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 indeterminable 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 indeterminable margins after ESD and evaluate the current empirical treatments for the patients with positive horizontal or indeterminable margins after ESD. We performed a multicenter survey of the treatment strategies for early gastric cancer with positive horizontal or indeterminable 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 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 indeterminable 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 indeterminable 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 indeterminable 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 indeterminable margins using obtained questionnaires.

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

Pooled estimates of positive or indeterminable 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 indeterminable margins ranged from 0.6% to 11%. The pooled estimate of positive horizontal or indeterminable 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).
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%.

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

| Hospitals | Positive or indeterminable margins (n = 229) |
|-----------|--------------------------------------------|
| High volume centers |
| 1         | 0.01 (0.01, 0.01)                           |
| 2         | 0.03 (0.02, 0.03)                           |
| 3         | 0.02 (0.02, 0.03)                           |
| 4         | 0.01 (0.00, 0.01)                           |
| 6         | 0.01 (0.00, 0.02)                           |
| LR Test RE vs. FE chi-squared test = 22.872, P = 0.00 |
| 0.01 (0.01, 0.02) |
| Non-high volume centers |
| 5         | 0.01 (0.01, 0.02)                           |
| 7         | 0.01 (0.00, 0.02)                           |
| 8         | 0.05 (0.03, 0.07)                           |
| 9         | 0.04 (0.02, 0.06)                           |
| 10        | 0.01 (0.00, 0.03)                           |
| 11        | 0.11 (0.08, 0.16)                           |
| 12        | 0.02 (0.01, 0.05)                           |
| 13        | 0.04 (0.01, 0.10)                           |
| 14        | 0.02 (0.00, 0.08)                           |
| LR Test RE vs. FE chi-squared test = 45.685, P = 0.00 |
| 0.02 (0.01, 0.04) |

Heterogeneity between groups: P = 0.191
LR Test RE vs. FE chi-squared = 84.44, P = 0.00

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 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 Fig. 4. 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 resection 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 indeterminable 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-
A second difficult decision is how to treat the cases with positive horizontal or indeterminable margins at an early date. Repeat 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 intramuscular 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 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
   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.
   I. Dual knife/Flush knife/Flex knife
   II. Hook knife
   III. SB knife/Clutch cutter
   IV. IT knife/IT knife 2
   V. 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 (Q2) | 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) | 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 (Q9II) | Surgery (Q9III) | No treatment (Q9IV) |
|--------------|----------------------------------------|--------------|-------------------|-----------------|---------------------|
| 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                                      | 0            | 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