Gastric Cancer (2017) 20:200–206
DOI 10.1007/s10120-015-0578-9

ORIGINAL ARTICLE

Effects of administration of a proton pump inhibitor before endoscopic submucosal dissection for differentiated early gastric cancer with ulcer

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Received: 21 July 2015 / Accepted: 13 November 2015 / Published online: 11 December 2015

Abstract

Background In ulcerative early gastric cancer, improvement and exacerbation of ulceration repeat as a malignant cycle. Moreover, early gastric cancer combined with ulcer is associated with a low curative resection rate and high risk of adverse events. The aim of this study was to investigate the ulcer healing rate and clinical outcomes with the administration of a proton pump inhibitor before endoscopic submucosal dissection for differentiated early gastric cancer with ulcer.

Methods A total of 136 patients with differentiated early gastric cancer with ulcer who met the expanded indications for endoscopic submucosal dissection were reviewed between June 2005 and June 2014. Eighty-one patients were given PPI before endoscopic submucosal dissection and 55 patients were not given PPI.

Results The complete ulcer healing rate was significantly different between the two groups (59.3 % vs. 23.6 %, $P < 0.001$). The procedure time was 38.1 ± 35.7 and 50.8 ± 50.2 min ($P = 0.047$). However, no significant differences were detected in the en bloc resection rate, complete resection rate, and adverse events including bleeding and perforation. Multivariate analysis showed that administration of PPI (OR = 10.83, $P < 0.001$) and mucosal invasion (OR = 24.43, $P < 0.001$) were independent factors that predicted complete healing of ulceration. The calculated accuracy for whether complete healing of the ulcer after PPI administration can differentiate mucosal from submucosal invasion was 75.3 %.

Conclusions Administration of PPI before ESD in differentiated EGC meeting the expanded criteria is effective to heal the ulcer lesion and reduce the mean procedure time. Complete healing of the ulcer after PPI administration suggests mucosal cancer.

Keywords Early gastric cancer · Endoscopic submucosal dissection · Proton pump inhibitor · Ulcer

Introduction

Minimally invasive treatment such as endoscopic submucosal dissection (ESD) is an effective alternative to surgical treatment for early gastric cancer (EGC) [1–3]. Endoscopic treatment for ulcerative EGC with differentiated mucosal cancer of less than 3 cm has been proposed in the expanded criteria [4]. However, improvement and exacerbation of ulceration repeat in patients with ulcerative EGC as a malignant cycle [5]. Moreover, EGC combined with ulcer is associated with a low curative resection rate and high risk of adverse events such as perforation and bleeding [3, 6–8].

Proton pump inhibitors (PPI) produce a high gastric pH by irreversibly binding to the proton pump on gastric parietal cells [9]. In previous studies, treatment with PPI led to improvement of the endoscopic signs in ulcerative EGC. Additionally, the degree of ulcer healing has been associated with the degree of submucosal invasion [10, 11]. However, these studies were limited because they were case reports or did not control for the use of antisecretory medication.

Therefore, the aim of this study was to evaluate ulcer healing, clinical outcomes, and adverse events such as

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perforation and bleeding after PPI administration before ESD for differentiated EGC with ulcer.

Patients and methods

Patients

We retrospectively reviewed 145 patients with differentiated EGCs with ulcer who met the expanded indications for ESD at the Soonchunhyang University Hospital (Bucheon, Korea) between June 2005 and June 2014.

The expanded indication was determined by pre-ESD clinical indications. Patients who had received endoscopic examination with a minimum interval of 1 week between the initial examination and follow-up were identified. The following exclusion criteria were applied: (1) patients whose endoscopic image was too poor to characterize the lesion, (2) patients who did not have a definite ulcer, and (3) patients who used other antisecretory medications (H2-receptor antagonists).

The study protocol was approved by the Institutional Review Board of the Soonchunhyang University Bucheon Hospital (SCHBC 2015-01-001).

