



# Radiothérapie des cancers rectaux : Past, Present & Futur !

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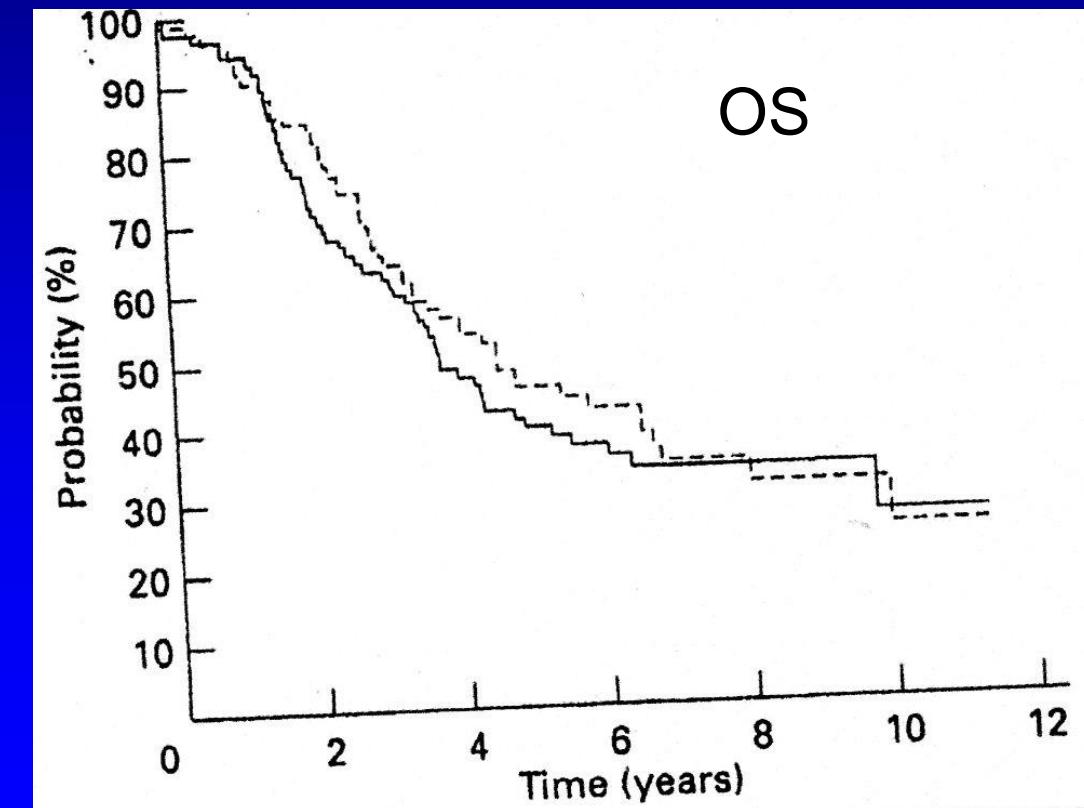
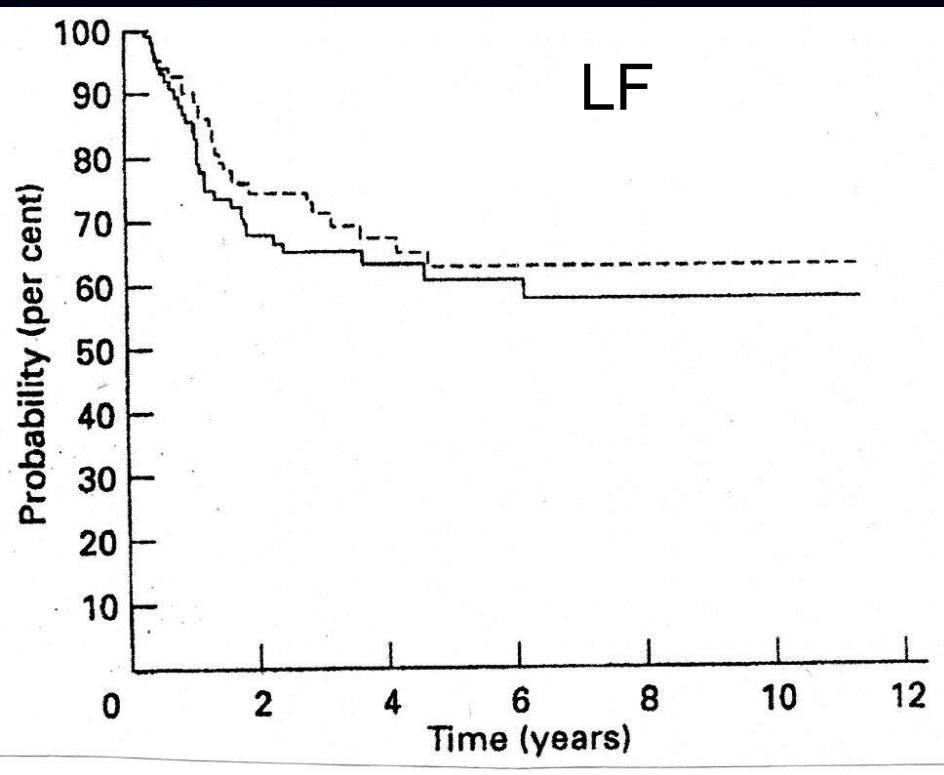
# 1980s = 5 year patterns of failure % Conventional surgery

➤ LR = 27

➤ DM = 29

From

- Galandiuk S, et al. Surg Gynecol Obstet 1992;174:27-32
  - Faivre J. Ann Chir 1994, 6, 520-524
- Swedish Rectal Cancer Trial. N Engl J Med 1997, 336, 980-987





# Postop XRT-CT and local control

	Scheme	Fup (y)	LF %	
			S	XRT-CT
GITSG	40 - 48 Gy	7	24	11
71 - 75	+ 5 FU-MECCNU			
Norway	46 Gy + 5 FU	> 4	30	12

> two fold LF reduction



# Acute toxicity and compliance in postoperative combined studies

	GITS1	NCCTG	GITS2	Intergroup	Bolus	PVI
<u>% grade 3 +</u>						
Haematol	26	33	33 } 50	11	2	
Diarrhoea	35	41	41 } 50	14	24	
<u>% treatment stopped</u>	35	35	14	2	3	
<u>% toxic death</u>	4	2	1	< 0.5		



# Alterations of bowel function after post-op XRT-CT

	Surgery	Post-op XRT-CT	
night movements	14	46	
incontinence	0	17	
wear a pad	10	41	
use Lomotil®	5	58	p<.001
unable to differentiate stools from gas	15	39	
unable to defer defecation	19	78	

*adapted from Kollmorgen, Ann Surg, 1994, 5, 676-682*



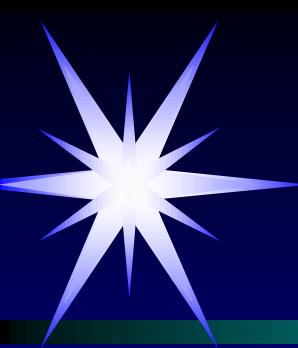
# US NIH statement 1990

- Postop XRT + 5-FU based CT  
standard treatment for stages II-III



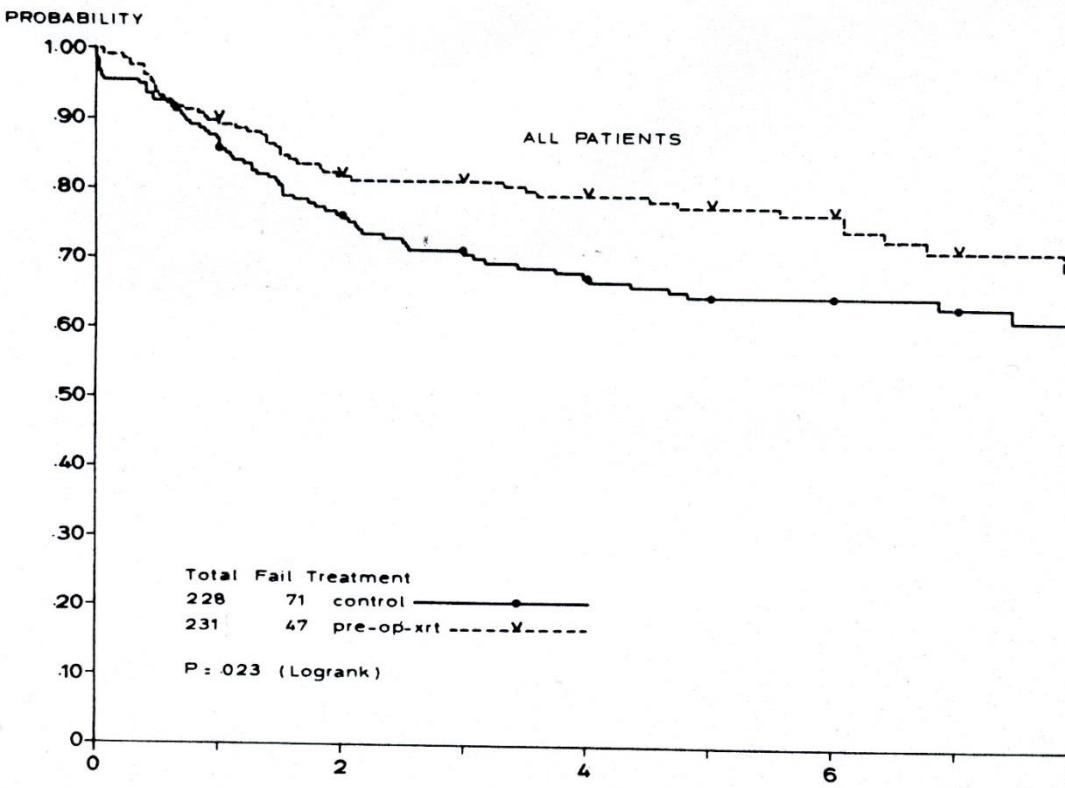
# Pre-op moderate dose XRT (15 Gy - 3 F to 40 Gy - 20 F)

	Nb	↓ LF	↗ Survival
Vasag II	361	NA	No
Norway	309	No	No
ICRF	468	No	No
Stockholm 1	849	< 0.01	No
EORTC	466	0.003	No
Manchester	284	0.0001	0.03
Stockholm 2	557	< 0.01	0.01
Swedish RCT	1168	< 0.001	0.004
MRC	279	0.02	No



# Main differences between short/conventional

	Short	Conventional
Dose/fraction	5	1.8-2
Total dose	25	40-50
Duration W	1	5
OTT W	$\leq 2$	$\geq 7$
Down staging	no	yes
Late effects	expected	?

