Retrospective Study

Additional laparoscopic gastrectomy after noncurative endoscopic submucosal dissection for early gastric cancer: A single-center experience

Yan-Tao Tian, Fu-Hai Ma, Gui-Qi Wang, Yue-Ming Zhang, Li-Zhou Dou, Yi-Bin Xie, Yu-Xin Zhong, Ying-Tai Chen, Quan Xu, Dong-Bing Zhao

ORCID number: Yan-Tao Tian (0000-0001-6479-7547); Fu-Hai Ma (0000-0003-2437-6881); Gui-Qi Wang (0000-0001-7767-1564); Yue-Ming Zhang (0000-0002-8406-5877); Dou-Li Zhou (0000-0003-1455-4701); Yi-Bin Xie (0000-0002-7887-1389); Yu-Xin Zhong (0000-0002-8865-3297); Ying-Tai Chen (0000-0003-4980-6315); Quan Xu (0000-0001-9246-3253); Dong-Bing Zhao (0000-0001-8339-687X).

Author contributions: Tian YT and Ma FH contributed equally to this work and they were involved in study concept, data acquisition, analysis, and interpretation, and production of tables, wrote the first draft, and revised it critically in light of comments from other authors; Zhao DB was involved in study conception and design, data interpretation, manuscript revision, and discussion; Wang GQ, Zhang YM, Dou LZ, and Xu Q were involved in data acquisition and literature review; Xie YB, Zhong YX, and Chen YT were involved in the manuscript revision and discussion; all authors approved the final version submitted.

Supported by the National Natural Science Foundation of China, No. 81772642; Beijing Municipal Science and Technology Commission, No. Z16110000116045; and Capital’s Funds for Health Improvement and Research, No. CFH 2018-2-4022.

Abstract

BACKGROUND

The necessity of additional gastrectomy for early gastric cancer (EGC) patients who do not meet curative criteria after endoscopic submucosal dissection (ESD) is controversial.

AIM

To examine the clinicopathologic characteristics of patients who underwent additional laparoscopic gastrectomy after ESD and to determine the appropriate strategy for treating those after noncurative ESD.

METHODS

We retrospectively studied 45 patients with EGC who underwent additional laparoscopic gastrectomy after noncurative ESD from January 2013 to January 2019 at the Cancer Hospital of the Chinese Academy of Medical Sciences. We analyzed the patients’ clinicopathological data and identified the predictors of residual cancer (RC) and lymph node metastasis (LNM).

RESULTS

Surgical specimens showed RC in ten (22.2%) patients and LNM in five (11.1%).
INTRODUCTION

Gastric cancer is the fourth most common cancer and the second leading cause of cancer-related death in the world[1]. Early gastric cancer (EGC) is defined as a tumor confined to the mucosa or submucosa, regardless of the regional lymph node metastasis (LNM)[2]. The detection rates of EGC have been improved with the increase in cancer surveillance and widespread endoscopic examinations[2]. Endoscopic submucosal dissection (ESD) as a treatment for EGC has been rapidly spreading due to the advantages of this technique including reduced postoperative complications, decreased medical cost, fast recovery, and improved quality of life[4]. As ESD is now performed more frequently, noncurative ESD is also becoming more and more frequent, thus warranting appropriate treatment[3].

For patients who have undergone noncurative ESD, some reports[5-9] recommend additional surgery to prevent residual cancer (RC) or LNM. However, high morbidity, poor quality of life, and medical cost of gastrectomy for these patients cannot be neglected, and it is controversial whether additional gastrectomy is necessary for all patients who do not meet the curative criteria after ESD[10]. Therefore, it would be valuable to determine which factors could increase the risk of residual cancer or lymph node metastasis in patients after noncurative ESD in order to avoid unnecessary surgery. We found that gastrectomy was necessary not only for patients who had a positive margin in ESD, but also for cases with neural invasion, undifferentiated type, and submucosal invasion more than 500 µm. Laparoscopic gastrectomy is a safe, minimally invasive, and feasible procedure for additional surgery after noncurative ESD.

CONCLUSION

Gastrectomy is necessary not only for patients who have a positive margin after ESD, but also for cases with neural invasion, undifferentiated type, and submucosal invasion more than 500 µm. Laparoscopic gastrectomy is a safe, minimally invasive, and feasible procedure for additional surgery after noncurative ESD. However, further studies are needed to apply these results to clinical practice.
inflammation causes edema, fibrosis, and intraabdominal adhesions, which might increase the difficulties and the risk of complications during subsequent LG\cite{13,14}. However, relatively few data are available on the influence of previous ESD on LG\cite{15,16}.

In the present study, we aimed to examine the predictive factors for LNM and RC as well as to explore the appropriate strategy for treating these patients after noncurative ESD. We also aimed to assess the feasibility and safety of LG as additional surgery after ESD.

**MATERIALS AND METHODS**

In this retrospective cohort study, the clinical data of consecutive EGC patients who underwent additional gastrectomy after ESD at the Cancer Hospital of the Chinese Academy of Medical Sciences, Chinese National Cancer Center between January 2013 and January 2019 were reviewed. The rate of LNM or RC was investigated. The associations between various clinicopathological factors and RC or LNM were examined by univariable and multivariable analyses. This retrospective study was approved by the Institutional Review Board at the Cancer Hospital of the Chinese Academy of Medical Sciences. The need for informed consent was waived due to the retrospective nature of the study, and the data were anonymously analyzed. The datasets in the current study are available from the corresponding author on reasonable request.

