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The Spanish Journal of Gastroenterology

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DOI: 10.17235/reed.2018.5674/2018
Link: PubMed (Epub ahead of print)

Please cite this article as:
Yu Yongjun, Li Yuwei, Xu Chen, Zhang Zhao, Zhang Xipeng . Comparison of long course and short course preoperative radiotherapy in the treatment of locally advanced rectal cancer: a systematic review and meta-analysis. Rev Esp Enferm Dig 2018. doi: 10.17235/reed.2018.5674/2018.

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OR 5674

Comparison of long course and short course preoperative radiotherapy in the treatment of locally advanced rectal cancer: a systematic review and meta-analysis

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Received: 27/04/2018

Accepted: 29/06/2018

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ABSTRACT

Background: rectal cancer (RC) is one of the most prevalent malignancies worldwide and different preoperative radiotherapies may lead to different outcomes. This meta-analysis aimed to compare the effectiveness of long-course (LC) and short-course radiotherapy (SC), with or without chemotherapy, for locally advanced rectal cancer.

Methods: studies published up to March 31st 2018 were retrieved from PubMed, Medline, Cochrane and EMABSE. Randomized control or consort control trials that reported the outcomes of short or long course radiotherapy were eligible. Either a fixed or random effects model was used to access the overall combined risk estimates.

Results: sixteen studies with a total of 2,773 RC patients were included in the analysis. There were no significant differences between LC and SC therapies with regard to the following: pathological complete response (PCR) (I^2 = 78%, $p < 0.05$, RR = 0.54, 95% CI: 0.26-1.10); tumor downstaging (I^2 = 79%, $p < 0.05$, RR = 0.83, 95% CI: 0.58-1.17); local recurrences (I^2 = 22%, p = 0.27, RR = 0.55, 95% CI: 0.26-1.16); distant

metastases (I^2 = 29%, p = 0.22, RR = 1.03, 95% CI: 0.77-1.37); mortality (I^2 = 0%, p = 0.78, RR = 0.95, 95% CI: 0.78-1.15) and serious late toxicity (I^2 = 74%, p = 0.01, RR = 1.10, 95% CI: 0.37-3.26). In the subgroup analysis, LC had a better PCR and tumor downstaging rate compared with SC in the RCT subgroup. Besides, LC also presented a better PCR rate compared with SC without chemotherapy.

Conclusions: LC and SC are both effective in the preoperative treatment of RC with regard to PCR, tumor downstaging, local recurrences, distant metastases, mortality and serious late toxicity. Furthermore, chemotherapy may enhance the efficacy of preoperative treatment.

Key words: Rectal cancer. Adjuvant treatment. Radiotherapy. Chemotherapy.

INTRODUCTION

Rectal cancer (RC) is one of the most common malignancies in both developed and developing countries and is also a leading cause of cancer-related morbidity and mortality (1,2). The current standard treatment for locally advanced RC is preoperative radiotherapy followed by total mesorectal excision (TME). It has been reported that the adoption of TME has notably improved local control rates, and overall survival (3) and short-course radiotherapy or conventional radiotherapy with fluorouracil can further improve local control (4-6). There are three preoperative radiotherapy methods that are generally used. Firstly, conventional chemoradiotherapy, also known as long-course chemoradiotherapy (LC), which includes 45-50.4 Gy in 25-28 fractions with concurrent chemotherapy followed by surgical resection after 4-8 weeks. Secondly, short-course chemoradiotherapy or short-course radiotherapy (SC), which consist of 25 Gy in 5 fractions with or without concurrent chemotherapy followed by immediate surgery within one week (7).

LC and SC have been extensively investigated in several studies and is thought to be a valuable approach in the preoperative treatment of RC. The German Rectal Cancer Study Group has demonstrated the benefit of LC with regard to local control and treatment-associated toxicity (8). Some randomized trials have also found that LC can lead to a higher pathological complete response (PCR) rate (9) and an improved

sphincter preservation (10). On the other hand, SC has advantages in terms of early toxicity (11,12), cost and convenience (13), which is preferred by many European centers (14).

Although radiotherapy is recommended for RC before surgery, different regions have different preferences and the results may vary in diverse studies. Therefore, this meta-analysis aimed to compare the outcome of LC and SC and identify the most beneficial approach for RC preoperative treatment.

METHODS AND MATERIALS

Search strategy

Relevant studies published up to March 31st 2018 were systematically searched within the PubMed, Medline, Cochrane and EMABSE databases by two authors. The main key search words were: “rectal cancer” OR “RC” AND “preoperative long course chemoradiotherapy” OR “preoperative short course radiotherapy” OR “preoperative short course chemoradiotherapy”. Citation lists of relevant articles and reviews were also reviewed to identify further studies of interest.

