Format for ANSWERING REVIEWERS

January 10, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 15244-review.doc).

Title: Clinicopathologic and molecular features associated with patient age in gastric cancer

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The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) **Reviewer #1**

① A flow chart or consort diagram of the excluded 758 patients will be helpful.

Reply: Thank you very much for your thoughtful comment. Flow chart of excluded patients was added in Figure 1. Detailed explanation of excluded patients was added in Result section: "Patients (n = 2416) with a diagnosis of gastric cancer were identified from electronic records from June 2003 to December 2010 at SNUBH. The following patients (n = 758) were excluded from further analysis: < 20 y of age (n = 1); diagnosis of gastric mucosa-associated lymphoid tissue lymphoma (n = 87), gastrointestinal stromal tumor (n = 18), metastatic cancer in the stomach (n = 3), pathologic diagnosis of gastric cancer was not confirmed (n = 11), did not undergo a staging workup (n = 32), lost in follow-up (n = 89), and diagnosed with gastric cancer and receiving treatment (n = 517) (Figure 1). The remaining patients (n = 1658) were analyzed." (Page 7, line 22-28)

② The primary outcome was given as mortality and recurrence of gastric cancer; but this is a retrospective study, thus besides giving primary outcome the authors should mention as; the primary aim of this study is to compare the survival effect of... should be better to define the study.

Reply: Thank you very much for your comment. We changed it, however, English editor modified it from 'aims' to 'outcomes'. We will change it again if 'outcome' seems inappropriate. (Page 7, line 3)

③ A higher rate of palliative resection was performed in young patients and previous studies showed that palliative gastrestomy can improve survival. More gastrectomy in young group may affect survival rate as found in univariate analyses. More details about the effect of gastrectomy on survival should be mentioned in discussion section.

Reply: Thank you very much for your critical comment. We added in Discussion section: "At the

same time, treatment differences do exist between the two groups. For example, in spite of the higher stage of gastric cancer, younger patients received more palliative resections than older patients. Because it is possible that palliative gastrectomy could improve overall survival, aggressive treatment in younger patients might have extended their overall survival. However, despite potential advantage in treatment strategies in younger patients, gastric cancer-related death did not differ between the two groups when adjusted by stage. Further support for this conclusion is gained from the results that only stage and distant metastasis could predict mortality, whereas age was not found to be an independent risk factor in a Cox proportional hazards model. Therefore, other factors, such as the diffuse pathology or size, might more strongly influence overall survival." (Page 10, line 13-21)

④ Higher rate of Chemotherapy was used in young group but we know that different subgroups of chemotherapeutics can affect survival. Additionally if the authors did not have this data, it should be mentioned as limitation

Reply: Thank you very much for your critical comment. We added in Discussion section: "Third, the influence of chemotherapeutic treatment or specific protocol was not evaluated. A greater proportion of younger patients received chemotherapy than older patients, and furthermore, different regimens could affect survival." (Page 10, line 27-30)

⑤ The manuscript should be reviewed for English translatation again.

Reply: Thank you very much for your important comment. We received English editing from AmEditor as you recommended.

(2) **Reviewer #2**

① A initial loss of 758 patients and follow up loss of 30% was observed, this issue may affect the results, however the findings are similar to was reported in even smaller series previously.

Reply: Thank you very much for your thoughtful comment. Since SNUBH is one of the largest tertiary hospital in Korea, many patients come from far provinces. However, some patients are sent back to or they hope to go back to their hometown during follow-up. We believe that this is the reason why rate of follow-up loss was high.

② It would be interesting to include a family history in analysis of each groups, I hope that young people are more cases of family disease.

Reply: Thank you very much for your important comment. In contrast with our expectation, family history was not different between the two age groups (11.9% in younger group vs 15.3% in older group, $P = 0.203$). However, due to the high percentage of missing data, reliability of this result is poor, and it was deleted.

③ The analysis of *H. pylori* strains or immune status was not included, in order to achieve more accurate data.

Reply: Thank you very much for your important comment. In SNUBH, analysis of H. pylori strains or immune status is not routinely checked for gastric cancer patients. Unfortunately, we could not include in result owing to the retrospective design.

④ Draws attention to the low proportion of patients with positive Her2, therefore FISH in gastric

cancer may be necessary.

Reply: Thank you very much for your important comment and we agree your opinion. Unfortunately, as we mentioned in discussion section, most of patients did not undergo FISH and we could not add FISH result. This could be a limitation of this study.

⑤ In this type of gastric cancer studies in young people a continue increase has been observed. This pathology has a different molecular pathogenic origin and evolution. This study gives encouragement for analysis in this population and to compare them in different geographical areas, eg East-West , East-Latin or Nordic-Mediterranean. We must do more detailed studies on the role of H. pylori in this population.

Reply: Thank you very much for your kind comment. We expect additional studies complementing our shortcomings.

(3) **Reviewer #3**

① Minor comments: They should highlight the differences of molecular pathology and pre-cancerous lesions between young and old cancer patients.

Reply: Thank you very much for your thoughtful comment. We highlighted the advantages of this study in Discussion section: "Nevertheless, our study presents several novel findings. To the best of our knowledge, this study is the first to identify differences based on age in the molecular pathology and H. pylori-associated precancerous changes of gastric cancer. Therefore, a novel concept on the basis of these results is that the disease pathogenesis differs between the two groups. However, additional studies are necessary to validate the role of H. pylori in disease progression, as well as the accompanying molecular changes in gastric cancer, of younger patients." (Page 10, line 31- page 11, line 1)

② The sample size isn't well defined - they should review why they excluded such patients in the study (and not just include it in the abstract).

Reply: Thank you very much for your thoughtful comment. As we mentioned above, detailed explanation was added in Results section: "Patients (n = 2416) with a diagnosis of gastric cancer were identified from electronic records from June 2003 to December 2010 at SNUBH. The following patients (n = 758) were excluded from further analysis: < 20 y of age (n = 1); diagnosis of gastric mucosa-associated lymphoid tissue lymphoma (n = 87), gastrointestinal stromal tumor (n = 18), metastatic cancer in the stomach (n = 3), pathologic diagnosis of gastric cancer was not confirmed (n = 11), did not undergo a staging workup (n = 32), lost in follow-up (n = 89), and diagnosed with gastric cancer and receiving treatment (n = 517) (Figure 1). The remaining patients (n = 1658) were analyzed." (Page 7, line 22-28)

③ The manuscript should be reviewed by an English translator.

Reply: Thank you very much for your important comment. We received English editing from AmEditor as you recommended.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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