Cytoreductive Nephrectomy

Stephen H. Culp, M.D., Ph.D.
Assistant Professor, Department of Urology
Outline

• The “Historics” of CN

• The current status of CN

• The importance of patient selection
Cytoreductive Nephrectomy: Tufts University

• 28 highly selected patients (61 pts. deferred)
  • >75% debulking, absence of CNS, Liver, Bone mets, PS 0-1, clear cell histology
  • 93% received systemic therapy
  • Response rate 39%
    » 18% CR
    » 21% PR
• Median survival: 20.5 months
• Systemic therapy: IL-2

Fallick ML et. al., J Urol, 1997
Role Of Cytoreductive Nephrectomy In The Setting Of Metastatic Disease: EORTC 30947

IFN + Nx - 5 CR, 3 PR (19%)

IFN - 1CR, 4 PR (12%)

Role Of Cytoreductive Nephrectomy In The Setting Of Metastatic Disease: SWOG 8949

IFN + Nx - 3 PR (3%)

IFN - 1 CR, 2 PR (4%)

Flanigan R et al., NEJM, 2001
2001 SWOG vs. UCLA

Retrospective

Survival vs. Months

P<0.05

IFN

Nx + IFN

Nx + IL-2
We Now Have “Better” Therapy...

- Sorafenib
- Sunitinib
- Pazopanib
- Axitinib
- Temsirolimus
- Bevacizumab +/- IFN
- Everolimus

But......

We lack any level 1 evidence for the continued use CN in advanced disease
Phase 3 Randomized Study Comparing Nephrectomy plus Sunitinib versus Sunitinib without Nephrectomy in 1st line Metastatic RCC

Randomization

N = 576

- Primary Objective:
  - To show that Sunitinib alone is not inferior to Nephrectomy plus Sunitinib (non-inferiority study) in terms of Overall Survival (OS)
- Hypothesis:
  - Median OS expected in the nephrectomy plus Sunitinib = 24 months
  - Sunitinib alone will be considered as a clinically valid option if median OS > 19.9 months

CARMENA Study
Pr Arnaud Mejean (CCAFU – Necker Hospital – Paris, France)
Pr Alain Ravaud (GETUG – Saint-André Hospital – Bordeaux, France)
Schematic for the European Organization for Research and Treatment of Cancer phase III trial assessing the scheduling of sunitinib therapy in the peri-nephrectomy setting in metastatic clear-cell renal cell carcinoma.

Randomization
N = 458

Nephrectomy Then Sunitinib

Sunitinib Then Nephrectomy

Examine progression-free survival

Biswas S et al. The Oncologist 2009
Problems with Current Trials

• Adequate Power?

• Contamination of results
  – Crossover of patients in CARMENA trial

• What about the multitude of other agents?

• Are we really answering the question?
  – CARMENA is an non-inferiority study
  – EORTC SURTIME deals with timing of sunitinib – Every patient gets CN
What is the current status of CN in the US?
Potentially surgically resectable primary with multiple metastatic sites

“Cytoreductive nephrectomy in select patients prior to systemic therapy”
Cytoreductive Nephrectomy Utilization

Tsao CK et. al., Clinical GU Cancer, 2011
SEER 1998-2011

• 21,062 patients diagnosed with Stage IV RCC

• 7,260 underwent cytoreductive nephrectomy

• Sub-analyses done based on age, race, and gender
CN Overall

Culp SH, unpublished data
CN Based on Age

Culp SH, unpublished data
CN Based on Race

Culp SH, unpublished data
CN Based on Gender

Culp SH, unpublished data
CN in Patients Younger than 75

[Graph showing the percentage of patients undergoing CN over different years with different lines representing different categories.

Culp SH, unpublished data]
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<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
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<tr>
<td>Female</td>
<td>0.88</td>
<td>0.82, 0.94</td>
<td>&lt;0.001</td>
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<tr>
<td>AA race</td>
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<td>1.00</td>
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Culp SH, unpublished data
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Data would suggest that CN use has been relatively stable despite the introduction of TT.
What are the existing data that support the continued use of CN?
The majority of patients who have had a good response to targeted therapy have done so in the context of a previous nephrectomy.
### Sunitinib in Patient With or Without Prior Nephrectomy in an Expanded Access Trial of mRCC: Response

