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[Original Article]

Gastric endoscopic submucosal dissection using sodium carboxymethylcellulose as a new injection substance

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Abstract

AIM : To investigate the feasibility of endoscopic submucosal dissection (ESD) using sodium carboxymethylcellulose (SCMC) for gastric cancer.

METHODS : During October 2011 through April 2013, 98 lesions from 98 patients who underwent ESD using SCMC (ESD-SCMC) for early gastric cancer were enrolled in this study. Two endoscopists, who had each performed fewer than 30 ESD procedures (less-experienced ESD physicians), performed ESD-SCMC under the supervision of two experts. The primary outcome was the *en bloc* resection rate. Secondary outcomes included the complete resection rate, the procedural time, the bleeding rate after SCMC injection, and complications. Patient characteristics, time necessary for hemostasis after SCMC injection, rate of treatment completion by less-experienced ESD physicians alone, and the effects of SCMC during ESD and on resected specimens were also evaluated.

RESULTS : The *en bloc* resection rate was 100%. Among these resections, 87.8% of the cases were completed by a less-experienced ESD physician alone. The complete resection rate was 98.0%. The mean total procedural time was 75.4 min. The mean incidence of intraoperative bleeding following SCMC local injection was 1.7 times. No bleeding was observed after SCMC injection in 29.6% of cases (29/98). Five complications occurred: one case of microperforation (1.0%) and four cases of postoperative bleeding (4.0%). SCMC remained in the submucosa. The submucosa was readily manipulated when the deep submucosa was dissected, even after placing the specimen on a slide.

CONCLUSION : ESD-SCMC is feasible for the resection of early gastric cancer.

Key words : endoscopic resection, gastric cancer, injection, sodium carboxymethylcellulose, training

Introduction

Endoscopic submucosal dissection (ESD) was developed for the resection of gastrointestinal

tumors¹⁻¹⁰⁾. However, this technically difficult procedure can cause adverse events such as perforation or bleeding. The maintenance of clear visualization of the submucosa is important to mini-

mize these events. Saline was used previously in endoscopic mucosal resection (EMR). Unfortunately, a saline-induced cushion subsides quickly, which renders this cushion ineffective in ESD. However, ESD requires that the cushion be retained for a longer period than for EMR. Several studies have evaluated the effectiveness of other injection substances, including glycerol¹¹, dextrose¹², sodium hyaluronate (SH)⁷⁻¹⁰, fibrinogen mixture¹³, sodium alginate^{14,15}, autologous blood^{16,17}, photocrosslinkable chitosan¹⁸, polymers^{19,20}, and mesna^{21,22}. Moreover, it is crucially important that nothing in the selected substance damage the submucosa or muscularis propria (MP)²³. Several comparative reports have described SH as superior to other substances²³⁻²⁵. However it gradually diminishes during the procedure. Therefore, substances that can be retained in the submucosa for long periods are expected to be more useful for ESD.

Sodium carboxymethylcellulose (SCMC), a cellulose ether with a carboxymethyl radical introduced into the hydroxyl, is generally used to increase the viscosity of water-based products²⁶⁻²⁸. Yamazaki *et al.*²⁹ reported SCMC as a submucosal injectant in a swine model. These investigators found that ESD was completed with no difficulty because the submucosa remained elevated for a sufficient period of time. These findings suggest that SCMC can support safe and reliable ESD in clinical applications. This study evaluated the feasibility of ESD-SCMC for the resection of early gastric cancer.

Methods

Patients

This study enrolled 98 gastric cancer patients who underwent ESD-SCMC at Fukushima Medical University Hospital during October 2011 through April 2013. Written consent was obtained from patients who satisfied the following eligibility criteria: intramucosal differentiated-type adenocarcinoma without ulceration, intramucosal differentiated-type adenocarcinoma with ulceration of 3 cm or lesser diameter, and intramucosal undifferentiated-type adenocarcinoma without ulceration of 2 cm or lesser diameter. Patients were excluded if they had major organ failure. This study was performed with the approval of the Ethics Committee at Fukushima Medical University (number 1122) and was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) as number UMIN000011489.

Preparation of 1.5% SCMC

Six grams of SCMC (Kosou Chemical Co. Inc., Tokyo, Japan) was mixed in 400 ml of saline and dissolved overnight using a rotor. An opaque 50-ml bottle was filled with the completely dissolved solution, which was sterilized at 115°C for 30 min using an autoclave. The bottle was stored at 4°C in a refrigerator. The solution was injected shortly after opening the bottle.

