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# Cytoreductive Nephrectomy for Metastatic Kidney Cancer

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# Introduction

- RCC : 3% of all cancers.
  - 17% of patients : distant metastasis at the time of diagnosis.
  - 20–40% localized disease develop metastasis.
- CN remove the primary tumor in the presence of metastatic disease : goal improve QoL and survival.

# Introduction

- Early reports of spontaneous regression of metastatic deposits following **CN**  **Therapeutic option.**
- Release of **cytokines** and **growth factors** promote **metastatic spread**  

- **Partially negated** with removal of the primary tumor.

# Introduction

- First cytokine: Interferon-alpha was identified in 1957 as a protein that interfered with viral replication.
- Cytokine-induced killer (CIK) cells.

# Introduction

- CN: demonstrated a survival benefit (Retrospective data ++++).
- Led to its widespread adoption.
- Favor of CN from retrospective data.

# Cytokine Period

- Early 2000s : SWOG and EORTC group prospective RCT if CN offered a survival benefit.
- CN **followed** by **interferon alpha** compared with interferon alpha alone.
- Combined analysis of their data:
  - OS : 13.6 months vs 7.8 months interferon group.
  - 31% decrease in risk of death in the CN group.

**Flanigan, R.C.** Nephrectomy Followed by Interferon Alfa-2b Compared with Interferon Alfa-2b Alone for Metastatic Renal-Cell Cancer. N. Engl.J. Med. 2001, 345, 1655–1659.

**Mickisch.** Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal- cell carcinoma: A randomised trial. Lancet 2001, 358, 966–970.

# Cytokine Period

- The combined analysis :
  - Significant survival difference when controlling for performance status.
- Prognostic factors were also better assessed.
- **Performance status** was shown to have prognostic importance.

# Cytokine Period

- Hypotheses explain beneficial effect CN:
- Removal of the immunologic sink :
  - diminished production of growth factors and cytokines by the tumour *in situ*
  - *postponed metastatic progression*

# Cytokine Period

- Long-term data : follow-up 9 years, show long-term OS with CN.
- Benefit was seen in all predefined patient strata:
  - performance status
  - presence or absence of lung metastasis
  - presence or absence of measurable disease
- Framework : future studies role of CN.

## **Predictors of Survival of Advanced Renal Cell Carcinoma: Long-Term Results From Southwest Oncology Group Trial S8949**

Primo N. Lara, Jr., Catherine M. Tangen, Sarah J. Conlon, Robert C. Flanigan  
and E. David Crawford

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# Prognostic factors

- Two risk prognostication models:
- MSKCC /Motzer criteria : **cytokine era**
  - low (KPS)
  - elevated (LDH)
  - elevated serum calcium
  - anemia
  - time to initiation of therapy < 1 year

Presence of 0, 1–2 and > 2 : stratifies patients into a good, intermediate and poor-risk with median OS **24, 14 and 5 months.**

# Rational targeted therapies

## Sporadic ccRCC

- Somatic alterations occur in the primary site : improved response of systemic therapy seen with CN.
- VHL-inactivation  over expression of:
  - VEGF
  - platelet derived growth factor (PDGF)
- Promote neo-angiogenesis.
- Development and progression of RCC.

# Rational targeted therapies

- Development of molecularly targeted therapies.
- Paradigm shift in treating advanced RCC in which **targeted therapy** replaced **immunotherapy**
  - VEGF inhibitors
  - mTOR inhibitors
  - tyrosine kinase inhibitors

# Targeted therapies

- Introduction of VEGFR-targeted therapy : increase in OS.
- Less than 1year to more than 2years for intermediate prognostic risk.



The NEW ENGLAND  
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## Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma

**Authors:** Robert J. Motzer, M.D., Thomas E. Hutson, D.O., Pharm.D., Piotr Tomczak, M.D., M. Dror Michaelson, M.D., Ph.D., Ronald M. Bukowski, M.D., Olivier Rixe, M.D., Ph.D., Stéphane Oudard, M.D., Ph.D., [+6](#), and Robert A. Figlin, M.D.\* [Author Info & Affiliations](#)

# VEGF Targeted Therapies/Choueiri

- In 2010, retrospective : VEGF or VEGF + CN.
  - Sunitinib
  - Sorafenib
  - bevacizumab.
- OS : 19.8 vs. 9.4 months in VEGF-alone group.

