Background

Endoscopic mucosal resection (EMR) was originally developed as an endoscopic treatment alternative to invasive surgery for early gastric neoplasms (EGN), with a negligible risk of lymph node metastasis and improved quality of life for patients. EMR is applied to lesions that meet the absolute indication: mucosal lesions smaller than 20 mm, dominated by differentiated adenocarcinoma, and not accompanied by ulcer (scar). Although EMR was originally developed as an endoscopic treatment alternative to invasive surgery for early gastric neoplasms, it is still a technically difficult and time-consuming procedure. Hybrid ESD (H-ESD) involves circumferential incision with partial submucosal dissection combined with subsequent mucosal resection by snaring, wherein the newly developed device allows us to perform H-ESD using a single device. This study aimed to determine the clinical outcomes of H-ESD compared with conventional ESD (C-ESD) for early gastric neoplasms.

Methods: In this multi-center, retrospective study, using propensity score-matched analysis, we reviewed the charts of patients with early gastric neoplasms smaller than 20 mm treated with H-ESD or C-ESD at three hospitals between January 2017 and October 2018. The primary outcome was the procedure time, and the secondary outcomes were other factors, including the en bloc resection rate, complete resection rate, curative resection rate, and rate of adverse events.

Results: Among 215 patients, 29 underwent H-ESD and 186 underwent C-ESD; 29 pairs were created by propensity score matching. In the H-ESD group, 82.8% of lesions met the absolute indication [mucosal lesions limited to 20-mm diameter, dominated by differentiated adenocarcinoma without ulcer (scar)] for endoscopic resection (ER). As a result, the procedure time of H-ESD was significantly shorter than that of C-ESD [20 (interquartile range, 12–27) min versus 40 (30–50) min; p < 0.001]. There was no significant difference in the secondary outcomes between the two groups.

Conclusion: H-ESD contributed to reduced procedure time. Therefore, H-ESD could be an alternative endoscopic treatment for gastric neoplasms when the lesion fulfills the absolute indication for ER.

Keywords: endoscopic submucosal dissection, gastric neoplasm, propensity score matching

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is a simple and useful technique, the problem of curability still remains.\textsuperscript{4} In previous studies, the en bloc resection rate was not satisfactorily high enough, especially when it was applied to lesions larger than 20 mm and/or with ulcer (scar).\textsuperscript{4–7} In this situation, endoscopic submucosal dissection (ESD) has been developed to overcome these problems, and it has been shown to achieve a considerably high rate of en bloc resection even for larger or ulcerative lesions,\textsuperscript{8} which enables us to make clear pathological diagnoses. ESD can be applied to the lesions with expanded indications,\textsuperscript{9–11} and it has become a gold standard of endoscopic treatment for EGN, facilitated by the development of the various ESD devices. However, the problem is that ESD for EGN is technically more difficult and time-consuming, with higher rates of adverse events, including perforation and bleeding, than EMR.\textsuperscript{6,12,13}

Hybrid ESD (H-ESD) is the procedure of circumferential incision with partial submucosal dissection combined with subsequent mucosal resection by snaring. H-ESD is, thus, an intermediate technique between conventional ESD (C-ESD) and EMR, which can combine the merits both of ESD and EMR. More recently, a novel multifunctional device for H-ESD called SOUTEN (Kaneka Medics, Tokyo, Japan) was invented (Figure 1). It combines the feature of a needle-type tip and a snare, enabling us to perform the procedure of H-ESD more easily with this single device.\textsuperscript{14}

Although H-ESD for EGN would have more advantages over C-ESD in terms of procedure time and complication risk, evidence on these aspects is still lacking. Thus, the objective of the present study was to determine the differences in clinical outcomes between H-ESD and C-ESD with lesions smaller than 20 mm using propensity score matching analysis.

Methods

Study design and ethics
This was a retrospective, multi-center, observational cohort study conducted at Nihon University School of Medicine Surugadai Hospital, Nihon University School of Medicine Itabashi Hospital, and Yuri-Kumiai General Hospital. We assessed the ESD database and reviewed the endoscopic reports and medical records, and obtained the necessary medical information and clinical outcomes of the ESD procedures. Written informed consent for endoscopic treatment was obtained from each patient. The study protocol was approved by the Institutional Review Board of Nihon University School of Medicine Surugadai Hospital, Nihon University School of Medicine Itabashi Hospital and Yuri-Kumiai General Hospital. The approval number was 20180904.

