Dear Editor,

Please find enclosed the edited manuscript in word format (file name 40553 revised manuscript .doc).

Title: Predictive factors for lymph node metastasis and defining a subgroup treatable for LLND after ESD in poorly differentiated early gastric cancer

Manuscript No: 40553

We have revised the manuscript carefully and all changes are highlighted in the revised version of the manuscript, according to the comments and suggestions of reviewers and editor, and responded, point by point to, the comments as listed below.
I would like to re-submit this revised manuscript to your journal, and hope it is acceptable for publication in the journal.
Looking forward to hearing from you soon.
Yours sincerely
Dengxiang Liu

Replies to Reviewers and Editor
First of all, we thank both reviewers and editor for their positive and constructive comments and suggestions.

Reviewer #1 This manuscript is about a retrospective study evaluating predictive factors for lymph node metastasis in poorly differentiated early gastric cancer (pd-EGC) as well as the potential relative benefit of the combination of “endoscopic submucosal dissection(ESD)” plus “laparoscopic lymph node dissection (LLND)” to avoid total gastrectomy for a suitable subgroup. The title reflects the main hypothesis of the manuscript. As we know, ESD is a recommended endoscopic excisional treatment for early-stage gastric cancer (EGC) when the lesion is ≤2 cm in diameter,

is shown on histopathology to be well or moderately differentiated, does not penetrate beyond the superficial submucosa, does not exhibit LVI and has clear margins. As the authors indicated also, additional therapy by gastrectomy and lymphadenectomy should be considered for patients with pd-EGC as a standard treatment. But among them, some patients with pd-EGC have N0 disease and they may be underwent "unnecessary" gastrectomy. In the patient population of this study, they found 15.2% (21/138) lymph node positivity. According to univariate and multivariate analyses, three independent risk factors for lymph node metastasis were identified in the study. According to Figure 1, the percentage of patients who have none of these 3 risk factors and have N0 disease is 56% (77/138). This is a considerable value. Authors concluded also that if patients with pd-EGC have one, two or three risk factors, lymph node positivity ratios are 7.7%, 47.6% and 64.3% respectively. Therefore, this study suggests the existence of a subgroup of patients with pdEGC to prevent overtreatment. Although its retrospective nature, this article brings new opinion for future multicentric prospective trials to change daily practice for a subgroup of patients with pd-EGC. My critics and recommendations:

1. I could not find any explanation of Figure 2 in the manuscript. It must be take place in the manuscript.

Response: Thank you for raising this issue. We have noticed that, and added some explanation of Figure 2 in the manuscript.

2. Some more comparative information (benefits and risks, adverse effects such as perforation rate, R1 resection ratio) of the proposed "ESD+LLND" versus "standard gastrectomy+lymphadenectomy" from the literature should be added to the manuscript. I believe that this manuscript should be addressed not only to surgeons, to the other readers like medical oncologists and gastroenterologists too.

Response: Thank you for raising this issue. I have noticed that, and added some information in the discussion. Some comparative information has been discussed in detail in the fifth paragraph of the discussion

3. The abbreviations LLND and ESD should be written open first even in the Title

Response: We accept your suggestion. We have noticed that, and made some changes in the title.

4. Word replacements; a. In pp 4, line 11-12, “a standard” in place of “an essential”. b. In pp 6, line 21, “multiple” in place of “multitude”. c. In pp 8, line 13, “Endoscopic” in place of “Endoscope”. After these corrections, this manuscript worth publishing.

Response: Thank you for raising this issue. We have noticed that, and replaced these wrong words in the manuscript.

Reviewer #2: Comments to the author The relevance of the research topic is unconditional, since the possibility of lymph node metastasis is the most important factor to consider when deciding whether to apply the minimally invasive therapies. Unfortunately, the authors did not provide any new data concerning the risk prediction of lymph node metastasis (LNM) in patients with poorly differentiated early gastric cancer (EGC). The manuscript presented for consideration only confirms the results of numerous studies by other authors (Shin N et al, 2014; Goto A et al, 2017; Lee IS, et al., 2016; Guo CG, et al., 2016) and results of own research done earlier (Li H et al, 2016). At the same time, in this manuscript the algorithm of "the therapeutic strategy for cases with poorly differentiated EGC" was proposed, that can be useful in clinical practice. The main remarks on the manuscript are as follows:

1. Title. The title reflects the main subject of the manuscript, but contains the abbreviations.

Response: Thank you for raising this issue. We have noticed that, and made some changes in the title.