**Indications and procedures for ESD**

Depth of tumor invasion and tumor stage were assessed initially before ESD by endoscopic ultrasonography and contrast-enhanced computed tomography of the abdomen and pelvis. The extended indications for ESD were as follows: (1) Differentiated mucosal cancer without ulceration regardless of lesion size; (2) Differentiated mucosal cancer, with ulceration, < 3 cm in diameter; (3) Differentiated minimally invasive submucosal cancer < 3 cm in diameter; and (4) Undifferentiated mucosal cancer ≤ 2 cm in size.

ESD was performed by one experienced gastrointestinal endoscopist in our hospital. An incision line were made at about 5 mm lateral to the margin of the cancerous lesion using a needle. Hypertonic saline mixed with epinephrine (1:10000) and sodium hyaluronate were injected into the submucosal layer to lift the lesion. A circumferential mucosal incision surrounding the marking dots was performed. The submucosa beneath the target lesion was dissected and the entire lesion was completely removed with a surgical electronic knife.

**Histopathological evaluation**

After being fixed in 10% formalin, resected specimens were sectioned perpendicularly at 2-mm intervals. The histological evaluation was based on the World Health Organization classification of gastric cancer. Gross types were categorized into elevated, flat, or depressed type. Well or moderately differentiated tubular adenocarcinoma and papillary adenocarcinoma were classified as differentiated adenocarcinoma type, while poorly differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma were classified as undifferentiated type. Tumor involvement in the lateral or vertical resection margin, tumor size, lymphovascular invasion, neural invasion, and the depth of tumor invasion were evaluated. The depth of tumor invasion was measured and quantified and was classified as M (mucosal invasion), SM1 (submucosal invasion < 500 μm of the lower margin of the muscularis mucosae), and SM2 (tumor invasion into submucosa > 500 μm from the muscularis mucosa).

**Criteria for noncurative resection of ESD**

The lesions that were considered not to meet the noncurative criteria for ESD were defined as lesions that met at least one of the following criteria based on histopathologic findings of the ESD specimens: (1) Positive horizontal margin; (2) Positive vertical margin; (3) Presence of lymphovascular involvement; (4) SM2 or deeper invasion; (5) Differentiated mucosal cancer with ulceration and size ≥ 30 mm; (6) Differentiated SM1 cancer ≥ 30 mm; and (7) undifferentiated cancer accompanied by submucosal invasion, size > 20 mm, or ulceration.

**Statistical analysis**

Univariate analyses by the χ² test or Fisher’s exact test were performed to explore the clinicopathological differences between the RC and non-RC groups, and between the LNM and non-LNM groups. Furthermore, multivariate logistic regression analysis
was used to identify independent risk factors for RC and LNM, including those factors with $P < 0.3$ in univariate analysis. A $P$-value $< 0.05$ was considered significant. All analyses were performed with SPSS for Windows version 22.0.

RESULTS

Demographics and clinicopathological characteristics of the patients
A total of 640 ESDs were performed, and 45 (7.0%) noncurative ESDs were found during the study period. The demographics and clinicopathological characteristics of the patients who received additional gastrectomy because of noncurative ESD are summarized in Table 1. The reasons for additional gastrectomy consisted of positive horizontal margin (7 cases), positive vertical margin (29 cases), SM2 (31 cases), lymphovascular invasion (19 cases), and undifferentiated type (14 cases). And two cases were suspected recurrence on esophagogastroduodenoscopy at the 3-month follow-up after ESD. Of the 45 patients, 34 (75.6%) were male and 11 (24.4%) were female. The mean age was 58.2 ± 9.3 years. The median interval between ESD and additional gastrectomy was 47 ± 26 d. The final depth of tumor invasion was M in 9 patients, SM1 in 5, SM2 in 26, muscularis propria in 2, and subserosa in 3.

Associations between clinicopathological characteristics and RC
RC was found in 10 (22.2%) of the 45 patients. The patients who did and did not have RC were compared in terms of their clinicopathological characteristics, as shown in Table 2. Univariate analyses determined that horizontal margin ($P = 0.034$) and neural invasion ($P = 0.007$) were significant factors for RC. In contrast, tumor location, macroscopic type, tumor size, histological differentiation, Lauren type, vertical margin, depth of invasion, and lymphovascular invasion did not show significant correlations. Multivariate analysis showed that horizontal margin [odds ratio (OR) = 13.393, 95% confidence interval (CI): 1.435-125, $P = 0.023$] and neural invasion (OR = 18.495, 95% CI: 1.585-215, $P = 0.020$) were associated with a higher incidence of RC within specimens after surgery (Table 3).

Associations between clinicopathological characteristics and LNM
LNM was detected in 5 (11.1%) out of 45 cases. Relationships between clinicopathological characteristics and LNM are summarized in Table 4. Undifferentiated type was the only significant factor for LNM ($P = 0.027$). Macroscopic type and depth of tumor invasion had weak relationships. Multivariate analysis revealed that undifferentiated type (OR = 12.000, 95% CI: 1.197-120, $P = 0.035$) was associated with a higher incidence of LNM within specimens after surgery. All five patients showed tumor depth of more than SM1 in the specimen from the initial endoscopic resection. Of the five patients with LNM, four previously exhibited undifferentiated type post-ESD treatment.

