

Gastric Cancer Caused by Adenoma: Predictive Factors Associated with Lesions Other Than the Expanded Indications

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Background/Aims: We aimed to investigate whether the current indications for curative endoscopic resection (ER) of gastric cancer (GC) can be applied to GC caused by adenoma. Additionally, we attempted to identify factors predictive of lesions subsequently found in addition to the expanded indications for ER. **Methods:** We retrospectively analyzed 342 patients diagnosed with GC caused by adenoma who underwent ER at a single tertiary center between February 2011 and December 2014. The gross whole tumor size was measured using the endoscopically resected specimen. The microscopic whole tumor size was measured using mapping paper. The estimated cancer size was calculated using the microscopic whole tumor size and the square root of the carcinoma component. **Results:** A gross whole tumor size ≥ 3 cm, carcinoma component $\geq 35\%$, and gross ulceration were predictive of lesions other than the expanded indications for ER. The overall rate of lymph node metastasis was 0.3% (1/327), which only occurred in one patient with a lesion other than the expanded indications (4.5%, 1/22). **Conclusions:** The current indications for curative ER in GC can be applied to GC caused by adenoma. In cases suspected of having lesions other than the expanded indications, patients should be cautiously selected for ER to reduce the risk of an inappropriate procedure. (**Gut Liver 2018;12:246-254**)

Key Words: Upper gastrointestinal track; Adenoma; Adenocarcinoma; Endoscopy

INTRODUCTION

Gastric adenoma is a premalignant lesion.¹ Although the risk of progression from adenoma to gastric cancer is relatively low,^{2,3} adenomas can progress to invasive carcinoma⁴ or even advanced gastric cancer.³ Endoscopic forceps biopsy is the gold standard for histological diagnosis of adenoma before endoscopic resection (ER). However, the histological discrepancy rate between the results of biopsy specimens and those obtained at ER was noted to be considerably high in recent studies.⁵⁻⁸ Reportedly, 6.4% to 30.1% of biopsy-diagnosed low-grade adenomas are finally diagnosed as high-grade ones and 3.8% to 11.0% as adenocarcinomas after ER.^{5,9} ER for early gastric cancer (EGC) is currently the established treatment of choice because it both minimally invasive and effective as a curative procedure for EGC.^{10,11} Recently, endoscopic submucosal dissection (ESD) has been developed to improve the *en bloc* resection rate over that of endoscopic mucosal resection (EMR).¹² ESD is performed for EGC lesions meeting the expanded indications for ER.^{13,14} Patients with EGC who undergo treatment based on the expanded indications have been reported to have similar long-term survival and outcomes to those treated according to the earlier absolute indications.¹⁵ However, if ER is performed and the lesion is subsequently found to be beyond the expanded indications, patients require additional treatment such as surgery. Thus, accurate prediction prior to ER of which EGC lesions will be found to be beyond the expanded indications could help physicians determine an appropriate treatment strategy and avoid unnecessary procedures. To the best of our knowledge, the criteria for evaluation of curative ER of gastric cancer arising from adenoma are rarely reported. Factors that might

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Received on March 16, 2017. Revised on September 2, 2017. Accepted on September 30, 2017. Published online February 8, 2018

pISSN 1976-2283 eISSN 2005-1212 <https://doi.org/10.5009/gnl17162>

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predict which lesions are actually beyond the expanded indications after ER are also rarely reported. This study was conducted to evaluate whether the current criteria for curative ER for EGC can be applied to gastric cancer arising from adenoma and to identify factors that can predict which lesions are beyond the expanded indications for ER.

MATERIALS AND METHODS

1. Patients

Between February 2011 and December 2014, 2,050 consecutive patients underwent ER for EGC at the Asan Medical Center, which is a tertiary academic center in Seoul, Korea. On reviewing the pathology report database, we found that 344 were diagnosed with gastric cancer arising from adenoma. After histological reanalysis, two patients were found to have *de novo* gastric cancer. We analyzed the medical records of the remaining 342 patients with gastric cancer arising from adenoma (Fig. 1). This study was approved by the Institutional Review Board of Asan Medical Center (IRB number: 2016-0825). Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. For full disclosure, the details of the study are published on the home page of Asan Medical Center, University of Ulsan College of Medicine.

