Active Surveillance of Localized RCC: What we think we know

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Case

- 62yo male with complicated history of Crohn's
- Incidental 1.5 cm right enhancing mass noted
- PMHx: Stable angina, COPD, CVA, HTN, IBD
- PSHx: Appy, perirectal abscess
- SHx: 1ppd
- Meds: Prednisone, flagyl, metoprolol, Asacol, hydralazine, clonidine, Cartia, famotidine
- PE: 145 lbs, 134/86, PS(1-2)
- Labs: Sr 1.3 mg/dl
Enhancing 1.5cm mass......kidneys otherwise clear

January '02

July '03

May '05
Case

• CT 7/01 – 1.5 cm enhancing lesion
• November 01 – CVA and aspiration, recovered
• CT 1/02 – 1.5 cm solid renal mass unchanged
• CT 6/02 – 1.5 cm solid renal mass unchanged
• CT 12/02 – 1.5 cm mass unchanged
• CT 7/03 – 1.5 cm mass unchanged
• CT 2/04 – 1.5 cm mass unchanged
• CT 5/05 – 1.5 cm mass unchanged
• CXR and further extent of disease negative

• Expired 2007 of other causes

Premise (s)

• Kidney cancer is:
  – Potentially lethal
  – Heterogeneous
  – Surgical

• NSS is underutilized

• Level I evidence is lacking
  – Only 3 prospective trials in localized RCC
  – Selection biases exist in ALL the published literature

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Kidney Cancer is Lethal

(Death Rates from RCC are Rising)

1. Pathology of localized SRM

predominantly (not always)

“low risk”
Size predicts histology and grade
Most are RCC - Most are low grade

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>Benign</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 cm</td>
<td>46%</td>
<td>54%</td>
</tr>
<tr>
<td>1.1-2.0</td>
<td>22%</td>
<td>78%</td>
</tr>
<tr>
<td>2.1-3.0</td>
<td>22%</td>
<td>78%</td>
</tr>
<tr>
<td>3.1 – 4.0</td>
<td>20%</td>
<td>80%</td>
</tr>
<tr>
<td>4.1 – 5.0</td>
<td>9.9%</td>
<td>90.1%</td>
</tr>
</tbody>
</table>

Mayo N= 2770
Frank et al J Urol 170: 2003

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>Low Grade (%)</th>
<th>High Grade (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4 cm</td>
<td>7729 (86)</td>
<td>1250 (14)</td>
</tr>
<tr>
<td>4-7 cm</td>
<td>5015 (79)</td>
<td>1361 (21)</td>
</tr>
<tr>
<td>&gt; 7 cm</td>
<td>2439 (70)</td>
<td>1024 (30)</td>
</tr>
<tr>
<td>Totals</td>
<td>15,183 (81)</td>
<td>3635 (19)</td>
</tr>
</tbody>
</table>

SEER analysis N=18,818
Uzzo et al J Urol 181: 2009

Preoperative Nomogram for Renal Tumors ≤ 7cm:
Will the tumor be “aggressive”? (n=862)

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Y</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor Size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Points</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggressive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Aggressive:
- Any high grade tumor
- Any fat, urothelial or vascular invasion
- 30% were potentially “aggressive”

Lane et al J Urol: 178, 429, 2007
2. Radiographic growth kinetics of localized SRM are slow

### Growth Potential of Lesions under Active Surveillance

<table>
<thead>
<tr>
<th># STUDIES</th>
<th>N</th>
<th>Mean Lesion Size (cm)</th>
<th>Mean Growth Rate (cm/yr)</th>
<th>Mean F/U Duration (months)</th>
<th>Progression to M+ Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>234</td>
<td>2.60</td>
<td>0.28 – 0.42</td>
<td>34</td>
<td>1%</td>
</tr>
</tbody>
</table>

*Chawla and Uzzo et al J Urol 175 (2): 425, 2006*

<table>
<thead>
<tr>
<th>N = 106</th>
<th>Zero Growth Tumors</th>
<th>Growing Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>34%</td>
<td>66%</td>
</tr>
<tr>
<td>Median Follow-up (mo)</td>
<td>28.7</td>
<td>36.4</td>
</tr>
</tbody>
</table>

*Kunkle and Uzzo et al J Urol 177 (3): 425, 2007*
**Growth and Progression of RCC under Active Surveillance 2010**

(18 non-redundant studies)

<table>
<thead>
<tr>
<th>N</th>
<th>Range Median Age (yrs)</th>
<th>Range Median Size (cm)</th>
<th>Median Growth Rate (cm/yr)</th>
<th>Range Median F/U Duration (mo)</th>
<th># progressed to mRCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>880</td>
<td>54-80</td>
<td>0.9 – 6.0</td>
<td>0.08 – 0.58</td>
<td>20-41</td>
<td>17 (1.9%)</td>
</tr>
</tbody>
</table>

Overall Mean follow-up = 34 months

35% of lesions exhibited *net ZERO* radiographic growth (none progressed)

*Smaldone, Kutikov and Uzzo et al in preparation*

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3. **No Relationship of Primary Tumor Size to Progression**

....smaller probably better

....but bigger isn’t universally worse
Does Primary Tumor Size Predict Growth Rates?

