National Institute for Health and Care Excellence

Draft for consultation

Colorectal cancer (update)

[C2] Preoperative radiotherapy and chemoradiotherapy for rectal cancer

NICE guideline TBC

Evidence reviews

July 2019

Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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ISBN:

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The effectiveness of preoperative radiotherapy and chemoradiotherapy for rectal cancer

This evidence review supports recommendation 1.3.3.

Review question

What is the effectiveness of preoperative radiotherapy and chemoradiotherapy for rectal cancer?

Introduction

The treatment of rectal cancer has become increasingly complex. The aim of this review was to assess how effective the use of preoperative therapy is in the treatment of rectal cancer, and to see whether there are any particular clinical situations where this treatment is beneficial, or alternatively, where it may be potentially omitted.

Summary of the protocol

Please see Table 1 for a summary of the population, intervention, comparison and outcomes (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Adults with non-metastatic rectal cancer • T any, N1 or N2 • T3 • T4 • M0
Intervention	• Preoperative chemoradiotherapy with or without prior chemotherapy • Preoperative radiotherapy ○ External - Short-course - Long-course ○ External and internal ○ Internal
Comparison	1. Any preoperative therapy versus no preoperative therapy 2. Short-course radiotherapy versus long-course radiotherapy with or without chemotherapy 3. Chemoradiotherapy with prior chemotherapy versus chemoradiotherapy without prior chemotherapy 4. Internal radiotherapy with or without external radiotherapy versus any external radiotherapy (without internal radiotherapy)
Outcomes	**Critical** • Overall survival • Complete (R0) resection rate • Overall quality of life

	Important • Local recurrence • Disease-free survival • Sphincter preservation/permanent stoma • Treatment-related mortality

M: distant metastasis stage; N: nodal stage; R0: complete resection; T: tumour stage

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy until 31 March 2018. From 1 April 2018, declarations of interest were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Register of Interests).

Clinical evidence

Included studies

Thirty-two publications from 22 RCTs (number of participants, N=9,210) were included in this evidence review (Appelt 2014; Atif 2012; CAO/ARO/AIO-94 trial [Sauer 2003; Sauer 2012]; Eitta 2010; Dutch TME trial [Marijnen 2005; Peeters 2005, 2007; van Gijn 2011; Wiltink 2014]; GCR-03 trial [Fernandos-Martos 2015]; Kacar 2009; Lithuanian trial [Kairevice 2017; Latkauskas 2016]; Lyon R96-02 trial [Gerard 2004]; Marechal 2012; MRC CR07 trial [Sebag-Montefiore 2009; Stephens 2010]; NSABP R03 trial [Roh 2009]; Park 2011; Polish trial 1 [Bujko 2006; Pietrzak 2007]; Polish trial 2 [Bujko 2016]; Stockholm III trial [Erlandsson 2017]; Swedish Rectal Cancer Trial [Cedermark 1997; Folkesson 2005]; Taher 2006; TROG 01.04 trial [McLachlan 2016; Ngan 2012]; Wang 2018; Zhang 2008).

The included studies are summarised in Table 2.

Twelve RCTs (19 publications) compared any preoperative therapy to no preoperative therapy (comparison 1) (Atif 2012; CAO/ARO/AIO-94 trial [Sauer 2003; Sauer 2012]; Fan 2015; Dutch TME trial [Marijnen 2005; Peeters 2005, 2007; van Gijn 2011; Wiltink 2014]; Kacar 2009; MRC CR07 trial [Sebag-Montefiore 2009; Stephens 2010]; NSABP R03 trial [Roh 2009]; Park 2011; Swedish Rectal Cancer Trial [Cedermark 1997; Folkesson 2005]; Taher 2006; Wang 2018; Zhang 2008). Six RCTs (9 publications) compared short-course radiotherapy to long-course radiotherapy with or without chemotherapy (comparison 2) (Eitta 2010; Lithuanian trial [Kairevice 2017; Latkauskas 2016]; Polish trial 1 [Bujko 2006; Pietrzak 2007]; Polish trial 2 [Bujko 2016]; Stockholm III trial [Erlandsson 2017]; TROG 01.04 trial [McLachlan 2016; Ngan 2012]). Two RCTs compared chemoradiotherapy with prior chemotherapy to chemoradiotherapy without prior chemotherapy (comparison 3) (GCR-03 trial [Fernandos-Martos 2015]; Marechal 2012). Finally, 2 RCTs compared internal radiotherapy with or without external radiotherapy to external radiotherapy without internal radiotherapy (comparison 4) (Appelt 2014; Lyon R96-02 trial [Gerard 2004]).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention/Comparison	Outcome
Comparison 1: Any preoperative therapy versus no preoperative therapy			
Atif 2012 RCT Egypt	N=100 people with resectable, non-metastatic rectal cancer within 15 cm from the anal verge (around 10% of the participants in preoperative radiotherapy group with early rectal cancer)	Preoperative radiotherapy versus postoperative radiotherapy	• Overall survival • Local recurrence-free survival • Disease-free survival
CAO/ARO/AIO-94 trial (Sauer 2003; Sauer 2012) RCT Germany	N=823 people with resectable, non-metastatic cancer within 16 cm from the anal verge Germany	Preoperative chemoradiotherapy versus postoperative chemoradiotherapy	• Overall survival • Complete (R0) resection rate • Local recurrence-free survival • Disease-free survival • Treatment-related mortality
Dutch TME trial (Marijnen 2005; Peeters 2005; Peeters 2007; van Gijn 2011; Wiltink 2014) RCT The Netherlands, Belgium, Canada, France, Germany, Italy, Sweden, UK	N=1,861 people with resectable, non-metastatic rectal within 15 cm from the anal verge (around 30% of the participants with early rectal cancer)	Preoperative short-course radiotherapy versus surgery alone	• Overall survival • Complete (R0) resection rate • Health-related quality of life • Local recurrence • Permanent stoma • Treatment-related mortality
Chi CTR-TRC-08000122 trial (Fan 2015; Wang 2018) RCT	N=192 people with resectable T3-T4 or N+ rectal cancer within 10 cm from the anal verge	Preoperative chemoradiotherapy versus surgery alone (with selective postoperative chemoradiotherapy)	• Overall survival • Complete (R0) resection rate • Local recurrence-free survival

Study	Population	Intervention/Comparison	Outcome
China			• Disease-free survival • Sphincter preservation • Treatment-related mortality
Kacar 2009 RCT Turkey	N=51 people with non-metastatic rectal cancer within 15 cm from the anal verge	Preoperative chemoradiotherapy versus postoperative chemoradiotherapy	• Local recurrence-free survival
MRC CR07 trial (Sebag-Montefiore 2009; Stephens 2010) RCT UK, Canada, New Zealand, South Africa	N=1,350 people with resectable, non-metastatic rectal cancer within 15 cm from the anal verge (a proportion of the participants might have early rectal cancer although not clearly reported)	Preoperative short-course radiotherapy versus surgery alone (with selective postoperative chemoradiotherapy)	• Overall survival • Complete (R0) resection rate • Local recurrence-free survival • Disease-free survival • Treatment-related mortality
NSABP R03 trial (Roh 2009) RCT US	N=267 people with non-metastatic rectal cancer within 15 cm from the anal verge	Preoperative chemoradiotherapy (and postoperative chemotherapy) versus postoperative chemoradiotherapy	• Overall survival • Disease-free survival • Sphincter preservation
Park 2011 RCT Republic of Korea	N=220 people with T3, potentially resectable cT4 or N+, non-metastatic rectal cancer within 10 cm from the anal verge	Preoperative chemoradiotherapy (and postoperative chemotherapy) versus postoperative chemoradiotherapy (and adjuvant chemotherapy)	• Overall survival • Complete (R0) resection rate • Local recurrence-free survival • Disease-free survival
Swedish Rectal Cancer trial (Cedermark 1997; Folkesson 2005) RCT Sweden	N=1,168 people with resectable, non-metastatic rectal cancer (around one third of the participants with early rectal cancer)	Preoperative short-course radiotherapy versus surgery alone	• Overall survival • Local recurrence-free survival • Treatment-related mortality
Taher 2006 RCT Egypt	N=50 people with previously untreated, locally advanced, resectable rectal cancer	Preoperative radiotherapy (and selective postoperative chemotherapy) versus postoperative chemoradiotherapy	• Local recurrence rate

Study	Population	Intervention/Comparison	Outcome
Zhang 2008 RCT China	N=260 people with Duke's stage B or C rectal cancer	Preoperative radiotherapy and postoperative radiotherapy versus postoperative radiotherapy versus surgery alone	• Local recurrence rate
Comparison 2: Short-course radiotherapy versus long-course radiotherapy with or without chemotherapy			
Eitta 2010 RCT Egypt	N=32 people with resectable, non-metastatic rectal cancer within 15 cm from the anal verge	Preoperative short-course radiotherapy (and selective postoperative chemotherapy) versus preoperative long-course radiotherapy (and selective postoperative chemotherapy)	• Local recurrence rate
Lithuanian trial (Kairevice 2017; Latkauskas 2016) RCT Lithuania	N=150 people with stage II or III rectal cancer within 15 cm from the anal verge	Preoperative short-course radiotherapy with delayed surgery versus preoperative long-course chemoradiotherapy (and postoperative chemotherapy)	• Overall survival • Complete (R0) resection rate • Local recurrence rate • Disease-free survival • Permanent stoma
Polish trial 1 (Bujko 2006; Pietrzak 2007) RCT Poland	N=316 people with T3 or T4, resectable rectal cancer with lower tumour margin accessible to digital rectal examination	Preoperative short-course radiotherapy (and selective postoperative chemotherapy) versus preoperative long-course chemoradiotherapy (and selective postoperative chemotherapy)	• Overall survival • Local recurrence-free survival • Disease-free survival • Permanent stoma • Treatment-related mortality
Polish trial 2 (Bujko 2016) RCT Poland	N=541 people with cT3 or cT4, non-metastatic rectal cancer within 15 cm from the anal verge	Preoperative short-course radiotherapy with consolidation chemotherapy versus preoperative long-course chemoradiotherapy (and selective postoperative chemotherapy)	• Overall survival • Complete (R0) resection rate • Disease-free survival • Treatment-related mortality
Stockholm III trial (Erlandsson 2017) RCT	N=840 people with resectable, non-metastatic rectal cancer within 15 cm from the anal verge (around 30% of the	Preoperative short-course radiotherapy versus preoperative short-course radiotherapy with delayed surgery	• Overall survival • Local recurrence rate • Disease-free survival

Study	Population	Intervention/Comparison	Outcome
Sweden	participants with early rectal cancer)	versus preoperative long-course radiotherapy	• Treatment-related mortality
TROG 01.04 trial (McLachlan 2016; Ngan 2012 RCT Australia and New Zealand	N=326 people with T3, non-metastatic rectal cancer within 12 cm from the anal verge	Preoperative short-course radiotherapy (and postoperative chemotherapy) versus preoperative long-course chemoradiotherapy (and postoperative chemotherapy)	• Overall survival • Complete (R0) resection margin • Local recurrence-free survival • Disease-free survival
Comparison 3: Chemoradiotherapy with prior chemotherapy versus chemoradiotherapy without prior chemotherapy			
GCR-3 trial (Fernandez-Martos 2015) RCT Spain	N=108 people with locally advanced, non-metastatic rectal cancer within 12 cm from the anal verge	Preoperative chemoradiotherapy with induction chemotherapy versus preoperative chemoradiotherapy and postoperative chemotherapy	• Overall survival • Complete (R0) resection rate • Local recurrence-free survival • Disease-free survival • Treatment-related mortality
Marechal 2012 RCT Belgium	N=57 people with resectable, T2-T4, N+, non-metastatic rectal cancer	Preoperative chemoradiotherapy with induction chemotherapy versus preoperative chemoradiotherapy without induction chemotherapy	• Complete (R0) resection rate • Treatment-related mortality
Comparison 4: Internal radiotherapy with or without external radiotherapy versus any external radiotherapy (without internal radiotherapy)			
Appelt 2014 RCT Denmark	N=224 people with T3-T4, N0-2, non-metastatic rectal cancer within 10 cm from the anal verge	Preoperative external chemoradiotherapy with brachytherapy boost versus preoperative external chemoradiotherapy without brachytherapy boost	• Overall survival • Complete (R0) resection rate • Locoregional recurrence-free survival • Disease-free survival
Lyon R96-02 trial (Gerard 2004) RCT France	N=90 people with T2-T3, non-metastatic rectal cancer within 6 cm from the anal verge (a small proportion of the participants might have T2N0 cancer although not clearly reported)	Preoperative external radiotherapy with endocavity contact X-ray boost versus preoperative external radiotherapy without endocavity contact X-ray boost	• Locoregional recurrence rate • Treatment-related mortality

N: number; RCT: randomised controlled trial; R0: complete resection; TNM: cancer classification system, standing for tumour, nodal, or metastasis stages

See the full evidence tables in appendix D and the forest plots in appendix E.

Quality assessment of clinical studies included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

Excluded studies

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Clinical evidence statements

Comparison 1: Any preoperative therapy *versus no preoperative therapy*

Critical outcomes

Overall survival

- One study (Zhang 2008) reported overall survival as observed events (n/N [%]) with no HR (95% CI), this study was not included in the pooled analysis.
- Moderate quality evidence from 8 RCTs (N=5,620; median follow-up 1.5 to 11.6 years) showed that receiving preoperative (chemo) radiotherapy produces a clinically important increase in overall survival compared to not receiving preoperative (chemo) radiotherapy in people with non-metastatic rectal cancer.

Complete (R0) resection rate

- Moderate quality evidence from 5 RCTs (N=4,356) showed no clinically important difference in complete (R0) resection rate between receiving and not receiving preoperative (chemo) radiotherapy in people with non-metastatic rectal cancer.

Overall quality of life

- Low quality evidence from 1 RCT (N not reported) showed no difference in overall health-related quality of life at 3, 6, 12 and 24 months after surgery (measured using a visual analogue scale) between receiving preoperative radiotherapy and undergoing surgery alone in people with non-metastatic rectal cancer. This result was reported narratively. Low quality evidence from the same RCT (N=478) showed no difference in global health status at median 14 years of follow-up

(measured using EORTC QLQ-C30) between receiving preoperative radiotherapy and undergoing surgery alone.

- Low quality evidence from 1 RCT (N=519) showed no clinically important difference in health-related quality of life general health subscale score or physical function subscale score at 2 year follow-up (measured using SF-36) between receiving preoperative short-course radiotherapy and undergoing surgery alone (with selective postoperative chemoradiotherapy) in people with non-metastatic rectal cancer.

Important outcomes

Local recurrence

- Moderate quality evidence from 9 RCTs (N=5,807; median 1.5 to 11.6 years of follow-up) showed that receiving preoperative (chemo)radiotherapy produces a clinically important increase in local recurrence-free survival compared to not receiving preoperative (chemo)radiotherapy in people with non-metastatic rectal cancer.
- Low quality evidence from 2 RCTs (N=240) showed that receiving preoperative (chemo)radiotherapy produces a clinically important decrease in local recurrence rate at median 5.2 year follow-up compared to receiving postoperative (chemo)radiotherapy in people with non-metastatic rectal cancer.
- Low quality evidence from 1 RCT (N=162) showed that receiving preoperative (chemo)radiotherapy produces a clinically important decrease in local recurrence rate (follow-up time not reported) compared to undergoing surgery alone in people with non-metastatic rectal cancer.

Disease-free survival

- Moderate quality evidence from 6 RCTs (N=2,937; median 1.5 to 11.2 years of follow-up) showed that receiving preoperative (chemo)radiotherapy produces a clinically important increase in disease-free survival compared to not receiving preoperative (chemo)radiotherapy in people with non-metastatic rectal cancer.

Sphincter preservation/permanent stoma

- Low quality evidence from 1 RCT (N=597) showed no clinically important difference in permanent stoma rate at median 5 year follow-up between receiving preoperative radiotherapy and undergoing surgery alone in people with non-metastatic rectal cancer.
- Moderately quality evidence from 2 RCTs (N=419) showed no clinically important difference in sphincter preservation at 5 year follow-up between receiving and not receiving preoperative chemoradiotherapy in people with non-metastatic rectal cancer.

Treatment-related mortality

- Low quality evidence from 4 RCTs (N=3,935) showed no clinically important difference in treatment-related mortality (preoperative or postoperative) between receiving and not receiving preoperative (chemo) radiotherapy in people with non-metastatic rectal cancer.
- Low quality evidence from 1 RCT (N=1,350) showed no clinically important different in 30-day and 60-day operative mortality between receiving preoperative short-course radiotherapy and undergoing surgery alone (with selective postoperative chemoradiotherapy) in people with non-metastatic rectal cancer.

Comparison 2: Short-course radiotherapy versus long-course radiotherapy with or without chemotherapy

Critical outcomes

Overall survival

- Meta-analysis of overall survival showed considerable heterogeneity, therefore, subgroup analysis according to treatment subtype was done.
- Moderate quality evidence from 2 RCTs (N=635; median 4 to 5.9 years of follow-up) showed no clinically important difference in overall survival between receiving preoperative short-course radiotherapy with immediate surgery and receiving preoperative long-course (chemo) radiotherapy in people with non-metastatic rectal cancer.
- Moderate quality evidence from 1 RCT (N=150; median 5 years of follow-up) showed that receiving preoperative short-course radiotherapy with delayed surgery showed a clinically important decrease in overall survival compared to receiving preoperative long-course chemoradiotherapy in people with non-metastatic rectal cancer.
- Moderate quality evidence from 1 RCT (N=515; median 2.9 years of follow-up) showed no clinically important difference in overall survival between receiving preoperative short-course radiotherapy with consolidation chemotherapy and receiving preoperative long-course chemoradiotherapy in people with non-metastatic rectal cancer.
- Moderate quality evidence from 1 RCT (N=357; median 5.2 years of follow-up) showed that receiving preoperative short-course radiotherapy showed no clinically important difference in overall survival compared with long-course radiotherapy in people with non-metastatic rectal cancer.

Complete (R0) resection rate

- Meta-analysis of complete (R0) resection rate showed considerable heterogeneity, therefore, the results are presented separately for each study.
- Moderate quality evidence from 1 RCT (N=140) showed no clinically important difference in complete (R0) resection rate between receiving preoperative short-course with delayed surgery or preoperative long-course chemoradiotherapy in people with non-metastatic rectal cancer.
- High quality evidence from 1 RCT (N=515) showed that receiving preoperative short-course radiotherapy with consolidation chemotherapy may produce a clinically important increase in complete (R0) resection rate compared to receiving preoperative long-course chemoradiotherapy and selective postoperative chemotherapy in people with non-metastatic rectal cancer, but there is uncertainty around the estimate.
- High quality evidence from 1 RCT (N=315) showed no clinically important difference in complete (R0) resection rate between receiving preoperative short-course or long-course radiotherapy in people with non-metastatic rectal cancer.

Overall quality of life

- Low quality evidence from 1 RCT (N=296) showed no clinically important difference in health-related quality of life global health status score change from baseline to 12 months (measured using QLQ-C30) between receiving preoperative short-course or long-course radiotherapy in people with non-metastatic rectal cancer.

- Low quality evidence from 1 RCT (N=221) showed no clinically important difference in health-related quality of life global health status score at 12 month follow-up (measured using EORTC QLQ-C30) between receiving preoperative short-course radiotherapy and receiving preoperative long-course chemoradiotherapy in people with non-metastatic rectal cancer.

Important outcomes

Local recurrence

- Moderate quality evidence from 2 RCTs (N=618; median 4 to 5.9 years of follow-up) showed no clinically important difference in local recurrence-free survival between receiving preoperative short-course or long-course radiotherapy in people with non-metastatic rectal cancer.
- Moderate quality evidence from 2 RCTs (N=286) showed no clinically important difference in local recurrence rate at median 1.5 to 5.2 years of follow-up between receiving preoperative short-course (with immediate surgery) or long-course radiotherapy in people with non-metastatic rectal cancer.
- Moderate quality evidence frm 2 RCTs (N=396) showed no clinically important difference in local recurrence rate at median 5 to 5.2 years of follow-up between receiving preoperative short-course (chemo)radiotherapy with delayed surgery or long-course (chemo)radiotherapy in people with non-metastatic rectal cancer.

Disease-free survival

- Meta-analysis for disease-free survival showed considerable heterogeneity, therefore, subgroup analysis according to treatment subtype was done.
- Moderate quality evidence from 3 RCTs (N=892; median 4 to 5.9 years of follow-up) showed no clinically important difference in disease-free survival between receiving preoperative short-course or long-course (chemo) radiotherapy in people with non-metastatic rectal cancer.
- Moderate quality evidence from 1 RCT (N=140; median 5 years of follow-up) showed that receiving preoperative short-course radiotherapy with delayed surgery produces a clinically important decrease in disease-free survival compared to receiving preoperative long-course chemoradiotherapy in people with non-metastatic rectal cancer.
- Moderate quality evidence from 1 RCT (N=515; median 2.9 years of follow-up) showed no clinically important difference in disease-free survival between receiving preoperative short-course radiotherapy with consolidation chemotherapy and preoperative long-course chemoradiotherapy in people with non-metastatic rectal cancer.

Sphincter preservation/permanent stoma

- Moderate quality evidence from 2 RCTs (N=252) showed no clinically important difference in permanent stoma rate at median 3.3 to 4 year follow-up between receiving preoperative short-course radiotherapy or receiving preoperative long-course chemoradiotherapy in people with non-metastatic rectal cancer.

Treatment-related mortality

- Moderate quality evidence from 2 RCTs (N=569) showed no clinically important difference in treatment-related mortality between receiving preoperative short-course radiotherapy with immediate surgery and receiving preoperative long-course (chemo)radiotherapy in people with non-metastatic rectal cancer.

- Low quality evidence from 1 RCT (N=256) showed no clinically important difference in treatment-related mortality between receiving preoperative short-course radiotherapy with delayed surgery and receiving preoperative long-course radiotherapy in people with non-metastatic rectal cancer.
- Moderate quality evidence from 1 RCT (N=515) showed no clinically important difference in treatment-related mortality between receiving preoperative short-course radiotherapy with consolidation chemotherapy and receiving preoperative long-course chemoradiotherapy in people with non-metastatic rectal cancer.

Comparison 3: Chemoradiotherapy with prior chemotherapy versus chemoradiotherapy without prior chemotherapy

Critical outcomes

Overall survival

- Moderate quality evidence from 1 RCT (N=108; median 5.8 years of follow-up) showed no clinically important difference in overall survival between receiving induction chemotherapy and not receiving induction chemotherapy before preoperative chemoradiotherapy in people with non-metastatic rectal cancer.

Complete (R0) resection rate

- Moderate quality evidence from 2 RCTs (N=165) showed no clinically important difference in complete (R0) resection rate between receiving induction chemotherapy and not receiving induction chemotherapy before preoperative chemoradiotherapy in people with non-metastatic rectal cancer.

Overall quality of life

No evidence was identified to inform this outcome.

Important outcomes

Local recurrence

- Low quality evidence from 1 RCT (N=108; median 5.8 years of follow-up) showed no clinically important difference in local recurrence-free survival between receiving induction chemotherapy and not receiving induction chemotherapy before preoperative chemoradiotherapy in people with non-metastatic rectal cancer.

Disease-free survival

- Low quality evidence from 1 RCT (N=108; median 5.8 years of follow-up) showed no clinically important difference in disease-free survival between receiving induction chemotherapy and not receiving induction chemotherapy before preoperative chemoradiotherapy in people with non-metastatic rectal cancer.

Sphincter preservation/permanent stoma

No evidence was identified to inform this outcome.

Treatment-related mortality

- Moderate quality evidence from 2 RCTs (N=165) showed no clinically important difference in treatment-related mortality between receiving induction

chemotherapy and not receiving induction chemotherapy before preoperative chemoradiotherapy in people with non-metastatic rectal cancer.

Comparison 4: Internal radiotherapy with or without external radiotherapy versus any external radiotherapy

Critical outcomes

Overall survival

- Moderate quality evidence from 1 RCT (N=221; median 5.4 years of follow-up) showed no clinically important difference in overall survival between receiving external chemoradiotherapy with brachytherapy boost and external chemoradiotherapy alone in people with non-metastatic rectal cancer.

Complete (R0) resection rate

- Moderate quality evidence from 1 RCT (N=194) showed no clinically important difference in complete (R0) resection rate between receiving external chemoradiotherapy with brachytherapy boost and external chemoradiotherapy alone in people with non-metastatic rectal cancer who underwent resection.

Overall quality of life

No evidence was identified to inform this outcome.

Important outcomes

Local recurrence

- Moderate quality evidence from 1 RCT (N=194; median 5.4 years of follow-up) showed that receiving external chemoradiotherapy with brachytherapy boost may have a clinically important decrease in locoregional recurrence-free survival compared to receiving external chemoradiotherapy alone in people with non-metastatic rectal cancer who underwent resection, but there is uncertainty around the estimate.
- Moderate quality evidence from 1 RCT (N=88; median 2.9 years of follow-up) showed no clinically important difference in pelvic local recurrence rate between receiving external radiotherapy with endocavity contact x-ray boost and external radiotherapy alone in people with non-metastatic rectal cancer.

Disease-free survival

- Moderate quality evidence from 1 RCT (N=221; median 5.4 years of follow-up) showed no clinically important difference in disease-free survival between receiving external chemoradiotherapy with brachytherapy boost and external chemoradiotherapy alone in people with non-metastatic rectal cancer.

Sphincter preservation/permanent stoma

No evidence was identified to inform this outcome.

Treatment-related mortality

- Moderate quality evidence from 1 RCT (N=88) showed no clinically important difference in 60-day operative mortality between receiving external radiotherapy with endocavity contact x-ray boost and external radiotherapy alone in people with non-metastatic rectal cancer.

Economic evidence statements

No economic evidence was identified which was applicable to this review question.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The aim of this review was to evaluate the effectiveness of preoperative radiotherapy or chemoradiotherapy on treating rectal cancer. Overall survival, complete (R0) resection rate and quality of life were considered critical outcomes for decision making. Overall survival was considered a critical outcome because ultimately the aim of cancer treatment is to improve survival. From the patient's perspective it is also critical to consider the treatment's effect on quality of life. Complete (R0) resection rate was considered a critical outcome because preoperative radiotherapy or chemoradiotherapy can downstage disease and facilitate complete surgical removal of the primary tumour. Local recurrence, disease-free survival, sphincter preservation/permanent stoma and treatment-related mortality were considered important outcomes.

The quality of the evidence

Evidence was available for the comparison of any preoperative therapy versus no preoperative therapy, short course radiotherapy versus long course radiotherapy with or without chemotherapy, chemoradiotherapy with prior chemotherapy versus chemotherapy without prior chemotherapy, and internal radiotherapy with or without external radiotherapy versus any external radiotherapy(without radiotherapy).

For comparison 1 and 2, evidence was available for all of the outcomes except quality of life. The quality of the evidence was assessed using GRADE and was mostly of moderate quality, varying from low to high quality. For comparisons 3 and 4, evidence was available for all outcomes except for overall quality of life and sphincter preservation/permanent stoma. The quality of the evidence, assessed using GRADE, was mostly of moderate quality varying from low to moderate quality.

The main reasons for downgrading the quality of evidence were population indirectness. Some of the trials included up to one third of participants who had early rectal cancer (T1-T2, N0).

Although the evidence was of moderate quality there was consistent benefit in terms of overall survival and local recurrence free survival which enabled the guideline committee to make a strong recommendation in favour of preoperative radiotherapy or chemotherapy.

Benefits and harms

Evidence showed that preoperative radiotherapy or chemoradiotherapy lowers the rate of local recurrence in people with T3-T4 or node positive, non-metastatic rectal cancer. The evidence also showed that preoperative therapy gives a small improvement in overall survival and disease-free survival.

The benefits of preoperative therapy on local recurrence and survival should be balanced against the potential adverse effects of preoperative radiotherapy or chemoradiotherapy. However, no difference was found in short-term or long-term quality of life, sphincter preservation or permanent stoma rate, or treatment-related mortality between people who received and did not receive preoperative therapy.

The risk of recurrence varies according to the stage and the height of the tumour (height meaning which part of the rectum (upper, middle or lower), the tumour is located in). The largest trials included in this review included a mix of participants with different clinical or pathological tumour stages and different tumour heights. This evidence review did not stratify outcomes according to tumour stage or height, and it is rare for papers to report results in such a way without losing statistical power. However, data from 2 large randomised trials, the Dutch TME trial and the MRC CR07 trial have shown that while the local recurrence rate for upper rectal tumours is lower, the beneficial effect of preoperative radiotherapy (compared to surgery alone or selective postoperative chemoradiotherapy) on local recurrence was stronger for upper rectal tumour compared to low or mid rectal tumours (van Gijn 2011; Sebag Montefiore 2009). No difference in overall survival was detected according to tumour height in the Dutch TME trial (van Gijn 2011).

In order to avoid the potential harmful effects of radiotherapy or chemoradiotherapy on people with lower risk rectal cancers, not all people with upper rectal tumours or T1-T2 N1-N2 tumours receive preoperative radiotherapy in current practice. Therefore, the committee recognised that with the new recommendation it is likely that there will be an increase in preoperative treatment for rectal cancer and there is a risk of overtreatment.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The recommendation largely reflect current practice and so no substantial resource impact is anticipated. However, the recommendation might increase preoperative radiotherapy or chemoradiotherapy for people with lower risk tumours and therefore there is a possibility of some increased costs.

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Wang F, Fan W, Peng J, et al. (2018) Total mesorectal excision with or without preoperative chemoradiotherapy for resectable mid/low rectal cancer: a long-term analysis of a prospective, single-center, randomized trial. Cancer Communications 38(1): 73

Dutch TME trial

Marijnen C, Van De Velde C, Putter H, et al. (2005) Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: Report of a multicenter randomized trial. Journal of Clinical Oncology 23(9): 1847-58

Peeters K, van de Velde C, Leer J, et al. (2005) Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients--a Dutch colorectal cancer group study. Journal of Clinical Oncology 23(25): 6199-206

Peeters K, Marijnen C, Nagtegaal I, et al. (2007) The TME trial after a median follow-up of 6 years: Increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Annals of Surgery 246(5): 693-701

van Gijn W, Marijnen C, Nagtegaal I, et al. (2011) Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncology 12(6): 575-82

Wiltink L, Chen T, Nout R, et al. (2014) Health-related quality of life 14 years after preoperative short-term radiotherapy and total mesorectal excision for rectal cancer: Report of a multicentre randomised trial. European Journal of Cancer 50(14): 2390-8

Eitta 2010

Eitta M, El-Wahidi G, Fouda M, et al. (2010) Preoperative radiotherapy in resectable rectal cancer: a prospective randomized study of two different approaches. Journal of Egyptian National Cancer Institute 22(3): 155-64

GCR-3 trial

Fernandez-Martos C, Garcia-Albeniz X, Pericay C, et al. (2015) Chemoradiation, surgery and adjuvant chemotherapy versus induction chemotherapy followed by chemoradiation and surgery: Long-term results of the Spanish GCR-3 phase II randomized trial. Annals of Oncology 26(8): 1722-8

Kacar 2009

Kacar S, Vanlsuha C, Grkan A, et al. (2009) Pre-operative radiochemotherapy for rectal cancer a prospective randomized trial comparing pre-operative vs. postoperative radiochemotherapy in rectal cancer patients. Acta chirurgica Belgica 109(6): 701-7

Lithuanian trial

Kairevice L, Latkauskas T, Tamelis A, et al. (2017) Preoperative long-course chemoradiotherapy plus adjuvant chemotherapy versus short-course radiotherapy without adjuvant chemotherapy both with delayed surgery for stage II-III resectable rectal cancer: 5-Year survival data of a randomized controlled trial. Medicina 53(3): 150-8

Latkauskas T, Pauzas H, Kairevice L, et al. (2016) Preoperative conventional chemoradiotherapy versus short-course radiotherapy with delayed surgery for rectal cancer: Results of a randomized controlled trial. BMC Cancer 16(1): 927

Lyon R96-02 trial

Gerard J, Chapet O, Nemoz, C et al. (2004) Improved sphincter preservation in low rectal cancer with high-dose preoperative radiotherapy: The Lyon R96-02 randomized trial. Journal of Clinical Oncology 22(12): 2404-9

Marechal 2012

Marechal R, Vos B, Polus M, et al. (2012) Short course chemotherapy followed by concomitant chemoradiotherapy and surgery in locally advanced rectal cancer: A randomized multicentric phase II study. Annals of Oncology 23(6): 1525-30

MRC CR07 trial

Sebag-Montefiore D, Stephens R, Steele R, et al. (2009) Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 373(9666): 811-20

Stephens R, Thompson L, Quirke P, et al. (2010) Impact of short-course preoperative radiotherapy for rectal cancer on patients' quality of life: Data from the Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 randomized clinical trial. Journal of Clinical Oncology 28(27): 4233-9

NSABP R-03 trial

Roh M, Colangelo L, O'Connell M, et al. (2009) Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. Journal of Clinical Oncology 27(31), 5124-30

Park 2011

Park J, Yoon S, Yu C, et al. (2011) Randomized phase 3 trial comparing preoperative and postoperative chemoradiotherapy with capecitabine for locally advanced rectal cancer. Cancer 117(16): 3703-12

Polish trial 1

Bujko K, Nowacki M, Nasierowska-Guttmejer A, et al. (2006) Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. British Journal of Surgery 93(10): 1215-23

Pietrzak L, Bujko K, Nowacki M, et al. (2007) Quality of life, anorectal and sexual functions after preoperative radiotherapy for rectal cancer: Report of a randomised trial. Radiotherapy and Oncology 84(3): 217-25

Polish trial 2

Bujko K, Wyrwicz L, Rutkowski A, et al. (2016) Long-course oxaliplatin-based preoperative chemoradiation versus 5 x 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: Results of a randomized phase III study. Annals of Oncology 27(5): 834-42

Stockholm III trial

Erlandsson J, Holm T, Pettersson D, et al. (2017) Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. Lancet Oncology 18(3): 336-46

Swedish Rectal Cancer Trial

Cedermark B, Dahlberg M, Glimelius B, et al. (1997) Improved survival with preoperative radiotherapy in resectable rectal cancer. New England Journal of Medicine 336(14): 980-7

Folkesson J, Birgisson H, Pahlman L, et al. (2005) Swedish rectal cancer trial: Long lasting benefits from radiotherapy on survival and local recurrence rate. Journal of Clinical Oncology 23(24): 5644-50

Taher 2006

Taher A, El-Baradie M, Nasr A, et al. (2006) Locally advanced rectal carcinoma: preoperative radiotherapy versus postoperative chemoradiation, 10-year follow-up results of a randomized clinical study. Journal of the Egyptian National Cancer Institute 18(3): 233-43

TROG 01.04 trial

McLachlan S, Fisher R, Zalcberg J, et al. (2016) The impact on health-related quality of life in the first 12 months: A randomised comparison of preoperative short-course radiation versus long-course chemoradiation for T3 rectal cancer (Trans-Tasman Radiation Oncology Group Trial 01.04). European Journal of Cancer 55: 15-26

Ngan S, Burmeister B, Fisher R, et al. (2012) Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. Journal of Clinical Oncology 30(31): 3827-33

Zhang 2008

Zhang X, Ma H, Ren H, et al. (2008) Prospective randomized trial of surgery combined with preoperative and postoperative radiotherapy for rectal carcinoma. Academic Journal of Xi'an Jiaotong University 20: 134-7

Appendices

Appendix A – Review protocol

Appendix B – Literature search strategies

Review protocol for review question: What is the effectiveness of preoperative radiotherapy or chemoradiotherapy for rectal cancer?

Table 3: Review protocol for the effectiveness of preoperative radiotherapy or chemoradiotherapy for rectal cancer

Field (based on PRISMA-P)	Content
Review question	What is the effectiveness of preoperative radiotherapy and chemoradiotherapy for rectal cancer?
Type of review question	Intervention
Objective of the review	To determine the effectiveness of preoperative radiotherapy or chemoradiotherapy for treating rectal cancer.
Eligibility criteria – population/disease/condition/issue/domain	Adults with non-metastatic rectal cancer defined according to TNM classification as: • T any, N1 or N2 • T3 • T4 • M0 Staging determined by ultrasound, MRI, computed tomography scan **Exclusions:** • Early rectal cancer T1, T2 + N0 M0 Rectal cancer defined as any tumour within 15 cm from anal verge excluding anal canal.
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• Preoperative chemoradiotherapy with or without prior chemotherapy • Preoperative radiotherapy o External - Short-course - Long-course o External and internal o Internal
Eligibility criteria – comparator(s)/control or reference (gold) standard	Comparisons: 1. Any preoperative therapy versus no preoperative therapy 2. Short-course radiotherapy versus long-course radiotherapy with or without chemotherapy 3. Chemoradiotherapy with prior chemotherapy versus chemoradiotherapy without prior chemotherapy

Field (based on PRISMA-P)	Content
	4. Internal radiotherapy with or without external radiotherapy versus any external radiotherapy (without internal radiotherapy)
Outcomes and prioritisation	**Critical outcomes:** • Overall survival (MID: statistical significance) • Complete (R0) resection rate (MID: statistical significance) • Overall quality of life measured using validated scales (MID: published MIDs from literature) **Important outcomes:** • Local recurrence (MID: statistical significance) • Disease-free survival (MID: statistical significance) • Sphincter preservation/permanent stoma (MID: statistical significance) • Treatment-related mortality (MID: statistical significance) Quality of life MIDs from the literature: • EORTC QLQ-C30: 5 points* • EORTC QLQ-CR29: 5 points* • EORTC QLQ-CR38: 5 points* • EQ-5D: 0.09 using FACT-G quintiles • FACT-C: 5 points* • FACT-G: 5 points* • 12 Item Short Form Survey (SF-12): > 3.77 for the mental component summary (MCS) and > 3.29 for the physical component summary (PCS) • 36 Item Short Form Survey (SF-36): > 7.1 for the physical functioning scale, > 4.9 for the bodily pain scale, and > 7.2 for the physical component summary (PCS) *Confirmed with guideline committee.
Eligibility criteria – study design	• Systematic reviews of RCTs • RCTs • Observational studies will not be considered.
Other inclusion exclusion criteria	**Inclusion:** • English-language • All settings will be considered that consider medications and treatments available in the UK • Studies published post 1997 Studies published post 1997 will be considered for this review question because the guideline committee considered that treatment techniques have evolved and evidence prior to 1997 would not be relevant any longer.
Proposed sensitivity/sub-group analysis, or meta-regression	In case of high heterogeneity, the following factors will be considered: • Type of chemotherapy drug • Radiotherapy technique

Field (based on PRISMA-P)	Content
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Resolution of any disputes will be with the senior systematic reviewer and the Topic Advisor. Quality control will be performed by the senior systematic reviewer. Dual sifting will be undertaken for this question for a random 10% sample of the titles and abstracts identified by the search.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations.
Information sources – databases and dates	Potential sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion Limit to RCTs and systematic reviews in first instance, but download all results Dates: from 1997
Identify if an update	Not an update
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10060 Developer: NGA
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Cochrane risk of bias tool for RCTs The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE.

Field (based on PRISMA-P)	Content
	The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	Synthesis of data: Pairwise meta-analysis of randomised trials will be conducted where appropriate. When meta-analysing continuous data, final and change scores will be pooled if baselines are comparable. If any studies report both, the method used in the majority of studies will be analysed. Minimally important differences: The guideline committee identified statistically significant differences as appropriate indicators for clinical significance for all outcomes except for quality of life for which published MIDs from literature will be used (see outcomes section for more information).
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan5 software to examine funnel plots.
Confidence in cumulative evidence	For details see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Peter Hoskin in line with section 3 of Developing NICE guidelines: the manual. Staff from The National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplement 1: methods.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds The National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	Not registered

1 *CCTR: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic*
2 *Reviews; DARE: Database of Abstracts of Reviews of Effects; EQ-5D: EuroQol five dimensions*

questionnaire; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Items; EORTC QLQ-CR29: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire colorectal cancer module (29 items); EORTC QLQ-CR38: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire colorectal cancer module (38 items); FACT-C: Functional Assessment of Cancer Therapy questionnaire (colorectal cancer); FACT-G: Functional Assessment of Cancer Therapy questionnaire (general); GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimal important difference; MRI: magnetic resonance imaging; NGA: National Guideline Alliance; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; R0: complete resection; RCT: randomised controlled trial; ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions; ROBIS: a tool for assessing risk of bias in systematic reviews; SD: standard deviation; TNM: cancer classification system, standing for tumour, nodal or metastasis stage

Literature search strategies for review question: What is the effectiveness of preoperative radiotherapy and chemoradiotherapy for rectal cancer?

A combined search was conducted for the following three review questions:

- What is the most effective treatment for early rectal cancer?
- What is the effectiveness of preoperative radiotherapy or chemoradiotherapy for rectal cancer?
- What is the optimal surgical technique for rectal cancer?

