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

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TABLE OF CONTENTS

[Intervention Review]

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

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ABSTRACT

Background

Preoperative radiotherapy (RT) decreases local recurrence rate and improves survival in stage II and III rectal cancer patients. The combination of chemotherapy with RT has a sound radiobiological rationale, and phase II trials of combined chemoradiation (CRT) have shown promising activity in rectal cancer.

Objectives

To compare preoperative RT with preoperative CRT in patients with resectable stage II and III rectal cancer.

Search methods

We searched the Cochrane Register of Controlled Trials, Web of Science, Embase.com, and Pubmed from 1975 until June 2012. A manual search was performed of Ann Surg, Arch Surg, Cancer, J Clin Oncol, Int J Radiat Oncol Biol Phys and the proceedings of ASTRO, ECCO and ASCO from 1990 until June 2012.

Selection criteria

Relevant studies randomized resectable stage II or III rectal cancer patients to at least one arm of preoperative RT alone or at least one arm of preoperative CRT.

Data collection and analysis

Primary outcome parameters included overall survival (OS) at 5 years and local recurrence (LR) rate at 5 years. Secondary outcome parameters included disease free survival (DFS) at 5 years, metastasis rate, pathological complete response rate, clinical response rate, sphincter preservation rate, acute toxicity, postoperative mortality and morbidity, and anastomotic leak rate. Outcome parameters were summarized using the Odds Ratio (OR) and associated 95% confidence interval (CI) using the fixed effects model.

Main results

Five trials were identified and included in the meta-analysis. From one of the included trials only preliminary data are reported. The addition of chemotherapy to preoperative RT significantly increased grade III and IV acute toxicity (OR 1.68-10, P = 0.002) and marginally affected postoperative overall morbidity (OR 0.67-1.00, P = 0.05) while no differences were observed in postoperative

mortality or anastomotic leak rate. Compared to preoperative RT alone, preoperative CRT significantly increased the rate of complete pathological response (OR 2.12-5.84, P < 0.00001) although this did not translate into a higher sphincter preservation rate (OR 0.92-1.30, P = 0.32). The incidence of local recurrence at five years was significantly lower in the CRT group compared to RT alone (OR 0.39-0.72, P < 0.001). No statistically significant differences were observed in DFS (OR 0.92-1.34, P = 0.27) or OS (OR 0.79-1.14, P = 0.58) at five years.

Authors' conclusions

Compared to preoperative RT alone, preoperative CRT enhances pathological response and improves local control in resectable stage II and III rectal cancer, but does not benefit disease free or overall survival. The effects of preoperative CRT on functional outcome and quality of life are incompletely understood and should be addressed in future trials.

PLAIN LANGUAGE SUMMARY

Radiotherapy alone versus radiotherapy combined with chemotherapy before operation of rectal cancer

Patients with cancer of the rectum, the end part of the large bowel immediately above the anus, are treated with surgery. When the tumour is deemed to present a high risk of recurrence after surgery, a course of radiotherapy (RT) is administered before the operation. It has been proven in clinical studies that this 'preoperative' radiotherapy improves the outcome in rectal cancer patients. Recently, several studies have investigated the combination of radiotherapy with chemotherapy (CRT) before surgery. In theory, adding chemotherapy enhances the antitumour activity of radiotherapy. This meta-analysis has summarized the results of five studies that compared preoperative RT alone with preoperative CRT in rectal cancer patients. All of these studies were randomized, which means that the decision to administer either RT or CRT was determined by chance (ballot draw). The results of the meta-analysis may be summarized as follows. Compared to RT alone, preoperative CRT leads to increased side effects during treatment. Also, postoperative complications are somewhat increased, although the risk of dying from postoperative complications is similar. Preoperative CRT is more effective in causing tumour shrinkage (downstaging), and in preventing local recurrence of the disease. However, addition of chemotherapy did not result in more sphincter preserving surgeries, and did not affect the overall survival in rectal cancer patients.

BACKGROUND

The incidence of fatal cases of colorectal cancer in Europe exceeds 200000 per year. Due to the specific anatomy and biology of rectal cancer, surgery alone historically has been associated with local recurrence in up to one in four patients. Locally recurrent disease is usually incurable, causes important morbidity and suffering and gives rise to systemic metastases. In the last few decades, improvements in surgical technique have dramatically lowered the incidence of locally recurrent disease. Careful pathological studies have clearly demonstrated that the major cause of local recurrence is the persistence of tumour foci within the mesorectum (Quirke 1986; Quirke 2003). Intact removal of the entire mesorectum (total mesorectal excision or TME) in cancers of the mid or lower third of the rectum was pioneered by Heald and has resulted in local recurrence rates lower than 5-10% (Heald 1982; Heald 1998; Enker 1999). The importance of complete removal of the surrounding mesorectum necessitates precise preoperative evaluation of the circumferential resection margin using imaging. Recently, magnetic resonance imaging (MRI) using a phased array coil has emerged as the imaging modality of choice in the preoperative evaluation of locally advanced rectal cancer (Beets-Tan 2003; Beets-Tan 2005; Brown 2004; Daniels 2005; Brown 2006).

Parallel to improvements in surgical technique, adjuvant therapy regimens have been tested in clinical trials in an effort to reduce local recurrence rates. Neoadjuvant radiotherapy (RT) has been shown to significantly decrease local recurrence rate and improve survival provided a biologically equivalent dose (BED) of at least 30 Gy is administered (Gray 2001). The advantages of preoperative over postoperative RT include enhanced effectiveness in well oxygenated tissue, downstaging of advanced tumors and better treatment compliance (Glimelius 2002). The theoretical superiority of the preoperative approach over postoperative adjuvant therapy has been confirmed in the recent German rectal cancer trial (Sauer 2004). The effect of preoperative RT on local recurrence rate is consistent even when optimal surgical technique (TME) is implemented. This was demonstrated by the results of the Dutch

rectal cancer trial which randomized rectal cancer patients to undergo either RT followed by TME or TME alone in the setting of a national surgical training programme (Kapiteijn 2001, Peeters 2007). Compared to TME alone, 5x5 Gray (Gy) of RT followed by TME resulted in a significantly lower local recurrence rate, although no improvement in overall survival (OS) was noted.

Although preoperative RT results in a complete pathological response in a minority of patients, significant downsizing is rarely achieved using short schedule RT regimens. In order to improve tumour response, preoperative RT has been combined with chemotherapeutic regimens. There is a strong radiobiological rationale to combine RT with chemotherapy. Combined chemoradiation (CRT) for rectal cancer was introduced in the adjuvant setting and subsequently in irresectable disease, where significant downsizing and downstaging was observed in many patients resulting in achievement of a resectable status in some cases (Minsky 1993; Minsky 1997). The argument for preoperative CRT in resectable disease is based primarily on possible downsizing and downstaging of tumors close to the circumferential resection margin or the sphincter apparatus, thereby enhancing both R0 resection and the sphincter preservation rate. The paramount importance of performing the resection with a negative CRM was shown in several clinical studies (Nagtegaal 2002). Secondly, the addition of chemotherapy could eliminate microscopic systemic disease present at the time of surgery. Possible concerns of preoperative CRT include an increase of both local and systemic toxicity and over treatment of inaccurately staged patients (Ammann 2003). Several phase I and II studies using preoperative CRT have shown a promising tumour response with acceptable toxicity (Rodel 2003; Osti 2004). A limited number of prospective randomized trials comparing preoperative RT alone with preoperative CRT in resectable rectal cancer are published or ongoing.

OBJECTIVES

To compare preoperative RT with preoperative CRT in patients with resectable stage II or III rectal cancer.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCT's) which randomized patients before surgery with curative intent to one of at least two schedules of preoperative therapy including RT and CRT.

Types of participants

Patients with clinical stage II or III resectable rectal cancer undergoing preoperative RT or CRT followed by surgery.

Types of interventions

Preoperative RT or CRT using fractionated external radiotherapy followed by surgery with curative intent (resectable rectal cancer). The surgical procedure must consist of rectal amputation or sphincter preserving anterior resection using an open or laparoscopic approach; local excisions are excluded.

Types of outcome measures

Primary
- local recurrence rate at 5 years
Secondary
- overall survival at 5 years
- disease free survival at 5 years
- systemic metastasis rate
- pathological complete response rate
- clinical response rate
- sphincter preservation rate
- postoperative mortality within 30 days
- postoperative morbidity
- anastomotic leak rate

Search methods for identification of studies

See: Colorectal Cancer Group methods used in reviews.
We searched the following electronic databases
- Cochrane Central Register of Controlled Trials
- ISI Web of Science (Science Citation Index, Current Contents) from 1975 until June 2012
- Embase.com
- Pubmed
Electronic database searches were performed with MeSH terms and free text terms:
-MeSH: \Rectal Neoplasms"[MeSH] AND\ Radiotherapy"[MeSH] AND \Drug Therapy"[MeSH]
-Free text terms:
rectal, rectum, cancer, adenocarcinoma, neoplasm, radiotherapy, irradiation, chemotherapy, chemoradiation, radiochemotherapy, combined modality, multimodal, preoperative, neoadjuvant
Manual search/abstract search
- Journals from 1990: Ann Surg, Arch Surg, Cancer, J Clin Oncol, Int J Radiat Oncol Biol Phys
- Proceedings from ASTRO, ECCO and ASCO
No language constraints were applied.