Patients
From January 2017 to October 2018, 285 patients with gastric tumors underwent endoscopic resection (ER) at three hospitals. Eight patients with non-neoplastic lesions, four patients treated for multiple lesions, and one patient with postoperative stomach lesions were excluded. ESD in the postoperative stomach was considered to be more difficult than that in non-operative stomach.\textsuperscript{15} Subsequently, 57 patients were excluded as their lesions were 20 mm or larger in diameter. Finally, 215 remaining patients with EGN lesions smaller than 20 mm, who underwent either C-ESD or H-ESD, were included in this study. H-ESD was performed in 29 patients, and C-ESD was performed in 186 patients (Figure 2).

ESD
All ESD procedures, including C-ESD and H-ESD, were conducted under intravenous sedation with midazolam and pentazocine hydrochloride with a standard single-channel endoscope (GIF-Q260J; Olympus Optical, Tokyo, Japan). A transparent cap was attached to the distal end of the endoscope. VIO 300D, ICC200 (ERBE...
Elektromedizin GmbH, Tübingen, Germany), or ESG100 (Olympus Optical, Tokyo Japan) was used as an electrical power unit.

**Conventional ESD**

C-ESD was performed as previously described. In brief, circumferential marking dots were placed using the tip of an endo-knife. A solution of mixed hyaluronate and a small amount of indigocarmine was injected into the submucosa to lift the lesion and secure a safe area for dissection of the submucosa. Then, a circumferential mucosal incision around the marking dots was made, and the submucosal layer was dissected out using an endo-knife. Several endo-knives, including needle-type knife, insulated tip knife, and scissors-type, were used according to the preference of attending endoscopists. The procedure-related bleeding was stopped by coagulation with the endo-knife itself or hemostatic forceps.

**Hybrid ESD**

H-ESD was performed with the newly developed SOUTEN, which enabled us to complete the procedure with one device. The technical steps of H-ESD are shown in Figure 3. In brief, a circumferential mucosal incision, followed by partial dissection, snaring, and mucosal resection, was performed. The procedure-related bleeding was stopped by coagulation with the endo-knife itself or hemostatic forceps.

**Figure 2.** A flow chart of enrollment of the patients in the present study. Initially, 285 patients with gastric neoplasms were reviewed. Finally, data from 215 patients were analyzed in the present study.

ER, endoscopic resection; ESD, Endoscopic submucosal dissection.

**Figure 3.** The procedures of H-ESD. (A–E) The schemas show each step of the H-ESD procedure: marking (A), mucosal incision (B), partial dissection (C), snaring (D), and mucosal resection (E). H-ESD, hybrid endoscopic submucosal dissection.
submucosal dissection, was performed using a needle-tip attached to the end of a snare in a manner similar to C-ESD. The procedure of submucosal dissection was continued until the point at which the attending operator judged that the lesion could be snared successfully. After completing the planned submucosal dissection, the lesion was resected by snaring in a manner similar to EMR.

**Histopathological evaluation**

After removal, ESD specimens were fixed in 10% formalin. The specimens were embedded in 10% paraffin, sectioned at 2-mm intervals, and stained with hematoxylin and eosin. Pathological diagnoses and evaluation of curability were made by the experts in gastrointestinal pathology according to the Japanese Gastric Cancer Classification and Japanese gastric cancer treatment guidelines.3,20

**Clinical outcomes**

The primary outcome was the procedure time, which was defined as the time from the start of mucosal incision to the completion of resection of the lesion. In addition, the secondary outcomes were the en bloc resection rate, complete resection rate, and adverse events (perforation and/or delayed bleeding). En bloc resection was defined as resection in a single piece, as opposed to piecemeal resection in multiple pieces. Complete resection was defined as en bloc resection with horizontal and vertical margins free of tumor. Curative resection was defined as complete resection with curative intention according to the guideline.3 Perforations were defined as a visible break of the gastric wall confirmed by endoscopy or free air confirmed by radiography or computed tomography scanning. Delayed bleeding was defined as clinical evidence of bleeding after ESD that required endoscopic hemostasis or transfusions. Endoscopists were divided into two categories: trainees and experts. Endoscopists having experience of no less than both 50 ESD procedures and 50 EMR procedures in gastrointestinal tract tumors were defined as experts. The others were defined as trainees. There was no specific training for H-ESD because H-ESD required a combined technique between EMR and ESD.

