Indication and role of surgical treatment in patients with metastatic RCC

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Question
In which country is world’s highest incidence of RCC?

1. USA
2. Germany
3. Czech republic
4. Lithuania
Epidemiology of RCC
Incidence and mortality in ČR

In 2008 in ČR

• 2841 new cases
• 1165 deaths
Epidemiology of RCC
Incidence and mortality of RCC in different countries

- High incidence and mortality in European countries
- Highest incidence and mortality in ČR
- Worldwide > 100,000 related deaths
Incidence and mortality of metastatic disease in ČR:

- In 2008 in ČR
  - 547 new cases
  - 420 deaths
  - Metastatic disease in > 25% cases at diagnosis
Epidemiology of mRCC

Age related incidence of RCC and metastatic disease in ČR

M1 disease in patients below age of 70 in ČR in 2008:

- **304 new cases**
- **214 deaths**
Prognosis of metastatic RCC

- During follow-up metastatic disease appears in ~ 30% of originally localized disease
- 5-year OS ~ 23%

Current therapy for RCC
Localised and locally advanced disease

Surgical therapy

Trends:
• Nephron sparing approach when possible
• Miniinvasive surgery (laparoscopy)

Limitations in efficacy:
• T3b,c tumors (thrombus)
• T4 tumors
• N+ tumors
## Current therapy for RCC

**Metastatic disease**

Targeted therapy combined with surgery

<table>
<thead>
<tr>
<th>Agent</th>
<th>Randomization</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib, 2007</td>
<td>vs. IF-alpha</td>
<td>PFS 11 vs. 5 Mo, improved OS</td>
</tr>
<tr>
<td>Sorafenib, 2007</td>
<td>vs. placebo</td>
<td>PFS 5.5 vs. 2.8 Mo, improved OS</td>
</tr>
<tr>
<td>Bevacizumab, 2010</td>
<td>+IF-alpha vs. IF-alpha</td>
<td>OS 23.3 vs 21.3, improved PFS</td>
</tr>
<tr>
<td>Pazopanib, 2010</td>
<td>vs. placebo</td>
<td>PFS 9.2 vs. 4.2 Mo, improved RR</td>
</tr>
<tr>
<td>Temsirolimus, 2007</td>
<td>vs. IF-alpha vs. combination</td>
<td>OS 10.9 vs. 7.3 vs. 8.4 Mo</td>
</tr>
</tbody>
</table>

**Limitations:**
- Non-curative effect of systemic treatment
Treatment options for metastatic RCC

• Cytoreductive nephrectomy and complete metastasectomy
• Cytoreductive nephrectomy followed by targeted therapy
• Presurgical targeted therapy followed by cytoreductive nephrectomy or even metastasectomy
• Targeted therapy only
• Male 61 Ys
• ICHS, hypertension
• Asymptomatic
• CT renal tumor and 3 lung lesions 3, 7 and 10 mm
• Bone scan negative
Question
Your recommendation?

1. Nephrectomy followed by targeted therapy
2. Nephrectomy + metastasectomy
3. Biopsy + Targeted therapy + radiation
4. Biopsy + Targeted therapy only
• Surgery of metastases in mRCC?
Surgical resection of metastases

• Resection of solitary metastasis (or limited number) can achieve long time survival in 35-50% of patients
• 5-year survival in 52% after resection of single metastasis and 29% after resection of more metastases
• 5-year survival in 54% with single lung and in 18% with brain metastasis

Kavolius, J Clin Oncol, 1998, 16, 2261

• Best results in lung metastases

Van der Poel, Eur Urol, 1999, 35, 197
Metastasectomy of multiple metastases

887 pts. with multiple metastases, 125 (14%) complete metastasectomy:

- Median CSS 4.8 years vs. 1.3 years
- 5-Year CSS 49% vs 14%
- In patients with lung-only metastases 5-Year CSS 73.6% vs. 19%
- Survival advantage also with multiple, non-lung-only metastases (5-Year CSS 32.5% vs 12.4%)

Alt et al., Cancer, 2011, 117, 2873
Survival prediction in metastatic disease

- 727 patients with simultaneous or subsequent metastatic disease
- All nephrectomy, clear-cell pathology

**Scoring algorithm:**
- Symptoms at nephrectomy (+2)
- Bone (+2), liver (+4) mets
- Multiple simultaneous sites (+2)
- Mets at nephrectomy (+1) or within 2 years (+3)
- Tumour thrombus (+3), nuclear grade 4 (+3), necrosis (+2)
- Complete resection of all metastatic sites (-5)

Leibovich, J Urol, 2005, 174, 1759
Surgery of metastases in the era of targeted therapies?

- Aggressive surgery for metastases after nephrectomy is advocated whenever possible (solitary or limited number)
- Female, 55 Ys ECOG PS 0
- Pain in right hip
- Lungs without lesions
Question
Your recommendation?

