Gel immersion endoscopic submucosal dissection: clinical experience with 13 cases of superficial esophageal cancer

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ABSTRACT

Esophageal endoscopic submucosal dissection (ESD) of tumors located on the gravity side is technically challenging. Given that gel immersion ESD (GIESD) is performed by immersing lesions in gel, we hypothesized that it could be used to eliminate the disadvantage associated with submerging the gravity side. Here, we performed GIESD using VISCOCLEAR for superficial esophageal cancer on the gravity side of the esophagus, with monopolar devices. This study aimed to evaluate the short-term outcomes of GIESD for superficial esophageal cancer. Fifteen patients with 16 superficial esophageal cancers underwent GIESD by a single operator, and 13 cases were evaluated. All patients were male, and GIESD was performed in the middle (12/13, 92.3 %) and lower (1/13, 7.7 %) thoracic esophagus. The lesions were located on the left (7/13, 53.8 %), posterior (5/13, 38.5 %), and right (1/13, 7.7 %) esophageal walls. The median procedure time was 27 minutes (interquartile range [IQR], 14–68), and the median dissection speed was 20 mm^2/min (IQR, 14–25.7). The median amount of gel used was 400 mL (IQR, 360–580), and no gel-related adverse events were observed. The median total dose of midazolam was 3 mg (IQR, 2–5). GIESD was completed with en bloc and R0 resections achieved in 100 % of the 13 cases. Delayed adverse events, such as bleeding or perforation, did not occur (0/13, 0 %).

Introduction

In Japan, esophageal endoscopic submucosal dissection (ESD) has been covered by medical insurance since April 2008 and is performed as a standard treatment for superficial esophageal cancer. However, esophageal ESD is technically challenging. One of the predictors of technical difficulty is a tumor located on the left esophageal wall [1]: as esophageal ESD is performed with the patient in the left lateral supine position, the left wall becomes the side affected by gravity and is submerged.

Gel immersion endoscopy has been reported as a novel method for securing the visual field using gel with an appropriate viscosity [2], and gel immersion ESD (GIESD) has been performed for esophageal tumors with good intraoperative visua-

lization and safe outcomes [3]. We hypothesized that because GIESD is performed by immersing the lesion in gel, it could be used to eliminate the disadvantage of submergence of the gravity side of the esophagus. Given that the gel (OS-1 Jelly; Otsuka Pharmaceutical Factory, Tokushima, Japan) contains electrolytes, monopolar hemostatic forceps would lead to energy being dispersed in the electrolyte solution. However, a recently developed gel (VISCOCLEAR; Otsuka Pharmaceutical Factory) does not contain electrolytes, thereby allowing the use of monopolar hemostatic forceps, and it has been reported to be useful for securing the field of view during endoscopic procedures [4, 5].

We decided to perform GIESD using VISCOCLEAR for superficial esophageal cancer to overcome the submergence on the gravity side of the esophagus with monopolar devices. We aimed to evaluate the short-term outcomes of GIESD for superficial esophageal cancer.

Patients and methods

Study design

This retrospective observational study was conducted at Saitama Medical University International Medical Center and was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the ethics committee of our institution (institutional ID: 2021–089). All patients provided written informed consent after having the risks and benefits of the procedure explained.

Patients and inclusion criteria

Fifteen consecutive patients with 16 superficial esophageal cancers underwent GIESD at our institution by a single operator between May 2021 and January 2022. Three of 16 patients were excluded because they did not meet the inclusion criteria in localization, and 13 patients were evaluated.

The inclusion criteria were as follows: (1) tumors diagnosed as superficial esophageal cancers through preoperative pathological biopsy; (2) lesions located in the middle and lower thoracic esophagus; (3) non-circumferential lesions; and (4) no lymph node or distant metastasis detected by contrast-enhanced computed tomography (CT) scan.

Data on tumor subsites, localization, and size; resected specimen size; procedure time; dissection speed; tumor invasion depth; en bloc resection rate; R0 resection rate; intraoperative perforation rate; delayed perforation rate; postoperative bleeding rate; gel-related adverse events rate; midazolam dose; MucoUp usage; gel usage; and fever (> 38 °C), and white blood cell (WBC) count, and C-reactive protein (CRP) levels on the day after ESD were analyzed.

All analyses were performed using STATA version 17 (StataCorp, College Station, Texas, United States).

