</td>
</tr>
<tr>
<td>Partial to Radical 1/54</td>
<td></td>
<td>1.8%</td>
</tr>
</tbody>
</table>

Reasons for Conversion From RMxPNx to Open Surgery

- Endophytic Mass: 3 (5.5%)
- Adhesions: 2 (3.7%)
- Renal Vascular Injury: 1 (1.8%) [radical nx]

Robotic MxPNx – Warm Ischemia

- WIT – 10/54 cases: 18.5%.
- Number of masses removed:
  - Mean 5.5 ± 2.64 (p=0.006)
  - Med 4.5
- Of the 10 cases on clamp:
  - WIT: 23.3±6.4mins
  - Min 15, max 37

Robot MxPNx – Renal Function Outcomes

<table>
<thead>
<tr>
<th>Pre- and post-operative renal function</th>
<th>Creatinine</th>
<th>eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>P-Value</td>
</tr>
<tr>
<td>Cr Preoperative</td>
<td>1.02±0.26</td>
<td></td>
</tr>
<tr>
<td>Cr post-op peak</td>
<td>1.47±0.53</td>
<td>p&lt;0.016</td>
</tr>
<tr>
<td>Cr at 3-month follow-up</td>
<td>1.07±0.33</td>
<td>p=0.101</td>
</tr>
<tr>
<td>eGFR Preoperative</td>
<td>85.4±21.5</td>
<td></td>
</tr>
<tr>
<td>eGFR post-op nadir</td>
<td>60.8±24.3</td>
<td>p&lt;0.031</td>
</tr>
<tr>
<td>eGFR 3-month follow-up</td>
<td>82.3±24.0</td>
<td>p=0.21</td>
</tr>
</tbody>
</table>

*Int J Urol Nephrol Nov 2016 Vol 48(11) pp1817-21*
Repeat Robotic Renal Surgery: Outcomes

Methods
- Identified patients who underwent complex multifocal partial nephrectomies:
  - January 2007 and December 2013
  - ≥ 2 ipsilateral renal or adrenal surgery, the second one being a RRPNx.
- Clinical characteristics, surgical parameters, complications and renal functional outcomes (preop and at 3 month f/u compared to patients undergoing initial ipsilateral robotic partial nephrectomy (iRPNx).

Results

Patient Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>iRPNx</th>
<th>RRPNx</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>124</td>
<td>98</td>
<td>26</td>
<td>-</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>47±13.8</td>
<td>46.5±14.1</td>
<td>48.8±12.8</td>
<td>0.56</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>30.1±5.5</td>
<td>30.1±7.4</td>
<td>30.1±5.2</td>
<td>0.90</td>
</tr>
<tr>
<td>Mean preop Cr (mg/dl)</td>
<td>0.97±0.3</td>
<td>0.96±0.27</td>
<td>1.02±0.27</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Patient Operative Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>iRPNx</th>
<th>RRPNx</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>124</td>
<td>98</td>
<td>26</td>
<td>-</td>
</tr>
<tr>
<td>Mean surgical time (min)</td>
<td>340.2±115.7</td>
<td>334.2±218.7</td>
<td>366.6±122.1</td>
<td>0.20</td>
</tr>
<tr>
<td>Mean EBL (cc)</td>
<td>930.7±1144.1</td>
<td>799±877.5</td>
<td>1426±1769</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean # tumors resected</td>
<td>4.5±7.1 (1-52)</td>
<td>4.6±7.4 (1-52)</td>
<td>4.3±7.8 (1-29)</td>
<td>0.44</td>
</tr>
</tbody>
</table>
Analgesia requirements and Length of Hospital stay for iRPNx vs RRPNx

<table>
<thead>
<tr>
<th>Patient Analgesia requirements and Length of Hospital stay</th>
<th>iRPNx</th>
<th>RRPNx</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>98</td>
<td>26</td>
<td>-</td>
</tr>
<tr>
<td>Mean # days of IV pain medication</td>
<td>2.4±1.7</td>
<td>2.9±2.0</td>
<td>0.316</td>
</tr>
<tr>
<td>Mean length of hospital stay (days)</td>
<td>5.4±2.7</td>
<td>7.1±2.9</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Mean % change Cr (Preop- to 3 month f/u) 10.9±26.9% 16.7±29.6% 0.69

