MANAGEMENT FOR EARLY STAGE KIDNEY CANCER
The Role of Biopsy and Possibility of Delayed Therapy

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THE MESSAGE

• POTENTIAL FOR INCREASED ROLE IN MANAGEMENT OF KIDNEY CANCER
• ROLE IN MANAGEMENT OF SMALL RENAL MASSES – PHYSICAL THERAPIES
• ROLE IN LOCALLY ADVANCED RCC BEYOND SURGERY ALONE
• POTENTIAL ROLE IN NEO- & ADJUVANT Rx
• INCREASED ROLE IN CYTOREDUCTIVE SURGERY
TARGETs
Maximum Percent Reduction in Tumor Measurement

![Graph showing maximum percent reduction in tumor measurement for Placebo and Sorafenib treatments.](image)

*Independently assessed measurements available for 574 patients.*
Trend in 5 Yr Survival

- URGENT TREATMENT IS NOT NECESSARY
- SOME PATIENTS DON’T NEED TREATMENT
- NEED TO BETTER CHARACTERIZE
- NEED TO REASSESS OUTCOMES OF TREATMENT
- CAN SPECULATE ON THE FUTURE MANAGEMENT
INCIDENCE IS INCREASING

During the last 20 years the incidence of RCC has been increasing

Pantuck et al., J Urol, 2001

Greatest increase in incidence of localized tumors - stage migration as a result of earlier detection?

Chow et al, JAMA 1999
INCIDENCE IS INCREASING

The incidental detection rate of RCC increased from 7-13% in the early 1970’s to 48-66% in recent years

Homma et al., Int J Urol, 1995
Jayson and Sanders, Urology, 1998

Incidental tumors are on average smaller and have earlier stage and lower grade if compared to symptomatic tumors

Breatheau et al., Eur Urol, 1995
Tsui et al., J Urol, 2000

LARGE INCIDENCE IN UNFIT

Many small renal masses are detected in elderly patients with comorbidities and therefore increased surgical risk

UNKNOWN NATURAL HISTORY

Natural history not well known - most removed soon after diagnosis
EXCELLENT Rx RESULTS

Results with surgical treatment of small, sporadic unilateral RCC’s are excellent

Cancer specific survival 97%, local recurrence <2%

Herr, J Urol, 1999

Cancer specific survival 91 +/- 4% for <4cm

Novick et al., J Urol, 1999

RESULTS TOO GOOD ?

DIFFERENT INTERPRETATONS

Retrospective studies suggest that renal tumors < 3 cm in diameter rarely metastasize and have a slow growth rate.

Bosniak et al., Radiol, 1995
DIFFERENT INTERPRETATIONS

>25% of incidental renal tumours are benign
  - risk unnecessary nephrectomy
  - partial nephrectomy ideal, particularly laparoscopic

Janetschek
Current Opinion Urology, 2003

Influence of Size

FIGURE 2. Mortality for renal carcinomas by tumor size estimated from
proportional hazards regression model.
Influence of Grade
UCLA, based on Fuhrman's grade 1-4

HISTOLOGY OF SMALL MASSES
40% of renal masses <2cm at Lap Partial Nephrectomy are benign (25% 2-4cm).

Steinberg et al. (Cleveland Clinic)
J Urol 169A, 2003

46% of 1cm renal masses at surgery are benign.

Frank et al. (Mayo Clinic)
J Urol 169A, 2003

And, most small RCC’s are low grade
INCLUSION CRITERIA

Radiologically detected small (< 4 cm) renal masses

Unfit or refused surgery

ACTIVE SURVEILLANCE WITH DELAYED NEPHRECTOMY STRATEGY

Abdominal imaging at least every 6 months

- U/S
- CT scan
- MRI
The Natural History of Incidentally Detected Small Renal Masses

**BACKGROUND:** The incidence of renal cell carcinoma (RCC) is increasing largely due to the widespread use of cross-sectional imaging. Most renal tumors are detected incidentally as small, asymptomatic masses. To study their natural history, the authors prospectively followed a series of patients with this type of lesion who were unsuitable for noninvasive surgery.

