Multidisciplinary Approaches to Cancer Symposium

Cytoreductive Nephrectomy: Is There a Role in Metastatic Renal Cell Cancer in 2024?

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City of Hope

Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

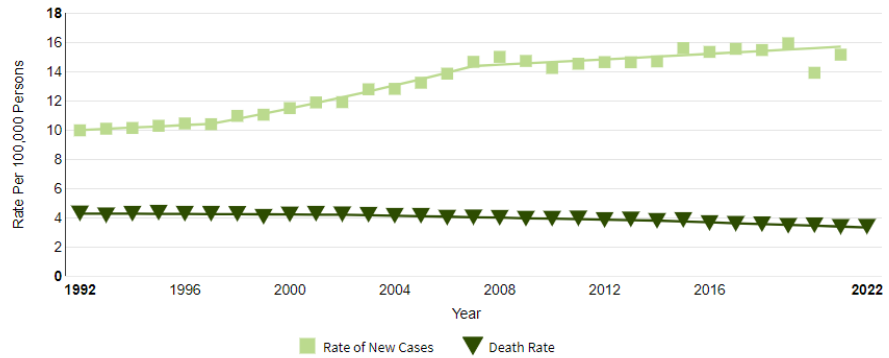
- *Disparities in surgery in mRCC.*

Renal Cell Cancer 2024

- ACS Estimates
  - 81,610 NEW CASES
  - 14,390 DEATHS
  - Average Age Diagnosis 65
  - Male Predisposition 2:1
  - Rate of new cases rising
  - Survival Improving

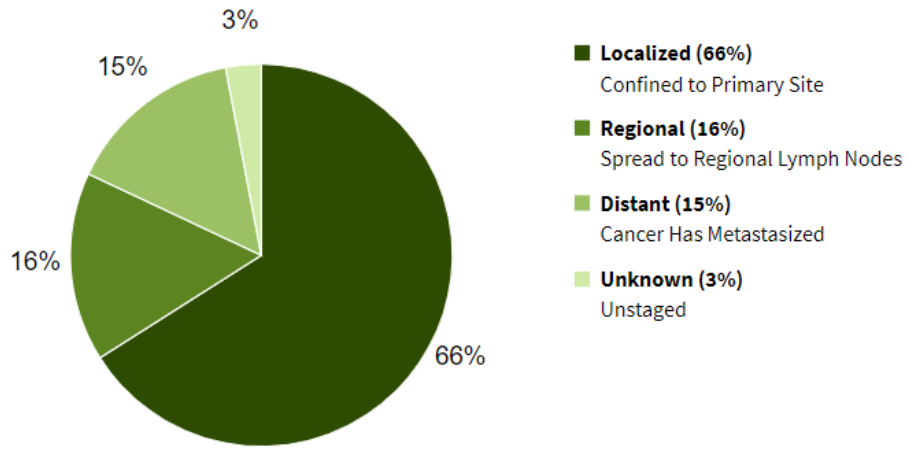
	Common Types of Cancer	Estimated New Cases 2024	Estimated Deaths 2024
1.	Breast Cancer (Female)	310,720	42,250
2.	Prostate Cancer	299,010	35,250
3.	Lung and Bronchus Cancer	234,580	125,070
4.	Colorectal Cancer	152,810	53,010
5.	Melanoma of the Skin	100,640	8,290
6.	Bladder Cancer	83,190	16,840
7.	**Kidney and Renal Pelvis Cancer**	**81,610**	**14,390**
8.	Non-Hodgkin Lymphoma	80,620	20,140
9.	Uterine Cancer	67,880	13,250
10.	Pancreatic Cancer	66,440	51,750

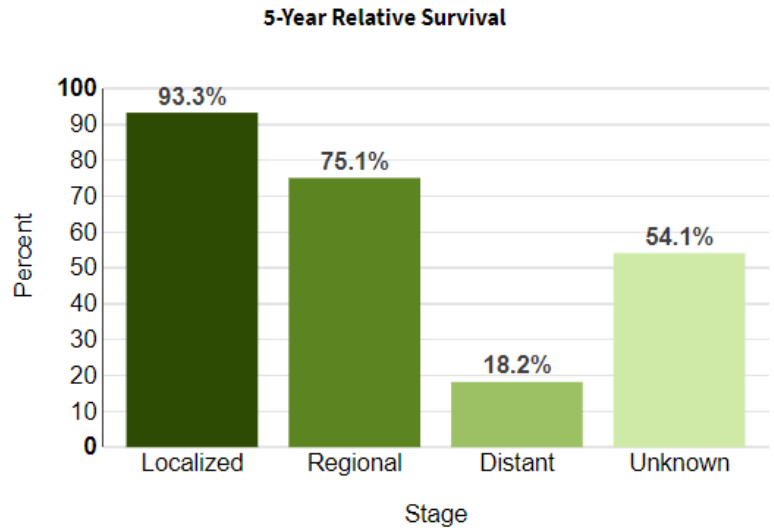
Kidney and renal pelvis cancer represents 4.1% of all new cancer cases in the U.S.



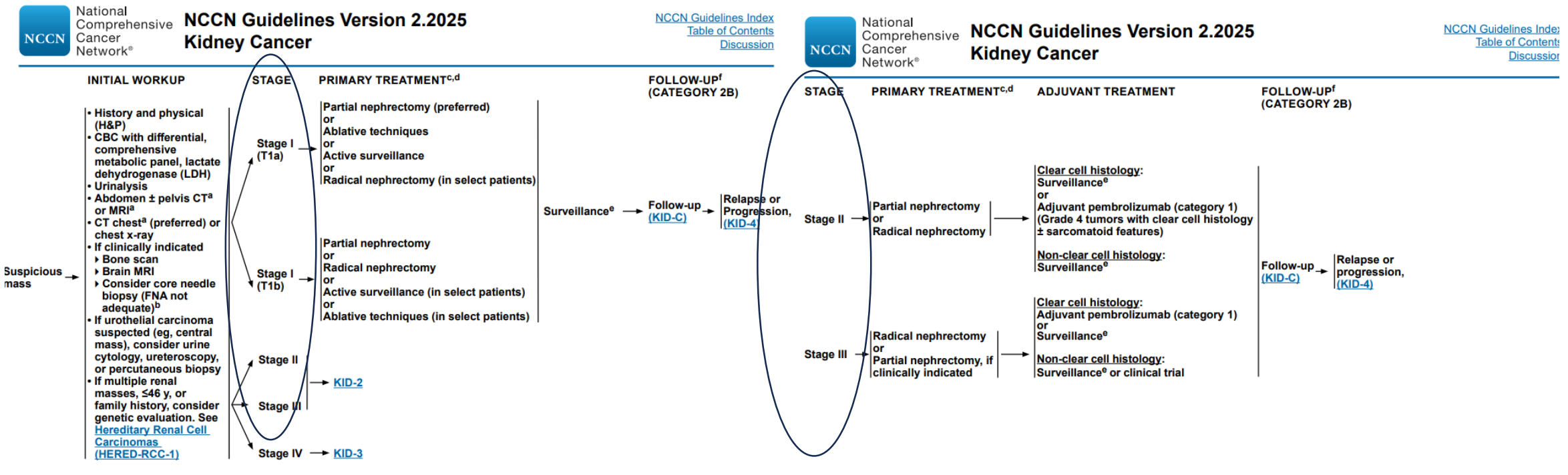
New cases come from SEER 12. Deaths come from U.S. Mortality.
All Races, Both Sexes. Rates are Age-Adjusted.

