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Capecitabine versus 5-fluorouracil in neoadjuvant chemoradiotherapy of locally advanced rectal cancer
A meta-analysis

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Abstract

Background: The differences in efficacy between capecitabine and 5-fuorouracil (5-FU) in neoadjuvant chemoradiotherapy (CRT) of locally advanced rectal cancer (LARC) are not well recognized. We performed this meta-analysis to analyze the effect of capecitabine and 5-FU on neoadjuvant CRT to more accurately understand the differences between the 2 drugs.

Methods: MEDLINE, EMBASE, Cochrane Library, China National Knowledge Infrastructure, and Wanfang Database were performed to identify all published studies investigating the efficacy of capecitabine in neoadjuvant CRT of LARC versus 5-FU before August, 2017. Primary endpoint was the odds ratio (OR) for improving pathological complete response (pCR) rate of patients with LARC. Secondary endpoints were the ORs of efficiency for downstaging tumor and increasing R0 resection in patients with LARC. Safety analyses were also performed. The OR was the principal measurement of effect, which was calculated as capecitabine group versus 5-FU group, and was presented as a point estimate with 95% confidence intervals (CIs). All calculations and statistical tests were performed using RevMan 5.3 software.

Results: In all, 2916 patients with LARC enrolled in the 10 studies were divided into capecitabine group (n = 1451) and 5-FU group (n = 1465). The meta-analysis showed that capecitabine improved pCR (OR 1.34, 95% CI 1.10–1.63), and R0 resection rate (OR 1.92, 95% CI 1.10–3.36). There were no statistically significant differences either in overall downstaging rate (OR 1.31, 95% CI 0.79–2.16) or in the tumor downstaging rate (OR 1.24, 95% CI 0.79–1.92), but there was a significant difference of the nodal downstaging rate between the 2 groups (OR 1.68, 95% CI 1.11–2.54). There was no statistically significant difference in sphincter preservation rate between the 2 groups (OR 1.36, 95% CI 0.96–1.92). No obvious safety concerns about mortality and complications were raised in these studies. There were no statistically significant differences in 3-year disease-free-survival (OR 1.29, 95% CI 0.75–2.20), and in grade 3 to 4 acute toxicity during CRT (OR 0.63, 95% CI 0.31–1.30).

Conclusions: Compared with 5-FU-based neoadjuvant CRT, capecitabine-based neoadjuvant CRT can safely improve pCR, nodal down-staging, and R0 resection of patients with LARC.

Abbreviations: 5-FU = 5-fluorouracil, cCR = clinical complete response, CI = confidence interval, CR = complete response, CRT = chemoradiotherapy, DFS = disease-free survival, IV = intravenous injection, LARC = locally advanced rectal cancer, LV = Leucovorin, NNT = number needed to treat, OR = odds ratio, pCR = pathological complete response.

Keywords: 5-fluorouracil, capecitabine, meta-analysis, neoadjuvant chemoradiotherapy, rectal neoplasms

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1. Introduction

Rectal cancer remains to be an important health issue worldwide, and is among the most commonly diagnosed cancer and leading causes of cancer-related death worldwide.[1] The treatment of the rectal cancer is dependent on the TNM staging of the tumor. Early-stage rectal cancer is curable with surgical treatment alone, with a 5-year overall survival rate of 90%.[2,3] However, the majority of rectal cancer patients are diagnosed with advanced diseases. The advanced rectal cancer without distant metastasis is still a potentially curable disease, but the prognosis is poorer than the early-stage diseases. Treatment of advanced rectal cancer is still a challenge for gastrointestinal surgeons. Localized tumors, limited to the submucosa, can be best treated surgically, with a long-term survival of over 90%,[3] but the prognosis of locally advanced tumors is poor due to a high unresectability rate at presentation, and a much higher relapse and metastasis rate after radical surgery. Locally advanced rectal cancer (LARC) without

evidence of distant metastasis are potentially curable, but these tumors usually present with a more advanced stage and are associated with a worse prognosis, so it is necessary and widely accepted that multidisciplinary treatment, including surgery, chemotherapy, and radiotherapy, is often employed. Neo-adjuvant chemoradiotherapy (CRT) has been recommended for the treatment of LARC, thus demanding further studies regarding the regimens of neoadjuvant CRT.

The employment of pelvic radiation may be the most significant development of the multidisciplinary treatment of LARC, and preoperative CRT, despite a moderate increase in acute toxicity and no impact on overall survival significantly improves local control, has become the standard of care for patients with LARC.[4–8] The Dutch rectal cancer total mesorectal excision (TME) trial showed that neoadjuvant radiation significantly improved 10-year survival in TNM stage III patients with a negative circumferential margin.[9] Compared with upfront surgery, the possible advantages of neoadjuvant CRT in the treatment of LARC include gained resectability and an increased rate of sphincter preservation.[7,10] According to the results of the German CAO/ARO/AIO-94 randomized phase III trial, preoperative CRT showed improved pelvic control and sphincter preservation and less acute/chronic toxicity than postoperative chemoradiotherapy,[7] and there is a persisting significant improvement of pre versus postoperative CRT on local control.[7,8] There is also evidence that showed that preoperative CRT reduce overall long-term surgical complications compared with postoperative CRT.[11]

The addition of 5-fluorouracil (5-FU) to preoperative radiotherapy has been shown to improve the treatment effect significantly compared with radiotherapy alone.[5,12] Fluorouracil has been limited by poor oral absorption and gastrointestinal toxicity, despite of its vital importance in regimens for the treatment of rectal cancer, whereas capecitabine, which is a prodrug of 5-FU, can be orally administered; the final step of its conversion to the active form of 5-FU is performed by thymidine phosphorylase, which is at higher concentrations in most tumor tissue than in most normal healthy tissue, this theoretically allows low systemic toxicity and should be more effective and much safer than 5-FU.[13,14] Recent large phase III studies have confirmed that capecitabine is noninferior to 5-FU as a component of neoadjuvant CRT for rectal cancer.[15] Therefore, 5-FU and the like, capecitabine-based neoadjuvant CRT is now a standard treatment for LARC.

