Cytoreductive Nephrectomy: Yes, No, Clinical Trial?

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European Association of Urology (EAU) Guidelines/Recommendation

Stage IV

Cytoreductive nephrectomy in appropriately selected patients

Recommended if:
- Good PS
- Large primary tumor
- Low metastatic burden

NOT recommended if:
- Poor PS
- IMDC or MSKCC poor-risk disease
- Small primary tumor with high metastatic burden
- Sarcomatoid disease

Ljungberg B. Eur Urol. 2014 and 2015
Stage IV

- **Primary Tumor Surgically Resectable + Resectable Solitary Met**
  - Cytoreductive Nephrectomy + Metastasectomy
- **Primary Tumor Surgically Resectable + Multiple Mets**
  - Cytoreductive Nephrectomy + Systemic Therapy
- **Surgically Unresectable**
  - Systemic Therapy

National Comprehensive Cancer Network (NCCN) Guidelines v2.2017
CYTOREDUCTIVE NEPHRECTOMY IN IMMUNOTHERAPY ERA
Cytoreductive Nephrectomy in “Immunotherapy” Era

SWOG 8949

- 246 patients (80 institutions)
- Biopsy-proven RCC
- SWOG PS 0-1
- Overall Survival
  - Surgery + IFNα → 11.1 months
  - IFNα alone → 8.1 months

Flanigan R. NEJM. 2001
Cytoreductive Nephrectomy in “Immunotherapy” Era

EORTC 30947

- 1995-1998
- 85 patients
- Biopsy-proven RCC
- WHO PS 0-1
- Overall Survival
  - Surgery + IFNα → 17 months
  - IFNα alone → 7 months

Mickisch GH. Lancet. 2001
Cytoreductive Nephrectomy in “Immunotherapy” Era

Combined Results (SWOG 8949 + EORTC 30947)

Overall Survival

- Nephrectomy + IFNα → 13.6 months
- IFNα alone → 7.8 months
Cytoreductive Nephrectomy in “Immunotherapy” Era

Role of Cytoreductive Nephrectomy + IL-2

- Retrospective
- 89 patients (UCLA)
- Met criteria for SWOG 8949
- Treated with IL-2 (not IFNα)
- Overall survival → 16.7 months

Pantuck AJ. NEJM. 2001
CYTOREDUCTIVE NEPHRECTOMY IN THE TARGETED THERAPY ERA
**CARMENA trial:** Phase 3 Randomized Study Comparing Nephrectomy plus Sunitinib versus Sunitinib without Nephrectomy in 1st line Metastatic RCC

- **PI:** Dr. Arnaud Mejean
- **Primary Endpoint:** Overall Survival
- **Start Date:** September 2009
- **Estimated completion date:** February 2020

ClinicalTrials.gov Identifier: NCT00930033
**SURTIME trial: Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients With Metastatic Kidney Cancer**

- **PI:** Dr. Axel Bex
- **Primary Endpoint:** Early postoperative progression (originally PFS)
- **Start Date:** April 2010
- **Stopped Accrual:** April 2016 at 99 patients

ClinicalTrials.gov Identifier: NCT01099423
Cytoreductive Surgery For Metastatic Renal Cell Carcinoma in 2016

What do we do while awaiting the SURTIME and CARMENA trial results (2017 at the earliest)?
CYTOREDUCTIVE NEPHRECTOMY IN TARGETED THERAPY ERA: RETROSPECTIVE STUDIES
The Impact of Cytoreductive Nephrectomy on Survival of Patients With Metastatic Renal Cell Carcinoma Receiving Vascular Endothelial Growth Factor Targeted Therapy


**Entire Study Population**

<table>
<thead>
<tr>
<th>KPS ≥ 80</th>
<th>KPS &lt; 80</th>
</tr>
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<tbody>
<tr>
<td>Median OS: 23.9 vs. 14.5 months</td>
<td>Median OS: 10.1 vs. 6 months</td>
</tr>
<tr>
<td>Hazard Ratio: 0.44 (95% CI: 0.32-0.59)</td>
<td>Hazard Ratio: 0.44 (95% CI: 0.32-0.59)</td>
</tr>
<tr>
<td>p &lt; 0.01</td>
<td>p = 0.08</td>
</tr>
</tbody>
</table>