Definitions

Conventional ESD was defined as ESD performed under insufflation. Procedure time was defined as the time from the initial mucosal incision to lesion removal. The area of the resected specimen (mm^2) was calculated using the following formula: major diameter of resected specimen (mm)/2 × minor diameter of resected specimen (mm)/2 × 3.14. Dissection speed was calculated using the area of the resected specimen (mm^2)/procedure time (min). Perforations were divided into intraoperative and delayed perforations; the former was defined as a perforation site detected in the mucosal defect during ESD, and the latter was defined as a perforation diagnosed by endoscopy or CT after the day of ESD. Delayed bleeding was defined as hematemesis or epistaxis requiring endoscopic hemostasis after the day of ESD. En bloc resection was defined as macroscopic one-piece resection including the whole tumor and did not include pathological confirmation of complete resection. R0 resection was defined as the pathological absence of tumor cells at the lateral and vertical margins of the specimen.

Equipment and preparation

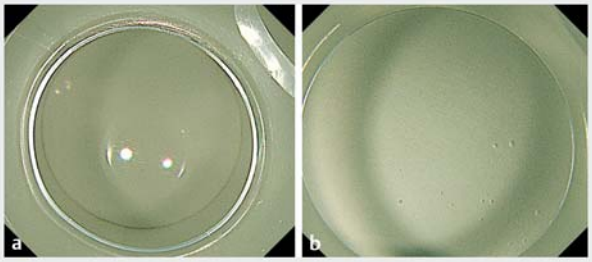
A therapeutic endoscope (GIF-H290T; Olympus, Medical Systems, Tokyo, Japan) with a distal attachment (D201–11804; Olympus Medical Systems) was used for all procedures.

A solution of 0.4 % sodium hyaluronate (0.4 %; MucoUp; Boston Scientific, Tokyo, Japan) combined with a small amount of indigo carmine and epinephrine (dilution 1:100,000) was locally injected into the submucosa.

A 1.5-mm Dual Knife J (KD655Q; Olympus Medical Systems) was used to make a mucosal incision or submucosal dissection. Using an electrosurgical unit (VIO3; ERBE Elektromedizin GmbH, Tübingen, Germany), soft coagulation (effect, 6.0) was used to mark the lesion with the tip of the dual knife; Endo Cut I (effect, 1; duration, 3; and interval, 1) was used for mucosal incision; forced coagulation (effect, 4.5) for submucosal dissection, spray coagulation (effect, 1.2) for hemostasis with the tip of the dual knife, and soft coagulation (effect, 7.0) for hemostasis with Coagrasper (Olympus Medical Systems) were used when hemostasis was still not achieved. The settings of VIO3 did not differ between conventional ESD and GIESD.

When performing GIESD, CO_2 insufflation was turned off, and the gel was injected through the accessory channel (BioShield irrigator, US Endoscopy, Mentor, Ohio, United States) (▶ **Fig. 1**). Compared with conventional ESD, gel immersion expands the field of view, making visualizing the distal attachment more difficult. As a result, the length of the attachment was adjusted to be longer than usual (▶ **Fig. 2**).

▶ **Fig. 1** Injection of the gel through the BioShield irrigator.



▶ **Fig. 2** **a** Conventional length of the distal attachment. **b** Adjusted length of the distal attachment for GIESD.