Achievement of complete pathological response (pCR) after neoadjuvant CRT is associated with greatly improved cancer outcomes in LARC.[16,17] Two meta-analyses[18,19] have shown that pCR is associated with excellent long-term survival, with low rates of local recurrence and distant failure, suggesting that achievement of pCR by neoadjuvant CRT may indicate a favorable biological tumor profile. So, we set the odds ratio (OR) for improving pCR as the primary endpoint of this meta-analysis.

The improvements in magnetic resonance and ultrasound endoscopy allows more accurate preoperative staging can be achieved,[20] and accordingly develop clinical studies with different regimens of neoadjuvant chemoradiotherapy.[15,21–29] Ten studies of 5-FU and capecitabine efficacies of neoadjuvant CRT in LARC were compared in this meta-analysis. All 10 studies have shown that preoperative CRT using capecitabine and 5-fluouracil is feasible and improves the pCR rate. The aim of the current meta-analysis under such circumstances was to evaluate the effectiveness of neoadjuvant CRT in treatment of rectal cancer and explore the optimal strategy for preoperative treating patients with LARC.

2. Materials and methods

2.1. Ethical approval

Because the present study is a meta-analysis of previously published studies, the ethical approval and patient consent are not required.

2.2. Data collection and selection

A comprehensive electronic data retrieval was in MEDLINE, EMBASE, Cochrane Library, China National Knowledge Infrastructure, and Wanfang Database until August, 2017. Electronic searches were carried out to identify all published studies that compared the capecitabine-based neoadjuvant CRT with 5-FU-based one for LARC. The search was done using four sets of terms: "rectal cancer"; "capecitabine"; "5-fluorouracil" and "neoadjuvant chemoradiotherapy/preoperative chemoradiotherapy", and the terms were set to title/abstract.

2.3. Inclusion and exclusion criteria

The following inclusion criteria were used: studies that compared the capecitabine-based neoadjuvant CRT with 5-FU-based one for LARC; blindness of the trial was not required; patients with pathologically diagnosed rectal adenocarcinoma, without prior treatment before entering the trial, but with a history of potentially curative surgery; and studies which were considered updated.

Exclusion criteria: studies on postoperative chemotherapy; studies that included patients with metastases at enrollment were excluded; and studies with the group not receiving surgery were excluded.

The data of each study were collected by 2 reviewers (J.F.Z. and W.Z.) independently. The results were consistent.

2.4. Data extraction

The following data were extracted from each study and recorded using a predesigned form: authors, year of publication, patient population, country of investigators, sample size (total, eligible, and per arm), CRT regimen, cycles of chemotherapy, follow-up period, curative effect (survival rate, rate of macroscopic radical resection and cancer stage at pathological examination), and adverse events. Two reviewers (J.F.Z. and W.Z.) did the extraction independently.

2.5. Meta-analysis protocol

Data were obtained directly from included articles or calculated by percentage in each article. The meta-analysis was performed using Review Manager 5.3 software (provided by Cochrane Collaboration). Outcomes assessed by this meta-analysis included the overall survival, 3-year progression-free survival rate, tumor down-staging rate, R0 resection rate, and safety analysis. Overall survival was defined as the time between the treatment randomization and the date of the last follow-up or of the patient's death. Patients who were lost to follow-up were considered as dead. Locoregional recurrence was measured either from the date of surgery to the occurrence of the event or to the
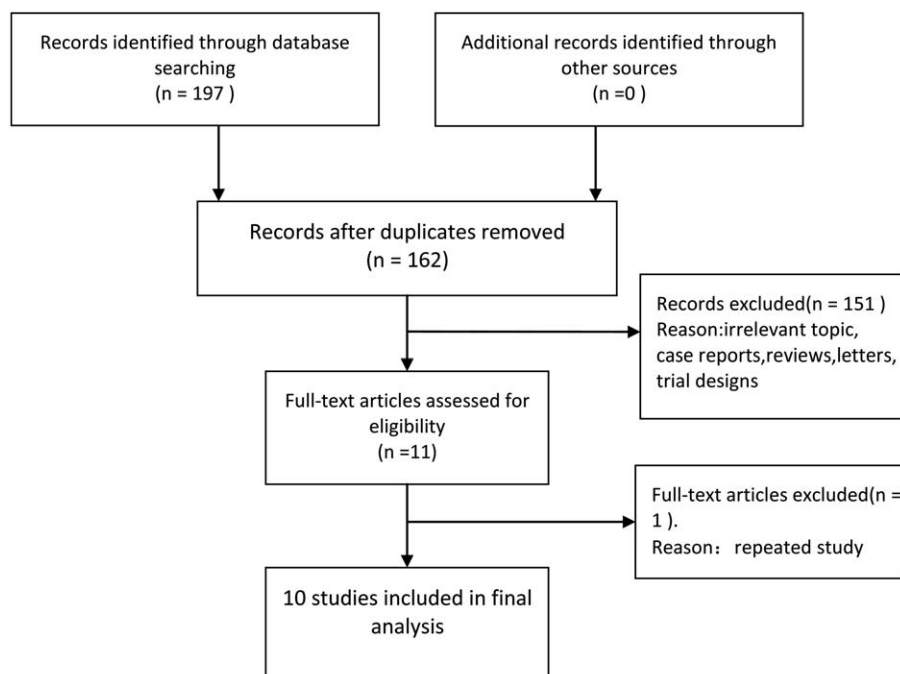
Figure 1. Flow diagram of studies selection process.