Selection criteria

In order to extract as much data as possible, randomized control trials (RCTs) or consort control trials (CCTs) published in English that conformed to following selection criteria were included in the meta-analysis: a) clinical tumor stage between T2 and T4, or clinical UICC stage between II and III; b) preoperative treatment within the study including long course and short course radiotherapy, with or without chemotherapy; c) consistent rectal resection surgeries in both groups; and d) a study with one or more available data related with PCR, tumor stage, local recurrence, distant metastases, mortality or late toxicity. Studies without assessable data for statistical analysis or non-original studies such as reviews, letters and comments were excluded. Discrepancies were resolved by referring to the original articles or via a group discussion of all the authors.

Data extraction

Data extraction was performed by two researchers independently and was recorded in a standard extraction form. The information, including the first authors' name, year of publication, number of enrolled patients, follow-up duration, study type, intervention methods and other baseline characteristics of enrolled patients were extracted.

Statistical analysis

Statistical analyses were performed using Review Manager 5.3 (The Nodic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014). Dichotomous data were analyzed using the risk ratio (RR) for RCTs and odds ratio (OR) for CCTs with 95% confidence intervals (CI). Heterogeneity among individual studies was studied using Cochran's Q statistic and the I^2 test. Significant heterogeneity was considered when the p value was < 0.05 (Q statistic) and/or $I^2 > 50\%$ and therefore, a random effects model was selected. If not, a fixed effect model was used. Sensitivity analysis was performed in order to confirm the robustness of the results by omitting one study at a time

Quality assessment and risk of bias

According to the Cochrane Handbook of Systematic Review of Interventions, RCTs were assessed using Review Manager 5.3 based on seven perspectives: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and others. These were scored as unclear, low or high risk of bias (Supplementary Figure 1). CCTs were assessed using NOS (The Newcastle-Ottawa Scale) based on three perspectives (selection, comparability and outcome of cohort), detailed in table 1.

RESULTS

Study selection

According to the search criteria (Fig. 1), 452 studies were originally included. A total of 289 articles remained after eliminating duplicates and irrelevant articles. Thus,

249 studies were excluded due to an inappropriate article style, such as reviews and comments, and finally 40 articles were fully reviewed. After scanning the full texts, 24 articles were excluded, including eight without raw data and 16 without crucial data. Finally, 16 eligible studies were included in this meta-analysis.

Characteristics of enrolled studies

Table 2 shows the basic information of the studies included in the meta-analysis. All included studies were published from 2001 to 2017, with a clinical tumor stage from cT2 to cT4, or UICC stage from II to III. Eight trials used chemotherapy (concurrent or adjuvant or both) in both groups, four trials only used chemotherapy (concurrent) in the LC group and two trials did not use chemotherapy. Four trials had a similar interval from the completion of radiation to the start of surgery in both groups. Two trials were performed in the Oceania region, eight in Europe, two in Asia, one in Africa and one in America.

Analysis

For the analysis, PCR and tumor downstaging served as primary endpoints. Local recurrences, distant metastases, mortality and serious late toxicity served as secondary endpoints.

Primary endpoints

PCR rate

Ten studies (13,15-22) with a total of 1,569 patients reported PCR rate. As shown in the forest plot (Fig. 2.1), significant heterogeneity (I^2 = 78%, $p < 0.05$) was observed. Therefore a random effect model was applied. Although the LC group had a higher prevalence of PCR after therapy, the difference did not reach statistical significance (RR = 0.54, 95% CI: 0.26-1.10). On the other hand, according to the sensitivity analysis, the diamond of the pooled point would favor the LC group if the study by Markovina et al. (21) or Read et al. were excluded (22).

Tumor downstaging rate

Twelve studies (15-25), with a total of 1,723 participants, reported a reduction in T or N stage based on the pretreatment clinical staging by CT or MRI *versus* the final pathological staging. As shown in figure 2.2, significant heterogeneity was observed (I^2 = 79%, p < 0.05) and a random effect model was applied. There was no statistical significance between the two groups (RR = 0.83, 95% CI: 0.58-1.17). However, the diamond of the pooled point would favor the LC group if the studies by Chung et al. (15) and Markovina et al. were excluded (21).

Secondary endpoints

Local recurrences and distant metastases

In terms of local recurrences, five studies (13,15-17) with a total of 669 patients were included. Low heterogeneity was observed (I^2 = 22%, p = 0.27) and this was not statistically significant (RR = 0.55, 95% CI: 0.26-1.16). With regard to distant metastases, five studies (13,15-17) with a total of 685 patients were included. Low heterogeneity was observed (I^2 = 29%, p = 0.22) and this was not statistically significant (RR = 1.03, 95% CI: 0.77-1.37). The results remained unchanged after the sensitivity analysis and the details are shown in figure 3.1 and 3.2.

Mortality

Six studies (13,15,17,18,23,26) with a total of 1,309 patients reported mortality. There was no heterogeneity (I^2 = 0%, p = 0.78) and this was not statistically significant (RR = 0.95, 95% CI: 0.78-1.15). The results remained unchanged after the sensitivity analysis and the details are shown in figure 3.3.

