II SIMPÓSIO INTERNACIONAL

GU - REVIEW 2018 - LACOG

23 E 24 | NOVEMBRO 2018 | HOTEL INTERCONTINENTAL | SÃO PAULO

Nephrectomy in metastatic patients: what changed in 2018?

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Previous knowledge: the era of interferon
(2 studies – SWOG e EORTC)

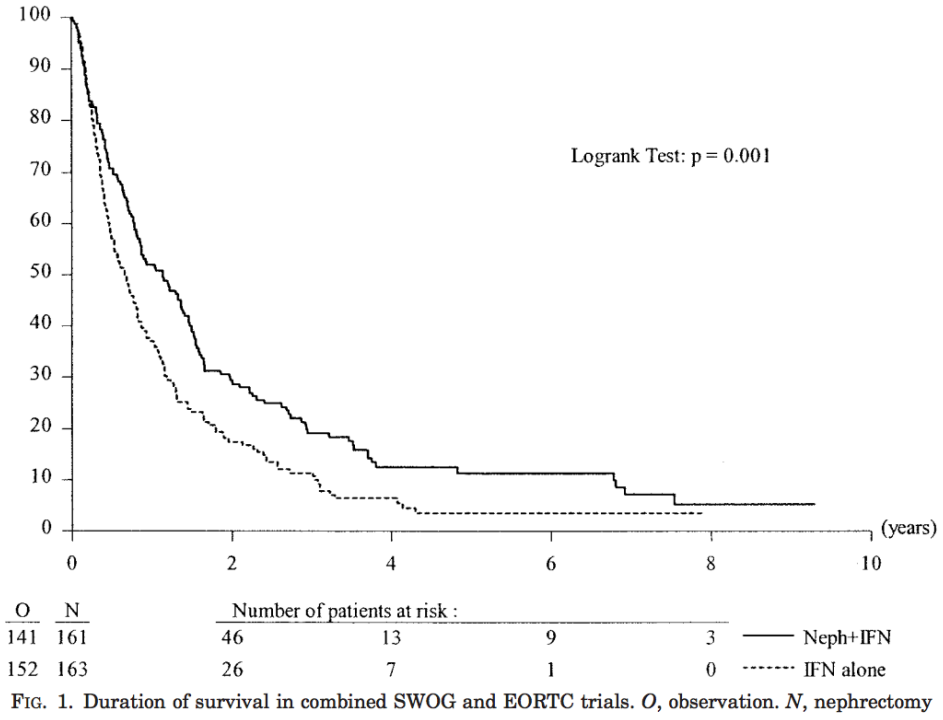
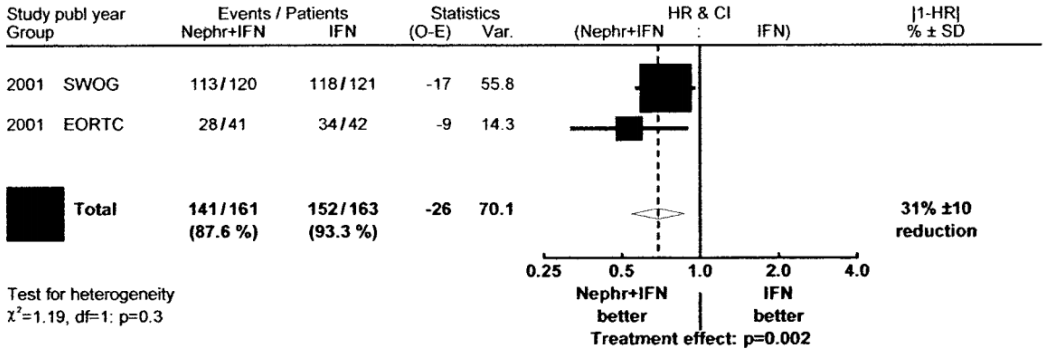


FIG. 1. Duration of survival in combined SWOG and EORTC trials. *O*, observation. *N*, nephrectomy

