

Management of early gastric cancer with positive horizontal or indeterminable margins after endoscopic submucosal dissection: multicenter survey



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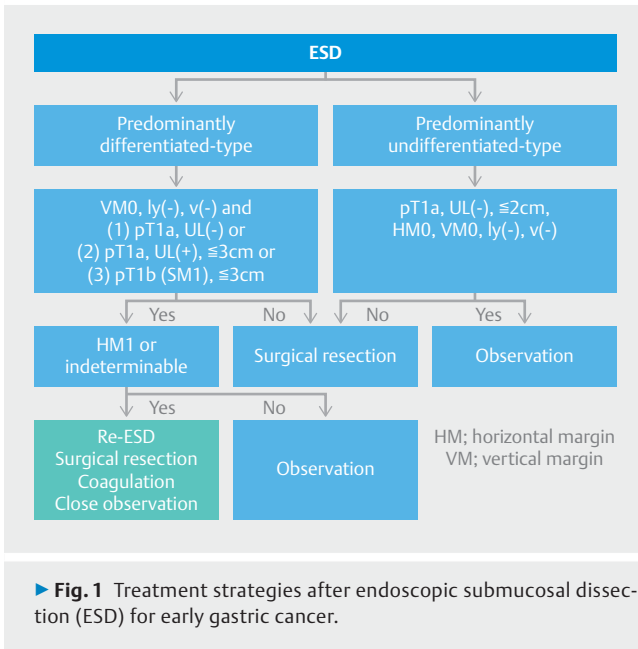
ABSTRACT

Background and study aims Positive horizontal margins in resected specimens are sometimes encountered after endoscopic submucosal dissection (ESD) for early gastric cancers, and appropriate treatment strategies for these cases are not established. The aim of this study was to evaluate current empirical treatments for patients with positive horizontal or indeterminable margins after ESD.

Patients and methods We performed a multicenter survey and data from 14 hospitals were collected. The pooled proportions of positive horizontal or indeterminable margins and those of patients followed up without early intervention were calculated using a logistic-normal random-effects model. For calculating pooled estimates, subgroup analyses of high- and non-high-volume centers were conducted.

Results A total of 11,796 ESD cases were enrolled and 229 patients (2%) had positive horizontal or indeterminable margins. Ninety-eight cases were treated within 30 days of ESD and 131 cases were followed up without early treatments. Pooled estimates of positive margins in high- and non-high-volume centers were 1% (95% CI: 1%–2%) and 2% (95% CI: 1%–4%), respectively, and were not heterogeneous ($P=0.191$). The proportion of patients followed up without early intervention ranged from 30% to 100%. The pooled estimate was 68% (95% CI: 50%–83%). The pooled estimates of high- and non-high-volume centers were 65% (95% CI: 38%–85%) and 72% (95% CI: 44%–89%), respectively, and were not heterogeneous ($P=0.692$).

Conclusion There was insufficient consensus regarding treatment strategies used for early gastric cancer with positive horizontal or indeterminable margins after ESD. Further studies are required to establish a consensus.



Introduction

Endoscopic submucosal dissection (ESD) was introduced for treating early gastric cancer with a minimal risk of regional lymph node and distant metastases [1]. ESD is currently performed worldwide because neoplasms can be resected *en bloc*, and a detailed pathological assessment of resected specimens can be performed [1,2]. However, positive horizontal margins in the resected specimens are sometimes encountered after ESD [1–9]. Nevertheless, appropriate treatment strategies for differentiated-type gastric cancers with positive horizontal or indeterminate margins after ESD have not yet been established (► **Fig. 1**) [10]. The aim of this study was to estimate the probability of positive horizontal or indeterminate margins after ESD and evaluate the current empirical treatments for the patients with positive horizontal or indeterminate margins after ESD. We performed a multicenter survey of the treatment strategies for early gastric cancer with positive horizontal or indeterminate margins after ESD.