Serious late toxicity

Four studies (13,22,25,27), with a total of 792 rectal cancer patients, reported serious late toxicity. Significant heterogeneity was observed (I^2 = 74%, p = 0.01) and therefore the random effect model was used. No statistical difference was found between the two groups (RR = 1.10, 95% CI: 0.37-3.26). The details are shown in figure 3.4.

Subgroup analysis

A subgroup analysis was performed based on study types and the use of chemotherapy (CT) in order to deliver a more accurate result and reduce the impact of high heterogeneity. In the first category, studies were stratified into RCTs and CCTs. LC had a higher prevalence of PCR and tumor downstaging than SC in the RCTs subgroup (RR = 0.18, 95% CI: 0.09-0.37; RR = 0.67, 95% CI: 0.54-0.82) and less heterogeneity was also observed (I^2 = 21%, p = 0.28; I^2 = 0%, p = 0.50). No significant difference was observed in the local recurrences, distant metastases, mortality and serious late toxicity subgroups.

In the second category, the analysis was stratified into three subgroups: LC and SC with chemotherapy (both CT), no chemotherapy in the SC group (SC non-CT) and no chemotherapy in both groups (both non-CT). The SC group had a poorer PCR rate compared with the LC group in the SC non-CT subgroup analysis (RR = 0.20, 95% CI: 0.08-0.52, I^2 = 16%, p = 0.31). However, in terms of tumor downstaging, no statistically significant differences were observed in the subgroups (RR = 0.92, 95% CI: 0.60-1.39; RR = 0.51, 95% CI: 0.19-1.36; RR = 1.19, 95% CI: 0.33-4.30, respectively). Due to inadequate studies, the subgroup analysis of local recurrences, distant metastases, mortality and late serious toxicity was not performed. Details of the subgroup analysis are presented in table 3.

DISCUSSION

LC and SC preoperative radiation are commonly adopted for the treatment of locally advanced RC, which can lead to better disease management after surgery. The outcomes of LC and SC therapies were compared in this meta-analysis and both were effective in the preoperative treatment of locally advanced rectal cancer with regard to PCR, tumor downstaging, local recurrence, distant metastases, mortality and serious late toxicity. Furthermore, the SC group without chemotherapy had a worse PCR rate compared to the LC group with chemotherapy, which may imply the benefit of chemotherapy in the preoperative treatment of RC.

PCR is commonly defined as the absence of viable tumor cells in the primary tumor, mesorectal fat and resected lymph nodes (28). This may confer a survival benefit as

well as a reference for selecting the candidates for organ-preserving strategies (29,30). There was no significant difference between the two groups in the overall analysis of PCR, although the LC group still had a higher PCR rate. Furthermore, statistically significant differences were observed in the sensitivity analysis when the studies by Markovina et al. (21) or Read et al. were excluded (22). An acceptable explanation was found after a more thorough review of these studies. There was a more frequent use of chemotherapy in the SC group for an unknown reason in the study by Markovina et al. (21), whereas there were three reasons which may account for the disparity in the study by Read et al. (22). Firstly, there were more patients with T3 or T4 stage tumors in the LC group. Secondly, a lower total dose of radiation was used in the LC group compared with the dose used in other studies. Thirdly, LC patients of this study did not receive chemotherapy, in contrast to other studies.

Tumor downstaging was recognized as a reduction in T stage based on pretreatment staging by TRUS and CT *versus* the final histology, which is also associated with the survival of patients undergoing treatment for RC (22). In contrast to the meta-analysis by Zhou et al. (31), the overall analysis of tumor downstaging did not reach statistical significance. Even though a higher downstaging rate was still found in the LC group. On the other hand, this analysis was statistically significant when the studies by Markovina et al. (21) and Chung et al. (15) were removed. Reasons for the former are mentioned previously and reasons for the later may be delayed surgery in both groups. Some researchers concede that immediate surgery in the SC group may lead to an inferior tumor downstaging (32,33) and delayed surgery in both groups may address this difference (19).

A subgroup analysis was performed based on study types and intervention with chemotherapy due to the significant heterogeneity within the meta-analysis. The results show that the LC group had a higher prevalence of PCR and tumor downstaging in the RCT subgroup, which are consistent with previous studies. Furthermore, the LC group also had a higher prevalence of PCR compared with the SC group without chemotherapy, which suggests that PCR may correlate with chemotherapy. Several randomized trials by EORTC (34) and the Foundation

Francaise de Cancerologie (35) have confirmed the benefit of chemotherapy for local control, PCR and tumor downstaging (6,13,35,36). Nevertheless, some studies have also revealed that chemotherapy was associated with grade 3 or 4 toxicity (13).

Some limitations within this study should not be ignored. Firstly, we combined RCTs and CCTs in the meta-analysis, which may lead to a notable heterogeneity in the overall analysis. Secondly, there were different types of surgery performed in the various studies; some studies performed TME while others adopted APR, LAR or Hartmann surgery, which may lead to bias. Thirdly, clinical staging is based on diagnostic imaging tests which may not be as accurate as histopathological staging. Finally, few studies reported the quality of TME and circumferential margin, therefore the influence of these variables cannot be evaluated.