2. Evaluation of endoscopic features

Endoscopic reports and photographs of the procedures were reviewed using electronic medical records for each patient, assessing morphological type, ulceration, and location of the lesions. Lesions with active ulceration or accompanying fibrous scarring were reported as ulcerated. Tumor location was categorized based on the longitudinal axis of the stomach: upper third, containing the fundus, cardia, and upper body; middle

third, containing the mid-body, lower body, and angle; and lower third, containing the antrum and pylorus.¹⁶ Macroscopic classification of tumors was as follows: type I (protruded), IIa (superficial elevated), IIb (flat), IIc (superficial depressed), and III (excavated).^{16,17}

3. Endoscopic procedures

Endoscopic procedures followed at our institution have been previously described.¹⁸ Briefly, for EMR, after we checked the lesion, saline solution containing epinephrine (0.01 mg/mL) mixed with indigo carmine was injected into the submucosal layer with a 23-gauge needle. The raised lesion was removed using an SD-9U-1 or SD-12U-1 snare (Olympus Co., Ltd., Tokyo, Japan) after circumferential mucosal incision. For ESD, the typical procedure involved marking, mucosal incision, and submucosal dissection with simultaneous hemostasis. After making several marking dots outside the lesion, saline solution containing epinephrine and indigo carmine was injected into the submucosal layer with a 23-gauge needle. A circumferential incision was made into the mucosa using a needle-knife (MTW Endoskopie Co., Ltd., Wesel, Germany) or insulated-tipped knife (Olympus Co., Ltd.). The submucosal layer was directly dissected with various knives until the lesion was completely removed. Hemostasis was achieved with hemoclips or hemostatic forceps (FD-410LR; Olympus Co., Ltd.) whenever bleeding or an exposed vessel was observed.

4. Histological analysis

The resected specimen was stretched, pinned to a polystyrene plate, and completely immersed in 10% neutral buffered formalin. After applying red, green, and yellow ink to the lateral resection margins and black ink to the deep resection margins, the entire specimen was sectioned into 2-mm thick slices parallel to an imaginary line drawn from the edge of the tumor to the closest resection margin (Fig. 2). Each sliced tissue specimen was

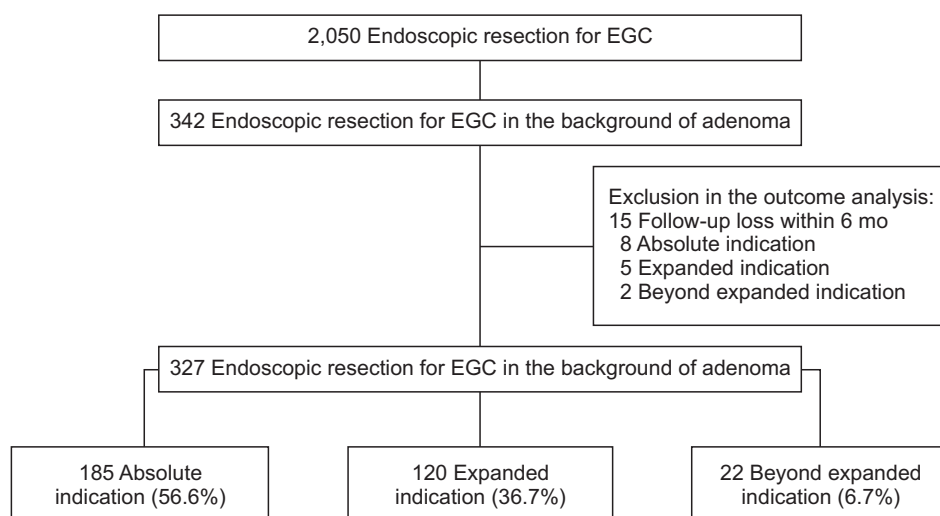


Fig. 1. Flow chart of patient enrollment. Median follow-up period was 24 months (interquartile range, 14.1 to 37). EGC, early gastric cancer.

