

XXII CONGRESSO
AIRO

ROMA 2012

17-20 novembre
Ergife Palace Hotel



Associazione
Italiana
Radioterapia
Oncologica



**Tossicità tardiva in radioterapia:
ipofrazionamento versus frazionamento
convenzionale
L'esperienza clinica nel retto**

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Preoperative Radiotherapy

Short course

immediate surgery



2-3 days

Long course

delayed surgery



5 weeks

6-8 weeks

Preoperative Radiotherapy

Short course

Local control

Fast

No Acute tox

Long course

Local control

Conc CT

Tumor shrinking



Late tox
difference

after 2000 randomized trials

Trial

Short ERT

Winner

Duch Trial

SC RT+TME vs TME

SC RT

MRC C07

SC RT+TME vs TME

SC RT

Trial

Long ERT

Winner

EORTC 22921

LC RT vs C-RT

C-RT

FFCD 9203

LC RT vs C-RT

C-RT

Scandinavian

LC RT vs C-RT

C-RT

Trial

Short vs Long

Winner

Polish Trial

SC RT vs C-RT

=

TROG Trial

SC RT vs C-RT

C-RT

after 2000 randomized trials

SURVIVAL

no improvement

Local control

improvement

Trial

Long ERT

Winner

EORTC 22921

FFCD 9203

Polish Trial

TROG Trial

Scandinavian

Acute Toxicity

increased

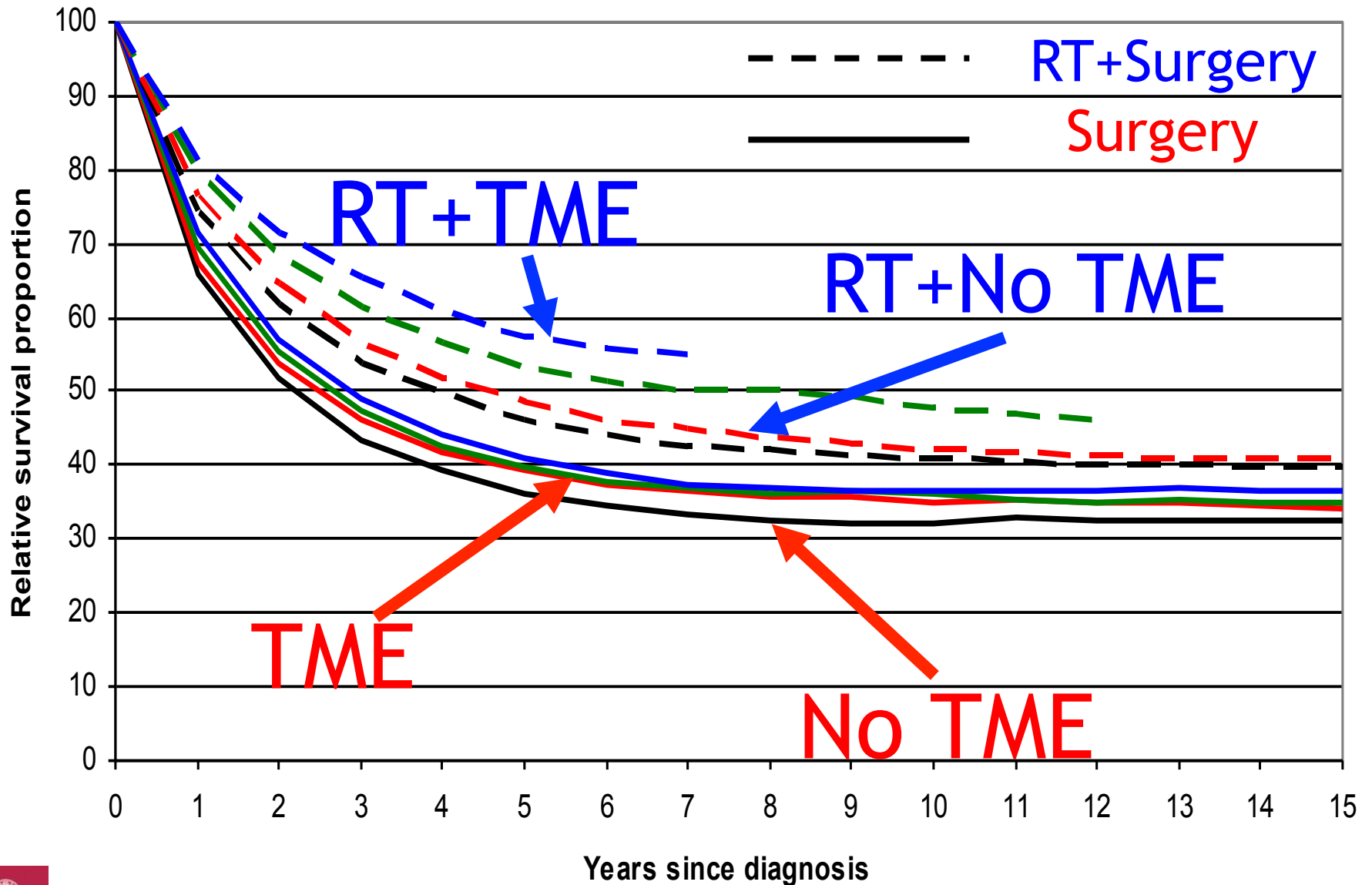
C-RT

C-RT

=

C-RT

Cumulativ relativ survival of Rectal cancer in Sweden



By the courtesy of L.Pahlman - ESTRO/ESSO/ESMO Course - 2009

LONG SURVIVORS

65%

LATE TOX

5-30%

Late adverse effect

COMMON

- Gastrointestinal disorders
- Anal/rectal dysfunction
- Sexual dysfunction
- Urinary dysfunction

RARE

- Fractures
- Tromboembolic disease
- Secondary cancers

Late adverse effect gastrointestinal disorders

COMMON

- Diarrhoea
- Bleeding
- Abdominal pain
- Obstruction (adhesion)

RARE

- Malabsorption
- Perforation

IRRADIATED

- SB volume
 - LB volume
- mucosal inflammation
increased secretion
malabsorption
- visceral peritoneum
(mesothelium)

Late adverse effect gastrointestinal disorders

COMMON

- Diarrhoea
- Bleeding
- Abdominal pain
- Obstruction (adhesion)

IRRADIATED

- SB volume
- LB volume
- mucosal inflammation
- increased secretion
- malabsorbtion

- visceral peritoneum
(mesothelium)

Late adverse effect anal-rectal dysfunction

- Incontinence
 - Rectal emptying problem
 - Bowel movement
 - Diarrhoea
- Surgery
- Stiffer rectal surroundings
- Sphincter muscle
- Sacral pudendal nerves

Late adverse effect sexual dysfunction

- Erection
- Ejaculation
- Orgasmic function

- Dryness
- Pain during intercourse

Surgery

Vessels damage

Nerves damage

Menopausa

Glands irradiation

Toxicity assessment

- **Scale:**
 - RTOG/EORTC
 - **Self reported: questionnaire:**
 - EORTC- QLQ-C30, 38
 - Others
-
- **Maximum**
 - **Over time:** baseline, FUP