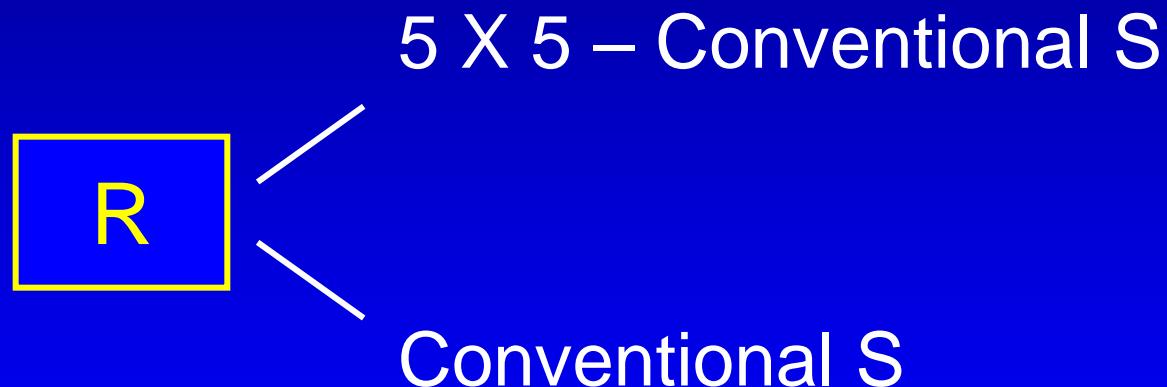


LF



# Swedish Rectal Cancer Trial

1168 pts ( $\approx$  30 % stage I)



LR % : 11 vs 27

OS % : 58 vs 48



# Functional results 5 years after treatment from SRCT

- bowel function < 0.01
- incontinence < 0.01
- urgency < 0.01
- emptying difficulties < 0.5
- impairment of social life < 0.1

Adapted from Dahlberg et al. Dis Colon Rectum 1998;41:543-549



# Early 90s : status and questions

## Status

Preop RT (Europe)

Postop CRT (US)

TME

## Questions

CT

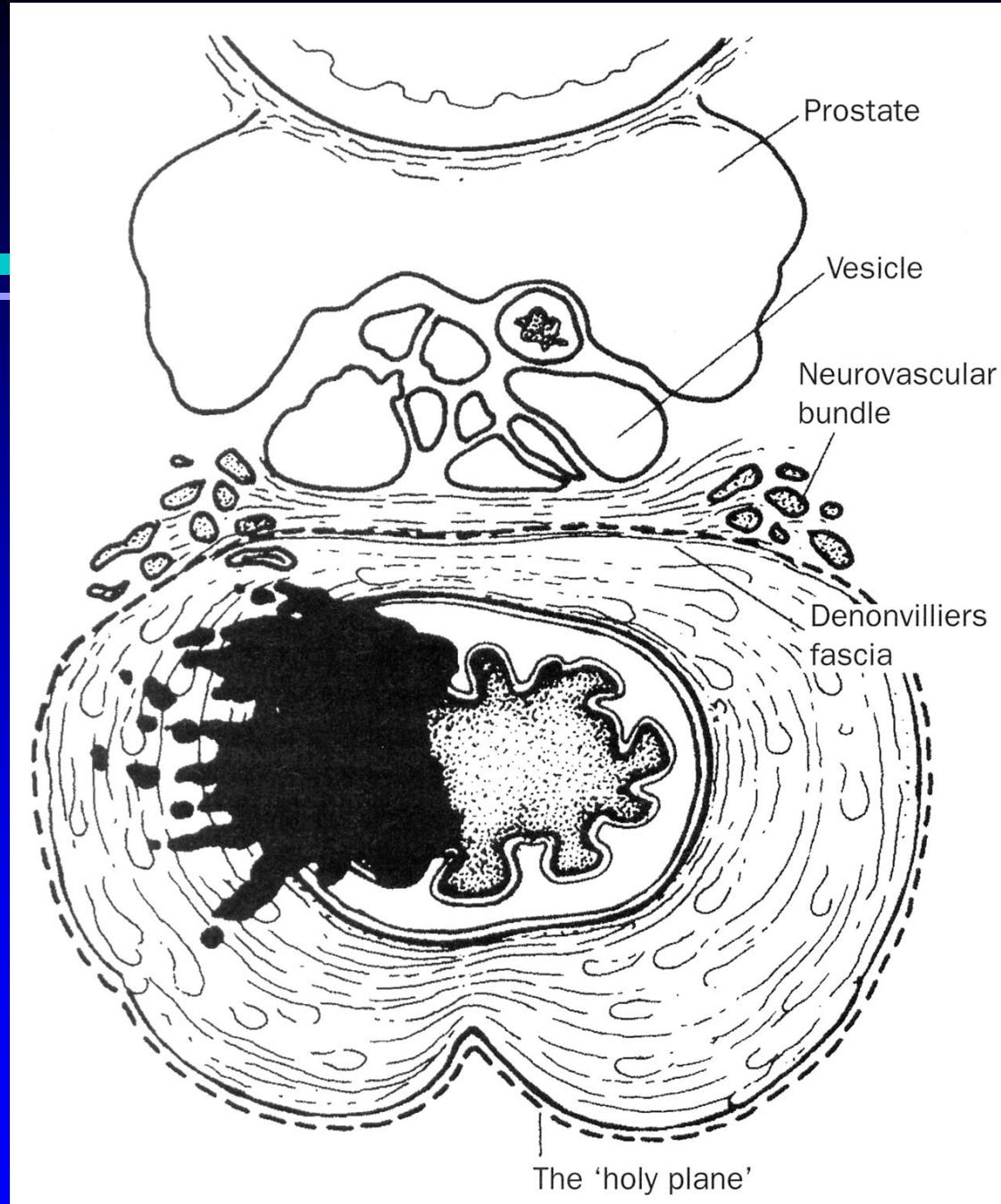
Pre vs postop CRT

Preop RT

# Definition

Tumour invasion  
outside the rectal wall

→ High risk of LF





# Implémentation TME

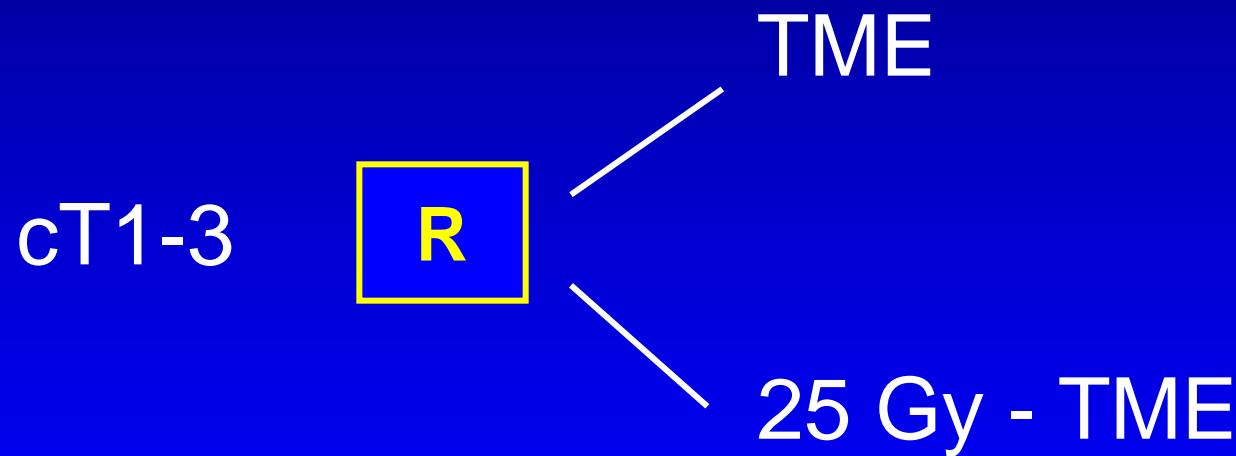
	Stockholm I (n=686)	Stockholm II (n=481)	TME project (n=381)	p*
➤ Local recurrence	103 (15 %)	66 (14 %)	21 (6 %)	<0.0001
➤ Distant metastases	107 (16%)	87 (18 %)	54 (14 %)	0.26
➤ Death from rectal K	104 (15 %)	77 (16 %)	35 (9 %)	0.002
➤ Death from	74 (11 %)	26 (5 %)	45 (12 %)	0.06
Intercurrent disease				