embedded in paraffin, and 5- μ m sections were cut from each paraffin block and stained with hematoxylin and eosin (H&E). Each slide was then examined to determine the extent of tumor involvement. The borders of the tumors were indicated on mapping paper (Fig. 2). The carcinoma component was analyzed by histological examination according to the area of the entire tumor tissue occupied by adenocarcinoma. All lesions were classified as gastrointestinal epithelial neoplasia according to Vienna classification, i.e., low-grade adenoma/dysplasia as category 3, high-grade adenoma/dysplasia or noninvasive carcinoma as category 4, and intramucosal or submucosal carcinoma or beyond as category 5.¹⁹ The histological type of gastric cancer was classified according to the World Health Organization (WHO) classification.²⁰ The degree of differentiation was classified as differentiated (well or moderately differentiated adenocarcinoma or papillary adenocarcinoma) or undifferentiated (poorly differentiated adenocarcinoma, signet ring cell carcinoma, or mucinous cell carcinoma). Patients with adenomatous components at the margin of the carcinoma were defined as cancers arising from adenomas. Lymphovascular invasion was defined as observable spread of tumor cells into the lymphatic vessels (e.g., carcinoma cells floating within the endothelia-lined space). In order to confirm the lymphovascular invasion, most cases were deciphered using the H&E stain. Only in case where it was unsure whether it is an artifact or true vessel, immunohistochemical CD34 stain or monoclonal antibody D2-40 were used. Depth of invasion was categorized as lamina propria, muscularis mucosa, or submucosa.¹⁶ Submucosal invasion was classified into three layers: SM1 (penetration of <500 μ m into the submucosal layer from the muscularis mucosa), SM2 (penetration of 500 to 1,000 μ m), and SM3 (penetration of \geq 1,000 μ m).

5. Size measurement and calculation

Gross whole tumor size was measured using a ruler based on the dimensions of the endoscopically resected specimen. Microscopic whole tumor size was measured on mapping paper (Fig. 2).

Maximum diameter was used as the measure for tumor size. Estimated cancer size was calculated using the microscopic whole tumor size and square root of the carcinoma component.

Estimate the cancer size was calculated by following equation: microscopic whole tumor size (cm) $\times\sqrt{\text{carcinoma component (\%)/100}}$

6. Indications for ER

Estimated cancer size was the basis for determining whether ER was indicated. The absolute indications include differentiated elevated cancer of <2 cm in diameter and depressed cancer of <1 cm in diameter without ulceration.²¹ Expanded indications include differentiated mucosal cancer of >2 cm in diameter without ulceration, differentiated mucosal cancer of up to 3 cm in diameter with ulceration, undifferentiated mucosal cancer of up to 2 cm in diameter without ulceration, or a submucosal cancer not deeper than SM1 and <3 cm in diameter.²² ER was considered to have been performed beyond the expanded indications if any of the values for the expanded indications were exceeded.

7. Evaluation after ER

Curative resection was defined when all of the following conditions were met: final mapping results within the expanded indications, *en bloc* resection, negative horizontal and vertical margins, and absence of lymphatic invasion and venous

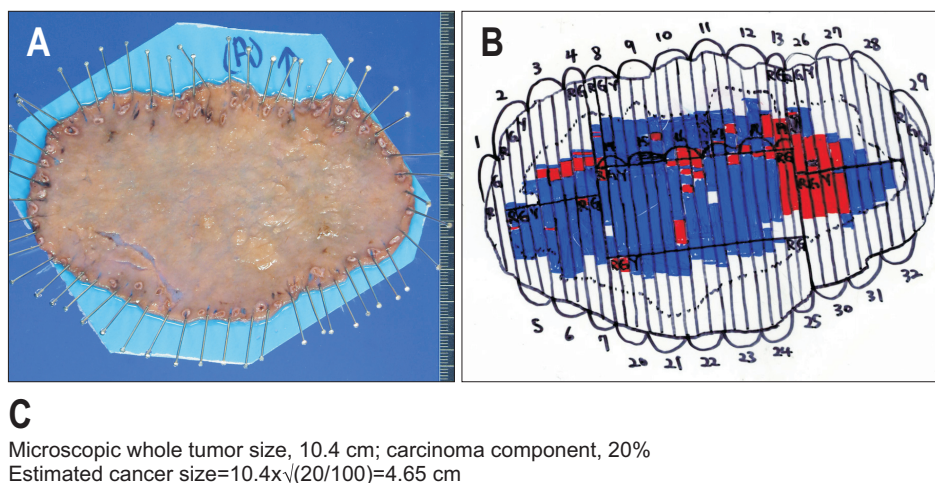


Fig. 2. Example of calculation of estimated cancer size. (A) The gross whole tumor size, which was measured using a ruler based on the dimension of the endoscopically resected specimen, was 12 cm. (B) Mapping paper showed cancer in the red area and adenoma in the blue area. The microscopic whole tumor size, which was measured using the mapping paper, was 10.4 cm. The carcinoma component, which was analyzed by a histological examination according to the area occupied by cancer within the whole tumor tissue, was 20%. (C) Example of calculation of estimated cancer size in this case. The estimated cancer size was 4.65 cm, and the degree of differentiation was the differentiated type (well-differentiated adenocarcinoma). The depth of invasion was submucosa. Thus, this case was classified as beyond absolute indication.