Administration of PPI

The enrolled patients were divided into two groups: the PPI group (patients who received PPI before gastric ESD) and non-PPI group (patients who did not receive PPI). PPI was orally administered once daily in patients with symptoms such as epigastric pain and dyspepsia. The duration of administration was from the date of diagnosis to the day of the procedure.

Endoscopic findings

Initial and follow-up endoscopic images were independently reviewed by a reviewer who was blinded to the clinical information and pathologic diagnosis. Initial endoscopic images were defined as the initial photos taken at the Soonchunhyang University Hospital.

We collected data from both groups regarding the ulcer stage, size, and location of the lesion. The ulcer stages of EGC were classified as active or healing according to the Sakita and Fukutomi system [12]. Endoscopic ulcer was defined as breaks in the mucosal surface >5 mm in size, with depth to the submucosa.

ESD

Two experienced endoscopists (M.S.L. and S.J.H) performed all of the procedures. All patients underwent procedures under sedation with intravenous administration of midazolam and propofol. The electrosurgical unit used was the VIO300D or ICC 200 (ERBE, Tuebingen, Germany). The circumferential margin was marked with argon plasma coagulation or a hook knife (KD-620L, Olympus, Tokyo, Japan). A mixture of indigo carmine and diluted epinephrine (1:100,000) in normal saline solution was used for submucosal injection. After submucosal injection, the mucosal layer around the lesion was incised with various knives such as a hook knife, insulated-tip knife (KD-610L, 611L Olympus, Tokyo, Japan), or flex knife (KD-630L, Olympus, Tokyo, Japan), and the submucosal layer was dissected. Hemostatic forceps (Coagrasper, FD-410LR, Olympus, Tokyo, Japan) were used to control bleeding during ESD and at any visible vessel in the post-ESD ulcer site.

Histopathology

Resected specimens were fixed in 10 % formaldehyde, sectioned at 2-mm sections, and embedded in paraffin. A pathologist (H.K.K) examined the embedded specimens and reported the histological diagnosis according to the World Health Organization. The size of the tumor, depth of invasion, presence of tumor cells in the dissected margin, and lymphatic and vascular involvement were reported.

En bloc resection was defined as resection in a single piece. Complete resection was defined as the absence of cancer in both the lateral and vertical resection margins and no evidence of lymphovascular invasion. Non-complete resection included EGCs that had incomplete margin resection or lymphovascular invasion.

Measured outcomes

The primary endpoint was the ulcer healing rate at the follow-up endoscopy compared with the initial endoscopy. Endoscopic ulcer healing was classified as complete, partial, no change, or exacerbation. Complete ulcer healing was defined as the ulcer improving to a scar lesion (Fig. 1). Partial ulcer healing was defined as the ulcer improving in depth and size, but not completely. We defined the outcome as exacerbation if a new ulcer developed or an existing ulcer was aggravated in depth or size (Fig. 2). The secondary endpoints were clinical outcomes such as en bloc resection and complete resection, procedure time, and adverse events. The procedure time was defined as the time from the submucosal injection to the removal of resected tumors by endoscopy. Assessed adverse events were significant bleeding and perforation. Significant bleeding was defined as follows: (1) hematemesis or melena that required endoscopic treatment or surgery after ESD or (2) depression of the hemoglobin count by more than 2 g/dl

