Pathologic Validation of Endoscopic Ablative Therapy for Gastric Epithelial Neoplasia: A Randomized Controlled Trial

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ABSTRACT

Background: *The effectiveness of endoscopic ablative therapy such as monopolar coagulation (MC) or argon plasma coagulation (APC) have not been validated histologically. The aim of this study was the histologic validation of endoscopic ablative therapy for gastric epithelial neoplasia.*

Methods: *We designed a prospective randomized controlled trial involving patients with gastric low-grade dysplasia. Patients were randomly assigned to either the APC or the MC group. Endoscopic ablative therapy was followed by endoscopic submucosal dissection (ESD) for histologic evaluation. The main outcome was histologic completeness of endoscopic ablative therapy.*

Results: *Sixty-eight patients were recruited, of whom 34 patients underwent APC and 34 patients underwent MC followed by ESD. The APC group showed significantly higher complete eradication rate compared to the MC group (55.9% vs. 11.8%, P < .001). APC was the only significant predictor of histologic complete eradication in multivariate analysis (OR: 7.66; 95% CI: 2.139-27.448). No adverse events related to the procedure occurred in either group.*

Conclusions: *Although APC is a more effective treatment option than MC in the management of gastric epithelial neoplasia, the effectiveness of both methods was limited in eradicating gastric epithelial neoplasia completely. Therefore, endoscopic resection should be a first option for treatment of gastric epithelial neoplasia until the optimal method is established with further studies.*

Keywords: *Gastric epithelial neoplasia, monopolar coagulation, argon plasma coagulation, endoscopic resection*

INTRODUCTION

Endoscopic ablative therapy, such as argon plasma coagulation (APC) and monopolar coagulation (MC), is widely used not only for hemostasis, but also for eradication of gastric epithelial neoplasia.[1-4] It causes tissue damage of limited depth that can result in complete ablation of superficial layers while minimizing the risk of perforation.[3-5] APC is a method of non-contact electrocoagulation that transfers high-frequency electric current through ionized argon gas to the lesion.[6] On the other hand, MC is a method of direct-contact electrocoagulation that transfers electric current to the lesion directly.[7]

Among gastric epithelial neoplastic lesions, gastric adenoma or dysplasia is a precancerous lesion. The Vienna classification divides gastric adenomas into 2 groups: high-grade dysplasia (HGD) and low-grade dysplasia (LGD).[8] Generally, endoscopic resection is performed for adenoma with HGD due to its coexistence and potential of progression to carcinomas.[9] However, treatments for adenomas with LGD remain controversial. Patients with LGD have been reported with low risk of progression to carcinoma. On the other hand, considering marked histologic discrepancies between forceps biopsy and specimens obtained after endoscopic resection, others insist on endoscopic resection for this lesion.[10]

Endoscopic resection, including endoscopic submucosal dissection (ESD), is technically difficult. Compared to endoscopic resection, endoscopic ablative therapy can be performed with low rates of complications by less experienced endoscopists. Several studies have reported that endoscopic ablative therapy, especially APC, is safe and effective for treatment of gastric epithelial neoplasia in patients with comorbidities or high risk of complications.[11-16] However, it has been applied to limited patients

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due to the difficulty in predicting depth of invasion and its inability to contribute to pathologic evaluation. Furthermore, these studies examined the effectiveness of endoscopic ablative therapy by recurrence rates after long-term follow-up in a retrospective cohort, instead of histologic validation. Therefore, the aim of this study was histologic validation of endoscopic ablative therapy for gastric epithelial neoplasia.

MATERIALS AND METHODS

Study Design and Patients

This study was a prospective randomized controlled trial involving patients who underwent endoscopic ablative therapy followed by ESD from August 2015 to December 2018 at a tertiary referral center in Korea. Patients older than 18 years who were diagnosed as gastric LGD were included. To minimize histologic discrepancy, we only enrolled patients diagnosed with forceps biopsy-proven LGD at our hospital by an experienced gastrointestinal pathologist. Lesions with high risk of discrepancies, such as large size (>2.0 cm in long diameter), color change, and/or depressed lesions were excluded.[17,18] HGD or carcinoma were also excluded to avoid inappropriate pathologic evaluation of submucosal invasion and/or lymphovascular invasion. Patients with coagulopathy, pregnancy, or inability to provide informed consent were excluded. Patients who showed hypersensitivity to proton pump inhibitor were also excluded. Written informed consents from the patients were obtained before the procedure. Randomization was performed when a lesion eligible for enrollment was confirmed after histologic confirmation of endoscopic forceps biopsy. Random sequence was generated by a statistical advisor and was concealed in an envelope. If a patient was eligible based on the inclusion criteria, the envelope was opened, and the endoscopist was informed of the method to be used for endoscopic ablative therapy.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of the Ethics Committee of Incheon St. Mary's Hospital, The Catholic University of Korea before initiating this study (approval number: OC15TISI0052). This trial was registered with the Primary Registries of the WHO Registry Network Platform (Clinical Research Information Service, CRiS, No. KCT0001587, https://cris.nih.go.kr/cris/index.jsp). All authors reviewed the study data and approved the final version of manuscript.