Furthermore, this was not a randomized control study. There were confounding differences between the two groups, which might have influenced the treatment outcomes of this study. Therefore, propensity score matching was adopted to compensate for the confounding bias.21–23 Logistic regression of the following factors with endoscopic procedures (H-ESD versus C-ESD) and calculation of propensity score were conducted for: age (years), sex (male/female), location (upper third of the stomach/others), position (lesser curvature/others), size (mm), depth (mucosa/submucosa), histology (differentiated/undifferentiated), ulcer (presence/absence), and operator skill (expert/trainee). This model yielded an area under the receiver operating characteristics curve of 0.69, which indicated a good predictive power. The propensity score for H-ESD was calculated using logistic regression analysis, which represented the possibility that a patient would undergo H-ESD. After estimating the propensity scores, patients in the H-ESD group were matched to patients in the C-ESD group. The matching algorithm used calipers with a width equal to one-quarter of the standard deviation (SD) of the log of the propensity score without replacement. The effect of the matching was evaluated in terms of the absolute standardized difference.

Continuous variables distributed non-normally were presented as median and interquartile range (IQR). The differences in the baseline clinico-pathological characteristics and treatment outcomes of this study were compared between the two groups using the Fisher’s exact test for categorical data, or the Mann–Whitney U test for non-normally distributed continuous data. \( p < 0.05 \) was considered statistically significant for all tests. All statistical data analyses were performed using JMP Pro 13.0 software (JMP, Marlow, UK).

**Results**

**Baseline clinico-pathological characteristics of the patients before matching**

All 29 patients for the H-ESD group and 186 patients for the C-ESD group completed their planned procedure. No patient was transferred from C-ESD to H-ESD or from H-ESD to C-ESD. The baseline clinico-pathological characteristics of the patients (29 for H-ESD group and 186 for C-ESD group) finally enrolled in the
present study are shown in Table 1. The median age of patients in the H-ESD group tended to be higher than that in C-ESD group, but it did not reach statistical significance. There was no significant difference in other factors between the two groups. As for histological types, the proportions of differentiated type in the H-ESD and C-ESD groups were 100% (29/29) and 92.5% (172/186), respectively. Regarding tumor depth, the proportions of lesions with submucosal invasion in the H-ESD and C-ESD groups were 10.3% (3/29) and 12.9% (24/186), respectively. As for the presence of ulceration, the proportion of the lesions with ulceration in H-ESD and C-ESD groups were 10.3% (3/29) and 10.8% (20/186), respectively. As a result, 82.4% (24/29) of lesions in the H-ESD group and 73.1% (136/186) in the C-ESD group met the absolute indication.

Comparison of treatment outcomes between H-ESD and C-ESD

The treatment outcomes, before propensity score matching, are shown in Supplemental Table S1. The results suggested that the median procedure time of the H-ESD group [20.0 min, (12.0–27.0)] was shorter than that of the C-ESD group [43.5 min, (30.0–62.0)] (p < 0.001). It seemed that there was no difference in the other outcomes between the two groups.

All 29 patients in the H-ESD group could be matched with patients in the C-ESD group by propensity score matching. The clinicopathological characteristics after matching between the two groups are shown in Table 2, which were quite similar without any significant differences. The matching of the two groups was considered to be well-balanced, with the absolute standardized differences of all factors ranging between ±1.96V/2n.24

The treatment outcomes of H-ESD and C-ESD after matching are summarized in Table 3. The median procedure time of H-ESD [20 min, (12–27)] was significantly shorter than that of C-ESD [40 min, (30–50)] (p < 0.001). This indicated that a nearly 50% reduction in procedure time could be achieved by H-ESD compared with C-ESD. Furthermore, lesions with a procedure time longer than 40 min were significantly fewer in H-ESD than in C-ESD (3.4% versus 48.3%, p < 0.001). There was no significant difference in other treatment outcomes between the two groups. The en bloc resection, complete resection, and curative resection rates of H-ESD were