Data collection and analysis

All three reviewers obtained the full text of all relevant studies and these were assessed for methodological quality according to the Cochrane Collaboration's tool for assessing the risk of bias (Higgins 2011). Methodological details relevant for potential bias included sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting. Disagreement was resolved by consensus.

Data were extracted by one reviewer (KF) on custom designed forms and entered in a computer database for transfer and statistical analysis in the Review Manager software. The data extracted included first author, year of publication, source, method of preoperative therapy and surgery, method of randomization, number of patients included, randomized, and analysed, and outcome parameters as listed above. Data accuracy was verified by the senior author (WPC).

RT dose was converted to the biologically equivalent dose (BED) using the linear quadratic equivalent formula (Dale 2005): BED = $nd(1+1/(\alpha/\beta)-(\gamma/\alpha)(T-T_k)$, with n = number of fractions, d = dose per fraction, α/β = the linear quadratic quotient (set at 10 Gy), γ/α= repair rate (set at 0.6 Gy/d), and T_k = the initial time delay in days (set at 7). Differences between categorical outcome parameters were quantified using the odds ratio (OR) and corresponding 95% confidence interval (95CI). Summary statistics were calculated using the Mantel-Haenszel methods. Heterogeneity analysis was performed using the Q test, with significance accepted when P<0.1. When present, heterogeneity was addressed as recommended by the Cochrane Collaboration Handbook (Higgins 2011).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of ongoing studies.

The initial search was performed in June 2007. Of a total of 17925 studies resulting from the primary search, 324 papers were selected for full review. In all, 320 papers were discarded (Table 1). Four randomized trials were identified comparing preoperative RT with preoperative CRT in resectable stage II or III rectal cancer (Bosset 2006; Boulis-Wassif 1984; Bujko 2006; Gerard 2006). The search was repeated, using similar criteria, in June 2012. A total of 1041 abstracts was selected and scrutinized, resulting in addition of one randomized trial (Latkauskas 2011) to the search results.

Boulis-Wassif 1984: From November 1972 through April 1976, Boulis-Wassif et al. recruited 247 patients with histologically proven localized adenocarcinoma of the rectum and no clinical of surgical evidence of distant metastases. All patients in both groups received preoperative RT by two parallel opposing diamond and chimney fields. All patients received a total dose of 34.5 Gy in 15 fractions of 2.3 Gy each over a total treatment time of 18 days (BED = 35.8 Gy). In the preoperative CRT group, intravenous 5-FU injection (375 mg/m^2) was administered during the first 4 days of irradiation. Surgery usually followed within 2 weeks after the last irradiation. Two patients died before surgery. Assessed outcomes included ease of surgery, type of operation, radical resectability rate, histopathological response, postoperative mortality, postoperative period of hospitalizations, local control of the disease, distant metastases, disease free survival, and median survival. Follow-up was available up to 7 years.

Bujko 2006: From April 1999 until February 2002, Bujko et al. included 316 patients with resectable T3-T4 rectal carcinoma without sphincter infiltration and with a lesion accessible to digital rectal examination. Patients were randomised to either preoperative 5 x 5 Gy short-term RT (BED = 37.5 Gy) with subsequent total mesorectal excision (TME) performed within 7 days or to CRT to a total dose of 50.4 Gy (1.8 Gy per fraction during 25 days; BED = 42.2 Gy) concomitantly with two courses of bolus 5-fluorouracil (325 mg/m^2) and leucovorin during weeks 1 and 5 of RT. Chemoradiation was followed by TME after 4-6 weeks. Three patients did not undergo surgery. Assessed outcomes were acute postirradiation toxicity, sphincter preservation rate, postoperative mortality, pathology, overall survival, disease free survival, local recurrence rate, distant metastases, late toxicity and incidence of permanent stoma. Median follow up was 48 months.

Gerard 2006: Between April 1993 and November 2003, Gerard et al. recruited 762 patients with a histologically confirmed, previously untreated rectal adenocarcinoma accessible to digital rectal examination (T3 or resectable T4 tumour with no evidence of distant metastases). Patients were allocated to two treatment arms: preoperative RT vs. preoperative CRT, both followed by surgery. RT was delivered with photons from a linear accelerator in a three- or four-field box technique. The dose per fraction was 1.8 Gy and all fields were treated each day with five fractions per week. The total dose was 45 Gy in 25 fractions during 5 weeks (BED = 42.2 Gy). Concurrent chemotherapy (CT) consisted of bolus 5-fluorouracil (350 mg/m^2) and leucovorin administered during week 1 and 5 of RT. Surgery was planned between 3 and 10 weeks after the end of the preoperative RT (+/- CT). TME was recommended. Assessed outcomes were surgical procedures and postoperative complications, pathology, overall survival, progression free survival, and local recurrence. Median follow-up was 81 months.

Bosset 2006: Between April 1993 and March 2003, Bosset et al. recruited 1011 patients with a T3 or resectable T4 M0 adenocarcinoma of the rectum within 15 cm from the anal margin and without previous treatment for this disease (EORTC 22921 trial). Patients were allocated to four treatment arms: preoperative RT, preoperative CRT, preoperative RT plus postoperative CT and preoperative CRT plus postoperative CT. Radiotherapy consisted of 45 Gy delivered to the posterior pelvis in 25 fractions of 1.8 Gy

over a period of 5 weeks (BED = 42.2 Gy). The target volume of RT was not a classical pelvic volume but was limited to the main field of tumour spread and to the perirectal nodes. Preoperative chemotherapy was delivered in two 5-day courses of 5-fluorouracil (350 mg/m^2) with leucovorin during the first and fifth weeks of RT. Surgery was scheduled to take place 3 to 10 weeks after treatment. TME was recommended beginning in 1999. Assessed outcomes were toxicity of the preoperative treatment, surgical procedures performed, rate of postoperative complications, pathology, late side effects, overall survival, disease free survival, and local and distant recurrence rate. Median follow-up of 5.4 years.

Latkauskas 2011: Latkauskas et al. evaluated 145 patients with histologically proven rectal cancer between 2007 and 2010. Eighty-three patients were e legible and randomized to receive either short term radiotherapy (5x5 Gy, N=37) or CRT (50 Gy in 25 fractions with 5-fluorouracil, N=46). In both groups, surgery was performed after a 6 weeks waiting period. Sample size was based on downstaging rate as primary endpoint; other endpoints were not defined. The included paper reports on preliminary data (surgical and pathological outcome).

Risk of bias in included studies

Randomisation was adequately performed in four studies using communication with a central office; the study by Latkauskas et al. does not specify the randomization method used. Three studies based randomisation on the minimization method (Bujko 2006; Gerard 2006; Bosset 2006). In the fourth study, the randomisation method is not specified (Boulis-Wassif 1984). None of the studies were described as double blind or used blinded outcome assessment. Description of withdrawals and dropouts was given in four out of five studies. There were no imbalances between treatment arms in the number of patients that did not undergo the complete trial procedure. Three studies were performed on an intention-to-treat basis (Bujko 2006; Gerard 2006; Bosset 2006); no imbalances were identified between treatment arms.

Effects of interventions

The main primary outcome parameter was the local recurrence rate at five years, which was reported in three studies (Bosset 2006; Boulis-Wassif 1984; Gerard 2006). In the RT group, 122 of 740 patients (16.5%) developed a local recurrence while in the CRT group this event was observed in 71 out of 754 patients (9.4%). (Figure 1, Figure 2) This difference was statistically significant (OR 0.53, 95%CI 0.39-0.72, P < 0.001). No statistically significant heterogeneity among studies was present (P = 0.12). Survival data at 5 years were available in three studies (Bosset 2006; Boulis-Wassif 1984; Gerard 2006). In the CRT group, 644 of 1007 patients (63.9%) were alive at 5 years while in the RT group 647 of 993 patients (65.2%) survived 5 years. (Figure 3, Figure 4) This difference did not reach statistical significance (OR 0.95, 95%CI 0.79-1.14, P = 0.58). No heterogeneity was present (P = 0.15).

