Long-term outcome of the endoscopic submucosal dissection of early gastric cancer: A comparison between patients with and without liver cirrhosis

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Abstract. Gastric cancer (GC) and liver cirrhosis (LC) have high incidence rates, particularly in Eastern Asia; however, the long-term clinical outcomes or recurrence of GC following endoscopic submucosal dissection (ESD) in patients with comorbid LC remain unclear. The present study aimed to compare the long-term efficacy and safety of ESD in patients with GC, with and without LC. Patients with early GC (EGC) who had underlying LC and underwent endoscopic treatment (LC-EGC group) were enrolled in the present study. In addition, patients with EGC without LC (non-LC-EGC group) were matched at a ratio of 1:3 via propensity score matching. The clinical outcomes and histopathological data of both groups were analyzed. No significant differences were observed in procedure type, complications [intraprocedural bleeding (11.8%) and perforation (0.0%)], en bloc resection rate (94.1%) and complete resection rate (100%) between the two groups. Multivariate Cox regression analysis demonstrated that procedure time was significantly associated with procedure-associated bleeding [adjusted hazard ratio (HR), 1.017; 95% confidence interval (CI), 1.001-1.032; P=0.033]. Furthermore, LC was significantly associated with cancer recurrence (adjusted HR, 5.482; 95% CI, 1.102-27.279; P=0.038). Taken together, the results of the present study suggest that endoscopic resection of EGC in patients with LC is an effective and safe treatment method. However, further studies are required to assess recurrence.

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Abbreviations: GC, gastric cancer; LC, liver cirrhosis; ESD, endoscopic submucosal dissection; EGC, early gastric cancer; HR, hazard ratio; CI, confidence interval

Key words: comorbidity, endoscopic resection, gastric cancer, prognosis, treatment

Introduction

Gastric cancer (GC), one of the most common gastrointestinal malignancies worldwide (1), has a high incidence rate in East Asia (2,3). The detection rate of early GC (EGC) has increased due to introduction of the national cancer screening system in the Republic of Korea. Endoscopic submucosal dissection (ESD) was recently accepted as an early treatment modality for EGC in several countries (2-8). ESD is considered a less invasive and more accessible treatment strategy for EGC compared with surgery (9-11). The extended criteria for the application of ESD for EGC are based on large-scale Japanese data (12). If performed accurately, recovery time and the return to normal life are notably faster for patients who undergo ESD compared with surgery, including open and laparoscopic surgery (13). Thus, ESD is a more desirable treatment strategy considering the perioperative risk in patients with comorbidities.

Liver cirrhosis (LC) is also prevalent in East Asia, owing to the high prevalence of hepatitis B and C viral infections (14-16). Several studies have demonstrated the association between LC and GC. A cohort study in Denmark reported an increased standardized incidence ratio of GC in patients with LC [a standardized incidence ratio of 1.9; 95% confidence interval (CI), 1.3-2.6] (17). Furthermore, a study on 1,379 patients with LC reported a 2.6-fold higher incidence of GC in cirrhotic patients compared with that in the general population (18).

Several studies have reported the effectiveness of ESD in patients with LC and EGC. A Korean study reported en bloc and curative resection rates of 96.8 and 89.9%, respectively (19). A Japanese study reported en bloc and R0 resection rates of 88.9 and 77.8%, respectively, in patients with EGC and LC (20).

Due to the high incidence of GC and LC in East Asia, and the favorable outcomes of endoscopic therapy, the prognostic expectations following ESD for EGC in patients with LC include improving the quality of life and compliance of the patients. However, this issue is yet to be investigated.

The present study aimed to compare the long-term clinical outcomes and prognosis of EGC following ESD in patients with and without LC.

Patients and methods

Patient enrollment. The present study retrospectively collected data on ESD procedures performed between March 2007 and March 2016. Patients were diagnosed according to the International Classification of Diseases, 10th edition (21), and the lesions were classified into lower third (C16.0, 16.1), middle third (C16.2) and upper third (C16.3, 16.4), according to their location. The total number of ESD procedures performed during the study period was 688. Patients diagnosed with LC, who underwent endoscopic treatment for EGC at Korea University Guro Hospital (Seoul, South Korea), were enrolled in the present study. The male to female ratio was 88.2:11.8, and the mean age was 62.64±7.85 years (age range, 51-79 years). All patients were Korean. The inclusion criteria were as follows: i) Presence of LC in imaging tests; ii) histologically diagnosed gastric cancer and iii) lesions localized in the mucosal layer. The exclusion criteria were as follows: i) Absence of LC in imaging tests; ii) incomplete clinical or blood test results, namely prothrombin time/international normalized ratio, presence of ascites, bilirubin level, albumin level or presence of encephalopathy, for calculating the Child-Pugh score (22); iii) history of receiving a liver transplant; and iv) biopsy results indicating a benign lesion. LC was diagnosed based on radiological examination, clinical data and medical history. Liver function was assessed using the Child-Pugh scoring system. To determine the therapeutic effect of ESD and the prognosis of EGC, propensity score-matched patients with EGC but without LC (n=51) were used as the controls. The present study was reviewed and approved by the Korea University Guro Hospital Institutional Review Board (approval no. 2019GR0467) and written informed consent was provided by all participants prior to the study start.

