Safety and feasibility of simultaneous endoscopic submucosal dissection for multiple gastric neoplasias

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Safety and feasibility of simultaneous endoscopic submucosal dissection for multiple gastric neoplasias

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The Master's Thesis
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Master of Medical Science

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December 2016

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December 2016

ACKNOWLEDGEMENTS

Above all, I would like to express my deep and sincere gratitude to Professor Sang Kil Lee for his supervision and encouraging suggestions throughout my academic life.

I am deeply indebted to Professor Seung-Ho Choi, who leads academic discussions and encourage me to broaden my horizons. I am grateful to Professor Hyunki Kim for his precious and constructive advices. Their guidance not only improved my dissertation but also will benefit my future work.

Finally I wish to thank my wife Jung Yoon Pyo and family members who have been with me and always given me lots of support and love.

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ABSTRACT

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Background: Synchronous gastric neoplasms are not infrequently detected, thus endoscopic submucosal dissection (ESD) for multiple early gastric neoplasia is occasionally considered. However, there have been few investigations of the safety and feasibility of simultaneous ESD for multiple gastric lesions. This study aims to evaluate the safety and feasibility of simultaneous ESD for multiple gastric neoplasia.

Methods : A total of 1,823 patients who underwent ESD for 1,929 gastric adenomas or early gastric cancers were retrospectively reviewed in this study. Two hundred gastric adenomas or early gastric cancers among 94 patients were treated by ESD simultaneously (multiple group) and 1,729 patients were treated with ESD for a single lesion (single group).

Results: *En bloc* resection (P = 0.060), complete resection (P = 0.362) and curative resection (P = 0.108) rates did not differ between the two groups. Rates

of adverse events including bleeding (P = 0.317), perforation (P = 0.316) and aspiration pneumonia (P = 0.563) were not higher in the multiple group. Long-term follow up showed more frequent local recurrence (P < 0.001), synchronous neoplasia (P = 0.041) and metachronous neoplasia (P < 0.001) per patient in the multiple group; however, local recurrence per lesion did not differ between the two groups (P = 0.103).

Conclusions: Simultaneous ESD for multiple synchronous gastric neoplasms is safe and feasible compared to single ESD. However, thorough examination for local recurrence and synchronous and metachronous neoplasia is required.

Key words: Endoscopic submucosal dissection; multiple gastric neoplasms; outcomes

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I. INTRODUCTION

The detection and diagnosis of early gastric cancer has increased due to advances in endoscopic examination and endoscopic screening. Endoscopic resection as a minimally-invasive therapy has been widely accepted in Asian countries, including Korea and Japan, for cases of gastric neoplasia that are confined to the mucosa and have little evidence of lymph node metastasis[1-3]. In particular, endoscopic submucosal dissection (ESD) is widely used because it allows for a single slice resection of gastric lesions, regardless of tumor size[4,5].

Two or more malignant foci in the stomach are often diagnosed during endoscopy and are known as synchronous multifocal gastric cancer. The incidence of concurrent multiple gastric carcinomas has been reported to range from 4.8 to 23.8% in studies of excised stomach specimens[6-9]. The incidence of synchronous multiple gastric carcinomas after endoscopic resection is reported

from 1.0 to 5.6%[10,11]. Epidemiologically, the risk factors known for multiple gastric carcinomas are old age and male sex[12]. Histologically, multiple gastric carcinomas often arise in the gastric mucosa with severe intestinal metaplasia[12-14].

Recent studies have shown that multiple synchronous EGCs have clinicopathologic features with respect to tumor size, depth of invasion, lymphovascular invasion, and incidence of lymph node metastasis similar to those of solitary EGCs[15,16]. Therefore, endoscopic treatment could be feasible when major and minor lesions are predicted to represent mucosal cancer without lymphovascular invasion.

However, ESD is a time-consuming procedure that requires great endoscopic skill[4,17]. Simultaneous ESD for multiple gastric neoplasms would increase procedure time and the amount of resected mucosa. Considering the reports describing large size and long procedure time as risk factors for adverse events, simultaneous ESD may increase the risk of complications and unfavorable outcomes[18,19]. On the other hand, separate procedures with a time interval between each gastric lesion would result in a longer period of hospitalization and increase medical expense.

