Advances in the Surgical Management of Renal Cancer

Grenville Oades
Consultant Urological Surgeon
Southern General Hospital
Landscape is Changing

Picture Removed
EORTC 30881

Overall survival

Overall log-rank test: $p = 0.869$

<table>
<thead>
<tr>
<th></th>
<th>135</th>
<th>389</th>
<th>No. of patients at risk</th>
<th>137</th>
<th>383</th>
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<tbody>
<tr>
<td></td>
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<td>0</td>
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<td>294</td>
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<td>90</td>
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<td>66</td>
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<td>16</td>
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<td>2</td>
</tr>
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<td>2</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Bloom JHM European Urology 2009
EORTC 30881: Conclusions

• In patients with low-stage (T1–T2) RCC and clinically negative lymph nodes, LND offers extremely limited staging information and no benefit in terms of decreasing disease recurrence or improving survival

• If pre op staging is Negative incidence of LN metastasis is low (<4%)

• In low-risk disease, risk of under staging by omission of LND is only 1%
  ▫ cNoMo with non-palpable nodes were pN+ in 1%
  ▫ cNoMo with palpable nodes were pN+ in 20% (80% non malignant)
Is Adrenalectomy Necessary?

- Multifocality
- Upper pole tumours (direct invasion)
- Associated renal vein involvement

<table>
<thead>
<tr>
<th></th>
<th>T1-2</th>
<th>T3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/164</td>
<td>0.6</td>
<td>28/347 (8.1)</td>
</tr>
</tbody>
</table>

Tsui J Urol 2000
Is Adrenalectomy Necessary?

- Synchronous ipsilateral adrenal involvement is rare (2.2%)
- Rate is low even in high risk tumours
- All but one identified on preoperative imaging, Remaining case identified perioperatively

<table>
<thead>
<tr>
<th>Feature</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper pole</td>
<td>2.43</td>
</tr>
<tr>
<td>Size +1cm</td>
<td>1.12</td>
</tr>
<tr>
<td>pT3a</td>
<td>4.27</td>
</tr>
<tr>
<td>pT3b</td>
<td>11.67</td>
</tr>
<tr>
<td>pT3c, pT4</td>
<td>10.52</td>
</tr>
<tr>
<td>N1</td>
<td>2.07</td>
</tr>
<tr>
<td>M1</td>
<td>14.49</td>
</tr>
</tbody>
</table>

Weight CJ European Urology 2011
Is there Ever a Role for “Open” Surgery

- Level I (10%)
- Level II
- Level III
- Level IV (1%)
Not Minimally Invasive

- Subcostal/Chevron
- Can be extended to include sternotomy if required
Sunitinib Trial in Adjuvant Renal Cancer (S-TRAC): A Randomized Double-Blind Phase 3 Study of Adjuvant Sutent vs Placebo in Patients With High-Risk RCC

Primary end points: Disease-free survival (DFS)
Secondary end points: Relapse-free survival (RFS), overall survival (OS), patient-reported outcomes (PRO), safety
Partial Nephrectomy

Picture Removed
Cancer Specific Survival for Renal Cancer

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Rationale for Partial Nephrectomy

<table>
<thead>
<tr>
<th>Estimated GFR</th>
<th>Death from Any Cause</th>
<th>Any Cardiovascular Event</th>
<th>Any Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60 ml/min/1.73 m²</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>45–59 ml/min/1.73 m²</td>
<td>1.2 (1.1–1.2)</td>
<td>1.4 (1.4–1.5)</td>
<td>1.1 (1.1–1.1)</td>
</tr>
<tr>
<td>30–44 ml/min/1.73 m²</td>
<td>1.8 (1.7–1.9)</td>
<td>2.0 (1.9–2.1)</td>
<td>1.5 (1.5–1.5)</td>
</tr>
<tr>
<td>15–29 ml/min/1.73 m²</td>
<td>3.2 (3.1–3.4)</td>
<td>2.8 (2.6–2.9)</td>
<td>2.1 (2.0–2.2)</td>
</tr>
<tr>
<td>&lt;15 ml/min/1.73 m²</td>
<td>5.9 (5.4–6.5)</td>
<td>3.4 (3.1–3.8)</td>
<td>3.1 (3.0–3.3)</td>
</tr>
</tbody>
</table>

*adjusted hazard ratio (95 percent confidence interval)

Go et al N Engl J Med 2004
Distribution of RCC and Benign Lesions by Tumour Size

20-30%
To Biopsy or Not?