Median overall survival
IFN: 7.8m
Nephrectomy-IFN: 13.6m

HR 0.69; p = 0.002



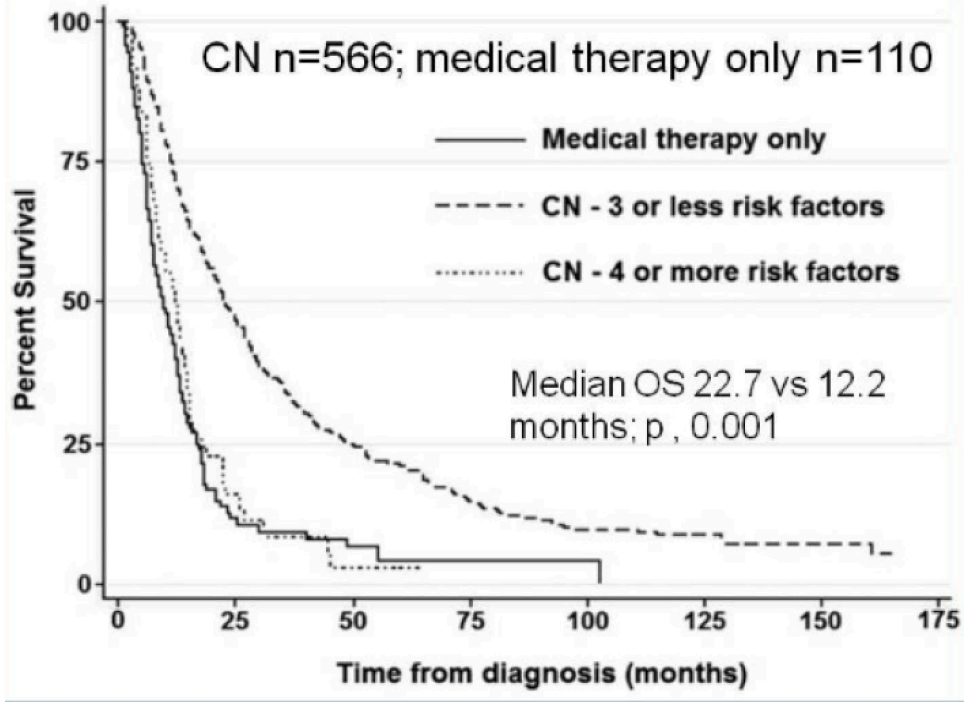
Flanigan RC, et al. J Urol. 2004 Mar;171(3):1071-6.

Previous knowledge: patient selection

- Prognostic factors
- Performance status
- Symptoms: pain, fatigue, weight loss, paraneoplastic syndromes
- Risk scores: IMDC or MSKCC
- Relationship between primary tumor volume and metastases
- Histology
- Site of metastasis (specially lymph nodes)

Important preoperative variables

- Hypoalbuminemia
- LDH > 1,5x UNL
- liver metastasis
- symptoms caused by a metastatic site
- retroperitoneal adenopathy
- supradiaphragmatic adenopathy
- T3 or T4



Culp SH, et al. Cancer. 2010 Jul 15;116(14):3378-88.

Consistent retrospective data

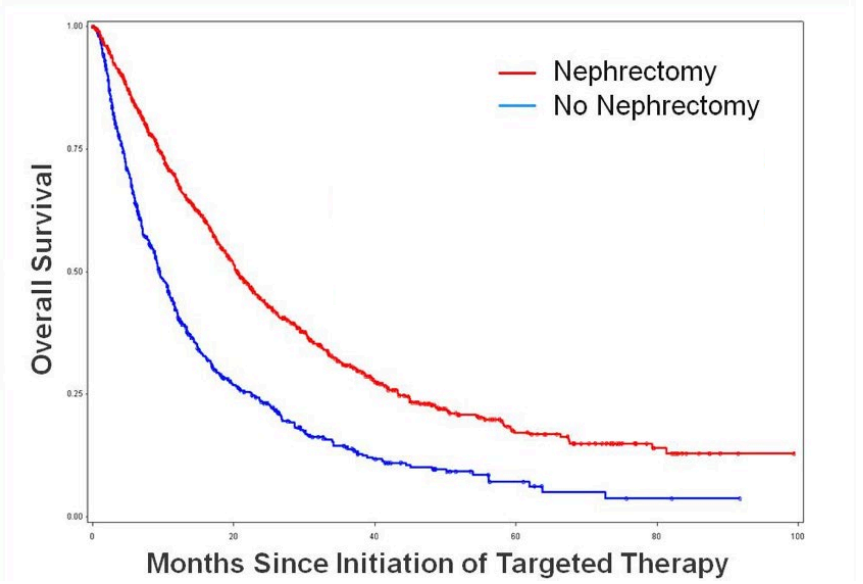
Database IMDC

1658 patients

- 676 (41%) no nephrectomy
- 982 (59%) with nephrectomy

Median overall survival

- With NC: 20.6 months
- Without NC: 9.5 months
- p<0.0001
- HR adjusted: 0.60 (p<0.0001)



