Efficacy of traction, using a clip-with-thread, for esophageal endoscopic submucosal dissection for esophageal lesions with fibrosis in an ex vivo pig training model

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ABSTRACT

Background/Aims: Endoscopic submucosal dissection (ESD) of recurrent esophageal carcinoma is technically difficult to perform due to submucosal fibrosis that develops after definitive chemoradiation therapy. Therefore, our aim was to evaluate the usefulness of clip-with-thread traction for ESD of esophageal lesions with submucosal fibrosis.

Materials and Methods: Four endoscopists excised 16 lesions by ESD in an ex vivo pig training model. Mock lesions (30 mm in diameter) were created, including a 10-mm area of submucosal fibrosis in the center of each lesion. Each endoscopist performed two ESDs with traction (ESD-T) and two without traction (ESD-N). The primary outcome was the time required for submucosal dissection. Secondary outcomes were the rate of en bloc (complete) resection and perforation during the procedure, and the total amount of solution injected.

Results: All esophageal ESDs were completed. The median dissection time was significantly shorter for the ESD-T group (median 12.5 min, interquartile range 10.2-14.5) when comparing to the ESD-N group (median 18.0 min, interquartile range 14.6-19.2) (P=0.040). The en bloc resection rate was 100% in both groups, with a rate of complete resection of 87.5% and a rate of perforation of 37.5% for both groups. The median amount of solution injected was not significantly different between the ESD-T (18.0 ml) and ESD-N (20.5 ml) groups (P=0.526).

Conclusion: Clip-with-thread traction improved the performance of ESD for lesions with submucosal fibrosis. However, the method might not reduce the risk of perforation, which remains an important clinical issue to resolve.

Keywords: Endoscopic mucosal dissection, traction, esophagus, fibrosis

INTRODUCTION

Endoscopic submucosal dissection (ESD) was originally designed as a treatment for early gastric cancer (1). Subsequently, the use of ESD was extended to the treatment of superficial esophageal squamous cell carcinoma (SCC), with reports of high en bloc resection rates (2-4). Furthermore, salvage ESD for superficial recurrence of esophageal SCC after definitive chemoradiation therapy (dCRT) is feasible and effective (5-7). However, this procedure is technically difficult to perform and time-consuming due to the formation of submucosal fibrosis after dCRT (5,6).

Various traction methods have been developed to assist ESD for the gastrointestinal tract (8), with the use of a clip-with-thread method proving to be simple and cost-effective (9-13). This method could be useful for esophageal ESD for SCC recurrence after dCRT, where lesions are complicated by submucosal fibrosis. The low number of patients with recurrence of esophageal neoplastic lesions after dCRT prevents clinical studies to be performed in order to determine the effects of the clip-with-thread traction on ESD for esophageal neoplasms with submucosal fibrosis. Therefore, in the absence of reports on the clinical outcome of using this technique, we

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created an *ex vivo* pig surgical training model to address this question.

MATERIALS AND METHODS

Statement of ethics

This study was conducted at our medical center. Our study protocol complied with the international guidelines for the use of animals in research and was approved by the Institutional Review Board of our medical center.

Generation of the ex vivo model

Four pig esophagi were obtained from fresh meat markets. To create the esophageal ESD model, an endoscopic overtube (TOP, Tokyo, Japan) was attached to one end of the esophagus for insertion of the endoscope, with the other end of the esophagus ligated. The esophagus was attached to a net that, itself, was fixed to a plastic case (Figure 1A). The plate electrode was attached around the esophagus. Four mock lesions were created in each esophagus for ESD. Lesions were located on the posterior wall of the middle or