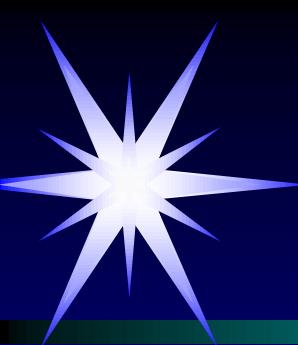
\*For Stockholm I and II vs TME project

From Lehander Martling A, et al. 2000;356: 93-96



# TME ± preop radiotherapy. Dutch trial 95.04





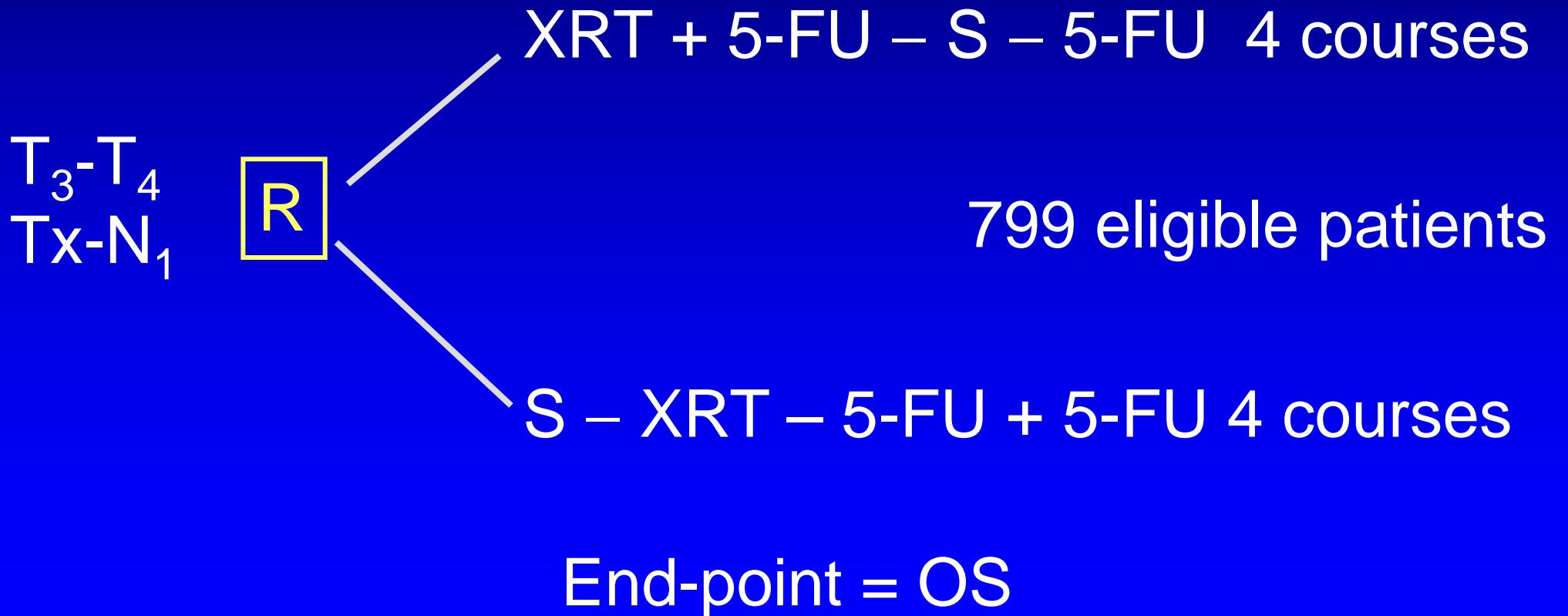
# Dutch trial. 5 y main results

End-point	%	p.	
	RT	S	
OS	64.2	63.5	0.87
LF	5.6	10.9	< 0.001
0-5 cm	10.7	12	0.57
5-10	3.7	13.7	< 0.001
>10	3.7	6.2	0.12
CRM+	19.7	23.5	0.39
CRM-	3.4	8.7	< 0.001



# The German Trial

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# G 3/4 toxic effects %

	Preop	Postop	p.value
Acute			
diarrhea	12	18	0.04
any	27	40	0.001
Late			
diarrhea	9	15	0.07
strictures	4	12	0.003



## 5-year results %

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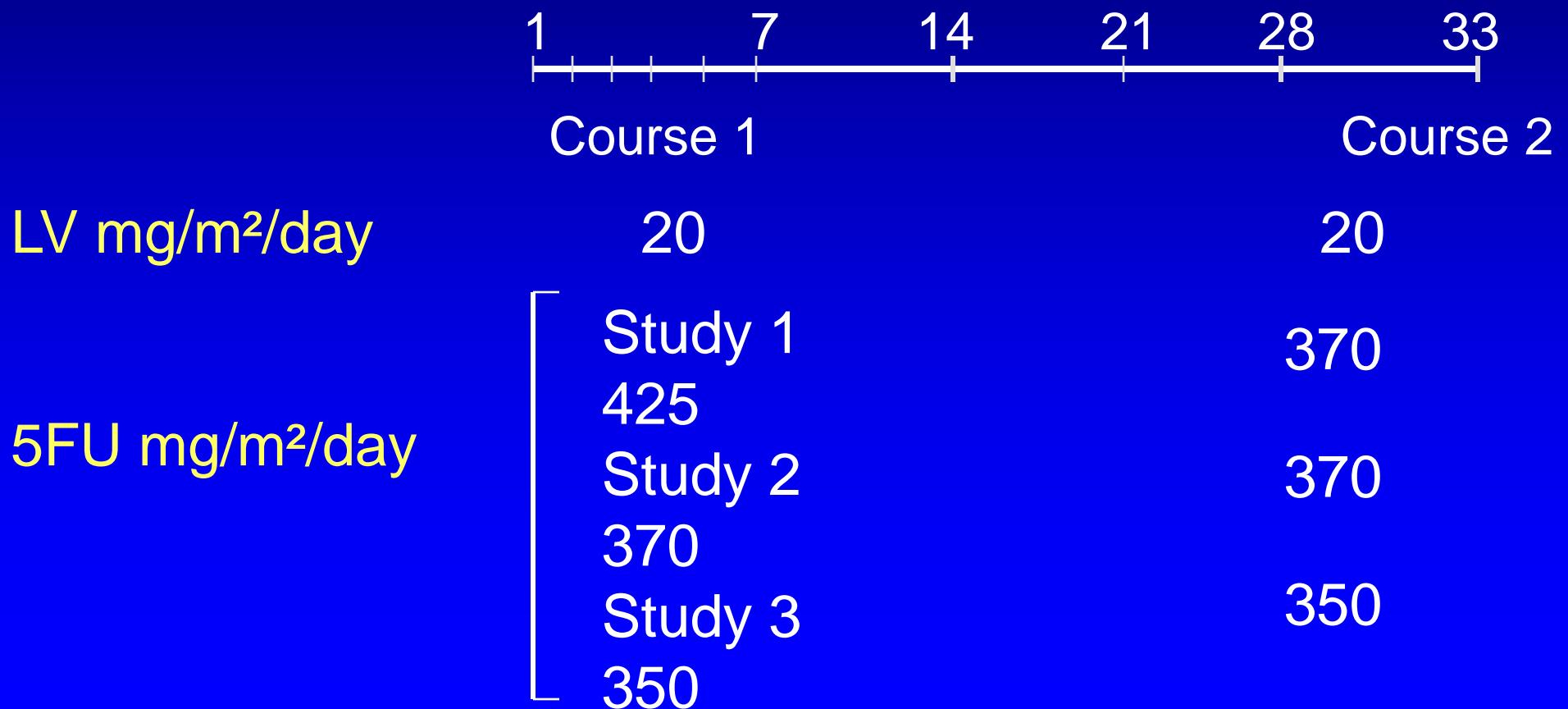
	OS	LF	DM
Preop	76	6	36
	0.8	0.006	0.8
Postop	74	13	36