• The Conventional Wisdom
  ▫ Limited benefit
  ▫ Inaccurate / unreliable
  ▫ Potential complications
  ▫ Use restricted to special situations
    • Concurrent malignancy
    • Single Kidney
    • Potential for haematological malignancy
  ▫ Synchronous Tumours
  ▫ Hybrid Tumours
To Biopsy or Not?

- Is it safe?
  - Risk of bleeding minimal
  - Mortality 0.031%
  - Only 8 reported cases of tumour seeding (All prior to 1994)
- Is it accurate?
- Is it necessary?
Sir Robert Muir

“Experience makes me more and more unwilling to give an opinion on a matter of doubt”
# To Biopsy or Not - Is it Accurate?

<table>
<thead>
<tr>
<th>IHC marker</th>
<th>Clear cell</th>
<th>Papillary</th>
<th>Chromophobe</th>
<th>Oncocytoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vimentin</td>
<td>Cyto/diffuse</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>CAIX</td>
<td>Membranous/cyto / diffuse</td>
<td>Cyto/focal tip necrosis</td>
<td>Cytoplasmic</td>
<td>Absent</td>
</tr>
<tr>
<td>CD10</td>
<td>Membranous/ cyto/ diffuse</td>
<td>Membr apical focal diffuse</td>
<td>Cyto /focal</td>
<td>Cyto/focal</td>
</tr>
<tr>
<td>AMA CR</td>
<td>Cyto/ focal or diffuse</td>
<td>Cyto/ granular diffuse</td>
<td>Membr/ diffuse</td>
<td>Cyto/focal</td>
</tr>
<tr>
<td>CK 7</td>
<td>Cyto/ focal</td>
<td>Membr /diffuse</td>
<td>Membr /diffuse</td>
<td>Cyto/ focal(rare)</td>
</tr>
<tr>
<td>CD117</td>
<td>Cyto /focal</td>
<td>Cytoplasmic</td>
<td>Membr /diffuse</td>
<td>Cyto/focal</td>
</tr>
</tbody>
</table>
To Biopsy or Not? - Technique

- Prone
- LA
- CT-Flouroscopy
- 17G sheath on tumour
- 18G core biopsy and FNA biopsy through same sheath

Schmidbauer Eur Urol 2008
# To Biopsy or Not? - Technique

<table>
<thead>
<tr>
<th></th>
<th>Aspiration</th>
<th>Core</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Insufficient</td>
<td>5/44</td>
<td>3/118</td>
</tr>
<tr>
<td>• Complications</td>
<td></td>
<td>4%*</td>
</tr>
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</table>

## Accuracy in defining:

<table>
<thead>
<tr>
<th></th>
<th>Aspiration</th>
<th>Core</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Malignancy</td>
<td>92%</td>
<td>97%</td>
</tr>
<tr>
<td>• RCC Subtype</td>
<td>86%</td>
<td>92%</td>
</tr>
<tr>
<td>• RC Grade 1/2 vs 3/4</td>
<td>28%</td>
<td>74%</td>
</tr>
</tbody>
</table>

Schmidbauer Eur Urol 2008
To Biopsy or Not - Is it Accurate?

- 7 studies, 362 patients
- Biopsy failure 5.2%
- Indeterminate 3.8%
- False negative 0.6%
- False positive 0%
- Accuracy 96%

Lane BR, Novick AC et al. J Urol 2008
To Biopsy or Not - Is it Necessary?

50-65 years
- Avoid unnecessary surgery

65-75 years
- Determine treatment modality

75+ years
- Allow decision to observe
SRM \leq 4\text{cm}

- Life expectancy > 10yr
- No surgical contraindication
- Adequate renal reserve

- Life expectancy < 10yr
- Relative surgical contraindication
- Inadequate renal reserve

**Is NSS feasible?**

- ? Biopsy

**NSS**

- Cancer
  - LRN
- Benign
  - Active Surveillance

**Biopsy**

- Active Surveillance if progression

**Active Surveillance**

- Biopsy if progression

**Biopsy**

- Cancer
  - Ablation
- Benign
  - Discharge
### Table 5. Bayesian Poisson model parameter estimates for risk of local recurrence or metastatic disease

