

Surgical outcome after incomplete endoscopic submucosal dissection of gastric cancer

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Background: Endoscopic resection of early gastric cancer is a relatively new and attractive treatment, but occasionally fails to remove all cancer lesions completely. This study aimed to elucidate clinicopathological factors that could be helpful in predicting residual tumour in the surgical specimen after incomplete endoscopic submucosal dissection (ESD).

Methods: Patients who underwent gastrectomy because of incomplete ESD between August 2004 and August 2008 were analysed. Clinicopathological characteristics were reviewed retrospectively from prospectively collected medical records. Patients were classified into groups with and without residual tumour. Pathology results following gastrectomy were compared with those of incomplete ESD.

Results: A total of 118 patients were included. The incidence of residual tumour in the surgical specimen was 24.6 per cent after incomplete ESD. Elevated/flat-type cancers, large tumours (at least 2 cm) and those limited to the mucosa had significantly higher incomplete ESD rates. Cancer limited to the mucosa and the presence of tumour in the lateral margin were associated with residual tumour in the surgical specimen (both $P = 0.001$).

Conclusion: Radical gastrectomy should be performed if pathological examination reveals a positive lateral resection margin after ESD.

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Introduction

Gastric cancer is the second commonest cause of death from malignancy in the world and the most common cancer in Korea^{1,2}. Advances in diagnostic techniques have led to an increased incidence of small and early-stage gastric cancers. The standard therapy is curative surgery, which involves gastric resection with D2 lymph node dissection. This has an excellent prognosis with survival rates in excess of 90 per cent, but is associated with high morbidity and mortality rates in the Western literature^{3–5}. Endoscopic resection, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), is now commonly performed in selected patients and enhances quality of life⁶. ESD is an innovative procedure that allows *en bloc* resection, which results in lower local recurrence rates than the piecemeal resection of EMR⁷. Indications for ESD proposed by the Japanese Gastric Cancer Association include differentiated adenocarcinoma and mucosal lesion size of 2 cm or less without ulceration^{8–10}. Recently, these

criteria have been expanded to include lesions greater than 2 cm and ulcerative lesions^{11,12}. Occasionally, it is difficult to predict whether an early gastric cancer is suitable for ESD, with consequent failure to remove the lesion completely. Causes of failure include residual cancer, advanced cancer, metastatic lymph nodes, cancer recurrence and complications such as bleeding or perforation. Following incomplete ESD, residual tumour has been reported in 29.0–39.5 per cent of definitive surgical specimens^{13,14}. This implies, on the other hand, that no residual tumour is found in about two-thirds of patients.

This study aimed to clarify clinicopathological factors that could predict residual tumour in the definitive surgical specimen after incomplete ESD.

Methods

All patients undergoing ESD at Samsung Medical Centre between August 2004 and August 2008 were enrolled. From these, all those who underwent gastrectomy because

of incomplete ESD were analysed. Clinicopathological characteristics were reviewed retrospectively from prospectively collected medical records.

Early gastric cancer was defined as a lesion confined to the mucosa or submucosa regardless of the presence or absence of lymph node metastases, according to the Japanese Classification of Gastric Carcinoma¹⁵. The indication for ESD in early gastric cancer was a non-ulcerative mucosal cancer smaller than 2 cm with differentiated histology and no evidence of lymph node metastases by abdominal computed tomography.

Incomplete ESD was defined as: presence of cancer cells in the lateral (anterior, posterior, proximal, distal) margins; presence of cancer cells at the deepest margin; invasion of the submucosa or muscularis propria; presence of lymphatic vessel invasion; or undifferentiated cell type. Patients meeting any one of these criteria underwent gastric resection and D2 lymph node dissection. Patients who had surgery for specific conditions, such as gastric perforation or uncontrolled bleeding during ESD, and those subjected to piecemeal resection were excluded from this study (Fig. 1). All patients with an incomplete ESD were transferred to the surgical department for operative treatment.