ESD-SCMC procedure

For this study, ESD was performed using an endoscope (GIF-Q260 J; Olympus Medical Systems Corp., Tokyo, Japan) and a VIO electrosurgical unit (ERBE Elektromedizin GmbH, Tübingen, Germany). Marking was performed with a dual knife (Olympus Medical Systems Corp., Tokyo, Japan) (Fig. 1a). A 1 : 1 solution of 0.4% SH (MucoUp; Johnson & Johnson K.K., Tokyo, Japan) and glycerol (Chugai Pharmaceutical Co. Ltd., Tokyo, Japan) was injected into the submucosa using a 25-G needle (Impact-flow; TOP Corp., Tokyo, Japan). A circumferential incision into the mucosa (Fig. 1b) was made using a Dual knife or an IT Knife2 (Olympus Medical Systems Corp., Tokyo, Japan). Submucosal dissection was done using an IT Knife2 after the mucosal incision. Once the submucosa was sufficiently visible, the 1.5% SCMC solution was injected into the submucosa (Figs. 1c, 1d). An inflation device (Alliance II; Boston Scientific Corp., Tokyo, Japan) was used to inject the solution (1-2 ml per injection) because 1.5% SCMC is highly viscous³⁰. Additional volumes of SCMC were injected as necessary when the "cushion" showed signs of subsiding. Any visible large vessel in the submucosa was cauterized using hemostatic forceps (Coagrasper; Olympus Medical Systems Corp., Tokyo, Japan), which were also used for ablation in case of bleeding. Hemostatic forceps were used to ablate any vessels on the surface that were cut during ESD and to eliminate any SCMC residue on the submucosa surface after ESD (Fig. 1e).

Two endoscopists (K.W. and J.N.), each of whom had performed fewer than 30 ESD procedures (less-experienced ESD physicians), performed ESD-SCMC under the supervision of two expert endoscopists (T.H. and M.S.), each of whom had performed more than 200 ESD procedures. An expert endoscopist took over when the procedural time was expected to exceed 2 hr or when complication such as perforation or respiratory depression occurred.

