MANAGEMENT OF RECTAL MALIGNANCIES SHORT VS LONG COURSE RADIOTHERAPY EVIDENCES

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Points of discussion

Evolution of locally advanced carcinoma of rectum

- Surgery
- Surgery plus RT
- Surgery plus RT/CRT
- Preop/vs postop RT
- Metaanalysis

NEED OF ADJUVANT TREATMENT

1 : Improved survival

2 : Local control

3 : QOL (sphincter preservation

STAGING AND PROGNOSIS

Stage	T, N, M	5-year Survival (%)
0 I	TIS, T1, N0, MO	□90
I	T2, N0, M0	80-85
II	T 3-4, NO, MO	70-75
III	T2, N1-3, M0	70-75
III	T3, N1-3, M0	50-65
III	T4, N1-2, M0	25-45
IV	M1	<3

PREOPERATIVE SETTING

Table 2. Anatomic Stage/Prognostic Gro

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b

es

Preop CT RT for Stage II –III disease

- Stage II (T3 and T4 disease)

&

- Stage III that is (any T with Nodal positivity)

SURGERY ALONE

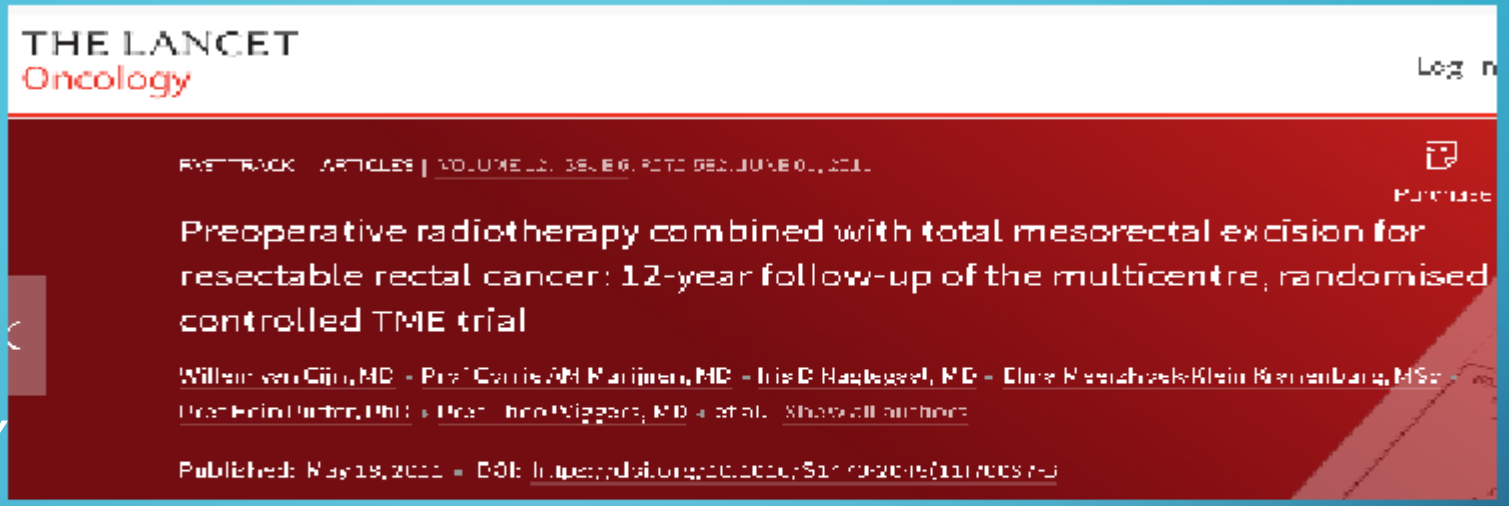
UPTO 50 % LOCAL FAILURE IN LOCALLY ADVANCED RECTAL CARCINOMAS

Local Failure of Rectal Cancer Surgery Alone (Local Failure Rate Percentage/Number of Patients in Cohort)

Analysis	Gunderson and Sosin[120]	Rich et al.[122]	Minsky et al.[221]	Martling et al.[123]	Mendenhall et al.[117]	Pilipshen et al.[119]	Bonadeo et al.[241]
	Reoperation (Crude)	Clinical Exam + Surgery (Crude)	First Failure—Clinical Exam + Surgery (5-y Actuarial)	Total Local Recurrence	Total Local Recurrence—5-y Follow-up Clinical	First Failure—Clinical	Total Local Recurrence—Clinical[a]
T1 N0		8%/39	11%/11	9%/78	0%/6	0%/5	3%/103
T2 N0			3%/36		38%/16	14%/128	
T3 N0	67%/6	24%/42	23%/60	34%/60	40%/30	30%/111	4%/161
T4 N0		53%/15	11%/9				
T1–2 N+	24%/17	50%/4	14%/11	37%/93	71%/17	22%/49	24%/133
T3 N+	83%/40	47%/34	25%/31		65%/17	49%/89	
T4 N+		67%/6	22%/10				
Total	64%/75	30%/142	15%/168	27%/251	46%/90		

[a]Local recurrence highly dependent on site in rectum—18% overall for tumors ≤7 cm from anal verge.

SURGERY (TME) VS RT PLUS SURGERY


THE LANCET
Oncology

Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial

RT PLUS SURGERY IS BETTER

THE DUTCH TME STUDY

- >50% reduction in recurrence risk for the radiotherapy group
- For negative circumferential margin, local recurrence 3% after radiotherapy versus 9% after surgery alone ,distant recurrence 19% versus 24
- Cancer-specific death at 10 years was 17% for the irradiated group versus 22% for surgery alone
- OS rates, were equivalent

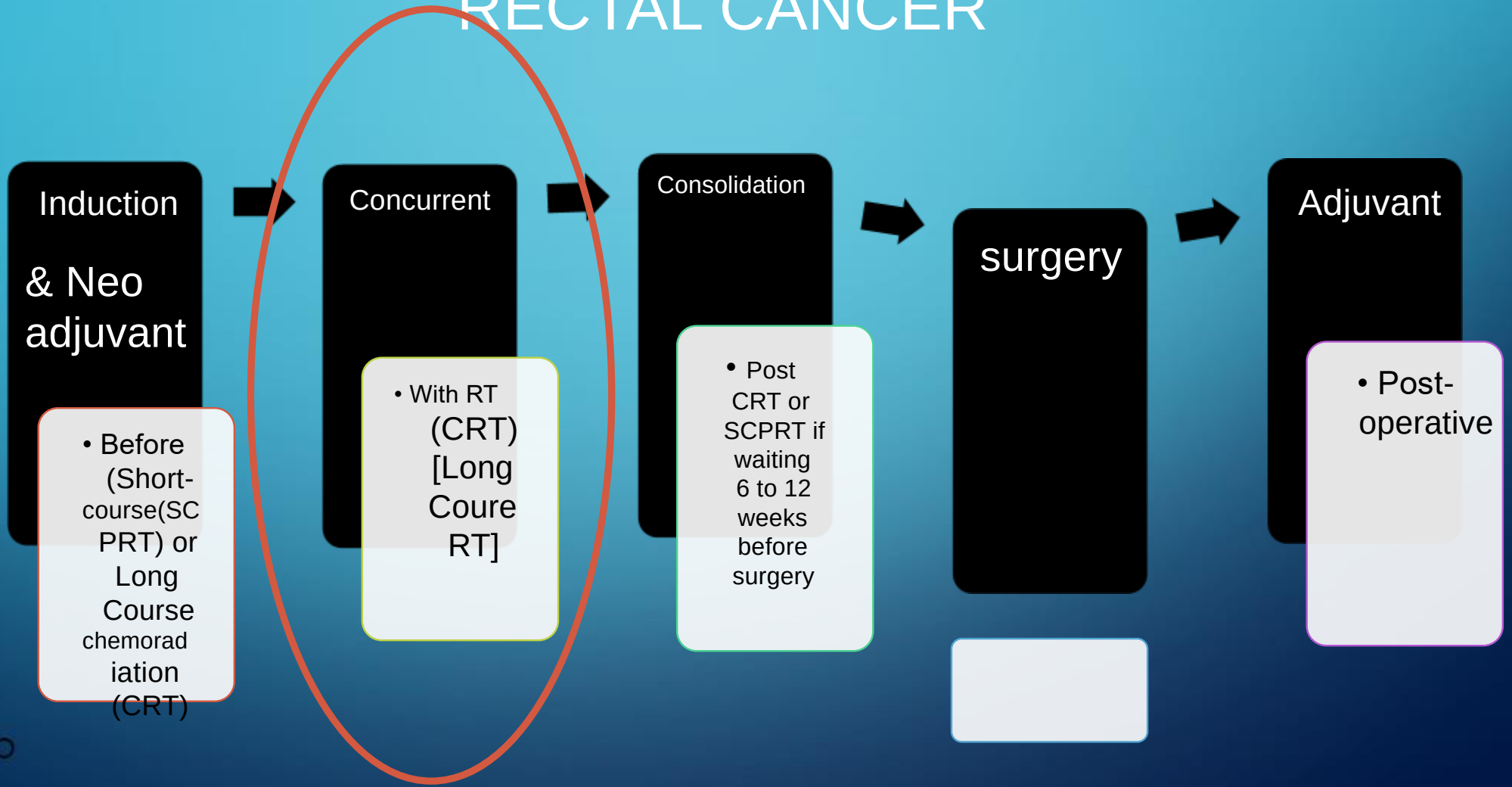
Local Control and Survival with and without Radiotherapy—Preoperatively, Postoperatively, and with or without Chemotherapy

Study/Institution[a] (Ref.)	No. of Patients	Local Failure (%)	Disease-Free Survival (%)	Survival (5 y) (%)
NSABP RO-1[132] Surg/Surg + RT (postoperative RT)	184/187	25/16	No difference	No difference
NSABP RO-2[133] Surg + chemo/Surg + chemo + RT (postoperative RT)	348/346	13/8		
GITSG[130] Surg/Surg + RT/Surg + chemo + RT (postoperative RT)	58/50/46	25/20/10	44/50/65	26/33/45
Swedish[224] Surg/Surg + RT (preoperative RT)		27/11		48/58
Stockholm II[123] Surg/Surg + RT (preoperative RT)		34/16 Stage II 37/21 Stage II		
MRC[135] Surg/Surg + RT (postoperative RT)	235/234	34/21		38/41

COMBINED MODALITY TREATMENT VS RT PLUS SURGERY VS SURGERY ALONE

LOCOREGIONAL FAILURE IS DECREASED BY THE USE OF RADIATION THERAPY AND IS FURTHER DECREASED BY THE USE OF CONCURRENT 5-FU–BASED CHEMOTHERAPY

CHEMOTHERAPY IN LOCALLY ADVANCED RECTAL CANCER



5FU INFUSIONAL VS 5FU BOLUS VS CAPACITABINE

- Initial trials - bolus 5-FU at a dose of 500 mg/m2/day for 3 days during weeks 1 and 5 of the radiation therapy
- North Central Cancer Treatment Group study- Continuous infusion 5-FU (only during radiation therapy) is better compared with bolus 5-FU in terms of local control

5FU INFUSIONAL VS 5FU BOLUS VS CAPACITABINE

- NSABP R-04 trial - Neoadjuvant use of capecitabine was found to be comparable with continuous 5-FU infusion when combined with radiation therapy
- Recommendation - Use capecitabine concurrently with radiation therapy, and use continuous infusion 5-FU or bolus 5-FU during radiation therapy only in patients unable or unwilling to take oral capecitabine

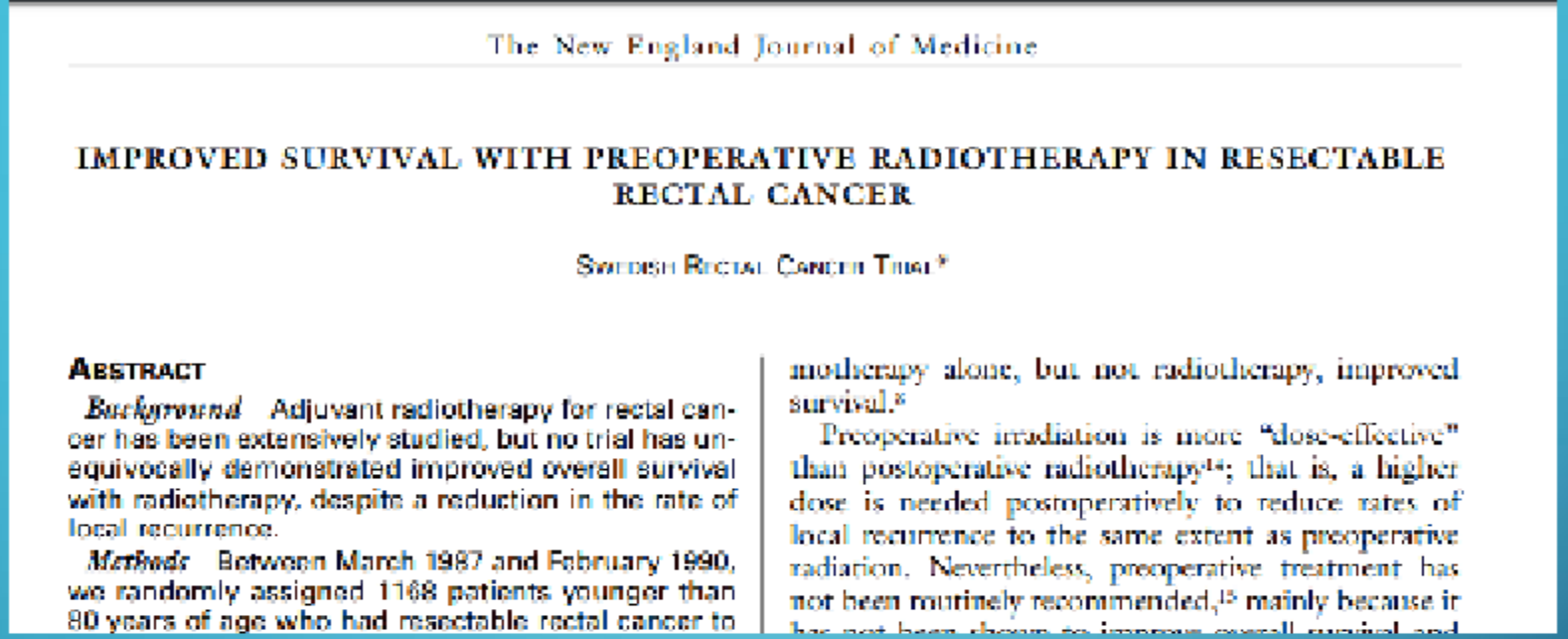
OPTIONS FOR RADIOTHERAPY IN LOCALLY ADVANCED RECTAL CANCER

Preoperative

- Short course radiotherapy SCPRT (5# X 5 Gy)
- Long course CRT (25-28# X 1.8Gy Gy)
  Phase I 45 Gy in 25 daily fractions of 1.8 Gy given in 5 weeks.
  Phase 2 (optional)
  5.4–9 Gy in 3–5 daily fractions of 1.8 Gy(2 lateral Fields)

Post-operative

- CRT as adjuvant



The New England Journal of Medicine

IMPROVED SURVIVAL WITH PREOPERATIVE RADIOTHERAPY IN RESECTABLE RECTAL CANCER

SWEDISH RECTAL CANCER TRIAL*

ABSTRACT

Background Adjuvant radiotherapy for rectal cancer has been extensively studied, but no trial has unequivocally demonstrated improved overall survival with radiotherapy, despite a reduction in the rate of local recurrence.

Methods Between March 1987 and February 1990, we randomly assigned 1168 patients younger than 80 years of age who had resectable rectal cancer to

motherapy alone, but not radiotherapy, improved survival.[5]

Preoperative irradiation is more "dose-effective" than postoperative radiotherapy[14]; that is, a higher dose is needed postoperatively to reduce rates of local recurrence to the same extent as preoperative radiation. Nevertheless, preoperative treatment has not been routinely recommended,[15] mainly because it

PRE OPERATIVE RT VS POST OPERATIVE RT

IMPROVING LOCAL CONTROL WITH THE USE OF RADIATION THERAPY (AND PRESUMABLY WITH CONCURRENT CRT) IS BENEFICIAL AND THAT TRIMODALITY THERAPY, ESPECIALLY WHEN CRT IS USED PREOPERATIVELY, CAN IMPROVE SURVIVAL.