On the basis of our findings, it can be concluded that both LC and SC therapies are effective and safe for the treatment of locally advanced disease with regard to PCR rate, tumor downstaging rate, local recurrence, distant metastases, mortality and serious late toxicity. Furthermore, chemotherapy may lead to a better PCR rate.

ACKNOWLEDGMENT

The authors declare that the research has not received any funding and there are no conflicts of interests.

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	Item	Chung MJ 2016	Guckenberger 2012	Krajcovicova 2012	Lee SW 2017	Markovina 2017	Read 2001	Vironen 2005	Yeh 2011
Selection	Representative nature of the exposed cohort	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Selection of the non-exposed cohort	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Ascertainment of exposure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Demonstration that the outcome of interest was not present at the start of the study	No	Yes	No	No	No	No	No	No
Comparability	Study controls for the most important factor	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Study controls for any additional factor	Yes	Yes	No	No	No	No	No	No
Outcome	Assessment of outcome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Was follow-up long enough for outcomes to occur	Yes	Yes	Yes	No	Yes	No	No	Yes
	Adequacy of follow up of cohorts	Yes	Yes	Yes	No	Yes	No	No	Yes

Table 1. Risk of bias of CCTs by the NOS

Table 2. Characteristics of the studies included in the meta-analysis

Study	Group	Age	Pretreatment tumor stage	Distance of lower border from anal verge (cm)	Radiotherapy	Surgery	Chemotherapy	Follow-up time (month)	Resources and study year	Type of study
Ansari 2016 (22)	SC: 161	63 (26-80)	cT3	0-5:60 > 5-10:94 > 10-12:7	25 Gy, 5 fractions, immediate surgery, adjuvant CT	TME; APR; LAR; AR; HP	5-FU	NA	2001-2006, Australian and New Zealand	RCT
	LC: 161	64 (29-82)		0-5:52 > 5-10:94 > 10-12:15	50.4 Gy, 28 fractions, concurrent CT, surgery after 4-6 weeks, adjuvant CT later					

Bujko 2006 (9)	SC: 155 LC: 157	NA	cT3-cT4	NA	25 Gy, 5 fractions, surgery within 7 days, optional postoperative CT 50.4 Gy, 28 fractions, concurrent CT, surgery after 4-6 weeks, optional postoperative CT	TME	5-FU, leucovorin	48 (31-69)	April 1999-February 2002, Poland	RCT
Chung MJ 2016 (11)	SC: 19 LC: 53	< 70:14 ≥ 70:5 < 70:14 ≥ 70:5	cT3-cT4	NA	25 Gy, 5 fractions, concurrent CT, surgery after 8 weeks, adjuvant CT 50.4 Gy, 28 fractions, concurrent CT, surgery after 8 weeks, adjuvant CT	LAR, APR	5-FU, Capecitabine	25 (3-58)	March 2010-June 2015, South Korea	CCT

Eitta MA 2010 (12)	SC: 14 LC: 15	53 (32-75) 45 (20-65)	cT3-cT4	NA	25 Gy, 5 fractions, surgery within 1 week, adjuvant CT 45 Gy, 25 fractions, surgery after 4-6 weeks, adjuvant CT	LAR, APR	Mayo Clinic or 5-FU	18 (6-28)	June 2007-September 2009, Egypt	RCT
Gucken berger 2012 (23)	SC: 108 LC: 117	64 66	UICC stage II-III	NA	29 Gy, 10 fractions, surgery within 1 week, adjuvant CT for patients with pathological stage UICC ≥ II 50.4 Gy, 28 fractions, surgery after 4-6 weeks, concurrent and adjuvant CT	TME, APR, TAR	5-FU 5-FU or 5-FU and oxaliplatin	49 (3-138)	1999-2008, Germany	CCT

Kairev 2017 (13)	SC: 68 LC: 72	65.6 ± 9.51 63.1 ± 10.13	cT2-cT4	0-5:34 5-10:29 11-15:5 0-5:30 5-10:37 11-15:5	25 Gy, 5 fractions, surgery after 6-8 weeks, optional postoperative CT 50 Gy, 25 fractions, concurrent CT, surgery after 6-8 weeks, adjuvant CT	TME	5-FU, leucovorin	NA	January 2007-June 2013, Lithuania	RCT
Krajcovicova 2012 (14)	SC: 96 LC: 55	62 (29-84) 63 (42-80)	UICC stage II-III	NA	25 Gy, 5 fractions, surgery after 5 days 45-46 Gy, 23-25 fractions, concurrent CT, surgery after 6 weeks	APR, SP	No 5-FU, leucovorin	48 (2-128)	January 1999-January 2008, Slovak	CCT
Latkauskas 2012	SC: 37	67.19 ± 9.56	cT3-cT4	0-5:18 5-10:16 11-15:2	25 Gy, 5 fractions, surgery after 6 weeks	TME, AR and anastomo	No	NA	2007-2010, Lithuania	RCT

