INSTITUTO DO CÂNCER DO ESTADO DE SÃO PAULO
OCTAVIO FRIAS DE OLIVEIRA
ORGANIZAÇÃO SOCIAL DE SAÚDE

URO USP

O papel da nefrectomia citorredutora no cancer de rim avançado: como integrar cirurgia e terapia sistêmica

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Therapy of Renal Cell Carcinoma Prior to 2006

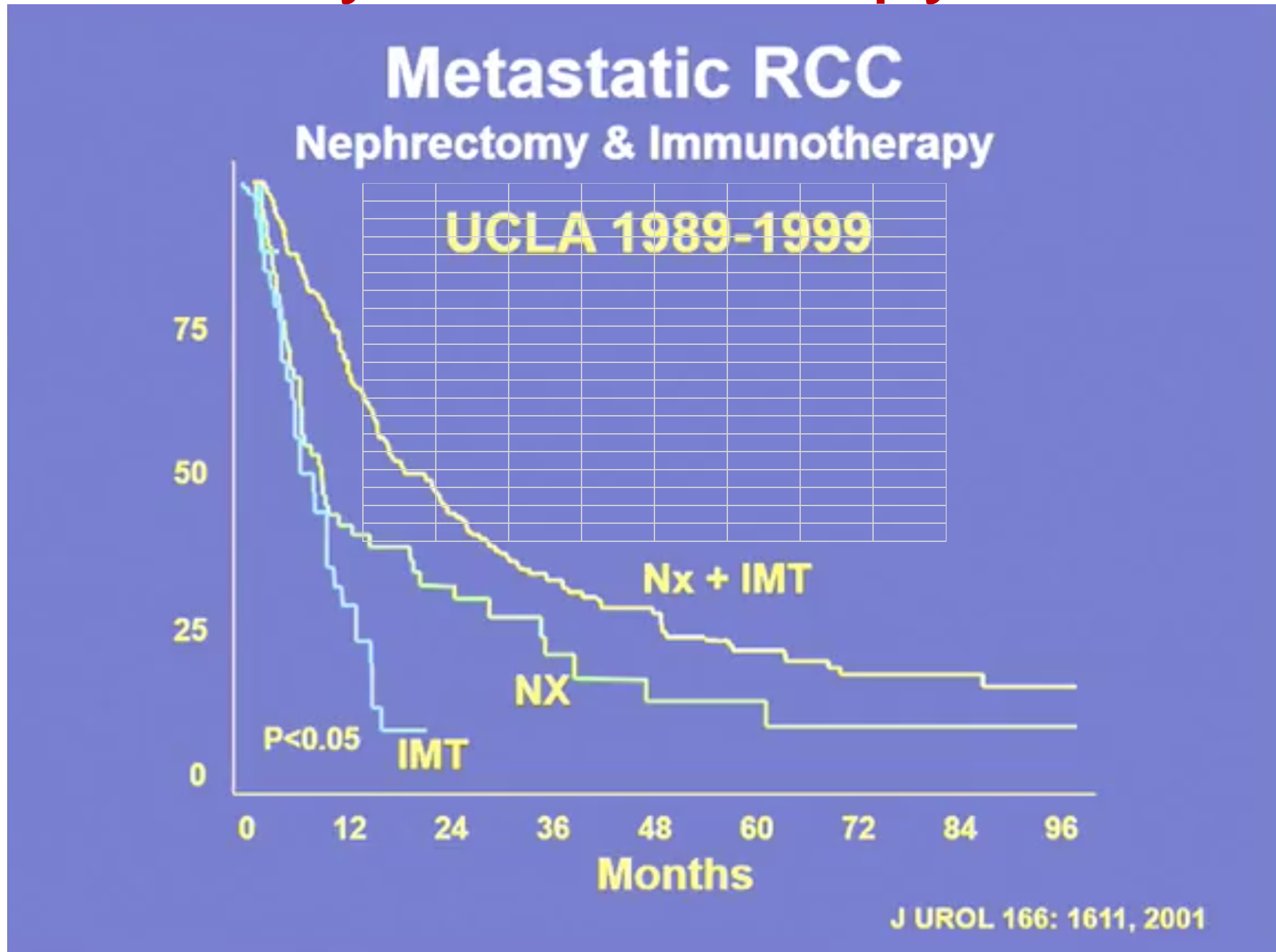
- Stage I-III: nephrectomy
- Stage IV: nephrectomy + systemic therapy

- Common therapies
  - Single-agent and combination regimens containing cytokines (eg, IFN-α, IL-2) and chemotherapeutics
  - Surgery
  - Radiation in selected cases

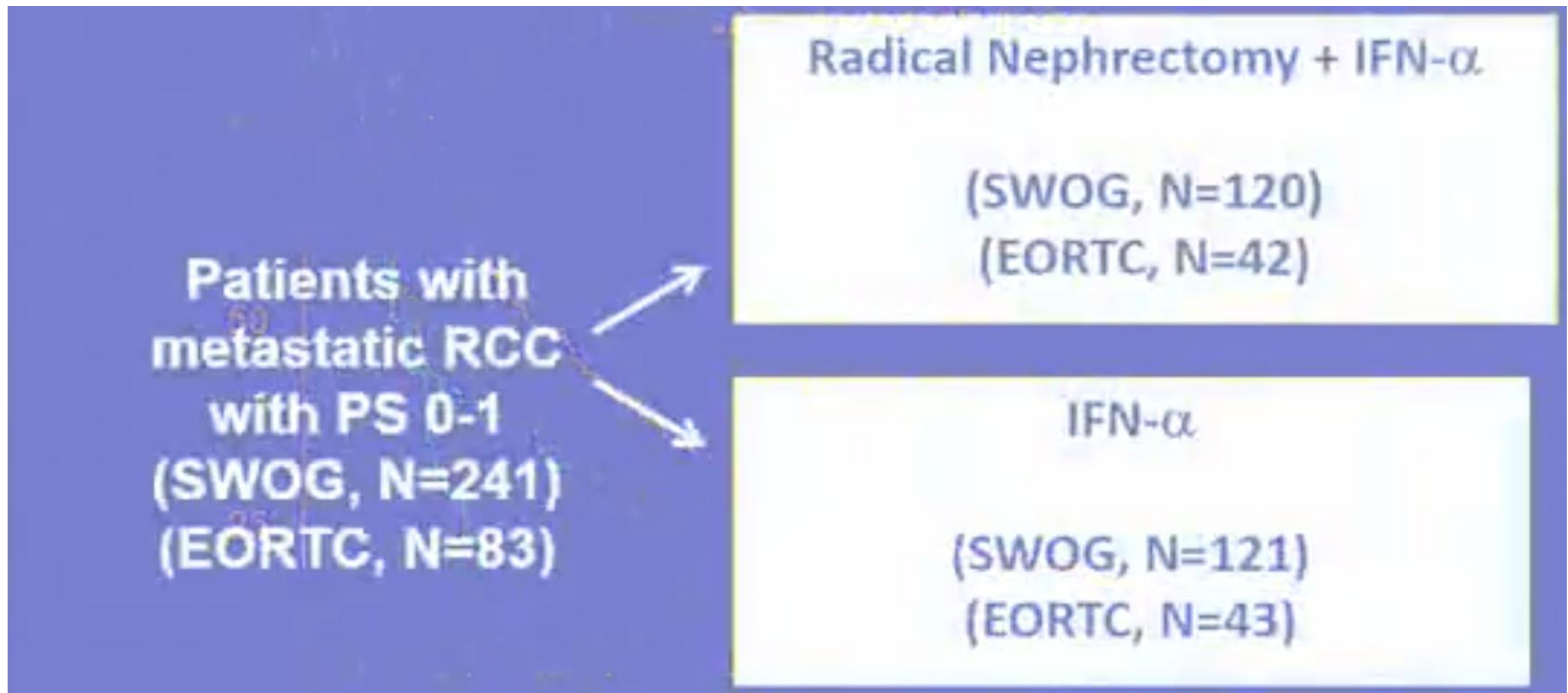
NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer. Available at: http://www.nccn.org/professionals/physician_gls/PDF/kidney.pdf. Yang et al. *N Engl J Med*. 2003;349:427-434. Ratain et al. *J Clin Oncol*. 2006;24:2505-2512. Motzer et al. *J Clin Oncol*. 2006;24:16-24. Motzer et al. *JAMA*. 2006;295:2516-2524. Motzer et al. *N Engl J Med*. 2007;356:115-124.

Como integrar a cirurgia no tratamento da doença avançada?

UCLA: Nephretomy and better systemic therapy?



