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Simultaneous endoscopic submucosal dissection for multiple early gastric cancers in a low volume center

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Abstract

The aim of the study is to evaluate the safety and efficacy of simultaneous endoscopic submucosal dissection (ESD) for multiple early gastric cancers.

A total of 70 solitary early gastric cancers from 70 patients and 20 multiple early gastric cancers from 10 patients were included in this retrospective study. The curative resection rate, en bloc resection rate, procedure-related complications, and local recurrence were compared between the 2 groups.

There was no statistical difference in the rate of complete resection, en bloc resection, and curative resection between the 2 groups ($P > .05$). No significant difference was found with respect to the occurrence of postoperative bleeding ($P > .05$). Procedure time was significantly longer in the simultaneous group than that in the single group (87.6 ± 25.1 min vs 54.6 ± 22.0 min, $P = .004$). The overall incidence of synchronous early gastric cancer was 7.5%.

Simultaneous ESD for multiple early gastric cancers is a safe and feasible choice in low-volume hospital. The entire stomach should be examined meticulously during and after ESD. Larger randomized studies are needed to validate our results.

Abbreviations: EGC = early gastric cancer, EMR = endoscopic mucosal resection, ER = endoscopic resection, ESD = endoscopic submucosal dissection, GI = gastrointestinal, L = lower, M = middle, ME-NBI = magnification endoscopy with narrow-band imaging, SDs = standard deviations, U = upper, WHO = World Health Organization.

Keywords: endoscopic submucosal dissection(ESD), multiple early gastric cancers

1. Introduction

The diagnosis of early gastric cancer (EGC) has been improved remarkably due to all kinds of new endoscopic imaging techniques. Reports regarding multiple early gastric cancers are increasing as well. The incidence of multiple early gastric cancers accounts for 6% to 14% of all gastric cancers.[1–3] Endoscopic submucosal dissection (ESD) have become the mainstay for treating EGC and precancerous lesions. Some ESD trials did conclude that quality-adjusted life expectancy was greater as compared to surgery.[4,5] gastrectomy for gastric cancer has been associated with substantial morbidity and mortality rates, especially at low-volume centers.[1,2] Recent studies have shown that multiple EGCs had clinicopathologic characteristics and risk of lymph node metastasis similar to those of solitary EGCs. Endoscopic resection (ER) could be adopted as curative treatment for multiple EGCs.[6,7] Multiple ESD would need more procedure time for the multifocal lesions as well. There have been studies evaluating safety and feasibility related to simultaneous ESD for multiple early gastric cancers in high volume hospitals.[8,9] To the best of our knowledge, there have been no reports about simultaneous ESD for multiple early gastric cancers in low-volume hospitals. This study aimed to introduce our initial experience about simultaneous ESD for multiple early gastric cancers. To date, such comparisons are relatively scarce, prompting further efforts in this respect. ESD allows en bloc resection regardless of tumor size and histology of the specimens.[4,5]

Because of these potential advantages, minimally invasive gastric surgery is being increasingly implemented; endoscopic resection (ER) including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) has become the mainstay for treating superficial neoplasms in the upper gastrointestinal (GI) tract.[8,9] However, little information is available regarding comparative efficacy of ER and minimally invasive esophagectomy.

2. Materials and methods

2.1. Patients

Between January 2014 and May 2015, medical records of early gastric cancer patients who underwent ESD in the Second Hospital of Shandong University were retrospectively analyzed. Clinical data included patient demographics, tumor locations, tumor size, tumor type, histologic findings, procedure-related adverse events including bleeding and perforation. All procedural

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Table 1

Clinicopathological characteristics of solitary and multiple EGCs.

	Solitary EGC	Multiple EGCs	*P*
Patients characteristics			
Number, n	70	10	
Sex			.711
Male	50	6	
Female	20	4	
Age, y			.230
Mean ± SD	62.8 ± 10.0	68.4 ± 6.8	
Range	43–83	62–78	
Tumor characteristics			
Location			.493
Upper	16	4	
Middle	12	8	
Lower	42	8	
Tumor size, mm			.562
Mean ± SD	12.4 ± 8.7	14.6 ± 11.1	
Range	3–37	8–33	
Specimen size, mm			.5
Mean ± SD	35.3 ± 9.6	33.0 ± 9.2	
Range	18–60	20–50	
Macroscopic type			.546
Elevated	22	8	
Flat	10	4	
Depressed	14	2	
Mixed	24	6	
Histological type			
Differentiated	70	20	
Undifferentiated	0	0	
Depth of invasion			.659
Mucosa	66	18	
Submucosal	4	2	
Venous invasion	0	0	
Lymphatic invasion	0	0	

EGC = early gastric cancer, SD = standard deviation.

data on patients and their lesions were consecutively stored in a database.