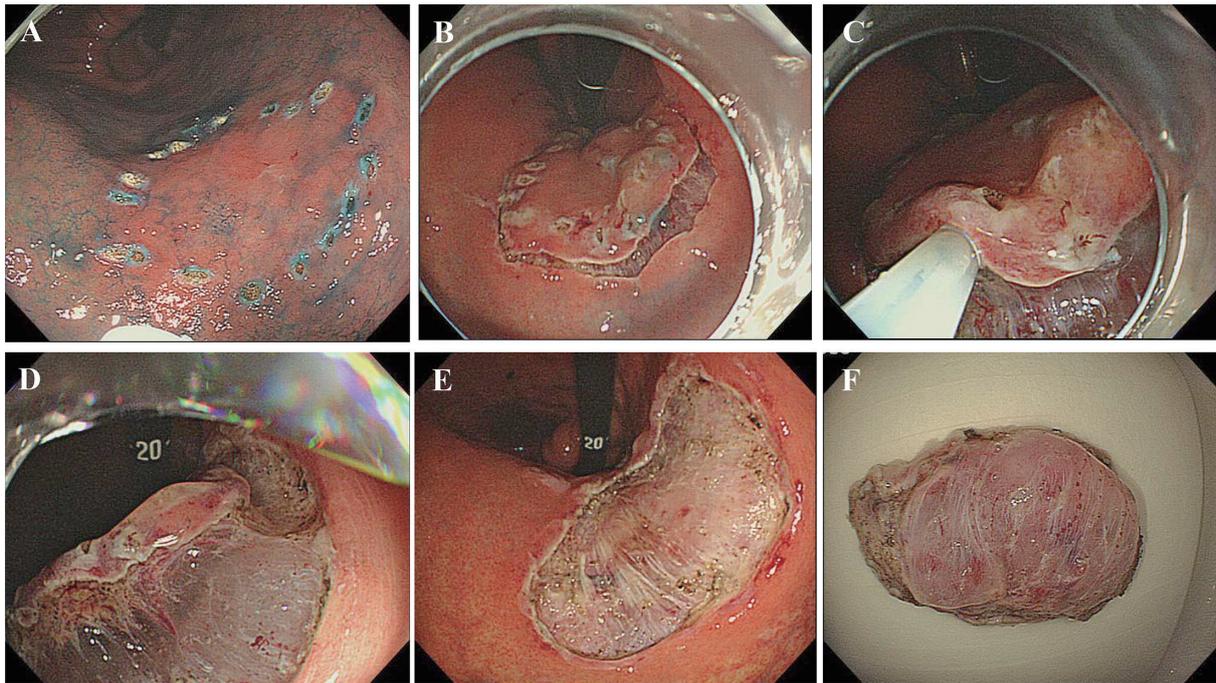


Fig. 1. ESD-SCMC procedure.

- a) Marking the outside of the tumor.
- b) Injecting the mixed sodium hyaluronate and glycerol solution outside the marking and proceeding to the circumferential mucosal incision.
- c) When the submucosa became sufficiently visible after the circumferential mucosal incision, SCMC was injected into the submucosa.
- d) During submucosal dissection. The submucosa elevated by SCMC was visible.
- e) Vessels on the dissected surface after ESD are ablated using hemostatic forceps. SCMC remaining on the dissected surface of the submucosa was removed to the greatest extent possible using hemostatic forceps. The ESD procedure was complete.
- f) Residual SCMC was visible on the surface on the submucosa side of the resected specimen.

Antiplatelet drugs were stopped 3-7 days before the procedure when the patient was administered an antithrombotic. These drugs were restarted 1-7 days after the procedure. Warfarin was stopped for seven days before the procedure. Heparin was administered intravenously until the day of the procedure. Heparin was stopped 4-6 hr before the procedure and was restarted immediately after the procedure. Warfarin was restarted the day after the procedure. Heparin was stopped.

Clinical outcomes

The primary outcome was the *en bloc* resection rate. Secondary outcomes included the complete resection rate, the procedural time, the bleeding rate after SCMC injection, and complications. Patient characteristics, time necessary for hemostasis after SCMC injection, rate of treatment completion by the less-experienced ESD physicians alone, and effects of SCMC during ESD and on resected specimens were also evaluated. The procedural time was de-

defined as the period of time from the start of the mucosal incision to the end of submucosal dissection. Perforation was defined as a case in which a hole toward the gastric wall was found during surgery or free air was observed in a postoperative radiograph. Postoperative bleeding was defined as a case in which bloody emesis or melena was observed after surgery. Advanced intraoperative bleeding was defined when the blood hemoglobin (Hb) content dropped by 2 g/dL or more in blood examinations the day after the procedure. The presence of free air was examined in radiographies immediately after the procedure. Histopathological diagnoses were conducted based on the Japanese classification of gastric carcinoma³¹. We initiated oral administration of a proton pump inhibitor from the morning of the procedure and continued the administration for eight weeks. Endoscopic examinations were performed one week and eight weeks after the procedure. The mean values are expressed as the mean value \pm standard deviation (range, minimum-maximum value).

Results

ESD-SCMC treatment outcomes

Table 1 presents patient characteristics. Patients included 69 men and 29 women with average age of 73.9 years. The mean tumor diameter and mean resected specimen diameter were, respectively, 18.0 mm and 40.8 mm.

The *en bloc* resection rate was 100%. Among these resections, 87.8% of the cases were completed by a less-experienced ESD physician alone. The complete resection rate was 98.0%. The incomplete resections occurred because of positive vertical margins in one MP cancer case and in one SM2 case. The mean total procedural time was 75.4 min. The mean count of intraoperative bleeding following SCMC local injection was 1.7 times. No bleeding was observed after SCMC injection in 29.6% of the cases (29/98). No difference was found in the bleeding count according to location (upper part, 1.8 times; middle part, 1.7 times; and lower part, 1.5 times). The mean time necessary to perform hemostasis after SCMC injection was 1.5

min (Table 2).

Two SM2 cases and one MP case underwent additional surgery after ESD-SCMC. No remaining cancer was observed in the surgically resected specimens. However, lymph node metastasis was detected in one SM2 cancer case. The average follow-up period was 29.1 months (20–38), until the end of December 2014. No local or metastatic recurrence was observed. One patient died of a different disease during this period.