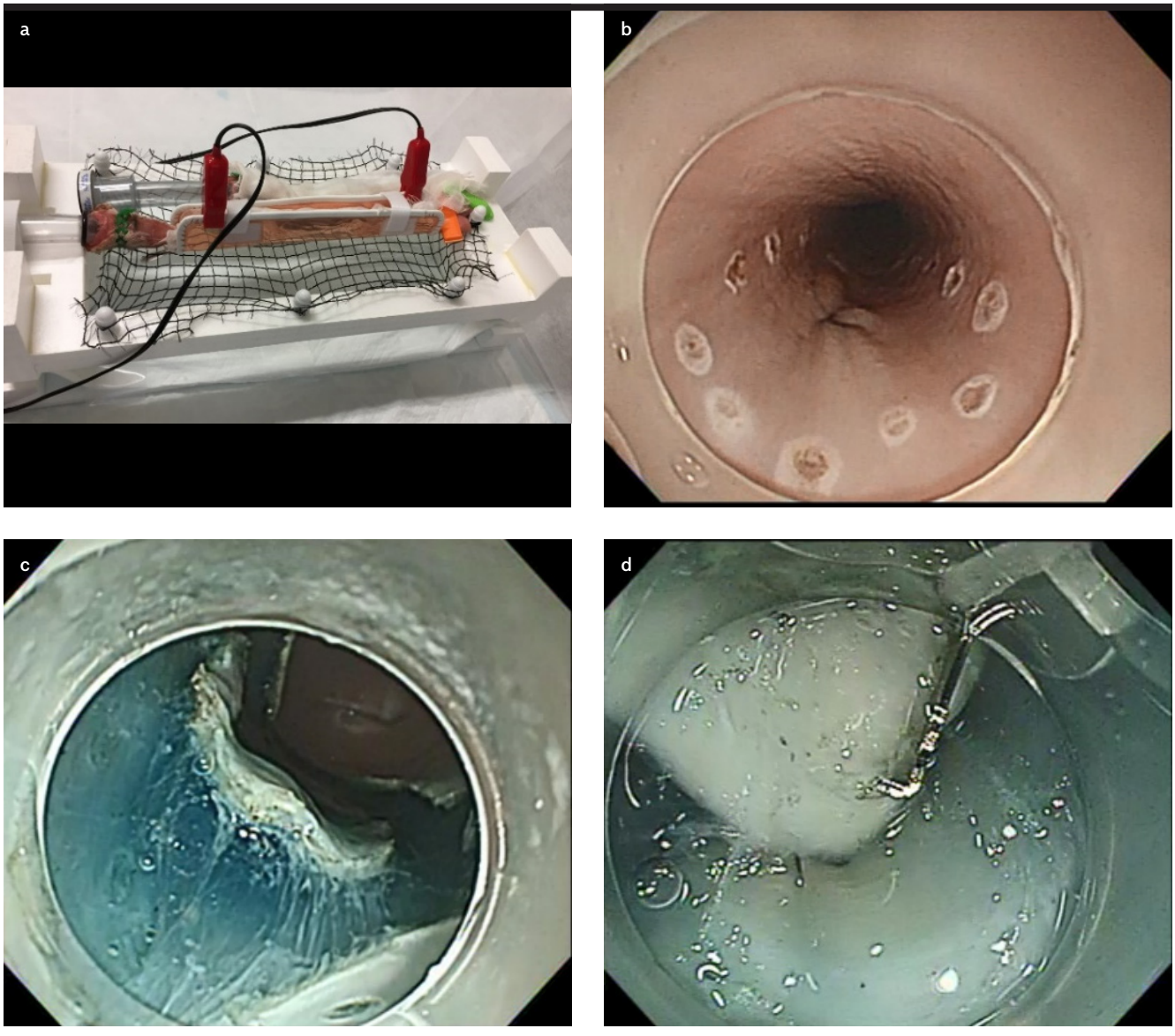

Figure 1. a-d. Experimental model showing. a) The esophageal ESD model using a pig esophagus. b) A mock lesion marked in a 30-mm area around the artificial submucosal fibrosis. c) A circumferential mucosal incision around the lesion. d) Submucosal dissection with clip-with-thread traction.

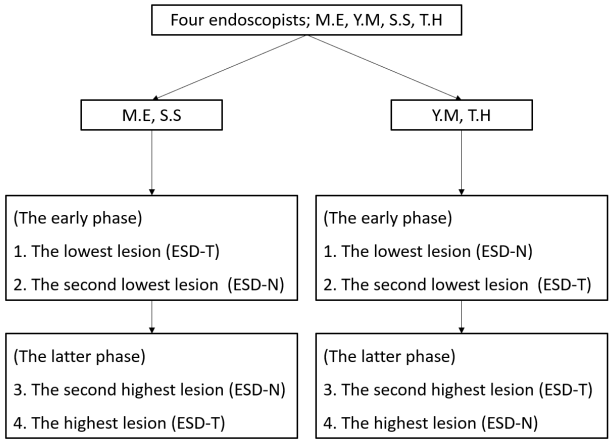

Figure 2. The schedule of ESD for each endoscopist.
ESD-T: endoscopic submucosal dissection with traction; ESD-N: endoscopic submucosal dissection with non-traction.

lower esophagus. At each lesion site, suturing (using 6-0 polypropylene thread, Proline®, Johnson & Johnson, Tokyo, Japan) was performed to create a 10-mm area of submucosal fibrosis, with marking dots made around each area using an Endo-knife. Therefore, in total, a 30-mm area was marked to recognize the mock lesions (Figure 1B).