date of last follow-up. Heterogeneity between the studies was assessed to determine which model would be used in the meta-analysis. A sensitivity analysis was performed by changing the meta-analysis model. An OR was the principal measurement of effect. It was calculated as the capecitabine group versus the 5-FU group.

2.6. Statistical analysis

All statistical analyses were performed spontaneously using Review Manager 5.3 software (Nordic Cochran Centre, Copenhagen, Denmark). Heterogeneity between the studies was assessed using chi-square test. I^2 statistics was used for the degree of heterogeneity evaluation, fixed-effects model methodology was applied when $I^2 < 50\%$, and random-effects model methodology was applied when $I^2 > 50\%$. The OR was calculated for dichotomous data with 95% confidence intervals (CIs) for all analyses. All P values were 2-sided, and $P < .05$ was considered statistically significant.

3. Results

3.1. Search results and characteristics of included studies

Figure 1 demonstrates a flow chart of the selection process that yielded a total of 10 studies included in the current meta-analysis. A total of 2916 patients (capecitabine group, n=1451; fluorouracil group, n=1465) were included in the analysis. The detailed characteristics of these studies are summarized in Table 1.

3.2. Complete pathological response

There was no significant heterogeneity between the studies ($P = .54$), and the fixed-effects model was used. The data in all the 10 studies[15,21–29] were available for the analysis of pCR. There

were 1408 patients in the capecitabine group and 1382 patients in the 5-FU group in this meta-analysis, and the pCR rates were 19.53% and 15.48%, respectively. The OR, expressed as capecitabine group versus 5-FU group, was 1.34 (95% CI 1.10–1.63, $P = .004$). The difference of the pCR between capecitabine group and 5-FU group was statistically significant. The pCR was increased by 4.05% in the capecitabine group compared with the 5-FU group (Fig. 2). The number needed to treat (NNT) was 25. Publication bias was not found in the included studies (Fig. 3).

3.3. Downstaging rate

Seven studies[21–23,25–27,29] describing the pathological down-staging of rectal cancer after resection (519 in capecitabine group and 466 in 5-FU group) were included in the analysis. Six studies[21,23–26,29] describing the tumor downstaging (425 in capecitabine group and 446 in 5-FU group), 3 studies[21,25,26] describing the nodal downstaging (214 in capecitabine group and 207 in 5-FU group) were included in the analysis respectively. There were no statistically significant differences either in overall downstaging rate (68.02% vs 62.23%; OR 1.31, 95% CI 0.79–2.16, $I^2 = 67\%$, $P = .29$) or in the tumor downstaging rate (51.29% vs 45.52%; OR 1.24, 95% CI 0.79–1.92, $I^2 = 57\%$, $P = .35$)between the 2 groups, but there was a significant difference of the nodal downstaging rate between capecitabine group and 5-FU group (66.36% vs 56.03%; OR 1.68, 95% CI 1.11–2.54, $I^2 = 42\%$, $P = .01$) (Fig. 4A, B, and C).

3.4. R0 resection rate

The R0 resection rate of rectal cancer was reported in 3 studies.[15,25,29] Because no obvious heterogeneity was observed in these studies ($P = .76$, $I^2 = 0\%$), the fixed-effect model was

Table 1

Characteristics of the included studies in the meta-analysis.