Renal Cell Cancer 2024

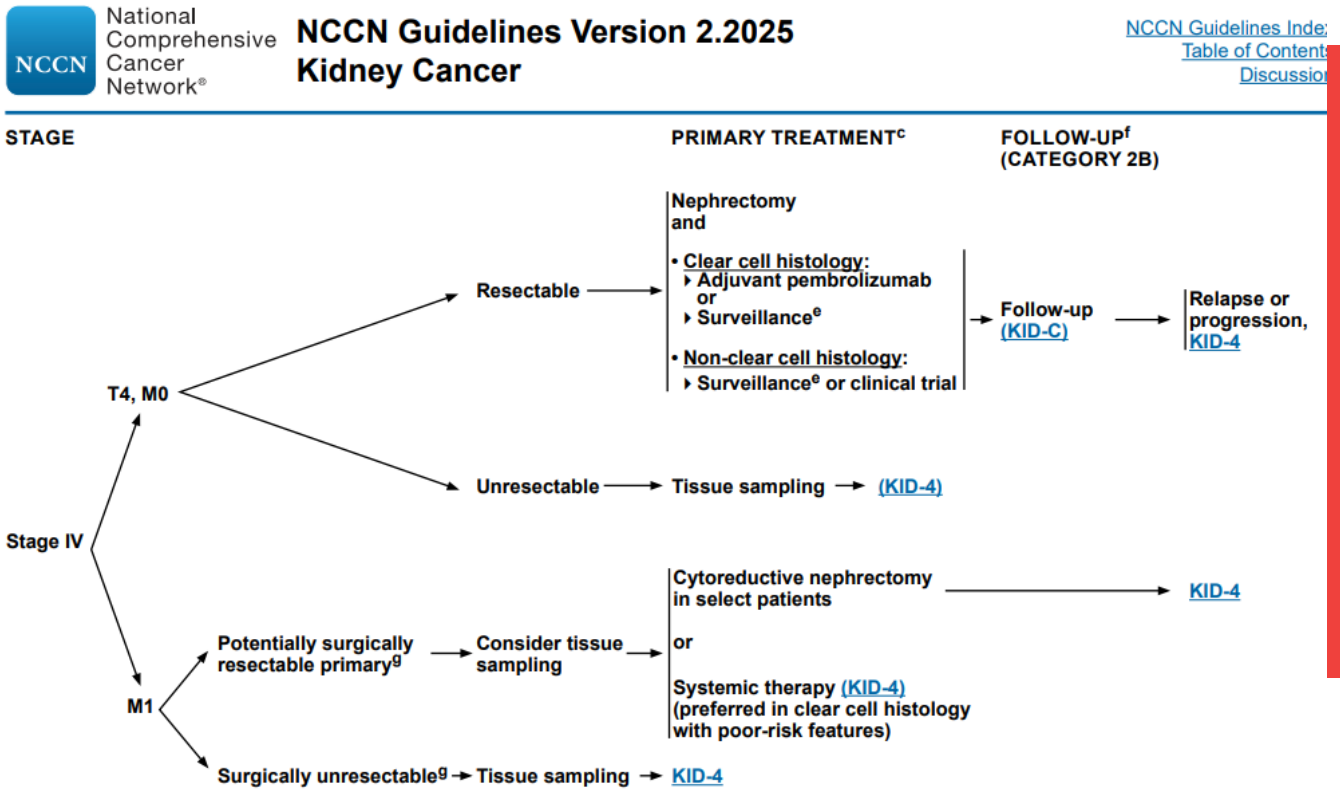




Localized and Localregional disease(Stage 1-3)



Stage 4 Disease



- Generally, patients who would be candidates for cytoreductive nephrectomy prior to systemic therapy have:
  - Excellent performance status (ECOG PS <2)
  - No brain metastasis
- Patients either with large-volume distant metastases or tumors with large sarcomatoid burdens should receive systemic therapy prior to cytoreductive nephrectomy.

Renal Cell Cancer 2024-General Principles of Management

- Surgical Disease , High Cure Rate for Most stages
- Nephron Sparing Surgery (Stage 1-3 when technically feasible)
- Minimally Invasive Surgery-Robotic(Less Complications/Pain)
- Ablation/SBRT an option for lesions <3cm-Stage 1A Lesions
- Active Surveillance
    - Predominate cystic component
    - Competing Risk of death, morbidity from intervention and Poor renal function

Why/Why not do surgery?

PROS

- CN can be performed as part of combined multimodal approach to decrease bulk of tumor before systemic therapy
- Palliative Nephrectomy to Remove Potential Source of Bleeding and Pain
- Metastastectomy can be performed in patients limited metastatic disease
- Eliminate Primary tumor as potential source of Immunosuppressive or Tumor Promoting Growth Factors and Resection of Resistant Clones

CONS

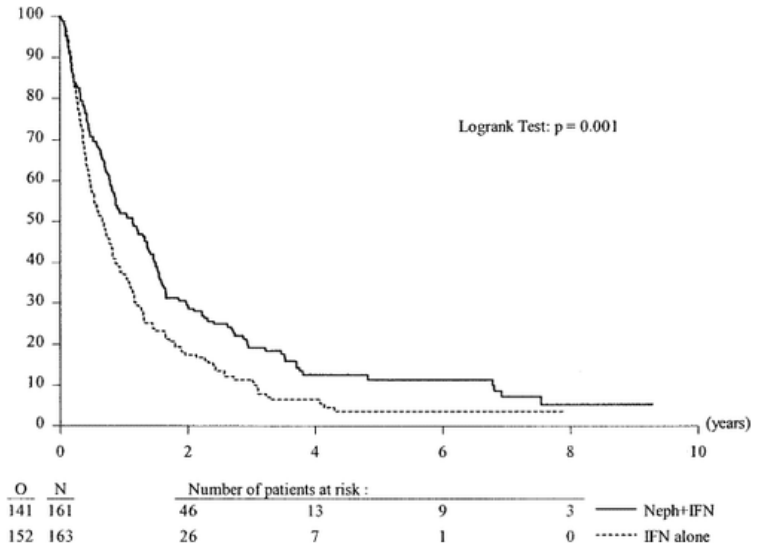
- Initial CN may delay start of systemic targeted therapies and patient may die prior to receiving them
- Avoid potential surgical or perioperative complications
- Uncertainty in who would be appropriate candidates

Pal et al. Cytoreductive Nephrectomy in 2021. European Urology . Feb 2022, V 36, P44-46

CN for mRCC in the INFN era (2001)

- **Southwest Oncology Group(SWOG) trial 8949** and **European Organization for the Research and Treatment of Cancer(EORTC) Trial 30947** - 331 total patients, identical trial design

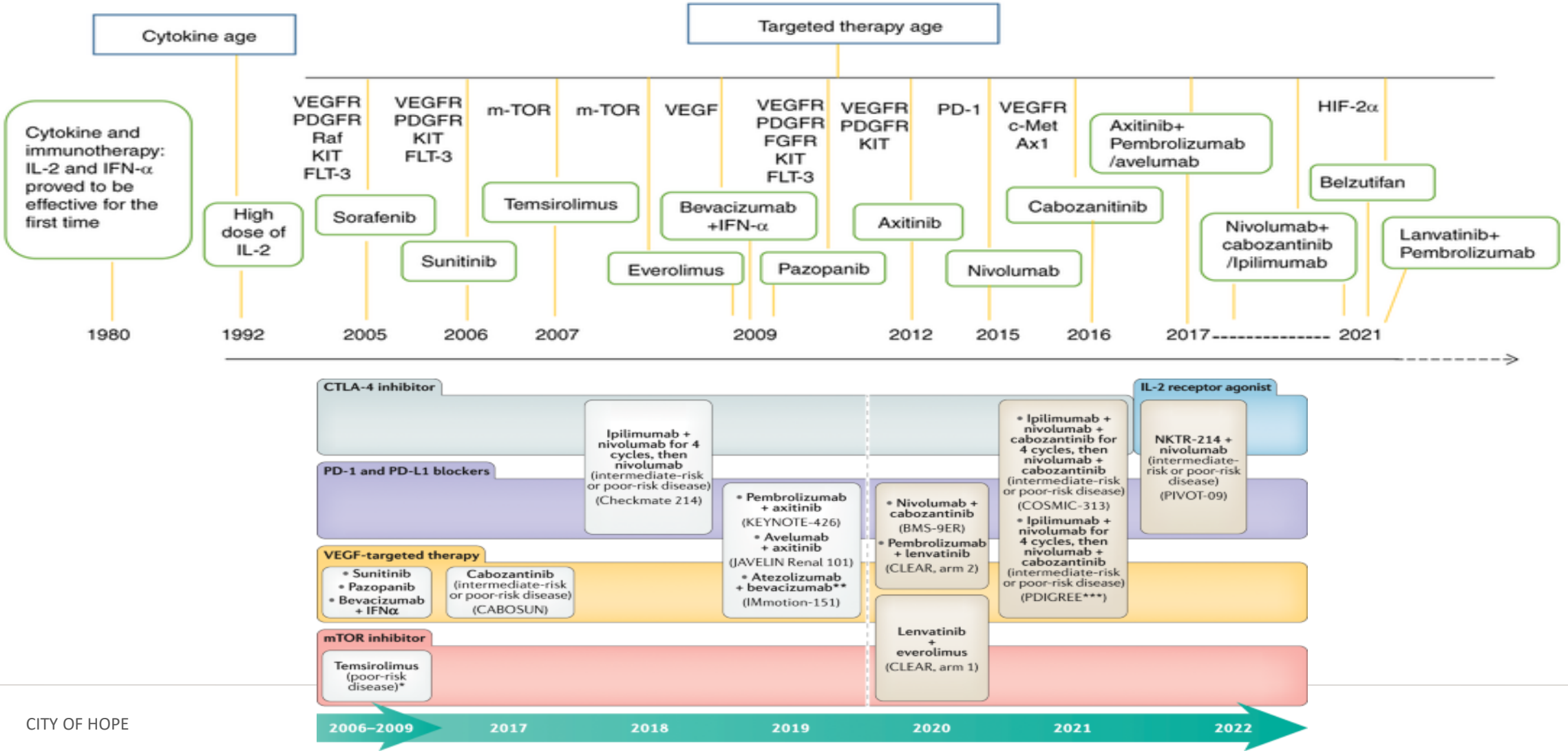
- mRCC, PS 0-1, Prospectively randomized to CN followed by IFN-Alpha versus INFN-Alpha alone



- Overall median Survival Was 13.6 months vs 7.8 months (HR 0.69, p=0002)
- OS survival advantage of 5.8 months
- 1 year survival (51.9% for CN vs 37.1% No CN)

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.* 345(23), 1655–1659 (2001).
Mickisch GH, Garin A, Van Poppel H, de Prijck L, Sylvester R. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet*358(9286), 966–970 (2001).