| Table 1. Comparison of baseline clinicopathological characteristics between the H-ESD and C-ESD groups. |
|-------------------------------------------------|-----------|----------------|-----------|
|                                                 | H-ESD n = 29 | C-ESD n = 186 | p value   |
| Age, years                                       | Median [IQR] | 77 [71–80]        | 73 [66–78] | 0.088     |
| Sex, n (%)                                       | Male          | 19 (65.5)          | 137 (73.7) | 0.38      |
|                                                | Female        | 10 (34.5)          | 49 (26.3)  | 0.38      |
| Tumor location, n (%)                           | Upper thirds  | 4 (13.8)           | 35 (18.8)  | 0.54      |
|                                                | Middle thirds | 9 (31.0)           | 71 (38.2)  |           |
|                                                | Lower thirds  | 16 (55.2)          | 80 (43.0)  |           |
| Morphology, n (%)                               | Flat or depressed | 17 (58.6)    | 115 (61.8) | 0.60      |
|                                                | Protruded     | 12 (41.4)          | 71 (38.2)  |           |
| Ulceration, n (%)                               | Presence      | 3 (10.3)           | 20 (10.8)  | 1         |
|                                                | Absence       | 26 (89.7)          | 166 (89.2) |           |
| Tumor size, mm                                  | Median [IQR] | 10 [6–15]          | 12 [8–16]  | 0.095     |
| Tumor depth, n (%)                              | Mucosa        | 26 [89.7]          | 162 [87.1] | 1         |
|                                                | Submucosa     | 3 [10.3]           | 24 [12.9]  |           |
| Histology, n (%)                                | Differentiated | 29 [100]           | 172 [92.5] | 0.37      |
|                                                | Undifferentiated | 0 [0]             | 14 [7.5]   |           |
| Indication, n (%)                               | Absolute indication | 24 [82.8]   | 136 [73.1] | 0.36      |
|                                                | Expanded indication | 5 [17.2]   | 50 [26.9]  |           |

p values were calculated using the Fisher’s exact test for categorical data and the Mann-Whitney U test for continuous data. C-ESD, conventional endoscopic submucosal dissection; H-ESD, hybrid endoscopic submucosal dissection; IQR, interquartile range.
### Table 2. Comparison of clinicopathological characteristics of the patients between H-ESD and C-ESD after propensity score matching.

| Variable matching between groups | H-ESD \( n=29 \) | C-ESD \( n=29 \) | \( p \) value | ASD |
|---------------------------------|-----------------|-----------------|--------------|-----|
| Age, years; median (IQR)        | 77 (71–80)      | 72 (67–80)      | 0.54         | 0.037 |
| Sex; Male/Female                | 19/10           | 18/11           | 1            | 0.072 |
| Tumor location; U/M or L        | 4/25            | 2/27            | 0.67         | 0.23 |
| Tumor position; Lessor curvature/others | 16/13          | 16/13           | 1            | 0    |
| Histology; differentiated/undifferentiated | 29/0         | 29/0            | –            | 0    |
| Morphology; protruded/others    | 12/17           | 10/19           | 0.79         | 0.28 |
| Tumor depth; mucosa/submucosa   | 3/26            | 3/26            | 1            | 0    |
| Ulcer [scar]; present/absent    | 3/26            | 1/28            | 0.61         | 0.27 |
| Tumor size; median (IQR)        | 10 (6–15)       | 10 (7–15)       | 0.92         | 0.0059 |
| Operator skill; expert/trainee  | 21/8            | 20/9            | 1            | 0.076 |

\( p \) values were calculated using the Fisher’s exact test for categorical data and the Mann-Whitney U test for continuous data. ASD, absolute standardized difference; C-ESD, conventional endoscopic submucosal dissection; H-ESD, hybrid endoscopic submucosal dissection; IQR, interquartile range; U/M or L, upper/middle or lower third.

### Table 3. Comparison of treatment outcomes between the H-ESD and C-ESD groups after propensity score matching.

| Procedure time, min | H-ESD \( n=29 \) | C-ESD \( n=29 \) | \( p \) value |
|---------------------|-----------------|-----------------|--------------|
| Median (IQR)        | 20 (12–27)      | 40 (30–50)      | <0.001       |
| Over 40 min, \( n \) (\%) | 1 (3.4%)     | 14 (48.3%)      | <0.001       |
| En bloc resection, \( n \) (\%) | 29 (100%)   | 29 (100%)       | –            |
| Horizontal margin negative, \( n \) (\%) | 100 (100%) | 28 (96.6%)      | 1            |
| Vertical margin, negative, \( n \) (\%) | 100 (100%) | 28 (96.6%)      | 1            |
| Complete resection, \( n \) (\%) | 29 (100%)   | 27 (93.1%)      | 0.49         |
| Curative resection, \( n \) (\%) | 28 (96.6%)   | 27 (93.1%)      | 1            |
| Adverse event, \( n \) (\%) | 0 (0%)      | 1 (3.4%)        | 1            |
| Perforation, \( n \) (\%) | 0 (0%)      | 0 (0%)          | –            |
| Delayed bleeding, \( n \) (\%) | 0 (0%)      | 1 (3.4%)        | 1            |

