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World Journal of Gastroenterology

Editor-in-Chief Prof. Damian Garcia-Olmo

Dear Editor:

We appreciate your review of our manuscript, entitled “Histological evaluation for chemotherapeutic responses of regional metastatic lymph nodes in gastric cancer” (Manuscript No. 21720), for *World Journal of Gastroenterology*.

We have addressed and incorporated all of the reviewer’s comments, improving the quality of the manuscript. We are sure that this revised manuscript is suitable for publication in *World Journal of Gastroenterology*. Please find the changes made in response to the reviewer’s suggestions (the revised sentences are in red in the attached manuscript).

Reviewer’s comments

English usage requires some correction. Not that the English is poor, which it is not, but some minor corrections will ease the understanding of the manuscript. Some examples: The expression “...practice around the world, including in Asian countries” should be changed to “...practice around the world, including Asian countries” (first paragraph of the Introduction, second paragraph of the Discussion). The sentence “This study investigated histological effects in each individual MLNs in patients with 28 advanced GC treated...” should be written as “This study investigated histological effects in each individual MLNs in 28 patients with advanced GC treated. . . .” along with some others throughout.

Reply: We greatly appreciate this constructive comment. Following the suggestion, we have changed the aforementioned phrases in the Introduction (p. 7, lines 8–9) and the Discussion (p. 14, lines 6–7). Furthermore, we have asked an experienced editor whose first language is English to proofread and polish the manuscript.

INTRODUCTION: A “...pathological N0 status...” is mentioned. Is it so? Is there a pathological N0 status? Could the word pathological be dropped and state simply “Xu et al. Reported that N0 status...”?

Reply: As per the suggestion, we have deleted the word “pathological” (p. 7, line 16).

MATERIALS AND METHODS: I think there is an overwhelming overload of information. Why mention 1,254 patients if all the work is done with 28 patients? And out of these 28, only 11 are truly informative. All the work should focus on these patients.

Reply: We fully agree with the reviewer’s comments. As per the comments, the phrase “A total of 1,254 patients with gastric cancer underwent gastrectomy at Kyoto Prefectural University of Medicine between January 2001 and January 2013” has been deleted, and we have rewritten the following phrase on p.8, lines 11–12 as follows:

From: Of these patients, those who had undergone pre-CTx ...

To: Of the patients with gastric cancer treated at Kyoto Prefectural University of Medicine between January 2001 and January 2013, those who had undergone pre-CTx ...

Is the MLNs grading as “complete response (CR) ...” etc. based on any already known or published criteria? If so, it should be adequately referenced. Furthermore, has the previous classification anything to do with the tumor regression grade? This needs to be clearly stated and referenced, if possible.

Reply: If we understand the reviewer’s question correctly, as described in p. 9, lines 14–15, the MLNs grading used in this study was adopted according to the new Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Further, Schwartz et al. successfully showed that the criteria could also be adapted to MLNs grading. Since our previous manuscript might confuse readers, we have added the phrase and the abovementioned reference on p. 9, line 16. If we did not interpret the reviewer’s question correctly, we would greatly appreciate further explanation.

Added reference: 17) **Schwartz LH**, Bogaerts J, Ford R, Shankar L, Therasse P, Gwyther S, Eisenhauer EA: Evaluation of lymph nodes with RECIST 1.1.

Eur J Cancer 2009; **45**: 261-267 [PMID: 19091550 DOI: 10.1016/j.ejca.2008.10.028]

RESULTS: It is stated that a total of 1,044 regional LNs were retrieved from 28 patients. How many were retrieved from the group of 11 patients?

Reply: According to the reviewer's suggestion, we have reassessed our data. Consequently, 436 regional LNs were retrieved from 11 patients, whose pre- and post-therapeutic MDCT images were available. We have rewritten the phrase on p. 13, lines 5–10, and accordingly, we revised Table 3.

DISCUSSION: Some nomenclature (cStage IV; ypM1, for instance) needs some explanation. I know it can be retrieved on the Internet, but providing some information will be helpful to potential readers.

Reply: Following the reviewer's suggestion, we have changed the phrase in p. 16, line 14, as follows:

From: cStage IV and/or ypM1 cases
To: advanced cases

The main conclusion (last paragraph of the Discussion) is a sound one, but it is based on a limited number of patients. This should be stressed in the manuscript. The authors should state whether pre-CTx is or is not of any use at all. It seems to me, as the authors state in the Introduction, that it markedly improves the survival rate of patients; thus, it should not be discarded. What the authors propose is that, in addition to this conditioning, an appropriate lymphadenectomy should be carried out in this type of patient; this should be made clear.