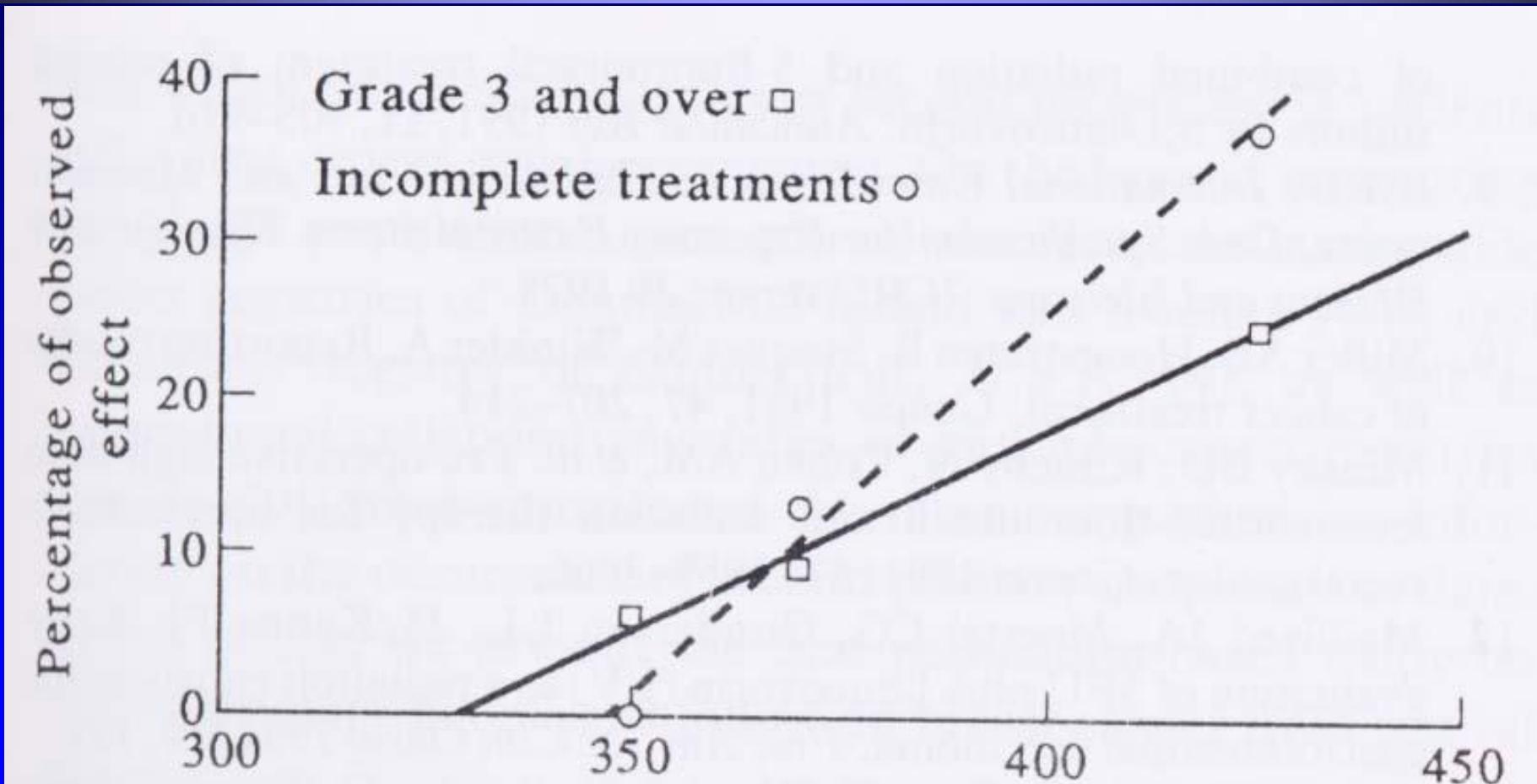
# Treatment scheme

## EORTC phase II studies

XRT : 45 Gy/ 5 weeks - 1.8 Gy/fraction



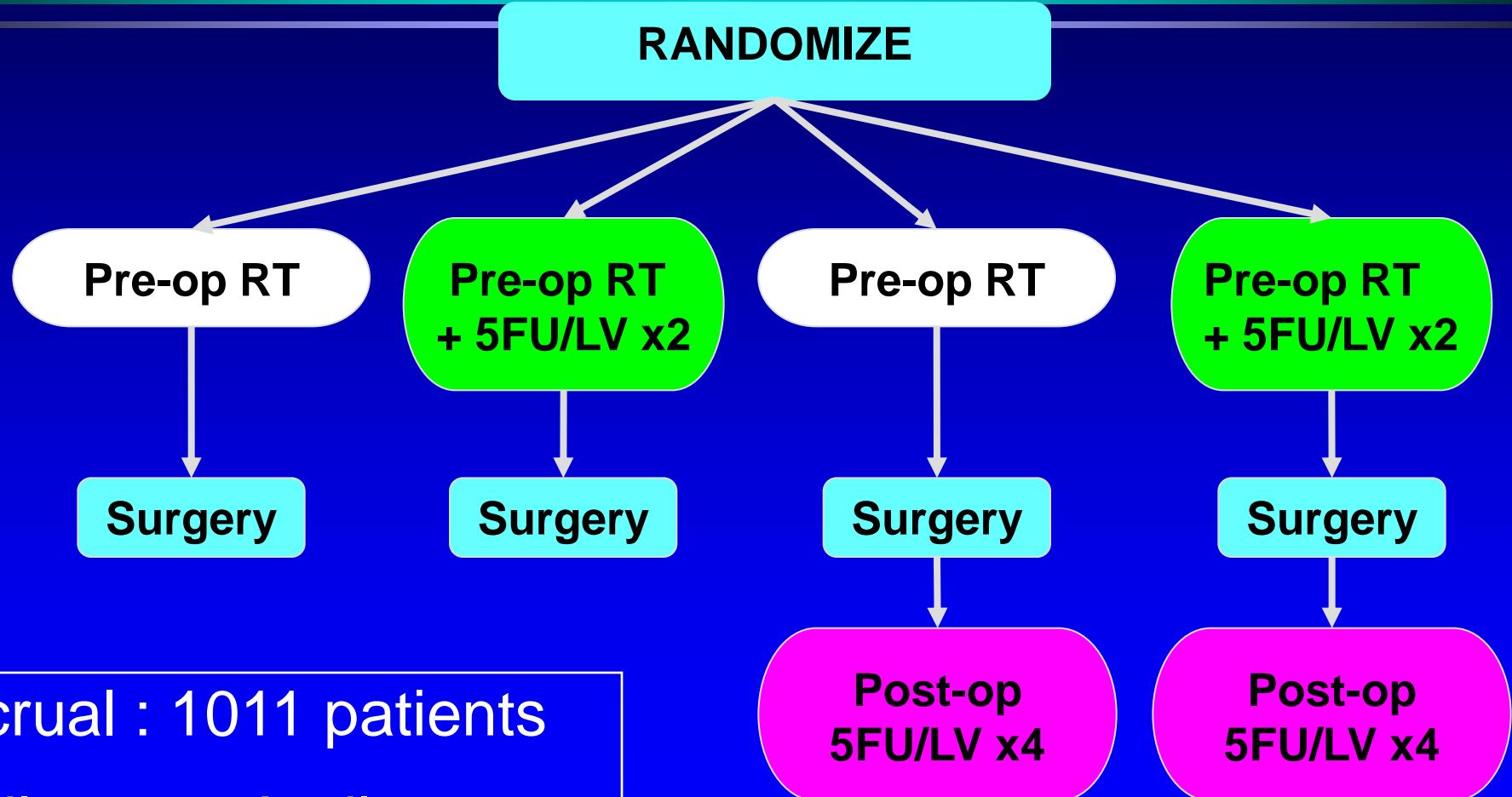
# 5-FU dose effect curve



*From Bosset J.F. et al. EJC 1993, 29A, 1406-10*



# Rectal cancer T3/T4 NX M0 (UICC 1987) by DRE or EUS Considered resectable, WHO PS 0-1, Age $\leq$ 80 y



Accrual : 1011 patients

April 1993 - April 2003

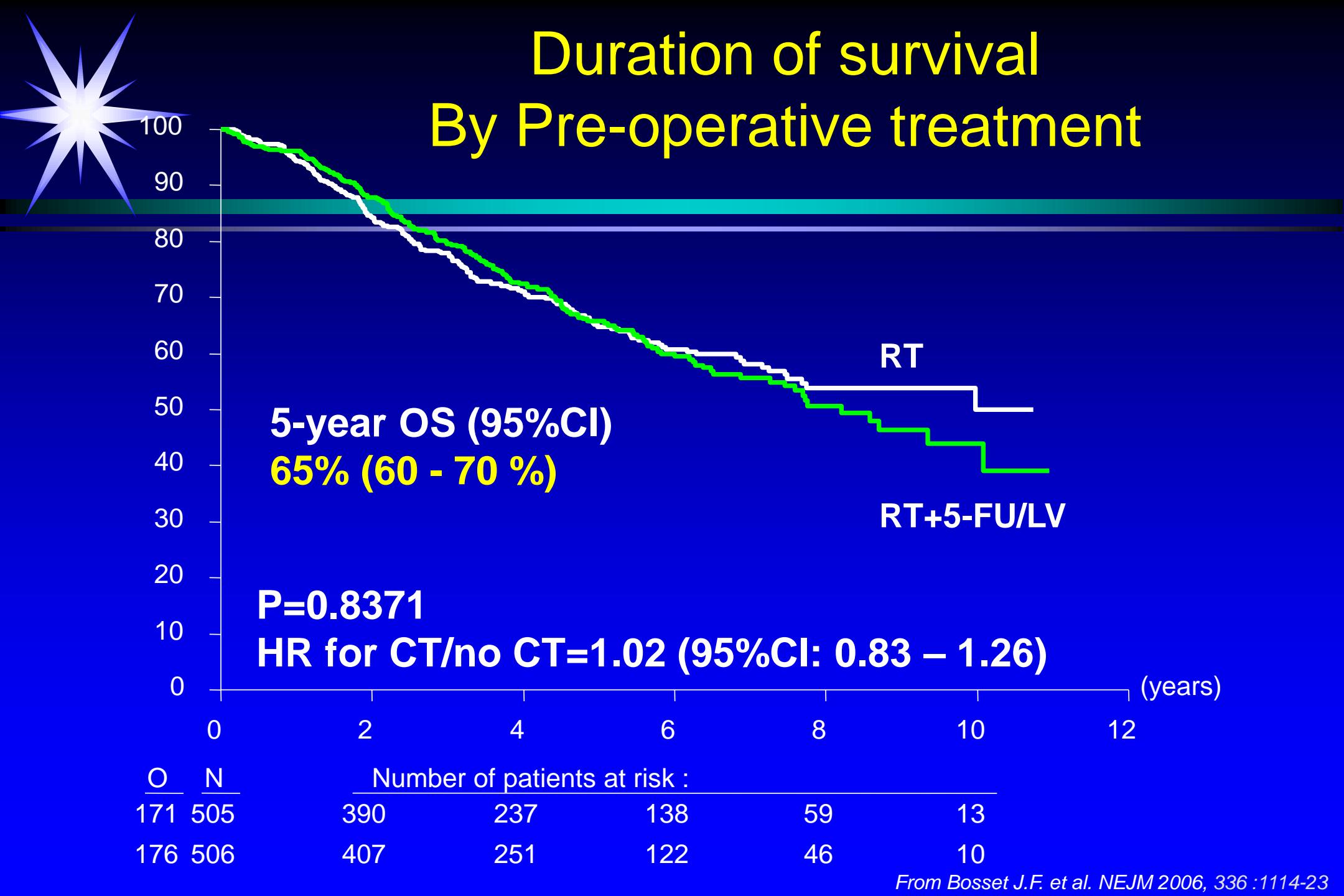


# EORTC trial main results

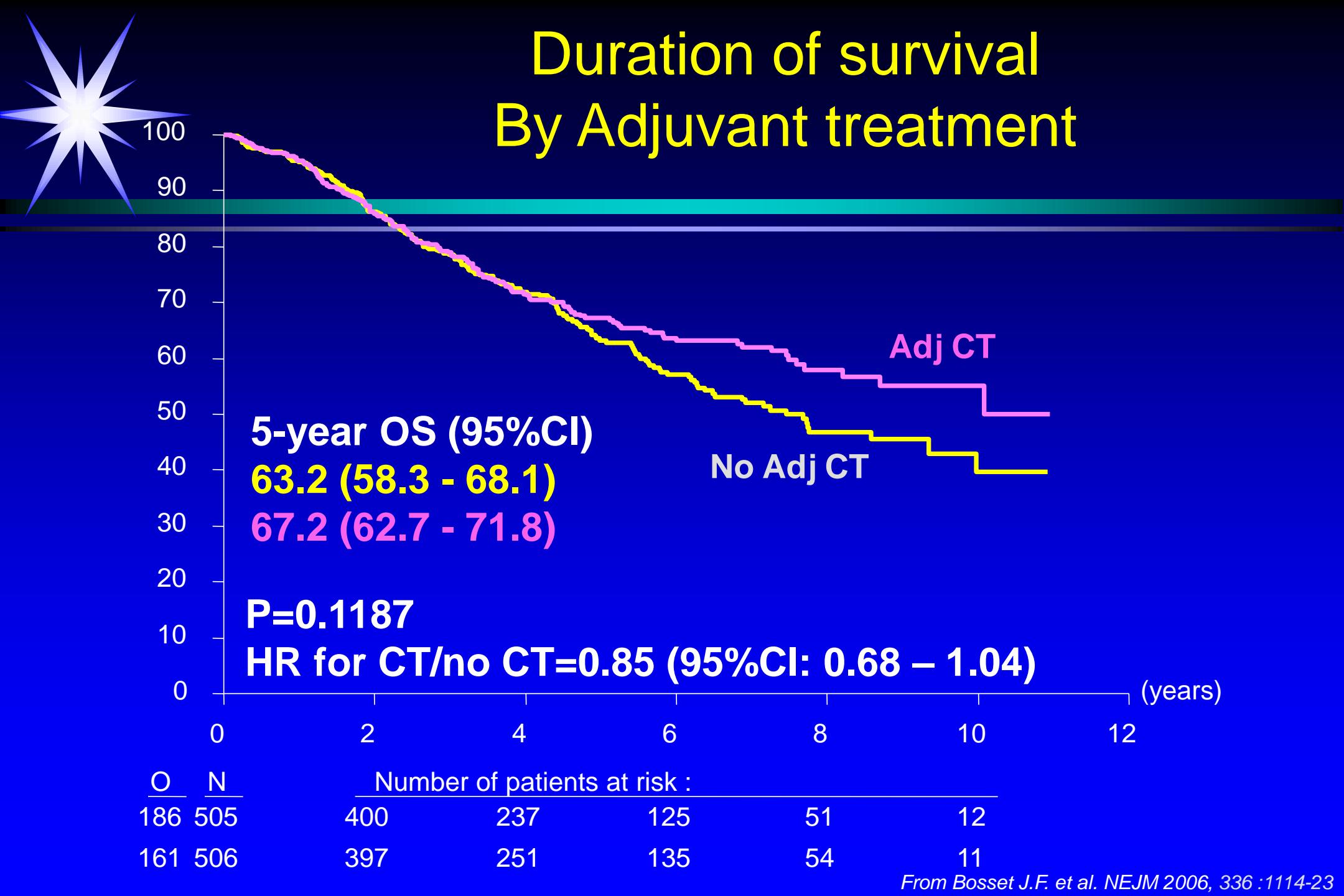
## Tumour efficacy

End point %	XRT-CT	XRT	p
pT0	14	5.3	< 0.001
< pT3	44.2	37.6	< 0.01