MAIN POINTS

- *Endoscopic ablative therapy is widely used for eradication of gastric epithelial neoplasia.*
- *Neither argon plasma coagulation nor monopolar coagulation was adequate to eradicate gastric epithelial neoplasia completely.*
- *Endoscopic resection should be the first option for treatment of gastric epithelial neoplasia.*

Endoscopic Ablative Therapy Protocol

All endoscopic procedures were performed under conscious sedation using midazolam (0.05 mg/kg) and meperidine (25-50 mg). All lesions were meticulously examined by white-light endoscopy followed by narrow-band imaging. To identify tumor shape and margin, the lesions were observed after spraying acetic acid (1.5%) and indigo carmine (0.2%). Lesion size was estimated using the opening width of the biopsy forceps (FB-230K; Olympus, Tokyo, Japan). If the lesion size was eligible for the study (≤2.0 cm), endoscopic ablative therapy was performed by using 1 of 2 randomized methods. All lesions were removed by ESD after endoscopic ablative therapy by an experienced GI endoscopist (B.W.K.). The electrocoagulation protocol was as follows (Figure 1 and 2): (1) marking dots were made 5 mm beyond the tumor margin with APC; (2) a mixture of diluted epinephrine (1 : 200 000) and normal saline was injected into submucosal layer; (3) after injection, an initial incision was made outside the marks with a hook knife (KD-620LR; Olympus, Tokyo, Japan) and the hook knife was then inserted into the initial incision and electrosurgical current was applied using an electrosurgical unit (VIO300D; ENDO CUT I mode, effect 2; ERBE, Tübingen, Germany), to complete circumferential mucosal incision around the lesion; (4) prior to endoscopic ablative therapy, the area around the lesion to be cauterized was additionally marked using APC; (5) the region inside the designated area was evenly ablated with APC probe (2200A; ERBE, Tübingen, Germany) or Coagrasper (FD-410LR; Olympus, Tokyo, Japan); and (6) the submucosal layer was dissected using a hook knife. There was no particular difference between the usual ESD method and ESD after ablation therapy. After removal, intravenous proton pump inhibitor was administered for 2 days followed by oral administration of proton pump inhibitors for 4 weeks.

The mode of APC was argon gas at flow rate of 2.0 L/min pulsed coagulation mode. Power was set at 80W (VIO 300D; ERBE, Tübingen, Germany). APC was performed