Patients and methods

Data from 14 hospitals (Cancer Institute Hospital, Toranomon Hospital, Kitasato University East Hospital, NTT Medical Center Tokyo, St. Luke's International Hospital, Tokai University School of Medicine, Kudanzaka Hospital, Koritsu Showa Hospital, Tokyo Metropolitan Bokuto Hospital, Juntendo University School of Medicine, Tokyo Women's Medical University Yachiyo Medical Center, Keio University School of Medicine, Foundation of Detection of Early Gastric Carcinoma, and Sanraku Hospital) that participated in the 30th endoscopic gastric mucosal resection (EGMR) conference were collected. The contents of the questionnaires in the current study are demonstrated in ► **Fig. S1**.

EGMR conference is a well-known research conference focusing on endoscopic therapy for early gastric cancer, which has been held biannually since 2000 in Tokyo, Japan and many endoscopists from more than 20 medical centers usually attend the conference. These institutions covered medical centers where the majority of endoscopists with expertise in ESD were working in Tokyo. Actually, at least 8 ESD opinion leaders worked in these institutions. It was expected that these doctors' behaviors would reflect current empirical therapeutic strategies after ESD in Japan. Survey questionnaires were sent to the representatives of each institution. Replies to our questionnaires and approval by the institutional review board (IRB) for the study were obtained from 14 institutions.

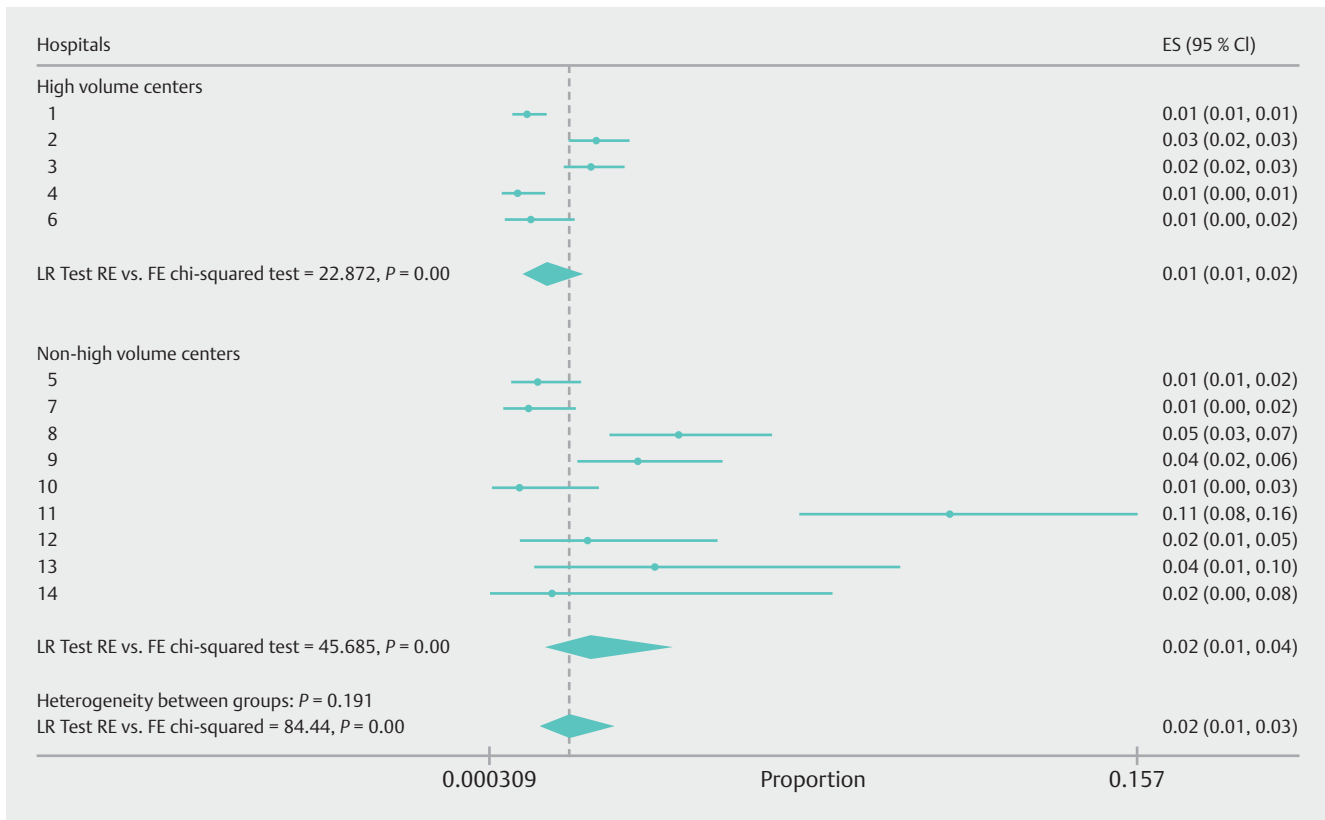
The proportion of patients with positive horizontal or indeterminate margins and the proportion of patients who were followed up without early interventions were calculated for each institution. Two-sided or 1-sided 95% confidence intervals (CIs) of those proportions were also calculated. Meta-analyses for proportions were performed to calculate pooled estimates of the above mentioned 2 proportions. The pooled proportions of positive horizontal or indeterminate margins and those of the patients who were followed up without early intervention were calculated by a logistic-normal random-effects model [11]. For calculating pooled estimates, subgroup analyses of high- and non-high-volume centers were also conducted. A high-volume center was defined as an institution with more than 100 ESD cases per year. All analyses were performed by STATA® version 14.1 (StataCorp, College Station, TX, USA).

