PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparison of paclitaxel in combination with cisplatin (TP), carboplatin (TC) or fluorouracil (TF) concurrent with radiotherapy for patients with local advanced esophageal squamous cell carcinoma: a three-arm phase III randomized trial (ESO-Shanghai 2)
AUTHORS	Ai, Dashan; Chen, Yun; Liu, Qi; Zhang, Junhua; Deng, Jiaying; Zhu, Hanting; Ren, Wenjia; Zheng, Xiangpeng; Li, Yunhai; Wei, Shihong; Ye, Jinjun; Zhou, Jialiang; Lin, Qin; Luo, Hui; Cao, Jianzhong; Li, Jiancheng; Huang, Guang; Wu, Kailiang; Fan, Min; Yang, Huanjun; Zhu, Zhengfei; Zhao, Weixin; Li, Ling; Fan, Jianhong; Badakhshi, Harun; Zhao, Kuaile

VERSION 1 – REVIEW

REVIEWER	Po-Kuei Hsu Taipei Veterans General Hospital, Taiwan.
REVIEW RETURNED	10-Dec-2017

GENERAL COMMENTS	This eligible patients are with locally advanced esophageal cancer, which should be offered the treatment option of surgical resection based on guidelines. However, none about surgery, and surgery related end-points is mentioned. Does this protocol met current guideline and ethic criteria? Please clarify.

REVIEWER	PAVANKUMAR TANDRA University of Nebraska Medical Center, Hematology-Oncology
REVIEW RETURNED	08-Feb-2018

GENERAL COMMENTS	After reviewing the study (NCT02459457), 1) Strengths of the study were mentioned on page 6; but I did not see any limitations, although the sub heading says “strenghths and limitations” 2) Why the radiation dose was chosen as 61.2 Gy. When I looked at NCCN guidelines, the radiation dose for definitive chemoradiation for patients unsuitable for surgery or those who refuse surgery was 50-50.4 Gy. As I am a medical oncologist, there must be a valid reason for the authors to choose this dose. This should be mentioned in the protocol. 3) Eligibility criteria 7: Life expectancy > 3 months. What was the reasoning for this? And also how they plan to calculate this?? Is it based on clinician`s discretion or do the authors use any charts or calculators to calculate this to avoid selection bias? 4) Do the authors consider concurrent chemo radiation (for locally advance ESSC) as palliative therapy or curative therapy? As usually 6 months or less expected life expectancy is considered for hospice evaluation. If we anticipate a minimal expected life expectancy beyond 6 months, and if the ECOG PS allows, we initiate definitive

	treatment. 5) In sample size calculation and statistical analysis part, the authors mentioned “the trial is designed to CONFIRM whether TF is superior to TP or TC ...." Does this mean, were they trying to confirm the results of RTOG 0113 which already showed that median survival of TF is 28.7 months, which is higher compared to other arms? (The authors clearly mentioned the limitations of the RTOG study in the protocol). In the interim analysis section, the authors were trying to "..if the superiority of ONE OF THE test arms is demonstrated with an adjusted alpha level, the study will be terminated... So what was exactly the hypothesis? Is it to a) To confirm the superiority of the TF arm ? or b) To know which arm is superior? I am not a statistician. So may be the study would benefit from a review by a statistician. But after a quick look, the statistical part appears to be appropriate to me. Finally, the study has no arm containing 2 of the category 1 regimens for definitive chemoradiation as per NCCN which are FU plus Cisp, FU plus Oxali platin. Thank you for allowing me to review this manuscript.

REVIEWER	Hao Daxuan Xuzhou NO.1 People’s Hospital, China
REVIEW RETURNED	11-Feb-2018

GENERAL COMMENTS	1. Is endoscopic ultrasound used as a routine method in tumor stage? 2. In arm A, 4 courses of TP every 4 weeks rather than 6 courses every week were used. Can you give us an explanation?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This eligible patients are with locally advanced esophageal cancer, which should be offered the treatment option of surgical resection based on guidelines. However, none about surgery, and surgery related end-points is mentioned. Does this protocol met current guideline and ethic criteria? Please clarify.

Thanks for your comments.
Our main purpose of this study is to find a proper treatment plan against esophageal cancer. As we all know, concurrent chemoradiation is one of the most effective treatment choices for those patients, which is recommended by NCCN guideline. We put forward multiple choices, including surgery and chemoradiation therapy after first diagnosis for patients. Before enrollment in this clinical trial, patients would choose to accept chemoradiation therapy as their first treatment plan in their first inform of consent (not within our trial). Only if they choose to accept chemoradiation therapy, we will continue to introduce our clinical trial plan and get their approval.

Reviewer: 2

1) Strengths of the study were mentioned on page 6; but I did not see any limitations, although the sub heading says “strenghths and limitations”

Limitations were added to the revised edition.

2) Why the radiation dose was chosen as 61.2 Gy. When I looked at NCCN guidelines, the radiation dose for definitive chemoradiation for patients unsuitable for surgery or those who refuse surgery was 50-50.4 Gy. As I am a medical oncologist, there must be a valid reason for the authors to choose this dose. This should be mentioned in the protocol.