involvement.¹³ Evaluation for lymph node (LN) metastasis was based on pathological results from surgery or surveillance computed tomography (CT), looking for perigastric LNs. Pathology was available if patients underwent additional gastrectomy with lymphadenectomy after ER; otherwise, patients were followed up with endoscopic examination and abdominal CT. Both were performed every 6 months for the first 2 years, and then annually for the next 3 years. Patients were excluded from outcome analysis if they were seen for less than 6 months of follow-up.

8. Statistical analysis

The chi-square or Fisher exact test was used to assess relationships among categorical variables and t-test was used for non-categorical variables. Factors associated with ER performed beyond the expanded indications were analyzed using logistic regression analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the effect of variables. All tests of significance were two-tailed, and $p < 0.05$ indicated statistical significance. All statistical analyses were performed using SPSS, version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

1. Clinicopathological characteristics

A total of 342 patients (256 men; mean age, 64.6 ± 9.5 years) were enrolled. The mean gross whole tumor size was 2.6 ± 1.8 cm. The most predominant gastric location was the lower third (221/342, 64.6%). In resected specimens, mucosal layer invasion was confirmed in 313 cases (91.5%), SM1 invasion in 16 (4.7%), and SM2 invasion in 13 (3.8%). Most tumors were differentiated (336/342, 98.2%), with only six (1.8%) being undifferentiated (poorly differentiated adenocarcinoma or signet ring cell carcinoma). The mean carcinoma component was $31.9\% \pm 27.1\%$, and the mean estimated cancer size was 1.3 ± 1.0 cm. Indications for ER were considered to have been absolute in 193 cases (56.5%), expanded in 125 (36.5%), and beyond the expanded indications in 24 (7%). The baseline, pathological, and endoscopic characteristics are shown in Table 1.

2. Outcomes of ER based on the type of indication for curative resection in gastric cancer

Fifteen patients were lost to follow up, leaving 327 available for the outcome analysis (Fig. 1). The median follow-up duration was 24 months (interquartile range, 14.1 to 37 months). The curative resection rate was 92.7% overall, 100% (185/185) for lesions meeting the absolute indications, 98.3% (118/120) for lesions meeting the expanded indications, and 0% (0/22) for lesions beyond the expanded indications. Immediate surgery was performed in 54.2% patients (13/24) who had a non-curative resection, including one of the two with expanded indications and 12 of the 22 with lesions beyond the expanded indications. The 11 patients who did not undergo surgery were

Table 1. Baseline, Pathological, and Endoscopic Characteristics

Characteristic	Value
Age, yr	64.6±9.5
Sex	
Male	256 (74.9)
Female	86 (25.1)
Gross whole tumor size, cm	2.6±1.8
Location	
Upper third	34 (9.9)
Middle third	87 (25.4)
Lower third	221 (64.6)
Endoscopic type	
I	13 (3.8)
IIa	161 (47.1)
IIb	47 (13.7)
IIc	120 (35.1)
III	1 (0.3)
Gross ulceration	
Negative	316 (92.4)
Positive	26 (7.6)
Initial forceps biopsy result	
LGD	126 (36.8)
HGD	117 (34.2)
WD	88 (25.7)
MD	11 (3.2)
Invasion layer	
M2	257 (75.1)
M3	56 (16.4)
SM1	16 (4.7)
SM2	13 (3.8)
Differentiation	
WD	301 (88.0)
MD	35 (10.2)
PD/SRC	6 (1.8)
LVI	
Negative	336 (98.2)
Positive	6 (1.8)
Microscopic whole tumor size, cm	2.6±1.8
Carcinoma component, %	31.9±27.1
Estimated cancer size, cm	1.3±1.0
Indication after endoscopic resection	
Absolute	193 (56.5)
Expanded	125 (36.5)
Beyond expanded	24 (7.0)

Data are presented as mean±SD or number (%).

