Chapter 9

Clinical Outcome of Endoscopic Submucosal Dissection for 352 Lesions of Superficial Gastric Neoplasms in 284 Patients

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1. Introduction

One of the most significant topics for therapeutic endoscopy in recent years is the development of new therapeutic strategies for gastric neoplasms, called endoscopic submucosal dissection (ESD)[1]-[7]. This technique was developed to allow resection of difficult lesions with characteristics such as large size, irregular shape, coexisting ulcer findings or difficult location that could not be resected en bloc using conventional endoscopic mucosal resection (EMR). One of the most important benefits of this procedure is to obtain accurate histological diagnosis. Additional benefits of ESD include that it is minimally invasive in nature and allows preservation of the entire stomach, resulting in the improved postoperative quality of life[8], [9]. Therefore, ESD is widely accepted as a standard treatment strategy for gastric neoplasm.

In this study, we conducted consecutive gastric ESD for superficial gastric neoplasms, and compared the results between under 64 years old (non elderly group; NEG) and over 65 years old (elderly group; EG) to evaluate the safety, efficacy and long-term outcomes, especially in the elderly people. We defined over 65 years old as EG according to a definition of World Health Organization (WHO).

Design: Retrospective, non-randomized, controlled clinical study

2. Patients and methods

Between April 2007 and March 2010, a total of 284 patients with superficial gastric neoplasm were treated with ESD at our institution. The resected specimens were evaluated histopathologically in all cases. Using a database, outcomes were compared between NEG and EG, retrospectively, including resected specimen size, tumor size, en-bloc resection rate, complete en-bloc resection rate, mean procedure time, hospital days after ESD, histopathological findings, complications and 1 and 3-year overall survival rate. After the initial treatment, all cases were observed (mean period: 796.5 days, range: 6-1812 days), and the local recurrence rate and overall survival period of the each group were analyzed. Data were collected and analyzed.

2.1. Preoperative diagnosis

The indication for ESD was determined from the endoscopic feature of the lesions, including white light observation, chromoendoscopy. Magnifying endoscopy with narrow band imaging (NBI) were also used, whenever necessary, in order to recognize the demarcated line between normal mucosa and lesion and to estimate the depth of the lesion[10]. Endoscopic ultrasonography (EUS) was also performed for the assessment of the invasion depth and/or presence of ulceration in cases in which submucosal invasion or ulceration is suspected. Contrast-enhanced computed tomography (CECT) was performed for preoperative detection of distant and/or lymph node metastases.

2.2. ESD technique

The ESD technique has been precisely described elsewhere[11]-[13]. In brief, ESD procedures were performed by using video endoscopes (GIF-Q260J; Olympus Optical Co, Ltd, Tokyo, Japan). A tip-transparent hood was attached to the top of the endoscope (Figure 1). A high-frequency power supply VIO300D (ERBE Elektromedizin, Germany) was used. Either flush knife (KD-2618 JN-15; Fujinon, Tokyo, Japan) (Figure 2a), dual knife (KD-650; Olympus, Tokyo, Japan) (Figure 2b), or flex knife (KD-630L; Olympus, Tokyo, Japan) (Figure 2c) was used as the electrosurgical knife for circumferential mucosal cutting around the tumor with a sufficient safety margin and also submucosal dissection beneath the lesion. Hook knife (KD-620LR; Olympus) (Figure 2d) was used if necessary. Sodium hyaluronate 0.4% (Mucoup; Johnson & Johnson, Tokyo, Japan), mixed with a small amount of indigo carmine dye and epinephrine, was used as the material for local injection into submucosal layer. By mixing a small amount of indigo carmine dye and epinephrine into sodium hyaluronate solution, visualization of the submucosal layer to be dissected was much easier, and bleeding during the procedure was also diminished. The resected specimen was removed and evaluated histopathologically. Hemostatic forceps (HDB2422W; Pentax, Tokyo, Japan) (Figure 2e) were used to control bleeding during the procedure or for ablation of visible vessels on the mucosal defect after resection. One day after the ESD, a second-look endoscopy was performed, along with preventive hemostasis, as needed. ESD was usually carried out under conscious sedation using midazolam and pethidine hydrochloride. The patients were preselected and treated under general anesthesia in cases that the treatment time was expected to exceed 2 hours.

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Figure 1. Endoscopy system

Figure 2. a. flush knife, b. dual knife, c. flex knife, d. fook knife, e. hemostatic forceps

2.3. Histological assessment

The resected specimen was cut into 2-mm slices after fixation in formalin. Histological type, size, depth of invasion, lateral and vertical margins, and lymphatic-vascular invasion were evaluated in each slice according to the Japanese Classification of Gastric Carcinoma[14].

2.4. Definition of complete and incomplete resection

It is usually easier to histologically evaluate the status of the resected specimen when the lesion is resected in one-piece. The quality of resection was also assessed by the status of the resected specimen: when the tumor was resected as a single piece and also when the margin was definitely free of tumorous glands, resection was considered to be complete. Multifragment resections were defined as incomplete when tumorous glands were histologically present at its edge, even if the lesion was completely removed by the endoscopical evaluation.

2.5. Definition of curative and non-curative resection

Gotoda et al studied surgically resected specimens from early gastric cancer (EGC) patients and assessed the rate of cases with EGC without lymph node metastasis, upon the following four indication criteria [15]; (1) differentiated intramucosal cancer without ulceration, regardless of size, (2) differentiated intramucosal cancer with ulceration, 30mm or less in size, (3) differentiated minute submucosal penetrative cancer (SM1), 30mm or less in size, (4) undifferentiated intramucosal cancer without ulceration, 20mm or less in size(Figures 3 to 8) [16]. If the lesion belongs to one of the four indication criteria with non-lymphatic and/or vascular involvement and the resected specimen was regarded as complete resection, the treatment was defined as curative resection. The remaining ones were defined as non-curative resection. In cases that the resected specimen was diagnosed histologically as possible node-positive cancer, additional gastrectomy with lymphadenectomy was considered.

