Approccio multidisciplinare nei tumori del retto

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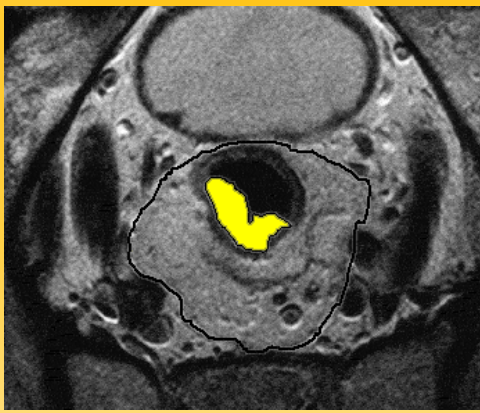
RECENT CHANGES IN RECTAL CANCER DIAGNOSIS AND THERAPY

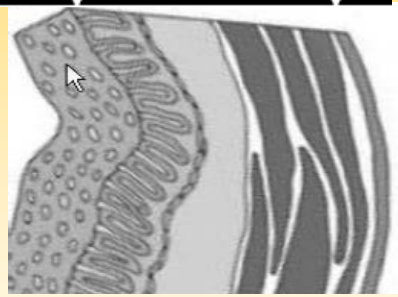
- Optimal staging by EUS and MRI
- The concept of TME surgery and CRM
- The role of radiotherapy
  - Preoperative RT vs postoperative RT
  - Evaluation of response
  - Impact of new technologies

Imaging Modalities

Local evaluation:



- **High resolution pelvic MRI**
  - High soft tissue contrast
  - Well visualization of perirectal soft tissue including
  - Mesorectal Fascia (MRF)
  - Well visualization of lateral lymph nodes



- **Transrectal ultrasonography (TRUS)**
  - Well differentiation of anorectal wall layers and perirectal tissue
  - Well depiction of the tumor including accurate dept of invasion

Local Staging: MRI

Table 1 Preoperative Staging: Modality Strengths

	CRM	T Stage	N Stage	EMVi	Peritoneum
EUS	NA	+++	++	NA	NA
CT	+	++	−	+	+
MRI	+++	+++	+++	+++	++
PET/CT	NA	NA	+	NA	NA

NA, not applicable.

Jessica Evans, Seminars in Rad oncol, 2011

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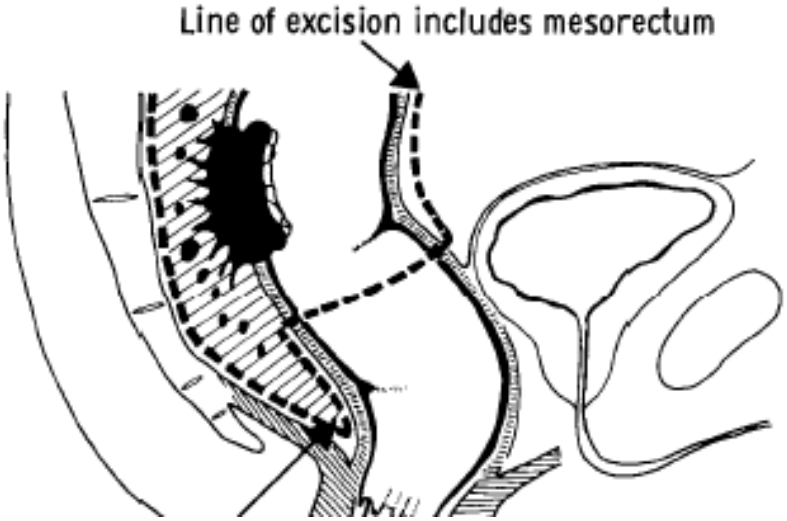
Br. J. Surg. Vol. 69 (1982) 613-616 Printed in Great Britain

The mesorectum in rectal cancer surgery—the clue to pelvic recurrence?

R. J. HEALD, E. M. HUSBAND AND R. D. H. RYALL
Basingstoke Bowel Cancer Clinic, Basingstoke District Hospital, Basingstoke, Hampshire.

Five cases are described where minute foci of adenocarcinoma have been demonstrated in the mesorectum several centimetres distal to the apparent lower edge of a rectal cancer. In 2 of these there was no other evidence of lymphatic spread of the tumour. In orthodox anterior resection much of this tissue remains in the pelvis, and it is suggested that these foci might lead to suture-line or pelvic recurrence. Total excision of the mesorectum has, therefore, been carried out as a part of over 100 consecutive anterior resections. Fifty of these, which were classified as 'curative' or 'conceivably curative' operations, have now been followed for over 2 years with no pelvic or staple-line recurrence.

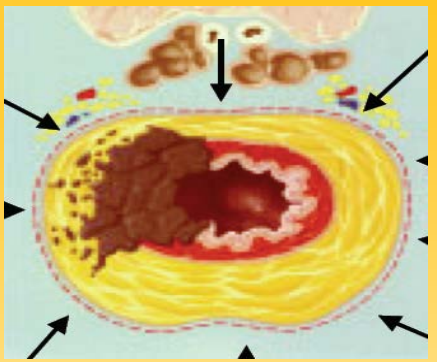
The incidence of locally recurrent disease is the most important measure of the success of any new operation for rectal cancer. Thus there has been anxiety (1) that the increase in sphincter-conserving surgery due to staplers might lead to more local recurrences. Four years ago, therefore, we combined the decrease in permanent colostomies in our unit with a change in the technique for pelvic dissection. In particular we determined that all cancers of the midrectum should be excised with the mesorectum intact. Thus the phase of dividing this during anterior resection, which is described in standard textbooks (2), was completely omitted and the whole mesorectum was encompassed by the plane of excision. In this way none of the usual 'block' of fatty lymphovascular tissue remains in the posterior half of the pelvis even though the anus, the levators, a small rectal reservoir and as much as possible of the nerve plexuses have been preserved.

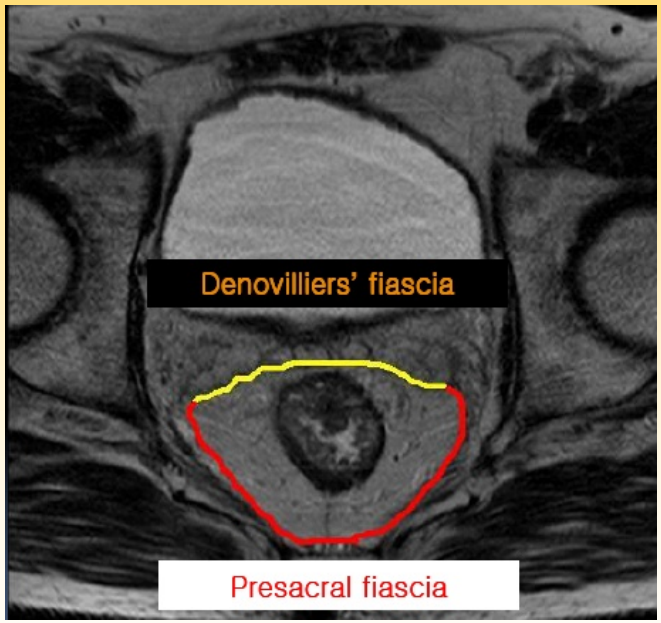


The concept of Total Mesorectal Excision

TME is the preferred technique for resection of mid to low rectal cancer

- Reduces bleeding
- Reduce pelvic recurrence
- Preserves pelvic autonomic nerves





TME - Radical en bloc resection of:

- Tumor
- Local drainage nodes
- Surrounding mesorectal fat
- Mesorectal fascia

[Heald et al, 1982]