Cytoreductive nephrectomy and survival in metastatic RCC



Flanigan RC, et al. NEJM 345:1655, 20
Mickish GH et al. Lancet 358:966, 200

EORTC 30947 IFN +/- Nx

Cytoreductive nephrectomy and survival in metastatic RCC

Time to progression

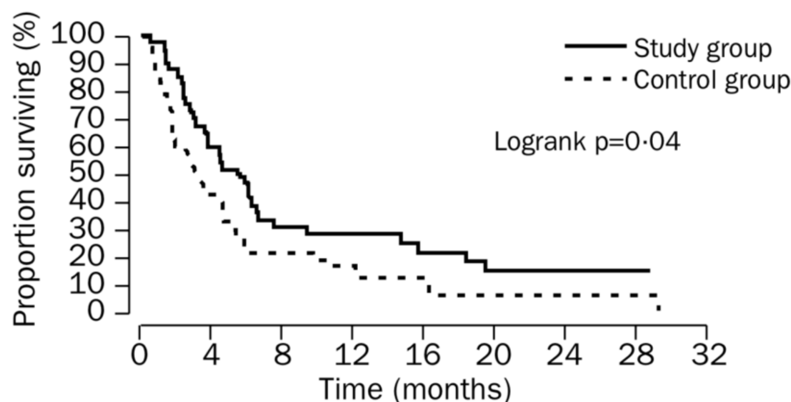


Figure 2: **Kaplan-Meier curves showing time to progression**

Overall survival

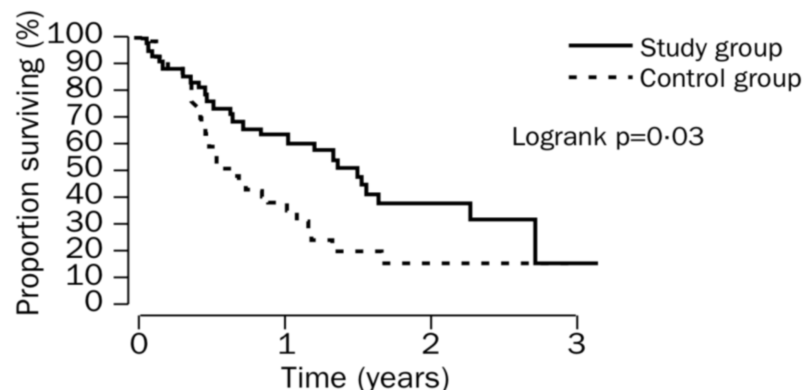


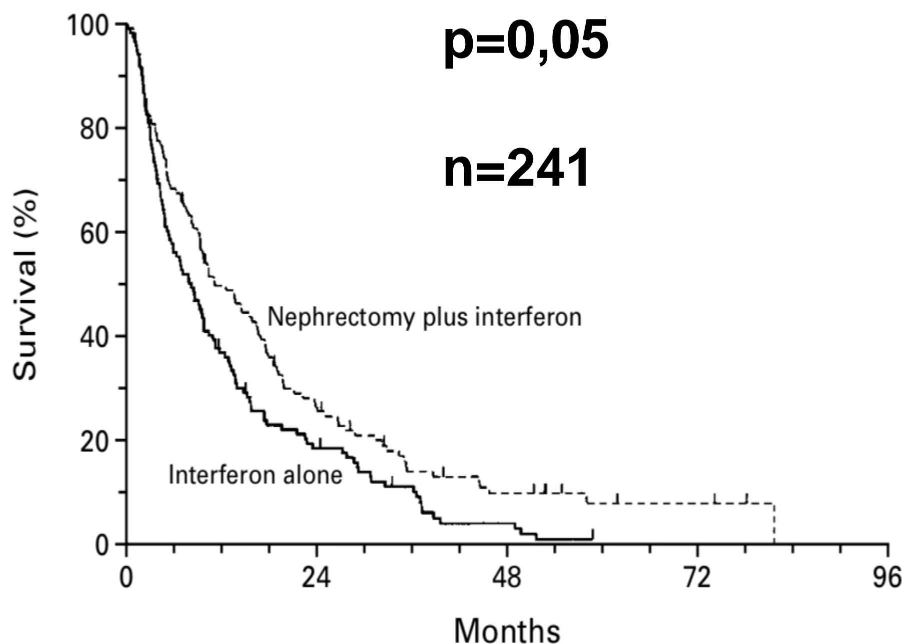
Figure 3: **Kaplan-Meier curves showing overall survival**
O=Observed number of events.

IFN +_Nx 5 CR, 3 PR (19%)

IFN 1 CR, 4 PR (12%)

G H J Mickisch Lancet **358:** 966, 2001

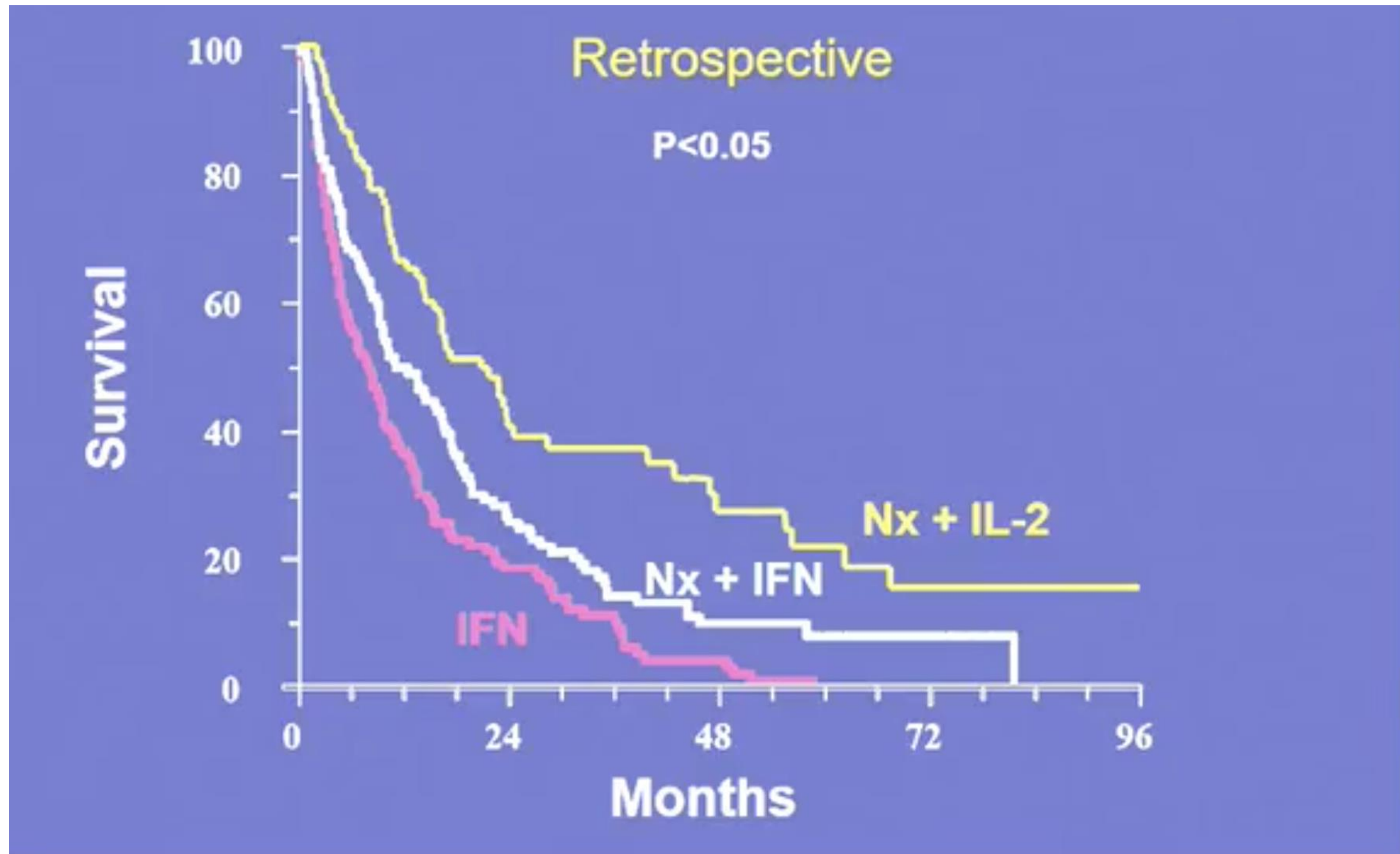
SWOG 8949 Nx FOLLOWED BY INTERFERON ALFA-2b vs INTERFERON ALFA-2b ALONE FOR METASTATIC RENAL-CELL CANCER



- IFN
  - 115 deaths
  - 1 CR, 2 PR (4%)
  - **median survival 8.1 ms.**
- Surgery + IFN
  - 106 deaths
  - 3 PR (3%)
  - **median survival 11.1 ms**

Flanigan RC et al N Engl J Med 345:165, 2

SWOG vs. UCLA (2001)



9 new better systemic therapies

- pan-tyrosine kinase inhibitors (TKIs)
- and those specifically targeting VEGF or mTOR are used
- Check point inhibitors