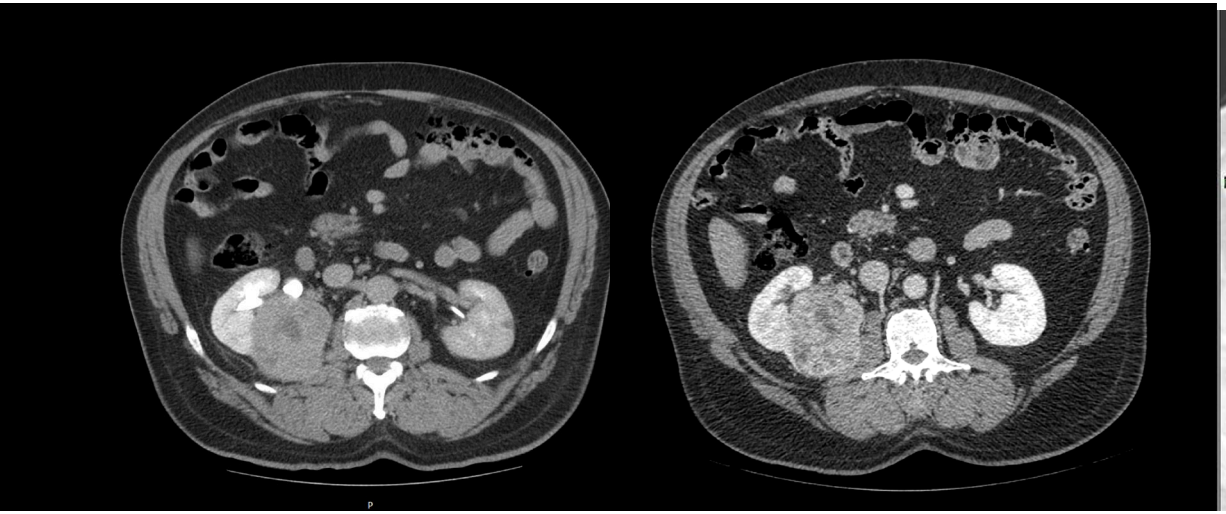
Patients without benefit

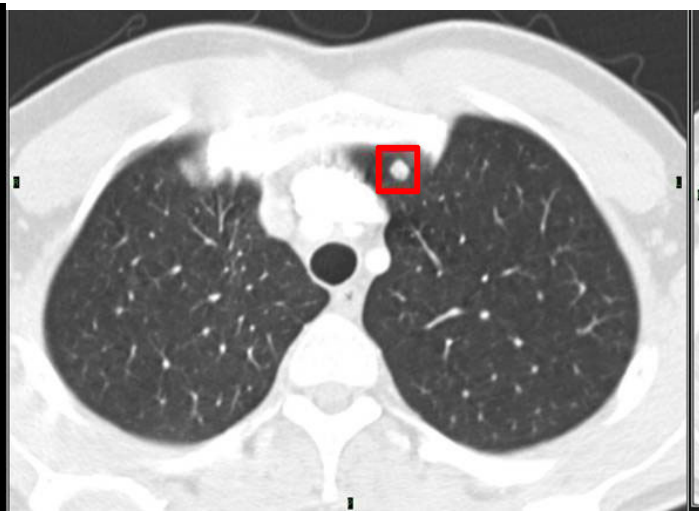
- with estimated survival times <12 mo
- with four or more IMDC prognostic factors

