The Role Of Cytoreductive Surgery In The Era Of Targeted Therapy For Metastatic Renal Cell Carcinoma

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City of Hope
Comprehensive Cancer Center

Cytoreductive Surgery

• Review indications and outcomes
• Examine specific subsets of patients where the role of cytoreductive surgery is not clear
  • Elderly
  • T4
  • Bulky nodal disease
• Integration of targeted therapies with surgery
  • Neoadjuvant strategies
Upfront Cytoreductive Surgery Is The Standard Of Care In Properly Selected Patients With Metastatic/Recurrent Renal Cell Carcinoma

Argument For Cytoreductive Nephrectomy

- Palliate local symptoms
- Primary tumor rarely responds to systemic therapy
- Delay time to disease progression
- Improve survival
- Systemic therapy ineffective
- Possibility of spontaneous regression
Argument Against Cytoreductive Nephrectomy

- Surgical morbidity/mortality significant
- Benefits remain unproven (except with interferon)
- Spend majority of time left on this earth recovering from surgery
- Significant disease progression during post-operative recovery period precludes systemic therapy
- Delays initiation of systemic therapy to treat metastatic disease

Results Of Therapy With Primary Tumor In Place

<table>
<thead>
<tr>
<th>Institution</th>
<th>Number of patients</th>
<th>Response Rate</th>
<th>Response in Primary Tumor</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI</td>
<td>51</td>
<td>6%</td>
<td>0%</td>
<td>13 months</td>
</tr>
<tr>
<td>Netherlands Cancer Institute</td>
<td>16</td>
<td>12.5%</td>
<td>0%</td>
<td>3 months</td>
</tr>
</tbody>
</table>
Cytoreductive Nephrectomy: Retrospective Series

<table>
<thead>
<tr>
<th>Institution</th>
<th>Number of patients</th>
<th>Periop Mortality</th>
<th>Eligible for systemic therapy</th>
<th>Therapy response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albert Einstein</td>
<td>30</td>
<td>17%</td>
<td>23%</td>
<td>13.3%</td>
</tr>
<tr>
<td>NCI</td>
<td>195</td>
<td>1%</td>
<td>62%</td>
<td>18%</td>
</tr>
<tr>
<td>UCLA</td>
<td>63</td>
<td>0%</td>
<td>88%</td>
<td>33.9%</td>
</tr>
<tr>
<td>Tufts</td>
<td>28</td>
<td>0%</td>
<td>93%</td>
<td>39%</td>
</tr>
<tr>
<td>MDACC</td>
<td>66</td>
<td>1%</td>
<td>95.5%</td>
<td>NR</td>
</tr>
</tbody>
</table>

Metastatic RCC
Nephrectomy & Immunotherapy
UCLA 1989-1999

% Survival vs Months

P<0.05

J UROL 166: 1611, 2001
Role Of Cytoreductive Nephrectomy In The Setting Of Metastatic Disease: EORTC 30947

**Time to Progression**
- IFN + Nx 5 CR, 3 PR (19%)
- IFN 1 CR, 4 PR (12%)

Mickisch G et al., Lancet, 2001

**Overall Survival**

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
Does the Application of Better Therapy Automatically Mean Better Outcomes With a Multidisciplinary Approach That Includes Cytoreductive Surgery?
Cytoreductive Surgery For Metastatic Renal Cell Carcinoma: Who, When, How Much?

MDACC Experience with Cytoreductive Nephrectomy in the Elderly

- Western society is aging
- Life expectancy is increasing
- The incidence of RCC increases with age and peaks in those aged 75 to 85
- There is an increase in presentation of advanced RCC
- Elderly patients with advanced malignancy are often not offered standard therapy

Kader et al., J Urol 3/07
MDACC Experience with Cytoreductive Nephrectomy in the Elderly

All Cytoreductive Nephrectomies at MDACC 1995-2005

24 ≥ 75 years 380 < 75 years

Outcomes Were Analyzed

Kader et al., J Urol, 3/07

Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Elderly N=24</th>
<th>Younger N=380</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>77.5 (75-84)</td>
<td>57 (14-74)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ECOG PS - 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 1</td>
<td></td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>- 2</td>
<td>12 (50.0)</td>
<td>219 (57.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 (45.8)</td>
<td>157 (41.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (4.2)</td>
<td>4 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (54.2)</td>
<td>273 (71.7)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11 (45.8)</td>
<td>107 (28.3)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Kader et al., J Urol, 3/07
### Tumor Characteristics