No.	Authors and year of publication	Country /area	Patients (n)		Chemotheraputic regimen		Radiotherapy	Time to surgery		Age
			Cape	5-FU	Cape	5-FU		Cape	5-FU	
1	Kim et al, 2006[21]	Korea	97	127	825 mg/m^2 b.i.d. + LV (20 mg/m^2/d, d1–14, 22–35	5-FU 500 mg/m^2/d + LV 20 mg/m^2 for 5 d, d1–5, d29–33	50.4Gy	Not specified	Not specified	25–80
2	Yerushalmi et al, 2006[22]	Israel	43	46	825 mg/m^2 b.i.d.	180 mg/m^2/d 24 h continuous infusion, 5 d/wk	50.4Gy	4.5–20 wks (median 7.5)	4–51 wks (median 7)	23–82
3	Kim et al, 2007[23]	Korea	133	145	825 mg/m^2 b.i.d.	5-FU 400 mg/m^2/d + LV 20 mg/m^2/d for 3 d. d1–3, d29–31	50.4Gy	4–8 wks (median 6)	4–8 wks (median 6)	27–82
4	Chan et al, 2010[24]	Canada	34	68	825 mg/m^2 b.i.d,	5-FU 20 mg/kg/d 6-h daily infusion + LV 200 mg/m^2/d, d1–4, d22–25 + mitomycin C 8 mg/m^2 dL	50Gy	8 wks	8 wks	30–79
5	Ramani et al, 2010[25]	United Kingdom	99	97	825 mg/m^2 (<70 y) 625 mg/m^2 (>70 y) b.i.d.	1000 mg/m^2/d (<70 y) 750 mg/m^2/d (>70 y) on d 1–4 and 22–26 as a 96-h infusion	50.4–54Gy	6–8 wks	6–8 wks	22–82
6	Chen et al, 2012[26]	Taiwan, China	47	27	850 mg/m^2 b.i.d.	5-FU 350 mg/m^2 IV + LV 20 mg/m^2 IV d1–5, d21–25	50.4Gy	6 wks	6 wks	18–85
7	Hofheinz et al, 2012[15]	Germany	73	74	825 mg/m^2 b.i.d.	1000 mg/m^2/d continuous infusion d1–5, d29–33	50.4Gy	4–6 wks	4–6 wks	30–86
8	Lu et al, 2013[27]	China	88	50	Capecitabine 1000 mg/m^2 b.i.d. d1–14, 29–42 + oxaliplatin 100 mg/m^2 d1, 29	Oxaliplatin 85 mg/m^2 d1, 22 + LV 200 mg/m^2 d1, 22 + 5-FU 400 mg/m^2 IV bolus on d1, then 600 mg/m^2/d continuous infusion for 2 d, d1–3, 22–24	50 Gy	5–8 wks	5–8 wks	18–75
9	Adnan et al, 2014	Turkey	35	25	825 mg/m^2 b.i.d.	5-FU 425 mg/m^2/d + LV 25 mg/ m^2/d, d1–4, 29–31	50.4Gy	6 wks	6 wks	36–80
10	O'Connell et al, 2014[28]	US	794	801	825 mg/m^2/d ± oxaliplatin 50 mg/m^2/wk	225 mg/m^2/d continuous infusion ± oxaliplatin 50 mg/m^2/wk	50.4–55.8 Gy	6–8 wks	6–8 wks	≥18

5-FU = 5-fluorouracil, Cape = capecitabine, IV = intravenous injection, LV = leucovorin.
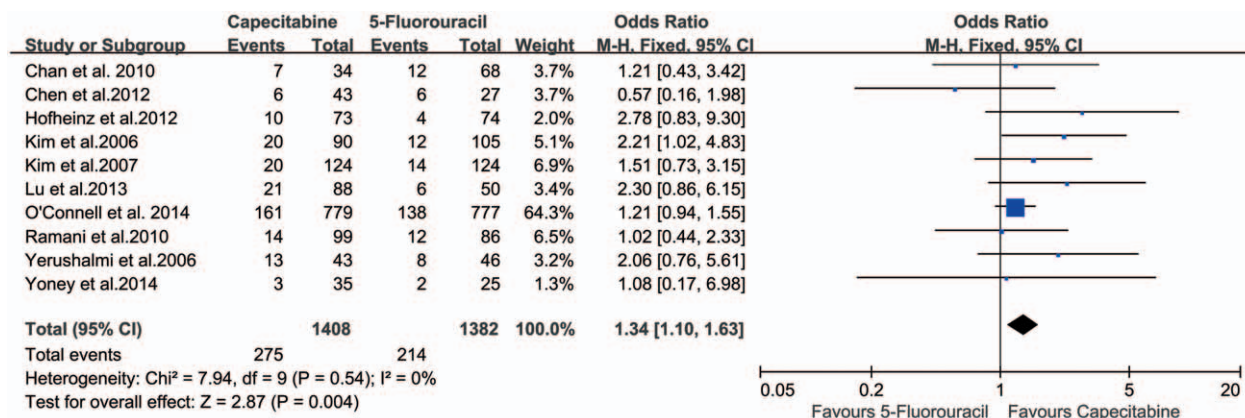
Figure 2. Effect of capecitabine-based and 5-fluorouracil-based neoadjuvant CRT on pCR rate. CRT = chemoradiotherapy, pCR = pathological complete response.

used. The R0 resection rate of the rectal cancer was higher in capecitabine group than in 5-FU group (87.86% vs 80.10%; OR 1.92, 95% CI 1.10–3.36, $I^2 = 0\%$, $P = .02$), and the NNT was 13 (Fig. 5).

3.5. Sphincter preservation

Eight studies[21–26,28,29] comparing the different sphincter preservation rate between the 2 groups (1247 in capecitabine group and 1272 in 5-FU group) were included in the analysis. There was no statistically significant difference in sphincter preservation rate between the 2 groups (63.67% vs 59.75%; OR 1.36, 95% CI 0.96–1.92, $I^2 = 53\%$, $P = .09$) (Fig. 6).

3.6. Three-year disease-free survival

Three studies[15,24,29] compared the 3-year disease-free survival (DFS) rates between the 2 groups. There were no statistically

significant differences in 3-year DFS (76.67% vs 75.72%; OR 1.29, 95% CI 0.75–2.20, $I^2 = 0\%$, $P = .35$) (Fig. 7).