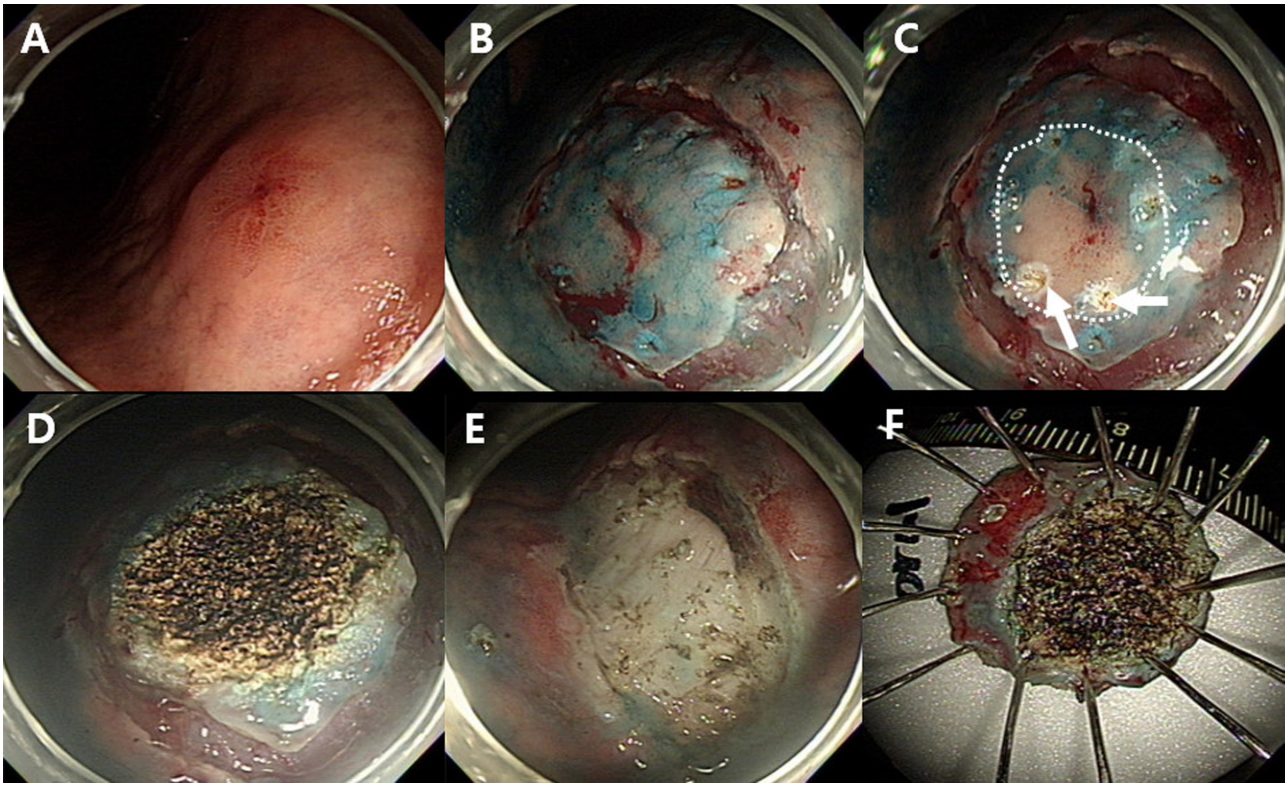

Figure 1. Argon plasma coagulation (APC) protocol. A, Lesion observed with white-light endoscopy. B, Circumferential mucosal incision after submucosal injection. C, Additional marking (white arrow) for area around lesion to be cauterized (white dot circle). D, After electrocoagulation with APC. E, Resected site after submucosal dissection. F, Resected specimen after submucosal dissection

with straight-type probe 3-5 mm from the lesion surface. The mode of MC was soft coagulation mode and the power was set at 80W (VIO 300D; ERBE, Tübingen, Germany). MC was performed with the Coagrasper having direct contact with the lesion surface. In our study, the electrical current was set at 80 W in both groups. According to the previous study, we tried to transfer energy of 1600 J/cm^2 of the lesion.[19] Therefore, coagulation time was determined by transferring 1600 J of energy per cm^2 of the lesion. For example, if the tumor area was 1 cm^2, coagulation time was determined to be 20 seconds (80 W × 20 seconds = 1600 J). The tumor area was assumed to have an oval shape and its area was calculated.

Histologic Examination of Thermal Lesions Made by Endoscopic Ablative Therapy: Endoscopically resected specimens were extended on a polystyrene board with pins and fixed in 10% formalin immediately. Specimens were embedded in paraffin and stained with hematoxylin and eosin for microscopic evaluation. The histologic complete eradication and depth of tissue necrosis were assessed by an experienced gastrointestinal pathologist (J.K.) who was blinded to the clinical information of the patient. Tissue necrosis was defined as complete destruction of microscopic structures. Histologic complete eradication was defined as no residual adenomatous tissues visible in the resected specimen.

Outcome

The primary outcome measured was complete histologic eradication rate after endoscopic ablative therapy using the 2 methods. The secondary outcomes measured were maximal depth of tissue necrosis and rate of adverse events, including bleeding and perforation.

