Imperative Indications for Partial Nephrectomy (Nephron Preservation)

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Disclosures

• Disclosures: Advisory Panel Member and Investigator for Altor Bioscience Corporation (Active)
• No conflicts of interest pertaining to this CME activity
Objectives

1. Describe imperative indications for nephron preservation and associated outcomes
2. Describe methods to manage complications associated with partial nephrectomy for renal cell carcinoma under imperative circumstances
3. Describe neoadjuvant therapy options to facilitate partial nephrectomy for suspected renal cell carcinoma under imperative circumstances
Nephron Preservation

– Imperative indications
  • Solitary kidney
    – Anatomic
    – Solitary “functioning” kidneys
    – Horseshoe kidneys/anatomic variants
  • Bilateral tumors
  • Hereditary syndromes
  • Compromised renal function

– Relative indications
  • Diabetes
  • Recurrent Urolithiasis
  • Renal function at risk (i.e. need for systemic chemo)
  • Any tumor amenable to partial nephrectomy
Nephron Preservation

Rationale

• Many tumors are benign
  – 20% to 34% SRM
• Many patients at baseline have CKD
  – 25% patients with serum Cr <1.4 with CKD stage III⁺
  – 47% patients ≥ 75 yrs with nL serum Cr have CKD III⁺
• CKD greater with radical Nx vs. NSS
• Decreased co-morbidity and improved survival with NSS

Huang et al, Lancet Oncol 7:735, 2006
“Solitary” Kidneys
Partial Nephrectomy
Solitary Kidney
Solitary Thoracic Kidney – Bochdalek Hernia

Anatomic Variant – Crossed Fused Ectopia
PT1aN0 4.0 cm Clear Cell RCCA
Margins negative
Horseshoe Kidney
THINK OUTSIDE THE BOX
Combined Modality Therapy
Partial Nephrectomy & Cryotherapy
Open Renal Cryo

* Few Indications *
Open Renal Cryo

Few Indications
Renal Vein Thrombus and NSS

Renal Vein Thrombus and NSS

• 305 patients underwent NSS over ~ 5 yrs
• Seven (2%) had pT3a venous thrombus
  – Six for imperative indications
  – Postoperative urine leak in one patient
  – One pt with new-onset renal failure
• Mean f/u 30 months:
  – Mean estimated eGFR decreased by 24%
  – Six were free of recurrence with no need for dialysis
  – One LR with level III IVC thrombus 9 mo after NSS - managed with rad Nx, IVC thrombectomy, dialysis

Bilateral Tumors and Hereditary Syndromes
Bilateral (Synchronous) Renal Tumors

- 1% to 6% of non-hereditary cases
- Stage surgeries (bilateral partials)
- Usually approach easier tumor first
  - Consider cStage and aggressive appearance of larger tumor
  - ? Initial surgery for advanced tumors
- Histologic concordance
  - Cancer 96%
  - Benign 46%
Familial Renal Cancer Syndromes

• All autosomal dominant inheritance
• 4% kidney cancers familial / hereditary
  – multifocal, bilateral, typically occur at a younger age (<35 years)
• No apparent increased genetic risk of kidney cancer with:
  – Autosomal dominant polycystic kidneys
  – Dialysis associated acquired renal cystic disease
  – Tuberous sclerosis
Familial Renal Cancer Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Phenotype</th>
<th>Renal cancer manifestation</th>
<th>Gene</th>
<th>Chromosome</th>
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</thead>
<tbody>
<tr>
<td>Von Hippel-Lindau (VHL)</td>
<td>Renal tumors, adrenal pheochromocytomas, retinal angiomas, CNS hemangioblastomas, pancreatic cysts and neuroendocrine tumors, endolymphatic sac tumors, epididymal and broad ligament cystadenomas</td>
<td>Clear cell renal cell carcinoma</td>
<td>VHL</td>
<td>3p25</td>
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<tr>
<td>Hereditary papillary renal carcinoma (HPRC)</td>
<td>Bilateral, multifocal renal tumors</td>
<td>Papillary renal cell carcinoma type 1</td>
<td>MET</td>
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<tr>
<td>Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)</td>
<td>Skin and uterine leiomyomas, renal tumors</td>
<td>Papillary renal cell carcinoma type 2</td>
<td>FH</td>
<td>1q42-43</td>
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<tr>
<td>Birt-Hogg-Dubé (BHD)</td>
<td>Cutaneous fibrofolliculomas, lung cysts, spontaneous pneumothorax, renal tumors</td>
<td>Hybrid oncocytic chromophobe, and clear cell renal cell carcinoma; oncocytoma</td>
<td>FLCN</td>
<td>17p11</td>
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</tbody>
</table>

