

Clinical Outcomes and Adverse Events of the Stomach Endoscopic Submucosal Dissection of the Mid to Upper Stomach Under General Anesthesia and Monitored Anesthetic Care

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Abstract

Background: Endoscopic submucosal dissection (ESD) of gastric tumors in the mid to upper stomach is a technically challenging procedure. This study compared the therapeutic outcomes and adverse events following ESD of tumors in this area, performed in conjunction with either general anesthesia (GA) or monitored anesthetic care (MAC).

Methods: Between 2012 and 2018, 674 patients underwent ESD of gastric tumors in the midbody, high body, fundus, or cardia (100 patients received GA; 574 received MAC). The results were analyzed using propensity score (PS)-matched (1:1) patients receiving either GA or MAC.

Results: PS matching identified 95 patients who received GA and 95 matched patients who received MAC. Both groups showed high rates of en-bloc resection (GA, 98.5%; MAC, 98.9%; $p = 0.18$) and complete resection, defined as tumors excised with histologically confirmed negative margins (GA, 82.1%; MAC, 90.5%; $p = 0.14$). There were no significant differences in the frequencies of adverse events (GA, 16.8%; MAC, 9.5%; $p = 0.13$) between the anesthetic groups. A logistic regression analysis indicated that the anesthetic method was not a factor impacting the frequencies of complete resection or adverse events.

Conclusion: At our high-volume center, good therapeutic outcomes were achieved following ESD of tumors in the mid to upper stomach, regardless of the anesthetic method used. Our results demonstrate the efficacy and safety non-inferiority of the ESD procedure performed in conjunction with MAC, compared with GA.

Background

Presently, endoscopic submucosal dissection (ESD) is widely used because it can achieve a higher rate of complete gastric tumor resection than endoscopic mucosal resection [1, 2]. Additionally, ESD is less invasive and can result in a better patient quality of life than surgical gastrectomy, if indicated [3]. However, ESD requires sophisticated endoscopic techniques. Thus, the adverse events, such as bleeding and perforations, and clinical outcomes following en-bloc resection are related to the technical skill of the endoscopists, especially in difficult ESD cases. A previous study demonstrated that tumors located in the upper third of the stomach are associated with longer procedure times and higher frequencies of incomplete resection than those located in other stomach areas [3]. Other studies also showed that the mid to upper stomach region has more vessels and is more likely to demonstrate early gastric cancers (EGCs) with submucosal invasion than other areas of the stomach [4, 5]. Therefore, ESD procedures for tumors located in the mid to upper stomach require high levels of endoscopic technical skill.

ESD also requires minimal patient movement during the procedure [6, 7]. Therefore, previous studies have discussed appropriate sedation methods for use during ESD. Specifically, these studies have compared different sedatives, such as midazolam and propofol, or have compared traditional sedation (delivered by endoscopists) with sedatives and anesthetic care delivered via intubation [1, 2, 6–9]. Some studies have also reported ESD outcomes involving patients under general anesthesia (GA) [1, 10].

The present study was based on the premise that ESD involving the mid to upper stomach is more difficult than that involving the lower part of the stomach. Hence, we assumed that the resection in the mid to upper stomach are less likely to be complete and are more likely to experience adverse events than those in the lower stomach occur than the other. ESD conducted under GA, with intubation, are recognized to be more effective and safer than procedures involving traditional sedation delivered by endoscopists [1, 2, 10]. However, a direct comparison between monitored anesthetic care (MAC), involving mask ventilation, and GA has not been previously reported. Thus, this study compared the therapeutic outcomes and adverse event rates following ESD of tumors located in the mid to upper stomach under either GA or MAC.

Methods

Study design, setting, and participants

This retrospective study was performed at Samsung Medical Center, Seoul, South Korea. Between January 2012 and December 2018, 3760 patients underwent ESD of gastric tumors involving either GA or MAC. The tumors were located in the mid to upper stomach, including in the midbody, high body, fundus, and cardia. Histologically confirmed EGCs, adenomas, and neuroendocrine tumors (NETs) were included, based on the final pathologic reports from the ESD specimens (Fig. 1). Patients with prior histories of esophagectomies for esophageal cancer were excluded. The study protocol was reviewed and approved by the institutional review board at Samsung Medical Center. Because this study was based on a retrospective analysis of existing clinical data, the requirement for informed patient consent was waived by the institutional review board (No. 2019-09-015-001).

