Ruolo della chirurgia citoriduttiva nel carcinoma renale metastatico

Clinica Urologica e Centro Trapianti di Rene
Scuola di Specializzazione in Urologia
Università degli Studi di Foggia

Cytoreductive surgery for metastatic renal cell carcinoma

- Spontaneous regression of metastases
- Palliation

Spontaneous regression of metastases after nephrectomy

Medline 1966 - 2008 → 53 Case-reports

- 0,8% Montie et al. J. Urol. 1977
- 4,4% Marcus et al J. Urol. 1993

Lung only metastases

The rational

(Empiric)

- Reduction in the disease burden
- Elimination of metastatic source

(Scientific)

- Mild renal failure
- Low grade metabolic acidosis

		Survival	
Serum creatinine	↕	17 months	
Serum creatinine	↕	4 months	p:0,01

Alexander JP et al Cancer Res 1993

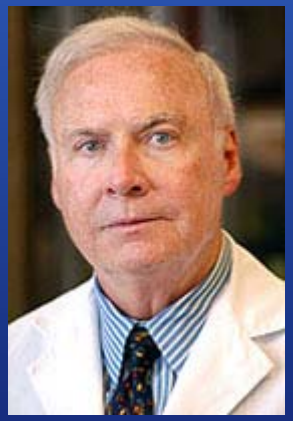
Palliation

- Pain related to the kidney mass
- Hematuria
- Erytrocytosis
- Hypertension
- Hypercalcemia

Walther et al. J. Urol. 1997

Debulking nephrectomy: *word of wisdom*

"…Survival of those who had adjunctive nephrectomy was no greater than that of the study population as a whole…"



Dekernion et al J Urol 1978

"…Palliative nephrectomy may be beneficial when…
…the primary tumor produces severe symptoms."

Immunotherapy Era
'80-'90

- IL-2
- IFN-α

Debulking Nephrectomy
A new prospective

Debulking nephrectomy pre-immunotherapy: Restrospective studies 1994-1998

Source	No. of patients	Surgical mortality, no. (%)	Unable to receive postoperative BMR therapy, no. (%)	Overall response, no. (%)	Complete response, no. (%)	Partial response, no. (%)
Rackley *et al.* (13)	37	1 (2.7)	8 (21.6)	3 (8.1)	0 (0.0)	3 (8.1)
Wolf *et al.* (20)	23	0 (0.0)	6 (26.1)	3 (13.0)	2 (8.7)	1 (4.3)
Bennett *et al.* (21)	30	5 (17)	23 (76.6)	4 (13.3)	3 (10.0)	1 (3.3)
Fallick *et al.* (22)	28	1 (3.6)	2 (7.1)	11 (39.3)	5 (17.9)	6 (21.4)
Walther *et al.* (23)	195	2 (1.0)	74 (37.9)	19 (17.8)	4 (3.7)	15 (14.0)
Figlin *et al.* (24)	62	0 (0.0)	7 (11.3)	19 (34.5)	5 (9.1)	14 (25.5)
Levy *et al.* (25)	66	2 (3.0)	12 (18.1)			
Total	441	11/441 (2.5)	132/441 (29.9)	59/375 (15.7)	19/375 (5.1)	40/375 (10.7)

Selection Bias

- Performance status
- Primary tumour extension

Flanigan et al. Clin. Cancer Res. 2004

Debulking nephrectomy pre-immunotherapy: Prospective studies

The NEW ENGLAND JOURNAL of MEDICINE

SWOG *(Flanigan et al N Engl J Med 2001)*

EORTC *(Mickisch et al Lancet 2001)*

Combined Analysis (Flanigan et al J Urol 2004)

EORTC e SWOG
Trial schema

Metastatic renal cell carcinoma

RANDOM

→ Radical nephrectomy + IFNα

→ IFNα

IFNα: $5x10^6$ IU/mg^2 subcutaneously 3 times a week
Continue for 52 weeks or until progression or unacceptable toxicity

Endpoints

- Survival
- Response to treatment

Mickisch et al Lancet 2001
Flanigan et al N Engl J Med 2001

EORTC + SWOG Trials
Inclusion criteria

- Any tumour, node, or metastatic 1 disease
- Carcinoma surgically removed
- Performance status 0 or 1
- No previous chemo-, hormonal or radiation therapy
- Pre-surgical biopsy

(Flanigan et al J Urol 2004)

EORTC + SWOG: Results

Study	Treatment arm	Patients	Perform status 1 (%)	Operative mortality	Operative morbidity	Overall survival (mo)	IFN-related complic.
SWOG	Nx+IFN	120	45*	0,08%	4,9%	11,1**	10
	IFN	121	58	N/A	N/A	8,1	14
EORTC	Nx+IFN	42	52	2,4%	14,3%	17***	12
	IFN	43	60	N/A	N/A	7	12

* p:0,04
** p:0,012
*** p:0,03

Mickisch et al Lancet 2001

Flanigan et al N Engl J Med 2001

Debulking nephrectomy pre-immunotherapy
The rational

Renal primary lesion: tumor sink

- Decreased expression of MHC by tumor cells
- Deficient processing of tumor antigens by limphocytes
- Enhanced expression of interleukin-10
- Decreased expression of caspases
- Imbalance in the helper T-cell profile