Operative data and postoperative outcomes
Details of the intraoperative course and postoperative course are shown in Table 5. The type of LG was determined based on the tumor location. Proximal gastrectomy was performed in 15 (33.3%) cases and distal gastrectomy in 23 (51.1%). Total gastrectomy was performed in five (11.1%) cases and partial gastrectomy in two (4.4%). The mean number of harvested lymph nodes was 29.7 ± 13.7. The mean operative time and mean estimated blood loss were 180 ± 47 min and 107 ± 69 mL, respectively. The time to first flatus was 3.4 ± 0.8 d, the time to recommencement of oral intake was 5.3 ± 1.4 d, and the length of hospital stay was 9.9 ± 2.9 d. Postoperative complications occurred five (11.1%) patients. Two patients developed leakage from the anastomotic site, and one each developed wound infection, hemorrhage, and abdominal infection. These complications were conservatively treated and consequently improved. None of these patients died.

DISCUSSION

The rate of RC in our series (22.2%) was similar to those in the previous reports (5.2%-28.6%)[9,16,20]. LNM was detected in 5 (11.1%) out of 45 cases. The majority of these cases harbored neither RC nor LNM, indicating that additional surgery may be unnecessary. Therefore, it is important to identify which patients will benefit the most from additional gastrectomy after noncurative ESD for EGC. However, the studies of predictive factors for RC and LNM in additional surgery gastrectomy specimens after ESD have been very limited. Our study revealed that positive horizontal and neural
### Table 1 Demographic characteristics of the patients

| Characteristic | All patients (n = 45) |
|---------------|----------------------|
|               | Number | Percent  |
| Age (yr)      | 58.24 ± 9.3 |
| Gender        |         |          |
| Male          | 34      | 75.6     |
| Female        | 11      | 24.4     |
| Abdominal operation history |         |          |
| Yes           | 8       | 17.8     |
| No            | 37      | 82.2     |
| ASA score     |         |          |
| I-II          | 34      | 75.6     |
| III-IV        | 11      | 24.4     |
| Comorbidity   |         |          |
| Any comorbidity | 15    | 33.3     |
| Hypertension  | 10      | 22.2     |
| Diabetes      | 5       | 10.5     |
| Coronary artery disease | 2 | 11.1 |
| Others        | 4       | 8.9      |
| Surgical indication |         |          |
| Vertical margin positive | 29 | 64.4 |
| SM2           | 31      | 68.9     |
| Horizontal margin positive | 7 | 15.6 |
| Lymphovascular invasion | 19 | 42.2 |
| Undifferentiated type | 14 | 31.1 |
| Suspected recurrence 3 mo after ESD | 2 | 4.4 |
| Interval (d)  | 47 ± 26 |
| RC            |         |          |
| Yes           | 10      | 22.2     |
| No            | 35      | 77.8     |
| LNM           |         |          |
| Yes           | 5       | 11.1     |
| No            | 40      | 88.9     |
| Depth of invasion |         |          |
| T1a           | 9       | 20.0     |
| T1b SM1       | 5       | 11.1     |
| T1b SM2       | 26      | 57.8     |
| T2            | 2       | 4.4      |
| T3            | 3       | 6.7      |

RC: Residual cancer; LNM: Lymph node metastasis; ASA: American Society of Anesthesiologists; ESD: Endoscopic submucosal dissection.

invasion were independent risk factors for RC. Undifferentiated type was an independent risk factor for LNM.

Regarding RC, positive vertical margin and positive horizontal margin were independent predictors in some previous studies[18], while many authors also reported only positive horizontal margin as a risk factor for RC, as found in our study[4,21,22]. Hyuk et al thought that the possibility of the tumor cells in the corresponding area opposite an involved resection margin being completely removed by the cautery effect was much lower in the horizontal rather than in the vertical direction[4,5]. The feasibility of secondary ESD for local control in positive horizontal margin cases has been reported; however, the management of these patients is debated[25]. If there is an additional noncurative factor combined with the positive horizontal margin, additional surgery should be considered. Neural invasion is a way of cancer spreading and is related to advanced stage, higher risk of recurrence, and poor long-
### Table 2 Characteristics of cases with and without residual cancer, \( n \) (%)