Choueiri, T.K. J. Urol. 2011, 185, 60–66.

## **The Impact of Cytoreductive Nephrectomy on Survival of Patients With Metastatic Renal Cell Carcinoma Receiving Vascular Endothelial Growth Factor Targeted Therapy**

Toni K. Choueiri,\* Wanling Xie, Christian Kollmannsberger, Scott North, Jennifer J. Knox, J. Geoffrey Lampard, David F. McDermott, Brian I. Rini and Daniel Y. C. Heng

# Targeted therapies

- Uncertain:
  - “ Improvement in outcome observed with systemic therapy would benefit from an additional CN at all ”
- To investigate the indication of CN combined with VEGFR-targeted therapy:
  - two prospective RCTs were initiated in 2010.



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Review – Kidney Cancer

## Systematic Review of the Role of Cytoreductive Nephrectomy in the Targeted Therapy Era and Beyond: An Individualized Approach to Metastatic Renal Cell Carcinoma

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[Thomas Powles](#)<sup>h</sup>, [Axel Bex](#)<sup>i</sup>

# CARMENA and SURTIME

- Changed the therapy paradigm of mRCC.
- Tempered the enthusiasm toward **initial CN** for mRCC, which was generated from retrospective data and **pre-TT era** randomized trials.
- CARMENA :whether (CN) is required in the targeted therapy area.
- SURTIME: **deferred** CN in combination with sunitinib can be used to identify patients with inherent targeted therapy resistance.

# CARMENA and SURTIME

- CARMENA and SURTIME used MSKCC risk.
- ICI trials: concept of using IMDC risk.
- IMDC and MSKCC risk factors have been shown in SURTIME and CARMENA to be associated with the outcome of patients in both trials.

# Prognostic factors

- **IMDC/Heng** criteria : targeted **therapy era**
- Similar of MSKCC, in addition to :
  - elevated platelet
  - elevated neutrophil count
  - without consideration of LDH

Established : poor-risk not benefit from CN

# CARMENA

- **Prospective RCT phase III trial**
- In 2018: the results of the CARMENA.
- Utility of CN in the targeted therapy era.
- **Immediate** CN followed by sunitinib vs. sunitinib alone:



- sunitinib alone was not inferior to CN followed by sunitinib with regard to OS in intermediate and poor prognosis MSKCC risk

# CARMENA

- **Post hoc analysis** of OS in patients who had a **secondary nephrectomy**.
- 18% in the sunitinib-alone group underwent secondary CN:
- OS benefit : **deferred CN approach +++++**
- Significantly longer OS :
  - 48.5 vs. 15.7 months in the deferred CN.
  - 32.4 vs. 15.0 months in the immediate CN.

# CARMENA

Major limitations :

- The first limitation of the CARMENA study is that the included patients were suitable candidates for nephrectomy
- the results are not generally applicable to patients with poor performance status
- Another limitation was **the inclusion of only patients with poor- and intermediate-risk disease according to the MSKCC scale**

# SURTIME

- RCT investigating three cycles of sunitinib prior to the decision to perform CN in the absence of systemic progression.
- Compared with immediate CN followed by sunitinib.
- Inclusion criteria required ccmRCC
  - Resectable primary tumour
  - $\leq 3$  risk factors associated with.

# SURTIME

- Shortly after the publication of the CARMENA trial.
- Immediate vs **deferred** CN in patients receiving sunitinib therapy.
- OS: *13.9 versus 18.4 months.*

# SURTIME

- *OS* : 32.4 vs 15.0 months in immediate CN



- Postponing systemic treatment by performing CN upfront may be questionable for those patients, who need early control of their progressive disease.

# SURTIME

- SURTIME was underpowered due to poor accrual that was in part a consequence of very stringent inclusion criteria to select only the most favourable candidates for CN
- Although the trial was successful in including predominantly MSKCC intermediate-risk patients, the sample size did not allow definite conclusions.

# SURTIME

- Addition of sunitinib did not increase the morbidity of CN.
- Inverse relationship between case volumes and morbidity.