ADVANTAGES OF PRE OPERATIVE CHEMO RADIATION

- Down staging, hence increased resectability
- Decreased risk of dissemination during surgery.
- Radiation more effective in tumour cells with highly vascularity.
- Less serious bowel toxicity due to easy exclusion.
- Possibility of increasing sphincter preservation in borderline cases.
- Decreased Local Recurrence.

DISADVANTAGES OF PRE-OPERATIVE RADIOTHERAPY

- Overtreatment of early stage tumors (18 % in german study)
- Delay in surgery
- Wound healing problem

Anorectal and sexual function is worse after preoperative Radiotherapy and TME compared with TME alone: Results from Some of the randomised studies

- Peeters K, J Clin Oncol 2015;25:6199
- Dahlberg M, Dis Colon Rectum 1998;41:543
- Stephens RJ, J Clin Oncol 2010;28:4233
- Marijnen CAM, J Clin Oncol 2005;23:1847
- Lundby L, Lancet 1997;350:564
- Lange MM, Br J Surg 2007;94:1278

RANDOMISED TRIALS

SC PRT (5# X 5GY)

Trial	MRI mandated	EUS mandated	TME mandated	Good Quality TME	Median no of nodes resected
Swedish Rectal	No	No	No	?No	Not stated
Dutch TME	No	No	Yes	50%	7
Polish	No	No	?	?	9
CR07	No	No	No	50%	11
TROG-0104	If US not possible	Yes	No	?	Not stated

RANDOMISED TRIALS

PRE-OP LONG COURSE CRT

Trial	MRI mandated	EUS mandated	TME	Good Quality TME	Median no of nodes resected
German (Sauer 2004)	No	Yes	?	No data	Collected but not stated
EORTC 22921	No	No	38%	No data	7 after CRT
FFCD 9203	No	No	No data	No data	Not stated
NSABP R03	No	?	No	No data	Not stated
Polish	No	No	?	No data	8
TROG-0104	some	Yes	?	No data	Not stated

PRE-OPERATIVE RADIOTHERAPY

TRIALS

- Pre-operative Long Course CRT
- 50 Gy at 1.8 to 2 Gy per fraction over 5 to 5.5 weeks

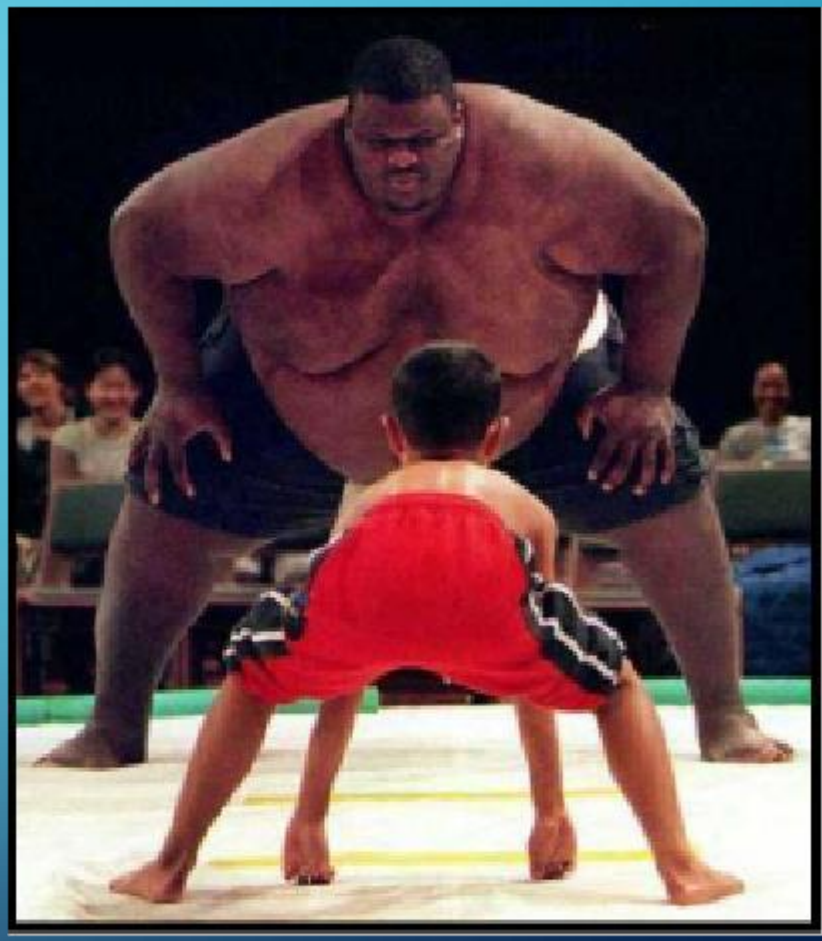
USA

- Pre operative Short Course
- 5# X 5Gy over 1 week
- (Stockholm Trials/ Swedish Rectal

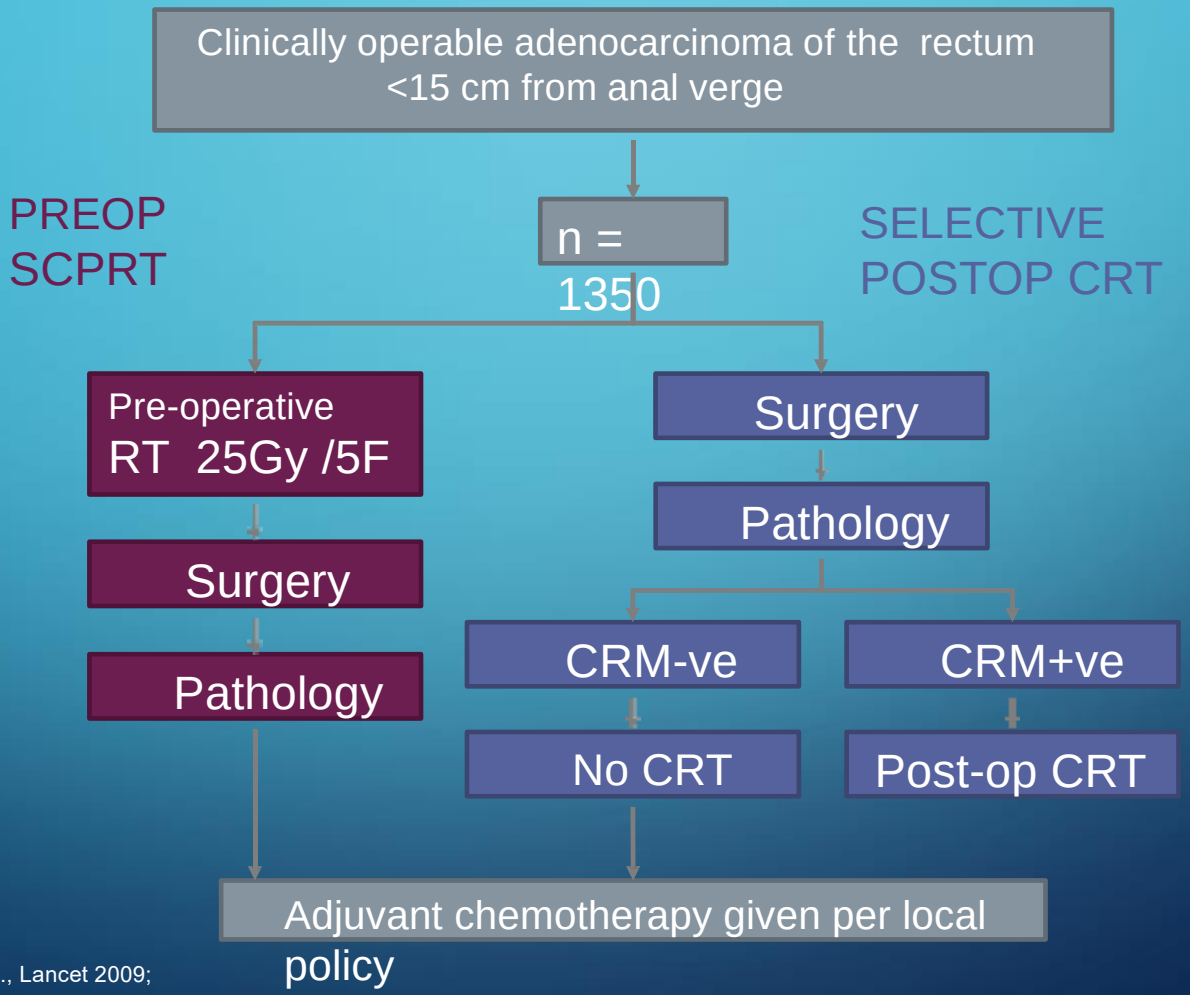
Europe

PRE OPERATIVE

SHORT COURSE VS LONG COURSE TRIALS

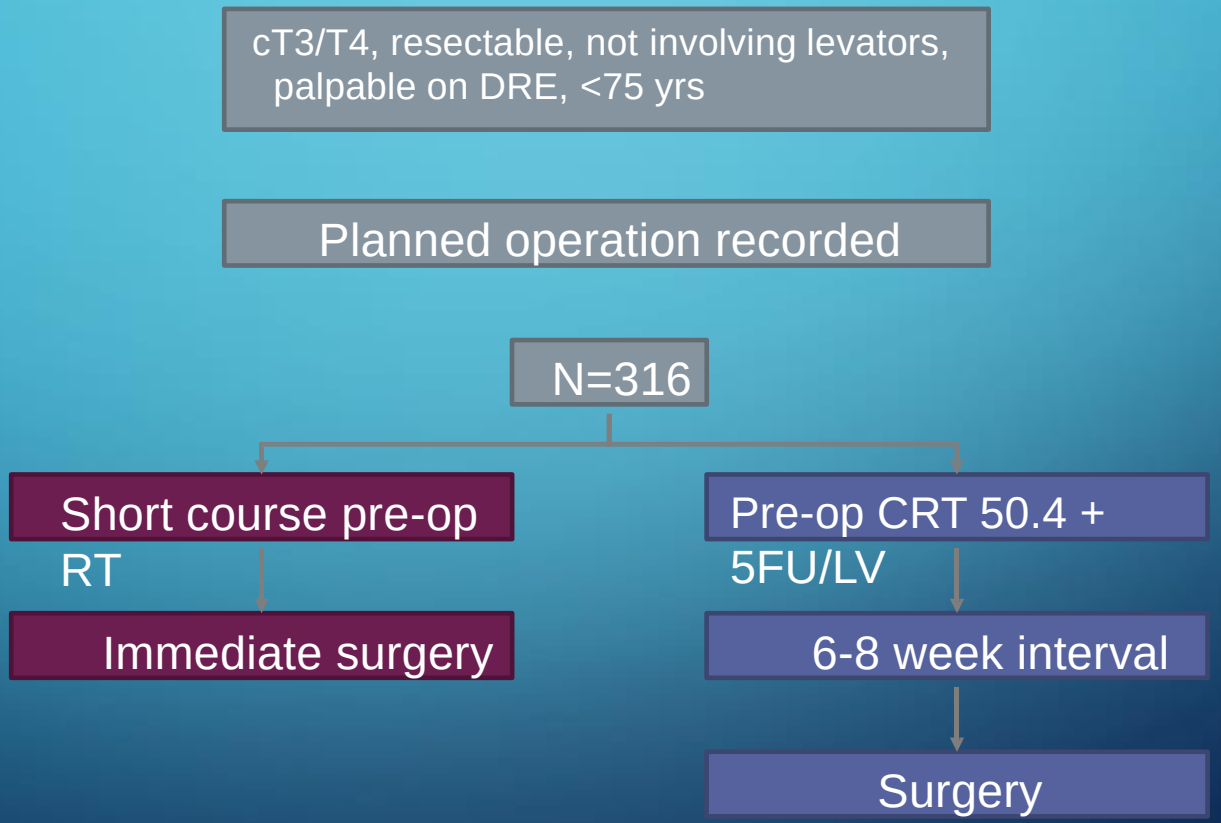


MRC CR07 NCIC C016 TRIAL



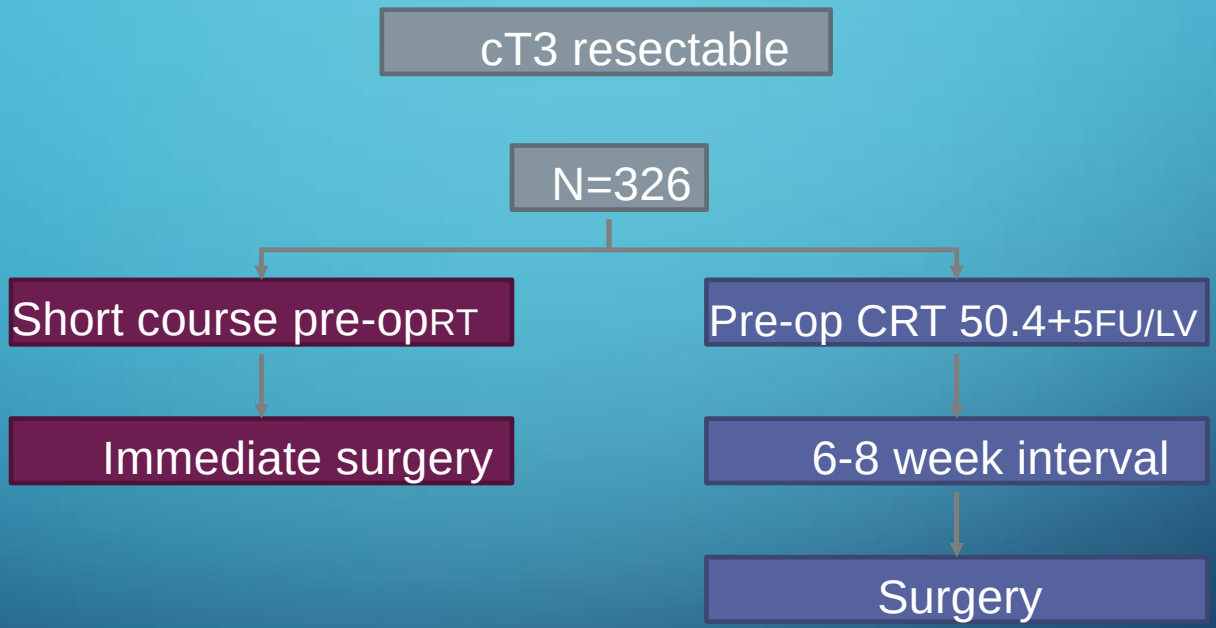
Sebag-Montefiore D, et al., Lancet 2009; 373(9666):811-20

POLISH TRIAL – BUJKO K, ET AL., RADIOTHERAPY AND ONCOLOGY 2004



Bujko K, et al., Radiother Oncol. 2004; 72:15–24

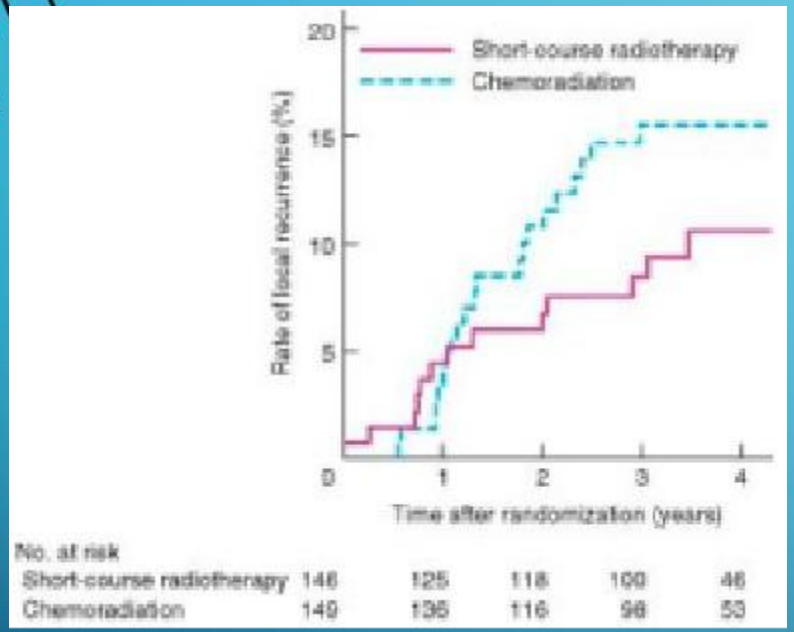
TROG AGIT LSSANZ RACS TRIAL NGAN, JCO 2012