Results

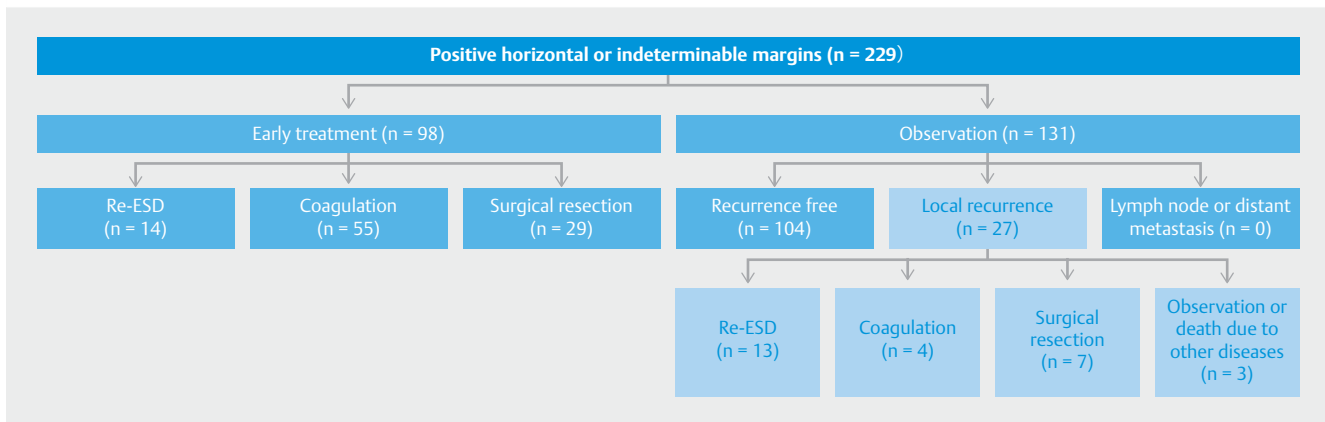
A total of 11,796 differentiated-type gastric adenocarcinomas that met the absolute or expanded indication for ESD in the Japanese gastric cancer treatment guidelines 2010 (tumors clinically diagnosed as T1a and either no ulcer findings regardless of size or positive ulcer findings in tumors sized ≤ 3 cm in diameter) [10] were treated with ESD from September 2002 to May 2014. Positive horizontal or indeterminate margins were observed in 235 resected specimens pathologically (2.0%). Six cases in which the description in the questionnaire was incomplete were excluded from the study, and 229 cases were enrolled. The treatment strategies were evaluated in 229 cases with positive horizontal or indeterminate margins using obtained questionnaires.

The number of total ESD cases and that of early gastric cancer with horizontal or indeterminate margins after ESD in each institution are presented in ► **Table S1**.