--J Endourol Vol 30(11) p1219-26

Complications iRPNx vs RRPNx

<table>
<thead>
<tr>
<th>Complication</th>
<th>iRPNx</th>
<th>RRPNx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Leak</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clavien grade I-II</td>
<td>3.0% (3/98)</td>
<td>19.2% (5/26)</td>
</tr>
<tr>
<td>Clavien grade III</td>
<td>1.5% (2/98)</td>
<td>7.7% (2/26)</td>
</tr>
<tr>
<td>Transfusion</td>
<td>9.3% (10/98)</td>
<td>19.2% (5/26)</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex. Diahphragm Injury</td>
<td>29.8% (29/98)</td>
<td>23.7% (21/26)</td>
</tr>
<tr>
<td>Ex. Pan (1), Fever (4), Bleeding (1), Liver laceration (1), Small bowel obstruction (1), Rhabdomyolysis (1)</td>
<td>Ex. Pan (2), Pleurysing (1)</td>
<td></td>
</tr>
</tbody>
</table>

--J Endourol Vol 30(11) p1219-26

Renal functional outcomes iRPNx vs RRPNx

<table>
<thead>
<tr>
<th>Patient Renal Functional Outcomes</th>
<th>iRPNx</th>
<th>RRPNx</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>98</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Mean Preop Cr (mg/dl)</td>
<td>0.96±0.2</td>
<td>1.02±0.27</td>
<td>0.27</td>
</tr>
<tr>
<td>Mean Cr 3 month f/u (mg/dl)</td>
<td>1.06±0.38</td>
<td>1.17±0.37</td>
<td>0.06</td>
</tr>
<tr>
<td>Mean % change Cr (Preop- to 3 month f/u)</td>
<td>10.9±26.9%</td>
<td>16.7±29.6%</td>
<td>0.69</td>
</tr>
</tbody>
</table>

--J Endourol Vol 30(11) p1219-26

Standard PNx vs MxPNx in Solitary Kidney

- 93 patients, 121 surgical procedures
  - 43 (35.5%) were SPNx
  - 78 (64.4%) were MxPNx
- Total and Major complication rates were similar (57.1% vs 70.1% p=0.2)(31% vs 35.1% p=0.3)
- Renal function preservation was similar
  - HD rate 4.7% vs 6.4%
  - Completion Nx was similar
- Metastasis rate 8.6% vs 4.1% (p=0.4)

--Unpublished data
OK. Your renal function outcomes are good but OR times are long and complications are high. Is it worth it??

Shortage of Transplantable Kidneys

- Wait list describe as a Darwinian ecosystem
- Most recent updates estimate nearly 350K on wait lists
  - >50% have been on dialysis between 12-36mos BEFORE being listed
- More patients being removed from the lists within the first year
- Transplant rates per 1000 patient/year have decreased recently
- At 5 years, only 37% of listed patients are alive without transplant which is up from 22%

- Schold JD, Arrigain S, et al Am J Trans 2018

QOL on HD

- Numerous studies show lower QOL scores for individuals on HD

Rationale for Pushing the Envelope

- Between 1989-2010
- Repeat renal surgery patients at NCI evaluated
- Costs calculated for RRS
- 33 patients underwent RRS on solitary kidney
- Hypothetical cohort of uncomplicated nephrectomy, fistula placement, dialysis
- Medicare reimbursement

- Agochukwu NQ, Metwalli AR et al J Urol 2012 p1695
Rationale for Pushing the Envelope

- 45% complication rate
- 87% maintained adequate renal function
- 96% metastasis-free
- Cost benefit realized at 0.68 years after surgery
- Benefit persists even calculating 50% underestimation of surgical costs
- HD cost estimated at $35,000/year (£18421/year)

Review

- Background on VHL hereditary Renal Cancer Surgery
- Technical aspects of partial nephrectomy
- Renal functional outcomes
- Impact of prolonged surgery on renal function
- Rationale for aggressive renal surgery

Acknowledgements

- Dr. W. Marston Linehan
- Dr. Peter A. Pinto
- Dr. Piyush K. Agarwal
- Dr. Ram Srinivasan
- The UOB fellows
- The Georgetown residents
- The Walter Reed residents
- UOB staff

The End

Questions?