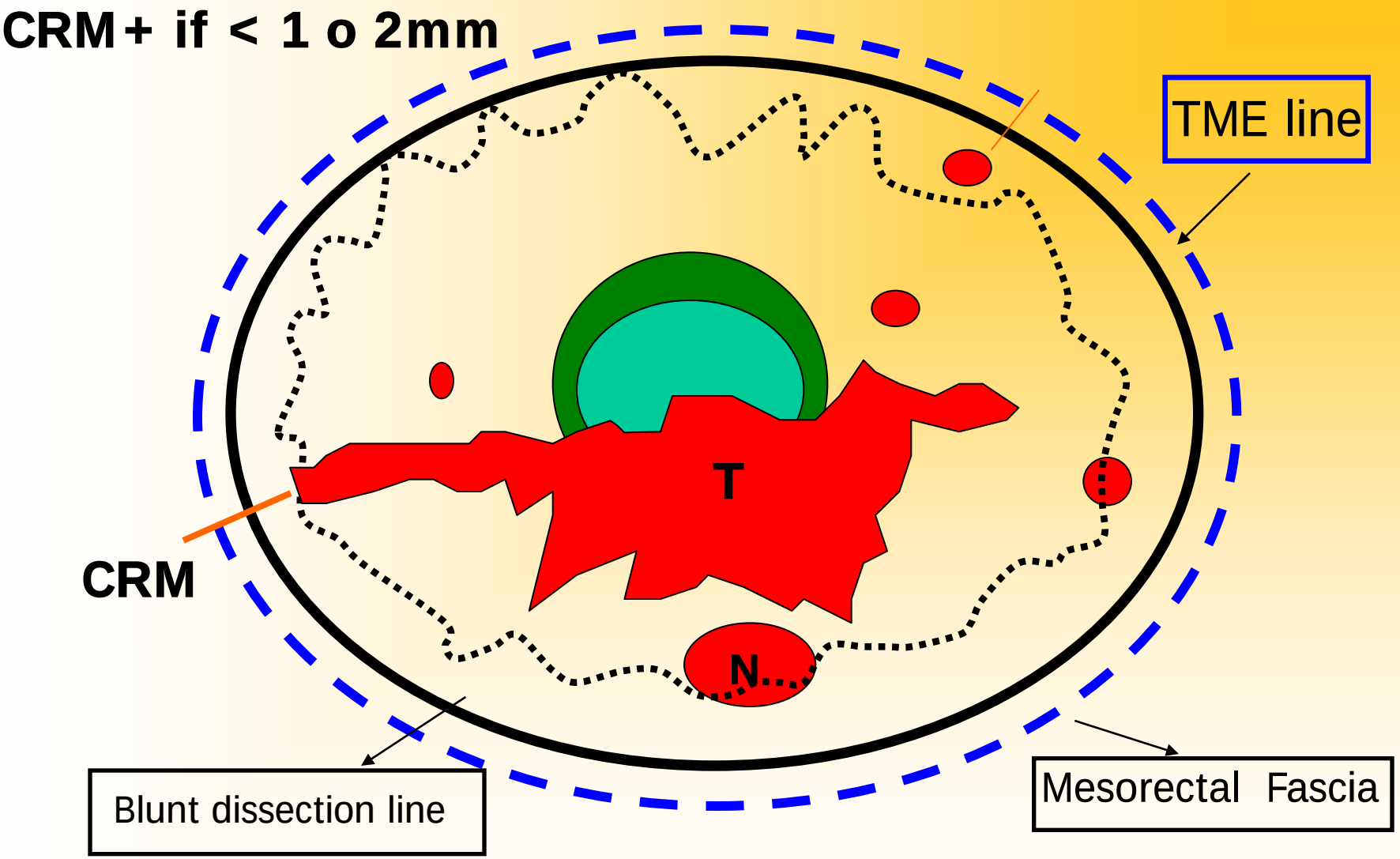
The Role of Total Mesorectal Excision in the Management of Rectal Cancer

Table 2. — Local Recurrence Rates Following TME From Selected Series With More Than 50 Patients*

Authors	No. of Patients	Study Design	Local Recurrence Rate (%)	Study Dates	Follow-Up
Heald[7] 1982	113	Retrospective	0	1978-82	2 yrs
McAnena[37] 1990	57†	Retrospective	3.5	1979-87	4.8 yrs (mean)
MacFarlane[8] 1993	135*	Retrospective	5	1978-91	7.7 yrs (median)
Enker[38] 1995	246	Retrospective	7.3	1980-92	5 yrs
Zaheer[39] 1998	514‡	Retrospective	5.7§	1982-89	5 yrs
Heald[40] 1998	519	Retrospective	6 8	1978-97 1978-97	5 yrs 10 yrs
Havenga[9] 1999	1,411†	Retrospective	7.6§	1978-94	5 yrs
Bolognese[41] 2000	71	Retrospective	12.6	1980-92	73.5 mos (median)
Martling[25] 2000	381	Prospective with historical controls	6	1994-97	24 mos
Bissett[15] 2000	124	Retrospective with controls	10	1980-96	5 yrs
Kapiteijn[36] 2001	1,748†	Randomized, controlled trial	8.2 and 2.4¶	1996-99	2 yrs
Tocchi[42] 2001	53	Retrospective	9	1990-95	68.9 mos (mean)
Wibe[43] 2002	686	Retrospective	7	1993-97	14-60 mos
Total	6,058		6.6	1978-99	2-10 yrs

[Ridgway F et al, 2003]

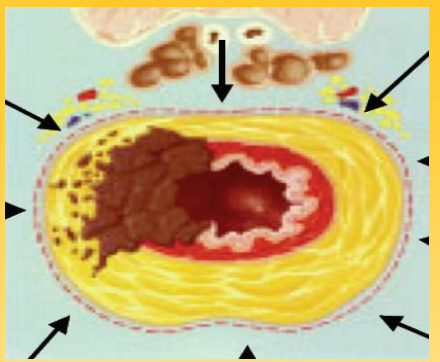
TME & CRM


CRM+ if < 1 o 2mm
TME line
T
CRM
N
Blunt dissection line
Mesorectal Fascia

Pathological examination of the CRM

Mode of CRM involvement:

- Direct (continuous) spread 45%
- Nodal 25%
- Satellite nodules 18%
- Intra-vascular spread 12%



Local Recurrence after Curative Surgery

Author	n.	CRM-	CRM+	Total	Follow-up (median)
Ng et al. (1993)	80	17%	60%	20%	26.6
Adam et al. (1994)	190	8%	66%	23%	63
HaasKock et al. (1996)	253	8%	29%	11%	29

Reducing CRM involvement for rectal cancer

- **more radical surgery**
- pre-operative radiotherapy or chemotherapy

Radiological findings do not support lateral residual tumour as a major cause of local recurrence of rectal cancer

incidence and location of LR in 880 patients from Stockholm after the introduction of TME surgery, and half of the group also received short-term preoperative RT

Results:

42% of LR originated from tumors in the upper rectum, and a majority of these patients had not received RT. In all these cases, the recurrence was at the anastomosis and virtually all had visible signs of residual mesorectal fat.

18% of the patients had LR involving the lateral wall of the pelvis, but only 6% of the tumors involved sites consistent with recurrence in iliac lymph nodes.

Conclusions:

an intentional or inadvertent partial mesorectal excision, combined with the absence of radiotherapy, may play a role in the recurrence of these tumours, and may be associated with an increased risk of local recurrence due to presacral and/or pelvic sidewall involvement in the upper rectum.

After surgery for rectal cancer, residual fatty tissue in the pelvis on postoperative CT or MRI appears to represent remaining mesorectum

[Syk E et al, 2006]

Reducing CRM involvement for rectal cancer

- more radical surgery
- **pre-operative radiotherapy**

Radiological findings do not support lateral residual tumour as a major cause of local recurrence of rectal cancer

[Syk E et al, 2006]

RECENT CHANGES IN RECTAL CANCER DIAGNOSIS AND THERAPY

- Optimal staging by EUS and MRI
- The concept of TME surgery and CRM
- The role of Radiotherapy

Why neo-adjuvant therapy in rectal cancer?

- To lower local failure rates
- To improve survival
- To allow surgery in primarily non-resectable cancers
- To facilitate a sphincter-preserving procedure in low-lying rectal cancers

Presentation Outline

- **Short course radiotherapy alone trials**
- **Combined CT-RT trials**
- **Critical points/Research**

Short-Course Radiotherapy Trials

TABLE 4. A comparison of the outcome data from the trials examining SCPRT: Swedish Rectal Cancer Trial, Dutch Trial, and MRC CR07 Trial

	Treatment						
	Swedish Rectal Trial		*Dutch Trial*		*MRC-CR07*		
	SCPRT	*Surgery*	*SCPRT*	*Surgery*	*SCPRT*	*Surgery*	*HR (95% CI)*
Local recurrence							
2-year	9%	24%**	2.4%	8.2%**	3.4%	8.3%**	
5-year	11%	27%**	5.6%	10.9%**	4.7%	11.5%	
LR by TNM	Median 13-y LR		5-y LR		3-y LR		
I	5%	15%*	0.4%	1.7%	1.9%	2.8%	0.68 (0.16–2.81)
II	6%	22%**	5.3%	7.2%	1.9%	6.4%	0.29 (0.12–0.67)
III	23%	46%**	10.6%	20.6%**	7.4%	15.4%	0.46 (0.28–0.76)
LR by CRM involvement			5-y LR		3-y LR[a]		HR (95% CI)
Involved (positive)	—	—	19.7%	23.5%	13.8%	20.7%	0.64 (0.25–1.64)
Not involved (negative)	—	—	3.4%	8.7%**	3.3%	8.9%	0.36 (0.23–0.57)
LR by distance from anal verge	Median 13-y LR		5-y LR		3-y LR		HR (95% CI)
>10–15 cm	8%	12%	3.7%	6.2%	1.2%	6.2%	0.19 (0.07–0.47)
>5–10 cm	9%	26%**	3.7%	13.7%**	5.0%	9.8%	0.5 (0.28–0.9)
0–5 cm	10%	27%*	10.7%	12%	4.8%	10.4%	0.45 (0.23–0.88)
Overall survival							HR (95% CI)
2-year	—	—	82%	81.8%	86.1%	84.8%	0.91 (0.73–1.13)
5-year	58%	48%*	64.2%	63.5%	70.3%	67.9%	

CRM = circumferential resection margin; LR = local recurrence; MRC = Medical Research Council; SCPRT = short-course preoperative radiotherapy.

[a]Recurrence date data from CR07 is from Kaplan-Meier estimates.

*$P < .01$, **$P < .001$. Significant results reflect a comparison of variables within the individual study. Only significant values are shown.