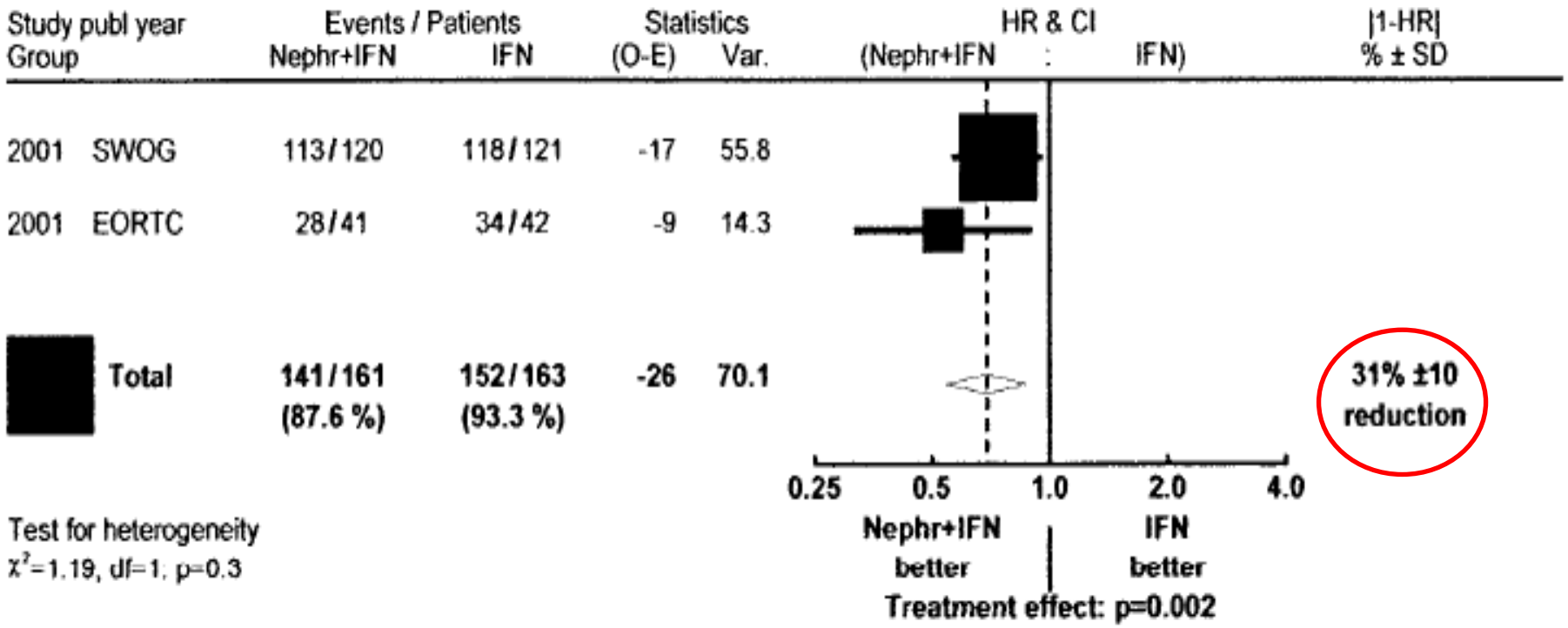
Rini et al J Urol 2007

Overall median survival

Nx + IFNα ➡ 13,6 months

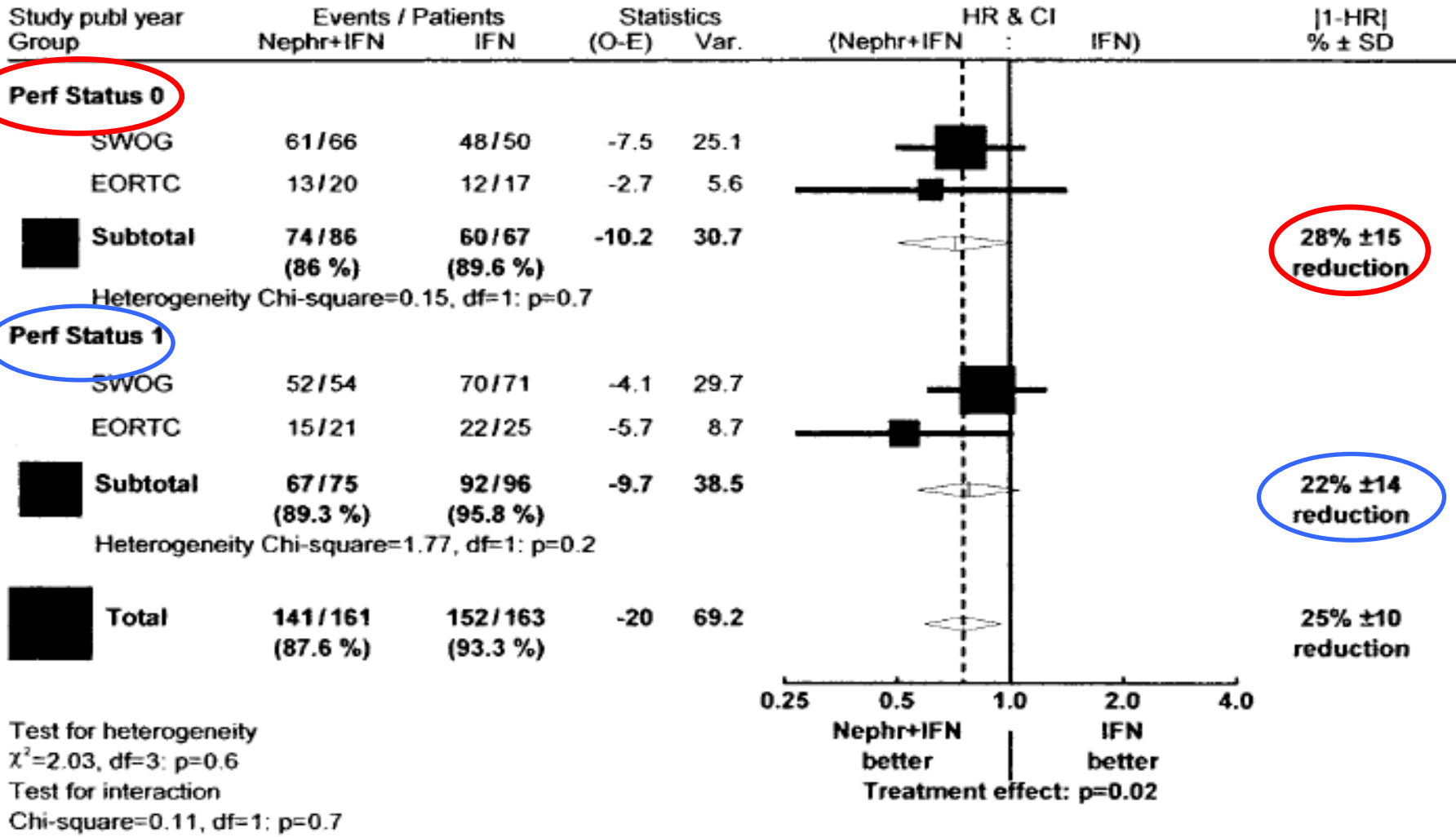
IFNα ➡ 7,8 months

➡ 5,8 months



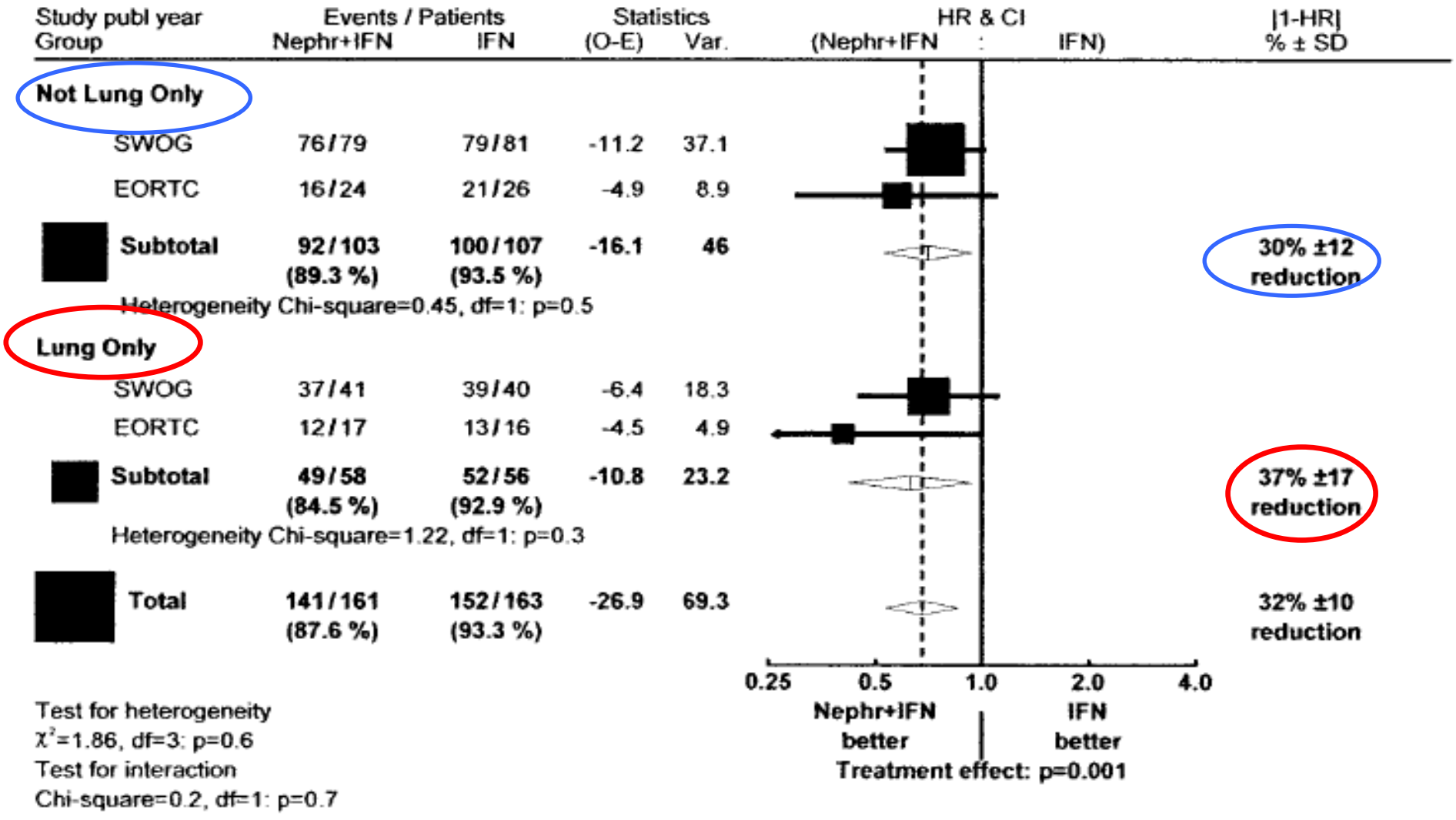
Flanigan et al J Urol 2004

Forest plot for performance status



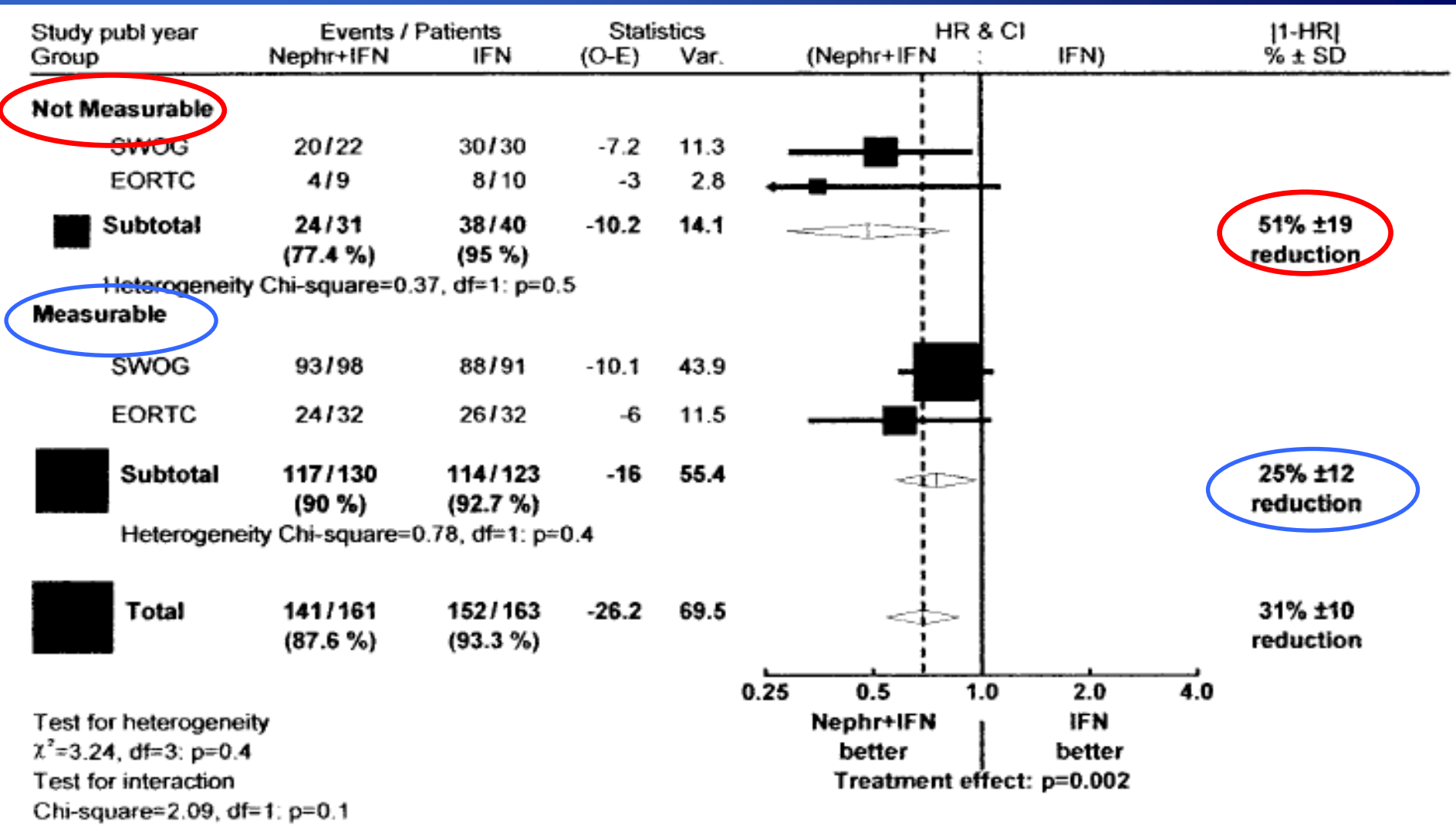
Flanigan et al J Urol 2004

Forest plot for lung only metastases



