World Journal of Gastroenterology,
Main Editorial Office
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December 24, 2014

Dear Professor Lian-Sheng Ma
President and Editor-in-Chief "**World Journal of Gastroenterology**"
Dear Jin-Lei Wang, Director,
Dear Yuan Qi, Science Editor, Editorial Office

Thank you for your kind letter concerning invited manuscript entitled "**Discrepancies in the histological type between biopsy and resected specimens; a cautionary note for mixed-type gastric carcinoma (ESPS Manuscript NO: 15033)**" by Komatsu et al. We have revised the manuscript according to reviewer's comments using a red color font (highlighted revise version) and presented the outlining responses to your comments below.

We thank you for the valuable suggestions and comments for the manuscript. We have carefully revised it accordingly. Explanations have been provided point by point. We believe that our revised manuscript has been improved by these revisions, and satisfy your concerns. We cordially appreciate your work regarding our manuscript. We hope that the revised manuscript is now acceptable for publication in the "**World Journal of Gastroenterology**".

Sincerely yours,

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Comments to authors from editor

The review of your manuscript (**ESPS Manuscript NO: 15033**) entitled "**Discrepancies in the histological type between biopsy and resected specimens; a cautionary note for mixed-type gastric carcinoma**", which you submitted to the World Journal of Gastroenterology, is now completed and the first decision for publication is available.

Based on the reviewers' comments, your manuscript may be accepted for publication if the suggested revisions are incorporated and the subsequent re-review is positive. In addition to revising your manuscript according to the reviewers' comments and the formatting and presentation standards of the **World Journal of Gastroenterology**, you are expected to address each of the points raised by the reviewers in a response letter that is to accompany your resubmission.

Response to editor's comments

Thank you for your kind and promising letter concerning invited manuscript. We have revised the manuscript according to reviewer's comments as follows. We believe that our revised manuscript have been improved by revisions, and satisfy your concerns. We cordially appreciate your work regarding our manuscript. We hope that the revised manuscript is now acceptable for publication in "**World Journal of Gastroenterology**".

Reviewer:
Reviewer code: 02441737
Date reviewed: 2014-11-21 05:11

Comments to Authors:
The manuscript is properly presented and discussed the incidence of discrepancies and associated factors, with special reference to pathological definitions by the Japanese classification of gastric carcinoma (JCGC) and TNM classification. Comments It is an article of great importance because the incidence of gastric cancer is increasing worldwide. Another reason that supports the conclusions of this study is the large sample size of 376 paired samples from gastric biopsy and resected specimens, derived from curative gastrectomy for gastric cancer. Because the researchers note that the incidence of mixed-type gastric cancer was significantly higher in specimens with discrepancies than in those without in both the JCGC ($p < 0.0001$) and TNM ($p < 0.0001$); 93.2 % (41/44) specimens with discrepancies in the JCGC and 97.1% (66/68) specimens with discrepancies in TNM were mixed-type gastric cancers.

Response to reviewer's comments
Thank you for your kind comments. We cordially appreciate your contribution to the review of our manuscript and found them to be great helpful. We have revised our manuscript accordingly. We hope that our manuscript has been more improved by these revisions and that we have adequately addressed your concerns.

Query
It is important that researchers indicate the name of the Ethics Committee approved the study and that the patients were treated according to the provisions of the Helsinki criteria to conduct research involving human subjects.

Reply
Thank you for your valuable comments. Off course, the Ethics Committee of our institute approved this study and patients were treated according to the provisions of the Helsinki criteria to conduct research involving human subjects. As you indicated, we revised our manuscript. Thank you for your helpful suggestion.

Query
It is recommended that the authors write down the number of biopsy specimens were reviewed by pathologists from other hospitals and if they followed the same procedures established by the original protocol.

Reply
Thank you for your important comment. As you mean, several number of biopsy specimens is very useful to evaluate the extent of histological mixed gastric cancer. Unfortunately, although we tried to investigate them, there was no complete data of the number of biopsy specimens which were reviewed by pathologists from other hospitals. We are sorry to reply your important comment. In near future, we will examine the correlation between the number of biopsy specimens and the rate of

discrepancies. We appreciate your reasonable and important comments.

Query

If it is possible the authors should explain in more detail the differences in histological type classifications of mixed-type gastric cancer, both in the case of classification JCGC and TNM classification (see page 6, second paragraph, lines 5-7).