pN0	71.9	60.5	< 0.001
Size mm	25	30	< 0.0001

# Duration of survival By Pre-operative treatment

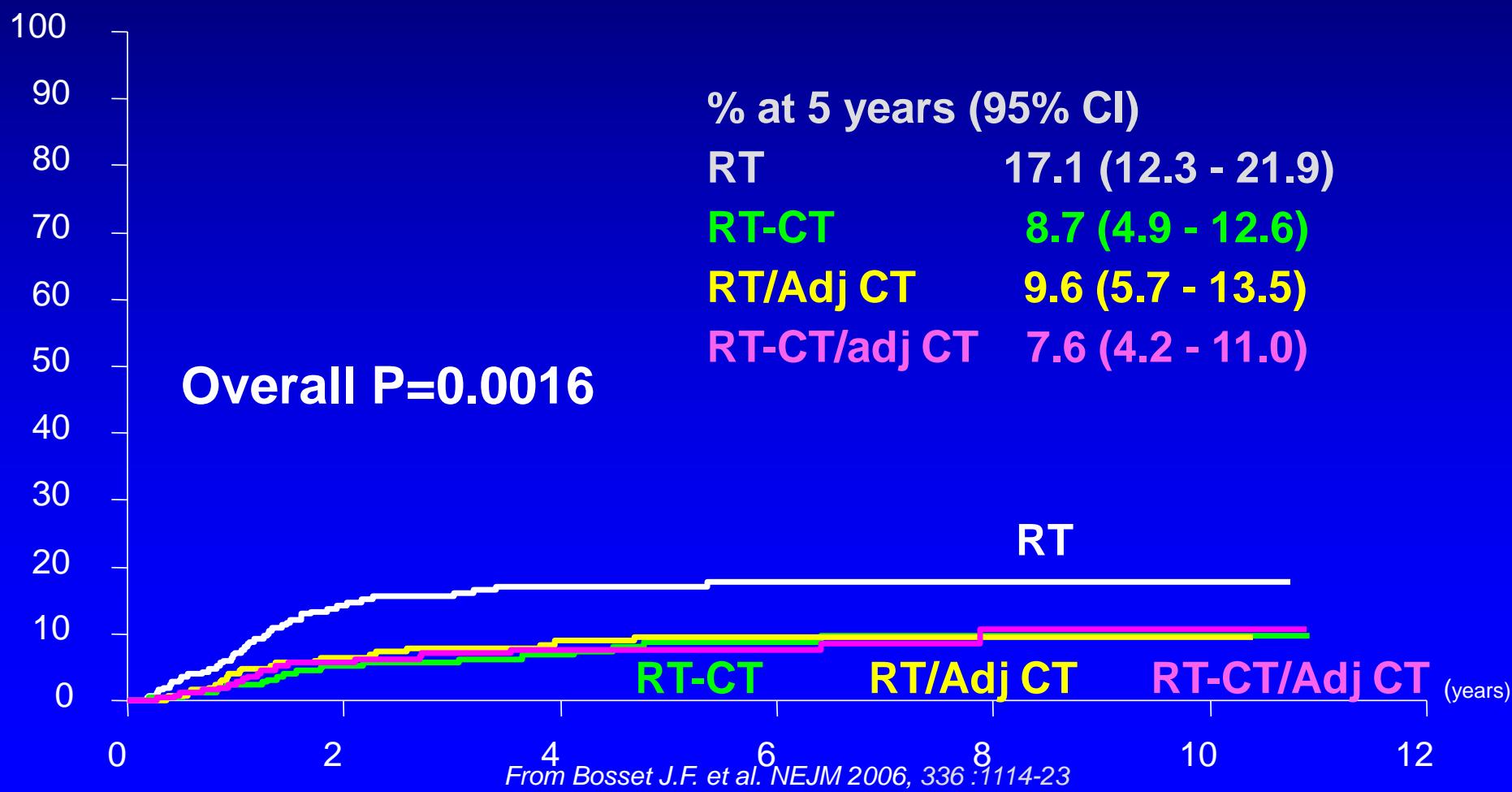


# Duration of survival By Adjuvant treatment

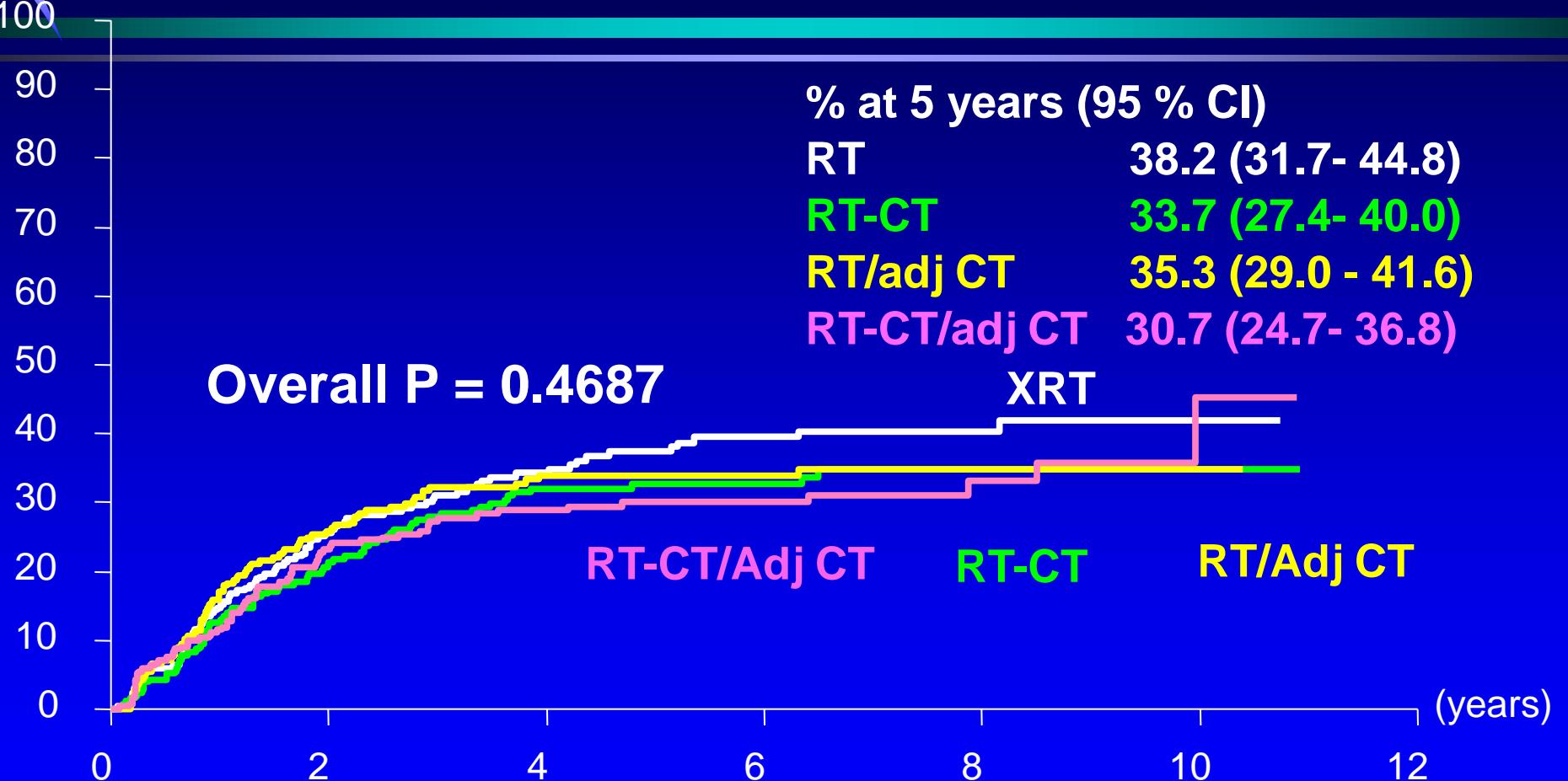




# Cumulative incidence of local relapse as first event



# Cumulative incidence of distant metastases



From Bosset J.F. et al. NEJM 2006, 336 :1114-23



# Current questions

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- Preop short RT course or preop CRT ?
- Preop Tt for upper rectum ?
- Tt intensification for bad prognostic tumors ?
- Recognizing and lowering toxicities



