

Cytoreductive Nephrectomy and Oligometastasectomy in 2020

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Disclosure

I have no actual or potential conflict of interest in relation to this presentation.

Objectives

- *Understand the rationale for cytoreductive nephrectomy in metastatic renal cell carcinoma*
- *Review the current indications for cytoreductive nephrectomy*
- *Examine the latest data on cytoreductive nephrectomy*
- *Discuss the management of oligometastases*

Kidney Cancer

- Kidney cancer is the 6th most common malignancy among men and the 10th among women
- Renal cell carcinoma (RCC) accounts for the vast majority of cases
- 25–30% of RCC patients present with metastases at the time of diagnosis

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7–30.

Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 1999;17:2530.

Cytoreductive Nephrectomy

- Removal of the kidney and primary tumour in the face of metastatic disease
- Occasional regression of metastatic deposits

Middleton RG, Surgery for metastatic renal cell carcinoma. J Urol 1967;97:973-7

Prospective Clinical Trials

Cytoreductive Nephrectomy in the Cytokine Era of Systemic Therapy

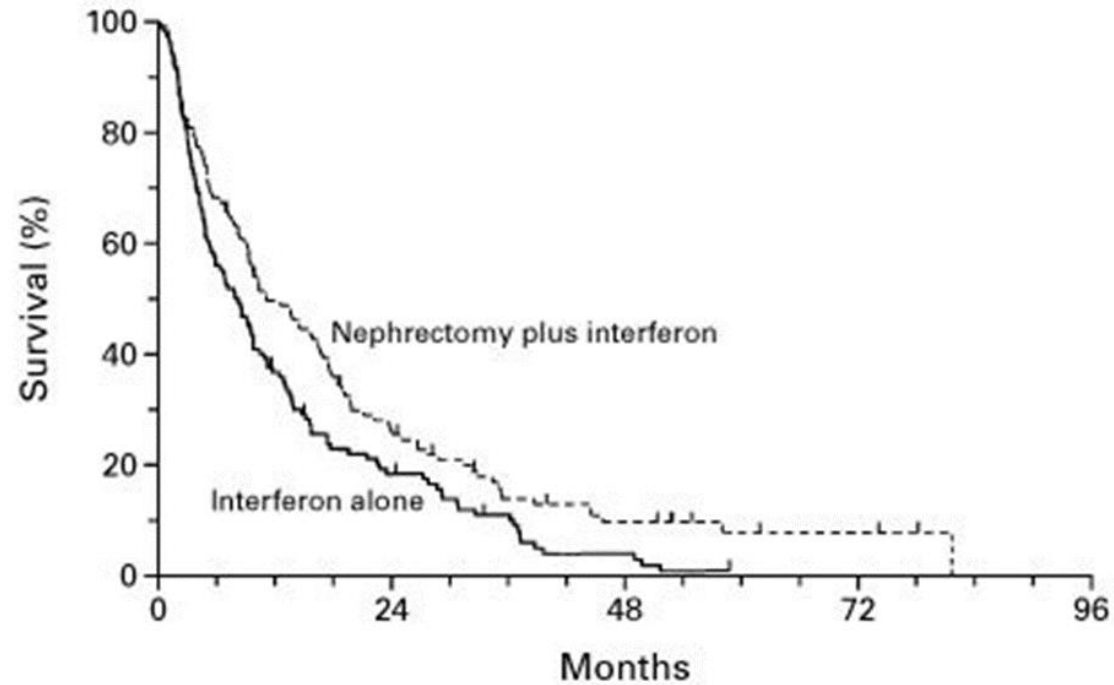
- **SWOG**

- *Flanigan RC, Salmon SE, Blumenstein BA, et al. 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.*

- **EORTC**

- *Mickisch GH, Garin A, van Poppel H, et al., European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group. 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.*

Prospective Trials for Cytoreductive Nephrectomy in the Cytokine Era of Systemic Therapy



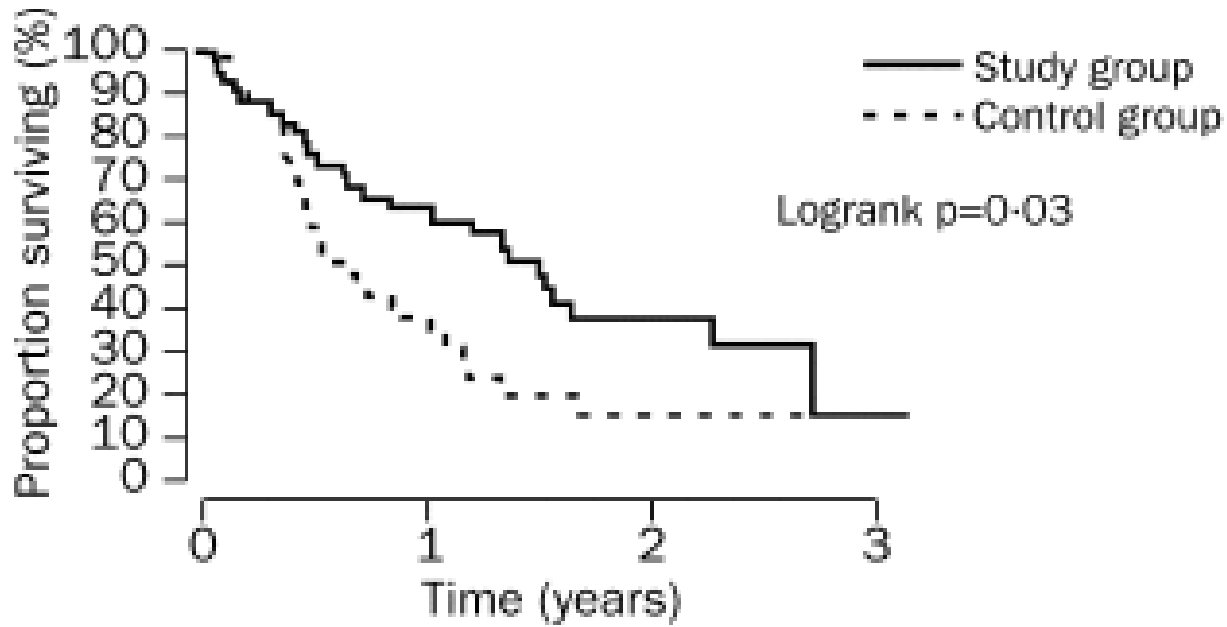
No. AT RISK					
Interferon alone	121	21	4	0	
Nephrectomy plus interferon	120	29	9	3	0

Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer.

Flanigan et al., N Engl J Med. 2001 Dec 6;345(23):1655-9.

Median overall survival of 11.1 vs. 8.1 months (p=0.05)

Prospective Trials for Cytoreductive Nephrectomy in the Cytokine Era of Systemic Therapy



Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial.

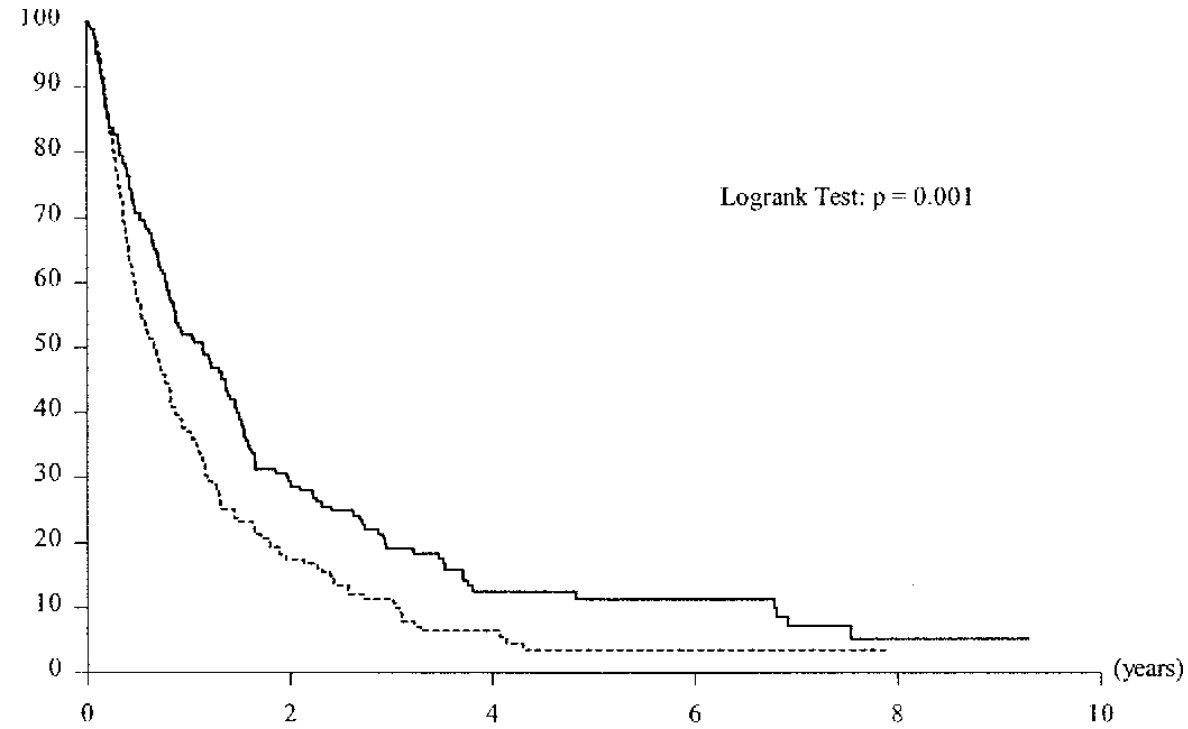
Mickisch et al., Lancet. 2001 Sep 22;358(9286):966-70.

Median overall survival 17 vs. 7 months

(p=0.03; HR 0.54; 95% CI 0.31-0.94)

	Observed number of events		Number of patients at risk		
	0	1	0	1	2
Study group	25	42	22	7	1
Controls	30	42	12	2	0

Prospective Trials for Cytoreductive Nephrectomy in the Cytokine Era of Systemic Therapy



<u>O</u>	<u>N</u>	<u>Number of patients at risk :</u>				
141	161	46	13	9	3	— Neph+IFN
152	163	26	7	1	0	- - - IFN alone

FIG. 1. Duration of survival in combined SWOG and EORTC trials. *O*, observation. *N*, nephrectomy

Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis.

Flanigan et al., J Urol. 2004 Mar;171(3):1071-6.