Reply

Thank you for your helpful comments. Concerning the differences in histological type classifications of mixed-type gastric cancer, we added the more detail explanation in "**MATERIALS AND METHODS,** ***Subgroups based on histological differentiation***", as follows. Thank you.

Original version

Subgroups based on histological differentiation

There has been no universal standard regarding the definition for the histological type, particularly in mixed-type gastric cancer. There are small differences in the definitions for the histological type according to the JCGC and TNM classifications. The histological type of mixed-type gastric cancer has been classified on the basis of the predominant component by the JCGC; however, it has been classified on the basis of the weakest differentiated component by the TNM classification.

Revised version

Subgroups based on histological differentiation

There has been no universal standard regarding the definition for the histological type, particularly in mixed-type gastric cancer. There are small differences in the definitions for the histological type according to the JCGC and TNM classifications. The histological type of mixed-type gastric cancer is defined by the quantitative predominance in JCGC classification and qualitative predominance in TNM classification. Namely, the histological type of mixed-type gastric cancer has been classified on the basis of the predominant component by the JCGC; however, however, it has been classified on the basis of the poorest differentiated component in TNM classification.

Query

In the statistical analysis of the data, it is recommended to the researchers (if possible) carrying out tests of sensitivity and specificity, predictive values, Relative Risk or Odds Ratio in order to determine the probability of presenting gastric cancer associated with certain histological factor consider the two classifications JCGC and TNM. The authors could also consider conducting logistic regression analysis to identify predictor's factors of mixed-type gastric cancer, both in the case of classification JCGC and TNM.

Reply

Thank you for your suggestions. In this study, we only focused on two factors such as the extent of undifferentiated components of gastric cancer and the presence of mixed gastric cancer. Therefore,

from important point of view in clinical settings, we added the data of the positive predictive values in the differentiated and undifferentiated type from biopsy specimens in both JCGC and TNM definition. Moreover, previously, we already reported clinical factors associated with mixed-type gastric cancer. Please refer to below paper (**Reference 15**). Therefore, in this study, we focused only on the mixed-type gastric cancer as a reason of diagnostic discrepancies between biopsies and resected specimens. We appreciate your reasonable and important comments.

Shimizu H, Ichikawa D, Komatsu S, Okamoto K, Shiozaki A, Fujiwara H, et al: The decision criterion of histological mixed type in "T1/T2" gastric carcinoma--comparison between TNM classification and Japanese Classification of Gastric Cancer. *J Surg Oncol* 2012; **105**:800-804. [PMID: 22189799 DOI: 10.1002/jso.23010]

Query

In Tables 1 to 3, it is advisable to record the results in absolute and relative values. Please write down a title in all tables, the Ji2 results and the "p" values. Also write down at the foot of the tables the meaning of the acronyms used. Table 4 needs a title and a foot of the table the meaning of the acronyms used. Note the meaning of the acronyms that are used throughout the manuscript.

Reply

Thank you for your valuable comments. We added the title to each table. Also, we added the meaning of the acronyms at the foot of the tables. Thank you for your reasonable suggestions.

Reviewer:
Reviewer code: 02445033
Date reviewed: 2014-11-19 18:41

Response to reviewer's comments
Thank you for your kind comments. We cordially appreciate your contribution to the review of our invited manuscript and found them to be great helpful. We have revised our manuscript accordingly. We hope that our manuscript has been more improved by these revisions and that we have adequately addressed your concerns.

Query
INTRODUCTION The studie's objective becomes clearer when reading the discussion than when reading the introduction. Perhaps the authors should re-write the objectives paragraph.

Reply
Thank you for your reasonable comments. We re-write the objective paragraph in INTRODUCTION. Thank you.

Query
METHODS - The retrospective design of the studie should be specified. - The reader gets confused about the groups for comparison when reading this section. There are many "groups" described, but statistical analysis is only performed on the "controversy yes/no" groups. However, when you first read this section you are initially expecting a direct comparison between biopsy and resection groups.

Reply
Thank you for your reasonable comments. We indicated in the ABSTRACT that this study was retrospective study. Thank you for your helpful comments.

