

Renal Cell Cancer

Is lymph node dissection
necessary?

EORTC GU GROUP PROTOCOL 30881

772 pts were randomized

Randomization between:

Radical nephrectomy without LND: 389 patients

Radical nephrectomy with complete LND: 383
patients

EORTC GU GROUP PROTOCOL 30881

Complication rate did not differ
between the two groups

Incidence of unsuspected lymph node
metastases was low, 3.3%

Conclusions 1

With modern imaging the incidence of unsuspected metastases is low

In locally confined tumors lymph node dissection seems to have no therapeutic benefit

New targets for the treatment of renal cell cancer or immunotherapy

- Peter Mulders
- Professor and chairman Department of Urology
- Radboud University Medical Centre
- Nijmegen, The Netherlands

MRC RE04/EORTC n°30012

A randomised controlled trial of

IL-2, IFN- α , 5FU

vs

IFN- α alone

in patients with advanced renal cell carcinoma

Coordinator: M. Gore / P. Mulders

Inclusion criteria:

ECOG 0 and 1

- Progressive disease

- 1100 patients have been included

Conclusions

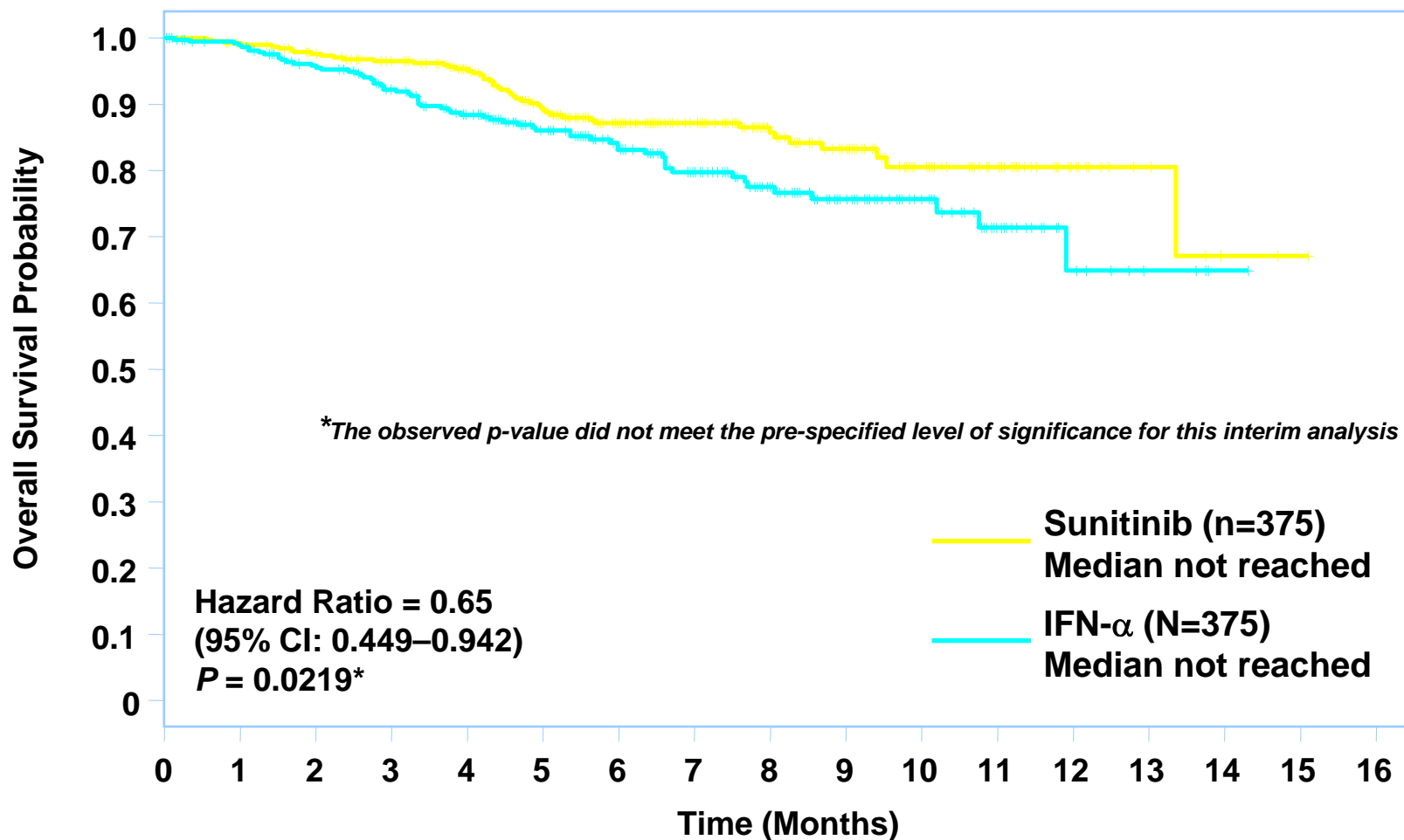
- Treatment of MRCC Prognostic factors should be regarded
- Only clearcell type histology show responders
- Take notice of the natural history of the disease
- IFN- α monotherapy gives a small but significant survival advantage
- High dose bolus IL-2 can give cure, especially in high CAIX expressing tumors
- There is no proven role for combination therapy
 - Results 30012 awaited 2007

