Management of Small Renal Mass: Focal Therapy, Partial Nephrectomy, Active Surveillance: What’s a Doctor to Do?

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Harvard Medical School
Disclosures

• None
Background: Renal cell carcinoma

Epidemiology
- 3.8% of all new cancers
- Affects more males than females (3:2)

Human Renal Epithelial Neoplasms

<table>
<thead>
<tr>
<th>Clear Cell</th>
<th>Papillary Type 1</th>
<th>Papillary Type 2</th>
<th>Chromophobe</th>
<th>Oncocytoma</th>
<th>Angiomyolipoma</th>
<th>TFE3</th>
<th>Oncocytic</th>
<th>Clear/Chromophobe</th>
</tr>
</thead>
<tbody>
<tr>
<td>VHL (89%)</td>
<td>Met (13%)</td>
<td>FH</td>
<td>FLCN</td>
<td>TSC1, TSC2</td>
<td>MITF</td>
<td>SDHB, SDHD</td>
<td>PTEN</td>
<td></td>
</tr>
<tr>
<td>TBD*</td>
<td>TBD*</td>
<td>TBD*</td>
<td>TBD*</td>
<td>TSC1, TSC2</td>
<td>TFE3, TFEB</td>
<td>TBD*</td>
<td>TBD*</td>
<td></td>
</tr>
</tbody>
</table>

NCCN Guidelines (2019)
Multilocular Cystic Clear Cell Neoplasm of Low Malignant Potential

- A histologic variant of clear cell RCC (<5% of clear cell RCC)
- Formerly known as “multi-locular cystic RCC”
- Well-circumscribed, entirely cystic
- Cysts lined with single layer of clear cells (grade 1 nuclei)
- No recurrence or metastasis reported after resection
Epidemiology

• Incidence of renal masses has increased due to surge in routine use of CT
  • RCC incidence rising by 3% per year
  • Many of the tumors are incidentally discovered and small in size (~66%)


• Cancer-specific mortality remains relatively unchanged
  • Many small masses may be treated too aggressively

Siegel CA. Cancer J Clin. 2018
Estimated New Cancer Cases* in the US in 2019

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>All other sites</td>
<td>22%</td>
<td>21%</td>
</tr>
</tbody>
</table>

*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.
<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Males 321,670</th>
<th>Females 285,210</th>
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<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>24%</td>
<td>23%</td>
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<tr>
<td>Prostate</td>
<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td>8%</td>
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<tr>
<td>Pancreas</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>All other sites</td>
<td>25%</td>
<td>24%</td>
</tr>
</tbody>
</table>
Small Renal Mass Dilemma

- Small Renal Mass (SRM):
  - Typically defined as small (<4cm), enhancing, organ confined tumor suspicious for RCC
  - Partial nephrectomy continues to be the ‘gold standard’
    - Improved preservation of renal function
    - Superior cardiac outcomes
Small Renal Mass Epidemic

• The most rapid increase is for tumors 2-4 cm
Incidence of Synchronous Metastases

**FIG. 1.** Predicted probability of metastasis at presentation based on primary tumour size. Dashed lines represent 95% CI.

Umbreit et al. *BJUI*. 2012
Treatment Disconnect

- Incidence of renal masses has increased due to surge in routine use of CT - 
  RCC incidence rising by 3% per year
- Mortality remains stable suggesting over-diagnosis and over-treatment

### Small Renal Mass Histology By Size (cm) n=798

<table>
<thead>
<tr>
<th>Size (cm)</th>
<th>#</th>
<th>Benign (%)</th>
<th>Malign (%)</th>
<th>FG&lt;2</th>
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<tbody>
<tr>
<td>0-1</td>
<td>19</td>
<td>32</td>
<td>68</td>
<td>100</td>
</tr>
<tr>
<td>1-2</td>
<td>183</td>
<td>22</td>
<td>78</td>
<td>85</td>
</tr>
<tr>
<td>2-3</td>
<td>259</td>
<td>22</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>3-4</td>
<td>172</td>
<td>20</td>
<td>80</td>
<td>70</td>
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<tr>
<td>4-5</td>
<td>95</td>
<td>16</td>
<td>84</td>
<td>68</td>
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<tr>
<td>5-6</td>
<td>38</td>
<td>8</td>
<td>92</td>
<td>60</td>
</tr>
<tr>
<td>6-7</td>
<td>32</td>
<td>9</td>
<td>91</td>
<td>72</td>
</tr>
</tbody>
</table>
Survival by tumor size in 637 patients with pathologically confirmed RCC

Overall survival

Cancer-specific survival

Years from surgery to last follow-up

Years from surgery to last follow-up

≤2
≤4
≤7
Competing Risks of Death in Patients with Localized Renal Cell Carcinoma: A Comorbidity Based Model