SCRT+TME vs TME

Dutch trial

MRC-CR07 trial

Dutch trial

Self reported: **3 yrs from last randomization**

Bowel

Urinary

Sexual

Neurologic

Hospital admission

General health status

Dutch trial

Self reported: 3 yrs from last randomization

Bowel

Urinary: incontinence 40%

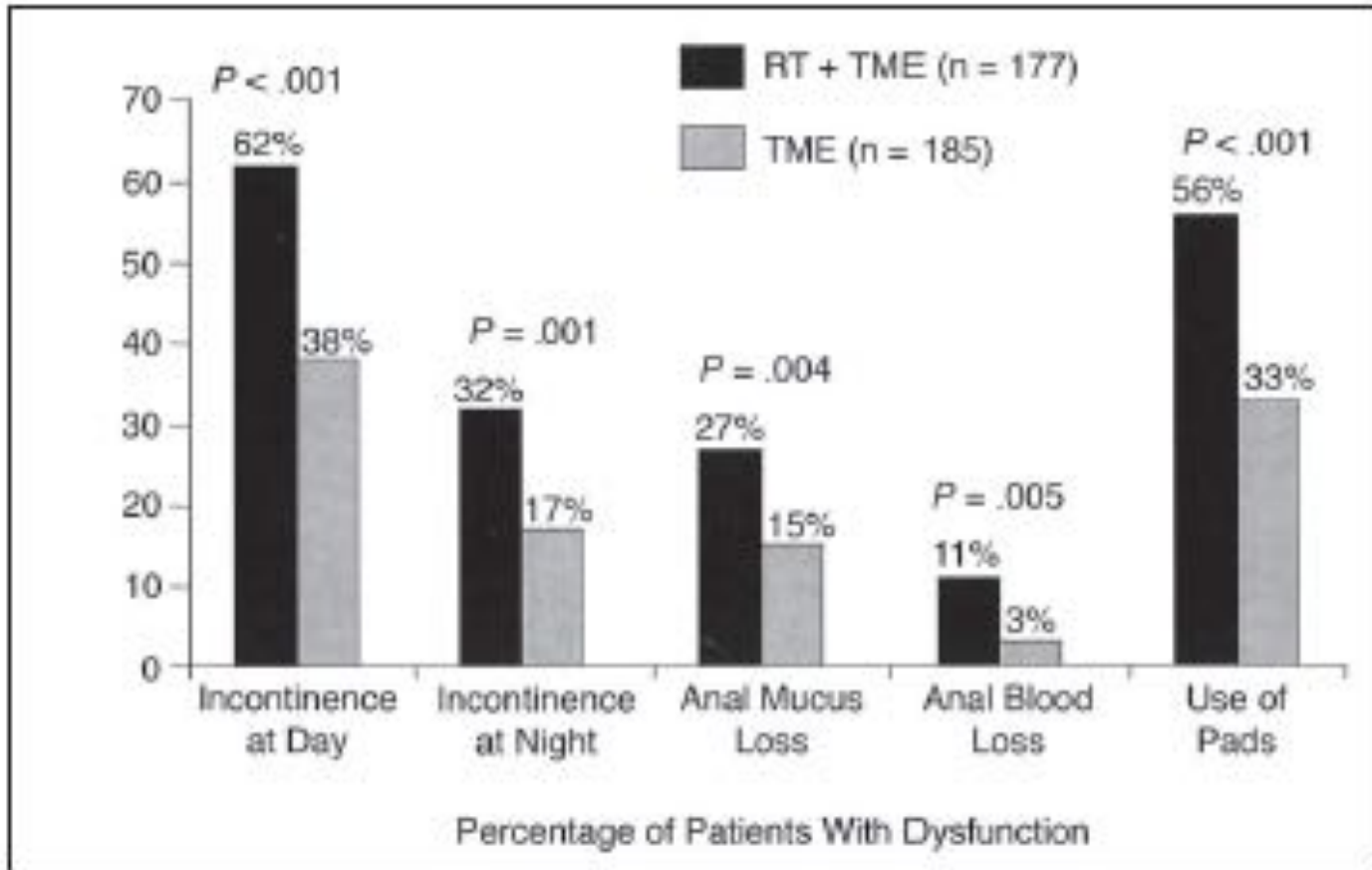
Sexual

Neurologic

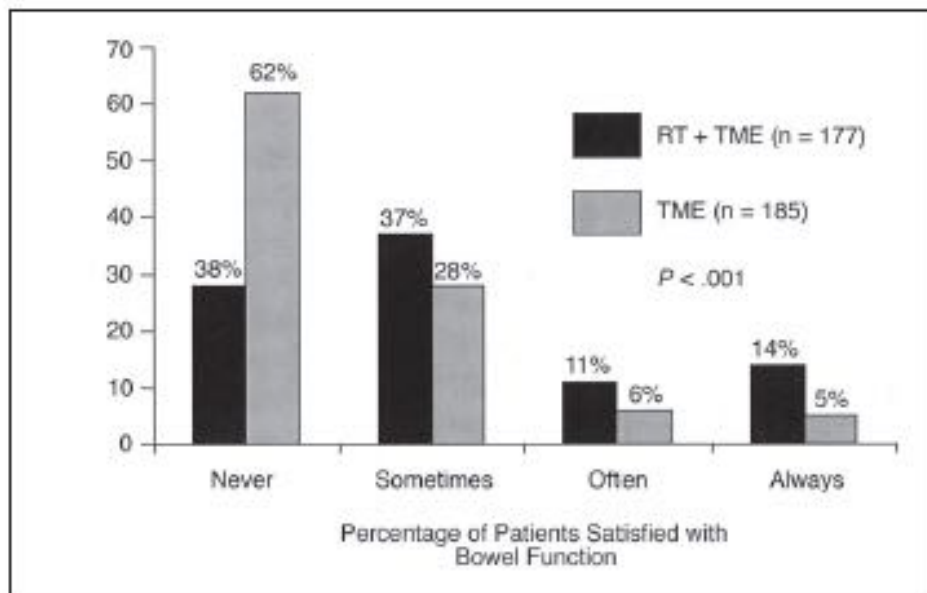
Hospital admission

General health status

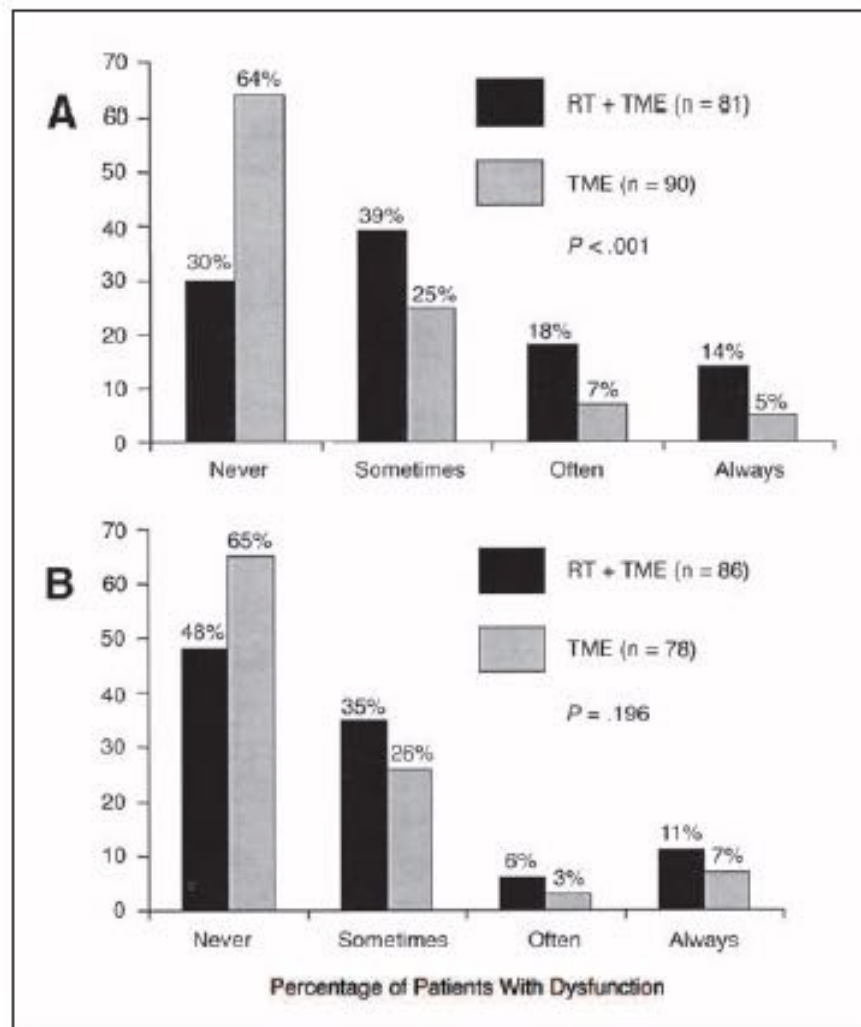
Bowel function (no stoma)



Bowel function: incontinence



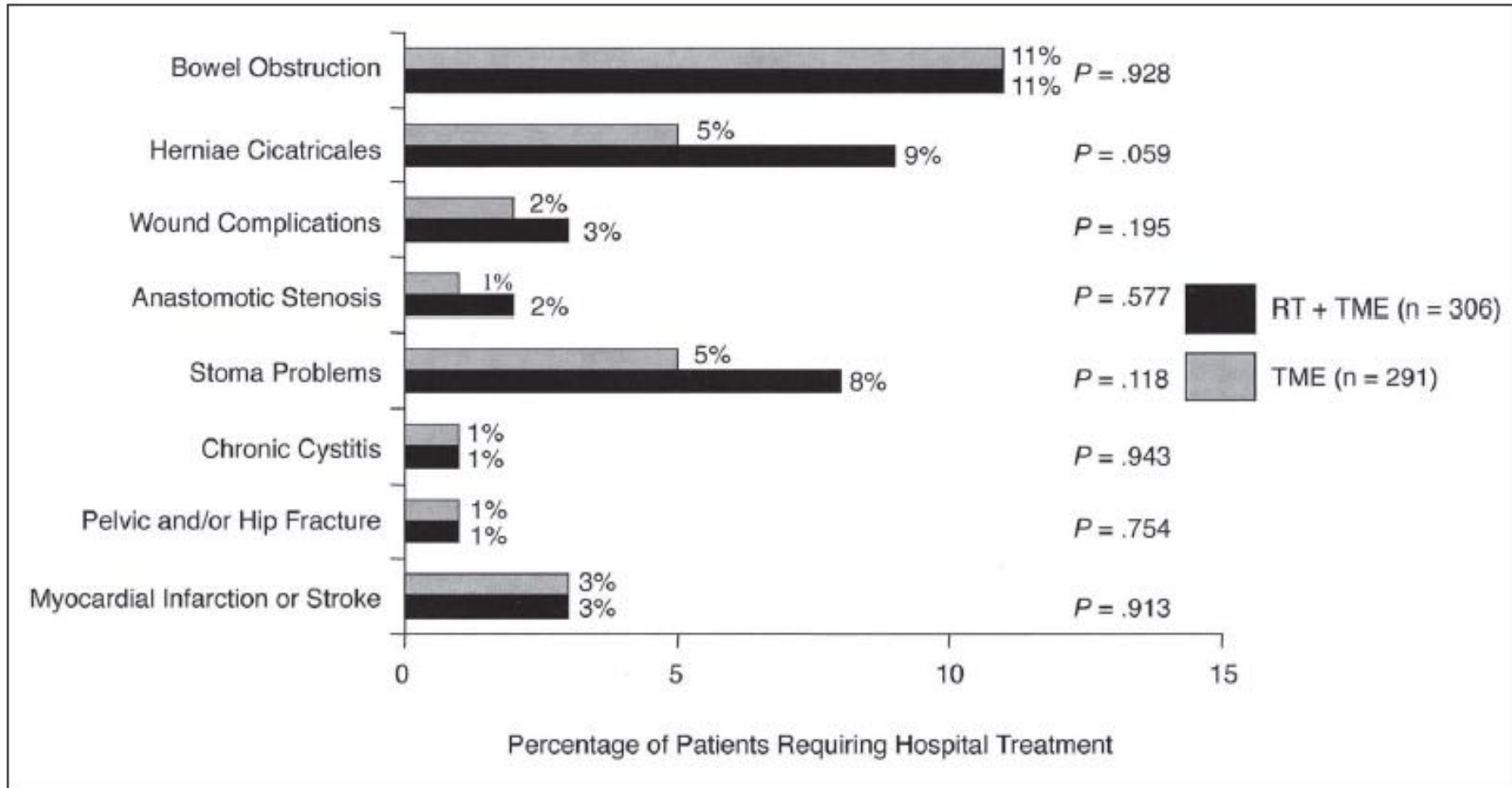
A: mid rectum (5-10 cm)
B: high rectum (10-15 cm)