Evolution of Systemic Therapy



Prognostic Factors in mRCC

- MSKCC/Motzer

- **Karnofsky performance status (KPS)**: Less than 80%
- **Time from diagnosis to treatment**: Less than one year
- **Serum lactate dehydrogenase (LDH)**: High
- **Anemia**: Present
- **Hypercalcemia**: Present

- IMDCC/Heng Criteria

International Metastatic Renal Cell Carcinoma Database Consortium criteria

Karnofsky performance status score <80
Time from original diagnosis to initiation of targeted therapy <1 year
Hemoglobin less than the lower limit of normal
Serum calcium greater than the upper limit of normal
Neutrophil count greater than the upper limit of normal
Platelet count greater than the upper limit of normal

- Favorable risk: None of the above risk factors present.
- Intermediate risk: 1 or 2 of the above risk factors present.
- Poor risk: 3 or more risk factors present.

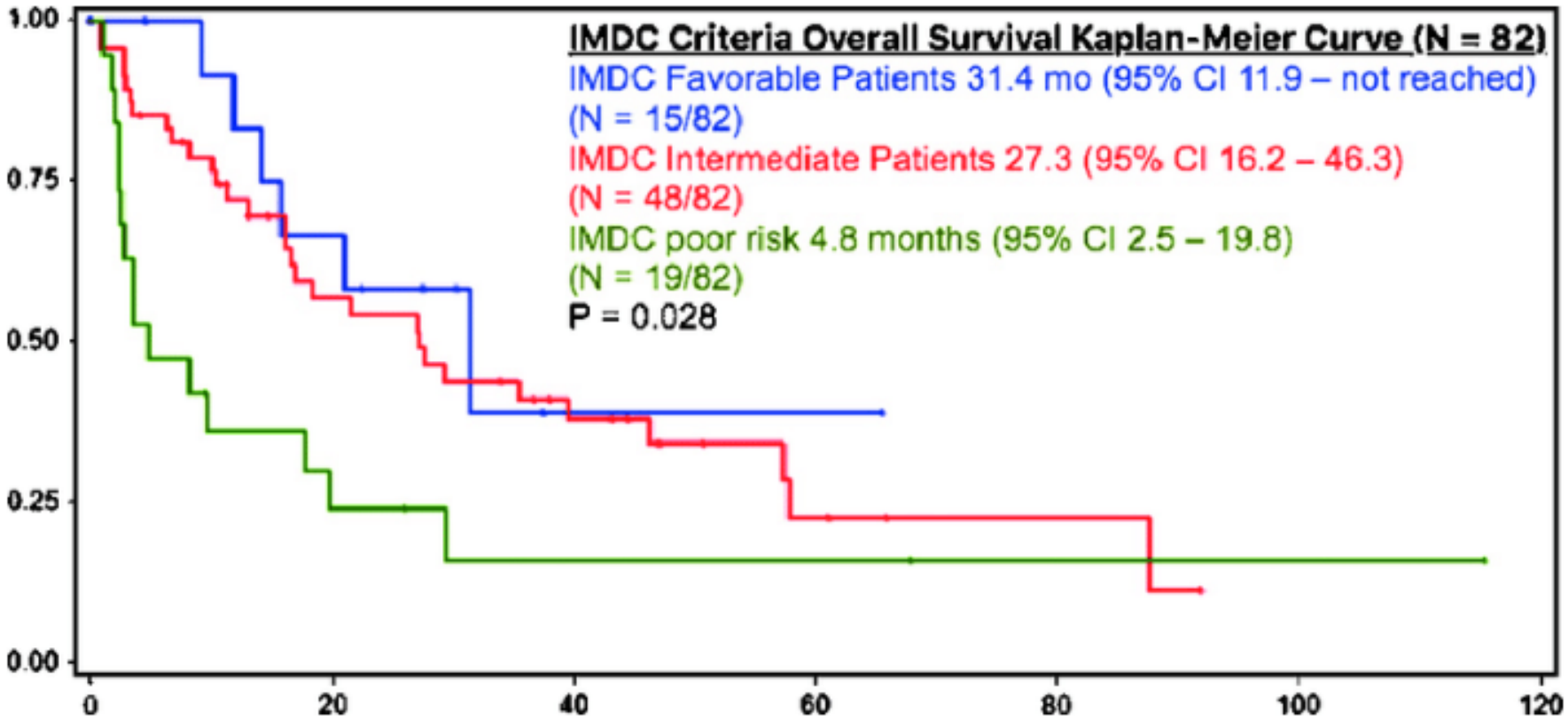
Adapted from: Heng DYC, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal Cell Carcinoma Database Consortium prognostic model: A population-based study. Lancet Oncol 2013; 14:141.

- **Favorable**: No poor prognostic factors
- **Intermediate**: One or two poor prognostic factors
- **Poor**: Three or more poor prognostic factors

About 50–60% of mRCC patients are classified as intermediate risk.

Heng et al, Lancet Oncology . The IMDC model as a prognostic tool in patient with mRCC. V 16, Issue 3, March 15 P 293-300

Prognostic Factors in mRCC



Heng et al, Lancet Oncology . The IMDC model as a prognostic tool in patient with mRCC. V 16, Issue 3, March 15 P 293-300

CN in Era of target therapies

- Data showed improved survival and tolerability of target therapy compared to immunotherapy
- CN usage after 2005 remained greater than 35% indication an **Assumption that there was a survival benefit regardless of the type of systemic therapy a patient would receive**

Tsao. Et al, CN for mRCC in the era of targerted therapy in the US:Seer analysis. World J Urol. 2013

Cancer
An International Interdisciplinary Journal of the American Cancer Society

Original Article | Free Access

Can we better select patients with metastatic renal cell carcinoma for cytoreductive nephrectomy?

Stephen H. Culp MD, PhD, Nizar M. Tannir MD, E. Jason Abel MD, Vitaly Margulis MD, Pheroze Tamboli MD, Surena F. Matin MD, Christopher G. Wood MD

First published: 17 May 2010 | https://doi.org/10.1002/cncr.25046 | Citations: 166

Volume 116, Issue 14
15 July 2010
Pages 3378-3388

- MDACC Retrospective review (1991-2007)
- 566 patients underwent CN/110 Medical Therapy Alone
- Multivariate Analysis **7 variables** were significant preoperatively that were Negative Predictors of Survivor:
  - •Low Albumin (HR-1.57)
  - •High LDH (HR-1.66)
  - •cT3 or4 (HR-1.37 /2.05)
  - •Presence of Liver metastasis (HR=1.47)
  - •Symptoms at metastatic site(Bone pain, SOB) (HR-1.35)
  - •Radiographic Retroperitoneal Lymphadenopathy > 1cm (HR-1.29)
  - • Radiographic Supradiaphragmatic Lymphadenopathy > 1cm (HR-1.48)

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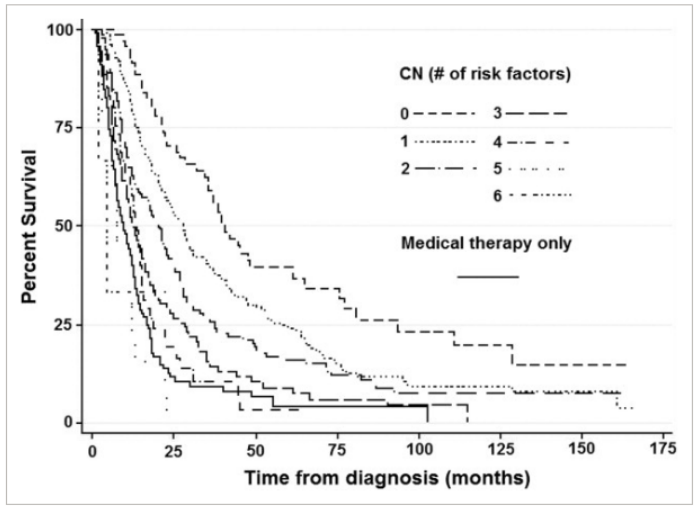

