Peer Review File

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Reviewer

Major Compulsory Revisions:

Comment 1: Figure 1 Selection flow diagram. 8 additional records identified through other sources. Please clarify the criteria of 8 additional records.

Reply 1: Your question is valuable to us, thank you for your reminder. Figure 1 was a searching process made before the whole inclusion criteria had been finally revised. At the beginning, we hoped not to omit any data that could be used for analysis including those clinical trials that were incomplete and had no full-text articles but might have some data displayed on clinicaltrials.gov. So we put them in the "additional records" box at first. And then carried out further checks. According to the final inclusion criteria, these records could be omitted.

Records like:

(1)Trial of Capecitabine With or Without Irinotecan Driven by UGT1A1 (CinClare). NCT02605265.

(2)Radiation-protection Effect of Amifostine in Locally Advanced Rectal Cancer. NCT03702985.

(3)Cetuximab, 5-FU and Radiation as Neoadjuvant Therapy for Patients With Locally Advanced Rectal Cancer. NCT00611858.

(4)Neoadjuvant Chemotherapy Combined With Cetuximab for EGFR Wild Type Locally Advanced Rectal Cancer. NCT03391843.

(5)CONVERT: Neoadjuvant Chemotherapy Alone Versus Preoperative Chemoradiation for Locally Advanced Rectal Cancer Patients. NCT02288195.

(6)Triplet Combination or Doublet Regimen Versus Chemoradiation as Neoadjuvant Therapy for Locally Advanced Rectal Cancer. NCT03975049.

(7)PROSPECT: Chemotherapy Alone or Chemotherapy Plus Radiation Therapy in Treating Patients With Locally Advanced Rectal CancerUndergoing Surgery. NCT01515787. The protocol was further explained in an article (PMID：30688523).
(8) A Pilot Study of Neoadjuvant Chemotherapy Combined With Bevacizumab for Locally Advanced Rectal Cancer. NCT03245203.

Changes in the text: Figure 1 has been omitted due to the suggestion below in "Minor Essential Revisions-comment 3".

Comment 2: The major flaw of the current study was that 19 studies of randomized controlled trials and one of cohort study, total 20 studies consisted of 12 regimens such as RT+XELOX, RT+IS, RT+FOLFOX, RT+CAPE, RT+FOLFIRI, RT+UFT, RT+5-FU, RT+CAPE+BEV, RT+XELIRI, RT+XELIRI+CET, RT, FOLFOX. As the manuscript entitled with "Comparison of different chemoradiotherapy regimen…."; therefore, The regimen of RT and FOLFOX should be excluded. Additionally, The keywords included colorectal or colon or rectal, and the term of colon for the selection should be excluded.

Reply 2: Your advice is valuable to us, thank you for your reminder. The main purpose of this paper was to explore how different preoperative treatments or neoadjuvant treatments of LARC worked. One of the reasons for the original protocol in the "Selection criteria" to allow regimens like "RT" and "FOLFOX" was that these treatment regimens were compared with chemoradiotherapy agent directly in researches and were used in LARC patients. If these regimens got removed, the researches should be excluded as well which means the exact sample size and comprehensiveness of LARC patients who had received CRT became unclear. For another, these attempts in LARC indicated the development of neoadjuvant treatment of LARC. Scholars firstly used RT alone and then shifted to the CRT field. And now they are trying to get rid of RT for lighter adverse events. Last but not least, the sample size would greatly be decreased after these changes which would influence the objectiveness of the network. For example, the network would now analyse "RT+5-FU" and

“RT+XELOX” directly or via “RT” and “RT+CAPE” node. If “RT” node was removed, the comparison between “RT+5-FU” and “RT+XELOX” would only depend on direct comparison (the line between these two circles was very thin) and “RT+CAPE”. It would finally make the network become too simple and rely on some weighted outcomes only. After careful discussion of all authors, we finally decided not to remove these two regimens temporarily and modified the “Selection criteria”. And the modification of the title was under consideration. Further, we attached the results of comparison among the rest regimens here to give the reviewers some references.

Another question about the keyword “colon” was considered as our fault and had been changed into “rectum”.

