Role of Cytoreductive Nephrectomy for Metastatic Kidney Cancer

Philippe E. Spiess, MD, MS, FRCS(C), FACS
Associate Member
Department of GU Oncology
Department of Tumor Biology
Moffitt Cancer Center
Associate Professor, Department of Urology
University of South Florida
NCCN Bladder and Penile Cancer, Vice-Chair
E-mail: philippe.spiess@moffitt.org
CASE PRESENTATION

• 60 yo male Pt presents with a 11 x 9 cm right renal mass, several retroperitoneal lymph nodes, 2 small pulmonary metastasis, and L3 bone metastasis extending into paravertebral/epidural space

• Completely asymptomatic

• ECOG is 0
CASE PRESENTATION

MAY 2011
• What would you offer this patient as upfront treatment at this point?
  – Systemic therapy (+/- XRT to bone)
  – Surgery (if so, what procedure?)
• Patient underwent a combined surgical procedure:
  – Right cytoreductive nephrectomy/RPLND
  – Anterior L3 vertebral resection, spinal internal fixation
• Final pathology:
  – Nephrectomy: pT3a, RCC, clear cell histology, Fuhrman grade 3, necrosis in 90% specimen, SM –ve
  – Retroperitoneal LN: metastatic RCC (2/2)
  – L3 vertebral bone: metastatic RCC
CASE PRESENTATION

July 2011
CASE FOLLOW-UP

• Received adjuvant XRT to the spine to consolidate his local response to bony metastasis

• Patient was started on systemic therapy post-op (sunitinib) with stability of disease for 26 months

• Then progressed and presently on axitinib with stability of disease for an additional 12 months
SURGERY IN THE SETTING OF METASTATIC RENAL CELL CARCINOMA
ROLE OF CYTOREDUCITIVE NEPHRECTOMY

• Pioneering work of Dr Flanigan and colleagues effectively demonstrating the improvement in overall survival in patients with metastatic RCC treated with cytoreductive nephrectomy (in the context of interferon immunotherapy)

• Combined analysis of SWOG 8949+85 and EORTC 30947 demonstrated a 5.8 month overall survival advantage with cytoreductive immunotherapy and immunotherapy

ROLE OF CYTOREDUCTIVE NEPHRECTOMY

Figure 1.

Duration of survival in combined SWOG and EORTC trials. O, observation; N, nephrectomy.

Logrank Test, $p = 0.001$
Fig. 2.
Role of Cytoreductive Nephrectomy

- A subsequent retrospective study conducted by Choueiri et al. assessing role of surgery in current TKI era

- A retrospective cohort of 314 patients treated with cytoreductive nephrectomy followed by anti-VEGF therapy

- Cytoreductive nephrectomy was associated with a median overall survival of 19.8 months versus 9.4 months if not performed prior to TKI (P<0.01)

On multivariate analysis, this overall survival benefit for cytoreductive nephrectomy persisted (P=0.04).

In subgroup analyses, patients in the poor risk (Motzer categories) had only a marginal benefit with surgery (P=0.06).

Patients with a Karnofsky performance status (less than 80%) had as well only a marginal benefit with surgery (P=0.08).
ROLE OF CYTOREDUCTIVE NEPHRECTOMY

Median OS: 19.8 vs. 9.4 months
Hazard Ratio: 0.44 (95% CI: 0.32-0.59)
p < 0.01

ROLE OF CYTOREDUCTIVE NEPHRECTOMY

• Study by Heng et al. evaluating the benefit of cytoreductive nephrectomy (CN) in patients with synchronous metastatic RCC (in present of targeted therapy)

• Retrospective assessment of the International Metastatic Renal Cell Carcinoma Database Consortium

• Median OS of patients undergoing CN versus without CN was 20.6 months vs 9.5 months (P<0.0001)
ROLE OF CYTOREDUCITIVE NEPHRECTOMY

Fig. 1 – Kaplan-Meier curve depicting the overall survival from the initiation of targeted therapy for 1633 metastatic renal cell carcinoma patients who did or did not receive a cytoreductive nephrectomy.

CI = confidence interval; CN = cytoreductive nephrectomy; HR = hazard ratio; OS = overall survival.

HENG DY et al. EUROPEAN UROLOGY, 2014
# Role of Cytoreductive Nephrectomy

**Table 4** - Overall survival differences in those with and without cytoreductive nephrectomy by number of International Metastatic Renal Cell Carcinoma Database Consortium criteria met

<table>
<thead>
<tr>
<th>No. of IMDC criteria met</th>
<th>No CN OS, mo (n)</th>
<th>CN OS, mo (n)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>92% of patients (65/71) had CN, insufficient number to compare</td>
<td>30.4 (n = 178)</td>
<td>0.002</td>
</tr>
<tr>
<td>1</td>
<td>22.5 (n = 72)</td>
<td>20.2 (n = 253)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>10.2 (n = 143)</td>
<td>15.9 (n = 106)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3</td>
<td>10.0 (n = 113)</td>
<td>6.0 (n = 67)</td>
<td>0.166</td>
</tr>
<tr>
<td>4</td>
<td>5.4 (n = 103)</td>
<td>2.8 (n = 14)</td>
<td>0.504</td>
</tr>
<tr>
<td>5</td>
<td>3.6 (n = 36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>25% of patients (3/12) had CN, insufficient number to compare</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall, 1168 of 1658 subjects (70%) had complete information about prognostic factors, nephrectomy, and outcomes and were used in this complete case analysis; the rest were excluded. Shaded rows indicate patient groups that may not benefit from cytoreductive nephrectomy.