1. Nephrectomy followed by targeted therapy
2. Biopsy + Targeted therapy alone
3. Symptomatic therapy
• Can cytoreductive nephrectomy improve outcomes in patients with mRCC?
Cytoreductive nephrectomy in immunotherapy era

- Prospective randomized studies „phase III“ (SWOG 8949, EORTC 30947)
- Nephrectomy + immunotherapy (IFNα-2b 5 MU/m²) x immunotherapy only

- 331 pts.
- Median OS 7,8 M x 13,6 M – p=0,002
- profit only 5,8 months
- 1-year survival 37,1 % x 51,9 %

Flanigan, J Urol, 2004, 171, 1071
Cytoreductive nephrectomy in immunotherapy era

Predictors of Survival of Advanced Renal Cell Carcinoma: Long-Term Results From Southwest Oncology Group Trial S8949

Primo N. Lara, Jr., Catherine M. Tangen, Sarah J. Conlon, Robert C. Flanigan and E. David Crawford

• Early progressive disease and PS strongerst predictors of OS

J Urol, 2009, 181, 512
Cytoreductive nephrectomy in immunotherapy era

- 5372 pts. from SEER database with M1 disease
- 45.5% cytoreductive nephrectomy
- 54.5% without surgery

Zini L, Urology, 2009, 73, 342
Cytoreductive nephrectomy in the era of targeted therapies?

- Performed in 67-100% of patients from targeted therapy trials

Potential reasons to perform Nx in mRCC:
- Progression of primary tumor
- Chance of long-term complete remissions with „drug holidays“
- Survival benefit of targeted therapy confirmed mostly on nephrectomized population
Cytoreductive nephrectomy in the era of targeted therapies?

The Impact of Cytoreductive Nephrectomy on Survival of Patients With Metastatic Renal Cell Carcinoma Receiving Vascular Endothelial Growth Factor Targeted Therapy


- Prolonged OS in patients with Nx
- Only marginal benefit in patients with poor risk features and Karnofsky PS less than 80

J Urol, 2011, 185, 60
Targeted therapy only in mRCC

188 pts., intermediate or high risk
OS 10.4 Mo, depending from risk stratification
Improved survival in comparison with historical cohorts
Carmina trial
NCT00930033

mRCC
ECOG PS 0-1

Randomization

Nephrectomy
+ sunitinib

Sunitinib

• Primary end point OS
• Results expected in 2016
Patients selection for cytoreductive nephrectomy

• Not all patients with mRCC will profit
In which patients was cytoreductive nephrectomy beneficial?

- Results of SWOG 8949, EORTC 30947

- Lower tumor volume (>75% of tumor volume removed by nephrectomy)
- Absence of CNS, liver (bones?) metastases
- Good cardiopulmonary condition
- ECOG PS 0 or 1
- Clear cell carcinoma (no sarcomatoid tumor, collecting duct carcinoma)
Role of surgery in the era of targeted therapies?

- Efficacy of surgery is dependent from the extent of tumor and extent of debulking
- Supports the role of extensive surgery in mRCC

BJUI, 2010, 106, 1266
mRCC treated between 1991 and 2007
566 pts with Nx and 110 pts with medical therapy (49% targeted therapy) alone
<3% ECOG PS 2, none 3

Predictors of inferior OS:
- Increased LDH level, low albumin level
- Symptomatic metastases
- Liver metastases
- Retroperitoneal or supradiaphragmatic adenopathy
- Clinically T3 or T4

Cancer, 2010, 116, 3378
Cytoreductive nephrectomy before systemic treatment should be performed if possible.

Profit can be expected particularly in patients:

• Good PS
• Absence of unfavourable histology
• Limited extend of the disease
• Absence of liver, extensive skeletal, brain mets.
- Male, 63 Ys ECOG PS 1
- Hypertension, diabetes
- cN+
- Metastases in lungs (4-5), in spine, in ribs
Question

Your recommendation?

1. Nephrectomy followed by targeted therapy
2. Biopsy + Targeted therapy
3. Chemotherapy
4. Symptomatic therapy
Targeted treatment before nephrectomy in mRCC?
Targeted treatment before nephrectomy in mRCC?

Potential benefits:

• Downstaging of unresectable disease
• Assessment of disease response
• Decreased time to initiation of systemic therapy

Important questions:

• Efficacy of targeted treatment on primary tumor?
• Morbidity of surgery after targeted treatment?
• Impact on patients survival?
Targeted therapy before Nx in mRCC - effect on primary tumor?

- 168 pts., various targeted treatments
- Primary tumor response is highly variable, median maximum response -7.2%
- Decrease of diameter >30% is rare, no complete response
- Early response is good prognostic sign
Targeted therapy before Nx in mRCC
- effect on primary tumor?

- Less response of primary tumor than metastatic sites
- **Response to sunitinib in phase 3 randomized trials:**
  - up to 37% in metastatic sites
  - 10-16% in primary tumor
- Low risk of progression under targeted treatment
Targeted therapy before Nx in mRCC - safety?

- Impaired wound healing, bleeding and thromboembolic complication after targeted therapies (bevacizumab)?