The results of the analysis of the secondary outcome parameters were as follows. Disease free survival at 5 years, available in the studies of Bosset 2006 and Gerard 2006, was 507/881 (57.5%) in the CRT group and 479/872 (54.9%) in the RT group. This difference was not statistically significant (OR 1.11, 95%CI 0.92-1.34, P = 0.27). (Figure 5, Figure 6) Significant heterogeneity did not occur (P = 0.64). Grade III or IV treatment related toxicity developed in 151 of 1015 patients (14.9%) treated with CRT while in patients treated with RT alone, this occurred in 52 of 1017 patients (5.1%). (Figure 7) This difference was statistically significant (OR 4.1, 95%CI 1.68-10, P = 0.002). There was, however, significant heterogeneity (P = 0.005) which remained when the data were reanalysed using the random effects assumption. Among patients who underwent surgery, sphincter preservation was possible in 583 of 1157 patients (50.4%) in the CRT group and in 553 of 1145 patients (48.3%) in the RT group; this difference failed to reach statistical significance (OR 1.09, 95%CI 0.92-1.30, P = 0.32). (Figure 8) No heterogeneity was observed (P = 0.48). Postoperative 30 day mortality was observed in 31 of 1122 (2.8%) patients in th CRT group and in 21 of 1117 (1.9%) patients in the RT group. This difference did not reach statistical significance (OR 1.48, 95%CI 0.84-2.6, P = 0.17); no heterogeneity was detected (P = 0.6).Figure 9 Postoperative morbidity was marginally higher in the CRT group (OR 0.67-1.00, P = 0.05) (Figure 10) while no differences in anastomotic leak rate were detected (OR 0.62-1.84, P = 0.81). (Figure 11) Pathological complete response (i.e., ypT0N0) of the resected specimen was observed in 135 of 1142 patients (11.8%) in the CRT group and in 40 of 1142 patients (3.5%) in the RT group. (Figure 12) This difference was statistically significant (OR 3.52, 95%CI 2.12-5.84, P < 0.00001) while significant heterogeneity for this parameter was not observed (P = 0.25).

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

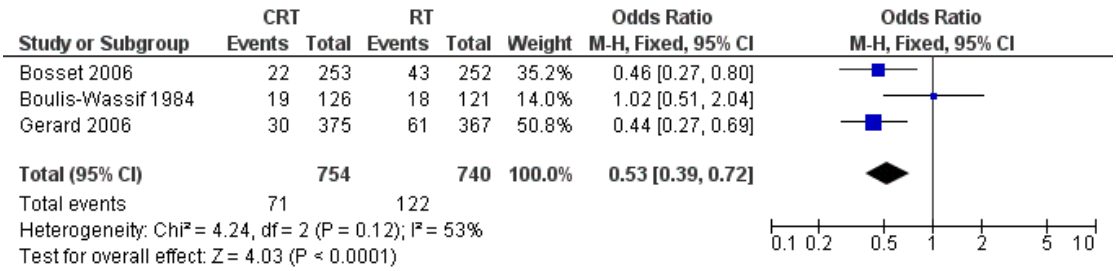


Figure 2. Forest plot of comparison: 1 radiotherapy vs radiochemotherapy, outcome: 1.12 HR˙LR.

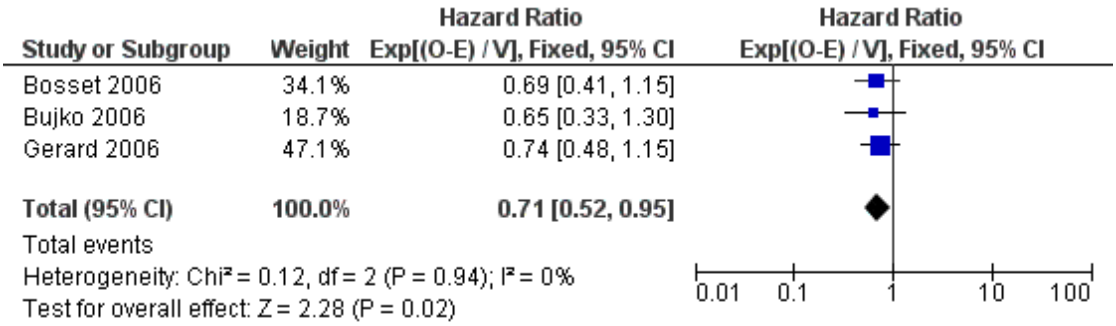


Figure 3. Forest plot of comparison: 1 radiotherapy vs radiochemotherapy, outcome: 1.1 Overall Survival at 5y.

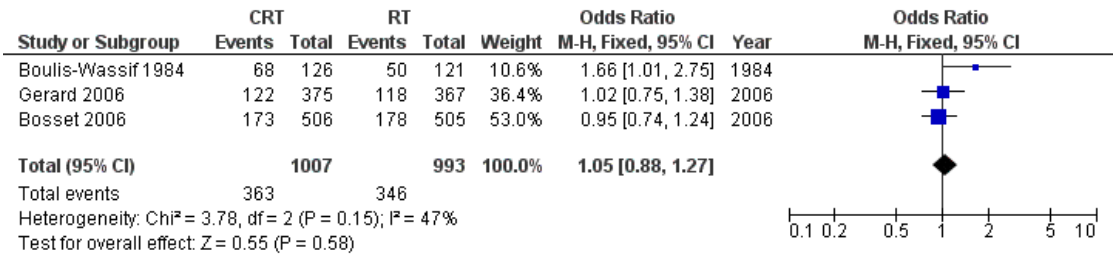


Figure 4. Forest plot of comparison: 1 radiotherapy vs radiochemotherapy, outcome: 1.2 HR˙OS.

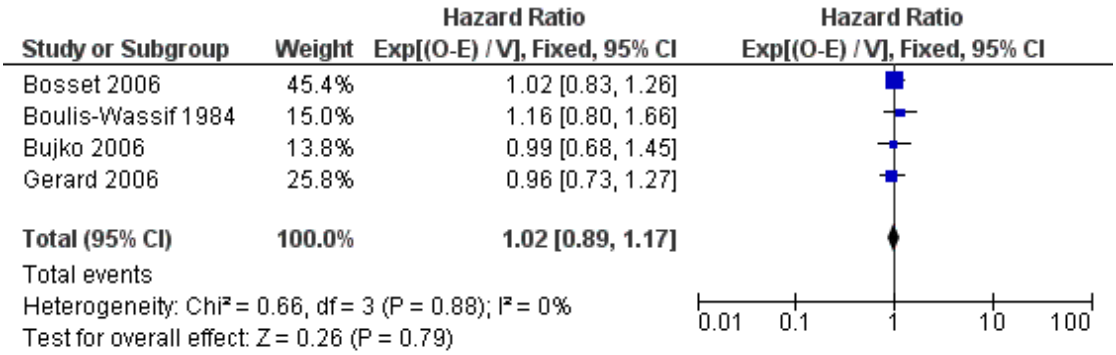


Figure 5. Forest plot of comparison: 1 radiotherapy vs radiochemotherapy, outcome: 1.3 Disease free survival at 5 y.

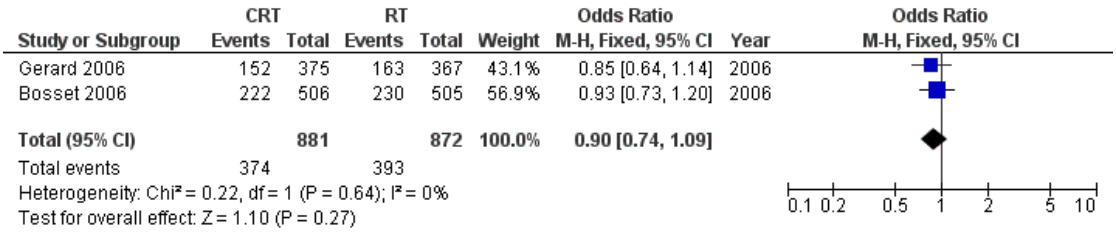


Figure 6. Forest plot of comparison: 1 radiotherapy vs radiochemotherapy, outcome: 1.11 HR˙DFS.

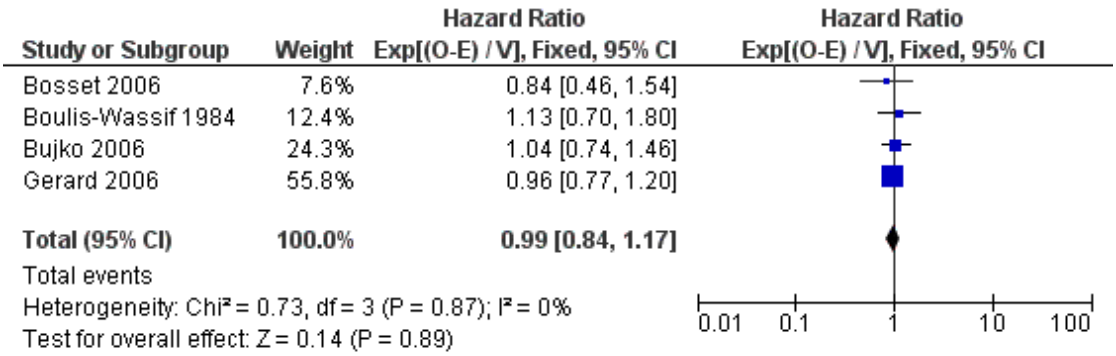


Figure 7. Forest plot of comparison: 1 radiotherapy vs radiochemotherapy, outcome: 1.6 Grade III - IV toxicity.

