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Reviewer's code: 03017516

SPECIFIC COMMENTS TO AUTHORS

Please clearly define longer and shorter waiting periods in the Methods.

Reply: Thank you for your suggestion. We have added the clear define of longer and shorter time interval of patients with the corresponding reasons. The cut-off value of 7-8 weeks was defined in order to compare the longer interval with the shorter time interval in our study. The reason for that are as follows: firstly, some studies have introduced the 7-8 weeks as a suggest time interval for esophageal cancer patients in terms of clinical practice (Table 1); secondly, similar classification was performed in a previous published meta-analysis of esophageal cancer (34).

> outcome, follow-up, clinical stage, histology HR type and HR with 95%CI. The time interval was defined as the period of time from the completion of nCRT to surgery. When several time interval groups were included in the study, the subgroup events were combined at the cut-off value of 7-8 weeks in order to compare the longer interval with the shorter time interval. The reason for that are as follows: firstly, some studies have introduced the 7-8 weeks as a suggest time interval for esophageal cancer patients in terms of clinical practice (Table 1); secondly, similar classification was performed in a previous published meta-analysis of esophageal cancer (34). OS was

Results: did you compare preoperative patients' characteristics of the two groups? Were the 2 groups comparable for baseline variables?

Reply: Thank you for your question. The basic statistics included in our meta-analysis are first author, study year, study region, study design, ethnicity, sample size, age, nCRT regimen, cut-off value, outcome, follow-up, clinical stage, histology HR type and HR with 95%CI. We have collected the data. Owing to some studies didn't provide the

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complete data and the different inclusion criteria of different studies, we summarized the data extracted from the included studies and compare the characteristics of the two groups. The 2 groups are comparable for baseline variables of Age and Histology.

	Short group ⩽7-8 weeks	Long group <7-8 weeks	P
	7522	5099	
Age			0.043
Male	6032	4597	
Female	1490	502	
Histology			<0.001
SCC	3955	2196	
AC	3567	2903	

A prolonged interval resulted in worse OS in the overall group and in SCC patients, whereas patients with AC had better survival with longer interval, may you better discuss this finding? It is related to different radiosensitivity? How does this observation affect clinical practice?

Reply: We appreciated your question very much. We are so sorry for mistaking the worse and better in Results. The authentic result was: Pooled data from the two studies demonstrated that a prolonged time interval was significantly associated with worse OS with a HR estimate of 1.385 (95% CI: 1.186-1.616, P<0.001; Table 2) without apparent heterogeneity (I2=22.00%, Ph=0.257; Figure 3). Meanwhile, we discussed the "A prolonged time interval from the completion of nCRT to surgery is associated with a

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significant decrease in OS" in Discussion session. We have revised the mistake in manuscript.

May you include quality assessment of the included studies?

Reply: We appreciated your question very much. We applied the quality assessment of Newcastle-Ottawa Scale (NOS) to evaluate the quality of included studies. The included studies quality was rated according to the Newcastle-Ottawa Scale (NOS) by two independent investigators (Yi-Min Gu, Wei-Peng Hu). Studies with NOS scores of 6 or higher were considered to be of high quality.

> selected as the primary end point, while PFS and DFS were secondary end points. The included studies quality was rated according to the Newcastle-Ottawa Scale (NOS) by two independent investigators (Yi-Min Gu, Wei-Peng Hu). Studies with NOS scores of 6 or higher were considered to be of high quality.

This meta-analysis has several potential bias, due to the methodological quality of the included studies (no randomized trials). Do you feel that your conclusion may modify the clinical management of these patients?

Reply: Thank you for your question. After searching through the database, there's no randomized controlled trail up to now and the included studies were assessed through NOS system, which represents the high quality of the studies of time interval between nCRT and esophagectomy until now. Therefore, we believe the results of us are evidential and further well-designed and large-scale studies are needed to determine whether the time interval from the end of nCRT to surgery has an effect on survival outcome and to assess whether disease-specific survival differs by type of pathological response.

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Reviewer's code: 03552525

SPECIFIC COMMENTS TO AUTHORS

Timing of surgery after neoadjuvant therapy is very important topic in treatment for esophageal cancer, but there are some points to revise. 1. Indeed, there were many evidence about nCRT following surgery. However, many of these article was from Western countries, where there were many patients with adenocarcinoma. So, authors should consider about this heterogeneity when thinking about this theme.