ESD procedure

Five gastroenterologists performed all the gastric ESD procedures using a standard technique. First, a circumferential mark was made around the lesion with either a needle knife or a dual knife. Thereafter, fluid (normal saline [100 mL], epinephrine [1 mL], and 0.8% indigo carmine [0.1 mL]) was injected into the submucosal layer, a circumferential mucosal precut was made, and the submucosal layer was dissected using various types of knives, such as the IT2 knife or dual knife. Endoscopic hemostasis was performed simultaneously whenever bleeding was observed (Fig. 2).

Anesthesia

The ESD procedure was performed under either GA, with endotracheal intubation, or MAC, with mask ventilation. GA was induced using rocuronium, remifentanyl, and propofol, and was maintained using propofol and remifentanyl. MAC was induced using midazolam and was maintained using propofol and remifentanyl. During anesthesia, the patients were monitored using end-tidal carbon dioxide level, tidal volume, respiratory rate, oxygen saturation, electrocardiogram, and non-invasive blood pressure, body temperature, and heart rate.

Study outcomes, variables, and definitions

Data in this study were retrospectively obtained from the electronic medical records of Samsung Medical Center. We collected data regarding patient demographics (age, sex, past medical history, and body mass index), tumor characteristics (tumor location, endoscopic tumor morphology, gross and pathologic tumor size, tumor specimen size, and tumor histopathology), and procedure-related factors (procedure time, anesthetic time, sedation method, and adverse events). The details of the pathologic findings, such as depth of invasion, tumor lateral and vertical margins, lymphatic and vascular involvement, and presence of ulceration, were obtained for EGC cases.

The study's primary outcomes were the frequencies of en-bloc and complete resection. The secondary outcomes were the associated adverse event (bleeding and perforations) frequencies. En-bloc resection was defined as tumor resection as a single piece. Complete resection was defined as en-bloc tumor resection with histologically confirmed tumor-free resection margins, both laterally and vertically. Curative resection, defined as complete resection without submucosal invasion deeper than 500 μm , lymphatic invasion, or vascular involvement, was assessed in EGC cases. We also compared procedure times, defined as the time from the first observation of the lesion to complete lesion removal, including hemostasis, for the two anesthetic method groups. A perforation was defined as evidence of free air in the radiographic findings, after finishing the ESD procedure. ESD-related bleeding was defined as the need for hemostatic procedures after the ESD procedure.

Statistical analysis

We used propensity score (PS) matched (1:1) analysis for patients who underwent GA with those who underwent MAC. For patients with EGCs, adenomas, and NETs, the PS matching involved the tumor locations and specimen sizes. In patients with EGCs, PS matching also included the depth of tumor invasion.

Baseline characteristics are summarized as means \pm standard deviation (SD) or as frequencies (percent). Categorical variables were compared using the Chi-square test or Fisher exact test, and continuous variables were compared using Student's *t*-test. Logistic regression was performed and the odds ratio was calculated to identify factors associated with therapeutic outcomes and adverse events; a *p*-value < 0.05 was considered statistically significant. Statistical analyses were performed using both SPSS, version 25.0 (SPSS, Chicago, IL, USA), and R, version 3.6.1 (R Foundation, Vienna, Austria).

Results

Clinicopathologic characteristics and clinical outcomes

The clinicopathologic characteristics of the analyzed patients with EGCs, adenomas, and NETs are shown in Table 1. PSs were used to match 95 patients who underwent GA with 95 who underwent MAC. The patients undergoing the two different anesthetic methods displayed similar clinicopathologic

characteristics, except for sex and numbers of lesions. Patients undergoing GA (20%) were more likely to have multiple lesions compared with those undergoing MAC (7.4%, $p = 0.03$).