Ngan SY, et al., J Clin Oncol. 2012 Nov 1;30(31): 3827-33

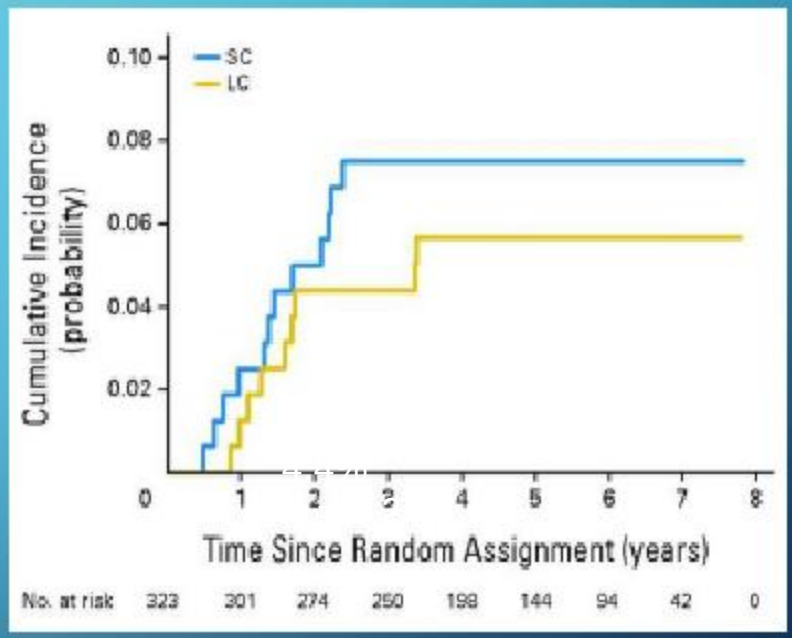
RESULTS OF PRE OPERATIVE SHORT COURSE VS LONG COURSE TRIALS

SHORT COURSE RADIATION VERSUS CHEMORADIATION
NO DIFFERENCE IN LOCAL CONTROL



14.4% vs 18.6%

P = 0.17

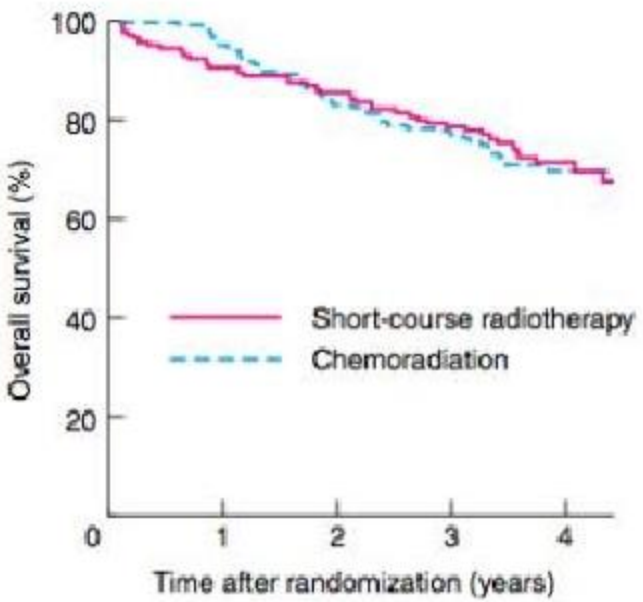


Polish Trial (Bujko 2006)[1]

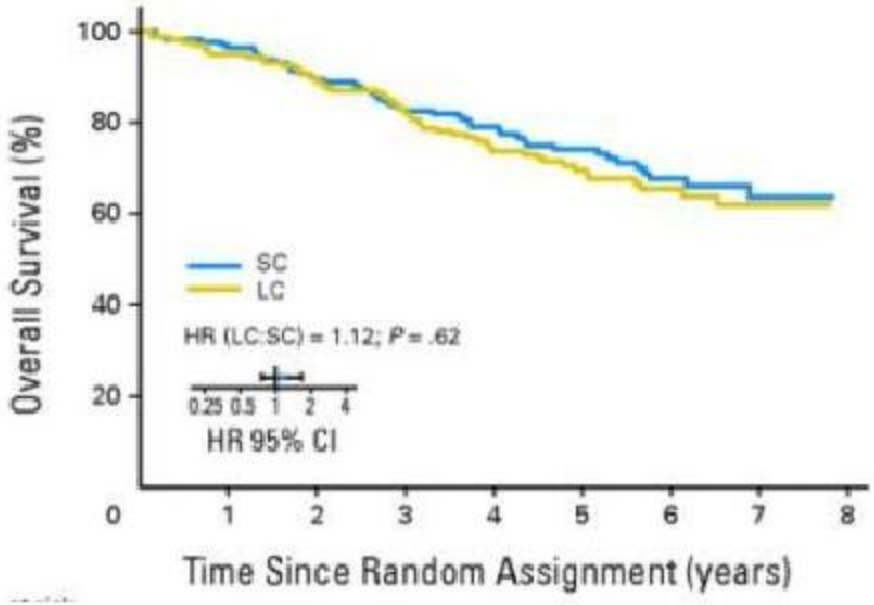
TROG-01 Trial (Ngan 2012)[2]

1.Bujko K, et al., Br J Surg 2006;93(10):1215–1223; Copyright © 2006 British Journal of Surgery Society Ltd. Published by John Wiley & Sons Ltd;
2.Ngan SY, et al., J Clin Oncol. 2012 Nov 1;30(31):3827-33. Reprinted with permission. © (2012) American Society of Clinical

SHORT COURSE RADIATION VERSUS CHEMORADIATION
EQUIVALENCE IN OVERALL SURVIVAL



Polish trial (Bujko 2006)



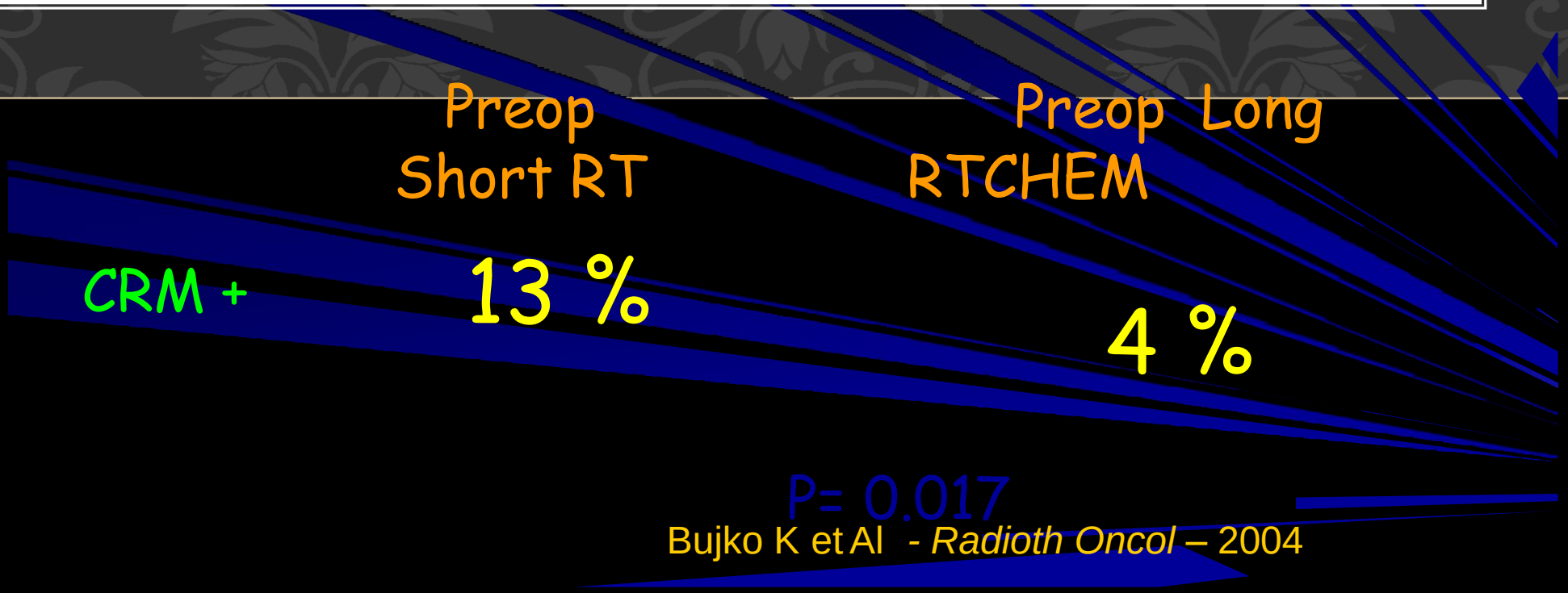
Trans-Tasman trial (Ngan 2012)

1.Bujko K, et al., Br J Surg 2006;93(10):1215–1223; Copyright © 2006 British Journal of Surgery Society Ltd. Published by John Wiley & Sons Ltd;
2.Ngan SY, et al., J Clin Oncol. 2012 Nov 1;30(31):3827-33. Reprinted with permission. © (2012) American Society of Clinical

SEVERE LATE TOXICITY SCPRT VERSUS CRT

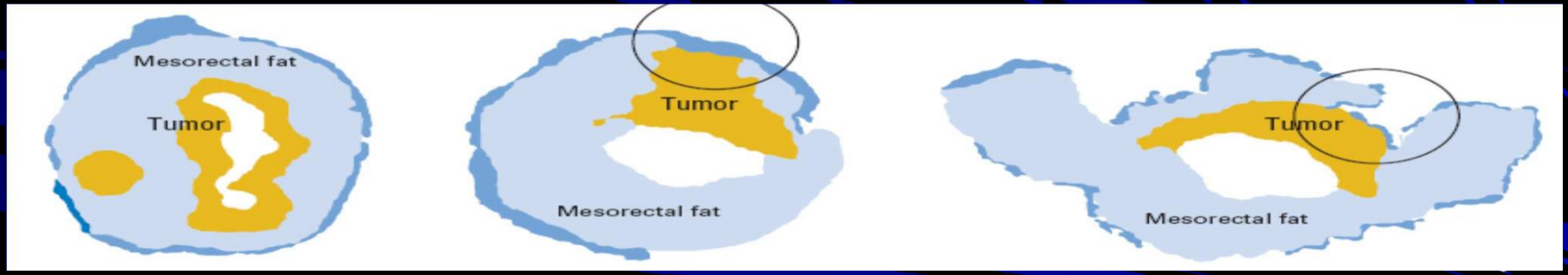
	SCPRT	CRT
Polish Study		
Severe late toxicity – G3/ G4	10%	7%
TROG 01.04		
Severe late toxicity – G3/ G4	9%	13%

CIRCUMFERENTIAL RESECTION MARGINS



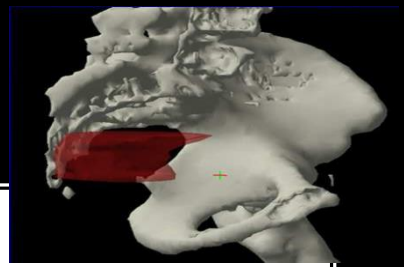
Bujko K et Al - *Radioth Oncol* – 2004

CIRCUMFERENTIAL RESECTION MARGINS



Nagtegaal I et Al - *JCO* – 2008

Optimized RT



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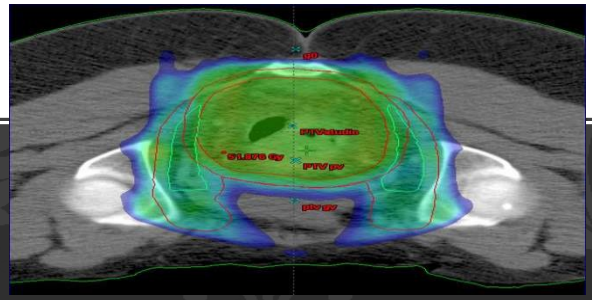


THEREFORE:
TAILORED TREATMENT

- “Small” T3 short-term RT and TME
- “Large” T3/T4 long-term CRT and TME


0:0

PRE OPERATIVE SHORT COURSE VS LONG COURSE QUALITY OF LIFE TRIALS

PRE OPERATIVE SHORT COURSE VS LONG COURSE QUALITY OF LIFE TRIALS

- Both SC-PRT (Short course) and CRT (long Course) have shown to reduce local recurrence rates without improving overall survival.
- So Health-related quality of life (HRQL) of the patient after these different treatment schedules may provides an insight for selecting the better one .
- SC-PRT uses a higher dose per fraction in a short overall treatment time, there may be a risk for more late radiation-related toxicity compared with CRT.

Original Study

Long-Term Health-Related Quality of Life in Patients With Rectal Cancer After Preoperative Short-Course and Long-Course (Chemo) Radiotherapy

Lisette M. Wiltink,[1] Remi A. Nout,[1] Jochem R.N. van der Voort van Zyp,[1,2] Heleen M. Ceha,[3] Marta Fiocco,[4,5] Elma Meershoek-Klein Kranenbarg,[6] Andreas W.K.S. Marinelli,[7] Cornelis J.H. van de Velde,[6] Corrie A.M. Marijnen[1]

Abstract

Long-term health-related quality of life is compared between patients with rectal cancer preoperatively treated with long-course chemo radiotherapy (CRT) or with short-course radiotherapy. Apart from less satisfaction with urinary function reported by patients who had CRT, no clinically relevant differences in health-related quality of life and patient-reported symptoms between patients who had CRT and short-course radiotherapy were found at 5 years after rectal cancer treatment.

LISETTE M. WILTINK ET AL

- The aim of this study was to compare patient-reported symptoms and HRQL of patients treated with CRT to patients treated with SC-PRT for rectal cancer with a long follow-up time

STUDY DESIGN LISETTE M. WILTINK ET AL

2003 to 2010

STUDY GROUP

Patients with Locally advanced rectal cancer received long course chemoradiation in Leiden University Medical Center

Total radiation dose of 50 to 50.4 Gy in daily fractions of 1.8 to 2.0 Gy delivered by a 4-field

Five to 8 weeks after the last radiation treatment, patients underwent surgery according to the TME principles

REFERENCE GROUP

Patients treated with SC-PRT in the Dutch TME trial with clinically resectable adenocarcinoma without evidence of distant metastases.

25 Gy in 5 fractions delivered with a 3 or 4-field Technique

Within 10 days of the start of radiotherapy, patients underwent surgery according to the TME principles

From 2011

HRQL questionnaires were sent to patients who were disease-free

Questionnaires includes

The EORTC QLQ-C30 is a general cancer HRQL-questionnaire composed of 30 items,
and

An additional questionnaire on bowel and urinary function

Statistic al Analysis

Reference data of the TME trial were matched for age and gender with the CRT group.

Linear regression and logistic regression models were used to compare the HRQL and symptoms between the groups that received CRT and SC-PRT.

