Renal Mass Biopsy: Needed Now More than Ever

Stuart G. Silverman, MD, FACR
Professor of Radiology
Harvard Medical School
Director, Abdominal Imaging and Intervention
Brigham and Women’s Hospital
Boston, MA

SCBTMR 2017
Renal Mass Biopsy: Needed Now More than Ever

Stuart G. Silverman, MD, FACR

No relevant financial Disclosures
Learning Objective

With this lecture the participant will be able to:

Diagnose renal masses by implementing percutaneous biopsy for patients with eight distinct clinical scenarios.
Learning Objective

With this lecture the participant will be able to:

Cite the historical rationale and evidence-based data used to derive the clinical indications for biopsying renal masses in clinical practice.
Learning Objective

With this lecture the participant will be able to:
Assess emerging data for using percutaneous biopsy to select a medically appropriate, ‘precision medicine’ approach to renal masses.
Renal Masses in the Adult Patient: The Role of Percutaneous Biopsy

Although percutaneous renal mass biopsy with cross-sectional imaging guidance has long been considered to be safe and accurate, there have been recent advances in imaging, interventional, and cytologic techniques that have increased the role of percutaneous biopsy in the diagnosis of renal masses. Today, biopsy always fundamental and it prompt the clinician to consider percutaneous biopsy.
Renal Mass Biopsy

Historical Indications

- Distinguish RCC from metastasis in patient with extrarenal malignancy
- Confirm unresectable suspected RCC
- Dx suspicious mass in poor surgical candidate
- Dx suspected pyelonephritis

Silverman SG et al Radiology 2006
Renal Mass Biopsy

Recently Established Indications

- Small, hyperdense, enhancing renal masses
- Renal masses referred for ablation
- Indeterminate cystic renal mass (Bosniak Category III), co-morbidity
- Multiple solid renal masses

Silverman SG et al Radiology 2006
Ever Increasing Role of Biopsy...

Solid renal masses thought to be RCC
Fat poor AML described
Immunocytochemistry diagnosis of AML, Oncocytoma
Benign tumors prevalent at surgery

Importance of pre-ablation tissue diagnosis
Biopsy diagnosis of Bosniak III cysts co-morbidity
Radiology suggests expanded role

Nephron loss decreases survival
Biopsy added to AUA guideline
Active surveillance safe

Biopsy suggested for all small masses to dictate care path
New call for biopsying multiple sites in each mass
Hyperdense + Enhancing

- RCC – typically papillary, or clear cell subtype that has bled
- Fat poor angiomyolipoma
- Oncocytoma
- Lymphoma
- Metanephric adenoma (rare)
- Leiomyoma (rare)
- Metastases (rare)

Fat poor angiomyolipoma

- Retrospective review of 175 resected lesions suspicious for RCC by imaging.
- All 6 AMLs were uniformly hyperdense, enhanced, and were T2-hypointense.
- Of 100 RCCs reviewed: only 2% were uniformly hyperdense and enhancing.

AML w/ minimal fat

Lipid poor AML

Jinzaki et al, Radiology 1997
Solid Masses may be benign

- Of 2,770 nephrectomies /NSS for “solid” renal masses, 1977-2000
  - 12.8% benign
  - Masses < 3 cm  25% benign
  - Masses < 2 cm  30% benign
  - Masses < 1 cm  44% benign

Frank et al J Urol 2003
# Solid Masses may be benign

<table>
<thead>
<tr>
<th>Benign Tumors resected</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oncocytoma</strong></td>
<td>73</td>
</tr>
<tr>
<td><strong>Angiomyolipoma</strong></td>
<td>18</td>
</tr>
<tr>
<td><strong>Papillary adenoma</strong></td>
<td>4</td>
</tr>
<tr>
<td><strong>Not otherwise specified</strong></td>
<td>4</td>
</tr>
<tr>
<td><strong>Metanephric adenoma</strong></td>
<td>1</td>
</tr>
</tbody>
</table>

*Frank et al J Urol 2003*
Hyperdense + Enhancing

- RCC – typically papillary, or clear cell subtype that has bled

- Fat poor angiomyolipoma

- Oncocytoma
- Lymphoma
- Metanephric adenoma (rare)
- Leiomyoma (rare)
- Metastases (rare)

Oncocytic Renal Neoplasms

- Oncocytoma
- Chromophobe RCC
- Granular RCC
- Eosinophilic variant of papillary RCC
- Angiomyolipoma

Oncocytic cells found in all oncocytic neoplasms
# Immunocytochemistry

<table>
<thead>
<tr>
<th></th>
<th>Oncocytoma</th>
<th>Oncocytic RCC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AE1/AE3</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>EMA</strong></td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>RCC</strong></td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Colloidal Fe</strong></td>
<td>-</td>
<td>+**</td>
</tr>
<tr>
<td><strong>S100A1</strong></td>
<td>+</td>
<td>- *</td>
</tr>
</tbody>
</table>

*refers to Chromophobe RCC only

Liu and Fanning Cancer Cytopath 2001
Li et al Histopathology 2007
Renal Oncocytoma

- Small oncocytomas can be diagnosed with biopsy using fine or large needles.
- Diagnosis is based on oncocytic cells and an immunocytochemical ‘signature’.
- Follow patients as oncocytomas rarely contain foci of RCC (almost always in large masses).