2.6. Complications

Postoperative bleeding was defined as hematemesis or melena requiring an endoscopic hemostatic procedure after ESD. Perforation during the procedure was sutured by clipping and confirmed by detection of free air on plain radiography[17].

2.7. Follow up care

All the patients who underwent ESD were regularly observed with endoscopic examinations to check for local recurrence and/or a 2nd primary lesion as well as CTs to evaluate the existence of distant or lymph node metastases once or twice a year. In cases that underwent surgical procedure after the endoscopic resection, the patients were observed in the same way.

2.8. Statistical analysis

Comparisons between groups were performed using the χ^2 test and Mann-Whitney test for categorical variables. A P value <.05 was considered statistically significant. The overall survival rate was assessed by Kaplan–Meier analysis. All analyses were performed on a personal computer using SAS JMP version 8.0.1 (SAS Institute Inc. USA).

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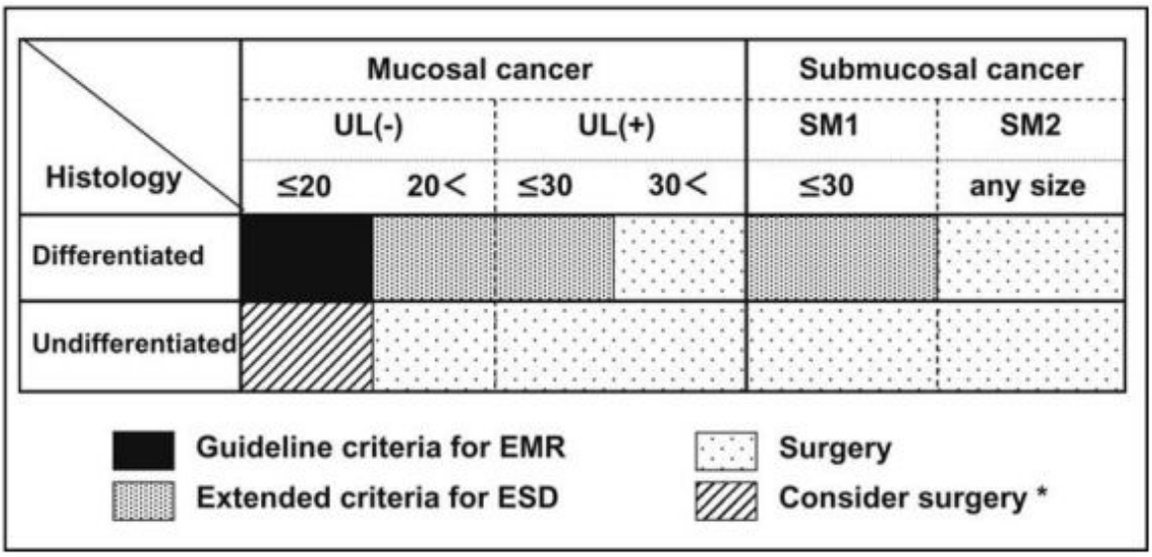

Figure 3. Extended criteria for endoscopic resection. Tumor size is shown in millimeters.UL; ulcerative findings,SM;submucosal

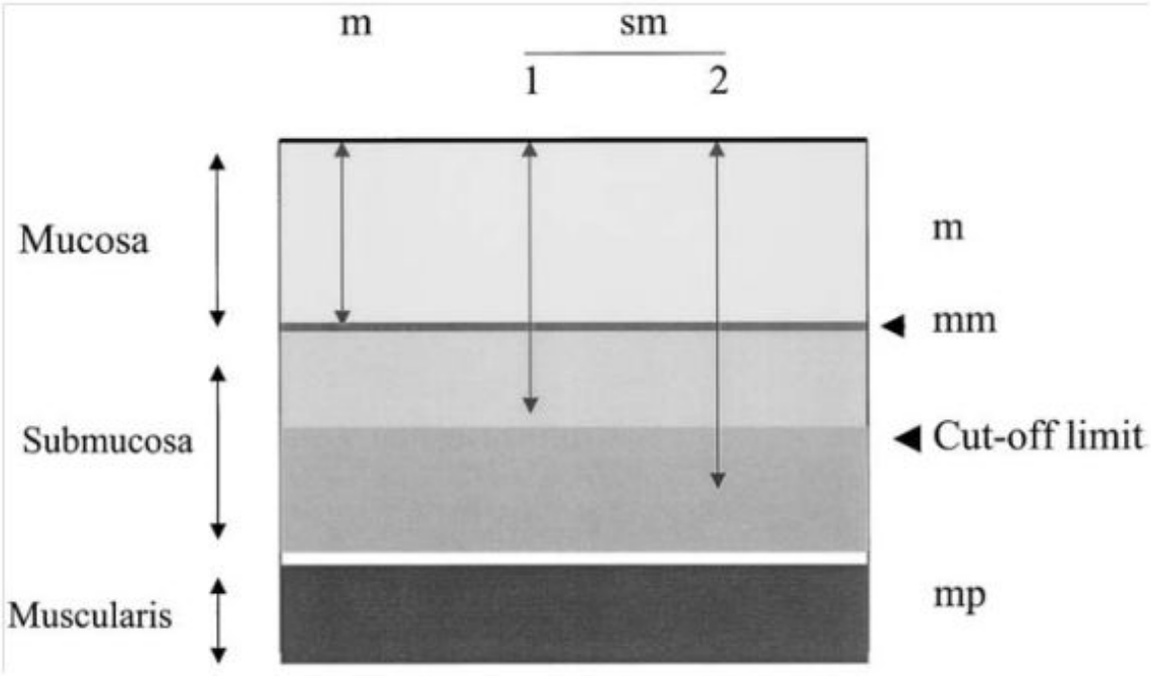

Figure 4. Depth of invasion of the submucosa in the columnar epithelium.Depth of invasion of the submucosa in the columnar epithelium assessed in the specimen obtained after surgery. Depth of submucosal invasion is divided into two groups: superficial (sm1) and deep (sm2) with respect to a cutoff limit determined on a micrometric scale (500 μ in the stomach).

