Is There Still A Role For Cytoreductive Nephrectomy In The Era of Targeted Therapy?

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62 y/o WM with hematuria

- **PMH:** DM, Htn
- **PSH:** Appy, Knee surgery
- **SH:** Denies Tobacco/ETOH use
- **PE:** unremarkable
- **PS = 1**
- **CT abdomen**
  - Locally advanced right renal mass
- **CT chest**
  - Bilateral pulmonary nodules
62 y/o WM with hematuria
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- Hb 9.8
- LDH 1000
- All other labs WNL
- Bone scan/MRI brain negative for mets
62 y/o WM with hematuria

- Patient undergoes cytoreductive nephrectomy
  - T3aN0M1 Clear cell RCC, FG 4
- Follow-up scans at 6 weeks show modest progression of pulmonary metastases
- Started on Sunitinib 4 weeks/2 weeks 50 mg
- Required dose reduction at 6 months to 37.5 mg due to toxicity
62 y/o WM with hematuria

- Disease progression at 14 months out from surgery
- Changed to everolimus
- Currently stable disease 2 years out from surgery
73 y/o WF presents with fatigue and anemia

- PS = 1
- PMH: Htn, Hypothyroidism, MVP, CKD (eGFR 36)
- CT chest: Bilateral pulmonary nodules
- Labs: Hb 9.5 (after transfusion), LDH 868, all other labs WNL
- Brain MRI and Bone Scan negative
73 y/o WF presents with fatigue and anemia
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- Undergoes right radical nephrectomy with RPLND. Mass noted in right fallopian tube (metastatic renal cell carcinoma)
- T3aN1M1 ccRCC with 30 – 40% sarcomatoid and rhabdoid features, FG 4
- 3/10 LN’s positive
- All surgical margins negative
73 y/o WF presents with fatigue and anemia

- Returns 1 month later, PS = 4
- Admitted through the emergency center for failure to thrive
- Hb 8.2, LDH 1094, Ca$^{2+}$ 12.3, eGFR 33
73 y/o WF presents with fatigue and anemia
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- Patient never received therapy due to poor performance status
- Died of disease 45 days after surgery
Therapy of Renal Cell Carcinoma Prior to 2006

- **Stage I-III**: nephrectomy
- **Stage IV**: nephrectomy + systemic therapy
- **Common therapies**
  - Single-agent and combination regimens containing cytokines (e.g., IFN-α, IL-2) and chemotherapeutics
  - Surgery
  - Radiation in selected cases

# RCC Treatment Algorithm: 2013 *

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<th>Setting</th>
<th>Therapy</th>
<th>Options</th>
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<tbody>
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<td>Treatment Naïve</td>
<td>MSK Risk : Good or Intermediate</td>
<td>Sunitinib ± IFNα</td>
<td>HD IL-2</td>
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<td>Patient</td>
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<td><strong>Treatment Refractory Patient (≥ 2nd Line)</strong></td>
<td>Cytokine Refractory</td>
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*Adapted from M Atkins, ASCO 2006

Non clear cell: Temsirolimus
Mechanisms of Therapeutic Effect and Angiogenic Escape

Response hypothesis: VHL status and circulating pathway elements could predict clinical benefit to VEGF targeting agents.

Resistance hypothesis: upregulation of alternative HIF and/or non-HIF mediated, pro-angiogenic genes/proteins (e.g., FGF, angiopoietin, IL-8, PIGF).
Strategy: more complete VEGF blockade or additional inhibitors of relevant proteins.

Response hypothesis: endothelial cell effects (e.g., hypertension, vascular imaging parameters) can identify patients who will benefit from VEGF-targeting agents.

Response hypothesis: inadequate target inhibition due to reduced drug levels and/or enhanced receptor signaling.

Rini, B Clin Cancer Res, 2010
Is there still a role for cytoreductive surgery in the setting of metastatic disease?
Metastatic RCC
Nephrectomy & Immunotherapy

UCLA 1989-1999

P<0.05

IMT

NX

NX + IMT

J UROL 166: 1611, 2001
Effect of Nephrectomy on Survival in Metastatic RCC

Radical Nephrectomy + IFN-α
(SWOG, N=120)
(EORTC, N=42)

IFN-α
(SWOG, N=121)
(EORTC, N=43)

Patients with metastatic RCC with PS 0-1
(SWOG, N=241)
(EORTC, N=83)


IFN = interferon
Role of Cytoreductive Nephrectomy in the Setting of Metastatic Disease: EORTC 30947

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

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
2001 SWOG vs. UCLA

Retrospective

P<0.05

Survival

Months
### RCC Treatment Algorithm: 2013 *

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Non clear cell: Temsirolimus
Cytoreductive Nephrectomy Utilization

Tsao CK et. al., Clinical GU Cancer, 2011
How Does It Work?