GIESD procedure

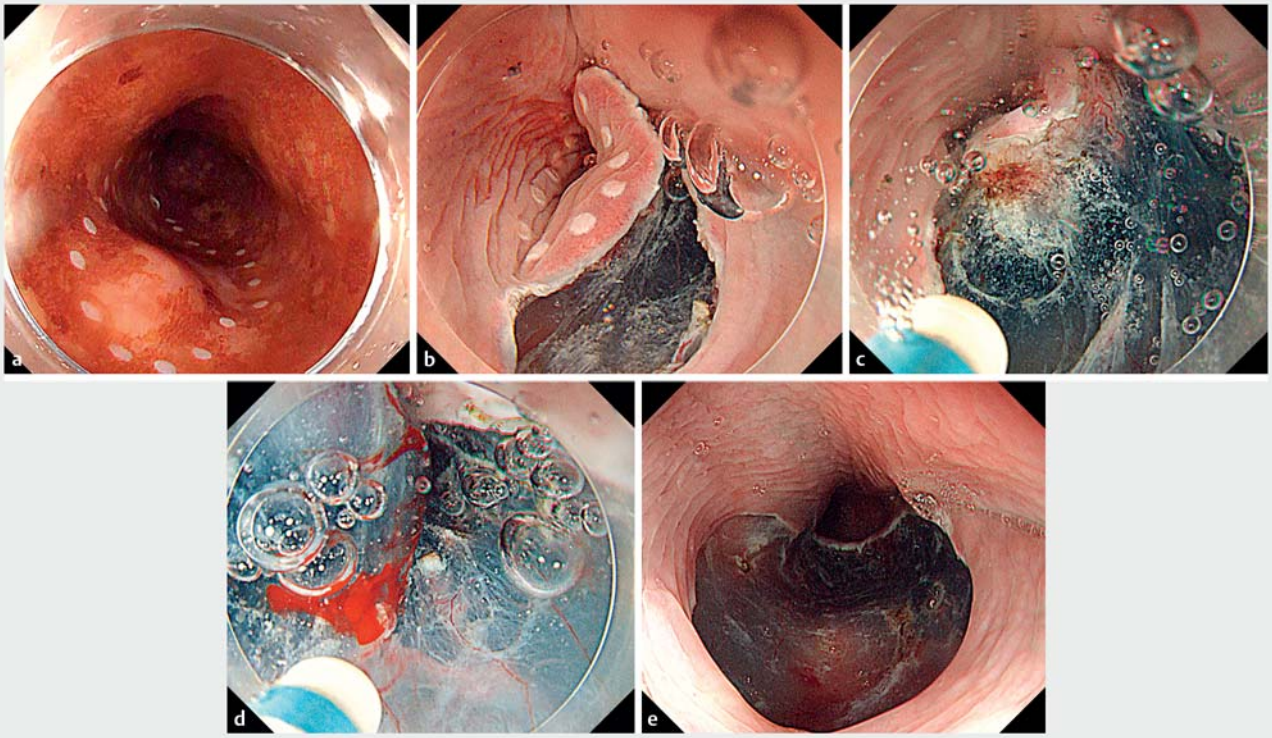
All procedures were performed in an endoscopy room, with the patient under conscious sedation. An initial dose of 35 mg of pethidine and 2 mg of midazolam for patients weighing < 50 kg or 3 mg of midazolam for patients weighing > 50 kg was administered [6, 7]. An additional dose of midazolam (1 mg) was administered when the patient moved.

The GIESD strategy is shown in ▶ **Fig. 3a**, ▶ **Fig. 3b**, ▶ **Fig. 3c**, ▶ **Fig. 3d**, ▶ **Fig. 3e** and ▶ **Video 1**. The endoscope was removed from the body after marking the area around the tumor. After adjusting the length of the distal attachment, the endoscope was reinserted, and CO_2 insufflation was turned off. The gel was injected manually by an assistant using a 50-mL syringe through the BioShield irrigator.

Gel immersion created a buoyancy effect on the lesion, facilitating the approach to the submucosal layer. However, to secure the field of view, bleeding and bubbles caused by incision and coagulation had to be removed by additional injection of the gel as needed. For posterior wall lesions, to complete the procedure with gel immersion from the start of the incision to the completion of excision, the strategy was to first make a mucosal incision on the side contralateral to gravity and move the lesion to the gravity side to facilitate gel immersion (▶ **Video 1**). After circumferential incision, we dissected from the proximal side and excised en bloc. After completion of the GIESD, the gel stored in the stomach was suctioned as much as possible.

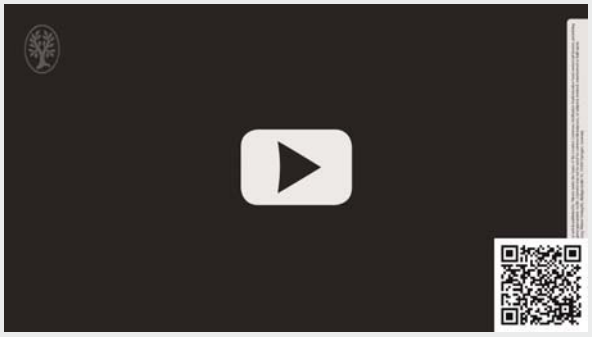
Results

In the three excluded patients, GIESD could not be completed, and the overall completion rate was 81.3 %. All results of 13 patients evaluated are summarized in ▶ **Table 1**. GIESD was completely performed in 13 male patients in the middle (12/13, 92.3 %) and lower (1/13, 7.7 %) thoracic esophagus. The median patient age was 73 years (range, 58–83), and the median body weight was 57.2 kg (range, 49.8–71.4). Lesions were located on the left (7/13, 53.8 %), posterior (5/13, 38.5 %), and right (1/13, 7.7 %) esophageal walls. The median procedure time was 27 (minimum [Min], 12; interquartile range [IQR], 14–68; maxi-