LGD, low-grade dysplasia; HGD, high-grade dysplasia; WD, well differentiated; MD, moderately differentiated; M2, lamina propria; M3, muscularis mucosa; SM1, submucosal 1 layer; SM2, submucosal 2 layer; PD, poorly differentiated; SRC, signet ring cell; LVI, lymphovascular invasion.

carefully followed up. Surgery was not performed in those cases because of severe comorbid illness, patient reluctance, or physician opinion. LN metastasis was found in only one patient; the overall rate of LN metastasis was 0.3% (1/327); 0% (0/185) in the absolute group, 0% (0/118) in the expanded group, and 4.5% (1/22) in the beyond the expanded group (Table 2).

Table 2. Outcomes of Endoscopic Resection According to Indications for Endoscopic Resection

	Absolute (n=185)	Expanded (n=120)	Beyond expanded (n=22)
Curative resection	185 (100)	118 (98.3)	0
Non-curative resection	0	2 (1.7)	22 (100)
Management of non-curative lesion			
Immediate surgery	0	1	12
Follow-up with surveillance CT	0	1	10
LN metastasis	0	0	1 (4.5)
LN metastasis (surgery group)	0	0	1
LN metastasis on CT (non-surgery group)	0	0	0

Data are presented as number (%) or number. CT, computed tomography; LN, lymph node.

Table 3. Baseline, Pathological, and Endoscopic Characteristics According to Indications after Endoscopic Resection in Patients Diagnosed with Adenomas Based on Forceps Biopsy

Clinicopathological feature	Absolute or expanded indications (n=227)	Beyond expanded indications (n=16)	p-value
Age, yr	65.1±9.1	66.0±8.6	0.71
Sex			0.25
Male	170 (74.9)	14 (87.5)	
Female	57 (25.1)	2 (12.5)	
Location			0.41
Upper third	26 (11.5)	3 (18.8)	
Middle third	58 (25.6)	2 (12.5)	
Lower third	143 (63.0)	11 (68.8)	
Endoscopic type			0.51
I	8 (3.5)	2 (12.5)	
IIa	115 (50.7)	8 (50)	
IIb	29 (12.8)	2 (12.5)	
IIc	74 (32.6)	4 (25)	
III	1 (0.4)	0	
Gross ulceration			0.05
Negative	213 (93.8)	13 (81.3)	
Positive	14 (6.2)	3 (18.8)	

Data are presented as mean±SD or number (%).

Table 4. Univariate and Multivariate Analyses of Clinicopathological Parameters Associated with Lesions Other Than the Expanded Indications in Patients Diagnosed with Adenomas Based on Forceps Biopsy

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Gross whole tumor size, cm				
<3 (n=147)	1		1	
≥3 (n=96)	2.7 (0.9–7.7)	0.06	4.4 (1.3–14)	<0.05
Initial forceps biopsy result				
LGD (n=126)	1			
HGD (n=117)	1.1 (0.3–2.9)	0.87		
Invasion layer				
Mucosa (n=221)	1			
SM (n=22)	104.9 (25.3–434.8)	<0.05		
Carcinoma component, %				
<35 (n=159)	1		1	
≥35 (n=84)	6.4 (2–20.7)	<0.05	8.1 (2.4–27.5)	<0.05
Estimated cancer size, cm				
<1.5 (n=172)	1			
≥1.5 (n=71)	6.1 (2–18.3)	<0.05		
Gross ulceration				
Negative (n=226)	1		1	
Positive (n=17)	3.5 (0.8–13.7)	0.07	4.2 (0.9–18.9)	0.058

OR, odds ratio; CI, confidence interval; LGD, low-grade dysplasia; HGD, high-grade dysplasia; SM, submucosa.

