Management of High Risk Renal Cell Carcinoma

Peter E. Clark, MD
Professor and Chair, Department of Urology
Carolinas HealthCare System
Chair, Urologic Oncology
Levine Cancer Institute

October 14, 2017
Cytoreductive Nephrectomy
Cytoreductive Nephrectomy is an Integral Part of the Treatment Algorithm for Metastatic RCC

NCCN, EAU, ESMO, and others
Combined SWOG 8949 & EORTC 30947

Log rank test: \( p = 0.001 \)

Nephrectomy & IFN
Take Away Points

• Level 1 evidence only for outdated therapy (IFN)
• Results critically dependent on performance status
• Unlikely to help the patient with rapidly progressive disease
Molecular Biology of Clear Cell RCC

1. HIFα
2. VHL mutation
3. low O2
4. TSC mutation

Protein stabilization

VEGF: Highly vascular tumor
IL-6: Paraneoplastic fever
Epo: Paraneoplastic polycythemia
ADRP: Lipid accumulation, clear cell histology
General Schema

• Low-Intermediate Risk disease
  • Pazopanib
  • Sunitinib

• Intermediate-Poor Risk/Papillary Histology
  • Temsirolimus

• Young, good performance status
  • High dose IL-2 still something to consider

• Second Line
  • Nivolumab
  • Cabozantinib
  • Everolimus +/- Lenvatinib
  • Axitinib
  • Sorafenib
Cytoreductive Nephrectomy in Patients with Synchronous Metastases from RCC

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.
The Impact of Cytoreductive Nephrectomy on Survival of Patients With Metastatic RCC Receiving VEGF Targeted Therapy

Figure 1. Kaplan-Meier curve depicting overall survival from initiation of VEGF targeted therapy for 314 patients who did or did not receive cytoreductive nephrectomy.
The Impact of Cytoreductive Nephrectomy on Survival of Patients With Metastatic RCC Receiving VEGF Targeted Therapy

Figure 2. Kaplan-Meier curve of overall survival from initiation of VEGF targeted therapy by cytoreductive nephrectomy, and KPS 80 or greater (A) or KPS less than 80 (B).
Risk Stratification in the Targeted Therapy Era

- KPS < 80%
- Time from diagnosis to treatment < 1 year
- Hemoglobin < LLN
- Calcium > ULN
- Neutrophils > ULN
- Platelets > ULN

![Graph showing overall survival by risk stratification categories](image-url)
Pre-operative Risk Criteria

- Culp et al
  - Low serum albumin
  - High LDH
  - cT3 or 4 disease
  - Symptomatic metastases
  - Liver metastasis
  - Retroperitoneal adenopathy
  - Supradiaphragmatic adenopathy
Conclusions

• Cytoreductive Nephrectomy likely has a role to play in the modern era

• Key is patient selection
  • Younger patients
  • Clear-cell histology
  • Good performance status
  • Limited metastatic burden
  • 3 or less MDACC or IMDC risk factors
Randomized Trial Underway

CARMENA STUDY

**Inclusion criteria:**
- ECOG PS 0-1
- Clear cell mRCC
- No previous systemic therapy
- Tumour amenable to nephrectomy

**Randomize**

**Arm A:** CN then sunitinib

**Arm B:** Sunitinib alone

n = 576

**End points:**
- Overall survival
- Objective response
- Progression-free survival
- Post-op morbidity

Galazi et al, Exp Rev Anticancer Therapy 14(3) 2014
Role of Neoadjuvant Systemic Therapy in Metastatic RCC
Fundamental Question

• Cytoreductive Nephrectomy has a significant role to play in M+ RCC

• The issue, what comes first
  • Surgery
  • Systemic therapy
Advantages of Surgery First

• Reduce the bulk of disease
  • Primary >>> metastatic burden

• Relieve local symptoms
  • Hematuria
  • Pain (be careful!)

• Psychological
  • “Doc, I just want it out!”
Advantages of Neoadjuvant Tx

• Litmus test
  • Avoid the patient with explosive disease

• Improve resectability
  • ? IVC Tumor Thrombus?

• Opportunity to Improve Performance Status or Nutrition
Potential Disadvantages/Concerns

• Timing of surgery relative to neoadjuvant therapy?
• Increased Risk of peri-operative complications?
• Will it actually improve survival
  • We know combination works w/ IFNα
  • No complete PhIII trial for targeted Tx
So, what is the evidence for Neoadjuvant Therapy in RCC?

