



PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Oncology

Manuscript NO: 40553

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

Reviewer’s code: 03004570

Reviewer’s country: Turkey

Science editor: Jin-Lei Wang

Date sent for review: 2018-07-03

Date reviewed: 2018-07-07

Review time: 4 Days

| SCIENTIFIC QUALITY | LANGUAGE QUALITY | CONCLUSION | PEER-REVIEWER STATEMENTS |
|---|---|--|---|
| <input type="checkbox"/> Grade A: Excellent | <input type="checkbox"/> Grade A: Priority publishing | <input type="checkbox"/> Accept | Peer-Review: |
| <input type="checkbox"/> Grade B: Very good | <input checked="" type="checkbox"/> Grade B: Minor language | (High priority) | <input type="checkbox"/> Anonymous |
| <input checked="" type="checkbox"/> Grade C: Good | polishing | <input type="checkbox"/> Accept | <input type="checkbox"/> Onymous |
| <input type="checkbox"/> Grade D: Fair | <input type="checkbox"/> Grade C: A great deal of | (General priority) | Peer-reviewer’s expertise on the |
| <input type="checkbox"/> Grade E: Do not | language polishing | <input checked="" type="checkbox"/> Minor revision | topic of the manuscript: |
| publish | <input type="checkbox"/> Grade D: Rejection | <input type="checkbox"/> Major revision | <input type="checkbox"/> Advanced |
| | | <input type="checkbox"/> Rejection | <input checked="" type="checkbox"/> General |
| | | | <input type="checkbox"/> No expertise |
| | | | Conflicts-of-Interest: |
| | | | <input type="checkbox"/> Yes |
| | | | <input checked="" type="checkbox"/> No |

SPECIFIC COMMENTS TO AUTHORS

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)”



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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. 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. 3. The abbreviations LLND and ESD should be written open first even in the Title, 4. Word replacements; a.



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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.

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

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- No



PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Oncology

Manuscript NO: 40553

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

Reviewer’s code: 03270609

Reviewer’s country: Russia

Science editor: Jin-Lei Wang

Date sent for review: 2018-07-03

Date reviewed: 2018-07-08

Review time: 5 Days

| SCIENTIFIC QUALITY | LANGUAGE QUALITY | CONCLUSION | PEER-REVIEWER STATEMENTS |
|---|--|--|---|
| <input type="checkbox"/> Grade A: Excellent | <input type="checkbox"/> Grade A: Priority publishing | <input type="checkbox"/> Accept | Peer-Review: |
| <input type="checkbox"/> Grade B: Very good | <input type="checkbox"/> Grade B: Minor language | (High priority) | <input type="checkbox"/> Anonymous |
| <input type="checkbox"/> Grade C: Good | polishing | <input type="checkbox"/> Accept | <input type="checkbox"/> Onymous |
| <input checked="" type="checkbox"/> Grade D: Fair | <input checked="" type="checkbox"/> Grade C: A great deal of | (General priority) | Peer-reviewer’s expertise on the |
| <input type="checkbox"/> Grade E: Do not | language polishing | <input type="checkbox"/> Minor revision | topic of the manuscript: |
| publish | <input type="checkbox"/> Grade D: Rejection | <input checked="" type="checkbox"/> Major revision | <input type="checkbox"/> Advanced |
| | | <input type="checkbox"/> Rejection | <input checked="" type="checkbox"/> General |
| | | | <input type="checkbox"/> No expertise |
| | | | Conflicts-of-Interest: |
| | | | <input type="checkbox"/> Yes |
| | | | <input checked="" type="checkbox"/> No |

SPECIFIC COMMENTS TO AUTHORS

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



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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: Title. The title reflects the main subject of the manuscript, but contains the abbreviations. 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. - 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." Key words. The key words reflect the focus of the manuscript, but the key word "'Poorly differentiated early gastric cancer" " seems incorrect. 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). 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). - The section contains erroneous links to some references. Methods. Patients The average age of patients is usually given along with the standard deviation. Dissection and classification of lymph nodes - It is not clear what authors understand by the "lymphatic vessel involvement". The presence of



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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. - The method of detecting metastases in lymph nodes is unclear. Usually, the staining with hematoxylin-eosin or immunohistochemical staining with cytokeratins is used. 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". 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].» 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 beneficial for long term quality of life in poorly differentiated EGC



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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. Illustrations and tables. Figures 1 and 2 have no abbreviations decryption. 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. Style,



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grammar, and spelling Correction of stylistic errors is necessary.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Oncology