BUT

Is there still a place for immunotherapy in the era of targeted therapies?

What is the exact place of these small molecules in the era of immunotherapy?

Overall Survival



No. at Risk Sunitinib:	341	190	84	15	1
No. at Risk IFN-α:	296	162	66	10	0

Conclusions

- Targeted therapies are an exciting development for patients with mRCC.
- Treatment plan for RCC at this moment can be:

	First-line	Second-line
● Good prognosis	<i>Sutent</i>	<i>Sutent/Nexavar</i>
● Intermediate prognosis	<i>Sutent</i>	<i>Sutent/Nexavar</i>
● Poor prognosis	<i>Temsirolimus</i>	

But

- No cure is achieved with targeted agents
- Cytokines can have benefit in a small cohort of patients
- Be aware of the biological behaviour of the tumour
- Timing of initiation is crucial.
- Combinations are feasible and do give encouraging results but should be proven valid in a randomized study.

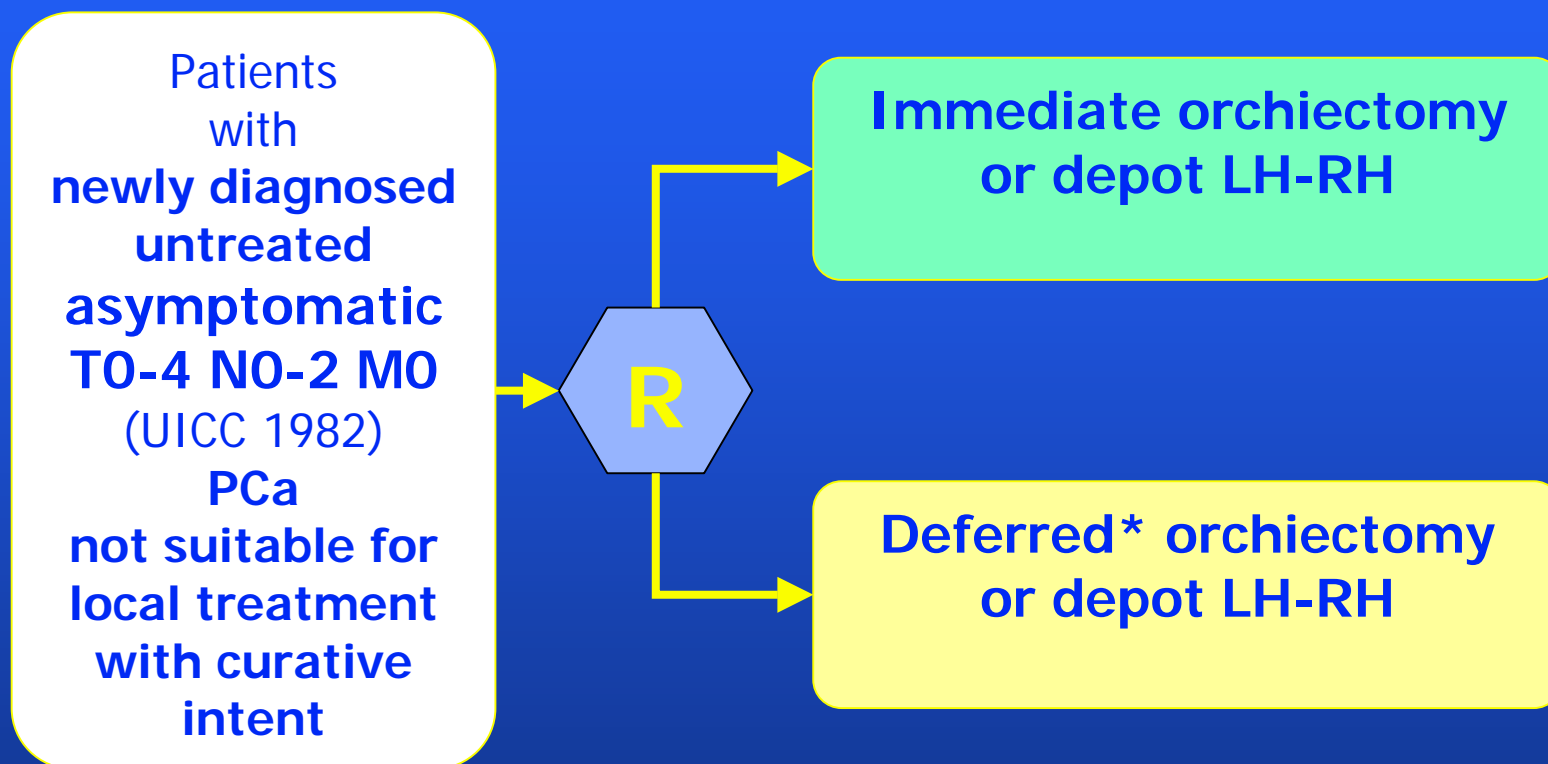
Unaddressed questions

- Can we stop ?
- Is there a rebound phenomenon?
- Are they effective in high risk patients?
- What is the effect on the primary tumor?
- Sequential use?
- etc

Locally advanced disease in older patients: in which patients is immediate hormonal treatment necessary