Fleming F et al, 2011

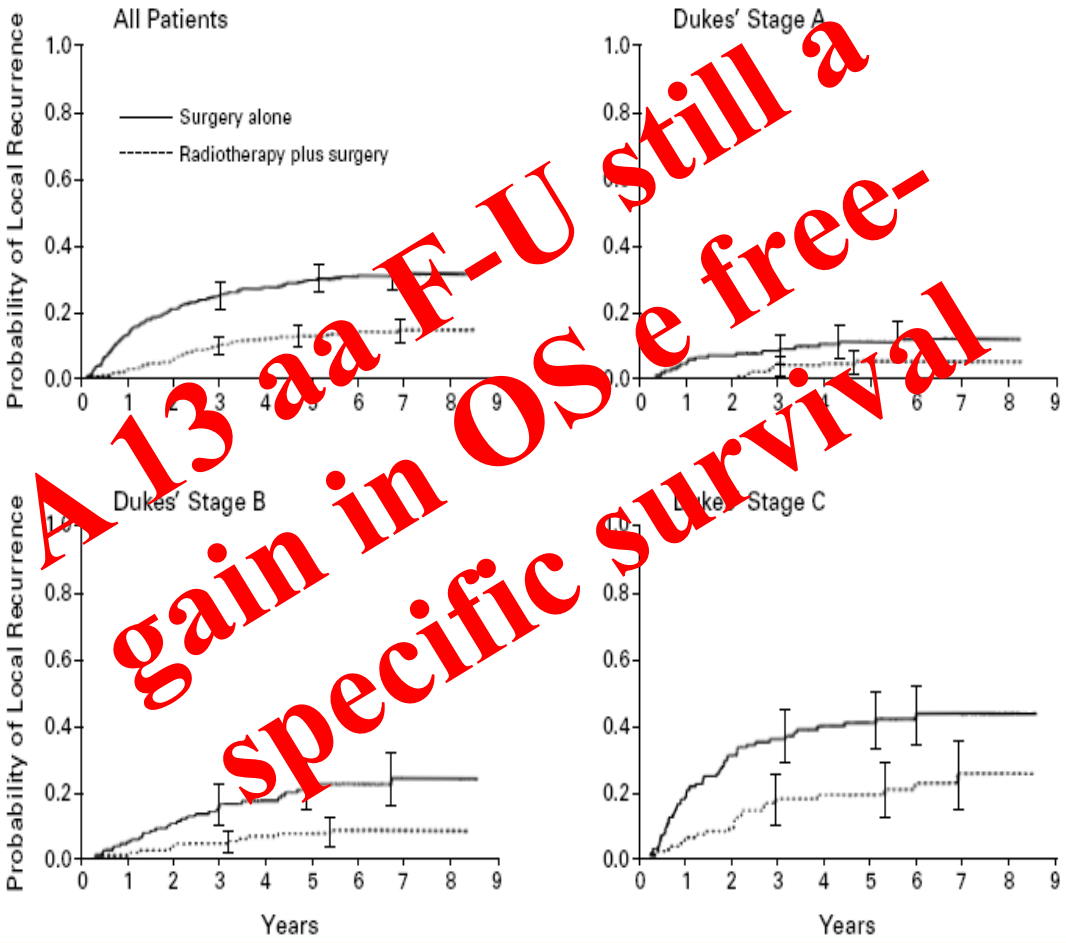
Short-term preoperative radiotherapy

IMPROVED SURVIVAL WITH PREOPERATIVE RADIOTHERAPY IN RESECTABLE RECTAL CANCER

1168 patients randomized to surgery alone or to surgery following a 1-wk of pelvic RT (25 Gy in 5 daily fractions)

5-year LR rate significantly improved with preoperative RT (23% vs 9%, among the curatively treated patients)
the 5-year survival rate significantly improved (58% vs 48%)

this trial was conducted in the surgical era prior to the adoption of TME



A 13 aa F-U still a gain in OS e free-specific survival

[SWEDISH RECTAL CANCER TRIAL, 1997]

Short-term preoperative radiotherapy

PREOPERATIVE RADIOTHERAPY COMBINED WITH TOTAL MESORECTAL EXCISION FOR RESECTABLE RECTAL CANCER

- **Dutch CKVO 95-04 trial**
- 1805 pts with T1-T3 disease
- randomized to TME alone or 25 Gy/5 fr pre-op followed by TME (3-4 days after the end of RT)

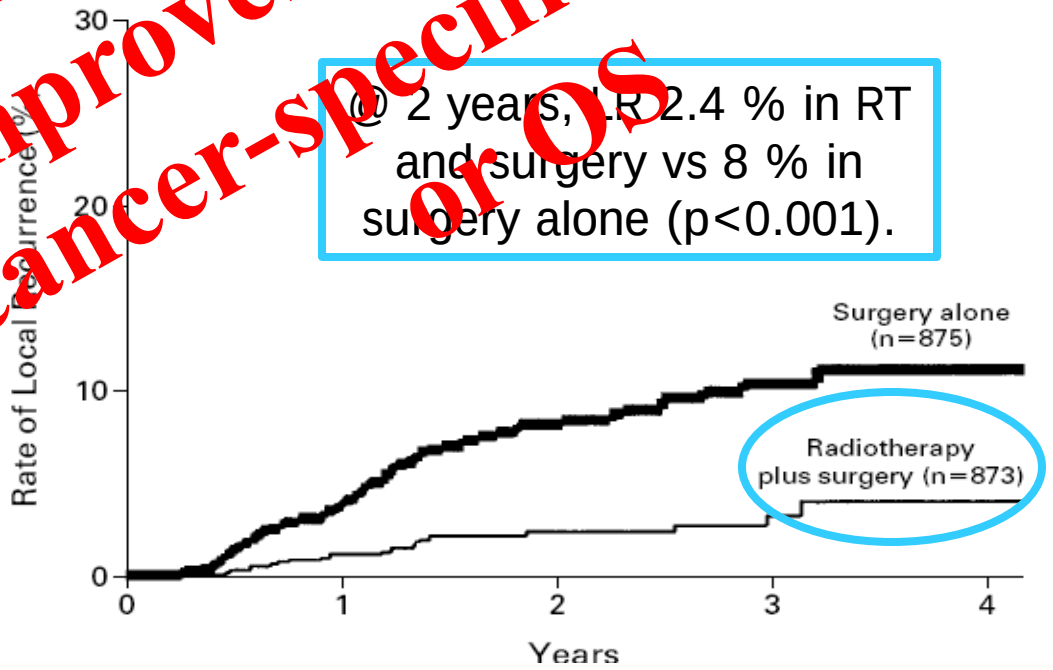
significant benefit was seen with preoperative RT in patients with TNM stage Ⅱ and Ⅲ disease, with the two-year local relapse rates decreasing from 5.7% to 1% and from 15% to 4.3%, respectively

[Kapiteijn E et al, 2003]

Variable	Radiotherapy plus Surgery		Surgery Alone		P Value
	No. of Patients at Risk	Local Recurrence at 2 yr	No. of Patients at Risk	Local Recurrence at 2 yr	
		%		%	
TNM stage					
I	265	[illegible]	244	[illegible]	0.15
II	[illegible]	1.0	241	5.7	0.01
III	[illegible]	4.3	[illegible]	15.0	<0.001
IV (distant metastases but complete local resection)	47	10.1	48	23.8	0.25

A 12 aa F-U still improves LR, but non cancer-specific survival or OS

@ 2 years, LR 2.4 % in RT and surgery vs 8 % in surgery alone (p<0.001).