Patient Group	No. (%)	HR	95% CI	*P*	Median OS, mo
Medical therapy only	110	Referent	—	—	9.6
CN group					
No. of preoperative risk factors					
0	70 (12.4)	0.22	0.15-0.31	<.001	40.6
1	194 (34.3)	0.33	0.26-0.43	<.001	27.9
2	153 (27)	0.45	0.34-0.58	<.001	20.2
3	88 (15.5)	0.66	0.49-0.88	.005	12.6
4	45 (8)	0.78	0.55-1.13	.191	13.8
5	13 (2.3)	1.57	0.88-2.81	.125	7.5
6	3 (0.1)	0.98	0.24-3.99	.982	4.3
≤3	505 (89.2)	0.39	0.31-0.48	<.001	22.7
≥4	61 (10.8)	0.89	0.64-1.24	.499	12.2

Figure 1 Open in figure viewer | PowerPoint

This chart illustrates a Kaplan-Meier analysis of overall survival for patients with metastatic renal cell carcinoma (mRCC) who underwent cytoreductive nephrectomy (CN) based on the number of preoperative risk factors. The solid line represents patients with mRCC who underwent medical therapy alone (reference line).

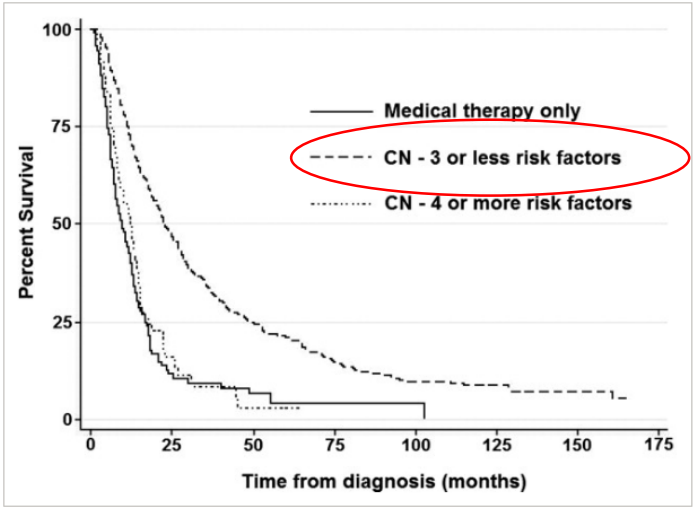

Figure 2 Open in figure viewer | PowerPoint

This chart illustrates a Kaplan-Meier analysis of overall survival for patients with metastatic renal cell carcinoma (mRCC) who underwent cytoreductive nephrectomy (CN) based on the number of preoperative risk factors (≤3 vs ≥4; $P < .001$). The solid line represents patients with mRCC who underwent medical therapy alone (reference line).

PLATINUM PRIORITY – KIDNEY CANCER | EDITORIAL BY STEPHEN H. CULP ON PP. 711–712 OF THIS ISSUE · Volume 66, Issue 4, P704-710, October 2014

Download Full Issue

Cytoreductive Nephrectomy in Patients with Synchronous Metastases from Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium

Daniel Y.C. Heng [a,†] · J. Connor Wells [a,†] · Brian I. Rini [b] · ... · Sun Young Rha [q] · Jenny J. Kim [r] · Toni K. Choueiri [s] ... Show more

Affiliations & Notes · Article Info · Linked Articles (1)

- Retrospective Review mRCC with synchronous Mets(n-1658) from IMDC (676 with CN, 982 Without CN) in targeted tx era
- Those that had CN, better IMDC profiles(Poor Risk 28% 54%)
- Even adjusted for Prognostic Profile there was an OS and PFS benefit for those undergoing CN
- Those did not benefit:
  - that had 4 or more risk factor

International Metastatic Renal Cell Carcinoma Database Consortium criteria

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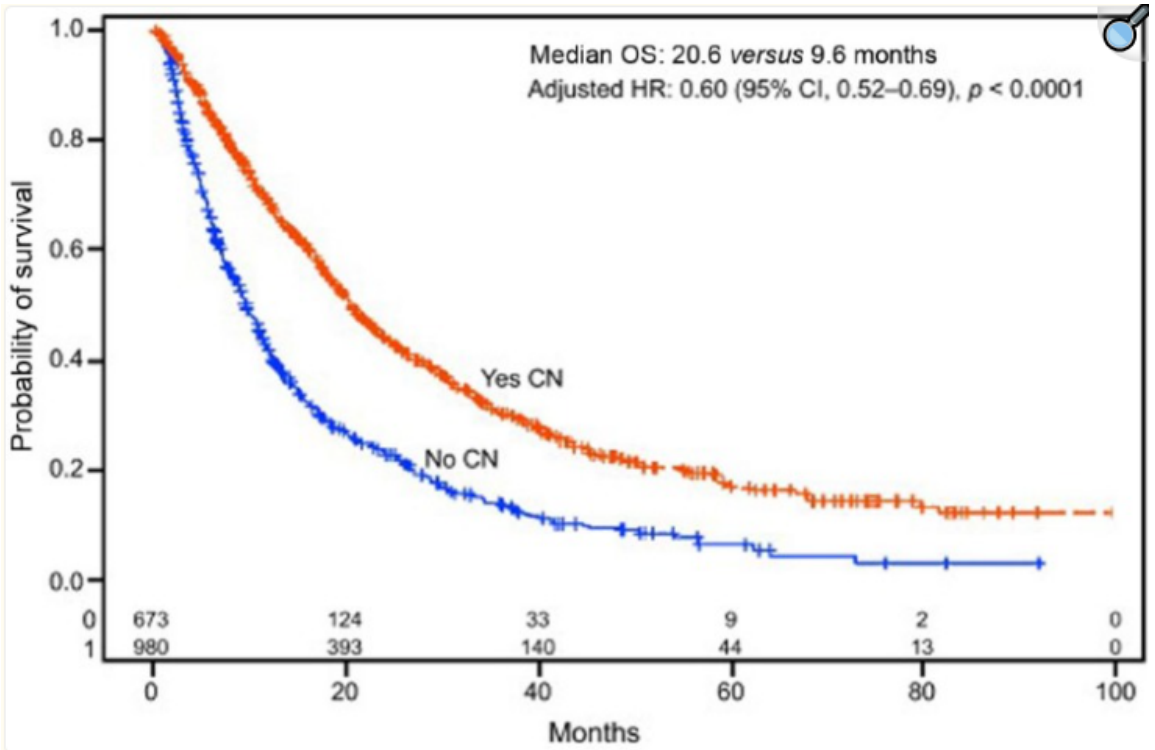

The NEW ENGLAND JOURNAL of MEDICINE

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SPECIALTIES TOPICS MULTIMEDIA CURRENT ISSUE LEARNING/CME AUTHOR CENTER PUBLICATIONS

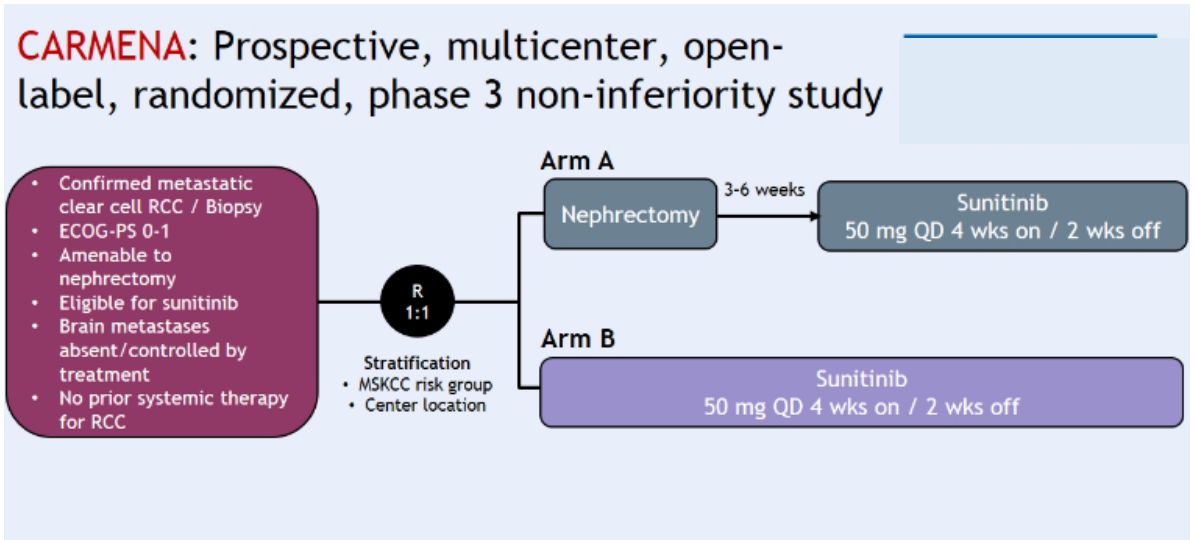
ORIGINAL ARTICLE

Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma

Authors: Arnaud Méjean, M.D., Ph.D., Alain Ravaud, M.D., Ph.D., Simon Thezenas, Ph.D., Sandra Colas, M.D., Jean-Baptiste Beauval, M.D., Karim Bensalah, M.D., Ph.D., Lionnel Geoffrois, M.D., +21, and Bernard Escudier, M.D. Author Info & Affiliations