**CN = 201 pts**
**No CN = 113 pts**

**Cytoreductive Nephrectomy**

- Yes
- No

**MD Anderson Cancer Center**

Choueiri T. J Urol. 2011
Entire Study Population

CN = 298 pts
No CN = 53 pts

ECOG 0-1

Log rank test p = 0.04

MSKCC Fav+Intermed

Log rank test p = 0.02

Mathieu R. Urol Oncol. 2015
Cytoreductive Nephrectomy in Patients with Synchronous Metastases from Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium


Median OS: 20.6 mo vs 9.6 mo
Adjusted HR: 0.60 (95% CI, 0.52–0.69), p < 0.0001

CN = 980 pts
No CN = 673 pts
Survival Analyses of Patients With Metastatic Renal Cancer Treated With Targeted Therapy With or Without Cytoreductive Nephrectomy: A National Cancer Data Base Study


Yes CRN ⇒ HR 0.49 (0.46-0.52) p<0.001
A CLOSER LOOK AT CYTOREDUCTIVE NEPHRECTOMY AND SURVIVAL AT 6 MONTHS
How Many Patients Died at 6 Months?

Dead at 6 months:
- Nephrectomy + IFN ~30%
- IFN alone ~40%

Flanigan RC. J Urol. 2004
How Many Patients Died at 6 Months?

Dead at 6 months:
Nephrectomy + Targeted Therapy ~20%
Targeted Therapy alone ~40%

Heng DY. Eur Urol. 2014
How Many Patients Died at 6 Months?

- Therapy alone → ~40%
- Cytoreductive nephrectomy + Therapy → ~20-30%
  - These patients did not benefit from surgery (even though PS 0-1, limited metastatic burden, etc...)
Can We Identify Patients Who Do **Not** Benefit from Cytoreductive Nephrectomy?

- Preoperative clinical and lab factors
- Preoperative response to therapy as “Litmus” test
- Molecular studies
1- USING PREOPERATIVE FACTORS AS A "BIOMARKER"
Preoperative Risk Factors

- Albumin < LLN
- LDH > ULN
- Liver metastasis
- Symptoms at presentation
- Retroperitoneal lymph node involvement
- Supra-diaphragmatic lymph node involvement
- Clinical T stage 3 or 4
Nomogram:
- Low Albumin
- High LDH

C-Index = 0.76

Externally validated (c-Index = 0.67)

[As a reference
- c-Index for IMDC = 0.70
- c-index for MSKCC = 0.66]

Low Albumin validated by an independent study

Margulis V. Eur Urol. 2013
Bex A. ASCO GU 2016. #556
Ko JJ. Lancet Oncol. 2015
Corcoran AT. BJU Int. 2015
### Criteria studied:
- Hb < LLN
- Calcium > ULN
- Neutrophils > ULN
- Platelets > ULN
- KPS < 80%
- Time from Dx to Rx < 1 year

<table>
<thead>
<tr>
<th>No IMDC Criteria</th>
<th>No CN OS (mo)</th>
<th>CN OS (mo)</th>
<th>P-value</th>
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<td>0</td>
<td>Insufficient number to compare</td>
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</tr>
<tr>
<td>1</td>
<td>22.5 (n = 72)</td>
<td>30.4 (n = 178)</td>
<td>0.002</td>
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<tr>
<td>2</td>
<td>10.2 (n = 143)</td>
<td>20.2 (n = 253)</td>
<td>&lt;0.001</td>
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<tr>
<td>3</td>
<td>10.0 (n = 113)</td>
<td>15.9 (n = 106)</td>
<td>&lt;0.001</td>
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<tr>
<td>4</td>
<td>5.4 (n = 103)</td>
<td>6.0 (n = 67)</td>
<td>0.166</td>
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<tr>
<td>5</td>
<td>3.6 (n = 36)</td>
<td>2.8 (n = 14)</td>
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<tr>
<td>6</td>
<td>Insufficient number to compare</td>
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</table>
2- USING RESPONSE TO PRESURGICAL THERAPY AS A “BIOMARKER” (LITMUS TEST)
The Role of Initial Immunotherapy as Selection for Nephrectomy in Patients with Metastatic Renal Cell Carcinoma and the Primary Tumor in Situ