Results without “RT” and “FOLFOX”:

pCR:

RT+5-FU									
0.84 (0.41, 1.81)	**RT+CAPE**								
0.66 (0.32, 1.24)	0.78 (0.27, 1.99)	**RT+FOLFOX**							
0.61 (0.22, 1.75)	0.72 (0.28, 1.81)	0.92 (0.28, 3.41)	**RT+XELOX**						
1.62 (0.23, 11.99)	1.93 (0.28, 13.21)	2∘ 47 (0.33, 21.22)	2.67 (0.51, 14.67)	**RT+XELIRI**					
0.58 (0.13, 2.59)	0.69 (0.12, 3.55)	0.89 (0.17, 4.78)	0.95 (0.15, 5.88)	0.36 (0.03, 4.08)	**RT+IS**				
1.00 (0.21,4.76)	1.18 (0.21, 6.40)	1.51 (0.29, 8.75)	1.64 (0.25, 10.47)	0.61 (0.05, 7.26)	1.72 (0.20, 14.78)	**RT+UFT**			
2.08 (0.16, 27.59)	2.50 (0.20, 30.15)	3.20 (0.23, 47.92)	3.43 (0.33, 36.08)	1.28 (0.25, 6.42)	3.64 (0.19, 73.54)	2.11 (0.11, 42.83)	**RT+XELIRI+CET**		
1.12 (0.15, 8.87)	1.33 (0.20, 9.07)	1.72 (0.21, 15.78)	1.83 (0.23, 15.57)	0.68 (0.05, 10.18)	1.96 (0.16, 25.79)	1.14 (0.09, 15.05)	0.54 (0.02, 12.80)	**RT+CAPE+BEV**	
1.00 (0.22, 4.29)	1.18 (0.21, 5.92)	1.52 (0.30, 7.84)	1.63 (0.25, 9.50)	0.61 (0.05, 6.89)	1.72 (0.20, 14.46)	1.00 (0.11, 8.27)	0.47 (0.02, 8.85)	0.87 (0.07, 10.77)	**RT+FOLFIRI**

DFS：

RT+5-FU							
0.89 (0.78,1.01)	**RT+CAPE**						
0.93 (0.86,1.01)	1.05 (0.90,1.23)	**RT+FOLFOX**					
0.83 (0.69,0.99)	0.94 (0.83,1.06)	0.89 (0.73,1.08)	**RT+XELOX**				
0.79 (0.53,1.16)	0.89 (0.62,1.28)	0.85 (0.57,1.26)	0.95 (0.67,1.34)	**RT+XELIRI**			
1.11 (0.79,1.57)	1.26 (0.87,1.82)	1.20 (0.84,1.70)	1.34 (0.91,1.98)	1.41 (0.84,2.38)	**RT+IS**		
1.06 (0.82,1.36)	1.19 (0.90,1.58)	1.14 (0.88,1.46)	1.28 (0.94,1.73)	1.34 (0.84,2.13)	1.22 (0.44,3.32)	**RT+UFT**	
0.62 (0.32,1.23)	0.70 (0.36,1.37)	0.67 (0.34,1.32)	0.75 (0.39,1.44)	0.79 (0.45,1.37)	0.95 (0.62,1.46)	0.59 (0.29,1.21)	**RT+XELIRI+CET**

OS:

RT+5-FU						
0.87 (0.87，1.02)	**RT+CAPE**					
0.98 (0.89,1.11)	1.12 (0.92,1.37)	**RT+FOLFOX**				
0.75 (0.60,0.94)	0.86 (0.74,1.00)	**0.77 (0.60,0.99)**	**RT+XELOX**			
0.69 (0.35,1.37)	0.79 (0.41,1.53)	0.71 (0.36,1.42)	0.92 (0.49,1.75)	**RT+XELIRI**		
0.94 (0.37,2.41)	1.08 (0.41,2.80)	0.96 (0.37,2.49)	1.25 (0.47,3.29)	1.35 (0.42,4.33)	**RT+IS**	
1.15 (0.83,1.60)	1.32 (0.92,1.89)	1.18 (0.83,1.67)	**1.53 (1.04,2.27)**	1.66 (0.78,3.52)	1.22 (0.44,3.32)	**RT+UFT**

SUCRA	pCR	DFS	OS
RT+5-FU	41.46%	24.24%	30.30%
RT+CAPE	53.67%	57.69%	59.89%
RT+FOLFOX	69.11%	47.83%	37.39%
RT+XELOX	74.11%	73.76%	83.42%
RT+XELIRI	29.55%	71.77%	77.46%
RT+IS	70.56%	16.88%	46.80%
RT+UFT	45.78%	20.55%	14.75%
RT+XELIRI+CET	25.22%	87.29%	
RT+CAPE+BEV	43.00%		
RT+FOLFIRI	46.11%		

Changes in the text: We added some settings to “Selection criteria” (see Page 8, line 166-167). And we would modified the title as “Comparison of different preoperative treatment regimens in patients with locally advanced rectal cancer: a network meta-analysis” if necessary (unperformed). Searching keyword “colon” was changed into “rectum” (see Page 7, line 143).