Data on 20 double early gastric cancers in 10 patients in the simultaneous ESD group and data 70 patients in the single ESD group were obtained. Approval was obtained by the local ethics committee of the Second Hospital of Shandong University, and informed consent was obtained from all patients both for data collection and endoscopic resections. Baseline characteristics of our clinical cohort are shown in Table 1.

2.2. Study definitions

Solitary EGC was defined as a single malignant focus in the stomach. According to Moertel's definition, multiple gastric cancers must meet the following requirements: (a) all the lesions must be pathologically malignant; (b) the malignant lesions must be separate from each other by intervals of normal gastric wall; (c) any lesion that is suspicious of a local extension or a metastatic neoplasm must be excluded; and (d) if the depth of invasion of 2 or more lesions is equal, the largest is regarded as the primary lesion, with all other lesions regarded as accessory.[10]

The location and the macroscopic type of EGCs were classified according to the Japanese Gastric Cancer Association classification system.[11] The lesions were classified into groups based on whether they were located in the upper (U), middle (M), or lower (L) third of the stomach, and the macroscopic type of each EGC was classified as type I (protruding), IIa (superficial, elevated), IIb (flat), IIc (superficial, depressed), III (excavated), or a combination of these. The histological type was classified as either differentiated (papillary adenocarcinoma, well-differentiated, and moderately differentiated adenocarcinomas) or undifferentiated (poorly differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma).

En bloc resection was defined as resection in 1 single piece. Complete resection was defined as tumor-negative lateral and vertical margins on pathologic examination. Curative resection was defined as en bloc and complete resection without submucosal invasion deeper than 500 μm from the muscularis mucosae, with no apparent lymphovascular involvement, and when the specimen had tumor-free margins.

Procedure time was defined as the time from marking of mucosa to complete removal of the lesion, including the time required for hemostasis. Bleeding was defined on the basis of clinical evidence, such as the occurrence of melena and/or hematemesis, or detection of blood or blood clots during the final endoscopic inspection. Perforation was diagnosed by endoscopy or by the presence of free air on a plain radiograph or CT of the abdomen.

2.3. ESD procedure

ESD was done with a single channel endoscope with jet function available (GIF Q260J, Olympus Optical Co. Ltd., Tokyo, Japan). Chromoendoscopy (using indigo carmine) and magnification endoscopy with narrow-band imaging (ME-NBI, GIF H260Z, Olympus Optical Co. Ltd., Tokyo, Japan) were used to define the carcinomatous area. A dual knife (KD-611L, Olympus Optical Co. Ltd., Tokyo, Japan) was used to mark the lesion. Saline mixed with epinephrine (0.01 mg/mL) and 0.5% indigo carmine was injected into the submucosa to lift the lesion. A circumferential mucosal incision was made around the lesion using a dual knife and/or IT knife 2 (KD-650L, Olympus Optical Co. Ltd., Tokyo, Japan). Lesions were completely removed by submucosal dissection using an IT knife 2 and/or a dual knife. Endoscopic hemostasis was performed either with hemostatic forceps (FD-410LR, Olympus Optical Co. Ltd., Tokyo, Japan) or the knife itself for bleeding or an exposed vessel. All visible vessels on the artificial ulcer were coagulated using hemostatic forceps, irrespective of the presence or absence of bleeding. For synchronous multiple lesions, marking was performed for all lesions initially. Resections subsequently were performed in the same way (Fig. 1A–H).

2.4. Histopathological evaluation

All resected specimens were sectioned into 2-mm slices and evaluated by histopathological examination. Two pathologists classified abnormalities according to guidelines stipulated by the World Health Organization (WHO). Disagreements between reviewers were resolved by consensus. Tumor size, depth of tumor infiltration, differentiation grade, tumor involvement in the resection margin, as well as *lymphatic* and *vascular* involvement in the tumor process were also assessed and recorded. Curative resection was histopathologically based on the expanded criteria proposed by Gotoda et al.[4]

2.5. Follow-up

Follow-up endoscopy after ESD was scheduled at 3, 6, 12 months and then annually until the patient's death. Local recurrence was

