Renal Mass Biopsy
Is it Time to Reconsider the Paradigm?

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Objectives

1. Outline the traditional indications for renal mass biopsy
2. Describe the techniques used for renal biopsy
3. List the contraindications, complications and limitations of renal mass biopsy
4. Review the accuracy, reliability, and clinical impact of renal biopsy in current series
5. Introduce the role of renal biopsy in the era of molecular medicine
6. Describe the role of renal biopsy in image guided therapy
• Started in 2004 in Australia
• $29 Million globally
• Prostate Cancer Research Foundation of Canada
The incidence of renal masses is increasing by approximately 1% per year. Incidental small masses now make up the majority of renal tumours. 28-32% of SRM are benign in current series (Gill et al. 2007; Venkatesh et al. 2006). Gold standard is surgical excision.
Natural History of SRMs

- <2cm: 30% benign
- 2-4 cm: 21% benign
- >4cm: <10%
- <4cm: 13% are high grade RCC
- 234 renal masses observed for 3 yrs → 4 metastases

Frank et al. 2003; Lane et al. 2007; Chawla et al. 2006.

Natural History of SRMs

- Growth rate does NOT predict benign vs. malignant
- No growth does NOT confirm benign disease
- Growth rate is NOT predicted by initial size

Chawla et al 2006; Bosniak et al. 2005; Wehle et al. 2004
History of Renal Biopsy

- Campbell’s 7th Edition
  - “biopsy only in the case of indeterminant or solid renal lesion in a patient with a known nonrenal cancer does it behoove the urologist to seek a tissue diagnosis”

Established Indications

- Suspected extrarenal metastatic disease
- Metastatic disease not amenable to cytoreductive nephrectomy
- Renal abscess
- Suspected lymphoma
Established Indications

- **Suspected Extrarenal Metastatic Disease**
  - 8-13% of renal masses in some series

- **Clinical Clues**
  - Multifocal
  - Lung, Colon, Liver, Melanoma
  - Short duration between diagnosis of primary and renal involvement
  - Solitary enhancing renal mass still most likely to be a primary renal mass

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**Established Indications**

- **Sanchez-Ortiz et al. 2004.**
  - 100 consecutive patients with renal mass and history of extrarenal cancer
    - 26 underwent nephrectomy w/o biopsy
      - 26 primary renal tumours
    - 74 underwent biopsy
      - 19 metastases
      - 45 primary renal tumours
      - 10 non-diagnostic
### Probability of Metastases to the Kidney

<table>
<thead>
<tr>
<th>Renal Mass Enhancement</th>
<th>Nonrenal malignancy progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>32% (7/22)</td>
</tr>
<tr>
<td>No</td>
<td>0% (0/50)</td>
</tr>
</tbody>
</table>

10 patients with non diagnostic biopsies were excluded.

*From Sanchez-Ortiz et al. 2004.*

### Established Indications

- **Unresectable or Metastatic Disease**
  - Precise histological diagnosis can guide management
  - Tyrosine kinase inhibitors indicated in clear cell RCC
  - Role of neo-adjuvant TKI under investigation

- **Renal Abscess**
  - Patients with pain, fever and UTI
  - Aspiration and drainage tube can be placed concomitantly
Renal Abscess

Established Indications

- Lymphoma
  - Massive retroperitoneal lymphadenopathy
  - Distant lymphadenopathy or splenomegaly
  - Sanchez-Ortiz et al. 2004
    - 21 patients with lymphoma
    - 12/21 in remission
**Established Indications**

<table>
<thead>
<tr>
<th>Primary Malignancy</th>
<th>N</th>
<th>Metastases (%)</th>
<th>RCC (%)</th>
<th>AML (%)</th>
<th>Oncocytoma (%)</th>
<th>Non-diagnostic (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma</td>
<td>21</td>
<td>4 (19%)</td>
<td>10 (48)</td>
<td>3 (14.3)</td>
<td>4 (19)</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>13</td>
<td>1 (7.7)</td>
<td>10 (77)</td>
<td>2 (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>13</td>
<td>4 (10.8)</td>
<td>8 (62)</td>
<td>1 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>11</td>
<td>1 (9.1)</td>
<td>7 (54)</td>
<td>1 (9.1)</td>
<td>2 (18.2)</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>8</td>
<td></td>
<td>7 (88)</td>
<td>1 (13)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- All 12 patients in remission had primary renal tumour
- Clinical status of lymphoma most predictive of renal mass histology

