Efficacy and Safety of Endoscopic Submucosal Dissection for Early Gastric Cancer in Patients with Comorbid Diseases

Beom Jin Kim*, Tae Hoon Chang[†], Jae J. Kim[†], Byung-Hoon Min[†], Jun Haeng Lee[†], Hee Jung Son[†], Poong-Lyul Rhee[†], Jong Chul Rhee[†], Kyung Mee Kim[‡], and Chul Keun Park[‡]

*Department of Internal Medicine, Chung-Ang University College of Medicine, Departments of [†]Medicine and [‡]Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Background/Aims: Endoscopic submucosal dissection (ESD), a new and potentially curative method for treating gastrointestinal neoplasms, may have longer procedure time and the risk of complications when compared to conventional endoscopic mucosal resection. This study evaluated the efficacy and safety of ESD in patients with comorbid diseases. **Methods:** The outcomes of 337 patients who underwent ESD for early gastric cancer at Samsung Medical Center from April 2003 to December 2006 were analyzed retrospectively. The Charlson comorbidity scale was used to divide the patients into low-risk (no risk factor) and high-risk (at least one risk factor) groups. The outcomes and complications were compared between the high- and low-risk groups. **Results:** The low- and high-risk groups comprised 240 and 97 patients with mean ages of 61.1 and 64.7 years, respectively ($p=0.002$). Tumor location, tumor size, depth of invasion, procedure duration, and rates of *en bloc* resection, complete resection, complication, and recurrence did not differ significantly between the two groups ($p>0.05$). **Conclusions:** ESD may be a safe and effective treatment for early gastric cancer in patients with comorbid diseases. (*Gut Liver* 2010;4:186-191)

Key Words: Early gastric cancer; Endoscopic submucosal dissection; Comorbid disease; Complication

INTRODUCTION

Endoscopic mucosal resection (EMR) is widely used as

a less invasive treatment for early gastric cancer than non-endoscopic surgical removal. Conventional EMR cannot resect lesions larger than 2 cm in diameter *en bloc*.¹⁻⁴ Pathological evaluation of a piecemeal specimen for curative resection is also difficult, and the recurrence rate is higher than with resection *en bloc*.⁵ In contrast to EMR, endoscopic submucosal dissection (ESD) can resect lesions larger than 2 cm *en bloc* and reduce local recurrence.⁶⁻⁹ But ESD may also cause serious complications such as bleeding or perforation more frequently than conventional EMR.^{5-7,10} As life expectancy has increased because of better living conditions and improvements in the treatment of chronic disease, more patients who undergo ESD have one or more chronic diseases.¹¹⁻¹³ However, the safety or complication rate of ESD for such patients is not well-known. The aim of this study is to evaluate the efficacy and safety of ESD as a treatment for early gastric cancer in patients with comorbid diseases.

MATERIALS AND METHODS

1. Patients

A retrospective analysis was performed on 337 patients who underwent ESD for early gastric cancer at Samsung Medical Center from April 2003 through December 2006. Follow-up endoscopic examinations and routine biopsies at the previous ESD site were performed biannually to check for local recurrence.

Correspondence to: Jae J. Kim

Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50, Irwon-dong, Gangnam-gu, Seoul 135-710, Korea

Tel: +82-2-3410-3409, Fax: +82-2-3410-0392, E-mail: jjkim@skku.edu

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B.J. Kim and T.H. Chang contributed equally to this work.

Table 1. Charlson Comorbidity Scale

Condition	Assigned weights	Condition	Assigned weights
Myocardial infarct	1	Hemiplegia	2
Congestive heart failure	1	Moderate or severe renal disease	2
Peripheral vascular disease	1	Diabetes with end organ damage	2
Cerebrovascular disease	1	Any tumor	2
Dementia	1	Leukemia	2
Chronic pulmonary disease	1	Lymphoma	2
Connective tissue disease	1	Moderate or severe liver disease	3
Ulcer disease	1	Metastatic solid tumor	6
Mild liver disease	1	AIDS	6
Diabetes	1		

2. Endoscopic mucosal dissection

The ESD procedures were performed under conscious sedation using midazolam (5-10 mg) and pethidine (25-50 mg) by one gastroenterologist (J.K.) with over 20 years of endoscopy experience. Several spots were marked 5 to 10 mm from the edge of the lesion with a needle knife, and diluted epinephrine solution (0.5%) plus indigocarmine dye was injected into the submucosal tissue around the lesion. The needle knife was used to place marking dots at the periphery of the lesion. These dots were used as a guide for the insertion of the tip of a insulation-tipped needle knife (IT knife; Olympus Co., Tokyo, Japan) into the submucosal layer. Circumferential mucosal cutting and submucosal dissection under the lesion were done with an electrosurgical knife such as the IT knife or Flex knife. When necessary diluted epinephrine solution was injected into the submucosal tissue. Perforation was avoided by using a tangential cutting angle. After complete ESD, electrocautery or hemoclipping was used for hemostasis. The procedure ended with the confirmation of complete hemostasis.

