Surgery of Renal Cell Carcinoma

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The Netherlands Cancer Institute

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Surgery of RCC

- Locally confined (small) renal tumours
- Locally advanced disease
- Metastatic disease

RCC = renal cell carcinoma.

Paul Grawitz
Changes in stage and surgical management of renal tumours during 1995-2005 in the Netherlands

N=12471 surgeries for renal cancer

Incidence of T1 tumours increased from 36,6 % to 44,2 %
Advanced tumours decreased from 46,4 % to 33,7 %

Partial nephrectomies in T1a tumours
1995 3,5 %
2005 10,1 %

Kummerlin et al., BJU Int 102:946-51, 2008
EORTC Intergroup trial of total versus partial nephrectomy

N=541 patients with masses ≤ 5 cm

<table>
<thead>
<tr>
<th></th>
<th>total nephrectomy</th>
<th>partial nephrectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood loss &lt; 0,5 l</td>
<td>96 %</td>
<td>87,2 %</td>
</tr>
<tr>
<td>Urinary fistulas</td>
<td>0</td>
<td>4,4 %</td>
</tr>
<tr>
<td>Pleural damage</td>
<td>9,3 %</td>
<td>11,5 %</td>
</tr>
<tr>
<td>Spleen damage</td>
<td>0,4 %</td>
<td>0,4 %</td>
</tr>
<tr>
<td>Post-op CT changes</td>
<td>2 %</td>
<td>5,8 %</td>
</tr>
<tr>
<td>Complications req sur</td>
<td>2,4 %</td>
<td>4,4 %</td>
</tr>
</tbody>
</table>

Data on DFS and OS not yet mature

## Benefit of partial nephrectomy

**Adjusted hazard ratio for death from any cause, cardiovascular events, and hospitalization among 1,120,295 ambulatory adults, according to the estimated GFR**

<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&lt;sup&gt;†&lt;/sup&gt;</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>

*The analyses were adjusted for age, sex, income, education, use or nonuse of dialysis, and the presence or absence of prior coronary heart disease, prior peripheral arterial disease, diabetes mellitus, hypertension, dyslipidemia, cancer, a serum albumin level of 3.5 g per deciliter or less, dementia, cirrhosis or chronic liver disease, chronic lung disease, documented proteinuria, and prior hospitalizations.

<sup>†</sup>This group served as the reference group.

US Trends in the Use of Partial Nephrectomy: A Rising Tide That Has Not Lifted All Boats

Increase in PN from 15.3 % in 2002 to 24.7 % in 2008

Robotic partial nephrectomies

Selective arterial branch Clamping

Ng et al., Eur Urol 2011
**R.E.N.A.L. Nephrometry score**

<table>
<thead>
<tr>
<th>Factor</th>
<th>1 pt</th>
<th>2 pts</th>
<th>3 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(R)adius</strong> (maximal diameter in cm)</td>
<td>\leq 4</td>
<td>&gt;4 but &lt; 7</td>
<td>\geq 7</td>
</tr>
<tr>
<td><strong>(E)xophytic/endophytic properties</strong></td>
<td>\geq 50%</td>
<td>&lt;50%</td>
<td>Entirely endophytic</td>
</tr>
<tr>
<td><strong>(N)earness of the tumor to the collecting system or sinus (mm)</strong></td>
<td>\geq 7</td>
<td>&gt;4 but &lt; 7</td>
<td>\leq 4</td>
</tr>
<tr>
<td><strong>(A)nterior/Posterior</strong></td>
<td>No points given. Mass assigned a descriptor of a, p, or x</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(L)ocation relative to the polar lines</strong></td>
<td>Entirely above the upper or below the lower polar line</td>
<td>Lesion crosses polar line</td>
<td>&gt;50% of mass is across polar line (a) or mass crosses the axial renal midline (b) or mass is entirely between the polar lines (c)</td>
</tr>
</tbody>
</table>

* suffix “h” assigned if the tumor touches the main renal artery or vein

**RENAL Nephrometry Score**

<table>
<thead>
<tr>
<th>RENAL Nephrometry Score</th>
<th>Degree of Case Complexity</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 to 6</td>
<td>HIGH</td>
</tr>
<tr>
<td>7 to 9</td>
<td>MEDIUM</td>
</tr>
<tr>
<td>10 to 12</td>
<td>LOW</td>
</tr>
</tbody>
</table>

RCC = renal cell carcinoma.
The small renal mass

Excise, ablate or observe?