Endoscopic procedure. Experienced endoscopists (n=2) used a GIF-H260 endoscope (Olympus Corporation) to perform the endoscopies in the present study. ESD was performed under standard conscious sedation induced by propofol (Daewon Pharm. Co., Ltd., https://www.daewonpharm.com/main/index.jsp, 1.5-2.5 mg/kg) and/or midazolam (Bukwang Pharm Co., Ltd., https://www.bukwang.co.kr, 2-2.5 mg) in patients placed in the left decubitus or prone position. Blood pressure and oxygen saturation were carefully monitored during endoscopy. Standard ESD procedures were performed, including lesion marking, mucosal dissection, submucosal dissection and hemostasis. Markings were made around the lesion via needle coagulation, and normal saline solution with epinephrine (Daihan Pharm Co., Ltd., http://www.daihan.com/main/main.php) 1:10,000 and indigo carmine (Korea United Pharm, Inc., https://www.kup.co.kr) was injected into the submucosa. After making a circumferential incision around the lesion, ESD was performed using an insulation-tipped electrosurgical knife (IT knife, KD-610L); until complete resection was achieved. When bleeding occurred, endoscopic hemostasis was performed using hemostatic forceps and an endoscope clip. Following endoscopic resection, all visible vessels were coagulated. All ESD procedures were performed the same in the LC and control groups. Patients were advised to drink water on the day of the procedure after a review of their blood test results and radiographs.

Definitions. En bloc resection was defined as the removal of the tumor lesion without its fragmentation. Complete resection was defined as resection with tumor-free lateral and deep resection margins following lesion removal. Procedure time was defined as the time from tumor marking to hemostasis completion and specimen retrieval. Bleeding was defined as the occurrence of bleeding requiring endoscopic hemostasis during second-look endoscopy, with clinical manifestations, such as melena or hematemesis. Perforation was confirmed based on direct observation during endoscopy or from abdominal imaging.

Patient follow-up. Patients were followed up until they were lost to follow-up or died. Following ESD, complete blood cell count determination and chest radiography were performed. Second-look endoscopy was performed a day after ESD to check for post-ESD ulcers. If no complications, such as bleeding or perforation, were observed, patients started an oral diet. An intravenous proton pump inhibitor was started on the morning of the procedure and replaced with an oral proton pump inhibitor following discharge. An endoscopy was performed 3, 6 and 12 months after endoscopic resection. Abdominal computed tomography was performed every 6 months for the first year and annually thereafter. Patient data were acquired from endoscopic results, radiological reports and clinical records.

Statistical analysis. Statistical analysis was performed using SPSS version 20.0 software (IBM Corp.). Endoscopy results were analyzed using an independent sample t-test and Fisher's exact test to compare the variables. Propensity score matching was used to match the LC-EGC group with the non-LC-EGC group in a 1:3 ratio, according to age, sex, lesion location, tumor histology and tumor size. Cox regression analysis was performed to assess the association between predictive factors and cancer recurrence or bleeding risk following ESD. P-values were derived from two-tailed tests and $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient population. Of the 688 patients enrolled in the present study, 73% were men and 27% were women (mean age, 64.36±14.43 years, range 46-81). No significant differences in variables were observed between the LC-EGC and non-LC-EGC groups (Table I). The average age of patients with EGC and LC was 64.4 years. Alcohol consumption was the main cause of LC in ~70% of all patients, followed by hepatitis B in 14% of patients. In the LC group, esophageal

Table I. Baseline characteristics of patients with EGC, with and without LC.