Weak! At best, smaller retrospective cohort and phase II studies
Feasibility in Locally advanced disease
Thomas et al, J Urol 182:881-886, 2009

- Cohort series CCF
- 19 patients surgery post-targeted tx
- Locally advanced/recurrent/M+
- Most open surgery
- Complications
  - Two wound complications (11%)
  - Anastomotic bowel leak
Cowey et al, JCO 28:1502-1507, 2010

• Ph II study Neoadjuvant Sorafenib Stg II+ RCC
• 30 patients
  • 17 localized dz
  • 13 metastatic dz
• 10% median reduction tumor size
• All able to undergo Nx
• No complications due to sorafenib
Hellenthal et al, J Urol 184:859-864, 2010

• Phase II trial
• Neoadj sunitinib M0 & M+ RCC
• 20 Patients
• No surgical complications attributable to sunitinib
• 85% tumors had some shrinkage
• Mean diameter change 12%
Karam et al, Eur Urol epub 2014

- Ph II axitinib in locally advanced ccRCC
  - Not metastatic disease
- Continued until 36 hrs prior to surgery
- 24 pts enrolled and tx’ed
  - All but 2 complete 12 weeks
- Median reduction tumor 28% (No CR)
- Complications
  - Gr 2 complications (n=13)
  - Gr 3 complications (n=2)
Helping resectability (IVC tumor thrombus)
Extensive Retroperitoneal Disease

Pre-TKI

Post-TKI
Extensive Retroperitoneal Disease

Pre-TKI

Post-TKI

- Phase II trial Neadjuvant Sunitinib
- 30 pts with unresectable RCC
  - $M_0=11$  $M+=19$
- Median 22% decrease in tumor size
  - ccRCC median 28%
  - 1.4% non-ccRCC
- 45% now able to undergo surgery
- Comparable complication rate to historical controls

- Retrospective cohort study
- Targeted Tx to shrink IVC thrombus
- 25 patients with level 2+ IVC thrombus
- Thrombus response (size)
  - 28% increase
  - 44% decrease
- Thrombus level
  - 4% higher
  - 12% lower
- One patient had approach changed
Metastatic disease

- Retrospective Cohort Series
- Compared Two Groups
  - Sunitinib then cytoreductive Nx (N=22)
  - Rad Nx for M0 RCC (N=28)
- Cytoreductive Nx safe and feasible
  - Little in the way of analysis
Powles et al, Eur Urol 60: 448-454, 2011

• Two Ph II studies Sunitinib in M+ RCC

• Disease Risk
  • Poor Risk: n=21
  • Intermediate Risk: n=45

• Nx not performed 19 (29%) due to progression

• Median Overall Survival
  • Intermediate Risk: 26 mo’s
  • Poor Risk: 9 mo’s
Chapin et al, Eur Urol 60: 964-971, 2011

• Retrospective Cohort Series MDACC

• CN plus targeted therapy
  • CN 1st  N=103
  • Neoadjuvant Tx  N=70

• Compared complications at 90 days
Chapin et al, Eur Urol 60: 964-971, 2011

• No difference in overall or severe (Clavien 3+) complications

• Increase in wound complications with neoadjuvant tx:
  • HR 4.14 (95% CI 1.6-10.6)
Conclusions from Studies

• Neoadjuvant Therapy is feasible and can be done safely
• In some cases can help resection
  • But don’t expect too much!
• Modest Tumor shrinkage
• Patient selection is key
  • The Litmus Test....
Does Neoadjuvant Targeted Therapy Improve Survival?

• Awaits a prospective, randomized trial

SURTIME STUDY

Inclusion criteria:
- ECOG PS 0-1
- Clear cell mRCC
- No previous systemic therapy
- Tumour *in situ* and amenable to nephrectomy

Randomize

Arm A:
CN then sunitinib

Arm B:
Sunitinib then CN

End-points:
- Overall progression-free survival
- Overall survival
- Morbidity

n = 458
Conclusions

• Surgery has a role to play in advanced RCC
• Timing of surgery relative to systemic therapy remains to be defined
• Patient selection remains the key to success
• Final answers await completion of prospective randomized trials
Thank You!