Figure 1. Predicted competing risks of mortality by tumor size and comorbidity status. Red areas indicate probability of kidney cancer death. Blue areas indicate chance of death from another cause.
- Patient factors;

70 yo female with 4.5 cm mass with Stage III CKD plus proteinuria has 50% chance of death due to other causes in 5 years while risk of progression to metastatic disease is ~ 6%

70 yo with 7 cm mass with no significant comorbidities has a 5 year risk of mortality of:

- 7.5% non-kidney cause
- 13% from RCC

Kutikov et al Jurol 2012 188,2077
TABLE 1
Meta-analysis of outcomes for patients with clinical T1 renal masses according to treatment approach

<table>
<thead>
<tr>
<th></th>
<th>Radical Nephrectomy*</th>
<th>Partial Nephrectomy*</th>
<th>Radiofrequency Ablation</th>
<th>Cryoablation</th>
<th>Active Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>6,235</td>
<td>6,418</td>
<td>745</td>
<td>644</td>
<td>390</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>63</td>
<td>60</td>
<td>70</td>
<td>66</td>
<td>68</td>
</tr>
<tr>
<td>Median tumor size (cm)</td>
<td>5.4</td>
<td>3.0</td>
<td>2.7</td>
<td>2.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Median follow-up (months)</td>
<td>58</td>
<td>47</td>
<td>19</td>
<td>17</td>
<td>29</td>
</tr>
<tr>
<td>Urologic complication rate (%)</td>
<td>1.3</td>
<td>6.3</td>
<td>6.0</td>
<td>4.9</td>
<td>NA</td>
</tr>
<tr>
<td>Local recurrence-free survival rate (%)</td>
<td>98.1</td>
<td>98.0</td>
<td>87.0</td>
<td>90.6</td>
<td>NA</td>
</tr>
<tr>
<td>Metastatic recurrence-free survival rate (%)</td>
<td>89.8</td>
<td>96.7</td>
<td>97.8</td>
<td>95.3</td>
<td>97.7</td>
</tr>
<tr>
<td>Reduction in renal function and potential impact on cardiovascular morbidity</td>
<td>High</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Minimal</td>
<td>None</td>
</tr>
</tbody>
</table>

*Both radical and partial nephrectomy data are from open approaches because these provide more mature data.
**AUA Guidelines**

**Patient with clinical T1 renal mass**

**EVALUATION**
- High-quality cross-sectional imaging study (CT or MR) with and without contrast (in the presence of adequate renal function) to assess contrast enhancement, exclude angiomyolipoma, assess for locally invasive features, define the relevant anatomy and evaluate the status of the contralateral kidney.
- Percutaneous renal mass core biopsy with or without FNA for patients in whom it might impact management, particularly patients with clinical or radiographic findings suggestive of lymphoma, abscess or metastasis.

**COUNSELING**
- Review the current understanding of the natural history of clinical T1 renal masses, the relative risks of benign vs. malignant pathology and the potential role of AS.
- Review the available treatment options and the attendant benefits and risks, including oncologic considerations, renal functional considerations and potential morbidities.
- Discuss the potential advantages of a nephron-sparing treatment approach in the impetuous and elective settings, including the avoidance of dialysis and reduced risk of CKD with its attendant morbidity and mortality.

**INDEX PATIENT 1:** Healthy; Clinical T1a

**STANDARD - PN:** Complete surgical excision by PN is a standard of care and should be strongly considered.

**STANDARD - RN:** Should be discussed as alternate standard of care if PN is not technically feasible as determined by the urologic surgeon.

**OPTION - TA:** Cysplatin or RFA should be discussed as less-invasive treatment options, but local tumor recurrence is more likely, measures of success are not well defined, and surgical salvage may be difficult.

**OPTION - AS:** As with delayed intervention should be discussed as an option for patients wishing to avoid treatment and willing to assume oncologic risk.

**INDEX PATIENT 2:** Major comorbidities Increased surgical risk Clinical T1a

**STANDARD - PN:** Complete surgical excision by PN should be discussed as a standard of care with increased surgical risk in this patient.

**STANDARD - RN:** Should be discussed as standard of care with increased risk of CKD and surgical complications in this patient.

**RECOMMENDATION - TA:** Cysplatin or RFA should be discussed as less-invasive treatment options which may be advantageous in this high surgical risk patient, acknowledging the increased risk of local tumor recurrence compared to surgical excision.

**RECOMMENDATION - AS:** Should be offered as an acceptable approach which can delay or avoid the need for intervention in this high-risk patient.

**INDEX PATIENT 3:** Healthy; Clinical T1b

**STANDARD - RN:** Should be discussed as standard of care for patients with a normal contralateral kidney.

**STANDARD - PN:** Complete surgical excision by PN should be discussed as an alternative standard of care, particularly when there is a need to preserve renal function.