Databases: Embase/Medline

Last searched on: 12/02/2019

#	Search
1	exp Rectal Neoplasms/ use prmz
2	*rectum cancer/ or *rectum tumor/
3	2 use oemezd
4	exp Adenocarcinoma/
5	(T1 or T2 or N0 or M0).ti,ab.
6	1 or 3
7	4 or 5
8	6 and 7
9	((rectal or rectum) adj3 (cancer* or neoplas* or malignan* or tumo?r* or carcinom* or adeno*)).ti,ab.
10	early rect* cancer.ti,ab.
11	6 or 8 or 9 or 10
12	exp radiotherapy/ or exp radiation oncology/ or exp external beam radiotherapy/ or exp Brachytherapy/ or exp preoperative care/ or exp neoadjuvant therapy/ or exp multimodality cancer therapy/ or exp chemotherapy/ or exp antineoplastic agent/ or exp drug therapy/ or exp chemoradiotherapy/ or exp fluorouracil/ or exp folinic acid/ or exp capecitabine/ or exp oxaliplatin/ or exp bevacizumab/ or exp methotrexate/ or exp radiation dose fractionation/ or exp tumor recurrence/
13	12 use oemezd
14	exp Radiotherapy/ or exp Radiation Oncology/ or exp Radiotherapy, Computer-Assisted/ or exp Brachytherapy/ or exp Preoperative Care/ or exp Neoadjuvant Therapy/ or exp Combined Modality Therapy/ or exp Chemoradiotherapy/ or exp Antineoplastic Combined Chemotherapy Protocols/ or exp Drug Therapy/ or exp Antineoplastic Agents/ or exp Fluorouracil/ or exp Leucovorin/ or exp Capecitabine/ or exp Bevacizumab/ or exp Methotrexate/ or exp Dose Fractionation/
15	14 use prmz
16	((radiotherap* or chemoradio* or radiation or brachytherapy* or chemotherapy*) adj (pre?op* or preop* or periop* or neoadjuvant)).ti,ab.
17	(5-fluorouracil or 5-FU or leucovorin or folinic acid or capecitabine or oxaliplatin or bevacizumab or methotrexate or dose* or fraction* or recurren*).ti,ab.
18	13 or 15 or 16 or 17
19	exp Laparoscopy/ or exp Transanal Endoscopic Microsurgery/ or exp Minimally Invasive Surgical Procedures/ or exp Endoscopy/ or exp Endoscopic Mucosal Resection/ or exp Surgical Procedures, Operative/ or exp Robotic Surgical Procedures/ or exp Surgery, Computer-Assisted/ or exp Dissection/
20	19 use prmz
21	exp laparoscopy/ or exp endoscopic surgery/ or exp transanal endoscopic microsurgery/ or exp endoscopy/ or exp minimally invasive surgery/ or exp endoscopic mucosal resection/ or exp surgery/ or exp robotic surgical procedure/ or exp computer assisted surgery/ or exp dissection/ or exp total mesorectal excision/ or exp excision/ or exp rectum resection/ or exp endoscopic polypectomy/ or exp polypectomy/ or exp endoscopic submucosal dissection/
22	21 use oemezd
23	(laparoscop* or endoscop* or transanal excision* or TAE or transanal endoscopic microsurger* or TEM or TEMS or transanal resection or TART or transanal minimally invasive surger* or TAMIS or total mesorectal excision* or TaTME or transanal total mesorectal excision* or TME or anterior resection* or abdominoperineal resection* or endoscopic resection* or polypectomy or endoscopic submucosal dissection* or ESD or endoscopic mucosal resection* or EMR or surger* or surgic* or operat*).ti,ab.
24	20 or 22 or 23
25	11 and 18
26	11 and 18 and 24
27	25 or 26
28	limit 27 to english language
29	limit 28 to yr="1997 -Current"
30	(conference abstract or letter).pt. or letter/ or editorial.pt. or note.pt. or case report/ or case study/ use oemezd
31	Letter/ or editorial/ or news/ or historical article/ or anecdotes as topic/ or comment/ or case report/ use prmz
32	(letter or comment* or abstracts).ti.
33	or/30-32
34	randomized controlled trial/ use prmz

#	Search
35	randomized controlled trial/ use oemezd
36	random*.ti,ab.
37	or/34-36
38	33 not 37
39	(animals/ not humans/) or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ use prmz
40	(animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ use oemezd
41	(rat or rats or mouse or mice).ti.
42	38 or 39 or 40 or 41
43	29 not 42
44	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
45	44 use prmz
46	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
47	46 use oemezd
48	or/45,47
49	43 and 48
50	epidemiologic studies/ or observational study/ or case control studies/ or retrospective studies/ or cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or cross-sectional studies/
51	50 use prmz
52	exp observational study/ or exp case control study/ or exp retrospective study/ or exp cohort analysis/ or exp longitudinal study/ or exp follow up/ or exp prospective study/ or exp cross-sectional study/
53	52 use oemezd
54	((retrospective* or cohort* or longitudinal or follow?up or prospective or cross section*) adj3 (stud* or research or analys*)).ti.
55	51 or 53 or 54
56	43 and 55
57	49 or 56
58	57 not 56
59	56 or 58

1 **Database: Cochrane Library**

2 Last searched on: 12/02/2019

#	Search
1	MeSH descriptor: [Rectal Neoplasms] explode all trees
2	MeSH descriptor: [Adenocarcinoma] explode all trees
3	T1 or T2 or N0 or M0
4	#2 or #3
5	#1 and #4
6	(rectal or rectum) near (cancer* or neoplas* or malignan* or tumo?r* or carcinom* or adeno*)
7	early rect* cancer
8	#1 or #5 or #6 or #7
9	MeSH descriptor: [Radiotherapy] explode all trees
10	MeSH descriptor: [Radiation Oncology] explode all trees
11	MeSH descriptor: [Radiotherapy, Computer-Assisted] explode all trees
12	MeSH descriptor: [Brachytherapy] explode all trees
13	MeSH descriptor: [Preoperative Care] explode all trees
14	MeSH descriptor: [Neoadjuvant Therapy] explode all trees
15	MeSH descriptor: [Combined Modality Therapy] explode all trees
16	MeSH descriptor: [Chemoradiotherapy] explode all trees
17	MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] explode all trees
18	MeSH descriptor: [Drug Therapy] explode all trees
19	MeSH descriptor: [Antineoplastic Agents] explode all trees
20	MeSH descriptor: [Fluorouracil] explode all trees
21	MeSH descriptor: [Capecitabine] explode all trees
22	MeSH descriptor: [Bevacizumab] explode all trees
23	MeSH descriptor: [Methotrexate] explode all trees
24	MeSH descriptor: [Dose Fractionation] explode all trees
25	(radiotherap* or chemoradio* or radiation or brachytherapy* or chemotherapy*) near (pre?op* or preop* or periop* or neoadjuvant)
26	5-fluorouracil or 5-FU or leucovorin or folinic acid or capecitabine or oxaliplatin or bevacizumab or methotrexate or dose* or fraction* or recurren*
27	#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
28	MeSH descriptor: [Laparoscopy] explode all trees
29	MeSH descriptor: [Transanal Endoscopic Microsurgery] explode all trees

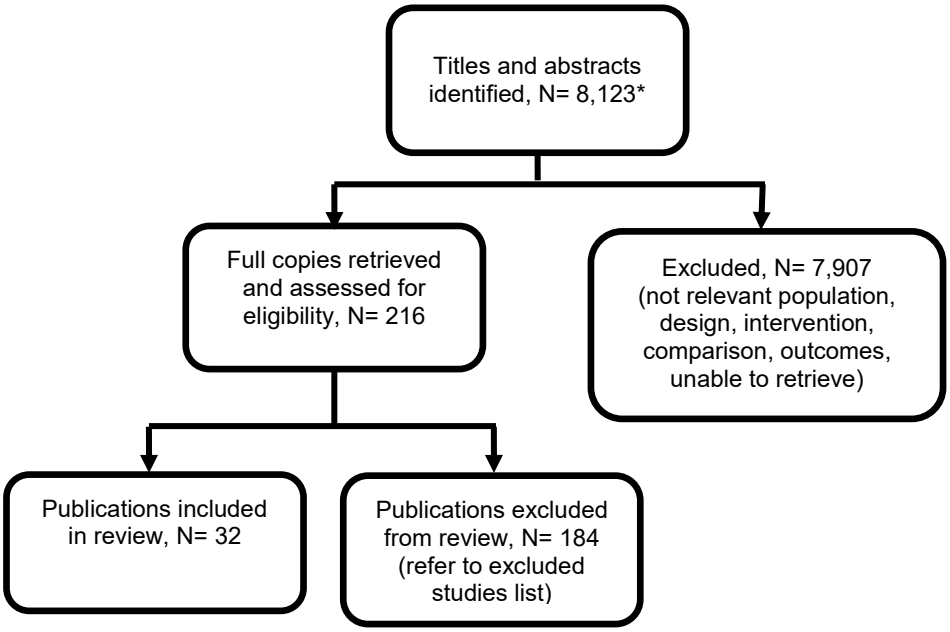
#	Search
30	MeSH descriptor: [Minimally Invasive Surgical Procedures] explode all trees
31	MeSH descriptor: [Endoscopy] explode all trees
32	MeSH descriptor: [Endoscopic Mucosal Resection] explode all trees
33	MeSH descriptor: [Surgical Procedures, Operative] explode all trees
34	MeSH descriptor: [Robotic Surgical Procedures] explode all trees
35	MeSH descriptor: [Surgery, Computer-Assisted] explode all trees
36	MeSH descriptor: [Dissection] explode all trees
37	laparoscop* or endoscop* or transanal excision* or TAE or transanal endoscopic microsurger* or TEM or TEMS or transanal resection or TART or transanal minimally invasive surger* or TAMIS or total mesorectal excision* or TME or anterior resection* or abdominoperineal resection* or endoscopic resection* or polypectomy or endoscopic submucosal dissection* or ESD or endoscopic mucosal resection* or EMR or surger* or surgic* or operat*
38	#28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37
39	#8 and #27
40	#8 and #27 and #38
41	#39 or #40 Publication Year from 1997 to 2017

1
2

Appendix C – Clinical evidence study selection

Clinical study selection for review question: What is the effectiveness of preoperative radiotherapy or chemoradiotherapy for rectal cancer

Figure 1: Study selection flow chart



**The literature search was done for 3 review questions at once including the current review and reviews 'What is the most effective treatment for early rectal cancer?' and 'What is the optimal surgical technique for rectal cancer after preoperative radiotherapy or chemoradiotherapy?'. Numbers screened at title and abstract (include and exclude) and full text were for the 3 specified review questions. Number publications included and excluded apply only to the current review. In addition, possibly relevant studies were added from systematic reviews.*

1 Appendix D – Clinical evidence tables

2 Clinical evidence tables for review question: What is the effectiveness of preoperative radiotherapy and chemoradiotherapy for 3 rectal cancer?

4 **Table 4: Clinical evidence tables**

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Appelt, A. L., Vogelius, I. R., Ploen, J., Rafaelsen, S. R., Lindebjerg, J., Havelund, B. M., Bentzen, S. M., Jakobsen, A., Long-term **Results** of a randomized trial in locally advanced rectal cancer: No benefit from adding a brachytherapy boost, International Journal of Radiation Oncology Biology Physics, 90, 110-118, 2014 **Ref ID** 745450 **Country/ies where the study was carried out** Denmark	**Sample size** N=224 randomised of which n=3 excluded (ineligible or withdrew consent); n=111 allocated to preoperative external CRT; n=110 allocated to preoperative external CRT with brachytherapy (internal RT) boost **Characteristics** Age in years, median (range): Preoperative CRT 62 (35-77) Preoperative CRT with brachytherapy boost 64 (38-78) Male sex, n (%): Preoperative CRT 68 (61)	**Interventions** Preoperative external CRT versus preoperative external CRT with brachytherapy boost External CRT: 50.4 Gy in 28 fractions (5 fractions per week). Computer tomography-based conformal treatment plans using 6 MV and/or 18 MV photon beams were used. The planning target volume consisted of the tumour and mesorectum (lower border 3 cm below the tumour), presacral lymph nodes, superior rectal, median and internal iliac lymph nodes, and obturator lymph nodes with a 1-cm isotropic margin to account for internal motion and setup uncertainties.	**Details** Randomisation and allocation concealment Randomisation based on a predefined, computer-generated list concealed to the treating physicians. Blinding Patients and treating physicians were not blinded but pathologist scoring for tumour response was blinded. Follow-up/outcomes Follow-up visits were done every 6 months for the first 3 years and once a year on the fourth and fifth year. Further follow-up was done in discretion of the treating physician. All electronic patient records were reviewed at	**Results** Outcome: Overall survival (median 5.4 years follow-up) Preoperative CRT n=111, 36 events Preoperative CRT with brachytherapy boost n=110, 43 events HR 1.24 95% CI 0.80 to 1.93, p=0.34 Outcome: Complete (R0) resection rate Preoperative CRT 90/99 Preoperative CRT with brachytherapy boost 89/95 Outcome: Locoregional control (median 5.4 years follow-up) Preoperative CRT n=99, 5 events	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: low risk Allocation concealment: unclear risk (Details not reported.) Performance bias Blinding of participants and personnel: high risk (No blinding.) Detection bias Blinding of outcome assessment: low/high risk (Pathologist examining the tumour response blinded. Physician examining

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type RCT **Aim of the study** To compare the outcomes of long-course neoadjuvant chemoradiotherapy (CRT) and adding a brachytherapy boost (internal radiotherapy, RT) to the regimen for locally advanced rectal cancer. **Study dates** March 2005 to November 2008 **Source of funding** The authors are supported by the following: CIRRO - The Lundbeck Foundation Center for Interventional Research in Radiation Oncology; the Danish Council for Strategic Research; the Region of Southern Denmark; the Global Excellence in Health program of the Capital	Preoperative CRT with brachytherapy boost 72 (65) Disease category, n (%): T3 Preoperative CRT 90 (81) Preoperative CRT with brachytherapy boost 93 (85) T4 Preoperative CRT 21 (19) Preoperative CRT with brachytherapy boost 17 (15) N0 Preoperative CRT 10 (9) Preoperative CRT with brachytherapy boost 13 (12) N1-2 Preoperative CRT 101 (91) Preoperative CRT with brachytherapy boost 95 (86) Received adjuvant chemotherapy, n (%)	Chemotherapy (CT) consisted of daily oral tegafur-uracil (3 x 100 mg/m²) and oral L-leuvocorin (3 x 75 mg) given on days when external RT was administered. Brachytherapy boost: 10 Gy high-dose-rate brachytherapy boost delivered in 2 fractions on weeks 4 and 6 of the treatment course, using a rigid, single-channel endorectal applicator. Dose was prescribed 1.0 cm from the applicator surface and was planned to provide uniform dose distribution along the central axis. Participants in the brachytherapy boost group who could not comply with brachytherapy were prescribed an external boost of 6 Gy or 12 Gy delivered with 2 Gy per fraction, according to protocol. Surgery: Total mesorectal excision (TME) was	the time of final analysis to verify all reported events and to identify disease relapse and death not otherwise reported. Overall survival was calculated from the date of randomisation to death from any cause. Progression-free survival was calculated from the date of randomisation to first clinical detection (preferably by biopsy) of distant metastasis, locoregional recurrence, determination of inoperability, or death from any cause. Locoregional failure was defined as clinically proven (preferably by biopsy) local failure or disease recurrence in pelvic lymph nodes included in the original external beam treatment volume, irrespective of distant failures. It was calculated from the date of surgery. **Statistical analysis** Intention-to-treat analysis was done on overall	Preoperative CRT with brachytherapy boost n=95, 12 events HR 2.60 95% CI 1.00 to 6.73, p=0.06 Outcome: Progression-free survival (median 5.4 years follow-up) Preoperative CRT n=111, 72 events (relapse + death) Preoperative CRT with brachytherapy boost n=110, 82 events (relapse + death) HR 1.22 95% CI 0.82 to 1.82, p=0.32	the participant not blinded.) Attrition bias Incomplete outcome data: low risk (Intention-to-treat analysis done for survival outcomes. Locoregional failure and complete (R0) resection rate analysis done per protocol. Very few losses to follow-up.) Reporting bias Selective reporting: low risk Other bias Other sources of bias: - **Other information** None

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Region of Denmark; National Cancer Institute.	Preoperative CRT 12 (12) Preoperative CRT with brachytherapy boost 15 (16) **Inclusion criteria** Histopathologically confirmed adenocarcinoma of the rectum; less than 10 cm from the anal verge; circumferential resection margin as estimated on MRI of less than 5 cm; T3-4N0-2M0 tumours based on MRI of the pelvis, rectal ultrasonography, chest and abdominal computer tomography scans and rectoscopy. **Exclusion criteria** None reported.	performed 8 weeks after the end of CRT. Adjuvant CT after surgery: Delivered at the discretion of the treating physician.	survival and progression-free survival. Analysis on locoregional failure was done on participants who underwent curative resection. Time-to-event endpoints were analysed using the Kaplan-Meier method, and log-rank test were used to compare the groups. Hazard ratios were calculated using Mantel-Haenzel type estimates.		
Full citation Atif, E., Sakr, H., Teama, S., Zayed, D., Effect of radical surgery combined with pre- or postoperative radiotherapy in treatment of resectable	**Sample size** N=100 randomised n=50 preoperative RT; n=50 postoperative RT **Characteristics**	**Interventions** Preoperative RT versus postoperative RT RT: given by high energy photon external beam irradiation using Co60 or linear accelerator (6 MV photons). The target	**Details** Randomisation and allocation concealment Randomised but method not reported. Allocation concealment not reported. Blinding	**Results** Outcome: Overall survival (median 18 months of follow-up) Preop RT n=50, 14 events Postop RT n=50, 26 events	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: unclear risk (Not reported.)

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
rectal cancer, Chinese-German Journal of Clinical Oncology, 11, 384-390, 2012 **Ref ID** 745502 **Country/ies where the study was carried out** Egypt **Study type** RCT **Aim of the study** To compare the effect between preoperative radiotherapy (RT) and postoperative RT in itreatment of resectable rectal carcinoma. **Study dates** Enrolment between January 2007 and September 2009 **Source of funding** None reported.	Age in years, median (range): Preop RT 48 (20-75) Postop RT 45 (22-80) Male sex, n (%): Preop RT 34 (68) Postop RT 27 (54) Site of tumour, n (%): Upper Preop RT 0 (0) Postop RT 3 (6) Middle Preop RT 9 (18) Postop RT 9 (18) Lower Preop RT 41 (82) Postop RT 38 (76) Pathologic stage, n (%): Stage 0: T0N0 Preop RT 3 (6) Postop RT 0 (0) Stage I: T2N0 Preop RT 8 (16) Postop RT 0 (0) Stage II: T3N1 Preop RT 19 (38) Postop RT 21 (42)	volume was defined as the sacral promontory superiorly, 3.5 cm below the inferior tumour extent, and in 1 cm lateral to the most lateral aspect of the bony true pelvis. The posterior border of the lateral field had to include the whole sacral canal target volume, and the anterior border of the lateral field must be at the anterior border of the symphysis pubis. The perineal scar was to be included postoperatively in patients with tumours <5 cm from the anal verge. Surgery: Abdominoperineal resection with a permanent colostomy or low anterior resection with colorectal or usually colo-anal anastomosis.	No blinding Follow-up/outcomes In the preoperative RT group, abdomino-pelvic computer tomography or MRI was done 3-4 weeks after the end of RT and compared to the pre-RT computer tomography or MRI. Participants were followed up to record early postoperative mortality and morbidity which occurred during hospitalisation or within 30 days of the surgery. Participants were followed up for detection of local recurrence or late effect every 1-2 months by clinical examination, every 3 months by tumour markers (CEA & CA19-9), abdomino-pelvic computer tomography or MRI and endoscopy, biopsies were taken and pathologically examined for suspicious lesion. Disease-free survival was calculated from the date of surgical resection until the date of recurrence and	p=0.227 Outcome: Local recurrence (median 18 months of follow-up) Preop RT 5/50 Postop RT 16/50 Outcome: Disease-free survival (median 15 or 17 months of follow-up, depending on the group) Preop RT n=50, 22 events Postop RT n=50, 31 events p=0.592	Allocation concealment: unclear risk (Not reported.) Performance bias Blinding of participants and personnel: high risk (No blinding.) Detection bias Blinding of outcome assessment: unclear risk (Not reported but likely not blinded.) Attrition bias Incomplete outcome data: unclear risk (No mention of intention-to-treat approach to analysis. None from the preoperative RT group and 5/50 of the postoperative RT group were lost to follow-up.) Reporting bias Selective reporting: low risk (Primary outcome points were reported.)

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Stage III: T3N1 Preop RT 14 (28) Postop RT 12 (24) Stage III T3N2 Preop RT 6 (12) Postop RT 17 (34) Type of surgery, n (%): Abdominoperineal resection Preop RT 31 (62) Postop RT 45 (90) Low anterior resection Preop RT 15 (30) Postop RT 5 (10) Palliative colostomy Preop RT 2 (4) Postop RT 0 (0) Exploration Preop RT 2 (4) Postop RT 0 (0) **Inclusion criteria** Histologically confirmed adenocarcinoma of the rectum (defined as the dital tumour <15 cm from the anal verge measured by recto-sigmoidoscopy) with no evidence of		overall survival was calculated from the date of diagnosis until the date of death. **Statistical analysis** Survival was compared using Kaplan-Meier method and log-rank test was used to compare the groups.		Other bias Other sources of bias: - **Other information** None

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	metastases (identified by abdominal computer tomograpgy scan and chest radiograph); the primary tumour had to be deemed resectable (defined as not fixed to the pelvis) as determined by digital rectal examination and preoprative abdnomino-pelvic computer tomography or MRI; Eastern Cooperative Oncology Group (ECOG) performance status score 0-1; no history of previous chemotherapy or radiotherapy to the pelvis. **Exclusion criteria** None reported.				
Full citation Bujko, K., Nowacki, M. P., Nasierowska-Guttmejer, A., Michalski, W., Bebenek, M., Kryj, M., Long-term **Results** of a randomized trial comparing preoperative	**Sample size** N=316 randomised of which n=4 excluded because did not meet **Inclusion criteria**, leaving n=312; n=155 allocated to short-course RT;	**Interventions** Preoperative short-course RT versus preoperative long-course CRT Short-course RT: 5 Gy in 5 fractions.	**Details** Randomisation and allocation concealment Randomisation was performed by telephone to the central trial office and was based on the minimisation method. Stratification was done	**Results** Outcome: Overall survival (median 4 years follow-up) Short-course RT n=155, 54 events Long-course CRT n=157, 53 events	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: unclear risk (details of randomisation

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer, British Journal of Surgery, 93, 1215-1223, 2006 **Ref ID** 745961 **Country/ies where the study was carried out** Poland **Study type** RCT **Aim of the study** To compare survival, local control and late toxicity between preoperative short-course RT and neoadjuvant CRT. **Study dates** Enrolment from April 1999 to February 2002. **Source of funding**	n=157 allocated to CRT **Characteristics** Not reported in this publication. **Inclusion criteria** TNM clinical stage T3 or T4 resectable primary tumour of the rectum; no evidence of sphincter involvement on digital rectal examination; lower tumour margin accessible to digital rectal examination; written informed consent. (All participants with freely movable tumours not involving the entire circumference of the bowel wall had endorectal ultrasound, pelvic computer tomography or MRI to exclude T1-2 lesions.) **Exclusion criteria** T1/T2 tumour	Long-course CRT: 50.4 Gy in 28 fractions of 1.8 Gy per fractions. CT consisted of 2 cycles administered during week 1 and 5 of RT. The cycle consisted of leucovorin 20 mg/m²/day and 10-20 min later fluorouracil (5-FU) 325 mg/m²/day, both administered as rapid infusions on 5 consecutive days. Postoperative CT: Optional but the protocol called for 4 months of bolus 5-FU and leucovorin in the long-course CRT group and 6 months of the same CT in the short-course RT group. Surgery: TME for low lying tumours and subtotal mesorectal excision for midrectal tumours. Sphincter preservation was based on the tumour status at the time of surgery. For the short-course RT group the surgery was performed within 7 days from completion of RT and for the long-course CRT group	according to institution, tumour character (movable or tethered) and most likely type of surgery (anterior resection, abdominoperineal resection or ambiguous decision). Blinding No blinding. Follow-up/outcomes Participants were followed-up at 6-month intervals for 3 years and once a year thereafter. Evaluations included physical examination, abdominal ultrasound or computer tomography and chest radiography. Other examinations were performed if there were symptoms. Local recurrence was defined as any reappearance of pelvic tumour mass located within the irradiated volume or in the perineum and it was detected by physical examination and/or pelvic computed tomography or MRI.	HR 1.01 95% CI 0.69 to 1.48, p=0.96 Outcome: Health-related quality of life – EORTC QLQ-C30 global health status mean score (median 12 months after surgery)* Short-course RT 57 (n=111) Long-course CRT 61 (n=110) p=0.22 Outcome: Local recurrence (median 4 years follow-up) (per-protocol) Short-course RT n=146, number of events not reported Long-course CRT n=149, number of events not reported HR 0.65 95% CI 0.32 to 1.28, p=0.21 Outcome: Disease-free survival (median 4 years follow-up)	methods not provided.) Allocation concealment: low risk (Randomisation done centrally and allocation done by telephone.) Performance bias Blinding of participants and personnel: high risk (No blinding.) Detection bias Blinding of outcome assessment: high risk (No blinding.) Attrition bias Incomplete outcome data: low risk (Intention-to-treat analysis done on all relevant outcomes but local recurrence. There were no losses to follow-up regarding vital status and only 3 participants were lost to follow-up regarding recurrence.)

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
The Polish State Committee for Scientific Research.		4-6 weeks after completion of CRT.	Histopathological verification was recommended. Time-to-event outcomes were calculated from the date of randomisation. Health-related quality of life was assessed at least 7 months after surgery using Quality of Life Questionnaire Core 30 Items (QLQ-C30) of the European Organization for Research and Treatment of Cancer (EORTC). The global health status score scale goes from 0-100, higher indicating better quality of life. The questionnaires were filled in by the participants at follow-up visit or returned by post. (Data extracted from Pitrzak 2007.) **Statistical analysis** Intention-to-treat analysis was done on all outcomes relevant for the review. Kaplan-Meier method was done to analyse time-to-event evidence and groups were compared suing log-rank test. HRs were calculated using the	Short-course RT n=155, number of events not reported Long-course CRT n=157, number of events not reported HR 0.96 95% CI 0.69 to 1.35, p=0.82 Outcome: Permanent stoma rate (median 4 years follow-up) Short-course RT 87/155 Long-course CRT 81/157 Outcome: Mortality due to treatment complications Short-course RT 5/155 Long-course CRT 5/157 *Data extracted from Pietrzak 2007. EORTC QLQ-C30 global health status scale 0-100, higher score indicating better quality of life.	Reporting bias Selective reporting: low risk (All main outcomes reported.) Other bias Other sources of bias: - **Other information** None

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Cox proportional hazards model.		
Full citation Bujko, K., Wyrwicz, L., Rutkowski, A., Malinowska, M., Pietrzak, L., Krynski, J., Michalski, W., Oledzki, J., Kusnierz, J., Zajac, L., Bednarczyk, M., Szczepkowski, M., Tarnowski, W., Kosakowska, E., Zwolinski, J., Winiarek, M., Wisniowska, K., Partycki, M., Beczkowska, K., Polkowski, W., Stylinski, R., Wierzbicki, R., Bury, P., Jankiewicz, M., Paprota, K., Lewicka, M., Cisel, B., Skorzewska, M., Mielko, J., Bebenek, M., Maciejczyk, A., Kapturkiewicz, B., Dybko, A., Hajac, L., Wojnar, A., Lesniak, T., Zygulska, J., Jantner, D., Chudyba, E., Zegarski, W., Las-Jankowska, M., Jankowski, M., Kolodziejski, L.,	**Sample size** N=541 randomised; n=271 allocated to short-course RT + consolidation CT of which 10 excluded due to entry criteria violation or withdrawal of consent, therefore, n=261 eligible for allocated treatment and included in analysis; n=270 allocated to long-course CRT of which 16 excluded due to entry criteria violation, withdrawal of consent, unknown reason, death before treatment, therefore n=254 eligible for allocated treatment and included in analysis **Characteristics** Age in years, median (IQR): Short-course RT+CT 60 (54-66)	**Interventions** Preoperative short-course RT with consolidation CT versus preoperative long-course CRT Preoperative short-course RT with consolidation CT: 5 x 5 Gy irradiation over 5 days and 3 cycles of FOLFOX4, the first cycle given a week after completion of RT. Preoperative long-course CRT: 50.4 Gy in 28 fractions of 1.8 Gy concomitantly with 5-day cycles of IV boluses of 5-FU 325 mg/m²/day and leucovorin 20 mg/m²/day during the first and fifth week of irradiation and five 1-day infusions of oxaliplatin 50 mg/m² given once a week at 1, 8, 15, 22 and 29 days of irradiation. From 2012 onwards, the use of oxaliplatin in both groups was left to the	**Details** Randomisation and allocation concealment Randomisation was based on the minimisation process done by telephone to a datacentre independent from investigators. Stratification done according to the institution and the type of tumour. Allocation concealment not reported. Blinding Participants not blinded. Not reported if outcome assessors were blinded. Data analyst was blinded. Follow-up/outcomes Participants were followed-up at 3-month intervals for 2 years and at 6-month intervals thereafter. Evaluations included physical examination and measuring blood CEA levels. Abdominal, pelvic and chest computer tomography (or chest	**Results** Outcome: Overall survival (median 35 months follow-up) Short-course RT+CT n=261, 64 events Long-course CRT n=254, 84 events HR 0.73 95% CI 0.53 to 1.01, p=0.046 Outcome: Complete (R0) resection rate Short-course RT+CT 202/261 Long-course CRT 178/254 Outcome: Disease-free survival (median 35 months follow-up) Short-course RT+CT n=261, number of events 216 Long-course CRT n=254, number of events 218 HR 0.96 95% CI 0.75 to 1.24, p=0.85	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: unclear risk (details not reported. Only reported that randomisation done by telephone in a data centre.) Allocation concealment: low risk (Randomisation done centrally and allocated by telephone.) Performance bias Blinding of participants and personnel: high risk (No blinding.) Detection bias Blinding of outcome assessment: unclear risk (Not reported if outcome assessor was blinded but presumably not.

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Radkowski, A., Zelazowska-Omiotek, U., Czeremszynska, B., Kepka, L., Kolb-Sielecki, J., Toczko, Z., Fedorowicz, Z., Dziki, A., Danek, A., Nawrocki, G., Sopylo, R., Markiewicz, W., Kedzierawski, P., Wydmanski, J., Albinski, J., Banas, R., Chmielowska, E., Bal, W., Baszczyk-Mnich, J., Bialas, M., Borowiec, T., Bujko, M., Cencelewicz, A., Chomik, K., Chwalinski, M., Ciepela, I., Dupla, D., Florek, A., Gornicki, A., Jeziorski, K., Jozwickil, W., Kobiela, J., Koda, M., Kolodziej, P., Kruszewski, P., Kryj, M., Kuciel-Lisiecka, G., Kwiatkowski, R., Lachowski, A., Liszka-Dalecki, P., Majewski, A., Majewski, W., Majsak, T., Maka, D., Malka, M., Mazurkiewicz, A., Morawiec, J., Nogal, E., Olejniczak, M., Olkowski, D.,	Long-course CRT 60 (56-65) Male sex, n (%): Short-course RT+CT 183 (70) Long-course CRT 169 (67) Type of tumour, n (%): Primary fixed cT3 Short-course RT+CT 88 (34) Long-course CRT 83 (33) Primary cT4 Short-course RT+CT 165 (63) Long-course CRT 163 (64) Recurrent Short-course RT+CT 8 (3) Long-course CRT 8 (3) Tumour distance from the anal verge, n (%): 0-5 cm Short-course RT+CT 148 (57) Long-course CRT 138 (55)	discretion of the local investigator. Surgery: The interval between start of RT and surgery was median 12.4 weeks in both groups. No other **Details** about surgery given.	radiography) was recommended at 1 and 2 years after treatment. The primary endpoint was complete (R0) resection rate. Secondary endpoints were overall survival, disease-free survival, acute toxicity of preoperative treatment, incidence of postoperative complications, pathological complete response rate, locoregional and distant failure rate and rate of late complications. Time-to-event endpoints were calculated from the date of randomisation. Disease-free survival was calculated to local or distant failure or death, whichever came first. **Statistical analysis** All analysis was done according to intention-to-treat. Survival data was analysed using the Kaplan-Meier method. The groups were compared by using the log-rank test stratified by oxaliplatin use.	Outcome: Mortality due to treatment complications (due to preoperative treatment, 30-day surgery, or late complications) Short-course RT+CT 6/261 Long-course CRT 13/254	However, data analyst was blinded.) Attrition bias Incomplete outcome data: low risk (Intention-to-treat analysis was done on all outcomes. No losses to follow-up regarding vital status and only 3 participants lost to follow-up regarding locoregional status.) Reporting bias Selective reporting: low risk (All primary and secondary endpoints reported.) Other bias Other sources of bias: - **Other information** None

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ostrowska-Cichocka, K., Pietruszka, M., Piotrkowski, G., Plewicka, M., Porzuczek-Zuziak, D., Reszke, J., Rychter, A., Sadowski, J., Salata, A., Serkies, K., Srutek, E., Szostak, B., Tuziak, T., Tyralik, D., Skoczylas, J., Wachua, E., Wandzel, P., Winkler-Spytkowska, B., Wojtasik, P., Wronski, K., Zemal, M., Zygulski, I., Long-course oxaliplatin-based preoperative chemoradiation versus 5 x 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: Results of a randomized phase III study, Annals of Oncology, 27, 834-842, 2016 **Ref ID** 745968 **Country/ies where the study was carried out** Poland	>5-10 cm Short-course RT+CT 106 (41) Long-course CRT 99 (39) >10-15 cm Short-course RT+CT 7 (3) Long-course CRT 16 (6) No data Short-course RT+CT 0 Long-course CRT 1 **Inclusion criteria** Primary or locally recurrent rectal cancer involving or abutting adjacent organs or structures (cT4) or palpably fixed cT3 lesion; pathologically proven adenocarcinoma; <=75 years of age; World Health Organization (WHO) performance status <=2; fit for major surgery and CT; signed informed consent. (Work-up included colonoscopy or rectoscopy, pelvic MRI or computed				

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type RCT (randomised phase III trial) **Aim of the study** To compare different schedules of preoperative CRT. **Study dates** 2008-2014 **Source of funding** Polish Ministry of Science and Higher Education	tomography, computed tomography of the abdomen, chest computed tomography or radiography, blood count and biochemistry.) **Exclusion criteria** Distant metastases; active coronary artery disease; cardiac arrhythmia; congestive heart failure; history of peripheral neuropathy; history of cerebral stroke.				
Full citation Cedermark, B, Dahlberg, M, Glimelius, B, Påhlman, L, Rutqvist, Le, Wilking, N, Improved survival with preoperative radiotherapy in resectable rectal cancer, New England Journal of Medicine, 336, 980-987, 1997 **Ref ID** 746072 **Country/ies where the study was carried out**	**Sample size** See Folkesson 2005. **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type **Aim of the study** **Study dates** **Source of funding**					
Full citation Eitta, M. A., El-Wahidi, G. F., Fouda, M. A., El-Hak, N. G., Abo El-Naga, E. M., Preoperative radiotherapy in resectable rectal cancer: a prospective randomized study of two different approaches, Journal of Egyptian National Cancer Institute, 22, 155-64, 2010 **Ref ID** 746717 **Country/ies where the study was carried out** Egypt **Study type** RCT	**Sample size** N=32 enrolled and randomised; n=16 allocated to short-course RT of which n=2 did not complete treatment protocol and were not followed up and are not included in the analysis, leaving n=14; n=16=allocated to long-course RT of which n=1 did not complete treatment protocol and was not followed up and is not included in the analysis, leaving n=15 **Characteristics** Age in years, median (range): Short-course RT 53 (32-75)	**Interventions** Preoperative short-course RT versus preoperative long-course RT Preoperative RT: Either short-course RT (2500cGy in 1 week in 5 fractions) or long-course RT (4500cGy in 5 weeks in 25 fractions) given with high energy photon radiation using Co60 or linear accelerator (6 MV photons). Two-dimensional three- or four-field techniques for the whole pelvis. Simulated in prone position with full bladder to reduce the volume of the small intestine in the irradiated fields. The target volume included the primary rectal tumour, the perirectal nodes, the mesorectum up to the level	**Details** Randomisation and allocation concealment No details reported. Blinding Not reported but presumably outcome assessors not blinded (participants not blinded). Follow-up/outcomes Early effects of radiation toxicity were recorded weekly during treatment and after 4 weeks. Late effects were recorded at 6 months then annually. Postoperative mortality was recorded during hospitalisation or within 30 days post-operation. After treatment participants were followed up every 1-2 months by clinical examination, every 3	**Results** Outcome: Local recurrence (median 18 months follow-up) Short-course RT 2/14 Long-course RT 1/15	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: unclear risk (Not reported.) Allocation concealment: unclear risk (Not reported.) Performance bias Blinding of participants and personnel: high risk (No blinding.) Detection bias Blinding of outcome assessment: unclear risk (Not reported but likely not blinded.) Attrition bias

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To compare between short-course and long-course preoperative RT for resectable rectal cancer. **Study dates** June 2007 to September 2009 **Source of funding** None reported.	Long-course RT 45 (20-65) Male sex, n (%) Short-course RT 9 (64) Long-course RT 10 (67) Tumour site, n (%): Upper Short-course RT 0 (0) Long-course RT 0 (0) Middle Short-course RT 3 (21) Long-course RT 2 (13) Lower Short-course RT 11 (79) Long-course RT 13 (87) Clinical stages, n (%): TNM stage IIa (T3N0) Short-course RT 6 (43) Long-course RT 8 (53) TNM stage IIb (T4N0) Short-course RT 2 (14) Long-course RT 1 (7) TNM stage IIIa (T3N+) Short-course RT 6 (43) Long-course RT 5 (33)	of the upper border of the first sacral vertebra and the lymph nodes along the internal iliac vessels. Surgery: Abdominoperineal resection (with a permanent colostomy) or lower anterior resection (with colorectal or usuallu coloanal anastomosis, diverting stoma was left to the surgeon's decision) performed within 1 week for the short-course RT group and after 4-6 weeks for the long-course RT group. Postoperative CT: Adjuvant CT was given 4-6 weeks after surgery. Depending on the postoperative pathology, either Mayo Clinic (leucovorin 20 mg/m² bolus followed by 5-FU 425 mg/m² bolus days 1-5 to be repeated every 4 weeks for 6 cycles, for low risk participants) or FOLFOX (oxaliplatin 85 mg/m² days 1 and 15 in glucose 5% over 2 hours infusion, leucoverin 20 mg/m² days 1, 8, 15 bolus and 5-FU 500 mg/m² days 1, 8, 15 bolus, to be repeated every	months by tumour markers (CEA & CA 19-9) and abdominopelvic computed tomography or MRI, or endoscopy every 6 months for the first 2 years. Disease-free survival was calculated from the date of surgery until recurrence (either local or distant). Overall survival was calculated from the date of surgery until death. **Statistical analysis** -		Incomplete outcome data: unclear risk (Intention-to-treat analysis was not done. Three of the 32 randomised were not included in the analysis.) Reporting bias Selective reporting: low risk (Primary outcome points were reported.) Other bias Other sources of bias: Poorly reported study. Number of events for survival outcomes not reported. No hazard ratios calculated. **Other information** The paper reports the percentage of overall survival and disease-free survival at 2 years and their log-rank p-values, however, no HRs or number of events are reported (and cannot

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	TNM stage IIIb (T4N+) Short-course RT 0 (0) Long-course RT 1 (7) Pathological stage, n (%): Stage 0 (T0N0) Short-course RT 0 (0) Long-course RT 2 (13) Stage I (T2N0) Short-course RT 2 (14) Long-course RT 3 (20) Stage II (T3N0) Short-course RT 6 (43) Long-course RT 5 (33) Stage IIIa (T3N1) Short-course RT 4 (29) Long-course RT 4 (27) Stage IIIb (T3N2) Short-course RT 2 (14) Long-course RT (error in reporting, does not make sense) Type of surgery, n (%): Abdominoperineal resection Short-course RT 10 (34) Long-course RT 8 (28)	4 weeks for 6 cycles, for high risk participants)			be calculated from the Kaplan-Meier curve), therefore, there is insufficient data for analysis.

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Lower anterior resection Short-course RT 3 (10) Long-course RT 6 (21) Palliative colostomy Short-course RT 0 (0) Long-course RT 1 (3) Exploration Short-course RT 1 (3) Long-course RT 0 (0) **Inclusion criteria** Histologically confirmed adenocarcinoma of the rectum with the inferior margin within 15 cm from the anal verge; resectable tumour (stage T2-4 N0-2) as determined by preoperative abdominopelvic computed tomography or MRI; ECOG performance status score 0-1; no evidence of distant metastases; no history of CT or RT to the pelvis. **Exclusion criteria**				

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	None reported.				
Full citation Erlandsson, J., Holm, T., Pettersson, D., Berglund, A., Cedermark, B., Radu, C., Johansson, H., Machado, M., Hjern, F., Hallbook, O., Syk, I., Glimelius, B., Martling, A., Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial, The Lancet Oncology, 18, 336-346, 2017 **Ref ID** 746776 **Country/ies where the study was carried out** Sweden **Study type** RCT, multi-centre, randomised, non-blinded, phase 3, non-	**Sample size** N=840 randomised in total N=385 in the 3-arm randomisation: n=129 short-course RT; n=128 short-course RT with delayed surgery; n=128 long-course RT with delayed surgery N=455 in the 2-arm randomisation: n=228 short-course RT; n=227 short-course RT with delayed surgery (this comparison is not of interest in this review) **Characteristics** **Characteristics** in the 3-arm randomisation: Age in years, median (IQR): Short-course RT 67 (62-74) Short-course RT with delay 67 (62-75) Long-course RT with delay 66 (61-73)	**Interventions** Short-course RT versus short-course RT with delayed surgery versus long-course RT Short-course RT: 5 Gy in fractions in 5 consecutive days (25 Gy in total). RT was given in three-beam or four-beam box technique including the primary tumour and primary and secondary lymph nodes in the pelvis. Long-course RT: 2 Gy in 25 fractions (50 Gy in total), no concomitant CT was given. RT was given in three-beam or four-beam box technique including the primary tumour and primary and secondary lymph nodes in the pelvis. Surgery: TME was performed (either anterior resection, abdominoperineal excision or Hartmann's procedure). Participants in the short-course RT group	**Details** Randomisation and allocation concealment Computer-generated randomisation lists were constructed using permuted blocks of 6 in the 3-arm randomisation and blocks of 4 in the 2-arm randomisation. Stratification according to participating centre. No reporting of allocation concealment. Blinding No blinding. Follow-up/outcomes According to trial protocol, follow-up was recommended at 3, 6, and 12 months after surgery and once a year thereafter but follow-up according to the national guidelines was also allowed (follow-up at 1 year and 3 years). The follow-up included chest radiography or computed tomography scan of the chest and computed	**Results** Outcome: Overall survival (median 5.2 years follow-up) Short-course RT n=129, 51 events Short-course RT with delay n=128, 43 events Short-course RT without delay (reference) versus short-course RT with delay: HR 0.81 (95% CI 0.53, 1.24) Long-course RT with delay n=128, 49 events Short-course RT without delay (reference) versus long-course RT with delay: HR 0.94 95% CI 0.63 to 1.40 Outcome: Local recurrence (median 5.2 years follow-up) Short-course RT n=129, 3 events Short-course RT with delay n=128, 4 events Long-course RT with delay n=128, 7 events	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: low risk Allocation concealment: unclear risk (Not reported.) Performance bias Blinding of participants and personnel: high risk (No blinding.) Detection bias Blinding of outcome assessment: high risk (No blinding.) Attrition bias Incomplete outcome data: low risk (Intention-to-treat approach to analysis used. All participants were followed-up minimum 2 years.) Reporting bias

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
inferiority trial (Stockholm III trial, NCT00904813) **Aim of the study** To study recurrence in patients randomised between three different RT regimens with respect to fractionation and time to surgery. **Study dates** October 5 1998 to January 31 2013 **Source of funding** Swedish Research Council; Swedish Cancer Society; Stockholm Cancer Society; the Regional Agreement on Medical Training and Clinical Research in Stockholm	Male sex, n (%): Short-course RT 81 (63) Short-course RT with delay 79 (62) Long-course RT with delay 73 (57) Tumour distance from anal verge, n (%): 0-5 cm Short-course RT 50 (39) Short-course RT with delay 57 (45) Long-course RT with delay 31 (25) 6-10 cm Short-course RT 49 (38) Short-course RT with delay 49 (39) Long-course RT with delay 60 (48) 11-15 cm Short-course RT 30 (23) Short-course RT with delay 21 (17) Long-course RT with delay 35 (28) Type of surgery, n (%):	underwent surgery within 1-7 days after RT. Participants in the short-course RT with delayed surgery and the long-course RT with delayed surgery underwent surgery within 28-56 days after completion of RT.	tomography scan of the abdomen to detect local; recurrence, distant metastases and adverse events. MRI was used if there was a suspicion of local recurrence and endoscopy was used at the discretion of the treating physician. Follow-up was done in person or by telephone with the participant. Data on all patients with rectal cancer are reported continuously to the nationwide validated Swedish ColoRectal Cancer Registry (SCRCR). The registry includes data on patient and tumour **Characteristics**, neoadjuvant therapy, short- and long-term complications, recurrences, and death. The primary endpoint was local recurrence, calculated from the date of randomisation to date of local recurrence. Local recurrence was defined as tumour growth below the level of the sacral promontory, related to the	Short-course RT without delay (reference) versus long-course RT with delay: HR 2.24 95% CI 0.71 to 7.10 Outcome: Disease-free survival (median 5.2 years follow-up) Short-course RT n=129, 44 events Short-course RT with delay n=128, 45 events Long-course RT with delay n=128, 44 events Short-course RT without delay (reference) versus long-course RT with delay: HR 0.99 95% CI 0.68 to 1.42 Outcome: 30-day mortality Short-course RT 2/129 Short-course RT with delay 3/128 Long-course RT with delay 1/128 Outcome: Death due to radiation toxicity (up to surgery)	Selective reporting: low risk Other bias Other sources of bias: - **Other information** Number of deaths in each group (used to calculate overall survival) is unclear. The paper reports in the same table the number of deaths in each group and the "number of patients with any lethal event" in each group - these numbers differ (higher numbers in the latter category). We have used the number of deaths reported in the overall survival.