3.7. Safety analysis

Safety analysis included both chemotherapy-induced acute adverse effects (grade 3/4, defined according to the Common Toxicity Criteria of the National Cancer Institute, version 2.0) and postoperative complication and mortality. Eight studies[21–26,28,29] reported grade 3/4 acute adverse effects of neoadjuvant CRT, and there were no statistically significant differences in grade 3 to 4 acute toxicity during CRT (26.82% vs 28.21%; OR 0.63, 95% CI 0.31–1.30, $I^2 = 82\%$, $P = .21$) (Fig. 8). Three studies[21,26,29] reported perioperative mortality without death in either group. Four studies[21,26,28,29] reported anastomotic leakage with no statistically significant difference ($P = .68$) between the 2 groups (2.18% vs 2.40%; OR 0.88, 95% CI 0.48–1.62, $I^2 = 0\%$) (Fig. 9).
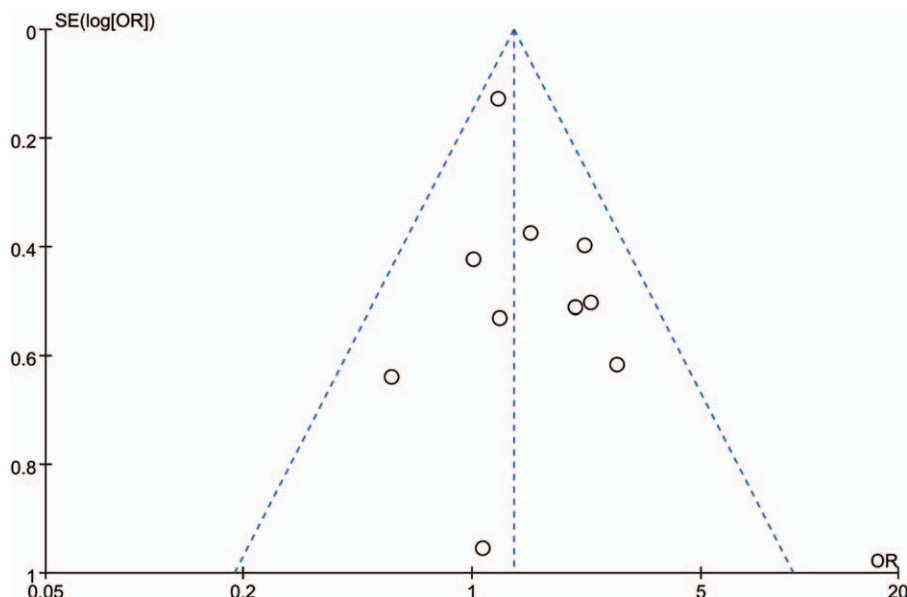

Figure 3. Publication bias in the included studies. Funnel plot analysis of potential publication bias. OR = odds ratio.
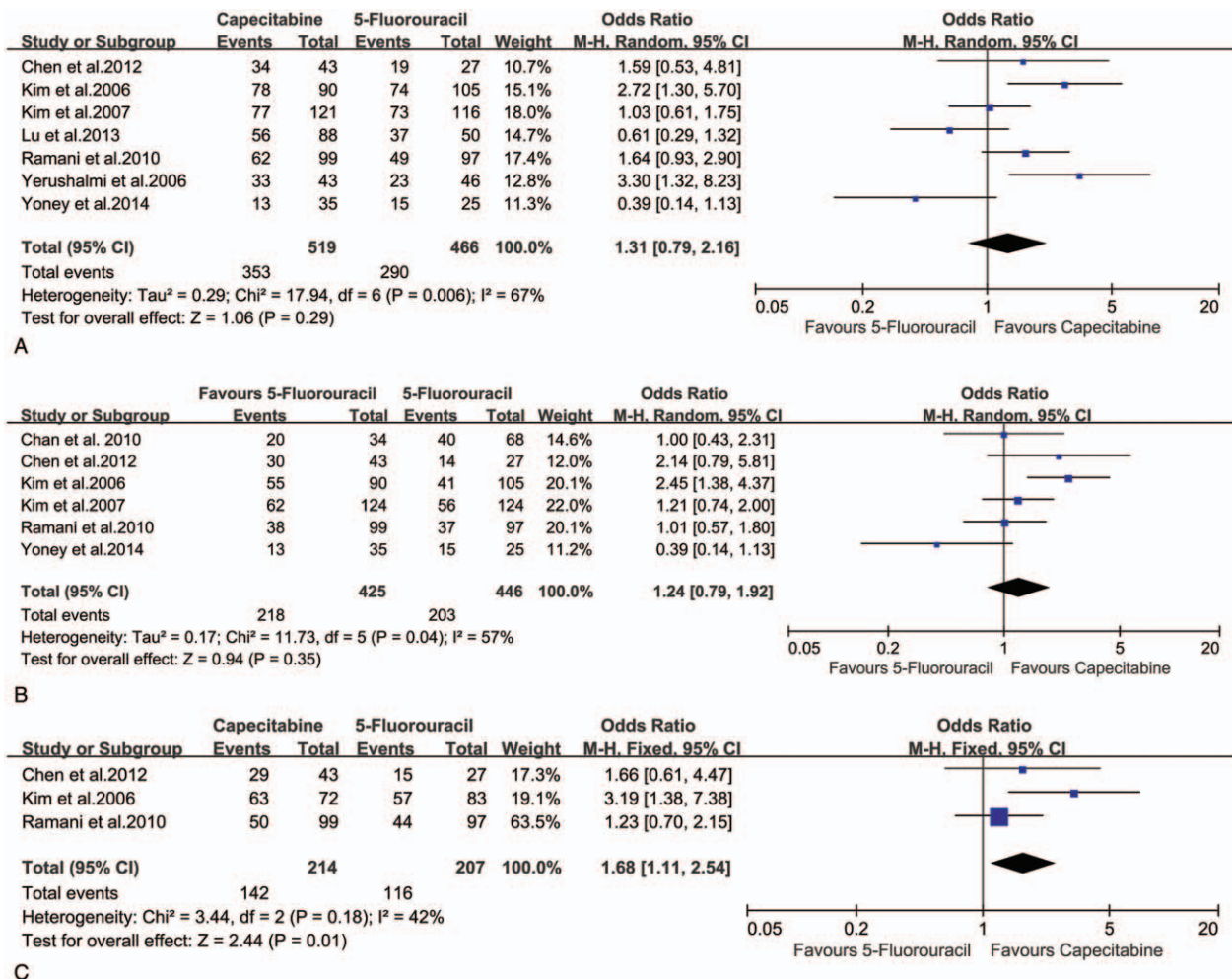
Figure 4. Effect of capecitabine-based and 5-fluorouracil-based neoadjuvant CRT on downstaging rate. (A) Overall downstaging rate; (B) tumor downstaging rate; (C) nodal downstaging rate.