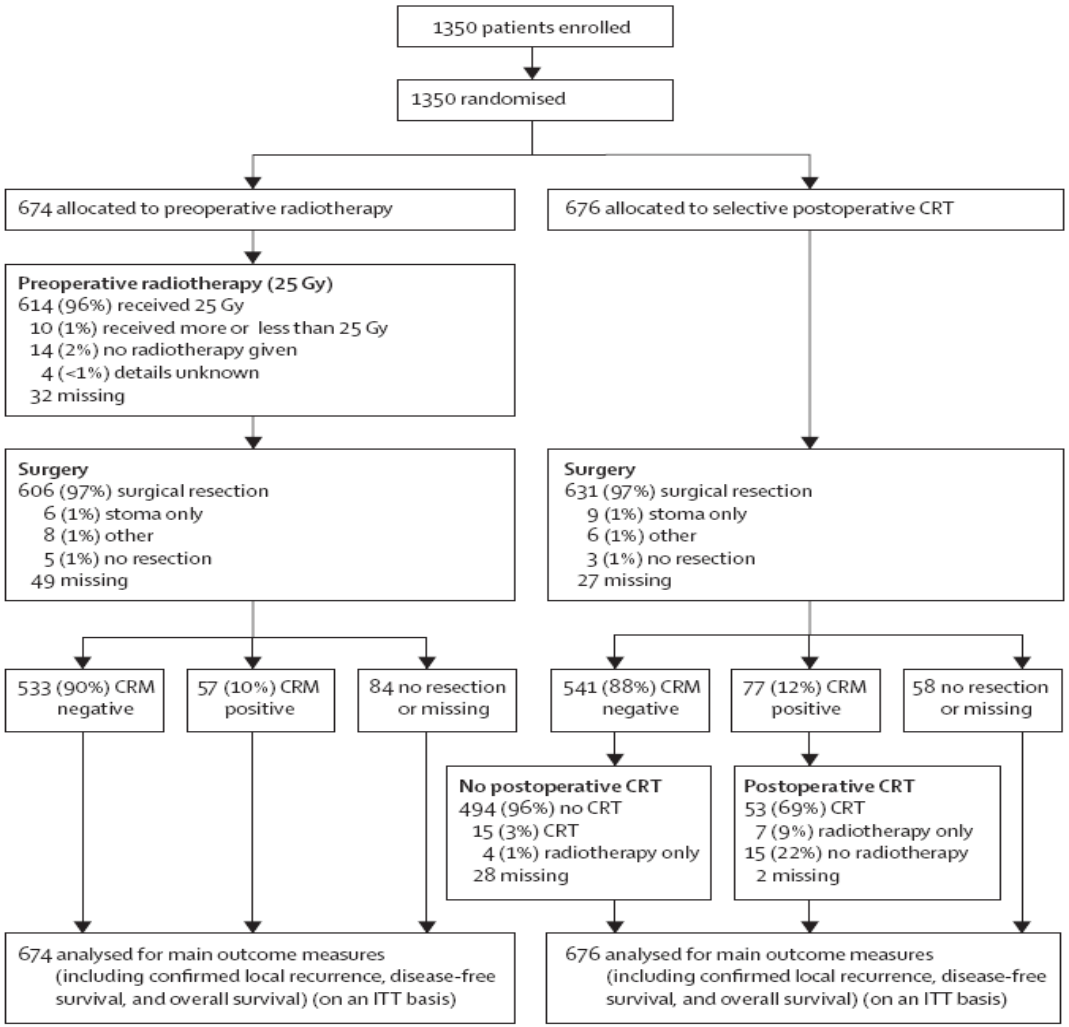


Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial

80 centres in four countries

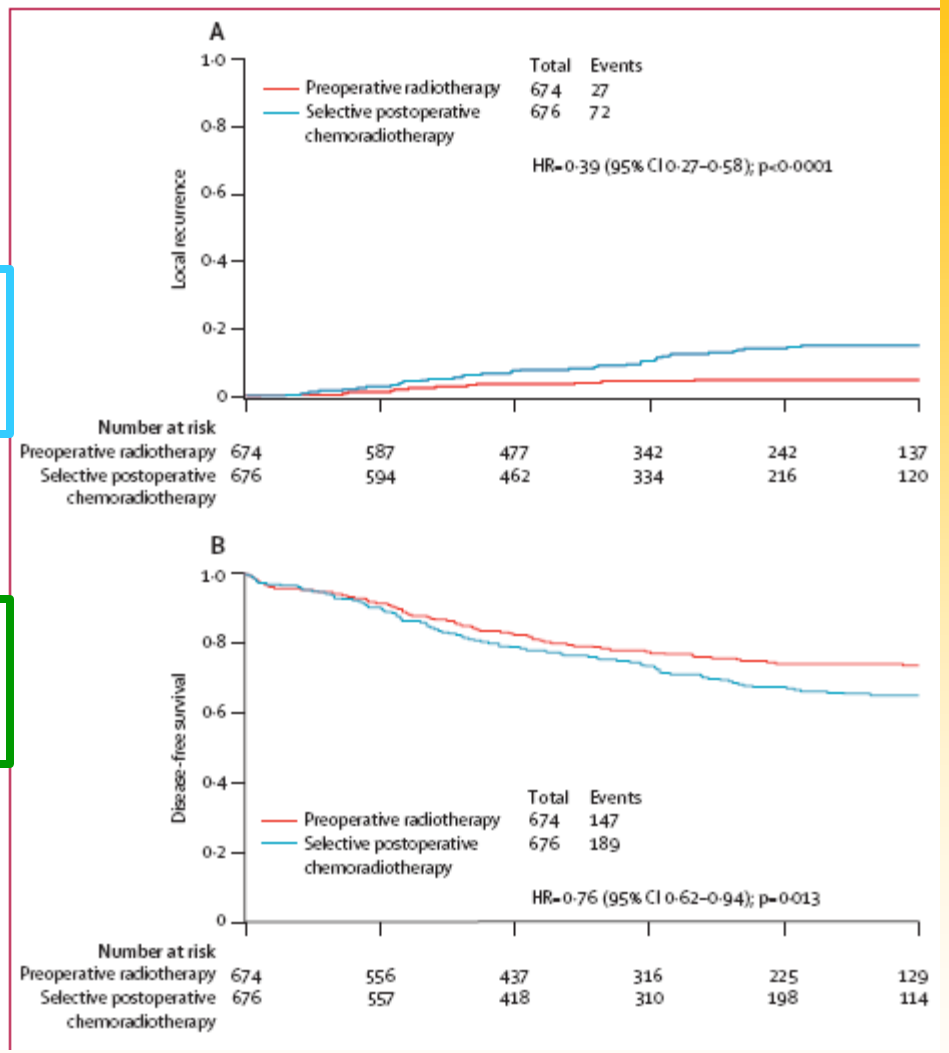
1350 patients with operable adenocarcinoma of the rectum randomly assigned to short-course preoperative RT (25 Gy/5 fr; n=674) or to initial surgery with selective postoperative CT-RT (45 Gy/25 fr with concurrent 5-FU restricted to patients with involvement of the CRM (n=676)

[Sebag-Montefiore D et al, 2009]



Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial

- Median follow-up: 4 years
- 99 patients had developed LR (27 preoperative RT vs 72 selective postoperative CT-RT)
- Reduction of 61% in the relative risk of LR in group of preoperative RT (HR 0.39, p<0.0001)
- Absolute difference at 3 years of 6.2% (95% CI 5.3–7.1) (4.4% preoperative RT vs 10.6% selective postoperative CT-RT)
- A relative improvement in DFS of 24% for patients receiving preoperative RT (HR 0.76, p=0.013)
- Absolute difference at 3 years of 6.0% (95% CI 5.3–6.8) (77.5% vs 71.5%)
- OS did not differ between the groups (HR 0.91, p=0.40)



[Sebag-Montefiore D et al, 2009]

Short-term preoperative radiotherapy

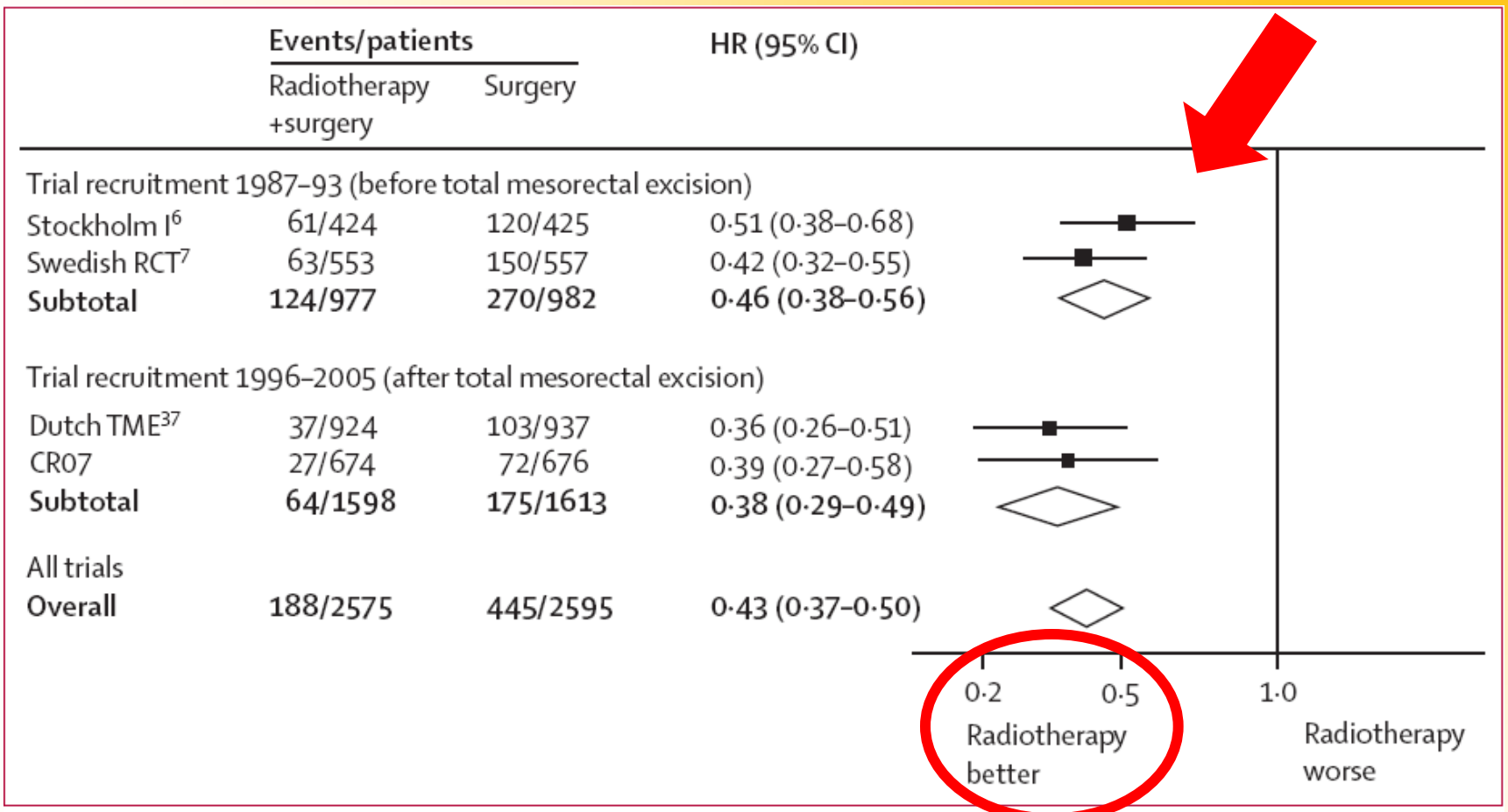


Figure 3: Summary of reduction in risk of local recurrence in phase III trials that have assessed short-course preoperative radiotherapy with 5 Gy per fraction

[Sebag-Montefiore D et al, 2009]

Presentation Outline

- **Short course radiotherapy alone trials**
- **Combined CT-RT trials**
- **Critical points/Research**