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Anterior resection Short-course RT 79 (61) Short-course RT with delay 68 (53) Long-course RT with delay 93 (72) Abdominoperineal excision Short-course RT 47 (36) Short-course RT with delay 53 (41) Long-course RT with delay 24 (19) Hartmann's procedure Short-course RT 3 (2) Short-course RT with delay 6 (5) Long-course RT with delay 8 (6) Local excision Short-course RT 0 (0) Short-course RT with delay 1 (1) Long-course RT with delay 0 (0) No resection Short-course RT 0 (0) Short-course RT with delay 0 (0) Long-course RT with delay 3 (2)		previous rectal cancer and diagnosed radiographically with MRI, CT or both, or clinically (preferably with histological confirmation). Secondary endpoints were overall survival (calculated from the date of randomisation to death from any cause or emigration); frequency of postoperative complications; frequency of reoperations; frequency of late complications; radiation toxicity; frequency of sphincter-preserving surgeries (anterior resections); and quality of life (added to protocol in May 1999 and reported elsewhere). Post-hoc exploratory endpoints were distant metastases-free survival and recurrence-free survival (calculated from date of randomisation to local or distant recurrence). **Statistical analysis** The trial was designed as a non-inferiority trial.	Short-course RT 0/129 Short-course RT with delay 0/128 Long-course RT with delay 0/128	

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Pathological stage after neoadjuvant treatment, n (%): ypI Short-course RT 38 (29) Short-course RT with delay 55 (43) Long-course RT with delay 37 (29) ypII Short-course RT 43 (33) Short-course RT with delay 31 (24) Long-course RT with delay 46 (37) ypIII Short-course RT 48 (37) Short-course RT with delay 31 (24) Long-course RT with delay 37 (30) ypIV Short-course RT 0 (0) Short-course RT with delay 7 (6) Long-course RT with delay 5 (4) Unknown Short-course RT 0 (0)		Survival was analysed using Kaplan-Meier method, log-rank test was used to compare differences between groups. HRs were calculated using proportional hazard regression. Participant data from the 3-arm and 2-arm randomisations were analysed separately (comparison in the 2-arm randomisation not relevant for this review).		

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Short-course RT with delay 3 (2) Long-course RT with delay 1 (1) **Inclusion criteria** Biopsy-proven primary adenocarcinoma of the rectum within 15 cm of the anal verge; scheduled for an open abdominal procedure; no signs of non-resectability or distant metastases; no previous RT to the abdominal or pelvic areas; no signs of severe ischaemic disease; no symptoms of severe arteriosclerosis. (No age restriction.) **Exclusion criteria** None reported.				
Full citation Fan, W. H., Wang, F. L., Lu, Z. H., Pan, Z. Z., Li, L. R., Gao, Y. H., Chen, G., Wu, X. J., Ding, P. R., Zeng, Z. F., Wan, D. S., Surgery with versus without	**Sample size** N=192 enrolled and randomised: n=97 allocated to preoperative CRT + TME; n=95 allocated to TME; of which n=8 were ineligible (were	**Interventions** Preoperative CRT + TME versus TME + selective postoperative CT RT: In the preoperative CRT group, three-dimensional conformal RT	**Details** Randomisation and allocation concealment A computer-generated scheme randomly allocated participants to the two arms. Identities were concealed in	**Results** Outcome: Overall survival* (median 71 months (range 4, 109 months) follow-up) Preop CRT + TME n=90, 83.5% (median	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: low risk Allocation concealment: low risk

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
preoperative concurrent chemoradiotherapy for mid/low rectal cancer: An interim analysis of a prospective, randomized trial, Chinese Journal of Cancer, 34 (9) (no pagination), 2015 **Ref ID** 746801 **Country/ies where the study was carried out** China **Study type** RCT (Clinical trial registration number Chi CTR-TRC-08000122) Aim of the study To compare the efficacy of TME with versus without preoperative concurrent CRT involving XELOX regimen (oxaliplatin plus capecitabine) in Chinese people with stages II and III mid/low rectal adenocarcinoma.	found to have metastasis or refused surgery); included in analysis n=90 preoperative CRT + TME; n=94 TME **Characteristics** Male sex, n (%): Preop CRT + TME 56 (62) TME 51 (54) Tumour distance from the anal verge, n (%): <=5 cm Preop CRT + TME 52 (58) TME 47 (50) >5-10 cm Preop CRT + TME 38 (42) TME 47 (50) T stage, n (%): cT2 Preop CRT + TME 2 (2) TME 8 (9) cT3	was planned with the Pinnacle 8 treatment planning system using a 3-field irrational technique with 8-MV X-rays. The gross tumour volume was defined as all known gross lesions, including abnormally enlarged regional lymph nodes. The clinical target volume included primary rectal tumour lesions, the two end portions of the rectum, perirectal tissues, and anterior sacral, iliac, obturator, and true pelvic internal iliac lymph drainage areas. In participants with T4 lesions or bladder-invading tumours the clinical target volume also included the external iliac lymph drainage area. The planned target volume was defined as the clinical target volume or the gross tumour volume with 8-mm margin extension. Before 2011, a total dose of 46 Gy was delivered to the clinical target volume in 23 fractions of 2 Gy each without a boost dose. From 2011 onwards, an addition	sequentially numbered, opaque, sealed envelopes. Blinding No blinding. Follow-up/outcomes Toxicity assessment included weekly monitoring of the participants medical history, clinical examination Results, blood counts, and biochemistry Results (including liver function) was done. The follow-up included evaluations every 3 months for the first 2 years after completion of all treatments and every 6 months thereafter. Evaluations at each visit included complete blood count, liver function test, CEA and cancer antigen 19-9 measurements, and physical examination. Chest, abdominal, pelvic computed tomography, pelvic endoscopic	follow-up 66 months (range 4, 109 months)) TME n=94, 86.5% (median follow-up 76 months (range 10, 106 months)) HR 0887 (95% CI 0.461, 1.707, p=0.719) Outcome: Complete (R0) resection rate Preop CRT + TME 90/90 TME 94/94 Outcome: Local recurrence* (median 71 months follow-up [range 4, 109]) Preop CRT + TME n=90, 5 events TME n=94, 4 events HR 1.318 95% CI 0.354 to 4.909, p=0.681 Outcome: Disease-free survival* (median 71 months follow-up) Preop CRT + TME n=90, 85.2%; TME n=94, 84.3%	Performance bias Blinding of participants and personnel: high risk (no blinding) Detection bias Blinding of outcome assessment: unclear risk (Not reported but presumably no blinding.) Attrition bias Incomplete outcome data: low risk (Eight randomised individuals (4% of the total) were excluded from analysis because of ineligibility. However, it was not reported if intention-to-treat analysis was performed.) Reporting bias Selective reporting: low risk (All primary and secondary outcomes were reported.) Other bias Other sources of bias: -

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates March 23 2008 to August 2 2012 **Source of funding** Funding from Sun Yat-sen University; CT medication provided by Sanofi and Roche.	Preop CRT + TME 60 (67) TME 69 (73) cT4 Preop CRT + TME 28 (31) TME 17 (18) N stage, n (%): cN0 Preop CRT + TME 33 (37) TME 48 (51) cN+ Preop CRT + TME 57 (63) TME 46 (49) Clinical stage, n (%): II Preop CRT + TME 33 (37) TME 48 (51) III Preop CRT + TME 57 (63) TME 46 (49) **Inclusion criteria** Pathologically confirmed rectal adenocarcinoma within	of 4 Gy boost dose that involved 2 fractions of 2 Gy each to the gross tumour volume increased the total dose to 50 Gy. CT: The preoperative CRT group received 2 cycles of a modified XELOX regimen (oxaliplatin at 100 mg/m² on day 1 and capecitabine at 1,000 mg/m² twice daily on days 1-14 with an interval of 7 days before surgery. The same group received 4 cycles of standard XELOX regimen (oxaliplatin at 130 mg/m² on day 1 and capecitabine at 1,000 mg/m² twice daily on days 1-14 with an interval of 7 days) and 2 cycles of capcitabine (1,000 mg/m² twice daily on days 1-14 with an interval of 7 days) after surgery. In the TME group, participants with postoperative pathologic stages II-III disease were recommended to receive 6 cycles of standard XELOX regimen.	ultrasonography, and/or MRI were conducted every 6 months. The primary endpoints was disease-free survival. The secondary endpoints were overall survival, local and distant recurrence, tumour response to CRT, toxicity, sphincter preservation, and surgical complications. **Statistical analysis** Survival analysis was done using the Kaplan-Meier method and compared using the log-rank test. A multivariate Cox regression model was used to calculated hazard ratios with 95% CI.	HR 1.030 (95% CI 0.540, 1.963; p=0.969) Outcome: Sphincter preservation Preop CRT + TME 63/90 TME 67/94 Outcome: Treatment-related deaths Preop CRT + TME 0/90 TME 0/94 *Data extracted from Wang 2018.	**Other information** None

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	10 cm from the anal verge; the presence of clinical T3-T4 or node-positive resectable tumour; no extension of the malignant disease to the anal canal; no evidence of distant metastasis; Karnofsky Performance Score >=70 points; age between 18-70 years; adequate bone marrow function (haemoglobin level >=100 g/L; white blood cell count >=3.5 x 10(9)/L; absolute neutrophil count >=1.5 x 10(9)/L; platelet count >=100 x 10(9)/L); adequate renal function (creatinine <=1.5 x the upper limit of the normal range; and adequate hepatic function (AST/ALT <=2.5 x the upper limit of the normal range; alkaline phosphatase <=2.5 x the upper limit of the normal range). (Staging was determined according to the 2002 American	All participants received standard antiemetic prophylaxis that consisted of 5-hydroxytryptamine receptor 3 antagonists and dexamethasone. Surgery: TME was performed according to standardised technique. For the preoperative CRT group the surgery was performed within 6-10 weeks after completion of CRT. The surgeon made the decision about a covering stoma during the surgery. When the completeness of the TME was doubted, a frozen section of the mesorectal margin was subjected to intraoperative pathologic examination.			

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Joint Committee of Cancer staging system, via the colonofiberscopy, endorectal ultrasonography, chest computer tomography, and/or abdominopelvic magnetic resonance imaging. Rigid sigmoidoscopy was performed to determine the distance of the tumour from the anal verge.) **Exclusion criteria** Previously administered pelvic RT or CT; inflammatory bowel disease; malabsorption syndrome; a history of other cancers; cardiac arrhythmia; coronary heart disease; peripheral neuropathy; psychiatric disorders or psychologic disabilities that might adversely affect treatment compliance; pregnant or lactating women; women of childbearing				

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	age who lacked effective contraception.				
Full citation Fernandez-Martos, C., Garcia-Albeniz, X., Pericay, C., Maurel, J., Aparicio, J., Montagut, C., Safont, M. J., Salud, A., Vera, R., Massuti, B., Escudero, P., Alonso, V., Bosch, C., Martin, M., Minsky, B. D., Chemoradiation, surgery and adjuvant chemotherapy versus induction chemotherapy followed by chemoradiation and surgery: Long-term Results of the Spanish GCR-3 phase II randomized trial, Annals of Oncology, 26, 1722-1728, 2015 **Ref ID** 746847 **Country/ies where the study was carried out** Spain **Study type**	**Sample size** N=108 randomised; n=52 allocated to preoperative CRT of which n=3 ineligible and excluded, leaving n=49; n=56 allocated to preoperative CRT with prior CT of which n=2 ineligible and exlcuded, leaving n=54 **Characteristics** Age in years, median (range): Preop CRT 62 (42-75) Preop CRT with prior CT 60 (38-76) Male sex, n (%): Preop CRT 34 (65) Preop CRT with prior CT 39 (70) ECOG performance status, n (%): 0 Preop CRT 36 (69) Preop CRT with prior CT 33 (59)	**Interventions** Preoperative CRT and postoperative CT versus preoperative CRT with prior induction CT Induction CT: Capecitabine plus oxaliplatin. Capecitabine 2,000 mg/m²/day for 14 days every 21 days for 4 cycles. Oxaliplatin was administered on day 1 of each of the 4 cycles at a dose of 130 mg/m². Preoperative CRT: Both groups received capecitabine plus oxaliplatin. Oral capecitabine 825mg/m² twice daily on days 1-5 for 5 weeks, first dose administered 2 hours before RT and the second dose 12 hours later. Oxaliplatin was administered as a 2-hour infusion on days 1, 8, 15, 22, and 29 at a dose of 50 mg/m² per day. RT was delivered concurrently with the CRT by a linear	**Details** Randomisation and allocation concealment Randomisation done centrally and stratification according to institution. No other details reported. Blinding No blinding. Follow-up/outcomes Follow-up was done at 3-month intervals for the first year and then at 6-month intervals for a total of 3 years. Evaluations included physical examination, a complete blood count and blood chemistry, chest radiography, abdominal ultrasound or computed tomography. Proctoscopy was also carried out according to the policy of each institution. The primary endpoint was pathological complete response. Secondary endpoints included disease-free survival (time	**Results** Outcome: Overall survival (median 69 months follow-up) Preoperative CRT and postoperative CT n=52, 11 events Preoperative CRT with induction CT n=56, 14 events p=0.6422 Outcome: Complete (R0) resection rate Preoperative CRT and postoperative CT 45/52 Preoperative CRT with induction CT 48/56 Outcome: Local recurrence (median 69 months follow-up) Preoperative CRT and postoperative CT n=52, 3 events* Preoperative CRT with induction CT n=56, 1 event* p=0.61	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: unclear risk (details not reported.) Allocation concealment: unclear risk (Not reported.) Performance bias Blinding of participants and personnel: high risk (No blinding.) Detection bias Blinding of outcome assessment: high risk (No blinding.) Attrition bias Incomplete outcome data: low risk (Intention-to-treat approach to analysis used. Only 3 participants lost to follow-up.)

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
RCT, phase II randomised open-label multicentre trial (the Spanish Grupo Cancer de Recto 3 [GCR-3] trial) **Aim of the study** To compare the outcomes of conventional preoperative CRT and the addition of CT before the CRT. **Study dates** Enrolment from May 2006 to December 2007. **Source of funding** None reported.	1 Preop CRT 15 (29) Preop CRT with prior CT 22 (39) Type of surgery, n (%): None Preop CRT 6 (11) Preop CRT with prior CT 2 (4) Low anterior resection Preop CRT 29 (56) Preop CRT with prior CT 27 (48) Abdominoperineal resection Preop CRT 17 (33) Preop CRT with prior CT 23 (40) Missing information Preop CRT 0 Preop CRT with prior CT 2 (4) Pathological stage after preoperative treatment, n (%): pCR Preop CRT 7 (13) Preop CRT with prior CT 8 (14) yl	accelerator ieht a minimum of 6 MV by using three- or four-field technique. The target volume included the primary tumour and the mesorectal, presacral, and internal iliac lymph nodes up to the level of the bottom part of the fifth lumbar vertebra. The total dose for all participants was 50.4 Gy in daily fractions of 1.8 Gy 5 days a week. In the induction CT arm, the CRT was started 3 weeks after the start of the fourth capecitabine plus oxaliplatin cycle. Surgery: TME was performed 5-6 weeks after completion of preoperative CRT. The choice of type of surgery (anterior resection or abdominoperineal resection) was at the surgeon's discretion. Postoperative CT: The preoperative CRT (without induction CT) group received postoperative capecitabine plus oxaliplatin CT 4-8 weeks after surgery.	from the date of trial entry to recurrence, second primary tumour or death from any cause), overall survival (time from the date of trial entry to death from any cause), toxicity, treatment compliance, downstaging, complete (R0) resection rates, 30-day surgical complications, local relapse, distant metastasis. **Statistical analysis** Intention-to-treat analysis was done on all outcomes. Survival was analysed using the Kaplan-Meier method, and log-rank test was used to compare the groups.	Outcome: Disease-free survival (median 69 months follow-up) Preoperative CRT and postoperative CT n=52, 18 events Preoperative CRT with induction CT n=56, 22 events p=0.85 Outcome: Treatment-related mortality Preoperative CRT with postoperative CT 2/52 Preoperative CRT with induction CT 2/56 *calculated from the Kaplan-Meier curve.	Reporting bias Selective reporting: unclear risk (Main outcomes are reported. However, some of the reporting is unclear regarding p-values (see Other information section below), and number of local recurrence events not reported. Other bias Other sources of bias: - **Other information** There is unclarity regarding the log-rank p-value for disease-free survival and local recurrence. In the abstract and in the text they are reported as p=0.85 and p=0.61, respectively, whereas in the figure with the Kaplan-Meier curve they are reported as reported as p=0.7395 and p=0.3470,

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Preop CRT 21 (40) Preop CRT with prior CT 12 (21) yII Preop CRT 9 (17) Preop CRT with prior CT 18 (32) yIII Preop CRT 9 (17) Preop CRT with prior CT 13 (23) yIV Preop CRT 0 Preop CRT with prior CT 1 (2) Missing information Preop CRT 0 Preop CRT with prior CT 2 (4) **Inclusion criteria** Age 18-75 years; histopathologically confirmed rectal adenocarcinoma; inferior margin within 12 cm from the anal verge; locally advanced rectal cancer on the basis of high-resolution, thin-slice MRI of the pelvis (Locally advanced	The capecitabine plus oxaliplatin regimen was the same as in for the induction CT (see above).			resepectively. The same p-value is reported in the abstract, text and figure for overall survival.

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	rectal cancer defined on MRI as tumours extending to within 2 mm of, or beyond, the mesorectal fascia that is an involved or threatened circumferential resection margin, lower third from the anal verge cT3 tumours, resectable cT4 tumours, and any cT3N+); ECOG performance status <=2; adequate haematologic, liver, and renal function (neutrophils >-1.5 x 10(9)/L; platelet count >=100 x 10(9)/L; creatinine clearance >=30 mL/min; total bilirubin concentration >= 2 times the upper normal limit; and liver transaminase or alkaline phosphatase concentrations >= 3 times the upper normal limit). **Exclusion criteria** M1 metastatic disease; previous RT top the				

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	pelvic region; previous CT; other cancers; clinically significant cardiovascular disease.				
Full citation Folkesson, J., Birgisson, H., Pahlman, L., Cedermark, B., Glimelius, B., Gunnarsson, U., Swedish rectal cancer trial: Long lasting benefits from radiotherapy on survival and local recurrence rate, Journal of Clinical Oncology, 23, 5644-5650, 2005 **Ref ID** 746909 **Country/ies where the study was carried out** Sweden **Study type** RCT (Swedish Rectal Cancer Trial) **Aim of the study** To evaluate the long-term effects of	**Sample size** N=1,168 randomised: n=583 allocated to preoperative RT of which n=10 were ineligible, leaving n=573; n=585 allocated to surgery alone of which n=11 were ineligible, leaving n=574 **Characteristics** Median age: 68 years (range 27-81 years) Male sex: 60% (542 of the 908 curatively treated participants) Disease stage among participants with R0 resections, n: Stage I Preop RT 174/454 Surgery alone 147/454 Stage II Preop RT 157/454	**Interventions** Preoperative short-course RT versus surgery alone Preoperative short-course RT: 5 x 5 Gy in 5 days delivered in 1 week Surgery: For the preoperative RT group, surgery performed within 1 week of completion of RT. Anterior resection or abdominoperineal excision.	**Details** Randomisation and allocation concealment Randomisation was done in the trial centre by telephone contact. Stratification according to hospital. No other details given. (Data is extracted from Cedermark 1997 paper.) Blinding Not reported but presumably outcome assessor not blinded (participant not blinded). Follow-up and outcomes This publication reports long-term follow-up of the Swedish Rectal Cancer Trial. The follow-up was done by matching the curatively treated participants in the trial database against the Swedish Cancer Register and the National Hospital	**Results** Outcome: Overall survival among curatively treated participants (median 6.3 years of follow-up)* Preop RT n=454, number of events not reported Surgery alone n=454, number of events not reported HR* 0.79 95% CI 0.66 to 0.92 Outcome: Local recurrence (median 6.3 years follow-up) (intention-to-treat)*: Preop RT 63/553 Surgery alone 150/557 Outcome: Treatment and postoperative mortality - in-hospital mortality (intention-to-treat)*: Preop RT 22/57	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: unclear risk (Not reported.) Allocation concealment: unclear risk (Not reported.) Performance bias Blinding of participants and personnel: high risk (No blinding.) Detection bias Blinding of outcome assessment: unclear risk (Not reported but likely not blinded.) Attrition bias Incomplete outcome data: high risk (Intention-to-treat analysis not done,

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
preoperative RT on survival and recurrence rates in the treatment of curatively operated rectal cancer. **Study dates** 1987-1990 **Source of funding** National Cancer Institute (Sweden)	Surgery alone 150/454 Stage III Preop RT 123/454 Surgery alone 157/454 **Inclusion criteria** Less than 80 years of age; histopathologically proven adenocarcinoma situated below the promontory as shown on a lateral projection on barium enema; informed consent given. (Data extracted from Cedermark 1997 paper.) Exclusion criteria Locally non-resectable tumour; a plan to perform only local excision; known metastatic disease; previous RT to the pelvis; other malignant disease (except squamous-cell carcinoma of the skin). (Data extracted from		Discharge Register and the Cause of Death Register until December 31 2001. The clinical records of all participants in two of the participating regions (30% of all participants) were checked manually for validity of the outcome of the register investigation. Out of these 353 participants 2 had distant metastasis and 1 had local recurrence that was not recorded in the data from the registries. **Statistical analysis** Survival and cumulative incidence of local recurrence was calculated using actuarial methods. Log-rank test was used to calculate the difference between the groups.	Surgery alone 15/574 *Data extracted from Cedermark 1997 paper.	only curatively treated participants included in the follow-up analysis. Only 78%, that is 908 out of 1,168 originally randomised included in the analysis. Registry data used for follow-up data.) Reporting bias Selective reporting: low risk Other bias Other sources of bias: - **Other information** Note that actuarial methods (not Kaplan-Meier method) were used to analyse survival and local recurrence data. Note that there is some overlap between the participants in the Stockholm II trial (Martling 2001) and this trial: 316 participants enrolled

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Cedermark 1997 paper.)				in Stockholm from March 1987 to February 1990 are included in this trial and the Stockholm II trial, whereas 238 participants enrolled to the Stockholm trial II from February 1990 onwards are not included in this trial.
Full citation Gerard, J. P., Chapet, O., Nemoz, C., Hartweig, J., Romestaing, P., Coquard, R., Barbet, N., Maingon, P., Mahe, M., Baulieux, J., Partensky, C., Papillon, M., Glehen, O., Crozet, B., Grandjean, J. P., Adeleine, P., Improved sphincter preservation in low rectal cancer with high-dose preoperative radiotherapy: The Lyon R96-02 randomized trial, Journal of Clinical Oncology, 22, 2404-2409, 2004 **Ref ID** 747125	**Sample size** N=90 randomised; n=44 allocated to preoperative external RT of which n=1 was ineligible, leaving n=43; n=46 allocated to preoperative external RT with boost endocavity contact X-ray of which n=1 was ineligible, leaving n=45 **Characteristics** Age in years, median (range): External RT 67 (28-79) External RT + contact X-ray 69 (40-82) Male sex, n/n: External RT 29/43	**Interventions** Preoperative external RT versus preoperative external RT with internal contact X-ray boost therapy External RT: A total of 39 Gy in 13 fractions, 3 Gy per fraction, delivered over 17 days. Three-field wedge technique with the participant in prone position and use of an 18-MV photon beam. The target volume included the primary rectal tumour, the perirectal nodes, the mesorectum up to the level of the upper border of the first sacral vertebra, and the lymph nodes along the internal iliac vessels. The anal canal was not	**Details** Randomisation and allocation concealment Randomisation done at a central office and was based on permuted blocks. No stratification. No reporting of allocation concealment. Blinding No blinding. Follow-up/outcomes Primary endpoint was sphincter preservation. Follow-up was done every 3 months during the first 3 years. Clinical examination with rigid proctoscopy was done every time. Relevant radiologic or biologic	**Results** Outcome: Pelvic local recurrence (median 35 months follow-up) External RT 3/43 External RT + contact X-ray 1/45 Outcome: 60-day postoperative death External RT 1/43 External RT + contact X-ray 0/45	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: unclear risk (No details reported.) Allocation concealment: unclear risk (Not reported.) Performance bias Blinding of participants and personnel: high risk (No blinding.) Detection bias Blinding of outcome assessment: unclear risk (Not reported if outcome

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out France **Study type** RCT (The Lyon R96-02 trial) **Aim of the study** To evaluate the role of escalating the dose of preoperative radiation to increase sphincter-saving procedures. **Study dates** 1996-2001 **Source of funding** None reported.	External RT + contact X-ray 28/45 Tumour distance from anal verge in cm, median (range): External RT 4 (1-6) External RT + contact X-ray 4 (0.5-6) T stage assessed by endorectal ultrasound, n/n (%)*: uT2 External RT 12/41 (29) External RT + contact X-ray 10/43 (23) uT3 External RT 29/41 (71) External RT + contact X-ray 33/43 (77) uN1 External RT 21/41 (51) External RT + contact X-ray 25/43 (58) *Reporting unclear in the publication. Type of surgery, n/n: No surgery External RT 0/43	irradiated except in participants who had the tumour invading the upper part of the anus. The mean field size was 14 x 12 cm and 14 x 11 cm for the posterior and lateral field, respectively. Contact X-ray: The context X-ray treatment was started 2 weeks before external RT. A total dose of 85 Gy in three fractions of 35 Gy, 30 Gy, and 20 Gy were delivered on days 1, 8, and 21. The fraction on day 21 was given at the end of the first week of external RT. Performed using a RT50 Philips unit delivering a beam of 50 kV with 0.5 mm aluminium filtration and a dose rate at 4 cm source-surface distance of 20 Gy per minute. Brachytherapy: For both groups, after a complete clinical response 4 weeks after completion of external RT, a final boost irradiation could be given to the tumour bed using an	examinations were performed according to presenting symptoms or signs. **Statistical analysis** Survival and local relapse-free rate were analysed using the Kaplan-Meier method and the difference between groups was tested using the log-rank test.		assessor was blinded but presumably not.) Attrition bias Incomplete outcome data: low risk (Intention-to-treat analysis done for survival outcomes. No losses to follow-up.) Reporting bias Selective reporting: unclear risk (Primary outcome reported but not clear which are the secondary outcomes. Poor reporting. P-values and hazard ratios not reported.) Other bias Other sources of bias: - **Other information** Reporting of T stage (by ultrasound) is a bit unclear in Table 1 in the publication and there is some

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	External RT + contact X-ray 7/45 Endoanal excision External RT 0/43 External RT + contact X-ray 3/45 Anterior resection External RT 19/43 External RT + contact X-ray 24/45 Abdominoperineal resection External RT 24/43 External RT + contact X-ray 11/45 Total sphincter-saving procedure**, n/n (%): External RT 19/43 (44) External RT + contact X-ray 34/45 (76) *including no surgery, endoanal excision and anterior resection) **Inclusion criteria** Histologically confirmed adenocarcinoma of the rectum without evidence of distant metastases; the inferior edge of the	interstitial iridium-192 brachytherapy implant. If the tumour was between 4 and 6 cm from the anal verge, a "fork" implant was used made of 2 iridium-192 wires 4 cm long and 1.6 cm apart delivering 25 Gy in 24 to 36 hours according to the Paris dosimetric system. When the tumour was located below 4 cm from the anal verge, a perineal template was used with 5 to 6 cm long iridium-192 wires 1 cm apart also delivering 25 Gy over 24 to 36 hours. (Only 6 participants underwent brachytherapy. It is not clear what was the decision to give brachytherapy was based on but in the discussion section, the authors say it was "arbitrary".) Surgery: TME, either abdominoperineal resection with a permanent colostomy or low anterior resection with colorectal or usually coloanal anastomosis, diverting stoma was left to the decision of the surgeon. In			uncertainty about the population

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	tumour located not further than 6 cm from the anal verge; T2 or T3 tumours staged with endorectal ultrasound; tumour not involving more than 2/3 of the rectal circumference (to be accessible to contact X-ray therapy); fit for surgery. (No age limit.) **Exclusion criteria** None reported.	case of complete clinical response after preoperative treatment, endoanal local excision was an alternative surgical approach. Surgery was carried out minimum 5 weeks after completion of the external RT. Adjuvant CT: Not specified in the trial protocol but in case of locally advanced evolutive cancer in the operative specimen, adjuvant CT with fluorouracil and folinic acid was possible and decided by the responsible physician.			
Full citation Gijn, W, Marijnen, Ca, Nagtegaal, Id, Kranenbarg, Em, Putter, H, Wiggers, T, Rutten, Hj, Påhlman, L, Glimelius, B, Velde, Cj, Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled	**Sample size** N=1861 randomised of which 56 excluded; N=1805 allocated to treatment: n=897 allocated to preoperative short-course RT + TME; n=908 allocated to TME **Characteristics** Age in years, median (range):	**Interventions** Preoperative short-course RT + TME versus TME alone RT: Short-course RT with 5 x 5 Gy was given to the preoperative RT group. In case of positive resection margin in the TME alone group, postoperative RT (28 x 1.8 Gy) was given. Surgery: TME was performed. The preoperative RT group	**Details** Randomisation and allocation concealment Computer-generated randomisation based on permuted blocks of six with stratification according to centre and the expected type of surgery. Randomisation was managed centrally. For every stratification group and participating centre, a list was printed by the Department of	**Results** Outcome: Overall survival (median 11.6 years of follow-up) Preop RT + TME n=897, 485 events TME 49% n=908, 488 events p=0.86 Outcome: Circumferential resection margin not involved (not defined	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: low risk Allocation concealment: low risk Performance bias Blinding of participants and personnel: high risk (No blinding.) Detection bias

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
TME trial, The lancet. Oncology, 12, 575-582, 2011 **Ref ID** 747166 **Country/ies where the study was carried out** The Netherlands mainly but also other European countries and Canada **Study type** RCT (The Dutch TME trial) **Aim of the study** To investigate the value of preoperative short-term RT in combination with TME. **Study dates** Enrolment between January 12 1996 and December 31 1999 **Source of funding** The Dutch Cancer Society; the Dutch National Health	Preop RT + TME 65 (26-88) TME 66 (23-92) Male sex, n (%): Preop RT + TME 573 (64) TME 578 (64) Tumour distance from the anal verge, n (%): <5 cm Preop RT + TME 244 (27) TME 265 (29) 5.0-9.9 cm Preop RT + TME 383 (43) TME 359 (40) >=10 cm Preop RT + TME 268 (30) TME 283 (31) Unknown Preop RT + TME 2 (<1) TME 1 (<1) Type of resection, n (%): None	underwent surgery within 1 week of completion of RT.	Medical Statistics. Participants were assigned to a treatment by these lists which were only available in the central data centre. Local investigators enrolling participants had no knowledge of the next assignment in the sequence. Blinding Participants were not blinded (not possible). Outcome assessors were not aware of the allocation. Data analysis was not blinded. Follow-up/outcomes Follow-up clinical examination was done every 3 months during the first year after surgery and annually thereafter. The primary endpoint was local control. Secondary endpoints were distant recurrence, overall survival, and cancer-specific survival. Local recurrence was defined as evidence of tumour within the pelvic or perineal	but assumed to indicate complete resection rate R0)* Preop RT + TME 729/897 TME 729/908 Outcome: Health-related quality of life - Overall health status (VAS) at 3, 6, 12, and 24 months after surgery** "Overall perceived health, measured by VAS, improved over time but did not differ significantly between treatment arms." Outcome: Health-related quality of life - Global health status score (QLQ-C30) at median 14 years of follow-up (scale 0-100, higher indicating better quality of life)*** Preop RT + TME 77.2 TME 78.5 p=0.16	Blinding of outcome assessment: low risk (Outcome assessment was blinded.) Attrition bias Incomplete outcome data: low risk (Intention-to-treat analysis was performed for overall survival. N=24 in arm 1 and n=33 in arm 2 excluded from local recurrence analysis because of macroscopically incomplete resection.) Reporting bias Selective reporting: low risk Other bias Other sources of bias: - Other information None

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Council; the Swedish Cancer Society.	Preop RT + TME 16 (2) TME 29 (3) Low anterior Preop RT + TME 579 (65) TME 604 (67) Abdominoperineal Preop RT + TME 251 (28) TME 235 (26) Hartmann Preop RT + TME 50 (6) TME 39 (4) Unknown Preop RT + TME 1 (<1) TME 1 (<1) TNM stage, n (%): 0 Preop RT + TME 11 (1) TME 17 (2) I Preop RT + TME 264 (29) TME 243 (27) II Preop RT + TME 251 (28)		area. All time-to-event outcomes were calculated from the date of surgery. At 3, 6, 12, and 24 months, overall health-related quality of life was measured using a 100-mm horizontal visual analogue scale (VAS), perfect health in one end and death in the other end. The score was calculated as millimeters from the death to the mark, with higher number indicating better health. (Data extracted from Marijnen 2005) At median 14 years of follow-up, health-related quality of life was measured with QLQ-C30 questionnaire. The questionnaire was sent out to all participants remaining alive in 2012. The scale for the item "global health status" is 0-100, with higher number indicating better health. (Data extracted from Wiltink 2014.) **Statistical analysis**	Outcome: Local recurrence (median 11.6 years of follow-up) Preop RT + TME n= 873, 46 events TME n=875, 97 events p<0.0001 Outcome: Stoma rate (median 5 years of follow-up)**** Preop RT + TME 129/306 TME 106/291 Outcome: Treatment-related mortality (RT complications or surgery complications) Preop RT + TME 22/897 TME 16/908 *Data extracted from Peeters 2007. **Data extracted from Marijnen 2005. *** Data extracted from Wiltink 2014. ****Data extracted from Peeters 2005, includes only Dutch participants of the Dutch TME trial.	

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	TME 245 (27) III Preop RT + TME 299 (33) TME 325 (36) IV Preop RT + TME 62 (7) TME 61 (7) Unknown Preop RT + TME 10 (1) TME 17 (2) **Inclusion criteria** Clinically resectable adenocarcinoma of the rectum without evidence of distant metastasis; tumour located below the level of S1/S2 with an inferior tumour margin 15 cm or less from the anal verge. **Exclusion criteria** None reported.		Intention-to-treat analysis was performed for overall survival using Kaplan-Meier method, compared using log-rank test. Local recurrence was done on all participants who underwent macroscopically complete local resection, cumulative incidence was calculated. HRs were calculated using Cox proportional hazards model.		
Full citation Kacar, S., Vanlsuha, C., Grkan, A., Karaca, C., Pre-operative radiochemotherapy for	**Sample size** N=51 randomised: n=26 allocated to preoperative CRT;	**Interventions** Preoperative CRT versus postoperative CRT	**Details** Randomisation and allocation concealment	**Results** Outcome: Local recurrence (mean follow-up time 25.5±12.6 months)	**Limitations** Cochrane risk of bias tool Selection bias

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
rectal cancer a prospective randomized trial comparing pre-operative vs. postoperative radiochemotherapy in rectal cancer patients, Acta chirurgica Belgica, 109, 701-707, 2009 **Ref ID** 747973 **Country/ies where the study was carried out** Turkey **Study type** RCT **Aim of the study** To find out whether preoperative CRT has any survival advantage over postoperative CRT for people with rectal cancer without metastasis or peritoneal carcinomatosis. **Study dates**	n=25 allocated to postoperative CRT **Characteristics** Age in years, mean (range): Preop CRT 57 (27-82) Postop CRT 52 (31-80) Male sex, n (%): Preop CRT 14 (54) Postop CRT 16 (64) Tumour distance from anal verge in cm, mean±SD: Preop CRT 6.96±3.68 Postop CRT 8.72±3.55 Tumour distance from the anal verge, n (%): 0-5 cm Preop CRT 9 (35) Postop CRT 4 (16) 6-10 cm Preop CRT 13 (50) Postop CRT 13 (52) 11-15 cm Preop CRT 4 (15) Postop CRT 8 (32)	RT: For the preoperative CRT group, RT was started immediately after clinical evaluation. 4500 to 5040 cGy was given in 25 to 28 fractions, 5 times a week, to the pelvis with individually shaped portals and by using a three-field or four-field box technique. For the postoperative CRT group, RT was started 2 to 4 weeks after their surgical wounds had completely healed. They received a total dose of 5040 cGy in 30 fractions and a 540 Gy boost delivered to the tumour bed. CT: For the preoperative CRT group, fluorouracil (5-FU) 425 mg/m² and leucovorin 20 mg/m² per day as a sensitiser for 2 to 5 days in the first and last week of RT. Postoperatively (for the preoperative CRT group), the same doses of these drugs were given as an adjuvant therapy in 4 to 6 five-day courses. For the postoperative CRT group, the same sensitiser and adjuvant therapy were	Randomisation was done by tossing the coin. No other **Details** are given. Blinding Participants were not blinded (impossible). Not reported if outcomes assessors were blinded. Follow-up/outcomes Primary endpoint was overall survival. Secondary endpoints were disease-free survival, local and distant recurrences. Participants were followed up every 3 months for 2 years and then every 6 months for 3 years. Evaluations consisted of physical examination, a complete blood count, and blood chemical analysis, proctoscopy, abdominal ultrasound scan, computer tomography of the abdomen, and chest X-ray. **Statistical analysis**	Preop CRT 4/26 Postop CRT 5/25	Random sequence generation: unclear risk (Coin toss method used, no other **Details** given.) Allocation concealment: unclear risk (Not reported.) Performance bias Blinding of participants and personnel: high risk (No blinding.) Detection bias Blinding of outcome assessment: unclear risk (Not reported.) Attrition bias Incomplete outcome data: unclear risk (Not reported if intention-to-treat analysis was performed. Losses to follow-up not reported.) Reporting bias Selective reporting: low risk of bias (Primary and secondary endpoints were reported.) Other bias

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
January 1998 to December 2003 **Source of funding** None reported.	Preoperative T-stage, n (%): IIB Preop CRT 2 (8) Postop CRT 0 (0) IIIA Preop CRT 3 (12) Postop CRT 2 (8) IIIB Preop CRT 12 (46) Postop CRT 10 (40) IIIC Preop CRT 9 (35) Postop CRT 13 (52) Surgery type, n (%): Anterior resection Preop CRT 12 (46) Postop CRT 19 (76) Abdominoperineal resection Preop CRT 14 (54) Postop CRT 6 (24) **Inclusion criteria** Biopsy-proven rectal cancer; no display of distant metastasis or peritoneal dissemination. Initial staging was determined by	administered in the same way as for the preoperative CRT group. Surgery: For the preoperative CRT group, surgery took place 5-8 weeks after completion of CRT. For the postoperative CRT group, surgery took place immediately after diagnosis. TME was the standard procedure for all participants. For the preoperative CRT group anterior resection or abdominoperineal resection with curative intent were performed depending on the tumour's pre-RT distance from the anal verge. Whenever possible, anastomosis was performed after resection with a distal tubular margin of at least 2 cm from the pre-RT localisation of the tumour and the tumour-free margin confirmed by frozen section. Otherwise abdominoperineal resection was done. For the postoperative CRT group, the surgical approach was the same. The anastomoses were	Survival outcomes were analysed using the Kaplan-Meier method. Log-rank test was used to compare survival in the 2 groups.		Other sources of bias: - Other information The paper reports the percentage of overall survival and disease-free survival at 1, 2, 3, and 4 years and their log-rank p-values, however, no hazard ratios or number of events are reported (and cannot be calculated from the Kaplan-Meier curve), therefore, there is insufficient data for analysis.