Compromised Renal Function & Potential for Compromised Function
(i.e. Relative Indications)
ESRD Survival Rates

5-yr survival

Age Range

Soderdahl DW et al, Urol Oncol, 2005
“Elective” Partial Nephrectomy

Poorly controlled IDDM & Hypertension
Incomplete Cryoablation

Cad and Hypertension

Persistent enhancement s/p cryotherapy

33 months s/p salvage partial nephrectomy
Outcomes for NSS Under Imperative Circumstances
Salvage Surgery

<table>
<thead>
<tr>
<th>Patients demographics</th>
<th>n=13</th>
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<tr>
<td>Age</td>
<td>64.2</td>
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<tr>
<td>Gender</td>
<td>Male 11</td>
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<table>
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<tr>
<th>Primary Treatment</th>
<th>Open surgery</th>
<th>Open CA</th>
<th>Hand assisted laparoscopy</th>
<th>Percutaneous CA</th>
<th>Laparoscopic CA</th>
<th>RFA</th>
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<tr>
<td></td>
<td>4</td>
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<td>2</td>
<td>3</td>
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<table>
<thead>
<tr>
<th>Pathological Characteristics</th>
<th>No. Pts 13</th>
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<tr>
<td>Tumor stage</td>
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<tr>
<td>pT1a</td>
<td>8</td>
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<tr>
<td>pT1b</td>
<td>2</td>
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<tr>
<td>pT3b</td>
<td>3</td>
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<tr>
<td>Grade</td>
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<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
</tr>
<tr>
<td>Clear Cell</td>
<td>8</td>
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<tr>
<td>Papillary</td>
<td>2</td>
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<tr>
<td>Oncocytoma</td>
<td>2</td>
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<tr>
<td>Fibrosis</td>
<td>1</td>
</tr>
<tr>
<td>Negative margins</td>
<td>13</td>
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<tr>
<td>Follow up(months)</td>
<td>26.5</td>
</tr>
<tr>
<td>Distant recurrence</td>
<td>1</td>
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<table>
<thead>
<tr>
<th>Renal Functional Outcomes</th>
<th>median mg/dl Serum Creatinine(range)</th>
<th>median ml/min/1.73 m² eGFR(range)</th>
</tr>
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<tbody>
<tr>
<td>No Pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>13</td>
<td>1.35(0.8-2.5)</td>
</tr>
<tr>
<td>Postop</td>
<td>13</td>
<td>1.43(0.8-2.6)</td>
</tr>
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</table>

Partial Nx vs. Ablation for Imperative Indications

- Of course there is a selection bias…
- Multicenter study – 284 patients (15 years)
- Indications:
  - Solitary kidney (n = 146)
  - Bilateral tumor (n = 78)
  - Chronic kidney disease (n = 60)
- Procedures:
  - PN, open (n = 146), lap (n = 9), robotic (n = 17)
  - AT, radiofrequency (n = 104), cryoablation (n = 8)

Partial Nx vs. Ablation for Imperative Indications

• Partial Nx (compared to ablation)
  – Larger tumors and higher RENAL score
  – Worse outcomes (transfusions, LOS, complications)
  – Better Recurrence free survival
  – Similar metastatic recurrence
  – Similar change in eGFR

• Partial Nx offers ability to manage larger, more complex tumors while providing better local control and similar renal function loss

Is R.E.N.A.L Nephrometry Predictive of Function?