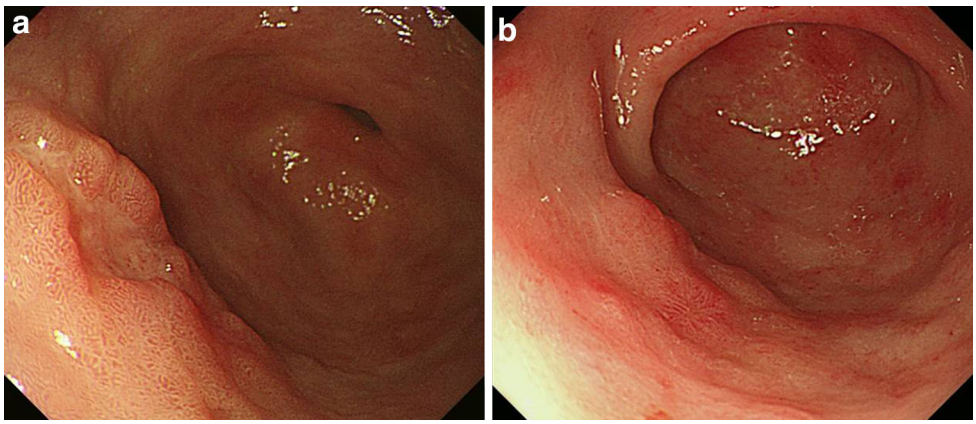


Fig. 1 A case of complete healing of ulcer stage in EGC. **a** Initial endoscopy shows an approximately 1.5-cm-sized EGC in the active stage located at the anterior wall of the antrum. **b** Follow-up endoscopy shows complete ulcer healing with scar formation after 21 days with PPI medication

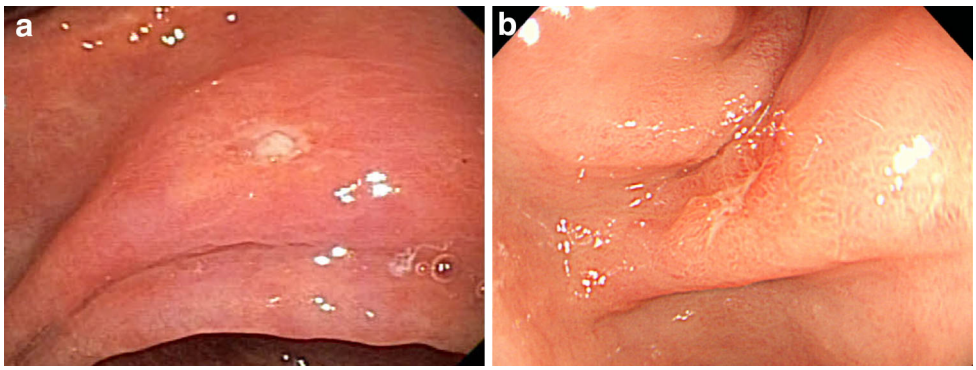


Fig. 2 A case of exacerbation of ulcer stage in EGC. **a** Initial endoscopy shows an approximately 1-cm sized EGC in the healing stage located at the lesser curvature of the antrum. **b** Follow-up endoscopy shows exacerbation of the ulcer after 7 days without PPI medication

after the procedure. Perforation was defined as a gross defect or the presence of free air on radiography following the procedure.

Statistical analysis

Statistically significant differences in baseline characteristics, clinical outcomes, and adverse events between the two groups were determined using Fisher's exact test, the χ^2 test, Mann-Whitney *U* test, or Student's *t* test, as appropriate. Independent factors to predict complete ulcer healing were evaluated by multiple logistic regression analysis and reported with 95 % confidence intervals (CIs). $P < 0.05$ was considered to indicate statistical significance. Variables are presented as mean ± standard deviation. All statistical analyses were performed using SPSS version 12.0 for Windows (SPSS; Chicago, IL, USA).

Results

Patient characteristics

During the study period, 145 eligible patients underwent gastric ESD. Six patients (4.1 %) with poor images and three (2.0 %) who used a H_2-receptor antagonist were subsequently excluded. Thus, 136 patients were ultimately enrolled. Of these 136 patients, 81 (59.5 %) received PPI and 55 (40.5 %) did not. Table 1 lists the clinical characteristics of the patients in the two groups. The PPI group included 64 males and 17 females with a mean age of 66.1 ± 10.5 years. The non-PPI group included 41 males and 14 females with a mean age of 65.2 ± 10.1 years. *Helicobacter pylori* infection was positive in 45 patients (55.6 %) in the PPI group and 32 patients (58.2 %) in the non-PPI group. They were not treated during PPI treatment. The ulcer stages at first endoscopy were 25 active (31 %) and 56 healing (69 %) for the PPI group as well as 11 active (20 %) and 44 healing (80 %) for the non-PPI group. The two groups did not differ significantly in age, gender ratio, tumor size, ulcer size and ulcer stage, tumor location, depth of invasion, *Helicobacter pylori* infection, and mean interval days.