To the best of our knowledge, there have been few studies evaluating adverse events, feasibility or outcomes related to ESD for multifocal gastric neoplasms. A recent study performed in Japan demonstrated comparable procedural outcomes and complication rates of simultaneous ESD to those of single ESD.

However, the literature reviewed relatively small number of patients, and did not evaluate long term outcomes[20]. Our study aimed to evaluate the safety, feasibility and outcomes of simultaneous ESD for multiple synchronous gastric neoplasia and compare it to that of ESD for solitary gastric lesion.

II. MATERIALS AND METHODS

1. Patients

Patients with gastric neoplasia who underwent ESD were prospectively followed at a single tertiary teaching hospital in Seoul, Korea from January 2008 to December 2011. Clinical data included patient demographics, pathologic data of gastric neoplasms, results of endoscopic resection, and procedure-related adverse events including bleeding and perforation. A total of 94 patients underwent simultaneous ESD for a total of 200 synchronous EGCs or gastric adenomas. They were compared to 1,729 patients who underwent ESD for single gastric neoplasm. Gastric neoplasms included in the study were selected based on the expanded criteria proposed by Gotoda et al.[3]. The patients in the multiple group were treated by ESD under a single anesthesia on a single day. Patients who had prior gastric resection were excluded. The institutional review board of the hospital approved this study. (Approval number: 4-2013-0382)

2. *Study definitions*

The macroscopic type and location of EGC were classified according to the Japanese Gastric Cancer Association classification system[21]. *En bloc* resection was defined as resection in a single piece as opposed to resection of multiple

pieces. Complete resection was defined as tumor-free 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, lymphatic invasion and vascular involvement. The main lesion was defined as being histologically more advanced, and larger, if the histology was the same. The accessory lesion was defined as histologically less advanced, and smaller, if histology was the same. The diameter of the lesion was defined as the longest diameter of the neoplasm measured in the resected specimen on pathologic examination. Procedure time was defined as the time from marking of mucosa to complete removal, including the time required for hemostasis. Bleeding was defined as (A) intraoperative bleeding that required blood transfusion, (B) clinical symptoms such as melena or hematemesis, or (C) a decrease in hemoglobin level greater than 2 g/dL following procedure. A diagnosis of perforation required direct endoscopic visualization of mesenteric fat or radiographic evidence of free air. Pneumonia was defined as new or progressive consolidation with one of the following newly developed criteria: (A) cough, (B) purulent sputum or change in character of sputum, or (C) rales or dullness to percussion on physical examination of the chest[22]. Parenteral administration of non-steroidal anti-inflammatory drugs or opioid analgesics was analyzed as the number of pain killer injections. Complete blood cell counts measured at the day of hospitalization and the day after ESD were retrospectively reviewed

3. ESD methods

Endoscopic procedure was done with single channel endoscope with jet function available (GIF Q260J or GIF-H260Z, Olympus Optical Co. Ltd., Tokyo, Japan). After endoscopic evaluation of the gastric lesions with indigocarmine stain, the surrounding lesion was marked by electrocautery (ICC 200; ERBE, Tübingen, Germany) using an argon plasma coagulation probe or a needle knife (KD-10Q-1-A, Olympus Optical Co. Ltd., Tokyo, Japan). Saline mixed with epinephrine (0.01mg/mL) and 0.8% indigo carmine was injected into the submucosa to lift the lesion. A circumferential incision (precut) was made along the outer border of the lesion using a needle knife and an insulated-tipped knife (IT knife, KD-610L, Olympus Optical Co. Ltd., Tokyo, Japan). The submucosal layer was then dissected with the IT knife until complete removal was achieved. Endoscopic hemostasis was performed with hemoclips or hemostatic forceps for bleeding or exposed vessels. For multiple synchronous lesions, marking was performed for all lesions initially. After complete dissection and hemostasis of the first lesion, an epinephrine mixture was injected, and a precut was made subsequently for the residual neoplasms.