**METHODS:** Twenty-nine patients with 32 masses that measured ≤4 cm in greatest dimension were included. The study population consisted of 20 men and 9 women with a mean age of 64 years (range: 34-87 years). The masses were detected during routine imaging or incidentally during workup for other complaints.

<table>
<thead>
<tr>
<th>Mass Type</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCC</td>
<td>8</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>1</td>
</tr>
</tbody>
</table>

**Surgical Treatment**

- **Radical:** 4 masses treated with radical nephrectomy.
- **Partial:** 5 masses treated with partial nephrectomy.

After an average follow-up of 3.1 years, all patients remained free of disease.

Cancer, 2004
• No patient progressed to metastatic disease

• Two patients died during the follow-up of tumor unrelated causes
CONCLUSIONS

About 1/3 small renal masses (SRM’s) presumed to be RCC appear to grow if managed conservatively with serial imaging.

The growth rate is slow or undetectable in some.

NATURAL HISTORY

<table>
<thead>
<tr>
<th>Study</th>
<th>Pts</th>
<th>Average patient age (years)</th>
<th>Average follow-up (months)</th>
<th>Average tumor growth (cm/year)</th>
<th>Masses eventually surgically removed</th>
<th>Histologically confirmed RCC</th>
<th>Progressions to metastatic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonniak et al.</td>
<td>40</td>
<td>65.5</td>
<td>39</td>
<td>0.36</td>
<td>26</td>
<td>22/26</td>
<td>0</td>
</tr>
<tr>
<td>Volpe et al.</td>
<td>32</td>
<td>71</td>
<td>27.9</td>
<td>0.1</td>
<td>9</td>
<td>8/9</td>
<td>0</td>
</tr>
<tr>
<td>Oda et al.</td>
<td>16</td>
<td>54</td>
<td>25.2</td>
<td>0.54</td>
<td>16</td>
<td>16/16</td>
<td>0</td>
</tr>
<tr>
<td>Kanoufi et al.</td>
<td>24</td>
<td>68.3</td>
<td>31.6</td>
<td>not reported</td>
<td>4</td>
<td>4/4</td>
<td>0</td>
</tr>
<tr>
<td>Wehle et al.</td>
<td>29</td>
<td>70.5</td>
<td>32</td>
<td>0.12</td>
<td>4</td>
<td>3/4</td>
<td>0</td>
</tr>
<tr>
<td>Kato et al.</td>
<td>18</td>
<td>56.5</td>
<td>22.5</td>
<td>0.42</td>
<td>18</td>
<td>18/18</td>
<td>0</td>
</tr>
</tbody>
</table>
Results

Combined Distribution of PSA doubling times (%) in 299 patients. Klotz L, J Urol 2004

- Median PSA DT 7.00 years
- Median F/U 62 months
- Median # measurements: 8 (3-19)
- 22% had PSA DT < 3 years
- 42% had PSA DT > 10 years
BELL’S
RENAI AL ADENOMA

Table 72.—Relation of the Size of the Tumor to the Presence of Metastases in the Adenoma—carcinoma Group.

<table>
<thead>
<tr>
<th>Diameter</th>
<th>Metastases</th>
<th>No metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 3 cm.</td>
<td>1</td>
<td>44</td>
</tr>
<tr>
<td>3 – 4 cm.</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>4 – 5 cm.</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>5 – 6 cm.</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>6 – 8 cm.</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>8–10 cm.</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Over 10 cm.</td>
<td>70</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>96</td>
<td>98</td>
</tr>
</tbody>
</table>

HYPOTHESIS

Possible period of initial observation in SELECTED patients particularly the elderly or infirm

Treatment reserved for those with
–rapid doubling times <12 mo’s?
–tumor size of >4cm?
volume > 30 cc?
BUT NEED PROGNOSTIC MARKERS

- Imaging
- Molecular
- Other
CANADA WIDE STUDY
ROLE FOR ACTIVE SURVEILLANCE AND IDENTIFICATION OF PROGNOSTIC FACTORS FOR PROGRESSION FOR EARLY STAGE RENAL CELL CARCINOMA