Complications

Complications occurred with one perforation (1.0%) and four postoperative bleedings (4.0%). However, no severe intraoperative bleeding was observed (Table 2). In the perforation case, no perforation was found during the procedure. However, a slight amount of free air was detected immediately after the procedure using chest radiography. Abdominal pain and rise of inflammatory reaction was not observed. Therefore, the patient conservatively healed by fasting and intravenous administration of antibiotics. All postoperative bleeding

Table 1. Patient characteristics

Number	98 patients, 98 lesions
Sex	Male 69, Female 29
Age (year)*	73.9 ± 8.0 (41–88)
Location	Upper 27, Middle 38, Lower 23
Tumor diameter (mm)	18.0 ± 11.1 (3–56)
Resected specimen diameter (mm)	40.8 ± 12.3 (22–80)
Tumor depth	M 84, SM1 4, SM2 9, MP 1
Ulceration	9.2% (9/98)
Intake of antithrombotics	15.3% (15/98)

*Mean values are expressed as the mean value ± standard deviation (range, minimum–maximum value).

M, mucosa; SM1, shallow submucosa; SM2, deep submucosa; MP, muscularis propria

Table 2. Treatment outcomes of ESD-SCMC

<i>En bloc</i> resection rate	100% (98/98)
Complete resection rate	98.0% (96/98)
SCMC dose (ml)*	5.2 ± 3.8 (1–25)
Total procedure time (min)*	75.4 ± 44.4 (15–340)
Time from the start of mucosal incision to SCMC injection (min)*	48.3 ± 26.6 (8–138)
Time from SCMC injection to dissection completion (min)*	27.0 ± 29.1 (2–248)
Case of bleeding after SCMC injection (times)	1.7 ± 1.8 (0–10)
Time taken for hemostasis of bleeding after SCMC injection (min)	1.5 ± 2.8 (0–17.3)
Complication (<i>n</i> (%))	Perforation: 1 (1.0%), Postoperative bleeding: 4 (4.0%)
Share of treatments completed solely by trainees (%)	87.8% (86/98)

*Mean values are expressed as the mean value ± standard deviation (range, minimum–maximum value).

cases were treated successfully using endoscopic hemostasis. The recovery process of post-ESD artificial ulcers in all 98 cases was similar to the recovery process of traditional ESD.

Effects of SCMC during ESD and on resected specimens

SCMC cushions in the submucosa were maintained during the procedure even after ablation of the vessels (Fig. 2a). The submucosal vessels are

easily identified. No additional injection was necessary after ablation of the vessels because the cushion was maintained. The SCMC weight also played an important role because it displaced the lesion downward in the direction of gravity and facilitated traction (Figs. 2b). SCMC remains in the submucosa (Fig. 3a). The submucosa was sufficiently easy to manipulate when the deep submucosa was dissected, even after placing the specimen on a slide. SCMC caused no growth in the nest of cancers that infiltrated the submucosa. The presence