\( p \) values were calculated using the Fisher’s exact test for categorical data and the Mann-Whitney U test for continuous data. C-ESD, conventional endoscopic submucosal dissection; H-ESD, hybrid endoscopic submucosal dissection; IQR, interquartile range.
100%, 100%, and 96.6%, respectively, while those of C-ESD were 100%, 93.1%, and 93.1%, respectively. As for adverse events, neither perforation nor delayed bleeding was observed in the H-ESD group. Although perforation was not observed in C-ESD, delayed bleeding occurred in one patient, which was successfully managed conservatively without surgery.

**Discussion**

In the present study, we compared the efficacy and safety of H-ESD and C-ESD for EGN using propensity score matching. We have shown for the first time that H-ESD yielded a significantly shorter procedure time than C-ESD, without any increase in adverse events, when the lesions were smaller than 20 mm. Therefore, H-ESD can be selected for endoscopic treatment of EGN that fulfilled the absolute indication for ER according to Japanese guidelines.

In previous reports, including a meta-analysis of endoscopic treatment for EGN, it was shown that the procedure time was significantly longer, and the complication rates, including perforation and postoperative bleeding, were significantly higher in C-ESD than those in EMR. The mean procedure time, postoperative bleeding, and intraoperative perforation rate in C-ESD reached up to 93.9 min, 15.6%, and 5.3%, respectively.25 Recently, a multicenter prospective study of gastric ER, which showed real-world evidence in Japan, showed favorable short-term outcomes.26 ESD consisted of 99.4% of ERs for EGN. Postoperative bleeding and intraoperative perforation were reduced in 4.4% and 2.3% of patients, respectively. However, the mean procedure time was still 91.4 min. Although the treatment outcomes, including en bloc resection rate, complete resection rate, curative resection rate, and adverse event rate for C-ESD, have been satisfactory enough owing to the development of ESD devices and improvement of endoscopic skills, the problem with long procedure time is yet to be resolved. For this reason, the procedure time was set as the primary outcome of the present study. We showed that the procedure time was significantly shorter in H-ESD than in C-ESD.

The en bloc resection rate in EMR decreases with larger lesions.6 The en bloc resection rate of EMR was significantly lower than that of ESD, especially for lesions larger than 10 mm.4,6 In contrast, according to Japanese guidelines, the absolute indication of EMR or ESD for EGN is as follows: a differentiated-type adenocarcinoma without ulcerative findings, a T1a depth of invasion diagnosed clinically, and a 20-mm diameter.3 In fact, the snare size of the multifunctional device used in the present study was not large enough to perform an en bloc resection for lesions larger than 20 mm. Thus, we determined that the EGNs that fulfilled the absolute indications per the Japanese guidelines were eligible for H-ESD in the present study. As a result, the horizontal and vertical margins of all lesions were both negative for any neoplastic component, while 100% en bloc and complete resection rate was achieved by H-ESD. However, lesions larger than 20 mm may be subjected to H-ESD when partial submucosal dissection is sufficient for snaring. Therefore, the indication of H-ESD should be further explored in future studies, especially considering lesion size.

Several clinicopathological factors, including tumor size, tumor location, tumor position, presence of ulceration (scar), tumor depth, tumor histology, and operator skill, are reported to be associated with the difficulty and adverse events of ESD.27–32 Before propensity score matching, there were no significant differences in the baseline of those factors between H-ESD and C-ESD groups. In this condition, the procedure time of H-ESD was significantly shorter than that of C-ESD (Supplemental Table S1). However, the median age of H-ESD tended to be older than that of C-ESD (p = 0.088), and the median tumor size of H-ESD tended to be smaller than that in C-ESD (p = 0.095). Thus, it was possible that some of those factors affected the treatment outcomes of the study. Therefore, propensity score matching was adopted to reduce the confounding bias between the two groups. As a result, the superiority of H-ESD over C-ESD in the procedure time could be also observed after propensity score matching in the present study.