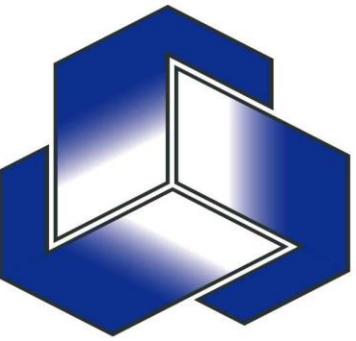
# Preop short RT vs long CRT

Trial	Short RT	Long CRT
Polish 316 pts	9	15.6
Australian 326 pts	7.5	4.4



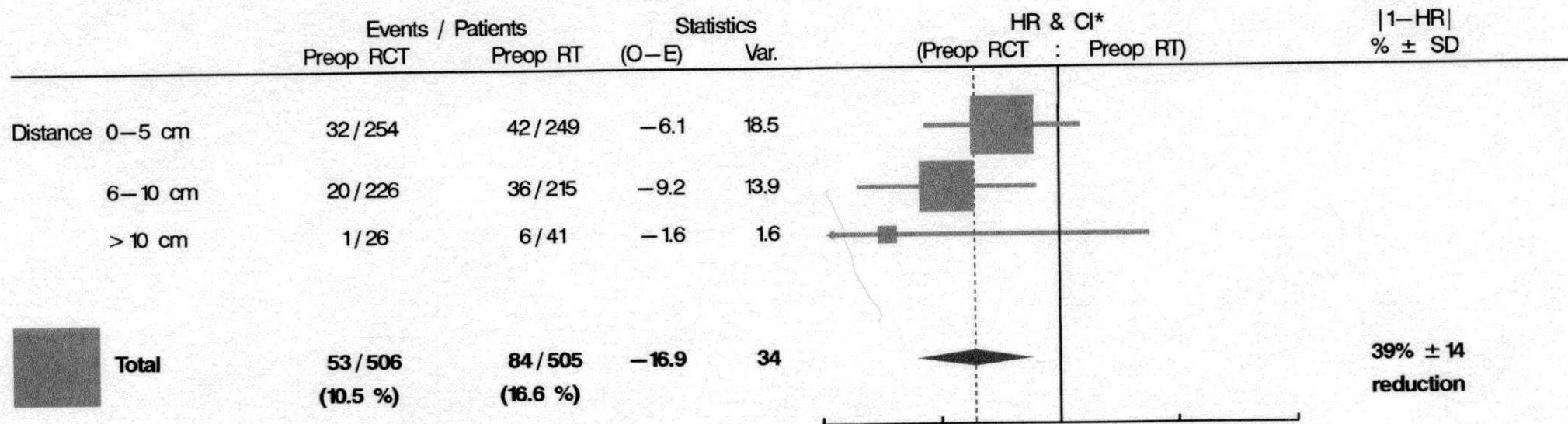
# Preop RT for upper rectum $\geq 10$ cm LR %

Study	Nb	RT-	RT+	p
Stockholm	126	21	5	0.01
SRCT	243	12	8	0.3
MRC	207	6.2	1.2	HR 0.19 (0.07-0.47)
TME	533	6.2	3.7	0.122



# Effet of preoperative treatment

## Time of local relapse : death competing



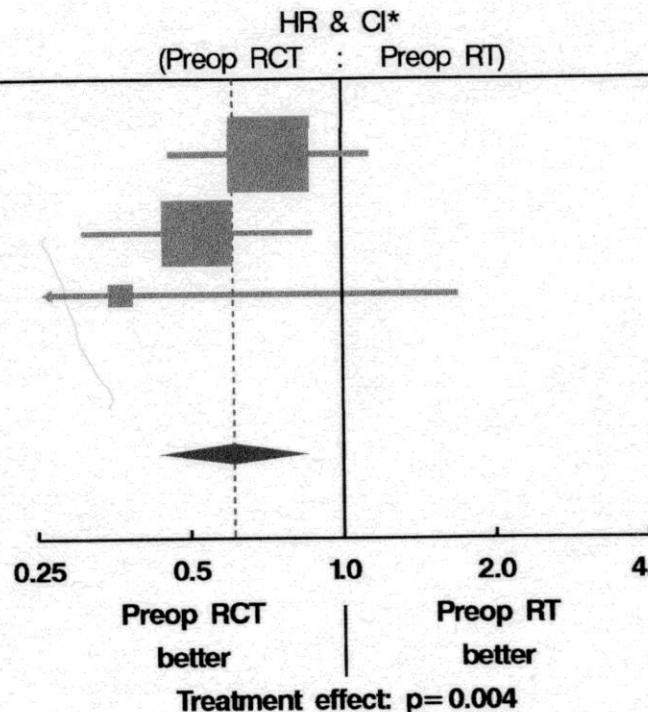
Test for heterogeneity

Chi-square= 1.29, df= 2: p= 0.52

Test for trend

Chi-square= 1.29, df= 1: p= 0.26

\*95% CI everywhere



22921 trial

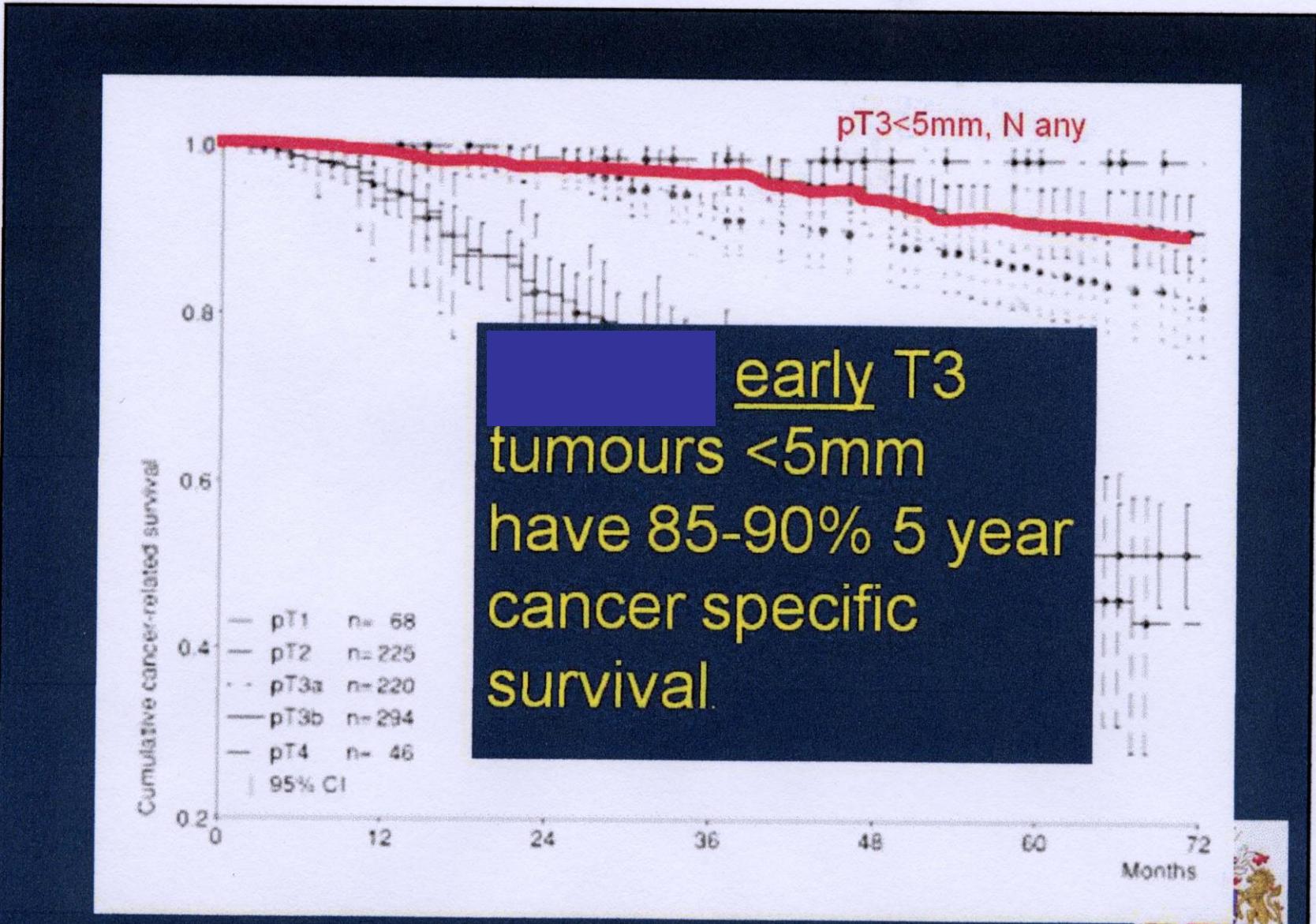


# Recognized prognostic factors

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- Importance of the extramural spread (> 5 mm)
- Tumor location at the sphincter level (APR ?)
- Nodal involvement
- CRM status