Pooled estimates of positive or indeterminate margins in 14 institutions are demonstrated in ► **Fig. 2**. Institutions 1 to 4 and 6 were allocated as high-volume centers. The proportion of patients with horizontal or indeterminate margins ranged from 0.6% to 11%. The pooled estimate of positive horizontal or indeterminate margins was 2% (95% CI: 1%–3%). The pooled estimates of positive margins in high- and non-high-volume centers were 1% (95% CI: 1%–2%) and 2% (95% CI: 1%–4%), respectively. Pooled estimates of these subgroups were marginally heterogeneous ($P=0.191$).



► **Fig. 2** Pooled estimates of positive or indeterminable margins in high and non-high volume centers.

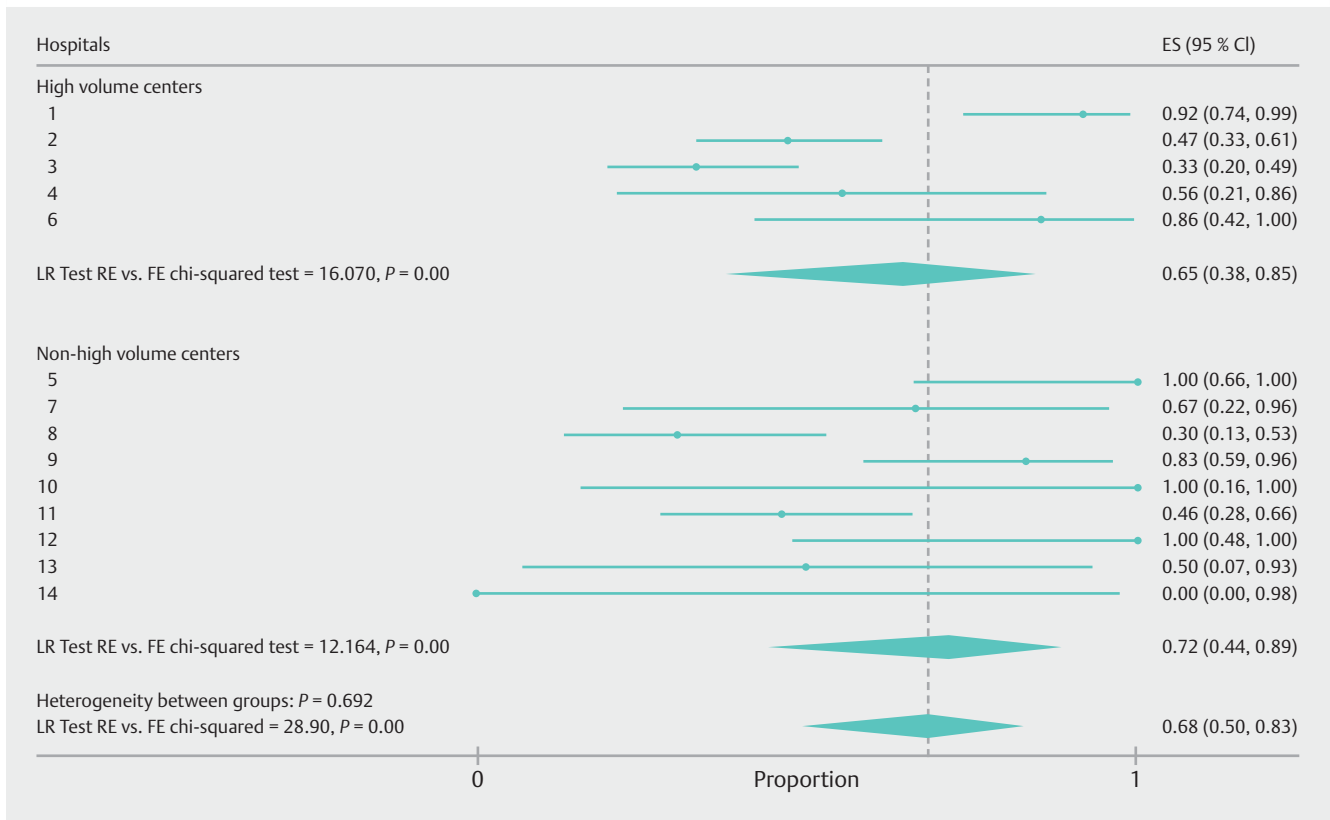


► **Fig. 3** Treatment strategy for early gastric cancer with positive horizontal or indeterminable margins after endoscopic submucosal dissection (ESD).