4. Follow-up

For EGCs, EGD was scheduled at 3, 6, 12, 18, 24 months after ESD to check

for local or metachronous lesions. After 24 months, EGD was performed annually. For adenomas, EGD was performed at 3, 12 months after ESD and annually thereafter.

Recurrent neoplasia detected at the curatively resected site was regarded as local recurrence. A second neoplasm detected at the gastric site other than the primary resection area within 12 months after endoscopic resection was defined as synchronous. A second neoplasm found at sites other than the primary resection area at 12 months or later was defined as metachronous.

5. *Statistical analysis*

For statistical analysis, χ^2 test, Fisher's exact test and *t* test were used. The Kaplan-Meier method and a log-rank test were used for survival analysis of long-term outcomes. A P-value <0.05 was regarded as a significant difference for group comparisons. Statistical analysis was performed using SPSS 18.0 for Windows (IBM., Chicago, IL, USA).

II. RESULTS

1. Baseline characteristics of patients

A total of 1,823 patients who had undergone endoscopic resection for 1,929 gastric adenomas or early gastric cancers were enrolled in this study. Ninety-four patients had two or more gastric lesions. The rate of simultaneous ESD for synchronous gastric neoplasia was 5.16% (94 out of 1,823). The baseline characteristics of patients who underwent endoscopic resection are shown in Table 1. The mean age was greater in patients with multiple lesions (67.03 ± 7.35 vs. 63.28 ± 9.44, $P < 0.001$). A history of cigarette smoking was more common (61.7% vs. 47.8%, $P = 0.009$), and underlying comorbid disease, including cardiovascular disease, renal disease, diabetes, and chronic viral hepatitis, were more frequent in patients with multiple lesions (62.8% vs. 48.0%, $P = 0.005$). Other baseline characteristics of the patients did not differ between the two groups.

Table 1. Baseline characteristics of patients

	Single group	Multiple group	P-value
Number of patients, n	1,729	94	
Sex, male, n (%)	1,217 (70.4%)	68 (72.3%)	0.686
Age, mean ± SD	63.28 ± 9.44	67.03 ± 7.35	< 0.001
Cigarette smoking, n (%)	827 (47.8%)	58 (61.7%)	0.009
Alcohol use, n (%)	917(53.0%)	55 (58.5%)	0.3
NSAID use, n (%)	196 (11.3%)	9 (9.6%)	0.599
Comorbidities[a], n (%)	830 (48%)	59 (62.8%)	0.005
H.pylori infection[b], n (%)	461/1,057 (43.6%)	17/52 (32.7%)	0.121

[a] Comorbidities include cardiovascular disease, renal disease, diabetes, and chronic viral hepatitis.
[b] *H.pylori* infection was investigated in a limited number of patients. *H.pylori* infection test methods: urea breath test, rapid urease test and H-E stain.
SD, standard deviation

2. Comparison of clinicopathologic characteristics of gastric neoplasms

In the multiple group, 12 patients had triple lesions and the remaining 82 had double lesions. Morphologic and pathologic characteristics of the main lesions, which were histologically more advanced or larger when histology was the same, were compared to those of the solitary lesions. The mean diameter of the main lesion of the multiple group was significantly longer than that of the single group (15.24 ± 9.89mm vs. 12.90 ± 9.30mm, $P = 0.020$). Histology, shape and location were comparable between the two groups (Table 2). When the main lesion was compared to the accessory lesions of the multiple group, shape and location did not differ (Table 3).

Table 2. Characteristics of gastric neoplasms

	Single group (N = 1,729)	Main lesion of multiple group (N = 94)	P-value
Histology			0.524
Grade of adenoma			
LGD, n (%)	600 (34.7%)	32 (34.0%)	
HGD, n (%)	212 (12.3%)	7 (7.4%)	
Differentiation of carcinoma[a]			
Differentiated (WD+MD), n (%)	813 (47.0%)	49 (52.1%)	
Undifferentiated (PD+SRC), n (%)	104 (6.0%)	6 (6.4%)	
Shape			0.217
Elevated, n (%)	1,362 (78.8%)	81 (86.2%)	
Flat, n (%)	122 (7.1%)	5 (5.3%)	
Depressed, n (%)	245 (14.2%)	8 (8.5%)	
Location			0.161
Upper third, n (%)	130 (7.5%)	7 (7.4%)	
Middle third, n (%)	360 (20.8%)	12 (12.8%)	
Lower third, n (%)	1,239 (71.7%)	75 (79.8%)	
Diameter of lesions, mean ± SD, mm	12.90 ± 9.30	15.24 ± 9.89	0.020

