Dear prof,

Thank you for giving us the opportunity to submit a revised draft of the manuscript "The impact of chemotherapy cycles≥9 for stage II and III gastric cancer patients undergoing D2+gastrectomy on survival and recurrence: A propensity score matching research" to "World Journal of Gastrointestinal Surgery". We appreciated the time and effort that you and the reviewers dedicated to providing feedback on our manuscript and are grateful for the insightful comments on and valuable improvements to our paper.

We have incorporated most of the suggestions made by the reviewers. Those changes are highlighted within the manuscript. Please see below, for a point-by-point response to the reviewers' comments and concerns. All page numbers refer to the revised manuscript file with tracked changes.

Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: The topic of this manuscript falls within the scope of Word Journal of Gastroenterology. The Authors restrospectively evaluated 412 patients in stage II and 902 patient in stage III gastric cancer who underwent D2+gastrectomy plus adjuvant chemotherapy or neo-adjuvant chemotherapy. The aim of this study was to affirm wether excessive chemotherapy cycles have extra survival benefits on stage II-III gastric cancer. The Authors pointed out that intestinal-type, proximal gastrectomy, maximum diameter of tumor (>= 6cm) had higher risk of total mortality in group of chemotherapy cycle >= 9 and disease progression in group of chemotherapy cycles <9. Chemotherapy cycles >= 9 is unnecessary for patients with stage II and III gastric cancer, owing to its insignificant role in prognosis in gastric cancer. Chemotherapy cycles >=9 has a major part to play in avoiding recurrence of patients with stage III, except for the role in stage II. It is a very interesting manuscript. Background, Methods, and Results are good. Discussion sound well. Complete the references.

Author response for Reviewer #1: Thank you for pointing this out. I corrected my references according to the format of this journal.

Reviewer #2:
Scientific Quality: Grade D (Fair)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors: The authors examined the prognosis by the number of cycles of chemotherapy for gastric cancer. Interesting study, but information is lacking. 1. The authors should state the chemotherapy regimen. 2. What does "D2+lymphadenectomy" mean? Is it same as D2 lymphadenectomy according to the Japanese guideline? 3. In the Abstract, please show how to divide the two groups. 4. Page 2, Line 4 from the bottom: adjuvant chemotherapy and adjuvant chemotherapy → adjuvant chemotherapy and neoadjuvant chemotherapy 5. Page 5, Line 17: the median OS → the median PFS? 6. In

Table 1, After PSM, ≧9cycles group, the total number of men and women is 107. 7. In the Discussion session, the first four lines are redundant with the Introduction session and should be omitted. 8. In the Discussion session, you mention chemotherapy cycles in various cancers, but it is better to focus your discussion on gastric cancer.

Author response for Reviewer #2:

Response1: I supplemented background of chemotherapy regimen for chemotherapy cycles ＜9 and ≥9. Stage II : The chemotherapy regimen applied to Chemotherapy cycle <9: S-1 alone was1, SOX was 28, S-1+docetaxel was 4, deofuridine alone was 10, XELOX was 3, FOLFOX was 32 and 18 multiple regimen combinations was 18. Composition of chemotherapy cycles≥9: S-1 alone was 61, SOX was 6, S-1+apatinib was 9, capecitabine alone was 15, FOLFOX was 2 and 5 cases were multiple regimen combinations. In group of chemotherapy cycle<9, neoadjuvant chemotherapy plus adjuvant chemotherapy was 3, 94 cases was used only postoperative adjuvant chemotherapy. Likewise, in group of chemotherapy cycle≥9, 21 cases was used to neoadjuvant chemotherapy plus adjuvant chemotherapy, postoperative adjuvant chemotherapy was 76. Stage III : The number of chemotherapy regimen in group of chemotherapy cycle <9: SOX was 30, S-1+apatinib was 5, S-1+DCF was 4, SOX+ FOLFOX was 10, S-1+ FOLFOX was 4, XELOX was 8, FOLFOX was 98 and 55 multiple regimen combinations was 18. Composition of chemotherapy cycles≥9: S-1 alone was 142, SOX was 2, S-1+DCF was 2, capecitabine alone was 29, doxifluridine alone was 9, SOX+ FOLFOX was 6, FOLFOX was 2 and 50 cases were multiple regimen combinations. In group of chemotherapy cycle<9, neoadjuvant chemotherapy plus adjuvant chemotherapy was 24, 218 cases was applied only postoperative adjuvant chemotherapy. Likewise, in group of chemotherapy cycle≥9, 41 cases was used to neoadjuvant chemotherapy plus adjuvant chemotherapy, postoperative adjuvant chemotherapy was 201.