(15)	LC: 46	63.5 ± 9.45		0-5:18 5-10:22 11-15:6	50 Gy, 25 fractions, concurrent CT, surgery after 6 weeks	sis, proctectomy with coloanal anastomosis; HP; APR	5-FU, leucovorin			
Latkauskas 2016 (13)	SC: 68	65.6 ± 9.5	cT3-cT4	0-5:34 5-10:29 11-15:5	25 Gy, 5 fractions, surgery after 6 weeks		No	NA	2007-2013, Lithuania	RCT
	LC: 72	63.14 ± 10.1		0-5:30 5-10:37 11-15:5	50 Gy, 25 fractions, concurrent CT, surgery after 6 weeks		5-FU, leucovorin			
Lee SW 2017 (16)	SC: 150	61 (35-83)	cT3-cT4	< 5:70 ≥ 5:94	25 Gy, 5 fractions (or 33 Gy, 10 fractions), concurrent CT, surgery after 4.9-14.7 weeks, optional postoperative CT	TME	5-FU; Capecitabine	NA	February 2010-July 2012	CCT

	LC: 150	63 (33-81)		< 5:58 ≥ 5:92	45-50.4 Gy, 25 fractions, concurrent CT, surgery after 4.9-14.7 weeks, optional postoperative CT		5-FU, leucovorin or capecitabine or 5-FU		January 2003-May 2014	
Markovina 2017 (17)	SC: 69	57.2 (28.3-84.6)	cT3-cT4	0-5:20 5-10:33 11-15:16	20-25 Gy, 5 fractions, adjuvant CT	LAR, APR	FOLFOX-6 (after radiotherapy)	49.4 (12.3-69.7)	November 2009-April 2012	CCT
	LC: 69	56.6 (31.0-82.5)		0-5:26 5-10:34 11-15:9	40-48 Gy, 25-30 fractions, concurrent CT		5-FU or capecitabine (during radiotherapy)	54.3 (9.8-112.3)	July 2002-April 2015	

	SC: 162	63 (26-80)		0-5:48 5-10:88 11-15:26	25 Gy, 5 fractions, surgery after 3-7 days, adjuvant CT later		FU, folinic acid			
Ngan 2012 (19)	LC: 161	64 (29-82)	cT3	0-5:31 5-10:88 11-15:42	50.4 Gy, 28 fractions, concurrent CT, surgery after 4-6 weeks, adjuvant CT later	APR, non-APR	FU (during radiotherapy); FU, folinic acid (postoperative)	NA	2001-2006, Australian and New Zealand	RCT
Petterson 2010 (24)	SC: 118	67 (41-86)	NA	> 6:41 6-10:45 > 10:32	25 Gy, 5 fractions, surgery within 1 week	TME, AR, APR, HP	No	NA	October 1998 to December 2005; Sweden	RCT
	LC: 65	68 (44-83)	NA	> 6:16 6-10:26 > 10:23	50 Gy, 25 fractions, surgery after 4-8 weeks					

Read 2001 (27)	SC: 82 LC: 122	61 ± 13	cT3-cT4	6.1 ± 3.7	25 Gy, 5 fractions, surgery in 1-2 days 45 Gy, 25 fractions, surgery after 5-7 weeks	TME, AR, APR, HP	No	NA	January 1990 to September 1999; US	CCT
Vironen 2005 (20)	SC: 42 LC: 44	68 (44-84) 65 (42-88)	cT2-cT4	NA	25 Gy, 5 fractions, surgery in 1 week 50 Gy, 28 fractions, concurrent CT, surgery after 4-5 weeks	TME, AR, APR, HP	5-FU	NA	January 1999-December 2003, Finland	CCT
Yeh 2011 (21)	SC: 28 LC: 37	67 (42-87) 60 (30-87)	cT3-cT4	≤ 4:21 5-7:9 ≥ 8:7 ≤ 4:21 5-7:9 ≥ 8:7	25 Gy, 5 fractions, surgery within 7 days, optional postoperative CT 50 Gy, 28 fractions, concurrent CT, surgery after 4-6 weeks, optional postoperative CT	TME	5-FU, leucovorin	3 (0.26-5.16) years	January 2005-December 2007, China (Taiwan)	CCT

AR: anterior resection; LAR: low anterior resection; APR: abdominoperineal resection; HP: Hartmann procedure; CT: chemotherapy; TAR: transanal resection; SP: sphincter preservation.