Median overall survival 13.6 vs. 7.8 months

($p=0.002$)

Targeted Systemic Therapy



- Introduction of new targeted agents (~2005)
- VEGFR-TKI
- E.g., sorafenib, sunitinib, pazopanib, bevacizumab, axitinib, cabozantinib, lenvatinib
- Substantial improvement in OS for patients with mRCC
 - 10 months to >40 months for good/intermediate-risk patients
- *Based on retrospective data*

Escudier B, et al., Cancer 2009;115:2321

Bhindi B, et al., J Urol 2018;200:528

Garcia-Perdomo H, et al., Investig Clin Urol 2018;59:2

RETROSPECTIVE DATA IN SUPPORT OF CYTOREDUCTIVE NEPHRECTOMY

- Many large retrospective studies on CN in the TT era
- Overwhelming support in favor of CN
- In January 2019, the largest systematic review evaluated the role of CN in over 40,000 patients with mRCC in the TT era
 - Total of 10 observational studies favored CN vs no CN
- Together, these studies suggest a strong favorable effect on OS for patients undergoing CN in the TT era

Heng DYC, Wells JC, Rini BI, et al. Cyto-reductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium. Eur Urol 2014; 66:704–710.

Pal S, Nelson R, Vogelzang N. Disease-specific survival in de novo metastatic renal cell carcinoma in the cytokine and targeted therapy era. PLoS One 2013; 8:e63341.

Bhindi B, Abel J, Albiges L, et al. Systematic review of the role of cyto-reductive nephrectomy in the targeted therapy era and beyond: An individualized approach to metastatic renal cell carcinoma. Eur Urol 2019; 75:111–128

Cytoreductive Nephrectomy

- Postulated mechanisms
 - removal of the “immunological sink”
 - decreased production of cytokines
 - reduced growth factors by the primary tumour
 - delayed metastatic progression
 - nephrectomy-induced azotemia

Robertson CN, Linehan WM, Pass HI, et al. Preparative cytoreductive surgery in patients with metastatic renal cell carcinoma treated with adoptive immunotherapy with interleukin-2 or interleukin-2 plus lymphokine activated killer cells. J Urol 1990;144:614–7.

Lahn M, Fisch P, Köhler G, et al. Pro-inflammatory and T cell inhibitory cytokines are secreted at high levels in tumor cell cultures of human renal cell carcinoma. Eur Urol 1999;35:70–80.

Kawata N, Yagasaki H, Yuge H, et al. Histopathologic analysis of angiogenic factors in localized renal cell carcinoma: the influence of neoadjuvant treatment. Int J Urol 2001;8:275–81.

Lara Jr PN, Tangen CM, Conlon SJ, Flanigan RC, Crawford ED. Predictors of survival of advanced renal cell carcinoma: long-term results from southwest oncology group trial S8949. J Urol 2009;181:512–7.

Gatenby RA, Gawlinski ET, Tangen CM, Flanigan RC, Crawford ED. The possible role of postoperative azotemia in enhanced survival of patients with metastatic renal cancer after cytoreductive nephrectomy. Cancer Res 2002;62:5218–22.

Comparison of Risk Factor Criteria for RCC:

Memorial Sloan-Kettering Cancer Center
(MSKCC)

and

International Metastatic Renal Cell
Carcinoma Database Consortium
(IMDC)

Table 1. Comparison Between the MSKCC and the IMDC Prognostic Risk Criteria for Renal Cell Carcinoma (RCC)

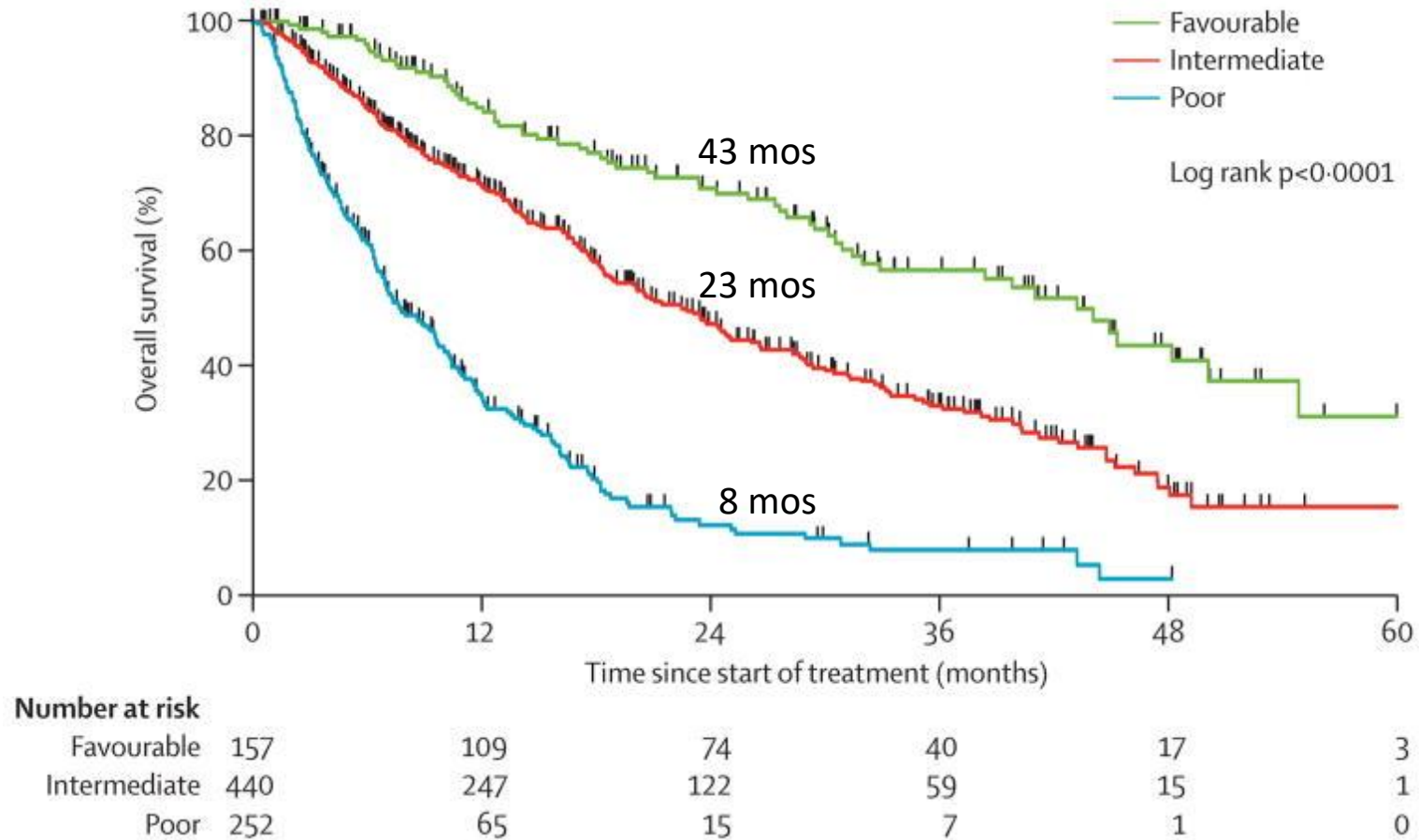
	MSKCC Criteria ^a	IMDC Criteria ^b
Risk Factors		
Karnofsky performance status < 80%	✓	✓
Time from diagnosis to treatment < 1 year	✓	✓
LDH level ≥ 1.5× ULN	✓	
Hemoglobin level below LLN	✓	✓
Corrected serum calcium level above ULN	✓	✓
Platelet counts above ULN		✓
ANC above ULN		✓
Entry Population Criteria		
Patients with metastatic RCC	Treated with interferon alfa as initial systemic therapy	Treated with first-line TKI therapy
Distribution of Risk Groups		
0 criteria (favorable)	80 pts (18%)	157 pts (18%)
1–2 criteria (intermediate)	269 pts (62%)	440 pts (52%)
≥ 3 criteria (poor)	88 pts (20%)	252 pts (30%)
Median OS, by Risk Group		
0 criteria (favorable)	29.6 mo (95% CI, 20.9–37.8 mo)	43.2 mo (95% CI, 31.4–50.1 mo)
1–2 criteria (intermediate)	13.8 mo (95% CI, 12.4–15.9 mo)	22.5 mo (95% CI, 18.7–25.1 mo)
≥ 3 criteria (poor)	4.9 mo (95% CI, 4.3–6.3 mo)	7.8 mo (95% CI, 6.5–9.7 mo)

ANC = absolute neutrophil count; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; LDH = lactate dehydrogenase; LLN = lower limit of normal; MSKCC = Memorial Sloan Kettering Cancer Center; OS = overall survival; pts = patients; TKI = tyrosine kinase inhibitor; ULN = upper limit of normal.

^aInformation from Motzer et al. J Clin Oncol. 2002.[8]

^bInformation from Heng et al. J Clin Oncol. 2009.[11] and Heng et al. Lancet Oncol. 2013.[68]

Risk stratification for first-line therapy in mRCC: IMDC Criteria



Central LHIN GU Update
A Multi-Disciplinary Forum:

Tuesday 12th April 2016

The Academy of Medicine Room
The Estates of Sunnybrook
2075 Bayview Avenue
Toronto, Ontario
M4N 3M5

6:00 PM Arrival and Reception

6:30 PM-8:30 PM

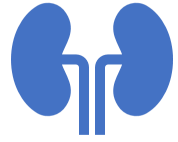
Management of RCC in 2016

Presentation & Discussion by Dr. Daniel Heng
Oncologist, Tom Baker Cancer Centre, Calgary

Case presentation – Dr. Victor Mak

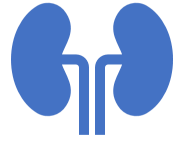
Moderator:

Dr. Yasmin Rahim, Stronach Regional Cancer Centre



Case

- **68-year-old lady**
- **Right renal mass**
- **Presented to ER on October 12, 2015**
- **3-month history of lower back pain**
- **No flank pain**
- **No gross hematuria**
- **Mild decrease in energy**
- **Remained active**
- **No significant weight loss**
- **Mild decrease in her appetite**
- **Otherwise healthy**
- **Physical examination unremarkable**



Case

- **LABORATORY INVESTIGATIONS:**
 - Hemoglobin low at 88
 - Platelet count high at 547
 - Neutrophil count high at 12.0
 - Corrected serum calcium normal at 2.61

[A]

LE
Study Date: 10/10/2011
Study Time: 8:00:00
MRN



[P]



Case

- **DIAGNOSTIC IMAGING STUDIES:**
 - **CT C/A/P**
 - Innumerable lung masses, up to 1.6 cm.
 - Right renal mass, 5.7 x 3.1 cm
 - Inferior vena caval thrombus
 - Right adrenal mass, 2.4 cm
 - No lymphadenopathy
 - **Bone Scan**
 - Negative
 - **CT Head**
 - Negative



Case

IMPRESSION & PLAN:

“This patient likely has metastatic right renal cell carcinoma. A biopsy of the right renal mass is being organized. I do agree with biopsy of the right renal mass to obtain histology. If the biopsy confirms evidence of clear cell renal cell carcinoma, the patient may be a candidate for vascular endothelial growth factor receptor-tyrosine kinase inhibitor targeted systemic therapy. The option of cytoreductive nephrectomy was also discussed in detail with the patient and her family members, in the context of either performing the operation prior to or after initiation of targeted therapy. *I did inform the patient and her family members that based on the International Metastatic Renal Cell Carcinoma Database Consortium (Heng) criteria, she has at least 4/6 factors, which is indicative of poor prognosis for overall survival (median overall survival of 7-8 months).”*”

Cytoreductive Nephrectomy

Randomised controlled trials demonstrated a survival benefit during the cytokine era

Retrospective studies showed survival benefit during the targeted therapy era

To prospectively assess the role the of CN in combination with targeted therapy, two randomised controlled trials were designed

ORIGINAL ARTICLE

Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma

A. Méjean, A. Ravaud, S. Thezenas, S. Colas, J.-B. Beauval, K. Bensalah, L. Geoffrois, A. Thiery-Vuillemin, L. Cormier, H. Lang, L. Guy, G. Gravis, F. Rolland, C. Linassier, E. Lechevallier, C. Beisland, M. Aitchison, S. Oudard, J.-J. Patard, C. Theodore, C. Chevreau, B. Laguerre, J. Hubert, M. Gross-Goupil, J.-C. Bernhard, L. Albiges, M.-O. Timsit, T. Lebre, and B. Escudier

Original Investigation

December 13, 2018

Comparison of Immediate vs
Deferred Cytoreductive
Nephrectomy in Patients With
Synchronous Metastatic Renal Cell
Carcinoma Receiving Sunitinib
The SURTIME Randomized Clinical
Trial

Axel Bex, et al.,

JAMA Oncol. 2019;5(2):164-170.

The Clinical Trial to Assess the Importance of Nephrectomy (CARMENA)

- Randomised patients
 - CN + sunitinib vs
 - sunitinib alone
- Investigate the role of CN in patients receiving targeted therapy

The Immediate Surgery or Surgery after Sunitinib Malate In Treating Patients with Kidney Cancer

(SURTIME)

- Randomised patients
 - CN -> sunitinib vs
 - sunitinib -> CN -> sunitinib
- Investigate the role of presurgical targeted therapy in combination with cytoreduction

Cytoreductive Nephrectomy Followed by Sunitinib vs Sunitinib Alone in mRCC (CARMENA): Background

- To date, no randomized head-to-head comparison of CN + TT vs TT alone in mRCC
- Retrospective analysis of IMDC data indicated CN + TT beneficial in patients with < 4 IMDC prognostic factors
- Unknown whether CN truly beneficial in mRCC patients in TT era
- CARMENA – phase III trial comparing CN + sunitinib vs sunitinib alone in patients with mRCC

Escudier B, et al. Ann Oncol. 2016;27(suppl 5):v58-v68.

Flanigan RC, et al. N Engl J Med. 2001;345:1655-1659.

Mickisch GH, et al. Lancet. 2001;358:966-970.

Bamias A, et al. Oncologist. 2017;22:667-679.

Heng DY, et al. Eur Urol. 2014;66:704-710.

CARMENA: Study Design

- Final analysis of multicenter, randomized, open-label noninferiority phase III trial
 - Steering committee closed trial after second interim analysis (prespecified at 326 events) due to slow recruitment; second interim analysis deemed sufficient to meet trial objectives

Stratified by center, MSKCC risk group (intermediate vs high risk)

Adult patients with biopsy-confirmed clear-cell mRCC, ECOG PS 0-1, treated brain mets without recurrence 3 wks post treatment permitted, suitable candidate for nephrectomy, eligible for sunitinib, no prior systemic treatment for kidney cancer

(N = 450) (Sept. 2009 - Sept. 2017)

Nephrectomy followed 3-6 wks later by Sunitinib 50 mg QD* 4 wks on/2 wks off (n = 226)

Sunitinib 50 mg QD* 4 wks on/2 wks off (n = 224)

Follow-up for minimum of 2 yrs

*Dose reductions/interruptions allowed for managing AEs.

Primary endpoint: OS

- Trial designed to have 80% power with 1-sided $\alpha = 0.05$ to show noninferiority with 576 patients enrolled (observed deaths, n = 456)

- Secondary endpoints: PFS, ORR (RECIST v1.1), clinical benefit, treatment adherence, nephrectomy in sunitinib-only arm, postoperative morbidity and mortality, safety

CARMENA: Baseline Characteristics

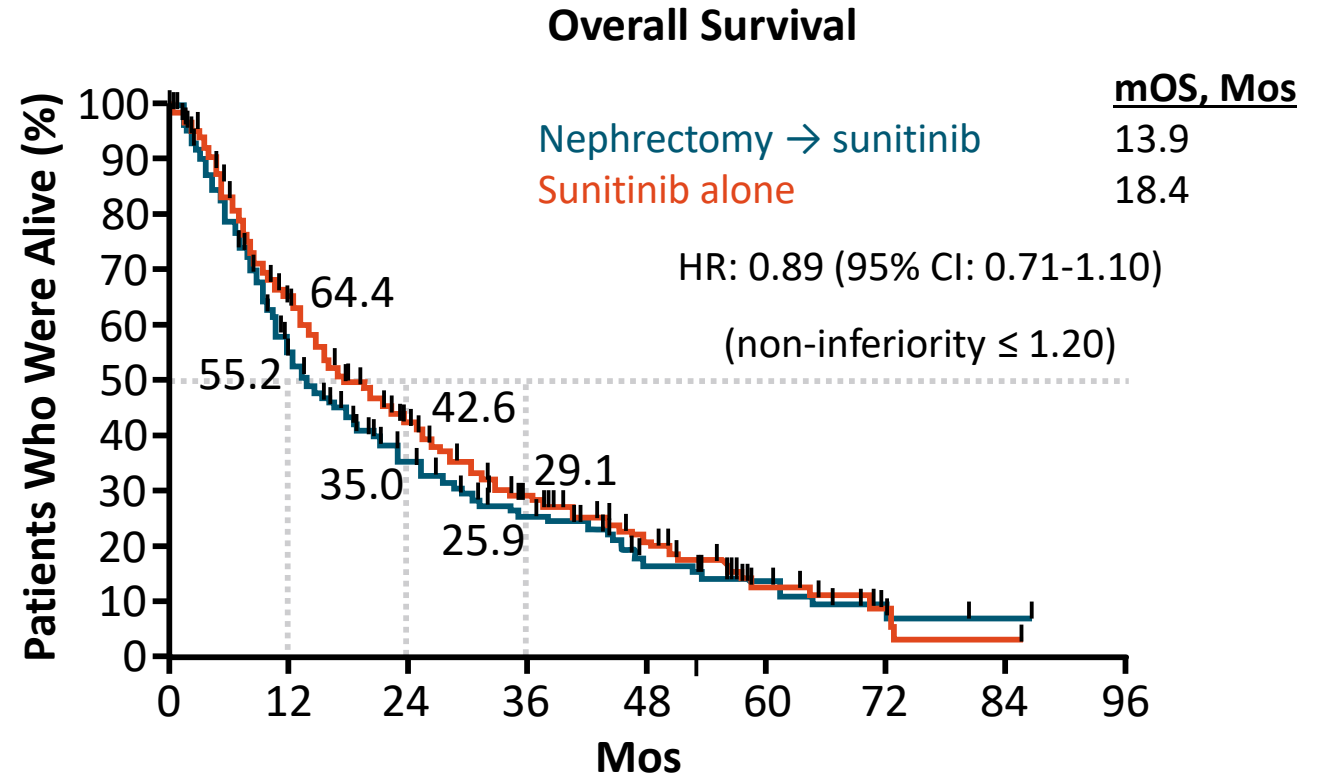
- Median follow-up of 50.9 mos at data cutoff (December 12, 2017)

Characteristic, n (%)	Nephrectomy → Sunitinib (n = 226)	Sunitinib (n = 224)
Median age, yrs (range)	63 (33-84)	62 (30-87)
Male	169 (74.8)	167 (74.6)
MSKCC risk category	n = 225	n = 224
▪ Intermediate	125 (55.6)	131 (58.5)
▪ Poor	100 (44.4)	93 (41.5)
ECOG PS		
▪ 0	130 (57.5)	122 (54.5)
▪ 1	96 (42.5)	102 (45.5)
Fuhrman grade of RCC	n = 150	n = 156
▪ 1 or 2	77 (51.3)	82 (52.6)
▪ 3 or 4	73 (48.7)	74 (47.4)
Tumor stage	n = 67	n = 49
▪ T1	5 (7.5)	7 (14.3)
▪ T2	13 (19.4)	13 (26.5)
▪ T3 or T4	47 (70.1)	25 (51.0)
▪ Tx	2 (3.0)	4 (8.2)

Characteristic, n (%)	Nephrectomy → Sunitinib (n = 226)	Sunitinib (n = 224)
Node stage	n = 66	n = 49
▪ N0	23 (34.8)	18 (36.7)
▪ N1	13 (19.7)	6 (12.2)
▪ N2	7 (10.6)	13 (26.5)
▪ Nx	23 (34.8)	12 (24.5)
Median primary tumor size, mm (range)	88 (6-200)	86 (12-190)
Median no. mets (range)	2 (1-5)	2 (1-5)
Median tumor burden, mm (range)	140 (23-399)	144 (39-313)
Location of mets	n = 217	n = 221
▪ Lung	172 (79.3)	161 (72.9)
▪ Bone	78 (35.9)	82 (37.1)
▪ LN	76 (35.0)	86 (38.9)
▪ Other	78 (35.9)	90 (40.7)

CARMENA: Overall Survival

- Sunitinib alone not inferior to nephrectomy → sunitinib (upper boundary of 95% CI ≤ 1.20)
- mOS longer with sunitinib alone vs nephrectomy → sunitinib:
 - MSKCC intermediate-risk: 23.4 vs 19.0 mos (HR: 0.92)
 - MSKCC poor-risk: 13.3 vs 10.2 mos (HR: 0.86)



mOS, Mos

Nephrectomy → sunitinib 13.9
 Sunitinib alone 18.4

HR: 0.89 (95% CI: 0.71-1.10)

(non-inferiority ≤ 1.20)

Patients at Risk

Nephrectomy → sunitinib	226	110	61	40	19	11	4	1	0
Sunitinib alone	224	128	76	44	26	8	3	1	0