Sample Size Calculation

A previous study has revealed that local recurrence rate after APC is 3.8% (14). Therefore, we assumed that the complete eradication rate after APC was 96.2% and that MC would not be inferior to APC in terms of complete

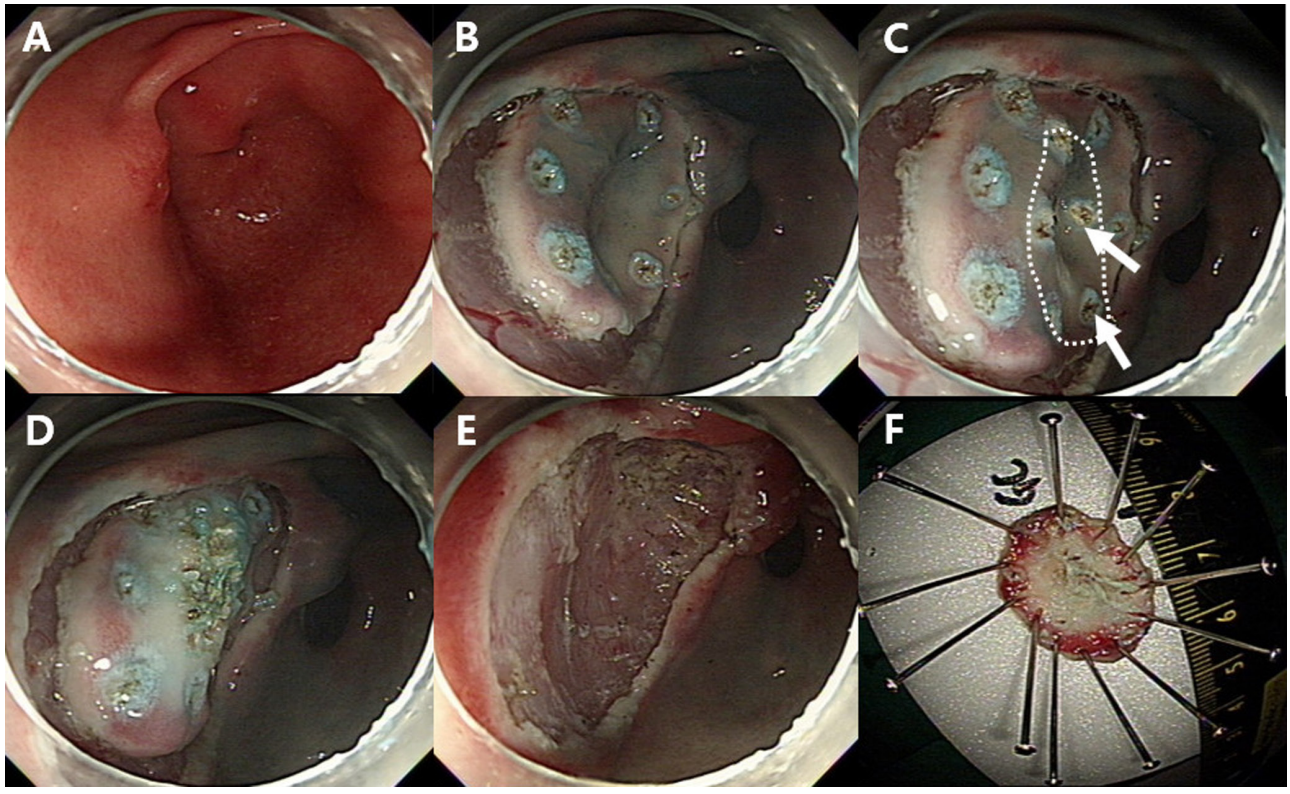

Figure 2. Monopolar coagulation (MC) protocol. A, Lesion observed with white-light endoscopy. B, Circumferential mucosal incision after submucosal injection. C, Additional marking (white arrow) for area around lesion to be cauterized (white dot circle). D, After electrocoagulation with Coagrasper. E, Resected site after submucosal dissection. F, Resected specimen after submucosal dissection.

eradication rate, with a noninferiority margin of –10%. With an α value of 0.05 and power of 80%, the estimated sample size of lesions was 68.

Statistical Analysis

Inter-group comparisons of clinical characteristics were conducted using the chi-square or Fisher's exact test for categorical variables and the Student's *t*-test for continuous variables. Logistic regression analysis was used to verify significant factors associated with histologic complete eradication. Statistical significance was set at $P < .05$. All statistical analyses were performed using SPSS version 20.0 for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

Baseline Characteristics

A total of 207 patients were screened. Of them, 68 patients satisfied the inclusion criteria. They were randomly assigned to the APC group (n = 34) or the MC group (n = 34) (Figure 3). The mean age of these patients was 66.2 ± 9.0 years. Of these 68 patients, 45 (66.2%) were males. The mean long diameter and tumor area were 1.4 cm and 1.3 cm^2, respectively. The mean total energy amount was 1605.3 J/cm^2. There were no significant differences in baseline characteristics between the 2 groups (Table 1).