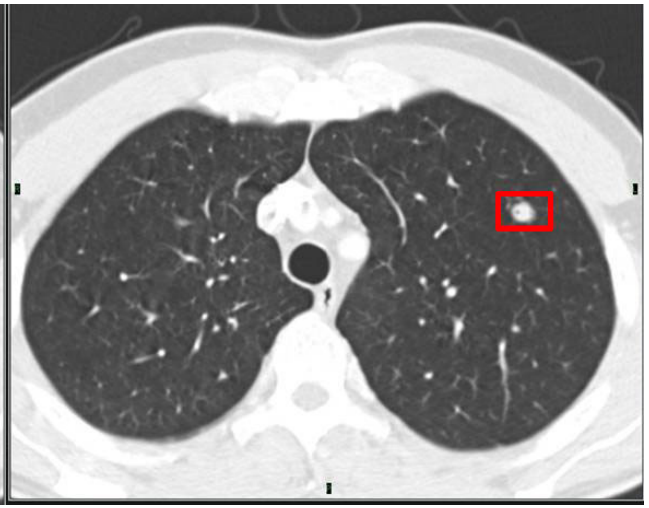
Heng DY, et al. Eur Urol. 2014 Oct;66(4):704-10.

Obvious cases always make sense

- Resectable primary tumor
- Small volume of metastatic disease
- Good performance status

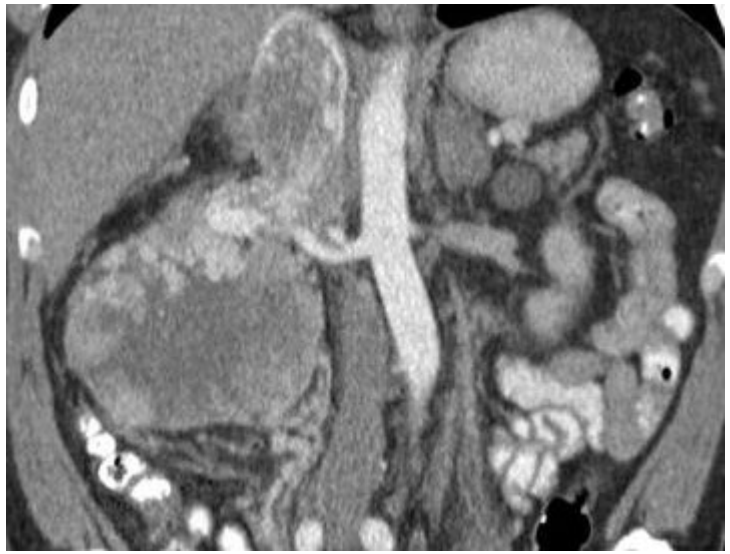


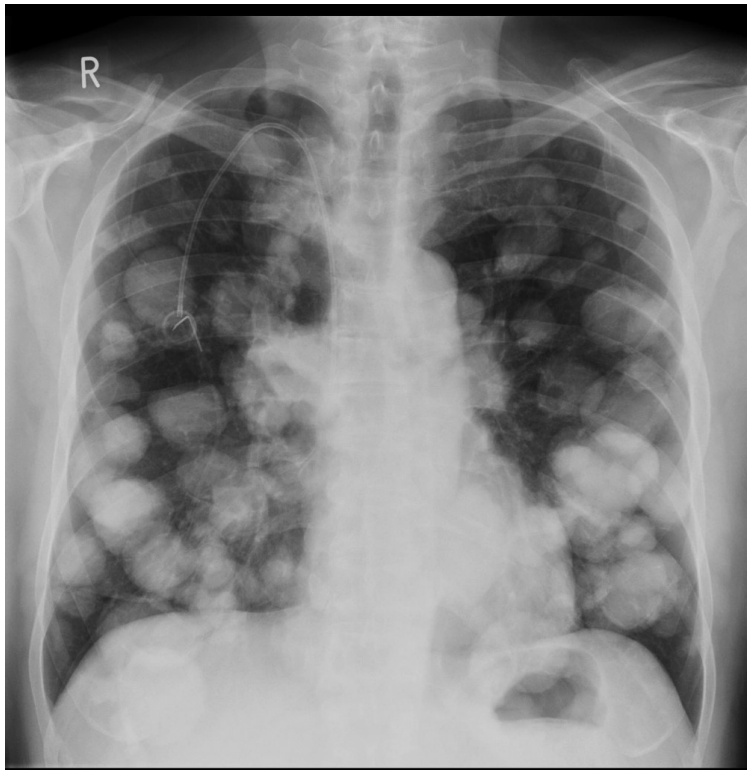




Obvious cases always make sense

- Primary tumor with great extension
- Large volume of metastatic disease
- Poor PS





The rule until early 2018 ...