- 42 patients - solitary kidneys assigned RENAL nephrometry score
  - 32 anatomic solitary kidney
  - 10 functionally solitary kidney
  - Median score of 8 (range 4 to 10)

- GFR - 11.6% reduction in eGFR was noted over 6 mo
  - mean pre-operative eGFR of 61.5 mL/min/1.73m²
  - 6 month f/u, mean eGFR (54.1 mL/min/1.73m²), (p=0.0002)

- Total or individual component of R.E.N.A.L. score not predictive of functional loss in solitary kidneys

Outcomes for Imperative Clinical Circumstances

- Post-op eGFR possibly more dependent on **Excisional Volume Loss** of affected kidney:
  - Surgical precision – excision of volume of benign parenchyma
  - Iatrogenic injury associated with reconstruction
- Functional loss attributed to warm ischemia recoverable
  - *Although some suggest cold ischemia for imperative indications*
- Tumor complexity not as important/predictive

Outcomes for Imperative Clinical Circumstances

- Associated with diminished Recurrence Free Survival
- Associated with diminished Cancer Specific Survival
  - For $\geq$ T2 RCC
  - Bilateral RCC
- Associated with major post-op complications (open & MIS)
- *Robotic imperative PNx vs. robotic elective PNx
  - Similar functional outcomes
  - Higher risk of major complications with imperative cases

Complications and Management
Neoadjuvant Therapy
“Neoadjuvant”

• Definition:
  – Treatment given as a first step to shrink or affect a tumor before the main treatment, which is usually surgery.
  – Strict application – treatment rendered in the absence of metastatic disease.
Neoadjuvant Therapies

Guiding Principals

• Define the benefit(s) of therapy
  – Improve survival
  – Facilitate surgery
• Minimal risk of local or distant progression
• Minimal risk of surgical delay or inability to deliver definitive treatment
• Acceptable toxicity
• Proof of concept based on prior studies
Neoadjuvant / Preoperative TKI Therapy

• Potential indications for patients with RCC

1) Facilitate a change in surgical approach
   • Radical ➔ partial nephrectomy
   • Open ➔ minimally invasive

2) Unresectable tumors ➔ resectable

3) Downstage IVC thrombus level
   • ? Intra-atrial (IV) ➔ sub-diaphragmatic (III)

4) Target micrometastatic disease early

5) Better select patients for cytoreductive nephrectomy?
Preoperative TKI Therapy Before Nephron-Sparing Surgery

• Clinical indications
  – Large mass in solitary kidney
    • Or solitary functioning kidney
  – Pre-existing CKD and need for NSS
  – Bilateral renal tumors
    • Caveat – anecdotal reports of “rebound growth”
    • ? Bilateral simultaneous vs. staged partials
  – Hereditary syndromes
    • VHL
Preoperative TKI Therapy Before Nephron-Sparing Surgery