3. Histological classification

The revised Vienna classification of gastrointestinal epithelial neoplasia was used for histological classification.¹⁴ The location was classified as antrum/angle, low body, midbody, high body and fundus. Criteria for "complete resection" were *en bloc* resections with margins free of neoplasms, with all of the following findings: 1) well or moderately differentiated type, 2) no angiolymphatic invasion, 3) mucosal or minimally invasive submucosal cancer (invasion depth $\leq 500 \mu\text{m}$, SM1), and 4) lateral safety margin ($\geq 2 \text{ mm}$). Resections that did not meet the above criteria were considered incomplete.

4. Complications

After the procedure, the presence of hematemesis or

melena was considered bleeding, as was a decrease in hemoglobin of more than 2.0 g/dL. If the patient required an endoscopic hemostatic procedures or surgical interventions within one month after ESD, then he or she was considered to have bleeding. Perforation was diagnosed endoscopically during the procedure or by the presence of free air on a chest PA view after the procedure.

5. Charlson comorbidity scale

The Charlson comorbidity scale has been used to estimate the risk of death from comorbid diseases in patients with cancer.¹⁵⁻¹⁸ Table 1 shows the diseases and the assigned weights for each disease considered in this assessment. The Charlson comorbidity index is the sum of the weights for the individual diseases in a given patient. Based on this scale, we assessed the comorbidity risks for various common conditions, including diseases of the pulmonary and cardiovascular systems, blood-forming tissues, and diabetes, as well as liver or renal disease. Patients with one or more comorbid diseases were assigned to the high-risk group, and the others were assigned to the low-risk group. We then compared the outcomes and complications of ESD between the two groups. We subdivided the high-risk group into two subgroups; mild subgroup with Charlson comorbidity index=1,2 and severe subgroup with Charlson comorbidity index ≥ 3 .

6. Statistical analysis

Data were analyzed using the unpaired *t*-test, Mann-Whitney U-test, χ^2 -test, and Fisher's exact probability test, as appropriate. All p-values were two-tailed, and a p-value <0.05 was considered statistically significant.

RESULTS

1. Characteristics of the patients and tumors

Among 337 patients who underwent ESD, 240 patients were included in the low-risk group, and 97 patients in

Table 2. Patient and Tumor Characteristics

	Low risk group (n=240)	High risk group (n=97)	p-value
Age, yr	61.1±10.1	64.7±8.7	0.002
Gender, M:F	181:59	79:18	0.233
Location			0.121
Antrum/Angle	187	73	
Low body	32	11	
Mid body	16	4	
High body	5	9	
Endoscopic pattern			0.244
I	8	2	
IIa	126	44	
IIb	17	11	
IIc	89	40	
Tumor size, mm	15.9±9.8	15.0±9.7	0.336
Specimen size, mm	40.7±12.4	37.9±11.5	0.133
Histology			0.072
Well differentiated	111	55	
Moderately differentiated	120	40	
Poorly differentiated	9	2	
Depth of invasion			0.257
Mucosal layer	205	78	
Submucosal layer	35	19

Fig. 1. Comorbid diseases in the high-risk group. Among patients in the high-risk group, the prevalence rates are higher for diabetes mellitus and cardiovascular disease than for hepatic, pulmonary, renal, and hematologic diseases.

the high-risk group. The characteristics of the patients and tumors are summarized in Table 2. The two groups did not differ significantly in gender, tumor location, endoscopic findings, tumor size, specimen size, histological classification, or depth of invasion. However, patients in the high-risk group were significantly older (mean age, 64.7 years) than those in the low-risk group ($p=0.002$).

The comorbid diseases in the high-risk group included diabetes, diseases of the cardiovascular system, liver, pul-

Table 3. Outcomes of Endoscopic Submucosal Dissection

	Low risk group (n=240)	High risk group (n=97)	p-value
Procedure time, min	47.2±26.1	52.4±32.0	0.188
<i>En bloc</i> resection (%)	220 (91.7)	87 (89.7)	0.564
Complete resection (%)	174 (72.5)	73 (75.3)	0.604
Local recurrence (%)	2/194 (1.0)	0/78 (0)	0.913
Metachronous cancer (%)	9/194 (4.6)	4/78 (5.1)	0.890
Complication (%)	28 (11.7)	9 (9.3)	0.525
Bleeding (%)	12 (5.0)	4 (4.1)	1.000
Perforation (%)	16 (6.7)	5 (5.2)	0.603