ESD was performed using a two-channel endoscope by medical endoscopists. The outer margin of the lesion was marked at 5 ± 10 mm with several spots using a needle knife. Following injection of normal saline and adrenaline (epinephrine) solution into the submucosa, the ESD procedure was carried out using a hook knife. Additional tissue was resected, if necessary, to ensure total removal of the lesion. Informed consent was obtained from all patients before ESD.

A standardized radical gastrectomy with D2 lymph node dissection was performed with curative intent by one of five expert surgeons, and surgical specimens were examined by a single pathologist.

All patients were assigned to one of two groups: those with and those without residual tumour. The residual tumour group included patients with tumour in the ESD margins (four lateral margins and the vertical margin) or metastatic lymph nodes in the surgical specimen.

Statistical analysis

Continuous values are expressed as mean(s.d.). Univariable analysis was performed using χ^2 or Fisher's exact test for categorical data. A binary logistic regression model was used for multivariable statistical comparisons. $P < 0.050$ was considered to indicate statistical significance. Statistical analyses were carried out using SPSS[®] software version 10.0 (SPSS, Chicago, Illinois, USA.).

Results

A total of 1743 patients had ESD during the study period. Incomplete ESD was performed in 118 patients and these underwent surgical resection. There were 92 men and 26 women of median age 64 (range 35–86) years. The clinicopathological outcomes of these patients are shown in Table 1. Invasion to the submucosa or muscle layer was most frequent (92 of 118, 78.0 per cent). The poorly differentiated/signet-ring cell type was found at pathological examination in 15 patients (12.7 per cent).

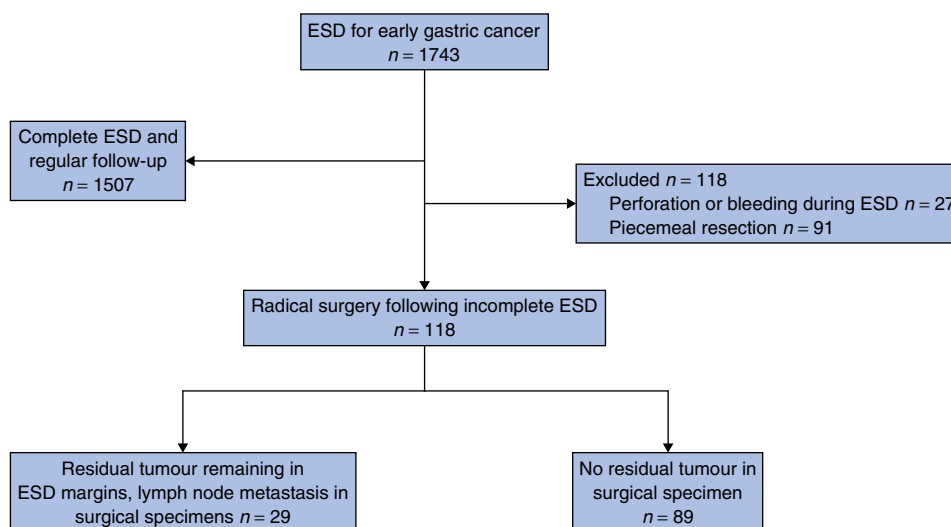


Fig. 1 Flow chart showing patient selection and treatment outcomes. ESD, endoscopic submucosal dissection

Table 1 Univariable analysis of clinicopathological characteristics of patients with incomplete endoscopic submucosal dissection according to residual tumour in surgical specimen