The treatment strategies used for early gastric cancer with positive horizontal or indeterminable margins after ESD are presented in ► **Table S1** and ► **Fig. 3**. A total of 98 patients with early gastric cancer were treated within 30 days of ESD treatment initiation: repeat ESD (re-ESD), n = 14 (14%), 4 institutions; coagulation, n = 55 (56%), 6 institutions; and surgical resection, n = 29 (30%), 7 institutions. Early re-ESD was completed safely in all 14 cases without any complications such as perforation or post-treatment bleeding. Residual cancer was demonstrated in the re-ESD specimens in 6 cases (43%). Coagulation

was performed safely in all 55 cases. Recurrence after coagulation was observed in 5 cases (9%) in which coagulation was performed additionally. Local residual cancers were observed in 13 of 29 surgically resected specimens (45%). Lymph node metastasis was not demonstrated in any surgically treated cases.

Pooled estimates of follow-up rate without early intervention in 14 institutions are demonstrated in ► **Fig. 4**. The proportion of patients who were followed up without early intervention in those with horizontal or indeterminable margins ranged from 30% to 100%. The pooled estimate was 68%



► **Fig. 4** Pooled estimates of follow-up rate without early intervention in high and non-high volume centers.

(95% CI: 50%–83%). The pooled estimates of high- and non-high-volume centers were 65% (95% CI: 38%–85%) and 72% (95% CI: 44%–89%), respectively. Pooled estimates of these subgroups were not heterogeneous ($P = 0.692$).

Results of follow-up cases without early intervention are demonstrated in ► **Table S2**. In total, 131 cases were followed up without additional early treatments after initial ESD; 27 cases (21%) recurred locally during the median follow-up period of 6 months (range, 1–74 months). The strategies used for the 27 recurrent cases more than 30 days after initial ESD were as follows (► **Table S3**): re-ESD, $n = 13$, 6 institutions; coagulation, $n = 4$, 3 institutions; surgical resection, $n = 7$, 5 institutions; and further observation or death due to other diseases, $n = 3$, 2 institutions. Late coagulation was performed safely in all 4 cases without any complications such as perforation or post-treatment bleeding. However, recurrence occurred in 3 coagulation cases (75%), in which additional coagulation was performed. Lymph node or distant metastases were not found in the resected specimens from the seven surgically-treated patients. Additional treatments were not performed and observation was done in three locally recurrent cases due to the patient's decision and/or comorbid cardiopulmonary diseases.

Results of late re-ESD for recurrent cases are demonstrated in ► **Table 1**. The median size of the residual cancers and that of the resected specimens were 12 mm (range, 6–41 mm) and 40 mm (range, 20–59 mm), respectively. The median procedural time was 133 min (range, 70–353 min). The rate of *en bloc* re-

section was 92% (12/13) in the late re-ESD group. Recurrence after late re-ESD occurred in the piecemeal resected case, in which a third ESD was performed and there was no recurrence during the follow-up period of 13 months after the third ESD. Needle-type knives (Dual knife/Flush knife/Flex knife), hook knives, and insulated tip (IT)-type knives (IT knife/IT knife 2) were preferred, and **scissor-type grasping knives** (SB knife/Clutch cutter) were not selected during re-ESD procedure. Perforation and post-ESD bleeding did not occur in any case.

Discussion

This is the first report of a multicenter survey of treatment strategies for early gastric cancer with positive horizontal or indeterminate margins after ESD. The pooled estimates of positive margins in high-volume centers (1%) were less than those in non-high-volume centers (2%) in our study. Although the heterogeneous test between above 2 groups was not statistically significant ($P = 0.191$), this test lacks power. Kakushima et al reported that there were 3 types of lesions that resulted in positive margins after resection (lesions with a flat spreading area, lesions with an unexpected nearby lesion, and lesions with lateral extension beneath non-cancerous mucosa) and tumor diameter, recurrent-type cancer, submucosal cancer, and undifferentiated-type cancer were factors significantly related to margin-positive resection [3]. Therefore, early gastric can-

► **Table 1** Results of repeat ESD for locally recurrent lesions (n = 13).