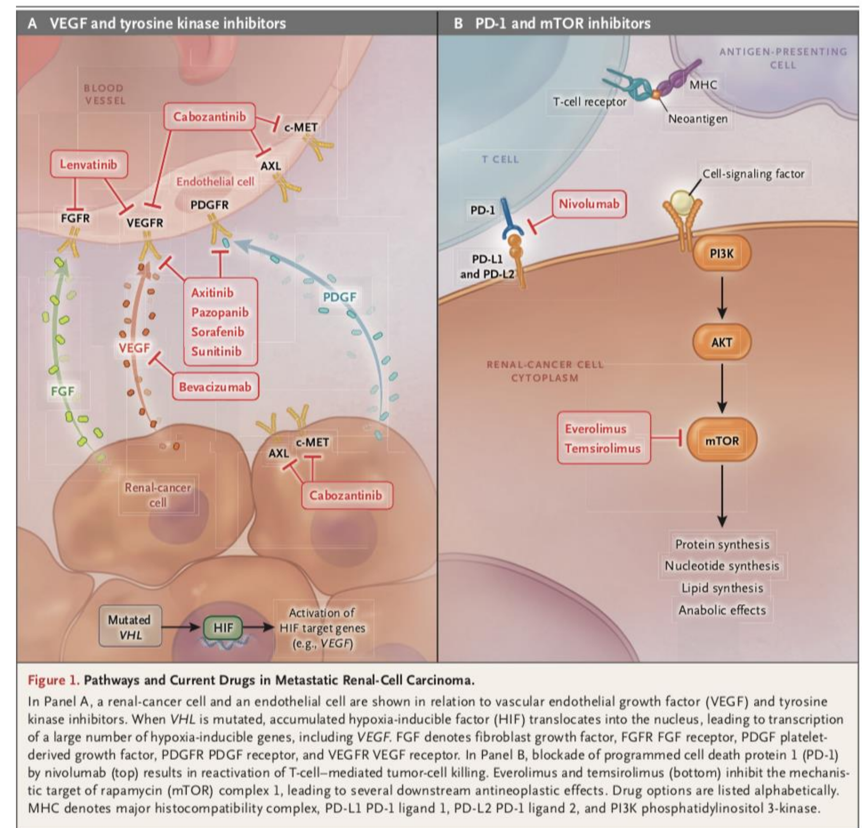
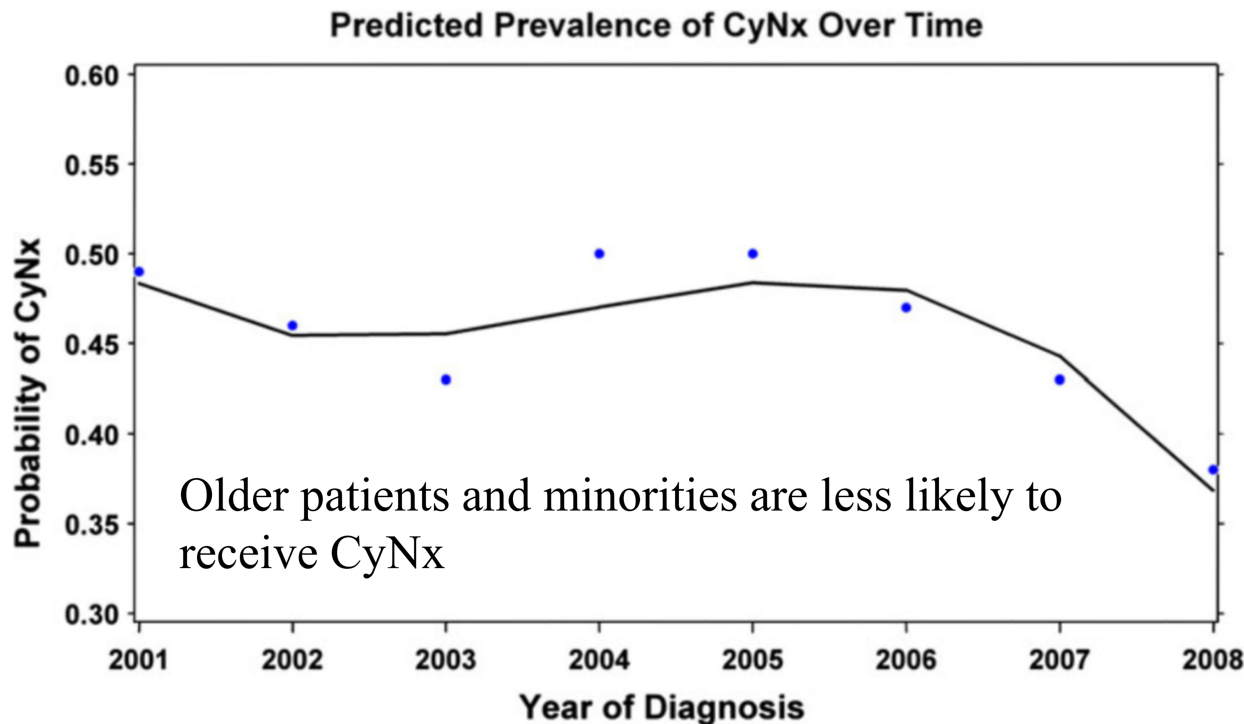


Figure 1. Pathways and Current Drugs in Metastatic Renal-Cell Carcinoma.

In Panel A, a renal-cancer cell and an endothelial cell are shown in relation to vascular endothelial growth factor (VEGF) and tyrosine kinase inhibitors. When *VHL* is mutated, accumulated hypoxia-inducible factor (HIF) translocates into the nucleus, leading to transcription of a large number of hypoxia-inducible genes, including *VEGF*. FGF denotes fibroblast growth factor, FGFR FGF receptor, PDGF platelet-derived growth factor, PDGFR PDGF receptor, and VEGFR VEGF receptor. In Panel B, blockade of programmed cell death protein 1 (PD-1) by nivolumab (top) results in reactivation of T-cell–mediated tumor-cell killing. Everolimus and temsirolimus (bottom) inhibit the mechanistic target of rapamycin (mTOR) complex 1, leading to several downstream antineoplastic effects. Drug options are listed alphabetically. MHC denotes major histocompatibility complex, PD-L1 PD-1 ligand 1, PD-L2 PD-1 ligand 2, and PI3K phosphatidylinositol 3-kinase.

Use of CyNx in the United States has declined in the VEGFR-TKI era



Older patients and minorities are less likely to receive CyNx

Fig. 1.
The use of CyNx in the United States, 2001–2008 (SEER database). There is a significant cubic trend in CyNx over time; $p = 0.0041$

Tsai CK, et al. World J Urol. ; 31(6): 1535 2013

Arguments against cytoreductive nephrectomy

- Surgical morbidity and mortality
- Randomized trials only with IFN (inferior)
- Patients with short life expectancy and long recovery time
- Explosive progression during recovery precluding systemic therapy
- Newer therapies may result in primary tumor regression

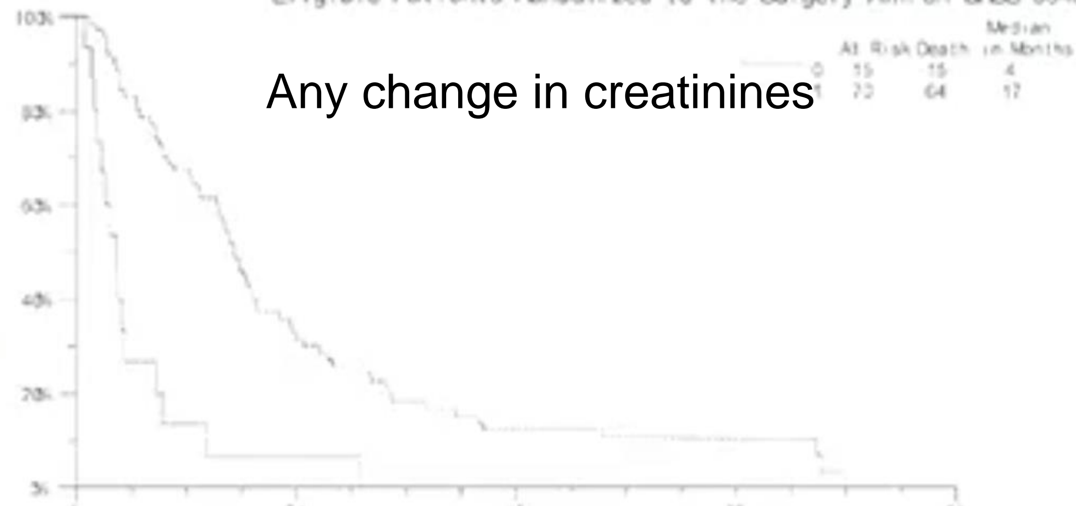
Potential benefits of cytoreduction surgery

- Prevent/treat local symptoms from primary tumor progression
- Diminish sources of metastasis
- Aliviate systemic symptoms
  - Paraneoplastic syndromes
  - Tumor cytokines and growth factors
- Tumor debulking
  - >75% of tumor burden (1 operation)

How does it work?

- Reduction in major tumor burden
- Exposure of new antigens or removal of immunologic “sink”
- Alteration of metabolism: partial loss of renal function = metabolic acidosis (anti-tumor effect)
- Removal of endocrine/paracrine factors that promotes progression and metastasis

Postoperative Azotemia and Survival after Cytoreductive Nephrectomy



Any change in creatinines

Gatenby R et al., Cancer Res 2002

Clinical Evidence For The Systemic Influence Of The Primary Tumor

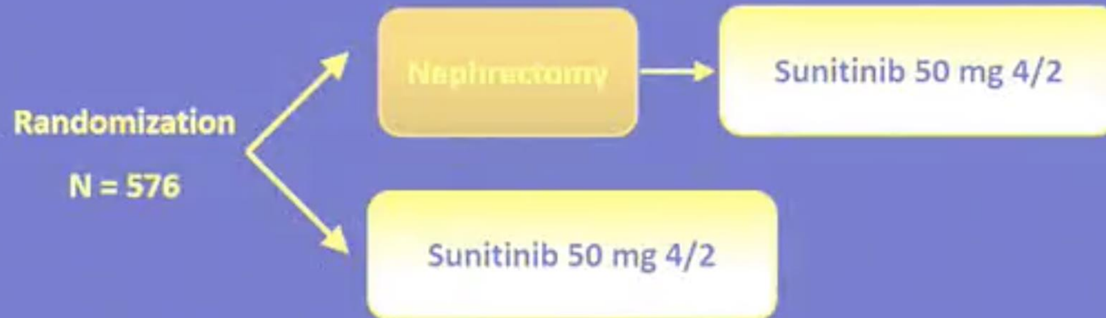
- Spontaneous regression of Mets after Cytoreductive surgery (1-2% for clear cell only)
- Paraneoplastic syndromes
- Explosive progression after cytireductive nephrectomy (5%)

Waiting for phase 3 evidence?