Published June 3, 2018 | N Engl J Med 2018;379:417-427 | DOI: 10.1056/NEJMoa1803675 | VOL. 379 NO. 5

CARMENA(Cancer du Rein Metastique Nephrectomie set Antiangiogeniques)



- Phase3 RCT
- 450 patients(France, UK, Sweden, and Norway). 425 from France
- Median FU-50.9 months
- Surgery 55.6% MSKCC Int risk 44.4% Poor Risk

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CARMENA: Prospective, multicenter, open-label, randomized, phase 3 non-inferiority study

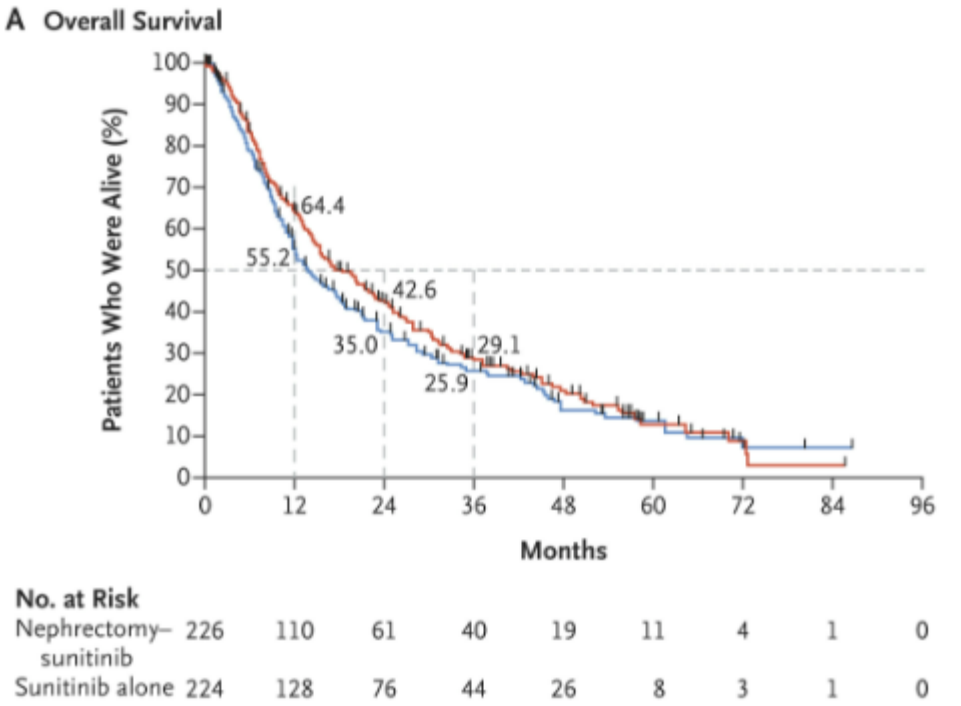
- Confirmed metastatic clear cell RCC / Biopsy
- ECOG-PS 0-1
- Amenable to nephrectomy
- Eligible for sunitinib
- Brain metastases absent/controlled by treatment
- No prior systemic therapy for RCC

R 1:1

Stratification
- MSKCC risk group
- Center location

Arm A: Nephrectomy → 3-6 weeks → Sunitinib 50 mg QD 4 wks on / 2 wks off

Arm B: Sunitinib 50 mg QD 4 wks on / 2 wks off



"Sunitinib alone was noninferior to nephrectomy"

	Overall Survival
Surgery +S	15.6 months
S alone	19.8 months

One IMDC Risk factor, OS was longer for nephrectomy +S 31.4 months vs 25.2 mo, HR 1.3,(p-0.2)

Mejean, et al., NEM, June 2018; 378: 417-427

Mejean, et al., NEM, June 2018; 378: 417-427

JAMA Oncology | Original Investigation

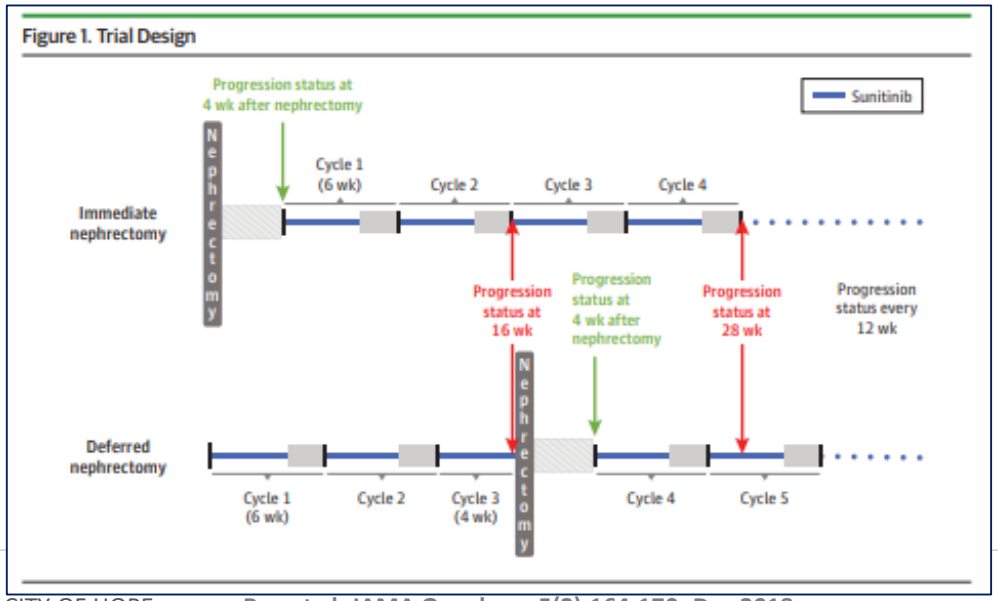
Comparison of Immediate vs Deferred Cytoreductive Nephrectomy in Patients With Synchronous Metastatic Renal Cell Carcinoma Receiving Sunitinib
The SURTIME Randomized Clinical Trial

Axel Bex, MD, PhD; Peter Mulders, MD, PhD; Michael Jewett, MD; John Wagstaff, MD; Johannes V. van Thienen, MD, PhD; Christian U. Blank, MD, PhD; Roland van Velthoven, MD, PhD; Maria del Pilar Laguna, MD, PhD; Lori Wood, MD, PhD; Harm H. E. van Melick, MD, PhD; Maureen J. Aarts, MD, PhD; J. B. Lattouf, MD; Thomas Powles, MD; Igle Jan de Jong, MD, PhD; Sylvie Rottey, MD, PhD; Bertrand Tombal, MD, PhD; Sandrine Marreaud, MD; Sandra Collette, MSC; Laurence Collette, PhD; John Haanen, MD

- Phase 3 RCT (2010-2016) EORTC,GU Cancer Group, National Cancer Research Institute Renal Clinical Studies/Wales Cancer Trials Unit-UK, and Candian UroOnc Group

- 99 patient(Resectable primary, No)

- Goal: To Identify patients with resistance to VEGGFR-TKI who would unlikely benefit from surgery . No CNS mets, 3 or less surgical prognostic factors(LDH, Albumin., Liver mets, LAD, cT3/4



Endpoints:

Primary-PFS

Secondary-OS, AE, Post op progression

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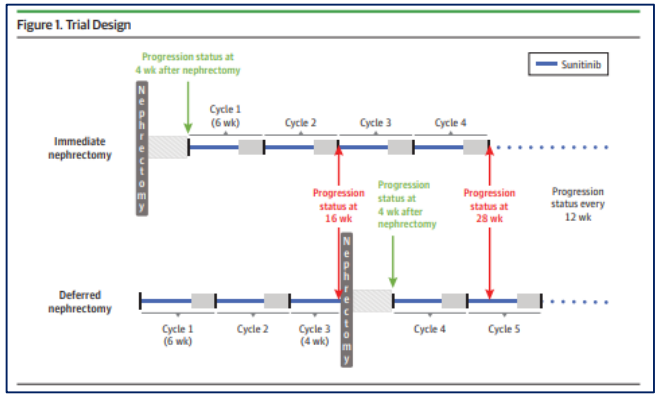
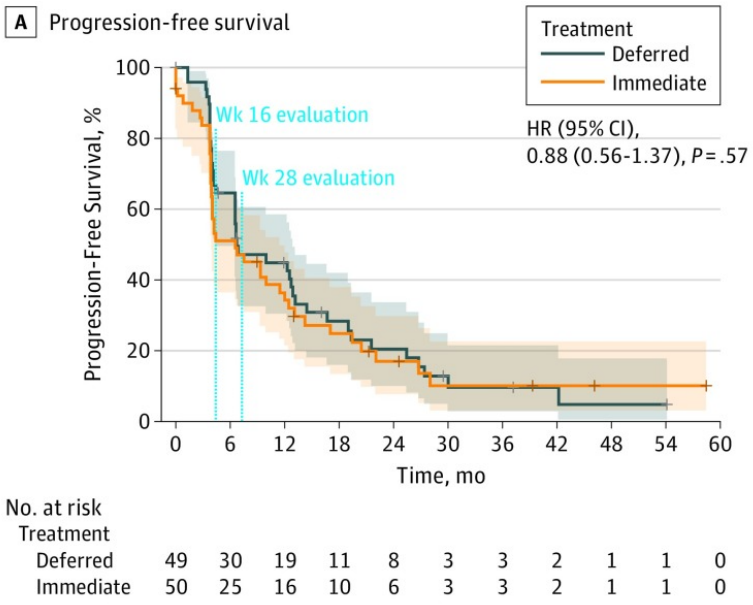
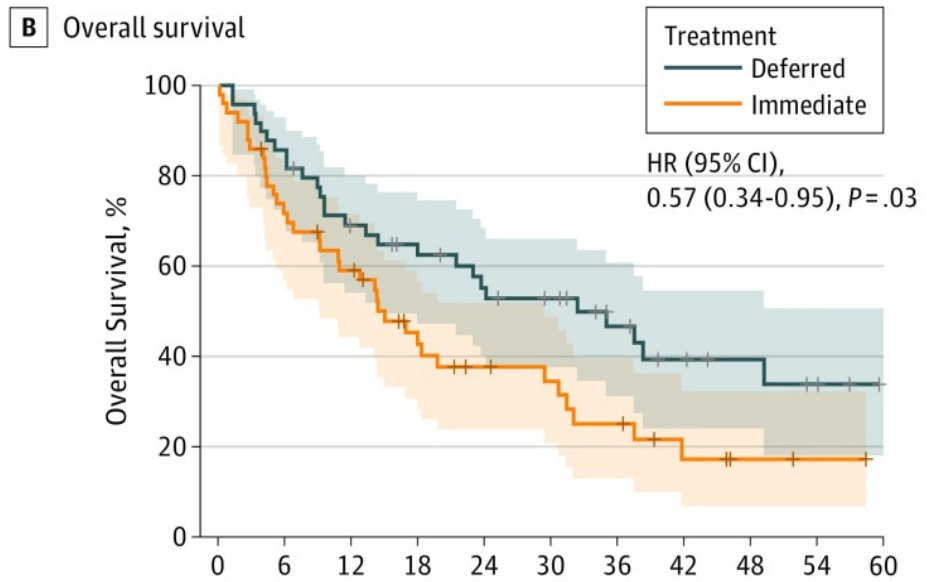


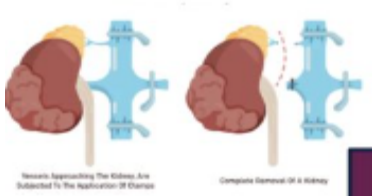




- 28-week PFS: 42% in the immediate CN arm (n = 50) and 43% in the deferred CN arm (n = 49) (P = .61).
- The intention-to-treat OS hazard ratio of deferred vs immediate CN was 0.57 (95% CI, 0.34-0.95; P = .03)
- Median OS of 32.4 months (95% CI, 14.5-65.3 months) in the deferred CN arm and 15.0 months (95% CI, 9.3-29.5 months) in the immediate CN arm
- 20% of Immediate CN group didn't receive Sunitinib
- Poor Accrural

Timeline on Role Cytoreductive Nephrectomy

Evolving Role of Nephrectomy in Kidney Cancer



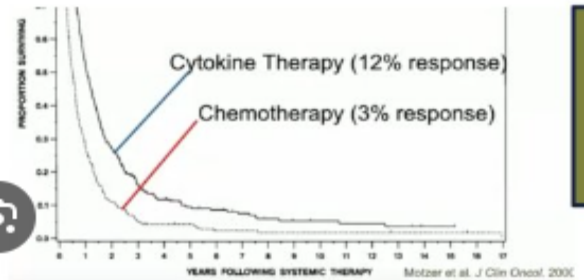
Radical Nephrectomy
Standard of Care for
RCC.