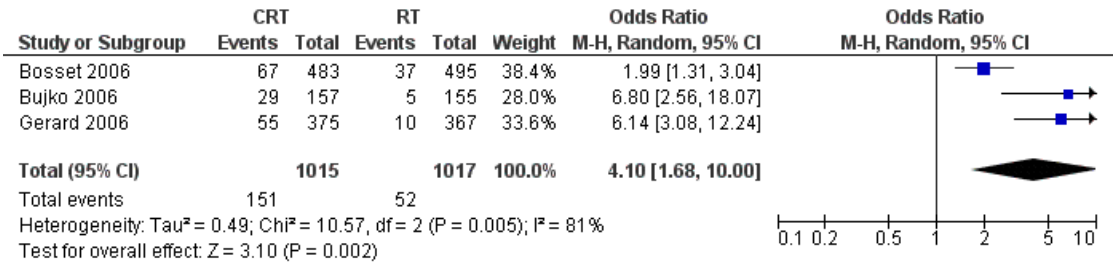


Figure 8. Forest plot of comparison: 1 radiotherapy vs radiochemotherapy, outcome: 1.7 Sphincter preservation.

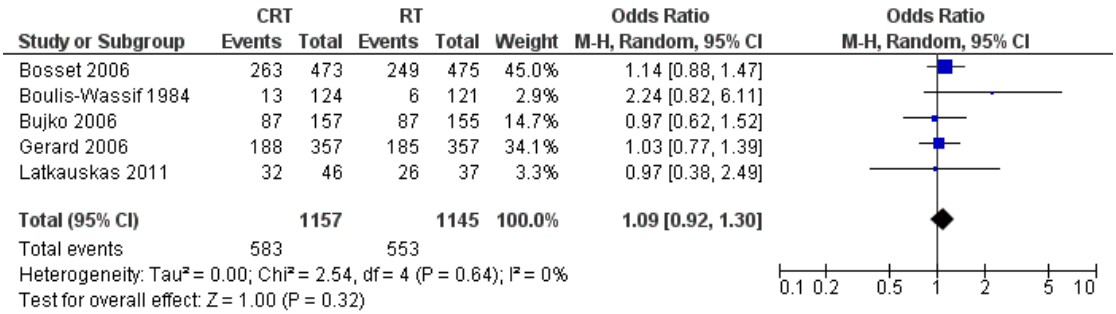


Figure 9. Forest plot of comparison: 1 radiotherapy vs radiochemotherapy, outcome: 1.4 Mortality 30 d.

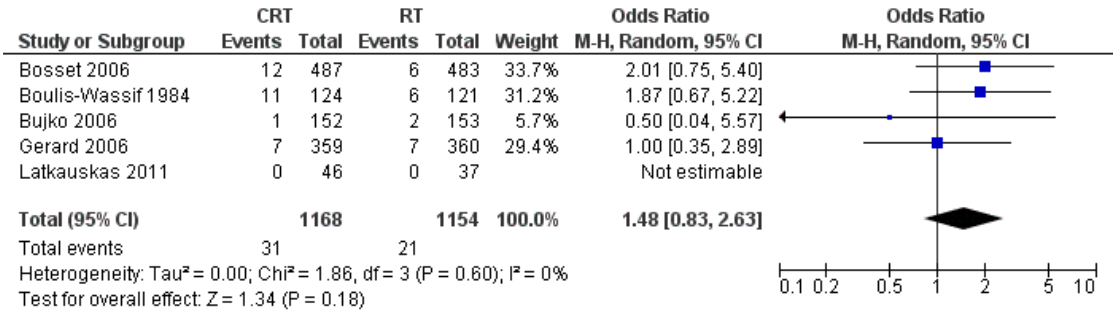


Figure 10. Forest plot of comparison: 1 radiotherapy vs radiochemotherapy, outcome: 1.5 Postop morbidity.

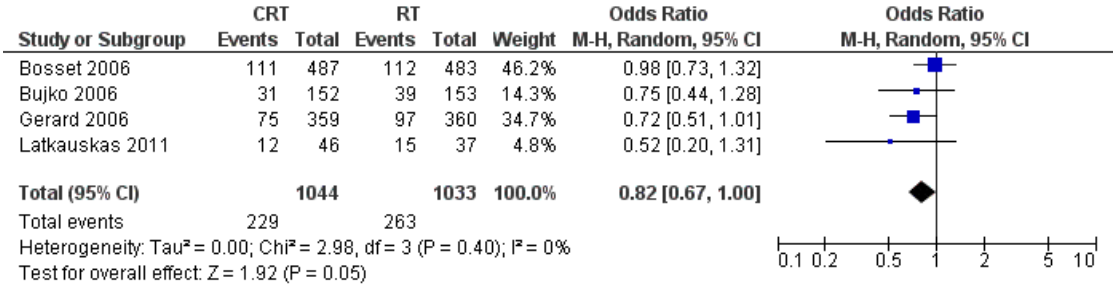


Figure 11. Forest plot of comparison: 1 radiotherapy vs radiochemotherapy, outcome: 1.9 Anastomotic leak.

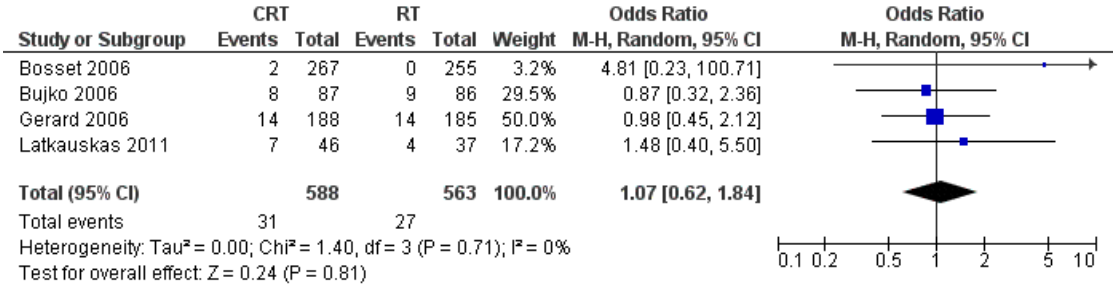
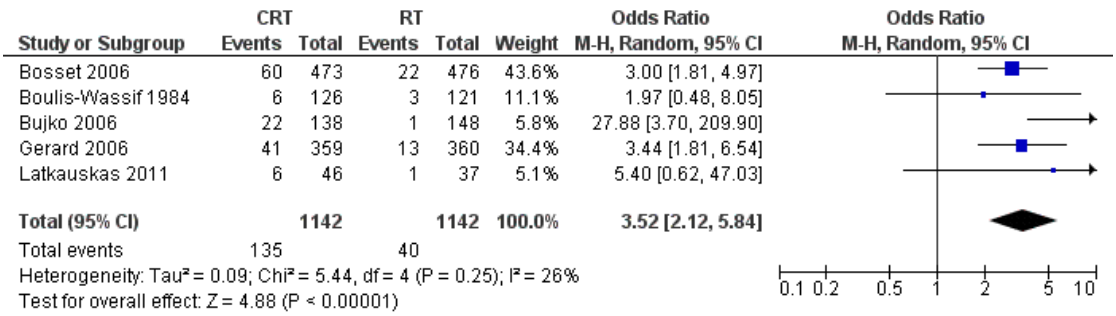


Figure 12. Forest plot of comparison: 1 radiotherapy vs radiochemotherapy, outcome: 1.8 pCR.



Because of the limited number of included studies, no sensitivity analysis was performed.