<table>
<thead>
<tr>
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<th>Elderly N=24</th>
<th>Younger N=380</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T Stage</strong> - T1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- T2</td>
<td>3 (12.5)</td>
<td>30 (7.9)</td>
<td>0.31</td>
</tr>
<tr>
<td>- T3a</td>
<td>4 (16.7)</td>
<td>53 (13.9)</td>
<td></td>
</tr>
<tr>
<td>- T3b/c</td>
<td>14 (58.3)</td>
<td>124 (32.6)</td>
<td></td>
</tr>
<tr>
<td>- T4</td>
<td>0 (0.0)</td>
<td>158 (41.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>4 (2-4)</td>
<td>3 (1-4)</td>
<td></td>
</tr>
<tr>
<td><strong>Size (cm)</strong></td>
<td>9.0 (4.0-25.0)</td>
<td>10.0 (2.0-35.0)</td>
<td></td>
</tr>
</tbody>
</table>

*Kader et al., J Urol, 3/07*

### Perioperative Events

<table>
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<tr>
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<th>Elderly N=24</th>
<th>Younger N=380</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EBL (L)</strong></td>
<td>0.58 (0-20)</td>
<td>0.6 (0-19.9)</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>OR Time (H:M)</strong></td>
<td>3:31</td>
<td>3:25</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Transfusion Rate</strong></td>
<td>11 (45.8)</td>
<td>182 (47.9)</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>Periop Mortality</strong></td>
<td>5 (20.8)</td>
<td>4 (1.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Length of Stay (d)</strong></td>
<td>6.0 (2-14)</td>
<td>6.0 (1-56)</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Time to Therapy (d)</strong></td>
<td>30.5 (10-97)</td>
<td>36.0 (7-152)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Survival Time (m)</strong></td>
<td>16.6 (0-115)</td>
<td>13.7 (.3-111.3)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

*Kader et al., J Urol, 3/07*
Survival Curves Comparing Younger to Older Cytoreductive Nephrectomy Patients

P = 0.89 by log-rank

Kader et al., J Urol, 3/07

T4NxM1 Cytoreductive Nephrectomy

Number of Patients 23
Median Age 55 (35-73)
Median Tumor Size 15 cm (7-30)
Sites of Metastases
  Pulmonary 20 (87%)
  Bone 4 (17%)
  Liver 3 (13%)
  Other 6 (26%)
Estimated Blood Loss 2445 ml (225-15000)
Length of Stay 7 days (5-19)
Time To Systemic Rx 39 days (24-113)

Kassouf et al., Urology, 2008
T4NxM1 Cytoreductive Nephrectomy: Survival

Probability of survival

Time in months

Cumulative # events

Patients at risk

Kassouf et al., Urology, 2008

T4NxM1 Cytoreductive Nephrectomy: Effect of Systemic Therapy

Received systemic Rx

No systemic Rx

p=0.003

Median DSS Systemic Rx 7.1 months (1.4-25.7)

Median DSS No Systemic Rx 2.5 months (0-5.2)

Kassouf et al., Urology, 2008
Nodal Metastases In Metastatic RCC

Presence of Nodal Metastases In Metastatic Renal Cell Carcinoma Predicts Survival

Survival

N- (82 pts): 14.7 mos
N+ (72 pts): 8.5 mos

Overall Survival for RCC Patients With and Without Nodal Metastases

Cytoreductive Surgery Prior To Systemic Therapy for mRCC

- Past
  - Remove kidney, adrenal, any threatening mets
  - Further cytoreduction of unproven benefit, increased morbidity
  - Leave additional lesions as index lesions for assessment of response to systemic therapy

- Present
  - Aggressive resection of all gross disease
  - Only proven for clear cell histology
    - Role in other histologies unproven
What is the role of cytoreductive surgery in the setting of targeted therapy?

Do We Need Randomized Trial(s)?