Outcomes

The overall complete eradication rate was 33.8% (23/68) histologically. There was no lateral margin positive case in both the APC and MC groups. The APC group showed significantly higher complete eradication rate compared to the MC group (55.9% vs. 11.8%, $P < .001$). Regarding the depth of tissue necrosis, it was deeper in the APC group than in the MC group. Of 45 incomplete histologic eradication cases, all residual tissues were LGD except one. All the residual lesions after endoscopic ablative therapy were removed histologically by endoscopic resection. No immediate or delayed adverse event such as bleeding or perforation occurred in either group (Table 2). Figure 4 shows the representative histology images in both groups.

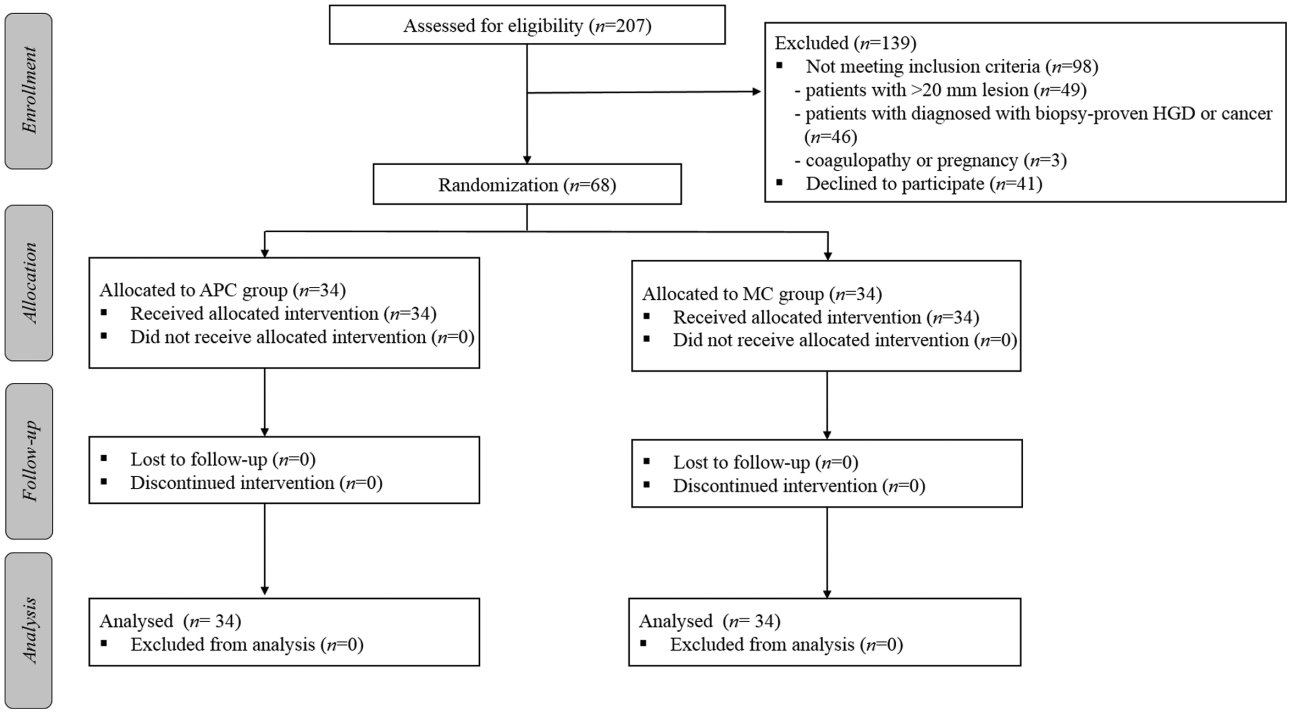

Figure 3. Study flow. APC, argon plasma coagulation; HGD, high-grade dysplasia; LGD, low-grade dysplasia; MC, monopolar coagulation.

Predictors of Histologic Complete Eradication

Univariate analysis revealed that tumor area and method of endoscopic ablative therapy were related to histologic complete eradication. Age, sex, tumor location, macroscopic finding, lesion lifting, or total energy amount were not related to histologic complete eradication (Table 3). In multivariate analysis, the endoscopic ablative therapy method (APC) was identified as a significant independent predictor of histological complete eradication (odds ratio [OR] = 7.66, 95% CI, 2.14-27.45; P = .002) (Table 4).