Sexual function

SEXUAL ACTIVITY	Sex	TME	RT-TME
	Male	76%	67%
	Female	90%	72%

Hospital admission



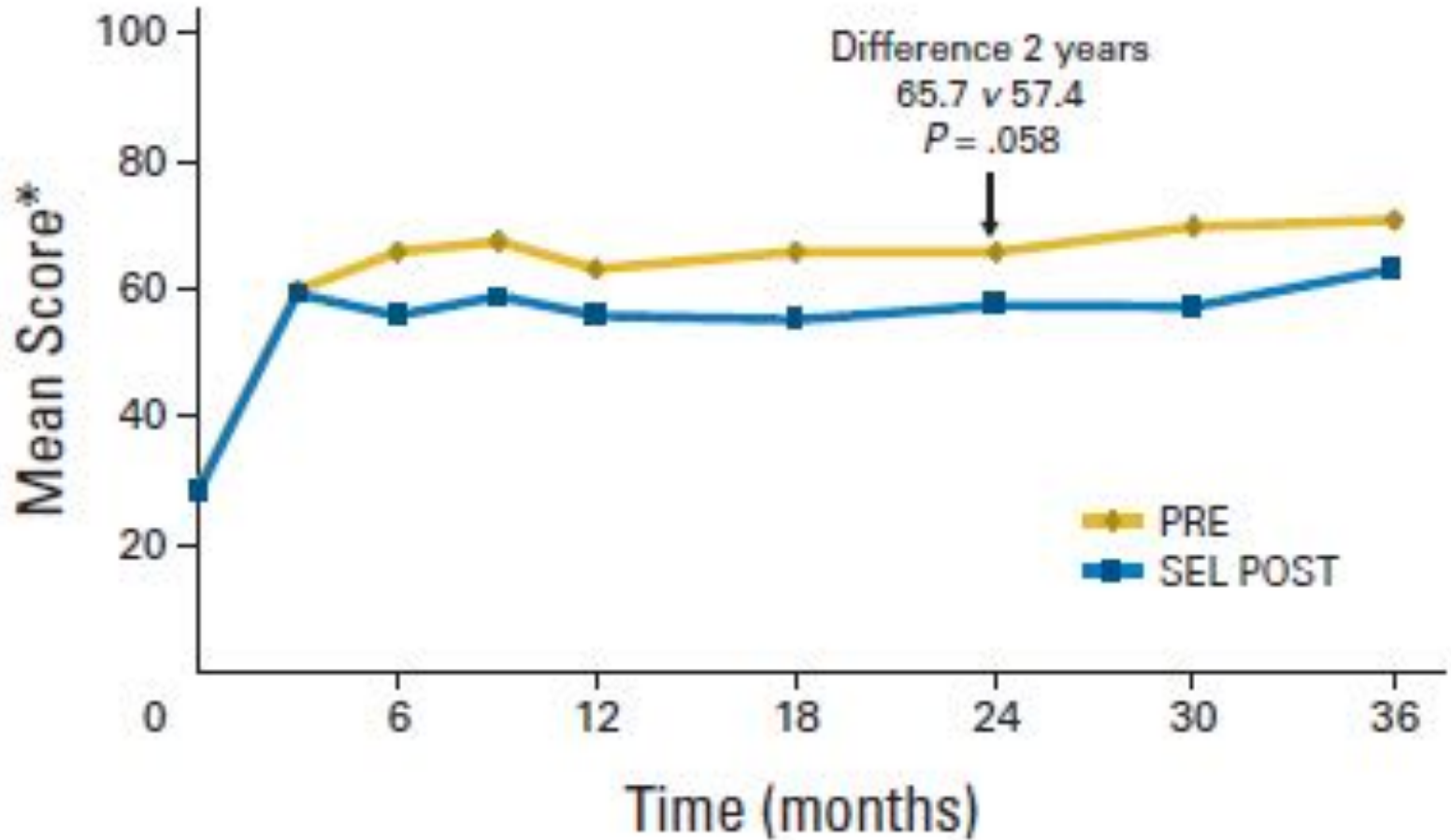
MCR-CR07

- **FUP min: 3 yrs**
- Self-reported: MOS SF-36 e EORTC-QLQ-CR 38, administered over time (BL, 3 mts for 1 y, than every 6 mts for 3 yrs)
- Sexual function
- Bowel function
- General e physical functions

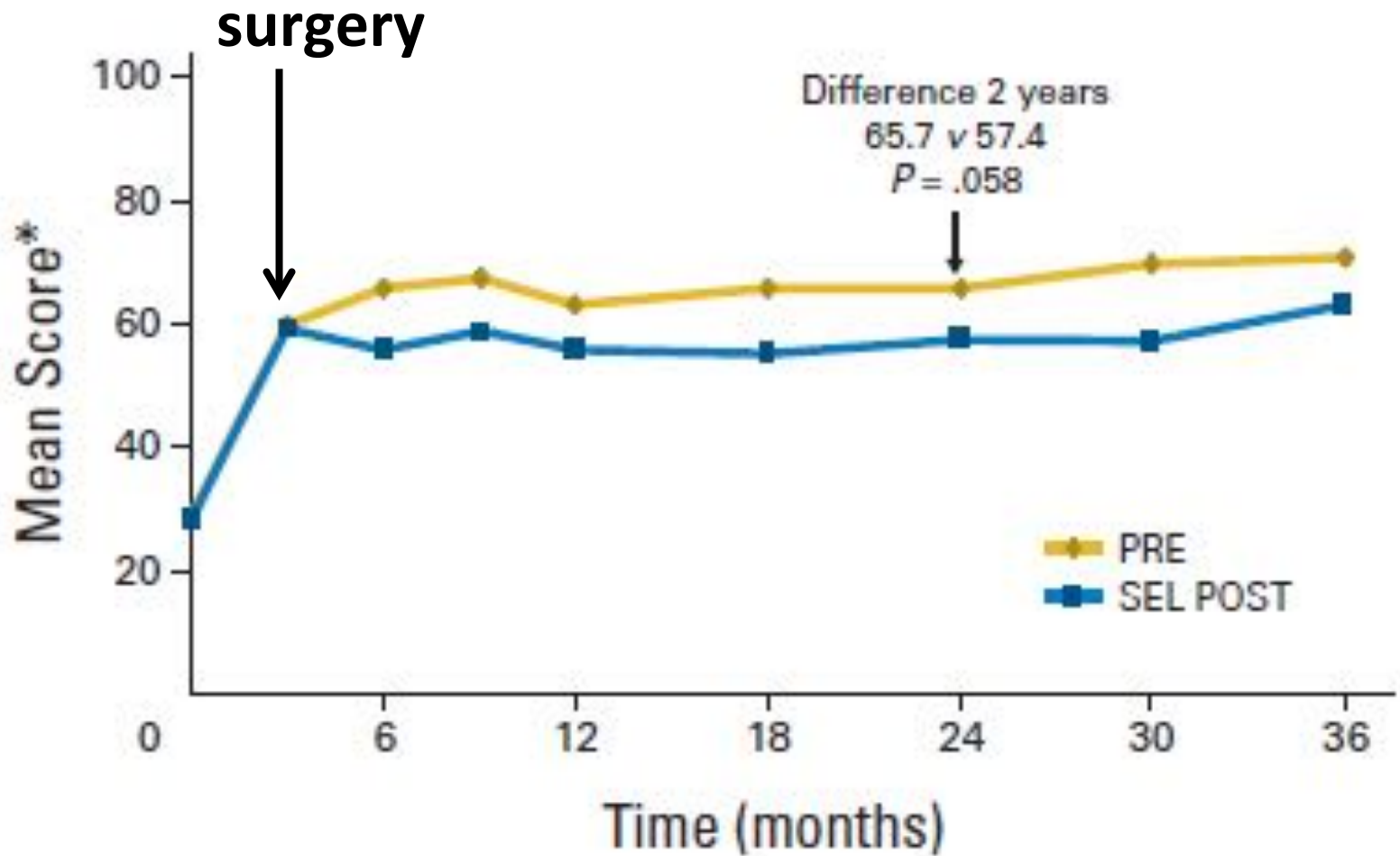
MCR-CR07

- Self-reported: MOS SF-36 e EORTC-QLQ-CR 38, administered over time (BL, 3 mts for 1 y, than every 6 mts for 3 yrs)
- Sexual function
- Bowel function
- General e physical functions