Carmena Study (French)

Only for clear cell carcinoma

Phase 3 Randomiz… ng Nephrectomy plus Sunitinib versus Sunitinib without Nephrectomy in 1st line Metastatic RCC



- Primary Objective:
  - To show that Sunitinib alone is not inferior to Nephrectomy plus Sunitinib (non inferiority study) in terms of Overall Survival (OS)
- Hypothesis:
  - Median OS expected in the nephrectomy plus Sunitinib = 24 months
  - Sunitinib alone will be considered as a clinically valid option if median OS > 19,9 months

CARMENA Study
Pr Arnaud Mejean (CCAFU – Necker Hospital – Paris, France)
Pr Alain Ravaud (GETUG – Saint-André Hospital – Bordeaux, France)

Timing of cytoreductive nephrectomy in metastatic clear cell carcinoma

SURTIME

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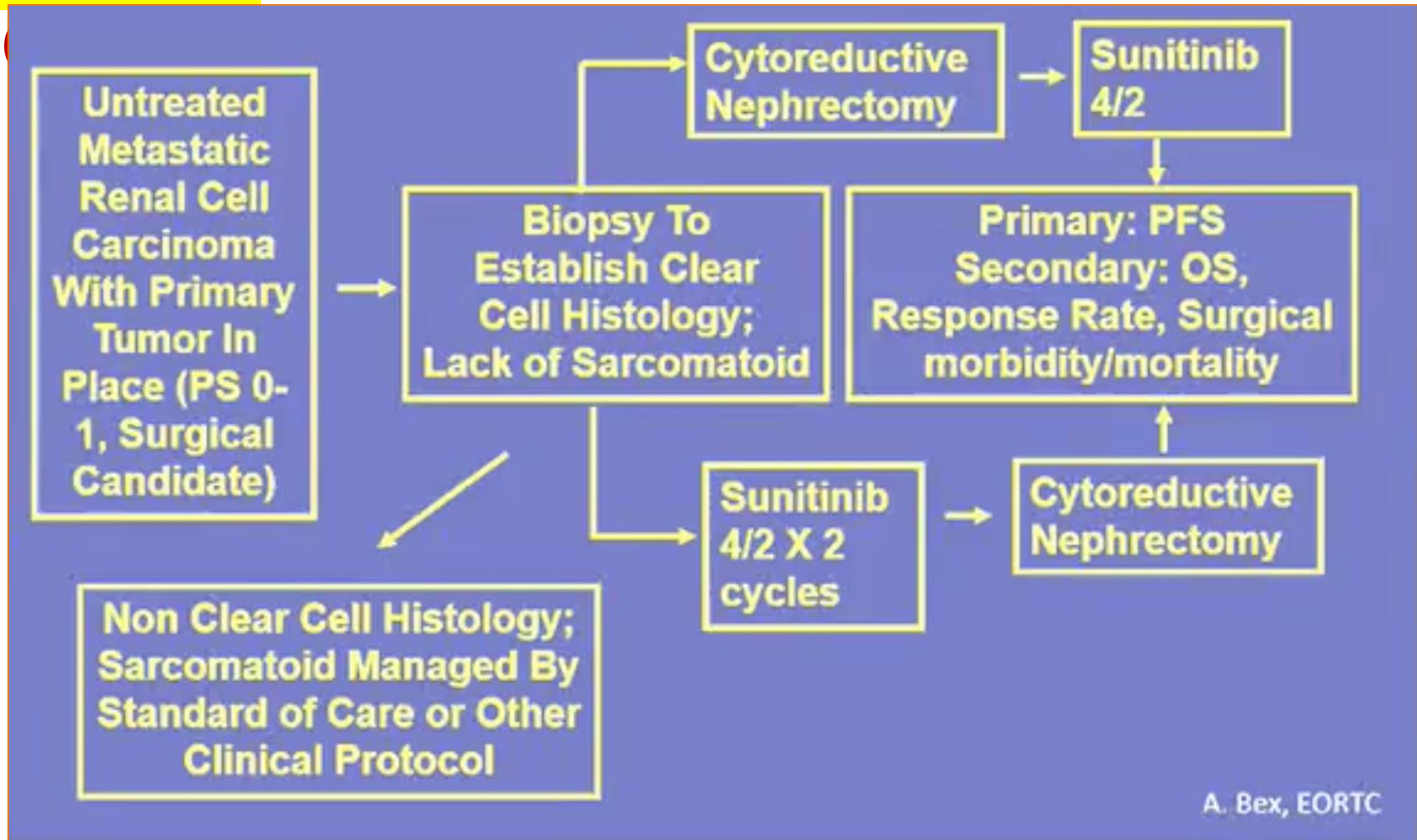


Harvard Experience: Retrospective study

Pts were treated with vascular endothelial growth factor targeted agents

- N= 314 metastatic renal cell carcinoma
- Anti-vascular endothelial growth factor therapy **naïve**
- On multivariable analysis, the **overall survival** difference (adjusted HR 0.68; 95% CI 0.46, 0.99; p 0.04)

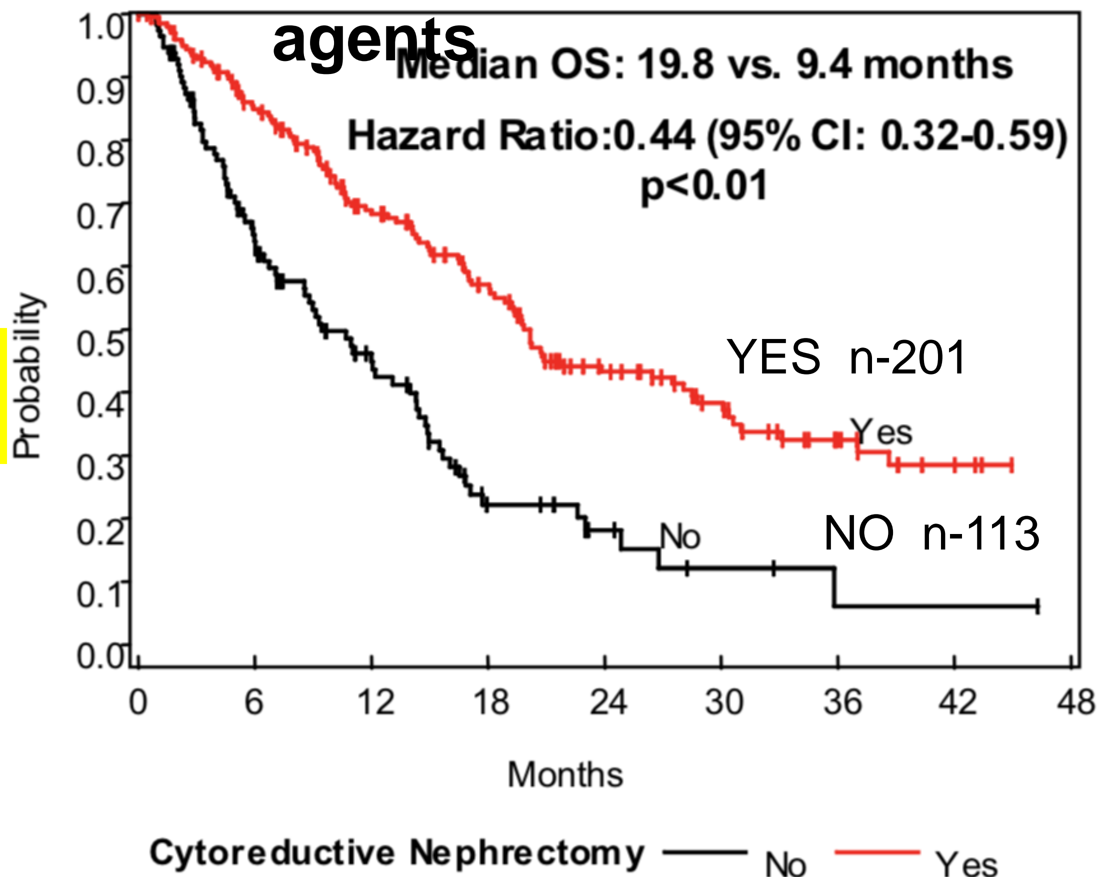
Choueiri TK et al, J Urol 185, 60-66, 2011

Harvard Experience:

Cytoreductive nephrectomy in the era of target therapy: What to do before results of prospective trials are completed?