Flanigan et al J Urol 2004

Forest plot for measurable disease



Flanigan et al J Urol 2004

Translating trial's results in clinical practice

YES

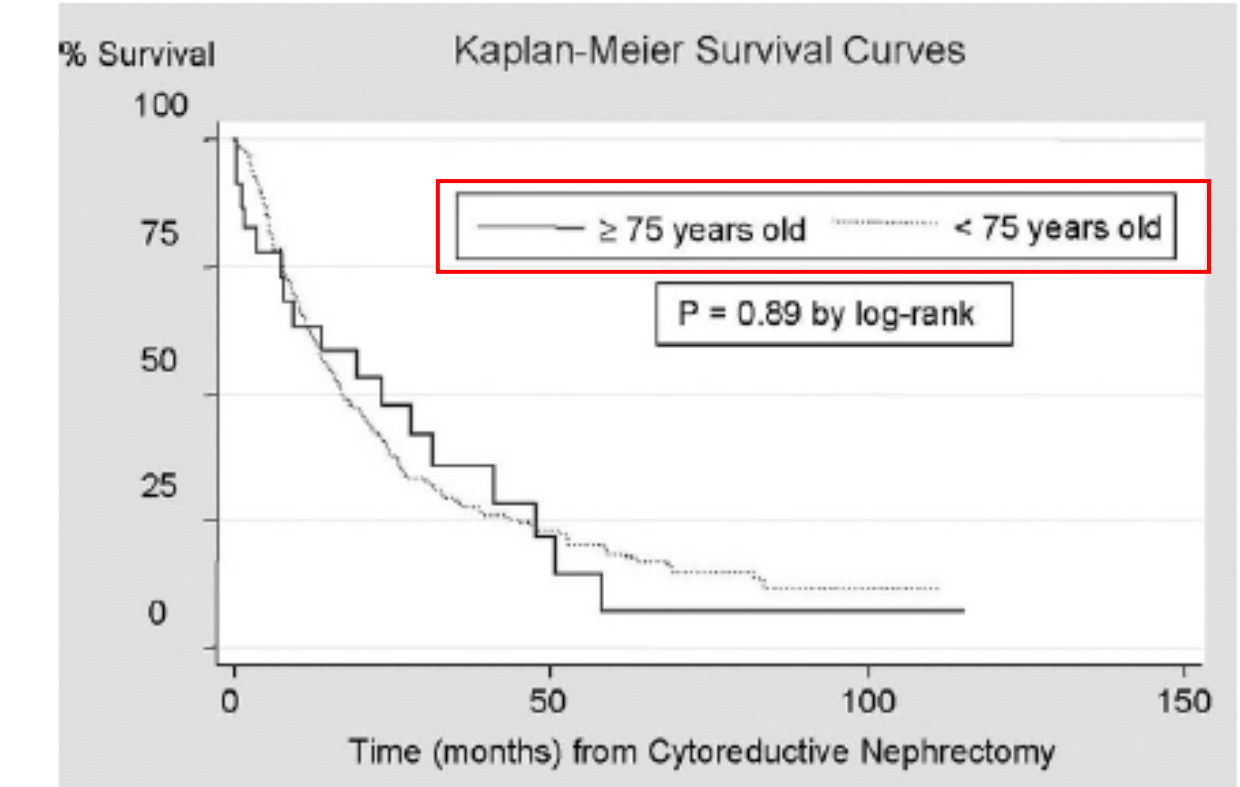
- Small, resectable primary tumors
- Small overall tumor burden
- Good performance status

NO

- Bulky nodal disease
- Large inferior cava thrombi
- Tumor extension into the psoas muscle (flank pain)