[a] Differentiated carcinoma includes well-differentiated carcinoma (WD) and moderately differentiated carcinoma (MD); undifferentiated carcinoma includes poorly-differentiated carcinoma (PD) and signet ring cell carcinoma (SRC)

LGD, low-grade dysplasia; HGD, high-grade dysplasia; SD, standard deviation

Table 3. Comparison of main and accessory lesions of the multiple group

	Main lesion (N = 94)	Accessory lesions (N = 106)	P-value
Histology			<0.001
Grade of adenoma			
LGD, n (%)	32 (34.0%)	72 (67.9%)	
HGD, n (%)	7 (7.4%)	17 (16.0%)	
Differentiation of carcinoma[a]			
Differentiated (WD+MD), n (%)	49 (52.1%)	17 (16.0%)	
Undifferentiated (PD+SRC), n (%)	6 (6.4%)	0 (0%)	
Shape			0.768
Elevated, n (%)	81 (86.2%)	89 (84.0%)	
Flat, n (%)	4 (4.3%)	7 (6.6%)	
Depressed, n (%)	9 (9.6%)	10 (9.4%)	
Location			0.730
Upper third, n (%)	7 (7.4%)	11 (10.4%)	
Middle third, n (%)	21 (22.3%)	21 (19.8%)	
Lower third, n (%)	66 (70.2%)	74 (52.9%)	
Diameter of lesions, mean ± SD, mm	15.24 ± 9.9	9.85 ± 5.80	<0.001

[a] Differentiated carcinoma includes well-differentiated carcinoma (WD) and moderately differentiated carcinoma (MD), undifferentiated carcinoma includes poorly differentiated carcinoma (PD) and signet ring cell carcinoma (SRC)

LGD, low-grade dysplasia; HGD, high-grade dysplasia; SD, standard deviation

3. Comparison of complications and morbidities

Table 4 shows a comparison of the procedure time, adverse events and variables related to morbidity in each group. The mean procedure time was longer in the multiple group (94.99 ± 48.96 min vs. 57.91 ± 42.73 min, $P < 0.001$), but adverse events including bleeding, perforation and aspiration pneumonia did not differ between the two groups. The mean number of hospital days and pain killer injections were not significantly different between the two groups. Also, the decrement of serum hemoglobin level was not significantly different between the two groups; however, the increment of white blood cell (WBC) count was larger in the multiple ESD group (4,335 ± 2,694/uL vs. 3,725 ± 2,610/uL, $P = 0.034$).

Table 4. Complications and morbidity related to endoscopic submucosal dissection

	Single group (N = 1,729)	Multiple group (N = 94)	P-value
Procedure time, mean ± SD, min	57.91 ± 42.73	94.99 ± 48.96	< 0.001
Adverse events			
Bleeding, n (%)	82 (4.7%)	2 (2.1%)	0.317
Perforation, n (%)	45 (2.6%)	4 (4.3%)	0.316
Aspiration pneumonia, n (%)	59 (3.4%)	4 (4.3%)	0.563
Δ WBC count, mean ± SD, /uL	3,725 ± 2,610	4,335 ± 2,694	0.034
Δ Hb, mean ± SD, g/dL	0.41 ± 0.94	0.44 ± 0.91	0.748
Hospital days[a], mean ± SD	4.24 ± 3.87	5.85 ± 15.42	0.136
Pain killers used[b], mean ± SD	0.99 ± 2.13	1.26 ± 1.45	0.094

[a] Statistical significance was determined by Mann-Whitney U-test since the parameter showed non-normal distribution
[b] Number of parenteral administration of NSAID or opioid analgesics for pain control during hospitalization after the procedure
Δ refers to elevation of the serologic value from baseline to the value tested at the day after the endoscopic procedure
SD, stand deviation; WBC, white blood cell; Hb, hemoglobin

4. Procedural outcomes and long-term outcomes

As shown in Table 5, the procedural outcome including *en bloc* resection, complete resection and curative resection did not differ between the two groups.