Michael A.S. Jewett - PI
### View Adverse Event

#### Patient Summary
- **Subject Initials:** ABC
- **Subject Study #:** 22-233

#### Adverse Event
- **Adverse Event:** Intestinal, Other
- **Start Date:** 23-Mar-2015
- **Stop Date:**
- **Frequency:** Single Episode
- **CTCAE grade:** 2
- **Relation to study:** Possible
- **Action taken:** Continued per protocol

### Edit Adverse Event

#### Patient Summary
- **Subject Initials:** ABC
- **Subject Study #:** 22-233

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- **Adverse Event:** Intestinal, Other
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**Note:** The images are of a web interface showing forms for viewing and editing adverse events in a cancer research setting.
ROLE NEEDLE BIOPSY
TRADITIONAL ROLE OF PERCUTANEOUS NEEDLE BIOPSY

• To diagnose metastatic disease to the kidney in patients with known extrarenal primary malignancy
• To establish a diagnosis of renal abscess or lymphoma
• To confirm the diagnosis of a renal primary tumour in patients with disseminated metastatic disease or unresectable retroperitoneal masses

UNCERTAINTIES

Percutaneous biopsy of renal tumours has not been widely used in North America because:

– Perceived to be unnecessary - increasing accuracy of noninvasive cross-sectional imaging tests and if –ve, operate anyway
– Safety issues - perceived risk of tumour implantation and other complications
– Technique - inadequate tissue and sampling
– Accuracy - intratumoural heterogeneity ?
UNCERTAINTIES

Percutaneous biopsy of renal tumours has not been widely used in North America because of:

– lack of familiarity by urologists with indications and utility

– lack of familiarity by pathologists on the interpretation of the cytologic findings (few detailed descriptions)

METASTATIC RCC

There is evidence that immunotherapy is effective only in clear cell RCC’s

A precise histological diagnosis is important in the management of patients that are diagnosed with metastatic renal tumours
UHN EXPERIENCE
(Jan 2001 – Dec 2004)

• **44** percutaneous needle core biopsies

• Core biopsy + FNA: **20/44** cases

• A retrospective chart review was performed to document complication rate, ability to obtain sufficient tissue for diagnosis and diagnostic accuracy

TECHNIQUE

The renal lesion was localized using ultrasound
TECHNIQUE

1% lidocaine was administered for local anesthesia

TECHNIQUE

Right to left

- 17 gauge guiding sheath
- 22 gauge fine needle for aspiration of cytological specimens
- 18 gauge biopsy automatic gun
TECHNIQUE

Guiding sheath was inserted to the tumour surface

TECHNIQUE

Inner stylet was removed from sheath
To obtain the specimen for cytology, mild suction was applied by drawing a syringe to 5-10 ml, while moving the 22 gauge needle rapidly but slightly within the lesion.

Cytological slides were prepared, rapidly fixed and tested for adequacy in the procedure room.
TECHNIQUE

18-gauge biopsy gun was inserted into lesion and a core of tissue is obtained.

TECHNIQUE

Three tissue cores were acquired from 18 gauge biopsy gun and stored in formalin or snap frozen for genetic studies.
TUMOUR SEEDING

• No cases in our experience but with short followup

• Only 5-6 cases of RCC seeding along the needle tract have been reported in the literature

COMPLICATIONS

• 3/44 biopsies (6.8%) produced minor bleeding that was easily controlled with the placement of gelfoam pledgets through the biopsy coaxial sheath – no admissions

• No other complications were reported
**DIAGNOSTIC ACCURACY**

- Diagnostic biopsies: 39/44 (88.6%)

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**INTRATUMORAL HETEROGENEITY**

(retrospective study)

- To assess intratumoural heterogeneity we reviewed the slides of 27 <3 cm RCC’s that were surgically removed
- Each case was examined by a blinded pathologist

Heterogeneity was defined as a two-point difference in Fuhrman score in different areas of the same tumor (i.e., grade 1 to 3 or 2 to 4)
• Only 1 of 27 diagnostic biopsies (4%) displayed tumor heterogeneity
  - Primary Grade 2 tumour spanning 80% of the lesion
  - Secondary Grade 4 tumour spanning 20% of the lesion
INTRATUMORAL HETEROGENEITY
(prospective study)