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Patients with prior Nx (n=3014*)</th>
<th>Patients without prior Nx (N=192)*</th>
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<tbody>
<tr>
<td>Objective response rate</td>
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<td></td>
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<tr>
<td>Complete response</td>
<td>538 (18)</td>
<td>17 (9)</td>
</tr>
<tr>
<td>Partial response</td>
<td>31 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Stable disease &gt;3 months</td>
<td>507 (17)</td>
<td>17 (9)</td>
</tr>
<tr>
<td>Clinical benefit†</td>
<td>1764 (59)</td>
<td>118 (61)</td>
</tr>
<tr>
<td></td>
<td>2302 (76)</td>
<td>135 (70)</td>
</tr>
</tbody>
</table>

Nx=nephrectomy
*Only patients with evaluable efficacy data included
†Clinical benefit=ORR + SD ≥ 3 months

Szczylik et al. ASCO 2008. Abstract 5124
Sunitinib in Patients With or Without Prior Nephrectomy in an Expanded Access Trial of mRCC: PFS (No Prior Cytokine Treatment)

- **Patients with prior nephrectomy (n=1020)**
  - Median = 12.0 mo
  - (95% CI, 10.9-13.4)

- **Patients without prior nephrectomy (n=146)**
  - Median = 6.5 mo
  - (95% CI, 5.4-10.2)
  - \( P=0.0021 \)

**mRCC** = metastatic renal cell carcinoma; **PFS** = progression-free survival

Sunitinib in Patients With or Without Prior Nephrectomy in an Expanded Access Trial of mRCC: OS (No Prior Cytokine Treatment)

OS probability

Patients with prior nephrectomy (n=1020)
Median = 19.0 mo
(95% CI, 18.2-21.4)

Patients without prior nephrectomy (n=146)
Median = 11.1 mo
(95% CI, 8.4-15.1)
P<0.0001

OS = overall survival

Cytoreductive Nephrectomy in Patients Treated with VEGF-Targeted Therapy

• Multi-institutional retrospective analysis
• Sunitinib, sorafenib, or bevacizumab
• 314 patients
  – 201 → CN
  – 113 → no surgery
• CN patients
  – Younger
  – Better KPS
  – > 1 site of metastasis
  – Lower corrected calcium levels

Cytoreductive Nephrectomy in Patients Treated with VEGF-Targeted Therapy

Cytoreductive Nephrectomy in Patients Treated with VEGF-Targeted Therapy

Cytoreductive Nephrectomy in Patients with Synchronous Metastases from Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium

Daniel Y.C. Heng\textsuperscript{a,*,†}, J. Connor Wells\textsuperscript{a,†}, Brian I. Rini\textsuperscript{b}, Benoit Beuselinck\textsuperscript{c}, Jae-Lyun Lee\textsuperscript{d}, Jennifer J. Knox\textsuperscript{e}, Georg A. Bjarnason\textsuperscript{f}, Sumanta Kumar Pal\textsuperscript{g}, Christian K. Kollmannsberger\textsuperscript{h}, Takeshi Yuasa\textsuperscript{i}, Sandy Srinivas\textsuperscript{j}, Frede Donskov\textsuperscript{k}, Aristotelis Bamias\textsuperscript{l}, Lori A. Wood\textsuperscript{m}, D. Scott Ernst\textsuperscript{n}, Neeraj Agarwal\textsuperscript{o}, Ulka N. Vaishampayan\textsuperscript{p}, Sun Young Rha\textsuperscript{q}, Jenny J. Kim\textsuperscript{r}, Toni K. Choueiri\textsuperscript{s}

- International Metastatic Renal Cell Carcinoma Database Consortium
- Patients with synchronous metastatic RCC
- CN $\rightarrow$ 982
- No CN $\rightarrow$ 676
PFS increased in CN patients – 7.6 vs. 4.5 months (p<0.001)

Heng DYC et al., Eur Urol, 2014
Cytoreductive Surgery For Metastatic Renal Cell Carcinoma:

It’s Not For Everyone!
The Importance of Patient PS

- Original data (Tufts) based on highly selected patients including ECOG 0 or 1
- All prospective trials enroll(ed) patients with a good (ECOG ≤ 1) PS
  - EORTC 30947 and SWOG 8949 (cytokine)
  - CARMENA and EORTC (SURTIME) (targeted therapy)
- Retrospective data including poor PS demonstrates no real benefit from surgery
Poor Prognostic Factors

- ↑ LDH
- ↑ Alkaline phosphatase
- ↓ Serum albumin
- Clinical stage ≥ T3
- Liver metastasis
- CNS metastasis
- Sx at presentation due to metastasis
- RPLN involvement

- Supra-diaphragmatic lymph node involvement
- Sarcomatoid histology
- ↑ Corrected serum calcium
- Dx to Tx < 12 months
- ↓ Hemoglobin
- Neutrophilia
- Thrombocytosis
Notably it is not one factor that determines benefit but rather the additive nature of poor prognostic factors.

