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NEW TECHNOLOGY

Colorectal endoscopic submucosal dissection using novel articulating devices: a comparative study in a live porcine model

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Abstract

Background and aims Colonic endoscopic submucosal dissection (ESD) is time-consuming and bears a high risk of perforation. The aim of the present study was to compare the safety and efficacy between novel articulating devices and conventional ESD in live porcine colon models.

Methods Thirty ESDs in ten pigs were carried out at three different locations (15, 25, and 35 cm from the anus) by the conventional method ($n=15$) and by the new method ($n=15$). Procedure times, adverse events (perforation, bleeding), and damage to the muscular layer were recorded, and the ESD time per unit area of the specimens was calculated.

Results The perforation rate using the conventional method was 6.7% (1/15), whereas that using the new method was 0.0%. The number of sites of muscular damage was significantly lower in the new than conventional method (6 vs. 37, respectively; $P=0.024$). The mean procedure time was significantly shorter in the new than conventional method (4.6 ± 2.0 vs. 7.0 ± 4.1 min/cm^2, respectively; $P=0.042$).

Conclusions Use of the new ESD method allows for reduced adverse events and a shortened resection time.

Keywords Endoscopic submucosal dissection · ESD · Novel device · Articulating device · Standard endoscope · Colon

Abbreviation

ESD Endoscopic submucosal dissection

Endoscopic submucosal dissection (ESD) is an effective treatment that provides high *en bloc* and curative resection rates for superficial gastrointestinal neoplasms [1–4]. However, major problems of ESD are the time-consuming nature of the procedure and the high risk of perforation, especially when used to treat colonic neoplasms [5–7]. These problems are mainly due to the limited degree of freedom of existing devices and the absence of traction during the procedure [8]. Thus, an articulating device with an easy-to-control system and a second device for raising the tissue is desirable. Several ESD tools have been developed, but their size or other technical parameters limit their use in daily practice [9–13].

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We have developed a 2.6-mm-diameter articulating device that can be used with standard endoscopes [14, 15] (Figs. 1, 2). Although we previously reported the usefulness of the device in ESD of the porcine stomach, the usefulness of the device in colonic ESD remains unknown. Therefore, the aim of the present study was to compare the safety and efficacy between this new ESD system and conventional ESD in an in vivo porcine colon.

Methods

Study design

This study was performed in ten healthy domestic pigs (weight range 29.2–35.8 kg). The experimental protocol was approved by the Animal Care and Use Committee of Kyushu University, Japan (Approval Number: A27-160-0). All study animals were handled according to national and institutional guidelines. The pigs were fasted for 24 h before each procedure. After the pigs had been placed under general anesthesia, tap water enemas of about 1000 ml were administrated through an endoscope channel to clear the distal part of the colon. ESD was performed at three locations in the colon: 15, 25, and 35 cm from the anus. The following procedure was used to create artificial lesions. The lesion area was marked by a device approximately 3 × 3 cm in size. The size of the lesion was estimated by the distance markers imprinted on the device; the space between the device tip and white marker ring measured 30 mm.

Fig. 1 Tip of an endoscope equipped with two novel articulating devices. One is a grasper inserted into the original channel, and the other is an electric knife inserted into the additional tube attached to the hood (hood outer diameter: 14 × 16.8 mm, additional tube outer diameter: 4.0 mm). The very small bending radius of these tools enables the camera to very closely approach the lesion, making the ESD procedure safer

ESD using the novel device was generally performed following the same steps as in the clinically established method. Markings and mucosal incisions were created by an electric knife only, while submucosal dissection was performed using both a grasper and a knife (Fig. 3, Video 1). Submucosal application of indigo-dyed glycerol by a standard injection needle was performed after marking and later if necessary. After completion of the whole procedure, the specimens were fixed on a corkboard and their sizes were measured (Fig. 4). All interventions were carried out by a single operator (Y.O.) with experience performing more than 50 ESD procedures. The locations were chosen according to the computer-generated randomization list, and ESD was conducted using either the conventional or newly designed technique. Computer randomization was programmed so that the case numbers of the new and conventional methods as well as the locations were evenly distributed (Fig. 5).

The primary endpoint was safety, assessed by the rate of adverse events (perforations and bleeding) during the ESD procedures, and efficacy, measured by the time needed to complete the procedures. The secondary endpoint was the number of sites of muscular damage.

