Author’s response to reviews

Title: Clinical implications of metastatic lymph node ratio in gastric cancer

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Author’s response to reviews: see over
Dear Dr. Lê,

Thank you very much for your letter and advice. We are also grateful to you for giving us another opportunity to re-submit our paper for your further consideration. We have revised the paper, according to the comments and suggestions made by you and the two reviewers, and point-by-point replies to the reviewers are enclosed in this letter. The revised manuscript as well as this reply letter has been further edited and proofread by a medical professional editing company in Hong Kong. We hope that the revised manuscript meets the standards of your journal and would be acceptable for publication in the journal.

I will be happy to provide any further additional information and answer any questions from you or the reviewers.

Look forward to hearing from you soon.

With best wishes,

Yours sincerely,

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Replies to Reviewers

First of all, we would like to express our sincere thanks to the reviewers for their constructive and pertinent comments that help us improve the presentation of our manuscript.

Replies to Reviewer Mario Lise

1) In the Patients and Methods section the Authors state that 224 patients were selected according to the following criteria: 1) that “more than D1 lymph node dissection had been performed” and 2) “more than 15 lymph nodes were pathologically examined.”

Were patients with D1 lymph node dissection thus excluded? Moreover, what does “more than D1 dissection” mean? Was this definition made on the basis of surgical or pathological criteria?

**Answer:** Yes, all patients with D1 lymph node dissection and/or less than 15 lymph nodes being removed and histologically examined were excluded from the study. This point has been clearly described in the revised version of the manuscript (page 5, line 10).

“more than D1 dissection” means “D1 lymph node dissection + dissection of lymph nodes along the left gastric artery, D1+ dissection of lymph nodes along the common hepatic artery, D1 dissection + dissection of lymph nodes along the celiac artery, D2, or D3 lymph node dissection”. The definition of “more than D1 dissection”, now modified as “beyond D1 dissection” was made on the basis of surgical criteria (page 5, line 11).

2) The Authors should describe the characteristics of the patient population from which their sample was selected; they should also specify how many patients were excluded because they had D1, or less extensive, lymph node dissection and how many patients classified as R0. The number of institutions and surgeons involved should also be given and the Authors should clarify whether they all used the same protocol. This information would allow the reader to have a general idea of the quality of surgery in the area, and the relevance of the sample in relation to the general population of gastric cancer patients.

**Answer:** Several sentences have been added or modified in the **Patients section** in the revised version to address this issue (page 5, line 22).

During the six years, 425 cases with gastric cancer (36 early and 389 advanced) were treated in our department. Based on the inclusion and exclusion criteria, 201 patients were excluded from the study; 57 received a palliative operation, 12 of the 36 cases with early gastric cancer and 132 cases with advanced gastric cancer received D1 lymph node dissection, and/or had less than 15 lymph nodes resected for pathologically examination. Therefore, a total of 224 patients with gastric cancer were included in the study.
The surgeons dissected lymph node in the operation and then removed lymph nodes for pathological examination, which was based on the Japanese Classification of Gastric Carcinoma.

3) No information is given about the methods used for the pathological examination resected specimen, and nor is it stated whether this analysis was conducted according to a standardized protocol. This may be relevant in order to understand the following sentence (Discussion, page 7): "1) the number of picked up lymph nodes from the resected specimen varies among surgeons or pathologist expended different efforts".

Answer: Several sentences have been added or modified in the Surgically dissection of lymph nodes (page 6, line 7).

In our study, the resected specimens were carefully examined for accurate pathologic staging according to the classification of the Japanese Research Society for Gastric Cancer. The classification of the dissected lymph nodes was made by surgeons who reviewed the excised specimens after surgery. Then, all lymph nodes retrieved were sectioned, stained with hematoxylin and eosin and examined for metastasis by specialized pathologists.

4) The clinico pathological parameters examined are reported in Table 1. Among the primary tumor characteristics, the Authors consider the diameter, but ignore T stage. Consequently the T parameter is not considered in the multivariate analysis. In other studies T stage has emerged as an independent factor. The Authors should therefore state the reason for their unusual choice. Nor is the number of metastatic nodes reported in this table. Moreover, for tumor differentiation the Authors distinguish between two groups (differentiated vs undifferentiated) instead of between the usual 3 categories (G1, G2 and G3). I have never heard of the histological classification used by the Authors (massive, next and diffuse). They might therefore state their reasons for choosing it, providing a reference, if available.