Concomitant Preoperative radiotherapy and chemotherapy

- **interaction (radiosensitization)**
- **increased local regression (pCR-rate)**
- **increase local control**
- **increased acute toxicity**

BUT…

Probably little effect on systemic control

Combined Chemotherapy and Radiotherapy Trials

TABLE 1. Comparison of comparable data from the FFCD 9203 and EORTC 22921 trials

	Long term RT		Treatment	Long term RT	
	FFCD 9203			*EORTC 22921*	
	RT 45 Gy	*RT 45 Gy and 5-FU/LV*		*RT 45 Gy*	*RT 45 Gy and 5-FU/LV*
No. of patients	367	375		505	506
Clinical staging					
T3	85.6%	88.5%		90%	90%
T4	11.2%	9.9%		10%	10%
Acute grade III/IV toxicity	2.9%	14.9%*		7.4%	13.9%**
Uniform TME policy	No			No	
Sphincter-sparing surgery	51.8%	52.6%		52.4%	55.6%
Postoperative complications	26.9%	20.9%		23.3%	22.8%
CRM positivity	6.8%[a]	6.2%		6.5%[b]	4.9%
Pathological complete response	3.6%	11.4%**		5.3%	13.7%**
5-y local recurrence	16.5%	8.1%*		17%[c]	8%*
5-y disease free survival	55.5%	59.4%		54.4%	56.1%
5-y overall survival	67.9%	67.4%		64.8%	65.8%

Fleming F et al, 2011

Preoperative Radiotherapy With or Without Concurrent Fluorouracil and Leucovorin in T3-4 Rectal Cancers: Results of FFCD 9203

661 patients withT3-4, Nx, M0 rectal adenocarcinoma randomized to preoperative RT vs preoperative CT-RT

Preoperative RT: 45 Gy in 25 fractions

CT: 5-FU 350 mg/m2/d during 5 days +leucovorin

Surgery: 3 to 10 weeks after the end of RT

Results

Grade 3 or 4 acute toxicity was more frequent with CT-RT (14.6% v 2.7%; p = 0 .05)

No difference in sphincter preservation

Complete sterilization of the operative specimen more frequent with CT-RT (11.4% v 3.6%; p= 0.05)

5-year LR: lower with CT-RT (p=0.05)

5-year OS in the two groups did not differ

Conclusion

Preoperative CT-RT despite a moderate increase in acute toxicity and no impact on OS significantly improves local control and is recommended for T3-4, N0-2, M0 adenocarcinoma of the middle and distal rectum

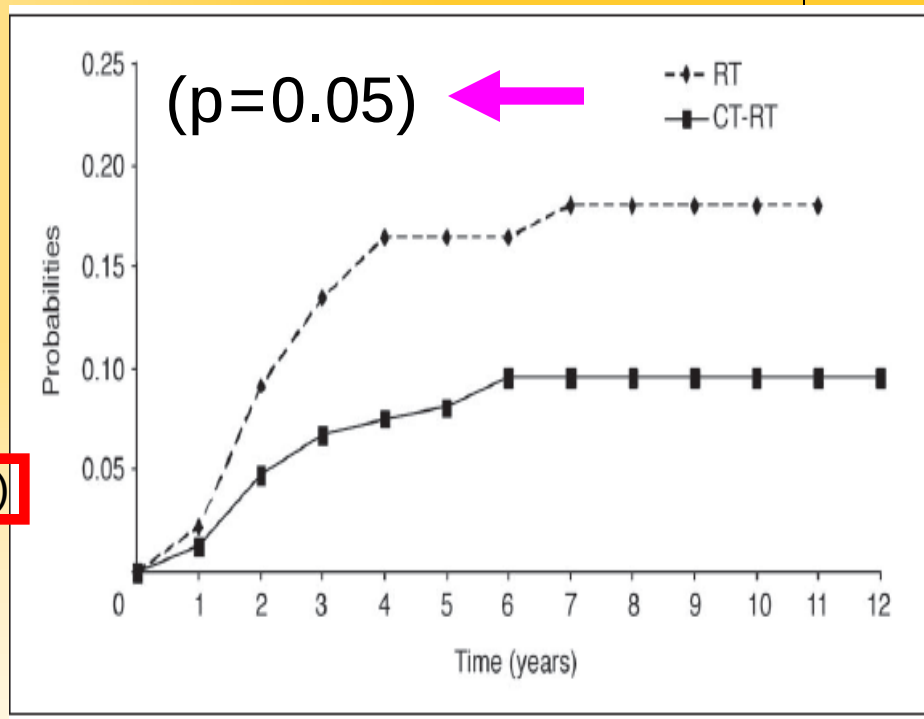


Fig 2. Cumulative incidence of local recurrence among 661 patients with treatment randomly assigned between preoperative radiotherapy (RT) and preoperative chemotherapy and radiotherapy (CT-RT). Estimate performed for patients who underwent surgery with a gross complete resection (R0-1).

Gerard JP et al, 2006

Chemotherapy with Preoperative Radiotherapy in Rectal Cancer

EORTC Radiotherapy Group Trial 22921

1011 patients with clinical stage T3 or T4 resectable rectal cancer

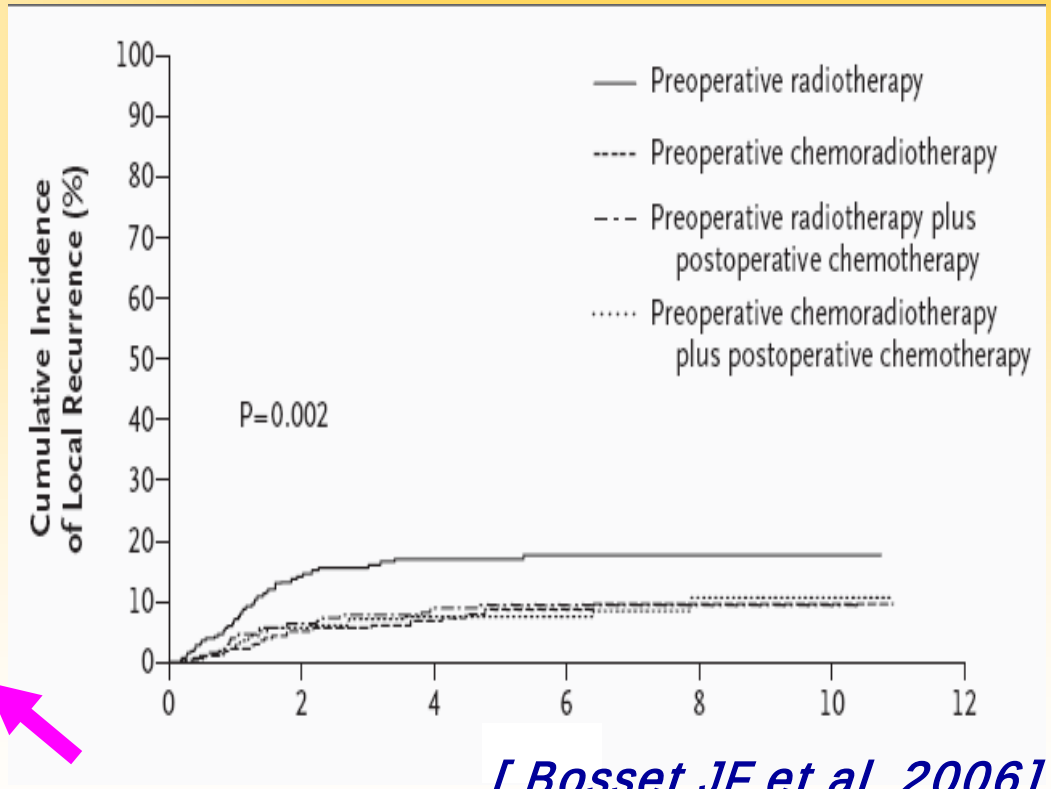
4 arms: preoperative RT, preoperative CT-RT, preoperative RT and postoperative CT, or preoperative CT-RT and postoperative CT

RT: 45 Gy/25 fr
CT: 350 mg/m2 5-FU and 20 mg/m2 of leucovorin for 5 days

no significant difference in OS between the groups that received CT preoperatively (p = 0.84) and those that received it postoperatively (p = 0.12)
5-year OS for all four groups was 65.2%

5-year LR: 8.7%, 9.6%, and 7.6% in the groups that received CT preoperatively, postoperatively, or both, respectively, and 17.1% in the group that did not receive CT (p = 0.002)

rate of adherence to CT: 82.0% preoperative and 42.9% postoperative



[Bosset JF et al, 2006]

Combined CRT and Short-Course Preop Radiotherapy Trials: the Polish Trial

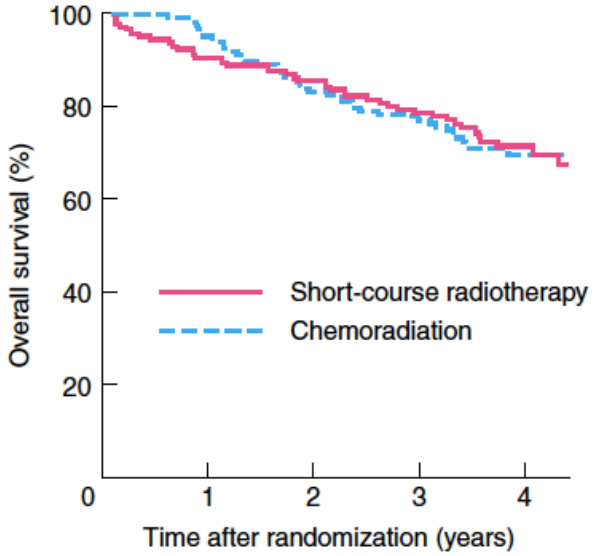
Randomized clinical trial

Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer

K. Bujko[1], M. P. Nowacki[2], A. Nasierowska-Guttmejer[3], W. Michalski[4], M. Bebenek[5] and M. Kryj[6] for the Polish Colorectal Study Group