CARMENA: Safety, Nephrectomy Outcomes

Severe (Grade 3/4) AEs in Sunitinib-Treated Patients, * n (%)	Nephrectomy → Sunitinib (n = 186)	Sunitinib (n = 213)
Any	61 (32.8)*	91 (42.7)*
Asthenia	16 (8.6)	21 (9.9)
Hand-foot syndrome	8 (4.3)	12 (5.6)
Anemia	5 (2.7)	11 (5.2)
Neutropenia	5 (2.7)	10 (4.7)
Kidney or urinary tract disorder	1 (0)	9 (4)

*P = .04

- In nephrectomy → sunitinib arm, 95% underwent nephrectomy with most (58%) having open surgery
 - Postop mortality within 1 mo of surgery: 2%
 - Postop morbidity: 82 pts (39%)
 - Clavien-Dindo grade 3: 11% of those with postoperative morbidity
 - Clavien-Dindo grade > 3: 5% of those with postoperative morbidity

- In sunitinib-alone arm, 38 patients needed secondary nephrectomy (7 for emergency treatment of primary tumor); 31.3% restarted sunitinib

CARMENA: Conclusions

- In final analysis of CARMENA, sunitinib alone not inferior to cytoreductive nephrectomy followed by sunitinib in patients with mRCC
 - HR for death: 0.89 (95% CI: 0.71-1.10; noninferior if upper boundary ≤ 1.20)
 - Median OS longer in sunitinib-alone arm for all patients and in intermediate-risk and poor-risk subgroups
- Clinical benefit rate significantly higher in sunitinib-alone arm (47.9% vs 36.6% with nephrectomy followed by sunitinib; $P = .02$)
- Investigators concluded that nephrectomy should no longer be part of standard of care for patients with mRCC requiring medical treatment

CARMENA: Limitations

- **Eight years were necessary to accrue 450 of a prespecified 576 patients over 79 sites**
- **Fewer than one (0.7) patient accrued per year at each institution**
 - **Suggest that many potentially eligible patients were never enrolled**
 - **Lack of clinical equipoise or patient unwillingness to be randomised?**
- **Comparative analysis of the baseline characteristics of patients in NCDB relative to CARMENA**
 - **Carmena participants -> more metastatic sites and more burden of lymph node, lung and bone metastasis**
 - **Suggest exclusion of potentially better candidates for CN from the trial**

Stewart GD, Aitchison M, Bex A, et al. Cytoreductive nephrectomy in the tyrosine kinase inhibitor era: a question that may never be answered. Eur Urol 2017;71:845–7.

Arora S, Sood A, Dalela D, et al. Cytoreductive nephrectomy: assessing the generalizability of the CARMENA trial to real-world National Cancer Data Base cases. Eur Urol 2019;75:352–3.

Motzer RJ, Russo P. Cytoreductive nephrectomy—patient selection is key. N Engl J Med 2018;379:481–2.

CARMENA: Limitations

- **Lower severe adverse event rate (Clavien-Dindo grade III-IV) observed among CN + sunitinib patients (33%) than sunitinib alone patients (43%, p = 0.04)**
- **Contamination / cross-over between study arms**
 - **17% of patients in sunitinib only arm undergoing CN**
- **Exclusion of patients for trial enrolment was left at the investigator's discretion**
- **Authors did not report on selection factors used to determine a patient's candidacy for CN**
- **Patients likely to benefit from CN were treated with surgery outside of trial?**

Stewart GD, Aitchison M, Bex A, et al. Cytoreductive nephrectomy in the tyrosine kinase inhibitor era: a question that may never be answered. Eur Urol 2017;71:845–7.

Arora S, Sood A, Dalela D, et al. Cytoreductive nephrectomy: assessing the generalizability of the CARMENA trial to real-world National Cancer Data Base cases. Eur Urol 2019;75:352–3.

Motzer RJ, Russo P. Cytoreductive nephrectomy—patient selection is key. N Engl J Med 2018;379:481–2.

CARMENA: Limitations

Overall survival by patient population

Population	Arm A (Nephrectomy + sunitinib)			Arm B (Sunitinib)			HR (95% CI), stratified by MSKCC risk group
	n	Events, n (%)	Median (95% CI), months	n	Events, n (%)	Median (95% CI), months	
ITT	226	165 (73)	13.9 (11.8-18.3)	224	161 (72)	18.4 (14.7-23.0)	0.89 (0.71-1.10)
PP1*	205	149 (73)	14.5 (11.9-20.2)	206	143 (69)	20.5 (15.6-25.2)	0.87 (0.69-1.1)
PP2#	176	122 (64)	18.3 (13.7-23.2)	206	143 (69)	20.5 (15.6-25.2)	0.98 (0.77-1.25)

*The PP1 analysis included only patients who had nephrectomy in Arm A, and patients who receive sunitinib in Arm B.

#The PP2 analysis included only patients who had nephrectomy and receive sunitinib after nephrectomy in Arm A, and patients who receive sunitinib in Arm B.
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; MSKCC, Memorial Sloan Kettering Cancer Center; PP, per-protocol.

- Per-protocol analysis
 - Included only those patients who were treated as assigned (sunitinib alone or CN + sunitinib)
 - The upper limit of the CI crossed the 1.20 threshold; median OS times were 20.5 (sunitinib alone) and 18.3 months (CN + sunitinib) with a hazard ratio of 0.98 (95% CI, 0.77 to 1.25)
 - Difficult to definitively conclude the non-inferiority of sunitinib without surgery when this patient population is treated as planned
 - Wider confidence interval may reflect the fact that many CARMENA patients were not treated as planned

CARMENA: Generalizability

- Selection of patients for CN in CARMENA is in discordance with what is seen in a real-world setting
- CN is not routinely performed in poor-risk patients anyway
- Generalizability of CARMENA trial to routine clinical practice may be limited

Arora S, Sood A, Dalela D, et al. Cytoreductive nephrectomy: assessing the generalizability of the CARMENA trial to real-world National Cancer Data Base cases. Eur Urol 2019;75:352–3.

Kokorovic A, Rendon, RA. Cytoreductive nephrectomy in metastatic kidney cancer: what do we do now? Curr Opin Support Palliative Care 2019;13:255-61.

Cytoreductive nephrectomy (CN) in metastatic renal cancer (mRCC): Update on Carmena trial with focus on intermediate IMDC-risk population

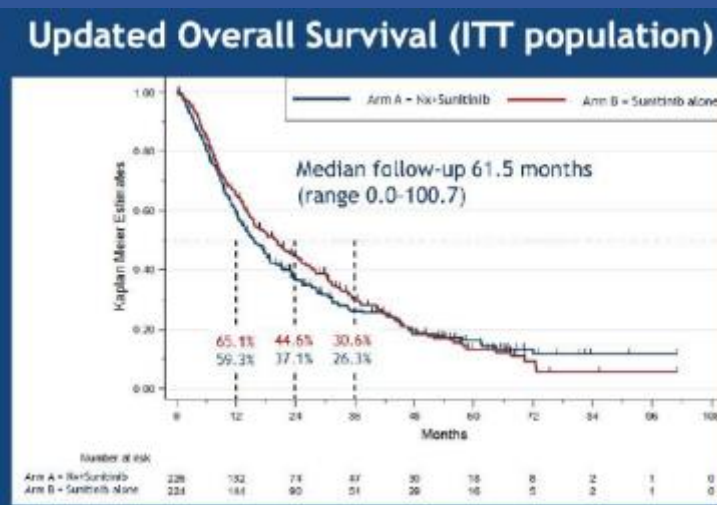
Arnaud Méjean, Simon Thezenas, Christine Chevreau, Karim Bensalah, Lionnel Geoffrois, Antoine Thiery-Vuillemin, Luc Cormier, Herve Lang, Laurent Guy, Gwenaelle Gravis, Frederic Rolland, Claude Linassier, Marc-Olivier Timsit, Laurence Albiges, Stephane Oudard, Thierry Lebret, Jean-Marc Treluyer, Sandra Colas, Bernard Escudier, Alain Ravaud



Cytoreductive nephrectomy (CN) in metastatic renal cancer (mRCC): Update on Carmena trial with focus on intermediate IMDC-risk population (Mejean A et al; Oral Abstract 4508)

Product (MOA)	Sponsor	Indication/patient pop	Phase and trial ID
Cytoreductive nephrectomy	Assistance Publique - Hôpitaux de Paris	mRCC	Phase 3 (NCT00930033 ; Carmena)

- **Background:**
 - Carmena data were presented in 2019 at EAU (testing external validity of Carmena) and AUA (patient perspectives and real-world role of CN)
 - ASCO 2019 analysis focused on which subgroups of patients, particularly those in intermediate IMDC risk group, benefit from CN
- **Patients and Treatments:**
 - Carmena was initially stratified by MSKCC risk group, but patients were reclassified by IMDC risk group, with no significant changes in patient risk: 56% remained intermediate and 44% remained poor risk in CN + sun vs 59% to 62% intermediate and 41% to 38% poor risk in sun
- **Results:**
 - Median OS (ITT) at 61.5 months follow-up: 15.6 months CN + sun vs 19.8 months sun (HR 0.97, 95% CI 0.79-1.19)
 - IMDC intermediate risk: 19.0 months CN + sun vs 27.9 months sun (HR 0.94, 95% CI 0.70-1.24)
 - IMDC poor risk: 9.5 months CN + sun vs 11.8 months sun (HR 1.01, 95% CI 0.74-1.37)
- **IMDC risk factors in intermediate risk patients:**
 - 28.0% had 1 risk factor with median OS: 31.4 months CN + sun vs 25.2 months sun (HR 1.29, 95% CI 0.85-1.98, P=0.232)
 - 31.1% had 2 risk factors with median OS: 17.6 months CN + sun vs 31.2 months sun (HR 0.63, 95% CI 0.44-0.97, P=0.033)
 - Comparing across number of risk factors within CN + sun arm, there was a significant difference in OS (HR 1.68, 95% CI 1.10-2.57, P=0.015)
- **Comparing across number of metastatic sites in CN + sun arm, there was a significant difference in OS (HR 1.42, 95% CI 1.03-1.96, P=0.032)**
- **Secondary nephrectomy: median OS 48.5 months (95% CI 27.9-64.4) sun + delayed CN vs 15.7 months (95% CI 13.3-20.5) sun**



Conclusions: The longer follow-up of 61.5 months confirms that CN is not superior to sun, with the authors recommending that CN still not be considered SOC for mRCC. With both MSKCC and IMDC risk group classification, CN was not superior to sunitinib in the ITT population, but for patients with only 1 IMDC risk factor (and particularly with 1 metastatic site), CN might be beneficial.