H-ESD was originally invented as a rescue treatment for colorectal neoplasms in which endoscopists faced technical difficulties in continuing the procedure of C-ESD. The safety and efficacy of H-ESD for colorectal neoplasms as a rescue therapy have been reported previously.33 The procedure time of H-ESD was significantly shorter than that of C-ESD, although H-ESD was applied only to colorectal neoplasms with difficulties in the ESD procedure. It was also
reported that there were no significant differences in the en bloc resection rate, perforation rate, and bleeding rate between H-ESD and C-ESD, and local recurrence did not occur in any case. Therefore, the planned H-ESD, not a rescue H-ESD, has been applied for colorectal neoplasms, where superior clinical outcomes were obtained compared with C-ESD. Later, H-ESD was also applied to EGN; however, a previous report could not prove the superiority in the procedure time of H-ESD. There was a limitation that a snare tip for polypectomy was used for both ESD and H-ESD procedures, which might not be suitable for mucosal incision or submucosal dissection, and the sample size was quite small. Therefore, it could not demonstrate shorter procedure time of H-ESD compared with C-ESD. In this situation, the recently developed multifunctional device could influence the treatment outcomes of H-ESD as previously reported. Thus, we conducted the present study to compare the treatment outcomes between H-ESD using a multifunctional device and C-ESD, wherein H-ESD was applied as a first-line therapy and not as a rescue therapy. The findings have shown that the treatment outcomes of H-ESD using a multifunctional device are sufficient for its consideration as a first-line endoscopic treatment for EGN. Considering H-ESD as a first-line endoscopic treatment, it is important to consider not only treatment outcomes, such as procedure time, but also the total cost of the procedure. When H-ESD-related procedures, including mucosal incision, submucosal dissection, and snaring, were performed using more than one device, similar to rescue H-ESD, the total cost of H-ESD was higher than that of C-ESD. The problem was solved by the development of a multifunctional device allowing us to complete all procedures with a single device. In fact, the SOUTEN used in the present study is less expensive than a conventional endo-knife, which contributes to the reduction of the medical cost for H-ESD. Taken together, compared with C-ESD, H-ESD using a multifunctional device yields not only comparable treatment outcomes but also cost-saving in the endoscopic treatment of EGN smaller than 20 mm.

The precutting EMR technique has already been applied to the gastrointestinal tract tumors including gastric neoplasms. This technique is defined as circumferential mucosal incision followed by snaring without any submucosal dissection. However, H-ESD includes the procedure of partial submucosal dissection, which assist in resecting the lesion completely. The complete resection rate was reported as 75.7–90.2% in precutting EMR for gastric neoplasms. In this study, 100% complete resection rate was achieved by adding partial submucosal dissection. Therefore, a higher rate of complete resection might be achieved in H-ESD than that in precutting EMR for gastric neoplasms.

Some limitations were associated with the present study. First, this was a retrospective study and not a study involving a randomized population. There was a possibility of selection bias, as lesions that were easy to snare were selected for H-ESD. Second, the sample size was relatively small, even though this was a multi-center study. Although 100% complete resection rate was achieved in H-ESD, and the procedure time of H-ESD was significantly shorter than that of C-ESD, this study did not prove a non-inferior outcome in curability and safety of H-ESD against C-ESD due to the small sample size. Therefore, a multi-center prospective study with a larger population should be conducted to clarify this point in future. Third, the indication for H-ESD was limited to lesions smaller than 20 mm, which met the absolute indication of ER by the Japanese guidelines. Therefore, the treatment outcomes of the present study could not be applied to EGN beyond the absolute indication: larger size than 20 mm, submucosal invasion, poorly differentiated component, and ulcers (scar). Third, this study included only short-term outcomes of H-ESD or C-ESD. Long-term outcomes, such as the rate of residual lesions or recurrent lesions, were not included in this study. Although an extremely low rate of residual or recurrent lesions are estimated due to 100% complete resection rate for H-ESD, a further study should also include the long-term outcomes.

In conclusion, the procedure time of H-ESD using a multifunctional device was significantly shorter than that of C-ESD, although there were no differences in the curability and adverse events between H-ESD and C-ESD for lesions smaller than 20 mm. Therefore, H-ESD could be an alternative endoscopic treatment of EGN when the lesion fulfils the absolute indication for ER.

