RE: Risk analysis of clinical metastasis of the lymph nodes along the proper hepatic artery (Station 12a) for patients with lower-third gastric cancer

Dear Editors and Reviewers,

Thank you very much for your letter and for the reviewers' comments concerning our manuscript entitled "Risk analysis of clinical metastasis of the lymph nodes along the proper hepatic artery (Station 12a) for patients with lower-third gastric cancer" (Manuscript ID: 64676). 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 Gastrointestinal Surgery*. 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 have presented a well written study which will add to the literature about Station 12a lymph node in gastric cancer. However need to add/

modify few aspects:

1. A general description of D2 and D2+ lymphadenectomy will add more depth to the introduction part.

Good suggestion. We quite agree with the reviewer' s recommendation and we have added the description in the table.

2. On page 8 under survival significance of No. 12 a lymph node the authors have mentioned the 5 year survival rate for patients with or without 12a metastasis was 39.5% and 5.6% respectively which seems to be contradictory to the general message provided by the manuscript that no. 12a lymph node metastasis carries a poor prognosis. This needs to be checked and corrected.

We quite agree with the Reviewer's suggestion and feel very sorry about the mistake on this description of the 5-year survival rate. And we have revised the value in the manuscript.

3. There is no mention about survival analysis with respect to adjuvant treatment wither in the form of adjuvant chemotherapy or radiotherapy. Which drugs were used as adjuvant chemotherapy treatment, were the treatment protocols similar in all the patients with 12a metastasis and whether that could have any part to play in the overall survival of the patients. The authors should mention more about adjuvant treatment details when commenting on survival analysis.

What a good question it is. But we feel very sorry for that we had no opportunities to record these details about adjuvant chemotherapy, because majority of patients in this study underwent adjuvant treatment after surgery in their local hospital. More details including drugs and treatment regimens, could not be fully recorded throughout the follow-up, so we did not consider these details in the survival analysis.

4. The authors should comment in the discussion section on whether having no. 12a metastasis changes the management of such cases. Since it is shown that it carries a poor prognosis the authors should comment on the management strategies of the same.

Thank you very much for the good suggestion. There was no consensus on neoadjuvant chemotherapy until 2015 in China. Patients with prior chemotherapy were excluded from this study as indicated by the exclusion criteria between 2003 to 2011. And all enrolled patients with No.12a metastasis had poorer prognosis without preoperative chemotherapy for this study. According to this, preoperative enhanced CT and endoscopic ultrasonography must be performed to evaluate preoperative CT staging, and preoperative chemotherapy should be given to patients with No.12a metastases in order to improve the survival rate of patients. Also, we have added comments in the discussion part of the manuscript.

5. The authors also need to comment on the morbidity of lymphadenectomy.

Good suggestion. There was no chylous fistula for all patients with No.12a lymph node dissection. As we all know, as a common complication for lymphadenectomy, there were three levels of mild, moderate and severe for lymphatic fistula. As well, as the most common complication in this study, mild lymphatic fistula accounted for 20%.

**Reviewer #2**: This topic is interesting. Also, I appreciate the authors' labors. The present manuscript needs some revisions for the publication of "World Journal of Gastroenterology". It is my great honour and pleasure to review such an interesting manuscript. The authors tried to prove that metastasis of No.12a is an independent prognosis factor for gastric cancer (GC) patients with lower third tumor. This study is retrospectively analyzed by the clinical data.

The study design,

1) Preoperative staging

The authors perform R0 gastrectomy for the 147 gastric cancer patients including 18 with No. 12a lymph node metastasis. In these cases, how about the preoperative CT staging ? Are there included, "bulky LN swelling cases" diagnosed, preoperatively ? Usually, for far advanced GC cases, preoperative chemotherapy should be considered. The authors should disclose and discuss the preoperative clinical stage based on CT.

Thank you very much for the good suggestion. However, all enrolled patients were recruited between 2003 to 2011 in this study, then there was no concept of bulky lymph nodes, which was introduced in 2017, only with the concept of lymph node metastasis that lymph nodes enlarged or fused or greater than 1cm in diameter. So, we were not entirely sure how many patients have bulky lymph node metastasis.