Partial nephrectomy?

Radiofrequency ablation

Cryo-therapy
# Benign lesions after partial nephrectomy in masses < 4 cm

N=376 patients

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign lesions</td>
<td>81/376</td>
<td>21.5%</td>
</tr>
<tr>
<td>Angiomyolipomas</td>
<td>35</td>
<td>9.3%</td>
</tr>
<tr>
<td>Complicated cysts</td>
<td>26</td>
<td>6.9%</td>
</tr>
<tr>
<td>Oncocytomas</td>
<td>11</td>
<td>2.9%</td>
</tr>
<tr>
<td>Others</td>
<td>9</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

Jeon et al., Urology March 17, 2010
Active surveillance

Canadian prospective phase II study
N=178 patients with 209 masses

Median follow up 28 mo
Local progression 25 (12%)
Growth rate/year 0.13 cm
Progression to metastasis 2 (1.1 %)

Presence of RCC at biopsy did not change growth rate

Caution: Data very short with the majority just above >12 months FUP. Conclusion is therefore limited to the ‘initial 2 years’

Jewett et al., Eur Urol 2011
Retrospective study comparing RFA to partial nephrectomy over a period of > 6 years

- For RFA versus PN, median follow-up was 6.5 yr versus 6.1 yr ($p = 0.68$), respectively.
- The 5-yr OS was 97.2% versus 100% ($p = 0.31$), CSS was 97.2% versus 100% ($p = 0.31$), DFS was 89.2% versus 89.2% ($p = 0.78$),
- local RFS was 91.7% versus 94.6% ($p = 0.96$), and MFS was 97.2% versus 91.8% ($p = 0.35$), respectively. Study limitations are retrospective data analysis, loss to follow-up, limited statistical power, and limited generalizability of our data.

Olweny et al, Eur Urol 2012
Recommendations from EAU guidelines on RCC – updated 2010

- For T1 RCCs, nephron-sparing surgery should be performed whenever possible. Open partial nephrectomy currently remains the standard.  
  
- Laparoscopic radical nephrectomy is recommended in T2 renal cell cancer when nephron-sparing surgery is not suitable
  
- Extended lymphadenectomy does not improve survival and can be restricted to staging purposes.
  
- Adrenalectomy is generally not recommended except when a normal adrenal gland cannot be excluded by imaging and palpation.

- Patients with small tumours and/or significant comorbidity who are unfit for surgery should be considered for an ablative approach (eg, cryotherapy and radiofrequency ablation).
# Ongoing Phase III Adjuvant Studies for RCC

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Patient Characteristics</th>
<th>Treatment Arms</th>
<th>Study Duration</th>
<th>Primary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-TRAC: Sunitinib Trial in Adjuvant Renal Cancer Treatment</td>
<td>600</td>
<td>High-risk patients according to UISS</td>
<td>Sunitinib, Placebo</td>
<td>1 yr</td>
<td>DFS</td>
</tr>
<tr>
<td>ASSURE: Adjuvant Sorafenib or Sunitinib for Unfavorable RCC</td>
<td>1,923</td>
<td>Non-metastatic RCC; disease stage II–IV</td>
<td>Sunitinib, Sorafenib, Placebo</td>
<td>1 yr (9 treatment cycles)</td>
<td>DFS</td>
</tr>
<tr>
<td>SORCE: Sorafenib in Patients with Resected Primary RCC at High/Intermediate Risk of Relapse</td>
<td>1,656</td>
<td>Patients with high- and intermediate-risk resected RCC</td>
<td>Sorafenib, Sorafenib/Placebo, Placebo</td>
<td>3 yrs</td>
<td>DFS</td>
</tr>
<tr>
<td>EVEREST: Everolimus for Renal Cancer Ensuing Surgical Therapy</td>
<td>1,218</td>
<td>Pathological stage intermediate or very high-risk patients with full or partial nephrectomy</td>
<td>Everolimus, Placebo</td>
<td>9 treatment cycles</td>
<td>RFS</td>
</tr>
<tr>
<td>PROTECT: Pazopanib as an Adjuvant Treatment for Localized RCC</td>
<td>1,500</td>
<td>Patients with moderately high or high risk of relapse with nephrectomy of localized or locally advanced RCC</td>
<td>Pazopanib, Placebo</td>
<td>1 yr</td>
<td>DFS</td>
</tr>
</tbody>
</table>

