



ESPS PEER-REVIEW REPORT

COMMENTS TO AUTHORS (reviewer 1)

The authors have written a thoughtful and comprehensive review of the analysis of predictive factors affecting the incidence of lymph node positivity in early gastric cancer, and what factors increase the risk of positive nodal involvement. The English and typographical errors require some correction. The graphic figures outline a treatment algorithm; this should be more clearly stated in the manuscript text. The summarized literature does not lead to clear treatment guidelines in the text. Specific comments are outlined below: Page 7: Pre and postoperative “values” is a poor choice of phrase. What are “receiver operating characteristics,” this is not defined clearly? It should clearly state that these assessments are done likely in EMR or ESD specimens, or not. Page 7: It states that molecular targeting is being studied, and this is followed by a litany of clinical factors. Light microscopy findings are not typically indicative of a molecular target, and this description should be limited to comments on IHC study of EBV, E-cadherin, and VEGF. The authors need to be careful to specify whether or not the listed factors have been validated in other clinical studies. Page 8: Is there really any utility or easy application of the “metastasis formula?” Any statements here need to be explained and linked to the Figure graphics with clearly treatment guidelines specified or proposed. Page 9 and on: A clear decision pathway and algorithm needs to be articulated here. Page 10: What is ICG and IREE? Page 13: Conclusion: More clear statements here are made, but again a clear treatment algorithm needs to be articulated or proposed.

Answer to reviewer 1

I am very pleased to see your thoughtful comments. I would like to reply my answers as follows.

Q1. Pre and postoperative “values” is a poor choice of phrase.

→Thank you for your comment. We exchanged the word “values” to “parameters”.

Q2. About “receiver operating characteristics,”

→The accuracy of the test depends on how well the test separates the group being tested into those with and without the disease in question. Accuracy is measured by the area under the ROC curve. An area of 1.0 represents a perfect test; an area of 0.5 represents a worthless test. A rough guide for classifying the accuracy of a diagnostic test is the traditional academic point system. In this point, the sentences (P6) **“As a result, produced areas under the ROC curve made of postoperative parameters including pathological data was 0.824. However, the area under the ROC curve made of preoperative factors obtained from CT or endoscopic examination was 0.660. Hence, they concluded that there are limitations in preoperative predictions of the presence of LN metastasis for EGC.”** mean that postoperative parameters are more worthwhile as compared to preoperative parameters as to LN metastasis.

The objective patients and method of the article (Nakagawa M et al.P6) were 1,042 patients with early gastric cancer who underwent gastrectomy with lymphadenectomy.

Q3. About “molecular targeting” (P8)

→Thank you for your appropriate comment. We exchange the sentence to “Immunohistochemical (IH) research is also useful for predicting LN metastasis.”

Q4. “Is there really any utility or easy application of the “metastasis formula?” Any statements here need to be explained and linked to the Figure graphics with clearly treatment guidelines specified or proposed. Page 9 an on: A clear decision pathway and algorithm needs to be articulated here.”

→We added explanation for the proposed algorithm which predicts lymph node metastasis. The added explanations for Fig.1 and Fig.2 are follows. It is written in green thick letter in P9 and 10.

“This flow chart is indicating that if resected tumor through ESD invaded 500 microns below the muscularis mucosae, the LN metastasis predicting score is available. $Y>0$ indicates that the tumor in question would be prone to lymph node metastasis. We defined patients who are satisfied with $Y>0$ as a high-risk group (HRG) for lymph node metastasis and $Y<0$ patients as a low-risk group (LRG) for lymph node metastasis. The flow chart means patients with HRG should undergo additional conventional gastrectomy. However, we think that less invasive treatment like as SNNS is more desirable for patients with LRG.”

→Added explanation as to Fig.2 is as follows.

“Lymphoid infiltration and the presence of lymphatic system invasion were scored as follows: +2 for lymphatic system invasion and -2 for involvement of lymphocystic infiltration, which was considered as a LN metastasis-inhibiting parameter. Next five pathological factors [minor axis length ≥ 2 cm, submucosal invasion depth $\geq 2,000$ microns, histological classification (undifferentiated) of submucosal cancer at the site of invasion, ulceration or scar in the lesion, and venous invasion] were scored +1 each when present. They concluded that a patient with total score 3 and more should be treated as high risk for LN metastasis and such patients are recommended to undergo additional gastrectomy. On the other hand, patients with total score less than 3 should be considered as low risk for LN metastasis and they don’t need to undergo additional gastrectomy.”

Q5. “What is ICG and IREE?”

→ICG is indocyanine green. We usually use this reagent to estimate potential function of liver. Recently, the reagent has been available for sentinel node navigation surgery as a tracer.

The added explanation for IREE is as follows. It is written in green thick letter in P11 and 12.

“Infrared ray has a wave length of around 805nm. It is able to penetrate fatty tissues up to a depth from 3 to 5 mm. In brief, before the ICG injection, the gastrocolic ligament is opened using ultrasonic coagulation incision device without disrupting the gastro-epiploic vessels. After that 0.5 ml ICG (5 mg/ml; Diagnogreen; Daiichi Pharmaceutical, Tokyo, Japan) is injected endoscopically in four points of the submucosa surrounding the tumor with an endoscopic puncture needle. 20 minutes after the injection, SN’s stained with ICG were observed with the naked eye and with IREE (Olympus Optical, Tokyo, Japan).”