*From Sanchez-Ortiz et al. 2004.*
Technique – Preparation

- Pre-biopsy blood work: CBC, INR, PTT
- Hold anticoagulants
  - ASA/Clopidogrel 7-10 days
  - Warfarin 5 days
  - Heparin infusion 4 hours
- Prone or lateral decubitus position
- Local anaesthetic or conscious sedation
Technique – Tru-Cut vs. Automatic Gun

- Tru-Cut yield of adequate tissue inferior to automatic gun (79 vs. 93%)
- Coaxial system
  - Decrease risk of seeding
  - 15% increase in success rate

Cozens et al. 1992; Appelbaum et al. 2002
**Fine Needle Aspiration**

- 22 gauge needle
- 15-20 moderately rapid reciprocations with negative pressure applied
- If core biopsy is also planned, perform FNA first
- Cytological detail often superior to core biopsy
- Cell blocks used for histoarchitectural, immunochemical, and FISH studies

**Technique-Post Biopsy Monitoring**

- Not standardized
- Monitor for 3-12 hours
- Check HCT at 6hrs
- 2nd look US post biopsy for hematoma with Doppler to identify active bleeding
Technical Considerations

- **Size of Core**
  - 18 gauge

- **Number of Cores**
  - 2-3 cores
  - 2 passes $\Rightarrow$ 97% success (Juul et al. 1985)
  - Avoid necrotic areas
  - Needle may fail to sample small lesions
  - If torn or less than 10mm, repeat biopsy at time

Technical Considerations

- **Approach**
  - Percutaneous access superior to laparoscopic or ex-vivo approach (Lane et al. 2008)
  - U/S, CT, MRI all have similar outcomes

- **Core vs. FNA Biopsy**
  - Core biopsy more likely to be diagnostic
  - Core biopsies provide histology rather than just cytology
  - FNA may have role in cystic masses and high grade, soft masses
Technical Considerations

♦ Cystic Masses
  ♦ Sampling error higher since tumour often focal within cyst
  ♦ Risk of cyst rupture and spread
  ♦ Increased yield with FNA biopsy
  ♦ Role of biopsy controversial
    • Use Bosniak classification system instead
    • 90% accuracy in Bosniak II/III cysts
    • 39% of patients with Bosniak III cyst can avoid surgery (Hasisignhani et al. 2003)
**Contraindications (Brenner)**

- **Absolute**
  - Uncorrected bleeding diathesis

- **Relative**
  - Solitary kidney
  - Morbid Obesity
  - Pyelonephritis
  - Perinephric abscess
  - Uncontrolled HTN
  - Hydronephrosis
  - PCKD
  - Severe Anemia
  - Pregnancy
  - Renal Masses
  - Renal artery aneurysms

**Complications**

- Death rate 0.031%
- Major complications 0.3%
- Minor Complications < 5%
- Time from biopsy to complication was <4hr in 52%, <8h in 79%, <12h in 100%

- Predictors
  - Number of cores, operator expertise
  - No apparent relationship to needle size
  - Not predicted by age, BP, Cr

*Smith 1991; Marwah et al. 1986; Volpe et al. 2007*
Complications

- Bleeding (Ralls et al. 1987; Lechevaillier et al. 2000)
  - Perinephric bleeding 44-90%
  - Gross hematuria 5-7%
  - Blood transfusion or admission rare (1%)

- Infection
- AVF
- Pneumothorax

Needle Track Seeding

- <0.01%
- Only 6 reported cases, last in 1992
- Most occur with poorly differentiated TCC
- Often associated with multiple biopsies and noncutting needles
"The Rockstar"  "The After Eight"  "The Trucker"

Limitations of Renal Biopsy

♦ Definitions

♦ Biopsy Failure: inability to obtain sufficient tissue

♦ Indeterminate Biopsy: unable to make definitive diagnosis with available tissue

♦ Inaccurate Biopsy: false-negative or false-positive based on final pathology
Limitations of Renal Biopsy

- Initial Biopsy Series (pre-2001)
  - Positive predictive value of 96%
  - Negative predictive value of 82%
  - Sensitivity 92% (70-100)
  - Specificity 90% (60-100)
    - Better than imaging (sens 60-90%, spec 5-50%)