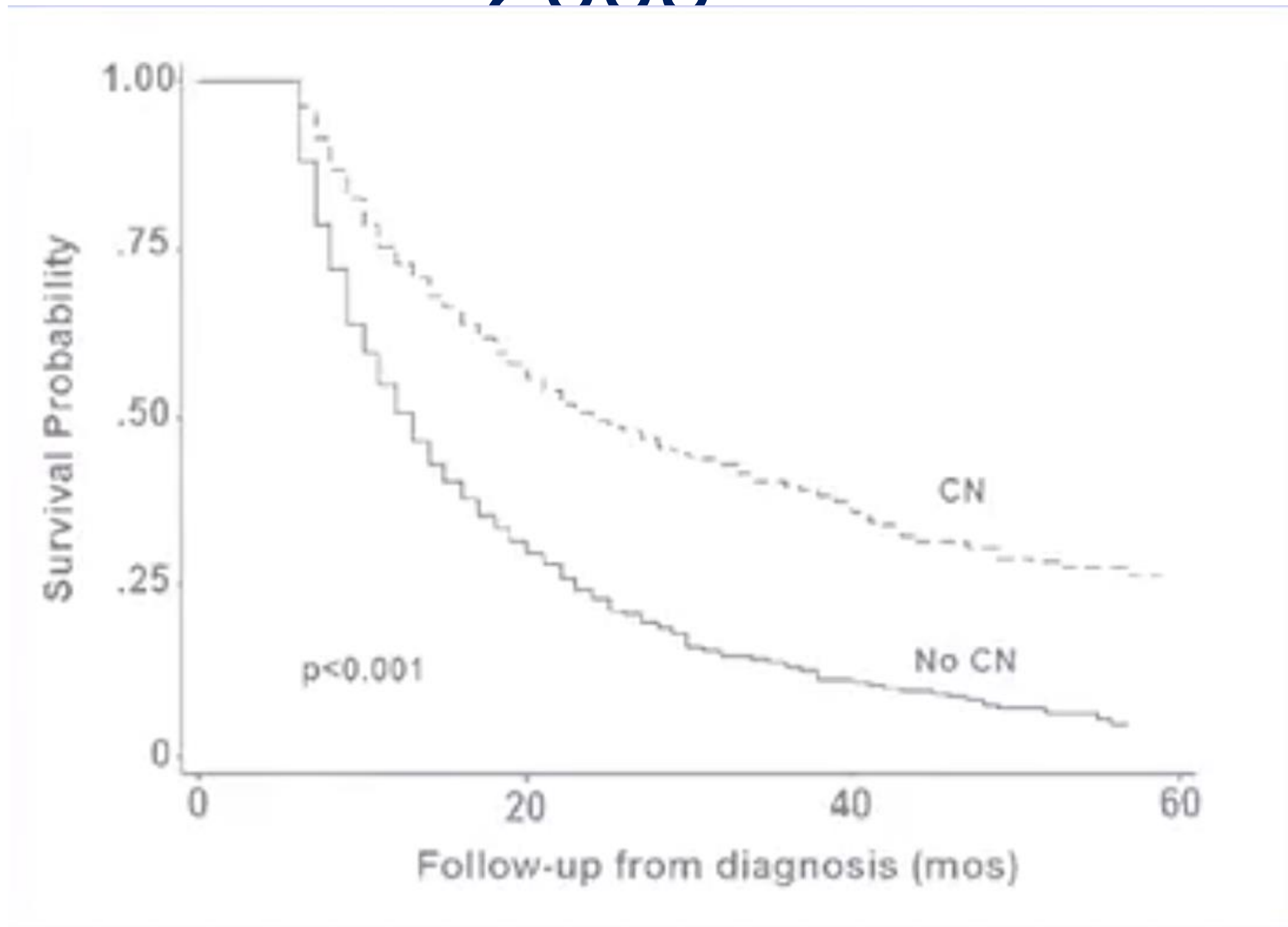
CyNx followed by vascular endothelial growth factor targeted agents

DOUBLING THE SURVIVAL. 19,8 VS 9.4 meses



Choueiri TK et al, J Urol 185, 60-66, 2011

Cytoreductive nephrectomy in the era of target therapy: SEER 2005 - 2009



CULP S ET AL UROL ONCOL 2014

Whose patients will not benefit from cytoreductive nephrectomy?

Patients who will not benefit from CN

n =566 CN (1991 – 2007)

Preoperative risk factors

- Serum albumin < lower limit of normal
- IDH > upper limit of normal
- Liver metastasis
- Symptoms of metastasis at presentation
- Retroperitoneal LN involvement
- Supra-diaphragmatic LN involvement
- Clinical T stage 3 or 4

Culp S et al Cancer 116:3378..2010

Patients who will not benefit from CN

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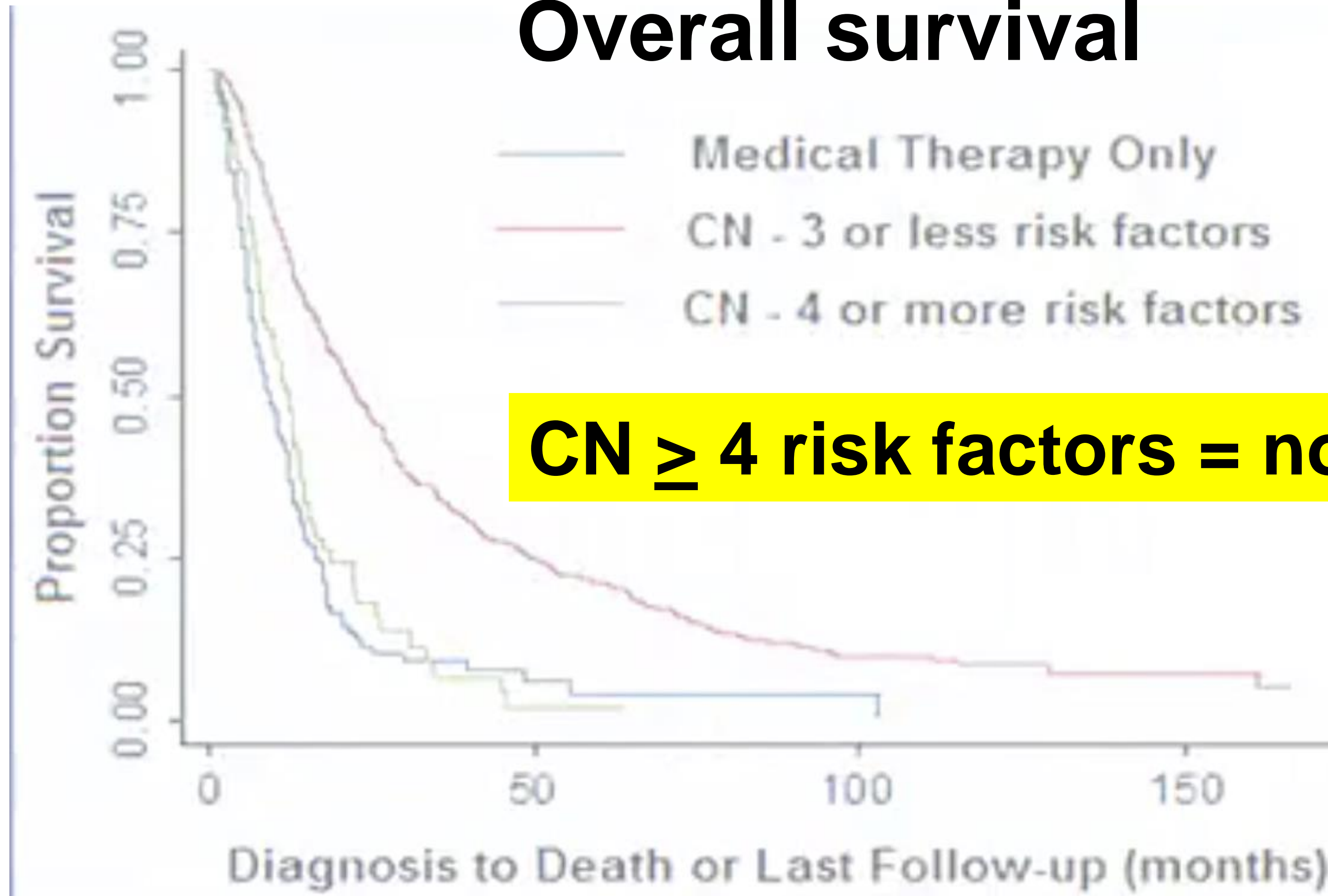