Conclusions (1)

- With longer FU of 61.5 months, Carmena trial confirms that CN is not superior to sunitinib alone in ITT population, both with MSKCC and IMDC risk groups for treating mRCC.
- **This update confirms that overall, CN should still not be considered as the SOC**

FU, follow up; CN, cytoreductive nephrectomy; ITT, intent to treat; MSKCC, Memorial Sloan Kettering Cancer Center; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mRCC, metastatic renal cell carcinoma; SOC; standard of care

Conclusions (2)

However further analyses suggest that :

1. CN might be beneficial for patients with only one IMDC risk factor, especially in case of one metastatic site
2. Number of metastatic sites per se is not helpful to define good candidates for surgery
3. Delayed nephrectomy after initial systemic treatment in good responders patients, is associated with long OS, supporting this approach as a good therapeutic strategy

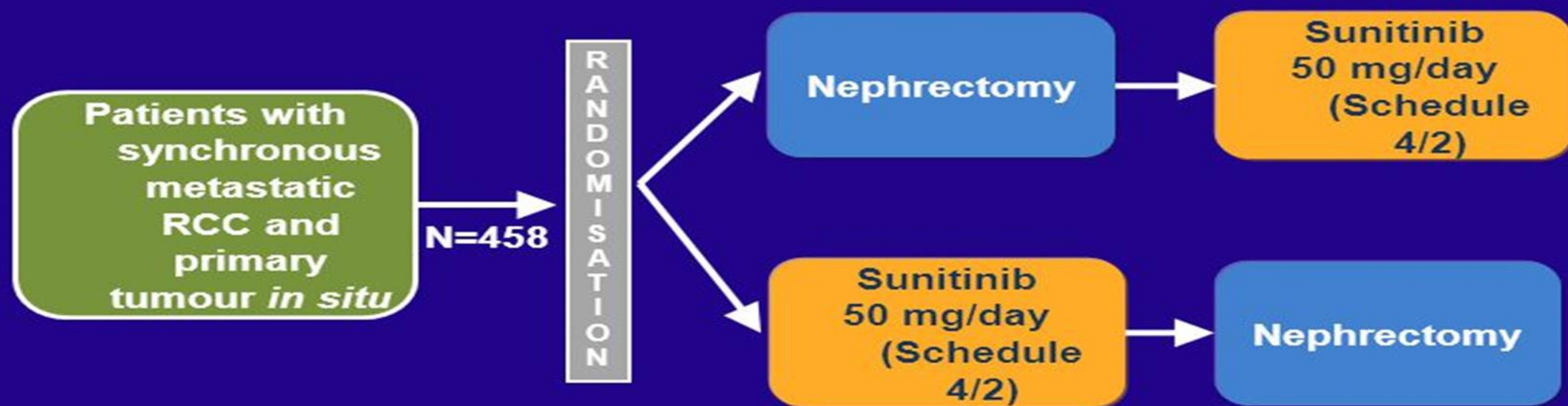
CN, cytoreductive nephrectomy; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; OS, overall survival

CARMENA

Overall, the results favor targeted therapy alone without cytoreductive nephrectomy in patients with mRCC

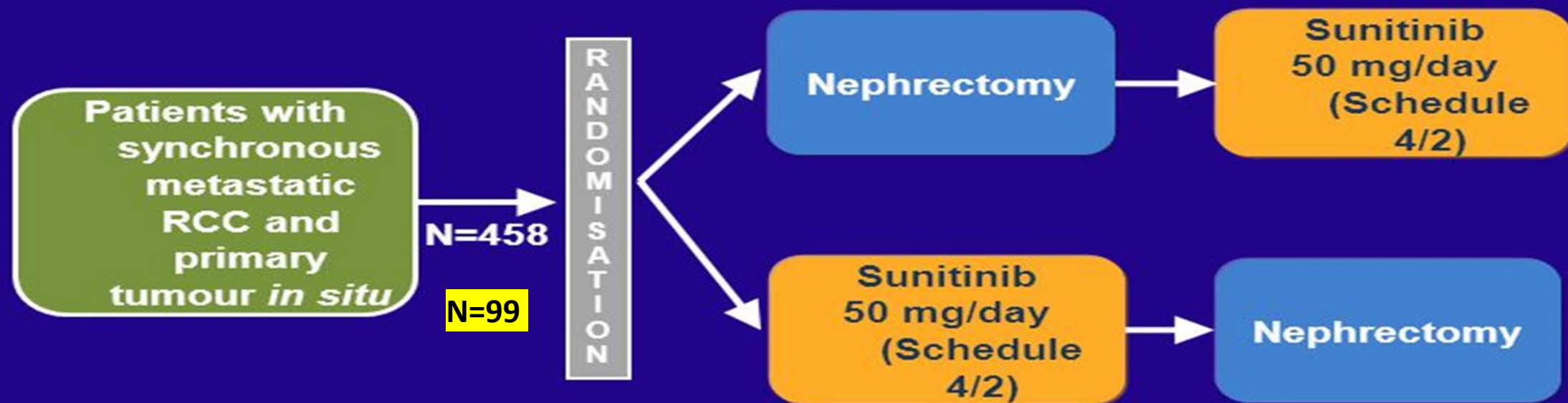
Refute the use of cytoreductive nephrectomy for poor risk and many intermediate-risk patients

SURTIME: The SURgery and TIME Phase III Study30073 of Sunitinib and Nephrectomy



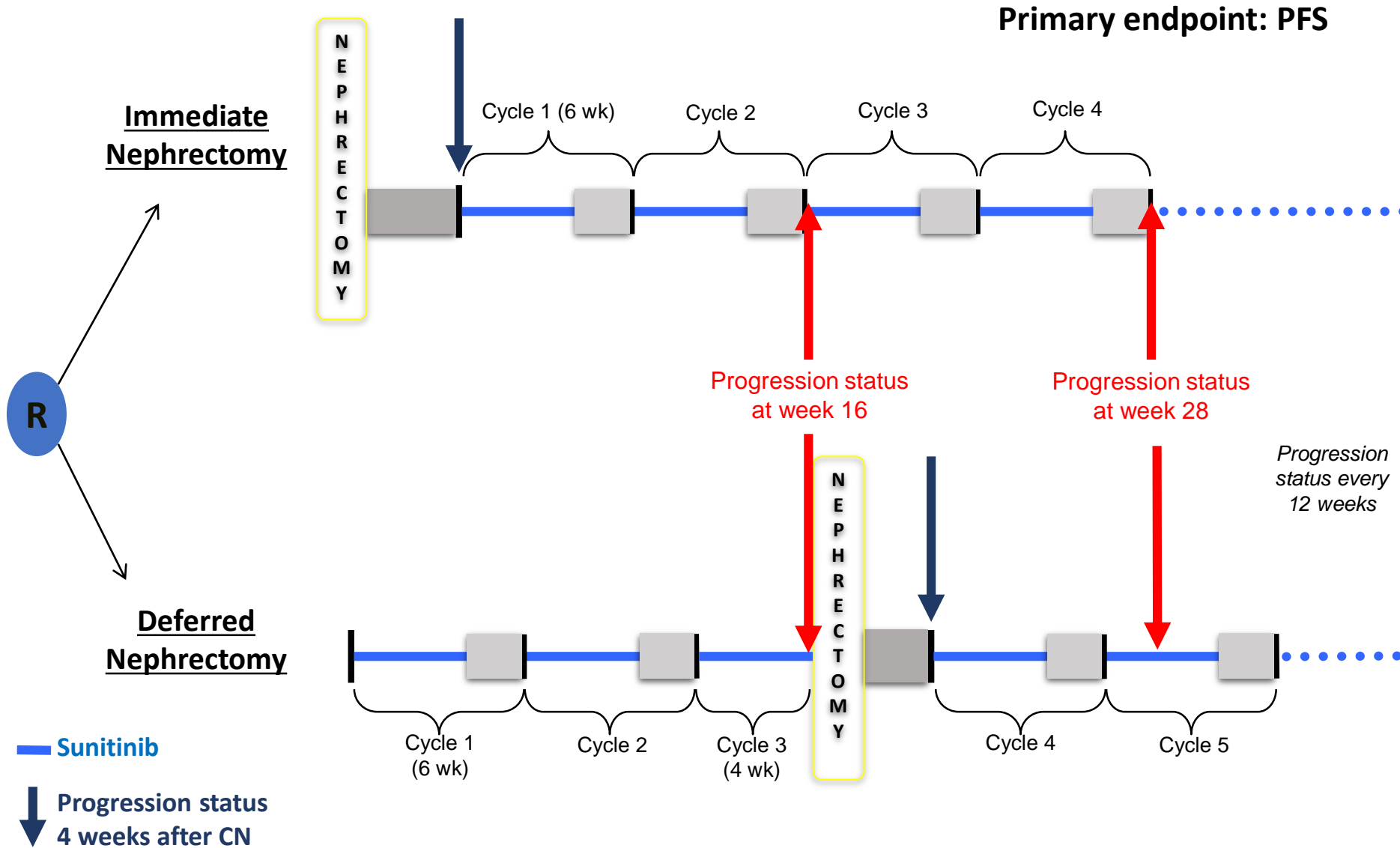
- Primary endpoint: progression-free survival
- Secondary endpoint: OS, association with prognostic gene and protein expression profiles

SURTIME: The SURgery and TIME Phase III Study30073 of Sunitinib and Nephrectomy



- Primary endpoint: progression-free survival
- Secondary endpoint: OS, association with prognostic gene and protein expression profiles

SURTIME: Study Design



SURTIME: Key Inclusion Criteria

Disease Characteristics

- **Histologically confirmed mRCC:**
 - Histology subtype: clear-cell subtype
 - Resectable *asymptomatic* primary in situ
- **Measurable disease (RECIST 1.1)**
- **Prior therapies:**
 - Prior systemic treatment for mRCC not allowed
 - Prior local radiotherapy for bone lesions allowed