Change of ulcer stage and clinical outcomes

Table 2 lists changes in ulcer stage and clinical outcomes for the two groups. Change in ulcer stage at follow-up endoscopy was observed in 65 patients (80.2 %) in the PPI group: 48 patients (59.3 %) had complete healing, 15

Table 1 Baseline characteristics of the enrolled patients

	PPI group ($n = 81$)	Non-PPI group ($n = 55$)	P-value
Age (years)[a]	66.1 ± 10.5	65.2 ± 10.1	0.496
Sex (M/F), n	64/17	41/14	0.542
Size (mm)[a]	16.3 ± 8.2	15.7 ± 7.4	0.592
Ulcer stage at first endoscopy, *n*			0.159
Active/healing	25/56	11/44	
Ulcer size (mm)[a,b]	10.0 ± 3.2	8.9 ± 2.4	0.108
Tumor location, *n*			0.558
Antrum/angle/body/fundus	51/12/17/1	30/15/10/0	0.277
Depth of invasion, *n*			0.364
Mucosa/submucosa	64/17	43/12	0.908
Helicobacter pylori infection			0.211
Positive/negative	45/22	32/19	
Median interval, days (range)	24 (7–85)	18 (7–84)	0.392

[a] Data are expressed as mean ± SD

[b] The size of the lesion represents the pre-ESD endoscopic size

Table 2 Clinical outcomes of the patients

	PPI group ($n = 81$)	Non-PPI group ($n = 55$)	P-value
Change of ulcer stage, *n* (%)			<0.001
Complete healing	48 (59.3)	13 (23.6)	
Partial healing	15 (18.5)	22 (40.0)	
No change	16 (19.8)	13 (23.6)	
Exacerbation	2 (2.5)	7 (12.7)	
En bloc resection, *n* (%)	78 (96.3)	54 (98.2)	0.647
Complete resection, *n* (%)	61 (75.3)	44 (80.0)	0.522
Procedure time (min)[a]	38.1 ± 35.7	50.8 ± 50.2	0.047
Adverse events			
Significant bleeding, *n* (%)	3 (3.7)	5 (9.1)	0.268
Perforation, *n*	1	0	1.000

[a] Data are expressed as mean ± SD

patients (18.5 %) had partial healing, and 2 patients (2.5 %) had exacerbation. Change in ulcer stage at follow-up endoscopy was observed in 42 patients (76.4 %) in the non-PPI group: 13 patients (23.6 %) had complete healing, 22 (40.0 %) had partial healing, and 7 (7.0 %) had exacerbation. There was a significant difference in change of ulcer stage ($P < 0.001$).

The two groups did not differ significantly in the en bloc resection rate (96.3 % in the PPI group and 98.2 % in the non-PPI group; $P = 0.647$) or complete resection rate (75.3 % in the PPI group and 80.0 % in the non-PPI group; $P = 0.522$). However, the procedure time for the PPI group was 38.1 ± 35.7 min compared with 50.8 ± 50.2 min for the non-PPI group, indicating a significantly shorter procedure time for the PPI group ($P = 0.047$). Moreover, when the patients were divided into two groups, the complete healing group and others group (partial healing, no change and exacerbation group), there was a significant difference in procedure time (33.0 ± 22.3 min and 43.6 ± 43.4, $P = 0.022$).

Significant bleeding occurred in three patients (3.7 %) in the PPI group and five patients (9.1 %) in the non-PPI group ($P = 0.268$). All cases were successfully managed endoscopically using endoclips or conservatively. Perforation occurred in only one patient in the PPI group. This patient was successfully managed endoscopically using endoclips (Table 2).