Liu Cancer 2001
Donat et al J Urol 2013
Fundamental facts...

• Unlike surgery where the mass may be examined, ablation is an in situ treatment and there is no opportunity for full pathology examination.

• Tissue diagnosis prior to ablation is entirely dependent on biopsy.
Masses referred for ablation

- Of 27 pts referred for ablation of suspected RCC, **10** had masses which were proven *not* to be RCC.
- Of these **10**, 3 were diagnosed as benign by biopsy, 3 by imaging, and 4 by a combination of both biopsy and imaging.
- Masses should be bxed pre-ablation.

Tuncali et al AJR 2004
Solid + Cystic Masses may be benign

- Of 815 nephrectomies /NSS for solid and cystic renal masses, 2000-2005
- 16.4% benign
- Masses 1- 2 cm  25% benign
- Masses 2- 3 cm  15% benign
- Masses 3- 4 cm  18% benign
- Masses 6- 7 cm  17% benign

Snyder et al J Urol 2006
Bosniak Category III Mass

- Biopsy and imaging follow-up may save patients with Category III cystic masses from having surgery. (Harisinghani et al AJR 2003)

- Benign results may lack specificity (eg, renal epithelium, fibrous tissue, atypical cells)

- No known time interval that proves benign results

- Unless a specific benign entity is rendered, benign results are not definitive alone.

- Benign results may be helpful as additional data.
Renal Mass Biopsy

Biopsy prevents benign masses from being treated unnecessarily.
Supportive Literature since ‘06

- **Lebret et al J Urol 2007** - Benign lesions diagnosed in 24 biopsies (20.1%), including oncocytoma (13), AML (5) and infection (5).
- **Veltri et al Eur Rad 2011** - FNAB correctly diagnosed 76.2% masses, Core biopsy, 93.2%. No major complications.
- **Leveridge et al Eur Urol 2011** - Biopsy diagnostic in 81%.
- **Mally et al Can J Urol 2012** Only 10%-15% of small renal mass biopsies were indeterminate.
- **Menoque et al BJU Intl 2012** - Biopsy was 100% accurate in distinguishing benign from malignant lesions.
- **Shannon et al J Urol 2012** - Of patients undergoing surgery, biopsy was 100% accuracy for distinguishing malignant from benign lesions. Complications in 2 pts (0.9%).
Nephron ‘loss’ is harmful

- Chronic kidney disease (CKD) is associated with increased cardiovascular and other cause mortality (Go et al, NEJM 2004).
- Survival after radical nephrectomy (RN) may be worse than partial nephrectomy (PN) (Tan et al, JAMA 2012)

Sun et al Eur Urol 2012 61 725-31
Van Poppel Eur Urol 2011;59:543-52
Tan JAMA 2012 307:1629-1635
Huang et al, Lancet Oncol 06
Nephron ‘loss’ is harmful

7138pts – 1925 PN, 5213 RN; At 8 yrs, PN had 15% increased survival.

Fig. 1. Kaplan-Meier estimate of all-cause survival among SEER-Medicare patients who underwent partial or radical nephrectomy for kidney cancers smaller than 4 cm in size. Copyright © 2012 American Medical Association. All rights reserved.

Tan JAMA 2012 307:1629-1635
Gore, GU ASCO 2013
CT or MRI; Percutaneous Biopsy as needed

T1a / Healthy
- Standard: PN
- Standard: RN
- Option: TA
- Option: AS

T1a / Surg risk
- Standard: PN
- Standard: RN
- Option: TA
- Option: AS

T1b / Healthy
- Standard: RN
- Option: TA
- Option: AS

T1b / Surg risk
- Standard: RN
- Recommend: PN
- Option: TA
- Recommend: AS

Biopsy now an accepted part of evaluation!