Sexual function

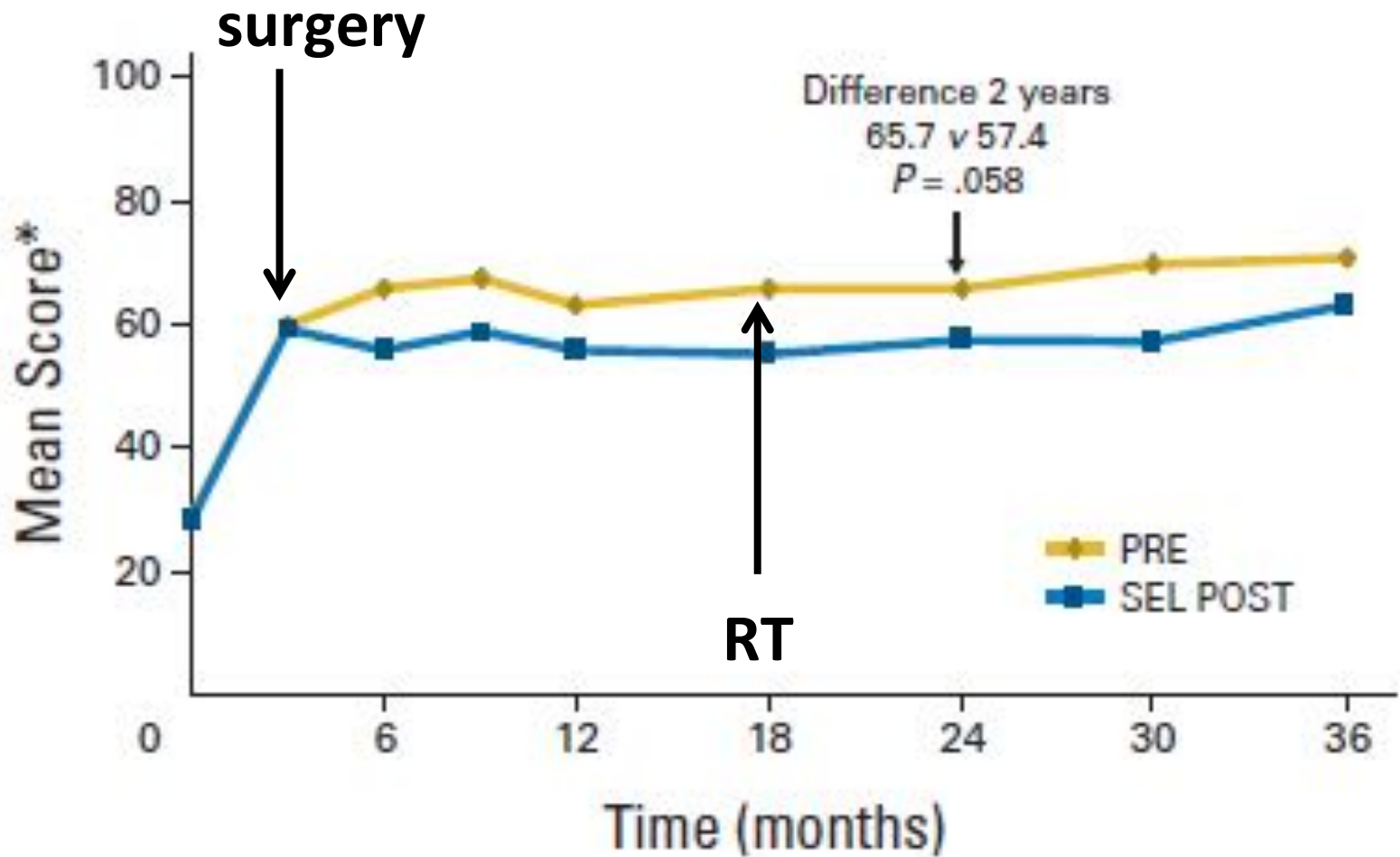


Sexual function (male*)



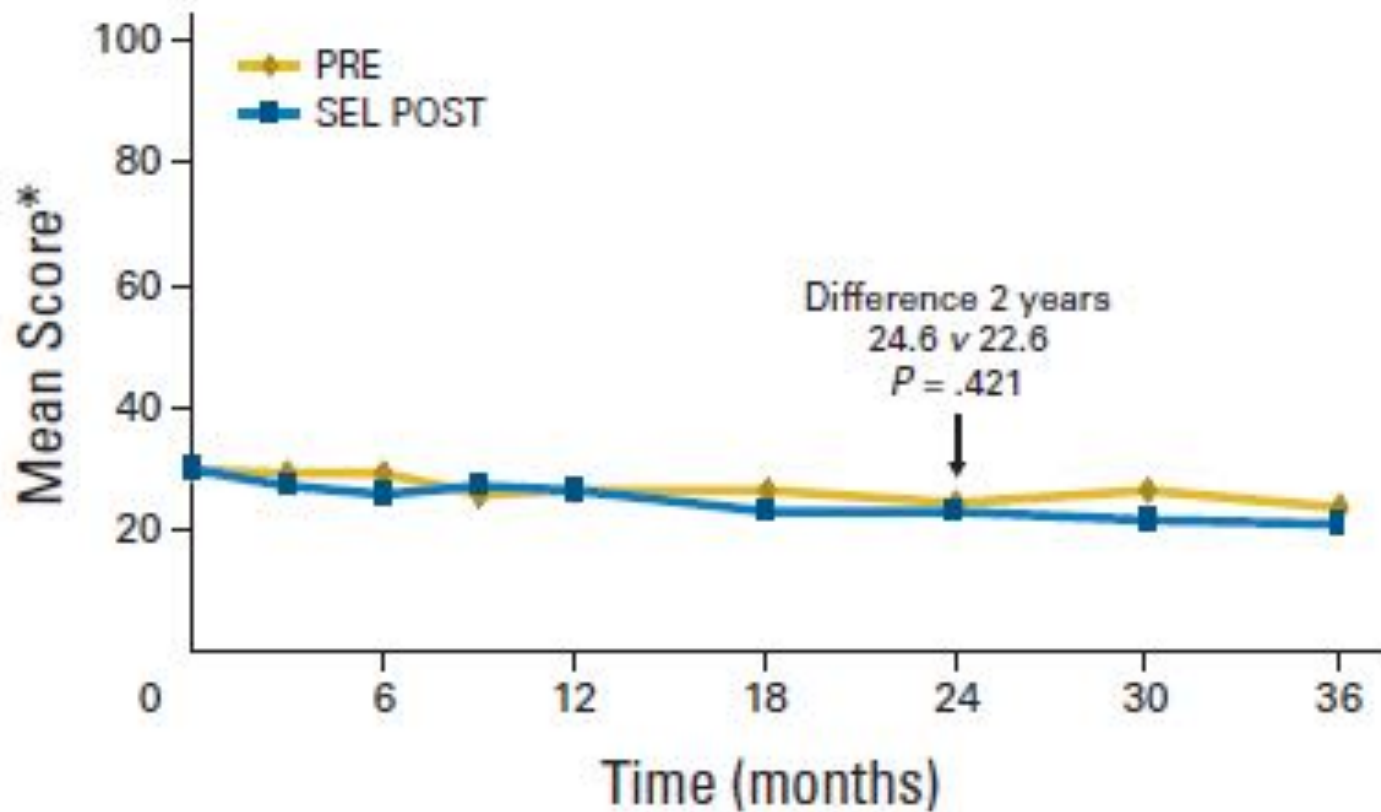
*Only 11% of women completed the questionnaire at 2 yrs

Sexual function (male*)

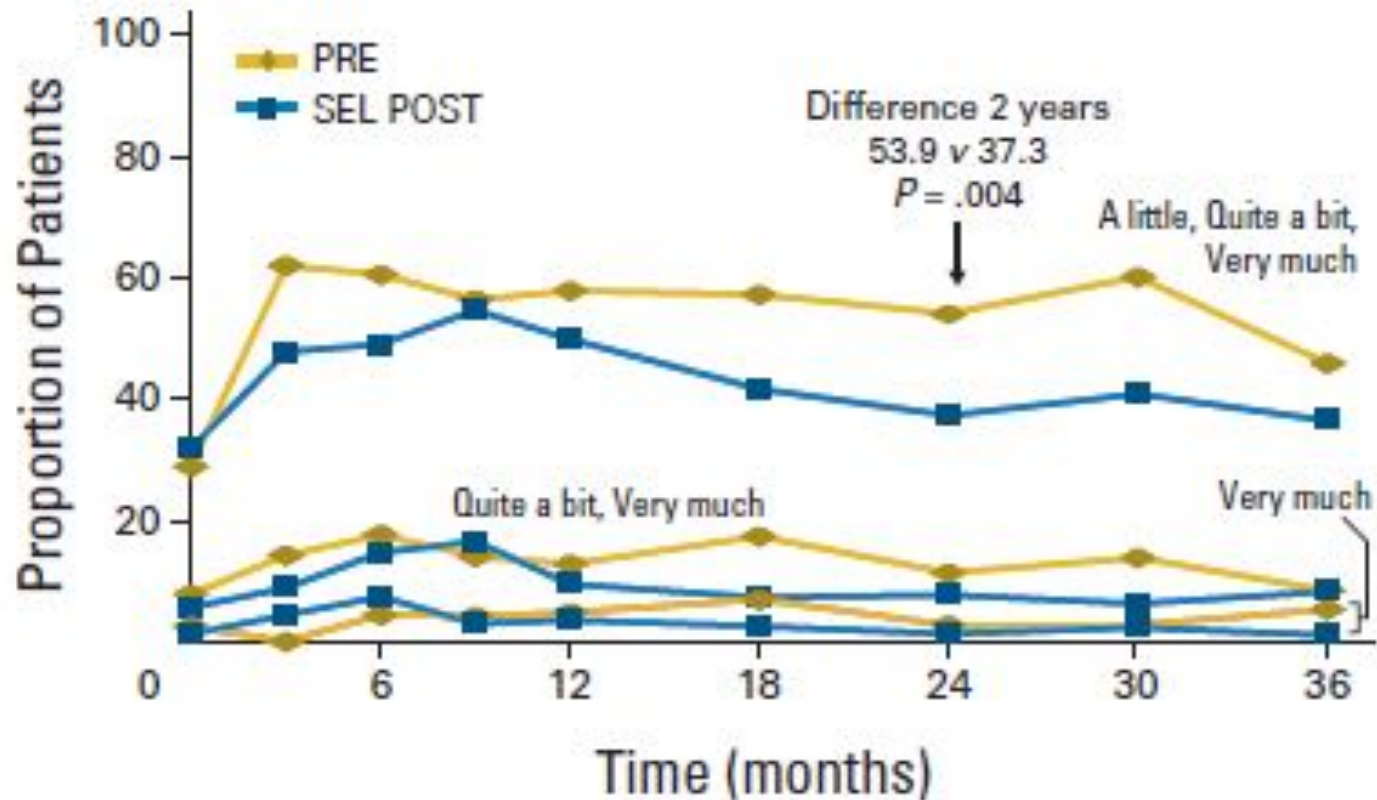


*Only 11% of women completed the questionnaire at 2 yrs

Bowel function: Defecation function (no stoma)