3. Comparison analysis between indications for ER (absolute or expanded vs beyond the expanded indications) in patients diagnosed as adenomas based on forceps biopsy

A total of 243 patients were diagnosed as adenomas with pre-procedural forceps biopsy. Among them, 16 patients were diagnosed as having lesions beyond expanded indications after ER. Gross whole tumor size, microscopic whole tumor size, estimated cancer size and carcinoma component were significantly larger in lesions beyond the expanded indications; submucosal invasion and gross ulceration were also more frequent (Table 3). By univariate analysis submucosal invasion, carcinoma component of $\geq 35\%$, estimated cancer size of ≥ 1.5 cm were significantly associated with lesions that were beyond the expanded indications (Table 4). By multivariate analysis, the following variables were independently associated with lesions beyond the expanded indications: gross whole tumor size of ≥ 3 cm (OR, 4.4; 95% CI, 1.3 to 14; $p < 0.05$), and carcinoma component of $\geq 35\%$ (OR, 8.1; 95% CI, 2.4 to 27.5; $p < 0.05$). Presence of gross ulceration was marginally significant (OR, 4.2; 95% CI, 0.95 to 18.9; $p = 0.058$) (Table 4).

DISCUSSION

Small *de novo* colorectal cancer, defined as tumors that have no demonstrable *in situ* (adenomatous) component, are reportedly more aggressive than conventional adenocarcinomas that develop from well-defined adenomatous precursor lesions.²³⁻²⁵ Analogously, gastric carcinoma arising from adenoma may be biologically different from *de novo* gastric cancer. However, to the best of our knowledge, clinical and biological features of gastric cancer arising from adenoma have rarely been reported. We conducted this study to evaluate whether the current criteria for curative resection of gastric cancer can be applied to gastric cancer arising from adenoma and to identify factors that can predict which lesions are beyond the expanded indications for ER. Previously reported rates of LN metastasis in cases where ER was performed beyond the expanded indications are as follows: (1) 3.0% (7/230) for >3 cm, predominantly differentiated, pT1a, and ulcerated lesions; (2) 2.6% (2/78) for >3 cm, predominantly differentiated, and pT1b (SM1) lesions; (3) 2.8% (6/214) for >2 cm, predominantly undifferentiated, pT1a, and non-ulcerated lesions; (4) 5.1% (52/1014) for predominantly undifferentiated, pT1a, and ulcerated lesions; and (5) 10.6% (9/85) for predominantly undifferentiated and pT1b (SM1) lesions.^{13,14,26} In this study, patients with gastric cancer arising from adenoma and considered suitable for ER by the absolute and expanded indications were believed to have a negligible risk of LN metastasis, and in fact, none of them did (Table 2). The LN metastasis rate of 4.5% in patients with lesions beyond the expanded indications was similar to that reported in previously published

data.^{14,26} Therefore, our results suggest that the current indications for curative resection of gastric cancer can also be applied to gastric cancer arising from adenoma.

Non-curative ER because of errors in preoperative diagnosis is an inevitable consequence of the fact that evaluations based on endoscopy, endoscopic ultrasonography (EUS), and even diagnostic biopsies before the procedure are not always accurate.^{27,28}

The discrepancy rates between forceps biopsy samples and post-resected specimens ranged from 20% to 40% in previous reports.²⁹⁻³² Discrepancies occur because the amount of tissue obtained by forceps biopsy is too small to represent the histology of the entire tumor lesions.³³ In this study, endoscopies and forceps biopsies were performed on a total of 233 patients (68.1%) at the Asan Medical Center prior to the ER. Since results of endoscopies conducted at other hospitals were missing, the numbers of forceps biopsies of 41 patients were unknown. Analyzing the remaining 301 patients, the mean frequencies of forceps biopsy in concordance group were 3 and the mean frequencies of forceps biopsy in discrepancy group were 2.7. But the frequencies of forceps biopsy between two groups did not show significant difference.

Mandai and Yasuda³⁴ measured the invasion depth of EGC using EUS. Among the 280 cases considered to have mucosal/SM1 cancer based on EUS findings, 20 (7.1%) had SM2 cancer. Of the tumors thought to be differentiated adenocarcinoma, 1.5% to 8.0% turn out to be undifferentiated after ESD.^{35,36} Histological discrepancy between pre- and post-ESD specimens can be attributed to inter- and intraobserver variability as well as to the fact that gastric cancer can have histological heterogeneity (containing both differentiated and undifferentiated areas).^{37,38} For these reasons, ESD has been recommended as a diagnostic tool for gastric lesions in cases where there is a discrepancy between the forceps biopsy pathology and endoscopic findings.³⁹

