Additional Surgery After Non-curative Resection of ESD for Early Gastric Cancer

TAKAO KATSUBE, MINORU MURAYAMA, KENTARO YAMAGUCHI, ATSUKO USUDA, ASAKO SHIMAZAKI, SHINICHI ASAKA, SOICH KONNNO, AKIRA MIYAKI, TAKEBUMI USUI, HAZIME YOKOMIZO, SCHUNICHI SHIOZAWA, KAZUHIKO YOSHIMATSU, TAKESHI SHIMAKAWA and YOSHIHIKO NARITAKA

Department of Surgery, Tokyo Women's Medical University Medical Center East, Tokyo, Japan

Abstract. *Aim: The appropriate additional surgery after non-curative resection of Endoscopic Mucosal Resection (ESD) for early gastric cancer is herein discussed. Patients and Methods: Data on 54 patients after non-curative resection of ESD were evaluated. These patients were broadly classified according to the risk of lymph node metastasis with lesions into group A (without risk) (n=26) and group B (with risk) (n=28). Their treatment results were evaluated. Results: The incidence of residual lesion was 7.7% in group A and 14.3% in group B. Risk factors were piecemeal resection, involvement of the horizontal margin (HM1) or unclear involvement of the horizontal margin (HMX) and with ulceration. Lymph node metastasis was detected in one patient with lymphatic invasion, total diameter of 3 cm or more and submucosal invasion over 0.5 mm (SM2). The 5-year survival rate was 93% and none of the patients died of gastric cancer. Conclusion: Follow-up observation was reasonable in group A. Patients who are judged as having undergone piecemeal resection, HM1 or HMX and with ulceration, should be treated by additional surgery and patients judged with SM2 or total diameter of 3 cm or more or lymphatic invasion should be treated by additional surgery with lymphadectomy in groupB.*

Favorable short-term outcomes of endoscopic submucosal dissection (ESD) for early gastric cancer including *en-bloc* resection have been reported (1-3). Two factors should be considered for assessment of curability of ESD for early gastric cancer: completeness of the primary tumor removal and nil possibility of lymph node (LN) metastasis. Early gastric cancer cases with a negligible LN metastasis can be defined based on a retrospective analysis involving a large number of surgical cases of early gastric cancer (4). The indications for ESD for early gastric cancer have been expanding. The Japanese guidelines clearly describe the criteria for lesions to be included in the indications for ESD and those included in the expanded indications for ESD, and classify curability after ESD into the following categories: curative resection, expanded-indication curative resection and non-curative resection (Table I) (5). Favorable long-term outcomes for patients with curative resection and curative resection of expanded indications were reported (6). In cases of curative resection or expanded-indication curative resection, additional surgical resection can be eliminated. However, when a judgment of non-curative resection is made, the risk of lymph node metastasis should be considered and additional surgical resection may be necessary. Most patients actually have no residual lesions and are simply followed-up.

In the present study, patients who suffered from early gastric cancer and underwent ESD resulting in non-curative resection were then classified broadly into two categories according to the risk of lymph node metastasis and, on the basis of their treatment results, the appropriate additional surgical resection was discussed.

Correspondence to: Takao Katsube, Department of Surgery, Tokyo Women's Medical University, Medical Center East, 2-1-10 Nisiogu Arakawa-ku, Tokyo, 116-8567, Japan. E-mail: katsusu@dnh.twmu.ac.jp

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Patients and Methods

Data on 54 patients (M/F ratio, 38:16; mean age=71.8 years) whose surgical outcome was judged to be non-curative resection among 231 patients having undergone ESD at this Department, for early gastric cancer between 2003 and 2013 were evaluated (Table II). The 54 patients were broadly classified according to the risk of lymph node metastasis into a group of patients with lesions included in the indications or expanded indications with neither lymphatic nor venous invasion (group A), and a group of patients with lymphatic or venous invasion or lesions not included in the indications (group B).

In group A, the median patient age was 74.5 years (range=55-83 years, n=26) and the ratio of males to females was 17:9. Twenty-five patients had mucosal cancer (HM1: horizontal margin involved, n=4; HMX: horizontal margin involvement unknown, n=19; VMX: vertical margin involvement unknown, n=2) and tumor in one patient had submucosal invasion within 0.5 mm with HMX.