Gold standard

Cytoreductive nephrectomy in the elderly



Median survival

16,6 months in elderly patients

13,7 months in younger patients

Perioperative deaths

21% in elderly patients

1,1% in younger patients

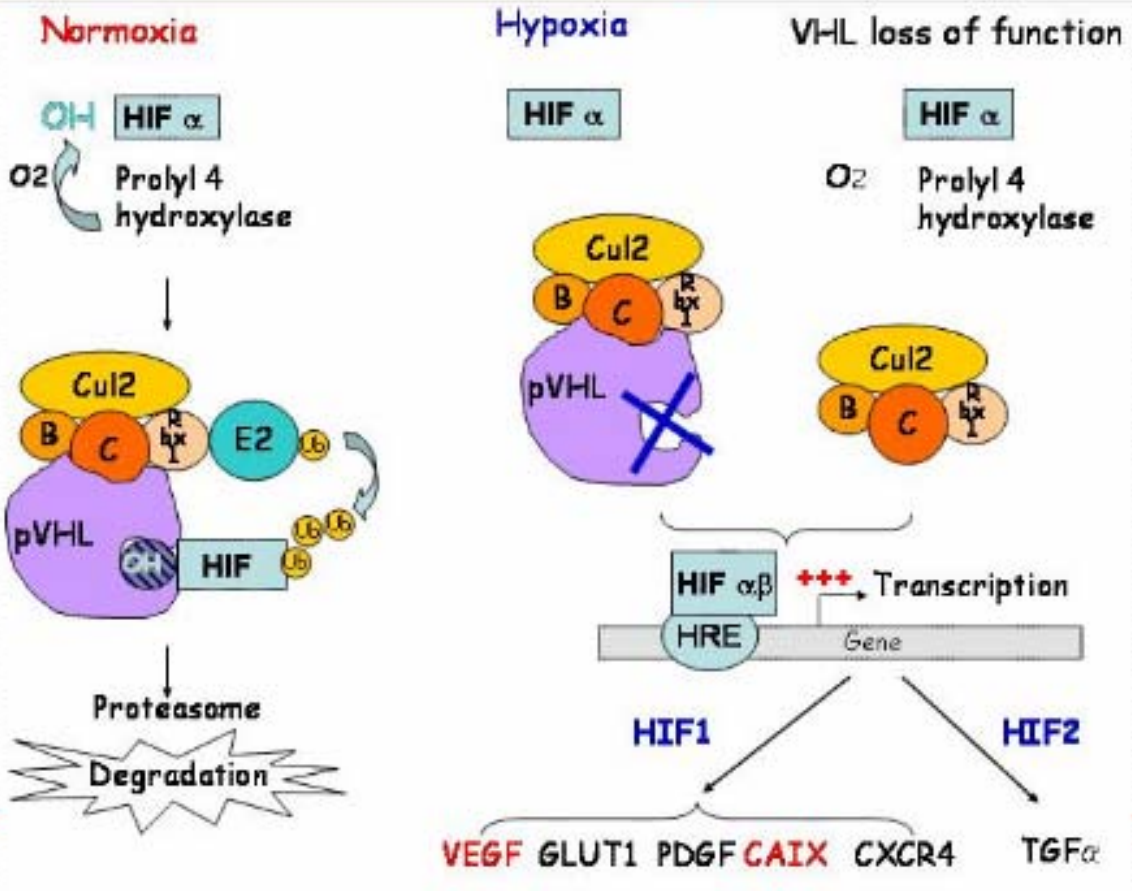
Kader et al J Urol 2007

Targeted therapy era
2005-2006

Current angiogenic drugs with proven efficacy in mRCC

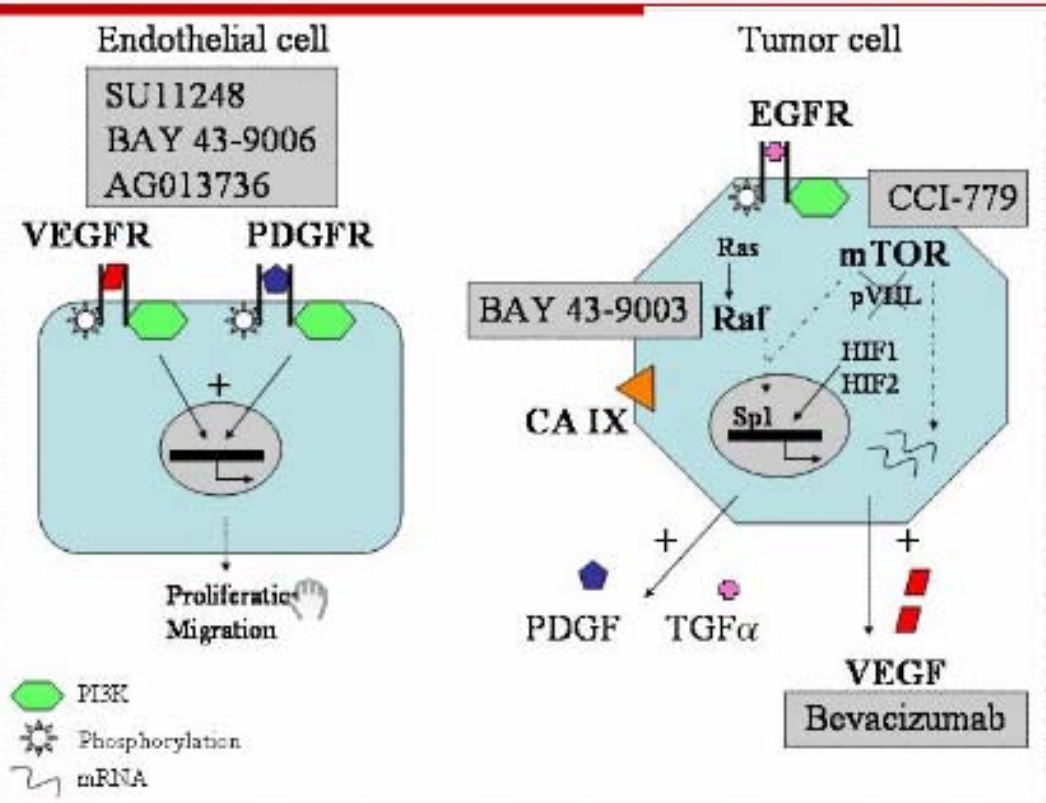
- SUTENT® (Sunitinib)
- NEXAVAR® (Sorafenib)
- TORISEL® (Temsirolimus)
- AVASTIN® (Bevacizumab)

Vascular phenotype of RCC: crucial role of the VHL/HIF/hypoxia/VEGF pathway



Patard JJ et al. Eur Urol 2006

Molecular targets in RCC



Patard JJ et al. Eur Urol 2006

Eligibility Criteria

- Clear cell histology
- No prior systemic treatment
- Measurable disease
- ECOG PS of 0 or 1
- Adequate organ function

(N=750)

RANDOMIZATION

(n=375) → **Sunitinib 50 mg PO QD (Schedule 4/2)**

(n=375) → **IFN-α 9 MU SQ TIW**

- Primary endpoint: Progression-free survival
- Secondary endpoints: Response rate, overall survival, patient-reported outcomes, safety

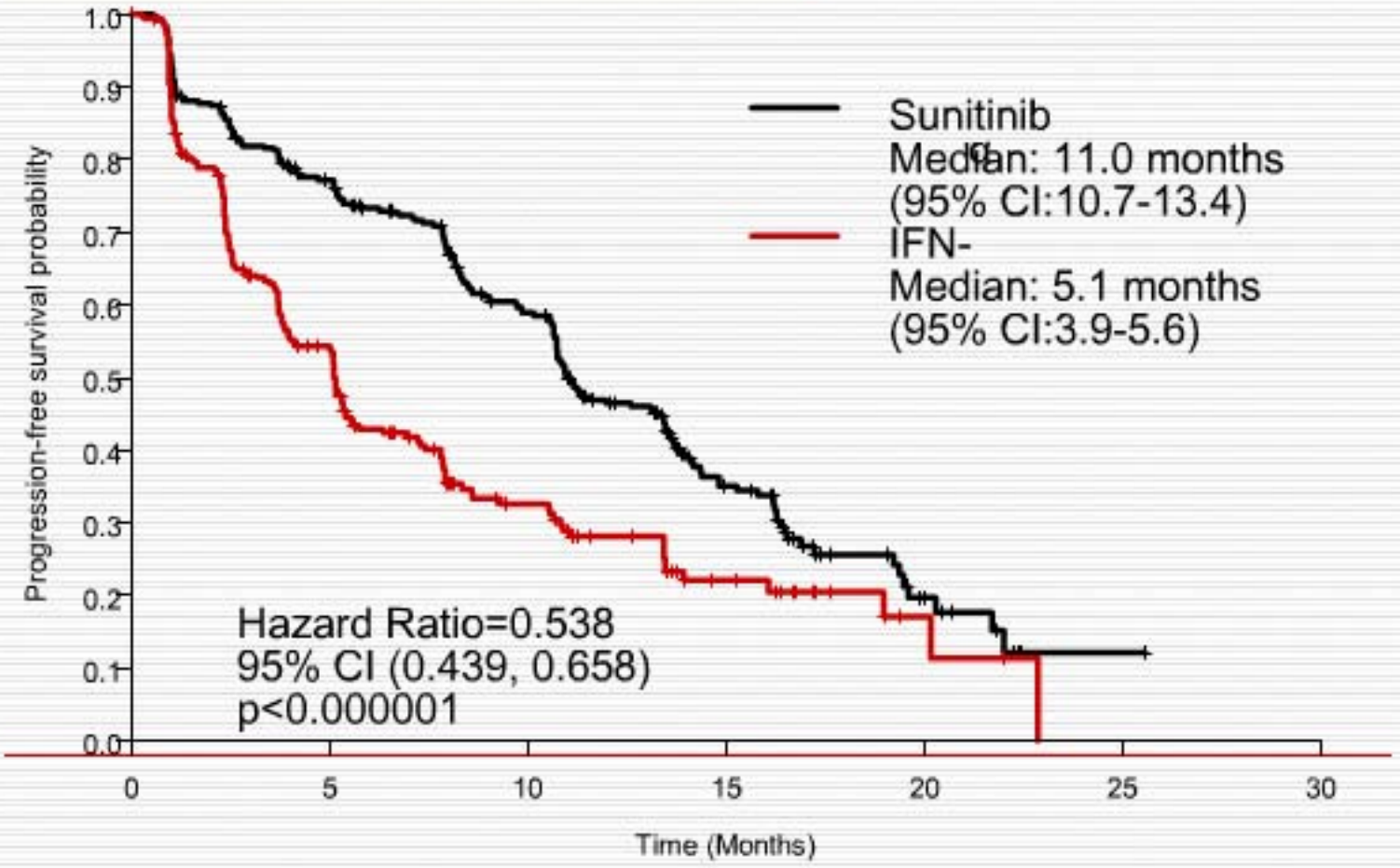
Motzer et al ASCO 2007

Sunitinib versus Interferon-alfa (IFN-α) as First-line Treatment of Metastatic Renal Cell Carcinoma (mRCC): Updated Results

	Sunitinib	INF-α
Nb patients	375	375
Treatment Median duration (months)	11 (<1 - 31)	4 (< 1-28)
Objective Response(%)	**46 %**	**12 %** **p < 0,000001**
Complete Response (CR) (%)	**1 %**	**1 %**
Partial Response (PR) (%)	**45 %**	**11 %**
Stable Disease (SD) (%)	**41 %**	**55 %**

Motzer RJ et al. Abstract 5024. ASCO 2007.

Progression-Free Survival
(Independent Central Review)



Motzer et al ASCO 2007

Treatment-Related Adverse Events

Event	Sunitinib (%)		IFN-α (%)	
	All grade	Grade 3/4	All grade	Grade 3/4
Fatigue	51	7	51	11/<1*
Diarrhea	53	5*	13	0
Nausea	44	3	33	1
Stomatitis	25	1	2	<1
Hypertension	24	8*	1	<1
Hand-foot syndrome	20	5*	1	0
Ejection fraction decline	10	2	3	1
Pyrexia	7	1	34	0
Chills	6	1	29	0
Myalgia	5	<1	16	<1
Flu-like symptoms	1	0	8	<1

Motzer et al ASCO 2007

Debulking nephrectomy in targeted therapy era: The rational

Renal primary lesion

- Increased serum VEGF
- Increased serum PDGF
- Angiopoietins growth factor
- Down-regulation anti-angiogenetic factors

Rini et al J Urol 2007

Questions

- Is a trial necessary?
- Timing of targeted therapy?