DISCUSSION

Preoperative RT has been shown to reduce local recurrence rates

and marginally improve survival over surgery alone provided a BED > 30 Gy is delivered to the target region (Gray 2001). The current review addresses the question whether the addition of chemotherapy to preoperative RT further improves pathological and clinical outcome parameters. Five randomized trials were identified comparing preoperative CRT with preoperative RT alone in resectable, locally advanced rectal cancer. Although there was considerable variation in radiotherapy dose and fractionation, all five studies have used a BED > 30 Gy. In three trials (Gerard 2006; Boulis-Wassif 1984; Bosset 2006), RT regimens were identical in both groups. The study by Latkauskas et al. compared two different regimens, but with a similar interval to surgery (Latkauskas 2011). In the Polish study (Bujko 2005, Bujko 2006), RT dose and fractionation as well as time interval until surgery were different in both groups (5x5 Gy followed by immediate surgery versus 50.4 Gy with chemotherapy followed by surgery after a waiting period of 4-6 weeks). In this study, therefore, it remains unclear whether the observed differences in tumour response between both arms are attributable to the addition of chemotherapy or to a different RT schedule and a different waiting period until surgery. Since, moreover, actuarial local recurrence data at five years are not available in this study, it was left out from the meta-analysis of local recurrence at five years. This analysis demonstrates a significant reduction in local recurrence rate with the addition of chemotherapy (OR 0.39-0.72, P < 0.001). Importantly, the cumulative incidence rates of local recurrence in the RT group of the studies of Bosset 2006 and Gerard 2006 (17%) and in both groups of the study of Boulis-Wassif 1984 (15%) seem high compared to the 5.5% local recurrence rate at five years achieved by the Dutch rectal cancer trial using 5x5 Gy preoperative RT followed by surgery (van den Brink 2004). Differences in stage distribution and variation in surgical technique might explain this observation. Indeed, during the Dutch rectal cancer trial a formal surgical training and quality control program was implemented in order to guarantee optimal surgery (TME). The study of Boulis-Wassif 1984 predated the introduction of TME surgery (inclusion period 1972-1976), whereas in the studies of Bosset 2006 and Gerard 2006, TME surgery was 'recommended' without any formal surgical training or quality control.

Although in the study of Boulis-Wassif 1984 a marginally significant five year survival benefit was associated with CRT, the combined analysis failed to demonstrate a significant difference in either overall or disease free survival at five years (OR 0.79-1.14, P = 0.58 and OR 0.92-1.34, P = 0.27, respectively). One of the hypotheses formulated to explain the observed lack of survival benefit found in many pre- or postoperative adjuvant therapy trials in rectal cancer is the existence of early, subclinical systemic disease present at diagnosis. This hypothesis is supported by the finding that the rate of distant metastatic disease in all four trials is consistently around 30%, without any difference between CRT and RT groups, indicating a future role of more effective systemic therapy to eradicate micrometastatic disease from the onset of therapy. Others have argued that the follow up time of the included trials is too short to observe a survival benefit, or that the incidence of local recurrence is too low to influence survival (Gerard 2006).

Grade III and IV acute treatment related toxicity was more pronounced in the CRT group in the three studies reporting this parameter (Bosset 2006; Bujko 2006; Gerard 2006), with an overall OR of 1.68-10 and a P value of 0.002. However, chemotherapy related toxicity was generally acceptable as evidenced by the high compliance rates in the studies mentioned (82%, 78.1%, and 69% respectively). In resected patients, no differences were observed in 30 day mortality or anastomotic leak rate, but a marginally significant difference in overall postoperative morbidity was found. The results concerning anastomotic leakage should be interpreted with caution, since the exceedingly low leakage rate in the study of Bosset compared to currently accepted and published leakage rates following anterior resection suggests underreporting of this specific complication.

Postoperative quality of life (QoL) is an important, though often underreported aspect of cancer trials. From the Swedish and Dutch rectal cancer trials, it is known that preoperative 5x5 Gy followed by surgery significantly worsens functional outcome in terms of bowel, sexual, and bladder function compared to surgery alone (Holm 1996; Dahlberg 1998; Peeters 2005). A number of phase II trials have suggested that preoperative CRT followed by surgery does not adversely affect functional outcome (Feliu 2002; Bosset 2000). The scarce available data in the four included studies did not allow to perform a meta-analysis of QoL related parameters. However, preliminary functional outcome data of the EORTC 22921 study (published as abstract only) demonstrated a significantly worse anorectal function in CRT patients compared to RT alone (Mercier 2005). Interestingly, in the final results paper of this study the incidence of 'late side effects' including fecal incontinence did not seem to differ between the four treatment arms (Bosset 2006).

The results of the meta-analysis confirm the enhanced cytotoxic efficacy of combined RT with 5-fluorouracil based chemotherapy. The incidence of a complete pathological response (pCR, ypT0N0) was 135 of 1142 patients (11.8%) in the CRT group and 40 of 1142 patients (3.5%) in the RT group; this difference was statistically highly significant (OR 3.52, 95%CI 2.12-5.84, P < 0.00001) while no heterogeneity was observed between the four studies. The results of the EORTC study moreover confirmed the difference in radioresponsiveness of the tumour in the bowel wall compared to that of mesorectal lymph nodes, as evidenced by nodal involvement in up to 12% of ypT0 patients (Bosset 2004). Although in two studies (Bosset 2006; Boulis-Wassif 1984) a trend towards increased sphincter preservation was observed in the CRT group, the overall results failed to demonstrate an increase in sphincter preserving surgery following CRT notwithstanding the downsizing and downstaging effect often noted with the combined therapy. This finding may be related to reluctance

of the colorectal surgeon to alter a preoperative assessment of the need to perform a rectal amputation, since reversal of this decision would possibly imply performing an anastomosis in previously macroscopically invaded tissue. Moreover, in at least two studies it was specifically advised not to change a preoperative decision to perform a rectal amputation even after a significant downsizing. Data from the German rectal cancer trial, however, suggested that a change in operative strategy (i.e., perform sphincter preserving surgery when a significant clinical response is observed) may be safely performed. Longer follow up will be needed to confirm the safety of this approach. Mature results (including recurrence and survival data) from the study by Latkauskas et al. are awaited. An ongoing study by the Berlin Cancer Society, randomises patients with histologically proven rectal cancer staged T2N+ or T3 to receive either SCRT (25 Gy in five fractions of 5 Gy) plus TME-surgery within 5 days or CRT (50.4 Gy in 28 fractions of 1.8 Gy, continuous infusion 5-fluorouracil) plus TME-surgery 4-6 weeks later (Siegel 2009). All patients receive adjuvant chemotherapy (12 weeks continuous infusional 5-FU) and are followed up for 5 years. TME-quality is independently documented by the surgeon and the pathologist; the primary endpoint is local recurrence at five years.

of chemotherapy causes a moderate increase in acute toxicity and overall postoperative morbidity, although anastomotic leakage rate or 30 day mortality are not enhanced. At this moment, it is unclear from the available data whether the addition of chemotherapy to preoperative RT influences sphincter preservation. Patients should be informed about the possible functional and QoL related aspects of preoperative therapy.

Implications for research

1. Since the improvement of local control obtained with CRT did not translate into a better overall or disease free survival and up to one third of all patients develop distant spread, priority should be given to trials addressing early subclinical systemic spread;

2. Trials are needed that specifically address the oncological safety of performing sphincter preserving surgery (including intersphincteric resection and colo-anal anastomosis) in patients deemed to require amputation before the start of CRT and in whom a significant clinical response is observed;

3. Preoperative therapy trials in rectal cancer should include formal evaluation of functional and QoL related aspects of therapy.

AUTHORS' CONCLUSIONS

Implications for practice

Compared to preoperative RT alone, preoperative CRT enhances tumour response and improves local recurrence rates. The addition

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bosset 2006

Methods	1.Randomization method: telephone to central office (assumed) 2. Abdominal imaging: CT 3. Chest imaging: CXR 4. 4 arm study: Arm 1 preop RT + S; Arm 2 preop XRT + concurrent 5FU LV + S;Arm 3 preop RT + S + post op 5FU LV ; Arm 4 preop RTCT+ S + postop 5FU LV 5. Total randomized 1011
Participants	1. Rectal Cancer 2. Location: within 15 cm from anal verge 3. Resectability: locally resectable 4. T3 or resectable T4 (defined by clinical criteria or endoscopic ultrasound) 5. WHO PS 0-1 6. </=80yr
Interventions	1.Surgery: AP/anterior resection or Hartman with TME 2. RT : 45 Gy in 25fr. 3. RT volume: 5cm above and below tumour and perirectal nodes below S2-3. If tumour above 10cm, include only 3 cm above tumour. If tumour in low rectum, S2-3 to perineum. Posteriorly to include entire sacrum with 3cm beyond macroscopic extension 4. RT-S: within 3-10 weeks of completing neoadjuvant therapy 5. 3 or 4 field 6. Chemotherapy: 5FU 325mg/m2/d; Leucovorin 20mg/m2/day Dy1-5 & 28-32 for arms 2 and 4, and postoperative for arms 3 and 4
Outcomes	1. Duration of FU: 5.4 yrs 2. Perioperative mortality: CRTS 2.4 % (12/506) RTS 1.2% (6/505) 3. Mets (liver) @ lap: Y 4. Curative resection: not stated 5. Overall resection: 94.5 % 6. Compliance to radiotherapy: CRTS 483/506 (95.5%) RTS 495/505 (98.0%) 7. OAS: Y 8. CSS? 9. Tox post RT: Y 10. Acute tox post S: Y 11. Late tox post S: Y 12. LR: Y 13. QOL: N 14. Proportion sfincter sparing: CRTS 267/506 (52.8%) RTS 255/505 (50.5%) 15. Proportion downstaging: Y
Notes	

Risk of bias

Bosset 2006 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Boulis-Wassif 1984