• Three needle cores were collected from 11 tumours after radical or partial nephrectomy
• The cores were obtained with a 14-gauge Tru-Cut needle from different regions in each tumor

INTRATUMORAL HETEROGENEITY
(prospective study)

• Adequate samples for grading were obtained from the 10 tumours that were found to be RCC’s
• None of the tumors displayed intratumoral heterogeneity
FUTURE APPLICATIONS

• Definition of prognostic factors
• To use the modern microarrays technology on needle biopsies of small renal masses
• To identify genes whose expression levels can help the urologist to distinguish aggressive tumors from indolent tumors

CONCLUSIONS

Percutaneous needle biopsy of renal tumours:

• is technically feasible
• is safe
• is accurate
  – intratumoural heterogeneity is a rare entity
  – needle biopsies are likely to provide tissue samples that are representative of the entire tumour in the vast majority of the cases
CONCLUSIONS

Percutaneous biopsy should be considered for:

– the management of small renal masses to establish malignancy and grade if considering active surveillance or minimally invasive ablative treatment

– patients with metastatic disease for cytoreductive surgery and/or therapy with biological modifiers

CURRENT THOUGHTS

• Most new SRM's are RCC but not all
• 33% of SRM’s grow, 40% small RCC’s
• Non selective treatment of SRM’s unlikely to reduce mortality from RCC
• Biopsy is useful
• Pathologist unable to distinguish clinically significant RCC from
• Can we learn from other tumour sites
• Is there an entity like RNLMP with potential to progress if one or more additional hits?
NEPHRECTOMY FOR KIDNEY CANCER

Robson, Churchill, Anderson
J Urol 1969;101;297-301

Treatment of RCC

• Surgery
• Surgery
• Surgery
LAPAROSCOPIQUE vs OPEN SURGERY

WELL KNOWN ISSUES

- PERCEIVED BETTER
- INITIALLY LONGER OR TIME AND HOSPITAL EXPENSE
- LESS PAIN
- BETTER COSMESIS, LESS HERNIA
- SHORTER RECOVERY

Partial Nephrectomy
REAL QUESTION IS WHEN AND HOW TO DO PARTIAL NEPHRECTOMY

- EVIDENCE FOR EFFICACY OF PARTIAL vs RADICAL NEPHRECTOMY FOR T1-2
- EVIDENCE FOR SAFETY OF PARTIAL NEPHRECTOMY
- COMPETITION BETWEEN LAP APPROACH FOR RADICAL vs USUALLY OPEN PARTIAL

ROLE OF LESS INVASIVE THERAPIES
Renal Cell Carcinoma
Ablative (Nonextirpative) Technologies

Modalities:
- Cryotherapy
- Electromagnetic (EM) Energy
  - Laser Induced Thermotherapy
  - Microwave Thermotherapy
  - Radiofrequency Ablation (Thermotherapy/RFA)
- Mechanical
  - High Intensity Focused ultrasound (HIFU)

Delivery:
- MIS-Laparoscopy vs Percutaneous vs Extracorporeal

Limitations
- Do not allow complete pathological evaluation of the treated lesion
- Correlation between treatment monitoring and actual tissue destruction is suboptimal
- Requires serial imaging for followup
Renal Cell Carcinoma
Ablative (Nonextirpative) Technologies

Issues:
• Safety
• Efficacy
RF Ablation: Mechanism of Action

Original Articles

THE UNCERTAINTY OF RADIO FREQUENCY TREATMENT OF RENAL CELL CARCINOMA: FINDINGS AT IMMEDIATE AND DELAYED NEPHRECTOMY

RICARDO A. PERDON, JOHN R. KACHURA, JOAN M. SWEET, MARK R. COYNE, MICHAEL D. SHEARER, MICHAEL R. BORNETT, JOHN TSHELIA, JOHN TRACHENBERG, HEATHER SANDSON, and MICHAEL A. S. JEWETT