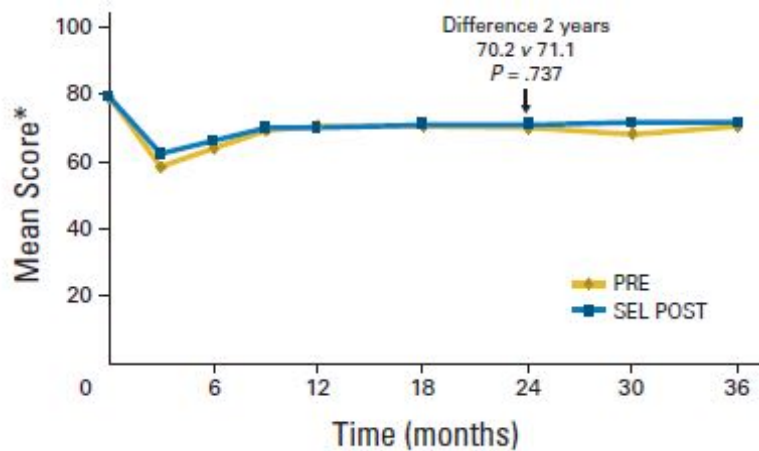


Unintentional release of stool

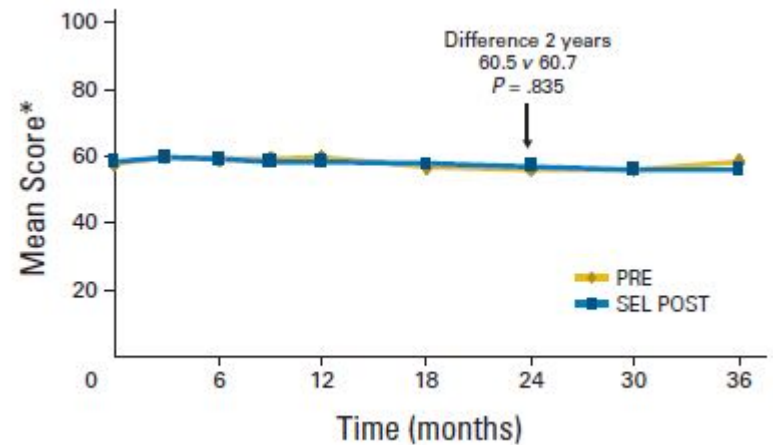


Physical/general health

Physical health



General health



Quality of life instrument: lack of sensitivity

Adaptation to symptoms: experience compared with expectation

Elderly patients accept dysfunctions as necessary cost of the treatment

LCRT+S vs RT-CT+S

EORTC trial

Scandinavian trial

EORTC 22921

- **Median time to random 4.6 yrs**
- Self assessed: EORTC-QLQ-C30 e QLQ-C-38
- Quality of life
- Anorectal function
- Sexual funcion

EORTC 22921: QLQ-C-30

Variables	Number of patients	Mean	S.D.
Physical functioning	204	88.29	15.21
Role functioning	202	85.40	20.48
Emotional functioning	202	82.01	20.39
Cognitive functioning	203	84.31	17.91
Social functioning	203	78.07	26.29
Global health status	201	73.32	19.06
→ Fatigue	204	→ 20.10	20.72
Nausea and vomiting	204	1.89	8.16
Pain	203	9.78	18.21
Dyspnoea	200	12.11	21.15
→ Insomnia	201	→ 19.51	28.36
Appetite loss	204	4.22	13.74
Constipation	202	11.16	21.14
→ Diarrhoea	199	→ 17.17	24.10
Financial difficulties	203	5.89	16.85

EORTC 22921: QLQ-C38

Variables	Number of patients	Mean	SD
Body image	198	79.63	24.95
Future perspective	200	67.91	32.16
Sexual functioning	184	18.91	23.43
Sexual enjoyment	74	49.59	33.77
Micturition problems	200	22.33	17.16
Gastrointestinal symptoms	199	16.60	15.25
Male sexual problems	119	62.47	36.63
Female sexual problems	14	25.00	21.41
Defecation problems	135	21.01	14.97
Stoma-related problems	54	35.59	24.81
Weight loss	198	5.19	15.39

Bowel

Endpoint	questionnaire	RT	RT-CT	p
Diarrhoea	QLQ-C30	6.9	21.3	0.001
Role functioning	QLQ-C30	90	83	0.03

Bowel

Endpoint	questionnaire	RT	RT-CT	p
Diarrhoea	QLQ-C30	6.9	21.3	0.001
Role functioning	QLQ-C30	90	83	0.03

Scandinavian trial

- **FUP min: 4 yrs**
- **Self assessed: EORTC-QLQ-C30, other**
 - Sexual function
 - Vaginal problem/change (score for GYN tumors)
 - Male IIEF (international index of erectile function)
- **measured:**
- **LENT SOMA**
 - Bowel
 - Urinary
- **St. Marks score**
 - Fecal incontinence

Scandinavian trial

- **Self assessed:** EORTC-QLQ-C30, other
 - **Sexual function**
 - Vaginal problem/change (score for GYN tumors)
 - Male IIEF (international index of erectile function)
- **Measured:**
- LENT SOMA
 - **Bowel**
 - Urinary: **about 25% incontinence**
- St. Marks score
 - Fecal incontinence

Bowel QLQ-C30 (no stoma)

Treatment	Incontinence for liquid	Incontinence for gas
RT	38%	56%
RT-CT	58%	75%
Treatment	Good function	P
RT	30%	0.046
RTCT	11%	

Bowel QLQ-C30 (no stoma)

Treatment	Incontinence for liquid	Incontinence for gas
RT	38%	56%
RT-CT	58%	75%
Treatment	Good function	P
RT	30%	0.046
RTCT	11%	

Male sexual function: IIEF

	CRT (<i>n</i> = 26)	RT (<i>n</i> = 18)	Maximum points on IIEF questionnaire
Age (y)	66 (42–79)	64 (51–78)	
Erectile function*	6.9 (1–29)	10.4 (1–29)	30
Orgasmic function	2.6 (0–10)	3.9 (0–10)	10
Sexual desire	4.8 (2–8)	5.6 (2–9)	10
Intercourse satisfaction	2.7 (0–13)	4.2 (0–13)	15
Overall satisfaction	4.5 (1–9)	4.9 (1–9)	10

***1-10: severe dysfunction**

11-16: moderate dysfunction

17-21: mild to moderate dysfunction;

22-25: mild dysfunction;

26-30: no dysfunction

Female sexual function

- < 50% sexually active during the last month
- vaginal dryness during intercourse
- Low interest in sex
- **Sex doesn't affect their life**

SCRT+S vs LCRTC+S

Polish trial

TROG trial

Polish trial

FUP med: 48 mts

RTOG-EORTC scale: skin, SB, LB, bladder; LENT-SOMA scale: nerves

	Short-course radiotherapy (<i>n</i> = 155)	Che- moradiation (<i>n</i> = 157)
Deaths		
Yes	52 (33.5)	53 (33.8)
Deaths related to rectal cancer	35	46
Deaths from treatment complications*	5	5
Deaths from causes not related to rectal cancer	8	1
Deaths from unknown causes	4	1
No	103 (66.5)	104 (66.2)
Late complications		
Yes	39 (28.3)	38 (27.0)
Severe late complications	14 (10.1)	10 (7.1)
No	99 (71.7)	103 (73.0)

Polish trial

Severe late tox	Short-course radiotherapy (n = 138)	Chemoradiation (n = 141)
Small/large intestine†	7 (5.1)	2 (1.4)
Urinary bladder	2 (1.4)	1 (0.7)
Skin (non-healing perineal wound)	0	4 (2.8)
Urether	1 (0.7)	1 (0.7)
Nerves: motor function	3 (2.2)	2 (1.4)
Nerves: sensory function	1 (0.7)	1 (0.7)
Nerves: pain	0	1 (0.7)
Postoperative hernia requiring surgery	1 (0.7)	1 (0.7)
Fracture of femoral neck	1 (0.7)	0
Total complications	16 in 14 patients	13 in 10 patients

TROG-trial

FUP med: 5.9 yrs

RTOG/EORTC scale: every 6 mts for 2 yrs, 1 yr for 5 yrs.

