

Risk stratification and management of non-curative resection after endoscopic submucosal dissection for early gastric cancer

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Abstract

Background Non-curative resection after endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) can contribute to local recurrence or lymphatic and distant metastasis of the tumor. We stratified the risk of local recurrence according to the histological characteristics in non-curative resection after ESD for EGC.

Methods Among 892 EGCs treated with ESD, 152 (17.0 %) were classified as non-curative resection based on the histology after ESD. The clinical outcomes and risk factors associated with local recurrence were analyzed retrospectively in non-curative resections.

Results Of 152 non-curative resections, 46 (30.3 %) were stratified as Group 1 (incomplete resection and met the ESD criteria), 31 (20.4 %) as Group 2 (complete resection and exceeded the ESD criteria), 41 (27.0 %) as Group 3 (incomplete resection and exceeded the ESD criteria), and 34 (22.4 %) as Group 4 (lymphovascular invasion regardless of complete resection). Group 3 [odds ratio (OR) 3.991; $p = 0.015$] and Group 4 (OR 4.487; $p = 0.014$) had higher rates of local recurrence after non-curative resection. In those high-risk groups, endoscopic surveillance without additional treatment detected significantly more

local recurrence than in those receiving additional treatment ($p = 0.029$).

Conclusion Risk stratification for non-curative resection is important for EGC prognosis after ESD. Moreover, additional treatment for non-curative resection influences long-term outcomes, especially in high-risk groups.

Keywords Non-curative resection · Early gastric cancer · Endoscopic submucosal dissection

Endoscopic submucosal dissection (ESD) is a minimally invasive and curative technique used to treat early gastric cancer (EGC) [1]. It enables higher rates of en bloc resection and complete resection than endoscopic mucosal resection (EMR) and allows histological evaluation, which is important for assessing the risk of local recurrence and lymph node metastasis [2, 3].

Advanced imaging techniques, including narrow-band imaging (NBI), magnifying endoscopy, and autofluorescence imaging, have been recently introduced [4, 5]. Although these diagnostic modalities can be helpful in predicting the precise margin or invasion depth of cancer during pre-ESD evaluation, these modalities have limited accuracy or are not widely available [4–8]. Inadequate evaluation before ESD or factors such as tumor size, location, ulcer, or submucosal fibrosis can influence non-curative resection after ESD for EGC [9]. Since additional surgery may be required for non-curative resection to reduce the risk of local recurrence or lymph node metastasis [10], stratifying the risk of local recurrence or lymph node metastasis is important in deciding on additional treatment for non-curative resection. This study analyzed the risk of local recurrence and assessed the long-term outcomes according to the histological characteristics in non-curative resection after ESD.

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Materials and methods

Patients

Among 892 patients with EGC treated with ESD from 2001 to 2012, 152 (17.0 %) were interpreted as non-curative resection based on the histology after ESD. They were classified into four groups according to the histological characteristics after ESD: Group 1, EGCs that had incomplete margin resection and met the ESD criteria; Group 2, EGCs that had complete margin resection and exceeded the ESD criteria; Group 3, EGCs that had incomplete margin resection and exceeded the ESD criteria; and Group 4, EGCs that had lymphovascular invasion regardless of complete resection margin (Fig. 1). Of the 152 patients, 45 underwent additional surgery for non-curative resection, and the histology of the surgical specimens was analyzed to evaluate the risk of local recurrence or lymph node metastasis. After excluding 35 patients with less than 12 months of follow-up, long-term clinical outcomes were assessed in 117 patients (Fig. 1). This study was approved by our institutional review board.

Endoscopic submucosal dissection

ESD was performed for EGC that met the absolute or expanded criteria and had no lymph node metastasis in the pre-ESD evaluation, which could include endoscopy,

endoscopic ultrasonography (EUS), and computed tomography of the abdomen [11, 12]. After careful observation, the tumor margin was marked using argon plasma coagulation (APC). Normal saline solution mixed with a small amount of indigo carmine and diluted epinephrine (1:100,000) was used for submucosal injection. A Hook Knife or IT Knife (Olympus, Tokyo, Japan) was used for margin cutting. The submucosal layer was dissected using various endoscopic knives. After ESD, exposed vessels on the artificial ulcer base were coagulated with a Coagrasper (FD-410LR; Olympus) or metal clips (Olympus).