Is a trial necessary?
NO

Table 1 Cytoreductive nephrectomy in molecular targeted therapy trials

References	Agent	Phase	Line	Number of patients	Nephrectomy (%)
[8]	Sunitinib	II	2	106	100
[5•]	Sunitinib	III	1	375	91
[9]	Sorafenib	II	1	97	98
[4•]	Sorafenib	III	2	451	94
[6•]	Temsirolimus ± IFN-α	III	1	419	67
[10]	Bevacizumab ± Tarceva	II	1	104	100
[11]	Bevacizumab	II	2	76	90
[12]	Bevacizumab + IFN-α	III	1	327	100

* Already in clinical practice in many Centers

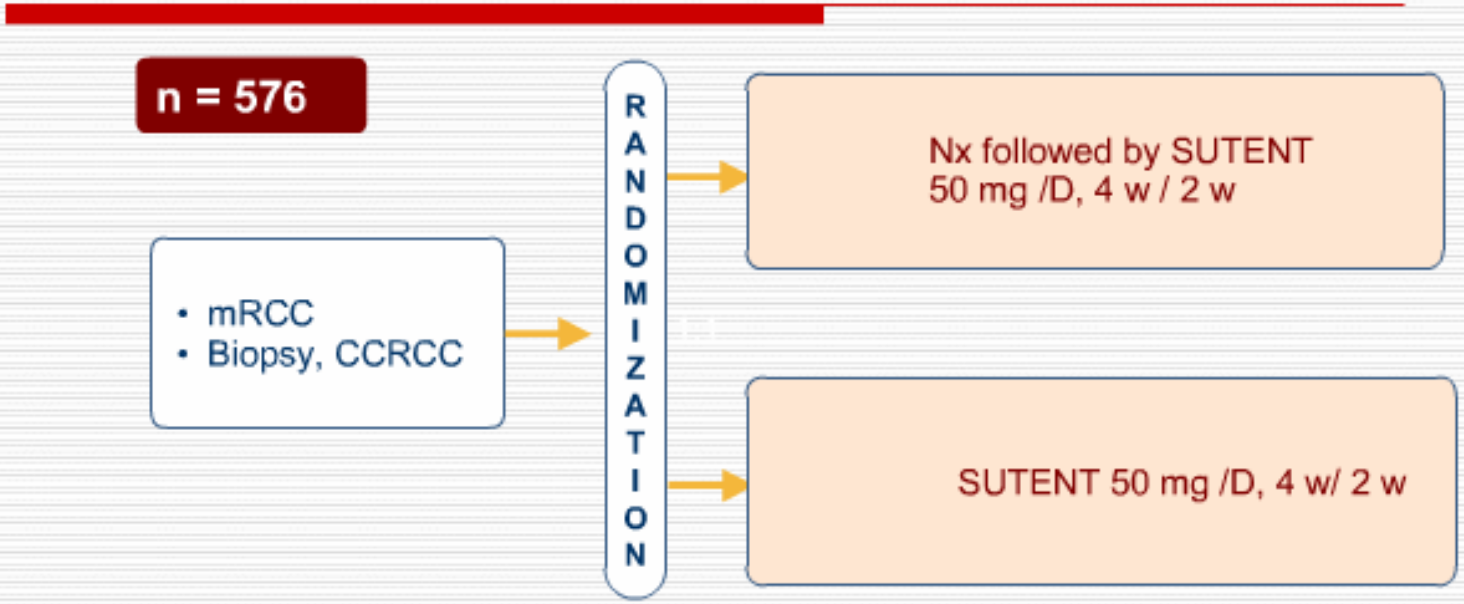
Margulis et al Curr Opin Urol 2008

Retrospective studies

Studies	Median PFS Nephrectomy	Median PFS NO Nephrectomy
Motzer	11 months	6 months
Rosenberg	20 months	10 months

Motzer et al ASCO 2007
Rosenberg et al ASCO 2007

CARMENA TRIAL : RANDOMIZED PHASE III TRIAL COMPARING NEPHRECTOMY FOLLOWED BY SUTENT TO SUTENT ALONE IN PATIENTS WITH METASTATIC RCC



- Role of nephectomy in metastatic setting
- Timing of nephrectomy?

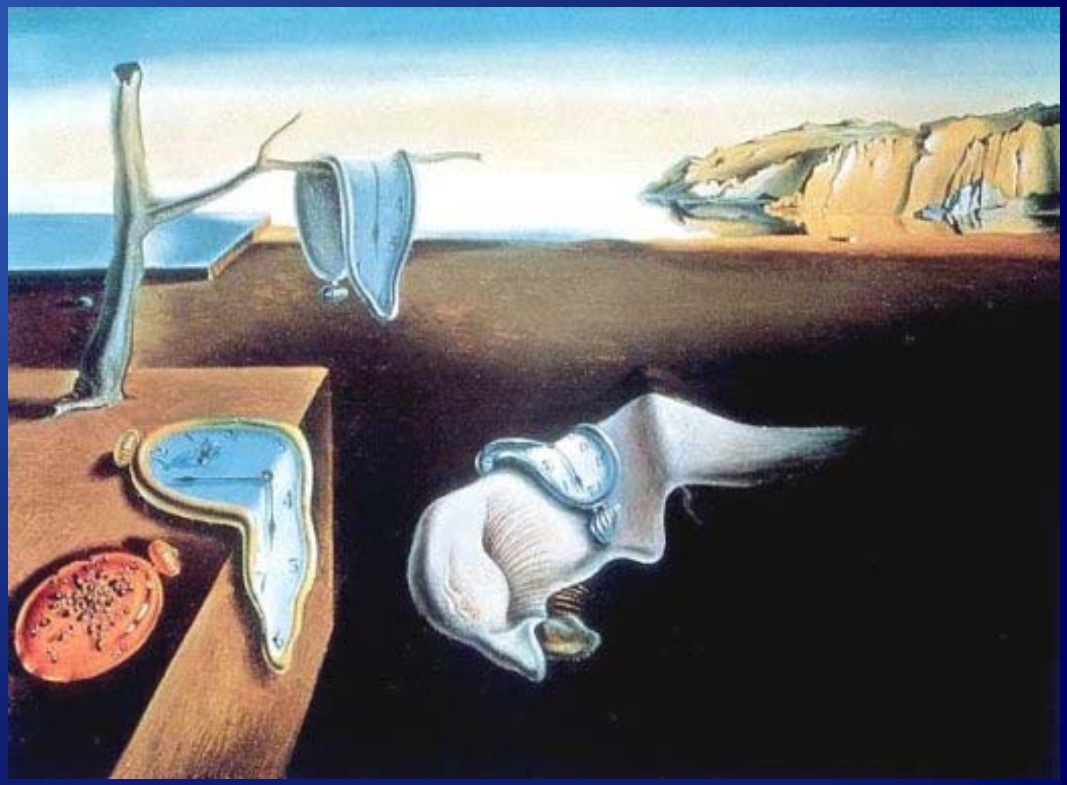
Answers

Questions

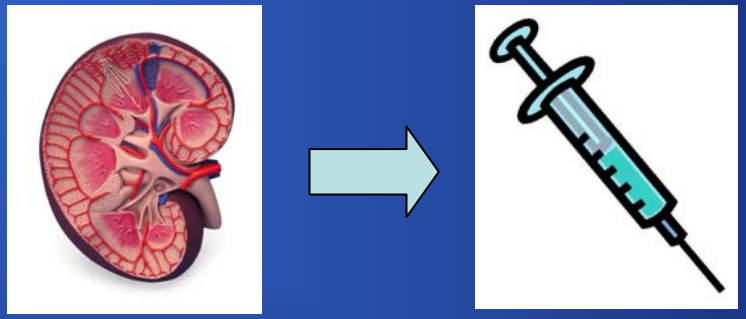
- Is a trial necessary?
- Timing of therapy?

Timing of targeted therapy

- Adjuvant ?
- Neo-adjuvant ?



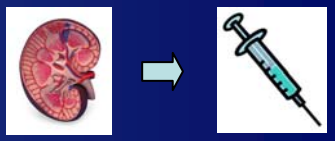
Adjuvant targeted therapy
Advantages



- Tumor burden
- New metastases
- Immunodepression
- Angiogenesis

Rini et al J Urol 2007

Adjuvant targeted therapy
Disadvantages



- Surgery → Systemic therapy

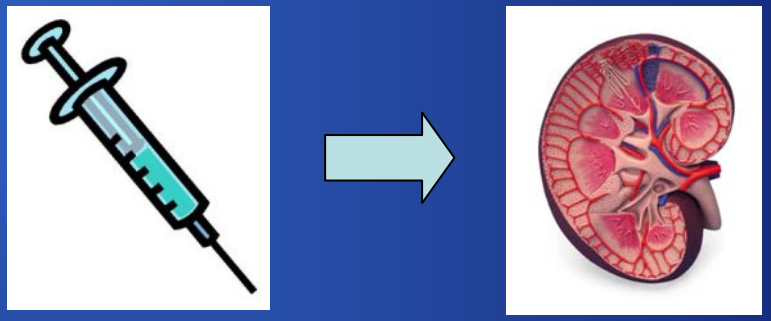
Disease progression

- Surgical morbidity and mortality

SWOG + EORTC: 20-25%
NO ADJUVANT SYSTEMIC THERAPY

Rini et al J Urol 2007

Neo-adjuvant targeted therapy
Advantages

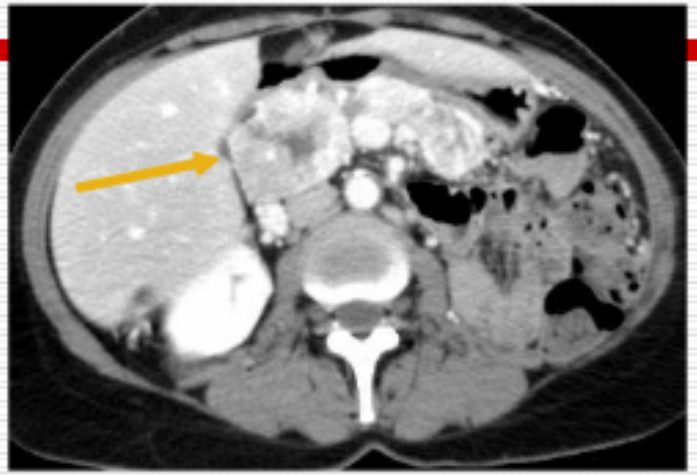


- Litmus test: to select patients who are responding to therapy

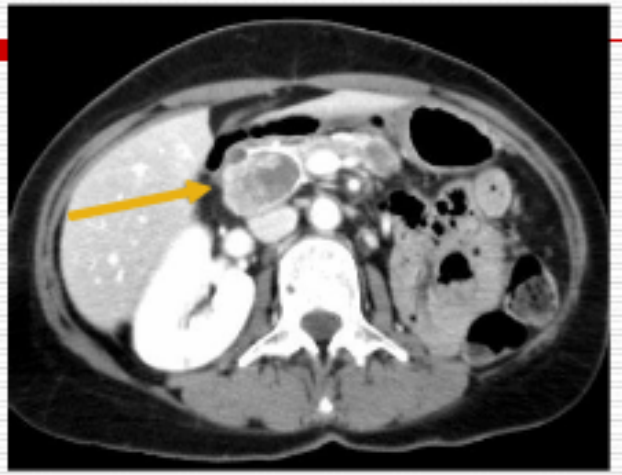
- Down-staging: down-sizing of the tumor that may facilitate surgical extirpation