CN = cytoreductive nephrectomy; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; OS = overall survival.
Which patients we operate on?

- Symptomatic/palliation
- Good/intermediate and selected poor risk
- Small number/favorable metastatic sites
- Predominant volume of disease in kidney
- Patient, physician, and tumor specific characteristics/anticipated outcomes
## Risk Categories in mRCC

### Motzer Risk Groups
- No prior nephrectomy status
- Karnofsky PS < 80%
- Low serum hemoglobin
- High corrected serum calcium
- High serum lactate dehydrogenase

### Heng Criteria
- Time from diagnosis to treatment less than 1 year
- Karnofsky PS < 80%
- Low serum hemoglobin
- High corrected serum calcium
- High serum neutrophil count
- High serum platelet count

---

Motzer Risk Groups

Heng Criteria


PRACTICAL APPROACH TO mRCC

Metastatic RCC Patient

Stratify Patients According to Motzer/Heng Risk Categories

Favorable Risk
- Upfront Cytoreductive Nephrectomy
- Post-Operative Systemic Therapy (likely TKI or IL-2 in Select Patients)

Intermediate Risk
- Choice of Nephrectomy vs Systemic Therapy (Based on ECOG/Karnofsky Performance Status, Tumor Histology, Symptomatic Primary or Metastatic Tumor Site, etc...)

Poor Risk
- Upfront Systemic Therapy +/- Clinical Trial*

Importance of Multidisciplinary Team Reviewing Pertinent Details of the Case

* Upfront cytoreductive nephrectomy can be considered in select poor-risk patients (e.g., as part of a clinical trial, patients with symptomatic primary tumor or metastatic tumor site)
Significant decline in # of surgeries

- Study by Tsao et al. revealing using SEER data that the # of patients undergoing surgery for mRCC declining by 38% in 2008

- On multivariate analysis, decrease use of cytoreductive nephrectomy was associated with advanced age (OR = 0.82), race (black OR= 0.64), hispanic (OR = 0.71), and onset of TKI era (OR = 0.82)
**SIGNIFICANT DECLINE IN # OF SURGERIES**

Fig. 1 The use of CyNx in the United States, 2001–2008 (SEER database). There is a significant cubic trend in CyNx over time, $p = 0.0041$.
### Significant Decline in # of Surgeries

#### Table: Nephrectomy Status in Selected Large, Single-Modality Medical Trials

<table>
<thead>
<tr>
<th>Study Sponsor and Reference</th>
<th>Systemic Therapy</th>
<th>Population Sample Size (No. of Patients)</th>
<th>Nephrectomy Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI15</td>
<td>Interleukin-2 (randomized)</td>
<td>154</td>
<td>100% nephrectomy</td>
</tr>
<tr>
<td>EDTG SWOG</td>
<td>Nephrectomy plus interferon vs interferon alone</td>
<td>331</td>
<td>Randomized 1:1</td>
</tr>
<tr>
<td>Bayer®</td>
<td>Sorafenib vs placebo</td>
<td>904</td>
<td>94%</td>
</tr>
<tr>
<td>Pfizer®</td>
<td>Sunitinib vs interferon</td>
<td>750</td>
<td>80% (of sunitinib arm)</td>
</tr>
<tr>
<td>Pfizer®</td>
<td>Sunitinib expanded access</td>
<td>4,617</td>
<td>80%</td>
</tr>
<tr>
<td>Wyeth®</td>
<td>Temsirolimus vs interferon vs both</td>
<td>416 (counting temsirolimus only and interferon only)</td>
<td>67%</td>
</tr>
<tr>
<td>Novartis®17</td>
<td>Everolimus vs placebo</td>
<td>410</td>
<td>96%</td>
</tr>
<tr>
<td>EDTG (Genentech)®</td>
<td>Bevacizumab + interferon vs interferon</td>
<td>649</td>
<td>Required (100%)</td>
</tr>
<tr>
<td>CALGB (Genentech)®</td>
<td>Bevacizumab + interferon vs interferon</td>
<td>732</td>
<td>85%</td>
</tr>
<tr>
<td>GlaxoSmithKline®</td>
<td>Pazopanib vs placebo</td>
<td>436</td>
<td>Required (100%)</td>
</tr>
</tbody>
</table>

NCI = National Cancer Institute, SWOG = Southwest Oncology Group, EDTG = European Organisation for Research and Treatment of Cancer, CALGB = Cancer and Leukemia Group B.