Device description

The novel devices were developed at the Center for Advanced Medical Innovation, Kyushu University, Fukuoka, Japan. The devices include forceps and electric knives that have an articulating part for movement in the up/down and right/left directions. The articulating forceps is inserted into the original channel of the endoscope, and the articulating electric knife is inserted into an additional channel that is made from elastic material and is attached to the hood (Fig. 1). The endoscope is fixed onto the same base structure and can be fully manipulated by a single operator without removing the endoscope from the base structure (Fig. 2). The details of the system and user interfaces have been previously described [9]. A dual knife (KD-650Q; Olympus Medical Systems, Tokyo, Japan) and transparent hood (D-201-11804; Olympus Medical Systems) were used for the conventional ESD procedure. A gastrointestinal endoscope (GIF-Q260J; Olympus Medical Systems) was used for all animal experiments. A fluid mixture of glycerol and indigo carmine was submucosally injected to create a cushion in the submucosal layer. A VIO 300 D generator (ERBE, Tübingen, Germany) was used as the source of radiofrequency energy. For the standard ESD procedure, the mucosal incisions were created with EndoCut I, effect 1, duration 3, interval 3, and the submucosal dissection and hemostasis were performed with SWIFT COAG 30W.

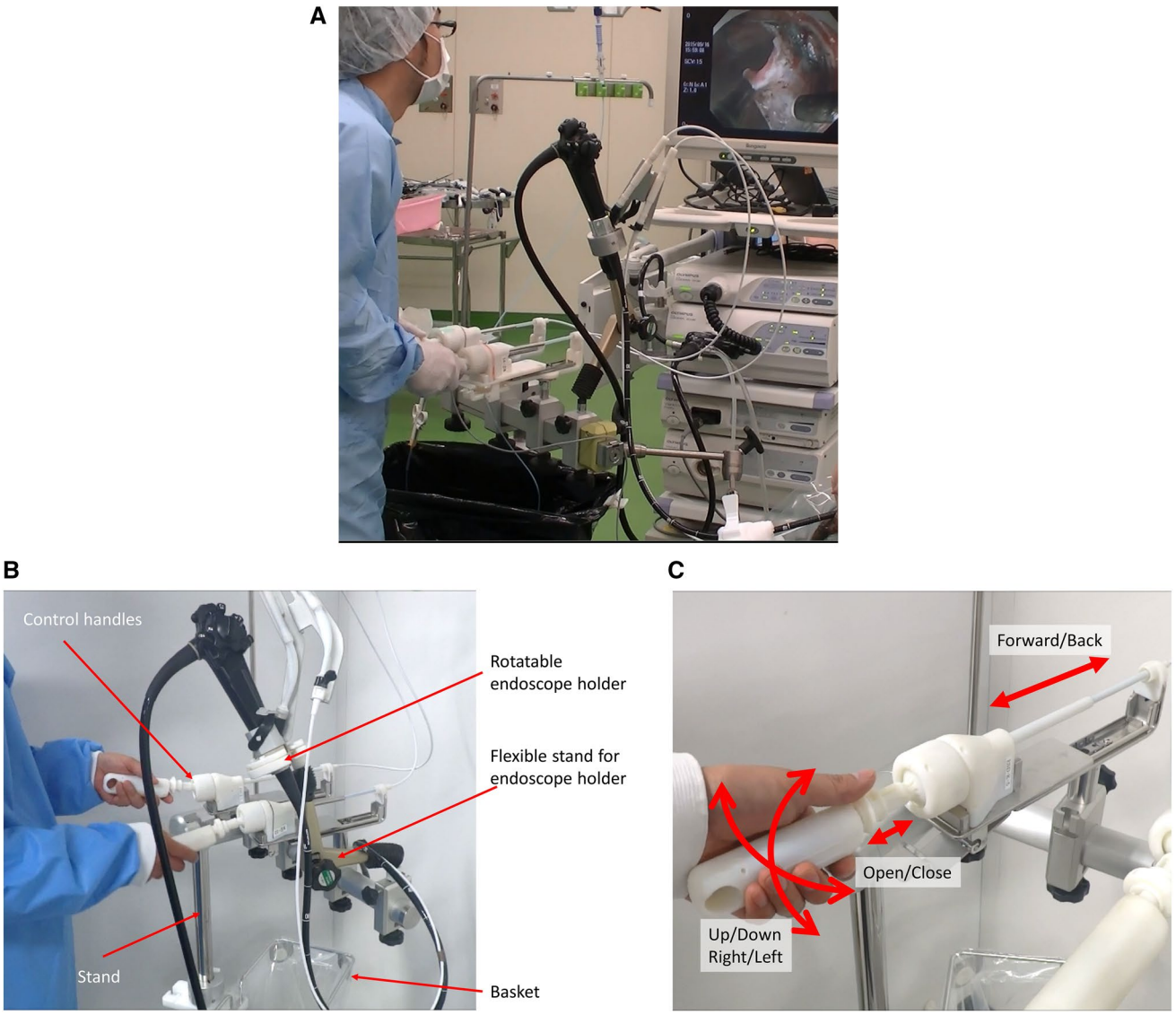

Fig. 2 **A** Experimental setup of in vivo porcine colonic ESD using the novel devices. The two handles that the operator is holding are controllers for the novel articulating devices. The endoscope is held by the same platform but is easily manipulated by a single operator. **B** Labeled photograph of the two articulating devices, including their handles and stand. **C** Labeled close-up of the handles

Outcome measurement

The following parameters were recorded for all ESD procedures: *en bloc* or piecemeal resection, procedure time, adverse events (perforation, bleeding), and number of sites of muscular damage. After completion of the whole procedure, the lengths of the long and short axes of the specimen were measured. The procedure time was recorded in minutes. Because the area of resected tissue was slightly different in each lesion, the time-to-area ratio was calculated for each ESD. The ESD time per unit area was then calculated using the formula $\pi ab/4$, where a is the length of the long axis and b is the length of the short axis. A perforation was defined as a visible hole in the colonic wall accompanied by air leakage in the abdominal cavity. Any bleeding that required use of an extra hemostasis device was defined as bleeding. We also counted the number of sites of damage to the muscular layer that were defined as resection bed muscle fiber degeneration, such as thermal injury, without the presence of perforation (Fig. 6).

Statistical analysis

Statistical analysis was performed by the two-sided Mann–Whitney U test to compare data that were not normally distributed. Differences with a P value of < 0.05