Manuscript NO: 40553

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

Reviewer’s code: 02624356

Reviewer’s country: Turkey

Science editor: Jin-Lei Wang

Date sent for review: 2018-07-03

Date reviewed: 2018-07-10

Review time: 6 Days

| SCIENTIFIC QUALITY | LANGUAGE QUALITY | CONCLUSION | PEER-REVIEWER STATEMENTS |
|--|--|--|---|
| <input type="checkbox"/> Grade A: Excellent | <input checked="" type="checkbox"/> Grade A: Priority publishing | <input type="checkbox"/> Accept | Peer-Review: |
| <input checked="" type="checkbox"/> Grade B: Very good | <input type="checkbox"/> Grade B: Minor language polishing | (High priority) | <input checked="" type="checkbox"/> Anonymous |
| <input type="checkbox"/> Grade C: Good | | <input type="checkbox"/> Accept | <input type="checkbox"/> Onymous |
| <input type="checkbox"/> Grade D: Fair | <input type="checkbox"/> Grade C: A great deal of language polishing | (General priority) | Peer-reviewer’s expertise on the |
| <input type="checkbox"/> Grade E: Do not publish | <input type="checkbox"/> Grade D: Rejection | <input checked="" type="checkbox"/> Minor revision | topic of the manuscript: |
| | | <input type="checkbox"/> Major revision | <input checked="" type="checkbox"/> Advanced |
| | | <input type="checkbox"/> Rejection | <input type="checkbox"/> General |
| | | | <input type="checkbox"/> No expertise |
| | | | Conflicts-of-Interest: |
| | | | <input type="checkbox"/> Yes |
| | | | <input checked="" type="checkbox"/> No |

SPECIFIC COMMENTS TO AUTHORS

In the abstract results section, authors should given patients demographic features. Patients'demographics and pathological features should given as a table.



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PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Oncology

Manuscript NO: 40553

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

Reviewer’s code: 03270518

Reviewer’s country: Italy

Science editor: Jin-Lei Wang

Date sent for review: 2018-07-03

Date reviewed: 2018-07-10

Review time: 7 Days

| SCIENTIFIC QUALITY | LANGUAGE QUALITY | CONCLUSION | PEER-REVIEWER STATEMENTS |
|---|---|--|---|
| <input type="checkbox"/> Grade A: Excellent | <input type="checkbox"/> Grade A: Priority publishing | <input type="checkbox"/> Accept | Peer-Review: |
| <input type="checkbox"/> Grade B: Very good | <input checked="" type="checkbox"/> Grade B: Minor language | (High priority) | <input type="checkbox"/> Anonymous |
| <input checked="" type="checkbox"/> Grade C: Good | polishing | <input type="checkbox"/> Accept | <input checked="" type="checkbox"/> Onymous |
| <input type="checkbox"/> Grade D: Fair | <input type="checkbox"/> Grade C: A great deal of | (General priority) | Peer-reviewer’s expertise on the |
| <input type="checkbox"/> Grade E: Do not | language polishing | <input checked="" type="checkbox"/> Minor revision | topic of the manuscript: |
| publish | <input type="checkbox"/> Grade D: Rejection | <input type="checkbox"/> Major revision | <input type="checkbox"/> Advanced |
| | | <input type="checkbox"/> Rejection | <input checked="" type="checkbox"/> General |
| | | | <input type="checkbox"/> No expertise |
| | | | Conflicts-of-Interest: |
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SPECIFIC COMMENTS TO AUTHORS

Fig. 1 should be accompanied with a chart.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Oncology

Manuscript NO: 40553

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

Reviewer's code: 03017458

Reviewer's country: Ukraine

Science editor: Jin-Lei Wang

Date sent for review: 2018-07-03

Date reviewed: 2018-07-11

Review time: 8 Days

| SCIENTIFIC QUALITY | LANGUAGE QUALITY | CONCLUSION | PEER-REVIEWER STATEMENTS |
|--|---|--|---|
| <input type="checkbox"/> Grade A: Excellent | <input type="checkbox"/> Grade A: Priority publishing | <input type="checkbox"/> Accept | Peer-Review: |
| <input checked="" type="checkbox"/> Grade B: Very good | <input checked="" type="checkbox"/> Grade B: Minor language | (High priority) | <input checked="" type="checkbox"/> Anonymous |
| <input type="checkbox"/> Grade C: Good | polishing | <input checked="" type="checkbox"/> Accept | <input type="checkbox"/> Onymous |
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| <input type="checkbox"/> Grade E: Do not | language polishing | <input type="checkbox"/> Minor revision | topic of the manuscript: |
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| | | <input type="checkbox"/> Rejection | <input type="checkbox"/> General |
| | | | <input type="checkbox"/> No expertise |
| | | | Conflicts-of-Interest: |
| | | | <input type="checkbox"/> Yes |
| | | | <input checked="" type="checkbox"/> No |

SPECIFIC COMMENTS TO AUTHORS

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



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the expense of patients with low-differentiated adenocarcinoma, which is not the standard today. Interesting results of multivariate analysis 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.

INITIAL REVIEW OF THE MANUSCRIPT

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