Patients who were curatively resected and who had a follow-up period longer than one year were analyzed for long-term outcome. In total, 1,184 patients for single group and 54 patients for multiple group were analyzed, and the median follow-up periods were 27 months (interquartile range (IQR) 18.3 to 36.3 months) and 19 months (IQR 13.0 to 24.2 months), respectively. The cumulative local recurrence ($P < 0.001$), cumulative incidence of synchronous neoplasia ($P = 0.041$) and metachronous neoplasia ($P < 0.001$) were higher in the multiple group. Among five cases of local recurrence in the multiple neoplasms, four occurred at the main lesion. However, when the cumulative incidence of local recurrence was considered per resected lesion, not per patient, there was no difference in the two groups ($P = 0.103$) (Figure 1).

Figure 2 shows that the estimated disease-free survival was significantly longer in the single group compared to the multiple group (45.41 ± 0.32 months vs. 38.90 ± 2.45 months, $P < 0.001$).

Table 5. Procedural outcomes

	Single group (N = 1729)	Multiple group (N = 200)	P-value
En bloc resection, n (%)	1,608 (93.0%)	193 (96.5%)	0.060
Complete resection, n (%)	1,594 (92.2%)	188 (94.0%)	0.362
Curative resection, n (%)	1,465 (84.7%)	178 (89.0%)	0.108

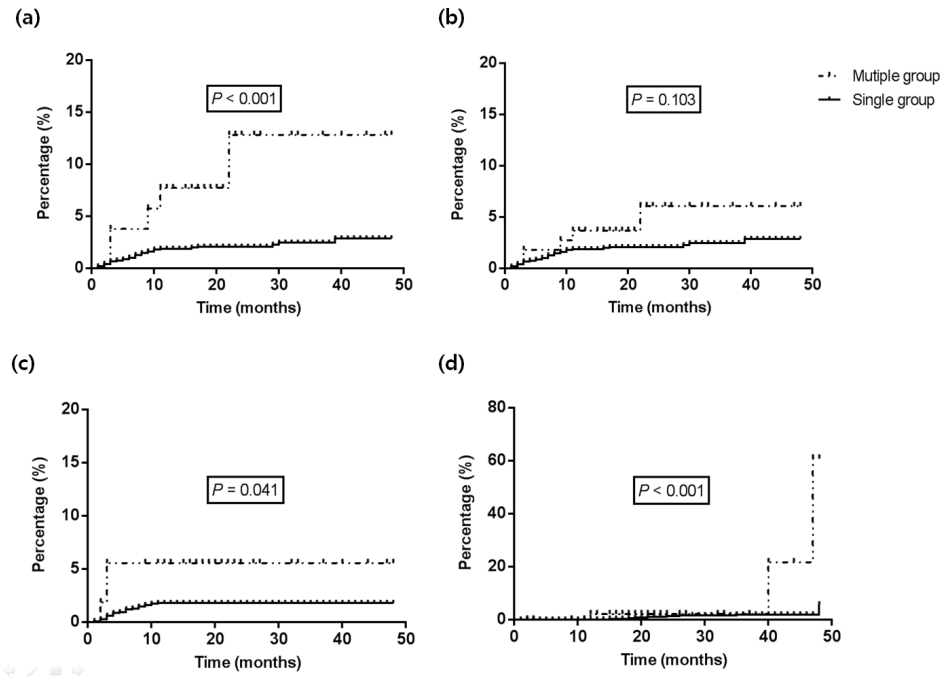

Figure 1. Kaplan Meier plot for long-term outcomes

(a) Cumulative incidence of local recurrence per patient and (b) per resected lesion. (c) Cumulative incidence of synchronous neoplasia and (d) metachronous neoplasia

Curatively resected patients who had a follow-up period longer than one year were analyzed for long-term outcomes. 1,184 patients from the single ESD group and 54 patients from the multiple ESD group were analyzed, and the median follow-up period was 27 months (IQR of 18.3 to 36.3 months) and 19 months (IQR of 13.0 to 24.2 months), respectively.