A. Bex\textsuperscript{a,*}, S. Horenblas\textsuperscript{a}, W. Meinhardt\textsuperscript{a}, N. Verra\textsuperscript{b}, G.C. de Gast\textsuperscript{b}

\[ \text{IL-2 + GM-CSF + IFNa} \quad (N=16) \]

- PR (2) or SD (9) - Nephrectomy (OS 11.5 mo)
- PD (5) - No Nephrectomy (OS 3 mo)

Bex A. Eur Urol. 2002
Interferon alpha 2b as Medical Selection for Nephrectomy in Patients with Synchronous Metastatic Renal Cell Carcinoma: A Consecutive Study

Axel Bex\textsuperscript{a*,} Martyn Kerst\textsuperscript{b,} Henk Malle\textsuperscript{b,} Wim Meinhardt\textsuperscript{a,} Simon Horenblas\textsuperscript{a,} Gy\textsuperscript{s}bert C. de Gast\textsuperscript{b}

IFNa alone
(N=16)

- PR (3) or SD (5)
- PD (8)

Nephrectomy
(OS NR, 1-yr OS 50%)

No Nephrectomy
(OS 4 mo)

Bex A. Eur Urol. 2006
Phase II Presurgical Feasibility Study of Bevacizumab in Untreated Patients With Metastatic Renal Cell Carcinoma

Jonasch, Christopher G. Wood, Surena F. Matin, Shi-Ming Tu, Lance C. Pagliaro, Paul G. Corn, Ana Aparicio, Pheroze Tamboli, Randall E. Millikan, Xuemei Wang, John C. Araujo, Wadih Arap, and Nizar Tannir
Overall Survival

- 2 Phase II studies
- 66 patients, ccRCC
- 2-3 cycles of Sunitinib
- 47 patients had surgery
- 17 pts (26%) with Progressive Disease in metastatic sites while on therapy
104 patients treated with pazopanib
- 63 (61%) underwent CRN
  - 14 (22%) complications. 1 postoperative death
- 41 did not have CRN
  - 13 PD
  - 9 patient choice
  - 7 died before surgery
  - 5 not surgical candidates
  - 7 other

MSKCC poor-risk disease $\rightarrow$ OS 5.7 months
PD prior to surgery $\rightarrow$ OS 3.9 months
Ongoing: Presurgical Immunotherapy Trial-MDACC (PI: P. Sharma)

60 patients, Resectable Primary, Randomized- 3 arms
No surgery if worsening PS and PD

**Metastatic Clear Cell RCC**

- Nivolumab
  - 4 wk
  - Nephrectomy
  - 4-6 wk

- Nivolumab + Bevacizumab
  - 4 wk
  - Nephrectomy
  - 4-6 wk

- Nivolumab + Ipilimumab
  - 4 wk
  - Nephrectomy
  - 4-6 wk

ClinicalTrials.gov Identifier: NCT02210117
Is an Early Minor (≥10%) PT Response Associated with Overall Survival?