DISCUSSION

Although APC was more effective than MC for ablating gastric LGD, both APC and MC showed disappointing results in histologic complete eradication in this study (55.9% vs. 11.8%, $P < .001$). It is plausible that APC is superior compared to MC, since the tip of the APC device is sharper than that of the MC device. So, the APC device allows a more even delivery of energy than the MC device. To the best our knowledge, this is the first study to validate histological complete eradication of endoscopic ablative therapy for gastric epithelial neoplasia. Our study also has several strengths methodologically. First, this study involved a sufficient number of adenoma lesions and was designed in a prospective, randomized, controlled manner. Second, based on previous studies, we delivered the most effective and sufficient energy to the lesion. Third, to minimize selection bias, we enrolled only patients with histologically proven gastric LGD, confirmed by an experienced gastrointestinal pathologist at our hospital.

Endoscopic ablative therapy has fewer complications, shorter hospitalization, and shorter procedure time compared to endoscopic resection for treatment of gastric epithelial neoplasia.[11,14] Endoscopic ablative therapy is also effective as a rescue therapy for residual gastric epithelial neoplasia after incomplete endoscopic resection.[12] The most advantageous aspect of endoscopic ablative therapy is its familiarity in the endoscopy unit. Most endoscopists can easily use this equipment in most situations. In particular, MC is more convenient than APC, since there is no need to change the generator or for additional argon gas. Several studies have shown that endoscopic ablative therapy, especially APC, is an effective and safe alternative treatment option for gastric epithelial neoplasia.[11-16] Previous reports indicated that the local recurrence rate was 3.8-15.3% after APC in early gastric cancer or in gastric adenoma.[13-16,20-22] The significant variations in recurrence rate among the studies might result from the different inclusion criteria and various electrocoagulation protocols (e.g., electrical current setting, coagulation time, etc.), and different follow-up periods. In addition,

Table 1. Baseline Characteristics of Patients

	Total (n = 68)	APC (n = 34)	MC (n = 34)	*P*
Age	66.2 ± 9.0	68.1 ± 8.8	64.2 ± 8.9	.075
Sex				.304
Male (n, %)	45 (66.2)	21 (61.8)	24 (70.6)	
Female (n, %)	23 (33.8)	13 (38.2)	10 (29.4)	
Tumor size (cm)	1.4 ± 0.4	1.4 ± 0.4	1.5 ± 0.3	.062
Tumor area (cm^2)	1.3 ± 0.5	1.2 ± 0.6	1.3 ± 0.4	.219
Vertical location or tumor (n, %)				.327
Upper/middle	29 (42.6)	17 (50.0)	12 (35.3)	
Lower	39 (57.4)	17 (50.0)	22 (64.7)	
Horizontal location of tumor (n, %)				.424
Anterior wall	19 (27.9)	9 (26.5)	10 (29.4)	
Posterior wall	8 (11.8)	6 (17.6)	2 (5.9)	
Lesser curvature	30 (44.1)	15 (44.1)	15 (44.1)	
Greater curvature	11 (16.2)	4 (11.8)	7 (20.6)	
Macroscopic finding (n, %)				.779
Elevated	17 (25.0)	9 (26.5)	8 (23.5)	
Flat/depressed	51 (75.0)	25 (73.5)	26 (76.5)	
Lesion lifting (n, %)				.314
Good	67 (98.5)	33 (97.1)	34 (100.0)	
Poor	1 (1.5)	1 (2.9)	0 (0.0)	
Energy amount (J/cm^2)	1605.3 ± 26.2	1601.6 ± 30.5	1608.9 ± 20.7	.256

APC, argon plasma coagulation; MC, monopolar coagulation.

the completeness of endoscopic ablative therapy for neoplastic tissue was judged based on follow-up endoscopic biopsy in previous studies. Therefore, it was impossible to ascertain whether the lesion was completely ablated, since the ablated tissues were not retrieved. If the patients had been observed for longer periods in previous studies, the recurrence rate might have increased due to the gastric epithelial neoplasia buried under the scar formed by endoscopic ablative therapy.