ESD, endoscopic submucosal dissection; IQR, interquartile range

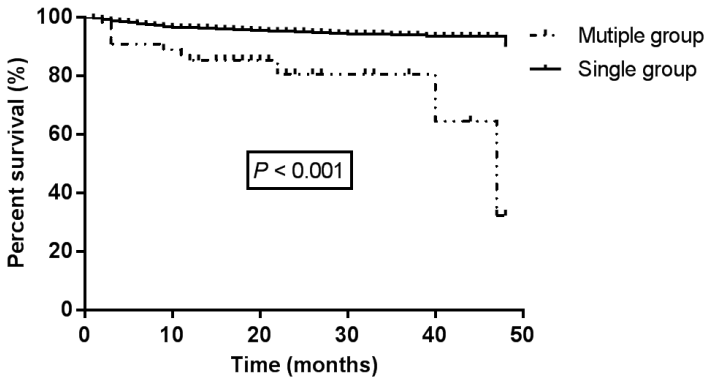

Figure 2. Comparison of disease-free survival between single ESD and multiple ESD group

ESD, endoscopic submucosal dissection

IV. DISCUSSION

Our study is the largest study to demonstrate the safety and feasibility of simultaneous ESD for multiple lesions as compared to ESD for a single lesion. A previous study evaluating safety and efficacy of simultaneous ESD for synchronous double EGCs only included double lesions (not triple), a relatively small number of patients and there was no analysis of long-term outcomes[20].

In this study, comparison of the single group and the multiple group revealed no significant difference in adverse events including bleeding, perforation and aspiration pneumonia. Also, patients in the multiple group showed neither longer hospitalization nor more pain killer injections. Review of the resected specimens showed no significant difference in the rate of *en bloc* resection, complete resection or curative resection. Our findings demonstrate that the technical safety and feasibility of simultaneous ESD for multiple gastric neoplasms is acceptable compared to ESD for a single neoplasm. On the other hand, metachronous recurrence after endoscopic resection in the multiple group was significantly higher than that in the single group.

In this present study, baseline characteristics showed that patients in the multiple group were older and more likely to have comorbidities than the patients in the single group. This corresponds to the previous studies reporting old age as one of the risk factors for multifocality in gastric neoplasms[8]. Frequent comorbidities in the multiple group may be ascribed to older age, since more comorbidities are generally expected in the elderly.

As expected, the procedure time was significantly longer in the multiple group. However, the mean procedure time for simultaneous ESD was not twice that of single ESD procedures. This may be due to ease of ESD of accessory lesions compared to the main lesion resulting from less advanced histology and smaller diameter.

Longer procedure time and poor visual field due to the previously resected specimen or blood clots may interfere with the resection of second or third target lesions. Nevertheless, our data did not show evidence of frequent adverse events such as bleeding, perforation or aspiration pneumonia related to simultaneous ESD. The rate of perforation was remarkably high in the multiple group (4.3% vs 2.6%), but did not reach statistical significance. The majority of perforation events were minimal and conservatively managed (39 out of 45 cases in the single group and all 4 cases in the multiple group). However, the increment of WBC count was significantly higher in the multiple ESD group. There were reports describing large size and long procedure time as risk factors for adverse events[18,19]. A previous study performed in our institute demonstrated a procedure time of more than two hours as a risk factor for aspiration pneumonia during ESD[23]. Moreover, a recent study performed in Japan indicated that procedure time longer than 150 minutes is an independent predictor of adverse events in simultaneous ESD for double EGC[20]. Though the mean procedure time did not reach two hours in our study, ESD took longer for the multiple group than for the single group, which may be related to minor

events of aspiration and pulmonary infection. Moreover, a larger amount of resected mucosa and mucosal injury from electrocauterization may account for inflammatory reactions which can lead to leukocytosis.