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	endorectal ultrasound scan and/or computerised tomography. **Exclusion criteria** None reported.	performed on resections with a distal margin of at least 2 cm from the palpable tumour and tumour-free margins in frozen sections.			
Full citation Kairevice, L., Latkauskas, T., Tamelis, A., Petrauskas, A., Pauzas, H., Zvirblis, T., Jarusevicius, L., Saladzinskas, Z., Pavalkis, D., Janciauskiene, R., Preoperative long-course chemoradiotherapy plus adjuvant chemotherapy versus short-course radiotherapy without adjuvant chemotherapy both with delayed surgery for stage II-III resectable rectal cancer: 5-Year survival data of a randomized controlled trial, Medicina (Kaunas, Lithuania), 53, 150-158, 2017	**Sample size** N=150 randomised; n=75 allocated to short-course RT, of which n=5 were judged ineligible and n=2 protocol violation, leaving n=68 for analysis; n=75 allocated to CRT, of which n=3 were judged to be ineligible, leaving n=72 for analysis **Characteristics** Age in years, mean±SD: Short-course RT 65.6±9.5 Long-course CRT 63.1±10.1 Male sex, n (%): Short-course RT 43 (63)	**Interventions** Preoperative short-course RT with delayed surgery versus conventional (long-course) preoperative CRT with delayed surgery and adjuvant CT Short-course RT: 5 Gy x 5 fractions for 5 days (in total 25 Gy). Individual 3-dimensional dose planning with photon beam energy 15 MV and beam shaping with multileaves collimator were used. The target volume included the primary tumour, adjacent lymph nodes and presacral region. The target volume extended from the top of the sacrum to 5 cm below primary tumour, laterally it included pelvic sidewalls and internal iliac nodes, posteriorly, the presacral lymph nodes and sacral	**Details** Randomisation and allocation concealment No details reported. Blinding No blinding. Follow-up/outcomes Follow-up visits were every 3 months for the first 2 years and thereafter every 6 to 12 months for at least 5 years. Evaluations included physical examination, abdominal ultrasound scan, chest X-ray and colonoscopy. Computed tomography and/or MRI were performed if there was a suspicion of local or distant recurrence. Primary outcomes were overall survival and disease-free survival. Overall survival was	**Results** Outcome: Overall survival (median 60.5 months follow-up) (intention-to-treat) Short-course RT n=75, number of events not reported Long-course CRT n=75, number of events not reported HR 2.28 95% CI 1.30 to 4.00, p=0.004 Outcome: "radical surgery" ("non-radical surgery" defined as R+ or CRM <=1 mm, therefore assumed to indicate complete resection rate R0)* Short-course RT 57/68 Long-course CRT 64/72	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: unclear risk (Not reported.) Allocation concealment: unclear risk (Not reported.) Performance bias Blinding of participants and personnel: high risk (No blinding.) Detection bias Blinding of outcome assessment: high risk (No blinding.) Attrition bias Incomplete outcome data: low risk (Intention-to-treat

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref ID 747982 **Country/ies where the study was carried out** Lithuania **Study type** RCT (NCT00597311) **Aim of the study** To compare overall survival and disease-free survival in two treatment groups: preoperative short-course RT and CRT both with delayed surgery plus adjuvant CT in CRT arm. **Study dates** January 2007 to June 2013 **Source of funding** None reported.	Long-course CRT 49 (68) Clinical stage, n (%): II Short-course RT 16 (24) Long-course CRT 15 (21) III Short-course RT 52 (77) Long-course CRT 57 (79) Clinical T category, n (%): cT2 Short-course RT 6 (9) Long-course CRT 4 (6) cT3 Short-course RT 56 (82) Long-course CRT 52 (72) cT4 Short-course RT 6 (9) Long-course CRT 16 (22) Clinical N category, n (%):	hollow, and anteriorly and adequate margin was left t cover the tumour (including posterior vaginal wall in women). Long-course CRT: In total 50 Gy in 25 fractions, 2 Gy per fraction over 5 weeks. Concomitant fluorourcil (5-FU) (400 mg/m²/day 1-hour IV infusion days 1-4) and lecovorin (20 mg/m²/day IV bolus injection days 1-4) CT on the first and fifth week of RT. The RT arrangement and technique was the same than in the short-course RT group (see above). Adjuvant CT was given within 8 weeks after surgery, 5-FU (400 mg/m²/day 1-hour IV infusion days 1-5) and lecovorin (20 mg/m²/day IV bolus injection days 1-5) for 4 cycles every 4 weeks. Surgery: TME for both groups, 6-8 weeks after completion of RT/CRT.	calculated from the first day of treatment to death from any cause. Disease-free survival was calculated from the first day of treatment to the first date of disease progression or date of confirmed tumour or death from any cause. **Statistical analysis** The trial was designed to test non-inferiority of overall survival in the short-course RT compared to the conventional long-course CRT. Survival analysis was done using Kaplan-Meier method and log-rank test was used to test for difference between groups. HRs were calculated using Cox proportional hazard ratios.	Outcome: Local recurrence (median 60.5 months follow-up) Short-course RT 4/68 Long-course CRT 5/72 Outcome: Disease-free survival (median 60.5 months follow-up) Short-course RT n=68, number of events not reported Long-course CRT n=72, number of events not reported HR 1.88 95 % CI 1.13 to 3.12, p=0.015 Outcome: Permanent stoma (median 39.7 months follow-up)* Short-course RT 27/68 Long-course CRT 25/72 *Data extracted from Latkauskas 2016.	analysis was done for overall survival. No losses to follow-up.) Reporting bias Selective reporting: low risk (Primary outcome points were reported.) Other bias Other sources of bias: - **Other information** None

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	cN0 Short-course RT 22 (32) Long-course CRT 21 (29) cN1 Short-course RT 33 (49) Long-course CRT 31 (43) cN2 Short-course RT 13 (19) Long-course CRT 20 (28) Tumour distance from the anal verge, n (%): <5 cm Short-course RT 34 (50) Long-course CRT 30 (42) 5-10 cm Short-course RT 29 (43) Long-course CRT 37 (51) 11-15 cm Short-course RT 5 (7) Long-course CRT 5 (7)				

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria Histopathologically confirmed stage II and III rectal cancer less than 15 cm from the anal verge; under 80 years of age; no other cancer in previous 5 years; normal cardiovascular, pulmonary, hepatic and renal function. (Data extracted from Latkauskas 2011.) **Exclusion criteria** Stage I or IV rectal cancer; cancer in previous 5 years; previous RT or CT; cardiovascular, pulmonary, hepatic or renal dysfunction; neurological and psychiatric disease; sepsis, pregnancy; breastfeeding. (Data extracted from Latkauskas 2011.)				
Full citation Latkauskas, T., Pauzas, H., Kairevice, L., Petrauskas, A., Saladzinskas, Z.,	**Sample size** See Kairevice 2017. **Characteristics**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Janciauskiene, R., Gudaityte, J., Lizdenis, P., Svagzdys, S., Tamelis, A., Pavalkis, D., Preoperative conventional chemoradiotherapy versus short-course radiotherapy with delayed surgery for rectal cancer: Results of a randomized controlled trial, BMC Cancer, 16 (1) (no pagination), 2016 **Ref ID** 748480 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Inclusion criteria** **Exclusion criteria**				
Full citation Marechal, R., Vos, B., Polus, M., Delaunoit, T., Peeters, M.,	**Sample size** N=57 randomised; n=29 allocated to preoperative CRT;	**Interventions** Preoperative CRT versus preoperative CRT with induction CT	**Details** Randomisation and allocation concealment	**Results** Outcome: Circumferential resection margin >1	**Limitations** Cochrane risk of bias tool Selection bias

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Demetter, P., Hendlisz, A., Demols, A., Franchimont, D., Verset, G., Van houtte, P., Van de stadt, J., Van laethem, J. L., Short course chemotherapy followed by concomitant chemoradiotherapy and surgery in locally advanced rectal cancer: A randomized multicentric phase II study, Annals of Oncology, 23, 1525-1530, 2012 **Ref ID** 748951 **Country/ies where the study was carried out** Belgium **Study type** RCT, a randomised, multicentre phase II trial **Aim of the study** To evaluate the feasibility and efficacy of a short-course	n=28 allocated to preoperative CRT with induction CT **Characteristics** Age in years, median (range): Preoperative CRT 62 (44-79) Preoperative CRT with induction CT 62 (22-80) Male sex, n (%): Preoperative CRT 16 (55) Preoperative CRT with induction CT 21 (75) Staging by ultrasound ± MRI, n (%): cT2 Preoperative CRT 3 (10) Preoperative CRT with induction CT 1 (4) cT3 Preoperative CRT 23 (79) Preoperative CRT with induction CT 25 (89) cT4	Induction CT: Modified FOLFOX6 for 2 cycles was administered before the preoperative CRT. Oxaliplatin 100 mg/m² 2-hour IV infusion on day 1, folinic acid 400 mg/m² on day 1, fluorouracil (5-FU) 400 mg/m² IV bolus on day 1, 5-FU 2,000 mg/m² continuous IV infusion over 46 hours on day 1 and day 14. Preoperative CRT: RT was delivered by a linear accelerator with a minimum of 6 MV by using three- or four-fields and three-dimensional conformal planning. Usually >=15 MV was necessary. A total dose of 45 Gy in daily fractions of 1.8 Gy was elivered 5 days a week. During RT, 5-FU was given as a continuous IV infusion with a dose of 225 mg/m²/day. Surgery: TME was carried out in both groups 6-8 weeks after the completion of CRT. The choice of the	Randomisation done centrally, stratification by institution. No other **Details** reported. Blinding Not reported but presumably no blinding. Follow-up/outcomes Primary endpoint was ypT0-1N0 rate. Standard pathology examination was carried out after surgery. **Statistical analysis** For outcomes relevant for this review, no Statistical analysis was carried out, data was reported descriptively.	mm (complete resection rate R0)* Preoperative CRT 25/29 Preoperative CRT with induction CT 27/28 Outcome: Chemotherapy-related death Preoperative CRT 0/29 Preoperative CRT with induction CT 1/28 *The paper reports the number of participants in each arm with positive circumferential margin (<=1 mm), from which complete (R0) resection was calculated: total number of participants - number of participants with positive circumferential margin (<=1 mm) = number of participants with complete (R0) resection.	Random sequence generation: unclear risk (Not reported.) Allocation concealment: unclear risk (Not reported.) Performance bias Blinding of participants and personnel: high risk (No blinding.) Detection bias Blinding of outcome assessment: unclear risk (Not reported but likely not blinded.) Attrition bias Incomplete outcome data: low risk Reporting bias Selective reporting: low risk (Primary endpoint was reported.) Other bias Other sources of bias: -

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
intense course of induction CT before preoperative CRT in people with locally advanced rectal cancer. **Study dates** Not reported. **Source of funding** None reported.	Preoperative CRT 3 (10) Preoperative CRT with induction CT 2 (7) Any cTN+ Preoperative CRT 25 (86) Preoperative CRT with induction CT 26 (93) Tumour location, n (%): Lower third Preoperative CRT 13 (45) Preoperative CRT with induction CT 11 (39) Middle third Preoperative CRT 9 (31) Preoperative CRT with induction CT 13 (46) Upper third Preoperative CRT 7 (24) Preoperative CRT with induction CT 4 (25) Total mesorectal excision performed, n (%): Preoperative CRT 23 (79)	type of surgery (abdominoperineal resection or sphincter preserving surgery) was according to the surgeon's discretion.			**Other information** The publication does not report if longer follow-up will be carried out and whether survival or disease recurrence outcomes will be studied.

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Preoperative CRT with induction CT 24 (86) Abdominoperineal resection performed, n (%): Preoperative CRT 5 (17) Preoperative CRT with induction CT 3 (11) **Inclusion criteria** Histologically proven resectable rectal adenocarcinoma; staged as clinically T2-4 N+; amenable to indication for CRT and resection; no prior treatment (CT or RT) of this cancer at the exception of colostomy; no evidence of metastatic disease on clinical examination and computer tomography of chest, abdomen and pelvis; ECOG performance status of <=2; age >=18 years; an adequate bone marrow reserve; normal renal and liver functions				

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	(polymorpjonuclear >1.5 x 10(9)/L, platelet >100 x 10(9)/L, creatitine clearance >=30 mL/min, total bilirubin concentration <1.5 x the upper normal limit, prothrombine time <=1.5 x the upper normal limit). **Exclusion criteria** Metastatic disease; previous treatment (CT or RT) for this cancer except colostomy; other cancers; known hypersensitivity to any components of study treatments; chronic inflammatory disease of the ileum or the colon; peripheral sensory neuropathy with functional impairment; clinically significant cardiovascular disease; major surgical procedure <=28 days before randomisation; medical or psychological condition that would not permit				

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	the participant to complete the study or sign informed consent; pregnancy or breast feeding.				
Full citation Marijnen, C. A. M., Van De Velde, C. J. H., Putter, H., Van Den Brink, M., Maas, C. P., Martijn, H., Rutten, H. J., Wiggers, T., Kranenbarg, E. K., Leer, J. W. H., Stiggelbout, A. M., Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: Report of a multicenter randomized trial, Journal of Clinical Oncology, 23, 1847-1858, 2005 **Ref ID** 748968 **Country/ies where the study was carried out** **Study type**	**Sample size** See van Gijn 2011. **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study **Study dates** **Source of funding**					
Full citation McLachlan, S. A., Fisher, R. J., Zalcberg, J., Solomon, M., Burmeister, B., Goldstein, D., Leong, T., Ackland, S. P., McKendrick, J., McClure, B., MacKay, J., Ngan, S. Y., The impact on health-related quality of life in the first 12 months: A randomised comparison of preoperative short-course radiation versus long-course chemoradiation for T3 rectal cancer (Trans-Tasman Radiation Oncology Group Trial 01.04), European Journal of Cancer, 55, 15-26, 2016 **Ref ID** 749082	**Sample size** See Ngan 2012. **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation Ngan, S. Y., Burmeister, B., Fisher, R. J., Solomon, M., Goldstein, D., Joseph, D., Ackland, S. P., Schache, D., McClure, B., McLachlan, S. A., McKendrick, J., Leong, T., Hartopeanu, C., Zalcberg, J., Mackay, J., Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04.[Erratum appears	**Sample size** N=326 randomised; n=163 allocated to short-course RT of which n=1 withdrew consent, therefore n=162 analysed; n=163 allocated to long-course RT of which n=2 withdrew consent, therefore n=161 analysed **Characteristics** Age in years, median (range): Short-course RT 63 (26-80) Long-course RT 64 (29-82)	**Interventions** Short-course RT versus long-course CRT Short-course RT: Total of 25 Gy in 5 fractions administered in 1 week. The radiation target volume included the primary rectal cancer, perirectal and internal iliac nodes, mesorectum, pelvic side walls, and presacral space with the upper border at the sacral promontory. Long-course CRT: A total of 50.4 Gy in 28 fraction as over 5 weeks and 3 days with continuous infusion of fluorouracil (5-FU) 225	**Details** Randomisation and allocation concealment Randomisation was done using an adaptive biased coin technique by stratification according to RT centre. No reporting of allocation concealment. Blinding Not reported but presumably no one was blinded. Follow-up/outcomes The status of participants were reviewed every 3 months for 2 years and then every 6 months until 5 years postsurgery and once a year thereafter.	**Results** Outcome: Overall survival (median 5.9 years follow-up) Short-course RT n=162, 47 events Long-course CRT n=161, 52 events HR 1.12 95% CI 0.76 to 1.67, p=0.62 Outcome: Negative resection margin (not defined but assumed to indicate complete (R0) resection rate Short-course RT 150/158 Long-course CRT 151/157	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: unclear risk (details not provided.) Allocation concealment: unclear risk (Not reported.) Performance bias Blinding of participants and personnel: high risk (No blinding.) Detection bias

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
in J Clin Oncol. 2013 Jan 20;31(3):399], Journal of Clinical Oncology, 30, 3827-33, 2012 **Ref ID** 749454 **Country/ies where the study was carried out** Australia and New Zealand **Study type** RCT (TROG 01.04, NCT00351598) **Aim of the study** To compare the local recurrence rate between short-course and long-course neoadjuvant RT for rectal cancer. **Study dates** 2001-2006 **Source of funding** The National Health and Medical Research Council; Cancer	Male sex, n (%): Short-course RT 117 (72) Long-course RT 120 (75) T3 stage, n (%): Short-course RT 162 (100) Long-course RT 161 (100) N stage, n (%): 0 Short-course RT 91 (56) Long-course RT 90 (56) 1 Short-course RT 59 (36) Long-course RT 59 (37) 2 Short-course RT 1 (1) Long-course RT 2 (1) X Short-course RT 11 (7) Long-course RT 10 (6) M0 stage, n (%):	mg/m²/day administered 7 days/week for the duration of radiation. Surgery: For the short-course RT group, surgery was performed 3-7 days after completion go RT. For the long-course CRT group surgery was performed 4-6 weeks after completion of CRT. Postoperative CT: For the short-course RT group: 6 monthly courses of 5-FU 425 mg/m² and folinic acid 20 mg/m² administered daily for 5 days starting 4-6 weeks after surgery for the short-course RT group. For the long-course CRT group: 4 monthly courses of the same CT starting 4-6 weeks after surgery.	Liver function and CEA level tests were done at each visit. Primary endpoint was local recurrence rate. Local recurrence was defined as recurrence within the true pelvis and either confirmed histologically or diagnosed from one or more of the following: progressive radiographic (computed tomography or MRI) changes in a pelvic soft-tissue mass; progressive pelvic pain with radiographic changes; abnormally high uptake in the true pelvis on positron emission tomography scan; visible or palpable tumour in the presence of distant metastasis. An independent review panel reviewed all cases of local recurrence. Recurrence outside the true pelvis was considered distant metastasis. Secondary endpoints were time to local recurrence, time to distant recurrence, recurrence-free survival, and overall survival.	Outcome: Health-related quality of life - QLQ-C30 global health/overall score change from randomisation to 12 months (scale 0-100)*: Short-course RT -9.9 (n=143) (baseline mean score 71.0 SE 1.7) Long-course RT -8.2 (n=153) (baseline mean score 70.0 SE 1.8) p=0.44 Outcome: Local recurrence cumulative incidence (median 5.9 years follow-up) Short-course RT n=162, events 12 Long-course CRT n=161, events 9 p=0.51 Outcome: Recurrence-free survival (median 5.9 years follow-up) Short-course RT n=162, 57 events Long-course CRT n=161, 64 events	Blinding of outcome assessment: unclear risk (Not reported but presumably no blinding.) Attrition bias Incomplete outcome data: low risk (Intention-to-treat analysis done. Very few losses to follow-up.) Reporting bias Selective reporting: low risk (Main outcomes reported.) Other bias Other sources of bias: - **Other information** None

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Council Victoria; the Royal Australian and New Zealand College of Radiologists.	Short-course RT 162 (100) Long-course RT 161 (100) Tumour distance from the anal verge, n (%): 0 to <5 cm Short-course RT 48 (30) Long-course RT 31 (19) 5 to <10 cm Short-course RT 88 (54) Long-course RT 88 (55) >=10 to 12 cm Short-course RT 26 (16) Long-course RT 42 (26) Type of surgery, n (%): Abdominoperineal resection Short-course RT 59 (37) Long-course CRT 48 (31) Non-abdominoperineal resection		Time-to-event outcomes were calculated from randomisation or operation, as appropriate. Overall survival was defined as time to death from any cause. Recurrence-free survival was defines as time to recurrence or death. Health-related quality of life was assessed with QLQ-C30 questionnaire at randomisation, and at 1, 2, 3, 6, 9, and 12 months thereafter. Questionnaires were filled in by the participants at the clinic visits or returned by post. (Data extracted from McLachlan 2016.) **Statistical analysis** Intention-to-treat analysis was done for local recurrence rate. Survival was analysed with Kaplan-Meier method, log-rank test were used to compare the groups, Cox proportional hazard methods were used to calculate HRs.	HR 1.15 95% CI 0.80 to 1.62, p=0.47 *Data extracted from McLachlan 2016.	

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Short-course RT 99 (63) Long-course CRT 109 (69) **Inclusion criteria** Histologically confirmed rectal adenocarcinoma with lower borders within 12 cm of the anal verge; ultrasound- or MRI-staged T3 disease; ECOG performance status 0 to 2; neutrophil count >=1.5 x 10(9)/L; platelet count >=100 x 10(9)/L; bilirubin and ALT <=1.5 times the upper limit of normal; serum creatitine ,=1.5 times the upper limit of normal. **Exclusion criteria** Evidence of distant metastasis; recurrent rectal cancer; unstable cardiac disease; active infection; other cancers within 5 years; prior RT. (No restriction on nodal stage.)				

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Park, J. H., Yoon, S. M., Yu, C. S., Kim, J. H., Kim, T. W., Kim, J. C., Randomized phase 3 trial comparing preoperative and postoperative chemoradiotherapy with capecitabine for locally advanced rectal cancer, Cancer, 117, 3703-3712, 2011 **Ref ID** 749709 **Country/ies where the study was carried out** Republic of Korea **Study type** RCT **Aim of the study** To compare preoperative CRT with postoperative CRT using capecitabine in survival, local control, sphincter preservation, and toxicity for the treatment of locally advanced rectal cancer.	**Sample size** N=240 enrolled N=220 randomised: n=107 allocated to preoperative CRT n=113 allocated to postoperative CRT **Characteristics** Age in years, median (range): Preop CRT 54 (29-73) Postop CRT 56 (33-75) Male sex, n (%): Preop CRT 67 (63) Postop CRT 71 (63) CEA level increased, n (%): Preop CRT 19 (18) Postop CRT 15 (13) Tumour location, n (%): Low (<5 cm) Preop CRT 64 (60) Postop CRT 52 (46) Middle (5-10 cm) Preop CRT 43 (40) Postop CRT 61 (54)	**Interventions** Preoperative CRT versus postoperative CRT RT: In the preoperative group a dose of 46 Gy in 23 fractions to the whole pelvis followed by a boost dose of 4 Gy in 2 fractions. In the postoperative group a dose of 50 Gy in 25 fractions to the whole pelvis. CT: Capecitabine (825 mg/m² twice per day without weekend breaks) was initiated on the first day of RT and was delivered concurrently with RT. Adjuvant CT was initiated 4 weeks after surgery in the preoperative CRT group and at 4 weeks after completion of CRT in the postoperative CRT group. Adjuvant CT consisted of either 4 cycles of capecitabine (2,500 mg/m²/day for 14 days followed by a 1 week break) or 4 cycles of bolus 5-FU/leucovorin (375 mg 5-FU/m²/day and 20 mg leucovorin/m²/day for 5 days every 4 weeks) depending on the	**Details** Randomisation and allocation concealment Randomisation done is a permuted block method using random number tables and included stratification by gender. No reporting of allocation concealment but the paper reports in the **Results** section that "...randomisation could have been affected by investigator preference for preoperative treatment for low-lying tumours; hence, we closed this protocol earlier than initially planned" which possibly indicates that there was no allocation concealment? Blinding No blinding. Follow-up/outcomes Treatment-related toxicity was evaluated according to National Cancer Institute Common Toxicity Criteria version 2.0. Participants were	**Results** Outcome: Overall survival (median follow-up of 52 months) Preop CRT n=107, 18 events* Postop CRT n=113, 16 events* p=0.6204 Outcome: Complete (R0) resection rate (median follow-up of 52 months) Preop CRT 105/105 Postop CRT 112/113 Outcome: Local recurrence (median follow-up of 52 months) Preop CRT n=107, 4 events Postop CRT n=113, 7 events p=0.3925 Outcome: Disease-free survival (median follow-up of 52 months) Preop CRT n=107, 30 events* Postop CRT n=113, 29 events*	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: unclear risk of bias (Reporting insufficient to know what was done.) Allocation concealment: high risk of bias (Not reported but mentioned in the **Results** section that the trial was ended prematurely partly because "randomisation could have been affected by investigator preference for preoperative treatment for low-lying tumours" which possibly indicated that allocation was not concealed?) Performance bias Blinding of participants and personnel: high risk of bias (No blinding.) Detection bias

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Enrolment between March 2004 and April 2006. **Source of funding** None reported.	Clinical stage, n (%): T3N0 Preop CRT 35 (32) Postop CRT 36 (32) T4N0 Preop CRT 0 (0) Postop CRT 1 (1) T2N+ Preop CRT 1 (1) Postop CRT 3 (2) T3N+ Preop CRT 70 (66) Postop CRT 72 (64) T4N+ Preop CRT 1 (1) Postop CRT 1 (1) Sphincter sparing procedures (low anterior resection), n (%): Preop CRT 84 (80) Postop CRT 81 (72) **Inclusion criteria** Locally advanced rectal cancer (cT3 or potentially resectable cT4 or positive regional lymph node) on endorectal	economic status of the participants (capecitabine is not covered by the medical insurance system of Korea). The participants were instructed to take capecitabine twice daily at 12-hour intervals and to take one of the doses 1 hour before RT to maximise the radiosensitisation effect. Surgery: Four to six weeks after completion of CRT (in the preoperative CRT group). TME was performed as the standard procedure and the particular type of surgery was determined at the time of resection. All operations were carried out by specialist colorectal surgeons who had performed more than 200 TMEs each year for the past 5 years.	examined weekly during CRT. After completion of CRT participants were followed-up every 3 months for the first 2 years and every 6 months from there on. Complete history and physical examination, complete blood count, biochemical profile, serum CEA and chest radiography were performed at each follow-up. Abdominopelvic computed tomography scan was performed every 6 months for the first 2 years and once a year after that. Colonoscopy was performed once a year. Pathologic confirmation of recurrent disease was encouraged. If histologic evidence was not available a clear demonstration of recurrent lesions or serial enlargement of the lesions based on radiology were accepted as the evidence of treatment failure. Local recurrence was defined as tumour recurrence within radiation field in pelvic cavity.	p=0.8656 Outcome: Treatment-related mortality Preop CRT 0/105 Postop CRT 0/113 *calculated from the Kaplan-Meier curve	Blinding of outcome assessment: high risk of bias (Not clear from the paper but appears to be that there was no blinding.) Attrition bias Incomplete outcome data: low risk of bias (Intention-to-treat analysis was performed. N=240 originally enrolled of which 20 were excluded for various reasons. Of the N=220 randomised only n=1 was lost to follow-up and not included in the analysis.) Reporting bias Selective reporting: low risk of bias (All primary and secondary endpoints were reported.) Other bias Other sources of bias: - **Other information** None

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	ultrasonography and abdominopelvic computed tomography; tumour located below 10 cm from the anal verge; >18 and <76 years of age; ECOG performance status 0-2; adequate bone marrow reserve (white blood cell count >=4,000/mm³, absolute neutrophil count >=1,500/mm³, platelet count >=100,000/mm³, haemoglobin >=10 g/dL); adequate renal function (serum creatinine level <=1.5 mg/dL, calculated creatinine clearance >=50 mg/min); adequate liver function (liver transaminase levels <=3 times the upper normal limits, serum bilirubin <=1.5 mg/dL); signed informed consent prior to randomisation. **Exclusion criteria** Evidence of distant metastasis; previous history of CT or RT;		**Statistical analysis** Primary endpoint was 3-year disease-free survival. Secondary endpoints were overall survival, local or distant relapses, sphincter preservation and treatment-related toxicities. Time-to-event outcomes were calculated from the first day of RT for the preoperative CRT group and from the day of surgery in the postoperative CRT group. Survival analysis was done using Kaplan-Meier method and the groups were compared using the log-rank test. Intention-to-treat analysis was done.		

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	history of malignancy during recent 5 years other than skin cancer; pregnant or lactating woman; family history of colorectal cancer.				
Full citation Peeters, K. C., van de Velde, C. J., Leer, J. W., Martijn, H., Junggeburt, J. M., Kranenbarg, E. K., Steup, W. H., Wiggers, T., Rutten, H. J., Marijnen, C. A., Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients--a Dutch colorectal cancer group study, Journal of Clinical Oncology, 23, 6199-206, 2005 **Ref ID** 749780 **Country/ies where the study was carried out**	**Sample size** See van Gijn 2011. **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type **Aim of the study** **Study dates** **Source of funding**					
Full citation Peeters, K. C. M. J., Marijnen, C. A. M., Nagtegaal, I. D., Kranenbarg, E. K., Putter, H., Wiggers, T., Rutten, H., Pahlman, L., Glimelius, B., Leer, J. W., Van De Velde, C. J. H., The TME trial after a median follow-up of 6 years: Increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma, Annals of Surgery, 246, 693-701, 2007 **Ref ID** 749782 **Country/ies where the study was carried out** **Study type**	**Sample size** See van Gijn 2011. **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study **Study dates** **Source of funding**					
Full citation Pietrzak, L., Bujko, K., Nowacki, M. P., Kepka, L., Oledzki, J., Rutkowski, A., Szmeja, J., Kladny, J., Dymecki, D., Wieczorek, A., Pawlak, M., Lesniak, T., Kowalska, T., Richter, P., Quality of life, anorectal and sexual functions after preoperative radiotherapy for rectal cancer: Report of a randomised trial, Radiotherapy and Oncology, 84, 217-225, 2007 **Ref ID** 749886 **Country/ies where the study was carried out** **Study type**	**Sample size** See Bujko 2006. **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study **Study dates** **Source of funding**					
Full citation Roh, M. S., Colangelo, L. H., O'Connell, M. J., Yothers, G., Deutsch, M., Allegra, C. J., Kahlenberg, M. S., Baez-Diaz, L., Ursiny, C. S., Petrelli, N. J., Wolmark, N., Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03, Journal of Clinical Oncology, 27, 5124-5130, 2009 **Ref ID** 750193 **Country/ies where the study was carried out** US **Study type** RCT (NSABP R-03)	**Sample size** N=267 randomised: n=130 allocated to preoperative CRT; n=137 allocated to postoperative CRT n=123 analysed in the preoperative CRT group; n=131 analysed in the postoperative CRT group **Characteristics** Age <=60 years, n (%): Preop CRT 53 (43) Postop CRT 59 (45) Male sex, n (%): Preop CRT 85 (69) Postop CRT 89 (68) Sphincter-sparing surgery as the intended surgical procedure, n (%): Preop CRT 43 (35) POstop CRT 44 (33)	**Interventions** Preoperative CRT versus postoperative CRT CT: Seven cycles CT in total given to both groups, the duration of cycle 1 and cycles 4 to 7 was 8 weeks including rest periods. RT was given during cycles 2-3. In the preoperative CRT group, cycles 1-3 were given before surgery and cycles 4-7 were given after surgery. RT: The pelvis was treated with 45 Gy in 25 fractions to the isocenter using a four-field box technique with a 5.4 Gy bvoost in 3 fractions to a restricted volume. Surgery: Type of surgery was determined by the treating physician. Either abdominoperineal resection, low anterior resection (including coloanal), and local	**Details** Randomisation and allocation concealment A biased coin minimisation algorithm was used to randomise participants, stratified by age (<=60 years or >60 years), sex, and institution. No reporting of allocation concealment. Blinding No blinding. Follow-up/outcomes Participants were assessed before allocation; every week before CT during RT; during CT every 8 weeks before the next cycle; and post-therapy every 3 months during the first and second year; every 6 months during years 3 to 5; and every 12 months after that.	**Results** Outcome: Overall survival (median 8.4 years follow-up) Preop CRT n=123, 44 events Postop CRT n=131, 62 events HR 0.693 95% CI 0.468 to 1.026, p=0.065 Outcome: Local recurrence (median 8.4 years of follow-up) Preop CRT n=123, 13 events Postop CRT n=131, 15 events HR 0.86 95% CI 0.41 to 1.81, p=0.693 Outcome: Disease-free survival (median 8.4 years follow-up) Preop CRT n=123, 51 events	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: unclear risk (Limited information reported.) Allocation concealment: unclear risk (Not reported.) Performance bias Blinding of participants and personnel: high risk (No blinding.) Detection bias Blinding of outcome assessment: unclear risk (Not reported but presumably not be blinded.) Attrition bias Incomplete outcome data: low risk of bias (Intention-to-treat analysis was done for the ones with follow-

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To compare neoadjuvant versus adjuvant CRT in the treatment of locally advanced rectal carcinoma. **Study dates** August 1993 to June 1999 **Source of funding** Public Health Service grants from the National Cancer Institute, Department of Health and Human Services.	Multiple tumours, n (%): Preop CRT 4 (3) Postop CRT 1 (0.8) Sphincter-sparing surgery, n (%): Preop CRT 55 (47.8) Postop CRT 47 (39.2) **Inclusion criteria** Histologic diagnosis of rectal adenocarcinoma (defined by the distal border of the tumour <=15 cm from the anal verge); able to begin treatment (surgery or CRT) within 49 days from histologic diagnosis; no radiologic evidence of metastases on abdominal or pelvic computer tomography scans; ECOG performance status <=2; adequate blood counts; adequate hepatic and renal function.	excision were acceptable according to trial protocol.	The diagnosis of recurrence was made on the basis of imaging and if possible cytologic analysis or biopsy. An elevated CEA level as a solitary finding was not considered evidence of treatment failure. Primary endpoints were disease-free survival and overall survival. Disease-free survival was defined as the time from randomisation to recurrence, second primary cancer (excluding basal cell carcinomas of the skin and carcinoma in situ of the cervix), or death without evidence of recurrence or second primary cancer. Overall survival was defined as the time from randomisation to death from any cause. Locoregional recurrence defined as time from the completion of therapy, including surgery, to evidence of tumour in the pelvis, including the presacrum, pelvic sidewalls, base of the	Postop CRT n=131, 74 events HR 0.629 95% CI 0.439 to 0.902, p=0.011 Outcome: Sphincter preservation at 5 years Preop CRT 39/115 Postop CRT 29/120 Outcome: Toxicity-related mortality (within 30 days of last CT) Preop CRT 4/126 Posop CRT 1/99	up data. Small numbers lost to follow-up not ineligible post-randomisation, thus, not included in analysis: 7 in preop CRT group and 6 in postop CRT group.) Reporting bias Selective reporting: low risk of bias (Main outcomes were reported.) Other bias Other sources of bias: None **Other information** None

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Detailed eligibility criteria: 1. The person must consent to be in the study. The informed consent form conforming to federal and institutional guidelines must be signed, witnessed, and dated prior to random assignment. 2. People in whom the diagnosis of invasive rectal cancer has been obtained by incisional (surgical or endoscopic) biopsy so that the majority of the tumour has not been removed are eligible. 3. Must be able to begin protocol therapy (surgery or CT) within 49 days from initial histologic diagnosis. 4. Must have a life expectancy of at least 10 years, excluding their diagnosis of cancer. 5. The tumour should be either palpable by clinical rectal		bladder and the perineum, or at the anastomotic site. **Statistical analysis** Kaplan-Meier method was used to analyse survival data, groups were compared using log-rank test. Cox proportional hazard models were used to calculate HRs with 95% CI. Intention-to-treat analysis was performed on all participants with follow-up data.		

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	examination or be accessible via a proctoscope or sigmoidoscope, and its distal border should be located no more than 15 cm from the anal verge. 6. The tumour should be movable on clinical examination without evidence of fixation to the pelvis or to surrounding organs (vagina, prostate, bladder) beyond the limits of resection via exenteration. 7. Must have no radiologic evidence of metastatic spread. The person must have a computer tomography scan of the abdomen and pelvis prior to random assignment. Any suspicious findings (liver nodule, retroperitoneal adenopathy) will render the person ineligible unless malignancy is ruled out				

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	by further tissue documentation (computed tomography- or ultrasound-guided biopsy, laparoscopic biopsy, or open biopsy) prior to random assignment. 8. Evidence by computed tomography scan of enlarged perirectal or pelvic lymph nodes is not a condition of ineligibility unless they appear to preclude adequate surgical removal. 9. The white blood cell count must be >= 4,000/µL and the platelet count must be >= 100,000/µL. 10. There must be evidence at random assignment of adequate hepatic and renal function (bilirubin and AST or ALT; creatinine must be <= 1.5 x the upper limit of normal for the performing laboratory). 11. People with more				

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	than one synchronous rectal lesion are eligible. 12. People with a performance status of 0, 1, or 2 are eligible. **Exclusion criteria** Detailed ineligibility criteria: 1. People with malignant rectal tumours other than adenocarcinoma (for example sarcoma, lymphoma, carcinoid, squamous cell carcinoma, or cloacogenic carcinoma). 2. People who have life expectancy of <10 years, excluding their diagnosis of cancer. 3. People who demonstrate, prior to random assignment, evidence of free perforation, as manifested by free air or free fluid in the abdomen. People with walled-off perforations are eligible. 4. People with a				

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	previous or concomitant malignancy, regardless of site, except patients with squamous or basal cell carcinoma of the skin, or carcinoma in situ of the cervix that has been adequately treated. 5. People who have received surgical treatment for rectal cancer, other than preliminary decompressing colostomy or diagnostic laparoscopy or laparotomy without any resection of primary tumour. 6. People who have received any other therapy (RT, CT) for rectal cancer prior to random assignment. 7. People in whom rectal cancer was diagnosed by excisional biopsy (removal of polyp with adenocarcinoma, removal of villous adenoma with adenocarcinoma,				

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	etc). 8. People who are unable to begin protocol therapy within 49 days from initial histologic diagnosis. 9. People with a tumour whose distal border is located more than 15 cm from the anal verge. 10. People whose tumour is fixed by clinical examination to surrounding structures, precluding the possibility of adequate surgical resection even with pelvic exenteration. 11. People who show radiologic evidence of advanced disease (inoperable locoregional disease, or metastatic disease). Evidence of biopsy-proven retroperitoneal lymph node involvement will deem a person ineligible. 12. People who				

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	demonstrate involvement of perirectal or pelvic lymph nodes with evidence of fixation to the pelvic side wall. 13. People with a performance status of 3 or 4. 14. People having nonmalignant systemic disease (cardiovascular, renal, hepatic, etc.), which would preclude their being subjected to the treatment (surgery, CT, and RT). 15. People with active inflammatory bowel disease. 16. People who are pregnant at the time of random assignment. 17. People with psychiatric or addictive disorders that would preclude obtaining informed consent. 18. People who have multiple primary tumours involving both the colon and rectum that would				

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	preclude them from being classified as having only rectal cancer. 19. People who are found, by endoluminal ultrasonography, to have a Dukes' A lesion				
Full citation Sauer, R., Fietkau, R., Wittekind, C., Rodel, C., Martus, P., Hohenberger, W., Tschmelitsch, J., Sabitzer, H., Karstens, J. H., Becker, H., Hess, C., Raab, R., German Rectal Cancer, Group, Adjuvant vs. neoadjuvant radiochemotherapy for locally advanced rectal cancer: the German trial CAO/ARO/AIO-94, Colorectal Disease, 5, 406-15, 2003 **Ref ID** 750394 **Country/ies where the study was carried out** **Study type**	**Sample size** See Sauer 2012. **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study **Study dates** **Source of funding**					
Full citation Sauer, R., Liersch, T., Merkel, S., Fietkau, R., Hohenberger, W., Hess, C., Becker, H., Raab, H. R., Villanueva, M. T., Witzigmann, H., Wittekind, C., Beissbarth, T., Rodel, C., Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: Results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years, Journal of Clinical Oncology, 30, 1926-1933, 2012 **Ref ID** 750396	**Sample size** N=823 enrolled and randomised, n=24 excluded (did not meet inclusion criteria or refused to participate) n=404 randomised to preoperative CRT (intention-to-treat population), of which n=18 requested change of arm or erroneously received other treatment arm, therefore, n=406 allocated to preoperative CRT n=395 randomised to postoperative CRT (intention-to-treat population), of which n=20 requested change of arm or erroneously received other treatment arm, therefore, n=393 allocated to postoperative CRT	**Interventions** Preoperative CRT versus postoperative CRT CRT: a total of 5040 cGy delivered (as at least 6-MV photons) in 28 fractions of 180 cGy 5 times a week to the pelvis with individually shaped portals and the use of three-field or four-fied box technique. In the 1st and 5th weeks of RT fluorouracil was given as a 120-h continuous infusion at a dose of 1000mg per m² per day. Treatment was identical in both groups except for a 540-cGy boost delivered to the tumour bed in the postoperative CRT group. Surgery: Total mesorectal excision. In the preoperative CRT group, surgery was scheduled to take place 4-6 weeks after completion of the CRT.	**Details** Randomisation and allocation concealment Randomisation performed using permuted blocks of 14 with stratification according to surgeon. No reporting of allocation concealment. In 16 out of the 26 centres, informed consent was obtained after randomisation result was told to the participant. Blinding No blinding. Follow-up/outcomes During treatment, participants were monitored weekly for signs of acute toxic effects with appropriate adjustments in CT and RT done if necessary. Follow-up occurred at 3-month intervals for 2 years and then at 6-month intervals for 3 years, for a total of 5 years. Evaluations	**Results** Outcome: Overall survival (intention-to-treat) (median 134 months of follow-up): Preoperative CRT n=404, number of events not reported Postoperative CRT n=395, number of events not reported HR 0.98 (95% CI 0.79 to 1.21), p=0.85 (postoperative CRT as reference) Outcome: Complete (R0) resection rate: Preoperative CRT 387/406 Postoperative CRT 381/393 Outcome: Local recurrence (only includes those with macroscopically	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: unclear risk (**Details** not reported, only reported that it was "performed centrally on permuted blocks of 14 stratifying by surgeon") Allocation concealment: unclear risk (not reported) Performance bias Blinding of participants and personnel: high risk of bias (no blinding) Detection bias Blinding of outcome assessment: high risk of bias (no blinding) Attrition bias

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Germany **Study type** RCT (CAO/ARO/AIO-94) **Aim of the study** To compare preoperative CRT and postoperative CRT for locally advanced rectal cancer. **Study dates** Trial was initiated in 1994 and participants were enrolled between February 1995 and September 2002. **Source of funding** German Cancer Aid (Deutsche Krebshilfe)	**Characteristics** Baseline **Characteristics** according to the treatment received: Age in years, median (range): Preop CRT 62 (30-77) Postop CRT 61 (33-76) No postop CRT 63 (40-76) Male sex, n (%): Preop CRT 293 (72) Postop CRT 164 (66) No postop CRT 91 (63) Tumour distance from the anal verge, n (%): 0-5 cm Preop CRT 117 (29) Postop CRT 59 (24) No postop CRT 27 (19) 5-<10 cm Preop CRT 189 (47) Postop CRT 102 (41) No postop CRT 66 (46)	Adjuvant CT: 4 cycles of of bolus fluorouracil (500mg per m² per day, 5 times a week, every four weeks) were started 4 weeks after surgery for the preoperative CRT group and 4 weeks after completion of the postoperative CRT in the postoperative CRT group.	consisted of physical examination, a complete blood count, blood chemistry, rectoscopy, abdominal ultrasound, computed tomography scan of the abdomen and chest radiography. Histologic confirmation of local recurrence (defined as a colorectal cancer within the true pelvis or perineal scar) and distant recurrence was encouraged. Alternate acceptable criteria included sequential enlargement of a mass in radiologic studies. To obtain long-term survival and tumour status, additional information was collected from all the participating hospitals and from general practitioners on additional case report forms and from German registy offices (survival status only). Primary endpoint was overall survival, defined as the time of randomisation to death for any reason or the day of last follow-up. Secondary endpoints were disease-	complete resection) (median 134 months of follow-up): Preoperative CRT n=397, 23 events Postoperative CRT n=393, 37 events HR 0.60 (95% CI 0.4 to 1.0), p=0.048 (postoperative CRT as reference) Outcome: Disease-free survival (intention-to-treat) (median 134 months of follow-up): Preoperative n=404, number of events not reported Postoperative CRT n=395, number of events not reported HR: 0.94 (95% CI 0.73 to 1.21), p=0.65 (postoperative CRT as reference) Outcome: Treatment-related mortality (death during CRT or surgical death)*: Preoperative CRT 5/406	Incomplete outcome data: low risk of bias (intention-to-treat analysis was done for main outcomes; low attrition at follow-up) Reporting bias Selective reporting: low risk of bias (primary and secondary outcomes were all reported) Other bias Other sources of bias: None **Other information** In the postoperative CRT group, 145 did not receive CRT because they had been histopathologically diagnosed as stage 0 or I (n=75) or as stage IV (n=19), because of postoperative complications (n=16), because of refusal to receive treatment or institutional error (n=28), and other reasons (n=7).

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	10-16 cm Preop CRT 85 (21) Postop CRT 79 (32) No postop CRT 45 (31) Unknown Preop CRT 15 (4) Postop CRT 8 (3) No postop CRT 7 (5) TNM stage, n (%): pCR/stage 0 Preop CRT 36 (9) Postop CRT 0 (0) No postop CRT 2 (1) yI/I Preop CRT 111 (27) Postop CRT 2 (<1) No postop CRT 73 (50) yII/II Preop CRT 117 (29) Postop CRT 87 (35) No postop CRT 28 (19) yIII/III Preop CRT 103 (25) Postop CRT 146 (59) No postop CRT 21 (14) yIV/IV Preop CRT 31 (8) Postop CRT 13 (5) No postop CRT 19 (13) Unknown		free survival, local and distant recurrences, postoperative complications, acute and long-term toxic effects and sphincter preservation. Local recurrence analyses were done on all participants who underwent a macroscopically complete local resection (participants with an R1 resection of the primary tumour or with distant metastases found at surgery were included but participants without surgery or with macroscopically incomplete local resection, R2, were excluded). All time-to-event outcomes were collected from the date of randomisation. All participants who were alive or free of recurrence or who died without having had a recurrence were censored in the analysis of disease-free survival and recurrences. **Statistical analysis**	Postoperative CRT 4/393 *Data extracted from Sauer 2003.	

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Preop CRT 4 (1) Postop CRT 0 (0) No postop CRT 1 (<1) Type of surgery: None Preop CRT 4 (1) Postop CRT 0 (0) No postop CRT 1 (<1) Low anterior resection Preop CRT 255 (63) Postop CRT 169 (68) No postop CRT 105 (72) Intersphincteric resection Preop CRT 36 (9) Postop CRT 18 (7) No postop CRT 5 (3) Abdominoperineal resection Preop CRT 109 (27) Postop CRT 61 (25) No postop CRT 33 (23) Other Preop CRT 2 (<1) Postop CRT 0 (0) No postop CRT 0 (0) **Inclusion criteria**		Overall- and disease-free survival were calculated with the Kaplan-Meier method and the groups were compared using the log-rank test. HRs (with 95% CI) were calculated using the Cox proportional hazards model. Analysis for overall and disease-free survival and cumulative incidence rates of recurrences were conducted with intention-to-treat basis.		