- The routine does not always follow the obvious
- Cytoreductive nephrectomy was indicated whenever possible
- First approach of the patient with advanced disease
- Biopsies usually not needed

CARMENA trial:

Histologically confirmed metastatic clear cell renal cancer
PS ECOG 0-1
Suitable to nephrectomy
Elegible for Sunitinib
No active brain metastasis
Without previous systemic treatment

R
1:1

Cytoreductive nephrectomy → 3 to 6 weeks → Sunitinib 50mg/d
4 w on / 2 w off

Sunitinib 50mg/d
4 w on / 2 w off

Primary endpoint: OS
Secondary endpoints: PFS, ORR clinical benefit, safety

Méjean A, et al. N Engl J Med. 2018 Aug 2;379(5):417-427.

Statistics

Non-inferiority trial

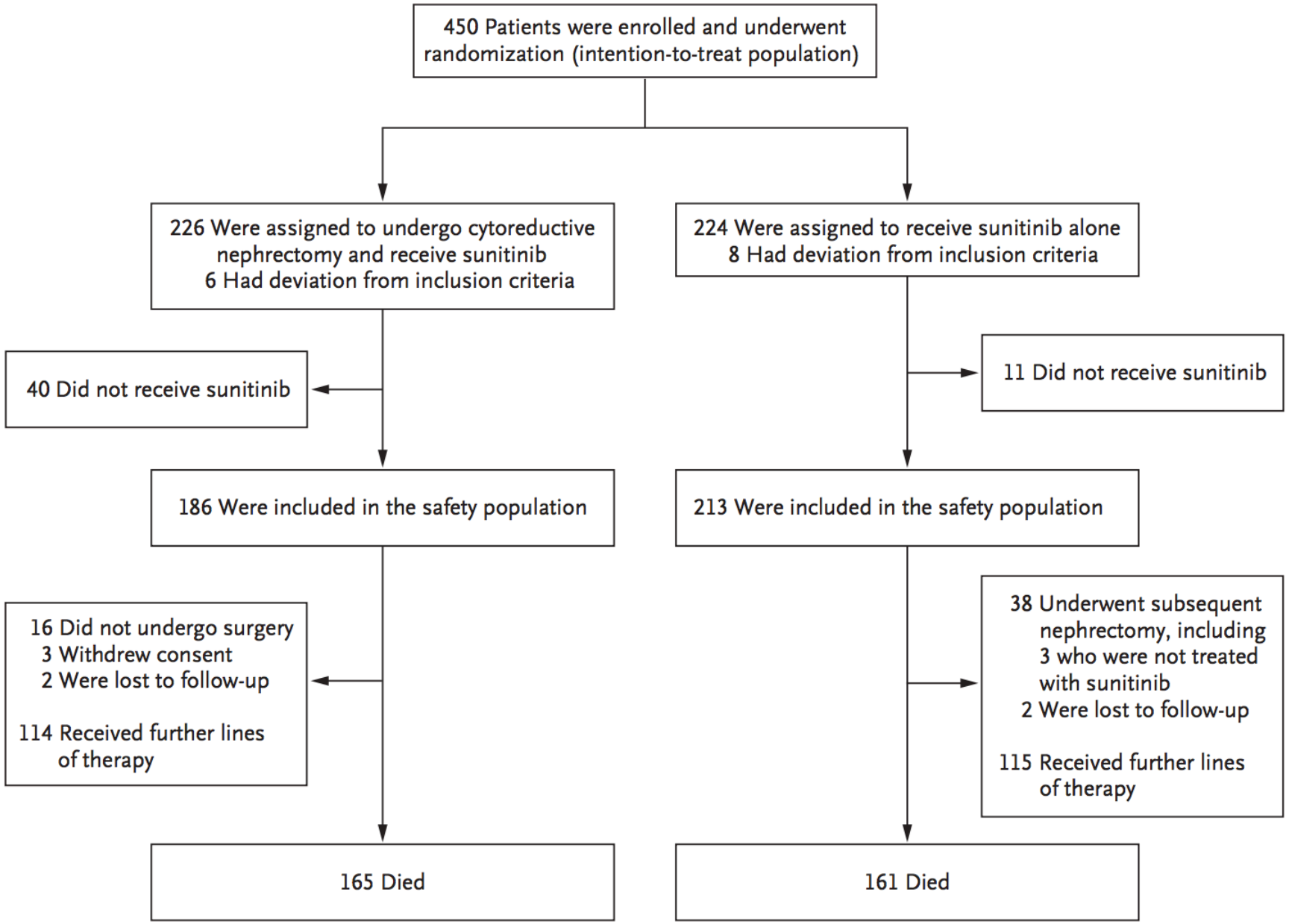
- Non-inferiority margin: upper 95% CI limit 1.20 to sunitinib alone
- 576 pacients needed
- 456 events