Margulis et al Eur Urol 2008

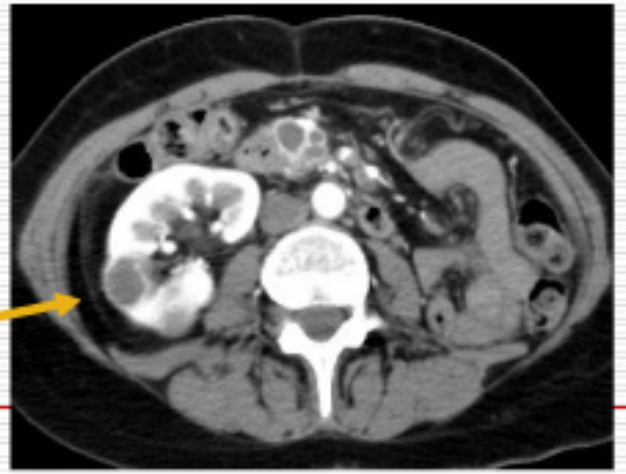
Efficacy of Sorafenib in various metastatic sites



June 21, 2005



October 17, 2005



Neoadjuvant Strategy: Down Staging IVC thrombi

European Association of Urology

Case Study of the Month

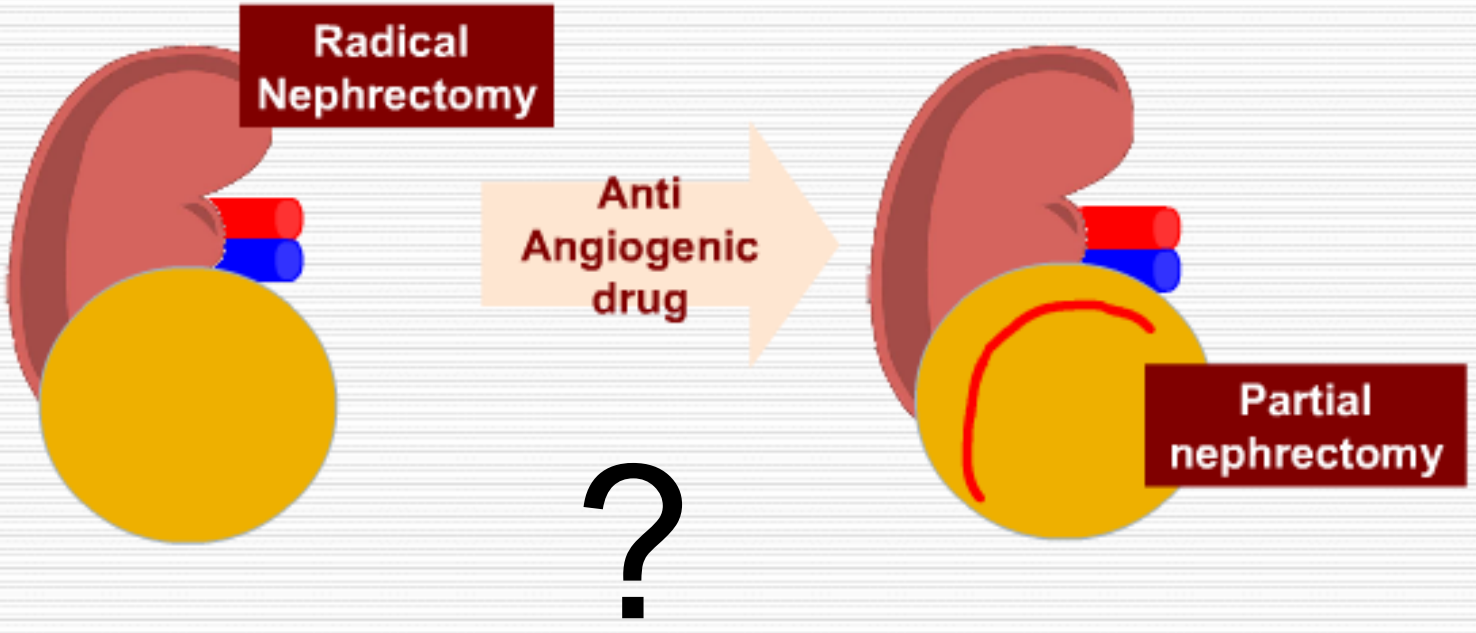
Neoadjuvant Sutent Induction Therapy May Effectively Down-Stage Renal Cell Carcinoma Atrial Thrombi

Pierre I. Karakiewicz [a,*], *Nazareno Suardi* [a], *Claudio Jeldres* [a], *Pascale Audet* [a], *Pierre Ghosn* [a], *Jean-Jacques Patard* [b], *Paul Perrotte* [a]

[a] Cancer Prognostics and Health Outcomes Unit, University of Montreal, Montreal, QC, Canada
[b] Department of Urology, Rennes University Hospital, Rennes, France

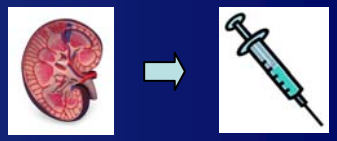
- 75 yrs old women, refusing sternotomy for left renal tumor and intra atrial thrombus
- Surgery by an exclusive abdominal acces was possible after 2 cycles of Sutent

Neoadjuvant strategy: Facilitating imperative nephron-sparing surgery by down-staging large primary tumors



Neo-adjuvant sistemic targeted therapy

Disadvantages



- Perioperative bleeding

- Thromboembolic phenomena

Rini et al J Urol 2007

No difference in:

- Blood loss
- Lenght of hospital stay
- Thromboembolic complications
- Cardiovascular complications

Margulis et al Eur Urol 2008

Ongoing neoadjuvant clinical trials

Principal Investifator	Clinical Stage	Nb pts	Drug	Primary objective
Jonasch E, US	mRCC	50	AVA + E	TTP/toxicity
Jonasch E, US	mRCC	45	SO	RR/toxicity/tolerance
Jonasch E, US	mRCC	50	SU	RR/toxicité/tolerance
Rathmell K, US	Locally Advanced/mRCC	30	SO	Surgical procedure
Rini B, US	Non resectable	50	SU	Surgical procedure
Powles T, UK	mRCC	40	SU	RR
Eisen T, UK	mRCC	50	SU	RR/toxicity/tolerance
Staehler F, Germany	mRCC	50	SU	RR/toxicity/tolerance
Oudard S, Fr	mRCC	100	SU	RR/imaging/trans res

AVA: Avastin ; E: Erlotinib ; SO: Sorafenib ; SU: Sunitinib

Conclusions

- Debulking nephrectomy before systemic immunotherapy improve survival in wisely selected patients
- In the era of targeted therapy, debulking nephrectomy will continue to play an important role (in many Centers already in clinical practice)
- Timing of targeted therapy (adjuvant vs neo-adjuvant) is at the moment a key question to be answered

NO nefrectomia debulking

- Carcinoma sarcomatoide
- Grado 4 Fuhrman
- Recente e considerevole perdita di peso
- Large inferior cava thrombi
- Tumor extension into the psoas muscle

Rendon et al. CUAJ 2007
Wood ASCO 2004

SURVIVAL

- Duration of survival Comparison (Stratified by Study)

	Deaths/ Patients	P Value	Median (Years)	% Alive at 1 Year, CI
Nephr + IFN	141/161	0.002	1.13	51.9% (44.2%, 59.7%)
IFN alone	152/163		0.65	37.1% (29.7%, 44.6%)

- Maximum follow up = 9.3 years

Flanigan et al J Urol 2004

A chi fare terapia?

- Greater than 75% surgical debulking of total tumor burden technically feasible
- No central nervous system, bone or liver metastases
- Adequate pulmonary and cardiac function
- No active infection or significant co-morbid condition
- ECOG performance status 0 or 1
- Predominantly clear cell histology

Fallick et al J Urol 1997

A chi fare terapia?