Table 1
Clinicopathologic characteristics of EGC, adenoma, NET patients

	GA (n= 95)	MAC (n= 95)	p value
Age at procedure (years)	64.9 ± 11.2	66.5 ± 9.4	0.28
Sex (male)	84 (88.4%)	64 (67.4%)	< 0.001
BMI (kg/m ²)	24.4 ± 3.3	24.2 ± 3.1	0.64
Smoking			0.19
Never	39 (41.0%)	50 (52.6%)	
Ex	43 (45.3%)	31 (32.6%)	
Current	13 (13.7%)	14 (14.8%)	
Pre-operative comorbidities* (yes)	51 (53.7%)	56 (52.3%)	0.47
Gastrectomy before ESD (yes)	8 (8.4%)	5 (5.3%)	0.39
Number of Lesion			0.03
1	76 (80.0%)	88 (92.6%)	
2	16 (16.8%)	7 (7.4%)	
3	2 (2.1%)	0 (0.0%)	
4	1 (1.1%)	0 (0.0%)	
Location (%)			0.99
Mid body	22 (23.2)	22 (23.2)	
High body + Fundus	31 (32.6)	30 (31.6)	
Cardia + EG junction	42 (44.2)	43 (45.3)	
Pathology of tumor			0.02
EGC	81 (85.3%)	69 (72.6%)	
Adenoma	11 (11.6%)	25 (26.3%)	
Neuroendocrine tumor	3(3.1%)	1 (1.1%)	
Morphology of tumor			0.24

ESD endoscopic submucosal dissection, *GA* general anesthesia, *MAC* monitored anesthetic care, *EGC* early gastric cancer, *NET* neuroendocrine tumor

*Pre-operative comorbidities: One of hypertension, diabetes mellitus, cardiovascular disease, arrhythmia, cerebrovascular disease, chronic pulmonary obstructive disease, chronic liver disease, chronic kidney disease, other malignancies

	GA (n= 95)	MAC (n= 95)	p value
Elevated	60 (63.2%)	48 (50.5%)	
Flat	8 (8.4%)	9 (9.5%)	
Depressed	27 (28.4%)	37 (38.9%)	
Endoscopic tumor size (cm)	2.02 ± 1.22	1.89 ± 1.13	0.44
Pathologic tumor size (cm)	2.39 ± 2.59	1.88 ± 1.24	0.08
Specimen size (cm)	4.82 ± 1.51	4.72 ± 1.38	0.63
<i>ESD</i> endoscopic submucosal dissection, <i>GA</i> general anesthesia, <i>MAC</i> monitored anesthetic care, <i>EGC</i> early gastric cancer, <i>NET</i> neuroendocrine tumor			
*Pre-operative comorbidities: One of hypertension, diabetes mellitus, cardiovascular disease, arrhythmia, cerebrovascular disease, chronic pulmonary obstructive disease, chronic liver disease, chronic kidney disease, other malignancies			

Supplementary Table 1 shows the clinicopathologic characteristics of the PS-matched EGC patients. In this analysis, the patients undergoing GA (19.5%) were also more likely to have multiple lesions compared with those undergoing MAC (3.9%, $p = 0.005$). The tumor morphologies and histologic differentiations were not significantly different between the two groups.

We compared the clinical outcomes between the two anesthesia groups of matched patients with EGCs, adenomas, and NETs. The procedure time per lesion was longer in the GA group than in the MAC group ($p < 0.001$) and the mean minimum resection margin was shorter in the GA group than in the MAC group ($p = 0.04$). Both anesthetic groups had high rates of en-bloc (GA, 98.5%; MAC, 98.9%) and complete (GA, 82.1%; MAC, 90.5%) resection. There were no significant between-group differences ($p = 0.13$) in the frequencies of adverse events (perforations and bleeding) (Table 2).