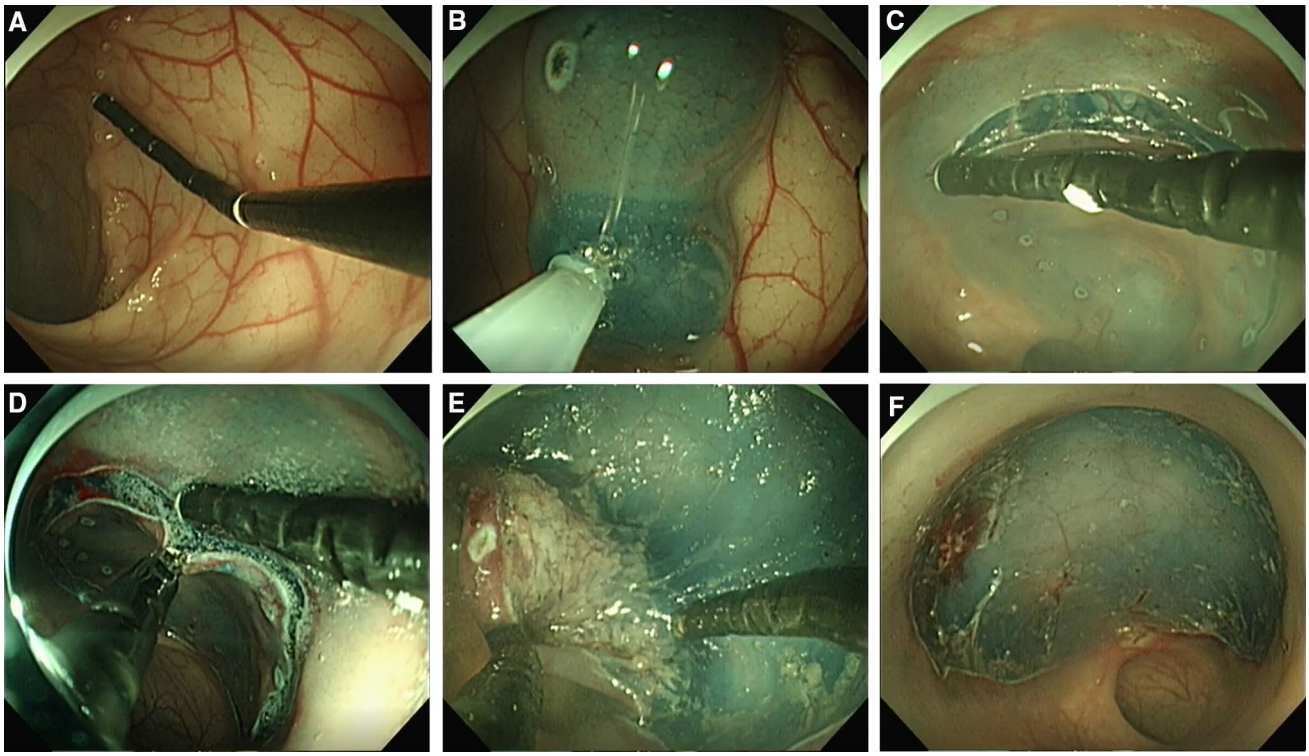

Fig. 3 Endoscopic view during in vivo porcine colonic ESD. **A** Marking by novel device. **B** Injection by conventional needle. **C** Circumferential incision by novel device. **D** Beginning of dissection using two novel devices. **E** Performance of dissection using novel devices. **F** After completion of the whole procedure

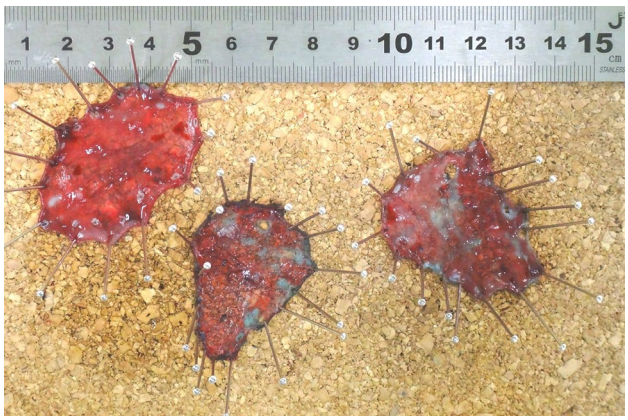

Fig. 4 Colonic specimens. The right and middle specimens were dissected by the conventional method. The left specimen was dissected by the novel devices. Some damage (discoloration) can be observed in the right and middle specimens

were considered significant. The statistical analyses were performed using JMP Pro 11.0.0 (SAS Institute Inc., Cary, NC, USA).

Results

Thirty ESD procedures were carried out at 3 different locations in the colon of 10 pigs (15, 25, and 35 cm from the anus). Of these ESD procedures, 15 were performed using the conventional method and 15 were carried out using