▶ **Fig. 3** **a** A flat lesion, 25 mm in diameter, located on the posterior mid-esophageal wall. **b** Mucosal incision. **c** Good approach to the submucosal layer after circumferential incision due to the buoyancy of the gel. **d** The viscosity of the gel slows bleeding, and good visualization is possible by additional gel injection. **e** Mucosal defect without perforation.

VIDEO



▶ **Video 1** Successful gel immersion endoscopic submucosal dissection for the posterior wall lesion.

mum [Max], 120) minutes, and the median dissection speed was 20 (Min, 11.4; IQR, 14–25.7; Max, 32.7) mm^2/min. The median gel use was 400 (Min, 290; IQR, 360–580; Max, 1,140) mL; no gel-related adverse events, such as abdominal pain, diarrhea, or aspiration, were observed. The median MucoUp volume used was 16 (Min, 7; IQR, 10–25; Max, 40) mL, and the median total dose of midazolam was 3 (Min, 2; IQR, 2–6; Max, 6) mg.

GIESD was completed without perforation, and en bloc or R0 resections were performed in 100 % of the 13 cases. The median major diameter of the resected specimen was 34 (Min, 17; IQR, 22–43; Max, 57) mm, and the median tumor size was 25 (Min, 5; IQR, 12–35; Max, 55) mm. Histopathologically, the invasion depths were as follows: epithelium, 3/13, (23.1 %); lamina propria mucosa, 4/13, (30.8 %); muscularis mucosa, 4/13, (30.8 %); shallow submucosal invasion, 1/13, (7.7 %); and deep submucosal invasion, 1/13, (7.7 %).

Regarding delayed adverse events (AEs), no bleeding or perforation occurred (0/13, 0 %). On the day after ESD, no patient developed a fever (> 38 °C), the median WBC count was 11.3 (Min, 6.4; IQR, 7.7–11.9; Max, 19.2) × 10^3/μL, and the median CRP levels were 1.4 (Min, 0.03; IQR, 0.6–1.8; Max, 6.4) mg/dL.

Discussion

GIESD was completed in 13 patients with middle and lower thoracic superficial esophageal cancer, without AEs.

The advantages of GIESD include a good approach to the submucosal layer owing to the buoyancy effect of the gel, clear visualization of the bleeding site, and the ability to perform the procedure with low pressure because insufflation is not required [8]. Even in a patient who moved constantly during marking with CO_2 insufflation, the gel immersion resulted in low-pressure endoscopy and the body movements subsided, allowing us to perform the procedure in a stable condition [9]. The median total dose of midazolam was as low as 3 mg, indicating the stability of the patients' condition during GIESD. The low bowel pressure due to the absence of insufflation may have resulted in less pain during the procedure and, therefore, less patient

▶ **Table 1** Patient characteristics and treatment outcomes.

	Value
Total patients, n	13
Age, median, years (range)	73 (58–83)
Sex, male/female, n	13 / 0
Body weight, median, kg (range)	57.2 (49.8–71.4)
Tumor subsites, n (%)	
▪ Middle esophagus	12 (92.3)
▪ Lower esophagus	1 (7.7)
Localization, n (%)	
▪ Left wall	7 (53.8)
▪ Posterior wall	5 (38.5)
▪ Right wall	1 (7.7)
Tumor size, median, mm (range)	25 (5–55)
Major diameter of resected specimen, median, mm (range)	34 (17–57)
Procedure time, median, min (range)	27 (12–120)
Dissection speed, median, mm^2/min (range)	20 (11.4–32.7)
Depth of invasion, n (%)	
▪ EP	3 (23.1)
▪ LPM	4 (30.8)
▪ MM	4 (30.8)
▪ SM1	1 (7.7)
▪ SM2	1 (7.7)
En bloc resection, n (%)	13 (100)
R0 resection, n (%)	13 (100)
Perforation, n (%)	
▪ Intraoperative	0 (0)
▪ Delayed	0 (0)
Postoperative bleeding, n (%)	0 (0)
Gel-related adverse events, n (%)	0 (0)
Midazolam dose, median, mg (range)	3 (2–6)
MucoUp usage, median, mL (range)	16 (7–40)
Gel usage, median, mL (range)	400 (290–1140)
The day after ESD	
▪ Fever (> 38 °C), n (%)	0 (0)
▪ WBC count, median, × 10^3/μL (range)	11.3 (6.4–19.2)
▪ CRP, median, mg/dL (range)	1.4 (0.03–6.4)

