Management of Local Recurrence After Radical Nephrectomy

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Local Recurrence following Radical Nephrectomy for Renal Cell Carcinoma (RCC)

- Disease progression following Radical Nephrectomy: 20-38%
  - *Local recurrence following radical nephrectomy: 0.8 – 3.6%*

- May represent:
  - Growth of residual disease
  - De novo metastasis

- May include:
  - Soft tissue/renal fossa, ipsilateral psoas, adrenal gland, regional lymph nodes

Presentation and Risk Factors Associated with Local Recurrence

• **Presentation:**
  - Often *asymptomatic*, discovered on surveillance imaging
  - Symptomatic 7 – 34%
  - **Present with synchronous metastases: ~50%**
  - Median time to local recurrence: 1.4 – 3.3 years

• **Risk factors for development of local recurrence**

<table>
<thead>
<tr>
<th>Features</th>
<th>Hazard Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Age /decade</td>
<td>1.42</td>
<td>0.004</td>
</tr>
<tr>
<td>Tumor size /cm</td>
<td>1.1</td>
<td>0.005</td>
</tr>
<tr>
<td>Tumor Stage (ref pT1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT2</td>
<td>2.56</td>
<td>0.048</td>
</tr>
<tr>
<td>pT3-4</td>
<td>3.77</td>
<td>0.003</td>
</tr>
<tr>
<td>Nuclear grade 4 (ref grade 1-2)</td>
<td>3.18</td>
<td>0.01</td>
</tr>
<tr>
<td>Coagulative Necrosis in Primary Tumor</td>
<td>1.81</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Local Recurrence Management Strategies

• To date, due to the rarity of localized recurrences, no large prospective series exist.

• Retrospective series demonstrate utilization of variable strategies...

Schrodt, Dresden, 2002
Master, USCF, 2005
Bruno, MSKCC, 2006
Paparel, France, 2013
Thomas, MDACC, 2015
Psutka, Mayo, 2015

Surgery
Systemic Therapy
Radiation
Ablation
Nonsurgical Therapy
Palliative Treatment
Operative Outcomes after Surgical Resection

• “...masses tended to have ill-defined margins, and often involved adjacent structures.”
  • Resection of adjacent organ 12 – 72%; > 2 organs: 32%
    • Adrenal, Spleen, Pancreas, Colon, Inferior Vena Cava, Liver, Psoas, Diaphragm, Body wall
  • Lymphadenectomy at the time of resection: 33%

• Operative Approach: Open vs. Laparoscopic (2-3%)
• Median Operative Time: 2 – 7.5 hours
• Median EBL: 400 – 3600 cc (Transfusion requirement: 44%)
• Complete surgical resection not possible: 40% (Paparel, 2014)
• Positive Surgical Margins: 12 – 59%
Postoperative Outcomes after Surgical Resection

- Length of stay 9.2 (7 – 20) days
  - Need for ICU stay 6/14 (43%)
- Overall Postoperative Complications: 29 – 43%
  - Clavien III/IV: 11 - 15%
  - Clavien V: 1 – 4%

Oncologic Outcomes

Median RFS: 1.9 years

Median CSS: 5.5 years

Thomas AZ et al., J Urol 2015; 194: 316.
Cancer Specific Survival: Local Recurrence Stratified by Presence of Synchronous Metastases

Psutka SP et al., J Urol 2015; 193 (4): e762

Median CSS
Isolated LR: 2.2 years
Synchronous Metastases: 1.3 years

Cancer-specific Survival (%)

Years from Renal Fossa Recurrence

N at Risk
Isolated 33 26 19 14 13 11
Synchronous 30 16 14 13 12 5

P = 0.06
Oncologic Outcomes (3)
Surgery vs. No Surgery, stratified by Synchronous Metastases

**Isolated Local Recurrence**
- Group I: Complete Surgical Resection: **71 mos**
- Group 2: Nonsurgical Therapy: **10 mos**

**Local Recurrence + Synchronous Metastases**
- Group 3: Complete Surgical Resection: **16 mos**
- Group 4: Nonsurgical Therapy: **12 mos**

In the Setting of Synchronous Metastases:
Median CSS: 1 – 1.3 years

Oncologic Outcomes (4)

A Margin Status at LR Resection

B Time To Local Recurrence

C Nodal Status at Nephrectomy

D Location of Local Recurrence

Thomas AZ et al., J Urol 2015; 194: 316.
Oncologic Outcomes (5)

Size of Local Recurrence

- Median CSS (months) ± SE
  - Size < 5 cm: 64.0 ± 3.6
  - Size ≥ 5 cm: 28.0 ± 9.7

Sarcomatoid Features

- Median CSS (months) ± SE
  - No sarcomatoid features: 65.0 ± 15.7
  - Sarcomatoid features: 6.0 ± 1.8

Margulis V et al., J Urol 2008; 181; 2044.
## Prognostic Features following Surgical Resection of Local Recurrence (1)

### Margulis et al., MDACC 2008, n=54

<table>
<thead>
<tr>
<th>Feature</th>
<th>RR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Surgical Margin after LR Resection</td>
<td>3.34</td>
<td>0.04</td>
</tr>
<tr>
<td>Recurrent Tumor Size</td>
<td>1.26</td>
<td>0.004</td>
</tr>
<tr>
<td>Sarcomatoid Features of LR</td>
<td>4.68</td>
<td>0.04</td>
</tr>
<tr>
<td>Abnormal Alkaline Phosphatase at LR</td>
<td>4.18</td>
<td>0.145</td>
</tr>
<tr>
<td>Abnormal Lactate Dehydrogenase at LR</td>
<td>2.21</td>
<td>0.481</td>
</tr>
</tbody>
</table>