Histologic assessment after endoscopic ablative therapy for gastric epithelial neoplasia revealed that histologic complete eradication could be achieved if sufficient energy was delivered to the lesion.[3-5,19,23] One study suggested that the optimal energy level to achieve complete removal of the mucosal and submucosal layer without damaging the muscularis propria was 800-1600 J.[19] Based on their ex vivo study, we tried to transfer energy of 1600 J/cm^2 of the lesion. Despite the use of sufficient total energy, total histologic complete eradication rate after endoscopic ablative therapy was only 33.8% in our in vivo human study. This is a disappointing result compared to previous clinical studies. There are some possible explanations of this result. First, the outcome of complete removal was measured histologically in our study, while previous studies measured the outcome by long-term follow-up. Second, the benign nature of gastric LGD can be one of the reasons. Gastric LGD can regress spontaneously in 38-49% of patients.[24-26] Therefore, in previous studies, even if there was remnant neoplastic tissue immediately after endoscopic ablative therapy, neoplastic tissue was not likely to be found in the follow-up endoscopic biopsy. Third, we calculated the total amount of energy based on the results of an ex vivo study. An increased amount of energy may be needed when performing ablation therapy in vivo.

Our study had several limitations. First, the endoscopist who performed the endoscopic ablative therapy was not blinded to the method, which might have led to bias. However, such blinding is not possible due the to distinct appearance of the 2 devices. Second, we assumed

Table 2. Outcomes of Endoscopic Electrocoagulation

	Total (n = 68)	APC (n = 34)	MC (n = 34)	*P*
Histologic complete eradication (n, %)				<.001
Complete eradication	23 (33.8)	19 (55.9)	4 (11.8)	
Lateral margin (+) only	4 (5.9)	4 (11.8)	0 (0.0)	
Deep margin (+) only	31 (45.6)	4 (11.8)	27 (79.4)	
Both lateral and deep margin (+)	10 (14.7)	7 (20.5)	3 (8.8)	
Pathology of resected specimen (n, %)				<.001
No tumor	23 (33.8)	19 (55.9)	4 (11.8)	
Low-grade dysplasia	44 (64.7)	14 (41.2)	30 (88.2)	
High-grade dysplasia	1 (1.5)	1 (2.9)	0 (0.0)	
Maximal depth of tissue necrosis (n, %)				<.001
Superficial mucosa	35 (51.5)	7 (20.6)	28 (82.4)	
Deep mucosa	21 (30.9)	18 (52.9)	3 (8.8)	
SM1* (<500 μm)	12 (17.6)	9 (26.5)	3 (8.8)	
Procedure-related adverse events				-
Immediate bleeding	0	0	0	
Delayed bleeding	0	0	0	
Perforation	0	0	0	

*SM1, 1st layer of submucosa.
APC, argon plasma coagulation; MC, monopolar coagulation.

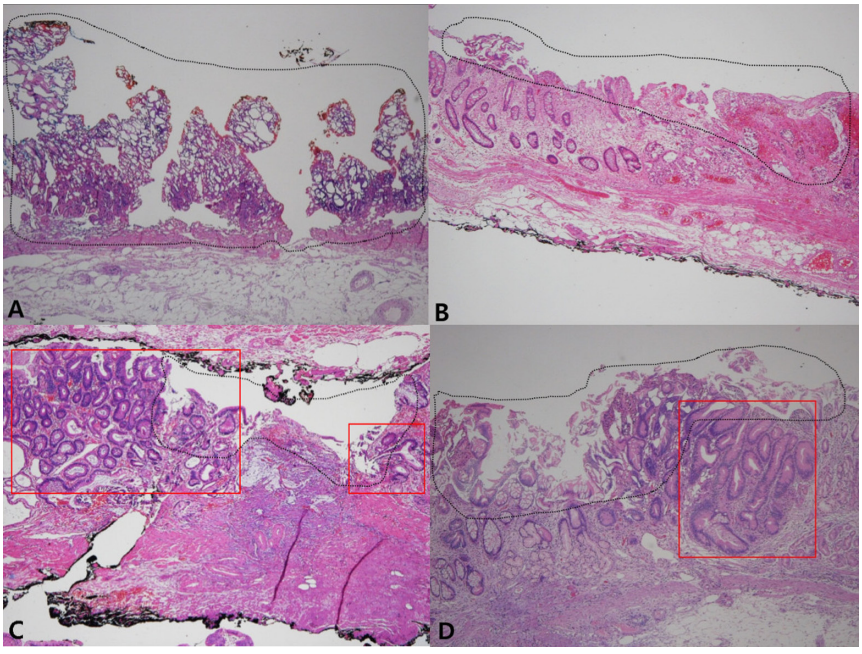

Figure 4. Representative images of the histology (H&E stain, ×40). A, Complete histologic eradication after argon plasma coagulation (APC) (black dot circle: cauterization area). B, Complete histologic eradication after monopolar coagulation (MC) (black dot circle: cauterization area). C, Incomplete histologic eradication after APC (black dot circle: cauterization area, red square: remnant adenoma). D, Incomplete histologic eradication after MC (black dot circle: cauterization area, red square: remnant adenoma).