RESULTS OF LISETTE M. WILTINK ET AL

SCORES OF EORTC QLQ-C30

GENERAL CANCER HRQL

Table 3 Scores of EORTC QLQ-C30

	Mean Scores CRT	Mean Scores SC-PRT	P[a]
Global health status	79.6	78.9	.90
Functional scales			
Physical functioning	84.5	82.6	.56
Role functioning	82.5	83.3	.73
Emotional functioning	86.9	86.3	.85
Cognitive functioning	84.0	84.1	.90
Social functioning	84.6	87.7	.27
Symptom items			
Fatigue	23.8	22.5	.59
Nausea and vomiting	5.9	1.3	<.01
Pain symptoms	11.2	11.1	.92
Dyspnoea	11.8	11.6	.89
Insomnia	15.4	18.5	.42
Appetite loss	8.5	4.6	.12
Constipation	8.6	10.8	.51
Diarrhea	5.8	10.6	.09
Financial difficulties	9.5	6.8	.27

A higher score for functioning reflects better functioning, whereas a higher score for symptoms represents a higher level of symptoms and decreased health-related quality of life.
Abbreviations: CRT = Preoperative long-course (chemo) radiotherapy; EORTC = European Organisation for Research and Treatment of Cancer; SC-PRT = preoperative short-course

RESULTS

LISETTE M. WILTINK ET AL

BOWEL AND URINARY FUNCTION

Table 2 Bowel and Urinary Function

	Mean Scores CRT	Mean Scores SC-PRT	*P*
Bowel function			
Fecal incontinence	42.2	34.6	.34
Fecal incontinence at night	22.9	13.4	.15
Ability to delay bowel emptying	65.6	66.5	.86
Anal blood loss	6.3	4.8	.78
Anal mucus loss	22.9	11.2	.07
Peristomal skin irritation	18.2	16.8	.54
Stoma smell	16.4	21.1	.27
Stoma bleeding	11.5	14.1	.47
Stoma leakage	10.6	12.0	.70
Painful stoma	7.0	6.3	.65
Noisy stoma	26.6	25	.65
Blood loss from stump	8.0	7.1	.60
Mucus loss from stump	14.6	17.9	.40
Impact of bowel dysfunction on			
Work or	22.5	15.5	.03

RESULTSLISETTE M. WILTINK ET AL

BOWEL AND URINARY FUNCTION

Table 2 Continued

	Mean Scores CRT	Mean Scores SC-PRT	*P*
Work or household activities	22.5	15.5	.03
Activities outside the house like shopping	24.8	22.2	.41
Social activities like theater or cinema visiting	23.8	24.8	.89
Urinary function			
Urinary frequency during the day	6.3	6.3	.77
Frequency urinary incontinence	57.1	54.2	.86
Use of pads for urinary incontinence	41.2	29.3	.18
Urine retention after miction	24.2	18.0	.08
Need to urinate again within 2 hours	26.2	25.9	.85
Stream hesitation	23.1	18.9	.24
Difficulty postponing miction	28.2	24.7	.35
Weak urinary stream	31.2	26.2	.16
Satisfaction			
Bowel function[a]	83.1	76.3	.11
Urinary function[a]	71.2	81.2	<.01

RESULTS OF LISETTE M. WILTINK ET AL

- Patients who received CRT and SC-PRT reported no clinically relevant differences in long-term HRQL and late symptoms after a median follow-up period of 58 months, apart from less satisfaction with urinary function reported by those who received CRT.
- These results indicate that both approaches have a comparable impact on long-term HRQL, and a preference for either of them can therefore not be based on long-term HRQL.

TIMING OF SX AFTER RT

WHAT IS THE OPTIMAL INTERVAL TO SURGERY?

- After SCPRT (5x5Gy)

AFTER SCPRT

- No downstaging
- SCPRT normally recommended to be followed by surgery within 1-7 days
- An “ideal” SCPRT schedule, delivers 5 X 5 Gy from Monday to Friday with surgery the following Monday or Tuesday – i.e. an interval of less than 10 days

STOCKHOLM III TRIAL

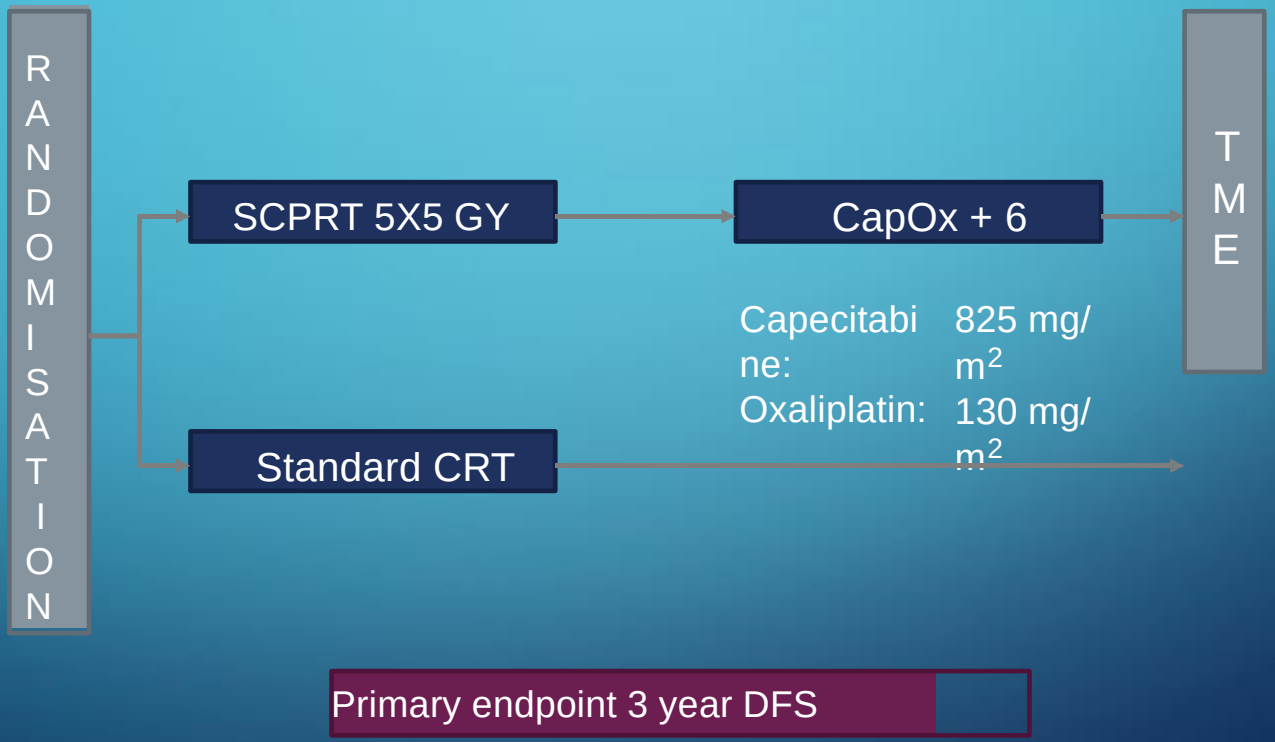
- But Short-course RT induces tumourdownstaging if surgery is performed after an interval of 4-8 weeks

Pettersson D, et al., Br J Surg 2015; 102(8):972-8

RAPIDO TRIAL
N = 885 PATIENTS

T 4
EMVI
+

N 2 CRM
+



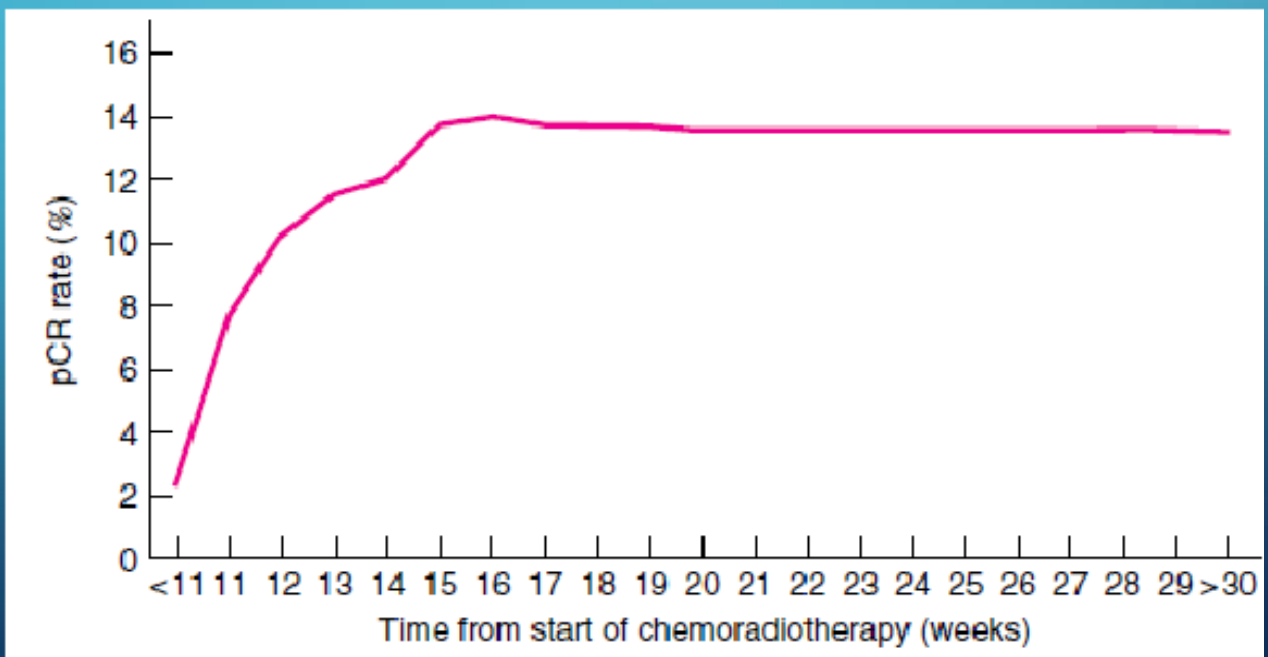
Nilsson PJ, et al., BMC Cancer. 2013; 13:279

WHAT IS THE OPTIMAL INTERVAL TO SURGERY?

- After SCPRT (5x5Gy)
- After long course CRT

HYPOTHESIS

- Longer intervals up 15 weeks
- Associated with an increased chance of a pCR (Sloothak, Kalady)
  - Cumulative complete pathological response (pCR) rate



Sloothaak DA, et al., Dutch Surgical Colorectal Audit. Br J Surg. 2013;100(7):933-9. © 2013 British

But no increase in negative

HYPOTHESIS

Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial

Julio Garcia-Aguilar, Oliver S Chow, David D Smith, Jorge E Marcet, Peter A Cataldo, Madhulika G Varma, Anjali S Kumar, Samuel Oommen, Theodore Coutsoftides, Steven R Hunt, Michael J Stamos, Charles A Tennert, Daniel O Herzig, Alessandro Fichera, Blase N Polite, David W Dietz, Sujata Patil, Karin Avila, for the Timing of Rectal Cancer Response to Chemoradiation Consortium

Summary

Background Patients with locally advanced rectal cancer who achieve a pathological complete response to neoadjuvant chemoradiation have an improved prognosis. The need for surgery in these patients has been questioned, but the proportion of patients achieving a pathological complete response is small. We aimed to assess whether adding cycles of mFOLFOX6 between chemoradiation and surgery increased the proportion of patients achieving a pathological complete response.

Methods We did a phase 2, non-randomised trial consisting of four sequential study groups of patients with stage II–III locally advanced rectal cancer at 17 institutions in the USA and Canada. All patients received chemoradiation (fluorouracil 225 mg/m² per day by continuous infusion throughout radiotherapy, and 45·0 Gy in 25 fractions, 5 days per week for 5 weeks, followed by a minimum boost of 5·4 Gy). Patients in group 1 had total mesorectal excision 6–8 weeks after chemoradiation. Patients in groups 2–4 received two, four, or six cycles of mFOLFOX6, respectively, between chemoradiation and total mesorectal excision. Each cycle of mFOLFOX6 consisted of racemic leucovorin 200 mg/m² or 400 mg/m², according to the discretion of the treating investigator, oxaliplatin 85 mg/m² in a 2-h infusion, bolus fluorouracil 400 mg/m² on day 1, and a 46-h infusion of fluorouracil 2400 mg/m². The primary endpoint was the proportion of patients who achieved a pathological complete response, analysed by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00335816.

Lancet Oncol 2015; 16: 957–66

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See Comment page 880

Department of Surgery (Prof J Garcia-Aguilar MD, O S Chow M D, E Avila MSc) and Division of Biostatistics (S Patil PhD), Memorial Sloan Kettering Cancer Center, New York, NY, USA; Division of Biostatistics, City of Hope, Duarte, CA, USA (Prof D D Smith PhD); Department of Surgery, University of South Florida, Tampa, FL, USA

TUMOUR RESPONSE –PCR

	Cohort 1 (60) SG1	Cohort 2 (67) SG2	Cohort 3 (67) SG3	Cohort 4 (65) SG3
pCR	11 (18%)	17 (25%)	20 (30%)	25 (38%)
Post CRT Chemo	None	2 cycles FOLFOX	4 cycles FOLFOX	6 cycles FOLFOX
Interval to surgery	8 weeks	11 weeks	15 weeks	19 weeks
N0/N+	75%/25%	75%/25%	?	?

Garcia-Aguilar J, et al., The Lancet Oncology 2015; 16(8): 957-966

TOXICITY/COMPLIANCE

	Cohort 1 (60) SG1	Cohort 2 (67) SG2	Cohort 3 (67) SG3	Cohort 4 (65) SG3
Post CRT Chemo	None	2 cycles FOLFOX	4 cycles FOLFOX	6 cycles FOLFOX
Interval to surgery	8 weeks	11 weeks	15 weeks	19 weeks
Treatment interruptions		7%	35%	40%
Dose reductions		2%	13%	35%

Garcia-Aguilar J, et al., The Lancet Oncology 2015; 16(8): 957-966

TOXICITY/COMPLIANCE

	Cohort 1 (60) SG1	Cohort 2 (67) SG2	Cohort 3 (67) SG3	Cohort 4 (65) SG3
Post CRT Chemo	None	2 cycles FOLFOX	4 cycles FOLFOX	6 cycles FOLFOX
Interval to surgery	8 weeks	11 weeks	15 weeks	19 weeks
Pelvic Fibrosis (1-10)	2.4	3.4	4.4	3.9 p=0.0001
Technical difficulty (1-10)	4.6	4.9	5.1	4.8 (p=0.8)

Garcia-Aguilar J, et al., The Lancet Oncology 2015; 16(8): 957-966

Preoperative Radiotherapy for Resectable Rectal Cancer

Article *in* JAMA The Journal of the American Medical Association · August 2000
DOI: 10.1001/jama.284.8.1008 · Source: PubMed