Modified from AUA 2009
Recent Data supporting AS

- **Prospective**, multi-institution, ‘DISSRM Registry; < 4cm
- Of 497 pts, 274 (55%) chose primary intervention (PI), 223 (45%) chose AS; 21 (9%) crossed over; median f/u 2.1 yrs
- AS patients: older, worse ECOG, co-morbidities (including CV disease), and had smaller tumors
- OS – overall survival vs. CSS – cancer specific survival
- At 2 yrs: AS-OS = 96%, PI-OS = 98%
- At 5 yrs: AS-OS = 75%, PI-OS = 92% (NOT significant)
- At 5 yrs: AS-CSS = 100%, PI-CSS = 99%
- Active surveillance was not inferior to primary intervention

Pierorazio et al Eur Urol 2015
Active surveillance is recommended in surgical risk patients with T1 masses.
Management flowchart...

Can biopsy be used to triage which patients should be treated or undergo surveillance?

Berland LL et al, JACR 2010
RCC Subtype and grade?

- Biopsy accuracy for histological tumor type and Fuhrman nuclear grade of 86% and 46%, respectively (Lebret et al J Urol 2007.)
- Histologic subtyping and grading of RCC was possible in 88.0% and 63.5% of cases, respectively (Leveridge et al Eur Urol 2011).
- Histologic subtyping reached 98% rate (Shannon et al J Urol 2012).

Grading difficult w/ Bx!
Benign Renal Mass Resections

- 19-study pooled estimate of the proportion of benign renal masses removed for suspected RCC in the US through July 1, 2014.

- Masses < 1 cm 40.4%
- Masses 1-2 cm 20.9%
- Masses 2-3 cm 19.6%
- Masses 3-4 cm 17.2%
- Masses 4-7 cm 9.2%
- Masses > 7 cm 6.4%

- Using SEER data, number in U.S. from 2000 to 2009 increased by 82%, from 3,098 to 5,624.

...are increasing nationwide!

Johnson DC et al. J Urol. 2015
Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

Marco Gerlinger, M.D., Andrew J. Rowan, B.Sc., Stuart Horsswell, M.Math., James Larkin, M.D., Ph.D.,
David Endesfelder, Dip.Math., Eva Gronroos, Ph.D., Pierre Martinez, Ph.D., Nicholas Matthews, B.Sc.,
Aengus Stewart, M.Sc., Patrick Tarpey, Ph.D., Ignacio Varela, Ph.D., Benjamin Phillimore, B.Sc., Sharmin Begum, M.Sc.,
Neil Q. McDonald, Ph.D., Adam Butler, B.Sc., David Jones, M.Sc., Keiran Raine, M.Sc., Calli Latimer, B.Sc.,
Claudio R. Santos, Ph.D., Mahrokh Nohadani, H.N.C., Aron C. Eklund, Ph.D., Bradley Spencer-Dene, Ph.D.,
Graham Clark, B.Sc., Lisa Pickering, M.D., Ph.D., Gordon Stamp, M.D., Martin Gore, M.D., Ph.D., Zoltan Szallasi, M.D.,
Julian Downward, Ph.D., P. Andrew Futreal, Ph.D., and Charles Swanton, M.D., Ph.D.

2017 Update...
Tumor Heterogeneity

A Biopsy Sites

B Regional Distribution of Mutations

C Phylogenetic Relationships of Tumor Regions

D Ploidy Profiling

2017 Update...
Tumor Heterogeneity

2017 Update…
Tumor Heterogeneity

2017 Update...
Tumor Heterogeneity

- Most T1a masses demonstrated nuclear grade heterogeneity, particularly in high grade tumors (Ball et al. J Urol 2015)
- Multi-quadrant (4 sites) technique to biopsy cT2 RCC (median 10 cm) identified more masses w/ sarcomatoid features c/w standard biopsy technique (13 of 15 (86.7%) vs. 2 of 8 (25.0%) (p=0.0062). (Abel et al J Urol 2015)

2017 Update...
Role of Biopsy today...

- Imaging is the first step and can be used to diagnose most renal masses.
- Biopsy reduces unnecessary surgeries and ablations.
- Biopsy masses in patients with eight clinical scenarios, including those with small, hyperdense, enhancing masses.
Surveillance

Biopsy used to diagnose benign masses and select patients for active surveillance

Herts et al JACR (in press)
Future Role of Biopsy

- Biopsy may eventually be used to diagnose many, if not all small, non-fat containing solid masses.
- Biopsy can help select patients for active surveillance.
- Sub-typing and particularly grading need improvement.
- Additional biomarkers needed, particularly those that predict clinical behavior.
Future Role of Biopsy

- Tumor heterogeneity once thought to be limited to large tumors shown to exist in small ones; these data prompt considering sampling masses in multiple locations.

- Data are not changing practice. Utilization rates low and benign renal mass resection rate is increasing.

- Role of biopsy needs to increase further…
Renal Mass Biopsy

- The current approach to the diagnosis of renal masses, centered largely on the burgeoning use of imaging and image-guided biopsy, is a success story on the ever increasing impact of radiology on an important area of oncology, and is an example of how radiology is contributing to 'precision medicine'.
Thank you