the new method. Both ESD methods led to complete *en bloc* resection in 100% of cases. The perforation rate using the conventional method was 6.7% (1/15), whereas that using the new method was 0.0% (0/15) (Table 1). However, perforation was a relatively rare event in our comparative study, and no significant reduction was revealed.

No significant bleeding occurred in any cases. The number of sites of muscular damage was significantly lower in the new than conventional method (6 vs. 37, respectively; $P=0.024$). The mean procedure time was also significantly shorter in the new than conventional method (4.6 ± 2.0 vs. 7.0 ± 4.1 min/cm^2, respectively; $P=0.042$) (Fig. 7).

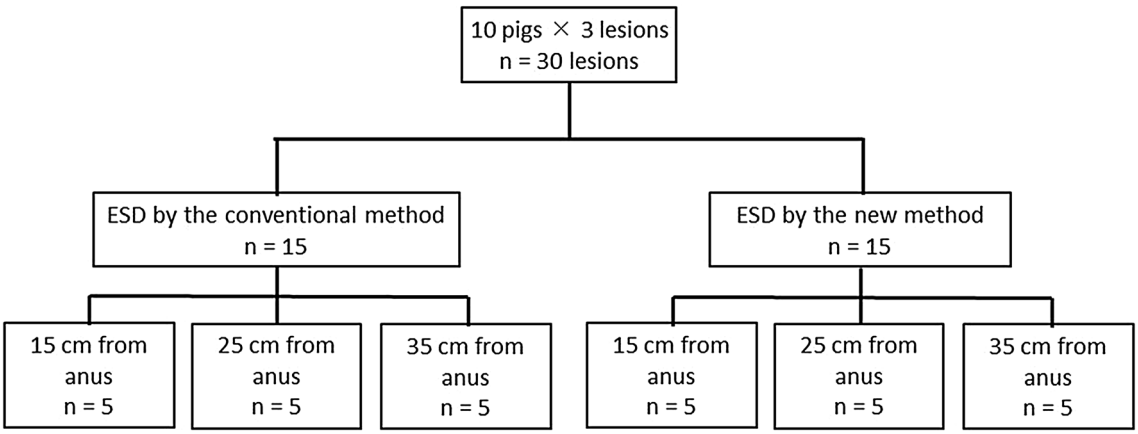

Fig. 5 Allocation of all cases in the present experiment. In each porcine colon, three lesions at 15, 25, and 35 cm from the anus were created. Computer randomization was performed so that the case numbers of the new and conventional methods as well as the locations were evenly distributed