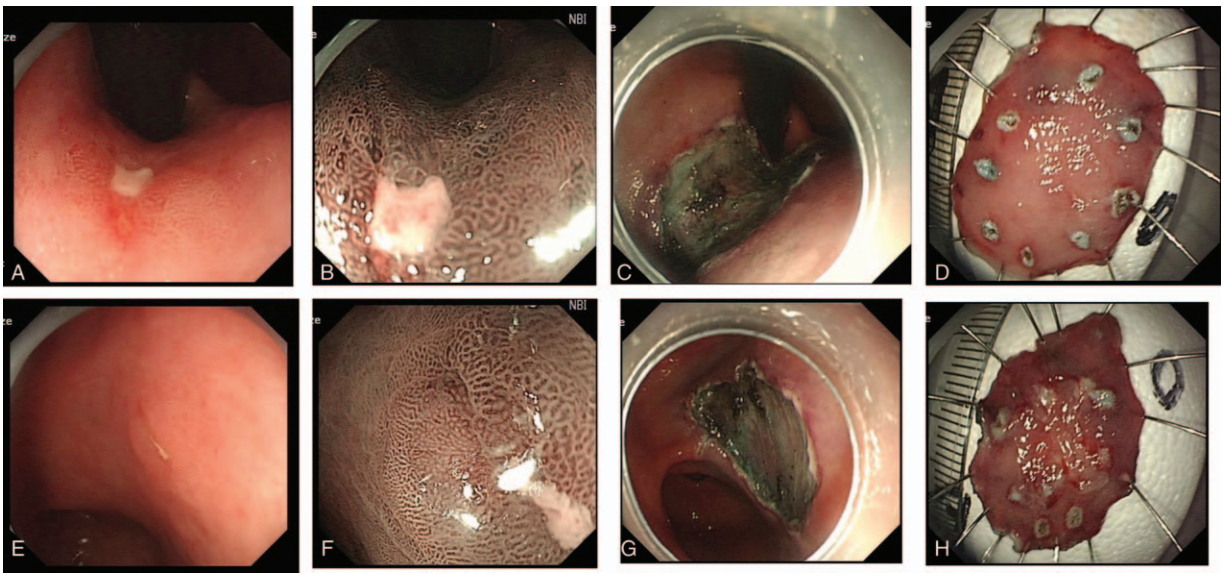

Figure 1. Simultaneous ESD procedure for synchronous double gastric cancer. (A) Conventional endoscopy showing the lesion of the lesser curvature of the gastric body. (B) Image of endoscopy with narrow band imaging. (C) Artificial ulcers after removal of lesion. (D) Endoscopic aspect of the lesion after ESD. (E) Conventional endoscopy showing the lesion of the antrum. (F) Image of endoscopy with narrow band imaging. (G) Artificial ulcers after the removal of lesion. (H) Endoscopic aspect of the lesion after ESD. ESD = endoscopic submucosal dissection.

defined as the postoperative detection of any carcinomatous lesion adjacent to the endoscopic resection scar. If a new tumor was detected at a different site from the initial ESD within 12 months it was defined as a synchronous EGC, and if it was found more than 1 year after the resection, it was called as a metachronous EGC.

2.6. Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences version 16.0.2 for Windows (SPSS, Chicago, IL). Quantitative data are presented as means and standard deviations (SDs). Potential differences between the experimental groups were assessed by using the $\chi 2$-test, Fisher's exact probability test, and Student's *t*-test. The Kaplan–Meier method was used to evaluate the difference of the local recurrence rate between the 2 groups. Differences with *P*-values $<.05$ were considered statistically significant.

3. Clinical results

3.1. Patient and lesion characteristics

A total of 80 patients were enrolled in this study. Twenty double early gastric cancers from 10 patients were treated by simultaneous ESD. The incidence of multiple early gastric cancers was 12.5%. The baseline characteristics of patients who underwent ESD are shown in Table 1. No significant differences were observed in gender and age, tumor location, and macroscopic aspect of the tumor type between the 2 groups.

The median patient age was 62.8 ± 10.0 years old in the single group and 68.4 ± 6.8 years old in the simultaneous group. The mean tumor size was comparable between the 2 groups (12.4 ± 8.7 mm vs 14.6 ± 11.1 mm, $P = .562$). All lesions were differentiated type gastric cancer histopathologically. The multiple early gastric cancers seemed to develop more frequently in different thirds of the stomach (8/10, 80%).

There were no statistically significant differences in the number of complete resections, en bloc resection, and curative resection between the 2 groups ($P = .99$, .99, .588, respectively; Table 2). Also, no significant difference was observed in the average length of stay between the 2 groups (3.8 ± 1.9 d, vs 4.2 ± 2.1 d, $P = .540$).

There was no perforation in these 2 groups. No significant differences were observed in the delayed bleeding rates ($P = .599$). Also, all the patients were successfully managed by endoscopic clipping, fasting, and intravenous administration of antibiotics.