Response 2: D2+lymphadenectomy means more than D2 lymph nodes were resected according to NCCN and AJCC guideline.

Response 3: For patients with TNM Stage II (n=412) grouping based on ten variables, inclusion of gender, age at surgery, vascular invasion, nerve invasion, depth of tumor invasion, number of positive lymph nodes, Lauren classification, maximum tumor diameter, type of gastrectomy, and Her-2, with 1:1 nearest-neighborhood propensity score matching (PSM) and without replacement, the caliper value was set to 0.05. patients with TNM Stage III (n=902) grouping based on eight variables, inclusion of gender, vascular invasion, nerve invasion, depth of tumor invasion, number of positive lymph nodes, Lauren classification, maximum tumor diameter, type of gastrectomy, with 1:1 nearest-neighborhood propensity score matching (PSM) and without replacement, the caliper value was set to 0.05.

Response 4: That is my fault. I corrected as adjuvant chemotherapy and neoadjuvant chemotherapy.

Response 5: Thank you for pointing this out. I corrected as the median PFS.

Response 6: That is my fault. In group of chemotherapy cycles≥9, male was 79 and female was 18.

Response 7: The first four lines are redundant and I omitted.

Response 8: I am sorry for this, paper about the chemotherapy cycles related to gastric cancer was rare and I cannot quote in my article.

Reviewer #3:
Scientific Quality: Grade C (Good)
Language Quality: Grade C (A great deal of language polishing)
Conclusion: Major revision
Specific Comments to Authors: Long-term results of gastric cancer treatment remain disappointing. This is primarily due to the late diagnosis of gastric cancer. For improving the survival of patients with advanced gastric cancer, adjuvant and neoadjuvant chemotherapy is widely used, but the effect of the chemotherapy courses number on long-term results of treatment has not been studied enough. Despite the urgency of the problem, there are a number of significant remarks concerning the submitted manuscript. Comments Title. The title seems to be long, with unnecessary details. Abstract. The results obtained should be presented more clearly and comprehensibly. Background. Information regarding the number of chemotherapy courses and the results obtained should be transferred to the appropriate sections (Methods and Results). It is necessary to explain why the authors believe that 9 or more courses are excessive chemotherapy cycles, and not, for example, 6 and 8 courses. There are inaccuracies in the text: "...the ratio of adjuvant chemotherapy and adjuvant chemotherapy were 97.78% (882/902), 13.41% (121/902)" Methods. The recitation of the clinical and pathological characteristics of gastric cancer is desirable to streamline: clinical data, pathological data, features of treatment, results. Information about the chemotherapy courses should include not only the average number of courses, but also information on how many patients (and their percentage of the total number of patients) received a certain number of courses of neoadjuvant chemotherapy only (if any), how many - only adjuvant chemotherapy and the number patients who received both courses. It is also necessary to provide information on chemotherapy regimens (given that the study included patients since 2002, they may be different). This data can be presented in the form of a table. Statistical methods should be removed from the "Data collection" section. "Neoadjuvant chemotherapy" is not listed in the inclusion criteria, why? Results. It should be taken into account that the prognosis for stages IIA and IIB of gastric cancer differs significantly. It is desirable to clarify whether only the stage IIA was included in the analysis, or the IIB as well. If both stages were included in the analysis, then I think the effect of different numbers of chemotherapy courses on the survival of patients with gastric cancer should be considered separately for stages IIA and IIB. Page 4, line 29. Error. Gender differences in groups before PSM (p=0.02). Page 5, line 14-16 «The diversity of 1-year OS rate（70.0% VS 80.0%，Log-Rank P=0.682, 3-year OS rate （78.2% VS 82.1%，Log-Rank P=0.981, 5-year OS rate （83.5% VS 60.0%，Log-Rank P=0.962)» - It cannot be that the 5-year OS rate is higher than 1 and 3-years ones. Page 5, line 17-18 «On the other side, the median OS were for chemotherapy cycles <9 was 82 months and the median OS for chemotherapy cycles≥9 has not reached.» - Apparently you mean PFS Page 5, line 18 – 20 «The outcomes were that 1-year PFS rate （50%VS 78.6%，Log-Rank P=0.042, 3-year PFS rate （74.1% VS 79.4%，Log-Rank P=0.367, 5-year PFS rate （75.3% VS 78.2%, Log-Rank P=0.924)» - Similar error as in Page 5, line 14-16 Page 5, line 22-26 «The recurrence rate of chemotherapy cycles<9 and chemotherapy cycles≥9 were 48.76% (22/97) and 24.38% (12/97), respectively and there was no obvious difference between the two groups(P=0.06)» and For group of chemotherapy cycles<9, the

