Individualizing Management of the Small Renal Mass with Percutaneous Renal Mass Biopsy

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Renal Mass Biopsy

• **Reasons to Forego Biopsy**
  - Don’t need it - we know it is cancer
  - Don’t need it - radiographic characteristics (CT, MRI, molecular imaging) are accurate to determine risk
  - Biopsy is unsafe
  - Biopsy is not accurate
Renal Mass Biopsy

• “We Know it is Cancer”
  – Wrong! For masses < 4 cm…
  – ~ 25% are benign
    • Frank et al, J Urol 170:2217, 2003
  – ~ 20% of malignancies are “aggressive”
    • Thompson et al, J Urol 181:2033, 2009
  – > 95% 5-year CSS * if malignant
    • Nguyen & Gill, J Urol 181:1020, 2009
  – ~ 1% 3-year risk of metastases
    • Thompson et al, J Urol 182:41, 2009
Renal Mass Biopsy

- “Radiographic Characteristics are Accurate” Getting better, but not enough…
  - Yes: Papillary v clear-cell
    - Sun et al, Radiology 250: 793, 2009
  - Yes: Oncocytoma v clear-cell
  - No: Papillary type 1 v type 2
    - Egbert et al, AJR 201:347, 2013
  - Cannot differentiate clear-cell grades
Renal Mass Biopsy

• “Biopsy is Unsafe”
  – Wrong!

  – Seeding risk estimated < 0.01%

  – Only 1 seeding report in last 20 years
    • Mullins & Rodriguez, J Can Urol Assoc 7:E176, 2013

  – Major complications < 1%
    • Lane et al, J Urol 179:20, 2008
Renal Mass Biopsy

• “Biopsy is not Accurate”
  – Wrong! Wrong! Wrong!
  – For determining malignancy
    • ~90% sensitivity, ~99% specificity
    • < 1% false -, < 1% false +, ~ 10% indeter
      – Lane et al, J Urol 179:20, 2008
  – For determining high v low risk cancer
    • 96% sensitivity, 100% specificity *
Renal Mass Biopsy to Risk Stratify

Accuracy of Determining Small Renal Mass Management with Risk Stratified Biopsies: Confirmation by Final Pathology

Schuyler J. Halverson,* Lakshmi P. Kunju,* Ritu Bhalla,* Adam J. Gadzinski,* Megan Alderman,* David C. Miller,† Jeffrey S. Montgomery,* Alon Z. Weizer,* Angela Wu,* Khaled S. Hafez* and J. Stuart Wolf, Jr.*,†

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Renal Mass Biopsy to Risk Stratify

- **Histologic Risk Groups**
  - **Benign** AML, Oncocytoma
  - **Favorable** Chromophobe, Gr 1 Papillary I
  - **Intermediate** Gr 1 / 2 Clear cell, Gr 2 Papillary I, Oncocytic or Papillary NOS
  - **Unfavorable** Gr 3 / 4 Clear cell, Papillary II, urothelial, unclassified, sarcomatoid, etc
Renal Mass Biopsy to Risk Stratify

- Favorable
- Intermediate
- Unfavorable

- < 2 cm
- 2 - 4 cm

AS
Treat
Renal Mass Biopsy to Risk Stratify

• Is Biopsy Reliable Enough?
  – 151 patients with core-biopsy and excised small renal mass
    • < 2 cm, n = 37; 2 – 4 cm, n = 114
  – Compare pathology on renal mass biopsy with final pathology
  – Determine management group as directed by biopsy
  – Confirm management group using final pathology
Renal Mass Biopsy to Risk Stratify

- Biopsy Results
  - Indeterminate - 14
  - Benign – 4
    (n = 18, excluded from analysis)
  - Favorable - 5
  - Intermediate - 110
  - Unfavorable – 18
    (n = 133, included in analysis)
Renal Mass Biopsy to Risk Stratify