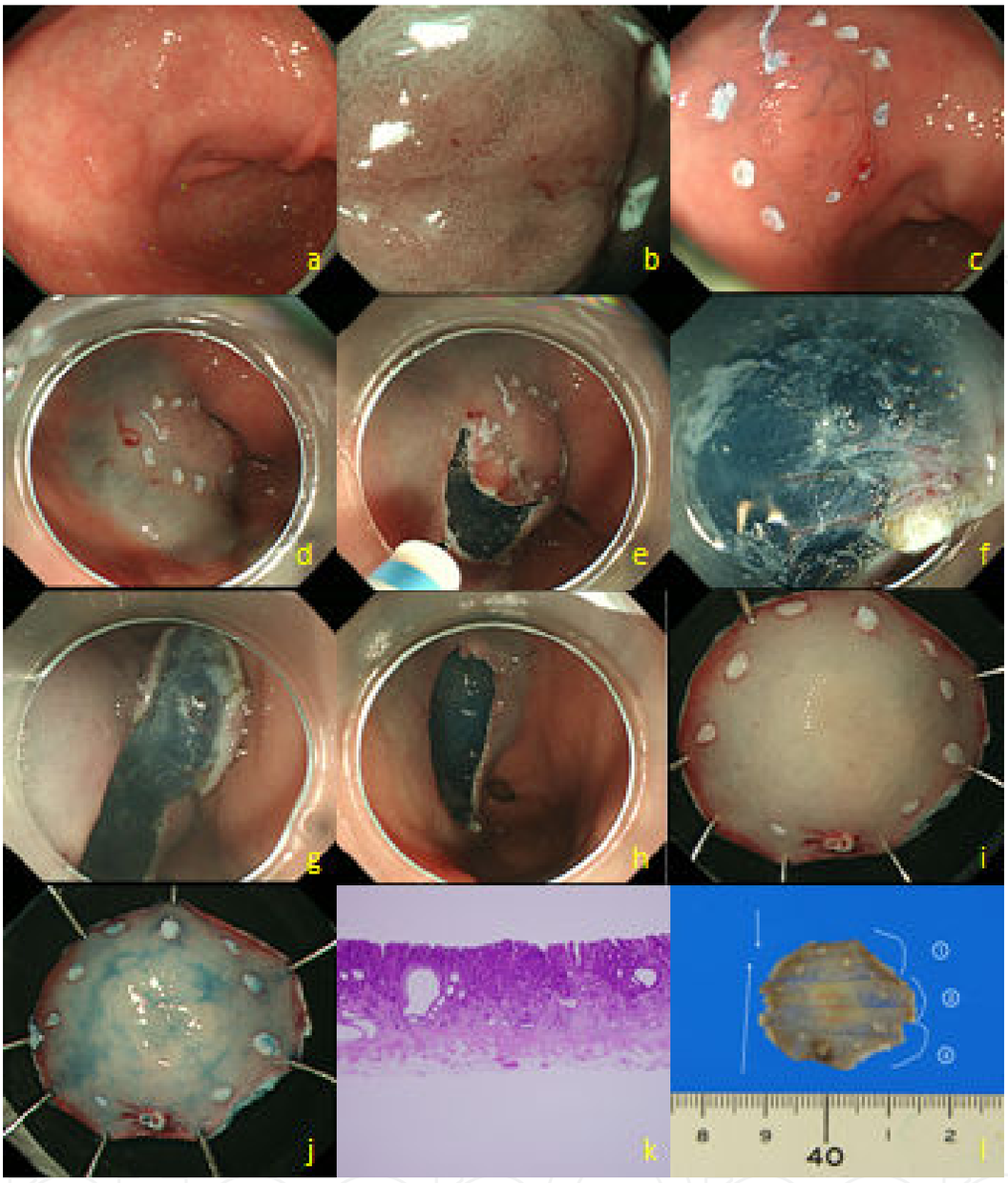

Figure 5. A case meet withguidline criteria. (a) Conventional endoscopic view revealed 0- II a, located in the lower part of the stomach. (b) Magnifying endoscopy with NBI.(c) After indigo carmine dye spraying. The border was well demarcated.(d) After injection of sodium hyaluronate. (e)to(g) Mucosal incision and dissection.(h) Gastric ulcer after ESD.(i) Resected specimen.(j) Resected specimen after indigo carmine dye spraying.(k) (l) Histopathological assessment of the resected specimen. 0- II a, 24 × 20 mm, intramucosal carcinoma, well-differentiated type. Tumor size was 5 mm.