monary system, kidneys and blood-forming tissues (Fig. 1). Seventy-six patients had only one disease and 21 patients had two or more. Cardiovascular diseases included ischemic heart disease (eight patients), congestive heart failure (four patients), arrhythmias (three patients), valvular heart disease (one patient), cerebrovascular disease and others (four patients). Although the Charlson comorbidity scale does not include hypertension, and this study did not combine it with cardiovascular disease, we monitored our patients for hypertension. In the high-risk group, 54 patients (55.7%) had hypertension, as did 72 patients (30.0%) in the low-risk group ($p<0.001$). Among the 18 patients with liver disease, 17 were Child-Pugh class A, and one was Child-Pugh class B. Four of 18 patients had platelet counts less than $1.0 \times 10^5/\text{mm}^3$. Pulmonary disease was defined as moderate or severe obstructive/restrictive dysfunction in a pulmonary function test. The FEV₁ of the patients with pulmonary disease was 1.80 ± 0.42 L (Mean±SD). Among the eight patients with chronic kidney disease (GFR<30 mL/min), three were receiving dialysis treatments. The GFR of the patients who didn't receive dialysis was 20.56 ± 3.96 mL/min (mean±SD). Two patients had hematologic diseases (paroxysmal nocturnal hematuria and lymphoma). Of the 95 patients in the high-risk group, 30 (31.6%) had taken antiplatelet agents or nonsteroidal anti-inflammatory drugs, and 15 of 234 patients (6.4%) in the low-risk group did the same ($p<0.001$). The history of medication was not available for the remaining patients. All patients were forbidden to take any drugs for at least one week before ESD.

2. ESD outcomes

Table 3 summarizes the results of ESD in the two groups. The two groups did not differ significantly in procedure time, or in rates of *en bloc* resection, complete resection, complications or recurrence. Patients who underwent the operation because of incomplete resection, or

who did not receive follow-up endoscopic examination were not included in the calculation of recurrence. The mean follow-up time was approximately 23 months for each of the two groups. During the follow-up, we identified two cases of local recurrence in the low-risk group, but found no recurrence in the high-risk group. One patient was treated for recurrence using a second ESD and argon plasma coagulation. After a few months, however, local recurrence was noted and subtotal gastrectomy was performed. The other case was found six months after incomplete resection and was also treated by subtotal gastrectomy. During the same period, metachronous cancers were diagnosed in nine patients in the low-risk group and four in the high-risk group. Among the patients with metachronous cancer, 11 received a second ESD, with complete resections achieved in eight patients. Five patients received surgery, including three in whom the initial resections were incomplete.

Bleeding occurred in 12 patients (5.0%) in the low-risk group and endoscopic management was successful in 11 of these. One patient required surgical intervention. Perforation occurred in 16 patients (6.7%) of the low-risk group, and 15 of these were successfully treated non-surgically with endoscopic clipping, fasting, and broad-spectrum antibiotics. Three of these patients, however, received further surgery with laparotomy because of submucosal invasion. Emergency surgery was performed on one patient.

Bleeding occurred in four patients (4.1%) in the high-risk group. Electrocauteries were performed in three of these patients, and injection hemostasis using hypertonic saline plus epinephrine solution was performed in one patient. Perforations were detected in five patients (5.2%) of the high-risk group, and medical care was successful in all. However, gastrectomy was performed in two of these patients because of submucosal invasion. One patient in the high-risk group experienced cerebrovascular accident after ESD. Immediately after the procedure, this 75-year-old male developed dysarthria and numbness in the left side of his face. His brain MRI before ESD had shown multiple chronic infarctions, and the post-ESD MRI suggested that new small infarctions had occurred. His symptoms did not intensify, and clopidogrel was prescribed in the neurologic outpatient clinic two weeks after ESD. The two groups did not differ significantly in rates of bleeding and perforation ($p > 0.05$). Furthermore, there was no significant difference between mild subgroup and severe subgroup ($p > 0.05$) (data not shown).

3. Complication rates for each comorbid disease

Fig. 2 shows the complication rates in the patients with

Fig. 2. Complication rates in patients with various comorbid diseases. The rates of bleeding and perforation are 5% and 7%, respectively, in the low-risk group, and they are highest in patients with cardiovascular disease or renal disease in the high-risk group. However, the rates does not differ significantly between the two groups.

each comorbid disease. Of the 47 patients with diabetes, two (4.3%) had post-ESD bleeding and only one (2.1%) had perforation. Among the patients with cardiovascular disease, two had postoperative bleeding (7.1%) and three had perforation (10.7%). Although the complication rates for hypertensive patients are not shown in the figure, post-ESD bleeding and perforation occurred in nine and nine patients, respectively (7.1% and 7.1%). Of the 18 patients with liver disease, one had post-ESD bleeding. His hepatic function status was Child-Pugh class A, but he also had chronic kidney disease and ischemic heart disease. Among patients with pulmonary disease, none developed bleeding, but perforation occurred in two (11.1%). Among the eight patients with renal disease, bleeding occurred in one patient (12.5%), the patient also had liver disease was mentioned above. Perforation also occurred in one of the patients with renal disease (12.5%). Although complication rates in patients with renal disease were higher than for patients without comorbid diseases, the difference did not reach statistical significance because of the small number of patients enrolled. None of the comorbid diseases made a statistically significant contribution to the occurrence of a specific complication (such as bleeding or perforation).