According to Chinese guidelines, 60-70Gy is a recommended dose for definitive treatment. Besides, the evidence of 50.4Gy in NCCN guideline is from RTOG 9405, in which high dose group didn't show any benefit in survival rate or local control rate and the side effects grew obviously. However, the result of 50.4Gy group was not satisfying, either. RTOG 9405 is a clinical trial from two-dimensional era. Under 3D-CRT or IMRT technique, the dose for organ at risk will be much lower than before and thus lower the side effects.
Zhang et al found the higher dose for esophageal cancer, the better local control rate and survival rate. Detailed data is as follows: Zhang Z, Liao Z, Jin J, Ajani J, Chang JY, Jeter M, Guerrero T, Stevens CW, Swisher S, Ho L et al: Dose-response relationship in locoregional control for patients with stage II-III esophageal cancer treated with concurrent chemotherapy and radiotherapy. International journal of radiation oncology, biology, physics 2005, 61(3): 656-664

3) Eligibility criteria 7: Life expectancy > 3 months. What was the reasoning for this? And also how they plan to calculate this?? Is it based on clinician`s discretion or do the authors use any charts or calculators to calculate this to avoid selection bias?

Our treatment will last for over 3 months. To assure the completion of whole treatment and ECOG prosperity score, we set this standard. Life expectancy is mainly based on the judgment of doctors.

4) Do the authors consider concurrent chemo radiation (for locally advance ESSC) as palliative therapy or curative therapy? As usually 6 months or less expected life expectancy is considered for hospice evaluation. If we anticipate a minimal expected life expectancy beyond 6 months, and if the ECOG PS allows, we initiate definitive treatment.

We regarded concurrent chemoradiation in our trial as curative therapy. We will deliver palliative therapy to whose expected life expectancy less than 3 months.

5) In sample size calculation and statistical analysis part, the authors mentioned “the trial is designed to CONFIRM whether TF is superior to TP or TC ...." Does this mean, were they trying to confirm the results of RTOG 0113 which already showed that median survival of TF is 28.7 months, which is higher compared to other arms? (The authors clearly mentioned the limitations of the RTOG study in the protocol).

In RTOG 0113, TF was found much longer than TP in median survival. However, it is still a phase II clinical trial with small sample size, and didn’t achieve the original hypothesis. In the limitations of RTOG study, the authors cannot recommend either of the two arms. Our aim is to confirm the hypothesis of RTOG 0113 rather than the result of that and thus we can provide our recommendations.

In the interim analysis section, the authors were trying to "..if the superiority of ONE OF THE test arms is demonstrated with an adjusted alpha level, the study will be terminated... So what was exactly the hypothesis?
Is it to
a) To confirm the superiority of the TF arm ?
or
b) To know which arm is superior?

In our protocol, if either of the following conditions become true when interim analysis:
a) TF arm is superior to TP arm
b) TF arm is superior to TC arm
The study will be terminated.

Finally, the study has no arm containing 2 of the category 1 regimens for definitive chemoradiation as per NCCN which are FU plus Cisp, FU plus Oxali platin.

We compared FU plus cisplatin with TF in ESO-Shanghai 1 trial. The protocol has been published on Radiation Oncology.
FU plus oxaliplatin may be an arm in the future research. Thank you for your kind reminds.

Reviewer: 3

1. Is endoscopic ultrasound used as a routine method in tumor stage?

We strongly recommend endoscopic ultrasound in the process of tumor staging, but it is not compulsory.

2. In arm A, 4 courses of TP every 4 weeks rather than 6 courses every week were used. Can you give us an explanation?

Our treatment combinations are from some classical studies, i.e. CROSS and famous centers, such as MSKCC and MDACC.
Cisplatin and carboplatin belong to the same category. Difference between TP and TC arm is because we also want to find a better treatment plan between qw and q28d.

VERSION 2 – REVIEW

REVIEWER	Pavankumar Tandra University of Nebraska Medical Center Omaha, NE 68198-6840, United States of America.
REVIEW RETURNED	19-Mar-2018

GENERAL COMMENTS	Thank you for addressing the concerns I raised during the initial review process. I am satisfied with the explanation. I would recommend this to the editor for publication. Please make sure all the explanation were added to the final manuscript to give readers the perspective of treating and standards of care in China which sometimes differ from United States.

REVIEWER	Daxuan Hao Xuzhou NO.1 People's Hospital,China

REVIEW RETURNED	23-Mar-2018

GENERAL COMMENTS	None

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: Pavankumar Tandra

Institution and Country: University of Nebraska Medical Center, Omaha, NE 68198-6840, United States of America.

Please state any competing interests: None

Please leave your comments for the authors below

Thank you for addressing the concerns I raised during the initial review process. I am satisfied with the explanation. I would recommend this to the editor for publication. Please make sure all the explanation were added to the final manuscript to give readers the perspective of treating and standards of care in China which sometimes differ from United States.

Response: Thank you for your useful comments. All the explanations and modifications were added to the final manuscript.