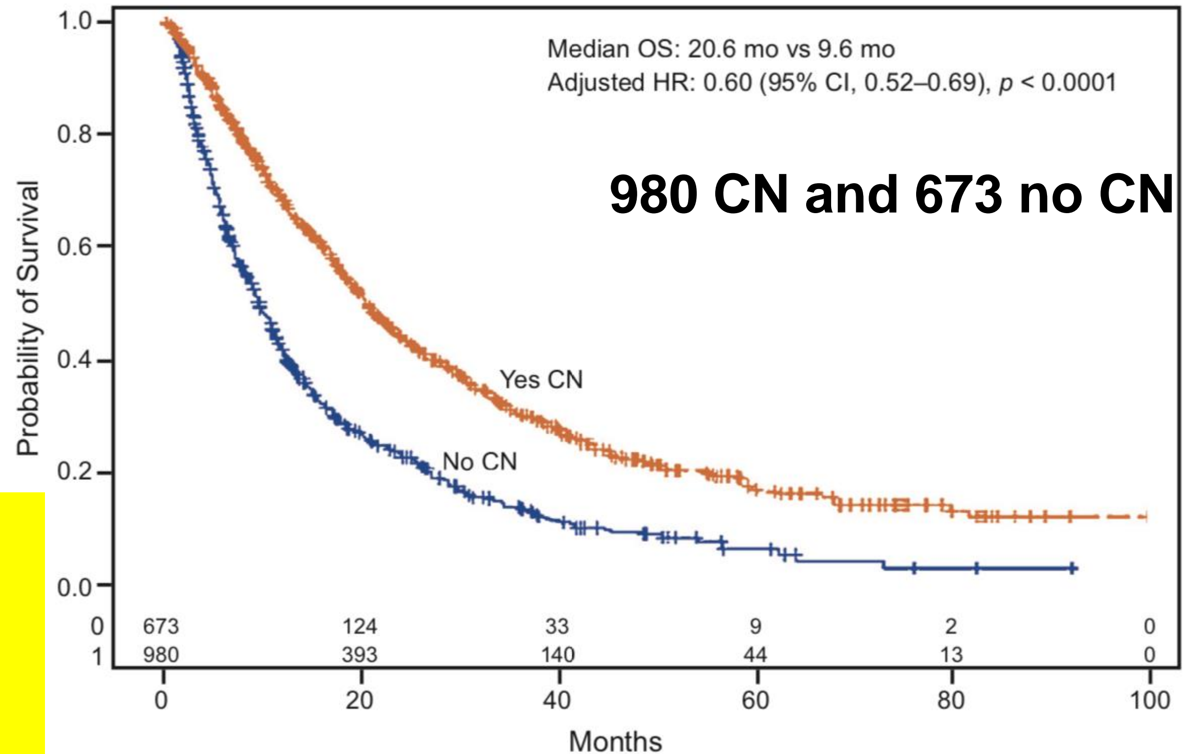
CN ≥ 4 risk factors = no CyNx

Culp S et al Cancer 116:3378, 2010

reductive Nephrectomy in the era of targeted therapy **(n= 1658)**

Synchronous Metastases

- Anemia
- Hypercalcemia
- Neutrophilia
- Thrombocytosis
- Karnosfsky < 80
- Dx to Rx < 1 year



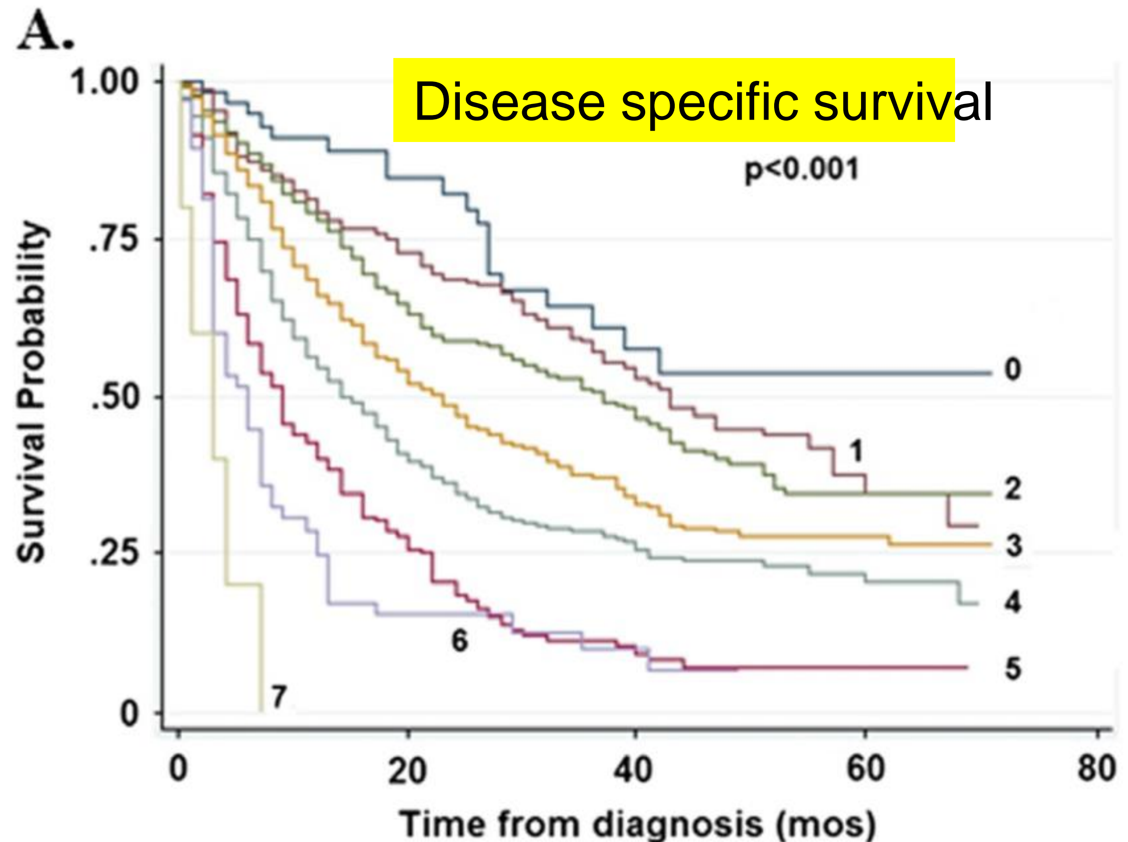
4 or more IMDC risk factors
no benefit

Limited expected survival
no benefit

Heng D et al Eur Urol 66: 704–710, 2014

Cytoreductive Nephrectomy in the era of targeted therapy (SEER 2005-2010)

1. age > 60 years
2. Size > 7 cm
3. cT3 or cT4 stage
4. High grade (3 or 4) **vs** (1 or 2)
5. Lymph nodes positives
6. Sarcomatoid histology **vs** clear cell
7. African americans **vs** caucasian
8. Visceral only **vs** visceral + lymph nodes