High-Dose IL-2:
- ✓ 15% RR
- ✓ 5% durable CR
- ✓ PS key
- ✓ Severe toxicities

INF-a:
- ✓ 10-15% RR
- ✓ Survival Benefit modest 3-7 mo
- ✓ Minimal Toxicities

mmunotherapy Era

1960 | 1980 | 1990 | 2010 | 2020 | 2024

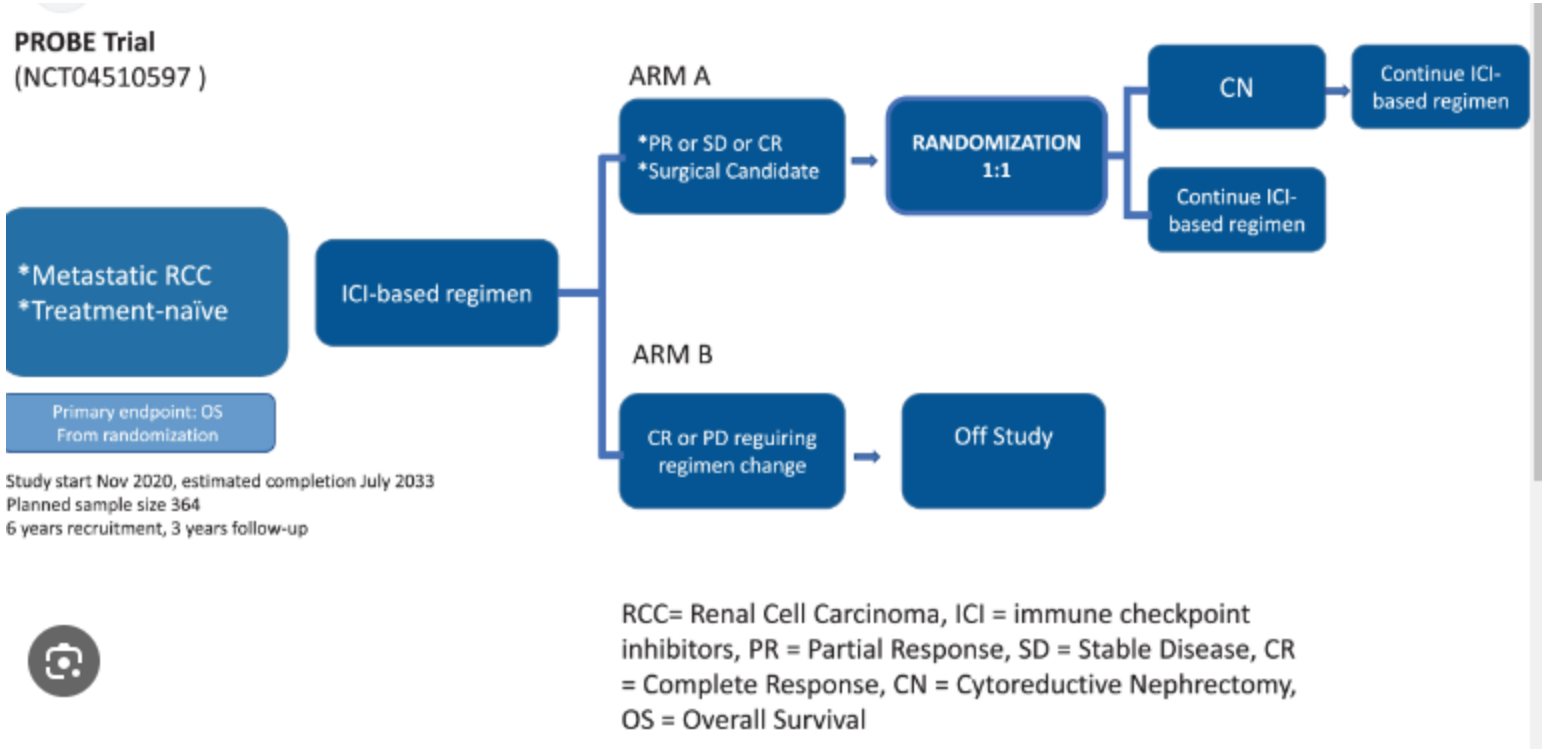


Cytoreductive Nephrectomy
Role? RCT
SWOG 8949
EORTC 30947

TKI Era

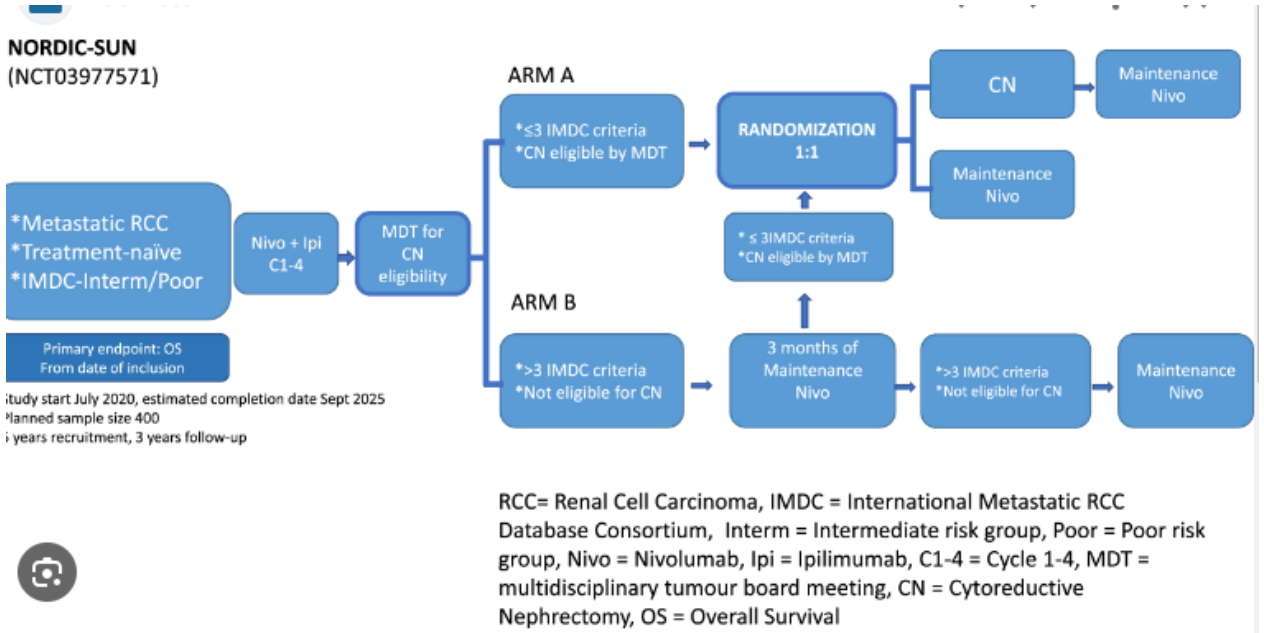
New Targeted Therapies Era

Ongoing Trials-PROBE



RCC= Renal Cell Carcinoma, ICI = immune checkpoint inhibitors, PR = Partial Response, SD = Stable Disease, CR = Complete Response, CN = Cytoreductive Nephrectomy, OS = Overall Survival

- SWOG 1931 Trial (Phase 3)
- Immune checkpoint-based combination therapy has now become the standard-of-care in the frontline setting for RCC. The role of nephrectomy or primary resection has not been evaluated in the setting of immune checkpoint-based systemic therapy
- FDA approved ICI based combinations: ipililumab and nivolumab, axitinib and pembrolizumab, or axitinib and avelumab. Cabozantinib + nivolumab and lenvatinib + pembrolizumab
- Primary Endpoint-OS

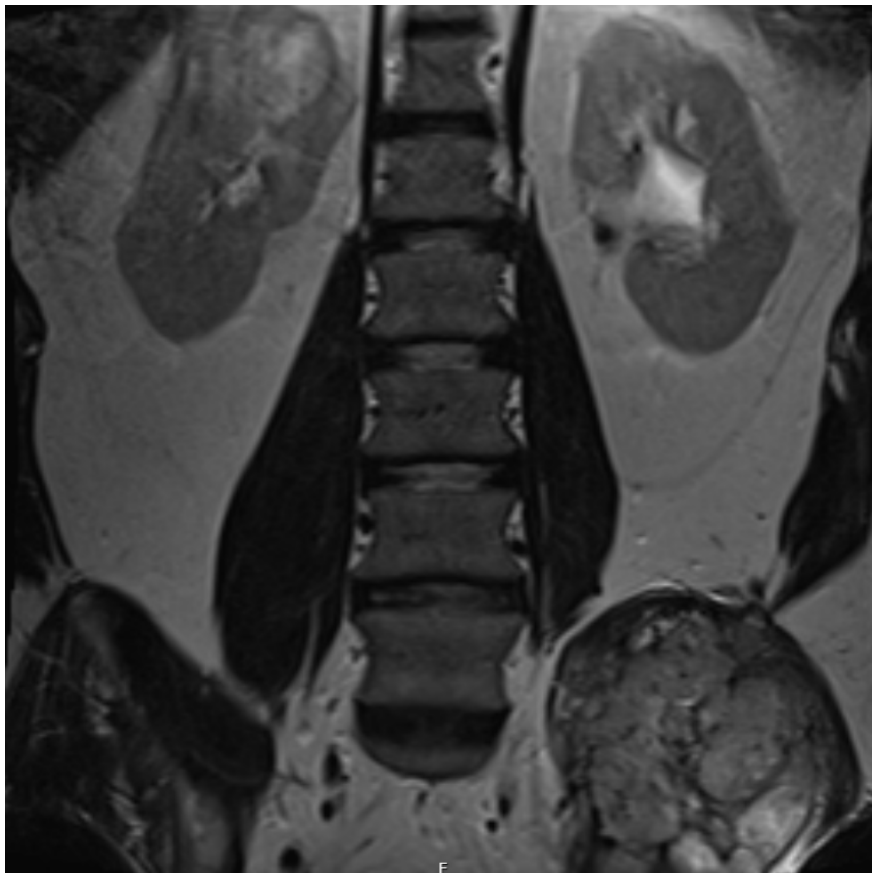


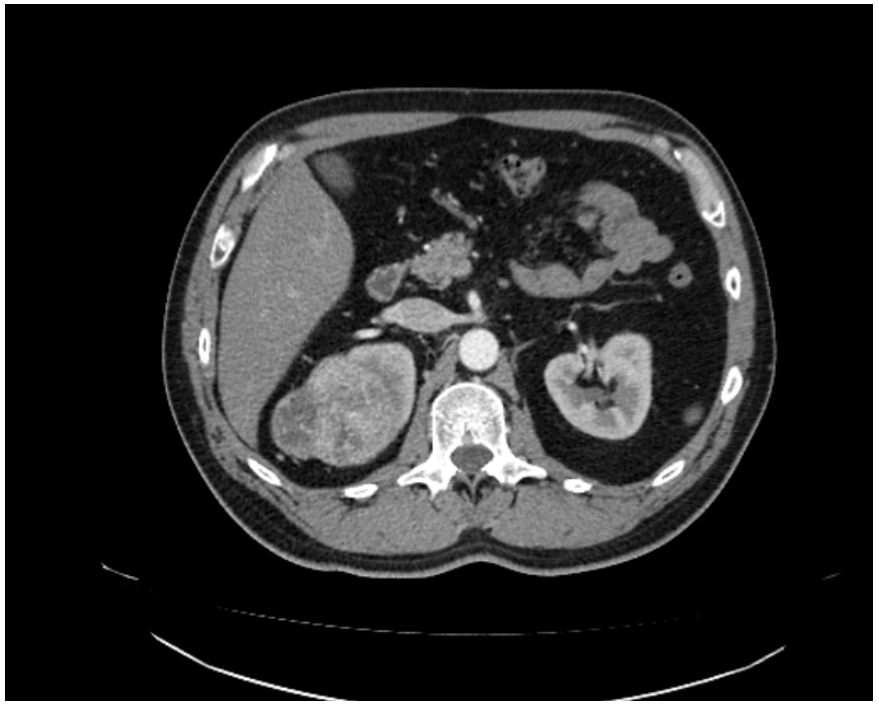
RCC= Renal Cell Carcinoma, IMDC = International Metastatic RCC Database Consortium, Interm = Intermediate risk group, Poor = Poor risk group, Nivo = Nivolumab, Ipi = Ipilimumab, C1-4 = Cycle 1-4, MDT = multidisciplinary tumour board meeting, CN = Cytoreductive Nephrectomy, OS = Overall Survival