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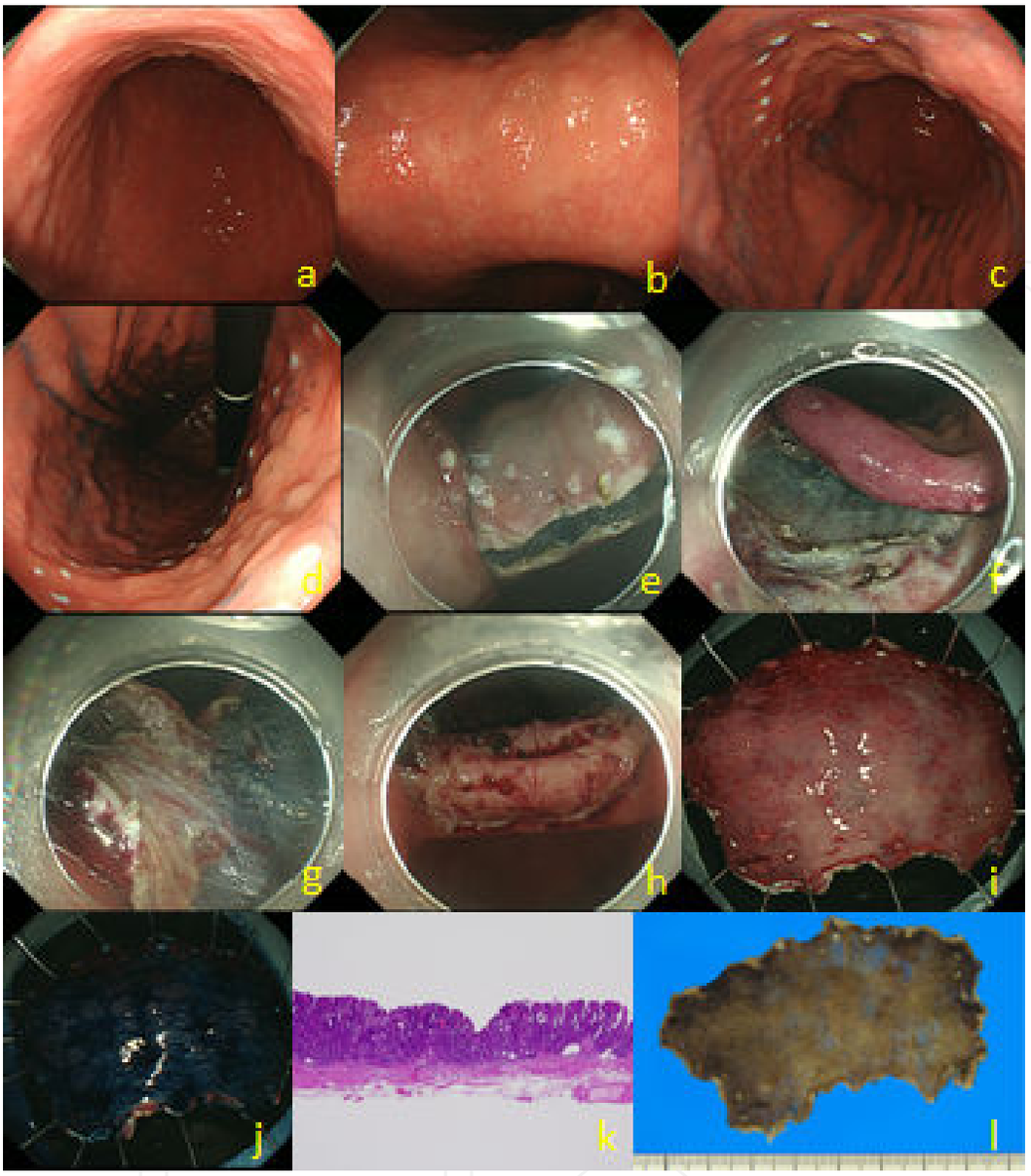

Figure 6. A case meet with extended criteria (20mm<). (a)(b) Conventional endoscopic view revealed 0- II a, located in the lower part of the stomach. (c)(d) After marking.(e)~(g) Mucosal incision and dissection.(h) Gastric ulcer after ESD.(i) Resected specimen.(j) Resected specimen after indigo carmine dye spraying.(k) (l) Histopathological assessment of the resected specimen. 0- II a, 75 × 45 mm, intramucosal carcinoma, well-differentiated type. Tumor size was 63 mm.