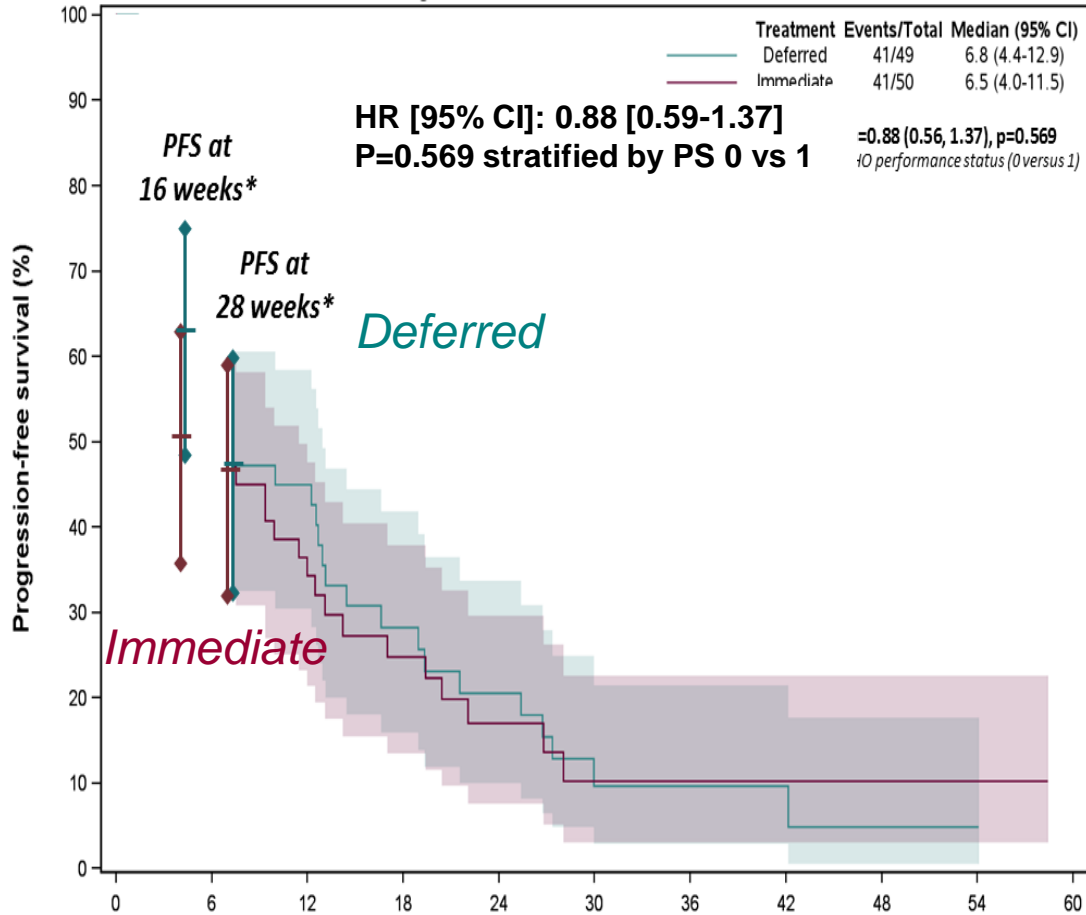
Patient Characteristics

- **WHO PS 0-1**
- **No more than 3 surgical risk factors¹:**
 - serum albumin CTCAE v4.0 grade 2 or worse
 - serum LDH > 1.5 x UNL
 - liver metastases
 - symptoms at presentation due to metastases
 - retroperitoneal lymph node involvement
 - supra-diaphragmatic lymph node involvement
 - clinical stage T3 or T4

SURTIME: Key Baseline Characteristics

	Immediate nephrectomy (N=50)	Deferred nephrectomy (N=49)
Median age (years)	60	58
Performance status (WHO)		
WHO 0	36 (72.0%)	31 (63.3%)
WHO 1	14 (28.0%)	18 (36.7%)
Male	41 (82.0%)	39 (79.6%)
MSKCC intermediate risk	43 (86.0%)	43 (87.7%)
≥ 2 measurable metastatic sites	43 (86.0%)	46 (93.9%)
Mean (SD) primary tumor size (mm)	93.1 (37.8)	96.8 (31.3)

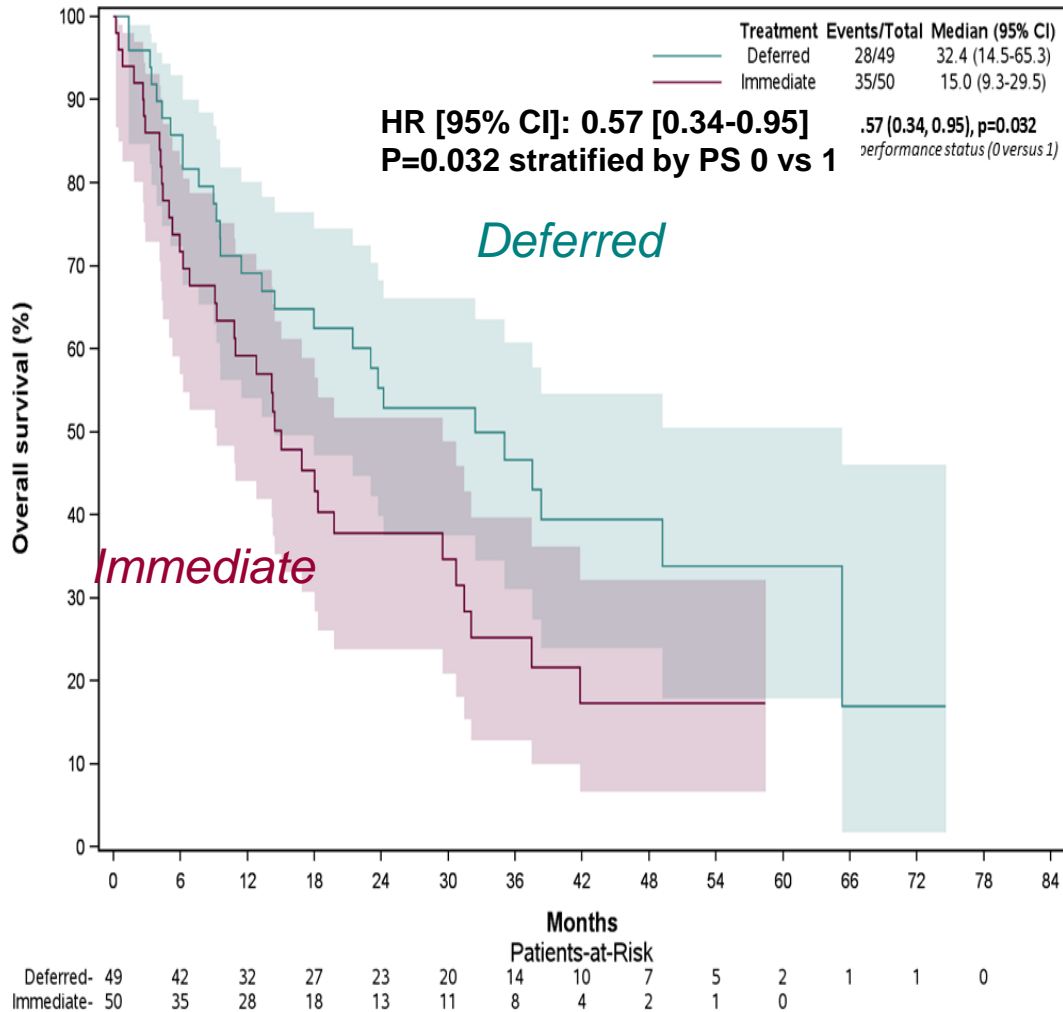
SURTIME: PFS (ITT population)



* With 15 days window

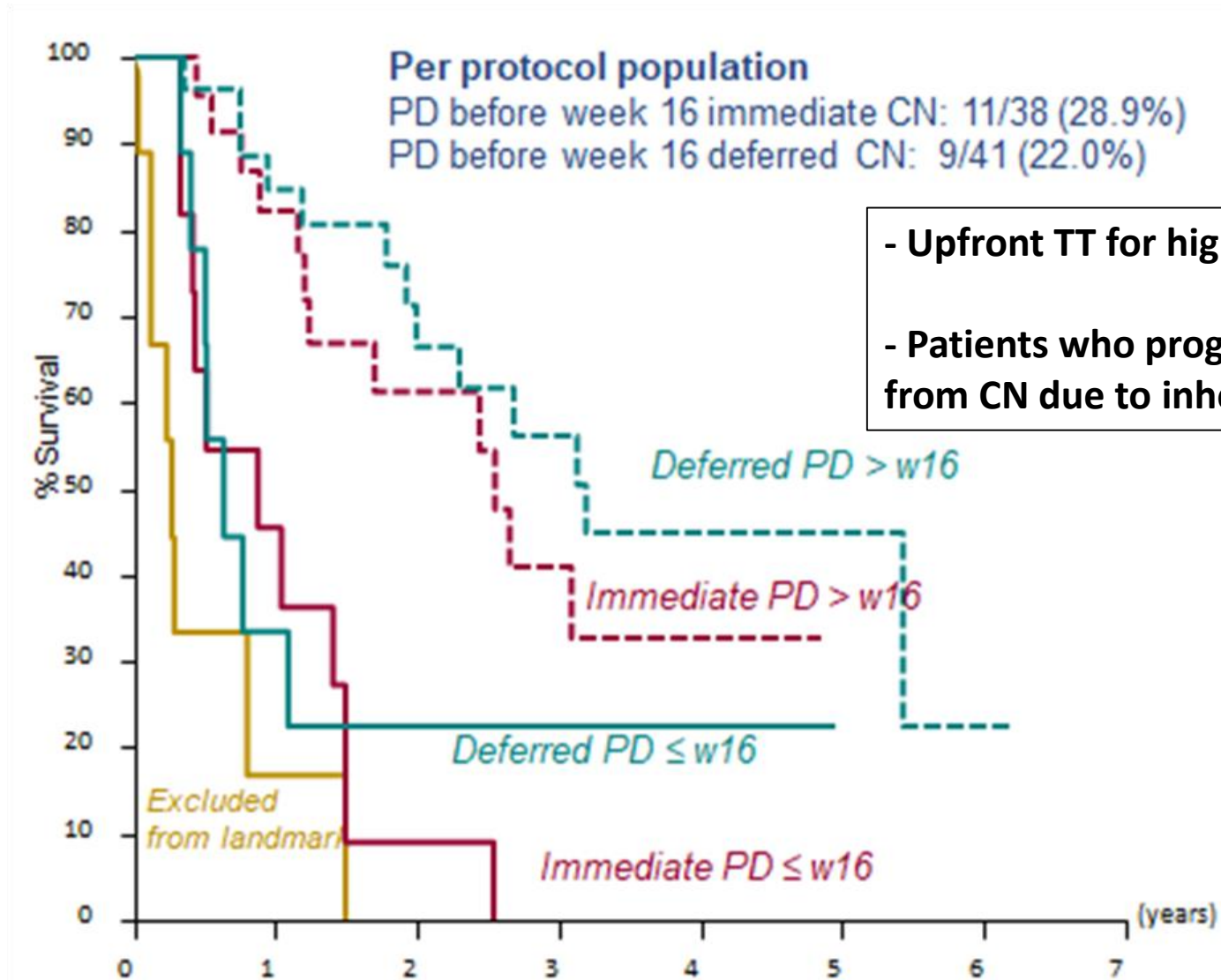
Progression-free status at w 28 (±15 days)	Immediate nephrectomy (N=50)	Deferred nephrectomy (N=49)
Progression-free at week 28 [95% CI]	21 (42.0%) [28.2% – 56.8%]	21 (42.9%) [28.8% – 57.8%]
p-value (Fisher exact test)	>0.99	
Progression before or at week 28, or treatment failure	25 (50.0%)	24 (49.0%)
Not assessable	4 (8.0%)	4 (8.2%)

