Peer Review File

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Author reply: Thank you very much for your letter and advice on our manuscript. We have resubmitted new version accordance with recommendations of the editor and reviewers. The reply for reviewers are as follows:

Reviewer A: The Authors present a series of gastric cancer patients treated by preoperative chemotherapy and surgery with particular interest for ypT0. The topic is relevant and worthy to be discussed, but the analysis is very limited from small figures and not so clear methods.

Comment 1: First of all, to conclude that ypT0 should be included in the TNM stage I is obvious. Similarly, to define ypT0N+ with a lower survival than stage I is obvious. Moreover, it could be interesting to specify ypT0N1, N2, and N3 (if possible with nodal pathologic response evaluation) with their survival.
Reply 1: The 5-year overall survival of ypT0N1 and ypT0N2 were both 75%. The prognosis was similar to ypstage II (71.6%), but different from ypstage I (97.5%) and ypstage III (32.7%). Despite the poor prognosis of ypT0N3 patient with survival time of 17 months, there was only 1 patient in this condition. Hence, we merged these three conditions together as ypT0N+. Large scale studies were needed to address these three conditions to the proper stage classifications.
Changes in the text: We added some data in our text. (See page 9 line 223-229).

Comment 2: Again, I suggest to verify if cTN stage before preoperative therapy did affect survival of ypT0 patients.
Reply 2: All patients in this study was evaluated as serosa invasion (cT4). There were 238 (75.8%) patients with cN (+) and 76 (24.2%) patients with cN (-). The proportion of cN (+) was not significantly different between ypT0 and notypT0 group (p=0.318). Generally, cN didn't affect patients' long-term outcome, the 5-year overall survival was 56.8% in cN (-) patients and 52.4% in cN (+) patients (p=0.571). The results were accordance with previous study in which postoperative stage rather than clinical stage determined the prognosis of patients receiving neoadjuvant chemotherapy (DOI: 10.1200/JCO.2014.55.9070). In ypT0 patients, the 5-year overall survival was 80.7% for cN (+) and 100% for cN (-) patients, the difference was not significant (p=0.358).
Changes in the text: 1. We added some data in our text (See page 9, line 230-232). 2. We added some data in our text (See page 15, Table 1).

Comment 3: Methodologically, the groups according to chemotherapy regimen are too inhomogeneous and the analysis should be corrected for this variable. It is not clear why 1-2 prep cycles are significantly associated with a better survival (Table 2).
Reply 3: In this study, we observed that patients receiving SOX regimen were more

likely to have ypT0. We included this variable in multivariate analysis and regimen wasn't an independent prognostic factor. It might indicate that the patients would benefit from complete response of primary lesion no matter what regimen patients received.

The majority of patients in this study received no more than 4 cycles of preoperative chemotherapy (90.8%). The 5-year overall survival of patients who received 1-2, 3-4 and >4 cycles preoperative chemotherapy was 60%, 51.3% and 34.5%. The difference between 1-2 and 3-4 cycles was not significant (p=0.228), but patients with >4 cycles had significantly worse prognosis.

One of the reasons probably was that patients with pronged cycles were lack of clinical response, more cycles of preoperative chemotherapy were administered in order to improve the response. Furthermore, we observed that less ypN (+) patients with 1-2 cycles (58.5%) than those with 3-4 (74%) or >4 cycles (75.9%), meanwhile the proportion of cN(+) before treatment was similar among three groups (77%, 74% and 79.3% for 1-2 cycles, 3-4 cycles and >4 cycles respectively, p=0.751). It indicated that patients with longer preoperative chemotherapy might be those lack of response and higher tumor burden even after chemotherapy.

Comment 4: I did not understand the single case of ypT0 R+. Anyway, the analysis should be performed excluding R+ patients.

Reply 4: The single case of ypT0 R+ is the condition that during the surgery, the common hepatic artery was encased by lymph nodes which cannot be dissected which was recorded as R2 resection. However, in pathological examination, no residual tumor cells were observed in primary lesion but still had 1 metastatic lymph node.

We include the patients with R+, as R+ resection was related to bad response. Even with the strong prognostic factor of R+, ypT0 remain an independent prognostic factor in multivariate analysis.

Comment 5: Neoadjuvant therapy can negatively affect the nodal count: specifying that generally authors for small simples (as ypT0) should indicate median and range, it needs to indicate median and range of retrieved nodes.

Reply 5: We added some data in our text (See page 7, line 171-172).