| Characteristic                   | Residual cancer | P-value |
|----------------------------------|-----------------|---------|
|                                  | Yes \( (n = 10) \) | No \( (n = 35) \) |       |
| Location                         |                 |         | 1.000 |
| Upper third                      | 4 (23.5)        | 13 (76.5) |       |
| Middle third                     | 2 (18.2)        | 9 (81.8)  |       |
| Lower third                      | 4 (23.5)        | 13 (76.5) |       |
| Macroscopic appearance           |                 |         | 0.694 |
| Elevated type                    | 1 (25.0)        | 3 (75.0)  |       |
| Surface type                     | 9 (23.1)        | 30 (76.9) |       |
| Depressed type                   | 0 (0)           | 2 (100)  |       |
| Tumor size                       |                 |         | 0.720 |
| \(< 3 \text{ cm} \)              | 5 (19.2)        | 21 (80.8) |       |
| \(\geq 3 \text{ cm} \)          | 5 (26.3)        | 14 (73.7) |       |
| Differentiation                  |                 |         | 1.000 |
| Differentiated                   | 7 (22.6)        | 24 (77.4) |       |
| Undifferentiated                 | 5 (21.4)        | 11 (78.6) |       |
| Lauren type                      |                 |         | 0.722 |
| Intestinal                       | 4 (18.2)        | 18 (81.8) |       |
| Diffused/Mixed                   | 6 (26.1)        | 17 (73.9) |       |
| Depth of invasion                |                 |         | 0.469 |
| Mucosal invasion/SM1             | 2 (14.3)        | 12 (85.7) |       |
| > SM1 invasion                   | 8 (25.8)        | 23 (74.2) |       |
| Horizontal margin                |                 |         | 0.034 |
| Positive                         | 4 (57.1)        | 3 (42.9)  |       |
| Negative                         | 6 (15.8)        | 32 (84.2) |       |
| Vertical margin                  |                 |         | 0.292 |
| Positive                         | 8 (27.6)        | 21 (72.4) |       |
| Negative                         | 2 (12.5)        | 14 (87.5) |       |
| Lymphovascular invasion          |                 |         | 1.000 |
| Yes                              | 4 (21.1)        | 15 (78.9) |       |
| No                               | 6 (23.1)        | 20 (76.9) |       |
| Neural invasion                  |                 |         | 0.007 |
| Yes                              | 6 (54.5)        | 5 (45.5)  |       |
| No                               | 4 (11.8)        | 30 (88.2) |       |

In previous studies of patients who underwent additional surgery following noncurative ESD of EGC, the LNM rates ranged from 5.1% to 9.8% [18,21,23,24,29,30], which are similar to the present finding of 11.1%. Previous reports have indicated that lymphovascular invasion, SM2 invasion, lesion size > 3 cm, and positive vertical margin were associated with a greater risk of LNM in patients with EGC [31-33]. Lymphovascular invasion has been proven to be an independent risk factor for LNM in those patients who underwent noncurative ESD [18,21,24,30]. However, lymphovascular invasion was not correlated with LNM in the present study and two patients without lymphovascular invasion were found to have LNM. Previous studies have demonstrated that the rate of LNM was higher in patients with differentiated EGC with undifferentiated components than in those with EGC without undifferentiated components [18,39]. Lee et al. [37] reported that the rate of LNM increased with the increase in undifferentiated components in differentiated type mucosal cancers. Kim et al. [38] investigated...
### Table 3 Multivariate analysis of the risk factors for residual cancer

| Risk factor               | OR     | 95% CI      | P-value |
|---------------------------|--------|-------------|---------|
| Vertical margin positive  | 0.670  | 0.065-6.909 | 0.737   |
| Depth of invasion: > SM1  | 0.637  | 0.075-5.423 | 0.680   |
| Horizontal margin positive| 13.393 | 1.435-125   | 0.023   |
| Neural invasion positive  | 18.495 | 1.585-215   | 0.020   |

OR: Odds ratio; CI: Confidence interval.

and Abdelfatah et al.[39] demonstrated that undifferentiated histology was an important risk factor for LNM. In the present series, undifferentiated histology was a major risk factor for LNM. SM2 invasion was another factor reported to be associated with a greater risk for LNM in patients with EGC[30,40]. This was thought to be due to the presence of larger diameter lymphatic vessels in the deeper third of the lamina propria, and the progressive increase in diameter as these vessels go deeper into the submucosal layer, where the lymphatic network is richer[39]. In our study, tumors in five lymph node-positive patients showed invasion deeper than SM1 in the surgical pathology specimen. Therefore, cases with submucosal invasion deeper than SM1 require additional gastrectomy and lymphadenectomy.

ESD in EGC causes an artificial gastric ulceration, local inflammation, subsequent fibrosis, and even adhesions in the outer gastric wall, which has a negative intraprocedural impact on additional LG in patients who have undergone noncurative ESD[14]. Previous studies have demonstrated that ESD is not associated with postoperative complications during or after an additional LG in patients who underwent noncurative ESD[15-17]. Our study found that LG can achieve good short-term surgical outcomes for gastric cancer after noncurative ESD.

This study had several limitations. First, it was a retrospective study conducted in a single center and the sample size was relatively small. Such limitations may lead to issues of selection bias and heterogeneous patient group. Second, we did not report long-term outcomes of patients with noncurative ESD because the mean follow-up period was too short.

