

Manuscript NO: 70329

Title: Long-term outcomes of endoscopic submucosal dissection and surgery for undifferentiated intramucosal gastric cancer regardless of size

We would like to thank the reviewers for their time and valuable comments. We have checked all their comments and answered them one by one as listed below. This response letter was also grammatically edited by a native speaker (Editage for English language editing, www.editage.com)

1. Peer-review report

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors:

The authors investigated the long-term outcomes of endoscopic submucosal dissection and surgery for undifferentiated intramucosal gastric cancer regardless of size. This is a valuable article on a very current topic. Unfortunately, it is not a prospective study, but it is appropriate to verify this topic in a retrospective study with propensity score matching. I, the reviewer, especially like the fact that the author presents honest data. It should be published in the World Journal of Gastroenterology. Unfortunately, there are some points that need to be corrected and some considerations that should be added. Please refer to the following.

1. Please review and check Figure 2. In legend of [B], ESD and surgery should be reversed. The legend for [F] also seems to have ESD and surgery reversed.

Reply: Thank you for your comment. We have carefully checked the figure and its legend; however, we could not identify any error. Surgery yields better overall survival than ESD in both cases, as shown in **Figures 2B** and **F**. However, the superiority is not statistically significant because the number of events that occurred during the observation period was low. While the graph declines vertically with

every event (death), there were no events reported in the ESD group around the mid-point. Though this suggests that surgery has worse outcomes, the p-value indicates no statistical difference. Therefore, we confirm that the legends of **Figures 2B** and **F** need no revision.

2. Table 5 is difficult to understand. Originally, ‘Table’ should be able to grasp the contents without reading the text. As it is, the difference between line 6 ‘Beyond expanded indication’ and line 7 ‘ESD with beyond expanded indication’ is not clear. I cannot understand.

Reply: Thank you for your valuable comment and for pointing out the error. We apologize for the confusion. In Table 5, we describe the three major criteria for analysis. First—the risk of recurrence was based on the type of treatment modality (surgery or ESD), regardless of the indication. Second—the recurrence was analyzed with regard to the ESD indication, regardless of the treatment modality. For each criterion, the HR was higher in the ESD than in the surgery group, and for the ‘beyond expanded indication’ than for the ‘within expanded indication’. Third,—the results were described after combining the two factors that increase the risk (treatment modality, i.e., ESD, and beyond expanded indication). In other words, it described ESD without surgery for beyond expanded indications. We have modified the table as follows to avoid confusion for the readers.

Before

Table 5. Cox proportional hazard model for risk of recurrence after initial treatment

Variables	Adjusted hazard ratio (95% confidence interval)	P value
Treatment modality		
Surgery	1.0	
ESD	5.2 (1.0-25.8)	0.045
ESD indication		
Within expanded indication	1.0	
Beyond expanded indication	1.4 (0.4-5.4)	0.585
ESD with beyond expanded indication ^a	2.8 (0.6-12.4)	0.183

ESD, endoscopic submucosal dissection

^aReference was ESD within expanded indication

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ESD, endoscopic submucosal dissection

3. In this article, all lesions larger than 2 cm are treated in the same way, but strictly speaking, There are two types of lesions, that, "lesions that were preoperatively diagnosed as 2 cm or less and ESD was performed in the diagnosis for expanded indication, but were larger than 2 cm" and "lesions that have been ESD with diagnosis of beyond the indication for larger than 2 cm." If it is possible to consider both types of lesion separately, please try it. This data will help to answer the clinical question, "What to do when the size of a lesion is unexpectedly large pathologically after ESD is performed with the preoperative diagnosis of indicated lesion?"

Reply: Thank you for your valuable comment and advice. We have re-reviewed the data, as per your suggestion. Below are the two conditions.

- 1) Lesions that were preoperatively diagnosed as 2 cm or less and ESD was performed when diagnosed as expanded-indication lesions but were pathologically larger than 2 cm
- 2) Lesions for which ESD was performed based on the diagnosis of beyond expanded indication and that were larger than 2 cm

Fifty cases were categorized under the second condition (ESD group: 19/119 [16.0%], Surgery group: 31/119 [26.1%]). While the size was less than 2 cm before treatment, there were 22 patients in the ESD group whose lesion sizes were pathologically > 2 cm. Among these cases, there was no mortality, but one case had a recurrence. In the surgery group, there were 20 patients whose lesion size was less than 2 cm before surgery but > 2 cm pathologically; among these, there were no cases with recurrence or mortality. As requested by the reviewer, we attempted to analyze the overall and recurrence-free

survival; however, unfortunately, the event number was too small and further analysis could not be performed.