Comment 6: Finally, authors should clarify if surgical complications and postoperative chemotherapy might affect patients survival.

Reply 6: There were 54 patients (17.2%) had surgical complications. The 5-year overall survival was 55.8% for patients who had surgical complications and 42.4% for those had not, the difference was marginally significant (p=0.076).

There were 245 (78%) patients received postoperative chemotherapy, 43 (13.7%) patients didn't continue postoperative chemotherapy and the other 26 (8.3%) patients' postoperative treatment status was unknown. The 5-year overall survival was 56% and 44.2% for patients receiving postoperative chemotherapy or not (p=0.157). Despite the difference was not statistically significant, we thought patients would benefit from postoperative chemotherapy and there were 26 patients' postoperative treatment status

was unknown, which might cause the bias of results.
As these two variable's p values were more than 0.05 in univariate analysis, they weren't included in the multivariate analysis.
Changes in the text: We added some data in the text. (See page 6, line 157-160; See page 16 Table 1).

Reviewer B
Comment 1: Abstract - Page2 line 40, ypT0 was a predictor for long-term outcomes → ypT0N0 was a predictor for long-term outcomes ?
Reply 1: As in the multivariable analysis, ypT0 was found to be an independent prognostic factor, we concluded "ypT0 was a predictor for long-term outcomes".

Comment 2: Page 2 line 39-42, author concluded that ypT0 was a predictor for long-term outcomes, however these have been reported in the past and are considered to have no novelty.
In this paper, we would like to convey that the prognosis of ypT0N＋ is the same as that of stage II and the prognosis is relatively poor. If so, author should change the conclusion.
Reply 2: We have modified our text as advised. (See page 2, line 42-43).

Comment 3: Methods - Page 4 line90-92, please describe the ethic committee approval number.
Reply 3: We added the ethic committee approval number in manuscript. (See page 4 line 94-95).

Comment 4: In page 5 line 113, please describe the postoperative chemotherapy in detail.
Reply 4: Postoperative chemotherapy was continued in patients with good physical status. The cycles and regimens were decided by the oncologist according to the response and adverse events.
Change: We have modified our text as advised. (See Page 5, line 117-118).

Comment 5: Equipment must have described the details (producer, city, country) in Page 6, line 133.
Reply 5: We have modified our text as advised. (See page 6 line 139).

Comment 6: In page 5 line 128, please describe the details of multivariate survival analysis (which parameters were chosen ex).
Reply 6: We have modified our text as advised. (See page 5 line 132-133).

Comment 7: Results - In page 6 line 139, the period was written as July 2004 to December 2105, but is it 2015?
Reply 7: We have modified our text as advised. (See page 6 line 145).

Comment 8: In table2, Which parameters were used in the multivariate analysis? Please list the all results of parameters you put in the multivariate analysis.
Reply 8: The variables for which the p value was <0.05 were included into multivariable analysis.
Changes: We added the results of univariate analysis and p value of all variable in multivariate analysis. (See page 8 line 198-202; Table 2).

Comment 9: In table 2, does ref means reference? Please write in full or in a footnote.
Reply 9: We have modified our text as advised. (See page 18 line 415).

Comment 10: The aim of this study is to propose the inclusion of ypT0 patients into TNM stage. Wouldn't it be necessary to compare T0N1, T0N2, T0N3 with Stage I-Ⅲ?
Reply 10: The 5-year overall survival of ypT0N1 and ypT0N2 were both 75%. The prognosis was similar to ypstage II (71.6%), but different from ypstage I (97.5%) and ypstage III (32.7%). Despite the poor prognosis of ypT0N3 patient with survival time of 17 months, there was only 1 patient in this condition. Hence, we merged these three conditions together as ypT0N+. Large scale studies were needed to address these three conditions to the proper stage classifications.
Changes: We added some data in our text. (See page 9 line 223-229).

Comment 11: Discussion - Why the long-term outcome of pCR patients was not better than that of ypStage Ⅰ ? Please describe the discussion of reasons.
Reply 11: The probable reasons for this condition were as follows: i) ypstage I was related to good response to neadjuvant chemotherapy, which resulted the 5-year overall survival of 97.5%. ii) Despite patients with pCR were likely to be cured, they still have chances of recurrence even after radical resection. As the limited cases of both conditions, it's hard to analyze the risk factors for recurrence and address the significant difference between pCR and ypstage I.
Changes: We added the discussion of reasons in our text. (See page 10, line 264-271).