In group B, the median patient age was 73.5 years (range=57-84 years, n=28) and the ratio of males to females was 22:6. Two

Table I. *Curability of endoscopic submucosal dissection.*

Curative Resection	
All of the following conditions are fulfilled for the included indications	•En-bloc resection •Negative horizontal margin (HM0) •Negative vertical margin (VM0) •No lymphovascular infiltration [ly(−), v(−)].
Indications:	•Tumor size≤2 cm •Histologically differentiated-type •Depth Mucosa(pT1a) , without ulceration [UL(−)]
Curative Resection for Expanded Indications	
All of the following conditions are fulfilled for the expanded indications:	•En-bloc resection •HM0 •VM0 •Negative lymphatic invasion (ly(−)) •Negative venous invasion (v(−))
Expanded indications:	•Tumor size>2 cm, histologically differentiated type, pT1a, UL(−), or •Tumor size≤3 cm, histologically differentiated type, pT1a, with ulcerarion (UL(+)), or •Tumor size≤2 cm, histologically undifferentiated type, pT1a, UL(−), or •Tumor size≤3 cm, histologically differentiated-type, Depth SM1 (SM1, <500 μm from *muscularis mucosae*).
Non-curative Resection	Does not satisfy any of the above criteria

Table II. *Characteristics of the non-curative and curative resection cases.*

	Non-curative n=54 (23.4%)	Curative n=177 (76.6%)	Total n=231 (100%)
Age, median (range)	73 (55-84)	71 (49-91)	72 (49-91)
≥80 years	8 (14.8%)	25 (14.1%)	33 (14.3%)
Sex (male/female)	40/14	138/39	178/53
En bloc ratio	85.2%	100%	96.5%
Length			
<20 mm	29 (53.7%)	137 (77.4%)	166 (71.9%)
20-30 mm	14 (25.9%)	27 (13.6%)	41 (17.7%)
>30 mm	11 (20.4%)	13 (9.0%)	24 (10.4%)
Histology			
Differentiated	47 (87.0%)	174 (98.3%)	221 (95.7%)
Undifferentiated	7 (13.0%)	3 (1.7%)	10 (4.3%)
Ulceration			
UL (−)	50 (92.6%)	173 (97.7%)	223 (96.5%)
UL (+)	4 (7.4%)	4 (2.3%)	8 (3.5%)
Depth			
M	27 (50%)	175 (98.9%)	202 (87.4%)
SM1	5 (9.3%)	2 (1.1%)	7 (3.1%)
SM2	22 (40.7%)	0	22 (9.5%)
Horizontal margin			
HM0	28 (51.9%)	177 (100%)	205 (88.7%)
HM1	5 (9.3%)	0	5 (2.2%)
HMX	21 (38.8%)	0	21 (9.1%)
Vertical margin			
VM0	46 (85.2%)	177 (100%)	223 (96.5%)
VM1	5 (9.3%)	0	5 (2.2%)
VMX	3 (5.5%)	0	3 (1.3%)
Lymphatic invasion			
Ly (−)	43 (79.6%)	177 (100%)	220 (95.2%)
Ly (+)	11 (20.4%)	0	11 (4.8%)
Venous invasion			
V (−)	49 (90.7%)	177 (100%)	226 (97.8%)
V (+)	5 (9.3%)	0	5 (2.2%)

UL(−): Without ulceration , UL(+): with ulceration, M: mucosa, SM1: <500 μm from muscularis mucosae, SM2: 500 μm or more into the muscularis mucosae, HM0: Negative horizontal margin, HM1: Positive horizontal margin, HMX: horizontal margin unclear, VM0: Negative vertical margin, VM1: Positive vertical margin, VMX: vertical margin unclear, Ly(−): Negative lymphatic invasion, Ly(+), Positive lymphatic invasion, V(−): Negative venous invasion, V(+), Positive venous invasion.

patients had mucosal cancer (lymphatic invasion: n=1, >30 mm HM1 with ulceration: n=1). Four patients had submucosal invasion within 0.5 mm (lymphatic invasion: n=3, >30 mm: n=1) and 22 patients had submucosal invasion greater than 0.5 mm.

In group A, 26 patients (100%) were followed-up and the data on residual lesions were evaluated. Seventeen out of the 28 patients (60.7%) of group B underwent an additional surgical operation. The remaining 11 patients (39.3%) were followed-up (Table III). The data on residual lesions and lymph node metastasis were evaluated. Moreover, the prognoses of all the patients were evaluated from the aspects of cumulative survival rate and causes of death. Statistical analysis was performed using the Fisher's exact test and Student's *t*-test (JMP Pro 11) using JMP 11 software (SAS Institute, Japan Tokyo).