Figure 1. Overall Mortality

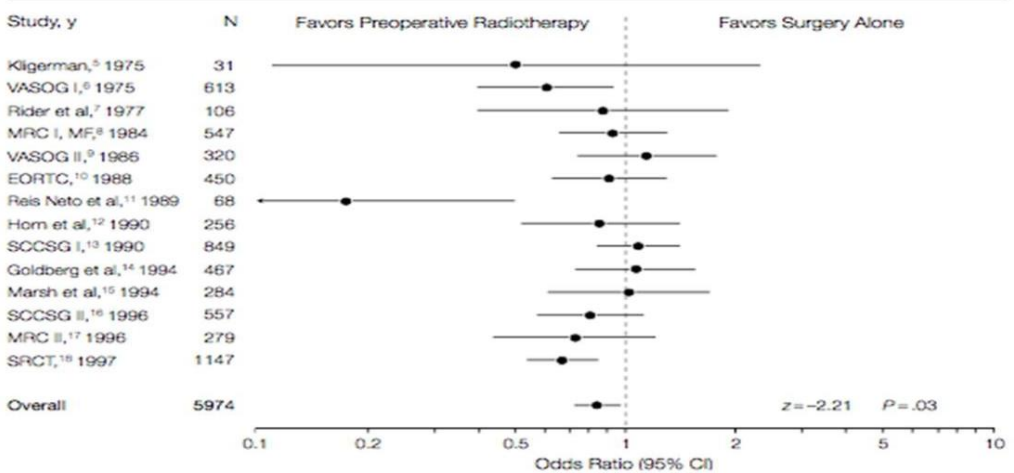


Figure 2. Cancer-Related Mortality

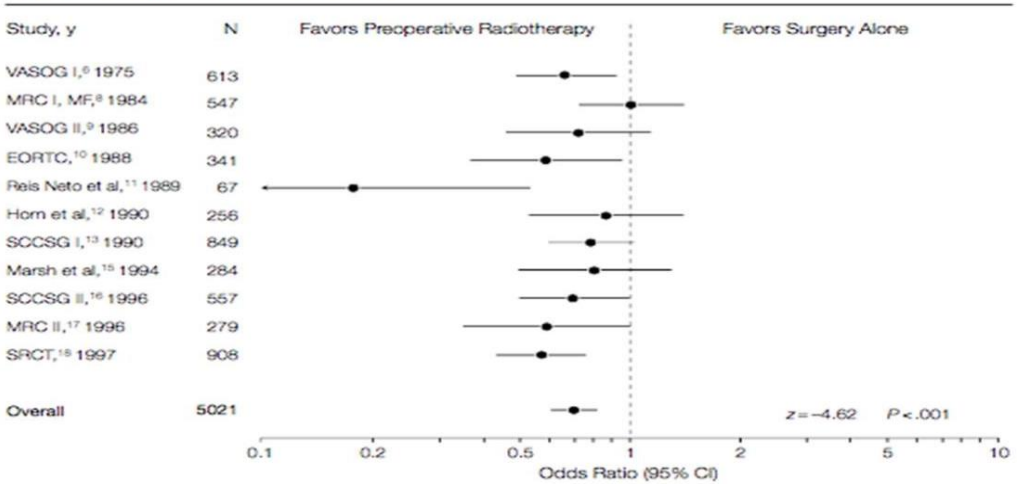
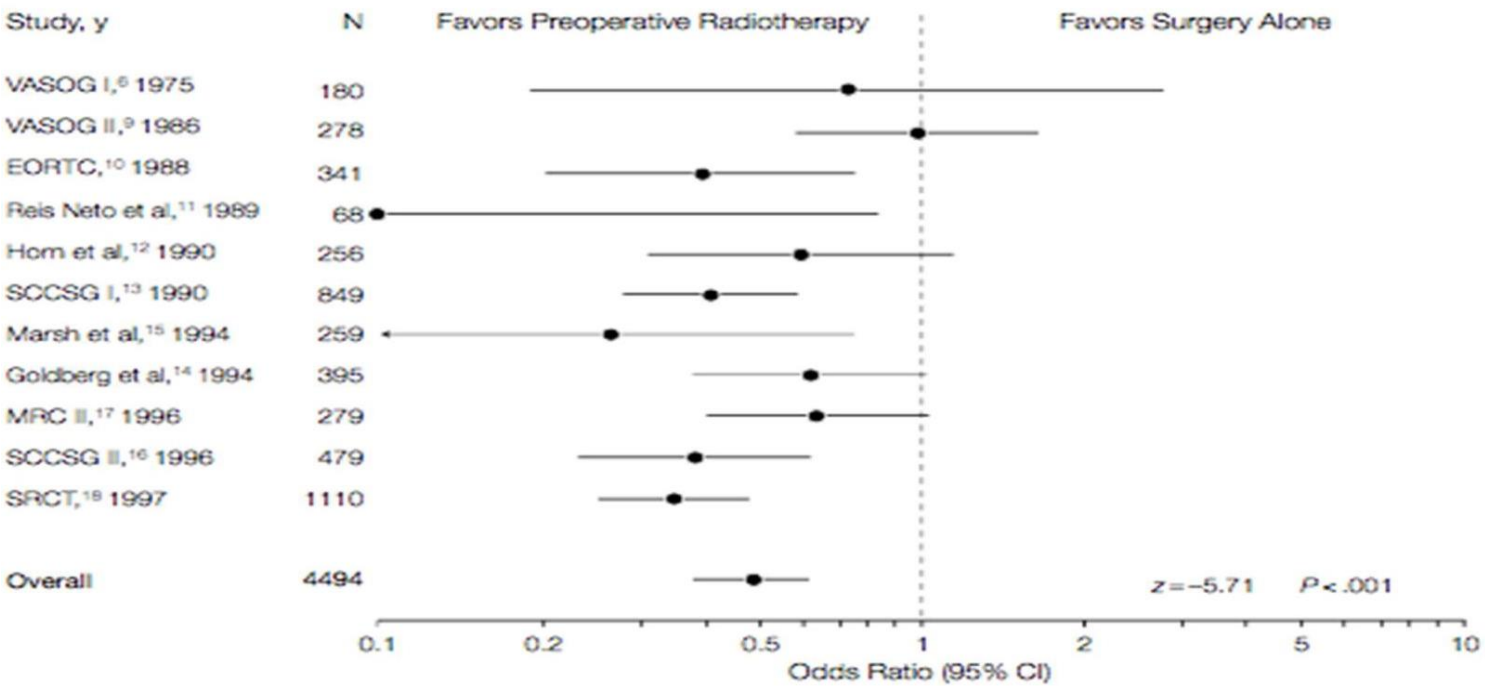


Figure 3. Local Recurrence



Ann Surg Oncol (2013) 20:4169–4182
DOI 10.1245/s10434-013-3198-9

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

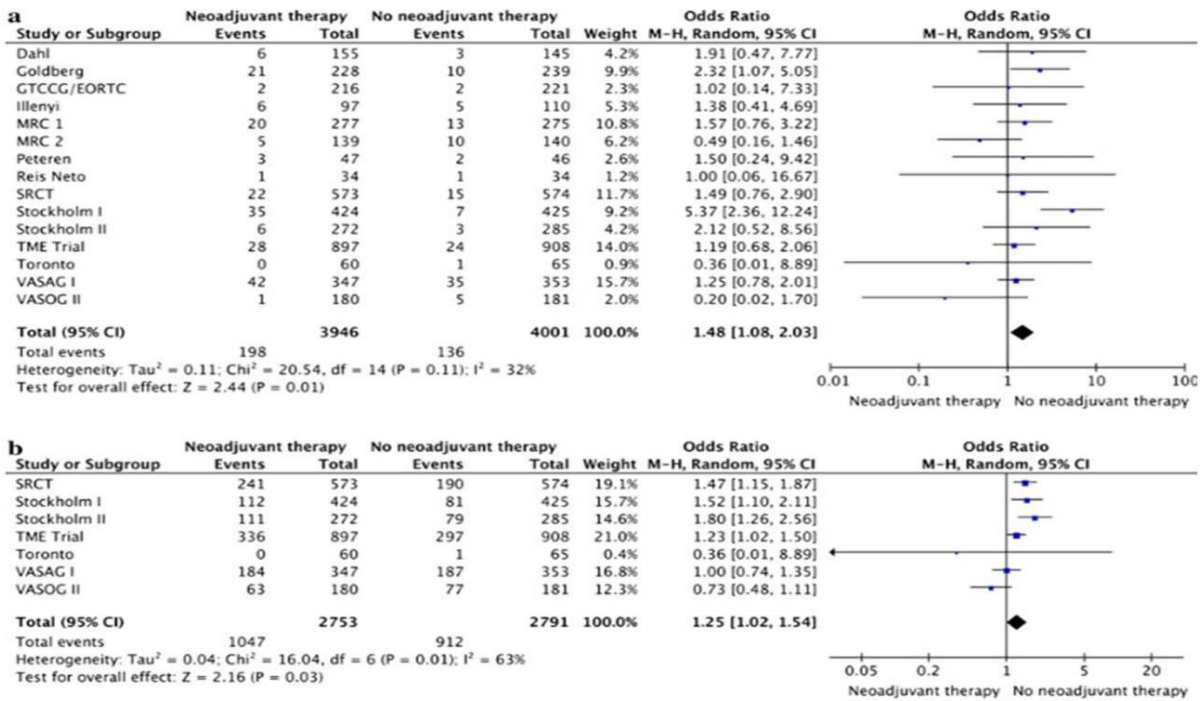
ORIGINAL ARTICLE – COLORECTAL CANCER

Neoadjuvant Radiotherapy for Rectal Cancer: Meta-analysis of Randomized Controlled Trials

Nuh N. Rahbari, MD[1], Heike Elbers, MD[1], Vasileios Askoxylakis, MD[2], Edith Motschall[3], Ulrich Bork, MD[4], Markus W. Büchler, MD[1], Jürgen Weitz, MD[4], and Moritz Koch, MD[4]

[1]Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Heidelberg, Germany; [2]Department of Radiation Oncology, University of Heidelberg, Heidelberg, Germany; [3]Institute of Medical Biometry and Medical Informatics, University of Freiburg, Freiburg, Germany; [4]Department of Gastrointestinal, Thoracic and Vascular Surgery, University of Dresden, Dresden, Germany

Meta analysis of Perioperative mortality



a

Study or Subgroup	Neoadjuvant therapy Events	Total	No neoadjuvant therapy Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Dahl	6	155	3	145	4.2%	1.91 [0.47, 7.77]
Goldberg	21	228	10	239	9.9%	2.32 [1.07, 5.05]
GTCCG/EORTC	2	216	2	221	2.3%	1.02 [0.14, 7.33]
Illenyi	6	97	5	110	5.3%	1.38 [0.41, 4.69]
MRC 1	20	277	13	275	10.8%	1.57 [0.76, 3.22]
MRC 2	5	139	10	140	6.2%	0.49 [0.16, 1.46]
Peteren	3	47	2	46	2.6%	1.50 [0.24, 9.42]
Reis Neto	1	34	1	34	1.2%	1.00 [0.06, 16.67]
SRCT	22	573	15	574	11.7%	1.49 [0.76, 2.90]
Stockholm I	35	424	7	425	9.2%	5.37 [2.36, 12.24]
Stockholm II	6	272	3	285	4.2%	2.12 [0.52, 8.56]
TME Trial	28	897	24	908	14.0%	1.19 [0.68, 2.06]
Toronto	0	60	1	65	0.9%	0.36 [0.01, 8.89]
VASAG I	42	347	35	353	15.7%	1.25 [0.78, 2.01]
VASOG II	1	180	5	181	2.0%	0.20 [0.02, 1.70]
Total (95% CI)		**3946**		**4001**	**100.0%**	**1.48 [1.08, 2.03]**
Total events	198		136			

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 20.54$, df = 14 (P = 0.11); $I^2 = 32\%$
Test for overall effect: Z = 2.44 (P = 0.01)

Odds Ratio M-H, Random, 95% CI

0.01 0.1 1 10 100
Neoadjuvant therapy No neoadjuvant therapy

b

Study or Subgroup	Neoadjuvant therapy Events	Total	No neoadjuvant therapy Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
SRCT	241	573	190	574	19.1%	1.47 [1.15, 1.87]
Stockholm I	112	424	81	425	15.7%	1.52 [1.10, 2.11]
Stockholm II	111	272	79	285	14.6%	1.80 [1.26, 2.56]
TME Trial	336	897	297	908	21.0%	1.23 [1.02, 1.50]
Toronto	0	60	1	65	0.4%	0.36 [0.01, 8.89]
VASAG I	184	347	187	353	16.8%	1.00 [0.74, 1.35]
VASOG II	63	180	77	181	12.3%	0.73 [0.48, 1.11]
Total (95% CI)		**2753**		**2791**	**100.0%**	**1.25 [1.02, 1.54]**
Total events	1047		912			

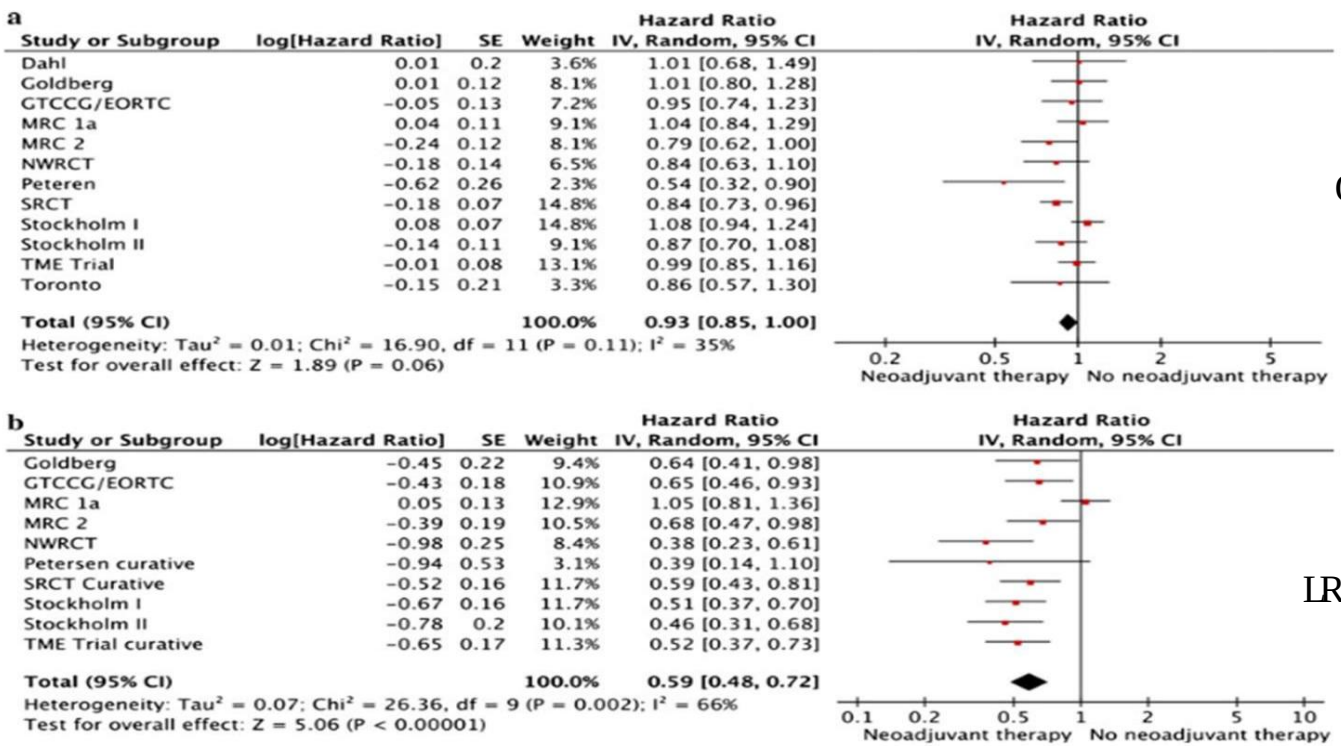
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 16.04$, df = 6 (P = 0.01); $I^2 = 63\%$
Test for overall effect: Z = 2.16 (P = 0.03)

Odds Ratio M-H, Random, 95% CI

0.05 0.2 1 5 20
Neoadjuvant therapy No neoadjuvant therapy

All studies

Subgroup analysis of studies with radiation dose of >5Gy/fr



. 3 Meta-analyses on **a** overall survival and **b** local recurrence-free survival in studies comparing neoadjuvant therapy to surgery alone

Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer (Review)

De Caluwé L, Van Nieuwenhove Y, Ceelen WP

Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD006041. DOI: 10.1002/14651858.CD006041.pub3.

Local Recurrence at 5yrs

Figure 1. Forest plot of comparison: 1 radiotherapy vs radiochemotherapy, outcome: 1.10 Local Recurrence at 5y.

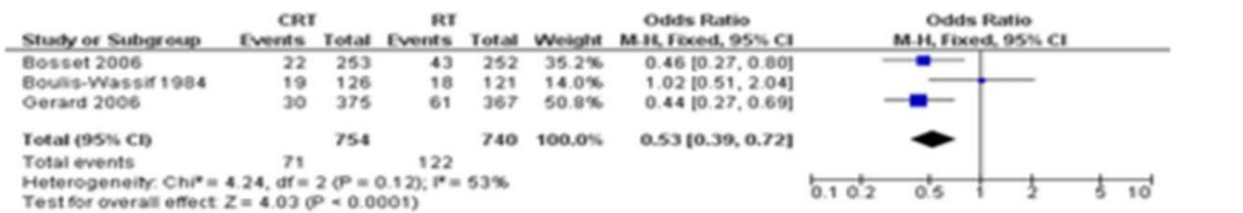


Figure 2. Forest plot of comparison: 1 radiotherapy vs radiochemotherapy, outcome: 1.12 HR LR.