	Total population			Propensity score-matched population		
Characteristic	LC-EGC group (n=17)	Non-LC-ECG group (n=671)	P-value	LC-ECG group (n=17)	Non-LC-ECG group (n=51)	P-value
Age, years	62.64±7.85	64.25±13.82	0.96	62.64±7.85	64.51±9.40	0.96
Sex			0.16			0.18
Male	15 (88.2)	490 (73.0)		15 (88.2)	37 (72.5)	
Female	2 (11.8)	181 (27.0)		2 (11.8)	14 (27.5)	
Smoking	5 (29.4)	116 (17.3)	0.27	5 (29.4)	9 (17.6)	0.14
Comorbidity						
Hypertension	4 (23.5)	258 (38.5)	0.21	4 (23.5)	23 (45.1)	0.11
Diabetes	5 (29.4)	110 (16.4)	0.15	5 (29.4)	11 (21.6)	0.50
Cardiovascular disease	1 (5.9)	36 (5.4)	0.92	1 (5.9)	6 (11.8)	0.48
Hx of other cancers	2 (11.8)	25 (3.7)	0.09	2 (11.8)	1 (2.0)	0.08
Medication						
Aspirin	1 (5.9)	59 (8.8)	0.90	1 (5.9)	6 (11.8)	0.65
Antithrombotic agent	0 (0.0)	25 (3.7)	0.41	0 (0.0)	5 (9.8)	0.18

Data are presented as the mean ± SD or n (%). ECG, early gastric cancer; LC, liver cirrhosis.

varices were present in 71% of all patients, gastric varices in 21% and ascites in 50%.

Most of the patients in both groups were men. No intergroup differences were observed in the rates of comorbidities, such as hypertension and diabetes mellitus. In addition, no intergroup differences in dosage associated with bleeding risk were observed. The propensity score matching of all patients produced matched pairs in a 1:3 ratio (LC-EGC group: non-LC-EGC group).

Clinical outcomes. The en bloc and complete resection rates were comparable between the LC-EGC and non-LC-EGC groups (Table II). The histological type was mainly differentiated cancer, with no significant intergroup differences. In the mean follow-up period of 33.15±26.58 months, four and three cases of recurrence occurred in the LC-EGC and non-LC-EGC groups, respectively. Surgery was performed in four cases, whereas repeat ESD was performed in the other three cases. During follow-up, one death occurred that was not associated with cancer or the procedure.

Factors associated with adverse events and recurrence. Cox regression analysis was performed to identify the factors associated with procedure-related bleeding and cancer recurrence (Tables III and IV). Multivariate analysis demonstrated that procedure time was an independent predictive factor for bleeding following ESD of EGC [adjusted hazard ratio (HR), 1.017; 95% CI, 1.001-1.032; P=0.033]. Furthermore, LC was significantly associated with cancer recurrence following ESD of EGC (adjusted HR, 5.482; 95% CI, 1.102-27.279; P=0.038; Fig. 1). In one patient from the LC-EGC group, cancer recurrence occurred 2 years after endoscopy. Repeat ESD and complete resection were performed (Fig. 2).

Discussion

The present study compared the long-term prognosis and effects of the endoscopic treatment of EGC in patients with and without LC. No significant differences were observed in the en bloc resection and complete resection rates between the LC-EGC and non-LC-EGC groups. The recurrence rate following ESD of EGC was higher in the LC-EGC group compared with that in the non-LC-EGC group (23.5 vs. 5.9%). No intergroup differences were observed in the incidence of periprocedural complications, such as bleeding. However, a higher risk of periprocedural bleeding was observed with longer procedure times.

ESD is a common treatment for EGC and is more effective than conventional endoscopic mucosal resection (23). Previous studies have reported that the incidence of gastrointestinal lesions, including GC, is high in patients with LC (17,18,24,25). However, surgical treatment in patients with LC is associated with high morbidity and mortality rates (26). Surgical resection in patients with LC is associated with several complications, including pneumonia, ascites, bleeding, infection and hepatic coma (27). Several studies have reported the safety and efficacy of ESD in cirrhotic patients (19,28). ESD is feasible in patients with early cirrhosis and is effective in patients with Child-Pugh class B cirrhosis (28). Bleeding complications tend to frequently occur following ESD procedures, and patients with LC have a higher risk of bleeding due to coagulation disorders and low platelet count (29). Thus, hemorrhagic complications associated with ESD procedures should be considered. However, in the present study, no significant differences in the incidence of bleeding complications following ESD were observed between the LC-EGC and non-LC-EGC groups, which is consistent with previous findings (19,30).

Table II. Clinical characteristics and outcomes of endoscopic submucosal dissection in patients with and without LC.