In conclusion, gastrectomy is necessary not only for patients who have a positive margin in ESD, but also for cases with neural invasion, undifferentiated type, and submucosal invasion more than 500 µm due to the risk of RC or LMN. In terms of short-term surgical outcomes, LG is a safe, minimally invasive, and feasible procedure for additional surgery after noncurative ESD. However, further studies are needed to apply these results to clinical practice.
| Characteristic                  | LNM | P-value |
|-------------------------------|-----|---------|
|                               | Yes (n = 5) | No (n = 40) |   |
| Location                      |     |         | 0.417 |
| Upper third                   | 3 (17.6) | 14 (86.7) |   |
| Middle third                  | 0 (0)  | 11 (100) |   |
| Lower third                   | 2 (11.8) | 15 (88.2) |   |
| Macroscopic appearance        |     |         | 0.125 |
| Elevated type                 | 1 (25)  | 3 (75)  |   |
| Surface type                  | 3 (7.7)  | 36 (92.3) |   |
| Depressed type                | 1 (50)  | 1 (50)  |   |
| Tumor size                    |     |         | 1.000 |
| < 3 cm                        | 3 (11.5) | 23 (89.5) |   |
| ≥ 3 cm                        | 2 (10.5) | 17 (89.5) |   |
| Differentiation               |     |         | 0.027 |
| Differentiated                | 1 (3.2)  | 30 (96.8) |   |
| Undifferentiated              | 4 (28.6) | 10 (71.4) |   |
| Lauren type                   |     |         | 0.665 |
| Intestinal                    | 3 (13.6) | 19 (86.4) |   |
| Diffused/Mixed                | 2 (8.7)  | 21 (91.3) |   |
| Depth of invasion             |     |         | 0.305 |
| Mucosal invasion/SM1          | 0 (0)  | 14 (100) |   |
| > SM1 invasion                | 5 (16.1) | 26 (83.9) |   |
| Horizontal margin             |     |         | 0.577 |
| Positive                      | 0 (0)  | 7 (100)  |   |
| Negative                      | 5 (13.2) | 33 (86.8) |   |
| Vertical margin               |     |         | 1.000 |
| Positive                      | 3 (10.3) | 26 (89.7) |   |
| Negative                      | 2 (12.5) | 14 (87.5) |   |
| Lymphovascular invasion       |     |         | 0.636 |
| Yes                           | 3 (15.8) | 16 (84.2) |   |
| No                            | 2 (7.7)  | 24 (92.3) |   |
| Neural invasion               |     |         | 1.000 |
| Yes                           | 1 (9.1)  | 10 (90.9) |   |
| No                            | 4 (11.8) | 30 (88.2) |   |

LNM: Lymph node metastasis.
Table 5  Operative data and postoperative outcomes

| Variable                        | n (%)     |
|---------------------------------|-----------|
| Type of gastrectomy             |           |
| Proximal                        | 15 (33.3) |
| Distal                          | 23 (51.1) |
| Total                           | 5 (11.1)  |
| Partial                         | 2 (4.4)   |
| Retrieved lymph node            | 29.7 ± 13.7|
| Complications                   |           |
| Any                             | 5 (11.1)  |
| Wound infection                 | 1 (2.2)   |
| Postoperative bleeding          | 1 (2.2)   |
| Anastomotic leakage             | 2 (4.4)   |
| Abdominal infection             | 1 (2.2)   |
| 30-day mortality                | 0         |
| Estimated blood loss (mL)       | 107 ± 69  |
| Operation time (min)            | 180 ± 47  |
| Time to resume soft diet (d)    | 5.3 ± 1.4 |
| Time until the first flatus (d) | 3.4 ± 0.8 |
| Postoperative hospital stay (d) | 9.9 ± 2.9 |

**ARTICLE HIGHLIGHTS**

Research background
Endoscopic submucosal dissection (ESD) as a treatment for early gastric cancer (EGC) has been rapidly spreading. As ESD is now performed more frequently, noncurative resection after ESD is also becoming more frequent. It is controversial whether additional gastrectomy is necessary for all patients who do not meet the curative criteria after ESD.

Research motivation
It would be valuable to determine which factors could increase the risk of residual cancer (RC) or lymph node metastasis (LNM) in patients after noncurative ESD of EGC in order to avoid unnecessary surgery.

Research objectives
The objectives of this study were to identify the predictive factors for LNM and RC as well as to explore the appropriate strategy for treating those after non-curative ESD. We also aimed to assess the feasibility and safety of LG as additional surgery after ESD.

Research methods
We analyzed the patients’ clinicopathological data and identified the predictors of RC and LNM.

Research results
Surgical specimens showed RC in ten patients and LNM in five. Multivariate analysis revealed that positive horizontal margin and neural invasion were independent risk factors for RC. Undifferentiated type was an independent risk factor for LNM. Tumors in all patients with LNM showed submucosal invasion more than 500 µm. Postoperative complications after additional laparoscopic gastrectomy occurred in five patients, and no deaths occurred among patients with complications.

Research conclusions
Our study revealed that positive horizontal and neural invasion are independent risk factors for RC. Undifferentiated type is an independent risk factor for LNM. Laparoscopic gastrectomy is a safe, minimally invasive, and feasible procedure for additional surgery after noncurative ESD. Gastrectomy is necessary not only for patients who have a positive margin in ESD, but also for cases with neural invasion, undifferentiated type, and submucosal invasion more than 500 µm due to the risk of RC or LNM. Laparoscopic gastrectomy is a safe, minimally invasive, and feasible procedure for additional surgery after noncurative ESD.