The accuracy of the lesion size on the endoscopic finding versus its pathology is a continuing issue. Personally, as an endoscopist, I believe that the treatment modality should be decided based on the size of the lesion during endoscopy. This is because morphology plays a major role in deciding between surgery and ESD. While we could not compare the two because of the small number of events, we included the following information in the Results section to provide more information to the readers (Page 10, lines 24 – 28).

The number of patients whose tumor size was ≤ 2 cm before ESD or surgery and therefore, satisfied the criteria for expanded-indication lesions but had a size of > 2 cm in the final pathology analysis was 22 (18.5%) and 20 (16.8%) in the ESD and surgery groups, respectively. Of these patients, one patient in the ESD group had a recurrence but no mortality in both groups.

4. Please add more considerations about the cause of local recurrence in ‘Discussion’. It is well known that sometimes the poorly differentiated adenocarcinoma may present with a spread that is greater than expected due to the coexistence of noncontiguous crypt progression, which is not obvious on endoscopy. How was the accuracy of the diagnosis of lateral margin in patients in your hospital? Is there a possibility that local recurrence can be reduced if a sufficient lateral margin is secured?

Reply: Thank you for your valuable comment and advice. As mentioned in the Discussion section (on Page 13, Lines 391 – 395), a pathologic review was performed for local recurrence in four cases to be reconsidered for curative resection, including those of lateral and deep resection margins; however, the original diagnosis, including the status of margin positive, did not change. According to the literature, the lateral margin negative resection rate for UD-type EGC was reported to be 72.7–94.8%^[21-24]. In our study, of 212 patients with undifferentiated EGC (before matching), the lateral margin negative resection rate in 121 patients with the lesion size < 2 cm was 92.6% (112/121), and this is within the range reported in previous studies. The rate was 92.0% (195/212) when evaluated in a total of 212 patients. Therefore, there was no significant difference in the lateral margin positive rate at the 2 cm

margin of the tumor. As a response, we have included the following in the Discussion section (on Page 14, lines 4 – 7):

In this study, in the 212 patients considered, the margin negative resection rate in the ESD group before matching was 92.0% (195/212). This was similar to previous studies where endoscopic resection was performed in UD EGC^[21-24].

We had an in-depth discussion regarding the reviewer's question "Is there a possibility that local recurrence can be reduced if a sufficient lateral margin is secured?" This is always a point of consideration for a therapeutic endoscopist. Therapeutic endoscopists always consider that a sufficient lateral margin can reduce the possibility of local recurrence. While it would be best to secure as much safety margin as possible, the operator should consider the duration of intervention, acute complications (bleeding or perforation), or delayed complications (bleeding, stricture). These considerations may be more prominent in UD EGC. A recently published study, however, mentioned that local recurrence may be related to sequential molecular changes in various cancer-related proteins in histological margin-free endoscopically resected early gastric cancers^[25]. In this study, a tumor-free distance of 5.5 mm was considered insufficient as a safety margin. Besides, undifferentiated EGC, especially signet ring cell cancer, may have a subepithelial spread beneath the normal mucosa, and this subepithelial spread could reach up to 6 mm^[26]. These studies suggest that securing sufficient margin during ESD for UD EGC could reduce the rate of local recurrence.

Moreover, it is possible that the endoscopically predicted range for the lesion is different from the actual location of the tumor during ESD for UD EGC. In the Japanese algorithm, an additional biopsy was recommended for a more accurate evaluation of the lesion margin^[26]. In addition, other studies have reported that narrow-band imaging with magnifying endoscopy may help in accurately predicting the tumor extent in UD EGC^[28]. Prospective randomized studies are needed to evaluate whether the various attempts to accurately determine the tumor margin endoscopically along with resection with sufficient margin can reduce the rate of local recurrence. We have included the following information in the Discussion section, as suggested by the reviewers (on Pages 14, lines 8 – 28).

Therapeutic endoscopists always consider that a sufficient lateral margin can reduce the possibility of local recurrence. While it would be best to secure as much safety margin as possible, the operator should consider the duration of intervention, acute complications (bleeding or perforation), or delayed complications (bleeding, stricture). These considerations may be more prominent in UD EGC. A recently published study mentioned that local recurrence may be related to sequential molecular changes in various cancer-related proteins in histological margin-free endoscopically resected early gastric cancers [25]. In this study, a tumor-free distance of 5.5 mm was considered insufficient as a safety margin. Besides, a subepithelial spread beneath the normal mucosa may exist in undifferentiated EGC, especially in signet ring cell cancer, and this subepithelial spread could reach up to 6 mm[26]. These studies suggest that securing sufficient margin in the endoscopic resection of UD EGC using the ESD method might reduce the rate of local recurrence. In the endoscopic resection of UD EGC using the ESD method, the endoscopically predicted and the actual size of the lesion is often different. In the Japanese algorithm, an additional biopsy was recommended from the surrounding mucosa of UD EGC to accurately evaluate the margin of the lesion[27]. In addition, other studies have reported that narrow-band imaging with magnifying endoscopy may help in accurately predicting the tumor extent in UD EGC[28]. Prospective randomized studies are required to evaluate whether the various attempts to accurately determine the tumor margin and resection with sufficient margin can reduce the rate of local recurrence.