Culp SH et al UROL ONCOL 2014

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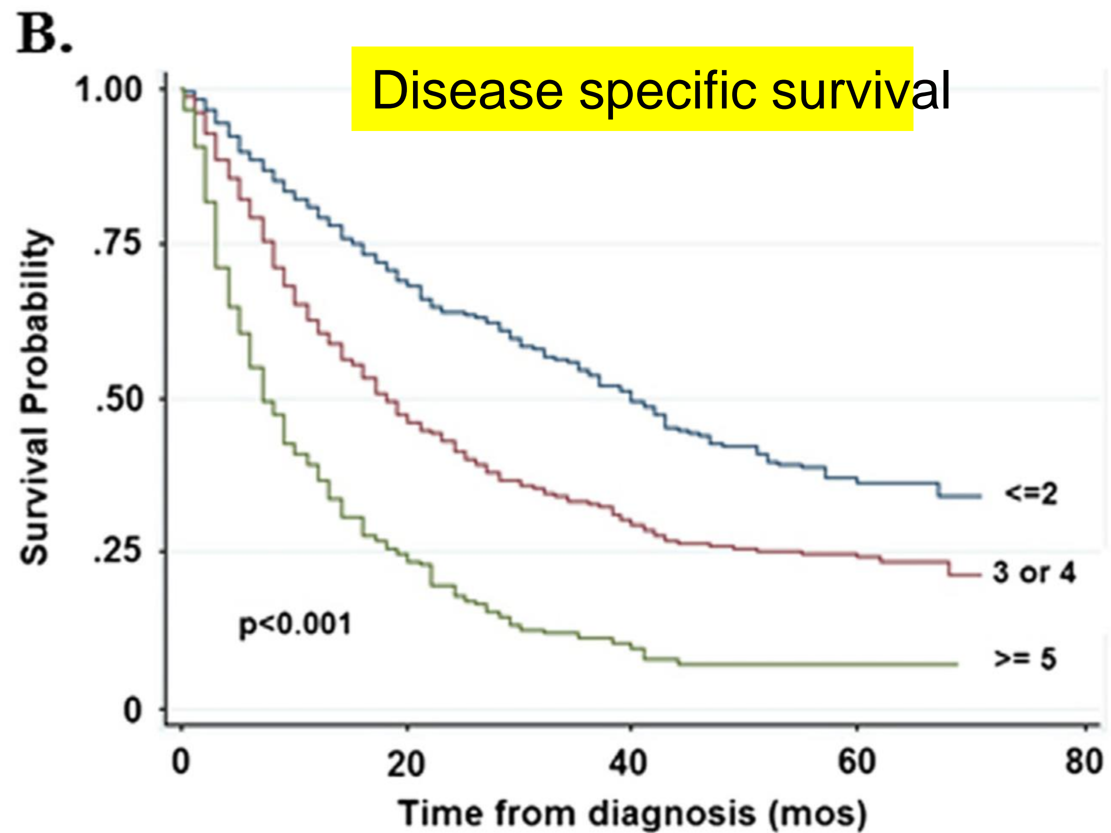
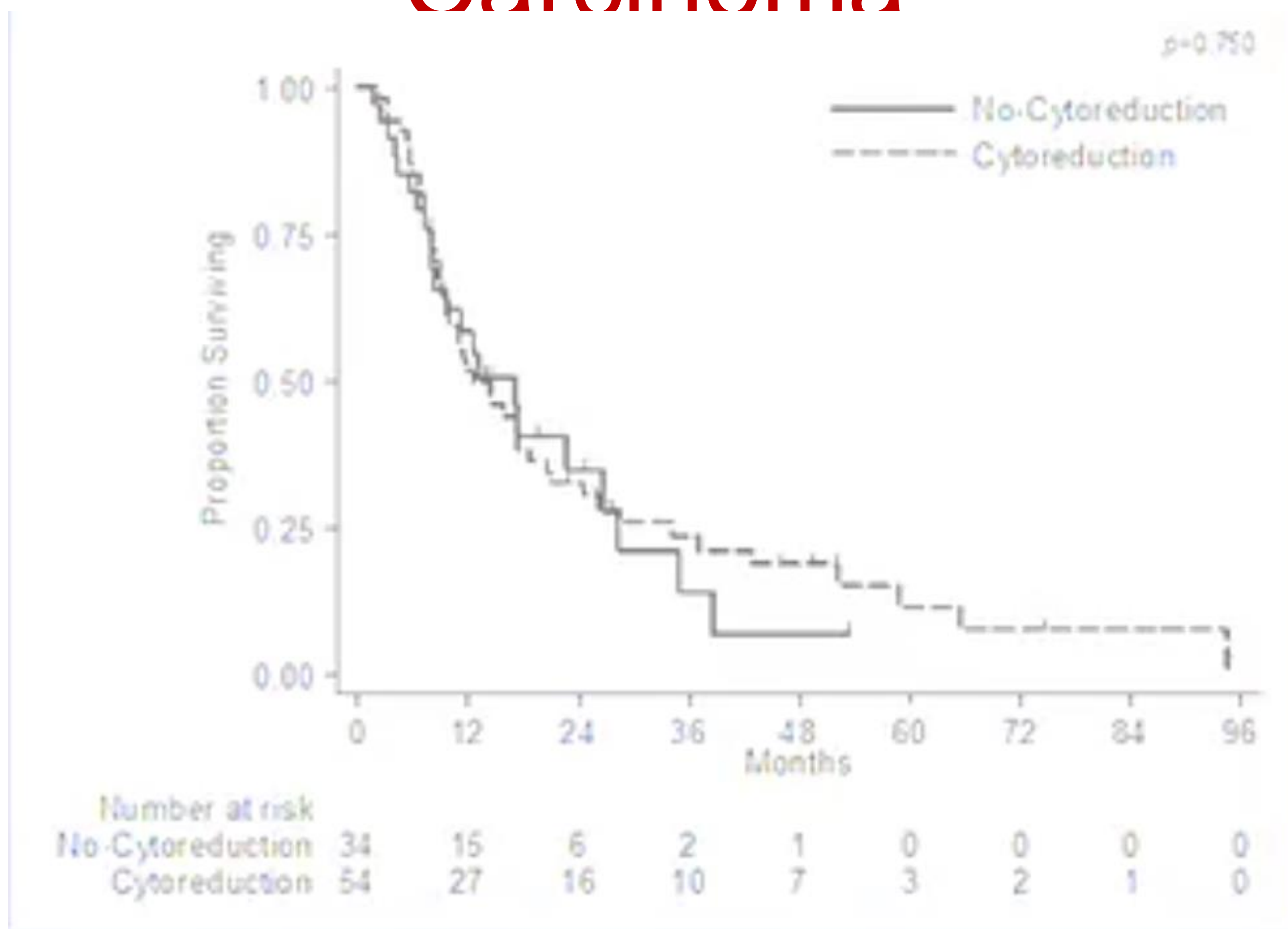


Culp S et al UROL ONCOL 2014

So, proper patient selection is fundamental !!!

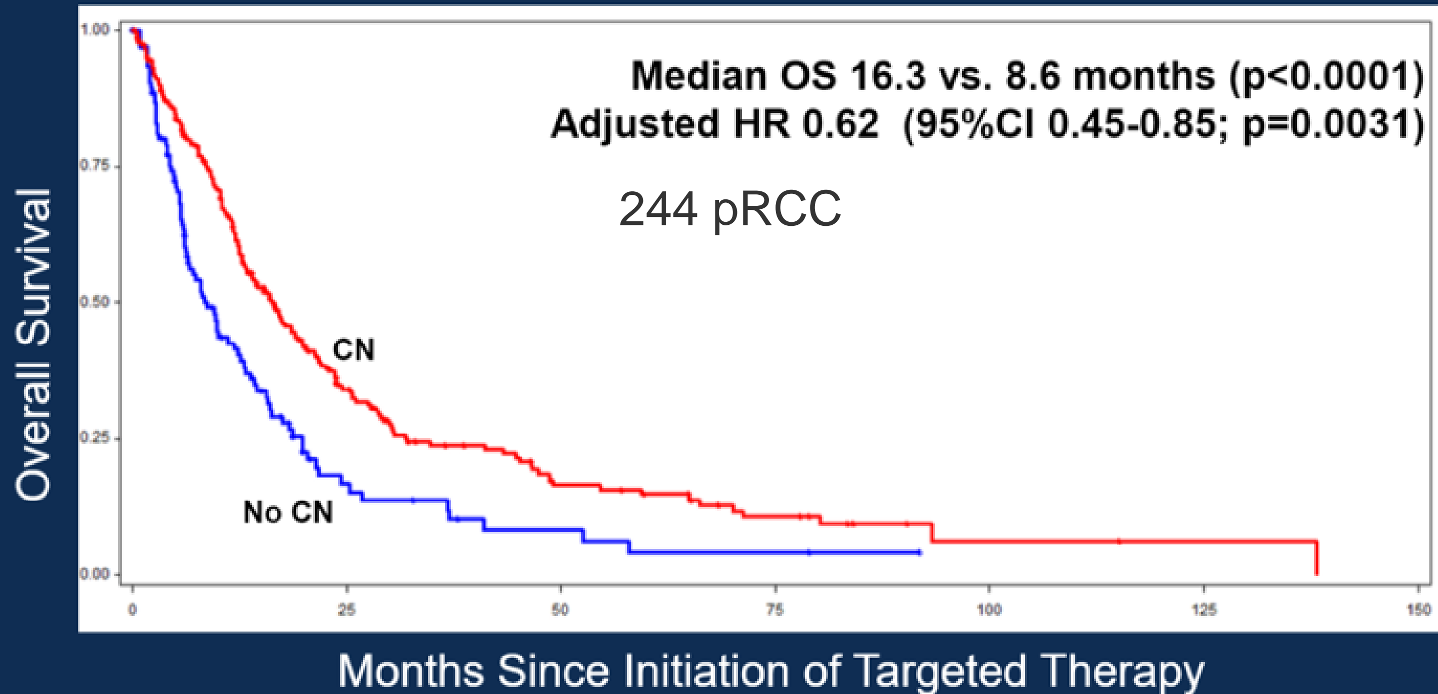
Does CyNx work for non-clear cell carcinoma?

