Management of Locally Remittent Renal Cell Carcinoma

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Definitions

• Definitive treatment
  – Aiming for cure
  – Ablation therapy
    • Radiofrequency ablation
    • Cryoablation
  – Surgery (Open, Laparoscopic, or Robotic)
    • Partial nephrectomy
    • Radical nephrectomy
Definitions

- Local recurrence
  - Recurrence of an already treated cancer
  - Location=retroperitoneum
    - The kidney itself
    - Where the kidney is/was (renal fossa)
    - Adrenal gland (same side of the affected kidney)
    - Lymph nodes (same side of the affected kidney)
How often does a local recurrence happen?

• With ablation therapy
  – Less than 10%

• With partial nephrectomy
  – Around 5%

• With radical nephrectomy
  – Less than 3%
How do we find a local recurrence?

• Routine imaging after treatment
  – CT scan
  – MRI

• Symptoms after treatment
  – Pain
  – Bleeding
  – Fatigue
  – Weight loss
  – Mass
What to do after discovery of local recurrence?

• Check for cancer in other areas
  – Chest Xray or CT chest
  – Careful review of the CT or MRI abdomen/pelvis
  – MRI brain if indicated
  – Bone scan if indicated

• Consider repeat imaging in 2-3 months if small

• Consider biopsy if indicated
Possible Scenarios?

- Local recurrence only (Best case scenario)
- Local recurrence + distant recurrence (metastasis)
Treatment Options?

- Observation
- Ablation
- Surgery
- Systemic therapy
Guidelines?

• AUA guidelines
• EAU guidelines
• NCCN guidelines

• No recommendations!!!
How do we decide what treatment?

- **Patient factors:**
  - Age
  - Performance status
  - Renal function
  - Comorbidities
  - Other cancers
  - Wishes and expectations

- **Tumor factors:**
  - Size
  - Location
  - Growth rate
  - Biopsy result (if available)
Outline

• Recurrence after ablation
• Recurrence after partial nephrectomy
• Recurrence after radical nephrectomy
1- RECURRENCE AFTER ABLATION THERAPY
Local Recurrence after Ablation
Local Recurrence after Ablation

• Ablation is done → local recurrence is <5% of patients

• Treatment options
  – Observation
  – Repeat ablation
  – Surgery
Surgery For Local Recurrence after Ablation : NCI

• 2001-2007
• 13 patients (VHL)
  – All had prior radiofrequency ablation (RFA)
  – 16 partial nephrectomies
• All had partial nephrectomy
• Average number of tumors removed = 7
• Average operating time ~ 8 hours
• Average blood loss = 1.5 liters

Kowalczyk KJ. J Urol. 2009
Surgery For Local Recurrence after Ablation : CCF (Updated)

- 27 patients (1997-2013)
  - 9 had radiofrequency ablation (RFA)
  - 18 had cryoablation
- 14 partial nephrectomy, 12 radical nephrectomy, 1 aborted surgery
- Median tumor size 3.6 cm
- Median blood loss ~ 225 mL
- Clavien III-IV complications– 6 (22%)
- Follow up (median 14.5 months):
  - NED- 67%
  - Recurrence- 8%
  - Lost to follow-up- 25%
Surgery For Local Recurrence after Ablation: MD Anderson Experience

• 2006-2013
• 14 patients
  – 10 had radiofrequency ablation (RFA)
  – 4 had cryoablation
• Surgery done ~ 2 years after ablation
• 11 partial nephrectomy
• 3 radical nephrectomy
Surgery For Local Recurrence after Ablation: MD Anderson Experience

- Median age at surgery = 65 years
- Median surgery duration ~ 3.5 hours
- Median blood loss ~275 mL
- Median size of tumor = 3.1 cm
- Major complications = 4 patients (all recovered)
- 1 recurrence only (Patient with VHL)