**OPTION - AS:** As with delayed intervention may be discussed as an option in patients who want to avoid surgery and are willing to accept an increased risk of tumor progression compared to PN or RN. As may represent suboptimal management for this healthy patient.

**INDEX PATIENT 4:** Major comorbidities; Increased surgical risk; Clinical T1b

**STANDARD - RN:** Should be discussed as standard of care for patients with a normal contralateral kidney, although it can be associated with surgical morbidity and an increased risk of CKD in this patient.

**RECOMMENDATION - PN:** Complete surgical excision by PN should be discussed as a recommended modality when there is a need to preserve renal function, although it can be associated with increased urologic morbidity in this patient.

**RECOMMENDATION - AS:** As should be discussed with patients who want to avoid surgery or risk.
(Under) Utilization of Active Surveillance for SRM

AS 6 → 11%
Yang et al. BJUI. 2012

AS 12 → 20%
Smaldone et al. Urology. 2013
### Prospective Trials of Active Surveillance

<table>
<thead>
<tr>
<th></th>
<th>Renal Cell Consortium of Canada (RCCC)</th>
<th>Delayed Intervention and Surveillance for Small Renal Masses (DISSRM)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eligibility</strong></td>
<td>cT1a+ not fit for surgery</td>
<td>&gt;18y.o cT1a, no personal hx of RCC, no familial RCC syndrome</td>
</tr>
<tr>
<td><strong>Surveillance</strong></td>
<td>CT, MRI, or US at 3 and 6 months, then q6m until year 3, then annually</td>
<td>US, MRI, or CT q6m for 2 years, then annually</td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td>Tumor diameter &gt;4cm or doubling of tumor volume in &lt;12 months</td>
<td>Tumor diameter &gt;4cm Growth rate &gt;0.5cm/year Symptoms(hematuria, flank pain) From SRM, patient preference</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>178</td>
<td>339</td>
</tr>
<tr>
<td><strong>Follow-up period</strong></td>
<td>28 (mean)</td>
<td>36 (median)</td>
</tr>
<tr>
<td><strong>Tumor growth rate</strong></td>
<td>0.13 cm/year</td>
<td>0.11 cm/year</td>
</tr>
<tr>
<td><strong>Local Progression Rate</strong></td>
<td>12%</td>
<td>16%</td>
</tr>
<tr>
<td><strong>Rate of Metastatic Disease</strong></td>
<td>1.1%</td>
<td>0%</td>
</tr>
</tbody>
</table>
78 yo male CAD, Afib, CHF, CKD (IV) Incidental 5cm Left Renal Mass. Left RMB 2017 Furhman Grade 1 RCC

Under Active Surveillance 3 yr  no progression

MRI 2016

CT Scan 2019
Available Thermal Ablation Techniques

- RFA
- Cryo ablation
- Microwave
Thermal Ablation Left Upper Pole Renal Mass
Practice Patterns Update: SEER Registry

- 2004-2007
- RFA and CA entered in 2004
- 1, 2 yr CSS
  - TA 99.4% and 98.0%
  - PN 99.6% and 99.3%
  - RN 98.9% and 98.0%
- Over 50% of T1a underwent RN

52 yo female with right flank pain/ hematuria  CT without contrast
Follow up CT reduction size
Renal MRI
New lesion lower pole cw lobar nephronia Rx antibiotics
Diagnostic Accuracy of Renal Mass Biopsy

- Sensitivity: 97.5% (for treatment)
- Specificity: 96.2% (for surveillance)
- Positive Predictive Value: 99.8%
- Negative Predictive Value: 68.5%
- Non-diagnostic rate: 14%
- Histology: 90% concordance
- Heterogeneity of Small Renal Mass
Safety of Renal Mass Biospy

- Major Complication rate – 1%

- Seeding risk - 0.01%
  - Only 1 seeding report in the last 20 years
57 yo underwent recent cardiac stenting and noted incidental solid left renal mass
Confirmed renal MRI decreased enhancement papillary v chromophobe/oncocytic lesion recommend RMB = chromophobe, low grade and ablated
Healthy 72 yo male referred for bilateral renal masses
RMB revealed oncocytoma pursuing AS
Active surveillance is an option for the initial management of patients with clinical stage T1 renal lesions, for example:

- Patient with small renal masses <4cm given the high rate of benign tumor and low metastatic potential for these masses
- Patient with clinical stage T1 masses and significant competing risks of death or morbidity from intervention
- Active surveillance entails serial abdominal imaging with timely intervention should the mass demonstrate growth (e.g., tumor size, growth rate, infiltrative pattern) indicative of increasing metastatic potential
- Active surveillance should include periodic metastatic survey including blood work and chest imaging, particularly if the mass demonstrates growth
Individualized Patient Approach for clinical T1a (<4cm) renal mass