UISS = UCLA integrated staging system.
Neoadjuvant Sunitinib for Surgically Complex Advanced RCC of Doubtful Resectability: Downsizing to Reconsider Cytoreductive Surgery

- Cytoreductive surgery in only 3 of 10 patients
- Sunitinib 50 mg/d for 4 wks on and 2 wks off until 48 hrs prior to surgery
Prospective Trial of 3 Mos Preoperative Sunitinib at 37.5 mg/d

- N = 20; cT1b-cT3b, any N/M category
- Sunitinib 90 days; discontinued day before surgery (n = 15)

- Non-metastatic neoadjuvant 67% (16/20)
- Reduced tumor size 85% (17/20)
- Mean change in diameter -11.8% (-27% to 11%)
- Partial nephrectomy 40% (5.3 [4.4–7.2] cm)

Primary Tumor Response to Targeted Agents in 168 Patients With mRCC

- Primary tumor maximum overall response to treatment with targeted agents
- Primary tumor response to a targeted agent according to the amount of response

mRCC = metastatic RCC.
Abel et al, 2011.
Onset of angiogenesis after discontinuation of sunitinib treatment

Linear regression analyses of EC proliferation (A), microvessel density (B) and gene expression (C) with the time-period between halting the sunitinib therapy and surgery. Correlation and p-values for all tested genes are shown in D.

Presented at the Genitourinary Cancers Symposium
Reluctance to perform a phase III trial with DFS and OS as endpoint

- Apart from subtype we lack predictive biomarkers

Why subject patients with localized RCC who are principally curable by surgery to a toxic therapy of which we cannot predict efficacy in the individual patient and delay definite treatment?
### RAND Appropriateness Panel on CN

<table>
<thead>
<tr>
<th>Symptomatic Primary</th>
<th>CN: IMT Planned Metastatic Burden</th>
<th>CN: Targeted Therapy Metastatic Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Limited</td>
<td>Extensive</td>
</tr>
<tr>
<td>Good Risk Yes</td>
<td>Appropriate</td>
<td>Appropriate</td>
</tr>
<tr>
<td>Good Risk No</td>
<td>Appropriate</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Poor Risk Yes</td>
<td>Uncertain</td>
<td></td>
</tr>
<tr>
<td>Poor Risk No</td>
<td>Inappropriate</td>
<td></td>
</tr>
</tbody>
</table>

Outcome of Patients With mRCC Treated With Targeted Therapy Without CN

Prognostic Factors

- LDH > ULN
- Calcium ≥ 10 mmol/L
- ECOG PS ≥ 2
- N2 disease
- Platelets > ULN
- Lymphocytes < LLN
- Bone metastases ≥ 2
- Smoker

LDH = lactate dehydrogenase; ULN = upper limit of normal; ECOG = Eastern Cooperative Oncology Group; PS = performance status; N2 = retroperitoneal lymph node metastasis; LLN = lower limit of normal.

CARMENA Phase III Study of Sunitinib Only Vs. Nephrectomy Followed by Sunitinib

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

N = 576

Metastatic clear cell RCC

RANDOMIZATION

Nephrectomy

Sunitinib 50 mg/day (schedule 4/2)

Sunitinib 50 mg/day (schedule 4/2)

Better survival in patients with mRCC after nephrectomy: A population based study in the Netherlands

N=328 patients, 37.5 % underwent nephrectomy; after adjustment for prognostic factors nephrectomy remained significantly associated with better survival (hazard ratio: 0.52, 95% CI: 0.37-0.73)

RCC = renal cell carcinoma.
Aben KK et al., Eur J Cancer 2011
Use of Systemic Treatment After CN in the Community Setting