Table 4. Late RT Toxicities by Worst Grade

Late RT Toxicity Type	SC (n = 155)		LC (n = 158)	
	Grade 3	Grade 4	Grade 3	Grade 4
Skin, pelvic	0	1	0	1
Subcutaneous tissue	0	1	0	1
Small or large intestine	2	3	6	2
Bladder	3	0	2	0
Other*	2	1	3	0
Any toxicity	6	3	10	3

Organo	Constraints	Endpoint	Rischio
Intestino tenue - Singole anse - Intera cavità peritoneale	V15 < 120 cc V45 < 195 cc	Tossicità acuta \geq G3	<10%
Vescica	D max < 65 Gy V65 < 50% V70 < 35% V75 < 25% V80 < 15%	Tossicità tardiva \geq G3	<6%
Teste femori (7)	V52 < 10% (70% della dose totale)	Osteonecrosi	<1%
Ano (8)	\leq 30 Gy SAI \leq 10 Gy SAE \leq 50 Gy PM \leq 40 Gy EA	urgenza	
Bulbo penieno (9)	D70 < 40 Gy	Disfunzione erettile	<1%
Vagina (9)	Evitare 1/3 inferiore	Secchezza Dispareunia	

Displacement devices

small bowel “displacement devices”:

full bladder

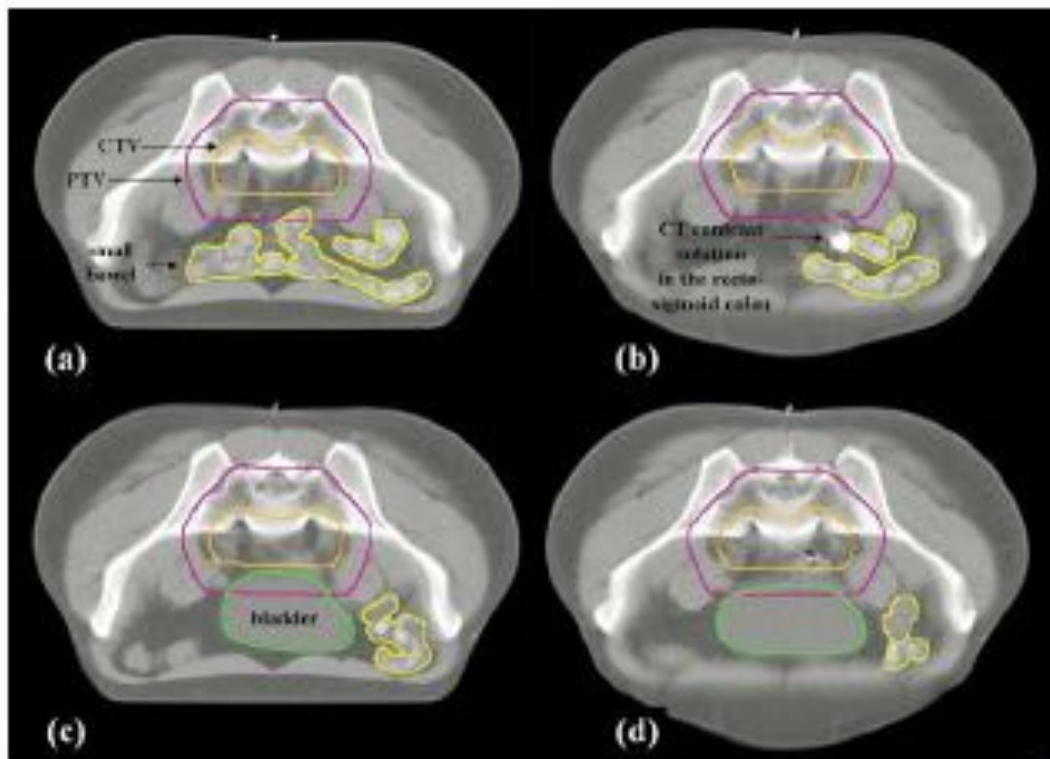
belly board/false table-top



Displacement devices

belly board vs full bladder:

nothing



BBD

FB

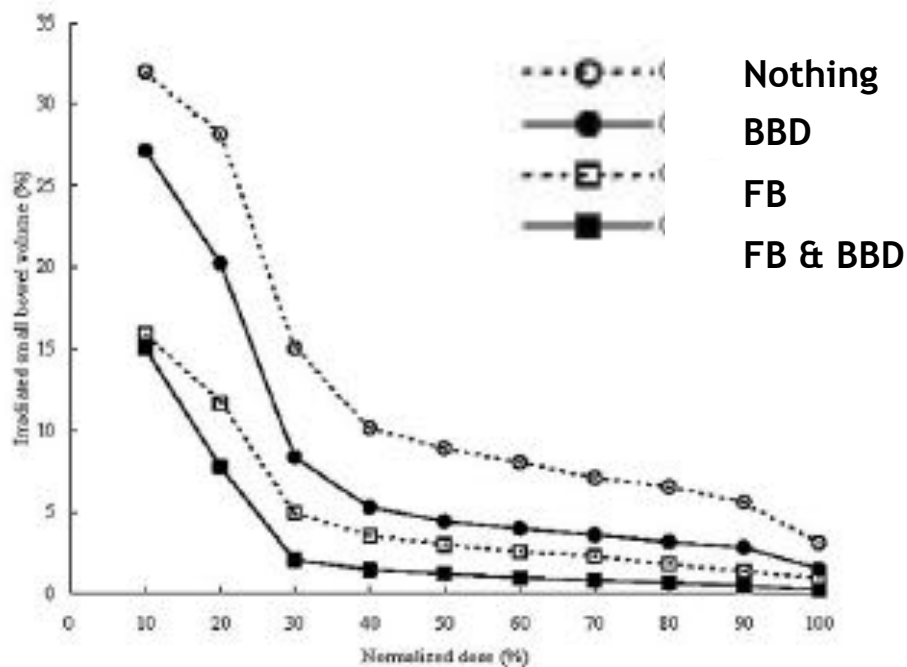
FB &
BBD

PRE-operative and POST-operative

Displacement devices

belly board vs full bladder:

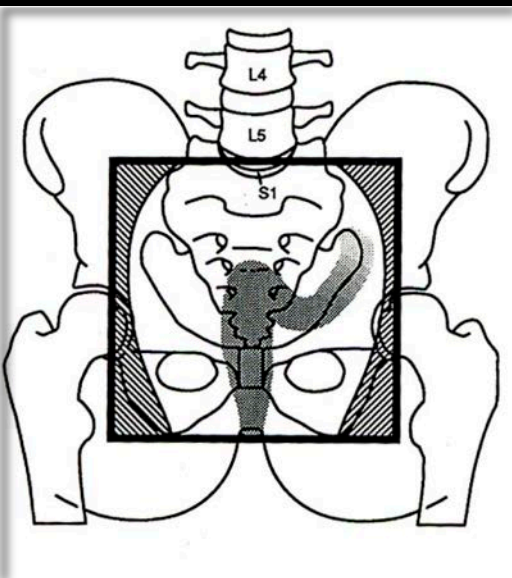
Belly-Board+Full-Bladder > Full-Bladder > Belly-Board



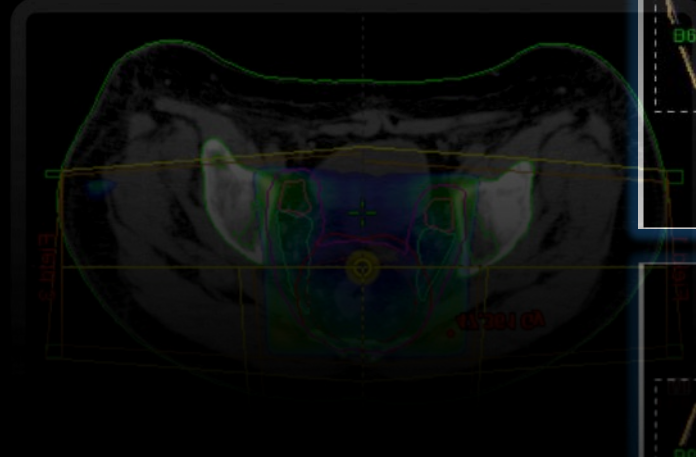
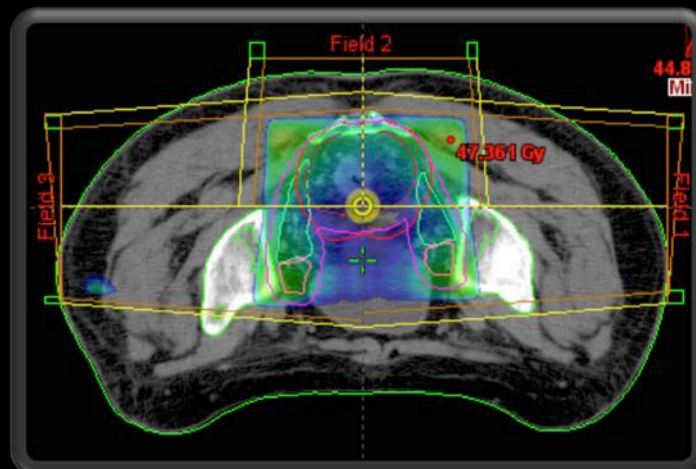
PRE-operative

Technique

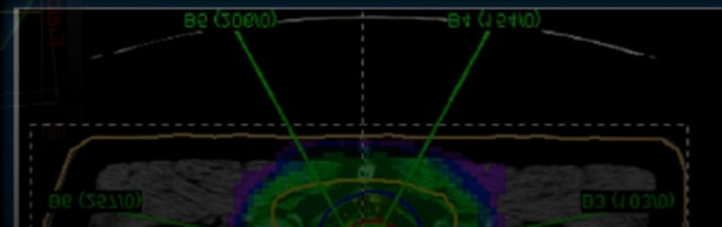
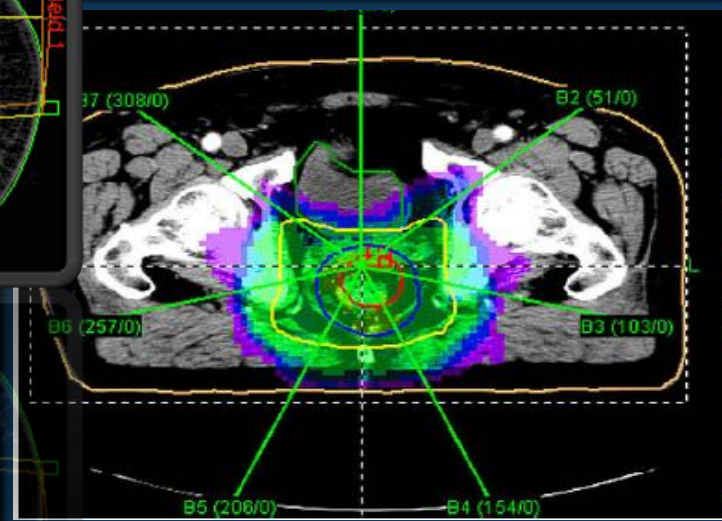
2D