These, in turn, translate into patient survival.
The greatest benefit seen in patients expected to survive > 12 months

Table 3 – Incremental overall survival benefit from cytoreductive nephrectomy separated by estimated survival times

<table>
<thead>
<tr>
<th>OS, mo</th>
<th>No CN OS, mo</th>
<th>CN OS, mo</th>
<th>Incremental benefit, mo</th>
<th>p value</th>
<th>HR (95% CI) adjusted for IMDC criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24</td>
<td>7.1</td>
<td>12.3</td>
<td>+5.2</td>
<td>&lt;0.0001</td>
<td>0.72 (0.62–0.85)</td>
</tr>
<tr>
<td></td>
<td>n = 456</td>
<td>n = 480</td>
<td></td>
<td></td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>n = 676&lt;sup&gt;∗&lt;/sup&gt;</td>
</tr>
<tr>
<td>&lt;18</td>
<td>6.7</td>
<td>10.0</td>
<td>+3.3</td>
<td>&lt;0.0001</td>
<td>0.85 (0.72–1.00)</td>
</tr>
<tr>
<td></td>
<td>n = 430</td>
<td>n = 395</td>
<td></td>
<td></td>
<td>p = 0.05</td>
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<td></td>
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<td>n = 602&lt;sup&gt;∗&lt;/sup&gt;</td>
</tr>
<tr>
<td>&lt;12</td>
<td>5.5</td>
<td>7.3</td>
<td>+2.2</td>
<td>&lt;0.0001</td>
<td>0.97 (0.81–1.17)</td>
</tr>
<tr>
<td></td>
<td>n = 366</td>
<td>n = 290</td>
<td></td>
<td></td>
<td>p = 0.761</td>
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<tr>
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<td>n = 483&lt;sup&gt;∗&lt;/sup&gt;</td>
</tr>
<tr>
<td>&lt;9</td>
<td>4.5</td>
<td>5.5</td>
<td>+1.0</td>
<td>0.0027</td>
<td>0.98 (0.79–1.20)</td>
</tr>
<tr>
<td></td>
<td>n = 303</td>
<td>n = 218</td>
<td></td>
<td></td>
<td>p = 0.811</td>
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<td></td>
<td></td>
<td>n = 385&lt;sup&gt;∗&lt;/sup&gt;</td>
</tr>
<tr>
<td>&lt;6</td>
<td>3.2</td>
<td>4.0</td>
<td>+0.8</td>
<td>0.0084</td>
<td>1.02 (0.80–1.31)</td>
</tr>
<tr>
<td></td>
<td>n = 230</td>
<td>n = 151</td>
<td></td>
<td></td>
<td>p = 0.856</td>
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<td>n = 280&lt;sup&gt;∗&lt;/sup&gt;</td>
</tr>
<tr>
<td>&lt;3</td>
<td>2.1</td>
<td>2.2</td>
<td>+0.1</td>
<td>0.9429</td>
<td>1.03 (0.72–1.46)</td>
</tr>
<tr>
<td></td>
<td>n = 118</td>
<td>n = 71</td>
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<td>p = 0.878</td>
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<td>n = 146&lt;sup&gt;∗&lt;/sup&gt;</td>
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CI = confidence interval; CN = cytoreductive nephrectomy; HR = hazard ratio; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; OS = overall survival.<sup>∗</sup> The n used in the adjusted HR does not match the sum of CN versus no CN patients in each row due to missing data on prognostic factors because a complete case analysis was used.
MDACC Series

No survival benefit with CN in patients not surviving > 8.5 months

Culp SH et al., CANCER, 2008
Summary

• CN usage (in the US) has remained relatively stable despite the introduction of TT
  – Discrepancies based race and gender

• Although we lack level 1 evidence in the TT era, existing data do support a continued benefit of CN
  – Is level 1 evidence even necessary or possible for every question?
Summary

• Patient selection is key!
  – Nomograms exist (or are in development) that can help stratify patients based on prognostic risk factors
  – Patients with expected survival < 12 months based on risk factors will likely not benefit from cytoreductive surgery
Thank You