- **Revised Risk Grouping**: ≤ 4 cm (n=133)

<table>
<thead>
<tr>
<th>Biopsy Pathology</th>
<th>Final Surgical Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surveillance</td>
</tr>
<tr>
<td>Surveillance</td>
<td>25</td>
</tr>
<tr>
<td>Treatment</td>
<td>0</td>
</tr>
</tbody>
</table>

Incorrect assignment in 4 / 133 (3.0%)
Kappa = 0.91
Renal Mass Biopsy to Risk Stratify

• **Accuracy of Biopsy Risk Assignment**
  – **Sensitivity (for Treatment)**
    • 104 / 108 (96%)
  – **Specificity (for Surveillance)**
    • 25 / 25 (100%)
  – **Positive Predictive Value (Treatment)**
    • 104 / 104 (100%)
  – **Negative Predictive Value (Surveillance)**
    • 25 / 29 (86%)
Renal Mass Biopsy to Risk Stratify

Evaluation of Renal Mass Biopsy Risk Stratification Algorithm for Robotic Partial Nephrectomy—Could a Biopsy Have Guided Management?

Haider Rahbar, Sam Bhayani, Michael Stifelman,* Jihad Kaouk, Mohamad Allaf, Susan Marshall, Homayoun Zargar, Mark W. Ball, Jeffrey Larson and Craig Rogers†,‡

From the Vattikuti Urology Institute, Henry Ford Hospital, Detroit, Michigan (HR, CR), Division of Urologic Surgery, Washington University School of Medicine, Saint Louis, Missouri (SB, JL), Department of Urology, New York University Langone Medical Center, New York, New York (MS, SM), The Glickman Urological Institute, Cleveland Clinic, Cleveland, Ohio (JK, HZ), and the James Buchanan Brady Urological Institute, The Johns Hopkins Medical Institutions, Baltimore, Maryland (MA, MWB)

http://dx.doi.org/10.1016/j.juro.2014.06.028
Vol. 192, 1337-1342, November 2014
Printed in U.S.A.
Materials and Methods: A simplified algorithm of biopsy directed small renal mass management previously reported using risk stratified biopsies was applied to 1,175 robotic partial nephrectomy cases from 5 academic centers. A theoretical assumption was made of perfect biopsies that were feasible for all patients and had 100% concordance to final pathology. Pathology risk groups were benign.

Conclusions: The theoretical application of a biopsy driven, risk stratified small renal mass management algorithm to a large robotic partial nephrectomy database suggests that about half of the patients might have avoided surgery. Despite the obvious limitations of a theoretical assumption of all
Renal Mass Biopsy to Risk Stratify

Comparison with Size Criteria

- Is biopsy any better than using size alone?
- Surveillance if < 2 cm (n = 31)?
- Treatment if 2 – 4 cm (n = 102)?

→ 9 of 31 on Surveillance would have unfavorable pathology (4 using biopsy)
→ 3 of 102 Treated would have favorable pathology (0 using biopsy)
Renal Mass Biopsy to Risk Stratify

Comparison with R.E.N.A.L. Nephrometry Score

- Kutikov et al, Eur Urol 2011, 60:241
- Nomograms predicting
  - benign v malignant (AUC = 0.76)
  - favorable v unfavorable (= 0.73)
- University of Michigan validation: 281 SRMs with nephrometry score, biopsy and final pathology from excision
Renal Mass Biopsy to Risk Stratify

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  - **Unfavorable** Gr 3 / 4 Clear cell, Papillary II, Urothelial, Unclassified, Sarcomatoid, etc
Renal Mass Biopsy to Risk Stratify

- **Collapsed Histologic Risk Groups**
  - **Favorable**, n = 157  
    - AML, Oncocytoma, Chromophobe, **Gr 1 / 2** Papillary I, Gr 1 / 2 Clear cell, Oncocytic or Papillary NOS
  - **Unfavorable**, n = 124  
    - **Gr 3 / 4** Clear cell, Papillary II, Urothelial, Unclassified, Sarcomatoid, etc
Nephrometry Score Nomogram Predicts Favorable vs Unfavorable Pathology