Characteristic	LC-ECG group (n=17)	Non-LC-ECG group (n=51)	P-value
Location			0.821
Lower third (C16.0, 16.1)	9 (52.9)	27 (52.9)	
Middle third (C16.2)	7 (41.2)	22 (43.2)	
Upper third (C16.3, 16.4)	1 (5.9)	2 (3.9)	
Gross type			0.672
Elevated	8 (47.1)	22 (43.1)	
Flat	7 (41.2)	18 (35.3)	
Depressed	2 (11.8)	11 (21.6)	
Presence of ulcer	2 (11.8)	12 (23.5)	0.299
Procedure type (:)			0.622
ESD	15 (88.2)	47 (92.2)	
EMR	2 (11.8)	4 (7.8)	
Procedure time, min	45.9±27.7	45.25±27.47	0.935
Complication			
Bleeding	2 (11.8)	11 (21.6)	0.373
Perforation	0 (0.0)	2 (3.9)	0.561
En bloc resection rate	16 (94.1)	49 (96.1)	0.733
Tumor size, mm	15.3±6.9	17.22±13.44	0.462
Histopathology			0.561
Differentiated type	14 (82.4)	48 (93.5)	
Undifferentiated type	3 (17.6)	3 (6.5)	
Invasion depth			0.399
Mucosa	12 (70.6)	41 (80.4)	
Submucosa	5 (29.4)	10 (19.6)	
Complete resection rate	100.0	43 (84.3)	0.554
Follow-up duration, months	23.71±20.21	36.29±27.84	0.091
Recurrence rate	4 (23.5)	3 (5.9)	0.038[a]
Death	1 (5.8)	0 (0.0)	<0.001[b]
Cancer-associated	0 (0.0)	0 (0.0)	1.000
Procedure-associated	0 (0.0)	0 (0.0)	1.000

[a]P<0.05; [b]P<0.001. Data are presented as the mean ± SD or n (%). ECG, early gastric cancer; ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection; LC, liver cirrhosis.

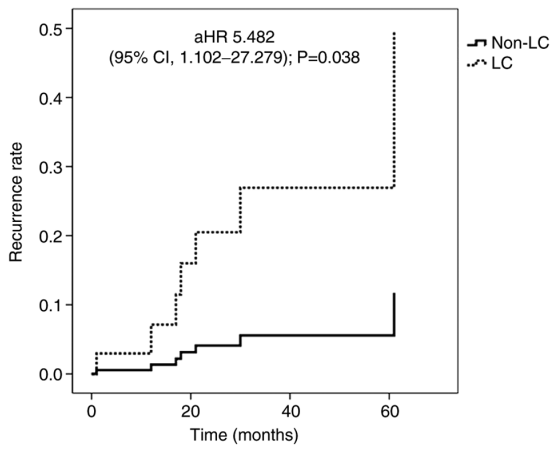

Figure 1. Recurrence of GC following ESD. Increased GC recurrence following ESD was observed in patients with LC (adjusted hazard ratio, 5.482; 95% confidence interval, 1.102-27.279; P=0.038). GC, gastric cancer; ESD, endoscopic submucosal dissection; LC, liver cirrhosis; HR, hazard ratio.

In the present study, LC was significantly associated with cancer recurrence following ESD of EGC. Previous epidemiological studies have also reported a high incidence of GC in patients with cirrhosis (17,18). The association between LC and GC development remains ambiguous. However, increased gastric epithelial cell proliferation is known to play an important role in the development of GC (31). A previous study reported that the presence of congestive gastropathy significantly increases the proliferation of epithelial cells in the gastric mucosa of patients with LC, and is further activated by *Helicobacter pylori* infection (24). Patients with LC have also been suggested to have zinc deficiency, which may play a role in epithelial carcinogenesis of the esophagus (32). Furthermore, LC may affect the metabolism of carcinogens and hormones, and increase the risk of cancer (33). It is important to consider the potential changes that occur in the body's immune system and the risk of infection in patients with LC, as liver dysfunction can affect the metabolism of lipids and

Table III. Cox proportional hazard analysis of the effect of factors on bleeding after endoscopic submucosal dissection.

	Univariate			Multivariate		
Variable	HR	95% CI	P-value	HR	95% CI	P-value
Diabetes	2.610	0.772-8.829	0.123	1.642	0.411-6.568	0.483
Hypertension	1.541	0.515-4.612	0.439	-	-	-
Liver cirrhosis	1.002	0.215-4.664	0.998	-	-	-
Aspirin	2.233	0.477-10.461	0.308	0.881	0.044-17.490	0.934
Other thrombotic agent	2.974	0.638-13.868	0.165	2.898	0.146-57.652	0.486
Procedure time, min	1.019	1.006-1.003	0.006[b]	1.017	1.001-1.032	0.033[a]

[a]P<0.05; [b]P<0.01. HR, hazard ratio; CI, confidence interval.

