

Cover letter

RE: Advances in para-aortic nodal dissection in gastric cancer surgery: A review of research progress over the last decade

Dear Editors and Reviewers,

Thank you very much for your letter and for the reviewers' comments concerning our manuscript entitled "Advances in para-aortic nodal dissection in gastric cancer surgery: A review of research progress over the last decade" (Manuscript ID:55161). It is our honor to receive your reply and reviewers' comments about the manuscript. Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. We have attached revised manuscript for your approval. Point-by-point responses to the reviewers' comments are appended.

We sincerely hope that all these changes fulfill the requirements to make the manuscript acceptable for publication on *World Journal of Clinical Cases*. Please don't hesitate to contact us if you have any questions.

Looking forward to hearing from you.

Thank you and best regards.

Yours sincerely,

Jingyu Deng

Reviewer #1: The authors discussed about the para-aortic nodal dissection in gastric cancer surgery, however, there are several problems in their manuscript and thus their manuscript cannot be accepted in the present form.

1) Their manuscript contains several inaccurate references as follows.

- In table 3, the ACTS-GC study (ref. 71) was listed as report for patients with pathological positivity of PAN, however, it was randomized trial of adjuvant chemotherapy for stage II/III gastric cancer. The population of the study do not include patients with pathologically positive lymph node metastases in PAN area.

Good suggestion. We quite agree with the reviewer's recommendation and we have deleted the the ACTS-GC study in the table.

- Similarly, the JCOG0001 and 0405 (ref. 33 and 72) were phase II trials for extended lymph node metastases. Some of the accrued patients has clinically positive metastasis in PAN area, however, many of the patients in these studies were pathologically negative in PAN area, although the results were acquired after neoadjuvant chemotherapy.

It is a very valuable suggestion. However, JCOG0001 and 0405 both were well-known trials designed for patients with PAN metastasis (no. 16a2/16b1) or bulky lymph nodes. Some patients in these studies were pathologically negative in PAN area, but the incidences of PAN metastasis is not very low as comparing with 1002, which were listed in the Table 3.

- In the PAN section of the manuscript, they stated the dissection of the No.16a2-lat was optional based on the report by Morita et al. (ref.34). But the description about No. 16a2-lat was limited for distal gastrectomy in the report.

This is a good suggestion. The reference is wrong and we have changed the note and added some details in the text.

2) There are too many points of discussion about PAN dissection for gastric cancer in the manuscript. For example, the indication, benefit, and risk of PAND, as well as the regimen and cycle number of neoadjuvant chemotherapies. They should limit the point of discussion in their manuscript.

That's a good suggestion. The main purpose of this article is to explore the progress of PAND for patients with AGC. So we deleted the discussion of regimen and cycle number of neoadjuvant chemotherapies.

3) There are redundant descriptions in the manuscript. For example, the classification of PAN such as No.16a1, No.16a2, No.16b1, and No.16b2 is not necessary in the manuscript because the classification is described in detail in the previous references.

This is a good suggestion. We have deleted the redundant description of the classification of PAN.

Reviewer #2: This review addresses the current problem of surgical oncology - the efficacy of advanced lymph node dissection in the surgical treatment of gastric cancer. After M. Sasako's et al, N Eng J Med, 2008 study, extended lymph node dissection is not included in any standard of surgical treatment for gastric cancer. A review of new scientific topics is needed in this field. The review article is well-structured and balanced. However, it has the following disadvantages:

- Keywords: "para-aortic, lymph node .." – superfluous comma;

Good suggestions. I have deleted the comma in the text.

- Introduction: “ ...the so-called D3 resection ...” - term D3 should be replaced by D2+ (according to Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer 2011; 14: 113-123). In Table 2, page 22 “ ... was significantly lower in D3 dissection, even with similar overall... “ at the same way;

Thanks for your suggestions. We quite agree with the reviewer' s recommendation and we have revised it by using the red colored text.

- Page 8: “PANs can be considered the terminal regional nodes of gastric lymphatic drainage, which can be dissected to avoid the threat of systemic metastases originating from the lymphatic system ... “ it is according to classical theory of William Halsted. But, the possibility of distant lymphogenous metastases or systemic dissemination without metastases in regional lymph nodes should be briefly mentioned;

Thanks for your suggestions. Distant lymphogenous metastases or systemic dissemination without metastases in regional lymph nodes were regarded as haematogenous metastasis, and we haven't seen this circumstance like that PAN metastasis without metastasis of regional lymph nodes before.

- serious comments to Conclusions:

- no words were mentioned about PAND in the conclusions (actually about the main essence of the article).

- “...To date, the CS chemotherapy combined with surgery plus extensive lymphadenectomy is considered the standard means for advanced gastric cancer... “ - only in Japan!

- “In the future, multimodal therapy including the extensive lymphadenectomy synergistically combined with appropriate chemotherapy and or immunotherapy ... “ - does not correspond to the main text of the article, which does not mention immunotherapy in any way. Given all of the above, as well as the lack of conceptually new results on this issue in the current literature, I recommend that after making all the corrections to accept the article for publication, but in World Journal of Gastrointestinal Oncology.

It is a very valuable suggestion. We have changed the description of conclusion and focused on PAND, please check it.

Reviewer #3: This review article was well written by means of thorough literature search in general. I have some comments as follows:

- 1.“Definitely, based on the current conclusions, intraoperative histological biopsy of the abovementioned relevant lymph nodes is feasible and effective to determine whether further PAND is needed”: This strategy is not practical and not accepted.

Thank you very much for the good suggestion. I agree with it and I have changed the inappropriate conclusion by using the red colored text.

- 2.“The 5-year survival of the patients with AGC with PAN metastasis ranges from 13% to 70.3%, as listed in Tables 2 and 3”, “For patients with AGC with positive PANs, the survivals ranged from 13% to 70.3% along with the corresponding treatment, as listed in Tables 2 and 3”: JCOG 9501 study included patients with AGC

without PAN metastasis (only 8.5% of patients had PAN metastasis). The 5-year survival of 70.3% was seen in those who underwent D2+PAND, irrespective of PAN status.

Thanks for your suggestions. We quite agree with the reviewer's recommendation and we have revised the value in the text according to the references of the Table by using the red colored text.

3. In “chemotherapy” and “radiotherapy” section, many studies that had not directly focused on patients with PAN metastasis were included, which would confuse the readers. The authors should have extracted the data about patients with PAN metastasis from these studies, if possible.

It is a very valuable suggestion. We have deleted the studies not directly focused on patients with PAN metastasis.

4.“For example, a phase III trial recommended adjuvant S-1 for patients with stage II or III gastric cancer after surgery with better survival than those with surgery only, and the 3-year overall survival (OS) rate reached 80.1% vs. 70.1% of the surgery only group”, “The most common adverse events of grade 3 or 4 (defined according to the Common Toxicity Criteria of the National Cancer Institute) of the S-1 single application comprised anorexia (6.0%), nausea (3.7%), and diarrhea (3.1%)”, “after preoperative chemotherapy followed by surgery, the relapse-free survival rate can reached as high as over 70% at 3 years by Sakuramoto and ...”: ACTS-GC trial should not be included in this review.

Good suggestion. We feel very sorry for our confusing discription and we have deleted the ACTS-GC trial in this review.

5.Difference in common adverse events among three JCOG trials with similar inclusion criteria but different preoperative chemotherapy regimens should be summarized in additional Table, which might help the readers understand.

Good suggestions. I have summarized it in the Table 4.

6.Each author's first name was unnecessary (see Tables).

Good suggestions. I have deleted the first name in the Table.