However, the mean procedure time was significantly longer in the simultaneous group than that in the single group (87.6 ± 25.1 min vs 54.6 ± 22.0 min, $P = .004$, Table 2).

3.2. Follow-up outcomes

All patients were followed up for at least 2 years. During the follow-up, no local recurrence was observed in both groups. Four synchronous early gastric cancers were detected in the single group (4/70), and these lesions were located in the lesser curvature of the upper third of the stomach (2/4) and the

Table 2

Clinical outcomes.

	Single ESD	Simultaneous ESD	*P*
Procedure time			.004
Mean ± SD	(54.6 ± 22.0) min	(87.6 ± 25.1) min	
Range	26–117	63–115	
Adverse events			.599
Bleeding, n, %	8 (11.4%)	2 (20%)	
Perforation, n, %	0	0	
Procedure outcomes			
En bloc resection, n, %	70 (100%)	10 (100%)	.99
Complete resection, n, %	70 (100%)	10 (100%)	.99
Curative resection, n, %	68 (97.1%)	10 (100%)	.588
Average hospital stay	(3.8 ± 1.9)d	(4.2 ± 2.1)d	.540

ESD = endoscopic submucosal dissection, SD = standard deviation.

posterior wall of the middle third of the stomach (2/4), respectively. However, 2 patients were found to be suffering from synchronous gastric cancers in the simultaneous group (2/10).

4. Discussion

Based on previous studies, multiple early gastric cancers accounts for 6% to 14% of all early gastric cancers.[1–3] The incidence of multiple early gastric cancers in this study was 12.5%, which is within the range of the rates reported by these studies. In our institute, we found that patients with multiple early gastric cancers were slightly older than those with solitary early gastric cancer. This observation was also consistent with the other studies.[3,7] The prevalence of gastric atrophy and intestinal metaplasia is increasing in the elderly people, and these precancerous conditions constitute the background in which gastric adenocarcinoma may develop.

In the present study, the location of early gastric cancer was predominant in the lower thirds of the stomach. This may be due to the pathogenetic importance of intestinal metaplasia; the distal gastric mucosa is the prevalent site for the development of intestinal mentaplasia and subsequently differentiated type cancer. The multiple early gastric cancers seem to develop frequently in different thirds of the stomach (upper, middle, or lower third). This phenomenon may be explained by the "field carcinogenesis" hypothesis which suggests that at the beginning of carcinogenesis, all parts of the stomach are exposed to the same cancerogen(s) and each part has the potential to develop gastric cancer. So, gastric cancer could develop simultaneously at 2 or more adjacent or distant sites.[12,13]

There were reports describing upper thirds of the stomach, large size, and long procedure time as risk factors for adverse events related to endoscopic resection.[14,15,16] A recent study performed in Japan demonstrated that procedure time longer than 150 minutes is an independent predictor for complications of simultaneous ESD.[8] There was no perforation in this study. Though the procedure time did not reach 150 minutes in this study, there were 8 and 2 patients suffered from delayed bleeding in the single group and the simultaneous group, respectively.

In our study, the delayed bleeding rate was 20% in the simultaneous group. It was a bit higher than that in some previous studies.[8,9] We believe that this discrepancy can be explained partly by the single-center nature of the present study and may have skewed results. The larger lesions and longer operation time in the multiple ESD group may account for the differences. Furthermore, there was much lower volume of ESD cases in this study, and our experience with ESD is somewhat limited.

The incidence rate of synchronous gastric cancer after ER ranges from 5.8% to 14.5%.[17–20] In our study, 4 synchronous early gastric lesions from 4 patients in the single ESD group were detected, whereas there were 2 lesions in the simultaneous ESD group. The overall incidence rate of synchronous gastric cancer was 7.5% in this study. The 4 lesions in the single ESD group were located in the lesser curvature of the upper third of the stomach and the posterior wall of the middle third of the stomach, respectively. However, the synchronous lesions in the multiple ESD group were of very small size, which were located in the anterior wall of the middle third of the stomach. These are important blind spots in the screening endoscopic examination before ER.[21] So, the entire stomach must be meticulously examined when ESD are to be performed. Novel imaging techniques such as mucosal staining techniques and magnifying endoscopy with narrow-band imaging are also needed.

The main limitation of this study is that it was a retrospective single institute study. This study is also limited by its small sample size and short follow-up. However, our study is the first report focus on simultaneous ESD for multiple early gastric cancers in low volume hospitals.

In summary, our initial experience has demonstrated that simultaneous ESD for multiple early gastric cancers is feasible and safe in the low volume hospital. However, the approaches used to evaluate for multifocal lesions are urgent to be improved. A large-scale prospective study is necessary to follow up on our findings.

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