Histological evaluation and definition

Complete resection was defined as the absence of cancer in both the lateral and vertical resection margins and no evidence of lymphovascular invasion. Curative resection was defined as resection that met the definition of complete resection and the ESD criteria in the histological evaluation after ESD. Non-curative resection included the EGCs with incomplete margin resection, lymphovascular invasion, or which exceeded the ESD criteria. Differentiated lesions exceeding the ESD criteria were defined as ulcerated and >30 mm in size or any size with SM2 invasion. Undifferentiated lesions exceeding the ESD criteria were defined as >20 mm in size, or the presence of ulceration or SM invasion regardless of size.

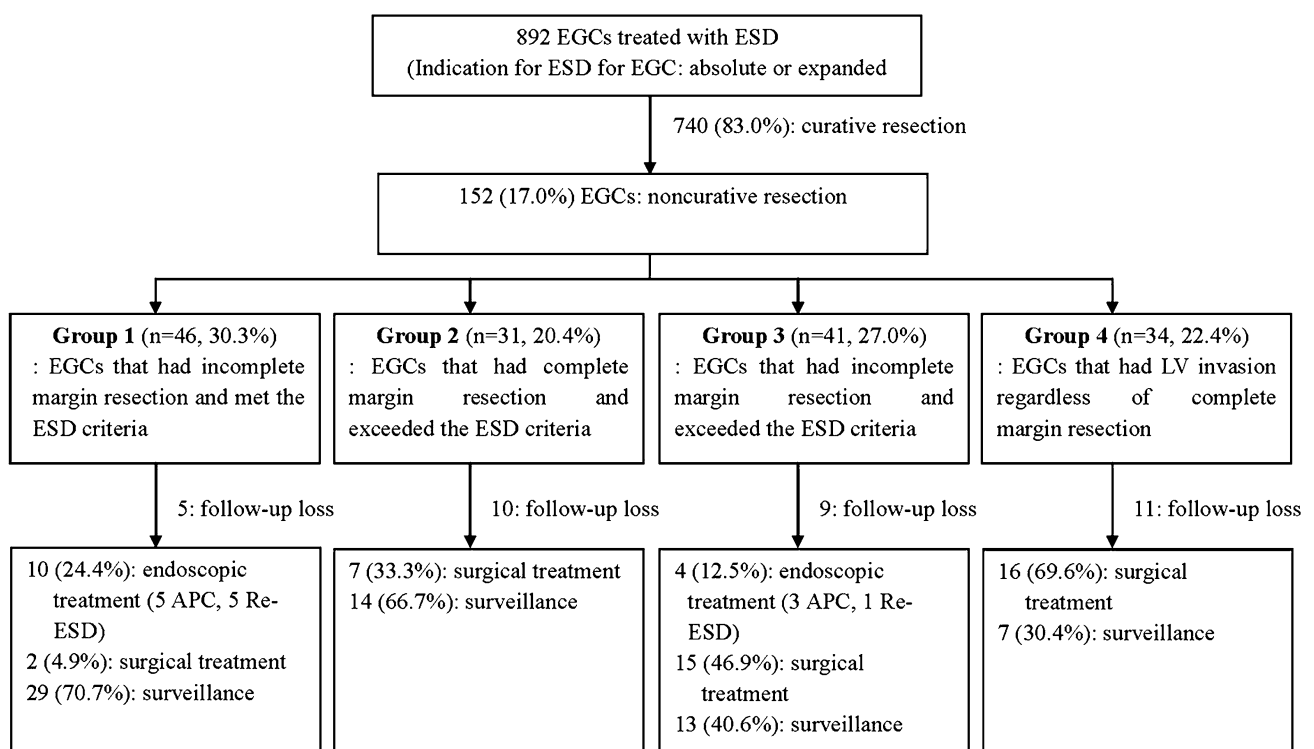


Fig. 1 Flowchart of the patients enrolled in the study. *EGC* early gastric cancer, *ESD* endoscopic submucosal dissection, *LV* lymphovascular

Clinical outcomes

Additional endoscopic procedures or surgery were performed within several months in non-curative resection after ESD. Before additional treatment, the patient's condition, including age, underlying disease, and consent to additional surgery, was considered. Patients who were at high risk or refused additional treatment underwent scheduled surveillance using endoscopy, computerized tomography, and chest X-ray. Local recurrence was defined as recurrent cancer confirmed by a follow-up forceps biopsy of the post-ESD ulcer scar regardless of the period. Metachronous recurrence was defined as newly detected cancers at other sites of previous ESD ulcers more than 12 months after ESD.