Table 3. Subgroup analysis

Outcome	Subgroup	No. of studies	Effect estimate	Test for overall effect	Heterogeneity	
PCR	RCTs	5	0.18 (0.08, 0.37)	$p < 0.05$	$I^2 = 21\%$	$p < 0.05$
	CCTs	5	1.09 (0.47, 2.54)	$p = 0.84$	$I^2 = 73\%$	$p = 0.28$
	Both CT	6	0.57 (0.22, 1.47)	$p = 0.25$	$I^2 = 76\%$	$p < 0.05$
	SC non-CT*	3	0.20 (0.08, 0.52)	$p < 0.05$	$I^2 = 16\%$	$p = 0.31$
	Both non-CT	1	1.57 (1.09, 2.27)	$p = 0.02$	NA	
	Overall	10	0.54 (0.26, 1.10)	$p = 0.09$	$I^2 = 78\%$	$p < 0.05$
Tumor downstaging	RCTs	5	0.67 (0.54, 0.82)	$p < 0.05$	$I^2 = 0\%$	$p = 0.50$
	CCTs	7	0.91 (0.36, 2.31)	$p = 0.84$	$I^2 = 84\%$	$p < 0.05$
	Both CT	7	0.92 (0.60, 1.39)	$p = 0.68$	$I^2 = 82\%$	$p < 0.05$
	SC non-CT	4	0.51 (0.19, 1.36)	$p = 0.18$	$I^2 = 84\%$	$p < 0.05$
	Both non-CT	1	1.19 (0.33, 4.30)	$p = 0.79$	NA	
	Overall	12	0.83 (0.58, 1.17)	$p = 0.29$	$I^2 = 79\%$	$p < 0.05$
Local recurrences	RCTs	4	0.49 (0.22, 1.07)	$p = 0.07$	$I^2 = 22\%$	$p = 0.28$
	CCTs	1	2.89 (0.17, 48.62)	$p = 0.46$	NA	
	Overall	5	0.55 (0.26, 1.16)	$p = 0.12$	$I^2 = 22\%$	$p = 0.27$
Distant metastases	RCTs	3	1.03 (0.76, 1.41)	$p = 0.84$	$I^2 = 9\%$	$p = 0.33$
	CCTs	2	0.71 (0.08, 6.67)	$p = 0.77$	$I^2 = 74\%$	$p = 0.05$
	Overall	5	1.03 (0.77, 1.37)	$p = 0.85$	$I^2 = 29\%$	$p = 0.22$
Mortality	RCTs	3	0.95 (0.76, 1.19)	$p = 0.64$	$I^2 = 0\%$	$p = 0.90$
	CCTs	3	0.93 (0.54, 1.59)	$p = 0.79$	$I^2 = 11\%$	$p = 0.33$
	Overall	6	0.95 (0.78, 1.15)	$p = 0.59$	$I^2 = 0\%$	$p = 0.78$
Serious late	RCTs	1	1.47 (0.71, 3.07)	$p = 0.30$	NA	
	CCTs	3	0.73 (0.08, 6.47)	$p = 0.77$	$I^2 = 82\%$	$p < 0.05$

toxicity	Overall	4	1.10 (0.37, 3.26)	p = 0.87	I^2 = 74%	p = 0.01

PCR: pathological complete response; RCTs: randomized control trials; CCTs: consort control trials; both CT: both the LC and SC group received chemotherapy; SC non-CT: SC group without chemotherapy; both non-CT: both groups without chemotherapy; NA: not applicable. *Statistical significance.

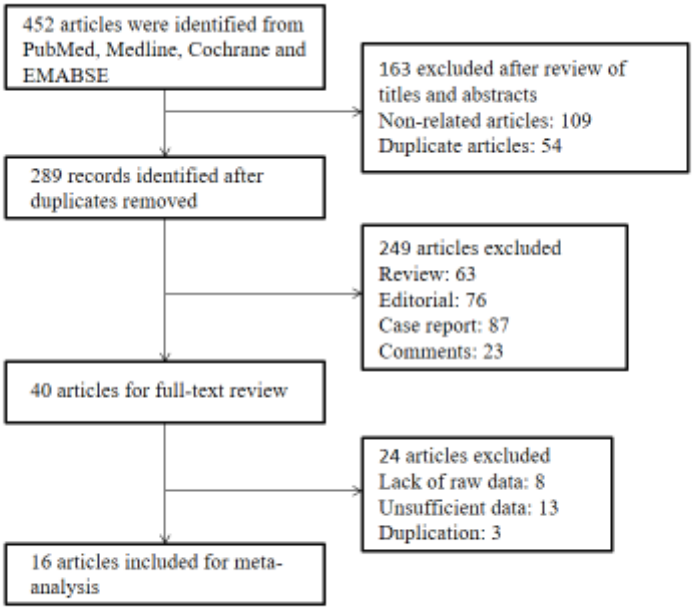


Fig. 1. Flow chart of the study selection process.