EP, epithelial; LPM, lamina propria; MM, muscularis mucosa; SM, submucosal; ESD, endoscopic submucosal dissection; WBC, white blood cell; CRP, C-reactive protein.

movement, resulting in less need for additional midazolam. As the risk of respiratory depression increases with increasing midazolam doses, low-pressure endoscopy may be useful for reducing midazolam doses in patients who respond poorly to midazolam, such as heavy alcohol consumers. Further investigations are required to clarify this.

However, GIESD is not suitable for every location. The cervical esophagus, upper esophagus, and right wall of the esophagus are not suitable sites for GIESD due to aspiration and poor gel immersion. In this study, we operated on one patient with middle esophageal cancer located on the right wall, but it was still difficult to maintain a good field of view because of contralateral gravity, which tended to cause stagnation of air, and bubbles generated by incision and coagulation. GIESD was also performed in patient with a non-enrolled right wall lesion of the esophagogastric junction, but it could not be completed. In conventional ESD, to improve the field of view, any interfering residues and bleeding are removed by suction. However, in the case of gel immersion, suction also removes the gel, making maintenance of the field of view impossible. Therefore, to remove bubbles and bleeding caused by incision and dissection in GIESD, additional gel injection is required instead of suction. In addition, in two non-enrolled patients with upper esophageal lesions, GIESD could not be completed because of aspiration. In both cases, the patients did not experience a drop in SpO_2. GIESD in the upper thoracic esophagus is not recommended due to safety issues.

Including the upper esophageal and esophagogastric junction cases, GIESD was completely performed in 13 of 16 cases, resulting in a completion rate of 81.3 %. Considering that GIESD is not always effective for localization other than on the gravity side of the middle and lower esophagus, the treatment strategy between GIESD and conventional ESD should be determined based on the location of each case.

Our study has some limitations. The number of patients reported was small, all cases were performed by only one operator, and this was a single-institution study, not a controlled trial. Hence, more cases and comparative studies are required in the future.

Conclusions

GIESD can be safely performed for superficial esophageal cancer of the middle and lower esophagus on the gravity side. GIESD may become an alternative approach in gravity-side lesions of the middle and lower esophagus.

Competing interests

The authors declare that they have no conflict of interest.

References

[1] Hazama H, Tanaka M, Kakushima N et al. Predictors of technical difficulty during endoscopic submucosal dissection of superficial esophageal cancer. Surg Endosc 2019; 33: 2909–2915

[2] Yano T, Nemoto D, Ono K et al. Gel immersion endoscopy: A novel method to secure the visual field during endoscopy in bleeding patients (with videos). Gastrointest Endosc 2016; 83: 809–811

[3] Akasaka T, Takeuchi Y, Ishida H et al. A novel gel immersion technique using a bipolar needle-knife in endoscopic submucosal dissection for superficial gastrointestinal neoplasms. Ann Gastroenterol 2018; 31: 247

[4] Yano T, Takezawa T, Hashimoto K et al. Gel immersion endoscopy: Innovation in securing the visual field – clinical experience with 265 consecutive procedures. Endosc Int Open 2021; 9: E1123–E1127

[5] Miyamoto S, Suzuki K, Kinoshita K. Efficiency of a novel gel product for duodenal ulcer bleeding. Dig Endosc 2021; 33: e63–e64

[6] American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology 2002; 96: 1004–1017

[7] Hamada K, Kawano K, Yamauchi A et al. Efficacy of endoscopic submucosal dissection of esophageal neoplasms under general anesthesia. Clin Endosc 2019; 52: 252–257

[8] Yano K, Yano T, Nagayama M et al. Hemostasis of an actively bleeding lesion at the ileocecal valve by low-pressure endoscopy using the gel immersion technique. VideoGIE 2021; 6: 184–186

[9] Nakano Y, Tashima T, Ryozawa S et al. Conversion from conventional esophageal endoscopic submucosal dissection to the gel immersion method. Endosc Int Open 2021; 12: E1756–E1757