Karam JA. BJU Int. 2014
Local Recurrence after Ablation

**Treatment**
- Open partial nephrectomy
- Clamp time = 8 minutes
- pT1a (3.8cm)
- Clear cell RCC
- Grade 2
- Negative margins
- NED 38 months postop
2- RECURRENCE AFTER PARTIAL NEPHRECTOMY
Local Recurrence after Partial Nephrectomy
Local Recurrence after Partial Nephrectomy

• Incidence ~5%
• Location
  – Kidney itself-same area of prior treated tumor
  – Kidney itself-different area
  – Around the kidney/lymph nodes/adrenal gland
Local Recurrence after Partial Nephrectomy: Mayo Clinic

• 2003-2012
• Patients had prior partial nephrectomy
• 48 patients with 68 tumors
• All local recurrences were treated with cryoablation
• Average tumor size 2.5cm
• Major complications = 5.7%
• Average follow up time = 1.5 years
• Another recurrence = 9.3%

Hegg RM. J Urol. 2013
Local Recurrence after Partial Nephrectomy: NCI

- 1992-2006
- Patients (with VHL) had prior partial nephrectomy
- 47 patients
- All local recurrences were treated with repeat partial nephrectomy
- Surgery time = 7.5 hours
- Blood loss = 1.8 liters
- Average number of tumors removed = 7
- Average size of largest tumor removed = 3.5cm

Johnson A. J Urol. 2008
Local Recurrence after Partial Nephrectomy: NCI

- Major complications = 19.6%
- 3 patients required radical nephrectomy
- Postoperative death = 1 patient
- Average follow up time ~5 years
- Another recurrence that needed surgery = 19.6%
- 46 patients were still alive

Johnson A. J Urol. 2008
Local Recurrence after Partial Nephrectomy: MD Anderson

- 44 patients with local recurrence after PN
- 163 controls (no recurrence)

Wood E, ..., Karam JA, Submitted
Local Recurrence after Partial Nephrectomy: MD Anderson

- Pathologic Stage at initial partial nephrectomy
  - pT1a = 20 (40.8%)
  - pT1b = 13 (26.5%)
  - pT3a = 7 (14.2%)
  - pT3b = 3 (6.1%)

- Histology at initial partial nephrectomy
  - Clear cell = 41 (93.2%)
Local Recurrence after Partial Nephrectomy: MD Anderson

Surgical Margin

Recurrence Free Survival Probability

Logrank P-value < 0.01

No. at Risk
Negative 193 143 91 52 27 16 6 0
Positive 12 5 4 4 2 0 0 0

Surgical Margin

Negative (n=193)
Positive (n=12)
Local Recurrence after Partial Nephrectomy: MD Anderson

Wood E, ..., Karam JA, Submitted

<table>
<thead>
<tr>
<th>Time (year)</th>
<th>Recurrence Free Survival Probability</th>
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<tbody>
<tr>
<td>0</td>
<td>1.0</td>
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<tr>
<td>2</td>
<td>0.8</td>
</tr>
<tr>
<td>4</td>
<td>0.6</td>
</tr>
<tr>
<td>6</td>
<td>0.4</td>
</tr>
<tr>
<td>8</td>
<td>0.2</td>
</tr>
<tr>
<td>10</td>
<td>0.0</td>
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<table>
<thead>
<tr>
<th>Group</th>
<th>No. at Risk</th>
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<tbody>
<tr>
<td>Under 6</td>
<td>56</td>
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<tr>
<td>7-9</td>
<td>118</td>
</tr>
<tr>
<td>10-12</td>
<td>16</td>
</tr>
</tbody>
</table>

Logrank P-value < 0.01
Local Recurrence after Partial Nephrectomy: MD Anderson

![Graph showing recurrence free survival probability with time (year) and no. at risk.](image)

- **Recurrence Free Survival Probability**
  - Time (year):
    - 0
    - 2
    - 4
    - 6
    - 8
    - 10
    - 12
    - 14
  - Probabilities: 0.0, 0.2, 0.4, 0.6, 0.8, 1.0

- **No. at Risk**
  - 1 (n=151)
  - 2 (n=15)
  - >2 (n=14)