### Thomas et al., MDACC 2015, n=102

<table>
<thead>
<tr>
<th>Feature</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN stage at Nephrectomy (pN1 vs. pN0/Nx)</td>
<td>4.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recurrent Tumor Size</td>
<td>1.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recurrence &lt; 1 year after Nephrectomy</td>
<td>1.77</td>
<td>0.12</td>
</tr>
<tr>
<td>Positive Margin after Resection of LR</td>
<td>2.09</td>
<td>0.14</td>
</tr>
<tr>
<td>Abnormal Hemoglobin after LR</td>
<td>1.45</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Prognostic Features following Surgical Resection of Local Recurrence (2)

Paparel P et al, French Multiinstitution Series (n=72)

<table>
<thead>
<tr>
<th>Feature</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to Recurrence &lt; 1 year</td>
<td>4.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Surgical Treatment of Recurrence</td>
<td>0.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Complete Surgical Resection</td>
<td>0.6</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Paparel P et al., J Surg Oncol 2014; 109: 126
Systemic Therapy for Local Recurrences

• Retrospective cohorts have listed variable regimens as neoadjuvant, adjuvant, and salvage therapies
  • *Chemotherapy*: 5-fluorouracil, Capecitabine, Gemcitabine, Thalidomide
  • *Immunotherapy*: Interferon-α, IL-2, Combination
  • *Targeted agents*: Bevacizumab/Erlotinib, Sunitinib, sorafenib, temsirolimus, pazopanib...

• *Lack of consensus regarding optimal regimen or sequencing with locally directed therapies*
  • Treatment of metastatic disease according to local protocol and guidelines
Management: Radiation Therapy

- Prior series have utilized EBRT or IORT in small numbers of the patients:

<table>
<thead>
<tr>
<th>Study</th>
<th>EBRT alone</th>
<th>Surgery + IORT</th>
<th>Surgery + EBRT</th>
<th>Surgery + IORT + EBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Master, UCSF, 2006 (n = 14)</td>
<td>0</td>
<td>10 (71.5%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Psutka, Mayo, 2015 (n=63)</td>
<td>5 (7.9%)</td>
<td>2 (3.2%)</td>
<td>2 (3.2%)</td>
<td>2 (3.2%)</td>
</tr>
</tbody>
</table>

- Master, UCSF, 2006: Median IORT Dose: 1500 cGy: **no difference in CSS observed**

Intraoperative Radiation Therapy; Multi-institutional series, n=98

- **IORT**: locally advanced (27%) vs. **locally recurrent (73%)** RCC with IORT at the time of resection
  - Preoperative/Postoperative EBRT: 27% (Median dose 40-45 cGy)
  - Median IORT dose: 15 Gy (9.5 – 20)
- 19% neoadjuvant or adjuvant systemic therapy
- Macroscopic complete resection: 87%
  - Positive Surgical Margin: 59%

**Multivariate Analysis: All-Cause Mortality (LR Only)**

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<thead>
<tr>
<th></th>
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<tr>
<td>Higher IORT dose</td>
<td>1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive Nodal Status</td>
<td>4.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Presence of Sarcomatoid Features</td>
<td>4.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Positive Surgical Margin Status</td>
<td>2.6</td>
<td>0.009</td>
</tr>
</tbody>
</table>

**Conclusion:** “Outcomes compare favorably to resection alone ... potential for improved outcomes with IORT”

Paly, JJ et al., International Journal of Radiation Oncology 2013; 8:618
Percutaneous Ablation

- 61 patients with 82 metastatic RCC lesions treated via percutaneous ablation (Single institution)
  - Retroperitoneal fat/soft tissue: 8 (10%)
  - Nephrectomy bed: 6 (7%)
  - Adrenal: 14 (17%)

- Technique
  - General anesthesia
  - Admitted for overnight observation
  - Cryoablation 59%, RFA 40%, Cryo + RFA 1%
    - 54% adjuvant systemic therapy
  - Outcomes: Median CSS (whole series): 1.5 years
    - 3/28 patients treated for local recurrences developed subsequent recurrent disease (20.5 months)
    - 3 Grade 3-4 complications (Adrenal)

- Potential option to obtain local control in select patients

Welch BT et al., J Urol 2014: 192; 357.
Summary: Management Strategies of Localized Recurrence

Cancer-specific Survival (%)

Years from Renal Fossa Recurrence

Primary Local Therapy = Surgery / Ablation / Radiation

Median CSS
- Local: 4.6 years
- Systemic: 2.8 years
- Expectant: 0.7 years

p=0.006

Mayo Clinic, N=63

French Multiinstitutional Series, N=72

Surgical Resection

No Surgical Treatment

Conclusions:
Management of Local Recurrence after Radical Nephrectomy

• Ideal approach has yet to be determined
  • Patient selection, consideration of competing risks is paramount

• **Retrospective series: benefit of multimodal approach with goal of obtaining local control**
  • Cornerstone: **Surgical Resection**
    • Complex, resection of neighboring organs en bloc, multidisciplinary team
  • Potential roles for **adjuvant IORT/EBRT, Ablation** in select patients
  • Use of **systemic agents** in patients with synchronous metastases per protocol for mRCC
Thank you

Questions & Discussion