Methods	1.Randomization method: not stated. conducted by cooperative group. Likely via central office 2. Abdominal imaging: Not stated 3. Chest imaging: Not stated 4. Study arm (Preop chemoradiotherapy arm) : 171randomized, 45 excluded. 5. Control arm (Preop radiotherapy arm): 168 randomized , 47 excluded
Participants	1. Rectal Cancer 2. Location: below within 15cm anal verge 3. Resectability: fit for surgery
Interventions	1.Surgery: AP/anterior resection 2. RT : 3450 cGy in 15fr. (for both arms) 3. BED: 35.2Gy1 4. RT volume: "chimney and diamond fields" paraaortic and pelvis. 5. RT-S: within 2 wk 6. 2 field 7. Cointervention: none 8. 2 arms, control (Radiotherapy followed by surgery), Study (Chemoradiotherapy followed by surgery) 9.Chemotherapy: 5FU 10mg/kg/d day 1-4
Outcomes	1.Duration of FU: mean 5.2yrs 2. Perioperative mortality: CRTS 19/126 RTS 11/121 3. Mets @ lap: CRTS 13/126 RTS 15/121 4. Curative resection: Not stated 5. Overall resection: CRTS 121, RTS 124 6. Compliance to radiotherapy: not given 7. OAS: Y 8. CSS: N 9. Tox post RT: not given 10: Acute tox post S: not given No complication not given 11. Late tox post S: not given 12: LR: N 13. QoL:N
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Boulis-Wassif 1984 (*Continued*)

Allocation concealment (selection bias)	Low risk	A - Adequate

Bujko 2006

Methods	1.Randomization method: telephone to central office 2. Abdominal imaging: ultrasound or CT 3. Chest imaging: CXR 4. XRT + S arm : (short XRT)155 randomized, 0 excluded. 5. Arm B: (Long XRT+CT): 157 randomized , 0 excluded
Participants	1. Rectal Cancer 2. Location: inferior edge palpable of digital exam 3. Resectability: locally resectable 4. T3 or resectable T4 5. not involving sphincter
Interventions	1.Surgery: AP/anterior resection or Hartman with TME 2. RT : XRT +S arm: 2500cGy cGy in 5fr. ; Arm B: 50.4Gy in 28 fr with concomitant CT weeks 1 & 5 3. BED: Arm A 38.7Gy10, Arm B 40.9Gy10 4. RT volume: Not stated 5. RT-S: XRT+S within 7 days; Arm B: within 4-6 weeks 6. 3 or 4 field 7. Arm B chemotherapy: 5FU 325mg/m2/d; Leucovorin 20mg/m2/day Dy1-5 & 28-32
Outcomes	1.Duration of FU: not stated 2. Perioperative mortality: XRT+S 0/155 Arm B 0/157 3. Mets @ lap: not stated 4. Curative resection: not stated 5. Overall resection: XRT+S 145/155 Arm B 147/157 6. Compliance to radiotherapy: XRT+S 152/155 Arm B 141/157 7. OAS: N 8. CSS: N 9. Tox post RT: no complications XRT+S 118/155 Arm B 24/157 Any complications XRT+S 37/155 Arm B 133/157 Gd 3-4 XRT + S 5/155 Arm B 26/157 Gd 5 (Death) XRT +S 0/155 Arm B 2/157 10: Acute tox post S: Not stated 11. Late tox post S: not given 12: LR: N 13. QoL:N 14. Proportion sphincter sparing 15. Proportion downstaged (by T stage, N stage, Tumor size)
Notes	

Risk of bias

Bujko 2006 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Gerard 2006

Methods	1.Randomization method: not stated 2. Abdominal imaging: liver sonography - CT scan 3. Chest imaging: CXR 4. Study arm: CRT 375 5. Control arm: RT 367
Participants	1. Rectal Cancer 2. Location: accessible by digital examination 3. Resectability: locally resectable
Interventions	2 arms: preop XRT vs preop CRT 1.Surgery: TME recommended 2. RT 45Gy in 25 fr for both arms 3. BED: 32.5Gy10 4. RT volume: NA 5. RT-S: NA 6. NA 7. Cointervention: postoperative CT (5FU FA) x 4 cycles
Outcomes	1.Duration of FU: 81m 2. Perioperative mortality (60 days): 2% for both arms 3. Mets @ lap: not stated 4. Curative resection: not stated 5. Overall resection: not stated 6. Compliance to radiotherapy: not stated 7. OAS: Y 8. CSS: Y 9. Tox (gr 3-4) post RT: Preop RT arm: 10/367 CRT arm: 55/375 10: Acute tox post S: not stated 11. Late tox post S: Y
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Latkauskas 2011

Methods	1. Randomization method: not stated 2. Abdominal imaging: abdominal US, EUS, CT scan and MRI pelvis 3. Chest imaging: CXR 4. Study arm: CRT 46 5. Control arm: RT 37
Participants	1. Rectal cancer stage II and III 2. less than 15 cm from anal verge 3. <80 years old, no other cancer during last 5 years
Interventions	1. CRT: 50 Gy in 25 fractions, 1.8-2 Gy/fraction over 5 weeks with 5-FU/LV during week 1 and 5 2. RT: 25 Gy in 5 fractions 3. Surgery: after 6 weeks in both groups
Outcomes	1. Duration of FU: not stated 2. Perioperative mortality: not stated 3. Mets @ lap: not stated 4. Curative resection: 91.3% (CRT), 86.5% (RT) 5. Overall resection: 37/37 (RT), 46/46 (CRT) 6. Compliance to radiotherapy: not stated 7. OAS: not stated 8. CSS: not stated 9. Tox (gr 3-4) post RT: not stated 10: Acute tox post S: not stated 11. Late tox post S: not stated
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	

Characteristics of ongoing studies *[ordered by study ID]*

Siegel 2009

Trial name or title	Preoperative short-course radiotherapy versus combined radiochemotherapy in locally advanced rectal cancer: a multi-centre prospectively randomised study of the Berlin Cancer Society
Methods	Prospective Randomized trial
Participants	Primary rectal cancer within 12 cm from anal verge, cT3N+, cT3N0, or cT2N+

Siegel 2009 (*Continued*)

Interventions	Short course RT consists of single doses of 5.0 Gy in five fractions within one week up to a total dose of 25 Gy. For CRT, standard fractions of 1.8 Gy/d are given 5 times a week up to a total dose of 50.4 Gy; concomitant chemotherapy consists of continuous 5-FU-infusion 225 mg per square meter per day
Outcomes	Local recurrence after five years follow up has been chosen as primary endpoint
Starting date	2008
Contact information	Peter M Schlag email: pmschlag@charite.de Department of Surgery and Surgical Oncology, Charité - Universitätsmedizin Berlin, Berlin, Germany
Notes	

DATA AND ANALYSES

Comparison 1. radiotherapy vs radiochemotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall Survival at 5y	3	2000	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.88, 1.27]
2 HR˙OS	4	0	Hazard Ratio (95% CI)	1.02 [0.89, 1.17]
3 Disease free survival at 5 y	2	1753	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.74, 1.09]
4 Mortality 30 d	5	2322	Odds Ratio (M-H, Random, 95% CI)	1.48 [0.83, 2.63]
5 Postop morbidity	4	2077	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.67, 1.00]
6 Grade III - IV toxicity	3	2032	Odds Ratio (M-H, Random, 95% CI)	4.10 [1.68, 10.00]
7 Sphincter preservation	5	2302	Odds Ratio (M-H, Random, 95% CI)	1.09 [0.92, 1.30]
8 pCR	5	2284	Odds Ratio (M-H, Random, 95% CI)	3.52 [2.12, 5.84]
9 Anastomotic leak	4	1151	Odds Ratio (M-H, Random, 95% CI)	1.07 [0.62, 1.84]
10 Local Recurrence at 5y	3	1494	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.39, 0.72]
11 HR˙DFS	4	0	Hazard Ratio (95% CI)	0.99 [0.84, 1.17]
12 HR˙LR	3	0	Hazard Ratio (95% CI)	0.71 [0.52, 0.95]

Analysis 1.1. Comparison 1 radiotherapy vs radiochemotherapy, Outcome 1 Overall Survival at 5y.