- **Logrank P-value**: <0.01

Wood E,..., Karam JA, Submitted
Local Recurrence after Partial Nephrectomy: MD Anderson

Wood E, ..., Karam JA, Submitted
Local Recurrence after Partial Nephrectomy: MD Anderson

No. at Risk
<table>
<thead>
<tr>
<th>Solitary Kidney</th>
<th>No (n=189)</th>
<th>Yes (n=18)</th>
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<tbody>
<tr>
<td>No</td>
<td>189</td>
<td>18</td>
</tr>
<tr>
<td>Yes</td>
<td>140</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>88</td>
<td>7</td>
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<td>6</td>
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Logrank P-value < 0.01
# Local Recurrence after Partial Nephrectomy: MD Anderson

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-value</th>
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<tr>
<td>Solitary kidney (Yes vs. No)</td>
<td>2.62</td>
<td>1.01</td>
<td>6.81</td>
</tr>
<tr>
<td>Positive margins (Yes vs. No)</td>
<td>5.53</td>
<td>2.02</td>
<td>15.13</td>
</tr>
<tr>
<td>Number of tumors (&gt;2 vs. 1)</td>
<td>16.65</td>
<td>6.52</td>
<td>42.54</td>
</tr>
<tr>
<td>R.E.N.A.L. score (High vs. Low)</td>
<td>5.53</td>
<td>1.52</td>
<td>20.21</td>
</tr>
<tr>
<td>pT stage (pT3 vs. pT1)</td>
<td>3.44</td>
<td>1.07</td>
<td>11.08</td>
</tr>
</tbody>
</table>

Wood E,..., Karam JA, Submitted
Local Recurrence after Partial Nephrectomy: MD Anderson

• Time between partial nephrectomy and local recurrence = 24 months (IQR 6-51)
Local Recurrence after Partial Nephrectomy: MD Anderson

• Salvage surgery
  – Open partial nephrectomy
  – Open radical nephrectomy
  – Laparoscopic radical nephrectomy
  – Robotic partial nephrectomy
• Salvage radiofrequency ablation
• Observation
• Systemic therapy

Wood E,..., Karam JA, Submitted
Local Recurrence after Partial Nephrectomy: MD Anderson

- OR time for salvage surgery = 135.5 minutes (IQR 110.25-241.75)
- Estimated blood loss = 575cc (IQR 256.25-850)
- Pathologic stage at salvage surgery
  - T1 = 13 (26.5%)
  - T3a = 7 (14.3%)
  - T3b = 3 (6.1%)
Local Recurrence after Partial Nephrectomy: MD Anderson

**Treatment**
- Laparoscopic radical Nx
- pT3a (5.5cm)
- ccRCC, Grade 3
- Negative margins
- NED 28 months postop
3- RECURRENCE AFTER RADICAL NEPHRECTOMY
Local Recurrence after Radical Nephrectomy
Local Recurrence after Radical Nephrectomy
Local Recurrence after Radical Nephrectomy
Local Recurrence after Radical Nephrectomy

• Incidence of <5%
Local Recurrence: USC

• 11 patients
  – 10 with no metastases at presentation
• Most patients had symptoms
• Presented 31 months after initial surgery
• 2 postoperative deaths
• 2 died of cancer at 8 and 22 months
• 3 died of causes unrelated to cancer recurrence
• 4 patients were without disease at a follow-up of 35, 46, 48 and 211 months
Local Recurrence: MDACC

- 16 patients with locally recurrent RCC
  - 8 patients received neoadjuvant Rx, 7 of these received additional adjuvant Rx
    - 7 IFNα based
    - 1 IL-2 based
  - Neoadjuvant group - 50% no evidence of cancer
  - Surgery alone group - 25% no evidence of cancer

Tanguay S. J Urol. 1996
Local Recurrence: MDACC

- 15 patients had complete resection (of the 16)
  - 12 had clear margins → 6 were free of cancer
- 12 of the 16 were alive at 2 years after second surgery
Local Recurrence: Mayo Clinic