4. Discussion

Our meta-analysis demonstrated the feasibility of capecitabine-based neoadjuvant CRT for LARC patients. Compared with 5-FU-based neoadjuvant CRT, capecitabine-based regimen could improve pCR (NNT=25) and increase the R0 resection rate (NNT=13) of rectal cancer. To examine the role of capecitabine-based neoadjuvant CRT in improving the 3-year DFS rate of LARC patients compared with the patients who received 5-FU-based regimen, data from 3 studies[15,24,29] were further

analyzed, showing that capecitabine had no effect on the 3-year DFS rate of LARC patients (OR 1.29, 95% CI 0.75–2.20). Although local failure reduced significantly, DFS has remained stable over these years.[4,8] Many studies showed that some of the complete responders with careful selection and strict surveillance may avoid surgery, and can get a similar oncological outcome compared with surgery, so the "watch and wait" policy can be considered instead of surgery.[30–33] Some studies showed that patients with pathological complete response have significant longer DFS and overall survival after neoadjuvant CRT and can
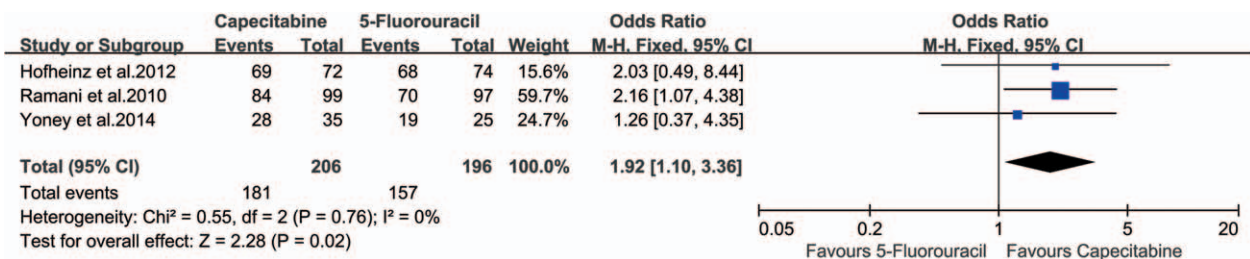

Figure 5. Effect of capecitabine-based and 5-fluorouracil-based neoadjuvant CRT on R0 resection. CRT=chemoradiotherapy.
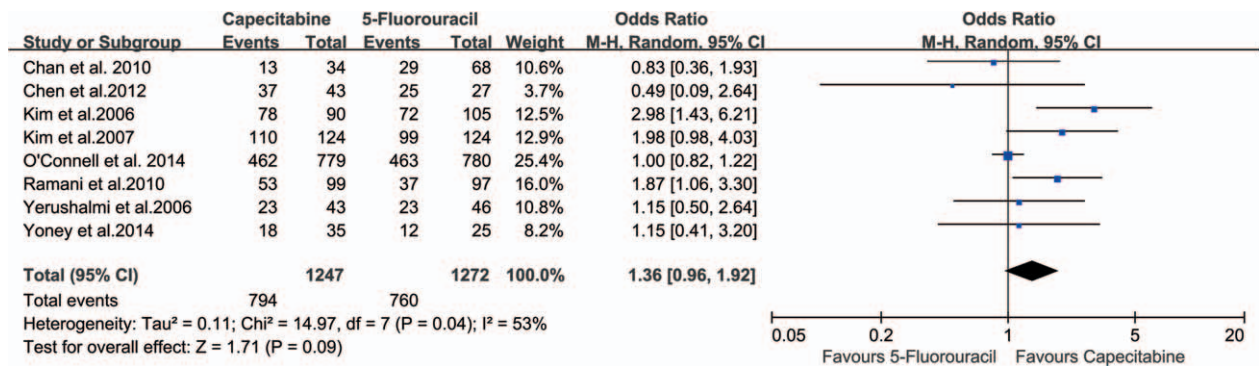
Study or Subgroup	Capecitabine Events	Total	5-Fluorouracil Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Chan et al. 2010	13	34	29	68	10.6%	0.83 [0.36, 1.93]
Chen et al.2012	37	43	25	27	3.7%	0.49 [0.09, 2.64]
Kim et al.2006	78	90	72	105	12.5%	2.98 [1.43, 6.21]
Kim et al.2007	110	124	99	124	12.9%	1.98 [0.98, 4.03]
O'Connell et al. 2014	462	779	463	780	25.4%	1.00 [0.82, 1.22]
Ramani et al.2010	53	99	37	97	16.0%	1.87 [1.06, 3.30]
Yerushalmi et al.2006	23	43	23	46	10.8%	1.15 [0.50, 2.64]
Yoney et al.2014	18	35	12	25	8.2%	1.15 [0.41, 3.20]
Total (95% CI)		1247		1272	100.0%	1.36 [0.96, 1.92]
Total events	794		760			