SURTIME: OS (ITT population)



	Immediate nephrectomy (N=50)	Deferred nephrectomy (N=49)
Survival status		
Dead	35 (70.0)	28 (57.1)
Reason of death		
Progression	30	25
Surgery related toxicity	1	0
Progression and surgery related toxicity	1	0
Cardiovascular disease (not due to toxicity or progression)	1	0
Other (not due to toxicity or progression)	1	0
Unknown	1	3

SURTIME: Landmark Analysis at Week 16



- Upfront TT for high-risk patients may act as a 'litmus test'
- Patients who progress despite TT were unlikely to benefit from CN due to inherent resistance

Surtime: Conclusions

- **SURTIME accrued poorly**
- **Results were mainly exploratory**
- **Sequence of CN and sunitinib did not affect PFS at 28 weeks**
- **Sample size precludes definitive conclusions from other endpoints, although OS signal present for deferred CN**
- **Survival in the deferred CN arm was comparable to data reported from previous single-arm phase II studies of presurgical sunitinib or pazopanib**
- **Deferred CN appeared to select out patients with inherent resistance to systemic therapy; confirms previous findings from single-arm phase II studies**
- **Advantages of deferred CN approach - initiate therapy quickly; still allows CN to be performed; surgery safe after sunitinib**

Journal of Urology 2017

Lymph Node Dissection is Not Associated with Improved Survival among Patients Undergoing Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma: A Propensity Score Based Analysis

Boris Gershman, R. Houston Thompson, Daniel M. Moreira, Stephen A. Boorjian, Christine M. Lohse, Brian A. Costello, John C. Cheville and Bradley C. Leibovici

From the Division of Urology, Rhode Island Hospital and the Miriam Hospital, Providence, Rhode Island (BG), Department of Urology (RHT, SAB, BCL), Department of Health Sciences Research (CML), Department of Oncology (BAC), and Department of Laboratory Medicine and Pathology (JCC), Mayo Clinic, Rochester, Minnesota, and Department of Urology, University of Illinois

The role of lymph node
dissection in the
management
of renal cell carcinoma:
a systematic review
and meta-analysis.

[BJU Int.](#) 2018 May;121(5):684-698.

[Bhindi B](#), [Wallis CJD](#), et al.

...Although LND yields independent prognostic information, the existing literature does not support a therapeutic benefit to LND in either M0 or M1 RCC.

METASTASECTOMY

Resection of metastatic disease (metastasectomy) has been performed in the following clinical scenarios:

- **Patients with mRCC at presentation; performed with nephrectomy**
- **Patients who develop metastatic disease following nephrectomy**
- **Patients who have persistent disease despite systemic therapy**

[Lancet Oncol.](#) 2014 Nov;15(12):e549-61.

Local treatments for metastases of renal cell carcinoma: a systematic review.

[Dabestani S](#), [Marconi L](#), [Hofmann F](#), [Stewart F](#), [Lam TB](#), [Canfield SE](#), [Stahler M](#), [Powles T](#), [Ljungberg B](#), [Bex A](#).

Local treatment of metastases such as metastasectomy or radiotherapy remains controversial in the treatment of metastatic renal cell carcinoma. To investigate the benefits and harms of various local treatments, we did a systematic review of all types of comparative studies on local treatment of metastases from renal cell carcinoma in any organ. Interventions included **metastasectomy, radiotherapy modalities, and no local treatment**. The results suggest that **patients treated with complete metastasectomy have better survival and symptom control (including pain relief in bone metastases) than those treated with either incomplete or no metastasectomy**. Nevertheless, the available evidence was marred by high risks of bias and confounding across all studies. Although the findings presented here should be interpreted with caution, they and the identified gaps in knowledge should provide guidance for clinicians and researchers, and directions for further research.

Surgical Metastasectomy in Renal Cell Carcinoma: A Systematic Review

*Eur Urol Oncol. 2019
Mar;2(2):141-149*

Young Academic Urologists
Kidney Cancer Working Group of the
European Association of Urology

- **No randomized clinical data available**
- **Published studies support the role of SM in selected patients in the modern era**
- **Complete SM allows sustained survival free of systemic treatment**
- **Integration of SM and systemic therapy in a multimodal approach remains a valid option for some patients**
- **Surgical resection of metastases originating from RCC may play a role in prolonging survival and avoiding systemic therapy when complete resection is achievable**
- **This strategy is an option for selected patients with a limited number of metastases who still have good general health status**

Lung Metastases: Cancer 2011

Original Article

Survival After Complete Surgical Resection of Multiple Metastases From Renal Cell Carcinoma

Angela L. Alt, MD¹; Stephen A. Boorjian, MD¹; Christine M. Lohse, MS²; Brian A. Costello, MD³;
Bradley C. Leibovich, MD¹; and Michael L. Blute, MD⁴

Lung Metastases: Cancer 2011

Surgical resection of isolated lung metastases in carefully selected patients has been associated with a 20 to 50% five-year survival

Complete resection of lung-only metastases is associated with markedly improved survival as compared with incomplete resection (five-year cancer-specific survival 73.6% versus 19%, respectively)

Isolated Bone Metastases

J Bone Joint Surg Am 2007

Patient Survival After Surgery for Osseous Metastases from Renal Cell Carcinoma*

By Patrick P. Lin, MD, Attiqah N. Mirza, MD, Valerae O. Lewis, MD,
Christopher P. Cannon, MD, Shi-Ming Tu, MD, Nizar M. Tannir, MD, and Alan W. Yasko, MD, MBA

Investigation performed at The University of Texas M.D. Anderson Cancer Center, Houston, Texas

Background: Skeletal metastases from renal cell carcinoma are highly destructive vascular lesions. They pose unique surgical challenges due to the risk of life-threatening hemorrhage and resistance to other treatments. The goal of this retrospective study was to evaluate factors that may affect survival after surgical treatment of metastases of renal cell carcinoma.

Methods: We performed a retrospective review of a series of 295 consecutive patients who had been treated for metastatic renal cell carcinoma at one institution between 1974 and 2004. There were 226 men and sixty-nine women. A total of 368 metastases of renal cell tumors to the extremities and pelvis were treated. The surgical procedures included curettage with cementing and/or internal fixation (214 tumors), en bloc resection (117), closed nailing (twenty-seven), amputation (four), and other measures (six). Overall survival was calculated with Kaplan-Meier analysis. The log-rank test was used to evaluate the effect of different variables on overall survival.

Results: The overall patient survival rates at one and five years were 47% and 11%, respectively. The metastatic pat-

Isolated Bone Metastases

- **Excision of bone metastases may be considered in carefully selected patients for both pain relief and tumor control**
- **295 consecutive patients with metastatic RCC who had a solitary lesion, intractable pain, or impending fracture underwent resection**
- **Overall, the one- and five-year survival rates were 47% and 11%**
- **Stereotactic radiosurgery (SRS) is increasingly being used to treat oligometastatic bony disease and may extend targeted therapy treatment**

Brain Metastasis

Clin GU Cancer Sep 2013

Original Study

Prognostic Factors of Survival for Patients With Metastatic Renal Cell Carcinoma With Brain Metastases Treated With Targeted Therapy: Results From the International Metastatic Renal Cell Carcinoma Database Consortium

Michael M. Vickers,¹ Hulayel Al-Harbi,¹ Toni K. Choueiri,²
Christian Kollmannsberger,³ Scott North,⁴ Mary MacKenzie,⁵
Jennifer J. Knox,⁶ Brian I. Rini,⁷ Daniel Y.C. Heng¹

Brain Metastasis

Clin GU Cancer Sep 2013

Brain lesions have been traditionally treated with surgical resection, whole-brain irradiation, or SRS

SRS alone may be an attractive therapeutic option for patients with incidentally identified brain metastases from RCC

Regardless of the treatment approach, the prognosis is poor, and median survival in patients with brain metastases is approximately 9 months

Liver Metastases

- **Despite the negative impact of liver metastases on survival, resections of solitary metachronous liver metastases are possible, although the morbidity may be high**
- **Contemporary reports suggest that with careful patient selection, two-year survival is greater than 50 percent**

Liver Metastases

Factors that may identify appropriate patients for hepatic metastasectomy

- Surgery is being performed with curative intent
- An interval of more than 24 months from RCC diagnosis to development of liver metastases
- Tumor size less than 5 cm
- The feasibility of repeat hepatectomy if necessary



ORIGINAL ARTICLE

Metastasis to the Thyroid Gland

Report of a Large Series From the Mayo Clinic

via Hegerova, MD,* Marcio L. Griebeler, MD,† Jordan P. Reynolds, MD,‡ Michael R. Henry, MD,§ and Hossein Gharib, MD, MACP, MACE†

Objectives: Metastases to the thyroid gland are not as unusual as commonly believed. This study reports the largest number of patients with metastatic disease of the thyroid to date, confirms the accuracy of fine needle aspiration (FNA) in diagnosing metastasis, and reviews the diagnosis and management through our institutional experience.

Methods: This study entailed review of all thyroid FNAs performed at the Mayo Clinic, Rochester during the period 1980 to 2010 and identified 100 patients with a metastatic solid neoplasm of the thyroid gland.