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Conflict of interest statement
Mitsuru Esaki, Sho Suzuki, Toshiki Horii, Ryoji Ichijima, Shun Yamakawa, Hitoshi Shibuya, Chika Kusano, Hisatomo Ikehara, and Takuji Gotoda have no conflicts of interest or financial ties to disclose.

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ORCID iD
Mitsuru Esaki https://orcid.org/0000-0001-7353-2153

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References
1. Tada M, Murakami A, Karita M, et al. Endoscopic resection of early gastric cancer. Endoscopy 1993; 25: 445–450.
2. Ono H, Yao K, Fujishiro M, et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. Dig Endosc 2016; 28: 3–15.
3. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer 2017; 20: 1–19.
4. Park YM, Cho E, Kang HY, et al. The effectiveness and safety of endoscopic submucosal dissection compared with endoscopic mucosal resection for early gastric cancer: a systematic review and metaanalysis. Surg Endosc 2011; 25: 2666–2677.
5. Nakamoto S, Sakai Y, Kasanuki J, et al. Indications for the use of endoscopic mucosal resection for early gastric cancer in Japan: a comparative study with endoscopic submucosal dissection. Endoscopy 2009; 41: 746–750.
6. Shimura T, Sasaki M, Kataoka H, et al. Advantages of endoscopic submucosal dissection over conventional endoscopic mucosal resection. J Gastroenterol Hepatol 2007; 22: 821–826.
7. Watanabe K, Ogata S, Kawazoe S, et al. Clinical outcomes of EMR for gastric tumors: historical pilot evaluation between endoscopic submucosal dissection and conventional mucosal resection. Gastroint Endosc 2006; 63: 776–782.
8. Ono H, Kondo H, Gotoda T, et al. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001; 48: 225–229.
9. Gotoda T, Yanagisawa A, Sasaki M, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer 2000; 3: 219–225.
10. Takizawa K, Takashima A, Kimura A, et al. A phase II clinical trial of endoscopic submucosal dissection for early gastric cancer of undifferentiated type: Japan clinical oncology group study JCG1009/1010. Jpn J Clin Oncol 2013; 43: 87–91.
11. Hasuike N, Ono H, Boku N, et al. A non-randomized confirmatory trial of an expanded indication for endoscopic submucosal dissection for intestinal-type gastric cancer (cT1a): the Japan clinical oncology group study (JCG0607). Gastric Cancer 2018; 21: 114–123.
12. Yamamoto S, Uedo N, Ishihara R, et al. Endoscopic submucosal dissection for early gastric cancer performed by supervised residents: assessment of feasibility and learning curve. Endoscopy 2009; 41: 923–928.
13. Zhao Y and Wang C. Long-term clinical efficacy and perioperative safety of endoscopic submucosal dissection versus endoscopic mucosal resection for early gastric cancer: an updated meta-analysis. Biomed Res Int 2018; 2018: 3152346.
14. Ohata K, Muramoto T, Minato Y, et al. Usefulness of a multifunctional snare designed for colorectal hybrid endoscopic submucosal dissection (with video). Endosc Int Open 2018; 6: E249–E253.
15. Esaki M, Suzuki S, Hayashi Y, et al. Propensity score-matching analysis to compare clinical outcomes of endoscopic submucosal dissection for early gastric cancer in the postoperative and non-operative stomachs. BMC Gastroenterol 2018; 18: 125.
16. Esaki M, Suzuki S, Hayashi Y, et al. Splash M-knife versus Flush knife BT in the technical outcomes of endoscopic submucosal dissection for early gastric cancer: a propensity score matching analysis. BMC Gastroenterol 2018; 18: 35.
17. Soetikno RM, Gotoda T, Nakanishi Y, et al. Endoscopic mucosal resection. *Gastrointest Endosc* 2003; 57: 567–579.

18. Ohkawa M, Hosokawa K, Boku N, et al. New endoscopic treatment for intramucosal gastric tumors using an insulated-tip diathermic knife. *Endoscopy* 2001; 33: 221–226.

19. Hayashi Y, Esaki M, Suzuki S, et al. Clutch Cutter knife efficacy in endoscopic submucosal dissection for early gastric neoplasms. *World J Gastrointest Oncol* 2018; 10: 487–495.

20. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; 14: 101–112.