**Institutions with experienced surgical teams  
and the appropriate resources**

# Targeted therapies / SURTIME

- Comparing the immediate and deferred CN groups:
- Adverse events were essentially the same—52% vs. 53%.
- CN is morbid procedure.
- Use of TKIs in either setting did not increase the rates of adverse events

**De Bruijn, R.E et al.** Surgical safety of cytoreductive nephrectomy following sunitinib: Results from the multicentre, randomised controlled trial of immediate versus deferred nephrectomy (SURTIME). *Eur. Urol.* 2019, 76, 437–440.

# SURTIME

- Deferred CN and surgery appear safe after sunitinib.
- In patients with poor PS or IMDC : CN is not recommended.
- Pre-surgical VEGFR-targeted therapy followed by CN seems to be beneficial.

# Morbidity and mortality of CN

- (SEER) registry database : 30-day mortality rate of:
  - 4.2% in mRCC patients undergoing CN
  - 0.3 – 1.3% for those with localized disease
- Range of **30–40%** within 6 months
- Major postoperative complications:
  - pulmonary and thromboembolic
  - bleeding events

# ICI era

- Despite the very recent evidence from CARMENA and SURTIME.
- Both, Performed with a certain class of drugs only.
- The question arises whether the management of patients with primary mRCC needs re-investigation in the era of immunecheckpoint inhibitors (ICIs).

**Hammers HJ** *et al.* Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: the CheckMate 016 study. *J Clin Oncol* 2017; 35: 3851–3858.

# Immuno-oncologic agents

- Immune Checkpoint Inhibitors (ICI)
- Utilize the body's own immune system to attack cancerous cells.
- More effective treatments in mRCC.
- Role of CN is unclear.
- Multiple ongoing trials may clarify the role of CN in this new era of cancer care.

# Immuno-oncologic agents

- Superiority of the combination of **nivolumab** and **ipilimumab** (ICI) over sunitinib, in terms
  - of survival
  - quality of life
- Changed the first-line therapy for patients with intermediate and poor-risk mRCC
- Limiting the applicability of the results of the SURTIME and CARMENA trials.

# ICI What We Know

- A recent National Cancer Database :
- Immunotherapy alone or combined with CN.

Patients who underwent CN better OS than those who received immunotherapy alone.

**Singla, N et al.** Improved survival after cytoreductive nephrectomy for metastatic renal cell carcinoma in the contemporary immunotherapy era: An analysis of the National Cancer Database. *Urol. Oncol. Semin. Orig. Investig.* 2020, 38, 604.e9–604.e17.

# ICI —Ongoing Trials

- In the ICI era, the role of CN has yet to be clearly elucidated by publications with high levels of evidence.
- Currently multiple trials looking at this question.

# NORDIC SUN

- Evaluating the role of **deferred** CN in patients who have at least **three IMDC high-risk** features and are receiving combination nivolumab and ipilimumab .
- The deferred CN is that it still provides the benefit of surgery.

# PROBE trial

- If CN offers a survival benefit in patients who had an objective response or stable disease after receiving any of the multiple first-line options for systemic therapy.
- Patients will be evaluated after 12 weeks of systemic immune checkpoint inhibition to assess their response to treatment
- whether there is benefit in performing a CN.

# Conclusion

- ST should generally represent the priority for the management of mRCC in the TT era and beyond.
- Upfront CN should not be standard management in patients with
  - poor performance status
  - poor IMDC/MSKCC-risk patients

# Conclusion

- Intermediate MSKCC risk group in CARMENA, and SURTIME support that:
- Immediate CN should not be performed in MSKCC intermediate- risk patients requiring sunitinib, or an equivalent VEGFR-TKI.
- The OS in the upfront CN arm in both studies was shorter than for patients receiving immediate sunitinib.

# Conclusion

- CN was found to have a survival benefit in patients with IMDC **intermediate-** and **poor-risk disease.**

**Kato, R.et al.** Significance of upfront cytoreductive nephrectomy stratified by IMDC risk for metastatic renal cell carcinoma in targeted therapy era—A multi-institutional retrospective study. *Int. J. Clin. Oncol.* 2022, 27, 563–573.

# Conclusions

- The role of CN has evolved over the past few decades.
- As we await the results of trials:
  - the Cyto-KIK
  - NORDIC-SUN
  - PROBE
- Help better elucidate the role of CN in the current landscape of immune-oncologic care
- Current data indicate that there is a benefit in performing CN in select patients with mRCC.

**Merci**