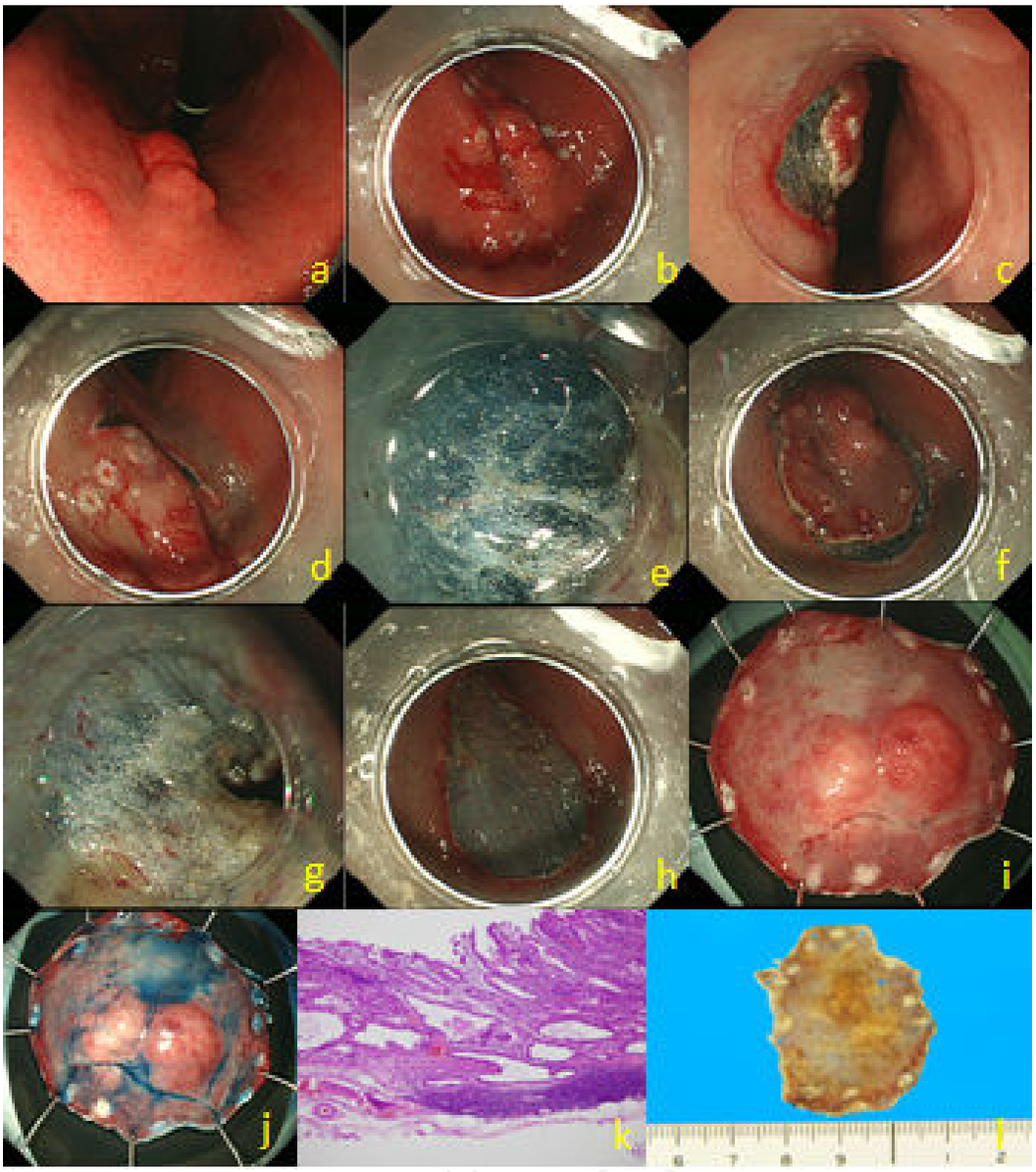

Figure 7. A case meet with extended criteria (sm invasion). (a) Conventional endoscopic view revealed 0-II a, located in the middle part of the stomach. (b) After marking.(c)~(g) Mucosal incision and dissection.(h) Gastric ulcer after ESD. (i) Resected specimen.(j) Resected specimen after indigo carmine dye spraying.(k) (l) Histopathological assessment of the resected specimen.0- II a, 35 × 32 mm, intramucosal carcinoma, well-differentiated type. Tumor size was 19 mm. One point with submucosal invasion is observed.

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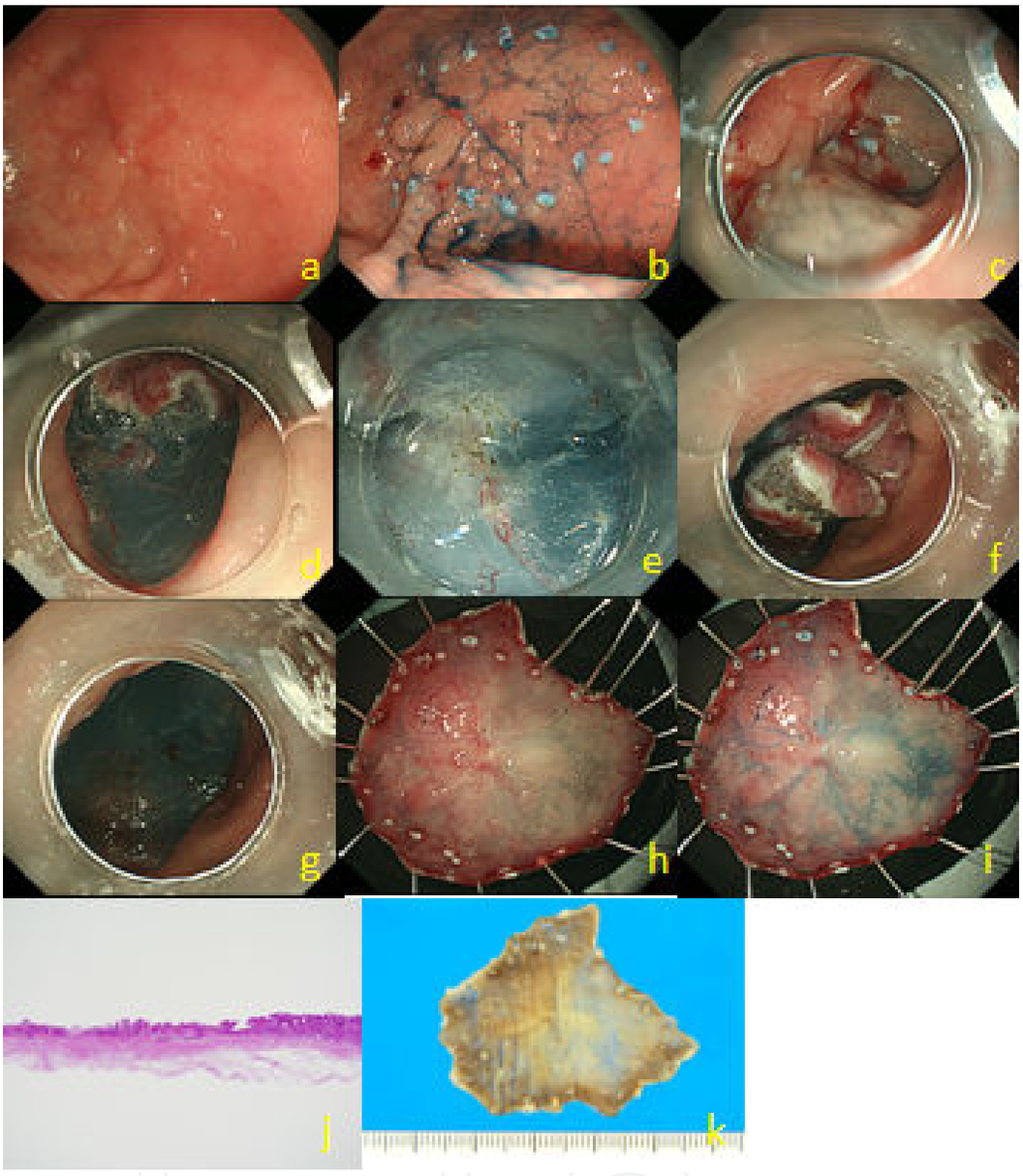