Added references:

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- 22 **Abe S**, Oda I, Suzuki H, Nonaka S, Yoshinaga S, Odagaki T, Taniguchi H, Kushima R, Saito Y. Short- and long-term outcomes of endoscopic submucosal dissection for undifferentiated early gastric cancer. *Endoscopy* 2013; **45**: 703-707 [PMID: 23990481 DOI: 10.1055/s-0033-1344396]
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2. Editorial Office's comments

Science Editor:

The study retrospectively compared 123 patients with ESD versus 562 patients with surgery for early-stage undifferentiated gastric carcinoma. The recurrence-free survival of the patients in ESD group is inferior to the surgery group. So any tumor beyond 2 cm should receive surgery to provide long-term disease-free survival. The quality of the paper is very good. The suggestions of the reviewer are objective and should be attended by the authors.

1. Please review and check Figure 2. In the legend of [B], ESD and surgery should be reversed.

The legend for [F] also seems to have ESD and surgery reversed.

Reply: Thank you for your comment. We have carefully checked the figure and its legend; however, we could not identify any error. Surgery yields better overall survival than ESD in both cases, as shown in **Figures 2B** and **F**. However, the superiority is not statistically significant because the number of events that occurred during the observation period was low. While the graph declines vertically with every event (death), there were no events reported in the ESD group around the mid-point. Though this suggests that surgery has worse outcomes, the p-value indicates no statistical difference. Therefore, we confirm that the legends of **Figures 2B** and **F** need no revision.

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Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, the author(s) must add a figure (medical imaging) to the manuscript. There are no restrictions on the figures (color, B/W).

Reply: Thank you for your favorable report. We have carefully considered all the reviewer's and editor's comments and answered them in a point-by-point manner. Thank you again for your effort.

Other Changes

1. We have deleted some references according to the guideline for the revised manuscript (Citing more than five references in a single citation, even when separated by a hyphen, should be avoided). Deleted references' list is as follows (The reference numbers are when we initially submitted it):

- ~~5. Choi MK, Kim GH, Park DY, Song GA, Kim DU, Ryu DY, Lee BE, Cheong JH, Cho M. Long term outcomes of endoscopic submucosal dissection for early gastric cancer: a single center experience. Surg Endosc 2013; 27: 4250-8 [PMID: 23765426 DOI: 10.1007/s00464-013-3030-4]~~
- ~~6. Choi JJ, Lee JH, Kim YI, Kim CG, Cho SJ, Lee JY, Ryu KW, Nam BH, Kook MC, Kim YW. Long term outcome comparison of endoscopic resection and surgery in early gastric cancer meeting the absolute indication for endoscopic resection. Gastrointest Endosc 2015; 81: 333-41.e1 [PMID: 25281498 DOI: 10.1016/j.gie.2014.07.047]~~
- ~~7. Hahn KY, Park CH, Lee YK, Chung H, Park JC, Shin SK, Lee YC, Kim HI, Cheong JH, Hyung WJ, Noh SH, Lee SK. Comparative study between endoscopic submucosal dissection and surgery in patients with early gastric cancer. Surg Endosc 2018; 32: 73-86 [PMID: 28639042 DOI: 10.1007/s00464-017-5640-8]~~
- ~~16. Hirasawa T, Gotoda T, Miyata S, Kato Y, Shimoda T, Taniguchi H, Fujisaki J, Sano T, Yamaguchi T. Incidence of lymph node metastasis and the feasibility of endoscopic resection for undifferentiated type early gastric cancer. Gastric Cancer 2009; 12: 148-52 [PMID: 19890694 DOI: 10.1007/s10120-009-0515-x]~~

2. We have modified the abstract section according to the guideline for the revised manuscript (word limit for each section in the Abstract).

Before

BACKGROUND

The clinical outcomes of endoscopic submucosal dissection (ESD) for undifferentiated (UD) intramucosal early gastric cancer (EGC) compared with those of surgery, regardless of lesion size, are not well known. Furthermore, there is a concern regarding the treatment plan before and after ESD in cases of UD intramucosal EGC within expanded indications.

AIM

To evaluate clinical outcomes of ESD compared with those of surgery in patients with UD intramucosal EGC who meet both the within expanded indications or beyond expanded indications with lesion size >2 cm (the only non-curative factor).

METHODS

We enrolled patients with UD intramucosal EGC after ESD with complete resection or surgery between January 2005 and August 2020. Overall, 123 and 562 patients underwent ESD and surgery, respectively. After propensity-score matching, clinical outcomes and long-term outcomes, i.e., recurrence-free survival (RFS) and overall survival (OS), were analyzed.