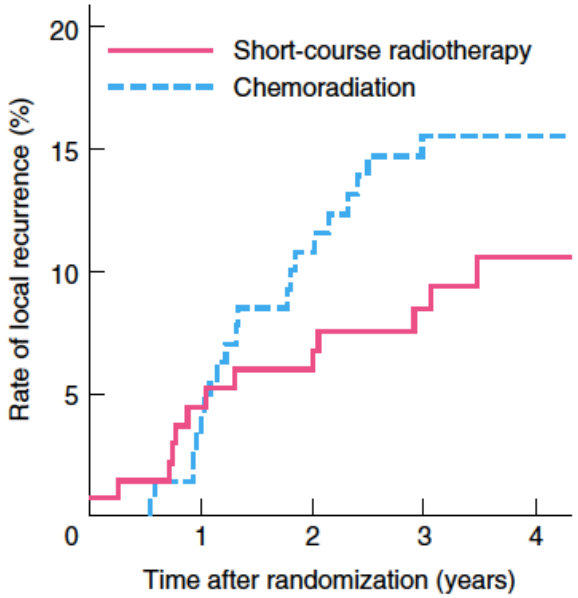
Departments of [1]Radiotherapy, [2]Colorectal Cancer, [3]Pathology and [4]Biostatistics, Maria Sklodowska-Curie Memorial Cancer Centre, Warsaw, [5]Department of Surgery, Silesian Oncological Centre, Wroclaw and [6]Department of Surgery, Maria Sklodowska-Curie Memorial Cancer Centre, Gliwice, Poland

Correspondence to: Dr K. Bujko, The Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, W. K. Roentgena 5, 02 781 Warsaw, Poland (e-mail: bujko@coi.waw.pl)



No. at risk

Short-course radiotherapy	155	135	125	110	50
Chemoradiation	157	145	125	110	56



No. at risk

Short-course radiotherapy	146	125	118	100	46
Chemoradiation	149	136	116	98	53

Not significant – different schedule – higher than expected

Combined Chemotherapy and Radiotherapy Trials

……..**Preoperative CRT trials**:

- Enhance tumor response
- Improve local recurrences rates
- When tumors close to < 2 mm CRM+ and low layer lesions
- Moderate increases of toxicity levels

Preoperative vs postoperative radiotherapy

Table 1.
Preoperative *vs.* Postoperative Radiotherapy

	Uppsala[7,8]		NSABP-R03[9]		CAO/ARO/AIO-94[10]	
	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative
Treatment	RT 25 Gy (1 week)	RT 60 Gy (8 weeks)	CRT 50 Gy	CRT 50 Gy	CRT 50 Gy	CRT 55 Gy
No. of patients	236	235	130	137	405	394
Acute toxicity G3–4	—	—	34%	23% ($p = 0.07$)	27%	40% ($p = 0.001$)
Postoperative complications	—	—	25%	22% (ns)	36%	34% (ns)
Late toxicity Grades 3–4	20%	41% (p=0.05)	-	—	14%	24% ($p = 0.01$)
pT0 N0	—	-	10%	0%	8%	0% ($p< 0.001$)
SSP	—	-	44%	34% (ns)	69%	71%
					39% (Subgroup of 194 pts)	19%($p = 0.004$)
Five-year local recurrence	13%	22% ($p=0.02$)	-	-	6%	13% ($p = 0.006$)
Five-year overall survival	47%	40% (ns)	74%	66% (ns)	76%	74% (ns)

RT = radiotherapy; CRT = concurrent chemoradiotherapy; SSP = sphincter-saving procedure; ns = not significant

No OS gain

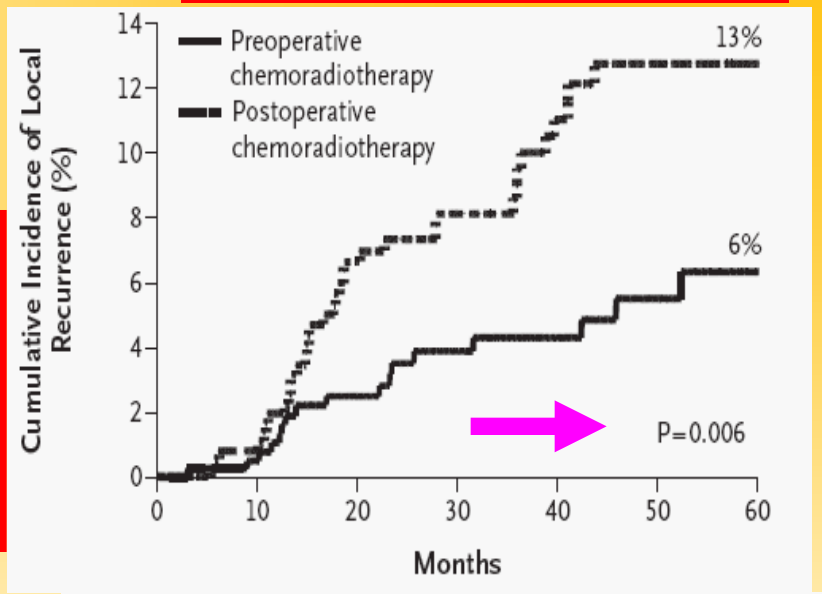
[Ortholan C et al., 2006]

Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer

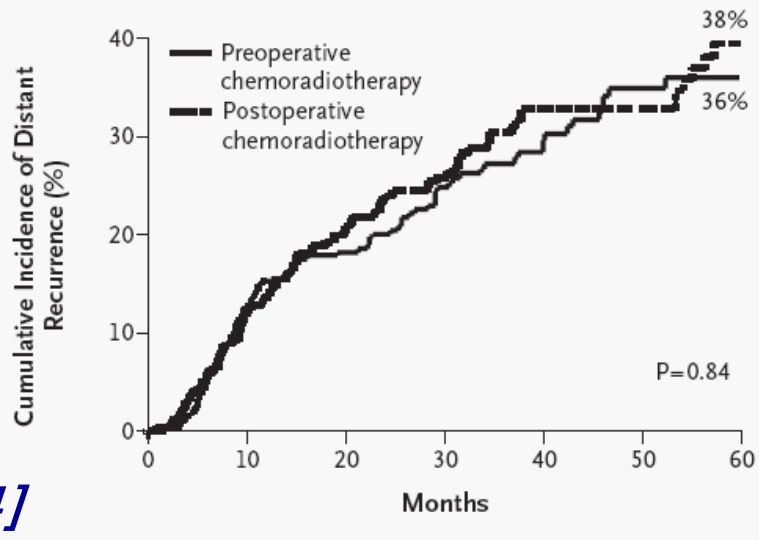
German Rectal Cancer Study Group

823 pts with T3 or T4 or N+ disease: 421 pts Randomized to preoperative CT-RT and 402 pts to postoperative CT-RT

Preoperative CT-RT: 50,40 Gy in fractions of 180 cGy and 5-FU 1000 mg/m2 in continuous IV
Surgery: 6 weeks after the completion of CT-RT
Postoperative CT-RT: 50,40 Gy + boost of 5,40 Gy and 5-FU



5-yr OS: 76% and 74% respectively (p=0.80)
5-yr LR: 6% preoperative CT-RT and 13% postoperative CT-RT (p=0.006)
G3 or G4 acute toxic effects: 27% in the preoperative-treatment group, as compared with 40% of the patients in the postoperative-treatment group (p=0.001)
G3 or G4 of long-term toxic effects: 14% and 24%, respectively (p=0.01)



[Sauer R et al, 2004]

Preoperative vs postoperative radiotherapy

- Relative risk reduction on LR of 50%
- No significatives difference in rates of sfhinter preservation (there is a trend)
- No differences in OS
- Higher toxicity in postoperative CRT group

Introduction of New Agents in preoperative CRT

TABLE 5. Phase III studies examining the impact of adding oxaliplatin to preoperative CRT in rectal cancer

	STAR-01		*ACCORD 12/0405*	
	DXT (59.4 Gy) and 5-FU	*DXT (59.4 Gy) and 5-FU/oxaliplatin*	*DXT (45 Gy) and capecitabine*	*DXT (45 Gy) and oxaliplatin/capecitabine*
No. of patients	379	368	299	299
Grade 3/4 toxicities	8%	24%*	11%	25%*
Sphincter-sparing surgery	72%	73%	73%	76%
pCR	16%	16%	14%	19%

CRT = chemoradiation; DXT = radiotherapy; 5-FU = 5-fluorouracil; pCR = pathological complete response; STAR = Studio Terapia Adiuvante Retto; ACCORD = Action Clinique Coordonnées en cancérologie Digestive.

*$P < .001$. Significant results reflect a comparison of variables within the individual study. Only significant P values are shown.

The failure was because:

-limited number of patients
-short follow-up
-suboptimal delivery therapy

Fleming F et al, 2011

A final answer on oxaliplatin?