Statistical analysis

Continuous variables were presented as the mean \pm SD. Logistic regression analysis was used for risk stratification for local recurrence after ESD, and Kaplan–Meier analysis was used to assess long-term outcomes according to additional treatment in the relatively low-risk groups and high-risk groups (ver. 14.0; SPSS Inc., Chicago, IL, USA). A p value <0.05 indicated statistical significance.

Results

Baseline characteristics of non-curative resection

In total, 152 patients (106 men, 46 women) were deemed non-curative resection after ESD. The mean patient age (\pm SD) was 62.9 ± 13.4 years, and the mean lesion size was 23.6 ± 12.7 mm (Table 1). Of the 152 non-curative resections, 46 (30.3 %) were included in Group 1 (39 incomplete resection of the lateral margin, five incomplete resection of the vertical margin, and two incomplete resection of the lateral and vertical margins), 31 (20.4 %) in Group 2, 41 (27.0 %) in Group 3, and 34 (22.4 %) in Group 4 (Fig. 1).

Histological result from additional surgery

Additional surgery was performed in 45 (29.6 %) of the 152 non-curative resections. Histologically, of the surgical specimens, 16 (35.6 %) had residual tumors, two (4.4 %) had lymph node metastases, and one (2.2 %) had residual cancer and lymph node metastasis. Residual cancer was detected in the surgical specimens of all four lesions that had incomplete resection of the vertical margin in criteria group (Table 2).

Table 1 Baseline characteristics of non-curative resection after ESD ($n = 152$)

Gender (Male–Female) [n (%)]	106 (69.7):46 (30.3)
Age (years, mean \pm SD)	62.9 ± 13.4
Location [n (%)]	
Antrum	78 (51.3)
Lower body	47 (30.9)
Mid-body	8 (5.3)
Upper body and cardia	19 (12.5)
Gross type [n (%)]	
Elevated	46 (30.3)
Flat	77 (50.7)
Depressed	29 (19.0)
En bloc resection [n (%)]	135 (88.8)
Size of lesion (mm, mean \pm SD)	23.6 ± 12.7
Ulceration [n (%)]	53 (34.9)
Differentiation [n (%)]	
Differentiated	108 (71.1)
Undifferentiated	44 (28.9)
Depth of invasion [n (%)]	
M	62 (40.8)
SM1	29 (19.1)
\geq SM2	61 (40.1)

ESD endoscopic submucosal dissection, *M* mucosa, *SM* submucosa

Risk stratification of local recurrence in non-curative resection

Table 3 shows the risk of residual cancer or local recurrence after ESD according to the histological characteristics of non-curative resection. Group 2 had similar risk [odds ratio (OR) 0.972, $p = 0.971$], but Groups 3 and 4 had a significantly higher probability of residual cancer or local recurrence (OR 3.991, $p = 0.015$; OR 4.487, $p = 0.014$, respectively) compared with Group 1.

Long-term outcomes of non-curative resection

Ten patients (24.4 %) underwent endoscopic procedures (five APC and five re-ESD) and two (4.9 %) had surgery as additional treatment in Group 1. In Group 2, seven patients (33.3 %) experienced additional surgery for non-curative resection. In Group 3, four patients (12.5 %) underwent endoscopic procedures (three APC and one re-ESD), and 15 (46.9 %) had additional surgery. Sixteen patients (69.9 %) in Group 4 experienced additional surgery (Fig. 1). Surveillance without additional treatment was performed in the remaining 63 patients. Table 4 shows the long-term clinical outcomes of patients who underwent surveillance without additional treatment such as

Table 2 Histological results from additional surgery for non-curative ESD resection ($n = 45$)

Findings	Criteria group ^a ($n = 4$)	Exceeded criteria group ^a ($n = 41$)	Total ($n = 45$)
No residual tumor	0 (0)	26 (63.4)	26 (57.8)
Positive residual tumor	4 (100)	12 (29.3)	16 (35.6)
LN metastasis	(0)	2 (4.9)	2 (4.4)
Positive residual tumor and LN metastasis	0 (0)	1 (4.4)	1 (2.2)

ESD endoscopic submucosal dissection, LN lymph node

^a Criteria group: group that met the ESD criteria based on the histological result after ESD, Exceeded criteria group: group that exceeded the ESD criteria based on the histological result after ESD