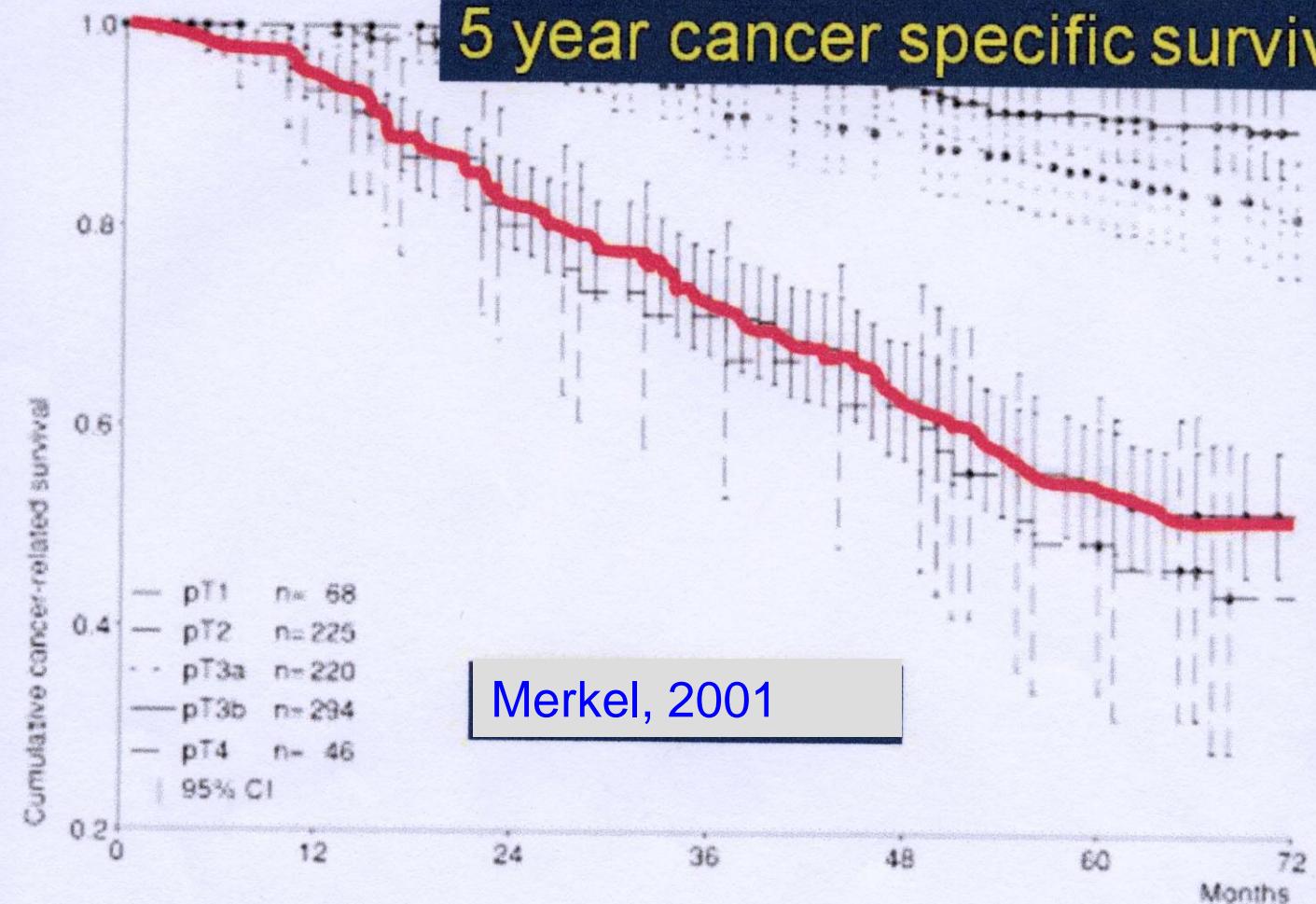
⇒ Heterogeneity of T3



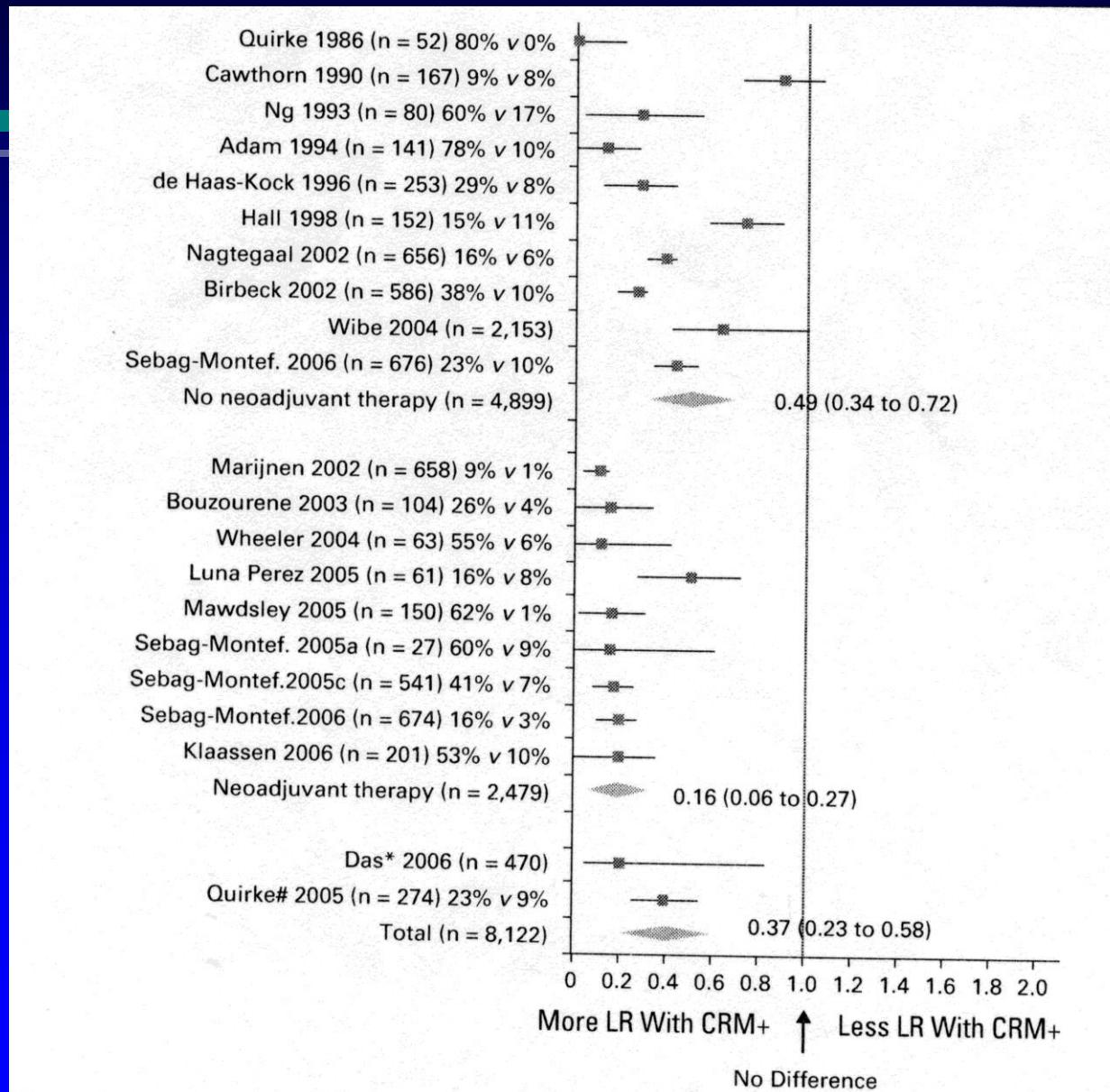
Merkel, 2001



T3 tumours >5mm spread 54%  
5 year cancer specific survival



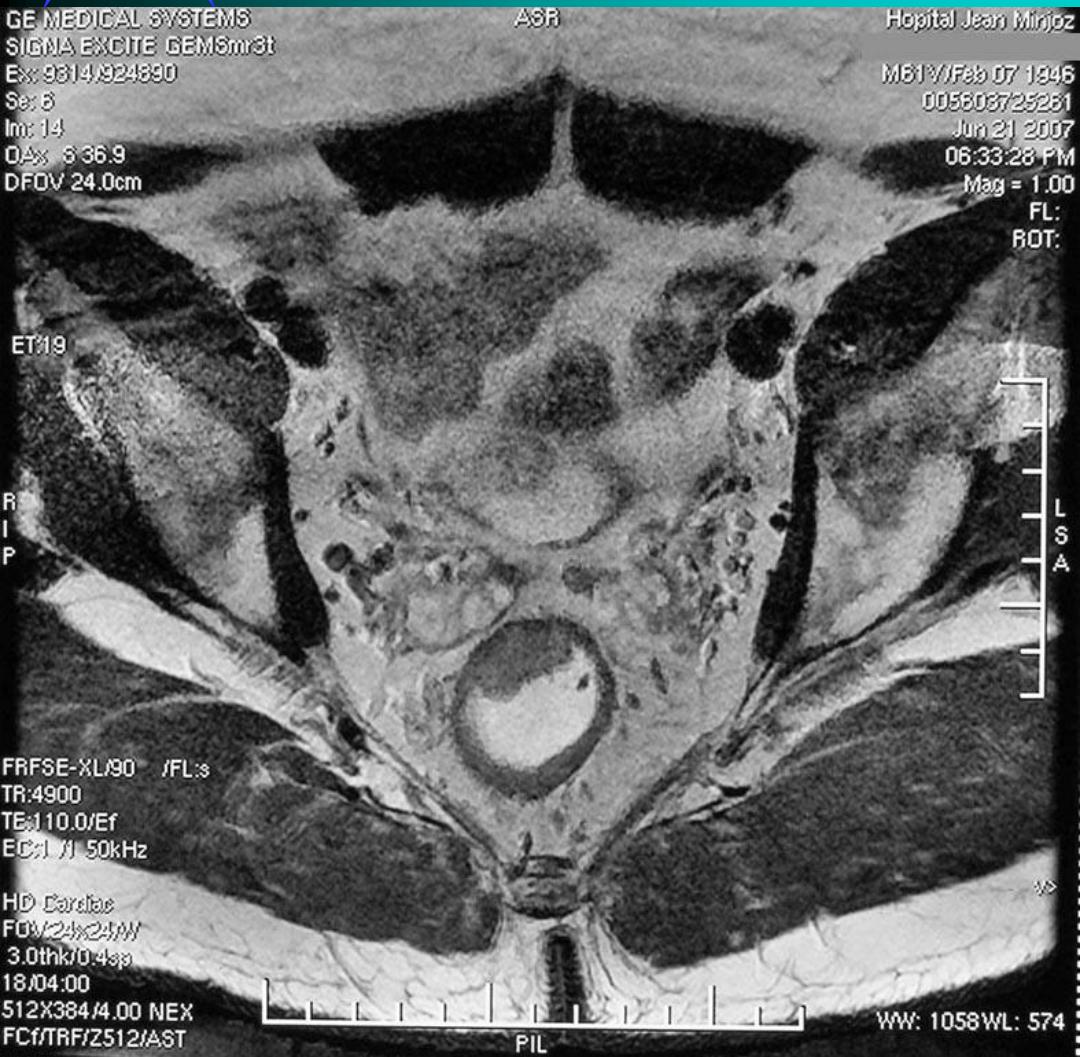
# Importance of CRM status



From Nagtegaal and  
Quirke, JCO 2008



# IRM Rectum T2 N0 ; T3 N2 CRM+





# IRM – Mercury group classification

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T 3a < 1 mm invasion

T 3b 1-5 m

T 3c > 5 mm

T 3d < 1 mm MRF

N = 58 % N+ < 5 mm Ø

T = Correct 85 – 88 %

Après CRT ≤ 60 %

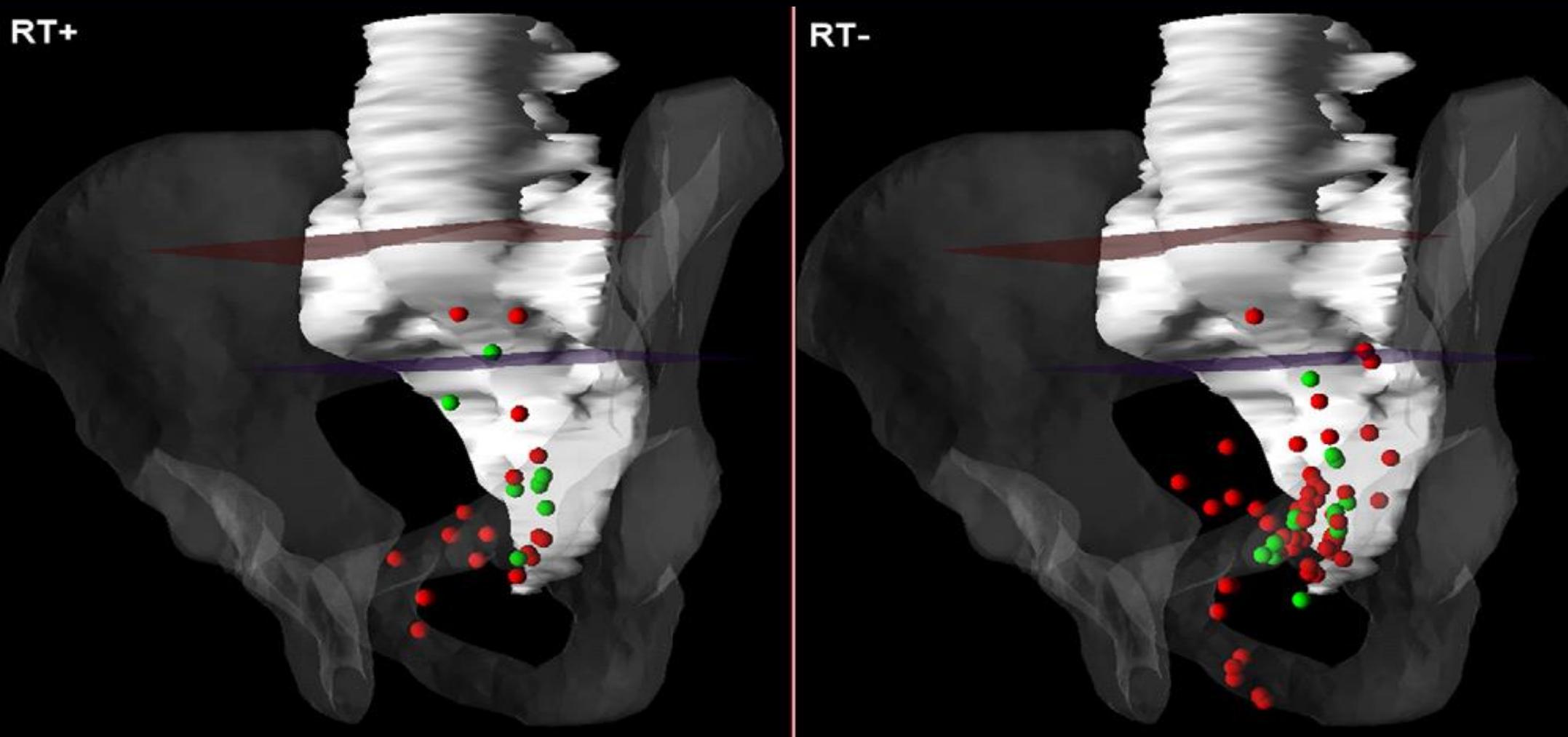


# Recommendations for lowering toxicity

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- Analysis of recurrence patterns in the TME era
  - ⇒ Reducing the classical CTV

RT+



Overview of the recurrence locations for RT+/RT- patients stratified by type of surgery. Note : recurrences above S2-S3 interspace rare (only if CRM+, N+, or both)

From Nijkamp et al. Int J Radiation Oncology Biol Phys 2010 (in press)



# Tailoring pretherapeutic strategies for T3-T4 on MRI/tumour location (next future ?)

Good T3a  
EMS < 1 mm  
N Θ  
Mid rectum  
CRM Θ

Bad T3b-T3c  
EMS 1 > 5 mm  
N +

T3a at sphincter level  
CRM Θ

Ugly T3d  
CRM +  
T4

↓  
5 x 5 Gy ?  
TME

↓  
CRT  
TME

↓  