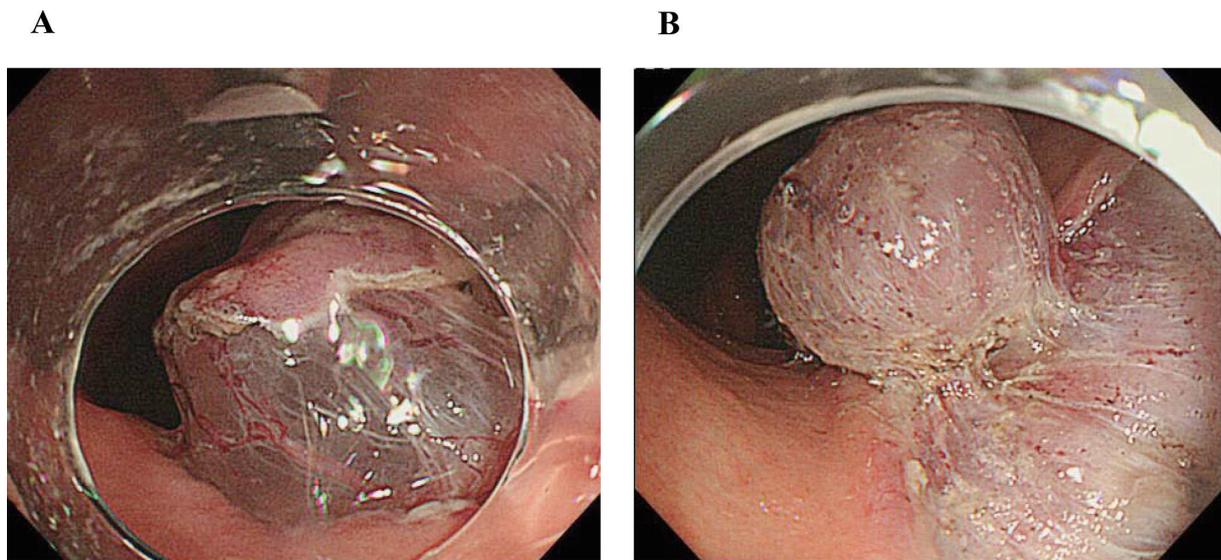


Fig. 2. Endoscopic views during submucosal dissection after SCMC injection.

- Production of a highly elevated cushion that rendered the submucosal vessels clearly visible.
- Weight of SCMC facilitated traction.

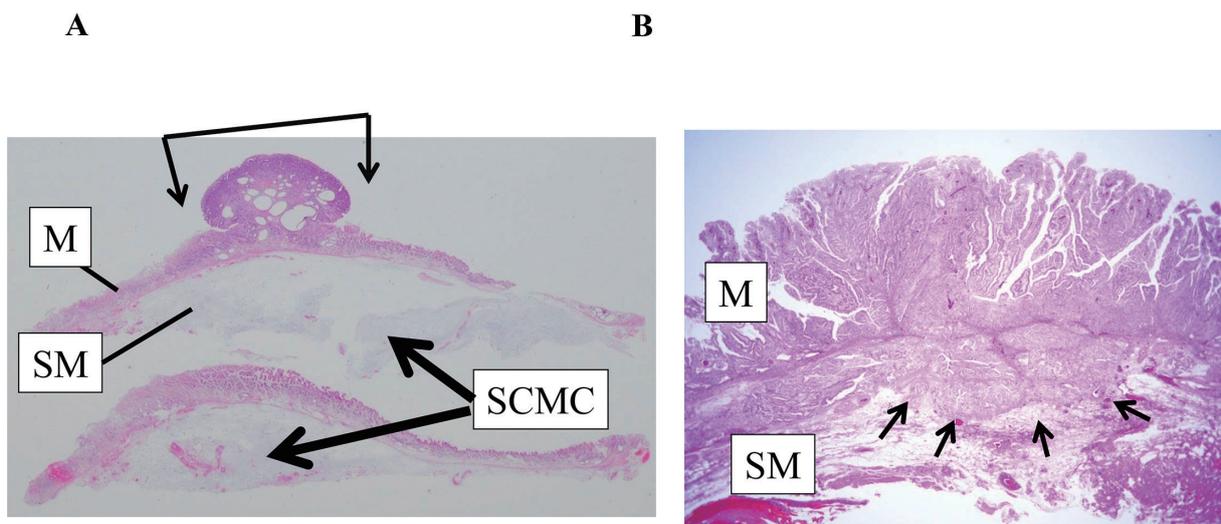


Fig. 3. Histopathological views of ESD-SCMC cases.

- M cancer case (hematoxylin and eosin stained): The tumor (indicated by the thin arrows) was localized in the mucosa (M). Sufficient residual SCMC (indicated by the thick arrows) was observed in the submucosa (SM).
- SM2 cancer case (hematoxylin and eosin stained): The tumor (indicated by the thin arrows) had infiltrated from the mucosa (M) to the submucosa (SM). However, no problem occurred with evaluation of the depth diagnosis.

of SCMC did not interfere with distinguishing SM1 or SM2 in histopathological cancer depth evaluations (Fig. 3b).

Similarly to other injection substances, in cases where insufficient space in the submucosa inhibited or prevented the entry of SCMC (e.g., in cases complicated by ulceration or scarring, cases with tumor infiltration deep in the submucosa, or cases with high submucosal vessel density), it was sometimes difficult to elevate the mucosa sufficiently to produce an adequate cushion. However, also in such cases, it was possible to perform submucosal dissection safely by SCMC injection around the scarring or vessels to produce a sufficient submucosal cushion and by recognizing the muscle layer accurately.