Factors associated with complete ulcer healing

We compared the changes in ulcer stage among patients with mucosal cancer. Patients in the PPI group were more likely to exhibit complete healing of ulceration than those

Table 3 Clinicopathologic factors associated with complete ulcer healing

	Univariate *P*-value	Multivariate *P*-value	Multivariate adjusted OR (95 % CI)
Age	0.334	\	\
Sex	0.203		
Ulcer stage at first endoscopy	0.219		
Morphologic finding	0.555		
Ulcer size	0.548		
Location	0.697		
Helicobacter pylori infection	0.974		
Administration of PPI (yes vs. no)	<0.001	<0.001	10.83 (4.10–28.45)
Depth of invasion (mucosa vs. submucosa)	<0.001	<0.001	24.43 (4.93–120.97)
Median interval days	0.633		

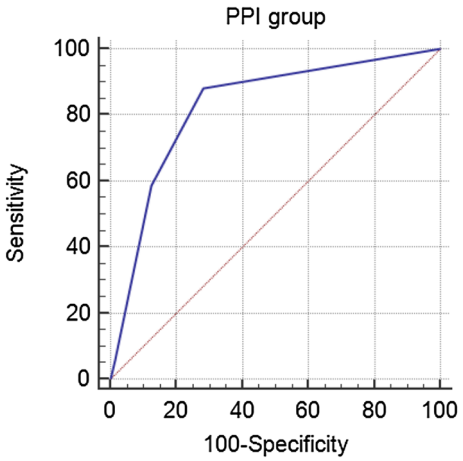
\ Administration of PPI and depth of invasion are factors associated with complete ulcer healing

in the non-PPI group (71.9 vs. 30.2 %; $P < 0.001$). Moreover, the complete ulcer healing rate of the PPI group among mucosal cancer patients was higher than that among submucosal cancer patients (71.9 vs. 11.8 %, $P < 0.001$). On multivariate logistic regression, mucosal cancer (OR = 24.43, 95 % CI 4.93–120.97, $P < 0.001$) and administration of PPI (OR = 10.83, 95 % CI 4.10–28.45, $P < 0.001$) were independently associated with complete healing of malignant ulcers (Table 3).

Diagnostic analysis in the prediction of mucosal cancer

We assessed whether complete healing of ulcers after PPI administration could differentiate mucosal from submucosal invasion (Table 4). The calculated sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of complete ulcer healing to differentiate mucosal invasion were 71.9, 88.2, 45.5, and 95.8 %, respectively. The overall accuracy for differentiating mucosal invasion from submucosal invasion was 75.3 %. The area under the receiver-operating characteristic (ROC) curve was 0.827.

Table 4 Diagnosis of mucosal cancer in patients with complete ulcer healing after PPI administration



	Complete ulcer healing
AUC	0.827
Sensitivity (%)	71.9
Specificity (%)	88.2
NPV (%)	45.5
PPV (%)	95.8
Accuracy (%)	75.3

AUC Area under the curve, *NPV* negative predictive value, *PPV* positive predictive value

Discussion

In the expanded indications for endoscopic treatment, the Japanese guidelines for gastric cancer include <30 mm differentiated gastric cancer confined to the mucosa with an ulcer [4]. According to the expanded indications, ESD is applicable to limited cases in EGC with ulcer. However, ESD of ulcerative EGC involves several problems. First, ulceration in EGC goes through phases of improvement and exacerbation in a malignant cycle [13]. Malignant ulceration is considered to arise at the site of the cancer in the presence of acid and pepsin. Healing takes place next, with benign tissue growing, and then malignant invasion occurs, forming a cycle [5]. Therefore, there is a risk in applying different indications in the same lesions depending on the presence of ulcer. Moreover, patients who are referred after biopsies have been performed at a private clinic are likely to be overestimated because of iatrogenic

ulcers. Second, precise pretreatment staging is difficult in EGC with ulcer. It is important to investigate the invasive depth of the tumor before ESD. However, the accuracy of T staging in EGC with ulcer is very low [14]. Third, the presence of ulceration interferes with complete resection and promotes a long procedure time and high risk of adverse events such as bleeding and perforation [3, 6–8].