Multi-Institutional Retrospective Analysis of 141 Patients After CN

Systemic Therapy 70% (98/141)

No Systemic Therapy 31% (43/141)

- Rapid PD 30% (13/43)
- Decision for surveillance 21% (9/43)
- Patient refusal 23% (10/43)
- Perioperative death 19% (8/43)
- Unknown reasons 7% (3/43)

Personalized medicine 2011
1.830.000 search results in 0.06 seconds
Arguments in Favor of Nephrectomy

- Palliate local symptoms
- Primary tumor has not responded to systemic therapy and progresses
- Long interval between progression and death with potential progression of the primary tumor if left in situ
- Possibility of CR more likely in combination with nephrectomy
- Benefit of pivotal phase III trials of targeted agents largely demonstrated in nephrectomised patients
- Adequate histology can be obtained
- Removal of the source of metastases, growth factors, cytokines, etc…

A Combined Analysis of 66 Patients With Clear Cell mRCC Treated With Presurgical Sunitinib in 2 Independent Phase II Trials

SURTIME, a EORTC-GU 30073 Phase III Study Investigating the Sequence of Nephrectomy and Sunitinib

- Primary end point: PFS
- Secondary end points: OS, association with prognostic gene and protein expression profiles

Patients with synchronous mRCC and primary tumor in situ

N = 458

Biswas et al, 2009; US NIH, 2010d.
Metastasectomy After Targeted Therapy in Patients With Advanced RCC (n = 22)

Retrospective analysis of consolidative metastasectomy (CR after surgery)

<table>
<thead>
<tr>
<th>No. cycles</th>
<th>1–10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>n = 11 after median of 42 wks</td>
</tr>
<tr>
<td>No recurrence</td>
<td>n = 11 after median of 43 wks</td>
</tr>
<tr>
<td>Alive</td>
<td>n = 21 at median FUP of 109 wks</td>
</tr>
<tr>
<td>Postoperative treatment</td>
<td>n = 9 (1–5 cycles)</td>
</tr>
</tbody>
</table>

FUP = follow-up.
Karam et al, 2011.
## Recommendations for surgery according to primary tumor T stage - EAU Guidelines

<table>
<thead>
<tr>
<th>T stage</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Nephron-sparing surgery</td>
</tr>
<tr>
<td></td>
<td>open</td>
</tr>
<tr>
<td></td>
<td>laparoscopic</td>
</tr>
<tr>
<td></td>
<td>Radical nephrectomy</td>
</tr>
<tr>
<td></td>
<td>laparoscopic</td>
</tr>
<tr>
<td></td>
<td>open</td>
</tr>
<tr>
<td>T2</td>
<td>Radical nephrectomy</td>
</tr>
<tr>
<td></td>
<td>laparoscopic</td>
</tr>
<tr>
<td></td>
<td>open</td>
</tr>
<tr>
<td></td>
<td>Nephron-sparing surgery</td>
</tr>
<tr>
<td></td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>T3,T4</td>
<td>Radical nephrectomy</td>
</tr>
<tr>
<td></td>
<td>Open, laparoscopic</td>
</tr>
</tbody>
</table>

Ljungberg et al., Eur Urol 2010
Key Takeaways: Locally Advanced Disease

- There is no evidence supporting the use of adjuvant therapy for patients with high risk of recurrence after nephrectomy. Multiple phase III trials are ongoing.
- There are no phase III trials investigating neoadjuvant therapy for high-risk disease.
- The effect of neoadjuvant therapy to downsize tumors, metastases, and CVT is limited with the available targeted agents.
- Neoadjuvant targeted therapy to downsize lesions and facilitate surgery is investigational. Patients with irresectable disease may receive targeted therapy after which surgery may be reconsidered in individual cases.
Key Takeaways: Metastatic Disease

- The role and the sequence of CN in the era of targeted therapy is under investigation in the CARMENA and SURTIME phase III trials.
- Presently, retrospective data suggest that patients with good performance, clear cell histology, and low metastatic burden may benefit from nephrectomy.
- Preliminary data suggest that metastasectomy following targeted therapy is feasible. Whether the outcome is due to complete resection or presurgical therapy or a combination of both remains investigational.
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