Comment 3: A network meta-analysis based on Bayesian methods, and please add the reference or website with access date in the text.

Reply 3: Thank you for your comments. Bayesian model and frequency model are two important methods for analysis. Bayesian methods could deal with some complex meta-analysis that is hard to be solved by frequency model [1-2].

Changes in the text: We added 2 reference to explain the Bayesian methods in “Statistical analysis” and changed the order of the references (see Page 10, line 193) [1-2].

[1] Bernardinelli L, Clayton D, Pascutto C, et al. Bayesian analysis of space—time variation in disease risk. Statistics in Medicine, 1995.14(21-22), 2433–2443.
[2] Carlin JB. Meta-analysis for 2 × 2 tables: A bayesian approach. Statistics in Medicine, 1992. 11(2), 141–158.

Comment 4: A funnel plot graph and Begg’s test to check for the existence of publication bias is highly recommended to be added.

Reply 4: Thank you for your suggestions. We also think it was necessary to check the existence of publication bias. With some evidence, we made a funnel plot graph as Figure5 with Stata 14 (Figure order had been changed) [1].
Changes in the text: We added a funnel plot graph as Figure5. The methods used were added in the “Statistical analysis” section (see Page 11, line 212-215). The results of Begg’s test were presented in a newly added section entitled “Results-Publication bias” (see Page 14, line 280-283). The figure legend for Figure 5 was added (see Page 29, line 594).

[1] Chaimani A, Higgins JPT, Mavridis D, et al. Graphical tools for network meta-analysis in STATA. PLoS ONE, 2013, 8(10), e76654.

Comment 5: Figure 4. Rankograms for pCR (A), DFS (B) and OS (C). Please clarify the term “rank1, rank2…” etc.

Reply 5: Thank you for your valuable question. The rankograms were to display the probability of ranking for each regimen. So the height of the columns for “rank1, rank2…” referred to the probabilities of each rank. If the height of the column belonging to interval A painted in the color of “rank1” was 0.4, it means the probability of intervention A to rank first was 40%. The probability was the result of the 300000 times attempts in the network

meta-analysis (75000 times to rank first).

Changes in the text: We added the explaining content to Figure legend-Figure3 (Figure order had been changed, Figure4→Figure3) (see Page 28, line 583-586).

Comment 6: As pCR is significantly associated with the interval between the completeness of RT and surgical intervention; therefore, this factor should be considered.

Reply 6: Thank you for your professional and valuable question. Completeness of RT and surgical intervention were also concerns in the treatment of LARC. The guidelines recommended both long-course and short-course radiation. The time for surgery was recommended to be about 6-8 weeks after neoadjuvant treatment to achieve higher pCR rate. These factors might lead to heterogeneity and were important to be discussed in the text [1-2].

Changes in the text: We added the meaning of completeness of RT and surgical intervention in the “discussion” section (see Page 15, line 301-313).

[1] Zhao N, Lin CJ, Wang Fei, et al. Short-course or long-course radiation therapy as a part of a neoadjuvant regimen for stage II & III rectal adenocarcinoma? Chin. J. Cancer Res, (2019) 31(6), 849-852.

[2] Petrelli F, Sgroi G, Sarti E et al. Increasing the Interval Between Neoadjuvant Chemoradiotherapy and Surgery in Rectal Cancer: A Meta-analysis of Published Studies.[J] .Ann. Surg., 2016, 263: 458-64.