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Histopathologically confirmed, resectable, rectal adenocarcinoma with the inferior margin within 16 cm from the anal verge, the tumour had to have evidence of perirectal fat (cT3-4) or lymph node involvement (cN+) by either endorectal ultrasound or computed tomography; 18-75 years of age. **Exclusion criteria** Over 75 years of age; TNM stage I tumours, distant metastases; previous cancer other than nonmelanoma skin cancer; previous CT; previous RT to the pelvis; contraindications to CRT.				
Full citation Sebag-Montefiore, D., Stephens, R. J., Steele, R., Monson, J., Grieve, R., Khanna, S., Quirke, P., Couture, J., de Metz, C., Myint, A. S., Bessell, E., Griffiths,	**Sample size** N=1350 randomised: n=674 allocated to preoperative RT; n=676 allocated to selective postoperative CRT	**Interventions** Preoperative short-course RT versus selective postoperative CRT	**Details** Randomisation and allocation concealment "Eligible consenting patients were randomly assigned to treatment groups by the MRC Clinical Trials Unit	**Results** Outcome: Overall survival (median 4 years of follow-up) Preop RT n=674, 157 events	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: unclear risk (**Details** of

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
G., Thompson, L. C., Parmar, M., Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial, The Lancet, 373, 811-820, 2009 **Ref ID** 750500 **Country/ies where the study was carried out** UK, Canada, South Africa, New Zealand **Study type** RCT (MRC CR07 and NCIC-CTG C016, trial registration number ISRCTN 28785842) **Aim of the study** To compare the effectiveness of short-course preoperative RT versus initial surgery with selective	**Characteristics** Age in years, median (range): Preop RT 65 (38-87) Selective postop CRT 65 (36-87) Male sex, n (%) Preop RT 499 (74) Selective postop CRT 482 (71) Tumour distance from anal verge, n (%) 0-5 cm Preop RT 229 (34) Selective postop CRT 217 (33) >5-10 cm Preop RT 345 (52) Selective postop CRT 337 (50) >10-15 cm Preop RT 95 (14) Selective postop CRT 112 (17) Missing Preop RT 5 Selective postop CRT 10	Preoperative RT: 25 Gy in 5 consecutive daily fractions. Selective postoperative CRT: Either a monthly (5-FU 370-425 mg/m² on days 1-5 every 28 days) or weekly (5-FU 370-425 mg/m² once per week) schedule combined with 20 mg/m² leucovorin with each 5-FU administration. Surgery: For the preoperative RT group, surgery was undertaken within 7 days of the last RT fraction. TME was encouraged although it was not mandated in the trial protocol.	by a minisation procedure, with stratification for surgeon, distance of distal tumour extent from the anal verge, and WHO performance status." No other **Details** of randomisation methods or allocation concealment reported. Blinding Follow-up/outcomes After randomisation, follow-up was done every 3 months for the first year and every 6 months for the next 3 years and once a year after that. Primary outcome as local recurrence. Secondary outcomes were overall survival, disease-free survival, local-recurrence-free survival, time to appearance of distant metastases, postoperative morbidity, quality of life and long-term complications. Local recurrence was defined as intraluminal tumour confirmed by a biopsy sample, positive	Selective postop CRT n=676, 173 events HR 0.91 95% CI 0.73 to 1.13, p=0.40 Outcome: Circumferential resection margin not involved (not defined but assumed to indicate complete resection rate R0) Preop RT 533/674 Selective postop CRT 541/676 Outcome: Health-related quality of life - SF-36 General health subscale score at 24 months* Preop RT 60.5 (n=258) Selective postop CRT 60.7 (n=261) p=0.835 Outcome: Health-related quality of life - SF-36 Physical function subscale score at 24 months* Preop RT 70.2 (n=244)	randomisation method not reported.) Allocation concealment: unclear risk (Not reported.) Performance bias Blinding of participants and personnel: high risk of bias (No blinding.) Detection bias Blinding of outcome assessment: unclear risk of bias (Not reported.) Attrition bias Incomplete outcome data: low risk of bias (Intention-to-treat analysis was performed. Relatively small numbers with missing data.) Reporting bias Selective reporting: low risk of bias (Primary and secondary outcomes reported in either this or other publication from the same trial.) Other bias Other sources of bias: None

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
postoperative CRT in people with operable rectal cancer. **Study dates** March 1998 to August 2005 **Source of funding** Medical Research Council (UK), National Cancer Institute of Canada	Type of surgery, n (%): Anterior resection Preop RT 383 (61) Selective postop CRT 409 (63) Abdominoperineal resection Preop RT 202 (32) Selective postop CRT 202 (31) Hartmann's Preop RT 21 (3) Selective postop CRT 20 (3) Other Preop RT 14 (2) Selective postop CRT 15 (2) None Preop RT 5 (1) Selective postop CRT 3 (1) Missing Preop RT 49 Selective postop CRT 27 **Inclusion criteria** Histologically confirmed adenocarcinoma of the rectum (defined as the		imaging or equivocal pelvic imaging with a raised serum CEA without distant metastases. Time to local recurrence was defined as the time from randomisation to a confirmed local recurrence. Participants without a confirmed local recurrence were censored at the time of last follow-up. Overall survival was defined as the time from randomisation to death from any cause, with survivors being censored at the time of last follow-up. Disease-free survival was defined as the time from randomisation to confirmed local recurrence, distant metastases, or death due to disease or treatment, whichever occurred first. Participants who were alive and disease free (or died od a non-rectal-cancer cause with no evidence of disease) were censored at the time of last follow-up.	Selective postop CRT 71.1 (n=250) p=0.737 Outcome: Local recurrence (median 4 years of follow-up) Preop RT n=674, 27 events Selective postop CRT n=676, 72 events HR 0.39 95% CI 0.27 to 0.58, p<0.0001 Outcome: Disease-free survival (median 4 years of follow-up) Preop RT n=674, 147 events Selective postop CRT n=676, 189 events HR 0.76 95% CI 0.62 to 0.94, p=0.013 Outcome: Operative 30-day mortality Preop RT 12/674 Selective postop CRT 15/676 Outcome: Operative 60-day mortality Preop RT 17/674	**Other information** None

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	dital tumour <15 cm from the anal verge) with no evidence of metastases (identified by liver ultrasound or computed tomography scan and chest radiograph); primary tumour deemed resectable (defined as not fixed to the pelvis and that complete excision was feasible, if operability could not be established by digital examination, examination under general anaesthesia supplemented when appropriate by pelvic computed tomography or MRI scan or by endoluminal ultrasound was recommended); regarded sufficiently fit to receive all treatments (no age limit). **Exclusion criteria** Previous or present malignant disease that likely to interfere with protocol comparisons.		Health-related quality of life was measured using Medical Outcomes Study Short-Form 36-item questionnaire (SF-36), scale range 0 to 100, higher score indicating better quality of life. (Data extracted from Stephens 2010.) **Statistical analysis** Intention-to-treat analysis was done for all outcomes reported. Time-to-event data was analysed by Kaplan-Meier method and compared with a 2-sided log rank test. HRs were calculated.	Selective postoperative CRT 20/676 *Data extracted from Stephens 2010.	

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Stephens, R. J., Thompson, L. C., Quirke, P., Steele, R., Grieve, R., Couture, J., Griffiths, G. O., Sebag-Montefiore, D., Impact of short-course preoperative radiotherapy for rectal cancer on patients' quality of life: Data from the Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 randomized clinical trial, Journal of Clinical Oncology, 28, 4233-4239, 2010 **Ref ID** 750799 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates**	**Sample size** See Sebag-Montefiore 2009. **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding					
Full citation Taher, A. N., El-Baradie, M. M., Nasr, A. M., Khorshid, O., Morsi, A., Hamza, M. R., Mokhtar, N., Ezzat, S., Locally advanced rectal carcinoma: preoperative radiotherapy versus postoperative chemoradiation, 10-year follow-up Results of a randomized clinical study, Journal of the Egyptian National Cancer Institute, 18, 233-243, 2006 **Ref ID** 750926 **Country/ies where the study was carried out** Egypt **Study type** RCT **Aim of the study** To compare local recurrence and survival between preoperative RT (+- postoperative CT) and postoperative	**Sample size** N=50 randomised: n=24 preoperative RT; n=26 postoperative CRT **Characteristics** Age in years, median (range): Preop RT 40 (15-59) Postop CRT 31.5 (20-55) Male sex, n(%) Preop RT 18 (75) Postop CRT 9 (35) Pathological Dukes' Stage, n (%): B Preop RT 8 (33) Postop CRT 5 (19) C Preop RT 16 (67) Postop CRT 21 (81) Mobility, n (%) Mobile Preop RT 4 (17) Postop CRT 19 (73)	**Interventions** Preoperative RT (with or without postoperative CT) versus postoperative CRT RT: 6MV linear accelerator was used. An isocentric technique was adopted at source-axis distance of 100 cm. All participants were treated in the prone position with a full bladder to displace the small bowel anteriorly and superiorly and to reduce the postero-anterior separation in obese patients. Irradiation was given in a dose of 50Gy/5 weeks for the postoperative group and 46Gy/4.5 weeks for the preoperative group. All the participants were treated with 2Gy/fraction, treating 5 days per week. Surgery: For preoperative RT group, surgery was performed 4 weeks after completion of irradiation. Abdominoperineal resection, posterior pelvic exenteration or low anterior	**Details** Randomisation and allocation concealment **Details** about randomisation not reported. Allocation concealment done "using closed envelope method". Blinding No blinding. Follow-up/outcomes During RT, all participants were evaluated weekly via RTOG/EORTC acute radiation morbidity scoring schema. In the preoperative RT group assessment of tumour response was done weekly during RT. Postoperative complications were reported. Chemotherapy-related toxicity was evaluated using the World Health Organisation (WHO) grading system. Clinical examination, complete blood count, liver and kidney function	**Results** Outcome: Locoregional recurrence (median follow-up time 62.5 months) Preop RT 1/24 Postop CRT 2/26	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: unclear risk of bias (Randomisation details not reported.) Allocation concealment: unclear risk of bias ("Closed envelope method" was used, no other details reported.) Performance bias Blinding of participants and personnel: high risk of bias (No blinding.) Detection bias Blinding of outcome assessment: high risk of bias (No blinding.) Attrition bias Incomplete outcome data: unclear risk of bias (Not reported if intention-to-treat analysis was done. No reporting of losses to follow-up.) Reporting bias

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
adjuvant CRT in people with locally advanced rectal cancer and to define prognostic parameters that can help in the choice of the optimum treatment modality. **Study dates** December 1994 to January 1999. **Source of funding** None reported.	Limited mobility Preop RT 20 (83) Postop CRT 7 (27) Performance status, n (%) I Preop RT 5 (20) Postop CRT 4 (15) II Preop RT 19 (80) Postop CRT 22 (85) Surgical tehcnique, n/N (%): Abdominoperineal resection/exentration Preop RT 19/26 (73) Postop CRT 15/16 (94%) Lower anterior resection Preop RT 7 (27) Postop CRT 1/16 (7) **Inclusion criteria** Previously untreated locally advanced resectable low rectal carcinoma. **Exclusion criteria**	resection were performed depending on the site and extent of the tumour. CT: For the postoperative CRT group, CT, as radio-sensitiser, was administered during the first 3 days of the first and last week of postoperative irradiation in the form of leucovorin (300 mg/m² as a short IV infusion over 1 hour followed in half an hour by 5-FU in a dose of 350 mg/m² as short IV infusion over 4-6 hours). Adjuvant CT was continued immediately after the end of irradiation if complete blood picture and laboratory investigations were satisfactory. Adjuvant CT consisted of 5-FU as 600 mg/m² short IV infusion weekly for 48 weeks in addition to levamisole tablet (1 tablet 3 times a day for 3 days every other week, also for 48 weeks). For the preoperative RT group, the same adjuvant CT was given 4-6	tests were done before each cycle of CT. Participants were followed up monthly for the first 6 months after completion of treatment and every 2 to 3 months for the following 2 years and every 6 months after that. The participants were score for both local and systemic failures and late treatment complications using the RTOG/EORTC late radiation morbidity scoring schema. The following evaluations were done: clinical examination, CEA, periodic chest X-ray, abdominopelvic ultrasound scan and pelvic computed tomography scan. Locoregional and/or distant failure were diagnosed clinically and radiologically and histopathological confirmation was done. **Statistical analysis** Survival analysis was done using Kaplan-Meier method and groups were		Selective reporting: low risk of bias (Main endpoints were reported.) Other bias Other sources of bias: None **Other information** The paper reports the percentage of overall survival and disease-free survival at 10 years and their log-rank p-values, however, no HRs or number of events are reported (and cannot be calculated from the Kaplan-Meier curve), therefore, there is insufficient data for analysis.

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
	None reported.	weeks after surgery for participants with pathologically positive lymph nodes and/or tumour had reached the pre-fatal fat.	compared using the log-rank test.		
Full citation Wiltink, L. M., Chen, T. Y. T., Nout, R. A., Kranenbarg, E. M. K., Fiocco, M., Laurberg, S., Van De Velde, C. J. H., Marijnen, C. A. M., Health-related quality of life 14 years after preoperative short-term radiotherapy and total mesorectal excision for rectal cancer: Report of a multicenter randomised trial, European Journal of Cancer, 50, 2390-2398, 2014 **Ref ID** 751545 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates**	**Sample size** See van Gijn 2011. **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations** **Other information**

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding					
Full citation Wang F, Fan W, Peng J, Lu Z, Pan Z, Li L, Gao Y, Li H, Chen G, Wu X, Ding P, Zeng Z, Wan D. Total mesorectal excision with or without preoperative chemoradiotherapy for resectable mid/low rectal cancer: a long-term analysis of a prospective, single-center, randomized trial. Cancer Commun (Lond). 2018 Dec 20;38(1):73. **Ref ID** 983081 **Country/ies where the study was carried out** **Study type** **Aim of the study** **Study dates** **Source of funding**	**Sample size** See Fan 2015	**Interventions**	**Details**	**Results**	**Limitations** **Other information** None

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments

Full citation
Zhang, X., Ma, H., Ren, H., Deng, H., Wang, X., Shi, F., Prospective randomized trial of surgery combined with preoperative and postoperative radiotherapy for rectal carcinoma, Academic Journal of Xi'an Jiaotong University, 20, 134-137, 2008
Ref ID
751800
Country/ies where the study was carried out
China
Study type
RCT
 	
Aim of the study
To assess the effect of surgery combined with preoperative and postoperative RT in rectal carcinoma.
 	
Study dates
October 1999 to January 2002
 	
Source of funding
	Sample size
	N=260 randomised:
	n=92 allocated to preoperative RT + postoperative RT;
	n=98 allocated to postoperative RT;
	n=70 allocated to surgery alone
	
	Characteristics
	Male sex, n/n:
	Preop RT + postop RT 51/92
	Postop RT 54/98
	Surgery alone 39/70
	
	Age in years, median:
	Preop RT + postop RT 57
	Postop RT 61
	Surgery alone 56
	
	Stage II cancer, n/n:
	Preop RT + postop RT 40/92
	Postop RT 41/98
	Surgery alone 36/70
	
	Stage III cancer, n/n:
	Preop RT + postop RT 52/92
		Interventions
		Preoperative RT + postoperative RT ("sandwich group") versus postoperative RT versus surgery alone
		
		Preoperative RT: Continuous hyper-fractionation accelerated RT by 6 MV or 10 MV X-ray. 15 Gy in 6 fractions over 3 days. The upper borders of anterior and posterior fields were located at the lower edge of 5th lumbar vertebrae and lateral borders were 2 cm outside of the pelvis. The lower border of anterior field was the lower border of obturator, and the lower border of posterior field was 1-1.5 cm under the anus.
		Surgery: Radical operation (not defined further). For the "sandwich group" performed on the 4th day (after 3 days of preoperative RT).
		Postoperative RT: In the "sandwich group" 3-4 weeks after surgery, 35 Gy over 3.5 weeks for Duke's
			Details
			Randomisation and allocation concealment
			Details not reported.
			
			Blinding
			Not reported but presumably no blinding for outcome assessor (participants cannot be blinded).
			
			Follow-up/outcomes
			Follow-up strategy, interval, methods etc. not reported. Outcomes reported include local relapse, distant metastasis, survival at 3 and 5 years, and complications.
			
			Statistical analysis
			Kaplan-Meier analysis done for survival and relapse data, differences between groups tested by log-rank test.
				Results
				Outcome: Overall survival (median follow-up time not reported)
				Preop RT + postop RT n=92, 29 events
				Postop RT n=98, 44 events
				Surgery alone n=70, 41 events
				p=0.003
				
				Outcome: Local relapse (median follow-up time not reported)
				Preop RT + postop RT 5/92
				Postop RT 16/98
				Surgery alone 45/70
					Limitations
					Cochrane risk of bias tool
					Selection bias
					Random sequence generation: unclear risk (Not reported.)
					Allocation concealment: unclear risk (Not reported.)
					Performance bias
					Blinding of participants and personnel: high risk (No blinding.)
					Detection bias
					Blinding of outcome assessment: unclear risk (Not reported but presumably no blinding.)
					Attrition bias
					Incomplete outcome data: unclear risk (No mention of intention-to-treat analysis. Around 5 participants in each group were lost to follow-up and treated as deaths.)
					Reporting bias
					Selective reporting: high risk (Reporting is very poor. No

Study Details	Participants	Interventions	Methods	Outcomes and Results	Comments
None reported.	Postop RT 57/98 Surgery alone 34/70 **Inclusion criteria** Duke's stage B (II) or C (III) rectal cancer; diagnosed by pathology; age range 28 to 70 years; Karnofsky Performance Status >=70; blood routine (?) test and urine routine (?) test normal; no heart, liver or kidney disease; surgery and RT can be tolerated; no other treatment received. **Exclusion criteria** None reported.	B and 40 Gy over 4 weeks for Duke's C (same fields as for preoperative RT). In the postoperative RT group the same fields were used, 50 Gy over 5 weeks.			**Details** given about methods, follow-up etc. Median follow-up time is not reported but follow-up was presumably done until May 2006, that is for 4-7 years from enrolment. There is a discrepancy between the chi² and p-value **Results** reported in the abstract and in the **Results** section. In the abstract it says the enrolment period was from 1990 to 2002 but in the text it says from 1999 to 2002 in two separate places so assumed to be from 1999 to 2002.) Other bias Other sources of bias: Generally, this publication raises a lot of questions and concerns due to poor reporting. **Other information** None

1 *ALT: alanine transaminase; AST: aspartate aminotransferase; c: stage assessed before treatment; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; cGy:*
2 *centigray unit; CI: confidence interval; CRM: circumferential resection margin; CRT: chemoradiotherapy; CT: chemotherapy; ECOG: Eastern Cooperative Group; EORTC:*
3 *European Organisation for the Research and Treatment of Cancer; GCR-3: Grupo Cancer de Recto 3 trial; Gy: Gray unit; IQR: interquartile range; HR: hazard ratio; IQR:*

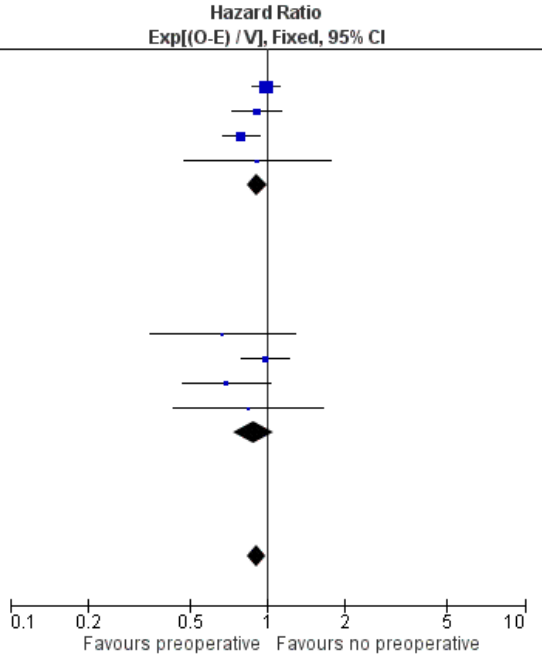
interquartile range; IV: intravenous; kV: kilovolt; L: litre; MRC: Medical Research Council; MRI: magnetic resonance imaging; MV: megavolt; N: number of participants; N0-2: nodal stage; NCIC: National Cancer Institute of Canada; NSABP R-03: National Surgical Adjuvant Breast and Bowel Project R03 trial; p: stage determined by histopathological examination; preop: preoperative; postop: postoperative; QLQ-C30: Quality of Life Questionnaire Core 30 Items; R+: positive resection margin; R0: complete resection; R2: macroscopic positive resection margin; RCT: randomised controlled trial; RT: radiotherapy; RTOG: Radiation Therapy Oncology Group; SD: standard deviation; SE: standard error; SF-36: 36 Item Short For m Survey; T: tumour stage; TME: total mesorectal excision; TNM: cancer classification system, stading for tumour, node, metastasis; TROG 01.04: Trans-Tasman Radiation Oncology Group trial 01.04; u: stage determined by ultrasound or endosonography; VAS: visual analogue scale; WHO: World Health Organization; x: staging cannot be assessed; y: stage assessed after neoadjuvant therapy; yp: pathological stage after neoadjuvant treatment; 5-FU: fluorouracil.

Appendix E – Forest plots

Forest plots for review question: What is the effectiveness of preoperative radiotherapy and chemoradiotherapy for rectal cancer?

Figure 2: Comparison 1 - Preoperative (chemo)radiotherapy versus no preoperative (chemo)radiotherapy for rectal cancer – Overall survival (median 1.5 to 11.6 years of follow-up, event is death from any cause)

Study or Subgroup	Preoperative therapy Events	Total	No preoperative therapy Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.1.1 Preoperative (chemo)radiotherapy versus surgery alone (median 3.2 to 11.6 years of follow-up)								
Dutch TME trial (van Gijn 2011)	485	897	488	908	-2.75	243.25	40.6%	0.99 [0.87, 1.12]
MRC CR07 (Sebag-Montefiore 2009) (1)	157	674	173	676	-7.59	80.49	13.4%	0.91 [0.73, 1.13]
Swedish RCT 1997 (2)	0	454	0	454	-32.83	139.29	23.3%	0.79 [0.67, 0.93]
Wang 2018 (3)	15	90	13	94	-0.84	8.97	1.5%	0.91 [0.47, 1.75]
Subtotal (95% CI)		**2115**		**2132**			**78.8%**	**0.91 [0.83, 1.00]**
Total events	657		674					
Heterogeneity: Chi² = 4.46, df = 3 (P = 0.22); I² = 33%								
Test for overall effect: Z = 2.03 (P = 0.04)								
1.1.2 Preoperative (chemo)radiotherapy versus postoperative (chemo)radiotherapy (median 1.5 to 11.2 years of follow-up)								
Atif 2012	14	50	26	50	-3.64	9.1	1.5%	0.67 [0.35, 1.28]
CAO/ARO/AIO-94 (Sauer 2012) (4)	0	404	0	395	-1.71	84.54	14.1%	0.98 [0.79, 1.21]
NSABP R03 (Roh 2009) (5)	44	123	62	131	-9.15	24.94	4.2%	0.69 [0.47, 1.03]
Park 2011 (6)	18	107	16	113	-1.44	8.47	1.4%	0.84 [0.43, 1.65]
Subtotal (95% CI)		**684**		**689**			**21.2%**	**0.88 [0.74, 1.05]**
Total events	76		104					
Heterogeneity: Chi² = 3.09, df = 3 (P = 0.38); I² = 3%								
Test for overall effect: Z = 1.41 (P = 0.16)								
Total (95% CI)		**2799**		**2821**			**100.0%**	**0.90 [0.84, 0.98]**
Total events	733		778					
Heterogeneity: Chi² = 7.66, df = 7 (P = 0.36); I² = 9%								
Test for overall effect: Z = 2.45 (P = 0.01)								
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%								



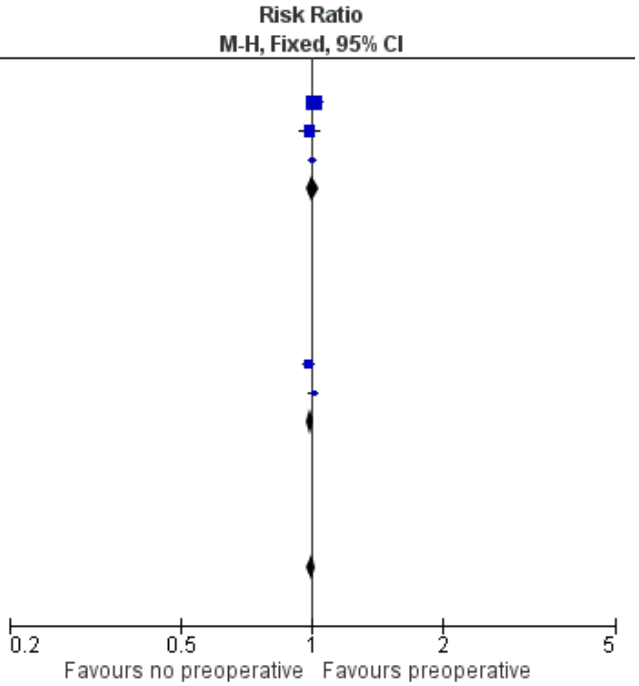
Footnotes

(1) Preoperative short-course radiotherapy. Less than 10% in the "surgery alone" group received postoperative (chemo)radiotherapy.
(2) Number of events not reported.
(3) Preoperative chemoradiotherapy. "Surgery alone" group received selective postoperative chemotherapy (Preliminary data reported in Fan 2015)
(4) Preoperative chemoradiotherapy versus postoperative chemoradiotherapy. Number of events not reported.
(5) Preoperative chemoradiotherapy (and selective postoperative chemotherapy) versus postoperative chemoradiotherapy.
(6) Preoperative chemoradiotherapy versus postoperative chemoradiotherapy, in addition both groups received postoperative adjuvant chemotherapy.

CI: confidence interval; O-E: observed minus expected; V: variance

Figure 3: Comparison 1: Preoperative (chemo)radiotherapy versus no preoperative (chemo)radiotherapy for rectal cancer – Complete (R0) resection rate

Study or Subgroup	Preoperative therapy Events	Total	No preoperative therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Preoperative (chemo)radiotherapy versus surgery alone						
Dutch TME trial (Peeters 2007)	729	897	729	908	39.1%	1.01 [0.97, 1.06]
MRC CR07 (Sebag-Montefiore 2009) (1)	533	674	541	676	29.2%	0.99 [0.94, 1.04]
Wang 2018 (2)	90	90	94	94	5.0%	1.00 [0.98, 1.02]
Subtotal (95% CI)		**1661**		**1678**	**73.3%**	**1.00 [0.97, 1.03]**
Total events	1352		1364			
Heterogeneity: Chi² = 0.48, df = 2 (P = 0.79); I² = 0%						
Test for overall effect: Z = 0.11 (P = 0.91)						
1.2.2 Preoperative (chemo)radiotherapy versus postoperative (chemo)radiotherapy						
CAO/ARO/AIO-94 (Sauer 2003) (3)	387	406	381	393	20.9%	0.98 [0.96, 1.01]
Park 2011 (4)	105	105	112	113	5.9%	1.01 [0.98, 1.03]
Subtotal (95% CI)		**511**		**506**	**26.7%**	**0.99 [0.97, 1.01]**
Total events	492		493			
Heterogeneity: Chi² = 2.59, df = 1 (P = 0.11); I² = 61%						
Test for overall effect: Z = 0.99 (P = 0.32)						
Total (95% CI)		**2172**		**2184**	**100.0%**	**1.00 [0.97, 1.02]**
Total events	1844		1857			
Heterogeneity: Chi² = 2.32, df = 4 (P = 0.68); I² = 0%						
Test for overall effect: Z = 0.13 (P = 0.89)						
Test for subgroup differences: Chi² = 0.43, df = 1 (P = 0.51), I² = 0%						



Footnotes

(1) Preoperative short-course radiotherapy. Less than 10% in the "surgery alone" group received postoperative (chemo)radiotherapy.

(2) Preoperative chemoradiotherapy. "Surgery alone" group received selective postoperative chemotherapy. (Preliminary data reported in Fan 2015)

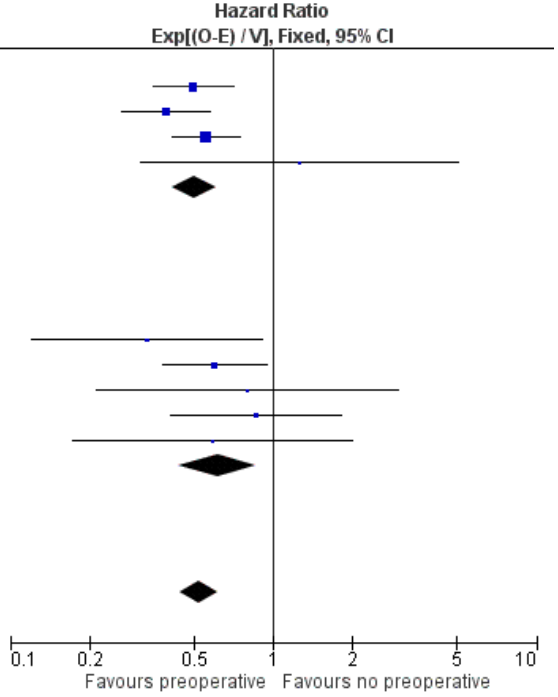
(3) Preoperative chemoradiotherapy versus postoperative chemoradiotherapy.

(4) Preoperative chemoradiotherapy versus postoperative chemoradiotherapy, in addition both groups received postoperative adjuvant chemotherapy.

CI: confidence interval; M-H: Mantel-Haenszel method

Figure 4: Comparison 1: Preoperative (chemo)radiotherapy versus no preoperative (chemo)radiotherapy for rectal cancer – Local recurrence-free survival (median 1.5 to 11.6 years of follow-up, event is local recurrence)

Study or Subgroup	Preoperative therapy Events	Total	No preoperative therapy Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.6.1 Preoperative (chemo)radiotherapy versus surgery alone (median 3.2 to 11.6 years of follow-up)								
Dutch TME trial (van Gijn 2011)	46	873	97	875	-21.88	31.2	22.7%	0.50 [0.35, 0.70]
MRC CR07 (Sebag-Montefiore 2009) (1)	27	674	72	676	-24.75	26.28	19.1%	0.39 [0.27, 0.57]
Swedish RCT 1997	63	553	150	557	-26.08	44.37	32.2%	0.56 [0.41, 0.75]
Wang 2018 (2)	5	90	4	94	0.46	2	1.5%	1.26 [0.31, 5.03]
Subtotal (95% CI)		**2190**		**2202**			**75.4%**	**0.50 [0.41, 0.60]**
Total events	141		323					
Heterogeneity: Chi² = 3.82, df = 3 (P = 0.28); I² = 22%								
Test for overall effect: Z = 7.09 (P < 0.00001)								
1.6.2 Preoperative (chemo)radiotherapy versus postoperative (chemo)radiotherapy (median 1.5 to 11.2 years of follow-up)								
Atif 2012	5	50	16	50	-4.21	3.81	2.8%	0.33 [0.12, 0.90]
CAO/ARO/AIO-94 (Sauer 2012) (3)	23	397	37	393	-9.35	18.3	13.3%	0.60 [0.38, 0.95]
Kacar 2009 (4)	4	26	5	25	-0.51	2.22	1.6%	0.79 [0.21, 2.96]
NSABP R03 (Roh 2009) (5)	13	123	15	131	-1.05	6.97	5.1%	0.86 [0.41, 1.81]
Park 2011 (6)	4	107	7	113	-1.36	2.55	1.9%	0.59 [0.17, 2.00]
Subtotal (95% CI)		**703**		**712**			**24.6%**	**0.61 [0.44, 0.86]**
Total events	49		80					
Heterogeneity: Chi² = 2.41, df = 4 (P = 0.66); I² = 0%								
Test for overall effect: Z = 2.83 (P = 0.005)								
Total (95% CI)		**2893**		**2914**			**100.0%**	**0.52 [0.44, 0.62]**
Total events	190		403					
Heterogeneity: Chi² = 7.34, df = 8 (P = 0.50); I² = 0%								
Test for overall effect: Z = 7.56 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.11, df = 1 (P = 0.29), I² = 10.2%								

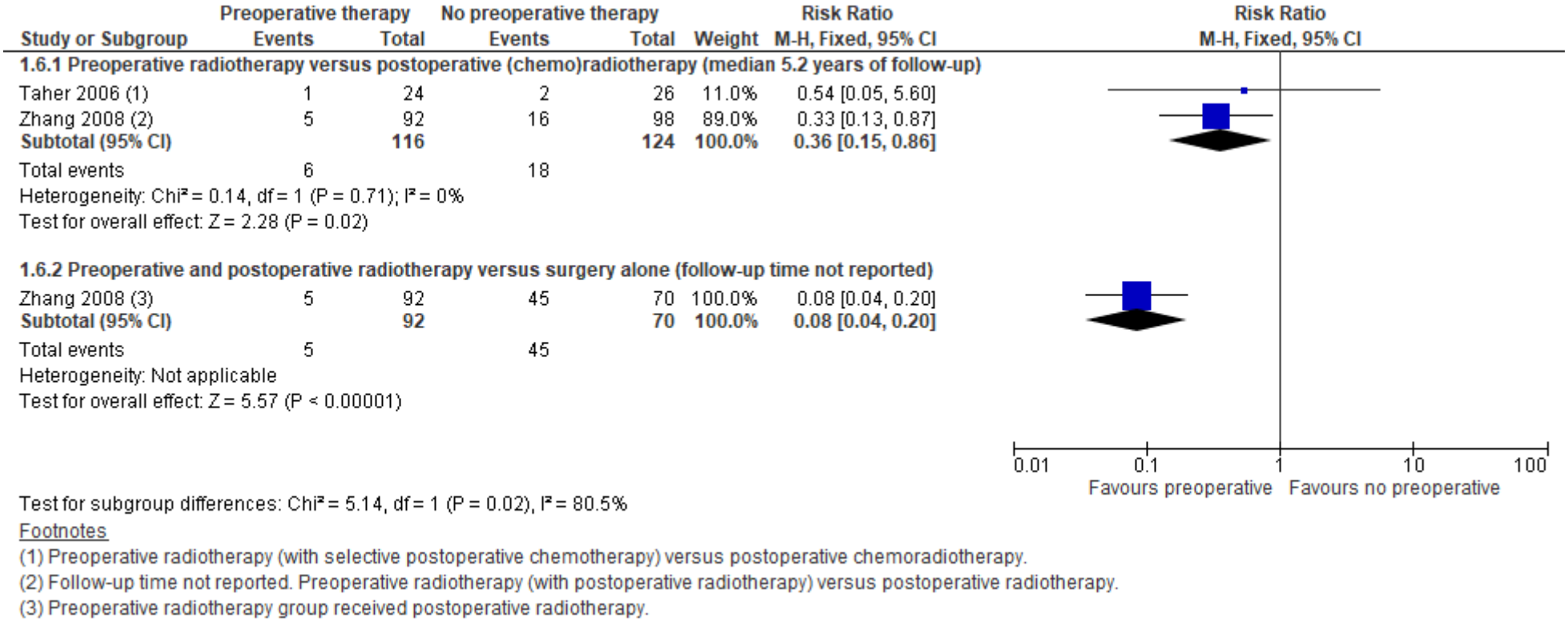


Footnotes

(1) Preoperative short-course radiotherapy. Less than 10% in the "surgery alone" group received postoperative (chemo)radiotherapy.
(2) Preoperative chemoradiotherapy. "Surgery alone" group received selective postoperative chemotherapy. (Preliminary data reported in Fan 2015)
(3) Preoperative chemoradiotherapy versus postoperative chemoradiotherapy.
(4) Preoperative chemoradiotherapy versus postoperative chemoradiotherapy.
(5) Preoperative chemoradiotherapy (and selective postoperative chemotherapy) versus postoperative chemoradiotherapy.
(6) Preoperative chemoradiotherapy versus postoperative chemoradiotherapy, in addition both groups received postoperative adjuvant chemotherapy.

CI: confidence interval; O-E: observed minus expected; V: variance

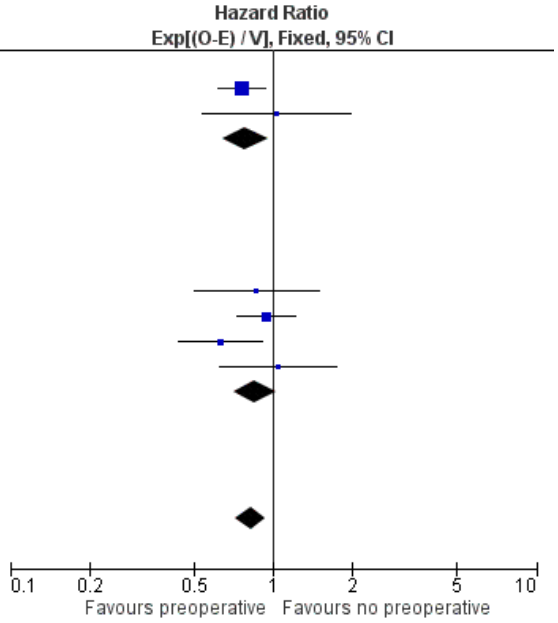
Figure 5: Comparison 1: Preoperative (chemo)radiotherapy versus no preoperative (chemo)radiotherapy for rectal cancer – Local recurrence rate (median 5.2 years of follow-up)



CI: confidence interval; M-H: Mantel-Haenszel method

Figure 6: Comparison 1: Preoperative (chemo)radiotherapy versus no preoperative (chemo)radiotherapy for rectal cancer – Disease-free survival (median 1.5 to 11.2 years of follow-up, event is local or distant failure or death)

Study or Subgroup	Preoperative therapy Events	Total	No preoperative therapy Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.8.1 Preoperative (chemo)radiotherapy versus surgery alone (median 3.2 to 4 years of follow-up)								
MRC CR07 (Sebag-Montefiore 2009) (1)	147	674	189	676	-24.35	88.72	41.2%	0.76 [0.62, 0.94]
Wang 2018 (2)	14	90	14	94	0.27	9.22	4.3%	1.03 [0.54, 1.96]
Subtotal (95% CI)		**764**		**770**			**45.5%**	**0.78 [0.64, 0.95]**
Total events	161		203					
Heterogeneity: Chi² = 0.77, df = 1 (P = 0.38); I² = 0%								
Test for overall effect: Z = 2.43 (P = 0.01)								
1.8.2 Preoperative (chemo)radiotherapy versus postoperative (chemo)radiotherapy (median 1.5 to 11.2 years of follow-up)								
Atif 2012	22	50	31	50	-1.92	12.87	6.0%	0.86 [0.50, 1.49]
CAO/ARO/AIO-94 (Sauer 2012) (3)	0	434	0	395	-3.72	60.17	27.9%	0.94 [0.73, 1.21]
NSABP R03 (Roh 2009) (4)	51	123	74	131	-13.74	29.63	13.8%	0.63 [0.44, 0.90]
Park 2011 (5)	30	107	29	113	0.65	14.75	6.8%	1.05 [0.63, 1.74]
Subtotal (95% CI)		**714**		**689**			**54.5%**	**0.85 [0.71, 1.02]**
Total events	103		134					
Heterogeneity: Chi² = 3.93, df = 3 (P = 0.27); I² = 24%								
Test for overall effect: Z = 1.73 (P = 0.08)								
Total (95% CI)		**1478**		**1459**			**100.0%**	**0.82 [0.72, 0.94]**
Total events	264		337					
Heterogeneity: Chi² = 5.10, df = 5 (P = 0.40); I² = 2%								
Test for overall effect: Z = 2.92 (P = 0.004)								
Test for subgroup differences: Chi² = 0.40, df = 1 (P = 0.53), I² = 0%								

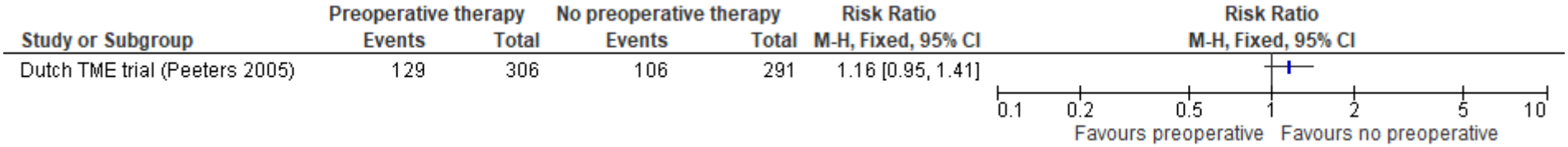


Footnotes

(1) Preoperative short-course radiotherapy. Less than 10% in the "surgery alone" group received postoperative (chemo)radiotherapy.
(2) Preoperative chemoradiotherapy. "Surgery alone" group received selective postoperative chemotherapy. (Preliminary data reported in Fan 2015)
(3) Number of events not reported. Preoperative chemoradiotherapy versus postoperative chemoradiotherapy.
(4) Preoperative chemoradiotherapy (and selective postoperative chemotherapy) versus postoperative chemoradiotherapy.
(5) Preoperative chemoradiotherapy versus postoperative chemoradiotherapy, in addition both groups received postoperative adjuvant chemotherapy.

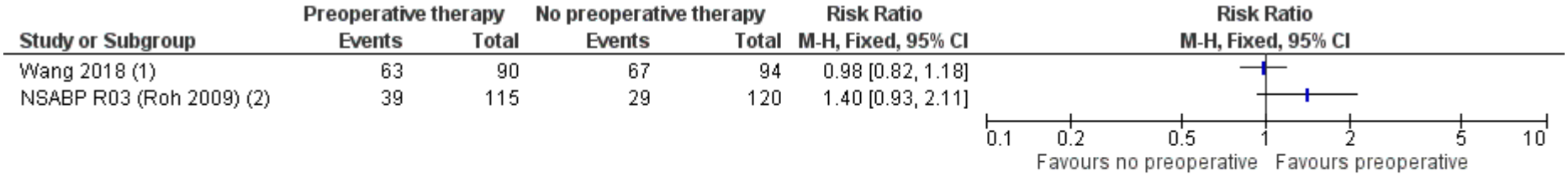
CI: confidence interval; O-E: observed minus expected; V: variance

Figure 7: Comparison 1: Preoperative (chemo)radiotherapy versus no preoperative (chemo)radiotherapy for rectal cancer – Permanent stoma (median 5 years of follow-up)



CI: confidence interval; M-H: Mantel-Haenszel method

Figure 8: Comparison 1: Preoperative (chemo)radiotherapy versus no preoperative (chemo)radiotherapy for rectal cancer – Sphincter preservation (at 5 years)

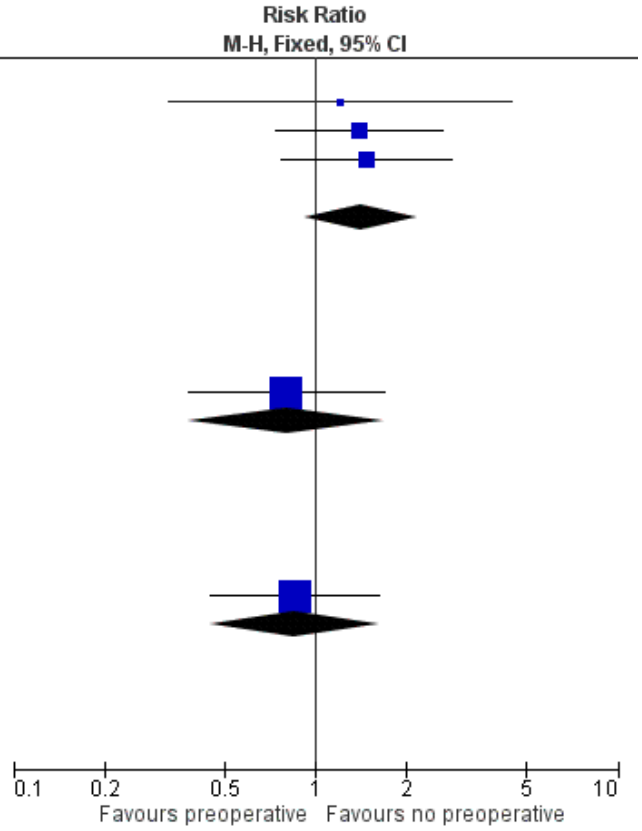


Footnotes
(1) Preoperative chemoradiotherapy versus "surgery alone" group received selective postoperative chemotherapy. (Preliminary data reported in Fan 2015.)
(2) Preoperative chemoradiotherapy (and selective postoperative chemotherapy) versus postoperative chemoradiotherapy (at 5 years)

CI: confidence interval; M-H: Mantel-Haenszel method

Figure 9: Comparison 1: Preoperative (chemo)radiotherapy versus no preoperative (chemo)radiotherapy for rectal cancer – Treatment-related mortality

Study or Subgroup	Preoperative therapy Events	Total	No preoperative therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.11.1 Treatment-related mortality (preoperative or postoperative)						
CAO/ARO/AIO-94 (Sauer 2003) (1)	5	406	4	393	11.6%	1.21 [0.33, 4.47]
Dutch TME trial (van Gijn 2011)	22	897	16	908	45.5%	1.39 [0.74, 2.63]
Swedish RCT 1997	22	573	15	574	42.9%	1.47 [0.77, 2.80]
Wang 2018 (2)	0	90	0	94		Not estimable
Subtotal (95% CI)		**1966**		**1969**	**100.0%**	**1.40 [0.91, 2.15]**
Total events	49		35			
Heterogeneity: Chi² = 0.07, df = 2 (P = 0.97); I² = 0%						
Test for overall effect: Z = 1.55 (P = 0.12)						
1.11.2 30-day operative mortality						
MRC CR07 (Sebag-Montefiore 2009) (3)	12	674	15	676	100.0%	0.80 [0.38, 1.70]
Subtotal (95% CI)		**674**		**676**	**100.0%**	**0.80 [0.38, 1.70]**
Total events	12		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
1.11.3 60-day operative mortality						
MRC CR07 (Sebag-Montefiore 2009) (4)	17	674	20	676	100.0%	0.85 [0.45, 1.61]
Subtotal (95% CI)		**674**		**676**	**100.0%**	**0.85 [0.45, 1.61]**
Total events	17		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.49 (P = 0.62)						



Test for subgroup differences: Chi² = 2.53, df = 2 (P = 0.28), I² = 20.9%

Footnotes

(1) Preoperative chemoradiotherapy versus postoperative chemoradiotherapy.