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

Comparison: 1 radiotherapy vs radiochemotherapy

Outcome: 1 Overall Survival at 5y

Study or subgroup	CRT n/N	RT n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Boulis-Wassif 1984	68/126	50/121		10.6 %	1.66 [1.01, 2.75]
Gerard 2006	122/375	118/367		36.4 %	1.02 [0.75, 1.38]
Bosset 2006	173/506	178/505		53.0 %	0.95 [0.74, 1.24]
Total (95% CI)	**1007**	**993**		**100.0 %**	**1.05 [0.88, 1.27]**

Total events: 363 (CRT), 346 (RT)

Heterogeneity: Chi^2 = 3.78, df = 2 (P = 0.15); I^2 =47%

Test for overall effect: Z = 0.55 (P = 0.58)

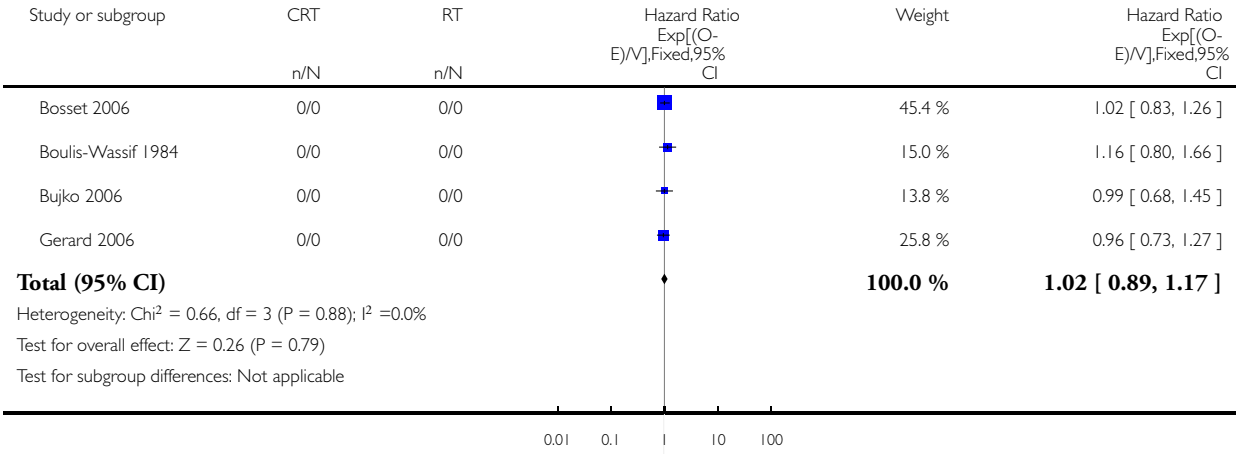
Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 radiotherapy vs radiochemotherapy, Outcome 2 HR˙OS.

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

Comparison: 1 radiotherapy vs radiochemotherapy

Outcome: 2 HR˙OS

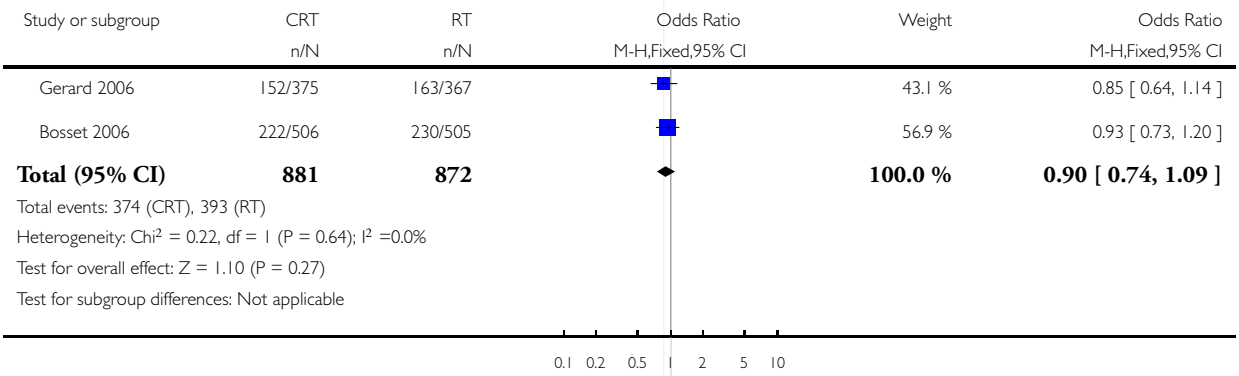


Analysis 1.3. Comparison 1 radiotherapy vs radiochemotherapy, Outcome 3 Disease free survival at 5 y.

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

Comparison: 1 radiotherapy vs radiochemotherapy

Outcome: 3 Disease free survival at 5 y

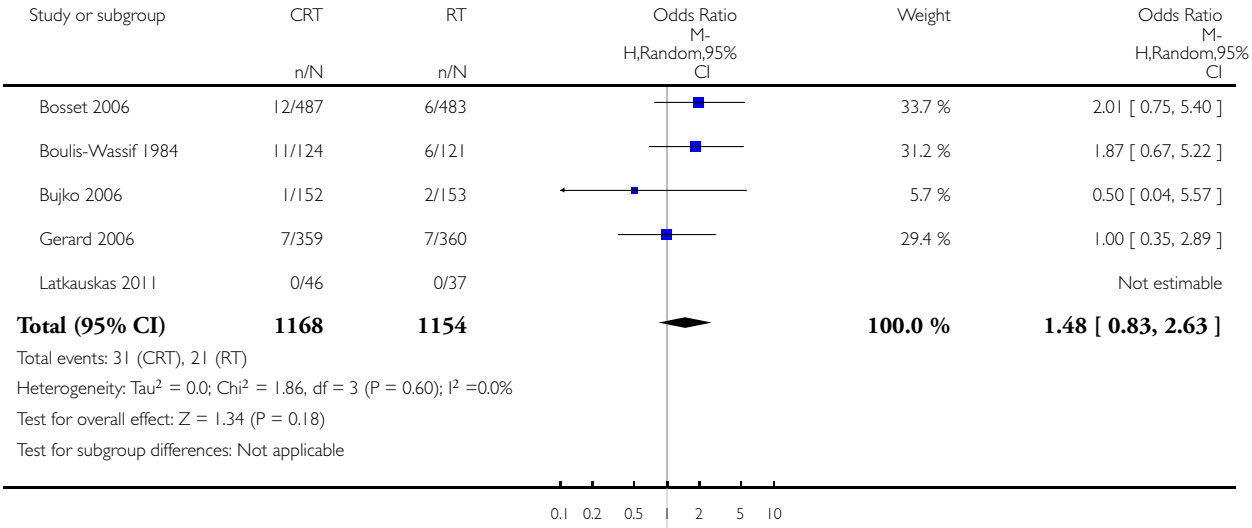


Analysis 1.4. Comparison 1 radiotherapy vs radiochemotherapy, Outcome 4 Mortality 30 d.

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

Comparison: 1 radiotherapy vs radiochemotherapy

Outcome: 4 Mortality 30 d



Analysis 1.5. Comparison 1 radiotherapy vs radiochemotherapy, Outcome 5 Postop morbidity.

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

Comparison: 1 radiotherapy vs radiochemotherapy

Outcome: 5 Postop morbidity

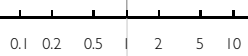
Study or subgroup	CRT n/N	RT n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Bosset 2006	111/487	112/483		46.2 %	0.98 [0.73, 1.32]
Bujko 2006	31/152	39/153		14.3 %	0.75 [0.44, 1.28]
Gerard 2006	75/359	97/360		34.7 %	0.72 [0.51, 1.01]
Latkauskas 2011	12/46	15/37		4.8 %	0.52 [0.20,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

Total events: 229 (CRT), 263 (RT)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.98$, df = 3 (P = 0.40); $I^2 = 0.0\%$

Test for overall effect: Z = 1.92 (P = 0.055)

Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1 radiotherapy vs radiochemotherapy, Outcome 6 Grade III - IV toxicity.

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

Comparison: 1 radiotherapy vs radiochemotherapy

Outcome: 6 Grade III - IV toxicity

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

Total events: 151 (CRT), 52 (RT)

Heterogeneity: $Tau^2 = 0.49$; $Chi^2 = 10.57$, df = 2 (P = 0.01); $I^2 = 81\%$

Test for overall effect: Z = 3.10 (P = 0.0019)

Test for subgroup differences: Not applicable

Analysis 1.7. Comparison 1 radiotherapy vs radiochemotherapy, Outcome 7 Sphincter preservation.

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

Comparison: 1 radiotherapy vs radiochemotherapy

Outcome: 7 Sphincter preservation

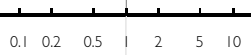
Study or subgroup	CRT n/N	RT n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Bosset 2006	263/473	249/475		45.0 %	1.14 [0.88, 1.47]
Boulis-Wassif 1984	13/124	6/121		2.9 %	2.24 [0.82, 6.11]
Bujko 2006	87/157	87/155		14.7 %	0.97 [0.62, 1.52]
Gerard 2006	188/357	185/357		34.1 %	1.03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

Total events: 583 (CRT), 553 (RT)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.54$, df = 4 (P = 0.64); $I^2 = 0.0\%$

Test for overall effect: Z = 1.00 (P = 0.32)

Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1 radiotherapy vs radiochemotherapy, Outcome 8 pCR.