<table>
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<tr>
<th></th>
<th>Hazard Ratio</th>
<th>95% CI</th>
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<tr>
<td>≥ 10% PT response in 60 days</td>
<td>0.26</td>
<td>0.08, 0.89</td>
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<tr>
<td>Renal vein or IVC thrombus</td>
<td>1.33</td>
<td>1.09, 1.63</td>
</tr>
<tr>
<td>Multiple bone metastases</td>
<td>2.05</td>
<td>1.00, 4.21</td>
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<tr>
<td>Lactate dehydrogenase &gt; ULN</td>
<td>2.42</td>
<td>1.26, 4.63</td>
</tr>
<tr>
<td>Local symptoms at presentation</td>
<td>3.03</td>
<td>1.57, 5.84</td>
</tr>
<tr>
<td>Number of metastatic sites &gt;2</td>
<td>3.28</td>
<td>1.65, 6.52</td>
</tr>
</tbody>
</table>

Abel EJ. Eur Urol. 2011
PT Response to Targeted Therapy and Overall Survival

• Phase II
• 22 patients
• Sunitinib
3- USING MUTATIONAL STUDIES ON TUMOR TISSUE AS A “BIOMARKER”
Genomic Studies to Identify Who Might Benefit from Cytoreductive Nephrectomy

- 194 patients who underwent cytoreductive nephrectomy
- Stratified patients into 3 groups based on the mutational status of BAP1 and PBRM1

Figure 1. Cancer-Specific Survival Based on BAP1 and PBRM1 Status

Manley BJ. AUA 2016 Annual Meeting. MP78-16
THOUGHTS TO CONSIDER...
CARMENA and SURTIME Eligibility Criteria

• Patients with low metastatic burden were not eligible for CARMENA or SURTIME
The CON Argument: Cytoreductive Nephrectomy was only Studied in “Immunotherapy” Era, so Results are no longer valid?

• If PD-1 inhibitor or PD-L1 inhibitor or VEGFGR/Met inhibitor (or others) become first line therapy, will we ignore CARMENA and SURTIME results?
• Do we really need a trial for every new drug or new class of drug?
• Or, can we test surgery as a concept of cytoreduction with the best systemic treatment available at the time (i.e. drug-du-jour)?
Two Questions!

**#1** - Can we pick the patients who **will** do poorly (whether nephrectomy is done or not) and avoid surgery in these patients?
  - Preoperative risk factors
  - Preoperative therapy as Litmus test
  - Molecular analyses

**#2** - In patients who are **not** expected to do poorly, does surgery help prolong survival?
How About This as an Example?

Stage IV

“Best” Systemic Treatment
How About This as an Example?

Can we pick the patients who will do poorly and avoid surgery?

Stage IV

“Best” Systemic Treatment

PD/Poor PS

No Nephrectomy
How About This as an Example?

Stage IV

“Best” Systemic Treatment

Can we pick the patients who will do poorly and avoid surgery?

PD/Poor PS

No Nephrectomy

PR/SD/Good PS

Nephrectomy

In patients who do NOT do poorly, does surgery help?

“Best” Systemic Treatment
Or This?

- Prospectively validate selection criteria (clinical, presurgical therapy, and/or molecular) for those who should undergo CRN?
**Take Home Messages- Cytoreductive Nephrectomy**

- Cytoreductive nephrectomy is **NOT** for everyone
- Cytoreductive nephrectomy *is* associated with longer survival in **well-selected** patients
  - Prospective data (IFN)
  - Retrospective data (IL-2 or targeted therapies)
- We **could** potentially predict who might benefit from cytoreductive nephrectomy
  - Preoperative risk factors
  - Preoperative therapy as Litmus test
  - Molecular analyses
Take Home Messages - Cytoreductive Nephrectomy

• In 2016, we should continue performing cytoreductive nephrectomy in
  – Younger patients
  – Clear-cell histology
  – Good performance status
  – Limited metastatic burden
  – 3 or less MDACC or IMDC risk factors
  – Preferably in high-volume centers

• **BUT**, patients who fall in other categories should not be automatically denied nephrectomy
Take Home Messages-
Cytoreductive Nephrectomy

• Most studies are retrospective, or small phase II
• Awaiting results of ongoing trials (SURTIME and CARMENA)
• We need to collaborate and perform:
  – Clinical trials with novel design
  – Molecular studies
THANK YOU

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