<table>
<thead>
<tr>
<th></th>
<th>Local Recurrence</th>
<th></th>
<th>Metastatic Disease</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Intercept (log scale)</td>
<td>-7.76</td>
<td>(-8.94, -7.73)</td>
<td>-8.84</td>
<td>(-11.0, -7.19)</td>
</tr>
<tr>
<td>Random intercept SD (log scale)</td>
<td>0.68</td>
<td>(0.40, 1.04)</td>
<td>1.36</td>
<td>(0.85, 2.06)</td>
</tr>
<tr>
<td>Partial nephrectomy</td>
<td>1.00</td>
<td>—</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>Cryoablation</td>
<td>7.45</td>
<td>(2.24, 6.92)</td>
<td>1.24</td>
<td>(0.10, 12.60)</td>
</tr>
<tr>
<td>RFA</td>
<td>18.23</td>
<td>(6.08, 60.64)</td>
<td>3.21</td>
<td>(0.39, 8.19)</td>
</tr>
<tr>
<td>Observation</td>
<td>—</td>
<td>—</td>
<td>0.11</td>
<td>(0.00, 0.14)</td>
</tr>
<tr>
<td>Mean age</td>
<td>1.06</td>
<td>(0.98, 1.14)</td>
<td>1.00</td>
<td>(0.86, 1.16)</td>
</tr>
<tr>
<td>Mean tumor size</td>
<td>2.13</td>
<td>(1.39, 3.35)</td>
<td>2.74</td>
<td>(1.53, 5.21)</td>
</tr>
<tr>
<td>Mean followup</td>
<td>0.99</td>
<td>(0.97, 1.01)</td>
<td>1.01</td>
<td>(0.99, 1.05)</td>
</tr>
</tbody>
</table>
“Gold Standard”-Partial Nephrectomy

Table 2: 2010 recommendations for primary surgical treatment of RCC according to T-stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Surgery</th>
<th>Open</th>
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<tbody>
<tr>
<td>T1</td>
<td>Nephron-sparing surgery</td>
<td>Laparoscopic</td>
</tr>
</tbody>
</table>
Long Term Survival Following Partial vs Radical Nephrectomy

Picture Removed
CONSERVE. A Feasibility Study of Randomisation to Partial Nephrectomy vs Minimally Invasive Treatment

Randomised study
T1a Tumour
Assessed a suitable for NSS

Partial nephrectomy (OPN/LPN)

Minimally invasive treatment
The Landscape is Changing

• SRMs account for 40+% of renal cancer diagnoses in the UK today
• Explained by increased use of diagnostic imaging
• Often detected in elderly patients or those with significant comorbidity
• Increasing and minimally invasive treatment options (PN, Observation, Thermal Ablation)
Treatment Type by Age Group (T1a): BAUS Cancer Registry Data
Unintended consequences of Laparoscopic Surgery on Partial Nephrectomy

Abouassaly J Urol 2010
Robot Assisted Laparoscopic Surgery
Da Vinci Robot

Picture Removed
Advantages of Robot Assisted Laparoscopic Surgery

- 3D
- Visual Magnification
- Ergonomics
- “Motion Scaling”
- Endowrist Technology
Da Vinci Robot
Ischaemia Time

- Ultimate renal function following PN is dependent on the "3 Qs":
  - Quality (renal function prior to surgery)
  - Quantity (renal parenchyma preserved during surgery)
  - Quickness (ischemia time).
Cytoreductive Nephrectomy
Cytoreductive Nephrectomy

- Flanigan et al. SWOG, 2001
- Mickisch et al. EORTC, 2001

Nx + IFN vs IFN
13.6 vs 7.8
The Impact of Cytoreductive Nephrectomy on Survival of Patients With Metastatic Renal Cell Carcinoma Receiving Vascular Endothelial Growth Factor Targeted Therapy


A

Median OS: 23.9 vs 14.5 months p<0.01

B

Median OS: 10.1 vs. 6 months p=0.08
MDACC Surgical Risk Factors for CN in patients with mRCC

1. Elevated LDH
2. Low albumin
3. Symptoms at presentation due to metastasis
4. Liver metastasis
5. Retroperitoneal adenopathy,
6. Supradiaphragmatic adenopathy
7. ≥T3.
**CARMENA**

- **Primary objective**: Is sunitinib alone non-inferior to nephrectomy plus sunitinib in terms of OS?
SURTIME

- Primary end point: PFS
- Secondary end points: OS, association with prognostic gene and protein expression profiles
Presurgical targeted therapy
Neoadjuvant Therapy

Potential Benefits

• Downsizing/downstaging of primary tumour or metastases (to allow surgical resection?)
• Avoid surgery in non-responding patients
• Eliminate micro-metastatic disease (in locally advanced setting)

Potential Drawbacks

• Primary tumor may not respond or in fact progress and/or metastasise
• Not clear how to integrate surgery and systemic therapy
• May see increased surgical morbidity due to deconditioning or wound healing complications
Glasgow University School for NHS Managers

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