Median size of residual cancers (range) (mm)	12 (6–41)
Median size of resected specimens (range) (mm)	40 (20–59)
Median procedure time (range) (min)	133 (70–353)
En bloc resection rate (%)	92% (12/13)
Pathological tumor-free margin rate (%)	92% (12/13)
Histopathologic depth (mucosa/submucosa)	13/0
Lymph vascular involvement (negative/positive)	13/0
Curative resection rate (%)	92% (12/13)
Complication (bleeding/perforation)	0/0
Preferred knives (Needle type/Hook type/IT type)	5/3/3
ESD, endoscopic submucosal dissection; IT type, Insulated-tip type	

cers with these factors may need to be treated in high-volume centers.

A first, and difficult, decision is whether the cases are treated promptly or followed up. In the current study, early treatment (early re-ESD, coagulation, or surgery) was performed in 98 cases (43%), and 131 cases (57%) were followed up without additional early treatments. In addition, pooled estimates of the follow-up rate without early intervention in high- and non-high-volume centers were not heterogeneous ($P=0.692$). Recently, a cancer-positive lateral margin length ≥ 6 mm in the ESD specimens has been reported as an independent risk factor for local recurrence after ESD [5,6]. Before deciding whether the cases with positive horizontal or indeterminable margins are treated promptly or followed up, the length of cancer-positive lateral margins may need to be evaluated in the ESD specimens.

A second difficult decision is how to treat the cases with positive horizontal or indeterminable margins at an early date. Re-ESD, coagulation, or surgery were used in additional treatments within 30 days in the enrolled cases. With time, submucosal fibrosis becomes severe and it can be considered difficult to resect the residual cancers endoscopically. Coagulation was performed in 55 cases at 6 institutions (56%). Admittedly, coagulation is easy and convenient. That may be the reason why coagulation was used to treat more than half of the enrolled cases. However, a specimen is not obtained and the state of residual cancers cannot be determined. Therefore, follow-up should be conducted more carefully. On the other hand, specimens can be obtained in re-ESD or surgery. In the early re-ESD group, ESD was completed safely in all cases and specimens were obtained. As a result, the re-ESD specimens could be evaluated pathologically and intramucosal residual cancer was demonstrated in 6 cases (43%). Early gastrectomy was performed in 29 cases. However, local residual cancers were observed in 13 of 29 surgically resected specimens (45%) and lymph node metastasis was not demonstrated in any cases. Early gastrectomy can be considered highly invasive.

The third choice is how to manage the later recurrent cases after follow-up. Application of coagulation to the later recur-

rent lesions may be easy and convenient as in the cases treated at an early date. However, the recurrence rate was high in late coagulation cases (75%) and coagulation may not be sufficient for the treatment of later recurrent lesions. As in the cases treated at an early date, lymph node or distant metastases were not found in the cases treated surgically at a later stage and local resection may be sufficient for the treatment of these lesions. *En bloc* resection rate was high (92%) and the recurrent case after late ESD was treated using a third ESD. In addition, there were no complications in the late re-ESD group. Because locally recurrent cancers were within the mucosal layer and ESD is less invasive than gastrectomy, ESD may be considered a more suitable additional treatment for locally recurrent lesions, as suggested in previous reports [7–9].

There were several serious limitations in our study. First, the probability of positive horizontal or indeterminable margin should be collected not from the questionnaire, but from official reports such as published literatures. Therefore, information bias was inevitable. Second, the selection criteria were insufficient because institutions that responded to our questionnaire were not selected randomly and limited in Tokyo, Japan. This study was approved by the internal review boards only in these 14 institutions. Third, the detailed follow-up results after ESD and additional treatments were not asked in our questionnaire. Therefore, the effectiveness of each strategy for early gastric cancer with positive horizontal or indeterminable margins after ESD could not be evaluated.