From sep/2009 until sep/2017

- 450 pacients recruited
- 326 events occurred

Steering Comitee decided stop the trial after preliminar analysis

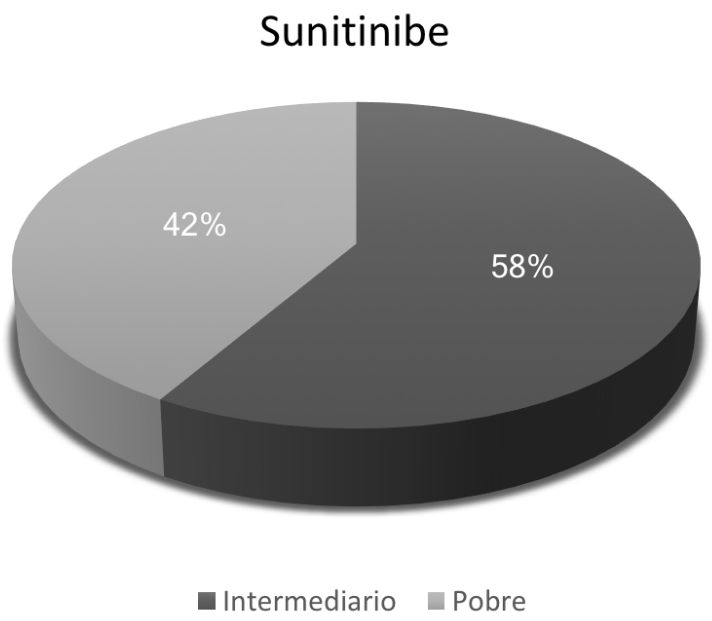
Méjean A, et al. N Engl J Med. 2018 Aug 2;379(5):417-427.

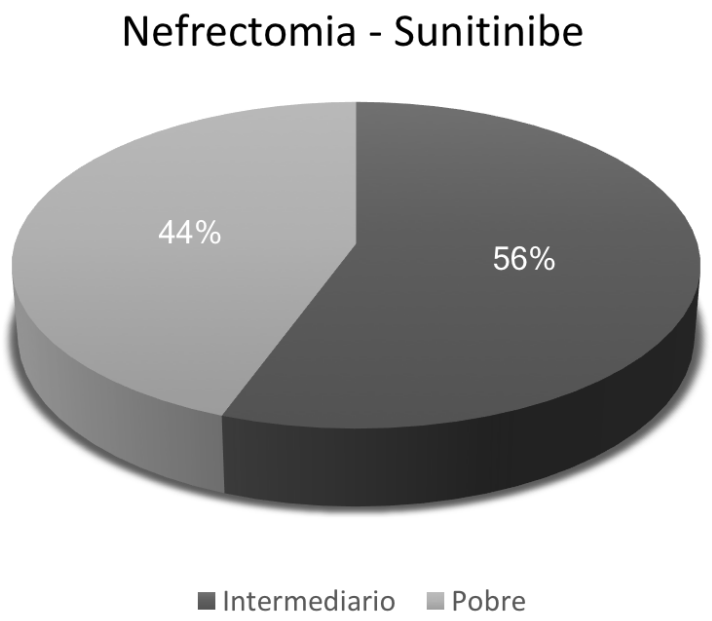


Méjean A, et al. N Engl J Med. 2018 Aug 2;379(5):417-427.

Main characteristics of patients included

Risk category - MSKCC





Méjean A, et al. N Engl J Med. 2018 Aug 2;379(5):417-427.