Despite the diagnostic effectiveness and safety of ESD, there is a low incidence of adverse events with endoscopic procedures. A multicenter study⁴⁰ showed that the incidences of post-ESD bleeding, perforation and serious adverse event were 5.5%, 4.7%, and 0.43%, respectively. Longer procedure times have been associated with an increased risk of adverse events,^{41,42} and tumor location and size may affect ESD procedure time.⁴³⁻⁴⁵ Although determining if the indications for curative ER have been met is difficult, accurate preoperative prediction of which EGC is beyond the expanded indications is very important to reduce the risks associated with an unnecessary procedure. Yamada *et al.*⁴⁶ described three risk factors for submucosal and lymphovascular invasion in ESD specimens of EGC: a dominant histology of moderately differentiated or papillary adenocarcinoma, non-flat gross morphology, and tumor size of ≥ 1.5 cm. In another study, SM2 invasion was correlated on multivariate analysis with tumor size, ulceration, undifferentiated histology, gross type, and tumor location.⁴⁷ We found several factors predictive of gastric carcinoma arising from adenoma being beyond the expanded

indications for ER.

Gross whole tumor size of ≥ 3 cm (OR, 4.4; 95% CI, 1.3 to 14; $p < 0.05$) and carcinoma component of $\geq 35\%$ (OR, 8.1; 95% CI, 2.4 to 27.5; $p < 0.05$) were independently associated with lesions that were beyond the expanded indications and gross ulceration (OR, 4.2; 95% CI, 0.95 to 18.9; $p = 0.058$) showed marginally significant association. Therefore, in cases suspicious of being beyond the expanded indications, very careful selection of the patients for ER is needed to reduce the risk associated with an unnecessary procedure.

There are several limitations to our study. First, this was a single-center retrospective study. Second, we defined the absence of LN metastasis radiologically in most patients, as pathology was unavailable for those not undergoing surgery. Considering the approximately 90% negative predictive value of stomach protocol CT,⁴⁸ it is possible that some patients with normal CT findings at 12 months of follow-up had LN metastasis that went undetected. Third, the carcinoma component is not a pre-procedure clinicopathological parameter. The endoscopic features suggesting the presence of carcinomatous foci in gastric adenoma, as reported by Kasuga *et al.*⁴⁹ include a lesion size of > 20 mm and central-depressed appearance. Further, Ko *et al.*³³ reported that surface redness seen on endoscopy suggested an underestimation on forceps biopsy. Although the carcinoma component is a post-procedure parameter, the aforementioned endoscopic findings suggest the presence of a carcinomatous component in gastric adenoma. For validation that such findings are predictive of carcinoma component before ER, further study is needed on the endoscopic appearance compared with subsequent findings on pathology (Fig. 2). Fourth, the calculation method to estimate the cancer size suggested in this research is under the hypothesis that the tumor is round. If it is hypothesized that the shape of the adenoma is oval, then the estimated cancer size using the calculation method suggested in this study overestimate the cancer size. However, most cancers are distributed in a mosaic pattern thus it is impossible to calculate the exact extent, as shown in the case (Fig. 2). Therefore, the size discrepancy can be considered as a limitation of this study.

Despite these limitations, our study is the first regarding EGC arising from adenoma. Our results suggest several clinicopathological characteristics predicting that the lesion is beyond the expanded indications for ER. The rate of standardized follow-up in our series was high (95.6%, 327/342), and the endoscopic procedures and pathology examinations were performed according to a standard protocol.

In this study, the LN metastasis rate was 0% (0/185) in the absolute indications, 0% (0/118) in the expanded indications, and 4.5% (1/22) in beyond the expanded indications. Therefore, the current indications for curative ER of gastric cancer can be applied to gastric cancer arising from adenoma. Gross whole tumor size of ≥ 3 cm and carcinoma component of $\geq 35\%$ were

independently associated with lesions that were beyond the expanded indications and gross ulceration showed marginally significant association. Accordingly, in cases with these clinicopathological parameters, cautious selection of patients for ER is needed to reduce the risk of an inappropriate procedure.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

Author contributions: K.D.C. designed and supervised the research; S.H.P. and K.D.C. reviewed medical records and analyzed the data; S.H.P. and Y.P. reviewed pathology; S.H.P., K.J., S.L., E.J.G., H.K.N. collected data; S.H.P., J.Y.A., K.W.J., J.H.L., D.H.K., H.J.S., G.H.L. interpreted data; H.Y.J. reviewed and supervised study concept.

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