

Lian-Sheng Ma
Science Editor
Company Editor-in-Chief
Editorial Office
World Journal of Gastrointestinal Surgery

Manuscript NO: 65429

Title: Oesophageal adenocarcinoma: In the era of extended lymphadenectomy, is the value of neoadjuvant therapy being attenuated?

16th August, 2021

Dear Lian-Sheng Ma,

Thank you for the interest you have shown in our manuscript. Thank you to the reviewers for their valuable criticism of this article.

We have considered the issues raised by your reviewers, and wish to submit a revised manuscript to be reconsidered for publication, which addresses those issues.

We again thank the reviewers, and sincerely hope that The World Journal of Gastrointestinal Surgery will find our revised manuscript favourable for acceptance.

Kind regards,

Dr. Jin-soo Park

In response to Reviewer #1:

Specific Comments to Authors: randomized control trials (Abstract) - controlled is right. references in Abstract are not acceptable. Please remove it.

We have removed the reference in the abstract.

Multiple randomized control trials (RCTs) have found neoadjuvant regimens to increase long-term survival compared to surgery alone.(2,3) However, a meta-analysis of eleven randomized controlled trials did not demonstrate a survival benefit when comparing NACT plus surgery versus surgery alone.(1) (Introduction) - reference numbers in the main text start with 2, not 1. This is a direct consequence of erroneous quotation in the abstract. To be corrected.

This correction has been made in the manuscript.

A three-incisional McKeown procedure with an additional left cervical incision was infrequently used for tumours in the mid third of the oesophagus (Surgical management) - "in the upper and middle thirds..." is better - judging by the data in the table, you have had cancers of the upper third of the esophagus. Comparison by NACT, Overall survival outcomes (NACT), Disease-free survival outcomes (NACT) - these three subheadings had to be improved. As possible better versions, I propose "Comparison of groups (NACT and surgery alone)", "Overall survival outcomes (NACT and surgery alone)" and "Disease-free survival outcomes (NACT and surgery alone)".

The changes to the three subheadings have been made.

Tumour location was similar between NACT and surgery groups amongst upper, middle, and lower parts of the oesophagus as well as the gastro-oesophageal junction (GOJ) (Page 8) - "as well as the EGJ" is right, because earlier in the text, namely this abbreviation was proposed.

The change to GOJ has been made in text (page 6) and in tables also.

Two-field lymphadenectomy, neoadjuvant chemotherapy (NACT) plus surgery (Page 12) - the abbreviation NACT can be used directly, because it was explained earlier.

We have revised this so that the abbreviation has been used alone.

Resectability may also have been effected by NACT (Page 12) - affected is better.

This change has been made.

This may reflect improved surgical and lymphadenectomy techniques contributing to improving survival outcomes (Page 15) - "improved surgical techniques including lymphadenectomy..." seems to be better.

This sentence has been rephrased as per reviewer suggestion (page 15).

Adenocarcinoma of the oesophagus and cardio-oesophageal junction (Conclusion) - "oesophagus and EGJ" is better, because it is logical to use once proposed abbreviation.

The suggested change has been made.

SCC - I think, this abbreviation was not explained in full.

We have explained this abbreviation (page 13).

In the discussion section, the authors quite often mention articles analyzing squamous cell carcinoma of the esophagus or mixed groups (squamous cell carcinoma and adenocarcinoma). For this work with pure material of adenocarcinoma, such references may be regarded as not entirely correct. Although, on the other hand, I do not recommend on removing these references, as they are still important to reflect the general trends in esophageal oncology.

We are in agreement with the reviewer.

The Reference List should be written in strict accordance with the Instructions for Authors. So, it will be extensively corrected (with Journal Title abbreviations as in PubMed, and adding PMID and DOI to each reference).

These changes to the reference list have been made to include PMID and DOI to each reference.