---

**Spiess PE et al, Cancer Control, 17:269, 2010**

---

**MOFFITT CANCER CENTER**
**Role of Cytoreductive Nephrectomy**

- Recent study by Hanna et al. published in the JCO evaluating the contemporary utilization rates of cytoreductive nephrectomy (CN) in mRCC and reassessing the survival benefit in the current era of targeted therapy.

- Data from the NCDB was assessed between 2006 and 2013.

- Of 15,390 Pts treated with targeted therapy, only 5,374 (35%) underwent cytoreductive surgery.

- Median OS of CN vs non-CN cohorts was 17.1 versus 7.7 months, respectively (P<0.001).
Role of Cytoreductive Nephrectomy

- Patients who were younger, privately insured, treated at an academic center, and had lower tumor stage and cN0 were more likely to undergo CN.

- Survival benefit of CN was +0.7 and +3.6 months who survived ≤ 6 and ≤ 24 months, respectively versus no CN.
ROLE OF CYTOREDUCTIVE NEPHRECTOMY

Fig 1. CONSORT diagram of patient selection within the National Cancer Data Base (NCDB), 2006 to 2013. CN, cytoreductive nephrectomy; ICD, International Classification of Diseases; mRCC, metastatic renal cell carcinoma; PUF, participant user file.
### Table 2. Multivariable Logistic Regression Predicting Receipt of Cytoreductive Nephrectomy Adjusting for Clustering Within Hospital and Multiple Patient and Hospital Characteristics in Patients With Metastatic Renal Cell Carcinoma Treated With Targeted Therapy Between 2006 and 2013, As Listed in the National Cancer Data Base (N = 15,390) (continued)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AJCC clinical N stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>1.0 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>0.51</td>
<td>0.47 to 0.56</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.56</td>
<td>0.50 to 0.63</td>
<td>&lt; .001</td>
</tr>
<tr>
<td><strong>Year of diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>1.0 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>0.93</td>
<td>0.78 to 1.10</td>
<td>.401</td>
</tr>
<tr>
<td>2008</td>
<td>1.23</td>
<td>1.03 to 1.47</td>
<td>.019</td>
</tr>
<tr>
<td>2009</td>
<td>1.08</td>
<td>0.90 to 1.29</td>
<td>.391</td>
</tr>
<tr>
<td>2010</td>
<td>1.18</td>
<td>0.98 to 1.43</td>
<td>.079</td>
</tr>
<tr>
<td>2011</td>
<td>1.08</td>
<td>0.90 to 1.31</td>
<td>.391</td>
</tr>
<tr>
<td>2012</td>
<td>1.13</td>
<td>0.94 to 1.36</td>
<td>.182</td>
</tr>
<tr>
<td>2013</td>
<td>1.06</td>
<td>0.88 to 1.26</td>
<td>.552</td>
</tr>
</tbody>
</table>

Abbreviations: AJCC, American Joint Committee on Cancer; CCI, Charlson comorbidity index; Ref, reference.
Role of Cytoreductive Nephrectomy

Fig 2. Kaplan-Meier survival analyses of patients with metastatic renal cell carcinoma treated with targeted therapy stratified according to cytoreductive nephrectomy (CN) status (yes or no), National Cancer Data Base, 2006 to 2012. Data were restricted to 12,895 patients with no missing information on vital status or follow-up time.
Recent retrospective study by Gerschman et al from the Mayo Clinic reporting on the contemporary outcomes of CN at their center over two decades (1990-2009)

- 294 Pts underwent CN at their center, with 15 Pts (5%) reported at least one Clavien grade ≥ 3 early complication

- Of those recommended post surgical systemic therapy, 61% did not receive it within 60 days of surgery (delay was surgery related in only 11%)

- On multivariate analysis, presence of liver metastasis was associated with periop complications (OR = 3.73) and increased LOS (OR = 2.46)
On multivariate analysis, MIS approach was associated with earlier administration of systemic Tx (HR = 5.05)

On a multivariate model incorporating OR parameters, intraop transfusion was associated with periop complications (OR = 1.14) and increased LOS (OR = 1.22) as well the presence of pN1 was associated with increased LOS (OR = 2.12) and delay in initiating systemic therapy (HR = 0.38)

GERSCHMAN B ET AL. EUR UROLOGY, 2016
**Contemporary outcomes of CN**

![Graph showing survival free of systematic therapy](image)

**No. at risk** 109 57 27 22 15 12 12

**Time since surgery (d)**

**Survival free of systematic therapy (%)**

**Fig. 1** – Kaplan-Meier plot of survival free of systemic therapy following cytoreductive nephrectomy.

*Gerschman B et al. Eur Urology, 2016*
Why are surgical rates declining?

EMERGENCE OF NEW SYSTEMIC THERAPIES

CHEN DS, ET AL. CLIN CANCER RES, 2012
WHERE IS THE FIELD GOING?

Era of personalized therapy
Conclusions

• Surgery has a clear and defined role in the management of metastatic and locally recurrent kidney cancer

• Risk categorization and personalized patient, physician, and tumor characteristics help delineate when surgery should be performed in this setting

• The importance of a multidisciplinary approach to such patients cannot be overemphasized and should be conducted routinely in such cases
He needed that vacation...