Table 2
Clinical outcomes and adverse events of EGC, adenoma, NET patients

	GA (n= 95)	MAC (n= 95)	p value
En-bloc resection (yes)	91 (98.5%)	94 (98.9%)	0.18
Complete resection (yes)	78 (82.1%)	86 (90.5%)	0.14
Resection margin (minimum, mm)	4.91 ± 3.31	6.09 ± 3.58	0.04
Anesthetic time, total (min)	131.6 ± 59.6	78.8 ± 44.9	< 0.001
Procedure time per, total (min)	105.5 ± 59.9	70.5 ± 44.4	< 0.001
Procedure time per 1 lesion (min)	91.7 ± 58.3	66.4 ± 44.4	0.001
Adverse events (yes)	16 (16.8%)	9 (9.5%)	0.13
Perforation (yes)	12(12.6%)	5 (5.3%)	0.08
Bleeding (yes)	5 (5.3%)	4 (4.5%)	1.00
GA general anesthesia, MAC monitored anesthetic care, EGC early gastric cancer, NET neuroendocrine tumor			

The matched EGC patients showed similar results. The rates of en-bloc (GA, 94.8%; MAC, 98.7%) and complete (GA, 79.2%; MAC, 84.4%) resection were high in both groups. However, the curative resection rates were lower than the complete resection rates, although the differences were not significant, due to the more severe tumor characteristics, such as tumor submucosal invasion > 500 µm, lymphatic invasion, or vascular involvement (GA, 61.0%; MAC, 70.1%) (Supplementary Table 2).

Association between therapeutic outcome and anesthetic modality

In the multivariable analysis, the anesthetic method was not a factor associated with complete ESD resection of gastric tumors (Table 3, Supplementary Table 3); a long resection margin was the only factor associated with complete resection of gastric tumors (Table 3). In the regression analysis, the anesthetic method was also not associated with the adverse event rate (Table 4, Supplementary Table 4).

Table 3
Factors associated with complete resection in EGC, adenoma, NET patients

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Age (years)	0.93 (0.96–1.04)	0.99		
Male (vs. female)	1.07 (0.40–2.86)	0.90		
Methods of anesthesia				
GA	1.00 (reference)		1.00 (reference)	
MAC	2.08 (0.88–4.94)	0.09	0.98 (0.30–3.18)	0.98
Number of lesion \geq 2 (vs.1)	0.62 (0.21–1.81)	0.38		
Endoscopic tumor size (cm)	0.72 (0.54–0.98)	0.03	0.49 (0.22–1.12)	0.09
Pathologic tumor size (cm)	0.83 (0.67–1.03)	0.09	0.96 (0.75–1.22)	0.72
Specimen size (cm)	0.82 (0.63–1.07)	0.14	1.26 (0.63–1.12)	0.52
Resection margin (minimum, mm)	1.70 (1.34–2.15)	< 0.001	1.77 (1.35–2.33)	< 0.001
Procedure time per 1 lesion (min)	0.99 (0.98–0.99)	0.002	0.99 (0.98–1.01)	0.14
Pathology of tumor				
EGC	1.00 (reference)	-		
Adenoma + NET	0.28 (0.06–1.22)	0.28		
<i>GA</i> general anesthesia, <i>MAC</i> monitored anesthetic care, <i>EGC</i> early gastric cancer, <i>NET</i> neuroendocrine tumor, <i>OR</i> odds ratio, <i>CI</i> confidence interval				

Table 4
Factors associated with adverse events in EGC, adenoma, NET patients

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Age (years)	1.03 (0.99–1.08)	0.16	1.06 (1.01–1.12)	0.045
Male (vs. female)	1.57 (0.51–4.86)	0.43		
Methods of anesthesia				
GA	1.00 (reference)	-	1.00 (reference)	
MAC	0.52 (0.22–1.24)	0.14	0.86 (0.29–2.56)	0.79
Number of lesion \geq 2 (vs.1)	1.71 (0.58–5.06)	0.33		
Location				
Mid body	1.00 (reference)	-	1.00 (reference)	-
High body + Fundus	0.86 (0.32–2.28)	0.76	0.59 (0.18–1.93)	0.59
Cardia + EG junction	0.24 (0.08–0.78)	0.02	0.33 (0.08–1.43)	0.14
Endoscopic tumor size (cm)	1.40 (1.04–1.89)	0.03	1.20 (0.55–2.61)	0.65
Pathologic tumor size (cm)	1.07 (0.92–1.26)	0.36		
Specimen size (cm)	1.44 (0.11–1.87)	0.006	0.89 (0.46–1.72)	1.72
Resection margin (minimum, mm)	1.09 (0.96–1.24)	0.19	1.09 (0.93–1.27)	0.28
Procedure time per 1 lesion (min)	1.01 (1.00–1.02)	0.04	1.01 (0.99–1.02)	0.20
Pathology of tumor				
EGC	1.00 (reference)	-		
Adenoma + NET	2.12 (0.60–7.48)	0.24		