Table 3. Univariate Analysis for Predictors of Histologic Complete Eradication After Electrocoagulation

	Total (n = 68)	Complete Eradication (n = 23)	Incomplete Eradication (n = 45)	*P*
Age	66.2 ± 9.0	66.8 ± 9.9	65.8 ± 8.7	.662
Sex (n, %)				.591
Male	45 (66.2)	14 (60.9)	31 (68.9)	
Female	23 (33.8)	9 (39.1)	24 (31.1)	
Tumor area (cm^2)	1.3 ± 0.5	1.0 ± 0.4	1.4 ± 0.5	.004
Vertical location or tumor (n, %)				.440
Upper/middle	29 (42.6)	8 (34.8)	21 (46.7)	
Lower	39 (57.4)	15 (65.2)	24 (53.3)	
Horizontal location of tumor (n, %)				.947
Anterior wall	19 (27.9)	7 (30.4)	12 (26.7)	
Posterior wall	8 (11.8)	2 (8.7)	6 (13.3)	
Lesser curvature	30 (44.1)	10 (43.5)	20 (44.4)	
Greater curvature	11 (16.2)	4 (17.4)	7 (15.6)	
Macroscopic finding (n, %)				.772
Elevated	17 (25.0)	5 (21.7)	12 (26.7)	
Flat/depressed	51 (75.0)	18 (78.3)	33 (73.3)	
Lesion lifting (n, %)				.471
Good	67 (98.5)	23 (100.0)	44 (97.8)	
Poor	1 (1.5)	0 (0.0)	1 (2.2)	
Energy amount (J/cm^2)	1605.3 ± 26.2	1597.7 ± 19.8	1609.1 ± 28.3	.088
Method of electrocautery (n, %)				<.001
Monopolar coagulation	34 (50.0)	4 (17.4)	30 (66.7)	
Argon plasma coagulation	34 (50.0)	19 (82.6)	15 (33.3)	

all tumor areas to have an oval shape while calculating the tumor area. Third, HGD and carcinoma were not included, due to ethical concerns. However, considering that HGD and carcinoma tend to invade more deeply than LGD, the histologic complete eradication rate for these lesions by endoscopic ablative therapy might be much lower than LGD.

Table 4. Binary Logistic Regression Analysis for Predictors of Histologic Complete Eradication

Factors	Odds Ratio (95% CI)	*P*
Tumor area (cm^2)		.073
<1	Ref	
≥1	2.93 (0.90-9.51)	
Method of electrocautery		.002
Monopolar coagulation	Ref	
Argon plasma coagulation	7.66 (2.14-27.45)	

In conclusion, our results suggest that endoscopic ablative therapy has a limited role in the treatment of gastric epithelial neoplasia. Therefore, endoscopic resection should be the first option for treatment of gastric epithelial neoplasia, until the optimal method is established with further studies.

Clinical Trial Registration: Primary Registries of the WHO Registry Network Platform (Clinical Research Information Service, CRiS, No. KCT0001587, https://cris.nih.go.kr/cris/index.jsp).

Ethics Committee Approval: The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of the Ethics Committee of Incheon St. Mary's Hospital, The Catholic University of Korea, before initiation (approval number: OC15TISI0052).

Informed Consent: Written informed consents from the patients were obtained before the procedure.

Peer review: Externally peer-reviewed.

Author Contributions: Concept – B.W.K.; Design - B.W.K.; Supervision - B.W.K.; Resource - B.W.K., C.W.H, J.K.; Materials - B.W.K., C.W.H., J.K.; Data Collection and/or Processing - C.W.H., J.K.; Analysis and/or Interpretation - C.W.H., J.K., B.W.K., J.S.K.; Literature Search - C.W.H., J.K., B.W.K., J.S.K.; Writing - C.W.H.; Critical Reviews - J.K., B.W.K., J.S.K.

Conflict of Interest: The authors have no conflict of interest to declare.

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