PPI may mask symptoms of early gastric cancer and even lead to complete or partial improvement of endoscopic signs of malignant ulcer [15, 16]. Previous studies have reported that ulcer healing in EGC was associated with antisecretory medications such as H2-receptor antagonists (H2RA) or PPI [10, 11]. In the current study, 48 (59.3 %) of the 81 patients exhibited complete improvement of ulceration, whereas exacerbation occurred in only 2 patients (2.5 %) in the PPI group. The complete healing rate of ulceration in the PPI group was significantly higher than in the non-PPI group. Additionally, the complete healing rate of ulceration was higher in mucosal cancer (78.0 %). We speculated that complete ulcer healing in EGC can be accelerated by PPI, especially in cases of mucosal cancer.

A previous study reported that the rates of en bloc resection and curative resection for ulcerative EGC were 94 and 72 %, respectively [7]. Our results were similar: rates of en bloc resection and curative resection were 98.2 and 80.0 %,respectively, in the non-PPI group. In contrast to our expectations, rates of en bloc resection and curative resection in the PPI group did not differ significantly from those in the non-PPI group. Additionally, adverse events such as bleeding and perforation did not differ between groups. However, the mean procedure time was significantly shorter in the PPI group than in the non-PPI group. A previous study reported that the presence of ulceration was associated with a long procedure time [7]. The presence of endoscopic ulceration was associated with submucosal fibrosis, and the fibrosis or inflammation caused by ulceration made it more difficult to lift the tumor tissue from the muscle layer, lengthening the procedure time [17, 18]. We speculate that PPI administration improved inflammation, made it easier to dissect the submucosa, and thereby shortened the procedure time.

Endoscopic ultrasonography (EUS) is thought to be a reliable method for determining the depth of invasion for EGC, and T staging accuracy of EGC has been reported to be about 80–90 % [19, 20]. However, the accuracy of T staging in EGC with ulcer has been reported at about 55–63 % [19, 21]. In our study, the calculated accuracy (75.3 %) of whether complete healing of the ulcer after PPI administration can differentiate mucosal invasion from submucosal invasion was higher than the accuracy in previous EUS studies. Therefore, complete ulcer healing after PPI administration is considered to indicate mucosal cancer.

Our study had several limitations. First, it was not a prospective study, which could have skewed the results regarding the effectiveness of PPI administration. However, the clinical characteristics of the patients in the two groups were similar, and factors that may have affected the results were controlled for using multiple logistic regression analysis. Second, the interval between initial and follow-up endoscopic examination was variable. However, there was no statistically significant difference between groups, and the interval of most patients was within 1 month. Third, the duration of PPI administration was variable because of the retrospective nature of the study. Fourth, ESD was performed by two expert endoscopists. Therefore, there was no difference in en bloc, complete resection and adverse event rates. If ESDs were performed by less experienced endoscopists, then those outcomes might have been affected significantly. Finally, the presence of ulceration was determined only by endoscopic findings without pathologic confirmation. However, concordance between the two methods of identifying ulceration was 99 % in a previous study [17]. Therefore, ulceration can be diagnosed solely on the basis of endoscopic examination.

In conclusion, administration of PPI before ESD in differentiated EGC with ulcer meeting the expanded criteria is effective in healing the ulcer lesion and reducing the mean procedure time. Also, complete healing of the ulcer after PPI administration suggests mucosal cancer.

Acknowledgments This work was supported in part by the Soonchunhyang University Research Fund.

Compliance with ethical standards

Conflict of interest All authors disclosed no financial relationships relevant to this publication.

Ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study. If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.
Identifying information on human subjects, including names, initials, addresses, admission dates, hospital numbers, or any other data that might identify patients, should not be published in written descriptions, photographs, or pedigrees unless the information is essential for scientific purposes and the patient (or parent guardian) gives written informed consent for publication. If any identifying information about patients is included in the article, the following sentence should also be included: Additional informed consent was obtained from all patients for which identifying information is included in this article.

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