Quality Cross Sectional Imaging (CT or MRI)
Consider RMB

Assess age, comorbidity, tumor size, location, invasiveness
Anticipate life expectancy (eGFR, Proteinuria, Vascular Calcification)

Benign 20%
Active Surveillance

Indolent Cancer (55%-60%)
Active Surveillance (elderly, comorbid)
Thermal Ablation (evidence for progression)
Partial Nephrectomy (young, healthy)

Potentially Aggressive Cancer (20%-25%)
Surgical Excision
Partial Nephrectomy preferred
Background

- greater than 50% of adults greater than 50 years old have renal cysts, the vast majority being benign simple cysts.

- cystic renal lesions are increasingly being detected with utilization of cross-sectional imaging

- the Bosniak Criteria for determining surgical cysts versus benign has been used for greater than 20 years in categorizing renal mass lesions

- 4-7% of renal cell carcinoma have cystic component
Bosniak III & IV  High Risk Cystic Lesions

- 67-100% are malignant

- the risk of malignancy is not clear-cut for Bosniak III and unnecessary surgery is a potential in up to 60% of lesions
Which one is malignant?
MEST
ccRCC
Benign Cystic
Epithelioid AML
59 year old male
Calcified cystic mass
Right kidney
Surveillance 5 yrs
Stable D/C from clinic
Managed by surveillance 11 years

Presents with thoracic inlet mass
Mediastinum mets
Isodense mass
Cystic renal lesion
Mini Flank Incision
Cyst Enucleation is safe as it is surrounded by fibrous wall
FG2 Cystic ccRCC
## Comparison of clinical and pathologic features by cystic architecture for 2431 patients with clear cell RCC

<table>
<thead>
<tr>
<th>Feature</th>
<th>Cystic architecture</th>
<th></th>
<th></th>
<th>P-Value</th>
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<tbody>
<tr>
<td>2002 TNM stage groupings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Yes n 85 n (%)</td>
<td>No n 2346</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>76 (89.4)</td>
<td>1078 (46.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>8 (9.4)</td>
<td>363 (15.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>1 (1.2)</td>
<td>510 (21.7)</td>
<td></td>
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<tr>
<td>IV</td>
<td>0 (0.0)</td>
<td>395 (16.8)</td>
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<tr>
<td>Nuclear grade</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>1</td>
<td>Yes n 85 n (%)</td>
<td>No n 2346</td>
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<td>&lt;0.001</td>
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<tr>
<td></td>
<td>35 (41.2)</td>
<td>227 (9.7)</td>
<td></td>
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</tr>
<tr>
<td>2</td>
<td>49 (57.7)</td>
<td>1007 (42.9)</td>
<td></td>
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</tr>
<tr>
<td>3</td>
<td>1 (1.2)</td>
<td>908 (38.7)</td>
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<tr>
<td>4</td>
<td>0 (0.0)</td>
<td>204 (8.7)</td>
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<tr>
<td>Coagulative tumor necrosis</td>
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<tr>
<td>No</td>
<td>Yes n 85 n (%)</td>
<td>No n 2346</td>
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<td>&lt;0.001</td>
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<tr>
<td></td>
<td>83 (97.7)</td>
<td>1650 (70.3)</td>
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<tr>
<td>Yes</td>
<td>2 (2.4)</td>
<td>696 (29.7)</td>
<td></td>
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<tr>
<td>Sarcomatoid differentiation</td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>Yes n 85 n (%)</td>
<td>No n 2346</td>
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<td>0.021</td>
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<td></td>
<td>85 (100.0)</td>
<td>2222 (94.7)</td>
<td></td>
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<tr>
<td>Yes</td>
<td>0 (0.0)</td>
<td>124 (5.3)</td>
<td></td>
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</table>
Cancer-Specific Survival

![Graph showing cancer-specific survival rates over years from surgery to last follow-up. The graph compares cystic and non-cystic conditions.](image-url)
Conclusion

- incidence of complex (HR) cystic renal lesions increasing with increasing cross-sectional imaging

- RMB is accurate and prevents unnecessary surgery or changes management in elderly/comorbidity

- the rate of malignancy for Bosniak III/IV is high but surgical outcomes are excellent. Bosniak classification does not predict aggressiveness (FG) or stage (ie no perinephric fat invasion) and cures for Bosniak IV lesions are high as compared to solid clear cell renal cell cancer; favor NSS when possible

- obey oncologic surgical principles (laparoscopic unroofing not acceptable)

- consider extending surveillance beyond midterm (5yrs) for high risk Bosniak lesions, especially young and healthy