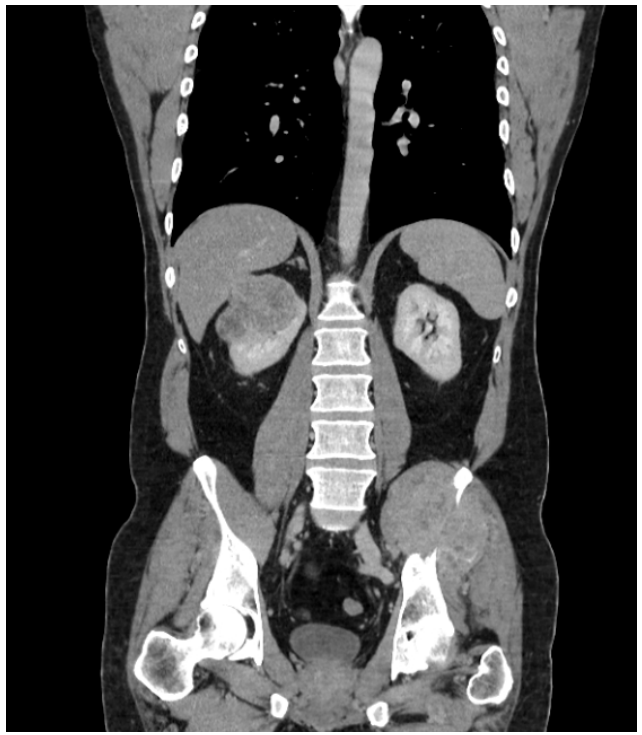
- Phase 3 RCT(All histologic types) Denmark, Nordic Countries
- Deferred CN Approach, allows all to receive systemic tx restricting those that have benefited from therapy to possibly receive surgery
- Primary Endpoint –Overall Survival
- Secondary Endpoints-PFS, TST, Surgery Complications
- Exploratory Endpoints: Immune cells, ctDNA, tumor cells, microbiome

Case 2024

- 48 year old healthy male
- Married, 4 kids, Business executive
- Back pain after vigorous exercise



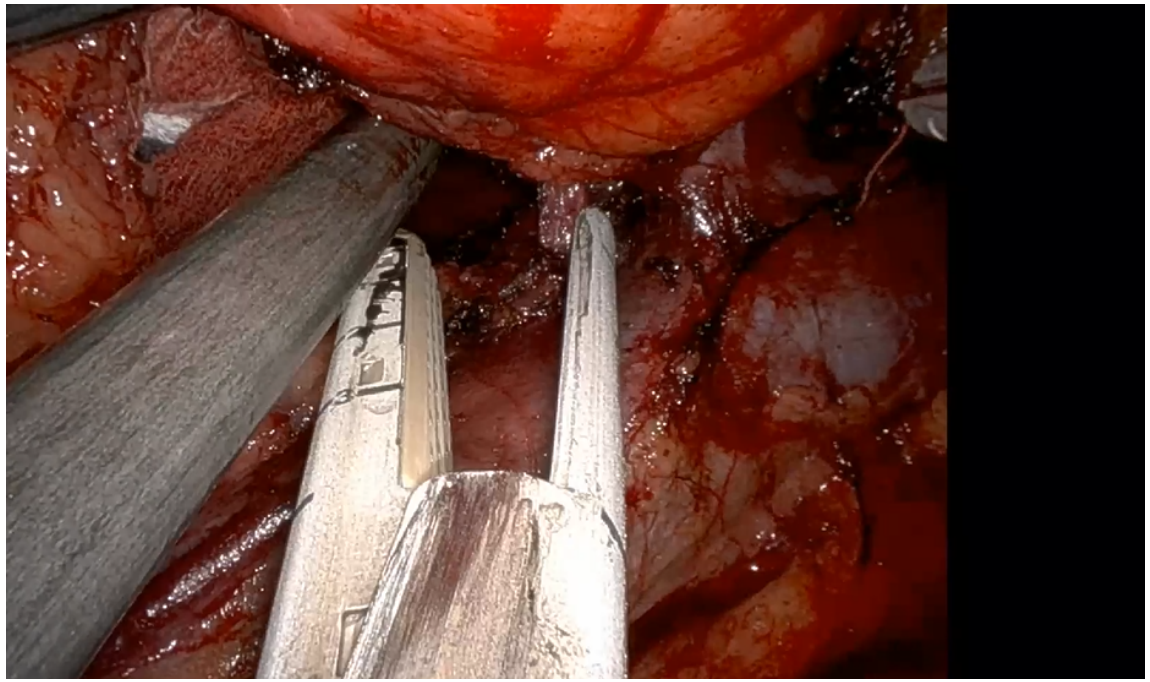




- 7 cm right solid renal mass abutting the right lobe of liver
- 14 cm Iliac bone met
- No other distant mets, No LAD, No CNS disease
- Hip Bx-ccRCC
- Normal Labs
- ECOG PS 0
- IMDCC Favorable Risk

•Ortho- Reports they can do a Type Hemipelvectomy – R0 resection

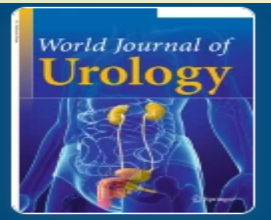
.



- Robotic Right CN
- 80 minutes
- Outpatient, stayed in hospital 3 hours post op
- No Complications
- Awaiting Ortho surgery in 2 weeks

Minimally invasive cytoreductive nephrectomy: a multi–institutional experience

Original Article | Published: 15 April 2016
Volume 34, pages 1651–1656, (2016) Cite this article



World Journal of Urology
Aims and scope →
Submit manuscript →

Luciano Nunez Bragayrac, Jan Hoffmeyer, Daniel Abbotoy, Kristopher Attwood, Eric Kauffman, Phillipe Spiess, Andrew Wagner & Thomas Schwaab

- Case Series-3 Prospectively Maintained IRB approved Kidney surgery databases(USF, BIDMC, Roswell Park) -2001-2013
- 120 patients, Median FU-67 months, 93.3% Lap, 3.4% Robotic)
- Mean size 7.8 cm, 63%- T3/T4
- LOS -2.4 days(mean)
- Conversion to open-3.3%
- Complications-23.3%, 71.4% were Minor CD I-II

LND During Cytoreductive Nephrectomy

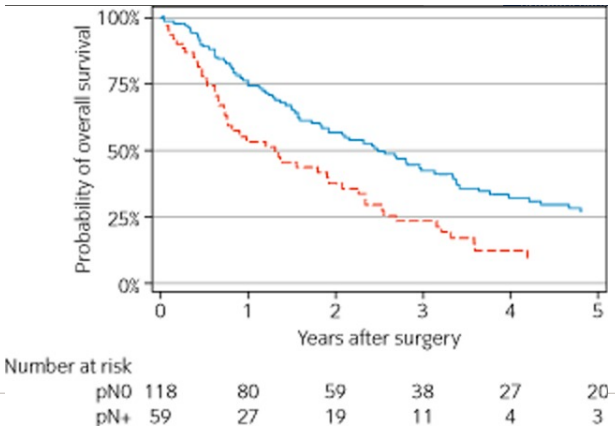
INTERNATIONAL JOURNAL OF UROLOGY

Original Article: Clinical Investigation | Full Access

Lymph node dissection during cytoreductive nephrectomy: A retrospective analysis

Michael A Feuerstein, Matthew Kent, Melanie Bernstein, Paul Russo

- MSKCC Retrospective Review of patients that underwent Cytoreductive Nephrectomy (1992-2013)
- 258 patients(69% Underwent Concurrent LND)
- **5 Year Overall Survival –No Difference**
- **5 year survival with those with N+ vs N0(9% vs 27%) P<0.0001**



Russso, et al, LND during Cytoreductive Nephrectomy , International Journal of Urology, April 2014

Summary and Key Takeaways Points

- Multidisciplinary Team Evaluation
- Favorable Risk Patients should be offered upfront CN, if a good surgical candidate
- Intermediate Risk , Good PS, Resectable Metastatic Lesions can be considered for upfront CN
- Palliative Surgery is an option-Hematuria, Symptomatic Thrombus
- Poor Risk IMDCC should have upfront Systemic therapy
- Await Nordic-SUN and Probe S1931 trials -Read out

Thank you

- Paul Liming, RN
- COH 1987-2024

Questions: cllau@coh.org