Laurence Collette, Urs Studer

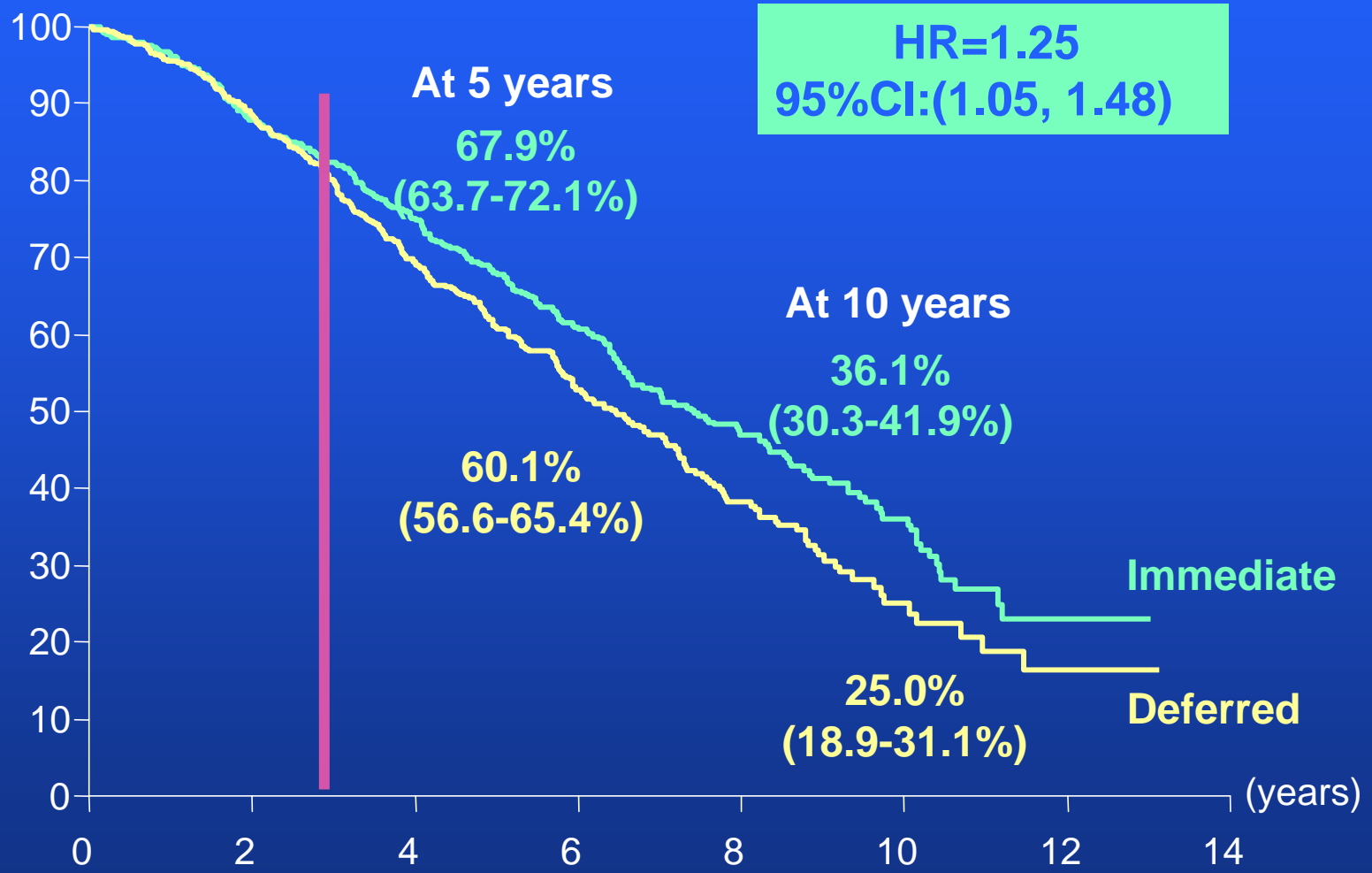
EORTC trial 30891 Trial Design



* **Start** at the time of symptomatic progression, ureteric obstruction, life threatening metastasis or PS decrease > 1 score. **Not for only** rise in PSA, new hot spots or asymptomatic mets.

EORTC 30891

Overall survival (ITT)



O	N	Number of patients at risk :							
257	492	428	349	221	112	48	2		
284	493	432	327	186	82	20	4		

Yes, there is a difference in survival

... but the benefit is not so huge

**Many patients may never suffer from symptoms
of the disease**

These patients may not need to be treated..

Can we identify them early after diagnosis?

**→ Likely those patients in risk of (HRPC)
disease progression or death due to PCa**

Those who clearly benefit:

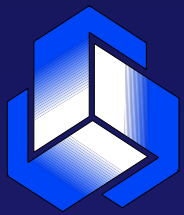
- Patients with baseline PSA > 50 ng/ml
- Patients aged ≤ 70 with baseline PSA > 20 ng/ml

Those who benefit less:

- Patients aged > 70 baseline PSA ≤ 70 ng/ml
- Patients aged ≤ 70 with baseline PSA ≤ 70 ng/ml

**Based on the findings from EORTC Trial 30891,
the following patients seem to benefit from
immediate androgen deprivation:**

- **Those who are likely to die from Prostate Cancer in the next 3 to 5 years.**
- **Those with a serum PSA > 50 ng/ml (the threshold may need to be lowered for younger patients)**
- **Those with a serum PSA > 8 ng/ml, if the serum PSA doubling time is < 12 months**