In response to Science Editor:

This prospective study presents a big series of 243 patients with oesophageal adenocarcinoma treated with radical oesophagectomy with or without neoadjuvant chemotherapy (NACT). The authors conclude that NACT did not appear to affect overall or disease-free survival, but extended lymphadenectomy (≥ 30 lymph nodes removal) had a positive impact on overall survival. However, the studied duration is too long (near 30 years) and the treatment strategy evolved considerably, such as surgical quality and neoadjuvant chemotherapy regimen. As American Joint Committee on Cancer (AJCC) stage is one of the three independent predictors for greater overall survival, the NACT group had less patients with pathologic stage I adenocarcinoma compared with the surgery only group (15.6% vs. 27.7%; $p=0.040$) is not acceptable. The difference in AJCC stage distribution would definitely have an impact on patient survival. A propensity-matched analysis is strongly suggested to address this difference before a conclusion could be made.

We have acknowledged this comment in the manuscript (page 15). We have previously addressed the fact that despite the long study time-frame, cohorts of participants were similar when analysed by the date at which they underwent oesophagectomy. For instance, the cohort was analysed by earlier in the series (1990-2004) or later (2005-2019), and were found to be similar in terms of demographic features.

The authors may describe the surgical technique more in details with photos or short video clips.

The surgical technique has been clarified and two new photos have been added.

The total references number ($n=18$) is too low. 28% (5/18, far lower than 50%) of the cited references represent publications from the recent 5 years. PMID and DOI numbers are missing in the reference list. Not all authors of the references were listed. The self-referencing rate is high ($1/18 = 6\% > 3\%$) in this study.

Changes have been made to include PMID and DOI numbers in each reference. Furthermore, all authors have been added to the reference lists. We believe that self-referencing with one citation is acceptable, and not excessive.

The abbreviation “NACT” should be explained in Figure 1 and 2.

These changes have been made.

The abbreviation “AJCC” should be explained in Table 1 and 2.

These changes have been made.

The tables should be properly annotated to easily read and interpret. The language quality is grade B and minor polishing is needed. All authors must provide their personal ORCID registration number.

The tables have been annotated. All authors have provided their personal ORCID numbers.

The “Author contributions” section is missing. Please provide it after “The institutions” section.

Author contributions section has been added.

The “Supportive foundations” section is missing. Please provide it after the “Author contributions” section.

This section has been added, there were no supports to disclose.

The ‘Key words’ list should provide 6 keywords (only 4 are provided in the manuscript) that reflect the main content of the study. The first letter of each keyword will be capitalized, and each keyword will be separated by a semicolon.

These changes have been made.

The “Core tip” section is missing. Please write a summary of no more than 100 words to present the core content of the manuscript, highlighting the most innovative and important findings and/or arguments. Please provide it after the “Key words” section.

Core tip section has been added.

The “Acknowledgements” section is missing. Please provide it after the “Conclusion” section in the main text.

We have no acknowledgements to be made, and have not added this section.

As a prospective study, the authors offered Institutional Review Board Approval Form, Signed Informed Consent Form, and Biostatistics Review Certificate. Clinical Trial Registration Statement, Conflict-of-Interest Disclosure Form, Copyright License Agreement, and CONSORT 2010 Statement are missing. The Signed Informed Consent Form provided by the authors seems incorrect as the consent should be for the studied patients instead for the Human Research Ethics Committee (HREC).

Clinical trial registration statement is not provided as this was a retrospective analysis.
CONSORT statement is not provided as this study was not a randomized control trial.
Copyright license agreement is attached in our revision.

Conflict of interest disclosure form has been attached in our revision.

Finally, all the issues raised by the peer-reviewer should be addressed.

Reviewer comments have been addressed.

In response to Company Editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Surgery, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, the author(s) must add a figure (medical imaging) to the manuscript. There are no restrictions on the figures (color, B/W).

We would like to extend our warm thanks to the peer reviewers and the editorial board. We feel that the need for language editing of the manuscript is unnecessary, as all authors in this manuscript are native English speakers – we are all born and educated in Australia. A medical image figure has been added to the manuscript.