Heterogeneity: Tau² = 0.11; Chi² = 14.97, df = 7 (P = 0.04); I² = 53%
Test for overall effect: Z = 1.71 (P = 0.09)

Figure 6. Effect of capecitabine-based and 5-fluorouracil-based neoadjuvant CRT on sphincter preservation. CRT = chemoradiotherapy.

Study or Subgroup	Capecitabine Events	Total	5-Fluorouracil Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chan et al. 2010	31	34	62	68	15.4%	1.00 [0.23, 4.27]
Hofheinz et al.2012	58	81	50	80	60.4%	1.51 [0.78, 2.93]
Yoney et al.2014	26	35	19	25	24.1%	0.91 [0.28, 3.00]
Total (95% CI)		150		173	100.0%	1.29 [0.75, 2.20]
Total events	115		131			

Heterogeneity: Chi² = 0.67, df = 2 (P = 0.72); I² = 0%
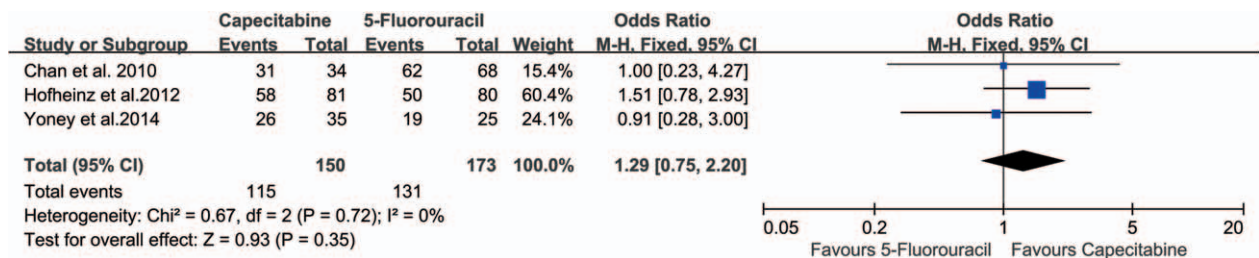Test for overall effect: Z = 0.93 (P = 0.35)

Figure 7. Effect of capecitabine-based and 5-fluorouracil-based neoadjuvant CRT on three-year disease-free survival. CRT = chemoradiotherapy.

Study or Subgroup	Capecitabine Events	Total	5-Fluorouracil Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Chan et al. 2010	3	34	1	68	6.4%	6.48 [0.65, 64.86]
Chen et al.2012	9	47	11	27	13.3%	0.34 [0.12, 0.99]
Kim et al.2006	16	97	66	127	16.3%	0.18 [0.10, 0.35]
Kim et al.2007	13	133	13	145	15.1%	1.10 [0.49, 2.47]
O'Connell et al. 2014	288	787	258	780	18.4%	1.17 [0.95, 1.44]
Ramani et al.2010	6	99	6	97	12.5%	0.98 [0.30, 3.15]
Yerushalmi et al.2006	7	43	12	46	13.4%	0.55 [0.19, 1.56]
Yoney et al.2014	0	35	4	25	4.5%	0.07 [0.00, 1.31]
Total (95% CI)		1275		1315	100.0%	0.63 [0.31, 1.30]
Total events	342		371			

Heterogeneity: Tau² = 0.73; Chi² = 39.90, df = 7 (P < 0.00001); I² = 82%
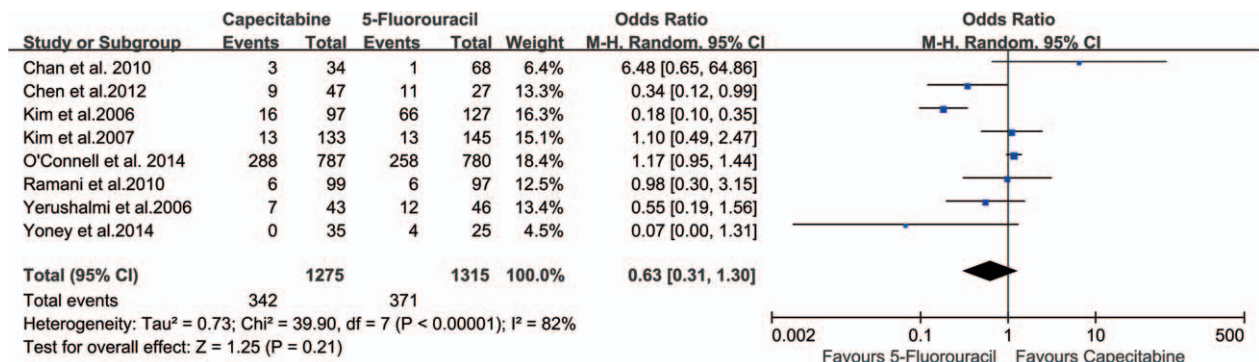Test for overall effect: Z = 1.25 (P = 0.21)

Figure 8. Effect of capecitabine-based and 5-fluorouracil-based neoadjuvant CRT on acute chemoradiotherapeutic toxicity. CRT = chemoradiotherapy.