Non-muscle invasive bladder cancer: when, what and how long to give adjuvant therapy



Prof Fred Witjes
Nijmegen, the Netherlands

ESOU/EORTC meeting
EAU, March 21, 8.30-12.30



When??

That depends on risk classification



Potential prognosticators to predict behaviour

- Molecular markers
- Histo-pathology:
 - The EORTC risk tables



Practical conclusion markers in 2007

- Many molecular markers are studied
- Many seem promising in initial reports
- However, clinical implication of molecular markers remains very limited and difficult



Potential prognosticators to predict behaviour

- Molecular markers
- Histo-pathology:
 - The EORTC risk tables





EORTC Risk Tables for Stage Ta T1 Bladder Cancer

Prior Recurrence Rate

- Primary
- Recurrent <= 1 per year
- Recurrent > 1 per year

Number of Tumors

- 1
- 2 to 7
- 8 or more

Tumor Diameter

- < 3 cm
- >= 3 cm

T Category

- Ta
- T1

Grade (WHO 1973)

- G1
- G2
- G3

Concomitant CIS

- No
- Yes

Calculate Probabilities

Clear

Exit

	1 Year	2 Years	3 Years	4 Years	5 Years
Probability of Recurrence	0.38	0.51	0.56	0.59	0.62
Probability of Progression	0.01	0.03	0.04	0.05	0.06

Reference: Sylvester RJ, van der Meijden APM, Oosterlinck W, Witjes JA, Bouffieux C, Denis L, Newling DWW, Kurth KH. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from 7 EORTC trials. *European Urology* 49: 466-477, 2006.