Table 2 Prognostic factors of oncologic outcome after cytoreductive nephrectomy and systemic therapy

Cytoreductive nephrectomy and cytokine therapy	Cytoreductive nephrectomy and targeted therapy
Patient performance status	Patient performance status
Constitutional symptoms	Number of metastatic sites
Number/sites of metastases	Time from diagnosis to systemic therapy
Percentage of cytoreduction achieved by surgery	Corrected serum calcium
Time from diagnosis to systemic therapy	Serum hemoglobin
Nodal metastases	Serum LDH
Histologic subtype	Serum neutrophil count
Sarcomatoid features	Serum platelet count
Corrected serum calcium	
Serum hemoglobin	
Serum LDH	
Serum neutrophil count	
Serum platelet count	
Serum TSH	
Tumor tissue levels of carbonic anhydrase IX	

LDH, lactate dehydrogenase; TSH, thyroid-stimulating hormone.

Margulis et al Curr Opin Urol 2008

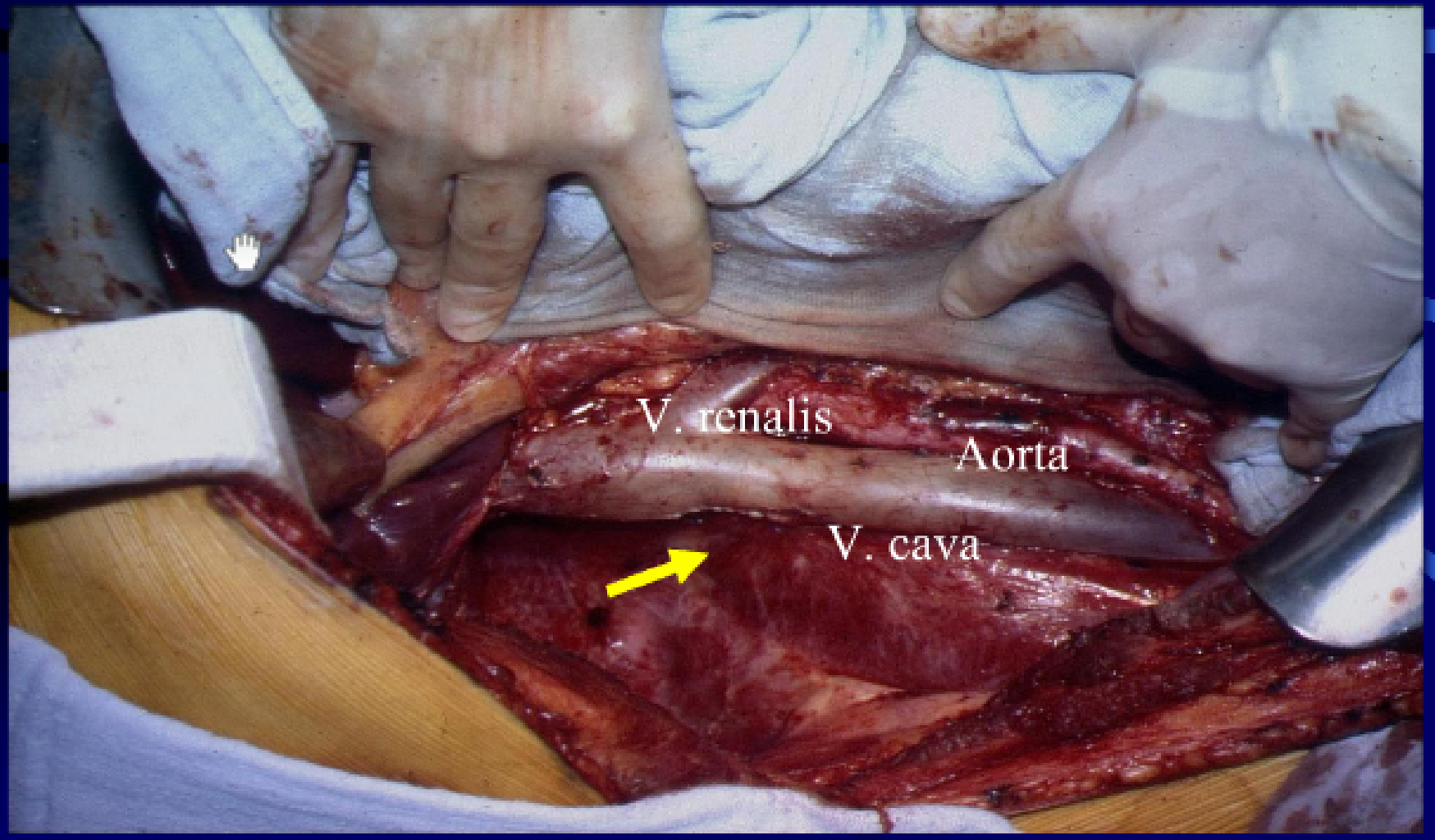
UCLA IL-2

	Immunoterapia	Nx + Immunoterapia
UCLA Median survival	-	16,7
SWOG Median survival	8,1 mo	11,1

Pantuck et al N Eng J Med 2001

Surgical Therapy of RCC

Lymphnode Dissection



Linfadenectomia

- Positive nodes were three to four times more common in patients with metastatic disease and most of these could be identified preoperatively
- Survival of patients with regional lymph node involvement only was identical to that of patients with distant metastatic disease only
- Patients with regional nodes and distant metastases had significantly lower survival than those with either condition alone

Wood Kidney Cancer J Int

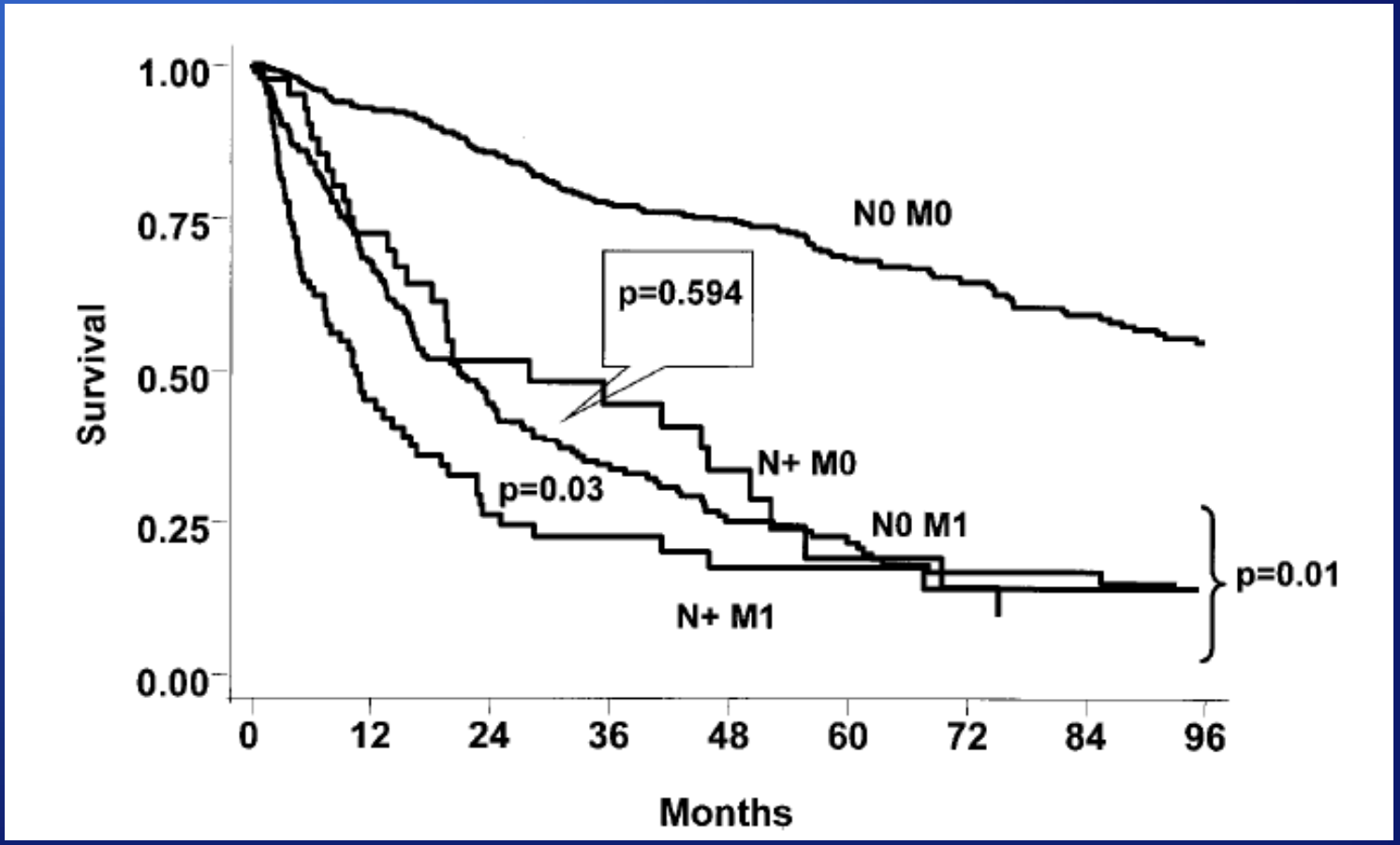
Linfadenectomia

- In node-negative cases lymph node dissection can be performed with no additional morbidity but it confers no survival advantage

- In node-positive cases lymph node dissection can also be performed safely but it is associated with improved survival and a trend toward an improved response to immunotherapy