RESULTS

After matching, 119 patients each were finally enrolled in the ESD and surgery groups. The median length of hospital stay was shorter in the ESD group than in the surgery group (4.0, interquartile range [4.0 – 5.0] vs. 9.0 [8.0 – 10.0] days, $p < 0.001$). Total recurrence was seven (5.9%) and two (1.7%) in the ESD and surgery groups, respectively. Four cases of recurrence after ESD were local recurrences, all of which occurred within 1 year. The ESD group had inferior RFS compared with the surgery group ($P = 0.031$). However, no difference was observed between the two groups with respect to OS ($P = 0.948$). In the Cox proportional hazard model, ESD was associated with the risk of recurrence after initial treatment in all enrolled patients (hazard ratio, 5.2; 95% confidence interval 1.0 – 25.8, $P = 0.045$).

CONCLUSION

The RFS was inferior in patients who underwent ESD with complete resection for UD intramucosal EGC regardless of lesion size, compared with those who underwent surgery; however, there was no difference in OS in both patient group. Since local recurrence is an important issue in the ESD group, despite complete resection being performed, surveillance endoscopy is essential. A short-term endoscopic follow-up is required in patients with UD intramucosal EGC with lesion sizes >2 cm after ESD.

After

BACKGROUND

The clinical outcomes of endoscopic submucosal dissection (ESD) for undifferentiated (UD) intramucosal early gastric cancer (EGC) compared with those of surgery, regardless of lesion size, are not well known. Furthermore, there is a concern regarding the treatment plan before and after ESD in cases of UD intramucosal EGC within expanded indications.

AIM

To evaluate clinical outcomes of ESD compared with those of surgery in UD intramucosal EGC patients regardless of tumor size.

METHODS

We enrolled patients with UD intramucosal EGC after ESD with complete resection or surgery from January 2005–August 2020 who met the within or beyond expanded indications with lesion size >2 cm (the only non-curative factor). Overall, 123 and 562 patients underwent ESD and surgery, respectively. After propensity-score matching, clinical and long-term outcomes, i.e., recurrence-free survival (RFS) and overall survival (OS), were analyzed. The multivariable Cox proportional hazard model with treatment modality and ESD indication was used to evaluate the recurrence risk.

RESULTS

After matching, 119 patients each were finally enrolled in the ESD and surgery groups. The

median length of hospital stay was shorter in the ESD group than surgery group (4.0 vs 9.0 days, $P < 0.001$). Four cases of recurrence after ESD were local recurrences, all of which occurred within 1 year. Total recurrence was seven (5.9%) and two (1.7%) in the ESD and surgery groups, respectively. No difference was observed between the two groups with respect to OS ($P = 0.948$). However, the ESD group had inferior RFS compared with the surgery group ($P = 0.031$). Additionally, ESD was associated with the risk of recurrence after initial treatment in all enrolled patients (hazard ratio, 5.2; 95% confidence interval 1.0–25.8, $P = 0.045$).

CONCLUSION

Although OS was similar between the two groups, surveillance endoscopy was important for the ESD than for the surgery group because RFS was inferior and local recurrence was an issue.

3. We have rewritten the core-tip section to reflect the word limit.

Before

This retrospective study evaluated the clinical outcomes of endoscopic submucosal dissection (ESD) compared with those of surgery in patients with undifferentiated (UD) intramucosal early gastric cancer (EGC) after propensity-score matching. No difference in overall survival was observed in the ESD and surgery groups, although recurrence-free survival was inferior in the ESD group. Lymph node metastasis was not observed after ESD; however, local recurrence was higher after ESD than after surgery. All local recurrences corresponded to lesion size > 2 cm. Surveillance endoscopy is important in ESD, even if complete resection is performed for UD intramucosal EGC. A short interval endoscopic follow-up is necessary when observing lesion sizes > 2 cm as the only non-curative factor.

After

This retrospective study evaluated the clinical outcomes of endoscopic submucosal dissection (ESD) compared with those of surgery in patients with undifferentiated (UD) intramucosal early gastric cancer (EGC) after propensity-score matching. No difference in overall survival was observed **between two groups**, although recurrence-free survival was inferior in the ESD group. Lymph node metastasis was not observed after ESD; however, local recurrence was higher after ESD than surgery. Surveillance endoscopy is important in ESD, even if complete resection is performed for UD intramucosal EGC. A short interval endoscopic follow-up is necessary when observing lesion sizes > 2 cm as the only non-curative factor.

Thank you again for your interest in our study and for your patience. If in your opinion other corrections are required, we will be pleased to do so in order to move the manuscript toward publication. We eagerly await your response.

Sincerely yours,

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