Figure 8. A case meet with extended criteria (UI+)(a) Conventional endoscopic view revealed 0- II c with ulcer finding, located in the lower part of the stomach. (b) After indigo carmine dye spraying and marking.(c)After injection of sodium hyaluronate. (d)~(f) Mucosal incision and dissection. Fibrosis was recognized.(g) Gastric ulcer after ESD.(h) Resected specimen.(i) Resected specimen after indigo carmine dye spraying.(k) (l) Histopathological assessment of the resected specimen.0-II a, 45 × 35 mm, intramucosal carcinoma, well-differentiated type. Tumor size was 30 mm.Considerable fibrosis was recognized under thelesion.

3. Results

3.1. Patient characteristics and short-term outcome

The demographic data of the patients is shown in Table 1. 72 patients were categorized as NEG (61 males, mean age: 59.4, range: 45-64) and 212 patients were EG (164 males, mean age: 73.5, range: 65-87), showing that major patients were elderly and male. Underlying disease was found as follows; liver cirrhosis in 2 and 3, chronic renal failure requiring hemodialysis in 0 and 4, diabetes in 3 and 13 in NEG and EG, respectively. Cancer was additionally found in the other parts of the body 3 and 16 cases in NEG and EG, respectively. Antithrombotic therapy was taken in 5 and 29 in NEG and EG.

	Total	**NEG**	**EG**	**p-value**
	(n=284)	(n=284)	(n=284)	
Age(years)	69.9	59.4	73.5	<0.0001
range	45~87	45~64	65~87	
Gender(male/female)	225/59	61/11	164/48	NS
Background				
Underlying disease				
Liver cirrhosis	5(1.8%)	2	3	NS
Hemodialysis	5(1.8%)	0	4	NS
Diabetes	16(5.6%)	3	13	NS
Double cancer	19(6.7%)	3	16	NS
Antithrombotic therapy	34(12%)	5	29	NS

Table 1. Patient characteristics

Clinical and histological data was shown in Table 2. Histopathologically, there were 66 cases of adnocarcinoma and 15 adenomas in NEG, and 250 adnocarcinoma cases and 21 adenomas in EG. Tumors were located less in the upper part of stomach. Tumor was confined to mucosa in most cases. The rate of the cases with ulceration was higher in EG. Tumor size was more than 20 mm in most cases. Gross type was many depressed and elevated type in most cases (Figure 9).

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	total	**NEG**	**EG**
	(n=352)	(n=81)	(n=271)
Histological type			
carcinoma	316	66	250
D/UD	313/3	64/2	249/1
adenoma	36	15	21
Tumor location			
U	61	17	44
M	131	35	96
L	160	29	131
Depth			
M	292	66	226
SM1	31	7	24
SM massive	29	8	21
Ulceration	61	18	43
Tumor size			
20mm≧	260	61	199
20mm<	92	20	72
Gross type			
Depressed	152	33	119
Flat	20	5	15
Elevated	180	43	137

Table 2. Clinical and histological data. D; differentiated carcinoma,UD; undifferentiated carcinoma

Short term outcomes are shown in Table 3. The mean size of the resected specimen was 36 mm in diameter (range: 10-60 mm) in NEG, and 35 mm in diameter (range: 12-110 mm) in EG (P=NS). The mean size of the tumor was 15 mm in diameter (range: 2-39 mm) in NEG, and 17 mm in diameter (range: 1-94 mm) in EG (P=NS). The en-bloc resection rates were 96.2% and 98.9% in NEG and EG, respectively (P=NS). The complete en-bloc resection rate were 90.1% and 89.7% in NEG and EG (P=NS). The curative resection rate were 81.4% and 87.8% in NEG and EG(P=NS).

	total	NEG	EG	p-value
	(n=352)	(n=81)	(n=271)	
Tumor size(mm)	16±11.6	15±8.3	17±12.4	NS
range	(1~94)	(2~39)	(1~94)	
resected specimen size(mm)	35±15.5	36±11.8	35±16.8	NS
range	(10~110)	(10~60)	(12~110)	NS
En block resection rate(%)	98.2(346/352)	96.2(73/81)	98.9(243/271)	NS
Complete en block resection rate(%)	89.7 (316/352)	90.1 (73/81)	89.7 (243/271)	NS
Curative resection rate(%)	86.36(304/352)	81.48(66/81)	87.82(238/271)	NS
Procedure time(min)	83.02	92.84	80.08	NS
Complication				
Perforation(%)	0.85(3/352)	1.23(1/81)	0.74(2/271)	NS
Postoperative bleeding(%)	1.42(5/352)	3.70(3/81)	0.74(2/271)	NS
Hospital days after ESD(day)	6.577(2~19)	6.432(2~14)	6.620(3~19)	NS