DISCUSSION

Gastric cancer is the most prevalent malignant neoplasm and the second leading cause of cancer death in Korea, despite a slight reduction in its incidence over the

past few decades.^{19,20} Since the adoption of endoscopic screening in Korea, the proportion of EGC cases has increased, and with it, the number of patients undergoing endoscopic treatment.^{3,21} The inclusion criteria for ESD are gradually extending.

The ESD technique permits the resection *en bloc* of larger lesions than before in EGC, and may possibly reduce local recurrence after the procedure. The procedure is especially useful for patients with EGC and comorbid diseases, because these patients show higher rates of morbidity and mortality with surgery. On the other hand, comparative studies show longer operation times, and higher risks for complications such as bleeding or perforation with ESD than with conventional EMR. The risk for bleeding with ESD approaches 7%, and delayed bleeding is associated with the size and location of the tumor.^{22,23} The risk for perforation, about 4%, varies with the location and morphology of the tumor.⁶ The increased risks for morbidity or mortality, associated with surgeries that are necessary to treat complications, raise concern for the availability and safety of ESD for patients with comorbid diseases.

Kakushima *et al.*²⁴ reporting on the feasibility of ESD in elderly patients (mean age, 78.9 years), found that 57% of the patients had comorbid diseases, and reported complication rates for bleeding and perforation as 7% and 2%, respectively. However, the number of enrolled patients was small (n=42), most of them had mild conditions, and the authors did not provide an analysis of complication risks for the specific diseases. Among patients with liver cirrhosis, Ogura *et al.*²⁵ reported the risk of postoperative bleeding after ESD as 20% (3/15 patients), which is high compared with the rate of 3.4-6.2% in previous studies. The patients who had postoperative bleeding were Child-Pugh class B. However, the availability and safety of ESD in patients with other comorbid diseases has not been evaluated.

In this study, we compared outcomes and complication rates for ESD in patients with and without other medical conditions, and found no significant differences. We also found that no specific comorbid condition significantly changed the outcomes and complication rates as compared to those in patients without that condition. Our findings support the safety and efficacy of ESD for patients with early gastric cancer and one or more of these common medical conditions. Although not shown specifically in this study, aspirin did not increase the risk for post-ESD bleeding in these patients, who were prevented from taking aspirin for at least seven days before ESD. None of the patients who enrolled had taken anti-coagulants, so the time after ESD at which patients may

safely resume aspirin or anticoagulant therapy must still be determined. We also used the Charlson comorbidity index to evaluate the influence of disease multiplicity and severity on complication rates. As Table 3 shows, the complication rates in the patients who had multiple comorbid diseases or a high Charlson comorbidity index did not significantly exceed those in the patients with a low Charlson comorbidity index.

Recent reports indicate that young age, large tumor size or high tumor locations may increase risk for post-ESD bleeding.^{22,26,27} Gotoda²⁸ demonstrated that the tumors located in the upper or middle third of the stomach, and those with ulcer were prone to perforate after ESD. In the present study, multivariate analysis failed to reveal a significant risk factor associated with post-ESD bleeding. In patients with post-ESD bleeding, the mean age was lower and the mean tumor size was larger, but these differences were not significant. We suspected hypertension as a risk factor for post-ESD bleeding, but could not confirm this statistically (p=0.077). Among patients with perforation, the proportion of proximal tumor locations was higher and the mean tumor size was larger; but, on multivariate analysis, only tumor location remained as an independent risk factor for perforation (p=0.002).

The non-randomized design and probable selection bias in this study limit its general application. Only a few patients had severe comorbid diseases, which precluded analysis with respect to disease severity and also introduced a probable selection bias. The small numbers of patients with each specific disease also excluded evaluation of complication rates by disease. For renal and pulmonary diseases, however, we minimized selection bias by defining "comorbid conditions" as moderate or severe cases with clinical significance, then analyzing the data by the number of diseases using the Charlson comorbidity index.

In conclusion, our findings support the use of ESD as a safe and effective treatment for EGC in patients with mild or moderate comorbid disease. In view of the risks from surgery, ESD stands out as the treatment of choice for selected patients with EGC and well-controlled comorbid diseases. Further study is needed to determine the safety and efficacy of EGD in the patients with severe comorbid diseases, and the risks imposed by each disease individually.

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