Initial Tumor Size did **not** correlate with linear growth rates

Rosales et al. J Urol 183: 2010

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Does Primary Tumor Size Predict Growth Rates?

*The Fox Chase Experience n=172*

Crispen and Uzzo Cancer 115:2009
**Does Primary Tumor Size Predict Growth Rates?**

*The Fox Chase Experience n=172*

**RCC and Gompertzian Growth Kinetics:**

- A tumor’s growth rate is initially exponential and then decreases with increasing size

- A significant association between presenting tumor size and volumetric growth

- Smaller tumors grow faster than larger tumors (p<0.05)

*Nguyen et al J Urol 181: 2009*

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**Relationship between 1° Tumor Size and Metastases at Diagnosis**

**Size vs Metastases at Diagnosis**

**Size vs 5 yr CSS**

*Nguyen et al J Urol 181: 2009*
Primary Tumor Size and Progression to mRCC
(n=17/880 published cases)

<table>
<thead>
<tr>
<th>#</th>
<th>Initial tumor size</th>
<th>Size at mRCC</th>
<th>Growth rate (cm/yr)</th>
<th>Follow-up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5</td>
<td>5.9</td>
<td>2.7</td>
<td>15 mo</td>
</tr>
<tr>
<td>2</td>
<td>2.7</td>
<td>4.5</td>
<td>0.9</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>2.7</td>
<td>5.8</td>
<td>0.95</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>8</td>
<td>1.2</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>6</td>
<td>0.59</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>3.2</td>
<td>4.8</td>
<td>0.3</td>
<td>63</td>
</tr>
<tr>
<td>7</td>
<td>4.3</td>
<td>6.3</td>
<td>0.89</td>
<td>52</td>
</tr>
<tr>
<td>8</td>
<td>4.5</td>
<td>4.8</td>
<td>0.28</td>
<td>37</td>
</tr>
<tr>
<td>9</td>
<td>8.8</td>
<td>10.7</td>
<td>0.2</td>
<td>111</td>
</tr>
</tbody>
</table>

VHL RULE – No patient* with localized tumor <3cm progressed to mRCC

Smaldone, Kutikov and Uzzo et al in preparation

4. Treatment (and Surveillance) decisions are overly subjective

....we can do better
We do not objectify Rx Decisions in RCC well

• Should Calculate
  – Performance status (ECOG/Karnofsky)
  – Co-morbidity Index (Charlson)
  – Competing Risks of Death (nomogram)
  – Complications
    • Clavien/Accordion/MSKCC/NCI-CTC
  – eGFR and Risk of CKD (nomogram)
  – Complexity of partial nephrectomy
    • Nephrometry Score

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Which are you more comfortable AS

75 year-old females with 3.5 cm SRM and comparable comorbidities

Nephrometry 1+2+3+a+3=9a

Nephrometry 1+1+a+1=4a
Objectifying AS Decisions

• Abstract #1359
  – Nephrometry scores on 540 of 1900 pts in FCCC prospective RCC database (2000 – present)
  – Patients on active surveillance had tumors that were:
    • smaller
    • further from the sinus/urothelium
    • more often polar
    • less often hilar

• Podium # 1238
  – higher anatomical complexity = worse pathological subtype and grade
  – AUC for Cancer Model = 0.78; AUC for Grade Model = 0.72

5. Metastases are a late event (even during Surveillance)

….but is there enough data?
Relative Risk of M+ Progression

Multivariate Regression (offset for log overall follow-up time)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Incidence Rate Ratio (IRR)</th>
<th>95% Credible Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Nephrectomy</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>Cryoablation</td>
<td>0.91</td>
<td>0.08-6.61</td>
</tr>
<tr>
<td>RFA</td>
<td>2.10</td>
<td>0.32-12.53</td>
</tr>
<tr>
<td>Active Surveillance</td>
<td>0.09</td>
<td>0.00-1.41</td>
</tr>
</tbody>
</table>

- Mean tumor size of 3.26 cm
- Mean follow-up of 47 months

Progression to mRCC under AS
(17/880 n=1.7%)

<table>
<thead>
<tr>
<th>N</th>
<th>Median Age (yrs)</th>
<th>Median Presenting Size</th>
<th>Median Size at mRCC</th>
<th>Median Growth Rate (cm/yr)</th>
<th>Median time to mRCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>75</td>
<td>4.3 cm</td>
<td>6.3 cm</td>
<td>0.89</td>
<td>52 mo</td>
</tr>
</tbody>
</table>