Wood Kidney Cancer J Int

Linfadenectomia

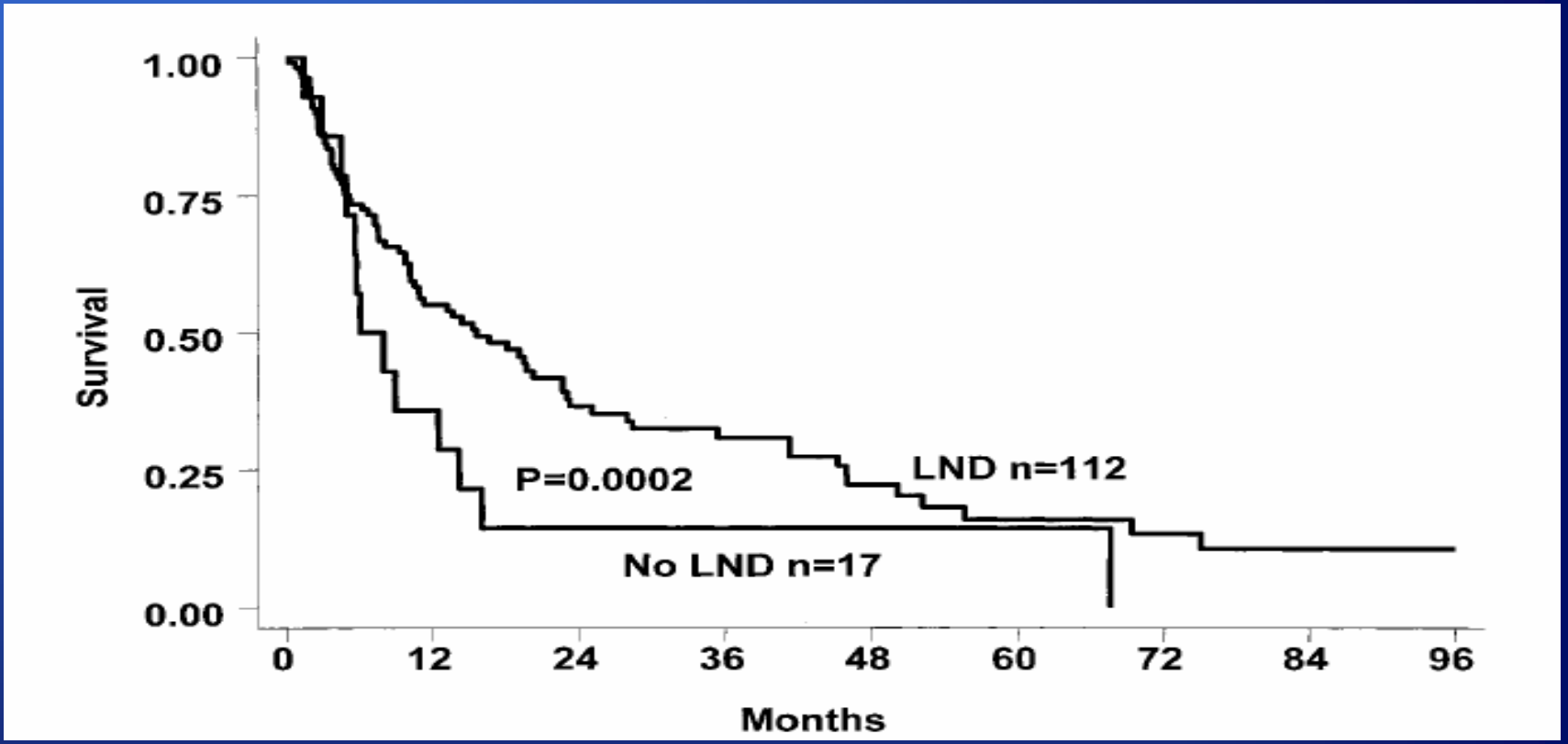


Pantuck et al J Urol 2003

Questioni aperte

- Serve un trial?
- Quando fare la terapia?
- Linfadenectomia?
- Nefrectomia debulking nei pz anziani?
- T4NxM1 ?

Linfadenectomia



When lymph nodes are present,
they should be resected when technically feasible

Pantuck et al J Urol 2003

Serve un Trial?
SI

- Nessun caso di risposta completa alla terapia (tumor in place)
- Razionale della nefrectomia debulking pre targeted therapy non ancora ben definito

Margulis et al Curr Opin Urol 2008

Questioni aperte

- Serve un trial?
- Quando fare la terapia?
- Linfadenectomia?
- Nefrectomia debulking nei pz anziani?
- T4NxM1 ?

Cytoreductive nephrectomy for T4NxM1

- 23 patients T4NxM1
- Median overall survival: 6,8 months
- No perioperative mortality

- Stage T4NxM1 RCC → symptom palliation
- Surviva benefit is unknown

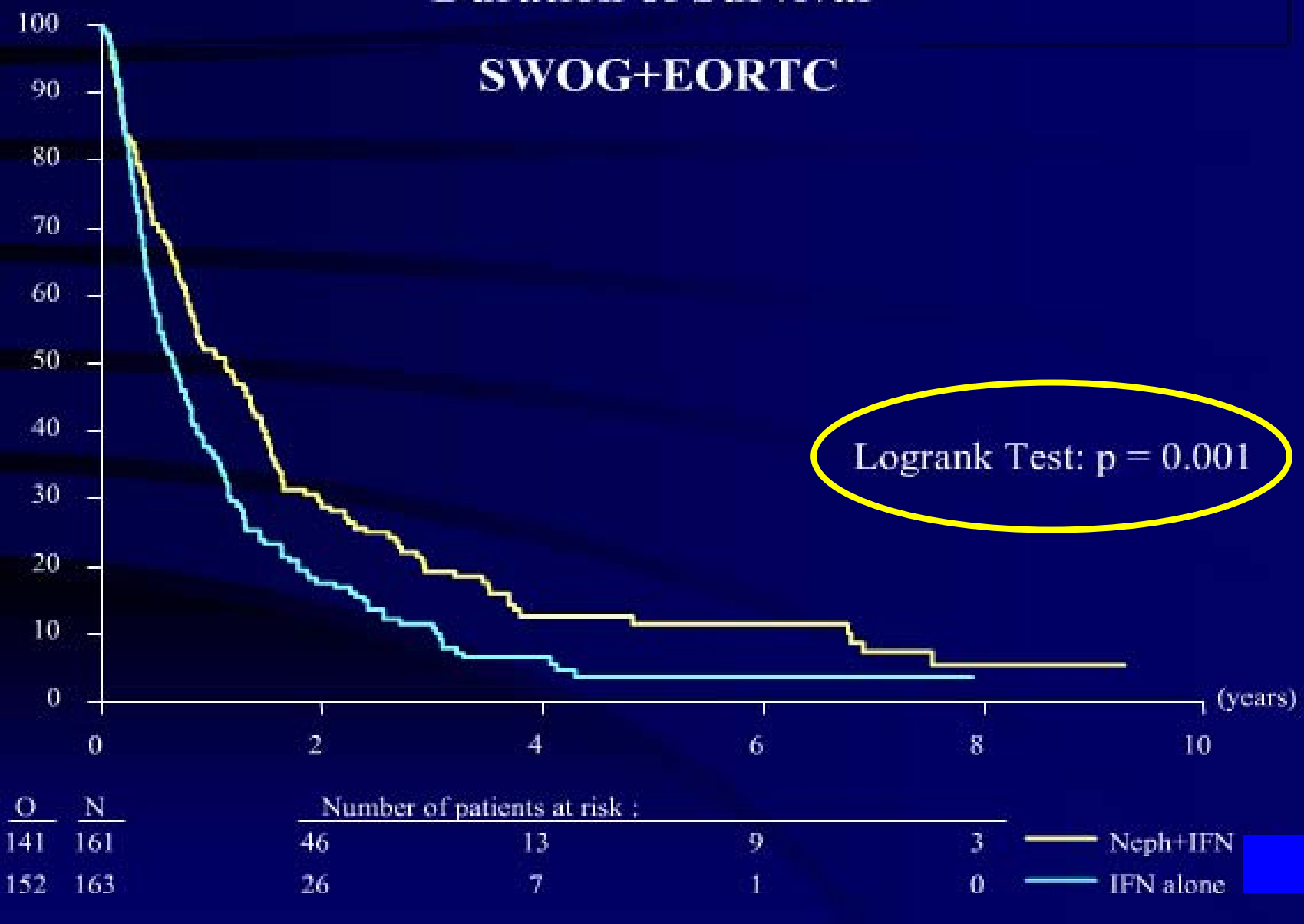
Kassouf et al Urology 2007

Nefrectomia debulking + IL-2 vs IL-2

	1 year survival rate	2 year survival rate
Nefrectomia + IL-2	67%	44%
IL-2	29%	4%

Belldegrun et al Cancer J Sci Am 2000

Flanigan et al J Urol 2004



Targeted therapy
Studi retrospettivi

References	Agent	Phase	Line	Number of patients	Nephrectomy (%)
[8]	Sunitinib	II	2	106	100
[5•]	Sunitinib	III	1	375	91
[9]	Sorafenib	II	1	97	98
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[12]	Bevacizumab + IFN-α	III	1	327	100

Margulis et al Curr Opin Urol 2008

Neoadjuvant strategy: down staging massive nodal invasion not amenable to initial excision