Main characteristics of patients included

Tumor stage		
T1	5/67 (7.5)	7/49 (14.3)
T2	13/67 (19.4)	13/49 (26.5)
T3 or 4	47/67 (70.1)	25/49 (51.0)
Tx	2/67 (3.0)	4/49 (8.2)
Node stage		
N0	23/66 (34.8)	18/49 (36.7)
N1	13/66 (19.7)	6/49 (12.2)
N2	7/66 (10.6)	13/49 (26.5)
Nx	23/66 (34.8)	12/49 (24.5)

Méjean A, et al. N Engl J Med. 2018 Aug 2;379(5):417-427.

Main characteristics of patients included

Size of primary tumor versus Global tumor burden

Nephrectomy - Sunitinib

PT 88mm (6-200)

TB 140mm (23-399)

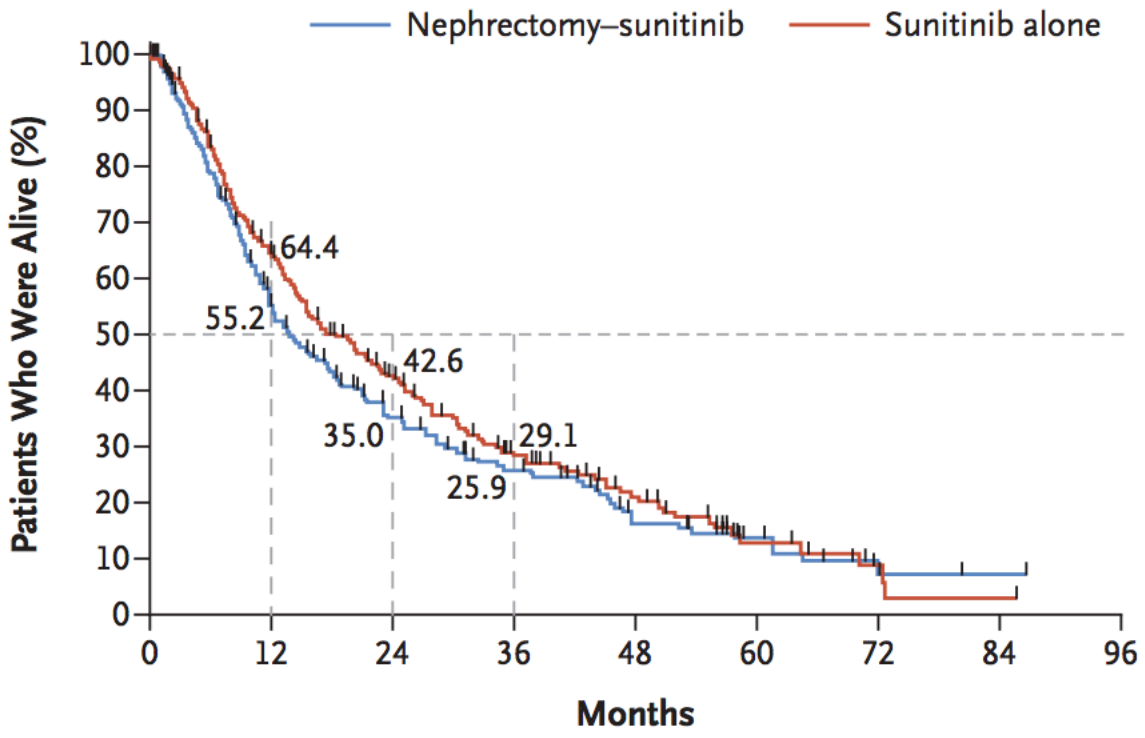
Sunitinib

PT 86mm (12-190)

TB 144mm (39-313)

Méjean A, et al. N Engl J Med. 2018 Aug 2;379(5):417-427.