35% of lesions exhibited net ZERO radiographic growth (none progressed)

Smaldone, Kutikov and Uzzo et al in preparation

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6. Treatment Tradeoffs are Real

…and should be objectified

AUA cT1 Renal Mass Guidelines
Major Urologic Complications
Significant Comparisons (p<0.05)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Complication Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPN (9.0%)</td>
<td></td>
</tr>
<tr>
<td>OPN (6.3%)</td>
<td></td>
</tr>
<tr>
<td>RFA (6.0%)</td>
<td></td>
</tr>
<tr>
<td>Cryo (4.9%)</td>
<td></td>
</tr>
<tr>
<td>LRN (3.4%)</td>
<td></td>
</tr>
<tr>
<td>ORN (1.3%)</td>
<td></td>
</tr>
</tbody>
</table>

www.auanet.org/guidelines
A 5y Comprehensive Nomogram of Competing Risks of Death

- At 78 yo
  - 30% 5y risk of non RCC death
  - 3% risk of RCC death

Kutikov, Uzzo et al
SEER (n=30,801)
JCO 10: 2010

7. Delayed Intervention unlikely to compromise efficacy/cure
AS with Delayed Intervention
8 non-redundant studies

<table>
<thead>
<tr>
<th>N</th>
<th>Median Size at Rx (cm)</th>
<th>Mean Linear Growth Rate (cm/yr)</th>
<th>Minimum Delay (mo)</th>
<th>% progressed to M+ disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>151</td>
<td>2.3</td>
<td>0.44</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

Only 3/880 developed mRCC within 3 years of active surveillance

Smaldone, Kutikov and Uzzo et al in preparation
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Five-Year Cancer Specific Survival

Death from kidney cancer during surveillance is rare
5-year Competing Cause Mortality

BETTER OBJECTIFY
our Treatment Decisions in RCC

86% of SRMs < 4cm are low grade

Average growth rate is 4-5mm/yr

17/880 tumors (1.9%) under AS have metastasized
  - All were > 4cm at time mRCC detected

No patient with AS and delayed intervention metastasized

Average time from detection to metastasis = 52 months
72 yo male with CAD, HTN, BPH
Creatinine 1.5 mg/dl
ECOG PS = 0
Weighted Charlson Co-morbidity Index of 2
1º caregiver to infirmed wife
Not interested in any risk of dialysis

6 months of Active Surveillance

L lesion: 3.9 → 3.8 cm
L cystic lesion: 4.8 → 4.9 cm
R lesion: 5.5 → 5.5 cm

1 year of Active Surveillance

L lesion: 5.5 → 5.5 cm
L cystic lesion: 4.8 → 4.9 cm
R lesion: 3.9 → 3.8 cm
2 years of Active Surveillance

L lesion: 5.5 → 5.5 → 5.6 cm

L cystic lesion:
4.8 → 4.9 → 4.7 cm

R lesion:
3.9 → 3.8 → 4.4 cm

3 years of Active Surveillance

L lesion: 5.5 → 5.5 → 5.6 → 5.8 cm

L cystic lesion:
4.8 → 4.9 → 4.7 → 4.4 cm

R lesion:
3.9 → 3.8 → 4.4 → 4.2 cm
4 years of Active Surveillance

L lesion: 5.5 → 5.5 → 5.6 → 5.8 → 5.5 cm

R lesion: 3.9 → 3.8 → 4.4 → 4.2 → 4.0 cm

L cystic lesion: 4.8 → 4.9 → 4.7 → 4.4 → 5.0 cm
4 years after Active Surveillance

- Large bilateral enhancing *localized* RCC:
  - 76 years old and asymptomatic
  - Creatinine = 1.5 mg/dl
  - No evidence of nodal or distant disease

These data do NOT suggest that...

1. That kidney cancer is not lethal…
2. That RCC is a ‘non-surgical’ disease…
3. That all patients want to be observed…
4. That we can precisely select patients for surveillance…
5. That we have a molecular marker for growth…

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These data DO suggest that…

1. Not all kidney cancers are equally lethal
2. Most SRMs grow slowly (0.28-0.42/cm/yr)
   - 30% exhibit zero radiographic growth
3. Progression to metastatic disease is low (1.5%)
   - CSS is 100% in the reported literature
   - Metastasis has always been associated with rapid growth
     (0.75cm/yr)
   - Mean of 65 months of AS prior to metastases
4. We are likely over interpreting the efficacy of our Rx (ablation)
5. Delayed management unlikely to jeopardize cure
6. Treatment biases exist when counseling patients
7. Surveillance (like intervention) is a calculated risk

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Manny Ramirez 1993 - 2009:

- 533 Career Home Runs
- Only 5 off Randy Johnson
HOME RUN
95-100% 5 yr CSS
Consider the published results of surgical interventions in the context of the formidability of the competition (the inherent biology of the tumor)