Results: Frequent primary tumor sites included kidney (22%), lung (18%), and head and neck (12%). The median age at discovery of metastasis was 63 years. The time from diagnosis of primary tumor to metastasis to the thyroid gland was most considerable for colorectal carcinoma (mean 113 mo). Forty-one patients underwent thyroid resection with an average tumor size of 3 cm. Median survival for patients with metastases was 20 months (range, 1 to 228 mo). Patients who underwent thyroid resection had a median survival of 30 months (range, 3 to 171 mo), whereas survival in patients without thyroid surgery was 12 months (range, 1 to 228 mo, log-rank test

Secondary thyroid malignancies often pose a diagnostic and management problem, particularly if they present years after identification and treatment of the primary cancer. This study reports the largest number of patients with metastatic disease of the thyroid to date, confirms the accuracy of fine needle aspiration (FNA) in diagnosing metastasis, and reviews the diagnosis and management through our institutional experience. Frequent primary tumor sites included kidney (22%), lung (18%), and head and neck (12%). The median age at discovery of metastasis was 63 years. The time from diagnosis of primary tumor to metastasis to the thyroid gland was most considerable for colorectal carcinoma (mean 113 mo). Forty-one patients underwent thyroid resection with an average tumor size of 3 cm. Median survival for patients with metastases was 20 months (range, 1 to 228 mo). Patients who underwent thyroid resection had a median survival of 30 months (range, 3 to 171 mo), whereas survival in patients without thyroid surgery was 12 months (range, 1 to 228 mo, log-rank test

This retrospective study reports the incidence and primary sites of metastatic disease to the thyroid gland, the accuracy of fine needle aspiration (FNA) in diagnosing metastasis, and the management of metastatic thyroid disease through our institutional experience. We report on 100 patients with metastatic disease to the thyroid gland. The median age at discovery of metastasis was 63 years. The time from diagnosis of primary tumor to metastasis to the thyroid gland was most considerable for colorectal carcinoma (mean 113 mo). Forty-one patients underwent thyroid resection with an average tumor size of 3 cm. Median survival for patients with metastases was 20 months (range, 1 to 228 mo). Patients who underwent thyroid resection had a median survival of 30 months (range, 3 to 171 mo), whereas survival in patients without thyroid surgery was 12 months (range, 1 to 228 mo, log-rank test

Thyroid metastases

American Journal of Clinical Oncology 2009



Thyroid Metastases

American Journal of Clinical Oncology 2009

- **RCC is one of the more common types of neoplasms to metastasize to the thyroid gland**
- **Fine needle aspiration is essential to make this diagnosis**
- **Limited data suggest that metastasectomy may confer a survival advantage**
- **97 patients with thyroid metastases (22% from a renal primary), median survival time was 30 and 12 months for those who underwent metastasectomy compared with those who did not**

Pancreatic Metastasis

BJS 2009

Systematic review

Systematic review of pancreatic surgery for metastatic renal cell carcinoma

P. J. Tanis, N. A. van der Gaag, O. R. C. Busch, T. M. van Gulik and D. J. Gouma

Pancreatic Metastasis

- **Patients with pancreatic metastases seem to have a better prognosis, which may be a result of a more indolent biology**
- **In addition, patients who present with pancreatic metastases also respond better to targeted agents, although the reason for this is unknown**

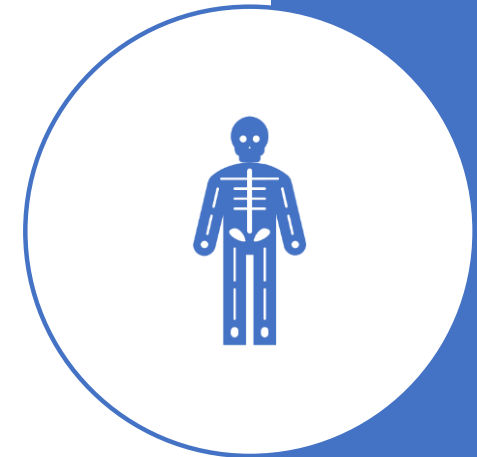
Pancreatic Metastasis

- A systematic literature review of 384 patients with RCC metastases to the pancreas managed with (n = 321) or without (n = 73) metastasectomy revealed five-year overall survivals of 73% and 14%, respectively
- The postoperative in-hospital mortality associated with pancreatic resection was 2.8 percent
- The presence of extrapancreatic RCC metastases was associated with worse disease-free survival, and symptomatic metastases were associated with worse overall survival
- Surprisingly, the size of the largest tumor resected, number of pancreatic metastases, type of pancreatic resection, and interval from diagnosis of RCC to pancreatic metastasis were not predictive of survival

Role of Stereotactic Body Radiation Therapy for the Management of Oligometastatic Renal Cell Carcinoma

[Franzese C, et al., J Urol. 2019 Jan;201\(1\):70-76.](#)

- **Considered to be a safe approach**
- **Effective local control of oligometastatic renal cell carcinoma**
- **Future prospective studies are necessary to evaluate the impact on survival and quality of life**



Local Recurrence

- **Although most patients who develop a local soft tissue recurrence die of metastatic disease, the limited data suggest that resection of the recurrence may prolong survival in carefully selected patients**
- **As with metastatic disease, patients with a longer time to recurrence following nephrectomy and with small-volume recurrent disease tend to do better**

Kidney Cancer Research Network of Canada (KCRNC)

Consensus statement on the role of cytoreductive nephrectomy for patients with metastatic renal cell carcinoma

[Mason RJ](#), [Wood L](#), [Kapoor A](#), [Basappa N](#), [Bjarnason G](#), [Boorjian SA](#), [Breau RH](#), [Cagiannos I](#), [Jewett MAS](#), [Karakiewicz PI](#), [Kassouf W](#), [Kollmannsberger C](#), [Lalani AA](#), [Lattouf JB](#), [Lavallée LT](#), [Pautler S](#), [Power N](#), [Richard P](#), [So A](#), [Tanguay S](#), [Rendon RA](#)

Can Urol Assoc J. 2019 Jun;13(6):166-174.

KCRNC consensus statement on the role of CN for patients with mRCC

Should patients with mRCC be offered CN and what is the optimal patient selection and timing?

1. Recognizing the complex nature of advanced kidney cancer management, decisions regarding CN should ideally be made in a **multidisciplinary** setting.
2. Patients with a **good performance status** (Eastern Cooperative Oncology Group [ECOG] ≤ 1 or Karnofsky performance status (KPS) $\geq 80\%$), **minimal symptoms** related to metastases, a **resectable** primary tumour, and a **limited burden** of metastatic disease should be **offered upfront CN** followed by metastases-directed therapy, a period of surveillance, or systemic therapy.
3. Patients with **significant systemic symptoms** from metastatic disease, active **central nervous system** metastases, a **limited burden of disease within the kidney relative to the cumulative extra-renal volume of metastases**, **rapidly progressing disease**, a **poor performance status** (ECOG > 1 or KPS $< 80\%$), and/or **limited life expectancy** should **not undergo CN**.
4. Patients with mRCC but **without characteristics of (2) or (3)** should be offered **initial treatment with systemic therapy** with consideration of CN given to those with a significant clinical response.

KCRNC consensus statement on the role of CN for patients with mRCC

- *Is there a role for CN in patients with non-clear-cell mRCC?*
 - **Patients with non-clear-cell mRCC should be offered CN with similar considerations to those with clear cell mRCC.**

Carrasco A, Thompson RH, Leibovich BC, et al. The impact of histology on survival for patients with metastatic renal cell carcinoma undergoing cytoreductive nephrectomy. Indian J Urol 2014;30:38-42. <https://doi.org/10.4103/0970-1591.124204>

Aizer AA, Urun Y, McKay RR, et al. Cytoreductive nephrectomy in patients with metastatic non-clear-cell renal cell carcinoma (RCC). BJU Int 2014;113:E67-74. <https://doi.org/10.1111/bju.12442>

Kassouf W, Sanchez-Ortiz R, Tamboli P, et al. Cytoreductive nephrectomy for metastatic renal cell carcinoma with non-clear-cell histology. J Urol 2007;178:1896-900. <https://doi.org/10.1016/j.juro.2007.07.037>

Graham JCW, Donskov F, Lee J-L, et al. Cytoreductive nephrectomy in metastatic papillary renal cell carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). Genitourinary Cancer Symposium 2018.

KCRNC consensus statement on the role of CN for patients with mRCC

- *Is there a role for biopsy prior to CN?*
 - **In patients receiving initial systemic therapy, biopsy of the primary lesion or a metastatic deposit should be performed prior to the initiation of therapy.**
 - **For patients receiving upfront CN, preoperative biopsy of the kidney tumour or metastatic deposit may be performed if the results of the biopsy will influence management.**

KCRNC consensus statement on the role of CN for patients with mRCC

- *Is there a role for concomitant regional LND during CN?*
 - In patients with mRCC undergoing CN who do not have clinical evidence of nodal disease, retroperitoneal LND is not recommended.
 - Surgical resection of clinically positive lymph nodes may be considered at the time of CN after weighing the potential for increased surgical morbidity and the uncertain clinical benefit.

KCRNC consensus statement on the role of CN for patients with mRCC

- *Is there a preferred surgical approach for CN?*
- **CN can be performed through both minimally invasive and open surgical approaches at the discretion of the treating surgeon.**

Rabets JC, Kaouk J, Fergany A, et al. Laparoscopic versus open cytoreductive nephrectomy for metastatic renal cell carcinoma. Urology 2004;64:930-4. <https://doi.org/10.1016/j.urology.2004.06.052>

Nunez Bragayrac L, Hoffmeyer J, Abbotoy D, et al. Minimally invasive cytoreductive nephrectomy: A multi-institutional experience. World J Urol 2016;34:1651-6. <https://doi.org/10.1007/s00345-016-1827-1>

Matin SF, Madsen LT, Wood CG. Laparoscopic cytoreductive nephrectomy: The MD Anderson Cancer Center experience. Urology 2006;68:528-32. <https://doi.org/10.1016/j.urology.2006.03.076>

Ganeshappa A, Sundaram C, Lerner MA, et al. Role of the laparoscopic approach to cytoreductive nephrectomy in metastatic renal-cell carcinoma: Does size matter? J Endourol 2010;24:1289-92. <https://doi.org/10.1089/end.2009.0401>

Eisenberg MS, Meng MV, Master VA, et al. Laparoscopic vs. open cytoreductive nephrectomy in advanced renal-cell carcinoma. J Endourol 2006;20:504-8. <https://doi.org/10.1089/end.2006.20.504>

Blick C, Bott S, Muneer A, et al. Laparoscopic cytoreductive nephrectomy: A three-centre retrospective analysis. J Endourol 2010;24:1451-5. <https://doi.org/10.1089/end.2009.0458>

CARMENA CONTROVERSY



“PRACTICE CHANGING”

CARMENA CONTROVERSY



“PRACTICE CHANGING”



“DOES NOT CHANGE MY PRACTICE”

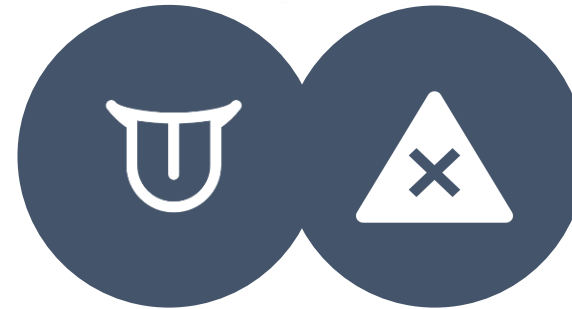
CARMENA CONTROVERSY



“PRACTICE CHANGING”



“DOES NOT CHANGE MY PRACTICE”



**IMHO...PRACTICE CHANGING
AND
PRACTICE CONFIRMING**

IMMUNOTHERAPY

IMMUNE CHECKPOINT INHIBITORS

What is the relevance of cytoreductive nephrectomy in the immunotherapy era?

What is the timing of cytoreductive nephrectomy in the immunotherapy era?

Thank you