AUC = 0.64
Final Pathology
Favorable, 122 Unfavorable, 170

Pathological grade

p<0.01, gamma=0.97

Biopsy grade

Low-risk
High-risk

154
91
35
1
Renal Mass Biopsy to Risk Stratify

• Concern about those “False Negatives”
  – Patients incorrectly assigned to surveillance, who in fact harbor worse pathology than suggested by biopsy and should get treated
  – 14% of those assigned to surveillance
  – (17% in updated series)
Renal Mass Biopsy to Risk Stratify

• Can we Salvage Patients Incorrectly Assigned to Surveillance?
  – Subset of University of Michigan SRM database
  – 495 treated SRMs from 2009 to 2015
  – 376 early intervention, 119 delayed intervention
  – Impact on Adverse pathology
    • Gr 3 / 4 Clear cell, Papillary II, Urothelial, Unclassified, Sarcomatoid, etc.
Renal Mass Biopsy to Risk Stratify

• Can we Salvage Patients Incorrectly Assigned to Surveillance?
  – Multivariable logistic regression comparing early and delayed intervention groups
  – Rates of partial v radical nephrectomy similar (p=0.6)
  – Delayed intervention not associated with adverse pathology (p=0.5)
Renal Mass Biopsy to Risk Stratify

• Can we Salvage Patients Incorrectly Assigned to Surveillance?
  – Multivariable logistic regression comparing early and delayed intervention groups
  – In patients who underwent surveillance, faster growth rates associated with adverse pathology

• 10% increase in odds of adverse pathology for each 1 mm/yr change in growth rate
Renal Mass Biopsy to Risk Stratify

• Can we Salvage Patients Incorrectly Assigned to Surveillance?

  – Answer … Yes, we can

  – This mitigates some of the concern about “false negatives” of biopsy
Renal Mass Biopsy to Risk Stratify

• **Summary:** Risk Stratification by Biopsy
  – Biopsy does not perfectly identify histologic type and grade
  – Biopsy does not need to perfectly identify histologic type and grade
  – Absolute accuracy not necessary when biopsy is paired with a risk-stratified management algorithm
Renal Mass Biopsy to Risk Stratify

• Reasons to Forego Biopsy
  – Don’t need it - we know it is cancer
  – Don’t need it - radiographic characteristics (CT, MRI, “advanced MRI”) are accurate to determine risk
  – Biopsy is unsafe
  – Biopsy is not accurate
Renal Mass Biopsy to Risk Stratify

• Reasons to Perform Biopsy - #1

  1) Avoid intervention in cases of benign or non-aggressive tumor

• Routine for all SRMs?
  – Young healthy patients unlikely to accept surveillance
  – Unlikely to treat older patients with major comorbidities

• Who are the best candidates?
Renal Mass Biopsy to Risk Stratify

• Reasons to Perform Biopsy - #2
  2) May change treatment plan if aggressive malignancy is found
    • Radical versus partial in some situations
    • Papillary Type 2 – risk of multifocality
    • Grade 4 clear cell – concern about margins
Renal Mass Biopsy to Risk Stratify

- **Biopsy Determines Management**
  - Subset of University of Michigan SRM database
  - 854 SRMs from 2007 to 2015
  - 366 interpretable biopsy, 488 no biopsy
  - Impact on initial management
    - 393 active surveillance
    - 49 ablative therapy
    - 275 partial nephrectomy
    - 37 radical nephrectomy
Renal Mass Biopsy to Risk Stratify

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  – **Benign** AML, Oncocytoma
  
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Renal Mass Biopsy to Risk Stratify

- **Collapsed Histologic Risk Groups**
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Renal Mass Biopsy to Risk Stratify