2. Abstract. Abstract summarizes and reflects the work described in the manuscript, but has the following drawbacks: The term of "lymphatic vessel involvement" was used incorrectly - The abbreviation "LVI" has no decoding.

Response: Thanks for your comments and suggestion. We have noticed that, and made some changes in the abstract.

3. In Conclusions: The correctness of the phrase "LLND may lead to the elimination of ESD in poorly differentiated EGC patients with a potential risk of LNM" raises doubts. Most likely, the authors had in mind: "ESD with laparoscopic LLND may lead to the elimination of" unnecessary "gastrectomy."

Response: Thanks for your comments and suggestion. We have changed the sentence of the conclusions into “ESD with LLND may lead to the elimination of unnecessary gastrectomy in poorly differentiated EGC.”

4. Key words. The key words reflect the focus of the manuscript, but the key word ""Poorly differentiated early gastric cancer" " seems incorrect.

Response: Thank you for raising this issue. We have changed the key word into “Poorly differentiated cancer”

5. Background. - The method of "Endoscopic submucosal dissection in early gastric cancer" has been used for more than 20 years and it can hardly be called "a newly developed endoscopic mucosal resection (EMR) technique" (Torii A et al, 1994; Oda I et al, 2006; Tanabe S et al, 2017).

Response: We accept your suggestion. We have corrected the sentence in the background.

6. The authors practically do not describe the present status of the problem, in spite of the fact that a large clinical experience of predicting the risk of LNM has been accumulated (Shin N et al, 2014; Goto A et al, 2017; Lee IS, et al., 2016; Guo CG, et al., 2016).

Response: Thanks for your comments and suggestion. We have noticed that, and made some changes in the text.

7. Patients The average age of patients is usually given along with the standard deviation.

Response: Thanks for your comments and suggestion. We have noticed that, and made some changes in the text.

8. Dissection and classification of lymph nodes - It is not clear what authors understand by the "lymphatic vessel involvement". The presence of lymphovascular invasion (LVI) is usually determined in a tumor tissue. The tumor emboli in vessels of lymph nodes are regarded as metastases. This retrospective study could be carried out only on archival paraffin blocks of the surgical specimens. Therefore, the main clinical and pathological data could be obtained only from archival documents: surgical report, conclusions of the pathologist, patient card. However, such information is not provided in this section.

Response: Thank you for raising this issue. We have corrected the sentence in the text. We have noticed that, and made some changes in the “Dissection and classification of lymph nodes”.

9. The method of detecting metastases in lymph nodes is unclear. Usually, the staining with hematoxylin-eosin or immunohistochemical staining with cytokeratins is used.

Response: Thank you for raising this issue. Lymph nodes of each case were meticulously dissected fromthe enbloc specimens. After careful review of specimens, a experienced surgeon gave the classification of the dissected lymph nodes. After that, the lymph nodes were sectioned and the histopathologic, and immunohistochemical features were detected by eosin and hematoxylin staining and immunohistochemistry. Pathological examination for metastasis and lymphatic vessel involvement was detected by immunohistochemistry with D2-40.

10. Results. The authors most likely misunderstand the term "Lymphatic vessel involvement". In the presented study, "Lymphatic vessel involvement - 21 cases" means the same as "Lymph node metastasis - 21 cases".

Response: Thank you for raising this issue. In the presented study， among the 138 patients who underwent radical gastrectomy, 21 cases had lymph node metastasis and 16 cases had Lymphatic vessel involvement (Table 1).

11. Discussion. The authors discuss the problem of predicting the risk of LNM playing a vital role in choosing ESD for EGC. Based on the obtained data, the specific recommendations on the therapeutic strategy for cases with poorly differentiated EGC are proposed. However, in this part of the manuscript there are also a number of significant shortcomings: Authors sometimes use incorrect links to references. For example, «The dominance of ESD over surgery is less invasive, less expensive and better preserves physiological function [17–18].

Response: Thanks for your comments and suggestion. I have noticed that, and made some changes in the reference (17-18).