Reply: Thank you for your question. Although many of included articles were from western countries and adenocarcinoma is the main histological type of esophageal cancer, there're still many squamous cell carcinoma in our included studies. Here shows the distribution of the different histological type in short and long time interval groups, and the baseline of the two groups are comparable. Meanwhile, the heterogeneity of it was taken into consideration before meta-analysis.

	Short group ≤7-8 weeks	Long group <7-8 weeks	P
	7522	5099	
Age			0.043
Male	6032	4597	
Female	1490	502	
Histology			<0.001
SCC	3955	2196	
AC	3567	2903	

2. The title is neoadjuvant therapy, but authors talked about only nCRT in this article. So, authors should revise title of this article.

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Reply: We appreciated your advice very much and we have revised the title of this article.

TITLE PAGE

Title:

Timing of surgery after neoadjuvant chemoradiotherapy affects oncologic outcomes in patients with esophageal cancer

3. Authors said that "Pooled data from the two studies demonstrated that a prolonged time interval was significantly associated with better OS with a HR estimate of 1.385 (95% CI: 1.186-1.616, P<0.001; Table 2)" in results section. I think worse OS, but not better OS, as you said that "In addition, a longer wait time indicated worse OS (HR: 1.385, 95%CI: 1.186-1.616, P<0.001) in patients with AC." in abstract section.

Reply: We appreciated your question very much. We are so sorry for mistaking the worse and better in Results. The authentic result was: Pooled data from the two studies demonstrated that a prolonged time interval was significantly associated with worse OS with a HR estimate of 1.385 (95% CI: 1.186-1.616, P<0.001; Table 2) without apparent heterogeneity (I2=22.00%, Ph=0.257; Figure 3). Meanwhile, we discussed the "A prolonged time interval from the completion of nCRT to surgery is associated with a significant decrease in OS" in Discussion session. We have revised the mistake in manuscript.

4. It is important result that longer wait time correlate worse OS, but articles were not randomized control studies about time interval between nCRT and surgery. Do you think about probability of existence of poorer factors in longer wait time patients?

Reply: Thank you for your question. After searching through the database, there's no

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randomized controlled trail up to now and the included studies were assessed through Newcastle-Ottawa Scale (NOS) system, which represents the high quality of the studies of time interval between nCRT and esophagectomy until now. Therefore, we believe the results of us are evidential and further well-designed and large-scale studies are needed to determine whether the time interval from the end of nCRT to surgery has an effect on survival outcome and to assess whether disease-specific survival differs by type of pathological response.

5. In this theme, authors should also consider about total treatment time of nCRT because some patients interrupt treatment.

Reply: Thank you for your question. This meta-analysis is Meta-analysis based on summary data (MAS), therefore, the included data were extracted from the data provided by published articles. We have considered the patients' treatment interruption, therefore, we defined the time interval as point of the end of the last therapy of nCRT to the point of beginning of the esphagectomy. The included studies we have evaluated met the definition of time interval in order to minimize the bias of patients' treatment interruption as much as possible.

6. Authors said that "Esophagectomy should not be performed beyond 8 weeks after nCRT in view of OS, especially in patients with good recovery and response to nCRT.". This article suggests that longer wait time correlate worse OS, but cannot indicate concrete best interval time. So, why do you think that esophagectomy should not be performed beyond 8 weeks after nCRT in view of OS?

Reply: Thank you for your question. We have group discussed the conclusion and found that the results we have gotten can only be concluded as esophagectomy should be performed within 7-8 weeks after nCRT, which are also reflected in Abstract. And we

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have revised our conclusion. As far as we concerned, although longer wait time correlate worse OS and patients in our study, there's no concrete evidence for that, especially for randomized controlled trails. Furthemore, a meta-analysis of Qin et al (34) also suggested that extending the surgical wait time to a period longer than 7–8 weeks after nCRT is significantly associated with increased pCR rate in patients with esophageal cancer, while related to a worsening of 30-day mortality and survival. Therefore, further well-designed and large-scale studies are needed to determine whether the time interval from the end of nCRT to surgery has an effect on survival outcome and to assess whether disease-specific survival differs by type of pathological response.

Reviewer's code: 03317348

SPECIFIC COMMENTS TO AUTHORS

I think that this paper is interesting for the esophageal surgeons, gastroenterologists, radiation oncologists, and medical oncologists. In order to better this manuscript, I have the following minor comments. 1. Do the authors misunderstand "Running Head" in TITLE PAGE ? Please change to, for example, "Timing of esophagectomy after neoadjuvant chemoradiotherapy".