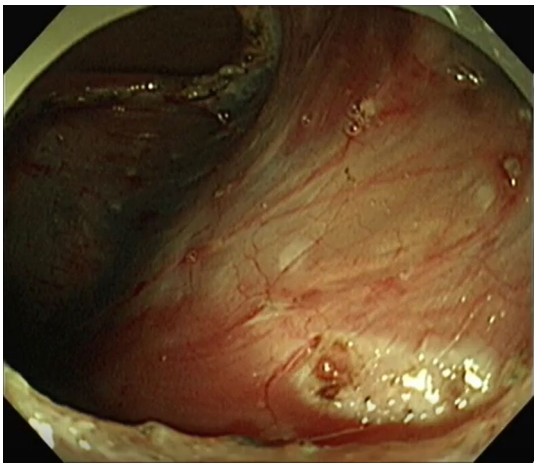

Fig. 6 The resection bed after performing ESD, with thermal damage to the muscle layer

Discussion

This is the first comparative study of the performance of the new ESD method versus conventional ESD in porcine colons. High safety and efficacy of the new ESD method in the porcine colon were proven this study.

Our new method for ESD is equipped with two independently movable devices: one is a grasping forceps that can lift up the lesion, and the other is an electrocautery knife that can dissect the exposed submucosal layer. This new method facilitates ESD by replicating the "traction" in the endoscopic environment. The grasping forceps is used to grasp the lesion and expose the submucosal layer by traction. The electrocautery knife has the ability to both cut tissue and coagulate bleeding, like other conventional knives. In addition, the articulating forceps and knives have a small radius of bending. Therefore, performance of an operation close to the lens is possible, which helps to maintain a clear visual field. This new method allows for adequate traction and controllable exposure of the submucosal layer to ensure precise dissection. This reduces both tissue damage and the risk of perforation and enables shortening of the resection time.

The new devices are still in the process of being developed into a commercial product and will likely be disposable, as with other devices. Because they are equipped with a bending mechanism, they will probably cost somewhat more than conventional devices. However, the new devices can also be used with standard endoscopes, and the new method requires only one operator. Therefore, hospitals do not have to invest in new endoscopes for ESD; furthermore, the staff costs are lower in association with the new ESD method.

Setup for the devices involves only donning of the hood attached to the additional tube and inserting the two devices into the tube and original channel of the endoscope. The only other preparation required is carrying the equipment in or out and cleaning it beforehand. Therefore the setup time for using these devices is almost the same as for conventional ESD.

In the present study, the operator had experience performing seven ESD procedures with the new devices both in vivo and *ex vivo* before the animal experiment began. Even just these few prior experiences with ESD using the new devices made the operator comfortable controlling the new devices. In our past report [15], novice endoscopists performed ESD using the new devices at a speed similar to that of experienced endoscopists. The new devices seem to be promising tools that can lower the technical hurdle of colorectal ESD.

Table 1 Outcomes by lesion

Location※ (cm)	Size※※ (cm^2)	Time† (min)	Dissection speed†† (min/cm^2)	Perforation (*n*)	Number of muscular damage
Conventional method					
15 (*n* = 5)	10.9	41	3.9	0	0
25 (*n* = 5)	10.1	81	9.3	0	17
35 (*n* = 5)	10.0	75	8.1	1	20
New method					
15 (*n* = 5)	12.8	42	3.2	0	0
25 (*n* = 5)	14.9	69	4.7	0	1
35 (*n* = 5)	13.2	76	5.9	0	5