The mean number of hospital days was greater in the multiple group, but the difference was not statistically significant. Also, patients in the multiple group received more parenteral pain killer injections after the procedure, but this difference was also not statistically significant. According to our results, it's unlikely that simultaneous ESD would cause more medical expense or morbidity. Rather, separate performance of endoscopic procedures would prolong hospitalization and consequently cause more medical expenses.

On long-term follow up, local recurrence was more frequent in the multiple group than the single group. However, considering the risk of recurrence per lesion, the risk of local recurrence may well be increased with multiple lesions. In fact, the cumulative incidence of local recurrence per resected lesion did not differ between the two groups (P = 0.103). Therefore, more thorough examination and biopsies of each resected site during follow up are important.

Reported overall incidence rates of metachronous gastric cancer after endoscopic resection range from 7.9 to 14% [24-28]. As for predictive factors, synchronous multiplicity of the gastric cancer and patient age at the time of the initial endoscopic resection have been reported to significantly affect the incidence of metachronous lesions[26]. Our results, which showed a higher incidence of synchronous neoplasia as well as metachronous neoplasia in the

multiple group, are consistent with the results from the previous report. However, this finding was not adjusted by known risk factor of metachronous neoplasia such as *H.pylori* status and extent of atrophy due to limited available data[29,30].

The main limitation of this study is that it was a retrospective single-center study. However, the number of patients included in this study was large, and most of the data used for this study were collected prospectively for future analysis, so there was little chance of bias. Future studies with a larger number of cases and a longer follow-up period would be useful to verify our results.

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V. CONCLUSION

Simultaneous ESD of multiple gastric neoplasms is safe, feasible and may reduce overall medical expense compared to multiple ESD separated by time intervals. However, in order to maintain optimal outcome, thorough examination for local recurrence, synchronous and metachronous neoplasia is essential.

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ABSTRACT(IN KOREAN)

다발성 위종양에 대한 동시적 내시경 점막하 박리술의 안전성 및 적합성

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조 동 후

배경: 다발성 위종양은 비교적 흔하게 발견되며 이들을 치료하기 위해 동시에 내시경 점막하 박리술을 시행하는 경우가 종종 있다. 하지만 다발성 위종양에 대한 동시적 내시경 점막하 박리술을 시행하는 것이 안전하고 적합한지에 대한 연구는 거의 없는 실정이다.

목적: 본 연구에서는 다발성 위종양에 대한 동시적 내시경 점막하 박리술의 안정성과 적합성에 대해 조사하였다.

방법: 총 94명의 환자가 200 개의 위선종 혹은 조기위암에 대해 동시에 내시경 점막하 박리술을 시행받았으며 (다발성 병변군), 1,729명의 환자가 단일 병변에 대해 내시경 점막하 박리술을 시행받았다 (단일 병변군). 두 환자군의 합병증, 시술 성과, 장기적인 치료 결과에 대해 비교하였다.

결과: 완전 절제율 (P = 0.362), 일괄 절제율 (P = 0.060), 근치적 절제율 (P = 0.108) 면에서 두 군의 차이는 없었으며 출혈 (P = 0.317), 천공 (P = 0.316) 및 흡인성 폐렴 (P = 0.563) 등의 합병증 면에서도 두 군간의 유의한 차이가 없었다. 장기적인 추적관찰

결과, 다발성 병변군에서 통계학적으로 유의하게 국소 재발 ($P < 0.001$), 동시성 병변 ($P = 0.041$) 및 이시성 병변의 ($P < 0.001$) 발견 빈도가 높았다.

결론: 다발성 위종양에 대한 동시적 내시경 점막하 박리술은 안전하고 적합하다. 그러나 장기적으로 국소 재발과 동시성 및 이시성 병변에 대해 유의하여 추적해야 한다.

핵심되는 말 : 다발성 위종양, 내시경 점막하 박리술, 결과

PUBLICATION LIST

Joh DH, Park CH, Jung S, Choi SH, Kim HK, Lee H, et al. Safety and feasibility of simultaneous endoscopic submucosal dissection for multiple gastric neoplasias. Surg Endosc 2015;29:3690-7.