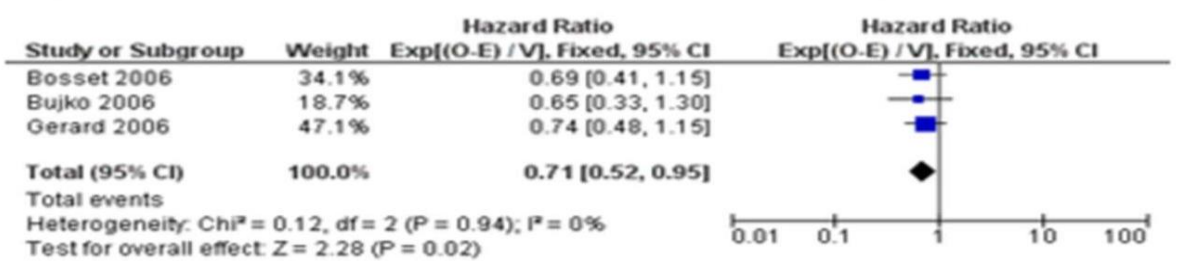
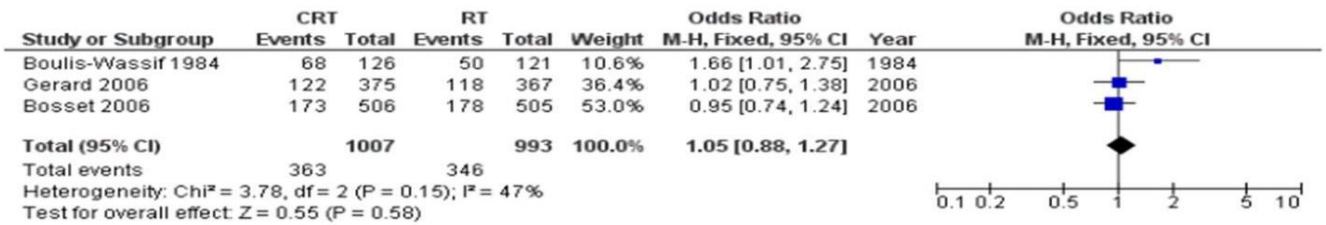


Figure 3. Forest plot of comparison: 1 radiotherapy vs radiochemotherapy, outcome: 1.1 Overall Survival at 5y.



5-ys OS

Figure 5. Forest plot of comparison: 1 radiotherapy vs radiochemotherapy, outcome: 1.3 Disease free survival at 5 y.

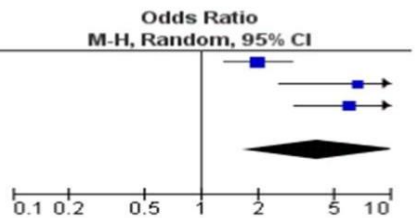
5-ys DFS

Toxicity

Figure 7. Forest plot of comparison: 1 radiotherapy vs radiochemotherapy, outcome: 1.6 Grade III - IV toxicity.

Study or Subgroup	CRT Events	CRT Total	RT Events	RT Total	Weight	Odds Ratio M-H, Random, 95% CI
Bosset 2006	67	483	37	495	38.4%	1.99 [1.31, 3.04]
Bujko 2006	29	157	5	155	28.0%	6.80 [2.56, 18.07]
Gerard 2006	55	375	10	367	33.6%	6.14 [3.08, 12.24]
Total (95% CI)		**1015**		**1017**	**100.0%**	**4.10 [1.68, 10.00]**
Total events	151		52			

Heterogeneity: Tau² = 0.49; Chi² = 10.57, df = 2 (P = 0.005); I² = 81%
Test for overall effect: Z = 3.10 (P = 0.002)



Sphincter preservation

Figure 8. Forest plot of comparison: 1 radiotherapy vs radiochemotherapy, outcome: 1.7 Sphincter preservation.

Study or Subgroup	CRT Events	CRT Total	RT Events	RT Total	Weight	Odds Ratio M-H, Random, 95% CI
Bosset 2006	263	473	249	475	45.0%	1.14 [0.88, 1.47]
Boulis-Wassif 1984	13	124	6	121	2.9%	2.24 [0.82, 6.11]
Bujko 2006	87	157	87	155	14.7%	0.97 [0.62, 1.52]
Gerard 2006	188	357	185	357	34.1%	1.03 [0.77, 1.39]
Latkauskas 2011	32	46	26	37	3.3%	0.97 [0.38, 2.49]
Total (95% CI)		**1157**		**1145**	**100.0%**	**1.09 [0.92, 1.30]**
Total events	583		553			

Heterogeneity: Tau² = 0.00; Chi² = 2.54, df = 4 (P = 0.64); I² = 0%
Test for overall effect: Z = 1.00 (P = 0.32)

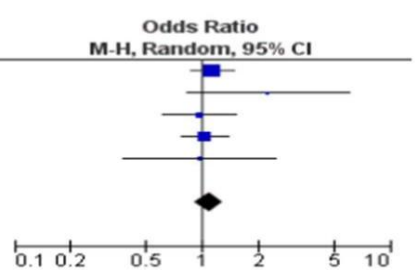
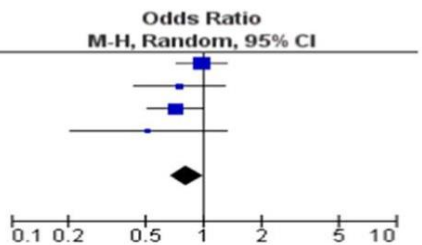


Figure 10. Forest plot of comparison: 1 radiotherapy vs radiochemotherapy, outcome: 1.5 Postop morbidity.

Study or Subgroup	CRT Events	CRT Total	RT Events	RT Total	Weight	Odds Ratio M-H, Random, 95% CI
Bosset 2006	111	487	112	483	46.2%	0.98 [0.73, 1.32]
Bujko 2006	31	152	39	153	14.3%	0.75 [0.44, 1.28]
Gerard 2006	75	359	97	360	34.7%	0.72 [0.51, 1.01]
Latkauskas 2011	12	46	15	37	4.8%	0.52 [0.20, 1.31]
Total (95% CI)		**1044**		**1033**	**100.0%**	**0.82 [0.67, 1.00]**
Total events	229		263			

Heterogeneity: Tau² = 0.00; Chi² = 2.98, df = 3 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.92 (P = 0.05)

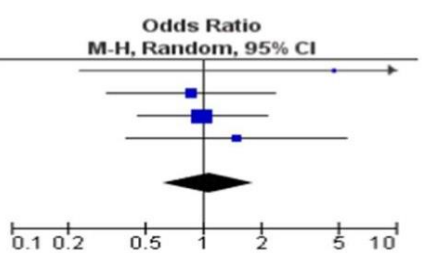


Post op morbidity

Figure 11. Forest plot of comparison: 1 radiotherapy vs radiochemotherapy, outcome: 1.9 Anastomotic leak.

Study or Subgroup	CRT Events	CRT Total	RT Events	RT Total	Weight	Odds Ratio M-H, Random, 95% CI
Bosset 2006	2	267	0	255	3.2%	4.81 [0.23, 100.71]
Bujko 2006	8	87	9	86	29.5%	0.87 [0.32, 2.36]
Gerard 2006	14	188	14	185	50.0%	0.98 [0.45, 2.12]
Latkauskas 2011	7	46	4	37	17.2%	1.48 [0.40, 5.50]
Total (95% CI)		**588**		**563**	**100.0%**	**1.07 [0.62, 1.84]**
Total events	31		27			

Heterogeneity: Tau² = 0.00; Chi² = 1.40, df = 3 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)

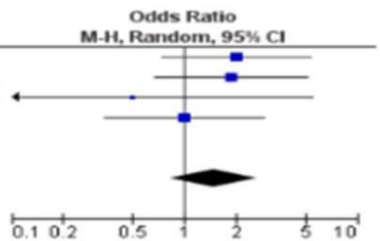


Anastomotic leak

Figure 9. Forest plot of comparison: 1 radiotherapy vs radiochemotherapy, outcome: 1.4 Mortality 30 d.

Study or Subgroup	CRT Events	CRT Total	RT Events	RT Total	Weight	Odds Ratio M-H, Random, 95% CI
Bosset 2006	12	487	6	483	33.7%	2.01 [0.75, 5.40]
Boulis-Wassif 1984	11	124	6	121	31.2%	1.87 [0.67, 5.22]
Bujko 2006	1	152	2	153	5.7%	0.50 [0.04, 5.57]
Gerard 2006	7	359	7	360	29.4%	1.00 [0.35, 2.89]
Latkauskas 2011	0	46	0	37		Not estimable
Total (95% CI)		**1168**		**1154**	**100.0%**	**1.48 [0.83, 2.63]**
Total events	31		21			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.86$, $df = 3$ ($P = 0.60$); $I^2 = 0\%$
Test for overall effect: $Z = 1.34$ ($P = 0.18$)

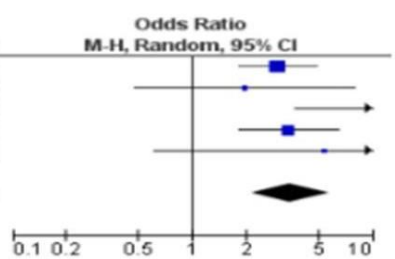


30-day mortality

Figure 12. Forest plot of comparison: 1 radiotherapy vs radiochemotherapy, outcome: 1.8 pCR.

Study or Subgroup	CRT Events	CRT Total	RT Events	RT Total	Weight	Odds Ratio M-H, Random, 95% CI
Bosset 2006	60	473	22	476	43.6%	3.00 [1.81, 4.97]
Boulis-Wassif 1984	6	126	3	121	11.1%	1.97 [0.48, 8.05]
Bujko 2006	22	138	1	148	5.8%	27.88 [3.70, 209.90]
Gerard 2006	41	359	13	360	34.4%	3.44 [1.81, 6.54]
Latkauskas 2011	6	46	1	37	5.1%	5.40 [0.62, 47.03]
Total (95% CI)		**1142**		**1142**	**100.0%**	**3.52 [2.12, 5.84]**
Total events	135		40			

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 5.44$, $df = 4$ ($P = 0.25$); $I^2 = 26\%$
Test for overall effect: $Z = 4.88$ ($P < 0.00001$)



pCR

ORIGINAL ARTICLE

Year : 2018 | **Volume** : 14 | **Issue** : 8 | **Page** : 224-231

Comparison of short-course with long-course preoperative neoadjuvant therapy for rectal cancer: A meta-analysis

Ke Chen, Guoming Xie, Qi Zhang, Yanping Shen, Taoqi Zhou

Department of Radiochemotherapy, Yinzhou Hospital Affiliated to Medical School of Ningbo University, Ningbo, China

Date of Web Publication 26-Mar-2018

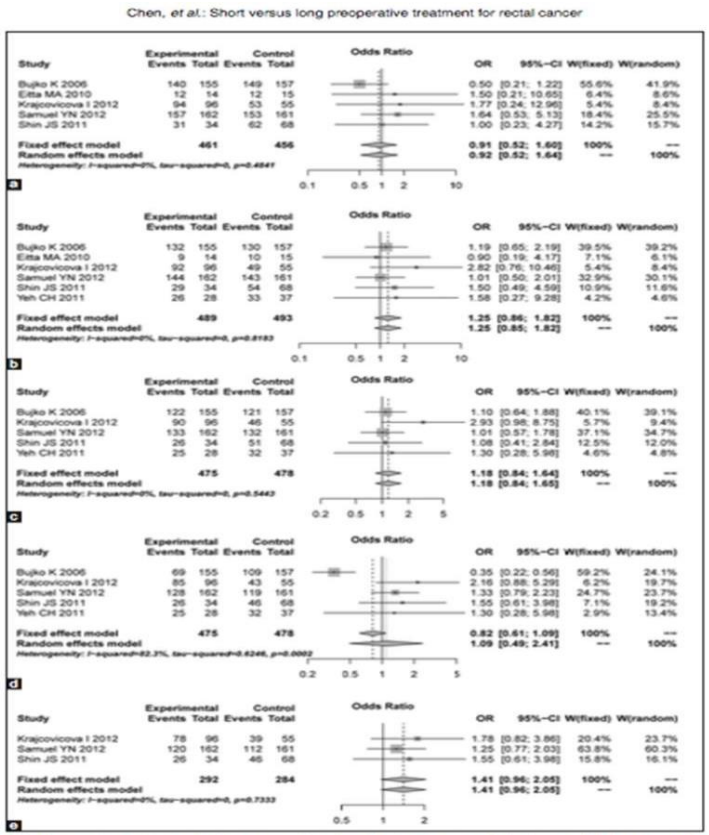


Figure 3: Forest plots of comparison between short-term versus long-term treatments on survival outcomes. (a) 1-year overall survival; (b) 2-year overall survival; (c) 3-year overall survival; (d) 4-year overall survival; (e) 5-year overall survival

1-yr OS

2-yr OS

3-yr OS

4 yr OS

5 yr OS

https://www.tandfonline.com/doi/full/10.1080/01635581.2017.1374418?scroll=top&needAccess=true

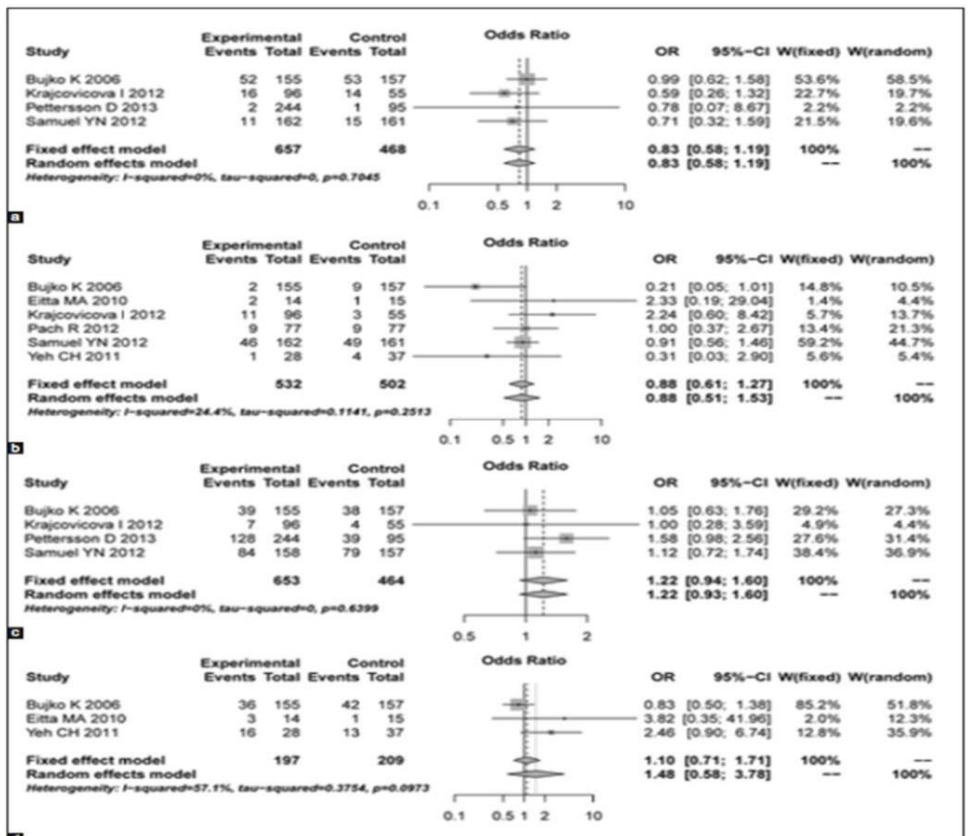


Figure 4: Forest plots of comparison between short-term versus long-term treatments on other outcomes. (a) death rate; (b) recurrence rate; (c) complications; (d) distant metastasis