**TARGETs**

Single, Planned Progression-Free Survival Analysis

- **Median PFS**
  - Sorafenib = 24 weeks
  - Placebo = 12 weeks
  - Hazard ratio = 0.44 (95% CI: 0.35, 0.55)
  - \( p \)-value < 0.000001

*Independently assessed

**PFS analysis performed March, 2005 (data cut-off Jan 28, 2005)

Escudier B et al. Oral presentation, ASCO, 2005
Sorafenib
Primary Tumor Response


Sorafenib
Maximum Percent Reduction in Tumor Measurement*

*Independently assessed measurements available for 574 patients
Progression-free Survival (Studies 014 and 1006)

Median PFS: 8.2 months (95% CI: 7.8, 10.4)

Sunitinib in mRCC: Example of a Tumor Response

Sunitinib for Renal Cell Carcinoma

MAXIMUM % REDUCTION OF TARGET LESIONS BY PATIENT

-100 -80 -60 -40 -20 0 20 40

Partial Responders by RECIST
SD/PD Patients

Role Of Cytoreductive Nephrectomy In The Era Of Targeted Therapy

Cytoreductive Nephrectomy → Sunitinib 4wks/2wks

Metastatic RCC with primary tumor in place

Sunitinib 4wks/2wks

Accrual: 572 patients

Primary Endpoint: Survival
Secondary Endpoints: TTP, RR
Cytoreductive Surgery Remains The Paradigm Of Choice

- Most patients in trials had previous nephrectomy
- Few if any complete responses
- Downstaging probably not “clinically relevant”
- Residual primary tumor still a source of morbidity and metastatic progression
- Has worked with other therapies in the past (immunotherapy)
- ?Need for another randomized trial?
  - Good Luck
  - Do we need to do another randomized trial combining surgery with every systemic therapy advance?

Metastatic Renal Cell Carcinoma Requires A Multidisciplinary Approach But Should Surgery Take The Lead Position?
Delayed Cytoreductive Nephrectomy: Neoadjuvant Approach

PRO
- Selects patients for surgery that are responding to therapy
- Downstaging
- Eliminates morbidity/mortality in those that won’t benefit anyway

CON
- May add to morbidity/mortality of surgery
- May “decondition” good surgical candidates
- No proven benefit
- Unclear when to pull the “trigger”

Surgical Issues Associated With Neoadjuvant Approaches

- Therapy may impact wound healing, recovery
  - Higher incidence of wound complications
- Local tumor progression increases complexity of the surgery
- Timing is everything
  - Why rock the boat in responders?
  - Risk of progression/death in nonresponders
Targeted Therapy Can Impact Wound Healing

Cytoreductive Nephrectomy For Metastatic Renal Cell Carcinoma In The Era Of Targeted Therapy: Not a question of “if” but “when”? 
Timing Of Cytoreductive Nephrectomy In Metastatic Renal Cell Carcinoma

Untreated Metastatic Renal Cell Carcinoma With Primary Tumor In Place (PS 0-1, Surgical Candidate)

Biopsy To Establish Clear Cell Histology; Lack of Sarcomatoid

Targeted Therapy

Survival, Response Rate, Time To Progression, Surgical Morbidity/Mortality

Cytoreductive Nephrectomy

Targeted Therapy

Non Clear Cell Histology; Sarcomatoid Managed By Standard of Care or Other Clinical Protocol

Timing Of Cytoreductive Nephrectomy In Metastatic Renal Cell Carcinoma: Issues

- Standardization of targeted therapy: Does it matter?
- Duration of targeted therapy prior to surgery
  - Defined period?
  - Maximum response?
- Time off therapy prior to surgery
- Time off therapy after surgery
- Non-responders/progressive disease prior to surgery
  - Base on performance status
  - Change to other systemic therapy and forego surgery
- Inclusion of unfavorable phenotypes
  - Bone, Liver, Brain Metastases?
Cytoreductive Nephrectomy In The Era Of Targeted Therapy

- Cytoreductive surgery benefits carefully selected patients that will be realized in the era of targeted therapy
- Surgically daunting- should be relegated to centers with significant track record
- Complete removal of all intraabdominal and retroperitoneal disease should be the goal
- Ongoing Surgeon/Medical Oncologist relationship at presentation critical to success

Cytoreductive Nephrectomy In The Era Of Targeted Therapy

- More effective systemic therapy should improve results
- Phase III trials for every agent not practical
  - No complete responses
  - Downstaging not clinically significant
  - More important question is timing of surgery
- New paradigm emerging (revisited?): Neoadjuvant Therapy With Delayed Nephrectomy