NSABP R-04 Phase III Preoperative

Stratify

- *T2 vs. T3*
- *M vs. F*
- *SP vs. APR*

R

n=1460
Closed
this Summer

Capecitabine (825 mg BID) 50.4 Gy ± Oxaliplatin (50 mg/m2 qw)

CI 5-FU (225 mg/m2/d) 50.4 Gy ± Oxaliplatin (50 mg/m2 qw)

Presentation Outline

- **Short course radiotherapy alone trials**
- **Combined CT-RT trials**
- **Clinical practice, Critical points/Research**

Clinical Practice

- **Short-course RT is effective (there is a warning on late toxicity)**
- **Preoperative CT-RT (long-course + 5-FU/5-FU analog) is considered a preferred choice when needing downsizing or in high risk patients, with a 50% increase in acute toxicity**
  - generally preferred in patients with high tumor burdens in order to allow more conservative surgery (even if it is unclear if CT can increase sphincter preservation rates → *data from the German trial suggest that a change in operative strategy may be safely performed)*
- **Informed patients on toxicity and QoL**

…a key-point for the future

Why chemotherapy did not show a survival benefit?

- In all 4 major trial the rate of distant metastases is around 30%
- One hypothesis: early metastatic spread
- Other explanation: Follow-up time too short?
- The benefit in terms of reduction in LR is too low to impact on survival?

Research / 1

- **Up to 1/3 of patients develop distant mts: priority to trials adressing early subclinical systemic spread?**

Intensification of preoperative chemoradiation and postoperative adjuvant treatment are currently addressed by 3 large trials (CAO/ARO/AIO-04 in Germany, PETACC 6 in Europe, and NSABP R-04 in the US)

Research / 2

Increasing pCR rates and LC: is the right strategy?

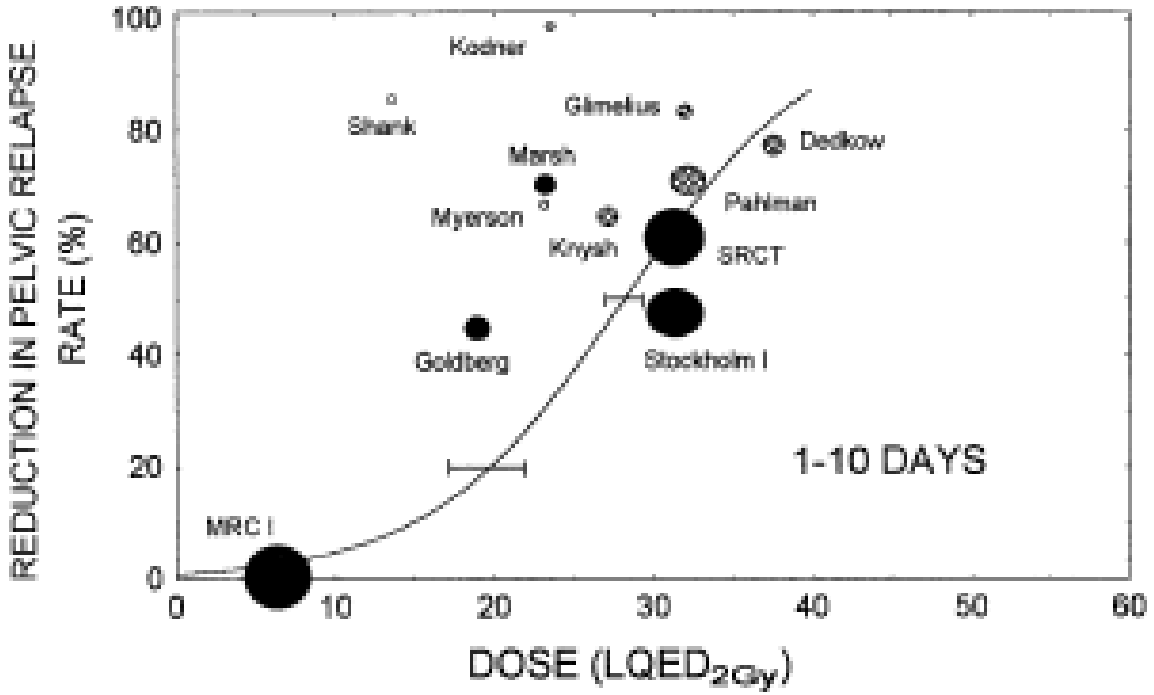
- *Prospective trials adressing the oncological safety of sphincter-preserving surgery in patients candidated to APR and responding to CT-RT (demonstrating that changing surgical strategy is safe)*

- *RT dose escalation without CT is a good option (primary enpoint pCR-local control)?.....*

Survival benefit for high Biologically Effective Doses

- Large randomized trials have shown that preoperative radiotherapy substantially decrease local failure rate

- The **survival benefit** was seen only in trials using a moderately high biologically effective dose (BED > 30 Gy) ***[Swedish Rectal Cancer Trial, 1997]***



Oheler C et al, 2006

UZ Brussel, Oncologisch Centrum, dienst Radiotherapie
Laarbeeklaan 101
B-1090 Brussel, België

CLINICAL TRIAL PROTOCOL

RANDOMIZED TRIAL OF PREOPERATIVE RADIOTHERAPY WITH AN INTEGRATED SIMULTANEOUS BOOST COMPARED TO CHEMORADIOTHERAPY FOR T3-4 RECTAL CANCER

Preoperative schedule

• **ARM 1:**
Radiotherapy (23 x 2 Gy) + Capecitabine 825 mg/m2 p.o. twice daily, excluding weekends

• **ARM 2:**
Radiotherapy (23 x 2 Gy) with a simulataneous integrated boost (SIB) up to 55.2 Gy on the primary tumour

Radiotherapy: rotational IMRT with daily CT-guided positioning

Adjuvant capecitabine chemotherapy

• 6-12 weeks after surgery: Capecitabine 1000 mg/m2 p.o. twice daily from the day 1 to day 15, every 3 weeks, 6 cycles

Which is the best strategy?

- A possible way could be: to maintain the same rate of LC (rt only –escalated?) and to try new drug combination in high-risk selected patients (molecular stratification)
- An example:

ASCO 2011

Phase II trial of five fractions of radiotherapy followed by four cycles of FOLFOX chemotherapy as preoperative therapy for rectal adenocarcinoma: Report of an interim response analysis.

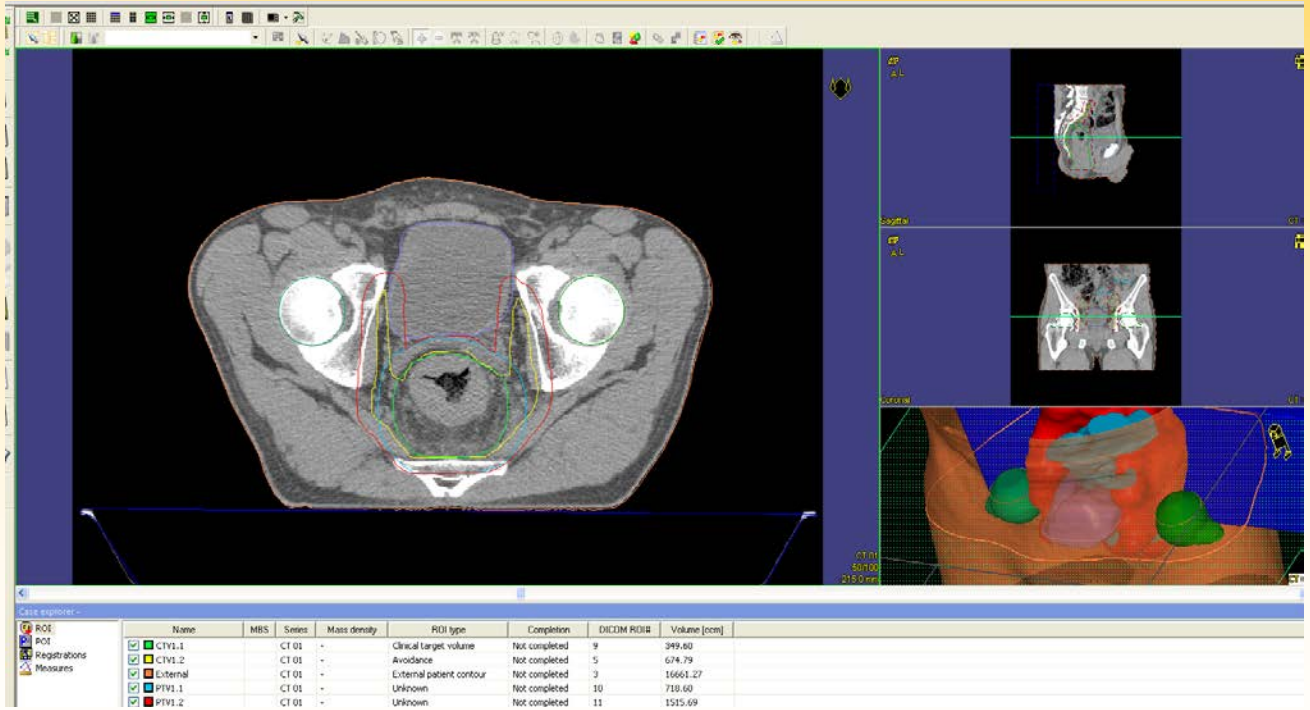
Author(s): R. J. Myerson, S. R. Hunt, B. R. Tan, P. Parikh, A. C. Lockhart, J. Picus, S. Sorscher, R. Suresh, A. Wang-Gillam, J. W. Fleshman, I. J. Kodner; Washington University School of Medicine, St. Louis, MO

