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Ying Dou
Science Editor, Editorial Office of Baishideng Publishing Group Inc

Dear Ying Dou

Thank you for considering our paper titled “HER2 heterogeneity is a poor prognosticator for HER2 positive Gastric cancer” for publication in *World Journal of Clinical Cases*.

We have improved the content in accordance with the reviewers’ comments and have attached a revised version of our manuscript. Please find our point-by-point responses to the reviewers’ comments below. The added text is indicated by red-colored font in the revised manuscript.

We confirm that all of the authors have approved the changes to the revised manuscript. We would be grateful if the revised manuscript could be further considered for publication in *World Journal of Clinical Cases*, and we look forward to hearing from you soon.

Yours sincerely,

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Point-by-point responses to the reviewers' comments

(The added text is indicated by red-colored font)

Response to Reviewer 1

We appreciate this reviewer's important suggestions and appropriate critiques.

1. **Comments from the Reviewer:** *One weakness of the work is the number of patients, that only 82 patients were included in the final evaluation of intratumoral HER2 heterogeneity, and only 20 were defined as hetero, which limits the reliability in further subgroup analysis. It will be good to include more patients after December, 2016 if possible.*

   We appreciate important suggestions. We reviewed our medical database and electrical medical records of 128 patients who received chemotherapy for advanced gastric cancer between Jan, 2017 and Dec, 2017, then 6 more patients were added to our current study. As a result, a total of 88 patients were included.

   Page 4, line 2-3: July 2011 and December 2017 were included in this study
   Page 6, line 16-17: Data were censored on May 31, 2019.
   Page 6, line 24-31: each number of patients was changed because total patients were changed from 648 to 776.
   Page 7, line 11: the median follow-up was 18.5 months
   Page 7, line 12-13: which was considerably worse than that in the Homo group (25.7 months, HR; 2.430, 95% CI: 1.389-4.273)
   Page 7, line 14: …in the Hetero group was 2.9 months
   Page 7, line 15-16: …in the Homo group (7.9 months, HR: 2.000, 95% CI: 1.203-3.333)

2. **Comments from the Reviewer** : *Please address more on possible explanations for the results in discussion section, i.e., why the overall response rate was significantly better in the patients without HER2 heterogeneity (Homo group), why the progression*

free survival of trastuzumab-based chemotherapy was significantly better in the Homo group, why the overall survival was also significantly better in the Homo group.

We appreciate valuable suggestions. The intrinsic mechanism of the correlation between HER2 heterogeneity and poor efficacy for trastuzumab-based chemotherapy is still unclear. Thus possible explanations for our results were addressed in discussion section (page 9, line 21 – page 10, line 2).

Page 9, line 21 – page 10, line 2:
Although intrinsic mechanism of the correlation between HER2 heterogeneity and poor efficacy for trastuzumab-based chemotherapy is still unclear, chemo-resistance can be one of the main reasons for the treatment failure. Fabi, et al reported the discordances of HER2 positivity between primary and metastatic lesions may be a possible cause of chemo-resistance of trastuzumab for metastatic breast cancers [25]. Park, et al reported these discordances between primary and metastatic lesions could often be observed also in HER2 positive gastric cancers [26], and HER2 heterogeneity of primary lesions was existed in such cases with discordances of HER2 positivity. Another explanation for the poor efficacy for trastuzumab might be genomic alterations. Pietrantonio, et al reported chemo-resistances for trastuzumab were more frequently observed in patients with genomic alternations including EGFR/MET/KRAS/PI3K/PTEN mutations than those without [27]. They stated such genomic mutations were correlated with IHC 2+, i.e. the existence of HER2 heterogeneity.

Response to Reviewer 3
Thank you very much for the reviewer's important suggestions and appropriate critiques.

1. **Comments from the Reviewer:** *The results part of this manuscript is too simple and short. The total words of results part were 347 with 5 figures and 2 tables. The authors should logically describe every figures and tables with more details.*

We appreciate your appropriate suggestions. We added the detailed explanations for our results (page 7, line 1-7, line 16-22), then the results part consists 456 words.

Page 7, line 1-7: Other background characteristics such as age, sex, performance status, TNM stage, metastatic site and chemotherapeutic regimens were not significantly different between both groups. Besides, the number of biopsy site for HER2 assessment were not significantly different, i.e. those numbers more than three was 46% for Homo group and 57% for Hetero group (P=0.393). Waterfall plot for tumor shrinkage and clinical responses for the patients…

Page 7, line 16-22: Multivariate analysis revealed IHC HER2 heterogeneity as one of the independent poor prognostic factors for OS (HR: 3.115, 95% CI: 1.610-6.024) and PFS (HR: 2.123, 95% CI: 1.225-3.676) (Table 2). Undifferentiated histological type (HR: 2.612, 95% CI: 1.388-4.916), number of non-curative factors (HR: 2.252, 95% CI: 1.113-4.553), clinical nodal status (HR: 2.119, 95% CI: 1.165-3.855), hepatic metastasis (HR: 2.084, 95% CI: 1.076-4.036) and HER2 score (2+) (HR: 2.008, 95% CI: 1.094-3.690) were also extracted as independent poor prognostic factors for OS.

2. Comments from the Reviewer:

1. *The supplementary figure 1 was not depicted in the manuscript.*

The supplementary figure 1 (patient flow chart) was changed to figure 2. The explanations for this figure were already described in the results part (page 6, line 23-30)

Page 6, line 23-30: A total of 776 patients with metastatic or unresectable adenocarcinoma of the stomach or gastro-oesophageal junction were treated in this study period, and HER2 positivity was observed in 127 (16.3%). Of these, patients who received upfront gastrectomy before chemotherapy (n=5) or chemotherapy without trastuzumab (n=21), and patients who underwent HER2 assessment from one portion of tumor (n=13) were excluded (Fig. 2). Finally, a

group of 88 patients were evaluated for their intratumoral HER2 heterogeneity, in which HER2 homogeneity was observed in 65 (Homo group) and HER2 heterogeneity was observed in 23 (Hetero group) patients, respectively.

2. *There are so many digraphs in the manuscript. They should be divided. For example, patientsthan (Line 2, Page 7), IHC 2+than (Line 2, Page 7). Many grammar errors need to be corrected: Line 3, Page 5: "XPT or FPT regimen were", Line 7, Page 14: "those portion", and so on. The duplicated table title in Page 24 should be deleted.*

   We appreciate your kind readings. Pointed digraphs and duplications were collected.

   Line 3, Page 5 : XPT or FPT regimens were …
   Line 32, Page 6: … patients than …
   Line 1, Page 7: … IHC 2+ than …
   Table 2: duplicated title was deleted

We added,

Line 7, page 1: "running title"
Line 22-29, page 1: "ORCID numbers"
Line 21, page 1 to Line 4, page 2: "author contributions"
Line 6-14, page 2: "Institutional review board statement" and "Informed consent statement"
Line 23-24, page 2: "Declarations of interest" and "founding source"
Line 30, page3 to Line 5, page 4: "core tip"
Line 7-9, page 4: "citation"
Line 9, page 13 to Line 26, page 16: "article highlights"

PMID and DOI are also added to references.