Table 3 Risk stratification of local recurrence in non-curative resection cases

	Odds ratio (95 % CI)	p value
Group 1	Reference	
Group 2	0.972 (0.217–4.348)	0.971
Group 3	3.991 (1.306–12.196)	0.015
Group 4	4.487 (1.357–14.834)	0.014

Group 1, EGCs that had incomplete margin resection and met the ESD criteria; Group 2, EGCs that had complete margin resection and exceeded the ESD criteria; Group 3, EGCs that had incomplete margin resection and exceeded the ESD criteria; Group 4, EGCs that had lymphovascular invasion regardless of complete resection margin
ESD endoscopic submucosal dissection

endoscopic procedures or surgery for non-curative resection. The local recurrence rate was 7.3 % in Group 1, 4.8 % in Group 2, 18.8 % in Group 3, and 13.0 % in Group 4. Lymph node or distant metastasis occurred in three patients (two in Group 3, one in Group 4), and cancer-related death occurred in three (9.4 %) of Group 3 (two patients who did not undergo treatment for metastatic cancer and one patient who had a complication after ESD). One patient with lymph node metastasis in Group 4 underwent surgical treatment, and no recurrence occurred subsequently. Four patients (two in Group 1, one in Group 2, and one in Group 3) died because of another malignancy, including neuroendocrine carcinoma, lymphoma, or lung cancer.

Table 4 Long-term clinical outcomes of non-curative resection during endoscopic surveillance without additional treatment

n (%)	Local recurrence	Metachronous recurrence	LN or distant metastasis	Cancer-related death
Group 1	3 (7.3)	2 (4.9)	0 (0)	0 (0)
Group 2	1 (4.8)	1 (4.8)	0 (0)	0 (0)
Group 3	6 (18.8)	2 (6.3)	2 (6.3)	3 (9.4)
Group 4	3 (13.0)	1 (4.3)	1 (4.3)	0 (0)

Group 1, EGCs that had incomplete margin resection and met the ESD criteria; Group 2, EGCs that had complete margin resection and exceeded the ESD criteria; Group 3, EGCs that had incomplete margin resection and exceeded the ESD criteria; Group 4, EGCs that had lymphovascular invasion regardless of complete resection margin

LN lymph node

The rate of local recurrence did not differ significantly according to additional treatment in the relatively low-risk groups, i.e., Groups 1 and 2 ($p = 0.129$; Fig. 2). However, Fig. 3 shows a significant difference in the local recurrence rate according to additional treatment in the high-risk groups, i.e., Groups 3 and 4 ($p = 0.029$).

Discussion

ESD has been accepted as an effective method for treatment of EGC [1, 13]. It provides higher en bloc and complete resection rates of EGC compared with conventional EMR [2, 3]. Many studies have reported that ESD also reduces the frequency of local recurrence, with excellent long-term outcomes after ESD for EGC [14–17]. Moreover, the procedure allows decisions regarding additional treatment following pathological assessment of resected specimens by ESD.

Since non-curative resection is strongly associated with the incidence of local recurrence of EGC, optimal treatment strategies are necessary for non-curative resection to reduce the risk of local recurrence or distant metastasis [18–20]. The limited accuracy of the assessment of the margin or depth of lesion and pathological discrepancy between forceps biopsy and final diagnosis can influence non-curative resection after ESD [4–8, 21, 22]. In this study, cases undergoing non-curative resection were

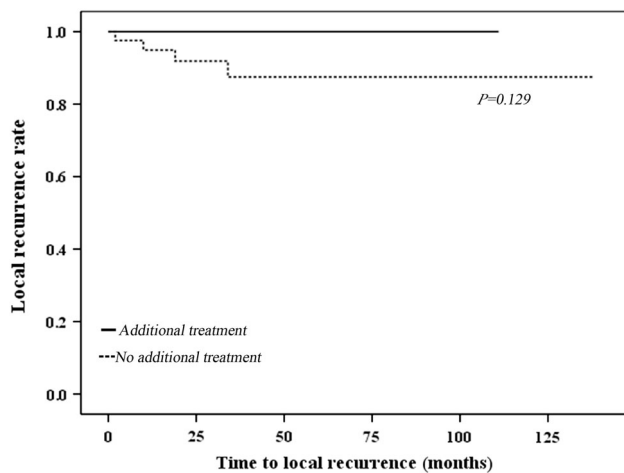


Fig. 2 Local recurrence according to additional treatment in the relatively low-risk groups (Groups 1 and 2)