*Lane et al. 2008*

Limitations of Renal Biopsy

- False negative rate pre-2001 0-21%
  - Actual misinterpretation uncommon
  - Most of false biopsies showed necrotic tissue, blood, normal kidney

- Reanalysis of pre-2001 series (Lane et al. 2008)
  - N=2474
  - Technical failure: 9%
  - Indeterminate 5.5%
  - FN 4.4%, FP 1.2%
  - Accuracy rate 89%
Non-diagnostic Specimen

- 5-10% of percutaneous biopsies

**Table 3. Multiple logistic regression analysis of possible diagnostic biopsy clinical predictors**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size*</td>
<td>6.0 (1.1–32.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Biopsy core length</td>
<td>3.7 (0.9–14.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>Tumor type (solid vs cystic)</td>
<td>5.9 (1.04–34.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Image guidance* (US vs CT or CT + US)</td>
<td>2.6 (0.7–9.6)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

* Square root transformation was used to approximate normality.

Volpe et al. 2007

So, why are more renal mass biopsies being performed?
Criteria for Proceeding with Biopsy

- Specimens must be reliable
- Accuracy must be high
- Ascertainment of a tissue diagnosis will change clinical management

Reliability

- Lane et al. 2008
  - 2474 renal mass biopsies
  - Pre-2001
    - Technical Failure 9%
    - Indeterminate 6%
  - Post-2001
    - Technical failure 5%
    - Indeterminate 4%
**Accuracy**

- Greater than 95%
- Sensitivity 70-100%
- Specificity 100%
- For patients who have sufficient tissue and diagnosis is possible, results are robust

*Lane et al. 2008*

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**Accuracy of Biopsy**

<table>
<thead>
<tr>
<th>Date</th>
<th>% Biopsy Failure</th>
<th>% Indeterminate Pathology</th>
<th>%FN</th>
<th>%FP</th>
<th>Accuracy %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre 2001</td>
<td>8.9</td>
<td>5.5</td>
<td>4.4</td>
<td>1.2</td>
<td>89</td>
</tr>
<tr>
<td>Post 2001</td>
<td>5.2</td>
<td>3.8</td>
<td>0.6</td>
<td>0</td>
<td>96</td>
</tr>
</tbody>
</table>

*From Lane et al. 2008*
Volpe et al. 2008

- 100 consecutive biopsies of incidental renal masses less than 4 cm in diameter
- 91% of which were solid
- 20 underwent surgical excision
- Core Biopsy: 84% diagnostic
- FNA: 61% diagnostic
- Biopsy and pathological diagnosis 100% concordant

From Volpe et al. 2008
The Issue of False Negatives

- Actual false negatives rare
- Most FN biopsies are due to insufficient tissue, necrosis, normal kidney, or blood
  - Should be labeled as indeterminate biopsies
- More common with small tumours
- Repeat biopsy or definitive management should be considered

From Volpe et al. 2008
**Subtype and Grade Accuracy**

- **Histological RCC Subtype**
  - 86-90% correlation

- **Grade**
  - 70-92% accurate
  - No more than 1 grade difference between biopsy and post-operative grade
  - 25% of tumours will have intratumour grade heterogeneity
  - Inter- and intra-observer reproducibility 90%

*Lebret et al. 2007; Volpe et al. 2007*

**Change in management**

- **Maturen et al. 2007**
  - 152 core biopsies of renal masses
  - 56% malignant
  - 6% non-diagnostic
  - No surgical confirmation of benign disease
  - 62% of biopsies changed clinical management
Maturen et al. 2007

152 renal masses

Known extrarenal malignancies (n = 40)

Benign result (n = 17)
- Infection, inflammation, or normal parenchyma (n = 9)
- Oncocytoma (n = 4)
- Mixed epithelial and stromal tumor (n = 2)
- No viable tumor after RFA (n = 2)

Malignant result (n = 23)
- RCC (n = 10)
- Solid organ metastasis (n = 7)
- Lymphoma (n = 6)

No known extrarenal malignancies (n = 112)

Post RFA (n = 18)
- Nondiagnostic (n = 1)
- Diagnostic (n = 17)

Other masses (n = 94)
- RCC (n = 48)
- Benign result (n = 28)
- Metastasis from occult extrarenal malignancy (n = 7)
- Carcinoma NOS (n = 6)
- Nondiagnostic (n = 5)
Diagnostic Advances

- Imaging has poor sensitivity and specificity
- Routine H&E staining may not differentiate between eosinophilic tumours with limited tissue
- Immunohistochemical and molecular characteristics can help
**Eosinophilic Tumours**

Renal tumours with eosinophilic cytoplasm, including conventional RCC (A), papillary RCC (B), chromophobe RCC (C) and oncocytoma (D). Differentiation between these eosinophilic variants can be difficult or limited pathological material.

