

ANSWERING REVIEWERS



January 20, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 16003-resubmission.doc).

Title: Clinicopathologic Features of Remnant Gastric Cancer Following Distal Gastrectomy for Cancer Correlate with Time Intervals

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Name of Journal: *World Journal of Gastroenterology*

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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.

Comment 1: The study is done carefully. Can you explain these two questions as described bellows?

Response 1: Thank you for your highly insightful comments and instructive suggestions and we have made corrections, accordingly.

Comment 2: “Nevertheless, we consider that there may be some differences in clinical pathology and prognosis between the RGC patients with a recurrence interval shorter than 10 years and those longer than 10 years.” The authors should check and explain it. Why they choose 10 years?

Response 2: Thank you very much for your meaningful comments. It is reported that time interval may be one of the most important factors for the development of RGC. The average latency time is reported to be 20-27 years and may go up to 40 years for patients with RGC after benign disease and most studies have reported a steep increase in the risk of developing gastric stump cancer from the 20th year after first gastrectomy. Few studies have studied that if there are some difference in clinical pathology and prognosis between RGC patients with RGC I recurrence interval shorter than 10 years (RGC I) and those longer than 10 years (RGC II). And we really found some difference between RGC I and RGC II, including, RGC II was easier to be located on the anastomotic site than RGC I, moreover, the predominant reconstruction type of the first operation is Billroth I for RGC I and Billroth for RGC II. However, more studies are needed to clarify our conclusion. We future will conduct several studies for the comparisons between difference time intervals. We really hope that it may address your concerns.

Comment 3: From table 3, we can see the predominant reconstruction type of the first operation is Billroth I for RGC I and Billroth II for RGC II. But there were 20 (60.6%) patients whose tumor stages of the initial cancer were III or IV stage in the RGC I subgroup. While only 3 (22.7%) of RGC II cases got III or IV stage initial cancer. Significant difference was observed between the two groups (60.6% vs. 22.7%, $P=0.006$). The authors should check and explain it.

Response 3: Thank you for your comment. We are so sorry for that we have made a mistake. Accordingly, corrections have been made (see in the Results Section). We have changed it into 5 (22.7%) of RGC II cases got III or IV stage initial cancer. Moreover, we added some information in the Result section. Hopefully, it will address your concerns.

Comment 4: This article is an important paper about clinicopathologic features of remnant gastric cancer (RGC). Original point of this paper is the comparison of RGC with time interval of >2 and 10≤ years after prior gastrectomy for gastric cancers. However, several questions for authors are remained.

Response 4: Thank you for your highly insightful and positive comments and instructive suggestions, accordingly, we have made the corrections.

Comment 5: From your data, long term bilious exposure owing to B-II reconstruction can occur RGC in RGC II. Do you have any data of anastomotic dysplasia or gene array to emphasize your affirmation?

Response 5: Thank you for your instructive comment and suggestions, we are sorry for that we didn't collect any data of anastomotic dysplasia or gene array to emphasize our affirmation before. We are grateful for your insightful comments and fully agree with you. Our team will add the data of anastomotic dysplasia and even gene array to emphasize our affirmation in our future study if conditions allow. Hopefully, this addresses your concerns.

Comment 6: In RGC I, there are too many early re-oncogenesis after prior gastrectomy. If you excuse this result as only background mucosal change, it is not reasonable (Because intensive follow-up must be conducted within 5-years after gastrectomy). You have to mention about it.

Response 6: Thank you for your important comment. We really understand your opinion. We have made corrections, accordingly. For RGC I, the tumor locations of re-oncogenesis including anastomotic site (n=13, 31.0%), non-anastomotic site (n=19, 45.2%) and total stump (n=10, 23.8%). For patients whose re-oncogenesis locations are non-anastomotic site and total stump, through preoperative gastroscopy and intraoperative check, we didn't find any other sites of re-oncogenesis, therefore, we consider these patients whose re-oncogenesis locations are non-anastomotic site and total stump may be associated with background mucosal change, however, it is only our conjecture. Moreover, all the 42 patients have achieved curative resection with safe margin (all the margins have been proven postoperatively to be safe or called "negative margin"). Thus, more studies should be conducted to find the most possible reason for these patients. For now, we only think of one possible hypothesis. The reasons for these patients with early re-oncogenesis after prior gastrectomy still need confirmed. Hopefully, this will address your concern.

Comment 7: According to non-anastomotic re-oncogenesis of RGC I, you suggest that the development of RGC I are likely to be due to residual carcinomas ignored at initial operation. Viewed in this way, it is doubtful of the quality of prior operation (plenty lymphadenectomy and safe margin); hence you have to present the results of detail of prior operations and histopathological characteristics.


Response 7: Thank you for your instructive comment. Your suggestion is very important. Firstly, in our study, we included patients with curative resection (RGC I, n=42; RGC II, n=32), palliative resection (RGC I, n=13; RGC II, n=8) and no operation (RGC I, n=10; RGC II, n=9) (see in Table 1). When we conducted next analyses, we only included patients with curative resection (safe margin) between RGC I (n=42) and RGC II (n=32). Therefore, all patients we included in the analyses were with safe margin. Meanwhile, all patients with curative resection have achieved plenty lymphadenectomy, and in our opinion, insufficiency lymphadenectomy shouldn't be associated with remnant gastric re-oncogenesis, it may lead to negative lymph nodes remained and lymph nodes metastasis. Secondly, we conducted

some comparisons of histopathological characteristics between RGC I and RGC II, including Bormann type ($p=0.322$), histology grade ($p=0.421$), Lauren grade ($p=0.308$), no significant difference was found between RGC I and RGC II (see in Table 3). Hopefully, this will address your concern.

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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