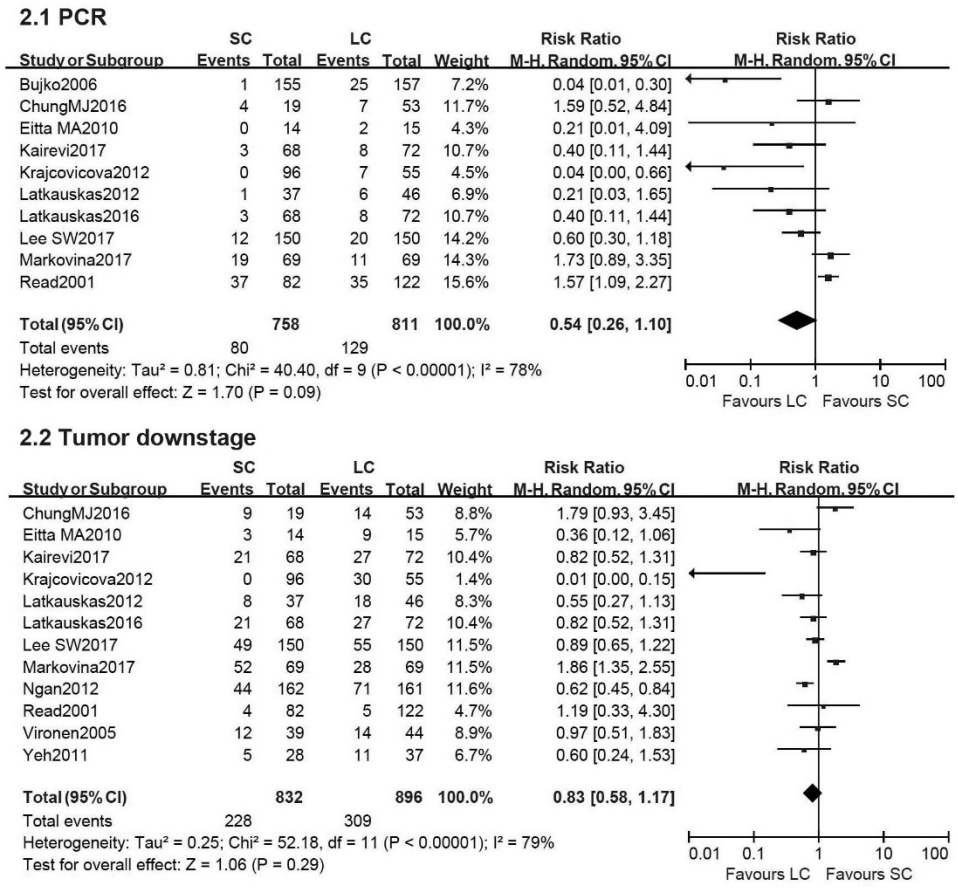


Fig. 2. Forest plots of primary endpoints.

Fig. 2.1. PCR.

Fig. 2.2. Tumor downstaging.