Conclusion

In conclusion, the rate of positive margins after ESD tended to be lower in high volume centers. There was insufficient consensus regarding the treatment strategies used for early gastric cancer with positive horizontal or indeterminable margins after ESD. Therefore, further studies are required to establish a consensus.

Acknowledgements

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Competing interests

None

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Questionnaires of the strategies used for early gastric cancer with positive horizontal or indeterminable margins after endoscopic submucosal dissection (ESD).

Hospital _____ Delegate _____

Q1. The number of gastric cancers treated with ESD so far?
_____ cases from month/year (____/____) to month/year (____/____)

Q2. The number of the cases in which the tumors were diagnosed as T1a and either no ulcer findings regardless of size or positive ulcer findings in tumors sized ≤ 3 cm in diameter, and positive horizontal or indeterminable margins were demonstrated in the ESD-specimens.
_____ cases

Q3. Strategies for Q2 cases

- ① Early repeat ESD (re-ESD) (ESD within 30 days after initial ESD)
_____ cases
- ② Early coagulation (coagulation within 30 days after initial ESD)
_____ cases
- ③ Early gastrectomy (additional gastrectomy without follow-up)
_____ cases
- ④ Follow-up without early treatments _____ cases

Q4. Results of early re-ESD (Q3 ①)

- A. Perforation _____ cases
- B. Uncontrollable bleeding _____ cases
- C. The number of the cases in which residual cancer was demonstrated in the re-ESD specimens _____ cases

Q5. Results of early coagulation (Q3 ②)

- A. Perforation _____ cases
- B. Uncontrollable bleeding _____ cases
- C. Recurrence after early coagulation _____ cases
Additional treatments for recurrent cases (_____)

Q6. Results of early gastrectomy (Q3 ③)

- A. The number of the cases in which residual cancer was demonstrated in the surgically resected stomach. _____ cases
- B. The number of the cases in which lymph node metastasis was observed in the resected specimens. _____ cases

Q7. Results of follow-up cases (Q3 ④)

- A. No recurrence _____ cases
- B. Local recurrence _____ cases
- C. Lymph node metastasis or distant metastasis _____ cases

Q8. Duration from initial ESD to recurrence in the follow-up cases (Q3 ④)

- a. Local recurrence (Q7 B)
 - Case 1 _____ months
 - Case 2 _____ months
 - Case 3 _____ months
- b. Lymph node metastasis or distant metastasis (Q7 C)
 - Case 1 _____ months
 - Case 2 _____ months
 - Case 3 _____ months

Q9. Additional treatments for local recurrent cases (Q7 B)

- I. Re-ESD _____ cases
- II. Coagulation _____ cases
- III. Gastrectomy _____ cases
- IV. No treatment _____ cases

Q10. Results of re-ESD in local recurrent cases after follow-up (Q9 I)

- I. En bloc resection _____ cases
- II. Piecemeal resection _____ cases
- III. Diameter of recurrent tumors
 - Case 1 _____ mm
 - Case 2 _____ mm
 - Case 3 _____ mm
- IV. Diameter of the resected specimens
 - Case 1 _____ mm
 - Case 2 _____ mm
 - Case 3 _____ mm
- V. Procedural time
 - Case 1 _____ min
 - Case 2 _____ min
 - Case 3 _____ min
- VI. Perforation _____ cases
- VII. Uncontrollable bleeding _____ cases
- VIII. R0 _____ cases R1 _____ cases
- IX. Recurrence after re-ESD _____ cases
Clinical course in recurrent cases after re-ESD _____
- X. Follow-up periods after re-ESD
 - Case 1 _____ mm
 - Case 2 _____ mm
 - Case 3 _____ mm

Q11. What devices do you prefer during re-ESD procedure?