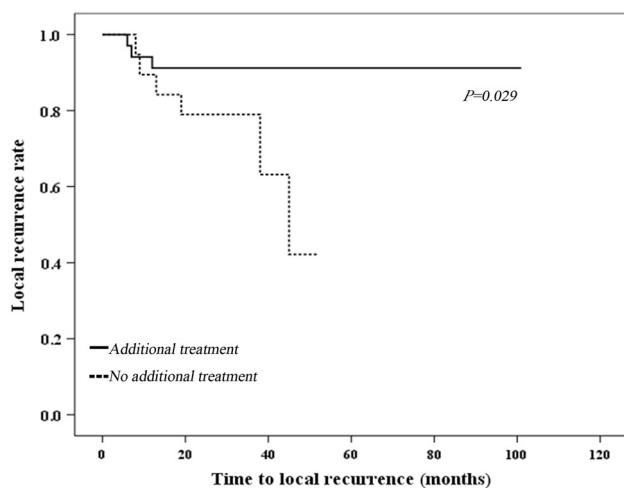


Fig. 3 Local recurrence according to additional treatment in the high-risk groups (Groups 3 and 4)

classified into four groups based on the complete or incomplete resection of the margin and the ESD criteria from the histological result after ESD, which showed that Groups 3 and 4 had significant higher rates of local recurrence. Moreover, residual tumor was observed in all four cases with incomplete resection of vertical margin in the criteria group, and residual tumor or lymph node metastasis was detected in 36.6 % of the cases exceeding the criteria at additional surgery for non-curative resection. These findings suggest that incomplete resection of the vertical margin and exceeding the criteria in the histological evaluation after ESD had a high risk of local recurrence or lymph node metastasis. Therefore, cases with a risk of residual cancer, including incomplete resection of the vertical margin or those exceeding the ESD criteria from ESD specimens, should be considered for additional treatment.

Assessing the risk of lymph node metastasis from specimens after ESD is also important when making decisions regarding additional treatment for non-curative resection. Lymph node metastasis in patients with EGC has only rarely been reported in differentiated mucosal cancer and submucosal cancers <20 mm in size and without depression [23]. Moreover, Gotoda et al. [11] reported no risk of lymph node metastasis in patients with non-ulcerated, differentiated intramucosal cancers; <30-mm ulcerated differentiated intramucosal tumors; <30-mm differentiated minute submucosal tumors (SM1, <500 μ m); and <20-mm non-ulcerated undifferentiated intramucosal tumors. Recently, ESD has been performed in selected undifferentiated tumors with no or low risk of lymph node metastasis [24–26]. These studies suggested that the risk of lymph node metastasis should be evaluated carefully from ESD specimens. Therefore, surgical gastrectomy with lymph node dissection for non-curative resection should be recommended in patients with high risk of lymph node metastasis, whereas additional endoscopic procedures can be considered for selected patients not at risk of lymph node metastasis to preserve gastric function and allow the patient to maintain a better quality of life [10, 18, 19].

In this study, we stratified the risk of local recurrence and lymph node metastasis in non-curative resection after ESD. Compared with the relatively low-risk groups (Groups 1 and 2), the high-risk groups (Groups 3 and 4) had significantly higher incidences of residual cancer or local recurrence. In the high-risk groups, local recurrence was less frequent in patients treated immediately than in patients who underwent endoscopic surveillance without immediate treatment. Therefore, additional surgery is necessary for non-curative resection, especially in patients at high risk of local recurrence or lymph node metastasis. If the patients in the relatively low-risk groups have a high risk of surgery or refuse additional surgery, additional endoscopic treatment can be considered.

Our study had several limitations. First, this was a retrospective study in a single center. Although most of the patients who underwent endoscopic surveillance without additional treatment were of advanced age or had other medical problems, additional information about these patients was lacking. Second, we could not exclude any bias associated with ESD procedures and the accuracy of modalities for pre-ESD evaluation, such as EUS and NBI and/or magnifying endoscopy.

In conclusion, risk stratification based on the risk of local recurrence and lymph node metastasis is important for predicting the long-term outcomes of non-curative resection after ESD for EGC. Additional surgery might be necessary for non-curative resection in groups at high risk of local recurrence or lymph node metastasis, whereas additional endoscopic treatment can be considered in

selected patients with a relatively low risk of lymph node metastasis, but who are a high risk for surgery.

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