Table 3. Short term outcomes

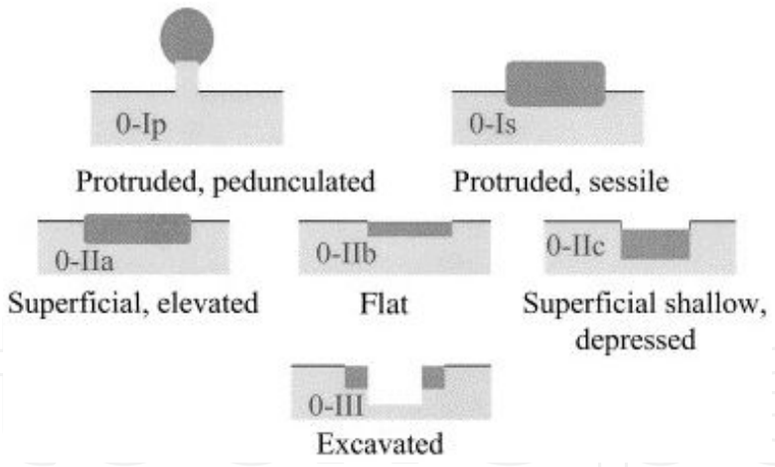

Figure 9. Schematic representation of the major variants of type 0 neoplastic lesions of the digestive tract.Schematic representation of the major variants of *type 0* neoplastic lesions of the digestive tract: polypoid*(Ip and Is)*, non-polypoid *(IIa, IIb, and II c)*, non-polypoid and excavated *(III)*. Terminology as proposed in a consensus macroscopic description of superficial neoplastic lesions

Of 15 cases that were judged as non-curative resection in NEG, 8 cases were additionally treated with surgical resection, while 7cases, including 1 adenoma, were followed up without surgical resection. In EG, of 33 cases judged as non-curative resection, 20 cases were additionally treated with surgical resection, while 13 cases, all adenocarcinoma, were followed up without surgical resection.

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The mean procedure time was 92 min in NEG and 80 min in EG (P=0.045). The hospital days after ESD was 6.4 days (range: 2-14) in NEG and 6.6 days (range: 3-19) in EG (P=NS). There were 4 cases of complications in NEG (1 cases of perforation and 3 cases of delayed bleeding), and 4 cases in EG (2 cases of perforation and 2 cases of delayed bleeding) (P=NS). All cases with perforation were managed and controlled conservatively.

3.2. Long-term outcomes

Four patients in NEG and 7 patients in EG died from irrelevant diseases during the follow up period. No patient in either group died from any associated complications of the endoscopic treatment or progression of gastric neoplasm. No cases of local recurrence or distant metastasis were observed during follow-up in each group. During the follow-up periods of median 843 days in NEG (range 14–1812 days) and 775 days in EG (range 6–1789 days), the 1–year overall survival rates were 100% and 99% in NEG and EG, respectively. The 3-year overall survival rates were 89% and 94% in NEG and EG, respectively (Figures 10,11, Table4).

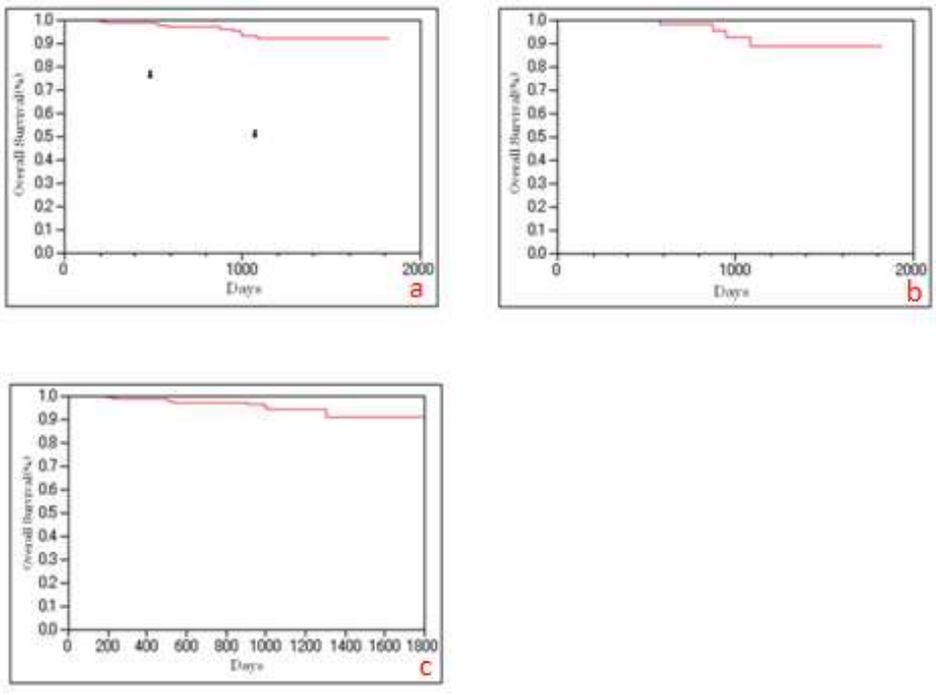

Figure 10. Overall survival (a) Overall survival(total), (b) Overall survival in NEG, (c) Overall Survival in EG