From Lane et al. 2008

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**Immunohistochemistry**

- **Oncocytoma vs. chromophobe**

<table>
<thead>
<tr>
<th></th>
<th>Oncocytoma</th>
<th>Chromophobe RCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hale's colloidal iron histochemical stain</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Cytokeratin 7</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>EMA</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Paralbumin</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Cytokeratin 20</td>
<td>+/-</td>
<td>+</td>
</tr>
</tbody>
</table>

Lebret et al. 2007
**Immunohistochemistry**

- **Clear Cell Carcinoma**
  - Pancytokeratin+, Vimentin+, CD10+, EMA+, CK7+
- **Chromophobe carcinoma**
  - Hale+, CK7+, P504S+, EMA+, CD10+/-, vimentin
- **Papillary Cell Carcinoma**
  - p504S+, CK7+, CD117+
- **Oncocytoma**
  - CK7-, pancytokeratin+/-, EMA+/-
- **AML**
  - Melanocytic markers (HMB-45)

**Molecular Advances**

- **PCR analysis**
  - Ex-vivo analysis of 77 tumours
  - PCR analysis of 4 gene products
  - Accuracy increased from 84 to 95%
- **FISH analysis**
  - Ex-vivo analysis of 42 tumours
  - FISH analysis on 6 chromosomes
  - Accuracy increased from 87 to 94%

Barocas et al. 2006 and 2007
**Molecular Advances**

- Biomarkers
  - Identify syndromes, genetic mutations
  - Prognostic
- Carbonic anhydrase IX
  - Positive correlation with cytokine response
  - Not an independent predictor of overall prognosis

Kim et al. 2008; Leibovich et al. 2007

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**Neoadjuvant Therapy**

- Neoadjuvant therapy (Jonasch et al. 2008)
  - Tumor downstaging
  - Assessment of primary tumor response
  - Decreasing circulating tumor cells and proangiogenic factors
  - Improve performance status
- Amin et al. 2008
  - 9 patients in retrospective surgery
  - Neoadjuvant sorafenib or sunitinib for a mean of 107 days
  - Median response of 8% tumor size reduction (1-54%)
Image Guided Therapy

- Cryotherapy
- Radiofrequency Ablation
- No pathological material
- NADH diaphorase staining indicative of cell viability along with conventional histology
Pre-therapy Biopsy

  - 138 patients undergoing laparoscopic RFA
  - Pre-treatment percutaneous biopsy (U/S and visual guidance)
  - RCC 95
  - Benign 35
  - Non-diagnostic 8 (5.8%)

- Impact on follow-up
  - Pre-treatment Biopsy recommended but not yet standard of care

Post Treatment Biopsy - RFA

- Weight et al. 2008
  - 109 consecutive patients treated with RFA
  - Pre-procedure FNA biopsy
  - Imaging at 3, 6, 12 months, then annually
  - 24% of those without enhancement (6 patients) were found to have a positive biopsy.
  - Post-procedure biopsy recommended
Post-Treatment Biopsy - Cryotherapy

- Weight et al. 2008
  - 192 consecutive patients treated with cryoablation
  - Intra-operative Tru-Cut biopsy
  - CT at 3, 6, 12 months and annually
  - 51% received biopsy at 6 months
  - 0 of 60 patients without enhancement had positive biopsies
  - Role of post-procedure biopsy less certain

Negative Predictive Value

- Weight et al. 2008
  - 4 patients had benign pre-procedure biopsy but follow-up biopsy demonstrated malignancy
Contemporary Role of Renal Mass Biopsy

- Safe
- Reliable
- >95% accurate
- False negatives rare
- Likely to significantly impact on management decisions

Contemporary Role of Renal Mass Biopsy

- Established indications
- Small Renal Masses
  - Elderly patients with multiple co-morbidities
  - Young and healthy patients
- Pre and Post Image Guided Therapy
Thank You