Programmed by Richard Sylvester, EORTC Data Center, 83 avenue Mounier, 1200 Brussels, Belgium.

Version 1.0, January 2006

Small Multiple Recurrent Ta G1 Tumours

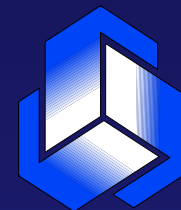
What?

Risk adapted therapy



Low risk:
one immediate instillation
indeed is standard





A meta-analysis of randomized trials investigating TUR with or without one immediate instillation of chemotherapy

Richard J. Sylvester, ScD

Willem Oosterlinck, MD, PhD

Adrian P.M. van der Meijden, MD, PhD

(J Urol June 2004)



Intermediate risk patients

- A course of intravesical MMC or epi (e.g. 4 times weekly followed by 5 times monthly)
- *Advantage:* <10% long term reduction in recurrence rate
- *Disadvantage:*
 - some side effects
 - Are these <10% worth the costs and effort?



High risk tumours

- High risk superficial tumours are:
 - any T1
 - any grade 3
 - any CIS

 - any multifocal
 - any highly recurrent



Intravesical *chemotherapy* and high risk superficial disease

- *no effect on progression!*



What about BCG and *progression* in high risk superficial disease

- 24 trial meta-analysis, 4863 patients, median follow up of 2.5 years
- Progression 9.8% in BCG group versus 13.8% in non BCG group (OR 0.73, $p=0.001$)
- Difference when only maintenance trials were used even larger: OR 0.63, $p=0.00004$

(Sylvester et al, J Urol 2002;168:1964-70)



However

- Relative short follow up, resulting in
- Low number of patients with progression:
 - 6.4% in papillary tumours and 13.9% in CIS
- Several small trials included
- No difference in tumour related survival



Take home messages (1)

Diagnosis / risk assessment

- Molecular markers remain largely experimental
- Know your patient and the tumour well
- Use nomograms or tables (EORTC tables) to inform your patient and chose therapy



Take home messages (2)

Therapy

- In low and intermediate risk one immediate instillation is effective and safe
- In intermediate risk patients use an additional course of chemotherapy
- In high risk patients use (maintenance) BCG



Take home messages (3)

High risk and BCG failures

- Progression is the problem and the window is small
- Standard therapy in BCG failures is cysto-prostatectomy
- Conservative possibilities for BCG failures are
 - BCG/IFN α
 - intravesical hyperthermia with chemotherapy





When to give neoadjuvant or adjuvant chemotherapy in muscle invasive bladder cancer?

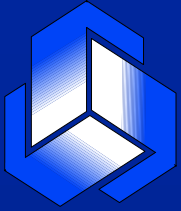
Cora N. Sternberg, MD, FACP

Chair, Department of Medical Oncology

San Camillo Forlanini Hospital

Rome, Italy

Neo-Adjuvant Chemotherapy



EORTC/MRC

Design (n=976)