• Biopsy Determines Management
  – Multivariable logistic analyses on initial management decision
    • Intervention vs Active Surveillance
    • Specific type of intervention
  – Factors
    • Age, gender, race, BMI, initial tumor size, and biopsy result
Management in All Patients

- Benign: Active surveillance
- Any malignancy: Treatment
Management in All Patients

Any malignancy on biopsy associated with increased rate of initial treatment (p<0.001)
Management in Patients 55 – 75 years old

- **Benign**
  - Active surveillance: 85%
  - Ablative therapy: 15%

- **Favorable/Intermediate**
  - Partial nephrectomy: 30%
  - Ablative therapy: 20%
  - Radical nephrectomy: 5%

- **Unfavorable**
  - Partial nephrectomy: 45%
  - Ablative therapy: 20%
  - Radical nephrectomy: 5%
Worse pathology on biopsy associated with increased rate of radical nephrectomy in patient aged 55 – 75 years (p=0.002)
Management in Patients 55 – 75 years old

Clinical utility of biopsy greatest in patients 55 to 75 years-of-age with tumors 2 - 4 cm in size
Partial Nephrectomy at University of Michigan for SRM: Rate of Benign Tumors by Year

- 2009
- 2010
- 2011
- 2012
- 2013
- 2014
- 2015
- ALL

Benign
Malignant
Renal Mass Biopsy to Risk Stratify

• **Reasons to Perform Biopsy - #3**

  3) ? More assurance on active surveillance
  • ? improve patient acceptance
  • ? increase urologist confidence

• Still follow benign lesions, but different endpoints
  – Angiomyolipoma
  – Oncocytoma
Renal Mass Biopsy to Risk Stratify

• Biopsy and Active Surveillance
  – Subset of University of Michigan SRM database
  – 118 SRMs initiating active surveillance from 2009 to 2011, > 5 months radiologic follow-up (unless limited by unexpected death or intervention)
  – Median radiologic follow-up of 29.5 months
  – Multivariable analysis on delayed intervention
Renal Mass Biopsy to Risk Stratify

- **Biopsy and Active Surveillance**
  - Increased risk of delayed intervention
    - Size > 2 cm (HR 3.65, p=0.015)
    - Growth rate, mm/yr (HR 1.26, p<0.001)
    - Not biopsy (p=0.29)
Renal Mass Biopsy to Risk Stratify

• Biopsy and Active Surveillance
  – So even at University of Michigan, don’t use biopsy to full potential

- Select patients for surveillance
- Select patients for treatment
- Select type of treatment
- Maintain patients on surveillance
Renal Mass Biopsy to Risk Stratify

• But, biopsy only going to get better…
  – “Prognostic Utility of a Multi-gene Signature (The Cell Cycle Proliferation Score) in Patients with Renal Cell Carcinoma after Radical Nephrectomy”
  – University of Michigan, Massachusetts General Hospital and Myriad Genetics
  – AUA Abstract 2016, MP78-20
Renal Mass Biopsy to Risk Stratify

- CCP Score and Resected RCC
  - CCP score
    - RNA-base expression of 46-gene-panel, from paraffin-embedded tissue, validated prognostic marker of cancer specific mortality (CSM) from prostate cancer
  - Karakiewicz nomogram
    - post-resection risk stratification
Multi-Institutional Validation of a New Renal Cancer–Specific Survival Nomogram


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**T-Stage**
- T1a
- T1b
- T2
- T3
- T4

**Nodes Involved by Cancer?**
- No
- Yes

**Metastases Present?**
- No
- Yes

**Tumor Size (cm):** 8.2

**Fuhrman Grade**
- I
- II
- III
- IV

**Symptoms?**
- Asymptomatic
- Local
- Systemic

---

**Results**
My chances of surviving my kidney cancer 1, 2, 5, 10 years after surgery are:

<table>
<thead>
<tr>
<th>Year</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 5</th>
<th>Year 10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95.6%</td>
<td>91.3%</td>
<td>85.8%</td>
<td>77%</td>
</tr>
</tbody>
</table>