	Residual tumour in surgical specimen			<i>P</i> †
	Total (<i>n</i> = 118)	No (<i>n</i> = 89)	Yes (<i>n</i> = 29)	
Tumour location				0.211‡
Lower third	63 (53.4)	48 (76)	15 (24)	
Middle third	41 (34.7)	33 (80)	8 (20)	
Upper third	14 (11.9)	8 (57)	6 (43)	
Endoscopic gross finding				0.005
Elevated/flat	47 (39.8)	29 (62)	18 (38)	
Depressed	71 (60.2)	60 (85)	11 (15)	
Differentiation				0.520‡
Well	36 (30.5)	26 (72)	10 (28)	
Moderate	67 (56.8)	53 (79)	14 (21)	
Poor/signet-ring cell	15 (12.7)	10 (67)	5 (33)	
Laurén's classification				0.165
Intestinal	106 (89.8)	82 (77.4)	24 (22.6)	
Diffuse	12 (10.2)	7 (58)	5 (42)	
Tumour size (long diameter) (cm)				0.002
< 2	58 (49.2)	51 (88)	7 (12)	
≥ 2	60 (50.8)	38 (63)	22 (37)	
Depth of invasion (T category)				0.001
Mucosa only	26 (22.0)	13 (50)	13 (50)	
Submucosa or muscularis propria*	92 (78.0)	76 (83)	16 (17)	
sm1	29	24 (83)	5 (17)	0.751§
sm2 or sm3	63	52 (83)	11 (17)	
Lymphatic invasion				0.103
No	79 (66.9)	56 (71)	23 (29)	
Yes	39 (33.1)	33 (85)	6 (15)	
Vascular invasion				1.000
No	116 (98.3)	87 (75.0)	29 (25.0)	
Yes	2 (1.7)	2 (100.0)	0 (0)	
Neural invasion				—
No	118 (100)	89 (75.4)	29 (24.6)	
Yes	0 (0)	0 (0)	0 (0)	

Values in parentheses are percentages. *The lesions were classified into three equal layers of the submucosa: sm1 (invasion of the upper third), sm2 (invasion of the middle third) and sm3 (invasion of the lower third). The average depth of upper third was 500 µm¹⁵. T, tumour. † χ^2 test except ‡Fisher's exact test. §Between sm1 and sm2 or sm3.

This probably resulted from discordance between the pre-ESD endoscopic biopsy and the final ESD pathology.

Results of radical surgery after incomplete endoscopic submucosal dissection

The most commonly performed surgical procedure was subtotal gastrectomy (90 patients, 76.3 per cent). The

Table 2 Pathological analysis of the surgical specimen in patients undergoing radical surgery following incomplete endoscopic submucosal dissection

	No. of patients (<i>n</i> = 118)
Residual tumour in surgical specimen	
No	89 (75.4)
Yes	29 (24.6)
Residual cancer at ESD margin	
No	91 (77.1)
Yes	27 (22.9)
Lymph node metastases	
No	114 (96.6)
Yes	4 (3.4)
Pathological tumour category	
Invasion of mucosa	26 (22.0)
Invasion of submucosa or muscularis propria	92 (78.0)

Values in parentheses are percentages. ESD, endoscopic submucosal dissection.

total mean number of harvested lymph nodes was 34.5(5.4). There was no major morbidity, but 11 patients (9.3 per cent) had a grade I complication according to Clavien's classification (fluid collection in the laparotomy wound)¹⁶. There was no surgery-related mortality.

Residual tumour was found in 29 patients (24.6 per cent) (Table 2), usually at the ESD margin (27 patients, 22.9 per cent). Lymph node metastases were found in four patients (3.4 per cent). Three patients had one metastatic lymph node each, and one patient had two such nodes. All positive lymph nodes were in the perigastric lymph node group (N1 level). Tumours in all four lymph node-positive patients showed submucosal invasion, differentiated cell types and were intestinal type in Laurén's classification. Only two of these patients had lymphatic vessel invasion in the surgical pathology specimen. Two patients with lymph node metastases presented simultaneously with residual cancer cells at the ESD margin of the surgical specimen.

Association between endoscopic submucosal resection result and residual tumour in surgical specimen

Elevated/flat-type cancers were associated with a significantly higher residual cancer rate following ESD compared with depressed lesions ($P = 0.005$) (Table 1). Likewise, large cancers (at least 2 cm) showed higher residual cancer rates than small cancers ($P = 0.002$). Cancers limited to the mucosa had higher residual tumour rates than those invading the submucosa or muscularis propria ($P = 0.001$).