Q6. “Conclusion (P14): More clear statements here are made, but again a clear treatment algorithm needs to be articulated or proposed.”

→Thank you for your constructive opinion. We changed conclusion as follows.

“When we predict LN metastasis for EGC, we need at least pathological information derived from resected tumor through ESD. In particular, lymphovascular invasion, tumor depth and tumor size are the strongest LN metastasis predicting parameters for EGC. Basic strategy of additional treatment after ESD for patients with EGC is conventional gastrectomy. However, providing less invasive surgery such as SNNS for patients with EGC has potentiality to improve the quality of life of patients after surgery by preserving gastric function as compared to conventional gastrectomy.”

COMMENTS TO AUTHORS (reviewer 2)

An interesting article in the field. In my opinion it could be published but author should give more complete and detailed explanations about the proposed score and the results of the pilot study to validate it. It would be interesting especially in order to accept the proposed algorithm.

Answer to reviewer 2

Q1. “the proposed score and the results of the pilot study to validate it.”

→Thank you for your constructive opinion. I added explanation for the proposed algorithm which predicts lymph node metastasis. The added explanation about Fig.1 is follows. It is written in green thick letter in P9 and 10.

“This flow chart is indicating that if resected tumor through ESD invaded 500 microns below the muscularis mucosae, the LN metastasis predicting score is available. $Y>0$ indicates that the tumor in question would be prone to lymph node metastasis. We defined patients who are satisfied with $Y>0$ as a

high-risk group (HRG) for lymph node metastasis and Y<0 patients as a low-risk group (LRG) for lymph node metastasis. The flow chart means patients with HRG should undergo additional conventional gastrectomy. However, we think that less invasive treatment like as SNNS is more desirable for patients with LRG.”

→Added explanation as to Fig.2 is as follows.

“Lymphoid infiltration and the presence of lymphatic system invasion were scored as follows: +2 for lymphatic system invasion and -2 for involvement of lymphocystic infiltration, which was considered as a LN metastasis-inhibiting parameter. Next five pathological factors [minor axis length \geq 2cm, submucosal invasion depth \geq 2,000 microns, histological classification (undifferentiated) of submucosal cancer at the site of invasion, ulceration or scar in the lesion, and venous invasion] were scored +1 each when present. They concluded that a patient with total score 3 and more should be treated as high risk for LN metastasis and such patients are recommended to undergo additional gastrectomy. On the other hand, patients with total score less than 3 should be considered as low risk for LN metastasis and they don’t need to undergo additional gastrectomy.”

Q2. “the results of the pilot study to validate it”

→The validation study for Fig. 1 is shown that sensitivity and specificity rates were 70% and 61.6%, respectively. However, regarding as Fig.2, we could not find any result of validation study. In this point, we definitely need further validation study for metastasis predicting score.

COMMENTS TO AUTHORS (reviewer 3)

This paper is an interesting review article concerning the prediction of lymph node metastasis and sentinel node navigation surgery for patients with early-stage gastric cancer. The authors precisely evaluated most of the literatures and concluded that CG-positive lymphatic basin dissection by SNNS with IREE seems to be an adequate method of lymph node dissection. However, there are some issues to be clarified. 1. In this paper, there are several mistakes of font or grammar. 2. The authors stated the sensitivity and specificity of SNNS but the authors should mention if the subject is sentinel node positive and the role of either completion lymphadenectomy or observation with nodal ultrasound. 3. In Figure 3 the IRRE should be corrected 4. Is there really the validity of scoring system that mentioned in Figure 2 and 1, it should be clearly stated and explained with statistical approach. 5. In page 7, “study showed that the 44 sensitivity and specificity rates were 70% and 61.6%, respectively [28].” The 44?

Answer to reviewer 3

Thank you for your reasonable and thoughtful comments. I would like to reply my answers as follows.

Q1. “In this paper, there are several mistakes of font or grammar.”

→I am very sorry. Regarding to my English skill, I completely agree with your opinion and I asked semi-native speaker of my colleague to check my article.

Q2. “The authors stated the sensitivity and specificity of SNNS but the authors should mention if the subject is sentinel node positive and the role of either completion lymphadenectomy or observation with nodal ultrasound.”

→I would like to explain our procedure of SNNS for early gastric cancer. Before SNNS, we necessarily conduct EUS in order to investigate depth of tumors. However, we do not estimate size of LN around tumors. Because we know the size of LN is not necessarily associated with LN metastasis. Most important thing is depth of tumor. If depth of tumor is within submucosa, we believe it is good indication for SNNS.

Q3. “In Figure 3 the IRRE should be corrected”

→I appreciate your comment. I corrected the ward IRRE to IREE.

Q4. “Is there really the validity of scoring system that mentioned in Figure 2 and 1, it should be clearly stated and explained with statistical approach”

→The validation study for Fig. 1 was shown that sensitivity and specificity rates were 70% and 61.6%, respectively. However, regarding as Fig.2, we could not find any result of validation study. In this point, we definitely need further validation study.

→The statistical method used in Fig.1 is linear discriminant analysis. Explanation for linear discriminant analysis (LDA) is as follows.

LDA is closely related to analysis of variance (ANOVA) and regression analysis, which also attempt to express one dependent variable as a linear combination of other features or measurements. LDA works when the measurements are made by independent variables.

A6. “In page 9, “study showed that the 44 sensitivity and specificity rates were 70% and 61.6%, respectively [28].” The 44?”

→Thank you for your comment. It was my mistake. I removed the “44” .