Research perspectives
A study of larger sample size is needed. Long-term outcomes of patients with noncurative ESD need to be investigated in a prospective multicenter trial.
REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108 [PMID: 25651787 DOI: 10.3322/caac.21262]

2. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 2011; 14: 101-112 [PMID: 21577343 DOI: 10.1007/s10120-011-0121-9]

3. Nozawa G, Ku HR, Kim YJ, Park SC, Kim J, Han CJ, Kim YC, Yang KY. Clinical outcomes of early gastric cancer with lymphovascular invasion or positive vertical resection margin after endoscopic submucosal dissection. Surg Endosc 2015; 29: 2583-2589 [PMID: 25480609 DOI: 10.1007/s00464-014-3973-0]

4. Toyosawa T, Ohta M, Tanaka H, Minamino H, Sakurai K, Nagami Y, Kubo N, Yamamoto A, Sano K, Murakami K, Tominaga K, Nebiki H, Yamashita Y, Arakawa T, Hirakawa K. Optimal management for patients not meeting the inclusion criteria after endoscopic submucosal dissection for gastric cancer. Surg Endosc 2016; 30: 2404-2414 [PMID: 26463497 DOI: 10.1007/s00464-015-4491-4]

5. Yone H, Kim SG, Choi I, Im JP, Kim JS, Kim WH, Jung HC. Risk factors of recurrent or recurrent tumor in patients with a tumor-positive resection margin after endoscopic resection of early gastric cancer. Surg Endosc 2013; 27: 1561-1568 [PMID: 23236643 DOI: 10.1007/s00464-012-2627-3]

6. Kusano C, Iwasaki M, Kakutenbach T, Conlin A, Oda I, Gotoda T. Should elderly patients undergo additional surgery after non-curative endoscopic resection for early gastric cancer? Long-term comparative outcomes. Am J Gastroenterol 2011; 106: 1064-1069 [PMID: 21470189 DOI: 10.1038/ajg.2011.49]

7. Lee HY, Kang YJ, Kim JH, Park SS, Park SH, Park JI, Kim SJ, Kim HS. Clinical Outcomes of Gastrectomy after Incomplete EMR/ESD. J Gastric Cancer 2011; 11: 112-13 [PMID: 22076221 DOI: 10.2520/jgc.2011.11.13.162]

8. Eom BW, Kim YJ, Kim KH, Yoon HM, Cho SJ, Lee JY, Kim CG, Kook MC, Kim YW, Nam BH, Ryu KW, Choi IJ. Survival benefit of additional surgery after noncurative endoscopic resection in patients with early gastric cancer. Gastrinostest Endosc 2017; 85: 155-163.e2 [PMID: 27460389 DOI: 10.1016/j.gie.2016.07.036]

9. Suzuki S, Gotoda T, Hatta W, Oyama T, Kawata N, Takahashi A, Yosihikou, Y, Hoteya S, Nakagawa M, Hirono M, Esaki M, Matsuda M, Ohtani K, Yamanoouki K, Yoshida M, Doi O, Takada J, Tanaka K, Yamada S, Tsuji T, Ito H, Hayashi Y, Shimosegawa T. Noncurative Endoscopic Submucosal Dissection for Early Gastric Cancer: A Propensity Score Matching Analysis. Ann Surg Oncol 2017; 24: 3353-3360 [PMID: 28795364 DOI: 10.1245/s10434-017-0639-1]

10. Hatta W, Gotoda T, Oyama T, Kawata N, Takahashi A, Yosihikou, Y, Hoteya S, Nakagawa M, Hirono M, Esaki M, Matsuda M, Ohtani K, Yamanoouki K, Yoshida M, Doi O, Takada J, Tanaka K, Yamada S, Tsuji T, Ito H, Hayashi Y, Nakamura T, Nakayama N, Shimosegawa T. Is the eCuras system useful for selecting patients who require radical surgery after noncurative endoscopic submucosal dissection for early gastric cancer? A comparative study. Gastric Cancer 2018; 21: 481-489 [PMID: 28936966 DOI: 10.1007/s10120-017-0776-z]

11. Heo J, Jeon SW. The clinical significance and management of noncurative endoscopic resection in early gastric cancer. Clin Endosc 2013; 46: 235-238 [PMID: 23703232 DOI: 10.5946/ce.2013.46.3.235]

12. Kim W, Kim HH, Han SU, Kim MC, Hyung WJ, Ryu SW, Cho GS, Kim CY, Yang HK, Park DJ, Song KY, Lee SI, Ryu SY, Lee JH, Lee HJ, Korean Laparo-endoscopic Gastrointestinal Surgery Study (KLASS) Group. Decreased Morbidity of Laparoscopic Distal Gastrectomy Compared With Open Distal Gastrectomy for Stage I Gastric Cancer: Short-term Outcomes From a Multicenter Randomized Controlled Trial (KLASS). Ann Surg Oncol 2016; 23: 28-33 [PMID: 25355329 DOI: 10.1245/s10434-015-4914-6]

13. Aoyama T, Sato T, Hayashi T, Yamada T, Cho H, Ogata T, Oba K, Yoshikawa T. Does a laparoscopic approach attenuate the body weight loss and lean body mass loss observed in open distal gastrectomy for gastric cancer? a single-institution exploratory analysis of the JCOG 0912 phase III trial. Gastric Cancer 2018; 21: 345-352 [PMID: 28623524 DOI: 10.1007/s10120-017-0775-8]

14. Akagi T, Shiraiishi N, Hiroshi K, Etoh T, Yasuda K, Kitano S. Case series of intra-abdominal adhesions induced by artificial ulceration after endoscopic submucosal dissection before additional laparoscopic gastrectomy. Gastrointest Endosc 2010; 72: 438-443 [PMID: 20541190 DOI: 10.1016/j.gie.2010.03.1066]