Table 3 Association between surgical indications and residual tumour in surgical specimen

	Residual tumour in surgical specimen		P*
	No (n = 89)	Yes (n = 29)	
Submucosa (sm) invasion			0.001
No	13 (50)	13 (50)	
Yes	76 (83)	16 (17)	
Deepest margin			0.360
Negative	78 (77.2)	23 (22.8)	
Positive	11 (65)	6 (35)	
Lateral margin			0.001
Negative	78 (89)	10 (11)	
Positive	11 (37)	19 (63)	
Lymphatic invasion			0.103
No	56 (71)	23 (29)	
Yes	33 (85)	6 (15)	
Undifferentiated cell type			0.520
No	79 (76.7)	24 (23.3)	
Yes	10 (67)	5 (33)	

Values in parentheses are percentages. * χ^2 test.

Table 4 Multivariable binary logistic regression analysis of risk of residual tumour in the surgical specimen

	Hazard ratio	P
Analysis according to ESD pathology		
Endoscopic gross finding (depressed lesion)	0.34 (0.13, 0.88)	0.026
Tumour size (≥ 2 cm)	3.65 (1.33, 10.02)	0.012
Depth of invasion (submucosa or muscularis propria)	0.34 (0.12, 0.95)	0.040
Analysis according to surgical indication following ESD		
Submucosa invasion	0.93 (0.26, 3.37)	0.909
Tumour in lateral margin	12.93 (3.83, 43.64)	0.001

Values in parentheses are 95 per cent confidence intervals. ESD, endoscopic submucosal dissection. Analysis was performed separately for ESD pathology and surgical indication following ESD; only dependent variables that were statistically significant ($P < 0.050$) in univariable analysis were included.

Association between surgical indication and residual tumour in surgical specimen

Surgical treatment (radical gastrectomy) was based on a single indication in 21 (17.8 per cent) of 118 patients, and on more than two indications in the remaining 97 (82.2 per cent). The group with cancer restricted to the mucosa had a significantly higher residual cancer rate than the submucosal invasion group ($P = 0.001$), and

the positive lateral margin group had a significantly higher residual cancer rate than the negative margin group ($P = 0.001$) (Table 3). In addition, the proportion of patients with a positive lateral margin was significantly higher in cancers limited to the mucosa (19 of 26; $P < 0.001$).

In multivariable analysis according to ESD pathology, large cancers (at least 2 cm), endoscopic gross findings and depth of invasion were significant independent predictors of residual tumour. Tumour in the lateral margin was significantly associated with residual tumour in the analysis according to surgical indication following ESD (Table 4).

Discussion

ESD is a novel endoscopic procedure that can facilitate *en bloc* resection of early gastric cancer. This is an elegant technique, but incomplete ESD has been associated with local recurrence and regional metastases. A gastric resection with lymph node dissection is inevitable after incomplete ESD, although it may be associated with a high risk of morbidity or death. The final pathology frequently reveals no residual tumour or lymph node metastases in the surgical specimen, raising the issue of whether unnecessary resection cannot be avoided^{17–20}. The present study was conducted to identify clinicopathological factors that might be used to predict residual tumour following incomplete ESD, and to establish appropriate indications for gastric resection that could contribute to avoiding unnecessary operation.

Few reports on surgical indications after incomplete ESD have been published, and this is an area of considerable controversy. One study concluded that surgery should be performed when pathological examination of the ESD specimen revealed tumour beyond the middle third of the submucosa (sm2) or a mucosal cancer larger than 3 cm¹³. Others suggested that gastrectomy should be carried out in patients with cancer invading the submucosal layer, whereas non-invasive treatment should be selected if the tumour extended only into the mucosa around the margin²⁰. In addition, it was shown that radical surgery was necessary if positive lateral margins, submucosal invasion or both were found after ESD²¹. The limitation of the above studies is the small number of patients. In the present study, which reported on a considerably larger number of patients, a positive lateral margin was the most important indication for gastric resection following incomplete ESD.