(2) Risk ratio not estimable because there were no events. Preoperative chemoradiotherapy. "Surgery alone" group received selective postoperative chemotherapy. (Preliminary data reported...

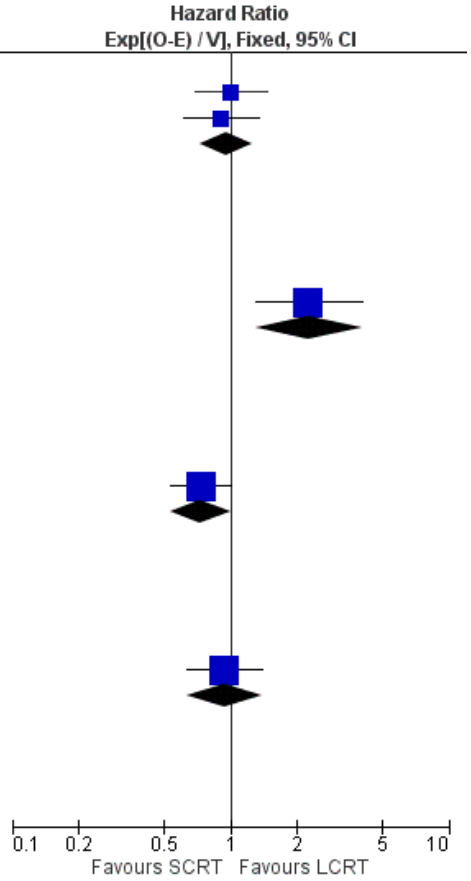
(3) Preoperative short-course radiotherapy.

(4) Preoperative short-course radiotherapy.

CI: confidence interval; M-H: Mantel-Haenszel method

Figure 10: Comparison 2: Short-course radiotherapy versus long-course radiotherapy with or without chemotherapy – Overall survival (median 2.9 to 5.9 years of follow-up, event is death from any cause)

Study or Subgroup	SCRT Events	SCRT Total	LCRT Events	LCRT Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
2.1.1 Short-course radiotherapy with immediate surgery versus long-course (chemo)radiotherapy (median 4 to 5.9 years of follow-up)								
Polish trial 1 (Bujko 2006) (1)	54	155	53	157	0.26	26.39	51.7%	1.01 [0.69, 1.48]
TROG 01.04 (Ngan 2012) (2)	47	162	52	161	-2.46	24.69	48.3%	0.91 [0.61, 1.34]
Subtotal (95% CI)		**317**		**318**			**100.0%**	**0.96 [0.73, 1.26]**
Total events	101		105					
Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%								
Test for overall effect: Z = 0.31 (P = 0.76)								
2.1.2 Short-course radiotherapy with delayed surgery versus long-course chemoradiotherapy (median 5 years of follow-up)								
Lithuanian trial (Kairevice 2017) (3)	0	75	0	75	10.03	12.16	100.0%	2.28 [1.30, 4.00]
Subtotal (95% CI)		**75**		**75**			**100.0%**	**2.28 [1.30, 4.00]**
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.88 (P = 0.004)								
2.1.3 Short-course radiotherapy with chemotherapy versus long-course chemoradiotherapy (median 2.9 years of follow-up)								
Polish trial 2 (Bujko 2016) (4)	64	261	84	254	-11.63	36.95	100.0%	0.73 [0.53, 1.01]
Subtotal (95% CI)		**261**		**254**			**100.0%**	**0.73 [0.53, 1.01]**
Total events	64		84					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.91 (P = 0.06)								
2.1.4 Short-course radiotherapy immediate surgery versus long course radiotherapy								
Stockholm III trial (Erlandsson 2017) (5)	51	129	49	128	-1.55	24.1	100.0%	0.94 [0.63, 1.40]
Subtotal (95% CI)		**129**		**128**			**100.0%**	**0.94 [0.63, 1.40]**
Total events	51		49					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.32 (P = 0.75)								



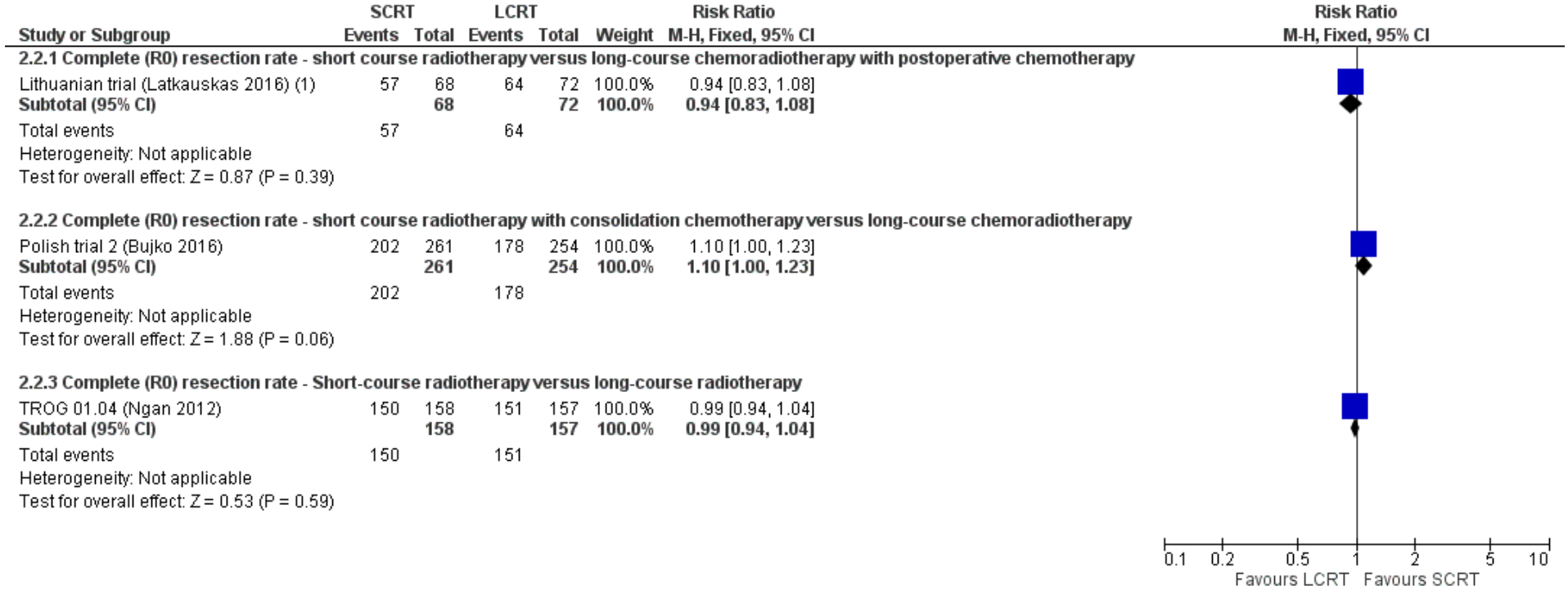
Test for subgroup differences: Chi² = 11.90, df = 3 (P = 0.008), I² = 74.8%

Footnotes

(1) Short-course radiotherapy (no chemotherapy) versus long-course chemoradiotherapy. Both groups received selective postoperative chemotherapy.
(2) Short-course radiotherapy versus long-course radiotherapy (no chemotherapy). Both groups received postoperative chemotherapy.
(3) Number of events not reported. Short-course radiotherapy (no chemotherapy) versus long-course chemoradiotherapy with postoperative chemotherapy.
(4) Both groups received selective popstoperative chemotherapy.
(5) Study also reported events for the comparison short-course radiotherapy with delayed surgery vs long-course radiotherapy but no HR (95% CI) reported

CI: confidence interval; LCRT: long-course radiotherapy; O-E: observed minus expected; SCRT: short-course radiotherapy; V: variance

Figure 11: Comparison 2: Short-course radiotherapy versus long-course radiotherapy with or without chemotherapy – Complete (R0) resection rate

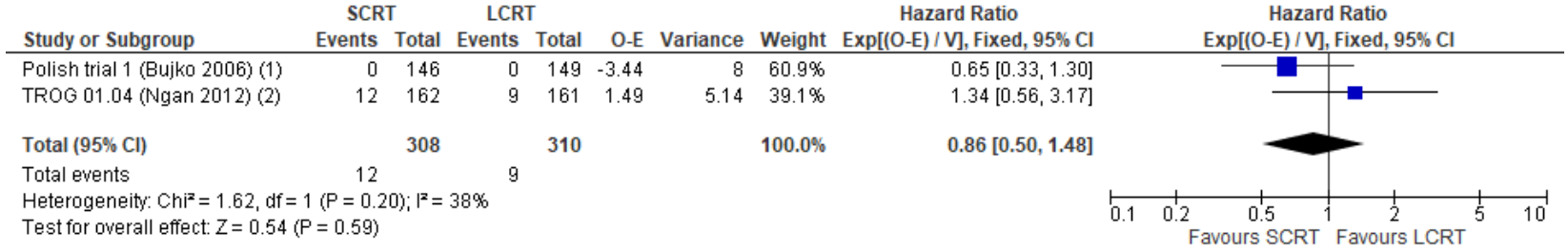


Footnotes

(1) Short-course radiotherapy (no chemotherapy) versus long-course chemoradiotherapy with postoperative chemotherapy.

CI: confidence interval; LCRT: long-course radiotherapy; M-H: Mantel-Haenszel method; SCRT: short-course radiotherapy

Figure 12: Comparison 2: Short-course radiotherapy versus long-course radiotherapy with or without chemotherapy – Local recurrence-free survival (median 4 to 5.9 years of follow-up, event is local reccurence)



Footnotes

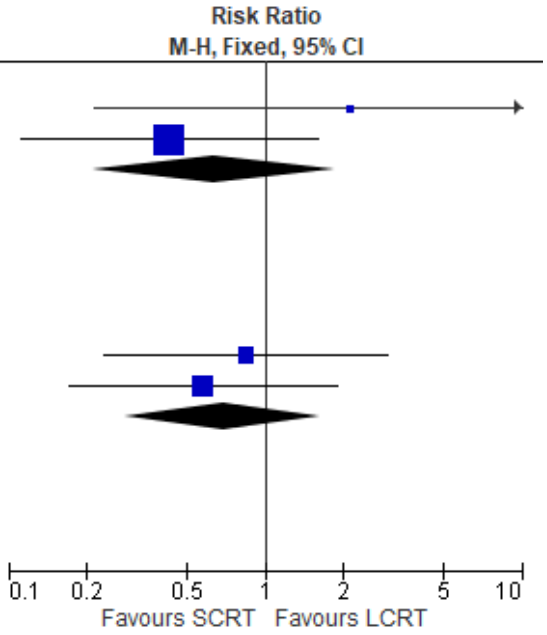
(1) Number of events not reported. Short-course radiotherapy (no chemotherapy) versus long-course chemoradiotherapy. Both groups received selective postoperative...

(2) Short-course radiotherapy versus long-course radiotherapy (no chemotherapy). Both groups received postoperative chemotherapy.

CI: confidence interval; LCRT: long-course radiotherapy; O-E: observed minus expected; SCRT: short-course radiotherapy; V: variance

Figure 13: Comparison 2: Short-course radiotherapy versus long-course radiotherapy with or without chemotherapy – Local recurrence rate (median 1.5 to 5.2 years of follow-up)

Study or Subgroup	SCRT Events	SCRT Total	LCRT Events	LCRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.5.1 Short-course radiotherapy with immediate surgery versus long-course radiotherapy (median 1.5 to 5.2 years of follow-up)						
Eitta 2010 (1)	2	14	1	15	12.1%	2.14 [0.22, 21.10]
Stockholm III trial (Erlandsson 2017)	3	129	7	128	87.9%	0.43 [0.11, 1.61]
Subtotal (95% CI)		**143**		**143**	**100.0%**	**0.63 [0.21, 1.87]**
Total events	5		8			
Heterogeneity: Chi² = 1.44, df = 1 (P = 0.23); I² = 30%						
Test for overall effect: Z = 0.83 (P = 0.41)						
2.5.2 Short-course radiotherapy with delayed surgery versus long-course (chemo)radiotherapy (median 5 to 5.2 years of follow-up)						
Lithuanian trial (Kairevice 2017) (2)	4	68	5	72	41.0%	0.85 [0.24, 3.02]
Stockholm III trial (Erlandsson 2017) (3)	4	128	7	128	59.0%	0.57 [0.17, 1.90]
Subtotal (95% CI)		**196**		**200**	**100.0%**	**0.68 [0.29, 1.63]**
Total events	8		12			
Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.85 (P = 0.39)						



Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%

Footnotes

(1) Selective postoperative chemotherapy.

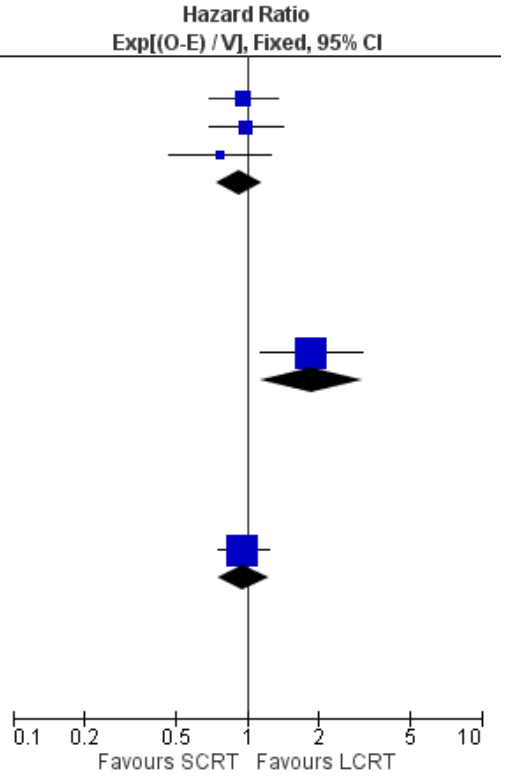
(2) Short-course radiotherapy (no chemotherapy) versus long-course chemoradiotherapy with postoperative chemotherapy.

(3) Short-course radiotherapy versus long-course radiotherapy (no chemotherapy).

CI: confidence interval; LCRT: long-course radiotherapy; M-H: Mantel-Haenszel method; SCRT: short-course radiotherapy

Figure 14: Comparison 2: Short-course radiotherapy versus long-course radiotherapy with or without chemotherapy – Disease-free survival (median 2.9 to 5.9 years of follow-up, event is local or distant failure or death)

Study or Subgroup	SCRT Events	SCRT Total	LCRT Events	LCRT Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
2.6.1 Short-course radiotherapy with immediate surgery versus long-course (chemo)radiotherapy (median 4 to 5.9 years of follow-up)								
Polish trial 1 (Bujko 2006) (1)	0	155	0	157	-1.39	34.11	44.0%	0.96 [0.69, 1.34]
Stockholm III trial (Erlandsson 2017) (2)	44	129	44	128	-0.28	28.34	36.6%	0.99 [0.69, 1.43]
TROG 01.04 (Ngan 2012) (3)	57	162	64	161	-3.97	15	19.4%	0.77 [0.46, 1.27]
Subtotal (95% CI)		**446**		**446**			**100.0%**	**0.93 [0.74, 1.16]**
Total events	101		108					
Heterogeneity: Chi² = 0.70, df = 2 (P = 0.70); I² = 0%								
Test for overall effect: Z = 0.64 (P = 0.52)								
2.6.2 Short-course radiotherapy with delayed surgery versus long-course chemoradiotherapy (median 5 years of follow-up)								
Lithuanian trial (Kairevice 2017) (4)	0	68	0	72	9.4	14.9	100.0%	1.88 [1.13, 3.12]
Subtotal (95% CI)		**68**		**72**			**100.0%**	**1.88 [1.13, 3.12]**
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.44 (P = 0.01)								
2.6.3 Short-course radiotherapy with consolidation chemotherapy versus long-course chemoradiotherapy (median 2.9 years of follow-up)								
Polish trial 2 (Bujko 2016) (5)	0	261	0	254	-2.48	60.78	100.0%	0.96 [0.75, 1.23]
Subtotal (95% CI)		**261**		**254**			**100.0%**	**0.96 [0.75, 1.23]**
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.32 (P = 0.75)								

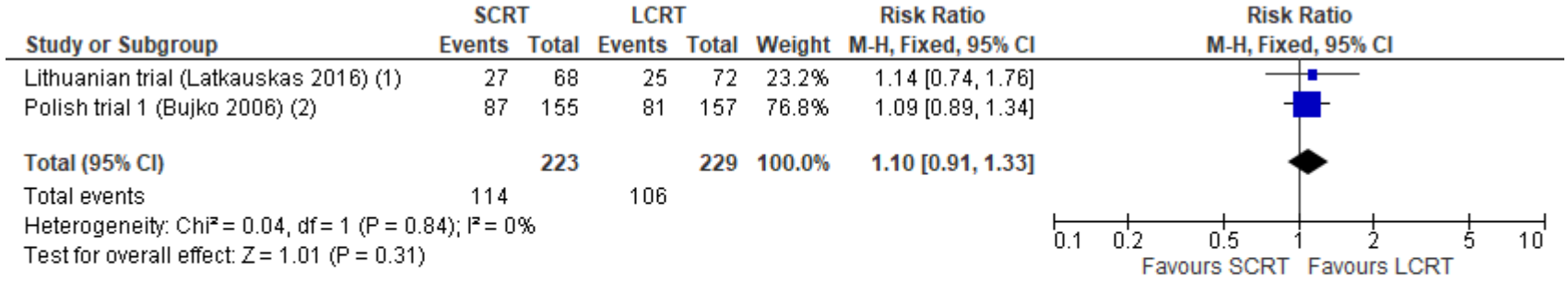


Footnotes

(1) Number of events not reported. Short-course radiotherapy (no chemotherapy) versus long-course chemoradiotherapy. Both groups received selective postoperative chemotherapy.
(2) Short-course radiotherapy versus long-course radiotherapy (no chemotherapy).
(3) Short-course radiotherapy versus long-course radiotherapy (no chemotherapy). Both groups received postoperative chemotherapy.
(4) Number of events not reported. Short-course radiotherapy (no chemotherapy) versus long-course chemoradiotherapy with postoperative chemotherapy.
(5) Number of events not reported. Both groups received selective postoperative chemotherapy.

CI: confidence interval; LCRT: long-course radiotherapy; O-E: observed minus expected; SCRT: short-course radiotherapy; V: variance

Figure 15: Comparison 2: Short-course radiotherapy versus long-course radiotherapy with or without chemotherapy – Permanent stoma (median 3.3 to 4 years of follow-up)



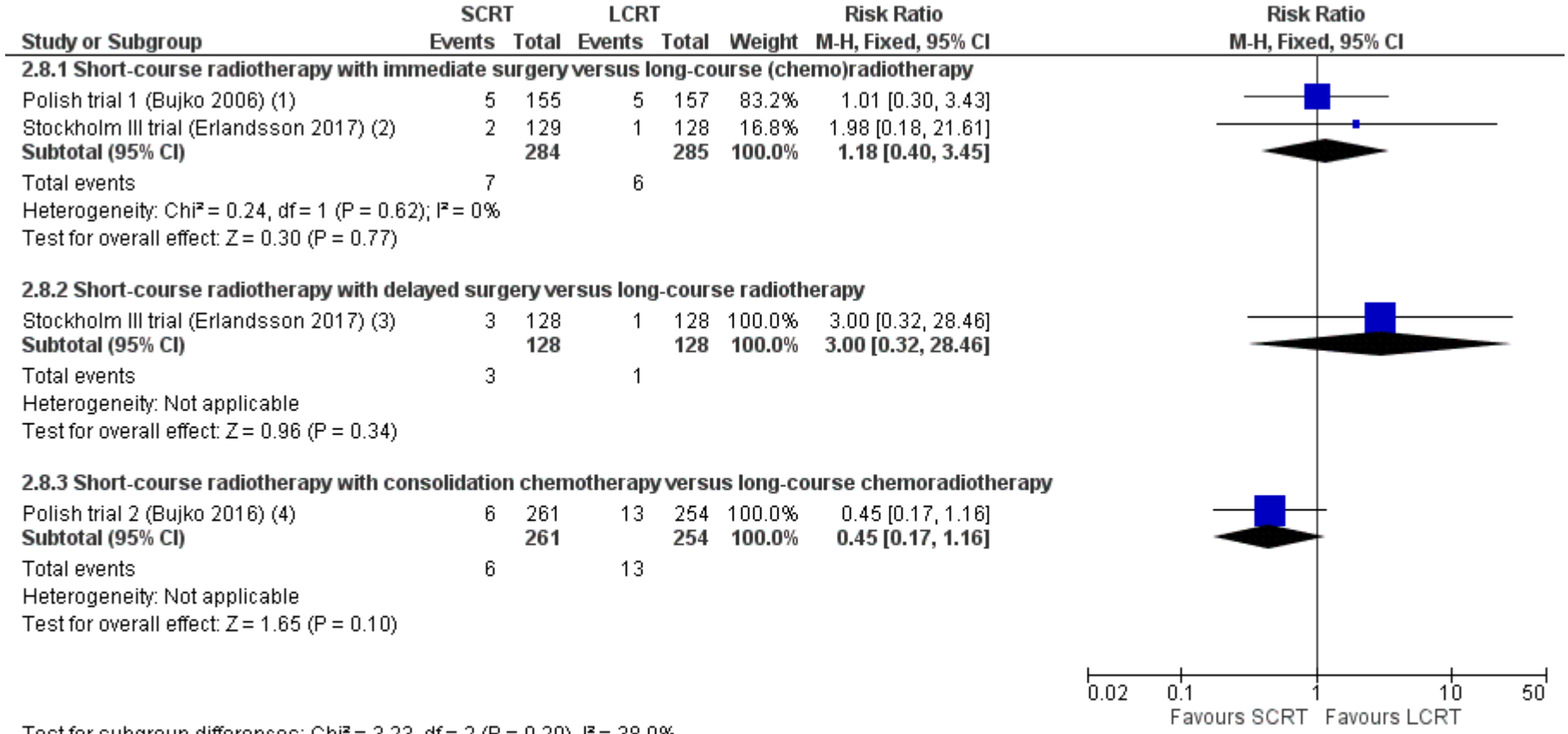
Footnotes

(1) Short-course radiotherapy (no chemotherapy) versus long-course chemoradiotherapy with postoperative chemotherapy.

(2) Short-course radiotherapy (no chemotherapy) versus long-course chemoradiotherapy. Both groups received selective postoperative chemotherapy.

CI: confidence interval; LCRT: long-course radiotherapy; M-H: Mantel-Haenszel method; SCRT: short-course radiotherapy

Figure 16: Comparison 2: Short-course radiotherapy versus long-course radiotherapy with or without chemotherapy – Treatment-related mortality



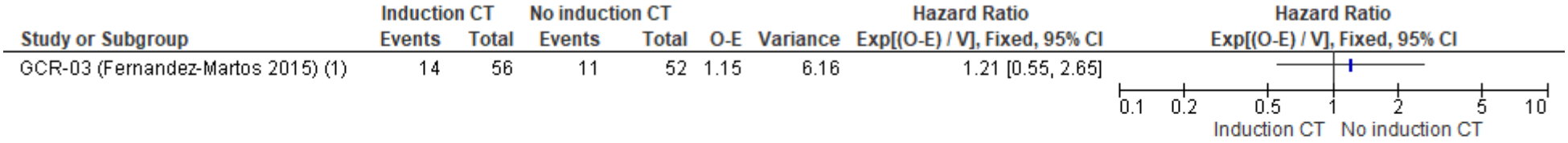
Test for subgroup differences: Chi² = 3.23, df = 2 (P = 0.20), I² = 38.0%

Footnotes

(1) Short-course radiotherapy (no chemotherapy) versus long-course chemoradiotherapy. Both groups received selective postoperative chemotherapy.
(2) Short-course radiotherapy versus long-course radiotherapy (no chemotherapy).
(3) Short-course radiotherapy versus long-course radiotherapy (no chemotherapy).
(4) Both groups received selective postoperative chemotherapy.

CI: confidence interval; LCRT: long-course radiotherapy; M-H: Mantel-Haenszel method; SCRT: short-course radiotherapy

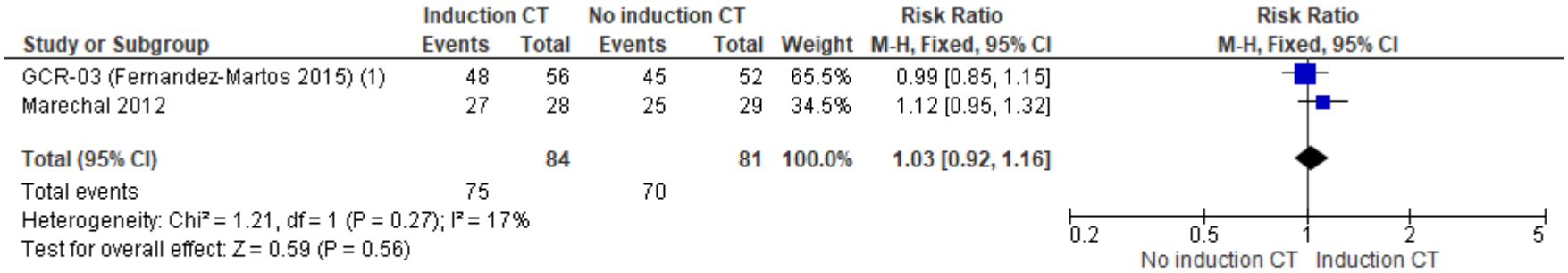
Figure 17: Comparison 3: Chemoradiotherapy with prior chemotherapy versus chemoradiotherapy without prior chemotherapy – Overall survival (median 5.8 years of follow-up, event is death from any cause)



Footnotes
(1) No induction group received postoperative chemotherapy.

CI: confidence interval; CT: chemotherapy; O-E: observed minus expected; V: variance

Figure 18: Comparison 3: Chemoradiotherapy with prior chemotherapy versus chemoradiotherapy without prior chemotherapy – Complete (R0) resection rate

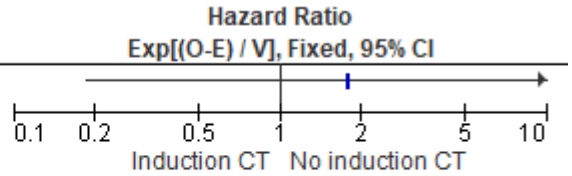


Footnotes
(1) No induction chemotherapy group received postoperative chemotherapy.

CI: confidence interval; CT: chemotherapy; M-H: Mantel-Haenszel method

Figure 19: Comparison 3: Chemoradiotherapy with prior chemotherapy versus chemoradiotherapy without prior chemotherapy – Local recurrence-free survival (median 5.8 years of follow-up, event is local recurrence)

Study or Subgroup	Induction CT Events	Total	No induction CT Events	Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
GCR-03 (Fernandez-Martos 2015) (1)	3	56	1	52	0.44	0.75	1.80 [0.19, 17.28]

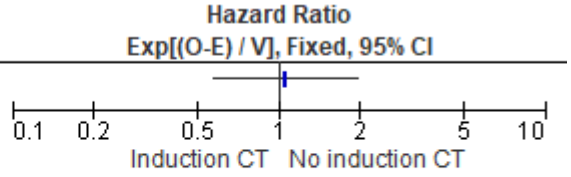


Footnotes
(1) No induction chemotherapy group received postoperative chemotherapy.

CI: confidence interval; CT: chemotherapy; O-E: observed minus expected; V: variance

Figure 20: Comparison 3: Chemoradiotherapy with prior chemotherapy versus chemoradiotherapy without prior chemotherapy – Disease-free survival (median 5.8 years of follow-up, event is local or distant failure or death)

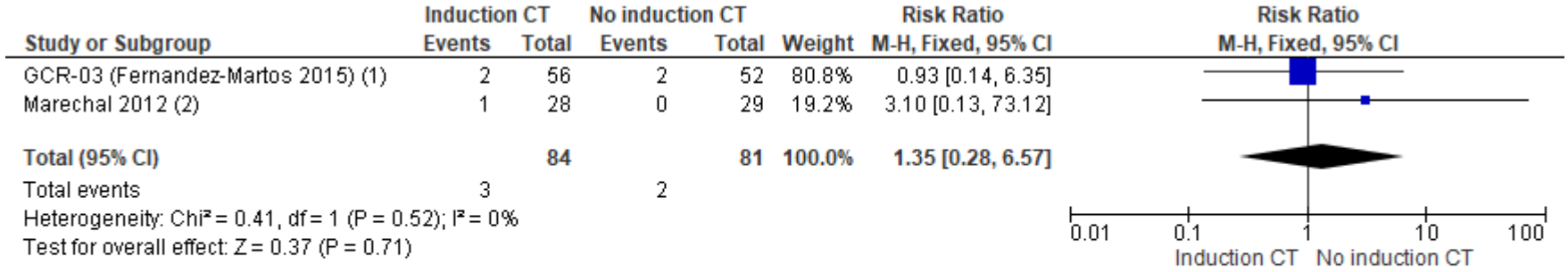
Study or Subgroup	Induction CT Events	Total	No induction CT Events	Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
GCR-03 (Fernandez-Martos 2015) (1)	22	56	18	52	0.6	9.9	1.06 [0.57, 1.98]



Footnotes
(1) No induction chemotherapy group received postoperative chemotherapy.

CI: confidence interval; CT: chemotherapy; O-E: observed minus expected; V: variance

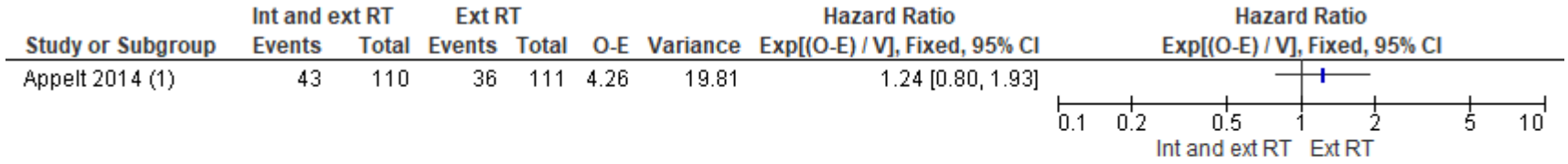
Figure 21: Comparison 3: Chemoradiotherapy with prior chemotherapy versus chemoradiotherapy without prior chemotherapy – Treatment-related mortality



Footnotes
(1) No induction chemotherapy group received postoperative chemotherapy.
(2) Chemotherapy-related death.

CI: confidence interval; CT: chemotherapy; M-H: Mantel-Haenszel method

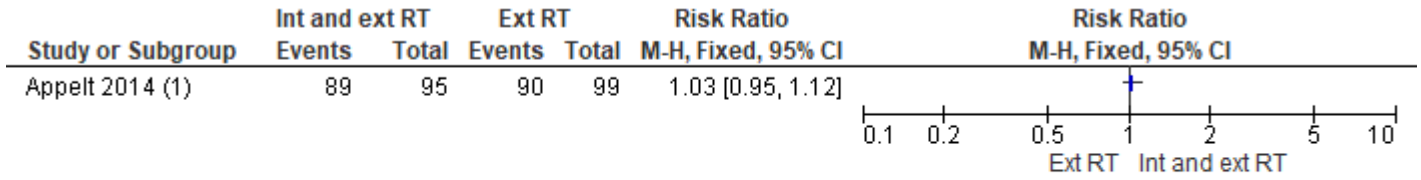
Figure 22: Comparison 4: Any external radiotherapy versus internal radiotherapy with or without external radiotherapy – Overall survival (median 5.4 years of follow-up, event is death from any cause)



Footnotes
(1) Internal brachytherapy boost. Both groups received preoperative chemotherapy.

CI: confidence interval; Int: internal; Ext: external; O-E: observed minus expected; RT: radiotherapy; V: variance

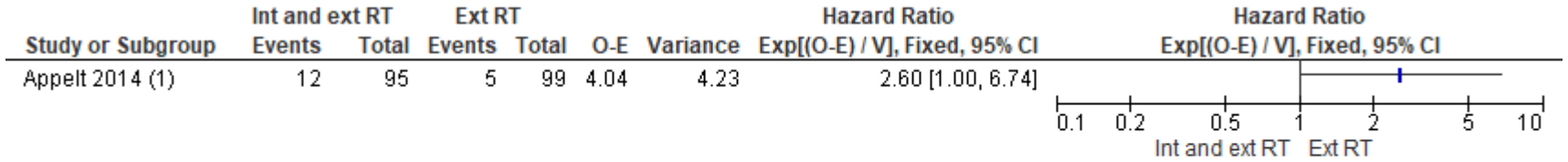
Figure 23: Comparison 4: Any external radiotherapy versus internal radiotherapy with or without external radiotherapy – Complete (R0) resection rate



Footnotes
(1) Internal brachytherapy boost. Both groups received preoperative chemotherapy.

CI: confidence interval; Int: internal; Ext: external; M-H: Mantel-Haenszel method; RT: radiotherapy

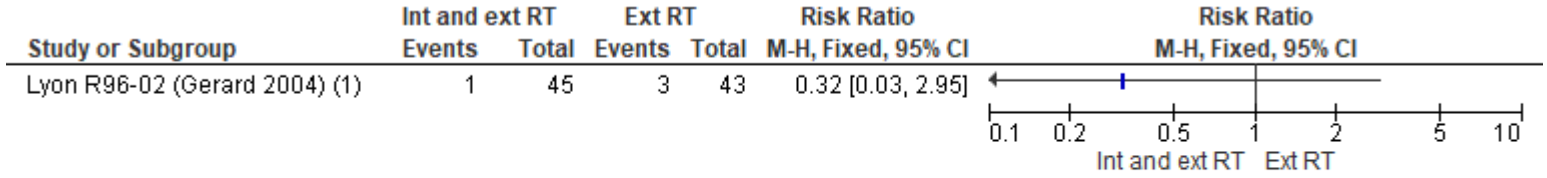
Figure 24: Comparison 4: Any external radiotherapy versus internal radiotherapy with or without external radiotherapy – Locoregional recurrence-free survival (median 5.4 years of follow-up, event is locoregional recurrence)



Footnotes
(1) Internal brachytherapy boost. Both groups received preoperative chemotherapy.

CI: confidence interval; Int: internal; Ext: external; O-E: observed minus expected; RT: radiotherapy; V: variance

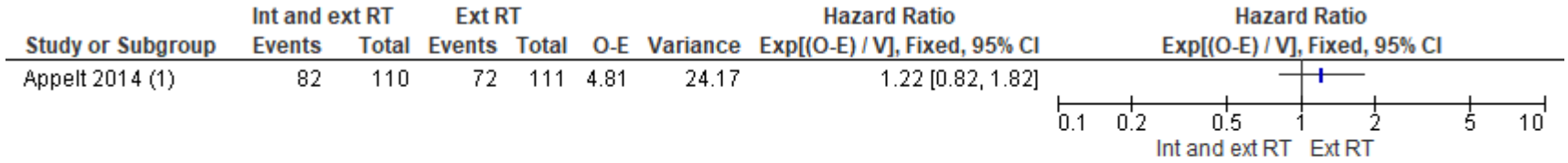
Figure 25: Comparison 4: Any external radiotherapy versus internal radiotherapy with or without external radiotherapy – Pelvic local recurrence rate (median 2.9 years of follow-up)



Footnotes
(1) Internal endocavity contact X-ray. Both groups received preoperative external radiotherapy (no chemotherapy).

CI: confidence interval; Int: internal; Ext: external; M-H: Mantel-Haenszel method; RT: radiotherapy

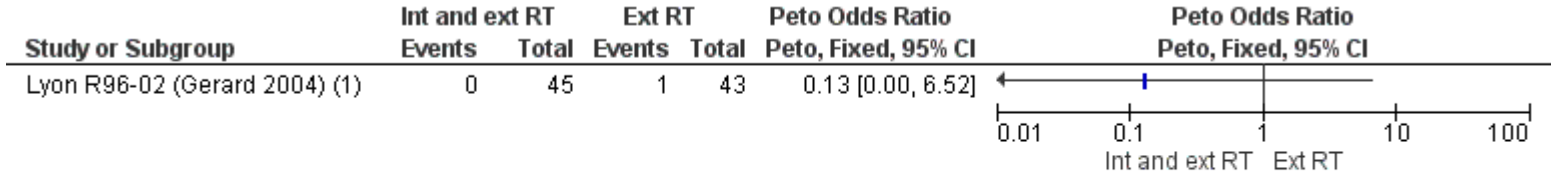
Figure 26: Comparison 4: Any external radiotherapy versus internal radiotherapy with or without external radiotherapy – Disease-free survival (median 5.4 years of follow-up, event is local or distant failure or death)



Footnotes
(1) Internal brachytherapy boost. Both groups received preoperative chemotherapy.

CI: confidence interval; Int: internal; Ext: external; O-E: observed minus expected; RT: radiotherapy; V: variance

Figure 27: Comparison 4: Any external radiotherapy versus internal radiotherapy with or without external radiotherapy – 60-day operative mortality



Footnotes
(1) Internal endocavity contact X-ray. Both groups received preoperative external radiotherapy (no chemotherapy).

CI: confidence interval; Int: internal; Ext: external; RT: radiotherapy

Appendix F – GRADE tables

GRADE tables for review question: What is the effectiveness of preoperative radiotherapy and chemoradiotherapy for rectal cancer?

Table 5: Clinical evidence profile for comparison 1: Any preoperative therapy versus no preoperative therapy

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Preoperative (chemo)radiotherapy**	**No preoperative (chemo)radiotherapy**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall survival (median 1.5 to 11.6 years of follow-up; event is death from any cause)												
8	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	N=2,799, number of events not reported in all studies	N=2,821, number of events not reported in all studies	HR 0.90 (0.84 to 0.98)	At 5 years no preoperative therapy 63.5%[a], preoperative therapy 66% (64.1% to 69%)	MODERATE	CRITICAL
Complete (R0) resection rate												
5	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	1,844/2,172 (84.9%)	1,857/2,184 (85%)	RR 1 (0.97 to 1.02)	0 fewer per 1,000 (from 26 fewer to 17 more)	MODERATE	CRITICAL
Overall health-related quality of life at 3, 6, 12, and 24 months after surgery (VAS; range of score 0-100; better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	serious[1]	no serious imprecision	none	N=497	N=493	"improved over time but did not differ significantly between treatment arms"	-	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative (chemo)radiotherapy	No preoperative (chemo)radiotherapy	Relative (95% CI)	Absolute		
Health-related quality of life – Global health status score at median 14 years of follow-up (QLQ-C30; range 0-100; better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	serious[1]	no serious imprecision	none	N=241	N=237	-	Preoperative therapy: 77.2 (SD not reported) No preoperative therapy: 78.5 (SD not reported) p=0.16 for difference	LOW	CRITICAL
Health-related quality of life - General health mean score at 2 years (SF-36; range of score 0-100; better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	N=258	N=261	-	Preoperative therapy: 60.5 (SD not reported) No preoperative therapy: 60.7 (SD not reported) p=0.835 for difference	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative (chemo)radiotherapy	No preoperative (chemo)radiotherapy	Relative (95% CI)	Absolute		
Health-related quality of life - Physical function mean score at 2 years (SF-36; range of score 0-100; better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	N=244	N=250		Preoperative therapy: 70.2 (SD not reported) No preoperative therapy: 71.1 (SD not reported) p=0.737 for difference	LOW	CRITICAL
Local recurrence-free survival (median 1.5 to 11.6 years of follow-up; event is local recurrence)												
9	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	190/2,893 (6.6%)	403/2,914 (13.8%)	HR 0.52 (0.44 to 0.62)	At 5 years no preoperative therapy 89%[a], preoperative therapy 94% (93% to 95%)	MODERATE	IMPORTANT
Local recurrence rate (median 5.2 years of follow-up) - Preoperative radiotherapy versus postoperative (chemo)radiotherapy												
2	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	6/116 (5.2%)	18/124 (14.5%)	RR 0.36 (0.15 to 0.86)	93 fewer per 1,000 (from 20 fewer to 123 fewer)	LOW	IMPORTANT
Local recurrence rate (follow-up time not reported) - Preoperative and postoperative radiotherapy versus surgery alone												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	5/92 (5.4%)	45/70 (64.3%)	RR 0.08 (0.04 to 0.2)	591 fewer per 1,000 (from 514 fewer to 617 fewer)	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative (chemo)radiotherapy	No preoperative (chemo)radiotherapy	Relative (95% CI)	Absolute		
Disease-free survival (median 1.5 to 11.2 years of follow-up; event is local or distant failure or death)												
6	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	N=1,478, number of events not reported in all studies	N=1,459, number of events not reported in all studies	HR 0.82 (0.72 to 0.94)	At 5 years no preoperative therapy 67%[b], preoperative therapy 72% (69% to 75%)	MODERATE	IMPORTANT
Permanent stoma (median 5 years of follow-up)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[5]	none	129/306 (42.2%)	106/291 (36.4%)	RR 1.16 (0.95 to 1.41)	58 more per 1,000 (from 18 fewer to 149 more)	LOW	IMPORTANT
Sphincter preservation at 5 years												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	63/90 (70%)	67/94 (71.3%)	RR 0.98 (0.82 to 1.18)	14 fewer per 1,000 (from 128 fewer to 128 more)	MODERATE	IMPORTANT
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	39/115 (33.9%)	29/120 (24.2%)	RR 1.4 (0.93 to 2.11)	97 more per 1,000 (from 17 fewer to 268 more)	MODERATE	IMPORTANT
Preoperative or postoperative treatment-related mortality												
4	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[5]	none	49/1,966 (2.5%)	35/1,969 (1.8%)	RR 1.4 (0.91 to 2.15)	7 more per 1,000 (from 2 fewer to 20 more)	LOW	IMPORTANT
30-day operative mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[5]	none	12/674 (1.8%)	15/676 (2.2%)	RR 0.8 (0.38 to 1.7)	4 fewer per 1,000 (from 14 fewer to 16 more)	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative (chemo)radiotherapy	No preoperative (chemo)radiotherapy	Relative (95% CI)	Absolute	Quality	Importance
60-day operative mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[5]	none	17/674 (2.5%)	20/676 (3%)	RR 0.85 (0.45 to 1.61)	4 fewer per 1,000 (from 16 fewer to 18 more)	LOW	IMPORTANT

CI: confidence interval; HR: hazard ratio; N: number; QLQ-C30: Quality of Life Questionnaire Core 30 Items; RR: relative risk; SD: standard deviation; SF-36: 36-Item Short Form Survey; VAS: visual analogue scale

1 Quality of evidence downgraded by 1 because a proportion of the people had early rectal cancer.

2 Quality of evidence downgraded by 1 because there was no blinding.

3 Quality of evidence downgraded by 1 because a proportion of the people likely to have early rectal cancer.

4 Quality of evidence downgraded by 1 because of high risk of reporting bias (poor reporting with discrepancies between the abstract and the text) and unclear risk of selection bias (details of random sequence generation not reported).