Overall survival - ITT



Median
Sunitinib alone: 18.4mo
Nephrectomy-Sunitinib: 13.9mo

HR 0.89 (0.71 – 1.10)
NI margin: 1.20

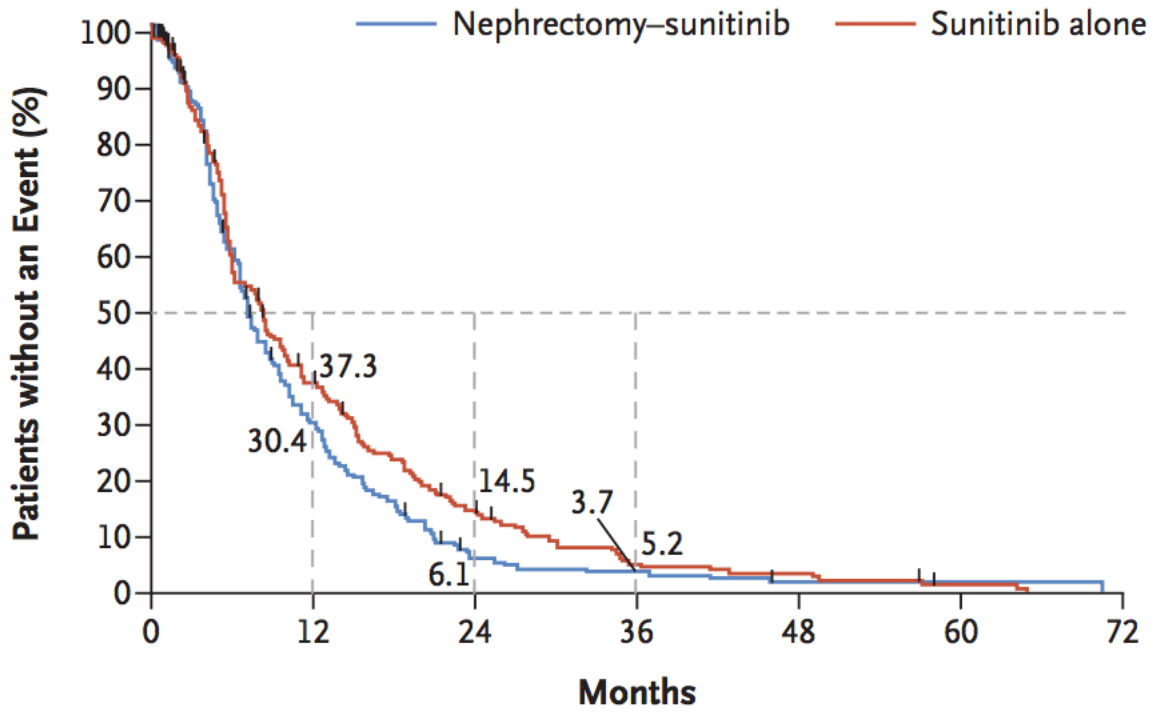
Méjean A, et al. N Engl J Med. 2018 Aug 2;379(5):417-427.

Results according to risk groups

median OS (months)	Nephrectomy-Sunitinib (n = 226)	Sunitinib alone (n = 224)	HR (IC 95%)
Total	13.9	18.4	0.89 (0.71 – 1.10)
Intermediate risk	19.0	23.4	0.92 (0.60 – 1.24)
Poor risk	10.2	13.3	0.86 (0.62 – 1.17)

Méjean A, et al. N Engl J Med. 2018 Aug 2;379(5):417-427.

Progression-free survival - ITT



Median
Sunitinib alone: 8.3mo
Nephrectomy-Sunitinib: 7.2mo

HR 0.82 (0.67– 1.00)

Méjean A, et al. N Engl J Med. 2018 Aug 2;379(5):417-427.

CARMENA trial - conclusions

Sunitinib alone was not inferior to nephrectomy followed by sunitinib in patients with metastatic renal-cell carcinoma who were classified as having intermediate-risk or poor-risk disease

The clinical benefit was better in the group allocated to Sunitinib alone

Cytoreductive nephrectomy should not be considered as standard treatment in these cases

Real life considerations

Retrospective data suggested a great benefit of cytoreductive nephrectomy

- Metanalysis of 16 trials: HR (for OS): 0.48 (CI 95% 0.42 – 0.56)
- Consistent results across all subgroups
- However, significant heterogeneity

Probable selection bias

Clear memory bias

Massari F, et al. Target Oncol. 2018 Oct 15. doi: 10.1007/s11523-018-0601-2. [Epub ahead of print]

Take home messages

The CARMENA trial results were surprising (shocking?)

The results did not confirm the findings of pre-TKI studies

Cytoreductive nephrectomy should not be considered as standard treatment in all cases

- Specially in intermediate and poor risk patients
- Specially considering immunotherapy

The question was: who should I exclude from the surgery indication?

The question is: who should I specifically select for surgery?

Final point of view

In the Brazilian Public Health System we are still experiencing the era of interferon

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