21. Suzuki S, Gotoda T, Kusano C, et al. The efficacy and tolerability of a triple therapy containing a potassium-competitive acid blocker compared with a 7-Day PPI-based low-dose clarithromycin triple therapy. *Am J Gastroenterol* 2016; 111: 949–956.

22. Suzuki S, Gotoda T, Hatta W, et al. Survival benefit of additional surgery after non-curative endoscopic submucosal dissection for early gastric cancer: a propensity score matching analysis. *Ann Surg Oncol* 2017; 24: 3353–3360.

23. Suzuki S, Gotoda T, Kobayashi Y, et al. Usefulness of a traction method using dental floss and a hemoclip for gastric endoscopic submucosal dissection: a propensity score matching analysis (with videos). *Gastrointest Endosc* 2016; 83: 337–346.

24. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009; 28: 3083–3107.

25. Oda I, Suzuki H, Nonaka S, et al. Complications of gastric endoscopic submucosal dissection. *Dig Endosc* 2013; 25(Suppl. 1): 71–78.

26. Suzuki H, Takizawa K, Hirasawa T, et al. Short-term outcomes of multicenter prospective cohort study of gastric endoscopic resection: ‘real-world evidence’ in Japan. *Dig Endosc* 2019; 31: 30–39.

27. Choi IJ, Kim CG, Chang HJ, et al. The learning curve for EMR with circumferential mucosal incision in treating intramucosal gastric neoplasm. *Gastrointest Endosc* 2005; 62: 860–865.

28. Kim JH, Nam HS, Choi CW, et al. Risk factors associated with difficult gastric endoscopic submucosal dissection: predicting difficult ESD. *Surg Endosc* 2017; 31: 1617–1626.

29. Imagawa A, Okada H, Kawahara Y, et al. Endoscopic submucosal dissection for early gastric cancer: results and degrees of technical difficulty as well as success. *Endoscopy* 2006; 38: 987–990.

30. Yoon JY, Shim CN, Chung SH, et al. Impact of tumor location on clinical outcomes of gastric endoscopic submucosal dissection. *World J Gastroenterol* 2014; 20: 8631–8637.

31. Ahn JY, Choi KD, Choi JY, et al. Procedure time of endoscopic submucosal dissection according to the size and location of early gastric cancers: analysis of 916 dissections performed by 4 experts. *Gastrointest Endosc* 2011; 73: 911–916.

32. Chung IK, Lee JH, Lee SH, et al. Therapeutic outcomes in 1000 cases of endoscopic submucosal dissection for early gastric neoplasms: Korean ESD study group multicenter study. *Gastrointest Endosc* 2009; 69: 1228–1235.

33. Okamoto K, Muguruma N, Kagemoto K, et al. Efficacy of hybrid endoscopic submucosal dissection (ESD) as a rescue treatment in difficult colorectal ESD cases. *Dig Endosc* 2017; 29(Suppl. 2): 45–52.

34. Bae JH, Yang DH, Lee S, et al. Optimized hybrid endoscopic submucosal dissection for colorectal tumors: a randomized controlled trial. *Gastrointest Endosc* 2016; 83: 584–592.

35. Kim SJ, Choi CW, Kang DH, et al. Endoscopic submucosal dissection of gastric neoplasms using a snare tip. *Scand J Gastroenterol* 2018; 53: 238–242.

36. Kobara H, Mori H and Masaki T. Effective and economical endoscopic resection using a novel multifunctional snare for small-sized gastric neoplasms. *Dig Endosc* 2018; 30: 800–801.

37. Tanaka S, Kashida H, Saito Y, et al. JGES guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. *Dig Endosc* 2015; 27: 417–434.

38. Sakamoto T, Matsuda T, Nakajima T, et al. Efficacy of endoscopic mucosal resection with circumferential incision for patients with large colorectal tumors. *Clin Gastroenterol Hepatol* 2012; 10: 22–26.

39. Min BH, Lee JH, Kim JJ, et al. Clinical outcomes of endoscopic submucosal dissection (ESD) for treating early gastric cancer: comparison with endoscopic mucosal resection after circumferential precutting (EMR-P). *Dig Liver Dis* 2009; 41: 201–209.

40. Park SM, Kim JS, Ji JS, et al. Efficacy of endoscopic mucosal resections for the management of small gastric adenomas with low-grade dysplasia. *Scand J Gastroenterol* 2015; 50: 1175–1182.