3D

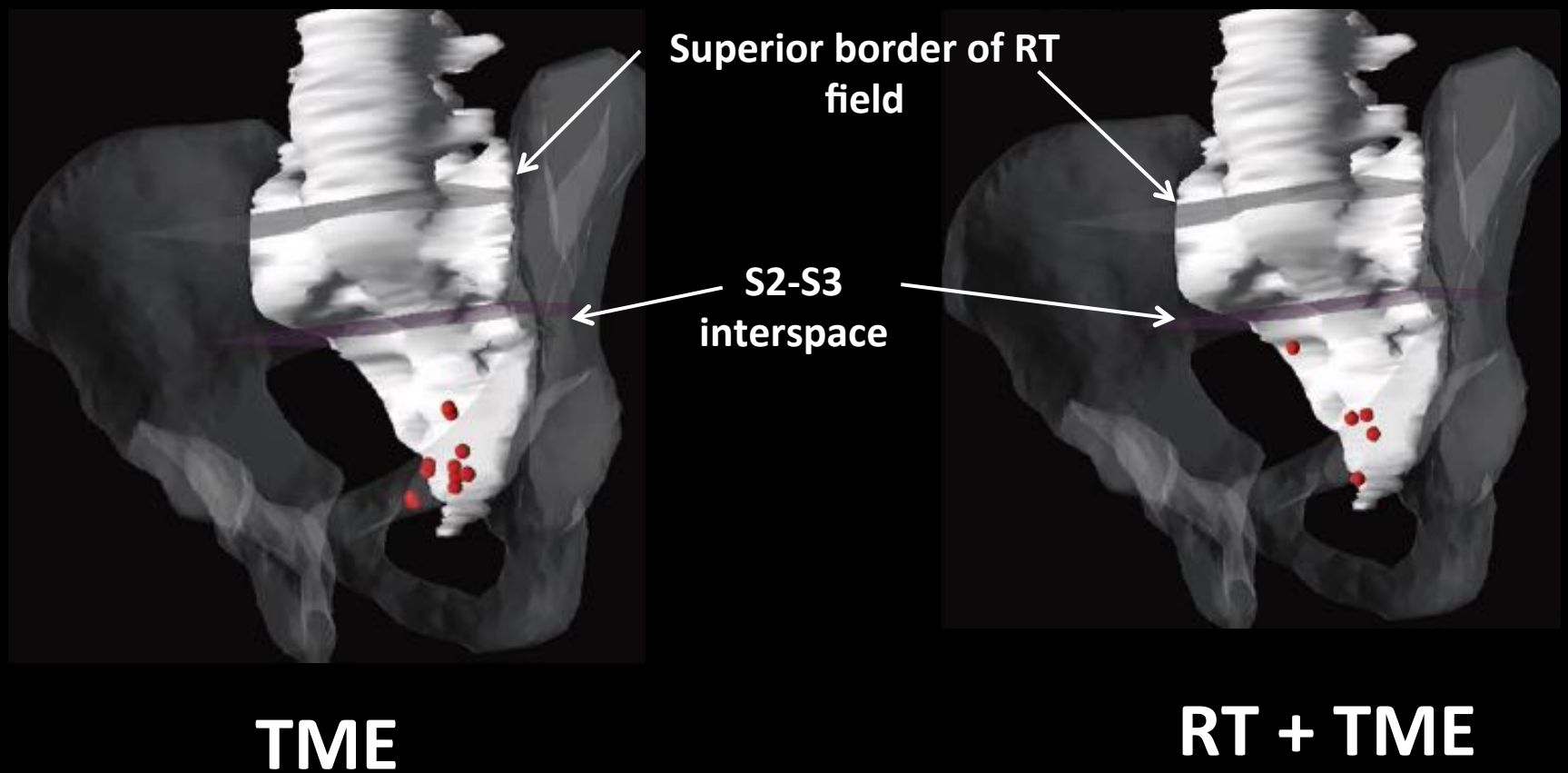


IMRT



CTV reduction

Local Relapse pCRM- & pN-



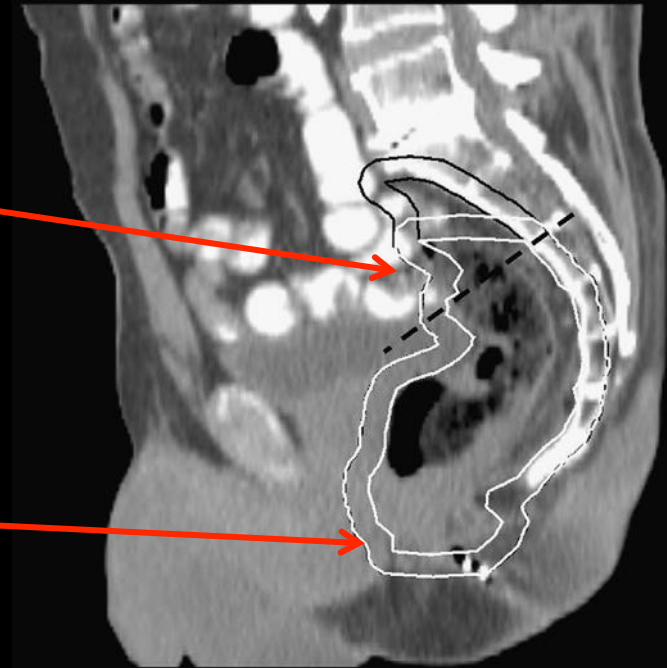
Nijkamp et al IJROBP 2011

Nijkamp *Multidisciplinary Management of Rectal Cancer 2012*

CTV: bowel/sphincter

Superior limit
(MRF-, cN0)

Inferior limit
(low, sphincter not invaded)



Levators barrier against cancer spread.

No lymph nodes in the ischiorectal fossa.

Recurrences in the ischiorectal fossa/perineum after APR (surgical contamination)

Nijkamp et al IJROBP 2011

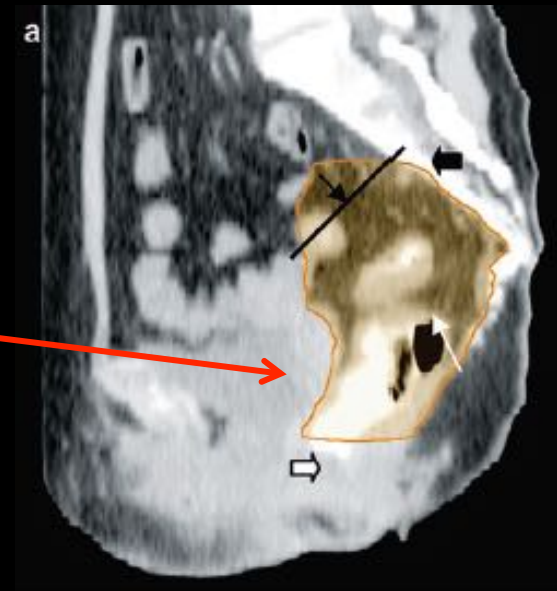
Bujiko *Multidisciplinary Management of Rectal Cancer* 2012

CTV: sexual

Anterior limit

Exclude inferior part of the vagina
(gh. Bartolini)

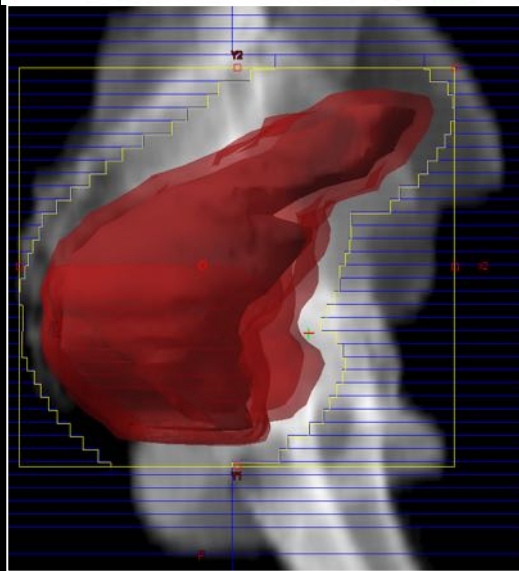
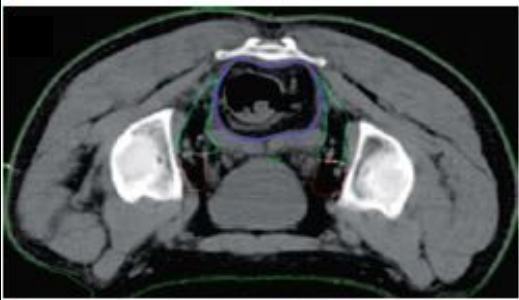
Inferior limit: penile bulb



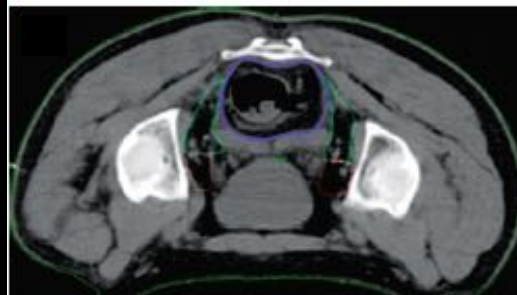
D 70	Erectile dysfunction
0-40	0%
40-70	80%
>70	100%