- Check up to 2 knives.
- Dual knife/Flush knife/Flex knife Hook knife
- SB knife/Clutch cutter IT knife/IT knife 2
- Others _____

Q12. Results of coagulation (Q9 II)

- I. Perforation _____ cases
- II. Uncontrollable bleeding _____ cases
- III. Recurrence after coagulation _____ cases
Additional treatments for recurrent cases _____

Q13. Results of gastrectomy (Q9 III)

- I. The number of the cases in which residual cancer was demonstrated in the surgically resected stomach. _____ cases
- II. The number of the cases in which lymph node metastasis was observed in the resected specimens. _____ cases
Detailed clinical course of recurrent cases _____

Q14. Reasons of follow-up without intervention (Q9 IV)

- Case 1 _____
- Case 2 _____

► **Fig. S1** Questionnaires of the strategies used for early gastric cancer with positive horizontal or indeterminable margins after endoscopic submucosal dissection (ESD).

► **Table S1** Management of early gastric cancers with positive horizontal or indeterminable margins after initial ESD.

Institutions	Total ESD (Q1)	Data collection period (From month/year to month/year)	ESD cases/year	HM1 cases (Q2)	Early ESD (Q3①)	Early coagulation (Q3②)	Early surgery (Q3③)	Follow-up (Q3④)
1	2686	Jan/2003 – Mar/2014	241	25	0	0	2	23
2	2042	Apr/2005 – Mar/2013	255	53	11	2	15	25
3	1819	Sep/2002 – Apr/2014	157	40	0	21	4	15
4	1274	May/2007 – Mar/2014	186	8	1	0	2	5
5	762	Apr/2004 – May/2014	75	9	0	0	0	9
6	690	Aug/2008 – May/2014	118	7	1	0	0	6
7	627	Oct/2003 – May/2014	59	6	0	0	2	4
8	500	Jan/2004 – Oct/2013	51	23	0	14	2	7
9	500	Jan/2006 – May/2014	60	18	1	2	0	15
10	270	Jan/2010 – Mar/2014	65	2	0	0	0	2
11	252	Dec/2006 – May/2014	34	28	0	15	0	13
12	209	Jun/2010 – Dec/2013	60	5	0	0	0	5
13	100	Jan/2003 – Apr/2014	9	4	0	0	2	2
14	65	Apr/2013 – Mar/2014	65	1	0	1	0	0
Total	11 796			229	14	55	29	131

ESD, endoscopic submucosal dissection; HM1, positive horizontal or indeterminable margins

Q2. The number of the cases in which the tumors were diagnosed as T1a and either no ulcer findings regardless of size or positive ulcer findings in tumors sized ≤ 3 cm in diameter, and positive horizontal or indeterminable margins were demonstrated in the ESD-specimens.

Q3. Strategies for Q2 cases

Early repeat ESD (re-ESD) (ESD within 30 days after initial ESD)

Early coagulation (coagulation within 30 days after initial ESD)

Early gastrectomy (additional gastrectomy without follow-up)

Follow-up without early treatments

► **Table S2** Results of follow-up cases without early interventions.

Institutions	Follow-up cases without early treatments (Q3 ④)	No recurrence (Q7A)	Local recurrence (Q7B)	Lymph node or distant metastasis (Q7C)
1	23	17	6	0
2	25	17	8	0
3	15	12	3	0
4	5	4	1	0
5	9	6	3	0
6	6	6	0	0
7	4	3	1	0
8	7	6	1	0
9	15	14	1	0
10	2	0	2	0
11	13	13	0	0
12	5	4	1	0
13	2	2	0	0
14	0	0	0	0
Total	131	104	27	0

► **Table S3** Additional treatments for local recurrent cases after initial ESD.

Institutions	Local Recurrence after follow-up (Q7B)	Re-ESD (Q9I)	Coagulation (Q9P II)	Surgery (Q9 III)	No treatment (Q9 IV)
1	6	4	0	2	0
2	8	5	1	2	0
3	3	1	2	0	0
4	1	0	0	0	1
5	3	1	0	0	2
6	0	0	0	0	0
7	1	0	0	1	0
8	1	0	0	1	0
9	1	1	0	0	0
10	2	1	1	0	0
11	0	0	0	0	0
12	1	0	0	1	0
13	0	0	0	0	0
14	0	0	0	0	0
Total	27	13	4	7	3

ESD, endoscopic submucosal dissection