<table>
<thead>
<tr>
<th>Study author</th>
<th>Number of total patients in study</th>
<th>Number of patients with MO/M1 disease in study</th>
<th>Number of patients with NSS/N of renal units with NSS</th>
<th>Targeted Molecular Therapy used before NSS</th>
<th>Duration of treatment before NSS</th>
<th>Time drug withheld before surgery</th>
<th>Mean diameter before/after NSS in cm</th>
<th>Mean change in Volume before NSS</th>
<th>N of patients with Positive Margins after NSS</th>
<th>Complications during/after NSS</th>
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</thead>
<tbody>
<tr>
<td>Silberstein et al. [21]</td>
<td>12</td>
<td>7/5</td>
<td>12/14</td>
<td>Sunitinib</td>
<td>90 days</td>
<td>14 days</td>
<td>7.1/5.6</td>
<td>-21.1%</td>
<td>0</td>
<td>3 urinary leaks in M1 patients with sunitinib after surgery</td>
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<tr>
<td>Hellenthal et al. [22]</td>
<td>20</td>
<td>4/16</td>
<td>8/8</td>
<td>Sunitinib</td>
<td>90 days</td>
<td>2–5 days</td>
<td>5.3/-</td>
<td>-11.8% (including nephrectomy patients)</td>
<td>1</td>
<td>1 arteriovenous fistula/1 ventral hema</td>
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<tr>
<td>Thomas et al. [23]</td>
<td>19</td>
<td>10/9</td>
<td>2/3</td>
<td>Sunitinib</td>
<td>135–180 days</td>
<td>7 days</td>
<td>-/-</td>
<td>-23.75%</td>
<td>0</td>
<td>1 acute renal failure</td>
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<tr>
<td>Shuch et al. [24]</td>
<td>4</td>
<td>1/3</td>
<td>1/1</td>
<td>Sunitinib</td>
<td>90 days</td>
<td>90 days</td>
<td>8.5/4</td>
<td>-56%</td>
<td>0</td>
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<td>Gorin et al. [25]</td>
<td>1</td>
<td>1/0</td>
<td>1/2</td>
<td>Sunitinib</td>
<td>180 days</td>
<td>21 days</td>
<td>5.1/2.9</td>
<td>-43.8%</td>
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<td>None</td>
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<tr>
<td>Ansari et al. [26]</td>
<td>1</td>
<td>1/0</td>
<td>1/1</td>
<td>Sunitinib</td>
<td>180 days</td>
<td>-</td>
<td>-/-</td>
<td>-20%</td>
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<td>None</td>
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<tr>
<td>Total</td>
<td>57</td>
<td>24/33</td>
<td>25/29</td>
<td>Sunitinib</td>
<td>90–180 days</td>
<td>2–30 days</td>
<td>6.5/4.1</td>
<td>-36.9%</td>
<td>1.8%</td>
<td>8.8%</td>
</tr>
</tbody>
</table>

NSS, nephron-sparing surgery.

✓ Pre-op/Neoadjuvant TKI therapy well tolerated
✓ Mean decrease in tumor diameter 15% to 30%

• Single institution, open-label, non-randomized
  – Biopsy proven clear cell RCC
  – cT2-T3b N0 M0 (all patients had cT3a tumors)
  – 24 patients

• Neoadjuvant Axitinib
  – 5 mg BID with upward titration (10 mg BID)
  – 12 weeks continuous therapy (off 36 hours prior to radical or partial nephrectomy)
• Response in 100% of tumors (23 patients)
  – Median reduction in diameter 28.3%
    • Median 10 cm ➔ 6.9 cm
  – No progression while on therapy

Neoadjuvant Axitinib
Complications & Quality of Life

• Surgical Complications
  – No Clavien grade 4-5 complications
  – Clavien grade III in 3 patients
    • Chylosus leak in 3 (conservative mgmt with drain)
    • Post-op bleed in 1 (return to OR same day)
  – Surrounding tissue reaction to kidney in 3

• QOL
  – Compared to baseline screening, significant impairment in QOL at week 3, 7, and 12 assessments
  – Returned to baseline by week 19 (7 weeks post-op)

Active Surveillance

Should AS be the “Norm” for Older Patients in Most Imperative Circumstances?
Active Surveillance for Renal Tumors

- Growth rate 0.21 cm to 0.31 cm per year
- Metastatic progression 1% to 5%
- Median tumor size at presentation ~ 2 cm
- Growth independent of:
  - Age
  - Gender
  - Tumor size at presentation
  - Multifocality
  - Radiographic characteristics (solid versus cystic)

Kunkle et al, J Urol 2008
Sometimes….Age is Relative
Active Surveillance for Patients > 75 Years of Age

- 537 patients with ≤ 7 cm tumors – median f/u 3.9 yrs
  - Surveillance (20%)…..**older, ↑’d comorbidities
  - Nephron-sparing (53%)
  - Nephrectomy (27%)
- 148 patients died (cardiovascular in 29%)
- Overall survival decreased:
  - Nephrectomy and surveillance groups
- Multivariate analysis predictors of survival
  - Age (p=.0004)
  - Comorbidity (p<.0001)
  - **NOT** Management type (p=.3)

*Lane BR et al, Cancer, 2010*
References