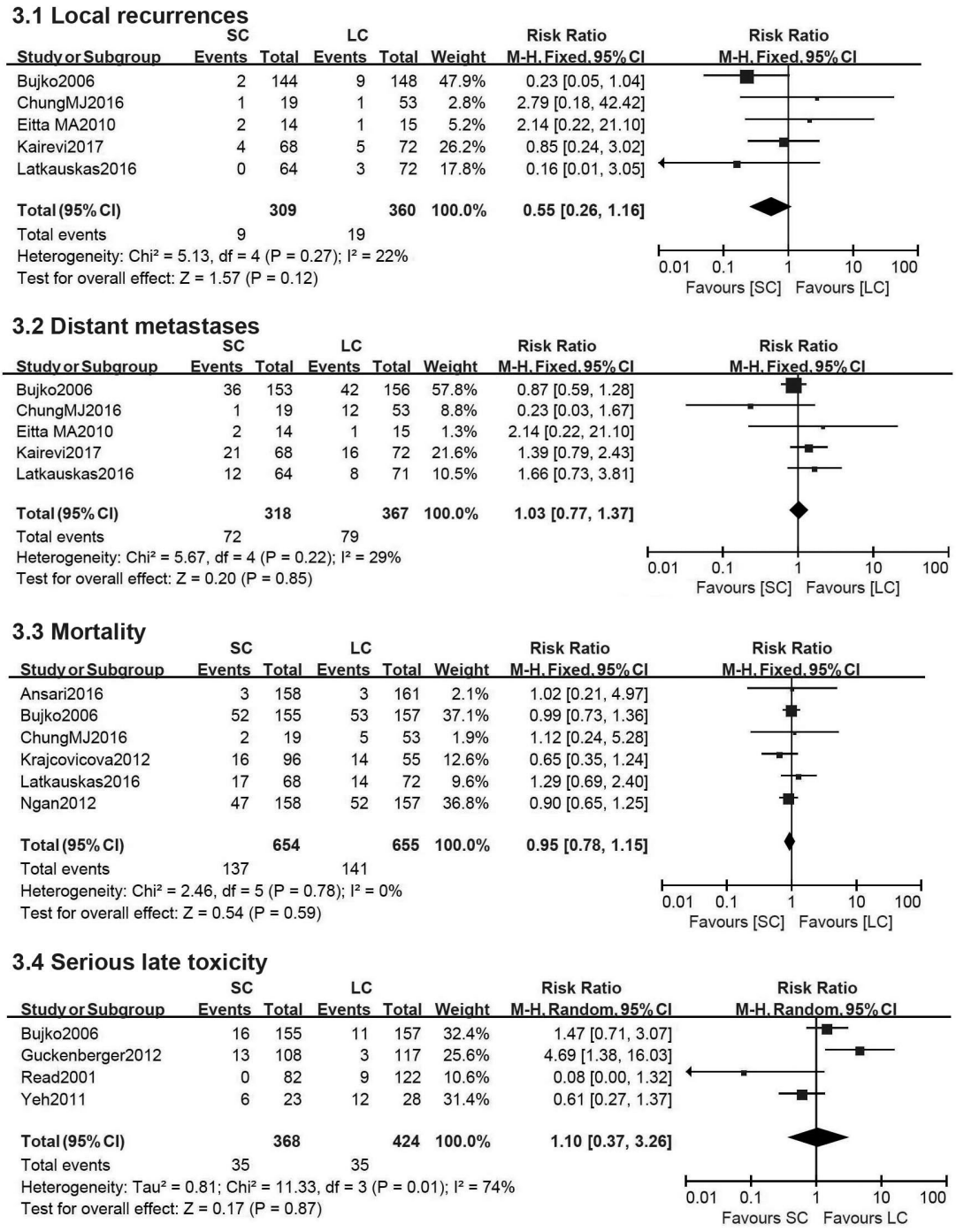


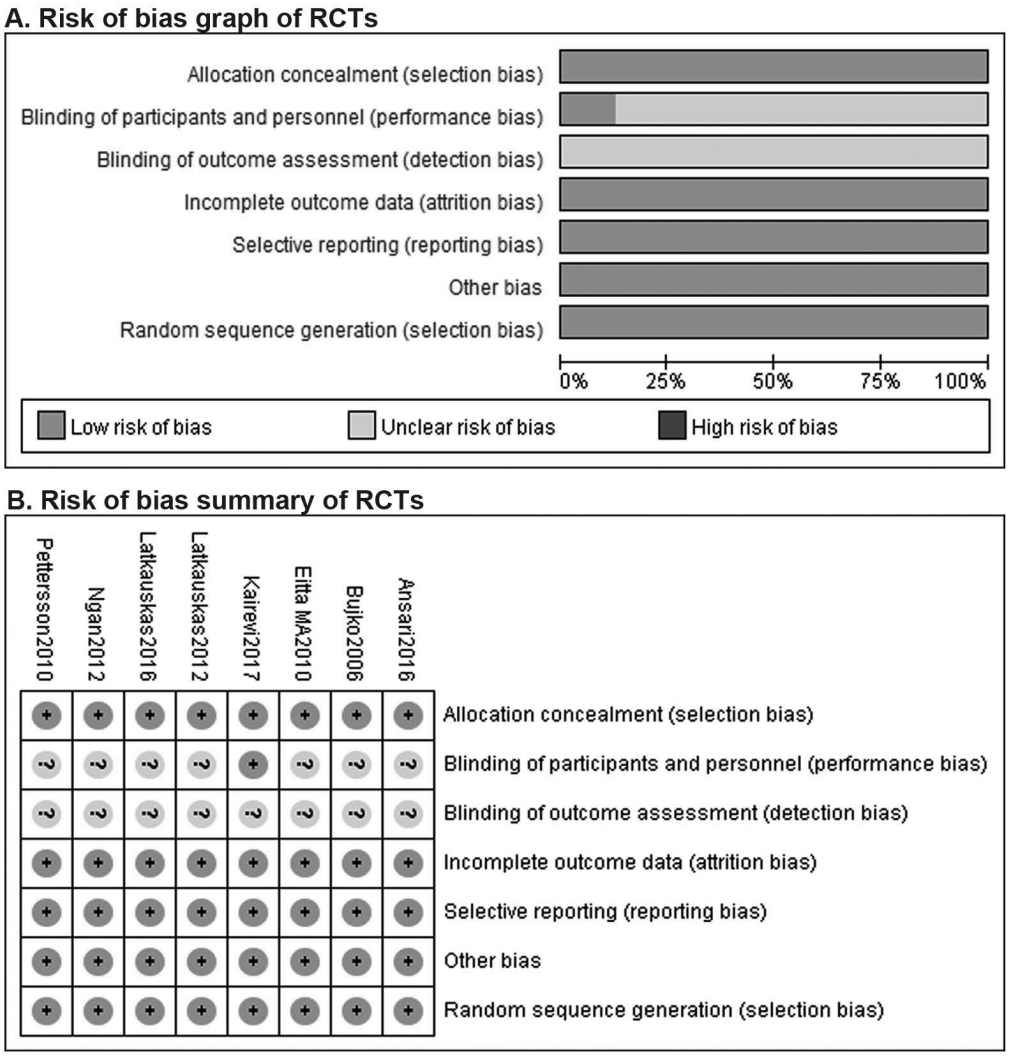
Fig. 3. Forest plots of secondary endpoints.

Fig. 3.1. Local recurrences.

Fig. 3.2. Distant metastases.

Fig. 3.3. Mortality

Fig. 3.4. Serious late toxicity



Supplementary Figure. Risk bias of included RCTs.