Results

In group A, out of 20 patients with HMX, 2 had residual lesions that were detected 398 days and 724 days after ESD, respectively. In these two cases, repeated ESD and laparoscopy-assisted distal gastrectomy (LADG) were additionally performed and the lesions were judged to be residual mucosal cancer (incidence of residual lesions: 7.7%). There were no factors significant for risk of residual cancer in group A.

In group B, 15 patients underwent additional surgery with lymphadectomy (D1+) (5) (LADG, n=7 patients; distal gastrectomy, n=2 patients; total gastrectomy, n=4; and proximal gastrectomy, n=2) and 2 patients underwent local resection. Local residual mucosal cancer occurred in two patients after local resection. Factors requiring follow-up by checkups in 11 patients included pulmonary complications (n=2), renal failure (n=1), age >80 years (n=2), another malignant tumor (n=2) and others (n=4). Of 11 patients who were followed-up, two had residual lesions confirmed 452 days and 572 days after ESD. One patient underwent additional distal gastrectomy and residual mucosal cancer was observed (incidence of residual lesions: 14.3%). For those patients with piecemeal resection, HM1 or HMX, or with ulceration, the incidence of residual lesions was over 50%. Risk factors for residual cancer in group B were piecemeal resection, HM1 or HMX and with ulceration (Table IV). Lymph node metastasis was detected in 1 out of 15 patients who underwent additional surgery with lymphadectomy (D1+). The metastatic lesion was limited to number 3 lymph node metastases while no residual lesion was observed (incidence of lymph node metastasis: 6.7%). This patient was a 70-year-old male, with a mucosal tumor of 32 mm in size, depressed macroscopic type, moderately differentiated adenocarcinoma, without ulceration, with lymphatic invasion but without vascular invasion, and submucosal invasion over 0.5 mm.

The five-year survival rate was 93% and none of the patients died of gastric cancer in the whole patient cohort. Three patients died of non-gastric cancer (Figure 1). Two patients of group A died, one 538 days (77-year-old male; cause of death: Chronic Obstructive Pulmonary Disease (COPD) and another 518 days (65-year-old male; cause of death: cardiovascular disorder) after follow-up/ESD. One patient of group B died 733 days after follow-up/ESD (80-year-old male; cause of death: renal failure).

Discussion

Endoscopic treatment has been increasingly introduced to treat patients with early gastric cancer because this procedure ensures excellent quality of life for patients after the treatment. However, conventional endoscopic mucosal resection often adopts the technique of fractional excision and the rate of local recurrence is high. ESD has been reported to allow for *en bloc* resection and contribute to reduction of the rate of non-curative resection on the horizontal margins (1-3). However, the rate of curative resection has been reported to be 96% for the lesions included in the indications and 67.5-87.5% for the lesions included in the expanded indications (7), and the presence of non-curative resection cases cannot be disregarded. In the present study of 231 patients, the rate of en bloc resection was 96.5% and the negative horizontal margin

Table III. *Characteristics of the additional surgical cases and followed-up cases in group B.*

	Additional Surgery (A) 17 (59.3%)	Follow_up(F) 11 (40.7%)	Total 28 (100%)	*p*-Value A *vs*. F
Sex				
Male	3 (17.6%)	2 (18.2%)	5 (17.9%)	0.6525
Female	14 (82.4%)	9 (81.8%)	23 (82.1%)	
Age	69.5 (57-82)	79 (59-84)	73.5(57-84)	0.02
En block				
Yes	14 (82.4%)	11 (100%)	25 (89.3%)	0.2579
No (Piecemeal resection)	3 (17.6%)	0	3(10.7%)	
Length				
−20mm	11 (64.8%)	5 (45.4%)	16 (57.1%)	
20-30mm	3 (17.6%)	4 (3.6%)	7 (25%)	0.5450
30mm-	3 (17.6%)	2 (1.8%)	5 (17.9%)	
Histology				
Differentiated	15 (88.2%)	6 (54.5%)	21 (75%)	0.0764
Undifferentiated	2 (11.8%)	5 (45.5%)	7 (25%)	
UL				
(−)	14 (82.4%)	10 (90.9%)	24 (85.7%)	1.0
(+)	3 (17.6%)	1 (9.1%)	4 (14.3%)	
Depth				
M	2 (11.8%)	0	2(7.1%)	
SM1	2 (11.8%)	2 (18.2%)	4 (14.2%)	0.3315
SM2	13 (76.4%)	9 (81.8%)	22 (78.7%)	
Horizontal margin				
HM0	15 (88.2%)	10 (90.9%)	25(89.3%)	1.0
HM1 or HMX	2 (11.8%)	1 (9.1%)	3 (10.7%)	
Vertical margin				
VM0	13 (76.5%)	9 (81.8%)	22(78.6%)	1.0
VM1 or VMX	4 (33.5%)	2 (18.2%)	6(21.4%)	
Lymphatic invasion				
Ly (−)	9 (52.9%)	8 (72.7%)	17(60.7%)	0.2530
Ly (+)	8 (47.1%)	3 (27.3%)	11 (39.3%)	
Venous invasion				
V (−)	13 (76.5%)	10 (90.9%)	23 (82.1%)	0.6145
V (+)	4 (33.5%)	1 (9.1%)	5(17.9%)	