percentage of local-regional metastasis and distant metastasis were 43.22% (11/97), 49.15 %(11/97), respectively» - Percentages calculated incorrectly! Page 6, line 27-29 and Page 7, line 2-4: «The diversity of 1-year OS rate (34.5% VS 30.8%, Log-Rank P=0.824), 3-year OS rate (38.3% VS 36.7%, Log-Rank P=0.816), 5-year OS rate (38.5% VS 35.0%, Log-Rank P=0.276) in both groups were not significant.»; « The outcomes were that 1-year PFS rate (24.2% VS 23.2%, Log-Rank P=0.263), 3-year PFS rate (36.3% VS 34.8%, Log-Rank P=0.085), 5-year PFS rate (40.3% VS 34.2%, Log-Rank P=0.411) of both two groups were similar.» - However, according to Figure 4c and 4d, the 1-year OS was clearly greater than 70% and the PFS was greater than 55%. And, as already noted, it cannot be that the 5-year OS rate is higher than 1 and 3-years ones. Table 2,3 and 5,6. It is not clear what is meant by "event": the number of patients who died and have relapse? Or something different? If this is the number of patients with disease recurrence, then these data do not match the number of patients given in the text of the manuscript (Page 5, line 22-24 and Page 7, line 6-8). According to the data shown in tables 1-3, patients with T4 were also assigned to the stage II - this is not true. Tables 2,3 and 5,6 do not allow understanding how patients with relapses were distributed in the group who received less than 9 courses of chemotherapy and in the group who received 9 or more courses. For this reason, it might think that you are comparing recurrence rates by gender, depths of tumor invasion, number of positive lymph nodes, vascular invasion, neural invasion, Lauren classification, maximum diameter of tumor, types of gastrectomy and Her-2. Figures 2 and 4. It is not clear what the table data under the survival curves means The text of manuscript contains stylistic errors. The submitted manuscript requires revision and correction of identified shortcomings.

Author response for Reviewer #3:

Response 1 title: corrected as "The survival benefits of excessive chemotherapy cycles for stage II and III gastric cancer patients after D2+gastrectomy"

Response 2 Abstract: I amended my abstract.

Response 3 Background: I added "According to clinical guidelines for the diagnosis and treatment of gastric cancer of Chinese Society of Clinical Oncology (CSCO), preoperative neoadjuvant chemotherapy is recommended for 2-4 cycles and Preoperative neoadjuvant chemotherapy is recommended for 2-4 cycles and 6-8 cycles. It should be pointed out that the chemotherapy cycles in our research including neoadjuvant chemotherapy before surgery and adjuvant chemotherapy after D2+gastrectomy. So chemotherapy cycles ⩾9 was consider as excessive chemotherapy cycles" and explain why chemotherapy cycles ⩾9 was consider as excessive chemotherapy cycles.

Response 4 menthod: Thank you for pointing this out. I supplemented background of chemotherapy regimen for chemotherapy cycles < 9 and ⩾9. Stage II : The chemotherapy regimen applied to Chemotherapy cycle <9: S-1 alone was1, SOX was 28, S-1+docetaxel was 4, deofuridine alone was 10, XELOX was 3, FOLFOX was 32 and 18 multiple regimen combinations was 18. Composition of chemotherapy cycles⩾9: S-1 alone was 61, SOX was 6, S-1+apatinib was 9, capecitabine alone was 15, FOLFOX was 2 and 5 cases were multiple regimen combinations. In group of chemotherapy cycle<9, neoadjuvant chemotherapy plus adjuvant chemotherapy was 3, 94 cases was used only postoperative adjuvant chemotherapy. Likewise, in group of chemotherapy cycle⩾9, 21 cases was used to