GA general anesthesia, *MAC* monitored anesthetic care, *EG* esophagogastric, *EGC* early gastric cancer, *NET* neuroendocrine tumor, *OR* odds ratio, *CI* confidence interval

Discussion

ESD is widely used to treat gastric tumors and is often performed under either anesthesia or traditional sedation, administered by endoscopists [1, 8, 10]. Previous studies have compared outcomes based on the sedatives or anesthetic methods used. However, there have been insufficient data comparing the anesthetic methods (GA and MAC) used during difficult gastric ESD cases. To the best of our knowledge,

this is the first study comparing the therapeutic outcomes and adverse events following ESD of tumors, performed under GA or MAC, in the upper region of the stomach.

In this present study, the en-bloc resection rates were > 98% for both anesthetic groups and the complete resection rates were > 82%; similar results were observed when the EGC cases were separately examined. In a previous meta-analysis of ESD clinical outcomes, the en-bloc resection rate for 1437 cases of EGC was 92.4% and the complete resection rate for 1495 cases of EGC was 82.4%, regardless of the anesthetic method or tumor location [11]. Thus, the en-bloc and complete resection rates in our study were above average. However, our curative resection rates, for EGC cases, were relatively low (GA, 61.0%; MAC, 70.1%). A previous study of post-ESD, short-term outcomes, involving 712 patients in a prospective multicenter cohort study in Korea, showed an en-bloc resection rate of 97.3% and a curative resection rate of 86.8%. The authors of that study suggested that non-curative resection were associated with large lesions, submucosal invasion, and moderately or poorly differentiated adenocarcinomas [12]. Also in that study, 26.1% of the patients had EGC lesions > 2 cm in size, 33.1% of the lesions were moderately or poorly differentiated adenocarcinomas, and 16.0% of the lesions had invaded the submucosal layer [12]. In our study, 35.1% of EGCs were > 2 cm in size, 63.6% were moderately or poorly differentiated adenocarcinomas, and 44.8% showed submucosal invasion. Thus, the lower curative resection rate, in our study, may have been due to the tumor characteristics of our study population.

In the present study, the rates of ESD-related perforations were 12.6% for patients receiving GA and 9.5% for those receiving MAC; the respective bleeding rates were 5.3% and 4.5%. Amongst EGC cases, the perforation rates were 13.0% for those receiving GA and 5.2% for those receiving MAC; the bleeding rates were 5.2% and 3.9%, respectively. In a previous meta-analysis of ESD adverse events, a perforation rate of 4.3% was observed among 1437 EGC cases and bleeding occurred in 9.4% of 876 EGC cases, regardless of the anesthetic method or tumor location [11]. The higher incidence of perforations, in our study, may also be related to the tumor characteristics of our study population, as described for the curative resection rates. ESD involving the upper part of the stomach is carries a higher risk of adverse events, such as perforations and bleeding, due to the difficulty of positioning the ESD knife, the relatively thin gastric wall, and the associated vasculature; therefore, the procedure requires longer procedure times and more advanced technical skills than procedures involving the lower portion of the stomach [4, 13, 14]. Moreover, EGC submucosal invasion occurs more frequently in the mid and upper parts of the stomach [5]. A previous study of the risk factors for procedure-related perforations demonstrated that longer procedure times are an associated risk factor. That study also showed that the perforation rate was higher when the upper stomach was involved (8% of 478 cases) than when the lower stomach was involved (0.5% of 478 cases) [15]. Another study showed that the perforation risk is 4.9-fold higher for procedures involving the upper stomach than for those involving other areas of the stomach, after adjusting for submucosal invasion and dyslipidemia [16]. In the present study, the procedure times were longer for patients receiving GA than for those receiving MAC. However, the perforation rates were not significantly different between the two anesthetic groups. The results show that the two anesthetic methods are not associated with ESD clinical outcomes or adverse events; thus, safe and efficacious ESD may be achieved using MAC in high-volume centers with specialized endoscopists.