Study or Subgroup	Capecitabine Events	Total	5-Fluorouracil Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chen et al.2012	1	43	3	27	16.3%	0.19 [0.02, 1.93]
Kim et al.2006	1	105	1	97	4.7%	0.92 [0.06, 14.96]
O'Connell et al. 2014	18	744	18	757	79.0%	1.02 [0.53, 1.97]
Yoney et al.2014	0	25	0	35		Not estimable
Total (95% CI)		917		916	100.0%	0.88 [0.48, 1.62]
Total events	20		22			

Heterogeneity: Chi² = 1.86, df = 2 (P = 0.39); I² = 0%
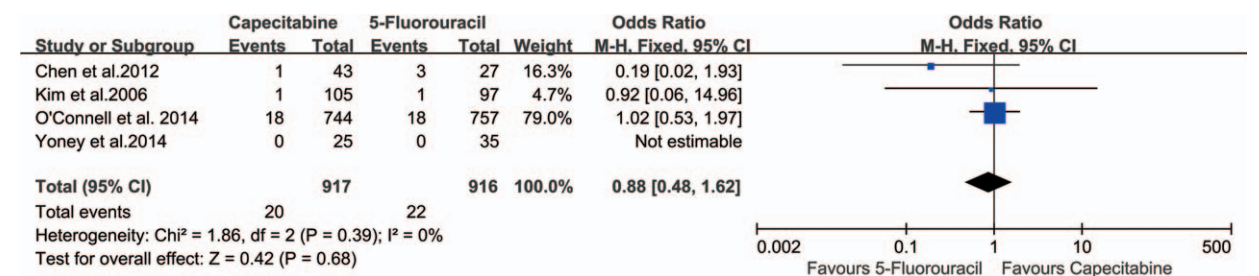Test for overall effect: Z = 0.42 (P = 0.68)

Figure 9. Effect of capecitabine-based and 5-fluorouracil-based neoadjuvant CRT on anastomotic leakage. CRT = chemoradiotherapy.

be an early response indicator.[17,18] What's more, in recent years, there has been growing interest in total neoadjuvant therapy (TNT), and a retrospective cohort analysis shows that TNT cohort has a higher CR rate (both pCR and cCR), suggest TNT may be adopted to avoid surgery and preserve organ.[34] Our study showed that capecitabine-based neoadjuvant CRT benefit the pCR of rectal cancer patients, which means more selected patients who get a cCR after neoadjuvant CRT or TNT may avoid surgery and can get a similar oncological outcome.

The regimen of the neoadjuvant chemotherapy affects the outcome of the treatment. Several regimens have been used in the neoadjuvant CRT of LARC. Our present meta-analysis showed that capecitabine-based combination regimen had a high efficiency for LARC patients. The effective response rate will help downstage tumors to the greatest extent and increase the probability of R0 resection. Outcome parameter as R0 resection depends highly on the quality of surgery; however, only 1 of the 3 included studies provided limited information about surgery.[15] Although there is a nonsignificant increase in sphincter preservation rate in this study, some oncologists hold the point that patients with a complete response managed by "watch and wait" strategy may avert permanent colostomy, thus improving the quality of life of the patients.[31,35]

Another major concern in our meta-analysis is the efficiency and safety of neoadjuvant CRT in the studies included. Our meta-analysis showed that LARC patients could well tolerate neoadjuvant CRT. Grade 3/4 gastrointestinal and leukopenia adverse events of neoadjuvant CRT occurred in 27.53% (713/2590) of LARC patients. The difference of complication rate between those 2 groups was not obvious, indicating that capecitabine-based neoadjuvant CRT is a safe modality for LARC (OR 0.63, 95% CI 0.31–1.30). The R0 resection rate of the rectal cancer was higher in capecitabine group than in 5-FU group (OR 1.92, 95% CI 1.10–3.36, NNT = 13). These results suggest that capecitabine can be considered as an alternative to 5-FU in the setting of CRT. Capecitabine was not inferior to 5-FU in safety concern.

There are several limitations to this study. The included studies recruited patients with different amount of capecitabine and 5-FU. The variable grades and clinical stages of disease could have potentially influenced overall survival and the incidence of local or distal recurrence. Only 2 of the included studies were randomized and 8 of them were retrospective.

Based on the evidence from 2 randomized and 8 retrospective studies, capecitabine-based neoadjuvant CRT appears to have clinically measurable advantages in patients with LARC. The reckonable impact on oncological endpoints awaits the findings from large high-quality randomized trials.

5. Conclusions

In conclusion, our study provides information on the efficacy of neoadjuvant CRT with capecitabine-based and 5-FU-based regimen in LARC patients. These regimens were regarded as the most effective ones in neoadjuvant CRT for treating LARC patients. The meta-analysis showed that compared with 5-FU-based neoadjuvant CRT, capecitabine-based neoadjuvant CRT can safely improve pCR, nodal downstaging and R0 resection of patients with LARC. With all these clinical and scientific efforts, these treatment strategies will definitely continue to further improve the outcome of LARC patients.

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