UL(-): Without ulceration , UL(+): with ulceration, M: mucosa, SM1: <500 μm from muscularis mucosae, SM2: 500 μm or more into the muscularis mucosae, HM0: Negative horizontal margin, HM1: Positive horizontal margin, HMX: horizontal margin unclear, VM0: Negative vertical margin, VM1: Positive vertical margin, VMX: vertical margin unclear, Ly(-): Negative lymphatic invasion, Ly(+), Positive lymphatic invasion, V(-): Negative venous invasion, V(+), Positive venous invasion.

Table IV. *Characteristics of the residual cancer cases and no residual cancer cases in group B.*

	Residual cancer (R) n=4 (14.3%)	No residual cancer (N) n=24 (85.7%)	Total n=28 (100%)	*p*-Value R *vs*. N
En block				
Yes	2 (50%)	23 (95.8%)	25 (89.3%)	0.0452
No (Piecemeal resection)	2 (50%)	1 (4.2%)	3 (10.7%)	
Length				
−20mm	3 (75%)	13 (54.2%)	16 (57.1%)	0.6132
21mm−	1 (25%)	11 (45.8%)	12 (42.9%)	
Histology				
Differentiated	4 (100%)	21 (75%)	21 (75%)	0.5453
undifferentiated	0	7 (25%)	7 (25%)	
UL				
(+)	2 (50%)	22(91.7%)	24 (85.7%)	0.0856
(−)	2 (50%)	2 (8.3%)	4 (14.3%)	
Depth				
M~SM1	1 (25%)	5 (20.8%)	6 (21.4%)	1.0
SM2	3 (75%)	19 (79.2%)	22 (78.6%)	
Horizontal margin				
HM0	2 (50%)	23 (95.8%)	25 (89.3%)	0.0452
HM1 or HMX	2 (50%)	1 (4.2%)	3 (10.7%)	
Vertical margin				
VM0	3 (75%)	19 (79.2%)	22 (78.6%)	1.0
VM1 or VMX	1 (25%)	5 (20.8%)	6 (21.4%)	
Lymphatic invasion				
Ly (−)	4 (100%)	12 (50%)	16 (82.1%)	0.1131
Ly (+)	0	12 (50%)	12(17.9%)	
Vascular invasion				
V (−)	4 (100%)	21 (87.5%)	25 (89.3%)	1.0
V (+)	0	3 (12.5%)	3 (10.7%)	

UL(-): Without ulceration , UL(+): with ulceration, M: mucosa, SM1: <500 μm from muscularis mucosae, SM2: 500 μm or more into the muscularis mucosae, HM0: Negative horizontal margin,HM1: Positive horizontal margin, HMX: horizontal margin unclear, VM0: Negative vertical margin, VM1: Positive vertical margin, VMX: vertical margin unclear, Ly(-): Negative lymphatic invasion, Ly(+), Positive lymphatic invasion, V(-): Negative venous invasion, V(+), Positive venous invasion.

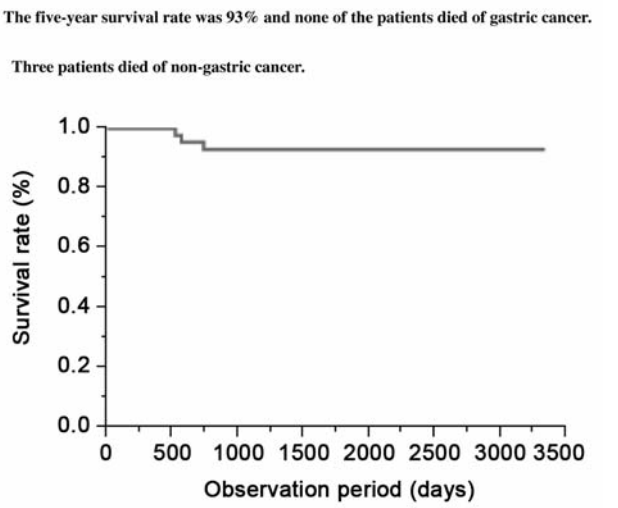

Figure 1. *Kaplan-Meier Survival curve of the patients after non-curative resection of Endoscopic Submucosal Dissection (ESD) for early gastric cancer*

rate was 88.7%. However, out of all patients, 23.4% were regarded as non-curative resection cases. It has been pointed-out that compared with endoscopic mucosal resection, ESD remarkably increases the number of non-curative resection cases that are at-risk of lymph node metastasis, and require additional surgical resection (8). In the present study, the cases regarded as non-curative resection at risk of lymph node metastasis accounted for about 50%.