Query
RESULTS - In the "Distribution of each histological type in the JCGC and TNM classification" paragraph, the described data correspond to the final diagnosis bases on respected specimens. However this is not so clear when reading the text. - In the "Comparison of each discrepancy" paragraph, the final sentence shows a 0.4 % (1 of 213 cases), but in table 2 that percentage is 0.5%. The latter is the correct one and it should be corrected in the text.

Reply
Thank you for your helpful comments. We apologize for the mistake. In the "Comparison of each discrepancy" paragraph, the data of final sentence was wrong. We corrected it to 0.5 % (1 of 213 cases), as shown in table 2. Thank you for your comment.

Query
DISCUSSION - In the third paragraph, third line it says: "29 (14.8%) of 195 specimens", but both in the results section and in table 1 it shows 28 (14.4%) of 195 specimens. - The authors state that "the

accuracy of the histological type is apparently inferior to that of the final diagnosis from respected specimens". Why not performing an analysis of sensitivity, specificity and overall accuracy?.

Reply

Thank you for your helpful comments. Again, we apologize for the mistake. In the DISCUSSION, third paragraph, third line, "29 (14.8%) of 195 specimens" was wrong. We corrected it 14.4% (28 of 195), as shown in table 1. Thank you for your comment.

Query

Some aspects from the author's comment on mixed-type cancer may be a bit confusing for the reader. First, they state that "it is not difficult for the pathologist to diagnose whether biopsy specimens include histological mixed type gastric cancer". But from their data you can see that 38% of pure D tumours and 35% of pure U were finally classified as mixed type.

Reply

Thank you for your reasonable and very important comments. We are sorry that our statement was a bit confusing. Detail meanings of this sentence "it is not difficult for the pathologist to diagnose whether biopsy specimens include histological mixed type gastric cancer" is as follows and we also revised this sentence as follows.

Revised, Discussion, paragraph 4

However, it is difficult for pathologists to accurately diagnose the histological differentiation of histological mixed-type gastric cancer due to the restricted tumor volume, even from several biopsy specimens, which only reflects a part of the tumor and the accuracy of the histological type is apparently inferior to that of the final diagnosis from resected specimens. It may be easier for pathologists to diagnose whether biopsy specimens include histological mixed-type gastric cancer. Therefore, in order to apply histological differentiation to clinical settings, the presence of the histological mixed-type itself could be a better indicative factor for limited treatments than the histological type, as proposed by recent studies [15, 18-20, 22]. Indeed, the positive predictive value was a bit higher in the histological mixed-type (90.2 % (55/61)) than that in the differentiated type (85.6 % (168/195)) from biopsy specimens according to the JCGC definition. These data suggest that it may be not difficult for pathologists to diagnose the histological mixed-type.

Query

Second, they also say that "mixed type may be a better indicative for limited treatments" (D1 lymphadenopathy following Japanese guidelines, as it is stated in the introduction, but also D1+ recommended for undifferentiated tumours in the same guidelines). But following the authors "These results indicate that the presence of the histological mixed-type itself could present malignant clinical behaviors". Therefore, it would seem logical to perform a standard D2 lymphadenectomy when a mixed type is diagnosed. In fact there is no recurrence in this series because all patients underwent a complete gastrectomy with radical lymphadenectomy irrespective of their stage (methods section)

Reply

Thank you for your reasonable comments. From only our results in this study, the recommended extent of lymphadenectomy for the mixed-type gastric cancer is difficult to discuss. Your query is very important issue and our future studies should be oriented as you mean. Indeed, in our previous study, we could not show the difference of recurrence pattern between the differentiated type and the mixed-type gastric cancer (**Reference 15**). Namely, we could not overcome and solve the malignant behavior of the mixed-type gastric cancer by the lymphadenectomy for gastric cancer.

Therefore, the sentence in Discussion "These results indicate that the presence of the histological mixed-type itself could present malignant clinical behaviors" does not only indicate the need for the extent of lymphadenectomy. Therefore, regardless of the extent of lymphadenectomy, the histological mixed-type itself could present malignant outcomes and close follow-up should be recommended for patients with the mixed-type gastric cancer. In this study, we presented the cautionary note of the mixed-type gastric cancer from viewpoint of the diagnosis. In near future, we will report the detail malignant behavior from viewpoint of the prognosis and molecular pathology. We cordially appreciate your review and various review points for our study.