![Graph showing cause-specific survival over time from recurrence to follow-up (years)]

- **Tx including surgery (n=10)**
  - 90.0±10

- **Tx excluding surgery (n=11)**
  - 63.6±15
  - 64.3±17

- **Observation (n=9)**
  - 38.1±17
  - 36.4±15
  - 12.7±12
  - P=0.02

- 51.4±18
- 18.2±12
- 12.7±12

Itano NB. J Urol. 2000
Local Recurrence: Royal Marsden

- 16 patients (9 year period)
  - 2 - unresectable
  - 2 - residual adrenal recurrence
  - 6 - retroperitoneal LN’s
  - 6 - renal bed
  - 1 liver; 1 stomach; 1 spleen
  - 2 - diaphragm

- 8 patients given neoadjuvant Rx
- Of 14 resected, 6 Margin +
  - Margin status predicted local and distant DFS (p < 0.05)
- Median f/u - 1 year
  - Median time to relapse - 2.4 months
  - Median time to metastasis - 4.3 months
  - 5 patients remain disease free

Sandhu S. BJU Int. 2005
Local Recurrence: MD Anderson Experience

- 1990-2014
- 102 patients had surgery for local recurrence
- 84.3% of the patients → radical nephrectomy at outside institutions → subsequently referred to MDACC for local recurrence surgery

Thomas AZ, ..., Karam JA. J Urol. 2015
Local Recurrence: MD Anderson Experience

- Time from nephrectomy to local recurrence diagnosis was 1.5 years
- At time of nephrectomy
  - Median age 55 years
  - 79.4% had open surgery
  - 60.8% were pT3-4 (invading renal vein/vena cava, fat or other organs)
  - 19.6% were pN1 (positive lymph nodes)
  - 13.7% had positive margins
Local Recurrence: MD Anderson Experience

• Area of local recurrence
  – 48% - Soft tissue/renal fossa
  – 40.2% - Lymph nodes
  – 11.8% - Adrenal gland

• At time of local recurrence surgery
  – 41.2% had symptoms
  – 45.1% received neoadjuvant Rx

Thomas AZ, ..., Karam JA. J Urol. 2015
Local Recurrence: MD Anderson Experience

- Median local recurrence size = 4.5 cm
- Open surgery for 97.1% of patients
- Major complications = 14.7%
- Blood loss = 700 mL
- Median surgery duration = 3.5 hours
- Median hospital stay = 1 week

Thomas AZ, ..., Karam JA. J Urol. 2015
Local Recurrence: MD Anderson Experience

• 58.8% of patients had cancer relapse after local recurrence surgery
  – Median time to second relapse ~ 2 years
  – Median survival after second relapse ~5.5 years

• Predictors of worse outcomes after surgery for local recurrence
  – Positive lymph nodes at time of initial nephrectomy
  – Larger size of local recurrence

Thomas AZ,..., Karam JA. J Urol. 2015
CSS-by Site of Recurrence

Median CSS (months) ± SE
- Soft tissue: 93 ± 27
- Lymph node: 61 ± 12
- Adrenal: NA

Graph showing survival rates for different sites of recurrence:
- Soft tissue
- Lymph node
- Adrenal

Thomas AZ, ..., Karam JA. J Urol. 2015
Local Recurrence after Radical Nephrectomy

**Treatment**
- Resection of all retroperitoneal masses
- Resection of renal artery and vein stump
- Distal pancreatectomy
- Splenectomy
- Left hemicolecotomy
- Left adrenalectomy
- Omentectomy
- Partial diaphragm resection
- RPLND

→ NED 17 months postop
Take Home Messages

• Local recurrences are rare but can occur after initial treatment
• Important to follow-up with urologist after initial treatment
• Best treated in referral medical centers
• Surgical resection in patients with good performance status
  – For recurrence after ablation or PN- excellent
  – For recurrence after radical Nx ~40% cure
Thank you!

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