Reply: Thank you for your suggestion. We did mistake the Running Head, therefor we took the advice of yours and revised the running head as "Timing of esophagectomy after neoadjuvant chemoradiotherapy", thank you very much!

2. Is "Pooled data from ..." (Page 9, Line 15-18) miswritten ? Is not "better" but "worse" correct?

Reply: We appreciated your question very much. We are so sorry for mistaking the worse and better in Results. The authentic result was: Pooled data from the two studies

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demonstrated that a prolonged time interval was significantly associated with worse OS with a HR estimate of 1.385 (95% CI: 1.186-1.616, P<0.001; Table 2) without apparent heterogeneity (I2=22.00%, Ph=0.257; Figure 3). Meanwhile, we discussed the "A prolonged time interval from the completion of nCRT to surgery is associated with a significant decrease in OS" in Discussion session. We have revised the mistake in manuscript.

3. Please provide figure legends especially figure 4 and 5 for wider readers. In addition, please add what staging method is used (e.g.8th UICC classification) to Table 1.

Reply: We appreciated your question very much. After confirmation, we have added the figure legends of figure 4 and 5 for wider readers and the method of staging each included study applied in Table 1.

1, 6th AJCC/UICC classification; 2, 7th AJCC/UICC classification;

Clinical stage
I-IV[1]
II-IVa[1]
II-IV[1]
cT1-4[2], N0-1[1]
I-III[2]
I-IV[2]
I-III[2]
I-IV[2]
cT1-3[2], N0-3[2]
I-IV[2]
II-III[2]
I-III[2]
NR
I-IV[2]
I-IV[2]
I-IVa[2]

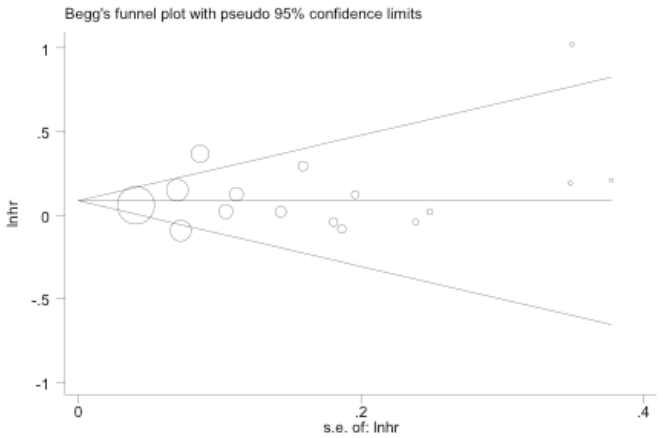

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Figure 5. Begg's funnel plot of the association between time interval and overall survival. The Begg's funnel plot did not indicate publication bias in the meta-analyses on the association between time to surgery and OS (Pr>|z|=0.344 for Begg's test).

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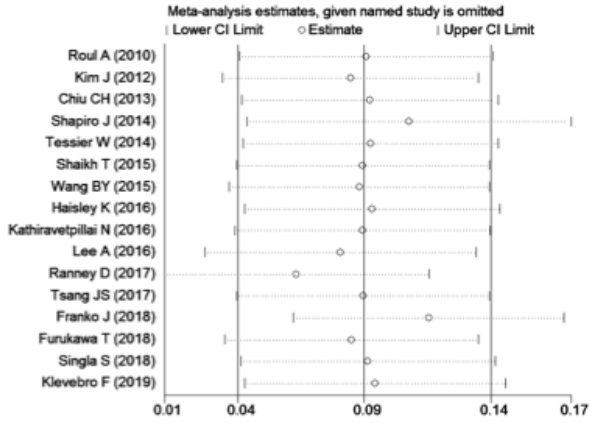

Figure 4. Sensitivity analysis of the association between time interval and overall survival. Combined results were still stable after the exclusion of any single study.

4. Could the authors provide the information of the method of esophagectomy?

Reply: We appreciated your question very much. After collection, 1029, 219 and 189 patients accepted the approaches of Ivor-Lewis, Mckeown and transhiatal esophagectomy, respectively, while six studies didn't provide the method of esophagectomy. And this was added in Results.

200 patients and was ≥200 patients in 11 studies. Meanwhile, 1029, 219 and 189

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patients accepted the approaches of Ivor-Lewis, Mckeown and transhiatal esophagectomy, respectively, while six studies[5,8,11,20-22] didn't provide the method of esophagectomy. The cut-off values in each study were not consistent and ranged from