5 Quality of evidence downgraded by 1 because of imprecision of the effect estimate (less than 300 events).

a The estimate of the absolute risk at 5 years in the control group taken from the Dutch TME trial.

b The estimate of the absolute risk at 5 years in the control group taken from the MRC CR07 trial.

Table 6: Clinical evidence profile for comparison 2: Short-course radiotherapy versus long-course radiotherapy with or without chemotherapy

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short-course radiotherapy	Long-course (chemo)radiotherapy	Relative (95% CI)	Absolute	Quality	Importance
Overall survival (median 4 to 5.9 years of follow-up; event is death from any cause) - Short-course radiotherapy with immediate surgery versus long-course (chemo)radiotherapy												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	101/317 (31.9%)	105/318 (33%)	HR 0.96 (0.73 to 1.26)	At 5 years LCRT 66%[a], SCRT 67% (59% to 74%)	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short-course radiotherapy	Long-course (chemo)radiotherapy	Relative (95% CI)	Absolute		
Overall survival (median 5 years of follow-up; event is death from any cause) - Short-course radiotherapy with delayed surgery versus long-course chemoradiotherapy												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	N=75, number of events not reported	N=75, number of events not reported	HR 2.28 (1.30 to 4.00)	At 5 years LCRT 78%[b], SCRT 57% (37% to 72%)	MODERATE	CRITICAL
Overall survival (median 2.9 years of follow-up; event is death from any cause) - Short-course radiotherapy with chemotherapy versus long-course chemoradiotherapy												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	64/261 (24.5%)	84/254 (33.1%)	HR 0.73 (0.53 to 1.01)	At 3 years LCRT 65%[c], SCRT 73% (65% to 80%)	MODERATE	CRITICAL
Overall survival (median 5.2 years of follow-up; event is death from any cause) - Short-course radiotherapy with immediate surgery versus long-course radiotherapy												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	51/129 (39.5%)	49/128 (38.3%)	HR 0.94 (0.63 to 1.40)	At 5 years SCRT 73% (64–80). LCRT 78% (70–84)	MODERATE	CRITICAL
Complete (R0) resection rate - Short-course radiotherapy versus long-course chemoradiotherapy with postoperative chemotherapy												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	57/68 (83.8%)	64/72 (88.9%)	RR 0.94 (0.83 to 1.08)	53 fewer per 1,000 (from 151 fewer to 71 more)	MODERATE	CRITICAL
Complete (R0) resection rate - Short-course radiotherapy with consolidation chemotherapy versus long-course chemoradiotherapy												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	202/261 (77.4%)	178/254 (70.1%)	RR 1.10 (1.00 to 1.23)	70 more per 1,000 (from 0 more to 161 more)	HIGH	CRITICAL
Complete (R0) resection rate - Short-course radiotherapy versus long-course radiotherapy												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	150/158 (94.9%)	151/157 (96.2%)	RR 0.99 (0.94 to 1.04)	10 fewer per 1,000 (from 58 fewer to 38 more)	HIGH	CRITICAL
Health-related quality of life - global health status score change from baseline at 12 months (QLQ-C30; range of score 0-100; better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N=143	N=153	-	Short-course radiotherapy: -9.9 (SD not reported)	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short-course radiotherapy	Long-course (chemo)radiotherapy	Relative (95% CI)	Absolute		
										Long-course radiotherapy: -8.2 (SD not reported) p=0.44 for difference		
Health-related quality of life - global health status mean score at 12 months (QLQ-C30; range of score 0-100; better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N=111	N=110	-	Short-course radiotherapy: 57 (SD not reported) Long-course radiotherapy: 61 (SD not reported) p=0.22 for difference	LOW	CRITICAL
Local recurrence-free survival (median 4 to 5.9 years of follow-up; event is local recurrence)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	N=308, number of events not reported in all studies	N=310, number of events not reported in all studies	HR 0.86 (0.5 to 1.48)	At 5 years LCRT 85%[a], SCRT 87% (79% to 92%)	MODERATE	IMPORTANT
Local recurrence rate (median 1.5 to 5.2 years of follow-up) – Short-course radiotherapy with immediate surgery versus long-course radiotherapy												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	5/143 (3.5%)	8/143 (5.6%)	RR 0.63 (0.21 to 1.87)	21 fewer per 1,000 (from 44 fewer to 49 more)	MODERATE	IMPORTANT
Local recurrence rate (median 5 to 5.2 years of follow-up) – Short-course (chemo)radiotherapy with delayed surgery versus long-course (chemo)radiotherapy												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	8/196 (4.1%)	12/200 (6%)	RR 0.68 (0.20 to 1.63)	19 fewer per 1,000 (from 43 fewer to 38 more)	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short-course radiotherapy	Long-course (chemo)radiotherapy	Relative (95% CI)	Absolute		
Disease-free survival (median 4 to 5.9 years of follow-up; event is local or distant failure or death) - Short-course radiotherapy with immediate surgery versus long-course (chemo)radiotherapy												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	N=446, number of events not reported in all studies	N=446, number of events not reported in all studies	HR 0.93 (0.74 to 1.16)	At 5 years LCRT 56%[d] SCRT 58% (51% to 65%)	MODERATE	IMPORTANT
Disease-free survival (median 5 years of follow-up; event is local or distant failure or death) - Short-course radiotherapy with delayed surgery versus long-course chemoradiotherapy												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	N=68, number of events not reported	N=72, number of events not reported	HR 1.88 (1.13 to 3.12)	At 5 years LCRT 67%[b], SCRT 47% (29% to 64%)	MODERATE	IMPORTANT
Disease-free survival (median 2.9 years of follow-up; event is local or distant failure or death) - Short-course radiotherapy with consolidation chemotherapy versus long-course chemoradiotherapy												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	N=261, number of events not reported	N=254, number of events not reported	HR 0.96 (0.75 to 1.23)	At 3 years LCRT 52%[c], SCRT 53% (45% to 61%)	MODERATE	IMPORTANT
Permanent stoma (median 3.3 to 4 years of follow-up)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	114/223 (51.1%)	106/229 (46.3%)	RR 1.10 (0.91 to 1.33)	46 more per 1,000 (from 42 fewer to 153 more)	MODERATE	IMPORTANT
Treatment-related mortality - Short-course radiotherapy with immediate surgery versus long-course (chemo)radiotherapy												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	7/284 (2.5%)	6/285 (2.1%)	RR 1.18 (0.4 to 3.45)	4 more per 1,000 (from 13 fewer to 52 more)	MODERATE	IMPORTANT
Treatment-related mortality - Short-course radiotherapy with delayed surgery versus long-course radiotherapy												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	serious[1]	none	3/128 (2.3%)	1/128 (0.78%)	RR 3.00 (0.32 to 28.46)	16 more per 1,000 (from 5 fewer to 215 more)	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short-course radiotherapy	Long-course (chemo)radiotherapy	Relative (95% CI)	Absolute		
Treatment-related mortality - Short-course radiotherapy with consolidation chemotherapy versus long-course chemoradiotherapy												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	6/261 (2.3%)	13/254 (5.1%)	RR 0.45 (0.17 to 1.16)	28 fewer per 1,000 (from 42 fewer to 8 more)	MODERATE	IMPORTANT

CI: confidence interval; HR: hazard ratio; LCRT: long-course radiotherapy; N: number; QLQ-C30: Quality of Life Questionnaire Core 30 Items; RR: relative risk; SCRT: short-course radiotherapy; SD: standard deviation

1 Quality of evidence downgraded by 1 because of imprecision of the effect estimate (less than 300 events).

2 Quality of evidence downgraded by 1 because there was no blinding.

3 Quality of evidence downgraded by 1 because of imprecision of the effect estimate (sample size of less than 400).

4 Quality of evidence downgraded by 1 because a proportion of the people had early rectal cancer.

a The absolute risk at 5 years in the control group estimated from the Polish trial 1 (Bujko 2006) and TROG 01.04 trial (Ngan 2012).

b The absolute risk at 5 years in the control group taken from the Lithuanian trial (Kairevice 2017).

c The absolute risk at 5 years in the control group take from the Polish trial 2 (Bujko 2016).

d The absolute risk at 5 years in the control group estimated from the Polish trial 1 (Bujko 2006) and the Stockholm III trial (Erlandsson 2017).

Table 7: Clinical evidence profile: Comparison 3: Chemoradiotherapy with prior chemotherapy versus chemoradiotherapy without prior chemotherapy

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Preoperative chemoradiotherapy with induction chemotherapy**	**No induction chemotherapy**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall survival (median 5.8 years of follow-up; event is death from any cause)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	14/56 (25%)	11/52 (21.2%)	HR 1.21 (0.55 to 2.65)	At 5 years no induction CT 78%[a], induction CT 74% (52% to 87%)	MODERATE	CRITICAL
Complete (R0) resection rate												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	75/84 (89.3%)	70/81 (86.4%)	RR 1.03 (0.92 to 1.16)	26 more per 1,000 (from 69 fewer to 138 more)	MODERATE	CRITICAL
Overall quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Local recurrence-free survival (median 5.8 years of follow-up; event is local recurrence)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	3/56 (5.4%)	1/52 (1.9%)	HR 1.80 (0.19 to 17.28)	At 5 years no induction CT 98%[a], induction CT 96% (71% to 100%)	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative chemoradiotherapy with induction chemotherapy	No induction chemotherapy	Relative (95% CI)	Absolute	Quality	Importance
Disease-free survival (median 5.8 years of follow-up; event is local or distant failure or death)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	22/56 (39.3%)	18/52 (34.6%)	HR 1.06 (0.57 to 1.98)	At 5 years no induction CT 64%[a], induction CT 62% (41% to 78%)	LOW	IMPORTANT
Sphincter preservation/permanent stoma												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Treatment-related mortality												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	3/84 (3.6%)	2/81 (2.5%)	RR 1.35 (0.28 to 6.57)	9 more per 1,000 (from 18 fewer to 138 more)	MODERATE	IMPORTANT

CI: confidence interval; CT: chemotherapy; HR: hazard ratio; RR: relative risk
1 Quality of evidence downgraded by 1 because of imprecision of the effect estimate (less than 300 events).
2 Quality of evidence downgraded by 1 because of high risk of reporting bias (poor reporting with inconsistencies in the results between the abstract, main text and the figures); unclear risk of selection bias (random sequence generation and allocation concealment not reported).
a The absolute risk at 5 years in the control group taken from the GCR-03 trial (Fernandez-Martos 2015).

Table 8: Clinical evidence profile: Comparison 4: Any external radiotherapy versus internal radiotherapy with or without external radiotherapy

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	External (chemo)radiotherapy with internal radiotherapy	External (chemo)radiotherapy without internal radiotherapy	Relative (95% CI)	Absolute	Quality	Importance
Overall survival (median 5.4 years of follow-up; event is death from any cause)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	43/110 (39.1%)	36/111 (32.4%)	HR 1.24 (0.80 to 1.93)	At 5 years no internal radiotherapy 71%[a], internal radiotherapy 65% (51% to 76%)	MODERATE	CRITICAL
Complete (R0) resection rate												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	89/95 (93.7%)	90/99 (90.9%)	RR 1.03 (0.95 to 1.12)	27 more per 1,000 (from 45 fewer to 109 more)	MODERATE	CRITICAL
Overall quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Locoregional recurrence-free survival (median 5.4 years of follow-up; event is locoregional recurrence)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	12/95 (12.6%)	5/99 (5.1%)	HR 2.60 (1.00 to 6.74)	At 5 years no internal radiotherapy 94%[a], internal radiotherapy 85% (65% to 94%)	MODERATE	IMPORTANT
Pelvic local recurrence (median 2.9 years of follow-up)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	1/45 (2.2%)	3/43 (7%)	RR 0.32 (0.03 to 2.95)	47 fewer per 1,000 (from 68 fewer to 136 more)	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**External (chemo)radiotherapy with internal radiotherapy**	**External (chemo)radiotherapy without internal radiotherapy**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Disease-free survival (median 5.4 years of follow-up; event is local or distant failure, inoperability or death)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	82/110 (74.5%)	72/111 (64.9%)	HR 1.22 (0.82 to 1.82)	At 5 years no internal radiotherapy 64%[a], internal radiotherapy 58% (44% to 69%)	MODERATE	IMPORTANT
Sphincter preservation/permanent stoma												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
60-day operative mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	0/45 (0%)	1/43 (2.3%)	Peto odds ratio 0.13 (0.00, 6.52)	20 fewer per 1,000 (from -0 fewer to 111 more)	MODERATE	IMPORTANT

1 *CI: confidence interval; HR: hazard ratio; RR: relative risk*
2 *1 Quality of evidence downgraded by 1 because of imprecision of the effect estimate (less than 300 events).*
3 *a The absolute risk at 5 years in the control group taken from Appelt 2014.*

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What is the effectiveness of preoperative radiotherapy and chemoradiotherapy for rectal cancer?

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information.

Appendix H – Economic evidence tables

Economic evidence tables for review question: What is the effectiveness of preoperative radiotherapy and chemoradiotherapy for rectal cancer?

No economic evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What is the effectiveness of preoperative radiotherapy and chemoradiotherapy for rectal cancer?

No economic evidence was identified which was applicable to this review question.

Appendix J – Economic analysis

Economic analysis: What is the effectiveness of preoperative radiotherapy and chemoradiotherapy for rectal cancer?

No economic analysis was conducted for this review question.

1 Appendix K – Excluded studies

2 Excluded clinical studies for review question: What is the effectiveness of 3 preoperative radiotherapy or chemoradiotherapy for rectal cancer?

4 **Table 9: Excluded studies and reasons for their exclusion**

Study	Reason for exclusion
Anon. Short-term surgical outcomes and patient quality of life between robotic and laparoscopic extralevator abdominoperineal excision for adenocarcinoma of the rectum. 2017	A conference abstract
Abdujapparov A, Ten Y, Korakhadjaev B. The results of neoadjuvant chemoradiation therapy in combined treatment of rectal cancer. European Journal of Cancer. 2017;72:S50.	A conference abstract.
Abraha I, Aristei C, Palumbo I, Lupattelli M, Trastulli S, Cirocchi R, et al. Preoperative radiotherapy and curative surgery for the management of localised rectal carcinoma. Cochrane Database Syst Rev. 2018;10:CD002102.	Systematic review and meta-analysis of RCTs comparing preoperative radiotherapy and surgery versus surgery alone. All included studies
Akpek, Ea, Kahraman, S, Bulutcu, E, Ozgen, S, Erdem, K, Randomised trial of surgery alone versus radiotherapy followed by surgery for potentially operable locally advanced rectal cancer, Cancer/Radiotherapie, 1, 268, 1997	A conference abstract.
Anonymous,, Randomised trial of surgery alone versus radiotherapy followed by surgery for potentially operable locally advanced rectal cancer, Cancer/Radiotherapie, 1, 268, 1997	A French summary of a Lancet publication from 1996.
Ansari, N., Solomon, M. J., Fisher, R. J., MacKay, J., Burmeister, B., Ackland, S., Heriot, A., Joseph, D., McLachlan, S. A., McClure, B., Ngan, S. Y., Acute Adverse Events and Postoperative Complications in a Randomized Trial of Preoperative Short-course Radiotherapy Versus Long-course Chemoradiotherapy for T3 Adenocarcinoma of the Rectum: Trans-Tasman Radiation Oncology Group Trial (TROG 01.04), Annals of Surgery, 265, 882-888, 2017	No outcomes of interest.
Auclin, E, Menard, J, Hennequin, C, Quero, L, Rectal cancer: short-or long-course radiotherapy, for which tumors and for which patients?, Hepato-gastro and oncologie digestive, 21, 431-438, 2014	Full text in French. A narrative review.
Aumock, A., Birnbaum, E. H., Fleshman, J. W., Fry, R. D., Gambacorta, M. A., Kodner, I. J., Malyapa, R. S., Read, T. E., Walz, B. J., Myerson, R. J., Treatment of rectal adenocarcinoma with endocavitary and external beam radiotherapy: results for 199 patients with localized tumors, International journal of radiation oncology, biology, physics, 51, 363-70, 2001	Not a RCT but an observational study.
Barendse RM, Musters GD, de Graaf EJR, van den Broek FJC, Consten ECJ, Doornebosch PG, et al. Randomised controlled trial of transanal endoscopic microsurgery versus endoscopic mucosal resection for large rectal adenomas (TREND Study). Gut. 2018;67(5):837-46.	Not a relevant comparison for this research question. Included study in review C1.
Bernstein, M. A., Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): A multicentre, randomised trial, Diseases of the Colon and Rectum, 52, 1532-1533, 2009	An abstract of a paper published elsewhere and considered for inclusion separately.
Birgisson, H., Pahlman, L., Gunnarsson, U., Adverse effects of preoperative radiation therapy for rectal cancer: Long-term	No outcomes of interest.

Study	Reason for exclusion
follow-up of the Swedish Rectal Cancer Trial, Diseases of the Colon and Rectum, 49, 537, 2006	
Birgisson, H., Pahlman, L., Gunnarsson, U., Glimelius, B., Adverse effects of preoperative radiation therapy for rectal cancer: Long-term follow-up of the Swedish Rectal Cancer Trial, Journal of Clinical Oncology, 23, 8697-8705, 2005	No outcomes of interest.
Birgisson, H., Pahlman, L., Gunnarsson, U., Glimelius, B., Late gastrointestinal disorders after rectal cancer surgery with and without preoperative radiation therapy, British Journal of Surgery, 95, 206-13, 2008	No outcomes of interest.
Birgisson, H., Pahlman, L., Gunnarsson, U., Glimelius, B., Occurrence of second cancers in patients treated with radiotherapy for rectal cancer, Journal of Clinical Oncology, 23, 6126-6131, 2005	No outcomes of interest.
Birnbaum, E. H., Ogunbiyi, O. A., Gagliardi, G., Fry, R. D., Myerson, R. J., Kodner, I. J., Fleshman, J. W., Selection criteria for treatment of rectal cancer with combined external and endocavitary radiation, Diseases of the Colon & Rectum, 42, 727-33; discussion 733-5, 1999	Not a RCT but an observational study.
Borg, C., Andre, T., Mantion, G., Boudghene, F., Mornex, F., Maingon, P., Adenis, A., Azria, D., Piutti, M., Morsli, O., Bosset, J. F., Pathological response and safety of two neoadjuvant strategies with bevacizumab in MRI-defined locally advanced T3 resectable rectal cancer: A randomized, noncomparative phase II study, Annals of Oncology, 25, 2205-2210, 2014	No outcomes of interest.
Borstlap, W. A. A., Deijen, C. L., den Dulk, M., Bonjer, H. J., van de Velde, C. J., Bemelman, W. A., Tanis, P. J., Aalbers, A., Acherman, Y., Algie, G. D., von Geusau, B. A., Amelung, F., Aukema, T. S., Bakker, I. S., Basha, S., Bastiaansen, A. J. N. M., Belgers, E., Bleeker, W., Blok, J., Bosker, R. J. I., Bosmans, J. W., Boute, M. C., Bouvy, N. D., Bouwman, H., Brandt-Kerkhof, A., Brinkman, D. J., Bruin, S., Bruns, E. R. J., Burbach, J. P. M., Burger, J. W. A., Buskens, C. J., Clermonts, S., Coene, P. P. L. O., Compaan, C., Consten, E. C. J., Darbyshire, T., de Mik, S. M. L., de Graaf, E. J. R., de Groot, I., de vos tot Nederveen Cappel, R. J. L., de Wilt, J. H. W., van der Wolde, J., den Boer, F. C., Dekker, J. W. T., Demirkiran, A., Derkx-Hendriksen, M., Dijkstra, F. R., van Duijvendijk, P., Dunker, M. S., Eijsbouts, Q. E., Fabry, H., Ferenschild, F., Foppen, J. W., Furnee, E. J. B., Gerhards, M. F., Gerven, P., Govaert, J. A., Van Grevenstein, W. M. U., Haen, R., Harlaar, J. J., Harst, E., Havenga, K., Heemskerk, J., Heeren, J. F., Heijnen, B., Heres, P., Hoff, C., Hogendoorn, W., Hoogland, P., Huijbers, A., Gooszen, J. A. H., Janssen, P., Jongen, A. C., Jonker, F. H., Karthaus, E. G., Keijzer, A., Ketel, J. M. A., Klaase, J., Kloppenberg, F. W. H., Kool, M. E., Kortekaas, R., Kruyt, P. M., Kuiper, J. T., Lamme, B., Lange, J. F., Lettinga, T., Lips, D. J., Logeman, F., Holzik, M. F. L., Madsen, E., Mamound, A., Marres, C. C., Masselink, I., Meerdink, M., Menon, A. G., Mieog, J. S., Mierlo, D., Musters, G. D., Neijenhuis, P. A., Nonner, J., Oostdijk, M., Oosterling, S. J., Paul, P. M. P., Peeters, K. C. M. J. C., Pereboom, I. T. A., Polat, F., Poortman, P., Raber, M., Reiber, B. M. M., Renger, R. J., van Rossem, C. C., Rutten, H. J., Rutten, A., Schaapman, R., Scheer, M., Schoonderwoerd, L., Schouten, N., Schreuder, A. M., Schreurs, W. H., Simkens, G. A., Slooter, G. D., Sluijmer, H. C. E., Smakman, N., Smeenk, R., Snijders,	Observational data.

Study	Reason for exclusion
H. S., Sonneveld, D. J. A., Spaansen, B., Bilgen, E. J. S., Steller, E., Steup, W. H., Steur, C., Stortelder, E., Straatman, J., Swank, H. A., Sietses, C., ten Berge, H. A., ten hoeve, H. G., ter Riele, W. W., Thorensen, I. M., Tip-Pluijm, B., Toorenvliet, B. R., Tseng, L., Tuynman, J. B., van Bastelaar, J., van beek, S. C., van de Ven, A. W. H., van de Weijer, M. A. J., van den Berg, C., van den Bosch, I., van der Bilt, J. D. W., van der Hagen, S. J., van der hul, R., van der Schelling, G., van der Spek, A., van der Wielen, N., van duyn, E., van Eekelen, C., van Essen, J. A., van Gangelt, K., van Geloven, A. A. W., van kessel, C., van Loon, Y. T., van Rijswijk, A., van Rooijen, S. J., van Sprundel, T., van Steensel, L., van Tets, W. F., van Westreenen, H. L., Veltkamp, S., Verhaak, T., Verheijen, P. M., Versluis-Ossenwaarde, L., Vijfhuize, S., Vles, W. J., Voeten, S., Vogelaar, F. J., Vrijland, W. W., Westerduin, E., Westerterp, M. E., Wetzel, M., Wevers, K., Wiering, B., Witjes, A. C., Wouters, M. W., Yauw, S. T. K., Zeestraten, E. C., Zimmerman, D. D., Zwieten, T., Benchmarking recent national practice in rectal cancer treatment with landmark randomized controlled trials, Colorectal Disease, 19, O219-O231, 2017	
Bosset, J. F., Calais, G., Daban, A., Berger, C., Radosevic-Jelic, L., Maingon, P., Bardet, E., Pierart, M., Briffaux, A., Preoperative chemoradiotherapy versus preoperative radiotherapy in rectal cancer patients: Assessment of acute toxicity and treatment compliance: Report of the 22921 randomised trial conducted by the EORTC Radiotherapy Group, European Journal of Cancer, 40, 219-224, 2004	Wrong comparison. This study compared preoperative radiotherapy with or without postoperative chemotherapy to preoperative chemoradiotherapy with or without postoperative chemotherapy.
Bosset, J. F., Collette, L., Calais, G., Mineur, L., Maingon, P., Radosevic-Jelic, L., Daban, A., Bardet, E., Beny, A., Ollier, J. C., Chemotherapy with preoperative radiotherapy in rectal cancer, New England Journal of Medicine, 355, 1114-1123, 2006	Wrong comparison. This study compared preoperative radiotherapy with or without postoperative chemotherapy to preoperative chemoradiotherapy with or without postoperative chemotherapy.
Bruin, Ec, Velde, Cj, Pas, S, Nagtegaal, Id, Krieken, Jh, Gosens, Mj, Peltenburg, Lt, Medema, Jp, Marijnen, Ca, Prognostic value of apoptosis in rectal cancer patients of the dutch total mesorectal excision trial: radiotherapy is redundant in intrinsically high-apoptotic tumors, Clinical Cancer Research, 12, 6432-6436, 2006	Wrong comparison. This publication studies the local recurrence between high apoptosis and low apoptosis of the tumour.
Bujko, K, Nowacki, Mp, Nasierowska-Guttmejer, A, Michalski, W, Bebenek, M, Pude?ko, M, Kryj, M, Oledzki, J, Szmeja, J, S?uszniak, J, Serkies, K, K?adny, J, Pamucka, M, Kuko?owicz, P, Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy, Radiotherapy and Oncology, 72, 15-24, 2004	Outcomes of interest reported in this publication reported in another publication of the same trial (Bujko 2006).
Bujko, K., Bujko, M., Point: Short-Course Radiation Therapy Is Preferable in the Neoadjuvant Treatment of Rectal Cancer, Seminars in Radiation Oncology, 21, 220-227, 2011	A combined report of 2 RCTs already included in this review.
Bujko, K., Nasierowska-Guttmejer, A., Wyrwicz, L., Malinowska, M., Krynski, J., Kosakowska, E., Rutkowski, A., Pietrzak, L., Kepka, L., Radziszewski, J., Olszyna-Serementa, M., Bujko, M., Danek, A., Kryj, M., Wydmanski, J., Zegarski, W., Markiewicz, W., Lesniak, T., Zygulski, I., Porzuczek-Zuziak, D., Bebenek, M., Maclejczyk, A., Polkowski, W.,	This publication reports interim results only, another publication from the same trial already included.

Study	Reason for exclusion
Czeremszynska, B., Cieslak-Zeranska, E., Toczko, Z., Radkowski, A., Kolodziejski, L., Szczepkowski, M., Majewski, A., Jankowski, M., Neoadjuvant treatment for unresectable rectal cancer: An interim analysis of a multicentre randomized study, Radiotherapy and Oncology, 107, 171-177, 2013	
Bujko, K., Nowacki, M. P., Kepka, L., Oledzki, J., Bebenek, M., Kryj, M., Bednarczyk, M., Chwalinski, M., Dziewiecki, A., Jaskola, K., Kosakowska, E., Kukawski, P., Liszka-Dalecki, P., Michalski, W., Nasierowska-Guttmejer, A., Nawrocki, G., Piotrowski, P., Sikora, D., Sopylo, R., Zawadzka, B., Andziak, P., Ziembinski, A., Biejat, Z., Polanski, J., Gornicka, B., Krasnodebski, I., Slodkowski, M., Chmielarz, A., Chmielik, E., Maciejewski, B., Maka, B., Nowicka, E., Plewicki, G., Poltorak, S., Samborska-Plewicka, M., Straczynski, M., Suwinski, R., Walichiewicz, P., Widel, M., Wydmanski, J., Osuch, C., Richter, P., Skibinski, J., Darasz, Z., Herman, K., Kowalska, T., Reinfuss, M., Rys, J., Stelmach, A., Al-Amawi, T., Husarski, T., Kozlowski, M., Jarema, A., Kladny, J., Rogowska, D., Fundowicz, D., Lozinski, C., Murawa, P., Nowakowski, W., Stryczynska, G., Teresiak, M., Drews, M., Kedziora, R., Majewski, P., Meissner, P., Szmeja, J., Pudelko, M., Szulc, R., Winkler-Spytkowska, B., Wojnar, A., Pamucka, M., Redelbach, W., Sachambinski, A., Szudrowicz, Z., Tokar, P., Florek, A., Gebski, A., Gluszek, S., Gozdz, S., Kedzierawski, P., Korejba, W., Kucharczyk, D., Kukolowicz, P., Ostrowski, M., Sadowski, J., Salata, A., Sluszniak, J., Sygut, J., Wieczorek, A., Zielinski, A., Chmielewska-Pytka, B., Harezga, B., Pawlak, M., Bocian, R., Cywinski, J., Postoperative complications in patients irradiated pre-operatively for rectal cancer: Report of a randomised trial comparing short-term radiotherapy vs chemoradiation, Colorectal Disease, 7, 410-416, 2005	The trial is included in the review but this publications does not report any outcomes of interest.
Bujko, K., Nowacki, M. P., Nasierowska-Guttmejer, A., Kepka, L., Winkler-Spytkowska, B., Suwinski, R., Oledzki, J., Stryczynska, G., Wieczorek, A., Serkies, K., Rogowska, D., Tokar, P., Prediction of mesorectal nodal metastases after chemoradiation for rectal cancer: Results of a randomised trial. Implication for subsequent local excision, Radiotherapy and Oncology, 76, 234-240, 2005	No outcomes of interest.
Cai, Yh, Huang, Mj, Deng, Yh, Wu, Xj, Wang, H, Yang, Zl, He, Xs, Wang, Jp, Meta-analysis of efficacy and safety on neoadjuvant therapy for rectal cancer (Provisional abstract), Database of Abstracts of Reviews of Effects, 1150-1155, 2012	Full text in Chinese.
Calvo, F. A., Sole, C. V., Serrano, J., Del Valle, E., Rodriguez, M., Munoz-Calero, A., Garcia-Sabrido, J. L., Garcia-Alfonso, P., Peligros, I., Alvarez, E., Preoperative chemoradiation with or without induction oxaliplatin plus 5-fluorouracil in locally advanced rectal cancer: Long-term outcome analysis, Strahlentherapie und Onkologie, 190, 149-157, 2014	Not a RCT but an observational study.
Camma, C., Giunta, M., Fiorica, F., Pagliaro, L., Craxi, A., Cottone, M., Preoperative radiotherapy for resectable rectal cancer: A meta-analysis, JAMA, 284, 1008-15, 2000	Systematic review and meta-analysis of RCTs comparing preoperative radiotherapy and surgery versus surgery alone. All included studies apart from 1 are published prior to 1997. The one published in 1997 is included in our review.
Ceelen, W., Boterberg, T., Pattyn, P., van Eijkeren, M., Gillardin, J. M., Demetter, P., Smeets, P., Van Damme, N.,	Not a RCT but an observational study.

Study	Reason for exclusion
Monsaert, E., Peeters, M., Neoadjuvant chemoradiation versus hyperfractionated accelerated radiotherapy in locally advanced rectal cancer, Annals of Surgical Oncology, 14, 424-31, 2007	
Ceelen, W., Willaert, W., Varewyck, M., Libbrecht, S., Goetghebeur, E., Pattyn, P., On behalf of, Procare, Effect of Neoadjuvant Radiation Dose and Schedule on Nodal Count and Its Prognostic Impact in Stage II-III Rectal Cancer, Annals of Surgical Oncology, 23, 3899-3906, 2016	Not a RCT but an observational study.
Chen K, Xie G, Zhang Q, Shen Y, Zhou T. Comparison of short-course with long-course preoperative neoadjuvant therapy for rectal cancer: A meta-analysis. J Cancer Res Ther. 2018;14(Supplement):S224-S31.	Systematic review of RCTs. All included studies are either included in our review or are too old for inclusion in our review.
Chen, C., Sun, P., Rong, J., Weng, H. W., Dai, Q. S., Ye, S., Short Course Radiation in the Treatment of Localized Rectal Cancer: A Systematic Review and Meta-Analysis, Scientific reports, 5, 10953, 2015	Systematic review and meta-analysis of the effectiveness of short-course radiotherapy. All included studies are either included in our review or are too old for inclusion in our review.
Chen, M., Song, X., Chen, L. Z., Xu, L., Lu, Y. P., Zhang, J. S., Adjuvant Second-Dose Chemotherapy before Surgery for Patients with Locally Advanced Rectal Malignancy Is Not Beneficial: A Systematic Review and Meta-Analysis, Gastroenterology research & practice, 2017, 1373092, 2017	Systematic review and meta-analysis of studies comparing preoperative CRT with or without additional CT. The RCTs that compared preop CRT with prior CT to preop CRT without prior CT were already included in our review. Other studies were not relevant for our review.
Chen, T. Y. T., Wiltink, L. M., Nout, R. A., Meershoek-Klein Kranenbarg, E., Laurberg, So, Marijnen, C. A. M., Van De Velde, C. J. H., Bowel function 14 years after preoperative short-course radiotherapy and total mesorectal excision for rectal cancer: Report of a multicenter randomized trial, Clinical Colorectal Cancer, 14, 106-114, 2015	No outcomes of interest.
Chmielik, E., Bujko, K., Nasierowska-Guttmejer, A., Nowacki, M. P., Kepka, L., Sopylo, R., Wojnar, A., Majewski, P., Sygut, J., Karmolinski, A., Huzarski, T., Wandzel, P., Distal intramural spread of rectal cancer after preoperative radiotherapy: The results of a multicenter randomized clinical study, International Journal of Radiation Oncology Biology Physics, 65, 182-188, 2006	No outcomes of interest.
Chua, Y. J., Barbachano, Y., Cunningham, D., Oates, J. R., Brown, G., Wotherspoon, A., Tait, D., Massey, A., Tebbutt, N. C., Chau, I., Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial, The Lancet Oncology, 11, 241-248, 2010	Phase II trial, no comparison group.
Ciria, J. P., Eguiguren, M., Cafiero, S., Uranga, I., Diaz de Cerio, I., Querejeta, A., Urraca, J. M., Minguez, J., Guimon, E., Puertolas, J. R., Could preoperative short-course radiotherapy be the treatment of choice for localized advanced rectal carcinoma?, Reports of Practical Oncology and Radiotherapy, 20, 1-11, 2015	A review, included studies checked for relevance. All relevant studies already included in our review.
Cleary RK, Morris AM, Chang GJ, Halverson AL. Controversies in Surgical Oncology: Does the Minimally Invasive Approach for Rectal Cancer Provide Equivalent Oncologic Outcomes Compared with the Open Approach? Ann Surg Oncol. 2018;25(12):3587-95.	A systematic review, included studies checked for relevance. All included studies are either included in our review or are too old for inclusion in our review.

Study	Reason for exclusion
Colorectal Cancer Chemotherapy Study Group of Japan - The 2nd, Trial, Results of a randomized trial with or without 5-FU-based preoperative chemotherapy followed by postoperative chemotherapy in resected colon and rectal carcinoma, Japanese Journal of Clinical Oncology, 33, 288-96, 2003	Relevant trial and comparison but insufficient data reported to be used in our analysis.
Craig-Schapiro, R., Kamel, I. R., Sacerdote, M., Canner, J., Pittman, M., Hicks, C. W., Hacker-Prietz, A., Hobbs, R. F., Armour, E. P., Efron, J. E., Wick, E. C., Azad, N. S., Herman, J. M., Gearhart, S. L., Radiographic predictors of response to endoluminal brachytherapy for the treatment of rectal cancer, Journal of Radiation Oncology, 6, 287-294, 2017	Not a RCT but an observational study.
Crane, C. H., Janjan, N. A., Mason, K., Milas, L., Preoperative chemoradiation for locally advanced rectal cancer: emerging treatment strategies, Oncology (Williston Park), 16, 39-44, 2002	A review, included studies checked for relevance.
Craven, I., Sebag-Montefiore, D., Is there a role for radiotherapy in operable rectal cancer?, Clinical Oncology (Royal College of Radiologists), 19, 687-92, 2007	A review, included studies checked for relevance.
Cui T, Sun W, He Y, Zhang G, Wang D, Xia Y, et al. The Feasibility and Safety of Interventional Occlusion Treatment of Intracristal Ventricular Septal Defects: Clinical Report of 56 Cases. Cardiology. 2017;137(4):218-24.	Non-randomised study
Dahlberg, M., Glimelius, B., Graf, W., Pahlman, L., Preoperative irradiation affects functional results after surgery for rectal cancer: results from a randomized study, Diseases of the Colon & Rectum, 41, 543-9; discussion 549-51, 1998	No outcomes of interest.
Dahlberg, M., Glimelius, B., Pahlman, L., Improved survival and reduction in local failure rates after preoperative radiotherapy: evidence for the generalizability of the results of Swedish Rectal Cancer Trial, Annals of Surgery, 229, 493-7, 1999	Other publications from the same trial (the Swedish Rectal Cancer Trial) already included in the review. This paper does not present any additional outcomes or data.
Dahlberg, M., Stenborg, A., Pahlman, L., Glimelius, B., Cost-effectiveness of preoperative radiotherapy in rectal cancer: Results from the Swedish Rectal Cancer Trial, International Journal of Radiation Oncology Biology Physics, 54, 654-660, 2002	A cost effectiveness analysis from the Swedish Rectal Cancer Trial (already included in the review).
D'Ambrosio G, Picchetto A, Campo S, Palma R, Panetta C, De Laurentis F, et al. Quality of life in patients with loco-regional rectal cancer after ELRR by TEM versus VLS TME after nChRT: long-term results. Surg Endosc. 2019;33(3):941-8.	Wrong comparison (comparison relevant to evidence review C1)
Das, P., Crane, C. H., Preoperative and adjuvant treatment of localized rectal cancer, Current Oncology Reports, 8, 167-173, 2006	A review, included studies checked for relevance.
De Felice, F., Musio, D., Izzo, L., Tombolini, V., Neoadjuvant chemoradiotherapy for locally advanced rectal cancer: The debate continues, World Journal of Gastrointestinal Oncology, 6, 438-40, 2014	A review, included studies checked for relevance.
Delaney, C. P., Lavery, I. C., Brenner, A., Hammel, J., Senagore, A. J., Noone, R. B., Fazio, V. W., Preoperative radiotherapy improves survival for patients undergoing total mesorectal excision for stage T3 low rectal cancers, Annals of Surgery, 236, 203-207, 2002	Not a RCT but a prospective cohort study.
Denost Q, Loughlin P, Chevalier R, Celerier B, Didailler R, Rullier E. Transanal versus abdominal low rectal dissection for	Wrong comparison (comparison relevant to evidence review C3)

Study	Reason for exclusion
rectal cancer: long-term results of the Bordeaux' randomized trial. Surg Endosc. 2018;32(3):1486-94.	
Dewdney, A., Capdevila, J., Glimelius, B., Cervantes, A., Tait, D. M., Brown, G., Wotherspoon, A., Gonzalez De Castro, D., Chua, Y. J., Wong, R., Barbachano, Y., Oates, J. R., Chau, I., Cunningham, D., EXPERT-C: A randomized, phase II European multicenter trial of neoadjuvant capecitabine plus oxaliplatin chemotherapy (CAPOX) and chemoradiation (CRT) with or without cetuximab followed by total mesorectal excision (TME) in patients with MRI-defined, high-risk rectal cancer, Journal of Clinical Oncology. Conference: ASCO Annual Meeting, 29, 2011	Conference abstract.
Dong, X-H, Zhang, X-F, Yang, Z, Liu, G-H, Efficacy and safety of preoperative radiochemotherapy combined with total mesorectal excision in treatment of stage II /III rectal cancer, World chinese journal of digestology, 21, 3163-3167, 2013	Full text in Chinese.
Draeger T, Volkel V, Gerken M, Klinkhammer-Schalke M, Furst A. Long-term oncologic outcomes after laparoscopic versus open rectal cancer resection: a high-quality population-based analysis in a Southern German district. Surg Endosc. 2018;32(10):4096-104.	Wrong comparison. Non-randomised study.
Feng B, Lu J, Zhang S, Yan X, Li J, Xue P, et al. Laparoscopic abdominoperineal excision with trans-abdominal individualized levator transection: interim analysis of a randomized controlled trial. Colorectal Dis. 2017;19(7):O246-O52.	Non-randomised study
Ferenschild, F. T. J., Dawson, I., De Graaf, E. J. R., De Wilt, J. H. W., Tetteroo, G. W. M., Preoperative radiotherapy has no value for patients with T2-3, n0 adenocarcinomas of the rectum, Digestive Surgery, 26, 291-296, 2009	Not a RCT but an observational study.
Fernandez-Martos, C., Pericay, C., Aparicio, J., Salud, A., Safont, M., Massuti, B., Vera, R., Escudero, P., Maurel, J., Marcuello, E., Mengual, J. L., Saigi, E., Estevan, R., Mira, M., Polo, S., Hernandez, A., Gallen, M., Arias, F., Serra, J., Alonso, V., Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo Cancer de Recto 3 study, Journal of Clinical Oncology, 28, 859-865, 2010	This trial is included in the review, however, this publication does not report any outcomes that is not already reported in the subsequent publication (Fernandez-Martos 2015).
Fernandez-Martos, C., Pericay, C., Salud, A., Alonso, V., Massuti, B., Safont, M., Vera, R., Escudero, P., Maurel, J., Aparicio, J., Randomized phase II trial comparing two strategies in high-risk rectal cancer (RC): Chemoradiation (CRT) followed by total mesorectal excision (TME) and adjuvant chemotherapy (CT) or induction CT followed by CRT and TME- Preliminary results of the multicenter GCR-3 study, Journal of Clinical Oncology, 26, 4087, 2008	Conference abstract.
Fernandez-Martos, C., Pericay, C., Salud, A., Massuti, B., Alonso, V., Safont, M. J., Vera, R., Escudero, M. P., Maurel, J., Aparicio, J., Three-year outcomes of GCR-3: A phase II randomized trial comparing conventional preoperative chemoradiation (CRT) followed by surgery and postoperative adjuvant chemotherapy (CT) with induction CT followed by CRT and surgery in locally advanced rectal cancer, Journal of Clinical Oncology. Conference: ASCO Annual Meeting, 29, 2011	Conference abstract.