Answer: We accept Dr. Lise’s comment, and in the revised version of the manuscript, T stage has been added in the multivariate analysis, and description of tumor differentiation and histological classification has been modified; the histological classification in the original manuscript has been replaced by the generally accepted classification (Table 4).

5) Again in Table 1, the number of cases reported for each category of involved nodes ratio does not correspond to those reported in Table 2.

Answer: Thanks for pointing out the mistake, which has been corrected the revised version of the manuscript.

6) The statistical methods used are not clearly described and serious doubts remain as
to whether the results of the analysis might have been different if the appropriate
TNM parameters had been included. Moreover, the data given in Tables 3 and 4
suggest that two meta-analyses were conducted, one including the number of involved
nodes and the other, the involved nodes ratio. Nor do the Authors explain the origin of
the different ratio percentages adopted. I believe that an expert statistician should be
asked to check that this that the statistical procedure used is sound.

Answer: Several sentences have been added or modified in the Statistical
analysis of revised version of the manuscript (page 7, line 14). The statistical results
have been described clearly in Tables and figure legends. In addition, the multivariate
analysis including both the number of metastatic nodes and the metastatic nodes ratio
has been rperformed, and the results are shown in Table 4 of the revised version and
manuscript.

7) In the Discussion section the AA state that the ratio has an important prognostic
value compared to other factors. Although these conclusions may be generally shared,
the issue has already been dealt with by others and similar results already reported in
literature. This should be clearly acknowledged by the Authors, and discussed in
relation to comparative criteria.

Answer: We thank Dr. Lise and accept this comment. A few references along
with several sentences have been added in the Discussion of the revised version of the
manuscript (page 11, line 13).

8) In the Conclusion section the AA state that "if classification of nodal status were
established by a combination category of the involved nodes number and ratio, it
could be the best category......." This statement is not clear and does not appear to be
in line with the issues considered in the discussion and with the conclusion in the
abstract.

Answer: The statement has been modified and several sentences have been added
in the Discussion of the revised version of the manuscript (page 12, line 10).

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a
term, which the author can be trusted to correct)ü
1) Legends in Tables 3 and 4 (upper bar) should be explained in notes at foot.

Answer: Legends (upper bar) in Tables 3 and 4 (previously 4 and 5) have been
self-explained. Legends in the figures have also been modified (pages 23 and 24).

Replies to Reviewer Masahide Ikeguchi

1. The authors did not prepare the legends of figures. Thus, I cannot understand the
meaning of Figure 2. Did the authors demonstrate the correlation between the numbers of dissected lymph nodes and the numbers of metastatic lymph nodes in Figure 1, and the correlation between pN and the involved node ratio in Figure 2?

**Answer:** We thank Dr. Ikeguchi for pointing out the problem and we are sorry for the confusion. Dr. Ikeguchi’s understanding is correct for the Figure 1, which demonstrates the correlation between the numbers of dissected lymph nodes and the numbers of metastatic lymph nodes. However, Figure 2 shows the correlation of the numbers of dissected lymph nodes with both pN category and the metastatic node ratio. In the revised version of the manuscript, we have deleted Figure 1 as we think it is unnecessary, and made Figure 2 (now Figure 1) clearer by modifying both the figure and the figure legend. Moreover, descriptions on these points have been modified in the Results of the revised version of the manuscript.

2. Did the authors excluded the patients who had metastatic lymph nodes in retropancreatic, mesenteric, or para-aortic lymph node metastasis (recognized as distant metastasis in the UICC-TNM classification system).

**Answer:** Yes, all patients who had metastatic lymph nodes in retropancreatic, mesenteric, duodenohepatic ligament, or para-aortic lymph node metastasis were excluded. This point has been clarified in the revised version of the manuscript (page 5, line 18).

3. Did the authors exclude the patients who underwent non-curative gastrectomy from this study?

**Answer:** Yes, the patients who underwent non-curative gastrectomy were excluded from this study. This point has been clarified in the revised version of the manuscript (page 5, line 27).