Cytoreductive Nephrectomy in Metastatic Non-Clear Cell Carcinoma



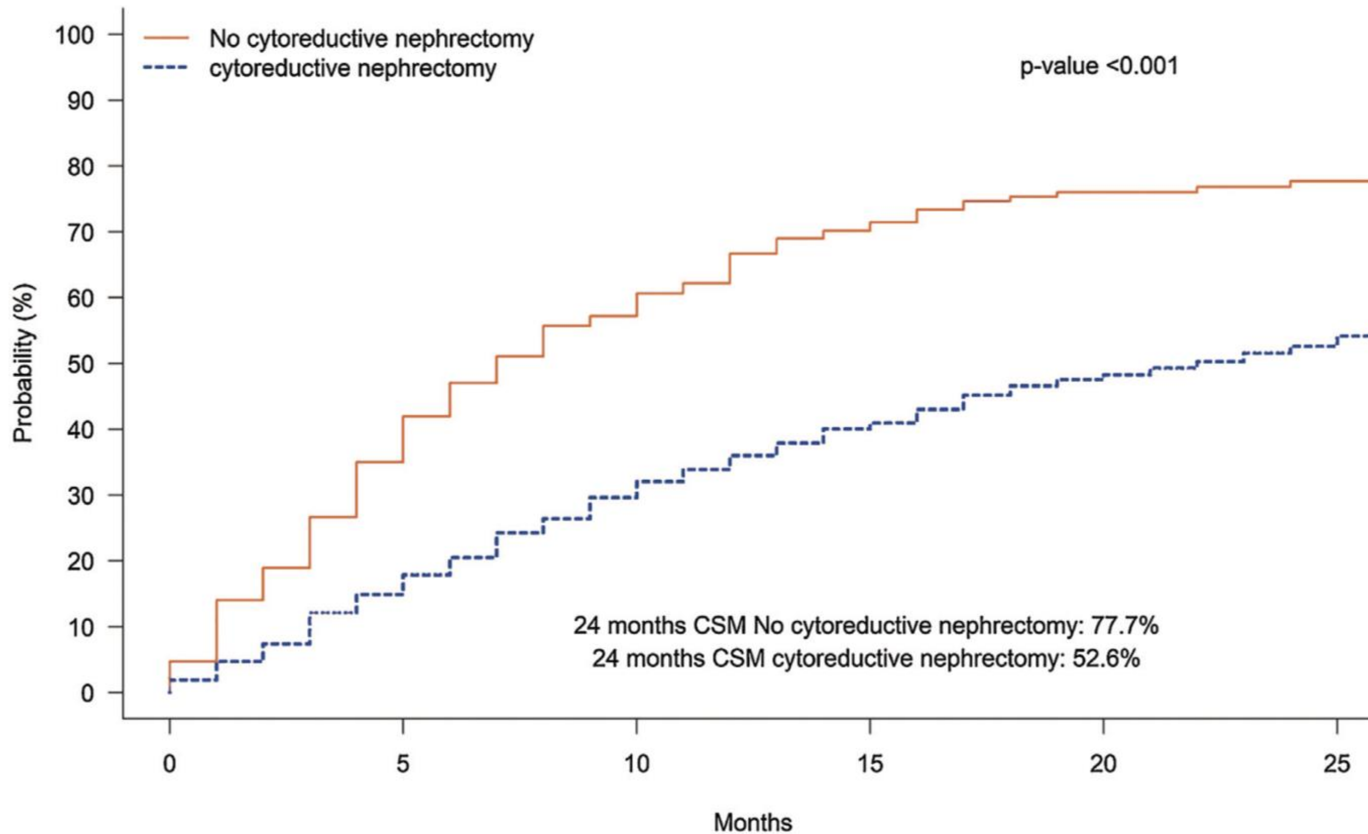
Kenney P et al, 2017

ASCO GU 2018: Cytoreductive Nephrectomy in Metastatic **Papillary** Renal Cell Carcinoma: the International Metastatic Renal Cell Carcinoma Database Consortium



Jeffrey Graham, et al. ASCO GU 2018

851 patients with non-ccmRCC, 67.6% underwent CyNx



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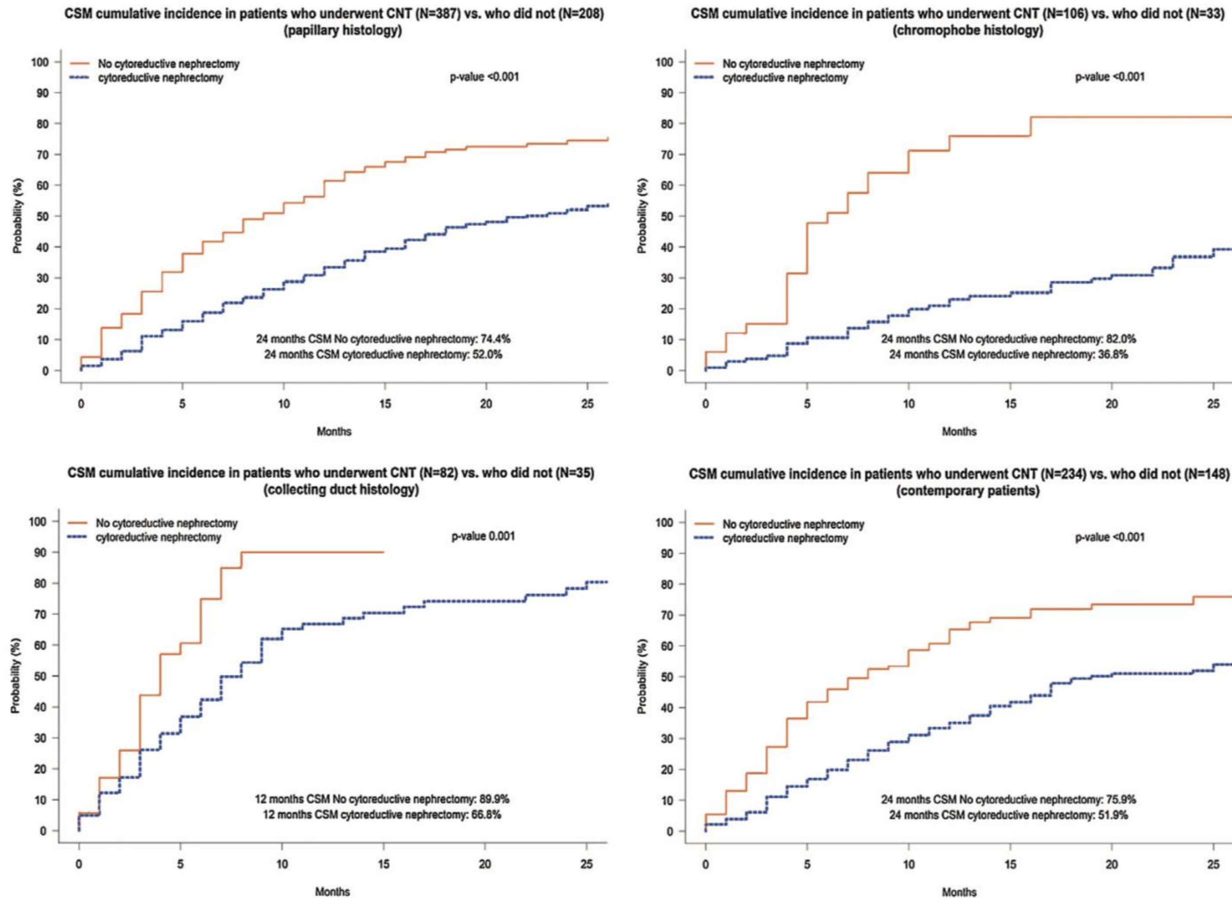

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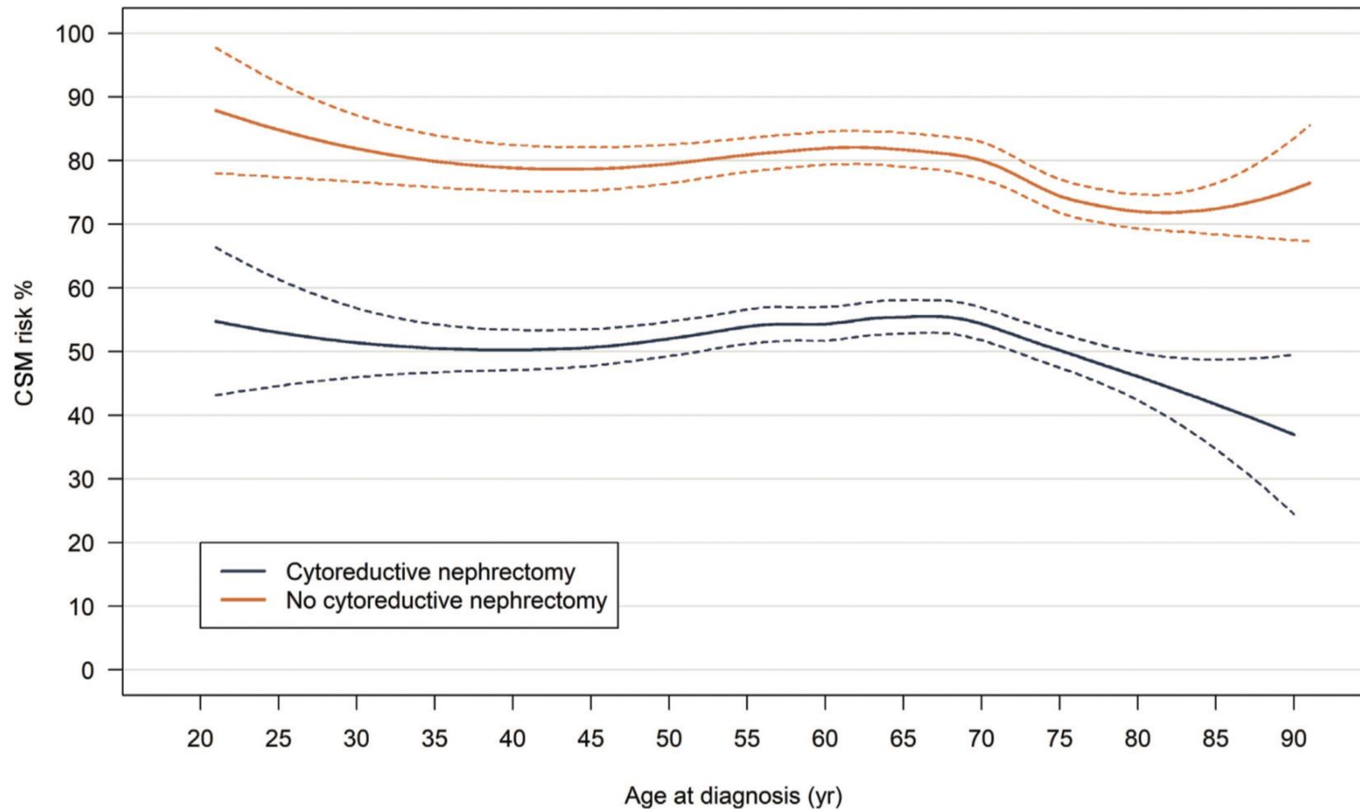

Cytoreductive nephrectomy (CN) in the era of target therapy

- Goal: removal of most tumor burden in one procedure
- CN improves survival in proper selected pts
- Adverse factors: **=> consider systemic therapy upfront and delayed surgery if**
  - poor performance status,
  - liver mets,
  - CNS mets,
  - extensive bone mets,
  - clinical nodal involvement
- **Consider CN for non-clear cell histology (paradigm shift)**

OBRIGADO