As this is a retrospective study between 2003-2011, and there was no consensus on neoadjuvant chemotherapy until 2015 in China. And then, the preoperative chemotherapy was included in the treatment guidelines for patients with advanced gastric cancer. As indicated by the exclusion criteria, patients with prior chemotherapy, radiotherapy, or endocrine therapy for any malignancies were excluded for this study. As we all know, preoperative CT staging was used to determine the methods of preoperative treatment. Due to the exclusion of patients with preoperative therapies, we didn't record the data about preoperative CT staging, but only with clinicopathologic data for patients including the depth of serosa invasion, enlargement of lymph nodes, or extranodal soft tissue invasion, and so on.

2) Operative procedure

The authors should comment the operative proceduress; laparoscopic, robotic, or laparotomy approaches, respectively. This is important, oncologically.

It is a very valuable suggestion. Because all enrolled patients underwent gastrectomy between June 2003 and March 2011. There was no selection of robotic gastrectomy for patients at that time, and the laparoscopic operation was not common for patients with advanced GC. Therefore, almost all patients underwent open surgery. And I have added it in the manuscript.

3) Extranodal soft tissue invasion

Anatomically, No.12a LN is located very near lower-third GC. The authors should clarify that the extranodal soft tissue invasion is differentially diagnosed from main tumor direct invasion, peritoneal dissemination, etc. Some typical histopathological photos are needed for the readers.

We are quite in favor of your point of view. Extranodal soft tissue invasion, as a histological term, was defined as the presence of tumor cells in an isolated tumor

nodule between extranodal adipose tissues that was discontinuous with either the primary lesion and beyond the capsule of the lymph node (Figure 1). And we have added the concept in the “Material and Methods” part of the manuscript.

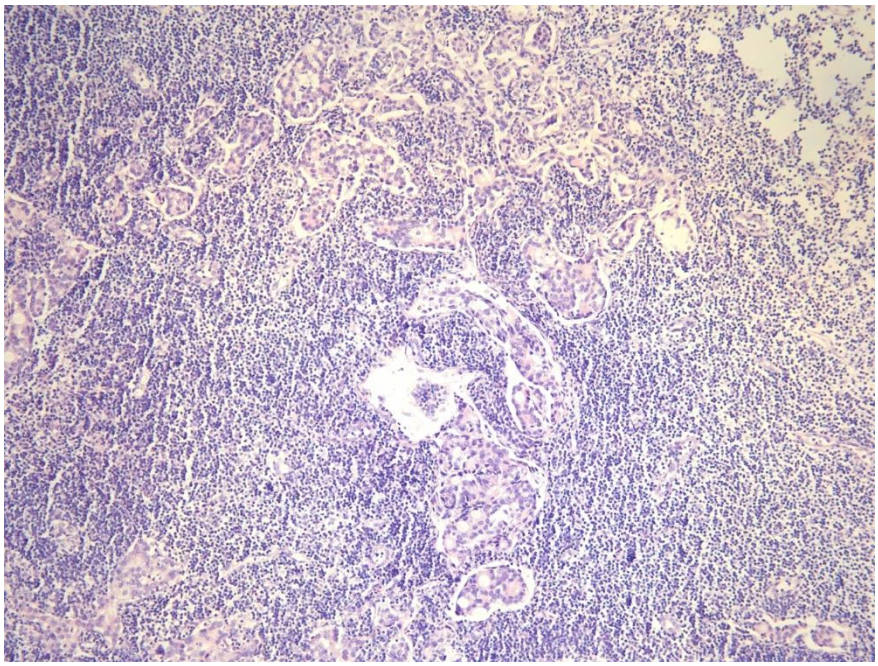

Figure 1. tumor cells deposit in adipose tissue discontinuous with the primary lesion and beyond the capsule of the lymph node (H&E, original magnifications ×40)

4) There are some limitations in this study as below;

1. The sample size is small.
2. This data is only retrospectively assessed by a single institute analysis.

It is very reasonable. We quite agree with the Reviewer’s suggestion. This study does have some limitations. The small sample size of included patients from a single institute analysis may constrain the number of patients with detection of other regional lymph nodes. Moreover, the number of patients with 12a metastasis was remarkably small. Thus, obtaining additional significant outcomes, including survival benefit and safety of No.12a lymph node dissection for GC patients, is difficult. Therefore, multicenter studies with large sample size are needed to investigate the clinical application of No.12a dissection and establish a more precise strategy of lymphadenectomy for advanced gastric cancer.

This topic is interesting. Also, I appreciate the authors’ labors. The present manuscript needs some revisions for the publication of “World Journal of Gastroenterology”.