Discussions

Although ESD is accepted as an effective treatment for early gastric cancers, it requires proficiency in endoscopic techniques. Therefore, ESD often requires prolonged procedures. A pressing issue during ESD is the means of obtaining clear visibility of the submucosa because the lack of a clear view might cause severe complications such as perforation and bleeding. Therefore, some submucosal injectant that can be sustained for a long time is needed. The results of our present study show a comparable technical success rate and an acceptable complication rate. Moreover, SCMC did not damage the surrounding tissues, which was demonstrated by other injectants.

Yamasaki *et al.*²⁹⁾ performed ESD-SCMC using a swine model. They reported that an appropriate cushion was produced and retained with local injection in the submucosa. This cushion was sufficient to enable dissection of the lesion from the MP because it provided viscosity of 200 mPa·S or greater. However, the use of 2.5% SCMC in their study posed problems for clinical applications because that concentration requires an extremely thick 18-G puncture needle. In addition, SCMC tends to leak through the puncture hole. Later, Yamasaki *et al.*³⁰⁾ retrospectively evaluated the efficacy of ESD-SCMC in gastric neoplasms in a clinical study. They compared the sectional height of the resected specimen among 1.5% and 3.0% SCMC and 0.2% SH. The sectional height of the resected specimen of 1.5% SCMC group (mean 7.8 mm) and 3.0% SCMC group (mean 7.7 mm) was greater than that of 0.2% SH group (mean 4.1 mm). However, the sectional height of resected specimen of 1.5% and 3.0% group was not significantly different.

Moreover, considering the ease of injecting the SCMC through a 25-G puncture needle, 1.5% SCMC was easier than 3.0% SCMC. They concluded that the 1.5% SCMC concentration is the most appropriate. Based on this report, we selected 1.5% SCMC for gastric ESD. Nevertheless, 1.5% SCMC is still too viscous for local injection using hand pressure. Therefore, we used an inflation device that is normally used for balloon dilation. Experienced assistants performed the 1.5% SCMC injections using an inflation device.

This study evaluated the feasibility of ESD-SCMC for the resection of early gastric cancer. The most important index of feasibility is the possibility of complete *en bloc* resection. Difficulties in submucosal dissection increase the probability of accidentally cutting the tumor in the mucosa, which can engender fractional excision. Additionally, the shallow dissection surface can make the deep margin positive even when the lesion is intramucosal. However, the dissection results in our study were favorable. The *en bloc* resection rate was 100%. The complete resection rate was 98.0%. The high complete resection rate likely occurred because the local injection of SCMC sufficiently elevated the submucosa. The heavy weight of the SCMC might facilitate the application of traction. SCMC has hardness in comparison to the conventional injectants. However, it was possible to dissect the submucosa easily using the Endocut mode and Coagulation mode of the electrosurgical unit, without special endoscopic techniques. The mean count of intraoperative bleeding was 1.7 times after SCMC injection. No hemostasis was necessary in 29.6% cases. This result was likely the result of the high, long-lasting cushion produced by the SCMC injection, which improved the submucosal vessel visibility and which enabled the application of preventive hemostasis to submucosal vessels that had a high risk of bleeding before actual bleeding occurred. Complications included only a single perforation and four cases of postoperative bleeding. These results demonstrate the safety of ESD-SCMC.

This study had some limitations. First, this study was a single-arm trial. However, the efficacy and safety of ESD-SCMC are likely to be similar to those of ESD using SH. We analyzed 79 early gastric cancer patients who underwent ESD using SH performed by expert surgeons from April 2009 through March 2010 as a historical control. The complete *en bloc* resection rate was 97.5%. The mean procedure time was 79.9 min in these data.

Perforation occurred in 2.5% of cases. Postoperative bleeding occurred in 6.3%. These results demonstrate that the efficacy and safety of ESD-SCMC are apparently equivalent to ESD using SH. Second, SCMC was used only during the submucosal dissection phase because of the possibility of injection into the MP when SCMC was used during the mucosal incision phase. Therefore, we subsequently conducted a randomized controlled trial between ESD using SCMC only and ESD with SH only (UMIN000015382). This study evaluated the feasibility of SCMC from the mucosal incision phase to the submucosal dissection phase.

In conclusion, ESD-SCMC enables performance with a high rate of *en bloc* resection and low incidence of complications. Therefore, ESD-SCMC is feasible for the resection of early gastric cancer.

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Conflicts of interest disclosure

The authors declare that they have no conflict of interest related to this study.

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