CRT intensification  
Extended resection



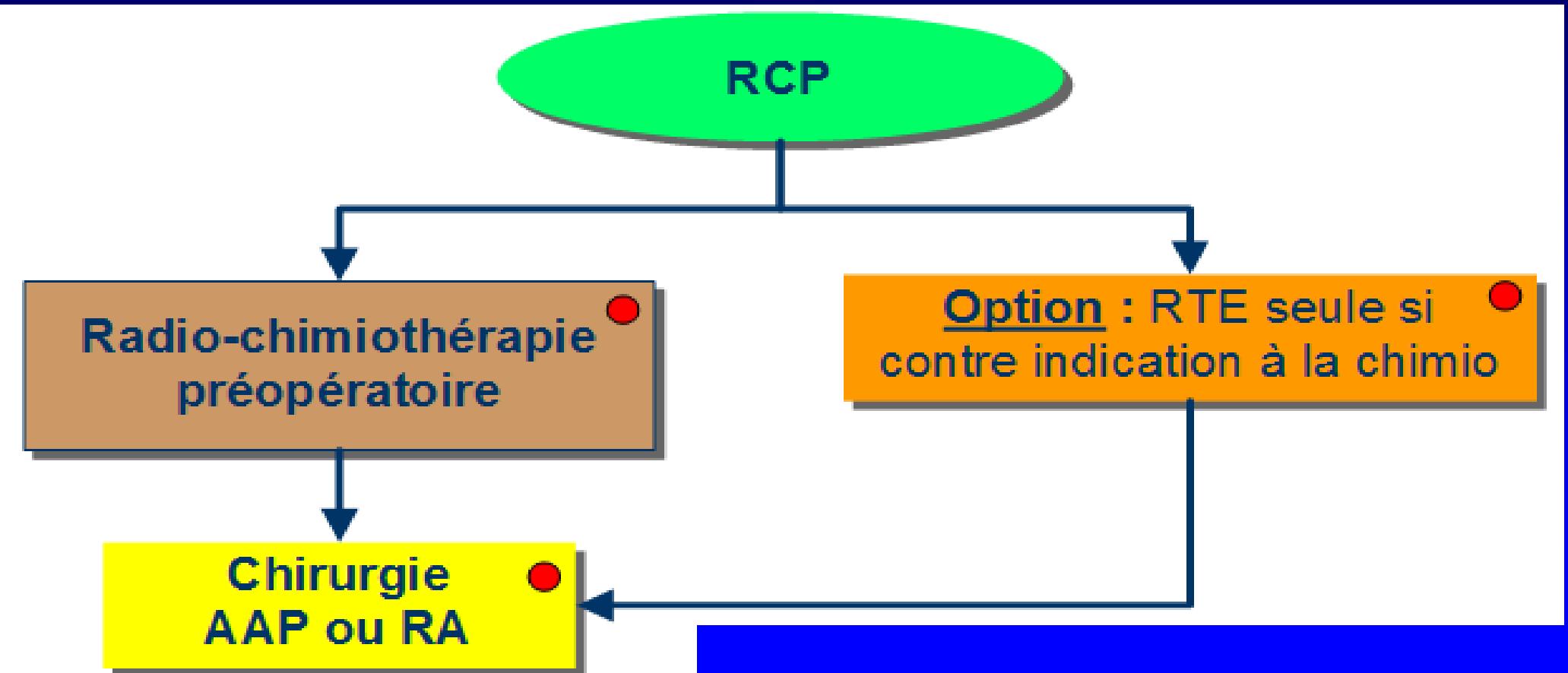
# Radiochimiothérapie préopératoire

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- Standard (NCCN, thésaurus national) pour toutes les lésions sous-péritonéales cT3-4 ou cN+
- 45 Gy/25 fr + 2 cures 5-FU/acid FOLinique : grade A thésaurus national 2013
- 50 Gy/25 fr/5 sem + capécitabine 1600 mg/m<sup>2</sup>/j (thésaurus national 2013, NCCN grade 1)
- Ne pas utiliser l'oxaliplatin ni l'irinotécan, le bévacizumab, le cétximab, et le panitumumab (NCCN, thésaurus national)
- Délai optimal entre radiochimiothérapie préopératoire et chirurgie ≥ -6 semaines



# Stratégie thérapeutique pour un cancer du rectum cT3 ou cT4 ou N+





# Take home messages

- Une radiochimiothérapie préopératoire avec 45, 50 ou 50,4 Gy permet :
  - un downstaging,
  - 15-16 % ypCR
  - une réduction des récidives locales
- La RCT préopératoire avec capécitabine est le standard à discuter en RCP pour tout cancer du rectum cT3-4 ou cN+
- CT adjuvant après CRT – Débat ! (NCCN, ESMO, Eureca, etc...),
- Du fait des problèmes d'observance de la chimiothérapie adjuvante, la chimio néoadjuvante est une approche prometteuse mais qui ne doit être utilisée que dans le cadre d'un essai clinique (consensus de l'ESMO 2012)