12. A number of statements are formulated incorrectly. For example: - «The factors that can help to predict LNM has not been verified by previous studies.». However, there are a large number of earlier studies that have obtained absolutely similar results (Shin N et al, 2014, Sunq CM et al, 2010 and other). - ".. gastrectomy with lymphadenectomy is preferable ... when number of factors is one, two or three". However, if there is only one factor, LNM rate is only 7.7%. In these cases, ESM can also be performed. This surgery does not affect on the long-term outcomes in patients with EGC, but requires monitoring of patients (Min BH et al, 2015). - «.the combination of ESD and LLND may be an effective, minimally invasive treatment and benefical for long term quality of life in poorly differentiated EGC patients». However, the authors of this method suggest using "the combination of ESD and LLND" in patients with a potential risk of LNM regardless of tumor differentiation degree (Abe N, et al, 2011). (Abe N, et al, 2011). To exclude these shortcomings, the authors should more clearly and correctly formulate their conclusions.

Response: Thank you for raising this issue. It is a limitation of the discussion. We have added some words describe the limitations of the study in the discussion section.

According to our study, we would propose a treatment strategy for patients with poorly differentiated EGC patients. We carried out a stratified analysis based on the risk factors. For only one factor, we recommend direct radical gastrectomy. In other words, we all recommend radical gastrectomy for any of the risk factors with poorly differentiated EGC patients.

13. Illustrations and tables. Figures 1 and 2 have no abbreviations decryption.
Response: Thank you for raising this issue. We have noticed that, and made some changes in the Figures 1 and 2.

14. References. Some important references to similar publications of other authors, as well as their own publications are not given. For example: Shin N, Jeon TY, Kim GH, Park DY. Unveiling lymph node metastasis in early gastric cancer. Unveiling lymph node metastasis in early gastric cancer. World J Gastroenterol. 2014 May 14;20(18):5389-95. doi: 10.3748/wjg.v20.i18.5389 Goto A, Nishikawa J, Hideura E, Ogawa R, Nagao M, Sasaki S, Kawasato R, Hashimoto S, Okamoto T, Ogihara H, Hamamoto Y, Sakaida I. Lymph node metastasis can be determined by just tumor depth and lymphovascular invasion in early gastric cancer patients after endoscopic submucosal dissection. Eur J Gastroenterol Hepatol. 2017 Dec;29(12):1346-1350. doi: 10.1097/MEG.0000000000000987. Lee IS, Lee S, Park YS, Gong CS, Yook JH, Kim BS. Applicability of endoscopic submucosal dissection for undifferentiated early gastric cancer: Mixed histology of poorly differentiated adenocarcinoma and signet ring cell carcinoma is a worse predictive factor of nodal metastasis. Surg Oncol. 2017 Mar;26(1):8-12. doi: 10.1016/j.suronc.2016.12.001 Guo CG, Chen YJ, Ren H, Zhou H, Shi JF, Yuan XH, Zhao P, Zhao DB, Wang GQ. A nomogram for predicting the likelihood of lymph node metastasis in early gastric signet ring cell carcinoma: A single center retrospective analysis with external validation. Medicine (Baltimore). 2016 Nov;95(46):e5393. Li H, Huo ZB, Chen SB, Li H, Wu DC, Zhai TS, Xiao QH, Wang SX, Zhang LL. Feasibility study on expanded indication for endoscopic submucosal dissection of intramucosal poorly differentiated early gastric cancer.

World J Gastroenterol. 2016 Aug 7;22(29):6736-41. doi: 10.3748/wjg.v22.i29.6736
There are many errors in links to references. Authors should carefully check all links.
Response: Thanks for your comments and suggestion. It is a limitation of the references. I have noticed that, and added above important references in the references

15. Style, grammar, and spelling Correction of stylistic errors is necessary.
Response: Thanks for your comments and suggestion. We have made the manuscript edited by a native English speaker. We sincerely hope that this revised version will meet the language requirements.

Reviewer #3: In the abstract results section, authors should given patients demographic features. Pagients' demographics and pathological features should given as a table.
Response: Thanks for your comments and suggestion. It is a limitation of the discussion. We have added some words describe the limitations of the study in the text.

Reviewer #4: Fig. 1 should be accompanied with a chart.
Response: We accept your suggestion. We have changed Figure 1 to Table 3 in the text.

Reviewer #5: This retrospective study deals with an important problem - the expansion of indications to a non-invasive organ-preserving surgical treatment for early gastric cancer.The authors have made a successful attempt to expand the indication for such treatment at the expense of patients with low-differentiated adenocarcinoma, which is not the standard today. nteresting results of multivariate analisys have been obtained. But it is very important that the authors propose a treatment algorithm for early low-differentiated gastric cancer. Congratulations to the authors with successful research. Although the results obtained require confirmation in prospective randomized trials.

Response: Thank you very much for the reviewers' approval of this article.