IMRT IN RECTAL CANCER
SIB PROTOCOL @ UNIVERSITY OF TURIN

- **Supine position**
- **Sinmed (Civco®)**

- **Target definition**
  - **Oncentra Masterplan**

PTV1.1: CTV1.1 + 10 mm
PTV1.2: CTV1.2 + 10 mm



IMRT IN RECTAL CANCER
SIB PROTOCOL @ UNIVERSITY OF TURIN

Elekta Synergy™

Procedures:

1. Immobilization
2. ConeBeam CT
3. Applied Shifts
4. Verification
5. Dose Delivery

IMRT IN RECTAL CANCER
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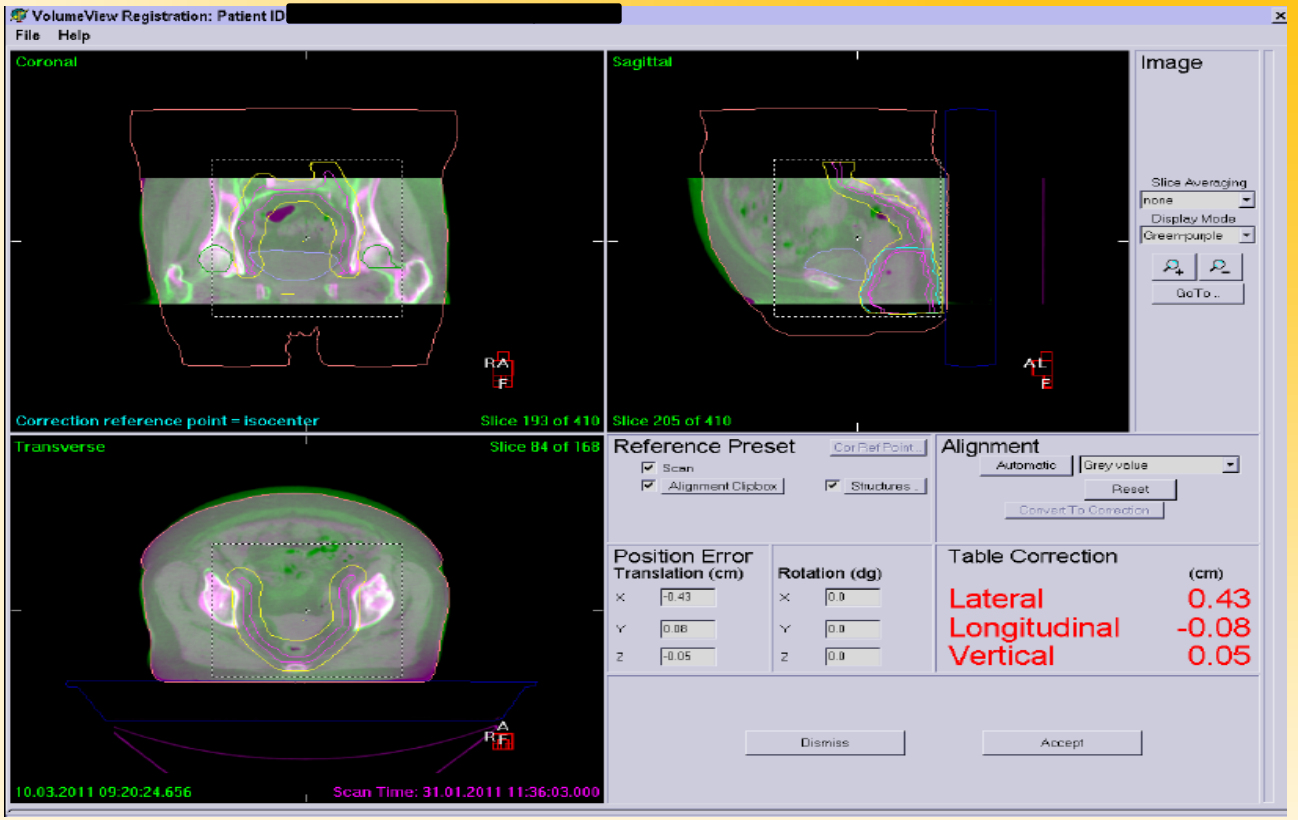


Rationale:

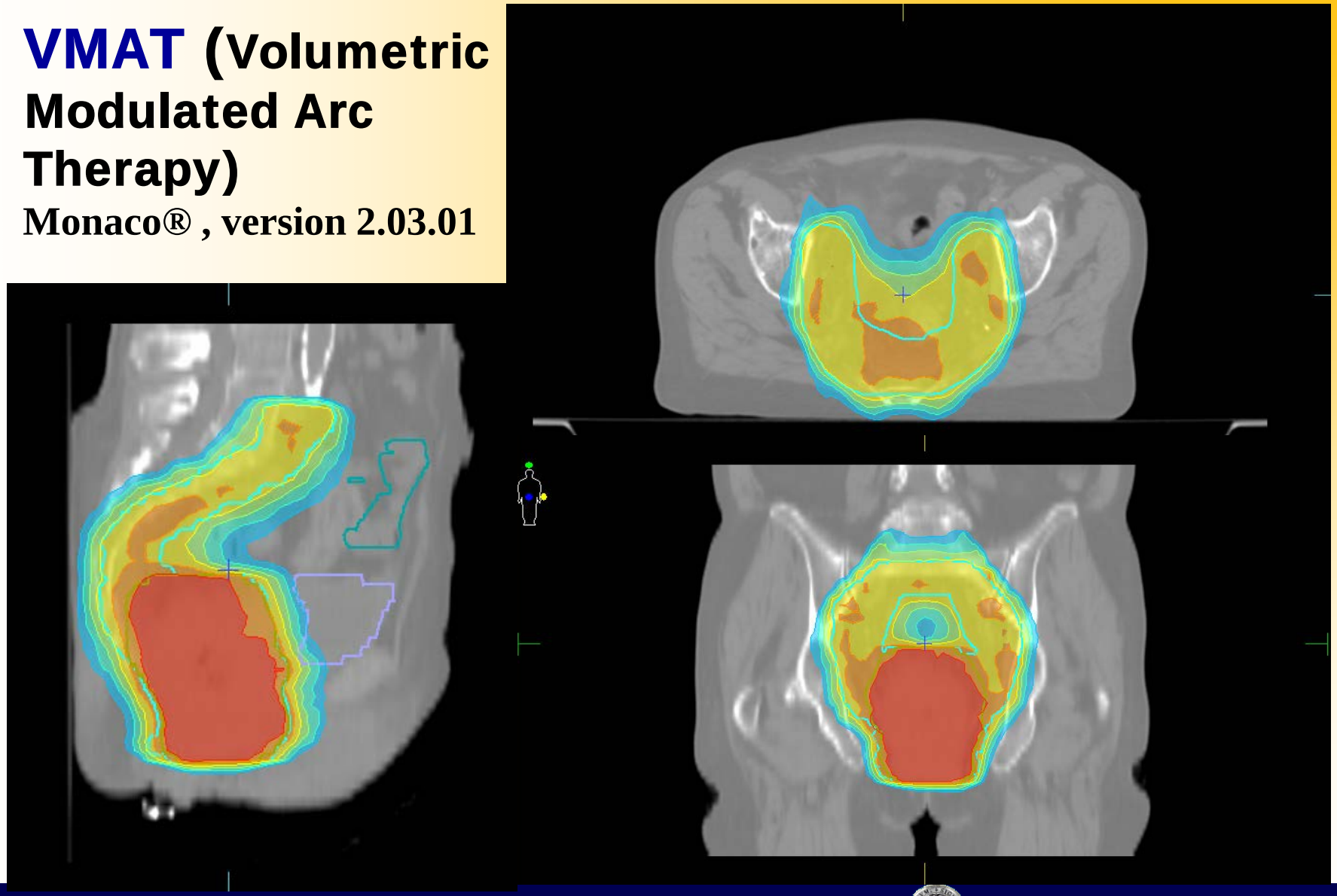
In order for the treatment to be executed adequately, the radiation has to be delivered exactly as specified in the treatment plan. In practice this is often difficult to achieve due to the flexibility and day-to-day variations in the patient's anatomy and also due to the difficulty of repositioning and aligning the patient in exactly the same position every day

(KV image based)

IMRT IN RECTAL CANCER
SIB PROTOCOL @ UNIVERSITY OF TURIN

VMAT (Volumetric Modulated Arc Therapy)

Monaco® , version 2.03.01



SELECTION OF PATIENTS FOR PREOPERATIVE THERAPY: A MAIN TASK FOR THE MULTIDISCIPLINARY TEAM

TREATMENT GROUP	MRI FEATURES	TREATMENT STRATEGY
A (stage I)	**T1-2, T3 <5mm, N0-1, PREDICTED CRM-**	**TME SURGERY SCRT or CRT if CRM + or low layer T**
B (stage II)	**T3>5mm, T4 PREDICTED CRM- N2**	**PREOP ChRT**
C (stage III , IV)	**T3/T4, PREDICTED CRM+**	**PREOP ChRT**

Burton et al, Br J Cancer 2006; 94:391-397

Take home.....

- **RT with TME surgery?**

YES!!! *But some subgroups may not benefit*

- **Neoadjuvant or adjuvant RT?**

Neoadjuvant!!! *But need for improved staging (MRI)*

- **5x5 Gy or long-course RCT?**

Risk-adapted!!! *If downsizing required: RCT*

- **RT with new drugs?**

Promising!!! *Ongoing phase III trials*

- **RT with new technique?**

Promising!!! *IGRT, Simultaneous Boost*