15. Jiang X, Hiki N, Yoshida N, Nunobe S, Kumagai K, Sano T, Yamaguchi T. Laparoscopy-assisted gastrectomy in patients with previous endoscopic resection for early gastric cancer. Br J Surg 2011; 98: 385-390 [PMID: 21254013 DOI: 10.1002/bjs.7358]

16. Tsujimoto H, Yaguchi Y, Kumano I, Takahata R, Matsuyomo Y, Yoshida K, Horiguchi H, Aosasa S, Ono S, Yamamoto J, Hase K. Laparoscopic gastrectomy after incomplete endoscopic resection for early gastric cancer. Oncol Rep 2012; 28: 2205-2210 [PMID: 22993111 DOI: 10.3892/or.2012.2046]

17. Ebihara Y, Okushita S, Kurashima Y, Noji T, Nakamura T, Murakami S, Tamoto E, Tsukahara T, Okamura K, Shichinohe T, Hirano S. Totally laparoscopic gastrectomy for gastric cancer after endoscopic submucosal dissection: A propensity score matching analysis. Langenbecks Arch Surg 2015; 400: 967-972 [PMID: 26476630 DOI: 10.1007/s00423-015-1349-0]

18. Sunagawa H, Kinoshita T, Kaito A, Shibasaki H, Kaneko K, Ochiai A, Ohno A, Nishida T. Additional surgery for non-curative endoscopic resection after endoscopic submucosal dissection for gastric cancer: A retrospective analysis of 200 cases. Surg Today 2017; 47: 202-209 [PMID: 27194020 DOI: 10.1007/s00595-016-1353-1]

19. Ishida R, Kanaji S, Maehara R, Hasegawa H, Yamamoto M, Matsuda Y, Yamashita K, Matsuda T, Oshikiri T, Sumi Y, Nakamura T, Suzuki S, Kakeji Y. Significance of Additional Gastrectomy Including Endoscopic Submucosal Dissection Scar for Gastric Cancer. Anticancer Res 2018; 38: 5289-5294 [PMID: 30194180 DOI: 10.21873/anticanres.12855]

20. Katsube T, Murayama M, Yamaguchi K, Usuda A, Shimazaki A, Asaka S, Konno M, Miyaki A, Usui T, Yokomizo H, Shizorai S, Yoshimatsu K, Shimakawa T, Naritaka Y. Additional Surgery After Non-curative Resection of ESD for Early Gastric Cancer. Anticancer Res 2015; 35: 2969-2974 [PMID: 25965838]

21. Ito H, Inoue H, Ikeda H, Odaka N, Yoshida A, Satodate H, Oinomaru M, Takayagami D, Santi EG, Kudo SE. Surgical outcomes and clinicopathological characteristics of patients who underwent potentially noncurative endoscopic resection for gastric cancer: A report of a single-center experience. Gastroenterol Res Pract 2013; 2013: 427405 [PMID: 23762335 DOI: 10.1155/2013/427405]

22. Jung H, Bae JM, Choi MG, Noh JH, Sohn TS, Kim S. Surgical outcome after incomplete endoscopic submucosal dissection of gastric cancer. Br J Surg 2011; 98: 73-78 [PMID: 21136563 DOI: 10.1002/bjs.7274]
Kim ER, Lee H, Min BH, Lee JH, Rhee PL, Kim JJ, Kim KM, Kim S. Effect of rescue surgery after non-curative endoscopic resection of early gastric cancer. Br J Surg 2015; 102: 1394-1401 [PMID: 26313295 DOI: 10.1002/bjs.9873]

Lee JH, Kim JH, Kim DH, Jeon TY, Kim DH, Kim GH, Park DY. Is Surgical Treatment Necessary after Non-curative Endoscopic Resection for Early Gastric Cancer? J Gastric Cancer 2010; 10: 182-187 [PMID: 22076184 DOI: 10.5230/jgc.2010.10.4.182]

Bae SY, Jang TH, Min BH, Lee JH, Rhee PL, Rhee JC, Kim JJ. Early additional endoscopic submucosal dissection in patients with positive lateral resection margins after initial endoscopic submucosal dissection for early gastric cancer. Gastrointest Endosc 2012; 75: 432-436 [PMID: 22246614 DOI: 10.1016/j.gie.2011.09.044]

De Franco L, Marrelli D, Voglino C, Vindigni C, Ferrara F, Di Mare G, Iudici L, Marini M, Roviello F. Prognostic Value of Perineural Invasion in Resected Gastric Cancer Patients According to Lauren Histotype for Early Oncol Res 2018; 24: 393-400 [PMID: 28555306 DOI: 10.1007/s10255-017-2527-8]

Liebl F, Demir IE, Mayer K, Schuster T, D’Haese JG, Becker K, Langer R, Bergmann F, Wang K, Rosenberg R, Novotny AR, Feith M, Reim D, Friess H, Ceyhan GO. The impact of neural invasion severity in gastrointestinal malignancies: A clinicopathological study. Ann Surg 2014; 260: 900-9; discussion 907-8 [PMID: 23579860 DOI: 10.1097/SLA.0000000000000968]

Kim YB, Han SU, Lee D. Prominent neural invasion of mucosal gastric cancer into the muscularis propria. Histopathology 2017; 71: 661-662 [PMID: 28524618 DOI: 10.1111/his.13259]