- Reduction in major portion of tumor burden
- Immunologic: Surgery induces exposure of new “tumor antigens” or removal of immunologic “sink”
- Altering the metabolic milieu: Relative renal insufficiency induces metabolic acidosis which is somehow anti-tumoral
- Endocrine/Paracrine: Removal of secreted factor that promotes progression/metastasis
Arguments Against Cytoreductive Nephrectomy

- Surgical morbidity/mortality significant
- Only proven benefit in combination with IFN (an “inferior” therapy)
- Spend majority of time left on this earth recovering from surgery
- Significant disease progression or morbidity during post-operative recovery period may preclude systemic therapy
- Newer therapies may result in primary tumor regression
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)
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>
<td>538 (18)</td>
<td>17 (9)</td>
</tr>
<tr>
<td>Complete response</td>
<td>31 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>507 (17)</td>
<td>17 (9)</td>
</tr>
<tr>
<td>Stable disease &gt;3 months</td>
<td>1764 (59)</td>
<td>118 (61)</td>
</tr>
<tr>
<td>Clinical benefit†</td>
<td>2302 (76)</td>
<td>135 (70)</td>
</tr>
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</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)


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)

**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 probability**

OS = overall survival

Cytoreductive Nephrectomy in the Era of Targeted Therapy: What do we do until the prospective trials are completed?

- KPS ≥ 80
  - Median OS: 19.8 vs. 9.4 months
  - Hazard Ratio: 0.44 (95% CI: 0.32-0.59) p < 0.01

- KPS < 80
  - Median OS: 23.9 vs. 14.5 months p < 0.01

Yes = 201, No = 113

Choueiri, T et al., J Urol, 2011
Cytoreductive Nephrectomy In The Era of Targeted Therapy (SEER 2005 – 2009)

Culp and Wood, Submitted
Cytoreductive Surgery For Metastatic Renal Cell Carcinoma:

It’s Not For Everyone!

Patient Selection Is CRITICAL!!!!!
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

J Urol, 1997
Patient Selection For Cytoreductive Nephrectomy

- ECOG Performance status 0-1
- Absence of significant co-morbidities
- Absence of CNS, Liver, Extensive Bone Mets
- Large primary tumor/Ability to resect “majority” of disease through single surgery
- Absence of sarcomatoid dedifferentiation
- Clear cell histology
Identifying Patients who will Not Benefit from Cytoreductive Nephrectomy: MDACC

• 566 pts undergoing CN between 1991 and 2007
• 110 pts undergoing medical therapy only
• Compared survival between groups and identified when survival diverged between surgical and non-surgical groups
• Identified pre-operative variables that differed between surgical groups based on follow-up
• Pre-operative “Risk Factors” based on significance in multivariate analysis

Culp et al., Cancer, 2010
Surgery vs. No Surgery

Overall Survival

Overall Survival Based on Follow-up of 8.5 months

Culp et al., Cancer, 2010
Pre-operative Risk Factors

- Serum albumin < lower limit of normal
- Serum LDH > upper limit of normal
- Liver metastasis
- Symptoms at presentation due to metastasis
- Retroperitoneal lymph node involvement
- Supra-diaphragmatic lymph node involvement
- Clinical T stage 3 or 4

Culp et al., Cancer, 2010
## Pre-operative Assessment

<table>
<thead>
<tr>
<th>Medical Therapy Only</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>Median Survival (mos)</th>
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<tr>
<td><strong>Referent</strong></td>
<td><strong>--</strong></td>
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<td><strong>9.6</strong></td>
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Culp et al., Cancer, 2010
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Culp et al., Cancer, 2010
Pre-operative Assessment

Culp et al., Cancer, 2010
Cytoreductive Nephrectomy In The Era of Targeted Therapy (SEER 2005 – 2009)

Predictive Clinical Factors:
1. Size > 7 cm
2. cT3 or cT4 Stage
3. High grade (3 or 4)
4. Clinically + LN’s
5. Sarcomatoid Histology

Culp and Wood, Submitted
Can we do better?

Is the relevant question whether or not surgery should be incorporated into the management of metastatic renal cell carcinoma?
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
- Non Clear Cell Histology; Sarcomatoid Managed By Standard of Care or Other Clinical Protocol

Cytoreductive Nephrectomy →

Sunitinib 4/2

Primary: PFS
Secondary: OS, Response Rate, Surgical morbidity/mortality

Sunitinib 4/2 X 2 cycles →

Cytoreductive Nephrectomy

A. Bex, EORTC
Conclusions

• Targeted therapy has dramatically improved the outcomes for patients with metastatic RCC

• Cytoreductive nephrectomy remains the standard of care in the treatment of appropriately selected patients with metastatic disease

• Without complete responses, surgery remains integral part of multi-disciplinary approach in metastatic disease
  • Control of primary tumor
  • Metastasectomy

• Reliable complete responses (including in the primary tumor) with any agent will force re-examination of current paradigm

• Ongoing studies to determine the best timing for surgery may further refine our treatment approach