TCC <7cm, T2 (G3), T3, T4a, N0, NX, M0

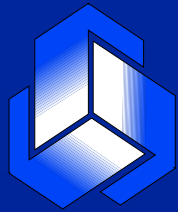
Randomize

3 cycles CMV

No CMV

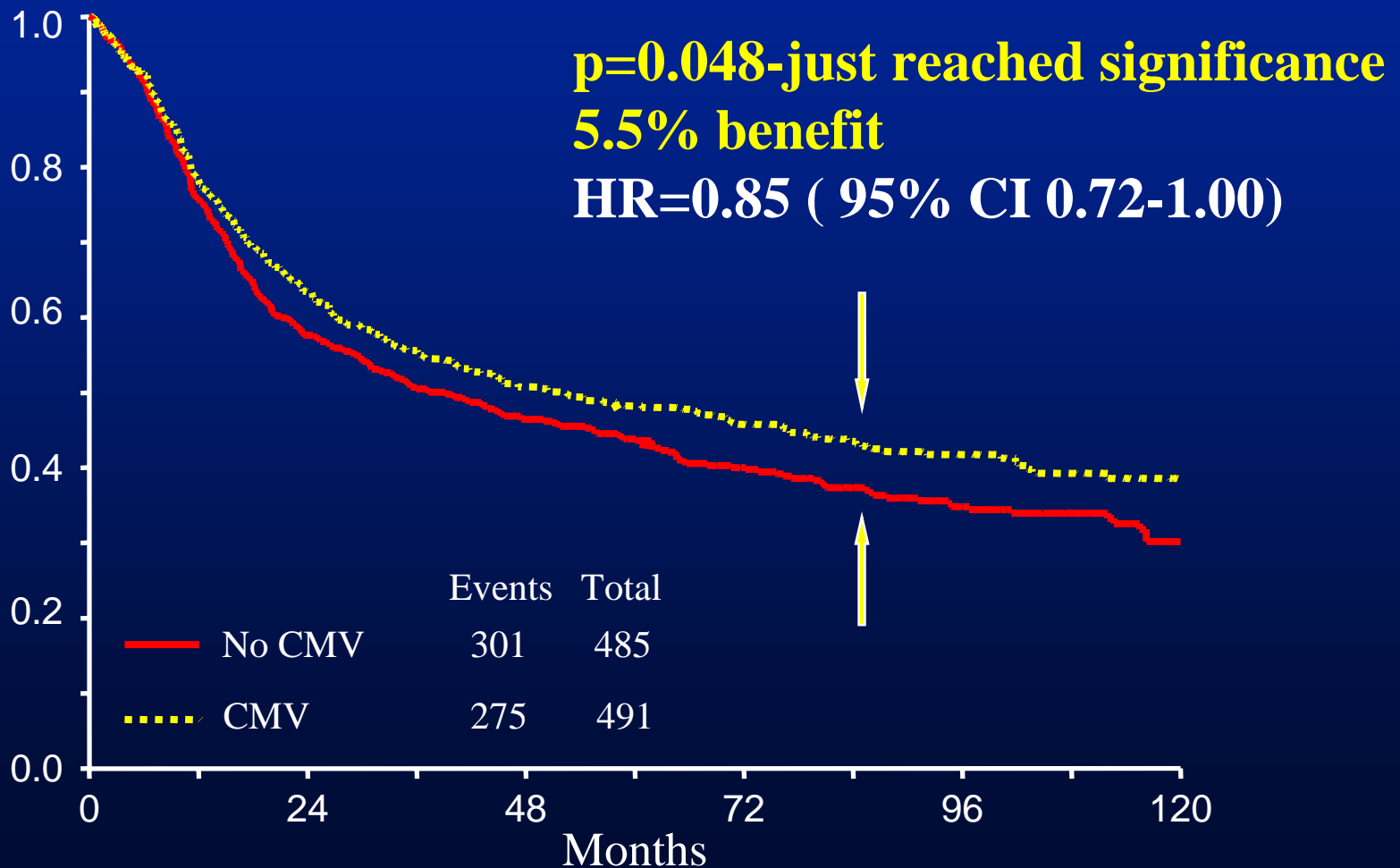
Cystectomy or RT

Cystectomy or RT



EORTC/MRC Overall Survival

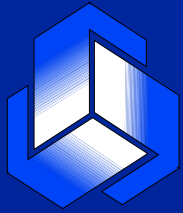
7.4 years follow-up (n=976)



Adjuvant Chemotherapy

Advantages of Adjuvant Chemotherapy

- Cystectomy is immediate
- Therapy is based on pathologic criteria
- Micrometastases are treated when at a low volume
- Orthotopic bladder substitution makes early cystectomy attractive