The indications for ESD are mainly dependent on endoscopic findings. Therefore, the gross findings at endoscopy may influence the decision to perform ESD, which means that accurate reporting of endoscopic gross findings is extremely important. Endoscopic ultrasonography, auto-

fluorescence imaging and narrow band imaging have been suggested to be useful in determining the margin of tumour and identifying lymph node metastases²². In the present study, the incidence of tumour exceeding 2 cm in the final ESD pathological examination was high (more 50 per cent). It seems likely that incomplete ESD was due to an error in size estimation on gastroscopy.

In this study, some patients had an undifferentiated cell type on ESD pathology, which differed from that of the initial diagnostic biopsy. It must be assumed that the ESD specimen frequently had mixed cell types that were not all present in the diagnostic biopsy because of the relatively small specimen size (for example moderately differentiated cells centrally with poorly differentiated cells in the periphery). This may imply that the pathological examination of initial diagnostic biopsies should preferably be done by a designated pathologist.

Interestingly, the present data suggest that gross estimation of tumour size in diagnostic endoscopy may be difficult in patients with elevated/flat-type mucosal tumours. This may result in tumour cells remaining around the lateral margins of ESD specimens in large cancers.

With regard to surgical indications, the residual tumour rate was higher in patients with cancers limited to the mucosa and those with positive lateral margins after incomplete ESD. This is in contrast to other reports. It may result from failure to achieve a lateral safety margin in large mucosal cancers because of underestimation of tumour size. The high incidence of residual tumour in cancers limited to the mucosa might be a result of selection bias in this retrospective analysis. On the contrary, favourable results were seen for relatively small submucosal cancers because complete dissection of the submucosal layer with sufficient safety margins was feasible using ESD. Although submucosal or lymphatic invasion and undifferentiated cell type have been reported as indications for surgical management in other studies^{13,14}, these factors were not associated significantly with the presence of residual tumour in the present series.

Several treatment strategies can be considered after incomplete endoscopic resection. Radical gastrectomy with lymph node dissection is commonly used, but the results of other procedures have been reported recently. The combination of ESD and laparoscopic lymph node dissection has enabled complete resection of the primary tumour and pathological confirmation of lymph node status, while obviating unnecessary gastrectomy¹⁸. Others have suggested laparoscopic gastrectomy with D1 + β (D1 + 7, 8a, 9 nodes dissection according to the JGCA classification) dissection as the treatment of choice for incomplete endoscopic resection²³. Repeat ESD may not

be feasible because the complication rate is likely to be increased owing to scar formation or thinning of the gastric wall after the first ESD procedure¹⁷.

A potential weakness of the present study is that long-term survival results were not available because of the short follow-up period. A comparative analysis of surgical modalities after incomplete ESD is required.