Table IV. Cox proportional hazard analysis of the effect of factors on recurrence after endoscopic submucosal dissection.

	Univariate			Multivariate		
Variable	HR	95% CI	P-value	HR	95% CI	P-value
Age, years	1.003	0.925-1.088	0.936	-	-	-
Sex	1.815	0.216-15.278	0.583	-	-	-
Diabetes	0.736	0.088-6.173	0.778	-	-	-
Hypertension	0.276	0.033-2.294	0.234	0.269	0.032-2.288	0.229
Liver cirrhosis	5.172	1.123-23.822	0.035[a]	5.482	1.102-27.279	0.038[a]
History of other cancer	0.044	0.000-18,963.051	0.638	-	-	-
Procedure type	0.038	0.000-423.832	0.491	-	-	-
Invasion depth	0.603	0.073-5.014	0.640	-	-	-

[a]P<0.05. HR, hazard ratio; CI, confidence interval.

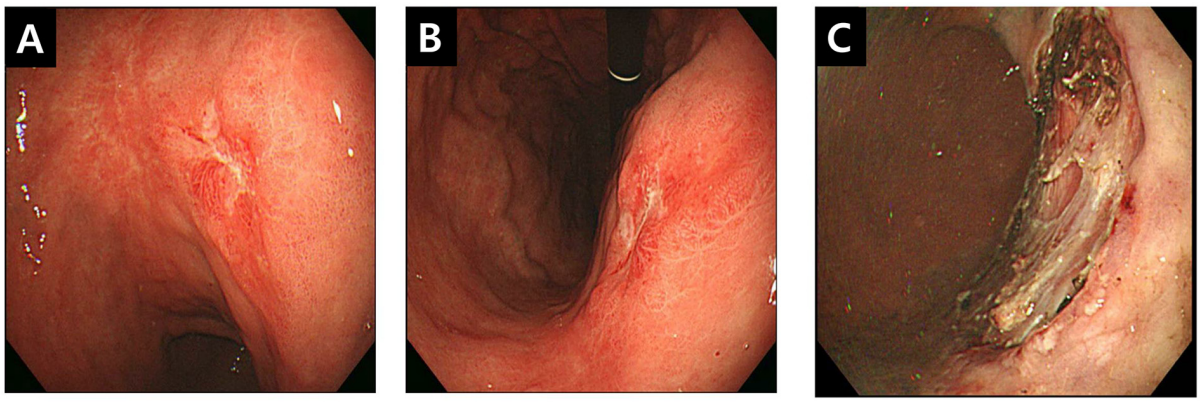

Figure 2. Recurred case of EGC after ESD in patients with LC. (A) EGC recurrence on posterior wall of supra-angle. (B) Retroflexed view of recurred EGC. (C) EGC recurrence on the posterior wall of the supra-angle 2 years after the first ESD. EGC, early gastric cancer; ESD, endoscopic submucosal dissection; LC, liver cirrhosis.

water-soluble drugs (34). As LC is an underlying disease accompanying GC regardless of early treatment, patients with LC are still at an increased risk of carcinogenesis even after undergoing ESD for EGC (33).

The present study is not without limitations. Given the retrospective design and limited sample size, the present study is susceptible to various biases and unmeasured confounding factors. However, an attempt was made to balance the variables through propensity score matching between the LC-EGC and non-LC-EGC groups.

Only a few studies to date have investigated ECG recurrence following endoscopic treatment in patients with LC.

The results presented in the current study may aid the decision-making process for patients with and without LC and EGC, and may encourage patient compliance. However, large-scale studies are required to confirm these results.

The recurrence rate was high in patients with LC. However, it was not associated with higher overall mortality. As the prognosis was good even in cases of relapse, repeat ESD can be recommended if the condition of the patient and the laboratory findings are satisfactory.

In conclusion, the present study demonstrated that the endoscopic resection of EGC in patients with LC is safe and effective, with high en bloc resection and complete resection rates. Thus, ESD can be actively performed in selected patients with LC. However, attention should be paid to potential cancer recurrence during clinical follow-up after ESD.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

SHK, MKJ and JJP designed the present study and drafted the initial manuscript. SHK and JJP critically revised the manuscript for important intellectual content. AYY, SMK, WSK and BJL acquired and analyzed the data. SHK, SWL and HJC analyzed the data. SHK and MKJ confirmed the authenticity of all the raw data All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was reviewed and approved by the Korea University Guro Hospital Institutional Review Board (Seoul, South Korea; approval no. 2019GR0467). Written informed consent was provided by all participants prior to the study start.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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