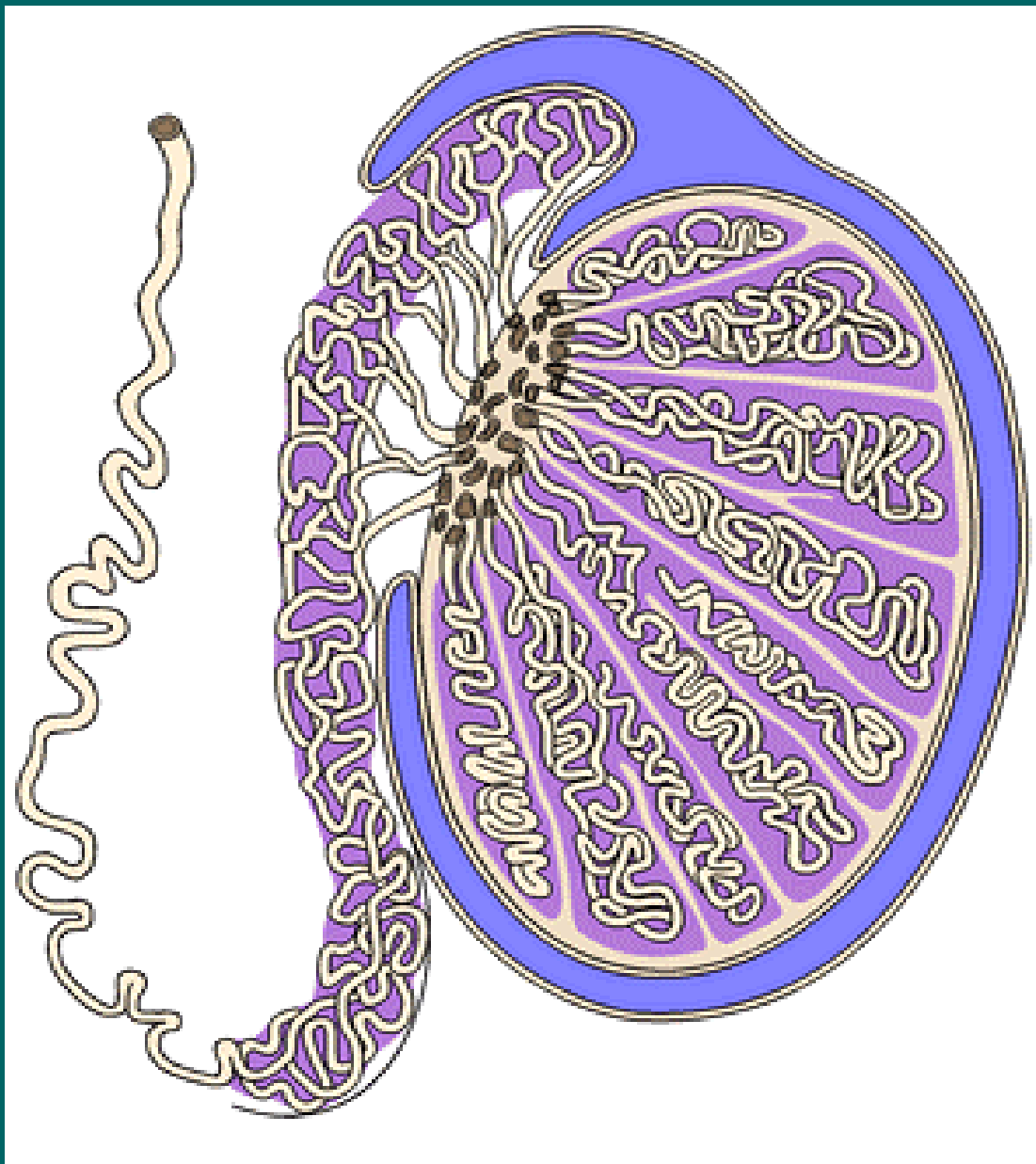
Randomized phase III trial comparing
immediate versus deferred
chemotherapy after radical cystectomy in
patients with pT3-pT4 and/or N+, M0
TCC of the bladder

Study Coordinator: Cora Sternberg (Oncology)

Study Co-coordinators: Pieter De Mulder
(Oncology), Karl Heinz Kurth (Urology),
Christer Busch (Pathology), Richard Sylvester
(Biostatistician)

EORTC Protocol 30994

TESTICULAR CANCER



Stage I seminoma

Gedske
Daugaard

Department of
Oncology,
Rigshospitalet

Denmark

Treatment modalities

Radiotherapy

Adjuvant chemotherapy

Surveillance only

Trial schema

Stage I seminoma, post-orchidectomy

Randomise
(ratio 3C: 5RT)

Carboplatin

Radiotherapy*

* including optional dose randomisation
20 Gy vs 30 Gy pending TE18 results

Non-inferiority trial powered to exclude absolute increase
in 2 year relapse rate of $>3\%$; ~1200 pts required
(90% power, 5% signif. level (1-sided))

Conclusions

With a median follow-up of 4 years, results indicate:

- 20 Gy associated with quicker recovery from lethargy and return to work than 30 Gy (both groups similar by 3 months)
- 20 Gy unlikely (probability < 5%) to increase relapse rates by more than 1-2% at 3 years

	Number of cases	Follow-up (months)	Relapses (crude relapse rate)	Second primary germ-cell tumours	Germ-cell tumour deaths	Non-germ-cell tumour deaths†
Two courses of carboplatin						
Oliver et al ¹⁴	57	128	2	0	0	2/0
Reiter et al ²³	107	74	0	n/a	0	1/5
Steiner et al ²⁴	108	60	2	n/a	0	0
Aparicio et al ²⁵	60	55	0	0	0	1/3
Aparicio et al ^{26*}	204	100	0	0	0	n/a
Krege et al ²⁷	47	100	0	0	0	1/0
Dieckmann et al ²¹	100	100	0	0	0	n/a
Total	683	617	4	0	0	4(0.6%)/8 (2.1%)
One course of carboplatin (doses 400 mg/m² × 7)						
Dieckmann et al ²¹ (400 mg/m ² × 7)	100	100	0	0	0	0
Present study (AUC×7)	100	100	0	0	0	0
Oliver et al ¹⁴ (AUC×7)	100	100	0	0	0	0
Total	300	300	0	0	0	0

n/a=not available. *High-n

Table 3: Overview of sta

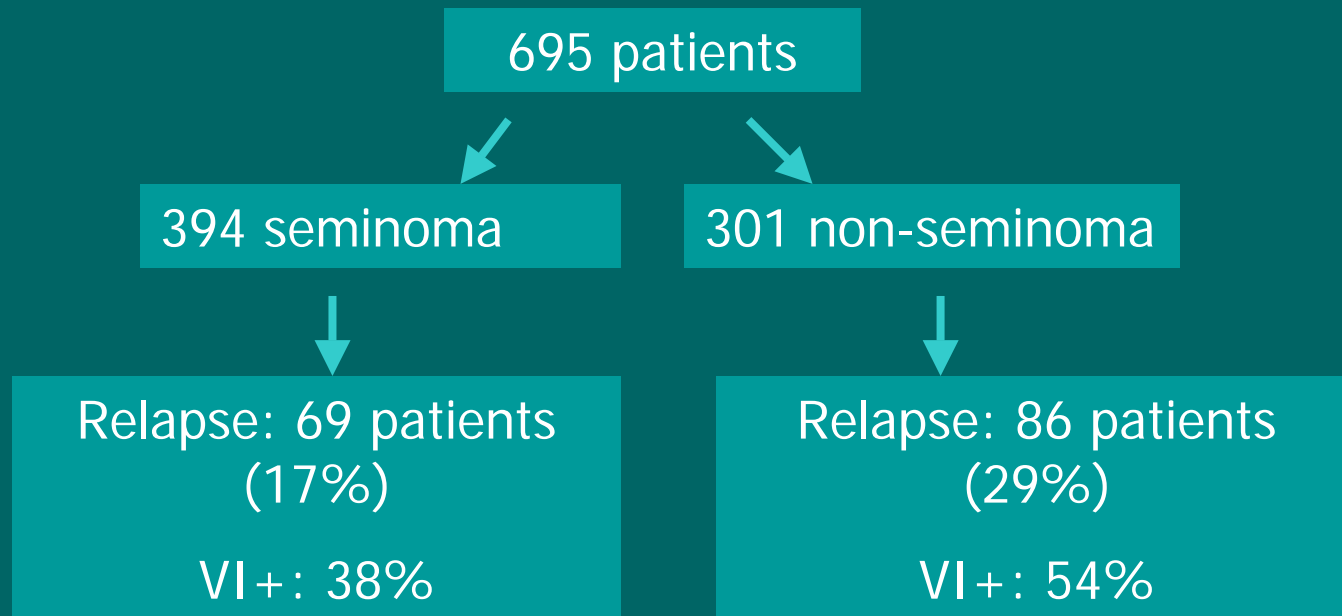
Carboplatin should only be given in clinical trials

Observation period not long enough

No known information about late relapses

Carboplatin still experimental

Results - surveillance



Median follow-up time 60 months (range 1 to 226 months)

Conclusion

The surveillance strategy gives optimal treatment results

Visualization of the retroperitoneal area is of key importance

Biopsy from the contralateral testis should be performed routinely

Surveillance cures the patient at the lowest possible risk