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References

- 1 Central Cancer Registry in Korea. 2002 Annual Report of the Central Cancer Registry in Korea. Ministry of Health and Welfare: Seoul, 2007.
- 2 Shin HR, Ahn YO, Bae JM, Shin MH, Lee DH, Lee CW *et al.* Cancer incidence in Korea. *Cancer Res Treat* 2002; **34**: 405–408.
- 3 Shimada S, Yagi Y, Shiomi K, Uebhiko H, Naoko H, Akinobu M *et al.* Characterization of early gastric cancer and proposal of the optimal therapeutic strategy. *Surgery* 2001; **129**: 714–719.
- 4 Itoh H, Oohata Y, Nakamura K, Nagata T, Mibu R, Nakayama F. Complete ten-year postgastrectomy follow-up of early gastric cancer. *Am J Surg* 1989; **158**: 14–16.
- 5 Lee HJ, Kim YH, Kim WH, Lee KU, Choe KJ, Kim JP *et al.* Clinicopathological analysis for recurrence of early gastric cancer. *Jpn J Clin Oncol* 2003; **33**: 209–214.
- 6 Amemiya T, Oda K, Ando M, Kawamura T, Kitagawa Y, Okawa Y *et al.* Activities of daily living and quality of life of elderly patients after elective surgery for gastric and colorectal cancers. *Ann Surg* 2007; **246**: 222–228.
- 7 Oka S, Tanaka S, Kaneko I, Mouri R, Hirata M, Kawamura T *et al.* Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. *Gastrointest Endosc* 2006; **64**: 877–883.
- 8 Eguchi T, Gotoda T, Oda I, Hamanaka H, Hasuike N, Saito D. Is endoscopic one-piece mucosal resection essential for early gastric cancer? *Dig Endosc* 2003; **15**: 113–116.
- 9 Soetikno RM, Gotoda T, Nakanishi Y, Soehendra N. Endoscopic mucosal resection. *Gastrointest Endosc* 2003; **57**: 567–579.
- 10 Nakajima T. Gastric cancer treatment guidelines in Japan. *Gastric Cancer* 2002; **5**: 1–5.
- 11 Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T *et al.* Incidence of lymph node metastases from early gastric cancer: estimation with a large number of patients at two large centers. *Gastric Cancer* 2000; **3**: 219–225.
- 12 Oda I, Saito D, Tada M, Iishi H, Tanabe S, Oyama T *et al.* A multicenter retrospective study of endoscopic resection for early gastric cancer. *Gastric Cancer* 2006; **9**: 262–270.
- 13 Ryu KW, Choi IJ, Doh YW, Kook MC, Kim CG, Park HJ *et al.* Surgical indication for non-curative endoscopic

- resection in early gastric cancer. *Ann Surg Oncol* 2007; **14**: 3428–3434.
- 14 Nagano H, Ohyama S, Fukunaga T, Seto Y, Fujisaki J, Yamaguchi T *et al.* Indications for gastrectomy after incomplete EMR for early gastric cancer. *Gastric Cancer* 2005; **8**: 149–154.
 - 15 Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma. 2nd English Edition. *Gastric Cancer* 1998; **1**: 10–24.
 - 16 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205–213.
 - 17 Oka S, Tanaka S, Kaneko I, Mouri R, Hirata M, Kanao H *et al.* Endoscopic submucosal dissection for residual/local recurrence of early gastric cancer after endoscopic mucosal resection. *Endoscopy* 2006; **38**: 996–1000.
 - 18 Abe N, Mori T, Takeuchi H, Yoshida T, Ohki A, Ueki H *et al.* Laparoscopic lymph node dissection after endoscopic submucosal dissection: a novel and minimally invasive approach to treating early-stage gastric cancer. *Am J Surg* 2005; **190**: 496–503.
 - 19 Kim JJ, Lee JH, Jung HY, Lee GH, Cho JY, Ryu CB *et al.* EMR for early gastric cancer in Korea: a multicenter retrospective study. *Gastrointest Endosc* 2007; **66**: 693–700.
 - 20 Korenaga D, Orita H, Maekawa S, Maruoka A, Sakai K, Ikeda T *et al.* Pathological appearance of the stomach after endoscopic mucosal resection for early gastric cancer. *Br J Surg* 1997; **84**: 1563–1566.
 - 21 Chung YS, Park DJ, Lee HJ, Kim SG, Jung HC, Song IS *et al.* The role of surgery after incomplete endoscopic mucosal resection for early gastric cancer. *Surg Today* 2007; **37**: 114–117.
 - 22 Ichikawa T, Kudo M, Matsui S, Okada M, Kitano M. Endoscopic ultrasonography with three miniature probes of different frequency is an accurate diagnostic tool for endoscopic submucosal dissection. *Hepatogastroenterology* 2007; **54**: 325–328.
 - 23 Song KY, Hyung WJ, Kim HH, Han SU, Cho GS, Ryu SW *et al.*; Korean Laparoscopic Gastrointestinal Surgery Study (KLASS) Group. Is gastrectomy mandatory for all residual or recurrent gastric cancer following endoscopic resection? A large-scale Korean multi-center study. *J Surg Oncol* 2008; **98**: 6–10.