To develop the hypothesis for our study, we presumed that ESD performed under GA would have better therapeutic outcomes and fewer adverse events than those not performed under GA, because GA would prevent patients from demonstrating even subtle movements during the procedure. As noted previously, previous study results involving esophageal or gastric ESD indicated that GA decreases the risk of adverse events, compared with traditional sedation administered by endoscopists [2, 17]. Further, a previous study of esophageal ESD procedures, conducted at our institute, showed that the en-bloc resection rate was significantly higher and perforation rate was significantly lower in patients receiving GA than in those receiving traditional sedation; GA was shown to be a factor associated with achieving complete resection and minimizing perforations [17]. Despite only a few studies comparing GA and MAC, MAC has been shown to provide more clinical benefits than GA. One retrospective study compared endovascular angioplasty outcomes, in patients with aortoiliac disease, according to the intra-operative use of GA or MAC. Interestingly, the post-operative adverse event rate was significantly lower for procedures performed using MAC than for those using GA [18]. Similarly, another retrospective study also suggested that MAC is a safe anesthetic method for mid-gestation pregnant women and its use is associated with a lower adverse event rate than GA [18].

Our study has limitations due to its retrospective design and its inclusion of procedures performed only at one medical center. However, as a high-volume center that employs several technically advanced endoscopists, many stomach ESD cases have been performed and were available for inclusion. Since 2012, when ESD was introduced at our center, most cases have utilized traditional sedation or MAC. However, a selection bias exists because endoscopists request specific anesthetic methods, before starting their procedures. Endoscopists tend to request GA for difficult cases, such as those involving tumors in the upper stomach or that are presumed to be more invasive, based on morphologic assessments. Moreover, procedures involving the mid to upper stomach are 5 times more likely to involve MAC than GA. To overcome this limitation, we applied PS matching.

In conclusion, our study results demonstrated that good clinical outcomes were achieved following ESD of tumors in the mid to upper stomach, regardless of the anesthetic method used in our high-volume center. Further, the results showed the non-inferiority of the safety and therapeutic outcomes following ESD procedures performed in conjunction with MAC, compared with those performed with GA. Regarding cost-effectiveness and less invasiveness, gastric ESD under MAC might be superior to ESD under GA.

Abbreviations

used in this paper: ESD, endoscopic submucosal dissection; GA, general anesthesia; MAC, monitored anesthetic care; PS, propensity score; EMR, endoscopic mucosal resection; EGC, early gastric cancer; NET, neuroendocrine tumor; OR, odds ratio; CI, confidence interval.

Declarations

Ethics approval and consent to participate

Ethical approval for the study was obtained from the institutional review board at Samsung Medical Center. Because this study was based on a retrospective analysis of existing clinical data, the requirement for informed patient consent was waived by the institutional review board (No. 2019-09-015-001).

Consent for publication

Not applicable

Availability of data and materials

All data were anonymous and stored in coded manner in a private domain. The dataset used and analysed during the current study is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interest.

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Author contributions

Study concept and design: Jae J Kim.

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Writing and Drafting of the manuscript: Jong-In Chang and Tae Jun Kim.

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Study supervision: Jae J Kim.

All authors approved the final submission.