We broadly classified the patients into two groups, one with lesions included in the indications or expanded indications with neither lymphatic nor venous invasion (group A) and a group of patients with lymphatic or venous invasion or lesions not included in the indications (group B), and evaluated the treatment results. In group A, the incidence of residual lesions was 7.7%. Twenty patients out of 26 (76.9%) were diagnosed as HMX because of burn effect in the present study. The ESD technique must be improved, thus reducing the potential for such an effect (9). Residual mucosal cancer of 20 patients with HMX was detected in two patients at over a year later. Another six patients with HM1 or VMX had no residual lesion. Tsujimoto *et al*. reported that cancer remaining on the vertical margins was related to the exposed tumor length in the ESD resection sample (10). Although the number of cases was limited, the possibility was suggested that even in the cases in which sufficient margins could not be ensured, no residual cancer might be detected for those patients with short exposed tumor length. For a long time after ESD, patients need monitoring with endoscopy. Hoteya *et al*. reported the usefulness of secondary ESD for residual lesions (11) For patients who suffer from residual mucosal cancer, treatment can be provided after confirmation of the residual cancer, and thus additional surgical resection is not necessarily indicated.

In group B, for which additional surgical resection should be considered, 11 patients (39.3%) with a mean age of 79 years were followed-up. An additional surgical resection was performed in about 60% of patients. Overall for this group, the incidence of residual cancer was 14.7%. However, for those patients with piecemeal resection, HM1, HMX, or with ulceration, the incidence of residual cancer was greater than 50% and such patients should be treated by additional surgery. Lymph node metastasis was detected in only one patient, and thus this case accounted for 6.7% of the cases of additional surgical resection with lymphadectomy (D1+) in group B. Oda *et al*. detected lymph node metastasis in 6.3% of patients who underwent ESD and insisted on the necessity for additional surgical resection (12). In the present study, lymphatic invasion and a total diameter of 3 cm or more were highlighted as risk factors for lymph node metastasis other than submucosal invasion over 0.5 mm. Toyokawa *et al*. pointed-out venous invasion as a risk factor for lymph node metastasis after ESD (13). Venous invasion is most closely related to lymph node metastasis in early gastric cancer. Son *et al*. found tumor size to be a risk factor for lymph node metastasis after endoscopic treatment (14), while Kim *et al*. found undifferentiated type and vascular invasion as risk factors (15). As the number of relevant cases is limited, we cannot make a clear declaration, but rather assume that the possibility of lymph node metastasis is low in differentiated cancer without lymphatic invasion, with total diameter of 3 cm or more and submucosal invasion over 0.5 mm.

Regarding prognosis, the results of surgical resection were generally favorable, as demonstrated by the 5-year survival rate of 94.3% in patients with mucosal cancer and that of 89.7% in those with submucosal cancer (16). Kusano *et al*. reported that in patients who were 75 years old or older and underwent ESD, the survival rate decreased unless non-curative ESD was followed by surgical resection (17). Abe *et al*. also reported that the 5-year survival rate in patients who were 80 years old and over with non-surgical follow-up after non-curative ESD was significantly lower than that in the patients with curative ESD (18). On the other hand, the 5-year survival rate was similar to the expected survival rate of the general population (18). In the present study, the 5-year survival rate was 93% and no patients died of gastric cancer. Because the median patient age was 73 years and those 80 years old and older accounted for 15%, the 5-year survival rate should to be satisfactory.

In conclusion, as the number of relevant cases is limited, follow-up observation was reasonable in patients who had lesions included in the indications or expanded indications and underwent non-curative ESD without lymphovascular invasion. In patients other than these, additional surgical resection should be considered. In particular, patients who were judged as having undergone piecemeal resection or were HM1, HMX or with ulceration should be treated by additional surgery and those patients who were judged as having submucosal invasion over 0.5 mm, total diameter of 3 cm or more or lymphatic invasion should be treated by additional surgery with lymphadectomy (D1+).

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