**RCC-Specific Survival**

Estimated Survival (%) vs. Years post-surgery
Renal Mass Biopsy to Risk Stratify

- **CCP Score and Resected RCC**
  - CCP score cut-offs, and optimal combination with Karakiewicz nomogram, derived after radical nephrectomy in 303 patients treated at MGH from 2000 to 2007
  - Validated using 345 patients treated at U-M from 2000 to 2009
  - Similar demographics, rate of informative CCP, etc.
CCP Score distributed across stage (validation cohort)
CCP Score & CSM (validation cohort)
## Renal Mass Biopsy to Risk Stratify

### CSM Multivariable analysis (validation)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCP (per 1.0 increase)</td>
<td>2.20 (1.25 – 3.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tumor size</td>
<td>1.16 (0.96 – 1.39)</td>
<td>0.12</td>
</tr>
<tr>
<td>T stage (referent: T1)</td>
<td></td>
<td>0.56</td>
</tr>
<tr>
<td>T2</td>
<td>3.69 (0.24 – 56.32)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>2.92 (0.30 – 28.46)</td>
<td></td>
</tr>
<tr>
<td>Fuhrman grade (High vs Low)</td>
<td>1.67 (0.34 – 8.16)</td>
<td>0.51</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>9.82 (2.75 – 35.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptoms (referent: none)</td>
<td></td>
<td>0.024</td>
</tr>
<tr>
<td>Local</td>
<td>3.09 (0.17 – 56.72)</td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>9.50 (1.12 – 80.78)</td>
<td></td>
</tr>
<tr>
<td>Positive surgical margins</td>
<td>0.83 (0.23 – 3.04)</td>
<td>0.78</td>
</tr>
</tbody>
</table>
Renal Mass Biopsy to Risk Stratify

**CSM Combined Score Validation**

**CCP + Karakiewicz Nomogram**

\[
\text{Combined Score} = 1.09 \times \text{CCP} + 0.023 \times \text{Karakiewicz}
\]

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th></th>
<th></th>
<th>Bivariate</th>
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<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-value</td>
<td>HR (95% CI)</td>
<td>P-value</td>
<td></td>
<td></td>
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<tr>
<td>Combined score</td>
<td>9.40 (3.94 – 22.44)</td>
<td>&lt;0.001</td>
<td>3.78 (1.10 – 12.93)</td>
<td>0.027</td>
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<tr>
<td>Karakiewicz score</td>
<td>19.79 (5.13 – 76.31)</td>
<td>&lt;0.001</td>
<td>6 (0.98 – 36.63)</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5-year CSM Risk: Comb. Score vs. Nomogram
Combined Score Risk Group

Cancer-specific survival (%)

Log rank P-value: $1.4 \times 10^{-3}$
Renal Mass Biopsy to Risk Stratify

- CCP Score and RCC
  - CCP score powerful predictor of CSM following radical nephrectomy
    - Most effective at identifying low risk group (100% CSM)
  - Next step: Obtain CCP from pre-operative biopsies
    - Correlate with CCP score from final pathology
    - Correlate with CSM
Renal Mass Biopsy to Risk Stratify

• Conclusion
  – Reasons to avoid biopsy are weak
  – Reasons to perform biopsy are strong
• University of Michigan SRM Team
  – Urology
    • Ganesh Palapattu
    • Alon Weizer
    • Jeff Montgomery
    • Todd Morgan
    • David Miller
    • Khaled Hafez
    • Sapan Ambani
    • Scott Hawken
    • Naveen Krishnan
  – Radiology & Pathology
    • Takahiro Osawa
    • Adam Gadzinski
    • Sky Halverson
    • Bruce Jacobs
    • Ray Tan
    • Elaine Caoili
    • Jim Ellis
    • Lakshmi Kunju