※Distance from anus

※※Mean size of resected tissue

†Mean dissection time

††Mean dissection speed

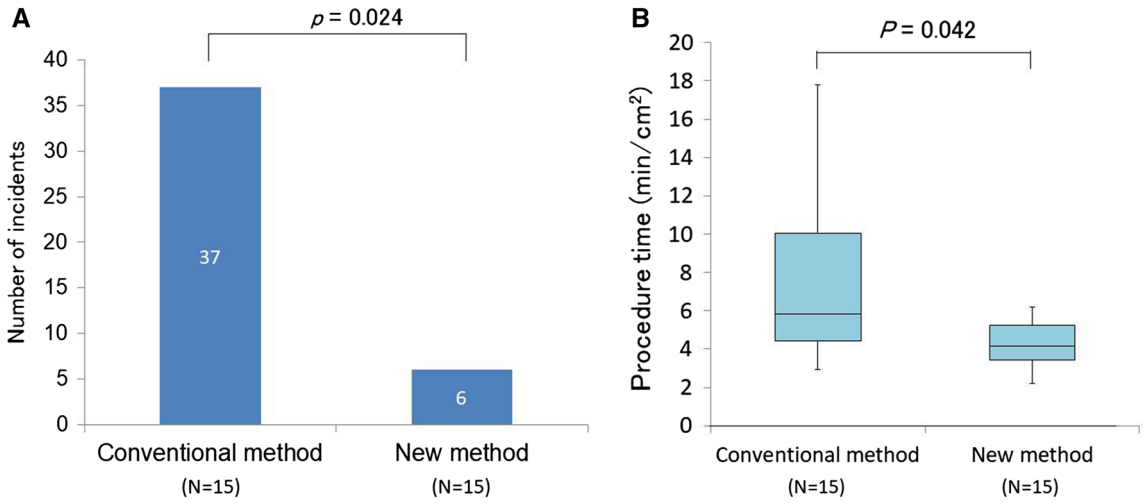

Fig. 7 **A** Number of sites of damage to the muscular layer. The new device significantly reduced the number of sites of damage. **B** Whole ESD procedure time per unit area. The procedure time using the new device was significantly shorter than that using the conventional method

This study had some limitations. First, the study included a limited number of cases. Second, a double-blind design could not be applied to this randomized controlled trial, and knowledge of the device might have introduced bias. Third, the procedure was conducted by a single operator in a single hospital. Although this likely allowed for better control of technical parameters, it may also mean that the results cannot be easily generalized. Therefore, future studies should assess whether these results can be obtained among different endoscopists and hospitals. Fourth, the structure of the pig colon differs from that of the human colon. Notably, performance of ESD in the pig colon is extremely difficult because the mucosal layer is thinner than that in a human. This makes it difficult to conduct precise submucosal dissection, increases the damage to the tissue, and finally leads to a higher perforation rate.

A further limitation of the study is that all ESDs were performed in locations that were easy to approach. We had to choose relatively standard locations and levels of difficulty to perform both ESD procedures in reproducible conditions. For example, we did not perform ESDs in retroflex positions or in the more proximal part of the colon, which requires deep insertion of the endoscope with formation of a long loop. Hence, we cannot deny the possibility that in locations that are more difficult to approach, conventional ESD might show better performance than the new method. However, the new devices can be used with standard endoscopes and can

be used in the retroflex position without problems and no difficulties were encountered with insertion into the porcine colons because the external tube and the new devices are thin and soft enough. We assume that the ability of the new articulating device and the use of two devices (electric knife and grasper) make dissection much easier in such difficult locations than when using the conventional method.

This study was an animal experiment involving in vivo porcine colons; hence, further trials under clinical conditions are necessary. Because the data from our study provided "proof of concept," we are now preparing for commodification of these novel devices.

In conclusion, colonic ESD using our novel devices was feasible in pig models. This comparative study showed that the new method can reduce adverse events and shorten the resection time in the thin porcine colon. Therefore, the feasibility of colonic ESD in humans using these novel devices appears promising.

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Author contributions YO: contributed to the study concept and design, the acquisition, analysis and interpretation of the data, the statistical analysis, and the initial drafting of the manuscript; RN: contributed to the study concept and design, the acquisition, the analysis and interpretation of the data, the drafting of the manuscript, and the critical revision of the manuscript for important intellectual content; SN, JA, SO, TM, ME, TI, KO, TA, TI: contributed to data collection and interpretation, and critically reviewed the manuscript; TK and MH: contributed to the critical revision of the manuscript for important intellectual content and approved the final draft for submission. All authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with ethical standards

Disclosures Drs. Okamoto, Nakadate, Nakamura, Arata, Ohuchida, and Hashizume have received research funding from Hogy Medical Co. Ltd., Japan. Drs. Oguri, Moriyama, Esaki, Iwasa, Akahoshi, Ikeda and Kitazono have no conflicts of interest or financial ties to disclose.

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