Death rate

Recurrence rate

Complications

Distant metastasis

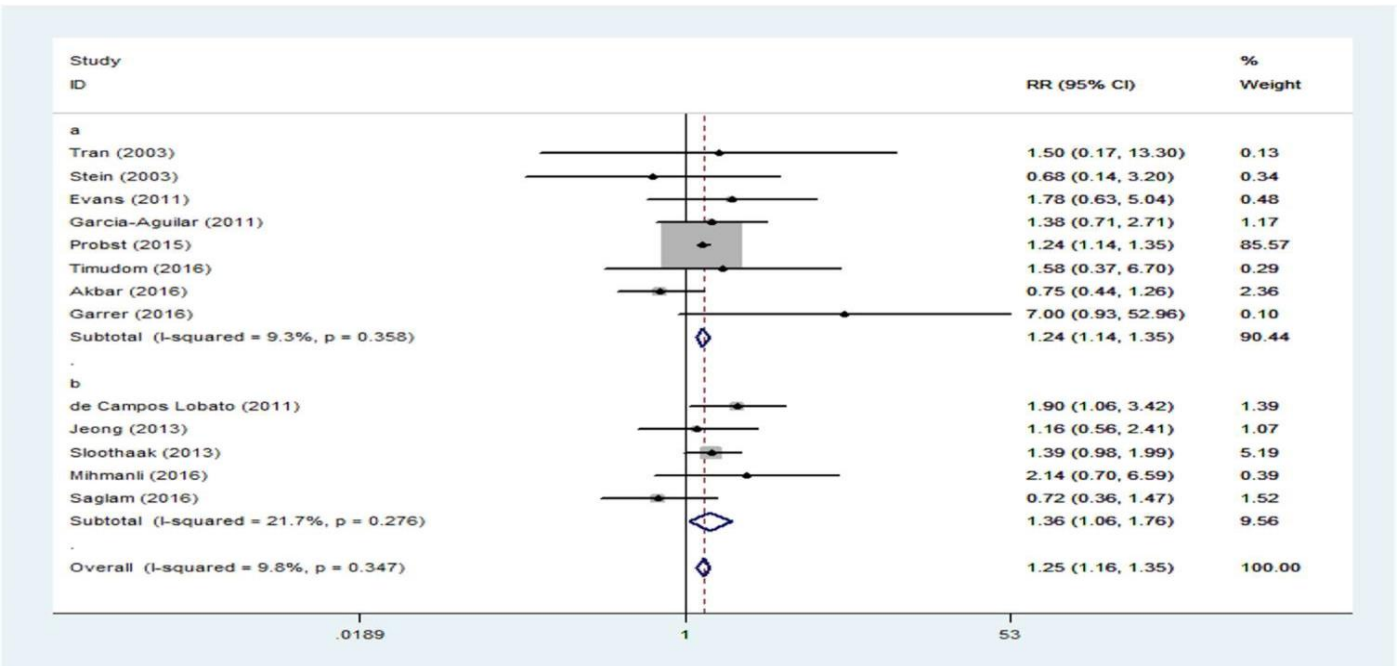
Optimal Interval to Surgery After NeoadJuvant Chemoradiotherapy in Rectal Cancer: A Systematic Review and Meta-analysis

Donglin Du, Zhourong Su, Dan Wang, Wenwen Liu, Zhangqiang Wei

Clinical Colorectal Cancer

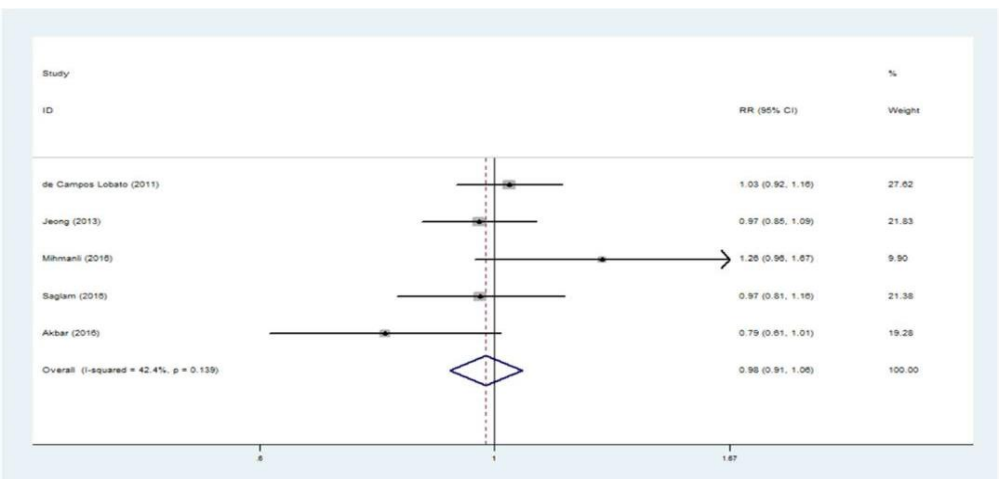
Volume 17, Issue 1, Pages 13-24 (March 2018)
DOI: 10.1016/j.clcc.2017.10.012

pCR with interval to surgery < vs > 8 weeks

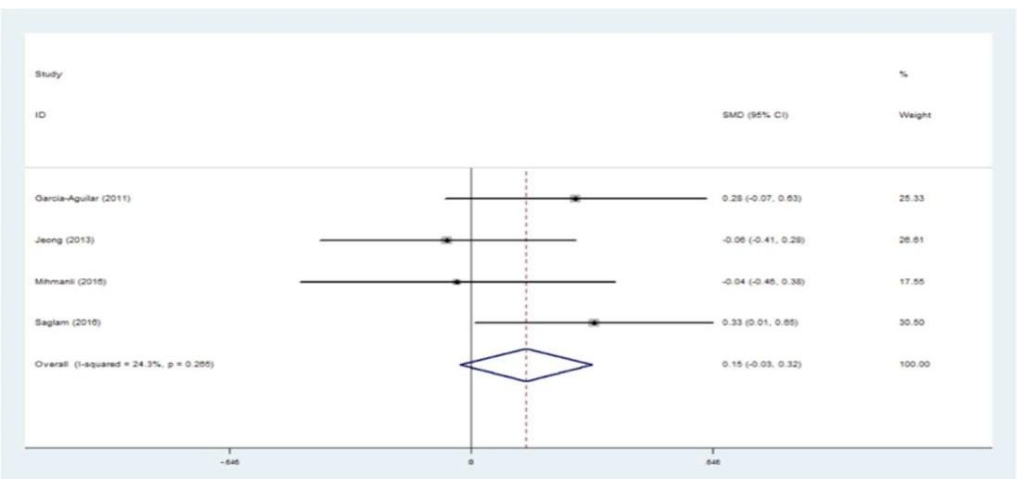


pCR was significantly higher with nCRT□Sx interval of > 8 weeks

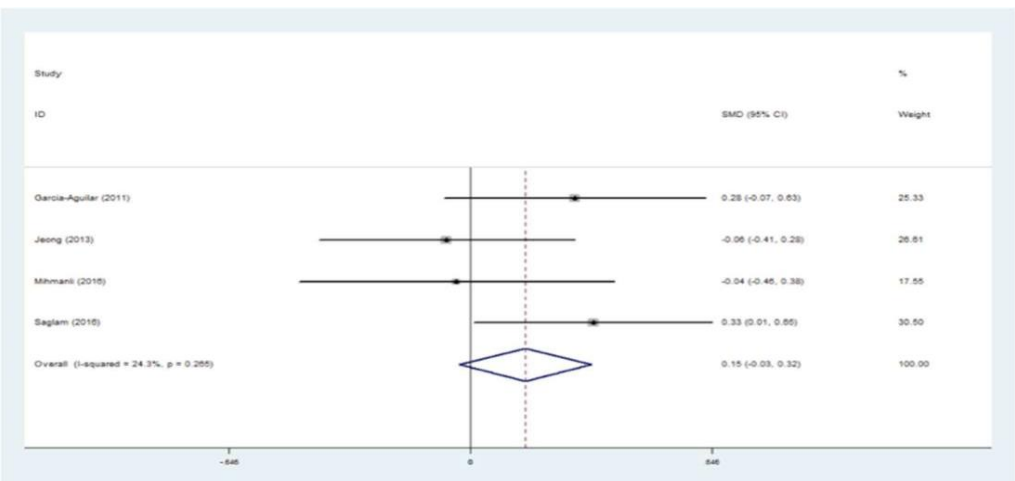
OS


Study
ID
RR (95% CI)
%
Weight
de Campos Lobato (2011)
1.03 (0.92, 1.16)
27.62
Jeong (2013)
0.97 (0.85, 1.09)
21.83
Mihmanli (2016)
1.26 (0.96, 1.67)
9.90
Saglam (2016)
0.97 (0.81, 1.16)
21.38
Akbar (2016)
0.79 (0.61, 1.01)
19.28
Overall (I-squared = 42.4%, p = 0.139)
0.98 (0.91, 1.06)
100.00
.6
1
1.67

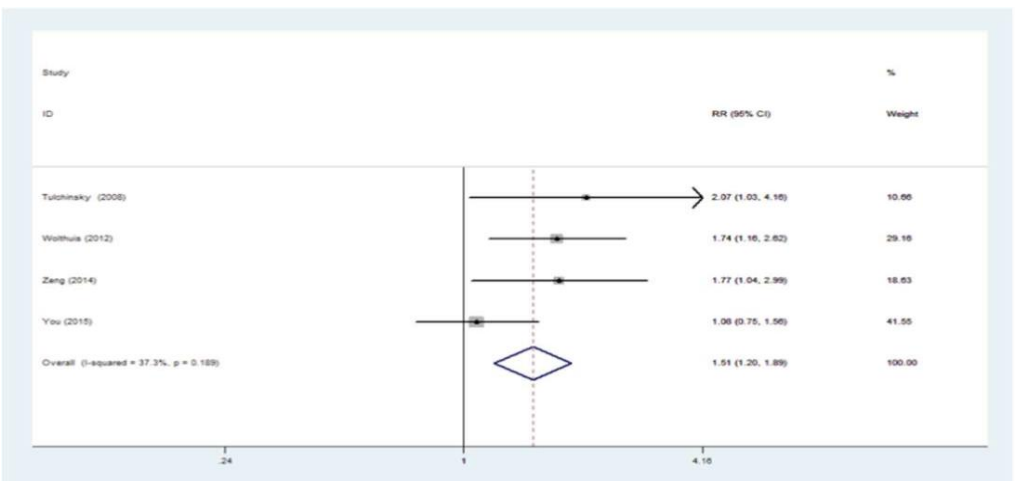
DFS


Study
ID
SMD (95% CI)
%
Weight
Garcia-Aguilar (2011)
0.28 (-0.07, 0.63)
25.33
Jeong (2013)
-0.06 (-0.41, 0.28)
26.61
Mihmanli (2016)
-0.04 (-0.46, 0.38)
17.55
Saglam (2016)
0.33 (0.01, 0.65)
30.50
Overall (I-squared = 24.3%, p = 0.266)
0.15 (-0.03, 0.32)
100.00
-.646
0
.646

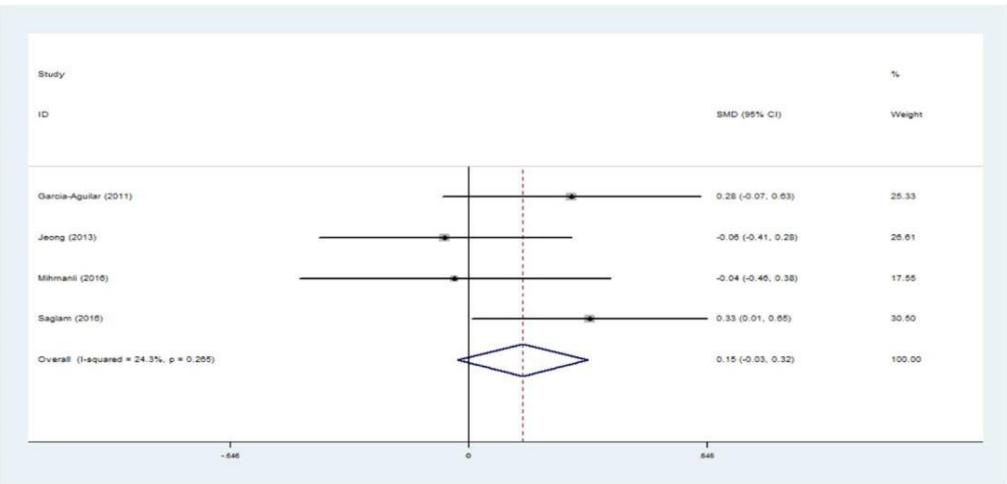
Local recurrence



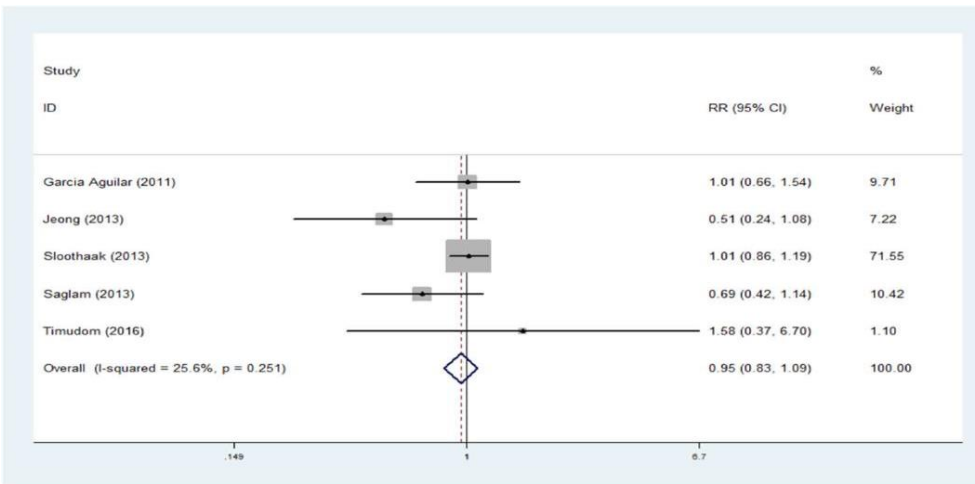
pCR



Operative time



Post op Complications



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Preoperative chemoradiotherapy versus postoperative chemoradiotherapy for stage II–III resectable rectal cancer: a meta-analysis of randomized controlled trials

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pCR

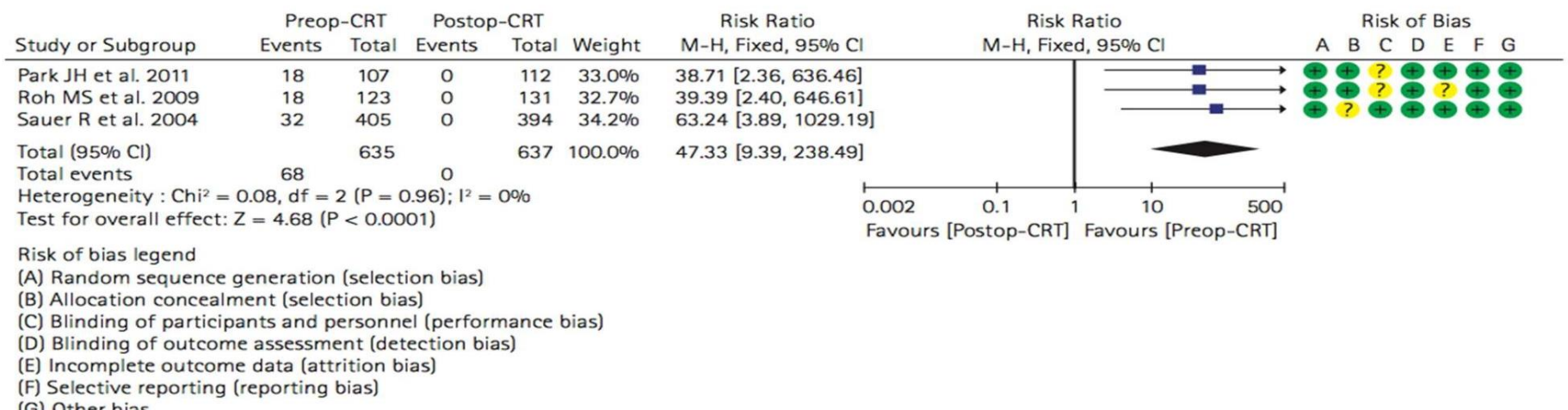
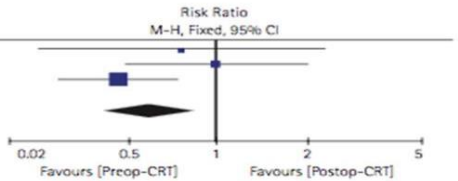


Fig. 2. Forest plot of comparison: pathologic complete response (ypT0N0) between preoperative and postoperative chemoradiotherapy.