Nakata B, Tendo M, Okuyama M, Nakahara K, Ishizu H, Masuda G, Lee T, Hori T, Ohswa M, Sato H, Ishikawa T. Additional surgical resection after endoscopic mucosal dissection for early gastric cancer: A medium-sized hospital’s experience. Int J Surg 2016; 36: 335-341 [PMID: 27871804 DOI: 10.1016/j.ijsu.2016.11.084]

Yang HJ, Kim SG, Lim JH, Choi J, Im JP, Kim JS, Kim WH, Jung HC. Predictors of lymph node metastasis in patients with non-curative endoscopic resection of early gastric cancer. Surg Endosc 2015; 29: 1145-1155 [PMID: 25171882 DOI: 10.1007/s00464-014-3790-7]

Hatta W, Gotoda T, Oyama T, Kawata N, Takahashi A, Yoshifuku Y, Hoteya S, Nakagawa M, Hizama N, Eski M, Matsuda M, Ohnita K, Yamasaki K, Yoshida M, Doi O, Takada T, Tanaka K, Yamada S, Tsuj I, Ito H, Hayashi Y, Nakay N, Nakamura T, Shimosegawa T. A Scoring System to Stratify Curability After Endoscopic Submucosal Dissection for Early Gastric Cancer: “cEcura system”. J Gastroenterol 2017; 112: 874-881 [PMID: 28397873 DOI: 10.1038/jgj.2017.95]

Li H, Hao ZB, Kong FT, He QQ, Gao YH, Liang WQ, Liu DX. Predictive factors for lymph node metastasis and defining a subgroup treatable for laparoscopic lymph node dissection after endoscopic submucosal dissection in poorly differentiated early gastric cancer. World J Gastrointest Oncol 2018; 10: 360-366 [PMID: 30364712 DOI: 10.4251/wjgo.v10.i360]

Zhou B, Zhang J, Zhang J, Luo R, Wang Z, Xu H, Huang B. Risk Factors Associated with Lymph Node Metastasis After Endoscopic Resection of Early Gastric Cancer Patients Who Underwent Non-curative Endoscopic Resection: A Systematic Review and Meta-analysis. J Gastrointest Surg 2019; 23: 1318-1328 [PMID: 30187319 DOI: 10.1007/s11605-018-3924-5]

Suzuki H, Oda I, Abe S, Sekiguchi M, Nonaka S, Yashina S, Saito Y, Fukagawa T, Katli H. Clinical outcomes of early gastric cancer patients after noncurative endoscopic submucosal dissection in a large consecutive patient series. Gastric Cancer 2017; 20: 679-689 [PMID: 27722825 DOI: 10.1007/s11605-016-0651-z]

Kawata N, Kakushima N, Takizawa K, Tanaka M, Makuuchi R, Tokunaga M, Tanizawa Y, Bando E, Kawamura T, Sugino T, Kusufuka K, Shimoda T, Nakajima T, Terashima M, Ono H. Risk factors for lymph node metastasis and long-term outcomes of patients with early gastric cancer after non-curative endoscopic submucosal dissection. Surg Endosc 2017; 31: 1607-1618 [PMID: 27495338 DOI: 10.1007/s00464-016-5148-7]

Takizawa K, Ono H, Kakushima N, Tanaka M, Hasuikke N, Matsubayashii H, Yamagichi Y, Bando E, Terashima M, Kusufuka K, Nakajima T. Risk of lymph node metastases from intramucosal gastric cancer in relation to histological types: How to manage the mixed histological type for endoscopic submucosal dissection. Gastric Cancer 2013; 16: 531-536 [PMID: 23926260 DOI: 10.1007/s10120-012-0220-z]

Lee JH, Choi JH, Han HS, Kim YW, Ryu KW, Yoon HM, Eom BW, Kim CG, Lee JY, Cho SJ, Kim YI, Nam BH, Kook MC. Risk of lymph node metastasis from differentiated type mucosal early gastric cancer mixed with minor undifferentiated type histology. Ann Surg Oncol 2015; 22: 1813-1819 [PMID: 25344305 DOI: 10.1245/s10434-014-4167-7]

Kim H, Kim JH, Park JC, Lee YC, Noh SH, Kim H. Lymphovascular invasion is an important predictor of lymph node metastasis in endoscopically resected early gastric cancers. Oncol Rep 2011; 25: 1589-1595 [PMID: 21455389 DOI: 10.3892/or.2011.1242]

Abdelfatah MM, Barakat M, Othman MO, Gimrin IS, Uedo N. The incidence of lymph node metastasis in submucosal early gastric cancer according to the expanded criteria: a systematic review. Surg Endosc 2019; 33: 26-32 [PMID: 30298447 DOI: 10.1007/s00464-018-6451-2]

Miyahara K, Hatta W, Nakagawa M, Oyama T, Kawata N, Takahashi A, Yoshifuku Y, Hoteya S, Hirano M, Eski M, Matsuda M, Ohnita K, Shimoda R, Yoshida M, Doi O, Takada T, Tanaka K, Yamada S, Tsuj I, Ito H, Aoyagi H, Shimosegawa T. The Role of an Undifferentiated Component in Submucosal Invasion and Submucosal Invasion Depth After Endoscopic Submucosal Dissection for Early Gastric Cancer. Digestion 2018; 98: 161-168 [PMID: 29870985 DOI: 10.1159/000488529]