- 70 pts with presurgical targeted therapy vs 103 pts with immediate Nx

Table 5 – Analysis of preoperative and postoperative characteristics by risk of overall complications for all patients undergoing cytoreductive nephrectomy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariable OR (95% CI)</th>
<th>p value</th>
<th>Multivariable OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG ≥2</td>
<td>9.1 (1.2–72.3)</td>
<td>0.036</td>
<td>9.0 (1.1–74.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Clinical N1 or N2</td>
<td>2.5 (1.3–4.8)</td>
<td>0.007</td>
<td>1.83 (0.96–3.5)</td>
<td>0.068</td>
</tr>
<tr>
<td>Clinical T3 or T4</td>
<td>2.0 (1.1–3.8)</td>
<td>0.023</td>
<td>8.95 (1.1–79.6)</td>
<td>0.042</td>
</tr>
<tr>
<td>Presurgical targeted therapy</td>
<td>1.8 (0.97–3.4)</td>
<td>0.064</td>
<td>1.50 (0.77–2.9)</td>
<td>0.237</td>
</tr>
<tr>
<td>BMI ≥30</td>
<td>1.5 (0.8–2.9)</td>
<td>0.222</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 4 – Analysis of preoperative and postoperative characteristics by risk for wound complications for all patients undergoing cytoreductive nephrectomy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariable OR (95% CI)</th>
<th>p value</th>
<th>Multivariable OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presurgical targeted therapy</td>
<td>4.42 (1.8–10.8)</td>
<td>&lt;0.001</td>
<td>4.14 (1.6–10.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>BMI ≥30</td>
<td>2.46 (1.1–5.7)</td>
<td>0.035</td>
<td>2.44 (0.96–6.2)</td>
<td>0.060</td>
</tr>
<tr>
<td>Diabetic</td>
<td>1.35 (0.5–4.0)</td>
<td>0.564</td>
<td>1.00 (0.3–3.3)</td>
<td>0.999</td>
</tr>
<tr>
<td>Smoker</td>
<td>1.03 (0.4–3.0)</td>
<td>0.999</td>
<td>0.73 (0.2–2.3)</td>
<td>0.597</td>
</tr>
<tr>
<td>Duration of surgery (per-minute increase)</td>
<td>1.00 (1.0–1.0)</td>
<td>0.361</td>
<td>1.00 (1.00–1.00)</td>
<td>0.929</td>
</tr>
<tr>
<td>Clinical N1 or N2</td>
<td>1.84 (0.8–4.2)</td>
<td>0.190</td>
<td>1.31 (0.5–3.3)</td>
<td>0.563</td>
</tr>
</tbody>
</table>
Targeted therapy before Nx in mRCC
- timing of surgery?

- Median time to maximum response was 5-6 Mo
- Pts. with decrease in diameter $\geq 10\%$ in first 60 days had significantly better overall response (24.5% vs. 7.2%)
Surtime
EORTC 30073

mRCC

Randomization

Primary end point PFS, secondary OS

Nephrectomy

Sunitinib

3 courses

Nephrectomy

Sunitinib
Consolidation metastasectomy after targeted therapy?

- Feasible with acceptable morbidity
- After 2 years 21/22 pts. were alive
Before systemic therapy

After 2 Mo of erlotinib
Neoadjuvant targeted treatment before nephrectomy in locally advanced RCC?

Argument is its better efficacy comparing to immunotherapy

Potential benefits:

• Achieve operability in unresectable disease
• Reduce the extent of surgery (tumor thrombus)
• Making laparoscopic approach possible
• Possible micrometastases elimination
• Assessment of disease response
• Detection of new tissue markers
Neoadjuvant targeted treatment before nephrectomy in locally advanced RCC?

Modest effect on primary tumor

Permitting resection:

- Pure definition of "unresectable lesion"
- In modern era only less than 1% of tumors deemed to be unresectable

Enabling nephron sparing surgery

- Not supported by evidence
- Male 53 years
- Temperature, Weight loss
- 10-08 Nephrectomy + liver resection
Downsizing caval tumor thrombus?

- 25 pts
- 7 increase, 7 no change, 11 decrease in thrombus height
- Only 1 case where surgical approach was potentially affected by targeted therapy

Conclusions: TMT had a minimal clinical effect on RCC tumor thrombi. Only patients treated with sunitinib had clinical thrombus regression; however, the clinical magnitude and relevance of this effect is not clear and should be investigated prospectively.
- Male 76 Ys
- Tumor thrombus
- cN0M0
Neoadjuvant targeted therapy in locally advanced RCC?

- No strong support by evidence
- Impact on patients’ survival?
Further questions?

Adjuvant targeted therapy after nephrectomy for localized disease?

• More trials ongoing
• ASSURE, S-TRAC, SORCE, PROTECT, EVEREST (compare targeted therapy with placebo)

• Theoretically promising, but data expected
Conclusions

• Surgery is only curative modality in RCC
• Proper integration of surgery and systemic therapy is essential for improving outcomes
• Further studies are necessary
• Education and production of experts in oncurology is critical for optimal results