CTV modulation

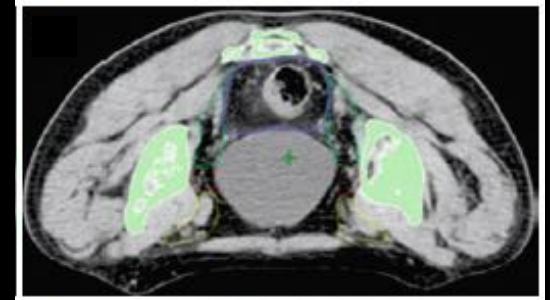
cT3 high



cT3 mid /low, IIN+

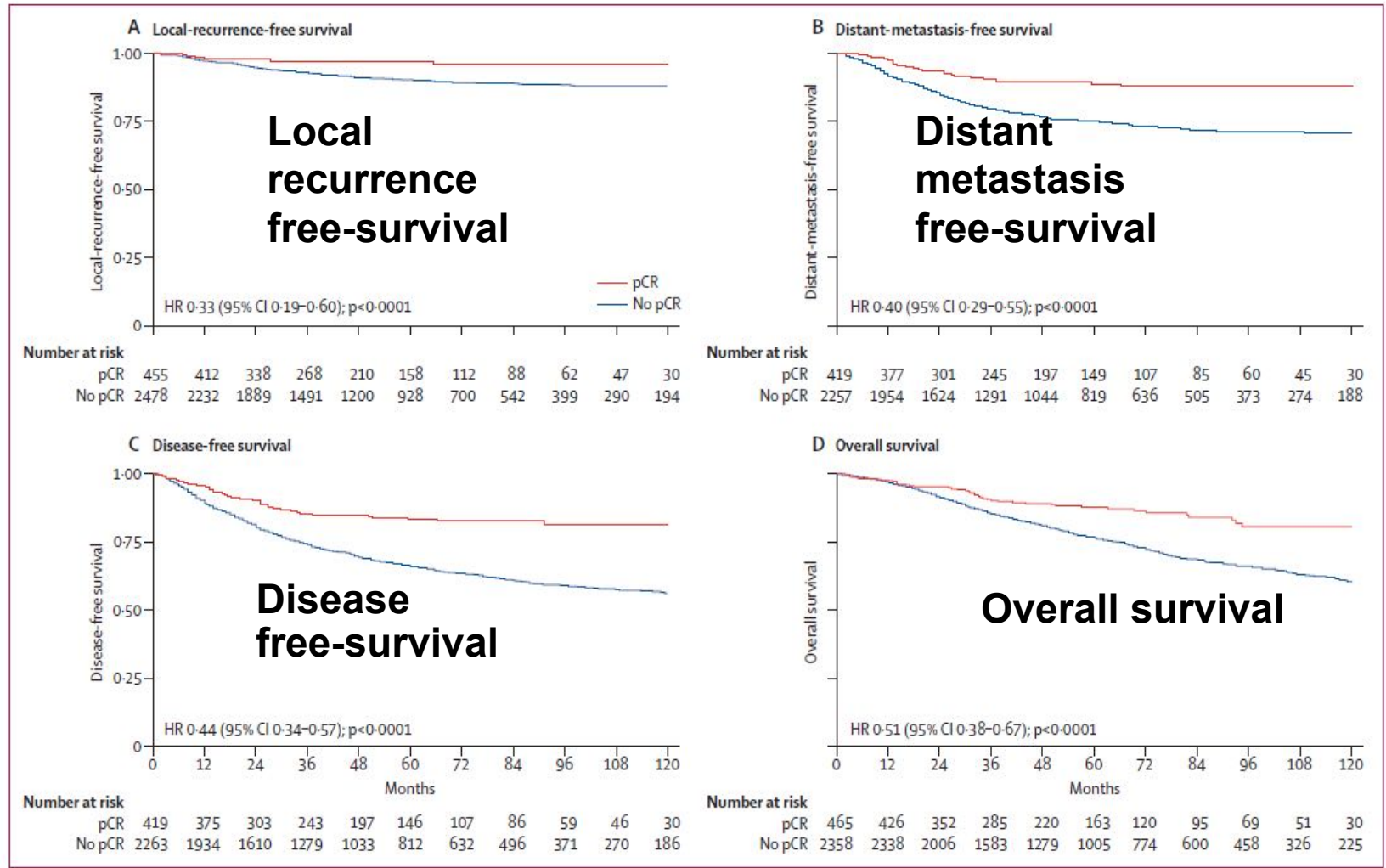


cT4 anterior organ,
cT3 ON +



ypCR pooled analysis

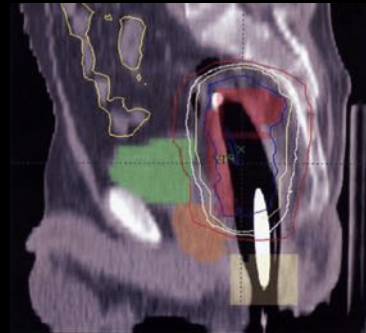
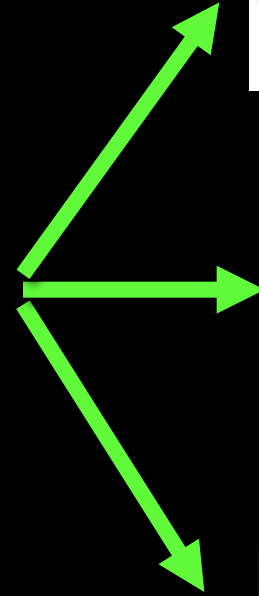
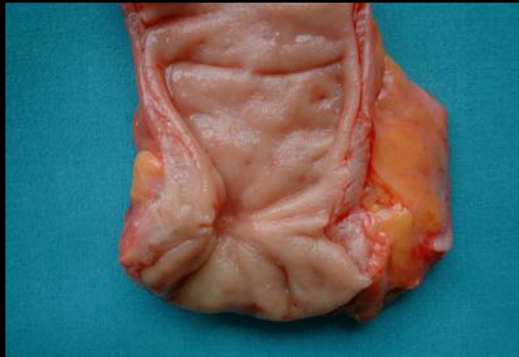
484 pCR on **3105** included patients (from 27 studies)



Surgery modulation



R
T
C
T



Cause of death, R0 patients

12 yrs FUP Dutch trial

	RT+TME (n=315)	TME alone (n=319)
Rectal cancer	119 (38%)	152 (48%)
Radiotherapy complications	2 (<1%)	0 (0%)
Surgery complications	20 (6%)	16 (5%)
Secondary malignancy	43 (14%)	30 (9%)
Cardiovascular cause	46 (15%)	45 (14%)
Pulmonary cause	16 (5%)	15 (5%)
Infectious cause	3 (1%)	2 (<1%)
Neurological cause	4 (1%)	4 (1%)
Ileus	3 (1%)	2 (<1%)
Other	39 (12%)	32 (10%)
Unknown	20 (6%)	21 (7%)

Data are number (%). Pearson χ^2 test between all causes of death p=0.448.
 RT=radiotherapy. TME=total mesorectal excision.

LR by treatment

Therapy	Specialized Centers	Total population
TME	11%	20% (in cT3)
Preop RT	5%	

LR by treatment

Therapy	Specialized Centers	Total population
TME	11%	20% (in cT3)
Preop RT	5%	10%

RT Indication by stage

		10-year local recurrence			
		n	RT+TME (%)	TME (%)	p
All eligible patients					
→	TNM I	507	<1%	3%	0.027
	TNM II	491	5%	8%	0.212
→	TNM III	622	9%	19%	<0.0001
Patients with a negative CRM					
→	TNM I	497	<1%	3%	0.027
	TNM II	421	4%	7%	0.355
→	TNM III	435	5%	17%	<0.0001

Age and comorbidities

Baseline co-morbidity	Number of patients	Percentage
Diabetes	51	7%
Hypertension	230	29%
Inflammatory bowel disease	35	4%
Previous pelvic surgery	43	5%
Previous TURP	95	12%

Age and comorbidities

	Age		Hypertension		Inflammatory bowel disease	
	HR*	95% CI	HR	95% CI	HR	95% CI
Rectal bleeding	1.04	1.01, 1.08	0.94	0.62, 1.40	0.42	0.13, 1.37
Proctitis	1.04	1.01, 1.08	0.57	0.34, 0.97	0.84	0.30, 2.37
Sphincter control	0.99	0.94, 1.05	0.42	0.16, 1.09	1.92	0.57, 6.45
Stool frequency	0.99	0.95, 1.03	1.10	0.68, 1.79	0.98	0.35, 2.79
Faecal urgency	1.02	0.99, 1.06	0.83	0.53, 1.30	2.28	1.09, 4.76
Loose stools	1.00	0.98, 1.03	0.92	0.65, 1.31	2.31	1.24, 4.31
Urinary frequency	0.98	0.95, 1.01	1.16	0.76, 1.77	0.91	0.36, 2.33
Nocturnal frequency	0.99	0.95, 1.02	0.91	0.56, 1.49	0.40	0.09, 1.66
Urine incontinence	0.99	0.95, 1.05	0.90	0.47, 1.70	1.27	0.39, 4.18
Decreased stream	0.98	0.94, 1.03	0.22	0.08, 0.62	0.81	0.19, 3.41
Haematuria	0.96	0.90, 1.04	0.63	0.21, 1.87		

Conclusions

- **LATE TOX**

- Surgery > RT-surgery > RT-CT-surgery
- More detailed reporting from **SC trials**
- **Random trials SC vs LC-CRT: NO DIFFERENCE**

- **Technique:** always 3D, selected IMRT
- **CTV modulation:** lowering upper border > IMRT
- **Surgery modulation:** CLINICAL TRIAL, (ycCR)
- **Right indication:** tumor and patient