Study	Reason for exclusion
Fietkau, R, Reduction of local recurrence and distant metastases in advanced rectal carcinoma by preoperative radiotherapy--results of a randomized study by the MRC (Medical Research Council), Strahlentherapie und Onkologie, 173, 488-489, 1997	A commentary, full text in German.
Figueredo, A., Zuraw, L., Wong, R. K., Agboola, O., Rumble, R. B., Tandan, V., Cancer Care Ontario's Program in Evidence-based Care's Gastrointestinal Cancer Disease Site, Group, The use of preoperative radiotherapy in the management of patients with clinically resectable rectal cancer: a practice guideline, BMC Medicine, 1, 1, 2003	A review, included studies checked for relevance.
Fleming, F. J., Pahlman, L., Monson, J. R. T., Neoadjuvant therapy in rectal cancer, Diseases of the Colon and Rectum, 54, 901-912, 2011	A systematic review, included studies checked for relevance.
Fleshman J, Branda ME, Sargent DJ, Boller AM, George VV, Abbas MA, et al. Disease-free Survival and Local Recurrence for Laparoscopic Resection Compared With Open Resection of Stage II to III Rectal Cancer: Follow-up Results of the ACOSOG Z6051 Randomized Controlled Trial. Annals of surgery. 2019;269(4):589-95.	Wrong comparison (comparison relevant for evidence review C3)
Garajova, I., Di Girolamo, S., De Rosa, F., Corbelli, J., Agostini, V., Biasco, G., Brandi, G., Neoadjuvant treatment in rectal cancer: Actual status, Chemotherapy Research and Practice, 2011 (no pagination), 2011	A review, included studies checked for relevance.
Gerard, J. P., Rostom, Y., Gal, J., Benchimol, D., Ortholan, C., Aschele, C., Levi, J. M., Can we increase the chance of sphincter saving surgery in rectal cancer with neoadjuvant treatments: lessons from a systematic review of recent randomized trials, Critical Reviews in Oncology-Hematology, 81, 21-8, 2012	A review, included studies checked for relevance. All relevant studies already included in our review.
Gerard, Jp, Cotte, E, Decullier, E, Doyen, J, Hannoun-Levi, Jm, Chapet, O, Pathological response is a marker but not a cause of good prognosis in rectal cancer: 15-year follow-up of the lyon r90-01 randomized trial, International journal of radiation oncology biology physics., 93, S126, 2015	Conference abstract.
Glimelius, B., Isacsson, U., Preoperative radiotherapy for rectal cancer: Is 5 x 5 Gy a good or a bad schedule?, Acta Oncologica, 40, 958-967, 2001	A review, included studies checked for relevance.
Glimelius, B., Neo-adjuvant radiotherapy in rectal cancer, World Journal of Gastroenterology, 19, 8489-8501, 2013	A review, included studies checked for relevance.
Glimelius, B., Pahlman, L., Preoperative radiotherapy for rectal cancer: hypofractionation with multiple fractions (15-25 Gy), Annali italiani di chirurgia, 72, 539-547, 2001	A review, included studies checked for relevance.
Glimelius, B., The role of short-term neoadjuvant radiotherapy for rectal cancer, Advances in Gastrointestinal Cancers, 5, 2-4, 2007	A review, included studies checked for relevance.
Glynne-Jones, R., Anyamene, N., Moran, B., Harrison, M., Neoadjuvant chemotherapy in MRI-staged high-risk rectal cancer in addition to or as an alternative to preoperative chemoradiation?, Annals of Oncology, 23, 2517-2526, 2012	A review, included studies checked for relevance.
Glynne-Jones, R., Chau, I., Neoadjuvant therapy before surgical treatment, European Journal of Cancer, Supplement, 11, 45-59, 2013	A review, included studies checked for relevance.
Glynne-Jones, R., Grainger, J., Harrison, M., Ostler, P., Makris, A., Neoadjuvant chemotherapy prior to preoperative	A review, included studies checked for relevance.

Study	Reason for exclusion
chemoradiation or radiation in rectal cancer: Should we be more cautious?, British Journal of Cancer, 94, 363-371, 2006	
Glynne-Jones, R., Harrison, M., Locally advanced rectal cancer: What is the evidence for induction chemoradiation?, Oncologist, 12, 1309-1318, 2007	A review, included studies checked for relevance.
Glynne-Jones, R., Neoadjuvant treatment in rectal cancer: Do we always need radiotherapy-or can we risk assess locally advanced rectal cancer better?, Early Gastrointestinal Cancers, Recent Results in Cancer Research. 196, 21-36, 2012	A review, included studies checked for relevance.
Gollins, S., Sebag-Montefiore, D., Neoadjuvant Treatment Strategies for Locally Advanced Rectal Cancer, Clinical Oncology (Royal College of Radiologists), 28, 146-51, 2016	A review, included studies checked for relevance.
Gray, R., Hills, R., Stowe, R., Clarke, M., Peto, R., Buyse, M., Piedbois, P., Adjuvant radiotherapy for rectal cancer: A systematic overview of 8507 patients from 22 randomised trials, Lancet, 358, 1291-1304, 2001	A systematic review, included studies checked for relevance. No relevant studies for our review. All included studies conducted or published between 1960s and 1980s.
Habr-Gama, A, Perez, Ro, Kiss, Dr, Rawet, V, Scanavini, A, Santinho, Pm, Nadalin, W, Preoperative chemoradiation therapy for low rectal cancer. Impact on downstaging and sphincter-saving operations, Hepato-Gastroenterology, 51, 1703-1707, 2004	Not a RCT but an observational study.
Harris, D. A., Thorne, K., Hutchings, H., Islam, S., Holland, G., Hatcher, O., Gwynne, S., Jenkins, I., Coyne, P., Duff, M., Feldman, M., Winter, D. C., Gollins, S., Quirke, P., West, N., Brown, G., Fitzsimmons, D., Brown, A., Beynon, J., Protocol for a multicentre randomised feasibility trial evaluating early Surgery Alone In LOw Rectal cancer (SAILOR), BMJ Open, 6 (11) (no pagination), 2016	A protocol of an on-going trial comparing preoperative CRT and surgery versus surgery alone. No results have been published yet.
Herrmann, T, Petersen, S, Hellmich, G, Baumann, M, Ludwig, K, Delayed toxicity of brief preoperative irradiation and risk-adjusted postoperative radiotherapy of operative rectal carcinoma. Results of a randomized prospective study, Strahlentherapie und Onkologie, 175, 430-436, 1999	Full text in German.
Hida K, Okamura R, Sakai Y, Konishi T, Akagi T, Yamaguchi T, et al. Open versus Laparoscopic Surgery for Advanced Low Rectal Cancer: A Large, Multicenter, Propensity Score Matched Cohort Study in Japan. Annals of surgery. 2018;268(2):318-24.	Wrong comparison – compares open versus laparoscopic surgery
Holmer C, Kreis ME. Systematic review of robotic low anterior resection for rectal cancer. Surg Endosc. 2018;32(2):569-81.	Systematic review of RCTs. (relevant for evidence review C3).
Hong, T. S., Kachnic, L. A., Preoperative chemoradiotherapy in the management of localized rectal cancer: the new standard, Gastrointestinal Cancer Research, 1, 49-56, 2007	A review, included studies checked for relevance.
Huh, J. W., Kim, C. H., Kim, H. R., Kim, Y. J., Oncologic outcomes of pathologic stage i lower rectal cancer with or without preoperative chemoradiotherapy: Are they comparable?, Surgery, 150, 980-984, 2011	Not a RCT but an observational study.
Hyams, D. M., Mamounas, E. P., Petrelli, N., Rockette, H., Jones, J., Wieand, H. S., Deutsch, M., Wickerham, L., Fisher, B., Wolmark, N., A clinical trial to evaluate the worth of preoperative multimodality therapy in patients with operable carcinoma of the rectum: a progress report of National Surgical	Another publication of this trial (NSABP R03) is already included in the review. This publication does not report any additional outcomes not already reported by the other paper and is

Study	Reason for exclusion
Breast and Bowel Project Protocol R-03, Diseases of the Colon & Rectum, 40, 131-9, 1997	superseded by the later publication with more follow-up data.
Isomoto, H., Tomita, M., Sugimachi, K., Ogawa, M., Yamada, K., Nakagoe, T., Mori, M., Takano, S., Kakegawa, T., Pre- and post-operative adjuvant chemotherapy in colorectal cancer, International Journal of Oncology, 23, 1103-1108, 2003	The intervention in this trial (tegafur suppositories) is not in use in the UK.
Jakobsen, A. K. M., Appelt, A. L., Lindebjerg, J., Ploeen, J., Rafaelsen, S. R., Vuong, T., The dose-effect relationship in preoperative chemoradiation of locally advanced rectal cancer: Preliminary results of a phase III trial, Journal of Clinical Oncology. Conference: ASCO Annual Meeting, 29, 2011	Conference abstract.
Jakobsen, A., Ploen, J., Vuong, T., Appelt, A., Lindebjerg, J., Rafaelsen, S. R., Dose-effect relationship in chemoradiotherapy for locally advanced rectal cancer: A randomized trial comparing two radiation doses, International Journal of Radiation Oncology Biology Physics, 84, 949-954, 2012	Later publication from the same trial included, this publication has no additional outcomes of interest.
Jakobsen, Akm, Appelt, Al, Lindebjerg, J, Ploeen, J, Rafaelsen, Sr, Vuong, T, The dose-effect relationship in preoperative chemoradiation of locally advanced rectal cancer: preliminary results of a phase III trial, Journal of Clinical Oncology, 29, 2011	Conference abstract.
Jensen, A. D., Roder, F., Cost-effectiveness analysis of preoperative radiotherapy in rectal cancer: 5 x 5 Gy versus chemoradiation, Strahlentherapie und Onkologie, 192 (1 Supplement 1), 30, 2016	Conference abstract.
Jimenez-Rodriguez, R., Quezada, F., Lynn, P., Strombon, P., Paty, P. S., Martin, W. R., Garcia Aguilar, J. Similar short-term oncolgical outcomes for robotic and open total mesorectal excision in patients with rectal cancer. 2018 American Society of Colon and Rectal Surgeons Annual Meeting, ASCRS 2018. United States	Wrong comparison – compares robotic and open TME
Jones K, Qassem MG, Sains P, Baig MK, Sajid MS. Robotic total meso-rectal excision for rectal cancer: A systematic review following the publication of the ROLARR trial. World J Gastrointest Oncol. 2018;10(11):449-64.	Systematic review of RCTs. (relevant for evidence review C3).
Kachnic, L. A., Adjuvant chemoradiation for localized rectal cancer: current trends and future directions, Gastrointestinal Cancer Research, 1, S64-72, 2007	A review, included studies checked for relevance.
Kachnic, L. A., Should Preoperative or Postoperative Therapy Be Administered in the Management of Rectal Cancer?, Seminars in Oncology, 33, 64-69, 2006	A review, included studies checked for relevance.
Kairevice, L, Pauzas, H, Janciauskiene, R, Latkauskas, T, Algimantas, T, Saladzinskas, Z, Petrauskas, A, Pavalkis, D, Factors, that may influence outcomes for stage II-III resectable rectal cancer patients treated with preoperative conventional chemoradiotherapy or short-term radiotherapy followed by delayed surgery. Data from the randomized single institution trial, European journal of cancer., 51, S328, 2015	Conference abstract.
Kaiser, A. M., Klaristenfeld, D., Beart, R. W., Preoperative versus postoperative radiotherapy for rectal cancer in a decision analysis and outcome prediction model, Annals of Surgical Oncology, 19, 4150-4160, 2012	A review with decision analysis and outcome prediction model. All relevant studies already considered for inclusion.
Kao, P. S., Chang, S. C., Wang, L. W., Lee, R. C., Liang, W. Y., Lin, T. C., Chen, W. S., Jiang, J. K., Yang, S. H., Wang, H.	Not a RCT but an observational study.

Study	Reason for exclusion
S., Lin, J. K., The impact of preoperative chemoradiotherapy on advanced low rectal cancer, Journal of Surgical Oncology, 102, 771-777, 2010	
Kapiteijn, E, Marijnen, Ca, Nagtegaal, Id, Putter, H, Steup, Wh, Wiggers, T, Rutten, Hj, Pahlman, L, Glimelius, B, Krieken, Jh, Leer, Jw, Velde, Cj, Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer, New England Journal of Medicine, 345, 638-646, 2001	Other publications of this trial (the Dutch TME trial) are already included in the review. This publication report 2-year survival but is superseded by a later publications with more follow-up data.
Kapiteijn, E, Marijnen, Cam, Nagtegaal, Id, Putter, H, Steup, Wh, Wiggers, T, Rutten, Hjt, Pahlman, L, Glimelius, B, Krieken, Jhjm, Leer, Jwh, Velde, Cjh, Improved local control following preoperative radiotherapy and total mesorectal excision in patients with resectable rectal carcinoma: a randomised multicentre trial, Nederlands tijdschrift voor geneeskunde, 145, 2272-2280, 2001	Full text in Dutch.
Kapiteijn, E, Marijnen, Cam, Nagtegaal, Ld, Putter, H, Steup, Wh, Wiggers, T, Rutten, Hjt, Pahlman, L, Glimelius, B, Krieken, Jhjm, Leer, Jwh, Velde, Cjh, Better local control after preoperative radiotherapy in patients with resectable rectum carcinoma and total mesoral excision; a randomized multicentre research, Nederlands tijdschrift voor geneeskunde, 145, 2272-2279, 2001	Full text in Dutch. Duplicate of another excluded publication.
Kapiteijn, E., Klein Kranenbarg, E., Steup, W. H., Taat, C. W., Rutten, H. J. T., Wiggers, T., Van Krieken, J. H. J. M., Hermans, J., Leer, J. W. H., Van De Velde, C. J. H., Total mesorectal excision (TME) with or without preoperative radiotherapy in the treatment of primary rectal cancer: Prospective randomised trial with standard operative and histopathological techniques, European Journal of Surgery, 165, 410-420, 1999	An interim analysis of the Dutch TME trial (included in this review). This publication does not report on any additional outcomes which are not already reported in other included papers from the same trial.
Kapiteijn, E., van De Velde, C. J., European trials with total mesorectal excision, Seminars in Surgical Oncology, 19, 350-7, 2000	Review and discussion of European trials with TME. All relevant trials discussed already considered for this review.
Kim HJ, Choi GS, Park JS, Park SY, Yang CS, Lee HJ. The impact of robotic surgery on quality of life, urinary and sexual function following total mesorectal excision for rectal cancer: a propensity score-matched analysis with laparoscopic surgery. Colorectal Dis. 2018;20(5):O103-O13.	Wrong comparison - compares robot-assisted versus laparoscopic surgery
Kim MJ, Park SC, Park JW, Chang HJ, Kim DY, Nam BH, et al. Robot-assisted Versus Laparoscopic Surgery for Rectal Cancer: A Phase II Open Label Prospective Randomized Controlled Trial. Annals of surgery. 2018;267(2):243-51.	Wrong comparison - compares robot-assisted versus laparoscopic surgery
Klenova, A., Georgiev, R., Kurtev, P., Kurteva, G., Short versus conventional preoperative radiotherapy of rectal cancer: Indications, Journal of B.U.ON., 12, 227-232, 2007	Not a RCT but an observational study.
Koedam TWA, Veltcamp Helbach M, Penna M, Wijsmuller A, Doornebosch P, van Westreenen HL, et al. Short-term outcomes of transanal completion total mesorectal excision (cTaTME) for rectal cancer: a case-matched analysis. Surg Endosc. 2019;33(1):103-9.	Non-randomised study comparing TaTME vs cTATME, compares versions of the same (like different doses same intervention
Kusters, M., Marijnen, C. A. M., van de Velde, C. J. H., Rutten, H. J. T., Lahaye, M. J., Kim, J. H., Beets-Tan, R. G. H., Beets, G. L., Patterns of local recurrence in rectal cancer; a study of	The trial (the Dutch TME trial) is included in this review, however, this publication has been superseded by a later publication

Study	Reason for exclusion
the Dutch TME trial, European Journal of Surgical Oncology, 36, 470-476, 2010	with more follow-up data and has no additional outcomes relevant for this review.
Latkauskas, T., Pauzas, H., Gineikiene, I., Janciauskiene, R., Juozaityte, E., Saladzinskas, Z., Tamelis, A., Pavalkis, D., Initial results of a randomized controlled trial comparing clinical and pathological downstaging of rectal cancer after preoperative short-course radiotherapy or long-term chemoradiotherapy, both with delayed surgery, Colorectal Disease, 14, 294-298, 2012	The trial is already included in the review but this publication presents interim results and does not report any outcomes not reported by the subsequent publications of the same trial.
Law WL, Foo DCC. Comparison of early experience of robotic and transanal total mesorectal excision using propensity score matching. Surg Endosc. 2019;33(3):757-63.	Non-randomised study comparing TaTME vs Robotic, population not clear, only reports important outcomes no critical outcomes reported
Lee SH, Kim DH, Lim SW. Robotic versus laparoscopic intersphincteric resection for low rectal cancer: a systematic review and meta-analysis. Int J Colorectal Dis. 2018;33(12):1741-53.	Review of RCTs - included studies checked and all accounted for
Lin Y, Lin H, Xu Z, Zhou S, Chi P. Comparative Outcomes of Preoperative Chemoradiotherapy and Selective Postoperative Chemoradiotherapy in Clinical Stage T3N0 Low and Mid Rectal Cancer. J Invest Surg. 2018:1-9.	Wrong comparison for review question- compares for preoperative CRT vs postoperative CRT
Liu, S. X., Zhou, Z. R., Chen, L. X., Yang, Y. J., Hu, Z. D., Zhang, T. S., Short-course Versus Long-course Preoperative Radiotherapy plus Delayed Surgery in the Treatment of Rectal Cancer: a Meta-analysis, Asian Pacific journal of cancer prevention : APJCP, 16, 5755-5762, 2015	A meta-analysis of RCTs comparing preoperative short-course RT to long-course RT. All included studies already considered for inclusion for this review.
Loos, M, Quentmeier, P, Schuster, T, Nitsche, U, Gertler, R, Keerl, A, Kocher, T, Friess, H, Rosenberg, R, Effect of preoperative radio(chemo)therapy on long-term functional outcome in rectal cancer patients: a systematic review and meta-analysis (Provisional abstract), Annals of Surgical OncologyAnn Surg Oncol, 20, 1816-1828, 2013	A systematic review and meta-analysis studying the effect of preoperative CRT on long-term functional outcomes. Most included studies are observational studies. The included RCTs either already included in our review or not relevant.
Maas, H. A. A. M., Lemmens, V. E. P. P., Nijhuis, P. H. A., De Hingh, I. H. J. T., Koning, C. C. E., Janssen-Heijnen, M. L. G., Benefits and drawbacks of short-course preoperative radiotherapy in rectal cancer patients aged 75 years and older, European Journal of Surgical Oncology, 39, 1087-1093, 2013	Not a RCT but an observational study.
Marijnen, C. A. M., Kapiteijn, E., Van de Velde, C. J. H., Martijn, H., Steup, W. H., Wiggers, T., Klein Kranenbarg, E., Leer, J. W. H., Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: Report of a multicenter randomized trial, Journal of Clinical Oncology, 20, 817-825, 2002	Other publications of this trial (the Dutch TME trial) are already included in the review. This publications has no additional relevant outcomes.
Marijnen, C. A. M., Nagtegaal, I. D., Klein Kranenbarg, E., Hermans, J., Van de Velde, C. J. H., Leer, J. W. H., Van Krieken, J. H. J. M., No downstaging after short-term preoperative radiotherapy in rectal cancer patients, Journal of Clinical Oncology, 19, 1976-1984, 2001	No outcomes of interest.
Martling, A., Holm, T., Johansson, H., ErikRutqvist, L., Cedermark, B., The Stockholm II trial on preoperative	Relevant trial but over half of the participants included in the Swedish Rectal Cancer Trial

Study	Reason for exclusion
radiotherapy in rectal carcinoma: Long-term follow-up of a population-based study, Cancer, 92, 896-902, 2001	which is included in the review. No additional outcomes reported.
Maschuw, K., Kress, R., Ramaswamy, A., Braun, I., Langer, P., Gerdes, B., Short-term preoperative radiotherapy in rectal cancer patients leads to a reduction of the detectable number of lymph nodes in resection specimens, Langenbeck's Archives of Surgery, 391, 364-368, 2006	Not a RCT but an observational study.
Minsky, B. D., Adjuvant treatment for rectal cancer: Short-course radiation vs. long-course chemoradiation, Seminars in Colon and Rectal Surgery, 24, 155-158, 2013	A review, included studies checked for relevance.
Minsky, B. D., Rodel, C., Valentini, V., Preoperative therapy for rectal cancer: Short-course radiation vs. long-course chemoradiation, Seminars in Colon and Rectal Surgery, 25, 19-21, 2014	A review, included studies checked for relevance.
Mullen, T. D., Kim, E. Y., Apisarnthanarax, S., Short-Course Radiation Therapy Versus Long-Course Chemoradiation in the Neoadjuvant Treatment of Locally Advanced Rectal Cancer: New Insights from Randomized Trials, Current Colorectal Cancer Reports, 13, 165-174, 2017	A review of RCTs studying preoperative short-course RT versus long-course RT. Included studies already considered for inclusion or not relevant.
NCT. Laparoscopic Surgery or Robotic-Assisted Laparoscopic Surgery in Treating Patients With Rectal Cancer That Can Be Removed By Surgery. 2010	Not full text; no usable data
NCT. Optimisation of Response for Organ Preservation in Rectal Cancer : neoadjuvant Chemotherapy and Radiochemotherapy vs. Radiochemotherapy. 2015	Non-randomised study comparing prior therapy vs no prior therapy. Study design not relevant. Not full text; no usable data.
NCT. Phase III Study Comparing Preoperative Chemoradiotherapy Alone Versus Neoadjuvant Chemotherapy With Folfirinox Regimen Followed by Preoperative Chemoradiotherapy for Patients With Resectable Locally Advanced Rectal Cancer. 2013	Not full text; no usable data
NCT. Preoperative Chemoradiotheray for Rectal Cancer. 2009	Not full text; no usable data
Nienhuser H, Heger P, Schmitz R, Kulu Y, Diener MK, Klose J, et al. Short- and Long-Term Oncological Outcome After Rectal Cancer Surgery: a Systematic Review and Meta-Analysis Comparing Open Versus Laparoscopic Rectal Cancer Surgery. J Gastrointest Surg. 2018;22(8):1418-33.	Not full text; no usable data
Nilsson, P. J., van Etten, B., Hospers, G. A. P., Pahlman, L., van de Velde, C. J. H., Beets-Tan, R. G. H., Blomqvist, L., Beukema, J. C., Kapiteijn, E., Marijnen, C. A. M., Nagtegaal, I. D., Wiggers, T., Glimelius, B., Short-course radiotherapy followed by neo-adjuvant chemotherapy in locally advanced rectal cancer - the RAPIDO trial, BMC CancerBMC Cancer, 13, no pagination, 2013	A protocol for a RCT. No results have been published yet.
O'Gorman, C, Denieffe, S, Gooney, M, Literature review: preoperative radiotherapy and rectal cancer ? impact on acute symptom presentation and quality of life (Provisional abstract), Database of Abstracts of Reviews of Effects, 333-351, 2014	A review, included studies checked for relevance..
Ohtani H, Maeda K, Nomura S, Shinto O, Mizuyama Y, Nakagawa H, et al. Meta-analysis of Robot-assisted Versus Laparoscopic Surgery for Rectal Cancer. In Vivo. 2018;32(3):611-23.	Systematic review and meta-analysis. Wrong comparison – compares robot-assisted versus laparascopic surgery
Okuno, K., Aoyama, T., Oba, K., Yokoyama, N., Matsuhashi, N., Kunieda, K., Nishimura, Y., Akamatsu, H., Kobatake, T., Morita, S., Yoshikawa, T., Sakamoto, J., Saji, S., Randomized phase III trial comparing surgery alone to UFT + PSK for stage	Wrong comparison, this study compares postoperative therapy to surgery alone.

Study	Reason for exclusion
II rectal cancer (JFMC38 trial), Cancer Chemotherapy and Pharmacology, 1-7, 2017	
Okuno, K., Aoyama, T., Oba, K., Yokoyama, N., Yoshida, K., Kunieda, K., Nishimura, E., Akamatsu, H., Obatake, T., Morita, S., Yoshikawa, T., Saji, S., Clinical trial comparing UFT-PSK combination adjuvant therapy and surgery-alone for stage II rectal cancer, Annals of Cancer Research and Therapy, 25, 15-16, 2017	A summary of a RCT protocol. Wrong comparison, this study compares postoperative therapy to surgery alone.
Ortholan, C., Francois, E., Thomas, O., Benchimol, D., Baulieux, J., Bosset, J. F., Gerard, J. P., Role of radiotherapy with surgery for T3 and resectable T4 rectal cancer: Evidence from randomized trials, Diseases of the Colon and Rectum, 49, 302-310, 2006	A review, included studies checked for relevance.
Palta, M., Willett, C. G., Czito, B. G., Short-course versus long-course chemoradiation in rectal cancer--time to change strategies?, Current Treatment Options in Oncology, 15, 421-8, 2014	A narrative review. All relevant studies already included in this review.
Petersen, S, Hellmich, G, Baumann, M, Herrmann, T, Henke, G, Ludwig, K, Brief preoperative radiotherapy in surgical therapy of rectal carcinoma. Long-term results of a prospective randomized study, Der chirurg; zeitschrift fur alle gebiete der operativen medizen, 69, 759-765, 1998	Full text in German.
Pettersson, D., Cedermark, B., Holm, T., Radu, C., Pahlman, L., Glimelius, B., Martling, A., Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer, British Journal of Surgery, 97, 580-7, 2010	This trial is included in the review, however, this publication reports interim results and does not report any additional outcomes and is therefore superseded by another publication from the same trial (Erlandsson 2017).
Pettersson, D., Glimelius, B., Iversen, H., Johansson, H., Holm, T., Martling, A., Impaired postoperative leucocyte counts after preoperative radiotherapy for rectal cancer in the Stockholm III Trial, The British journal of surgery, 100, 969-975, 2013	This trial is included in the review, however, this publication reports interim results and does not report any additional outcomes and is therefore superseded by another publication from the same trial (Erlandsson 2017).
Pettersson, D., Lorinc, E., Holm, T., Iversen, H., Cedermark, B., Glimelius, B., Martling, A., Tumour regression in the randomized Stockholm III Trial of radiotherapy regimens for rectal cancer, The British journal of surgery, 102, 972-978, 2015	Wrong comparison, compares preoperative short course RT with immediate surgery to preoperative short course RT with delayed surgery. The third arm of this trial (long course RT) was not analysed in this publication.
Pollack, J., Holm, T., Cedermark, B., Altman, D., Holmstrom, B., Glimelius, B., Mellgren, A., Late adverse effects of short-course preoperative radiotherapy in rectal cancer, British Journal of Surgery, 93, 1519-1525, 2006	No relevant outcomes.
Pollack, J., Holm, T., Cedermark, B., Holmstrom, B., Mellgren, A., Long-term effect of preoperative radiation therapy on anorectal function, Diseases of the Colon and Rectum, 49, 345-352, 2006	Relevant RCT but no relevant outcomes reported. Reports fecal incontinence.
Popek, S., Tsikitis, V. L., Hazard, L., Cohen, A. M., Preoperative radiation therapy for upper rectal cancer T3,T4/Nx: selectivity essential, Clinical Colorectal Cancer, 11, 88-92, 2012	A review. All relevant studies already included in this review.

Study	Reason for exclusion
Popek, S., Tsikitis, V. L., Neoadjuvant vs adjuvant pelvic radiotherapy for locally advanced rectal cancer: Which is superior?, World Journal of Gastroenterology, 17, 848-854, 2011	A review. All relevant studies already included in this review.
Preoperative high dose rate brachytherapy for rectal cancer (Structured abstract), Health Technology Assessment Database, 2, 2006	A bibliographic record of a NICE IPG.
Prytz M, Ledebo A, Angenete E, Bock D, Haglind E. Association between operative technique and intrusive thoughts on health-related Quality of Life 3 years after APE/ELAPE for rectal cancer: results from a national Swedish cohort with comparison with normative Swedish data. Cancer Med. 2018;7(6):2727-35.	Review, included RCTs accounted for in the review
Quirke, P., Steele, R., Monson, J., Grieve, R., Khanna, S., Couture, J., O'Callaghan, C., Myint, A. S., Bessell, E., Thompson, L. C., Parmar, M., Stephens, R. J., Sebag-Montefiore, D., Mrc Cr Ncic-Ctg Co Trial Investigators, Ncri Colorectal Cancer Study Group, Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial, Lancet, 373, 821-8, 2009	Analysis from a relevant RCT but this publication reports comparison of outcomes between plane of surgery and resection margin not by interventions.
Rahbari, N. N., Elbers, H., Askoxylakis, V., Motschall, E., Bork, U., Bu Chler, M. W., Weitz, J., Koch, M., Neoadjuvant radiotherapy for rectal cancer: Meta-analysis of randomized controlled trials, Annals of Surgical Oncology, 20, 4169-4182, 2013	Meta-analysis. Relevant included studies already included in our review. Meta-analysis includes many old studies which are not relevant for our review.
Reibetanz, J., Germer, C. T., Preoperative chemoradiotherapy and postoperative chemotherapy with 5-fluorouracil and oxaliplatin in rectal cancer: Initial results of the CAO/ARO/AIO-04 study. [German, English], Chirurg, 83, 995, 2012	Full text in German.
Rodel, C., Arnold, D., Becker, H., Fietkau, R., Ghadimi, M., Graeven, U., Hess, C., Hofheinz, R., Hohenberger, W., Post, S., Raab, R., Sauer, R., Wenz, F., Liersch, T., Induction chemotherapy before chemoradiotherapy and surgery for locally advanced rectal cancer: Is it time for a randomized phase III trial?, Strahlentherapie und Onkologie, 186, 658-664, 2010	A review, included studies checked for relevance.
Rodel, C., Trojan, J., Bechstein, W. O., Woeste, G., Neoadjuvant short-or long-term radio(chemo)therapy for rectal cancer: How and who should be treated?, Digestive Diseases, 30, 102-108, 2012	A review, included studies checked for relevance.
Rouanet P, Bertrand MM, Jarlier M, Mourregot A, Traore D, Taoum C, et al. Robotic Versus Laparoscopic Total Mesorectal Excision for Sphincter-Saving Surgery: Results of a Single-Center Series of 400 Consecutive Patients and Perspectives. Ann Surg Oncol. 2018;25(12):3572-9.	Wrong comparison, robotic versus laparoscopic TME
Ruo, L., Tickoo, S., Klimstra, D. S., Minsky, B. D., Saltz, L., Mazumdar, M., Paty, P. B., Wong, W. D., Larson, S. M., Cohen, A. M., Guillem, J. G., Long-term prognostic significance of extent of rectal cancer response to preoperative radiation and chemotherapy, Annals of Surgery, 236, 75-81, 2002	Not a RCT but an observational study.
Sadahiro, S., Suzuki, T., Ishikawa, K., Fukasawa, M., Saguchi, T., Yasuda, S., Makuuchi, H., Murayama, C., Ohizumi, Y., Preoperative radio/chemo-radiotherapy in combination with	Not a RCT but an observational study.

Study	Reason for exclusion
intraoperative radiotherapy for T3-4Nx rectal cancer, European Journal of Surgical Oncology, 30, 750-758, 2004	
Sadahiro, S., Suzuki, T., Maeda, Y., Tanaka, A., Kamijo, A., Murayama, C., Nakayama, Y., Akiba, T., Effects of preoperative immunochemoradiotherapy and chemoradiotherapy on immune responses in patients with rectal adenocarcinoma, Anticancer Research, 30, 993-1000, 2010	Wrong comparison - compares preoperative CRT with preoperative CRT with PSK.
Saglam, S., Bugra, D., Saglam, E. K., Asoglu, O., Balik, E., Yamaner, S., Basaran, M., Oral, E. N., Kizir, A., Kapran, Y., Gulluoglu, M., Sakar, B., Bulut, T., Fourth versus eighth week surgery after neoadjuvant radiochemotherapy in T3-4/N0+ rectal cancer: Istanbul R-01 study, Journal of Gastrointestinal Oncology, 5, 9-17, 2014	Wrong comparison - compares the interval between preoperative CRT (4 weeks versus 8 weeks).
Sajid, M. S., Siddiqui, M. R., Kianifard, B., Baig, M. K., Short-course versus long-course neoadjuvant radiotherapy for lower rectal cancer: a systematic review, Irish Journal of Medical Science, 179, 165-71, 2010	A systematic review. Included studies checked for relevance.
Sauer, R., Becker, H., Hohenberger, W., Rodel, C., Wittekind, C., Fietkau, R., Martus, P., Tschmelitsch, J., Hager, E., Hess, C. F., Karstens, J. H., Liersch, T., Schmidberger, H., Raab, R., Preoperative versus postoperative chemoradiotherapy for rectal cancer, New England Journal of Medicine, 351, 1731-1740+1810, 2004	Other publications of this trial (CAO/ARO/AIO-94) are already included in the review. This publication does not report any additional outcomes not already reported by other papers from the same trial and is superseded by a later publication with more follow-up data.
Sauer, R., Fietkau, R., Wittekind, C., Martus, P., Rodel, C., Hohenberger, W., Jatzko, G., Sabitzer, H., Karstens, J. H., Becker, H., Hess, C., Raab, R., Adjuvant versus neoadjuvant radiochemotherapy for locally advanced rectal cancer, Strahlentherapie und Onkologie, 177, 173-181, 2001	Other publications of this trial (CAO/ARO/AIO-94) are already included in the review. This publication does not report any additional outcomes not already reported by other papers from the same trial and is superseded by a later publication with more follow-up data.
Sebag-Montefiore, D., Steele, R., Grieve, R., Monson, J., Pugh, C., Nichols, L., Thompson, L., Quirke, P., Routine short course pre-op radiotherapy or selective post-op chemoradiotherapy for resectable cancer? Long term follow up of the MRC CR07 trial, Colorectal Disease, 14, 9, 2012	A conference abstract.
Serra-Aracil X, Pericay C, Golda T, Mora L, Targarona E, Delgado S, et al. Non-inferiority multicenter prospective randomized controlled study of rectal cancer T2-T3s (superficial) N0, M0 undergoing neoadjuvant treatment and local excision (TEM) vs total mesorectal excision (TME). Int J Colorectal Dis. 2018;33(2):241-9.	Wrong comparison – TEM vs TME
Seshadri RA, Swaminathan R, Srinivasan A. Laparoscopic versus open surgery for rectal cancer after neoadjuvant chemoradiation: Long-term outcomes of a propensity score matched study. J Surg Oncol. 2018;117(3):506-13.	Study protocol CRT TEM vs TME
Short-term surgical outcomes and patient quality of life between robotic and laparoscopic extralevator abdominoperineal excision for adenocarcinoma of the rectum	A conference abstract
Siegel, R., Burock, S., Wernecke, K. D., Kretzschmar, A., Dietel, M., Loy, V., Koswig, S., Budach, V., Schlag, P. M., Preoperative short-course radiotherapy versus combined	A protocol of a RCT.

Study	Reason for exclusion
radiochemotherapy in locally advanced rectal cancer: A multi-centre prospectively randomised study of the Berlin Cancer Society, BMC Cancer, 9 (no pagination), 2009	
Simillis C, Lal N, Thoukididou SN, Kontovounisios C, Smith JJ, Hompes R, et al. Open Versus Laparoscopic Versus Robotic Versus Transanal Mesorectal Excision for Rectal Cancer: A Systematic Review and Network Meta-analysis. Annals of surgery. 2019.	A non-randomised study
Song, J. H., Jeong, J. U., Lee, J. H., Kim, S. H., Cho, H. M., Um, J. W., Jang, H. S., Korean Clinical Practice Guideline for, Colon, Rectal Cancer, Committee, Preoperative chemoradiotherapy versus postoperative chemoradiotherapy for stage II-III resectable rectal cancer: a meta-analysis of randomized controlled trials, Radiation Oncology Journal, 35, 198-207, 2017	A systematic review and meta-analysis of preoperative chemoradiotherapy versus postoperative chemoradiotherapy. All included studies included in our review.
Spiegel DY, Boyer MJ, Hong JC, Williams CD, Kelley MJ, Moore H, et al. Long-term Clinical Outcomes of Nonoperative Management With Chemoradiotherapy for Locally Advanced Rectal Cancer in the Veterans Health Administration. Int J Radiat Oncol Biol Phys. 2019;103(3):565-73.	A systematic review and NMA - included studies accounted for in the GC review.
Stevenson ARL, Solomon MJ, Brown CSB, Lumley JW, Hewett P, Clouston AD, et al. Disease-free Survival and Local Recurrence After Laparoscopic-assisted Resection or Open Resection for Rectal Cancer: The Australasian Laparoscopic Cancer of the Rectum Randomized Clinical Trial. Annals of surgery. 2019;269(4):596-602.	Wrong comparison - laparoscopic-assisted resection or open resection
Takiyama H, Kawai K, Ishihara S, Yasuda K, Otani K, Nishikawa T, et al. Different Impacts of Preoperative Radiotherapy and Chemoradiotherapy on Oncological Outcomes in Patients with Stages II and III Lower Rectal Cancer: A Propensity Score Analysis. Dig Surg. 2018;35(3):212-9.	A non-randomised study
Van Den Brink, M., Van Den Hout, W. B., Stiggelbout, A. M., Kranenbarg, E. K., Marijnen, C. A. M., Van De Velde, C. J. H., Kievit, J., Cost-utility analysis of preoperative radiotherapy in patients with rectal cancer undergoing total mesorectal excision: A study of the Dutch colorectal cancer group, Journal of Clinical Oncology, 22, 244-253, 2004	A cost-utility analysis using clinical evidence from a RCT which is already included in our review.
Veltcamp Helbach M, Koedam TWA, Knol JJ, Velthuis S, Bonjer HJ, Tuynman JB, et al. Quality of life after rectal cancer surgery: differences between laparoscopic and transanal total mesorectal excision. Surg Endosc. 2019;33(1):79-87.	Wrong comparison – compares laparoscopic versus transanal TME
Veness, M. J., Does preoperative radiotherapy improve outcome in patients with resectable rectal cancer?, Medical Journal of Australia, 177, 563-564, 2002	This publication is a summary and "review" of the Dutch TME trial paper by Kapiteijn 2001.
Viani, G. A., Stefano, E. J., Soares, F. V., Afonso, S. L., Evaluation of biologic effective dose and schedule of fractionation for preoperative radiotherapy for rectal cancer: Meta-analyses and meta-regression, International Journal of Radiation Oncology Biology Physics, 80, 985-991, 2011	Meta-analysis. References checked but most studies old and not relevant for this review.
Wang X, Zheng B, Lu X, Bai R, Feng L, Wang Q, et al. Preoperative short-course radiotherapy and long-course radiochemotherapy for locally advanced rectal cancer: Meta-analysis with trial sequential analysis of long-term survival data. PLoS One. 2018;13(7):e0200142.	A review of RCTs and non-randomised studies. All RCTs accounted for in review.

Study	Reason for exclusion
Wiltink, L. M., Marijnen, C. A. M., Kranenbarg, E. M. K., Van De Velde, C. J. H., Nout, R. A., A comprehensive longitudinal overview of health-related quality of life and symptoms after treatment for rectal cancer in the TME trial, Acta Oncologica, 55, 502-508, 2016	The Dutch TME trial is already included in the review. This paper reports detailed results for health-related quality of life at 14 years of follow-up which, in less detail, was already reported in another publication (Wiltink 2014) which is included in this review.
Wiltink, L. M., Nout, R. A., van der Voort van Zyp, J. R. N., Ceha, H. M., Fiocco, M., Meershoek-Klein Kranenbarg, E., Marinelli, A. W. K. S., van de Velde, C. J. H., Marijnen, C. A. M., Long-Term Health-Related Quality of Life in Patients With Rectal Cancer After Preoperative Short-Course and Long-Course (Chemo) Radiotherapy, Clinical Colorectal Cancer, 15, e93-e99, 2016	Not a RCT but an observational study.
Wisniowska, K., Nasierowska-Guttmejer, A., Polkowski, W., Michalski, W., Wyrwicz, L., Pietrzak, L., Rutkowski, A., Malinowska, M., Krynski, J., Kosakowska, E., Zwolinski, J., Winiarek, M., Oledzki, J., Kusnierz, J., Zajac, L., Bednarczyk, M., Szczepkowski, M., Tarnowski, W., Pasnik, K., Radziszewski, J., Partycki, M., Beczkowska, K., Stylinski, R., Wierzbicki, R., Bury, P., Jankiewicz, M., Paprota, K., Lewicka, M., Cisel, B., Skorzewska, M., Mielko, J., Danek, A., Nawrocki, G., Sopylo, R., Kepka, L., Bujko, K., Does the addition of oxaliplatin to preoperative chemoradiation benefit cT4 or fixed cT3 rectal cancer treatment? A subgroup analysis from a prospective study, European Journal of Surgical Oncology, 42, 1859-1865, 2016	Wrong comparison. This study is a subgroup analysis from a RCT and compares different chemotherapies.
Wong, R. K., Tandan, V., De Silva, S., Figueredo, A., Pre-operative radiotherapy and curative surgery for the management of localized rectal carcinoma, Cochrane Database of Systematic Reviews, CD002102, 2007	A Cochrane Systematic review from 2007. All included publications checked for inclusion in our review. Many of the included trials are from the 1980s and published in the 1980s or early 1990s and are therefore not relevant for our review.
Wu C, Lu C, Xu C. Short-term and long-term outcomes of laparoscopic versus open surgery for low rectal cancer. 2018;97(35):e12026.	Wrong comparison -compares laparoscopic vs open surgery
Wzietek, I., Wydmanski, J., Suwinski, R., Clinical outcome of three fractionation schedules of preoperative radiotherapy for rectal cancer, Reports of Practical Oncology and Radiotherapy, 13, 135-143, 2008	Non-randomised study.
Xanthis A, Greenberg D, Jha B, Olafimihan O, Miller R, Fearnhead N, et al. Local recurrence after 'standard' abdominoperineal resection: do we really need ELAPE? Ann R Coll Surg Engl. 2018;100(2):111-5.	Wrong study design - no comparison
Xiao, J., Teng, W. H., Liu, S., Wei, C., Liu, W. J., Chen, S., Zang, W. D. Short-course radiotherapy with delayed surgery versus conventional chemoradiotherapy: Comparison of short-term outcomes in patients with rectal cancer. 2018	Wrong comparison – compares short course RT + delayed surgery vs conventional chemotherapy). Non-randomised study.
Xu J, Wei Y, Ren L, Feng Q, Chen J, Zhu D, et al. Robot-assisted vs laparoscopic vs open abdominoperineal resections for low rectal cancer: Short-term outcomes of a single-center prospective randomized controlled trial. Annals of Oncology. 2017;28(suppl_5).	Wrong comparison – compares robot-assisted vs laparoscopic vs open abdominoperineal resections

Study	Reason for exclusion
Zhang X, Gao Y, Dai X, Zhang H, Shang Z, Cai X, et al. Short- and long-term outcomes of transanal versus laparoscopic total mesorectal excision for mid-to-low rectal cancer: a meta-analysis. Surg Endosc. 2019;33(3):972-85.	Wrong comparison – compares CRT vs RT
Zhang X, Wu Q, Hu T, Gu C, Bi L, Wang Z. Laparoscopic Versus Conventional Open Abdominoperineal Resection for Rectal Cancer: An Updated Systematic Review and Meta-Analysis. J Laparoendosc Adv Surg Tech A. 2018;28(5):526-39.	Wrong comparison - compares laparoscopic versus conventional open abdominoperineal resection
Zhou, Yf, Xie, Ch, Liu, H, Ge, W, Deng, D, A prospective randomized study of the effect of field in field preoperative radiotherapy in operable rectal carcinoma, Chinese journal of radiation oncology, 6, 90-93, 1997	Full text in Chinese.
Zhou, Z. R., Liu, S. X., Zhang, T. S., Chen, L. X., Xia, J., Hu, Z. D., Li, B., Short-course preoperative radiotherapy with immediate surgery versus long-course chemoradiation with delayed surgery in the treatment of rectal cancer: A systematic review and meta-analysis, Surgical Oncology, 23, 211-221, 2014	A systematic review and meta-analysis. Includes mostly observational studies. RCTs included already considered or included for this review.

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Appendix L – Research recommendations

Research recommendations for review question: What is the effectiveness of preoperative radiotherapy and chemoradiotherapy for rectal cancer?

No research recommendations were made for this review question.