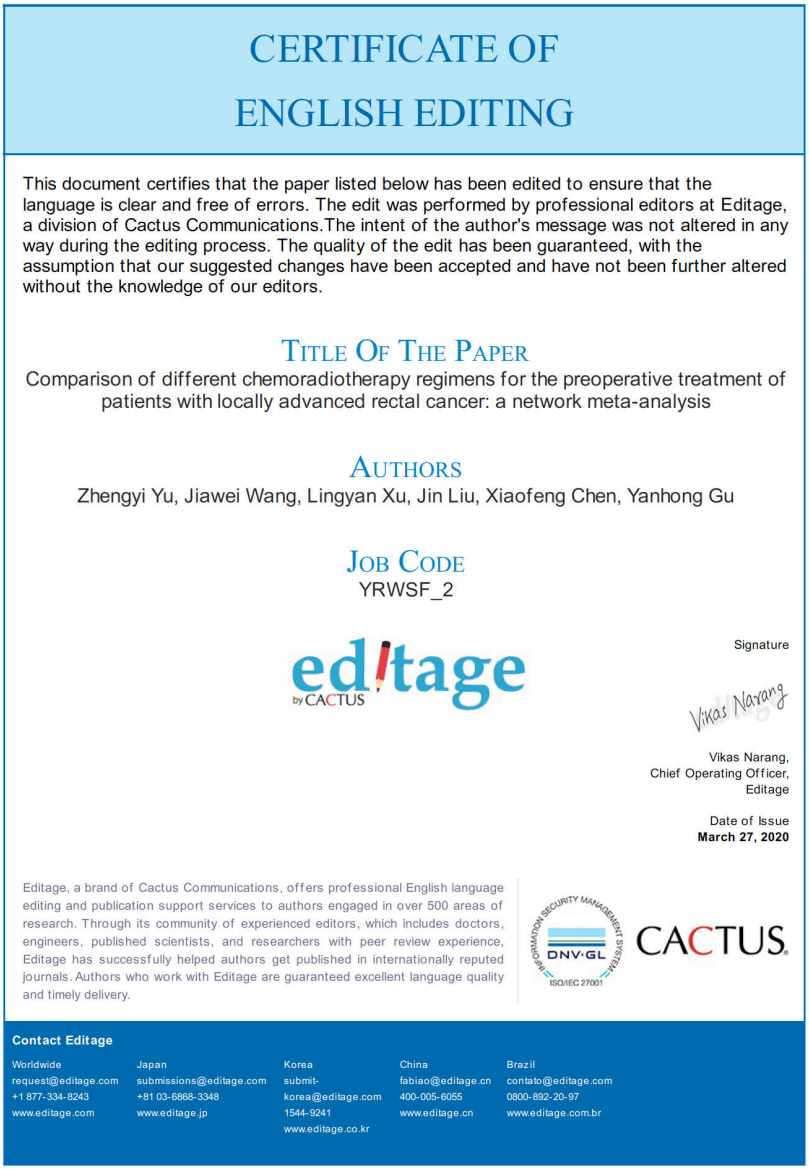
Minor Essential Revisions:

Comment 1: Typo and grammatical error need to be improved by an expert good at English-editing. For example, trails vs. trials.

Reply 1: Thank you for your reminder. We employed a professional English editing service (Shang Hai YiDEJI Info-tech Co. Ltd; https:// www.editage.cn) to re-check and modulate the

English for the previous version.

Changes in the text: We corrected the typo and grammatical error over the text. We had checked the manuscript carefully once again and made sure that grammatical mistakes were corrected.



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TITLE OF THE PAPER

Comparison of different chemoradiotherapy regimens for the preoperative treatment of patients with locally advanced rectal cancer: a network meta-analysis

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Comment 2: Table 1. RT+OUTF. Please clarify the term of OUTF.

Reply 2: Thank you for your reminder. This term was a careless mistake and had been

changed into “RT+UFT”.

Changes in the text: This term in Table1 had been changed into “RT+UFT”.

Comment 3: Figure 1 was redundant and could be omitted.

Reply 3: Thank you for your suggestion. Figure 1 has been omitted and all figure order has been changed.

Changes in the text: Figure 1 had been omitted and all figure order had been changed (Figure2→Figure1; Figure3→Figure2; Figure4→Figure3; Figure5→Figure4). Contents associated with “Figure 1” had been removed (see Page 28, line 572).

Comment 4: Please merge Table 2 into the Figure 5.

Reply 4: Thank you for your suggestion. Table 2 had been merged into Figure 4 and the figure legend had been re-write (Figure order had been changed ,Figure5→Figure4).

Changes in the text: Table 2 had been merged into Figure 4 and the figure legend had been rewritten (Figure order had been changed, Figure5→Figure4) (see Page 29, line 591-592). Content associated with “Table 2” had been removed (see Page 30, line 608).