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Figures

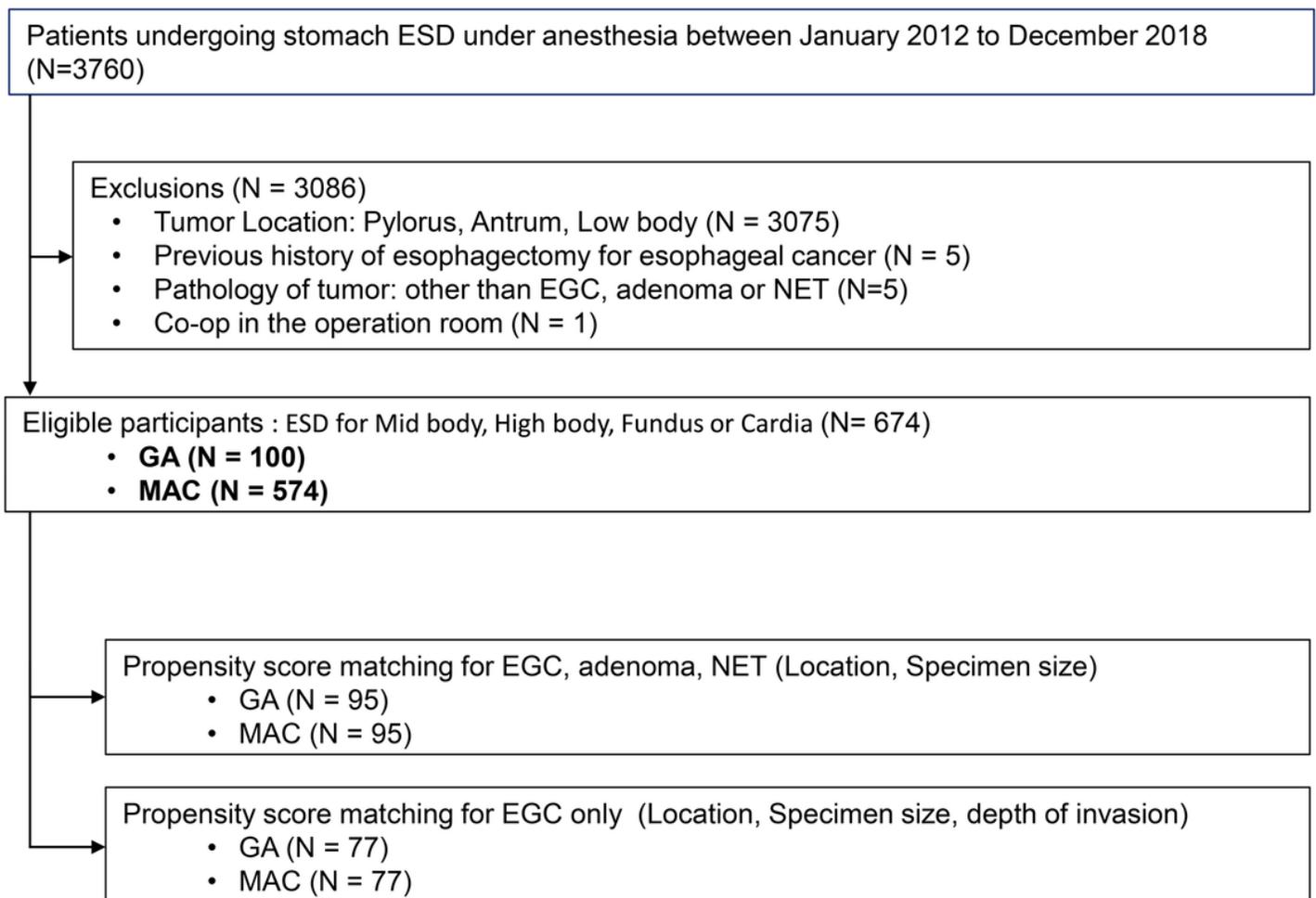


Figure 1

Flow diagram of study patients.