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

Comparison: 1 radiotherapy vs radiochemotherapy

Outcome: 8 pCR

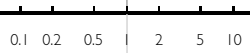
Study or subgroup	CRT n/N	RT n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Bosset 2006	60/473	22/476		43.6 %	3.00 [1.81, 4.97]
Boulis-Wassif 1984	6/126	3/121		11.1 %	1.97 [0.48, 8.05]
Bujko 2006	22/138	1/148		5.8 %	27.88 [3.70, 209.90]
Gerard 2006	41/359	13/360		34.4 %	3.44 [1.81,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

Total events: 135 (CRT), 40 (RT)

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 5.44$, df = 4 (P = 0.25); $I^2 = 26\%$

Test for overall effect: Z = 4.88 (P < 0.00001)

Test for subgroup differences: Not applicable

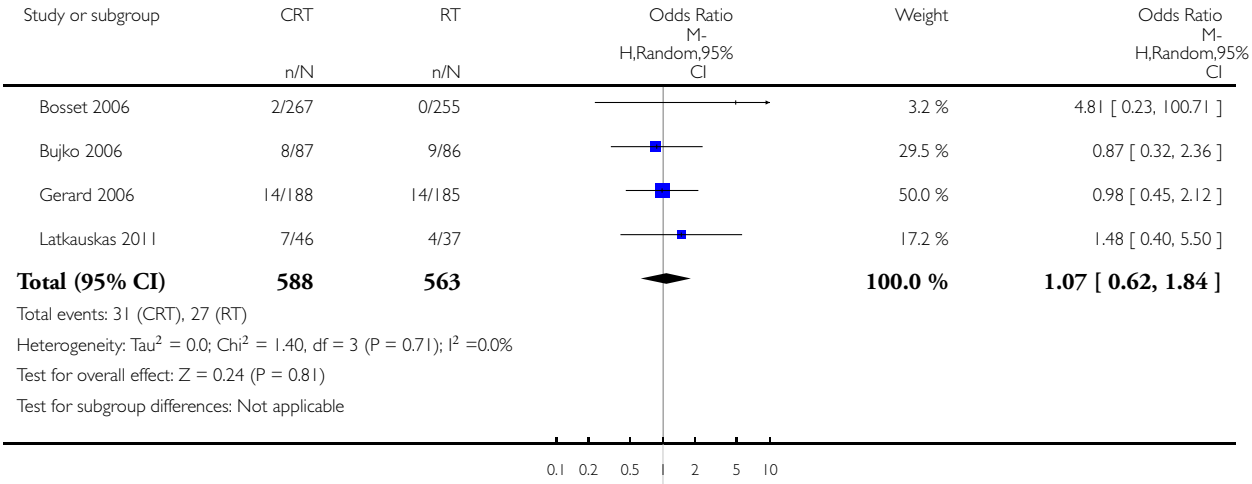


Analysis 1.9. Comparison 1 radiotherapy vs radiochemotherapy, Outcome 9 Anastomotic leak.

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

Comparison: 1 radiotherapy vs radiochemotherapy

Outcome: 9 Anastomotic leak

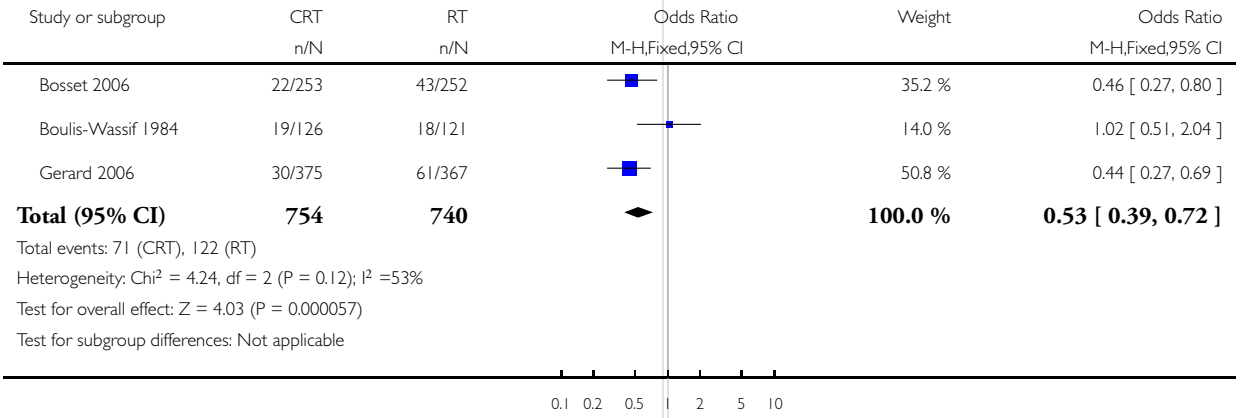


Analysis 1.10. Comparison 1 radiotherapy vs radiochemotherapy, Outcome 10 Local Recurrence at 5y.

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

Comparison: 1 radiotherapy vs radiochemotherapy

Outcome: 10 Local Recurrence at 5y



Analysis 1.11. Comparison 1 radiotherapy vs radiochemotherapy, Outcome 11 HR˙DFS.

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

Comparison: 1 radiotherapy vs radiochemotherapy

Outcome: 11 HR˙DFS

Study or subgroup	CRT n/N	RT n/N	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI
Bosset 2006	0/0	0/0		7.6 %	0.84 [0.46, 1.54]
Boulis-Wassif 1984	0/0	0/0		12.4 %	1.13 [0.70, 1.80]
Bujko 2006	0/0	0/0		24.3 %	1.04 [0.74, 1.46]
Gerard 2006	0/0	0/0		55.8 %	0.96 [0.77, 1.20]
Total (95% CI)				**100.0 %**	**0.99 [0.84, 1.17]**

Heterogeneity: $Chi^2 = 0.73$, df = 3 (P = 0.87); $I^2 = 0.0\%$

Test for overall effect: Z = 0.14 (P = 0.89)

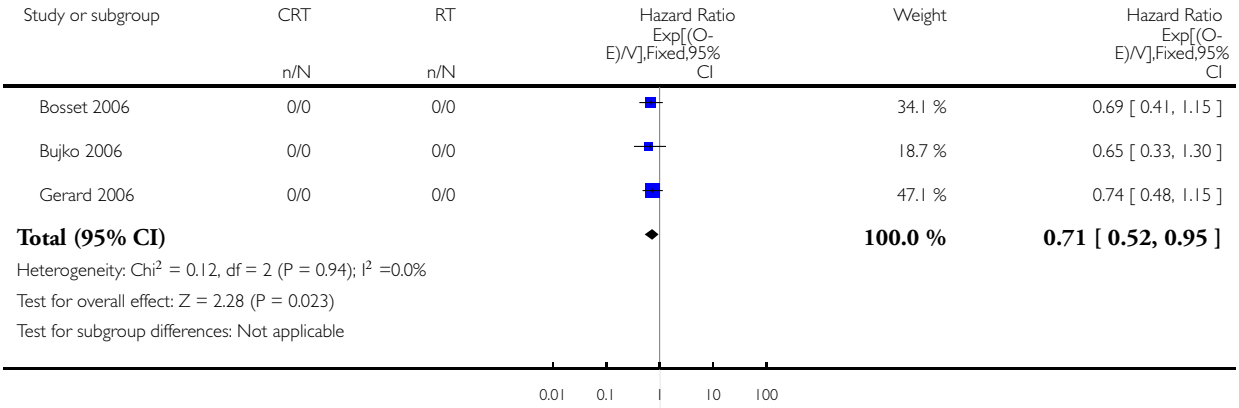
Test for subgroup differences: Not applicable

Analysis 1.12. Comparison 1 radiotherapy vs radiochemotherapy, Outcome 12 HR˙LR.

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

Comparison: 1 radiotherapy vs radiochemotherapy

Outcome: 12 HR˙LR



ADDITIONAL TABLES

Table 1. excluded studies

Type	N
Non randomized trials	144
Adjuvant therapy trials	28
Trials not including at least one chemotherapy arm combined with radiotherapy	71
Trials not including radiotherapy	27
Trials using local or no resection	18
Trials including other tumour types	25
Trials not including stage II/III cancer	7
Total	320

WHAT'S NEW

Last assessed as up-to-date: 16 July 2012.

Date	Event	Description
25 January 2013	New search has been performed	Review update with one new trial included
25 January 2013	New citation required but conclusions have not changed	Review update with one new trial included

HISTORY

Protocol first published: Issue 2, 2006

Review first published: Issue 1, 2009

Date	Event	Description
26 February 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

General coordination and writing: Wim Ceelen, Yves Van Nieuwenhove

Literature search, data extraction, data verification: Laura De Caluwé, Wim Ceelen, Yves Van Niewenhove

DECLARATIONS OF INTEREST

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [therapeutic use]; Chemoradiotherapy [*methods]; Neoplasm Recurrence, Local [prevention & control]; Preoperative Care [methods]; Randomized Controlled Trials as Topic; Rectal Neoplasms [pathology; *therapy]

MeSH check words

Humans