Reply: We fully agree with the reviewer's comment and have added information to the end of the Conclusion (p. 17, lines 10–13). Although cumulative evidence showed that some patients benefited from pre-CTx, our study suggested that pre-CTx could not provide a promising effect, especially on MLNs. However, as the reviewer suggested, we also believe that pre-CTx "should not be discarded," since some patients certainly benefit from pre-CTx. It seems to us that the type of patients that should undergo a D2

lymphadenectomy requires further discussion. Indeed, many previous studies with large sample sizes examining the usefulness of pre-CTx selected patients with a variety of pathological stages (Ib–IVa) of gastric cancer. In this sentence, further improvement of pre-CTx and patient selection would be required. We have added a statement to this effect on p. 16, line 9.

Related to the previous point, the conclusion reached in the present work is relevant in patients with advanced GC, but no information is given concerning patients in earlier stages of the disease. This should also be clearly stated in the manuscript.

Reply: We think that what the reviewer suggested is one of the limitations in this study. Accordingly, we have added a phrase addressing this in the Discussion (p. 16, lines 14–15)

REFERENCES: Is there a more recent reference to replace ref. #1, which is somewhat outdated?

Reply: We greatly appreciate this constructive suggestion and have replaced it with a more recent reference. Accordingly, the phrase “the second most frequent cause of ...” has been changed to “the third most frequent cause of ...” (p. 7, line 3).

Reference 1:

From: Hohenberger P, Gretschel S: Gastric cancer. *Lancet* 2003; **362**: 305-315 [PMID: 12892963]

To: Niccolai E, Taddei A, Prisco D, Amedei A: Gastric cancer and the epoch of immunotherapy approaches. *World J Gastroenterol* 2015; **21**: 5778-5793 [PMID: 26019442 DOI: 10.3748/wjg.v21.i19.5778]

Minor changes

1) p. 7, line 11

From: ... are in rates of tumor resectability ...

To: ... are an increased rate of tumor resectability ...

2) p. 7, line 12 and line 15

From: metastases

- To: metastasis
- 3) p. 8, line 3
From: ... to examine effects of pre-CTx on MLNs...
To: ... to examine the effects of pre-CTx on the MLNs...
- 4) p. 8, line 6
From: ... if limited lymph node ...
To: ... whether limited lymph node ...
- 5) p. 8, line 7
From: GC patients treated by pre-CTx.
To: GC patients treated with pre-CTx.
- 6) p. 9, line 5
From: ... from all the patients ...
To: ... from all of the patients ...
- 7) p. 10, line 3
From: ..., according to the RECIST guidelines.
To: ..., which is according to the RECIST guidelines.
- 8) p. 11, line 3)
From: ... gastrointestinal disorders (M.K.)
To: ... gastrointestinal disorders (M.K. and A.Y.)
- 9) p. 11, line 17
From: ... Stage III; 13 (46%) as Stage IV.
To: ... Stage III; 13 (46%) were diagnosed as Stage IV.
- 10) p. 12, line 4
From: ... pre-CTx were performed ...
To: ... pre-CTx was performed ...
- 11) p. 12, line 6
From: Of those, ...
To: Of these, ...
- 12) We rewritten the phrase on p. 14, lines 4–5
- 13) p. 14, line 14
From: yield
To: yielded
- 14) p. 14, line 15
From: proved
To: proven
- 15) p. 15, line 3

From: ... who come to be candidates ...

To: ... who become candidates ...

16) p. 15, lines 7–8

From: Hayashi et al. called attention that ...

To: Hayashi et al. called attention to the fact that ...

17) p. 15, line 9

From: ... higher surgical complications.

To: ... greater surgical complications.

18) p. 16, line 10

From: ..., the first is its small ...

To: ..., the first of which is its small ...

20) p. 17, line 8

From: ... and its clinical evaluation.

To: ... and their clinical evaluation.

21) The first author, Osamu Kinoshita, recently joined another affiliation.

Thank you again for your comments on our paper. We believe that the revised manuscript is suitable for publication in *World Journal of Gastroenterology*.

Sincerely,

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