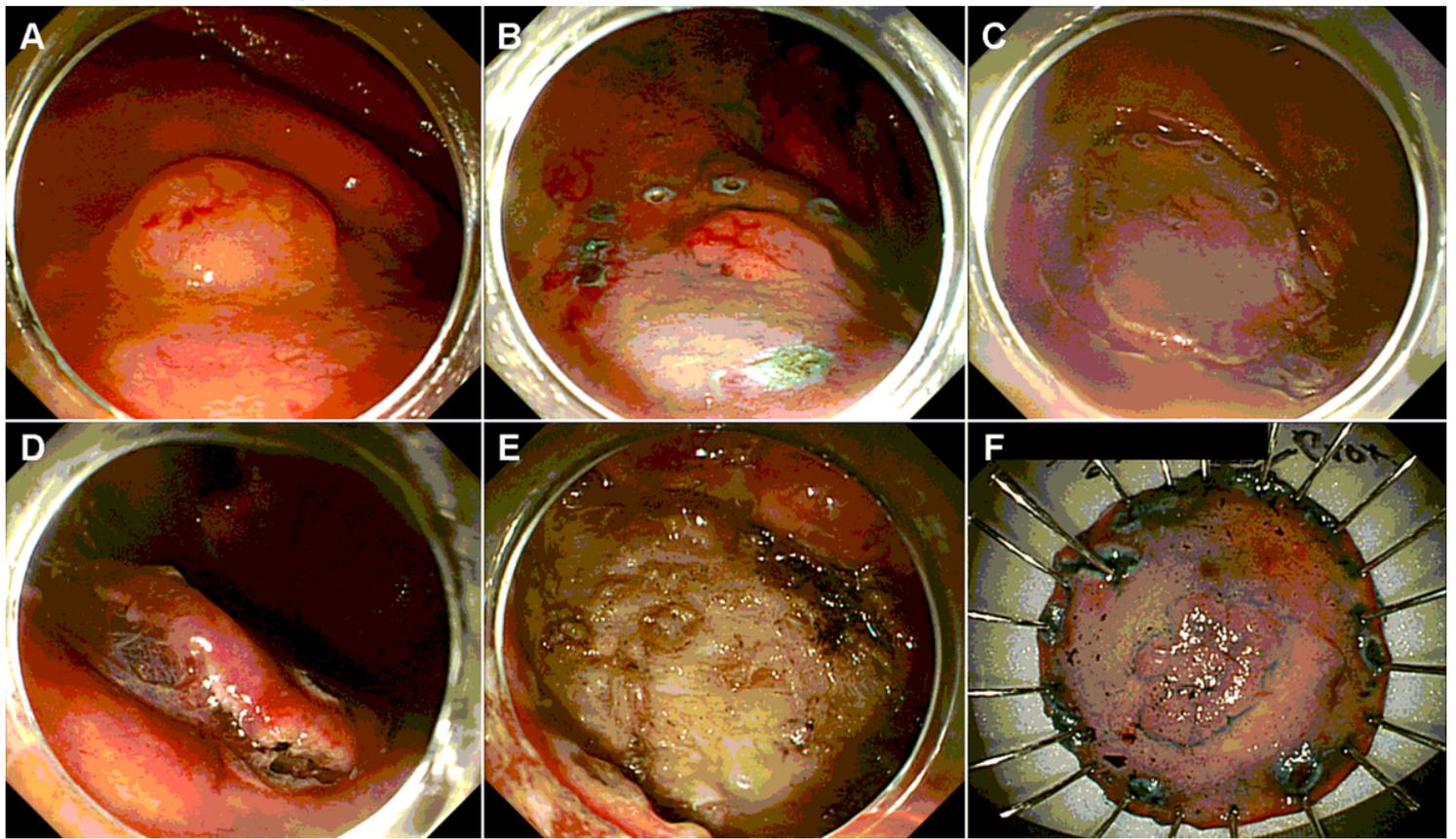


Figure 2

Endoscopic submucosal dissection procedure; (A) On the posterior wall of high body, a 1.2cm sized flat elevated mucosal lesion was noticed. (B) After indigo carmine solution was sprayed for visualization of the lesion, marking around the lesion with needle knife was performed. (C) Circumferential mucosal cutting was performed with needle knife. (D) After Submucosal injection with mixed fluid of normal saline, epinephrine, indigo carmine and glycerol, dissection of submucosal layer with IT2 was performed. (E) A procedure induced artificial ulcer was seen. (F) The resected specimen was fixed on a board for pathologic examination.

Supplementary Files

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