A. 5-year locoregional recurrence

Study or Subgroup	Preop-CRT Events	Preop-CRT Total	Postop-CRT Events	Postop-CRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Park JH et al. 2011	5	107	7	112	9.5%	0.75 [0.24, 2.28]
Roh MS et al. 2009	13	123	14	131	18.8%	0.99 [0.48, 2.02]
Sauer R et al. 2004	24	405	51	394	71.7%	0.46 [0.29, 0.73]
Total (95% CI)		635		637	100.0%	0.59 [0.41, 0.84]
Total events	42		72			

Heterogeneity : Chi² = 3.33, df = 2 (P = 0.19); I² = 40%
Test for overall effect: Z = 2.89 (P = 0.0004)

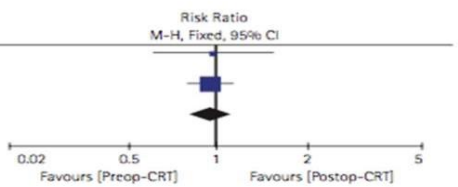


5-yr LR

B. 5-year distant recurrence

Study or Subgroup	Preop-CRT Events	Preop-CRT Total	Postop-CRT Events	Postop-CRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Park JH et al. 2011	25	107	27	112	14.8%	0.97 [0.60, 1.56]
Roh MS et al. 2009	0	0	0	0		Not estimable
Sauer R et al. 2004	146	405	150	394	85.2%	0.95 [0.79, 1.13]
Total (95% CI)		512		506	100.0%	0.95 [0.80, 1.13]
Total events	171		177			

Heterogeneity : Chi² = 0.01, df = 2 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.55)

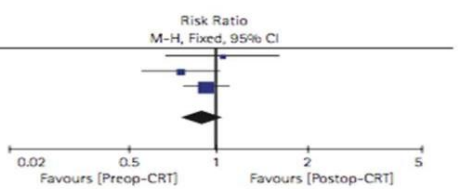


5-yr DM

C. 5-year relapse-free survival

Study or Subgroup	Preop-CRT Events	Preop-CRT Total	Postop-CRT Events	Postop-CRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Park JH et al. 2011	29	107	29	112	12.5%	1.05 [0.67, 1.63]
Roh MS et al. 2009	43	123	61	131	26.0%	0.75 [0.55, 1.02]
Sauer R et al. 2004	130	405	138	394	61.5%	0.92 [0.75, 1011]
Total (95% CI)		635		637	100.0%	0.89 [0.76, 1.04]
Total events	202		228			

Heterogeneity : Chi² = 1.82, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.49 (P = 0.14)

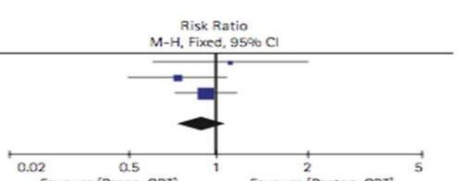


5-yr RFS

D. 5-year overall survival

Study or Subgroup	Preop-CRT Events	Preop-CRT Total	Postop-CRT Events	Postop-CRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Park JH et al. 2011	18	107	17	112	10.2%	1.11 [0.60, 2.03]
Roh MS et al. 2009	31	123	45	131	26.8%	0.73 [0.50, 1.08]
Sauer R et al. 2004	96	405	102	394	63.2%	0.92 [0.72, 1.17]
Total (95% CI)		635		637	100.0%	0.89 [0.73, 1.08]
Total events	145		164			

Heterogeneity : Chi² = 1.51, df = 2 (P = 0.47); I² = 0%
Test for overall effect: Z = 1.22 (P = 0.22)

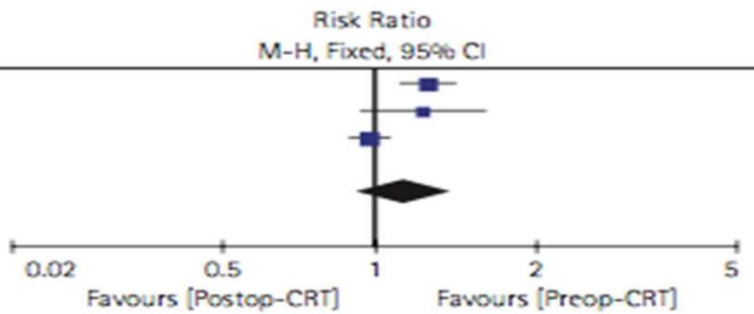


5-yr OS

A. sphincter preservation rate

Study or Subgroup	Preop-CRT Events	Preop-CRT Total	Postop-CRT Events	Postop-CRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Park JH et al. 2011	98	107	7	81	36.7%	1.27 [1.11, 1.44]
Roh MS et al. 2009	59	123	14	51	24.0%	1.23 [0.93, 1.63]
Sauer R et al. 2004	279	405	51	280	39.4%	0.97 [0.89, 1.06]
Total (95% CI)		635		637	100.0%	1.13 [0.92, 1.40]
Total events	436		412			

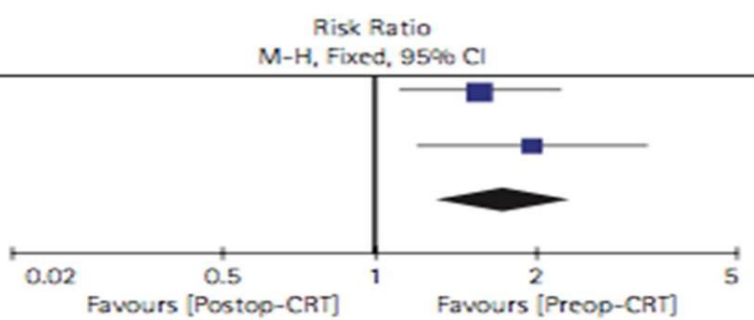
Heterogeneity : $Tau^2 = 0.03$; $Chi^2 = 12.24$, df = 2 (P = 0.002); $I^2 = 84\%$
Test for overall effect: Z = 1.16 (P = 0.24)



B. conversion rate from APR to LAR

Study or Subgroup	Preop-CRT Events	Preop-CRT Total	Postop-CRT Events	Postop-CRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Park JH et al. 2011	42	62	22	52	57.2%	1.60 [1.12, 2.30]
Roh MS et al. 2009	0	0	0	0		Not estimable
Sauer R et al. 2004	45	116	15	78	42.8%	2.02 [1.21, 3.36]
Total (95% CI)		178		130	100.0%	1.78 [1.31, 2.41]
Total events	87		37			

Heterogeneity : $Chi^2 = 0.56$, df = 1 (P = 0.45); $I^2 = 0\%$
Test for overall effect: Z = 3.72 (P = 0.0002)

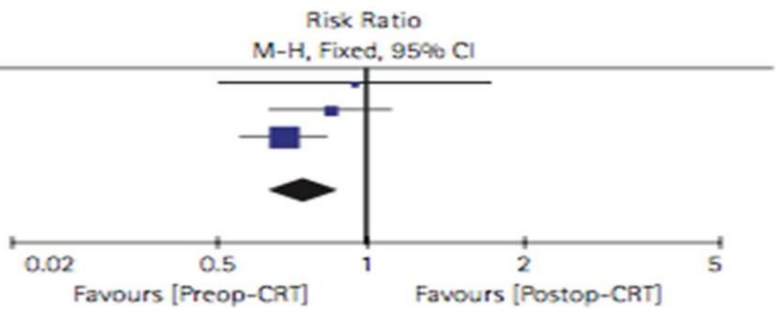


A. ≥ grade 3 acute complication

Study or Subgroup	Preop-CRT Events	Preop-CRT Total	Postop-CRT Events	Postop-CRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Park JH et al. 2011	16	107	18	112	7.3%	0.93 [0.50, 1.73]
Roh MS et al. 2009	51	123	65	131	26.2%	0.84 [0.64, 1.10]
Sauer R et al. 2004	109	405	158	394	66.5%	0.67 [0.55, 0.82]
Total (95% CI)		635		637	100.0%	0.73 [0.63, 0.86]
Total events	176		241			

Heterogeneity : $Chi^2 = 2.20$, $df = 2$ ($P = 0.33$); $I^2 = 9\%$

Test for overall effect: $Z = 3.87$ ($P = 0.0001$)

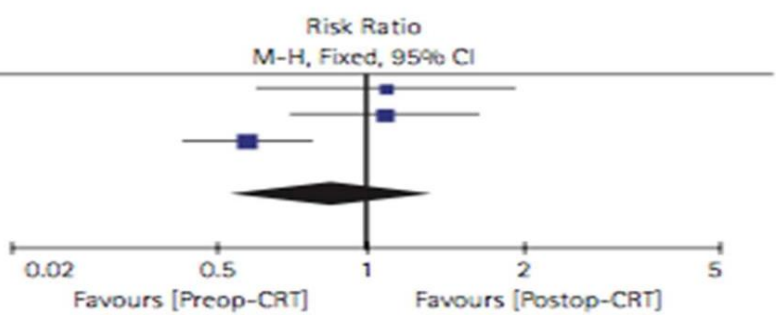


B. ≥ grade 3 perioperative or chronic complication

Study or Subgroup	Preop-CRT Events	Preop-CRT Total	Postop-CRT Events	Postop-CRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Park JH et al. 2011	18	107	17	112	26.7%	1.11 [0.60, 2.03]
Roh MS et al. 2009	31	123	30	30	33.7%	1.10 [0.71, 1.70]
Sauer R et al. 2004	57	405	95	95	39.7%	0.58 [0.43, 0.79]
Total (95% CI)		635		637	100.0%	0.86 [0.53,1.38]
Total events	106		142			

Heterogeneity : $Tau^2 = 0.13$; $Chi^2 = 7.26$, $df = 2$ ($P = 0.03$); $I^2 = 72\%$

Test for overall effect: $Z = 0.63$ ($P = 0.53$)



SO WHAT ARE THE INDICATIONS FOR SCPRT/ CRT

RESECTABLE CANCERS

- To reduce the risk of local recurrence
- To compensate for inexperienced surgeon
- If the surgeon finds other reasons for which he is not convinced that an R0 resection can be achieved

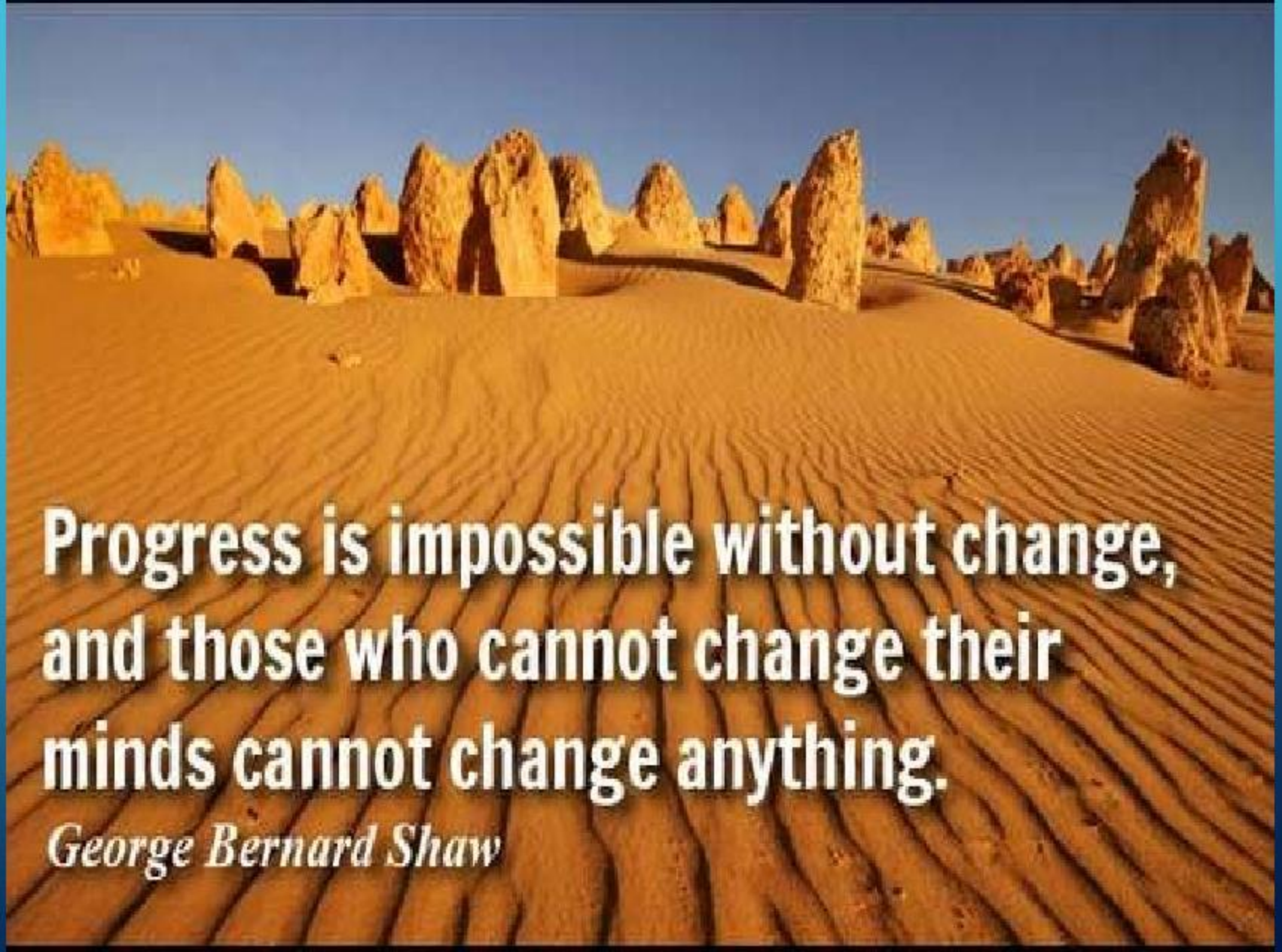
- To treat lateral pelvic lymph nodes
- Anatomy and vasculature are well preserved
- To help to achieve sphincter sparing?
- Frail, aged or unsuitable for radical surgery because co-morbidity

Clinical Practice points

- Pre-op RT significantly reduces local recurrence
- Pre-op CRT results in higher rates of pCR compared to RT alone
- CRT is associated with higher toxicity c/w RT alone
- Pre-op RT is associated with better local control compared to post op RT
- pCR rates are higher when interval from CRT to Sx is more than 8 weeks
- Longer interval to surgery did not compromise outcomes and was not associated with difference in toxicity rates
- Hypofractionation with doses >5Gy appears to increase perioperative mortality and post op morbidity in some reports

No benefit of CRT over SCPRT was seen based on long term HRQL, acute toxicity, local control and survival

Sometimes wait and watch can be offered to few patients after good response to CRT


Progress is impossible without change,
and those who cannot change their
minds cannot change anything.
George Bernard Shaw

THANK YOU