neoadjuvant chemotherapy plus adjuvant chemotherapy, postoperative adjuvant chemotherapy was 76. Stage III : The number of chemotherapy regimen in group of chemotherapy cycle <9: SOX was 30, S-1+apatinib was 5, S-1+DCF was 4, SOX+ FOLFOX was 10, S-1+ FOLFOX was 4, XELOX was 8, FOLFOX was 98 and 55 multiple regimen combinations was 18. Composition of chemotherapy cycles≥9: S-1 alone was 142, SOX was 2, S-1+DCF was 2, capecitabine alone was 29, doxifluridine alone was 9, SOX+ FOLFOX was 6, FOLFOX was 2 and 50 cases were multiple regimen combinations. In group of chemotherapy cycle<9, neoadjuvant chemotherapy plus adjuvant chemotherapy was 24, 218 cases was applied only postoperative adjuvant chemotherapy. Likewise, in group of chemotherapy cycle≥9, 41 cases was used to neoadjuvant chemotherapy plus adjuvant chemotherapy, postoperative adjuvant chemotherapy was 201. I removed from statistical methods from data collection. Neoadjuvant chemotherapy added in the inclusion criteria.

Response 5:

Both IIA and IIB were included in the analysis and I will talk about this in my next paper. Gender differences in groups before PSM (p=0.022) and I corrected. The following is the result of revision, stage II :"The diversity of 1-year OS rate （96.9% VS 97.9%, Log-Rank P=0.650）, 3-year OS rate （89.7% VS 89.7%, Log-Rank P=1.000）, 5-year OS rate （79.4% VS 83.5%, Log-Rank P=0.460）in both groups were not palpable. On the other side, the median PFS were for chemotherapy cycles <9 was 82 months and the median PFS for chemotherapy cycles≥9 has not reached. The outcomes were that, 3-year PFS rate （76.3% VS 81.4%, Log-Rank P=0.379）, 5-year PFS rate （69.1% VS 77.3%, Log-Rank P=0.195）of both two groups were similar, only 1-year PFS rate （82.4%VS 93.8%, Log-Rank P=0.015）proved that chemotherapy cycles≥9 was better than chemotherapy cycles <9 in short-term."

Stage III :"The diversity of 1-year OS rate (91.7% VS 92.5%, Log-Rank P=0.735), 3-year OS rate (67.4% VS 63.6%, Log-Rank P=0.389), 5-year OS rate (47.1% VS 42.5%, Log-Rank P=0.315) in both groups were not significant. On the other side, the median PFS of chemotherapy cycles <9 and chemotherapy cycles≥9 roughly analogous, were 42, 41 months, respectively. The outcomes were that 1-year PFS rate (62.0%VS 80.1%, Log-Rank P<0.001), 3-year PFS rate (44.2% VS 54.5%, Log-Rank P=0.023) of both two groups were dissimilar, except for 5-year PFS rate (38.4% VS 33.9%, Log-Rank P=0.298)."

It should be noted that the meaning of event in Table 2 and Table3 were different, the event in Table 2 represented by death, but in Table 3 the event indicated recurrence or death. It should be noted that the meaning of event in Table 5 and Table6 were different, the event in Table 5 represented by death, but in Table 6 the event indicated recurrence or death.

According to 8th AJCC TNM stage, T4N0M0 was stage II B.

The Chi-square test was used to compare the differences in recurrence, local-regional recurrence, peritoneal metastasis, and distant metastasis between the two groups and the result was analyzed by number of each group, rather than ratio.

I had to admitted that some patients with relapses were unwilling to accomplish chemotherapy cycles and for patients with TNM Stage II (n=412) grouping based on ten variables, inclusion of gender, age at surgery, vascular invasion, nerve invasion, depth of tumor invasion, number of positive lymph nodes, Lauren classification, maximum tumor diameter, type of gastrectomy, and Her-2, with 1:1 nearest-neighborhood propensity score matching (PSM) and without replacement, the caliper value was set to 0.05. patients with

TNM Stage III (n=902) grouping based on eight variables, inclusion of gender, vascular invasion, nerve invasion, depth of tumor invasion, number of positive lymph nodes, Lauren classification, maximum tumor diameter, type of gastrectomy, with 1:1 nearest-neighborhood propensity score matching (PSM) and without replacement, the caliper value was set to 0.05.