From the Division of Urology, Department of Surgery, University Health Network, University of Toronto, Toronto; Division of Vascular and Interventional Radiology, Department of Medical Imaging, Toronto General Hospital, Mount Sinai Hospital, University of Toronto, Department of Radiology, Central General Hospital, University of Toronto; Division of Medical Physics, Ontario Cancer Institute, Mount Sinai Hospital, University Health Network, and Department of Medical Biophysics and Radiation Oncology, University of Toronto, Toronto, Ontario, Canada
Partial Nephrectomy post RF (acute)

Partial/Nephrectomy post RF (chronic) Intraoperative
Partial/Nephrectomy post RF (chronic)
Intraoperative post partial nephrectomy

Partial/Nephrectomy post RF (chronic)
Surgical Specimen
**Current Status RF Thermotherapy/Ablation (RFA)**

Characteristics of Ideal Tumors

- Peripheral
- Well circumscribed
- Enhancing

**Treatment Follow Up**

- Less than 4 cm

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**Current Status RF Thermotherapy/Ablation (RFA) – Relative Contraindications**

- Location
  - Central
  - Collecting system
  - Contiguous with bowel
- Large lesion size
- Bleeding Diatheses
  - Radiofrequency Ablation
  - Coagulation from heat
Current Status RF Thermotherapy/Ablation (RFA) – Conclusions

• Lower morbidity: Open or Laparoscopic
• Safe, Focused – Controlled
• Mostly Reproducible Lesions
• Real-time Monitoring of Lesion Formation Limited
• Limited Ability to Determine Treatment Success
• Cancer Control – Complete Destruction
  *NOT* Equal or better than Open or Lap NSS

EMERGING THERMAL ABLATION METHODS

• **HIFU** (High Intensity Focused Ultrasound)
• **MICROWAVE ABLATION**
• **LITT** (Laser Induced Thermotherapy)
HIFU

- Possible complete non invasive treatment
- Clinical experience in PCa and BPH
- Application in human renal tumors are in early feasibility stages

Vallencien et al., Semin Urol 1993
Hacker et al., Curr Op Urol 2003
Wu et al., J Urol 2003

HIFU (High Intensity Focused Ultrasound)

CHALLENGES

- Energy deposition control
- Heat sink effect (high renal blood flow)
- Adjustment for moving of the target
- Monitoring of treatment (US? MRI?)
- Length of treatment
MICROWAVE ABLATION

- Experience in liver, uterus and BPH
- Small ablation zone
- Technique and ideal energy settings have still to be clarified
- No documented clinical experimentation in renal tumors
RENAL CRYOABLATION

- Good local control rates (85-95%) in small peripheral exophytic tumors
- Percutaneous approach may become the preferred choice
  - MRI guidance (multiple planes)
  - lower morbidity
  - shorter OR time

SMALL TUMOURS NEED TO BE STRATIFIED BY SIZE AND LOCATION
TRIAGE MANAGEMENT OF SMALL RCC’S BY

SIDE
LOCATION-
  UPPER, MID, LOWER
  ANTERIOR, POSTERIOR
  PERIPHERAL, CENTRAL

SIZE
SOLID, CYSTIC
TRIAGE MANAGEMENT OF SMALL RCC’S
SIDE
LOCATION-
UPPER, MID, LOWER
ANTERIOR, POSTERIOR
PERIPHERAL, CENTRAL
SIZE
SOLID, CYSTIC
IN CONCLUSION

- We have come a long way from routine radical nephrectomy for renal masses assumed to be RCC.
- We can characterize small renal masses with biopsy.
- Active surveillance with delayed treatment is an option to be studied.
- The indications for partial nephrectomy are increasingly broad.
- Less invasive technologies may replace most surgery.
University of Toronto UroOncology Fellowship

Training program in clinical and research UroOncology
Dr. Antonio Finelli
Dr. Neil Fleshner
Dr. Michael Jewett
Dr. Laurie Klotz
Dr. Rob Nam
Dr. Sharon Sharir
Dr. John Trachtenberg

Rotations in Medical and Radiation (incl Brachy) Oncology

SUO Approved

One clinical year and up to two research years
Clinical Research Fellows
Postdoctoral Fellows
Graduate Students

Remuneration includes:
Salary
Travel expenses
Graduate Program encouraged with tuition