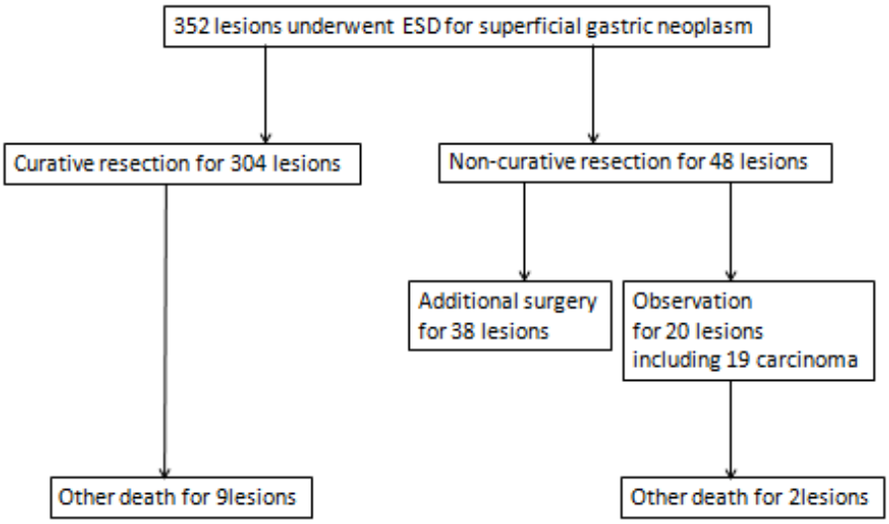

Figure 11. Flow diagram in this study

	total	NEG	EG	p-value
	(n=352)	(n=81)	(n=271)	
Madian follow-up	796.5	843	775	NS
Local recurrencerate(%)	0 (0/352)	0 (0/81)	0 (0/271)	NS
distant metastasis rate(%)	0 (0/352)	0 (0/81)	0 (0/271)	NS
the 1–year overall survival rates (%)	99	100	99	
the3–year overall survival rates (%)	92	89	94	

Table 4. Long term outcomes

3.3. Limitations

A single-center, retrospective analysis.

4. Discussion

It is a great advancement that ESD has been introduced into endoscopic therapy of early gastric cancer (EGC). However, in the present status, ESD requires difficult skills that can be obtained only after intensive training. With less trained skills, there is a high risk of hemorrhage, perforation, etc., which hampers the wide prevalence of this technique. Since it also takes a longer time to perform ESD than other endoscopic treatments, this method would be better regarded as an endoscopic surgery. In order to acquire complete curability by EMR, it

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is necessary to meet two conditions: "a tumor is resected in one piece without residual tumor" and "there is no metastasis." Introduction of ESD into the therapeutics for EGCs practically met the former condition. Therefore, the latter condition, the possibility of metastasis, is an important factor to determine the indication. At the present time, the possibility of lymph node metastasis is judged from pathological features of the primary lesion, and the indication is considered as standard for such lesions that have practically no probability of metastasis. However, there are many EGCs without metastasis even if lesions do not meet the ongoing criteria of indication for endoscopic therapy that has been described in the previous section. Indication of EMR could be extended if another index is established, that indicates the probability of lymph node metastasis more precisely. Introduction of molecular biological techniques or sentinel node navigation may bring about a new standard of determination of EGCs without metastasis that have not been predicted by conventional diagnostic methods. In the future, we would be able to extend the indication of EMR without impairing complete curability by establishing a reliable prediction factor on lymph node metastasis.

The criteria of indication of endoscopic therapy for EGCs described in this chapter has been set based on the data analyzing the outcomes of the therapeutic efforts for EGCs that have been done in Japan thus far. However, most reports, evaluating the risk of lymph node metastases, have been based on the pathological examinations of surgically resected specimens, which contain some problems. For example, surgical specimens were sectioned at 5 mm intervals to prepare pathological specimens in most cases. Therefore, there was a possibility that submucosal invasion might have been unrecognized between the sections examined. Micro metastases might be missed by routine pathological examinations of the surgically resected lymph nodes, which could influence the prognosis as reported.To evaluate the validity of endoscopic therapy of EGCs, particularly of ESD that enables extended indication, we need to verify it based on the follow-up data of long-term prognosis after the therapies. There are differences between Japanese and western classification systems used to define the pathology of early forms of GI cancers. These differences have made it difficult for western endoscopists to extrapolate the outcomes of EMR reported in Japanese studies to their own practices.Efforts are ongoing among pathologists to correlate the two classifications.

Early gastric cancer cases included in the indication of endoscopic resection are those with high surgical curability, and the achievement of an equivalent outcome by endoscopic treatment is an absolute requirement. However, ESD is frequently selected for elderly patients because surgery for them is high-risk[18]. Since our hospital is a specializedinstitution comprised of Cancer, Heart Disease, Stroke, and Emergency and Critical Care Centers, many elderly patients are at high-risk, and course observation without additional treatment is selected even after non-curable resection in many cases.

In many reports on the investigation of surgery for elderly gastric cancerpatients, the prevalence of preoperative complications was high. In our study, the prevalence of underlying diseases, such as those requiring hemodialysis, diabetes, and double cancers, and antithrombotic therapy was high in the elderly group, although no significant difference was detected.

However, the short- and long-termoutcomes were favorable, and no significant differences were noted between the 2 groups[18]. A significant difference was observed only in the treatment time, but it may have been due to the fact that trainees performed treatment under supervision by experts in many patients in the non-elderly group because they had no risk factor.

It would be beneficial for patients if this type of reliable endoscopic therapy that is less invasive than surgery would prevail. Thus, it is certainly warranted to develop and improve safer and more reliable maneuvers as well as to establish a training program to teach correct maneuvers. In addition, from the medico economical aspect, a new concept of endoscopic surgery should be taken into consideration so that the technique, labor and benefit to patients are recognized with an appropriate reimbursement.

5. Conclusion

On the basis of our results, ESD was safe and effective even in the elderly people. ESD is a feasible method for the treatment of superficial gastric neoplasm. The long-term outcomes following ESD are promising. This method has a potential to spread our indications and to reduce the need for surgery in patients with early gastric cancer.

Nomenclature (where applicable)-

Endoscopic submucosal dissection; ESD, endoscopic mucosal resection; EMR, elderly group; EG, non elderly group; NEG, World Health Organization; WHO, narrow band imaging; NBI, endoscopic ultrasonography; EUS, contrast-enhanced computed tomography; CECT, early gastric cancer; EGC, ulcerative findings; UL, submucosal; SM, early gastric cancer; EGC

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