ESD procedure

Conventional ESD techniques have previously been described in detail (2,3). Briefly, ESD was performed using a single-channel-endoscope (GIF Q260J, Olympus Medical Systems, Tokyo, Japan), with a transparent hood (D-201-11804, Olympus, Tokyo, Japan) attached to the tip. A Splash M-knife (DN-D2718B, HOYA Corp., Pentax, Tokyo, Japan) was used as an Endo-knife (14,15) with the VIO3 electrosurgical unit (ERBE Elektromedizin, GmbH, Tübingen, Germany). Hyaluronic acid with a small amount of 0.8% indigo carmine stain was injected using a needle (01841; Top Corporation, Tokyo, Japan) into the submucosal layer of the area surrounding each mock lesion. After injection, a circumferential mucosal incision was performed around each lesion using the Endo-knife in the Endo Cut mode (effect 3, interval 3, duration 3) (Figure 1C). Submucosal dissection was performed using the Endo-knife in the Forced Coagulation mode (effect 3, 30 W) (Figure 1D). ESD was performed either *with* clip-with-thread traction (ESD-T group) or *without* (ESD-N group). In the ESD-T group, the traction was applied to the lesion after completion of the mucosal incision around the marked area.

Four endoscopists (ME, SS, MY, and TH), each having performed >50 cases of gastric and/or esophageal ESD, performed the ESD procedures for the four mock esophageal lesions, two using ESD-T and two ESD-N. The order of the procedure type and location was allocated as per a fixed order between surgeons to minimize the bias effect (Figure 2). Specifically, ME and SS first performed ESD-T for the lowest esophageal lesion, followed by ESD-N for the second lowest esophageal lesion, then ESD-N for the second highest esophageal lesion, and, lastly, ESD-T for the highest esophageal lesion. The other endoscopists performed ESD-N for the lowest esophageal lesion, followed by ESD-T for the second lowest esophageal lesions, ESD-T for the second highest esophageal lesion, and ESD-N for the highest esophageal lesion. Overall, the data of the 16 lesions resected by ESD were included in our analysis, eight ESD-T and eight ESD-N. The first two ESD procedures were defined as early phase training, with the last two ESD procedures defined as late phase training.

Traction method

Before the ESD procedure, a non-replaceable hemoclip (HX-610-090, Olympus Medical, Tokyo, Japan) was loaded on the reusable delivery/deployment catheter (HX-110LR, Olympus, Tokyo, Japan). Approximately 50 cm of dental floss (Johnson & Johnson K.K., Tokyo, Japan) was tied directly to the loaded, half-open, clip. The endoscope was then withdrawn to apply the clip-with-thread, after completion of the mucosal incision in the ESD-T group. The endoscope was then re-inserted into the esophagus, the clip opened and applied to the edge of the lesion; the lesion could then be elevated by pulling the thread through the opening. To apply traction, the thread was either attached to a sinker, with a weight of approximately 10 grams, or pulled by hand.

Outcome measurements

The following outcomes were compared between the ESD-T and ESD-N groups to determine the efficacy of the traction method. The primary outcome was the time of submucosal dissection, which was measured from the start to the completion of the submucosal dissection procedure. Secondary outcomes were the rate of en bloc resection, the rate of complete resection, the rate of perforation during the procedure, and the total amount of solution injected. En bloc resection was defined as the removal of the whole lesion in one piece. Complete resection was defined as en bloc resection with all marking confirmed in the specimen without any pin-hole. Perforation was defined as any hole created in the muscle layer during the ESD procedure. In a sub-analysis, technical outcomes were compared between the early and late training periods.

Statistical analysis

This was a pilot study with no previous data available regarding the clinical outcomes of ESD for esophageal lesions with fibrosis performed using traction before excision. Therefore, a sample size could not be calculated *a priori*. Continuous data were expressed as a median (interquartile range, IQR). Between-group comparisons (ESD-T and ESD-N) were evaluated using a Mann-Whitney U test for continuous variables with a non-normal distribution. Categorical data were expressed as frequencies, with between-group differences evaluated using Fisher's exact test. For all analyses, a P value <0.05 was considered significant. All analyses were performed using JMP Pro 13.0 software.

RESULTS

Technical outcomes of ESD according to the traction method

A total of 16 esophageal ESDs were performed, with data summarized in Tables 1 and 2. The median dissection time was significantly shorter for the ESD-T group (12.5 min, IQR 10.2-14.5 min) when comparing to the ESD-N group (18.0 min, IQR 14.6-19.2 min) (p=0.040). The rate of en bloc resection was 100% in both groups, with a rate of complete resection of 87.5% and a rate of perforation of 37.5% for both groups. There was no significant difference in the amount of injected solution between

Table 1. All data for ESD procedures.

Surgeon	Sequence of Resection	Traction method	En bloc	Complete Resection	Perforation	Injection (mL)	Dissection time (min/s)
ME	1	Yes	Yes	Yes	Yes	22	6.0/359
ME	2	No	Yes	No	No	16	11.2/671
ME	3	No	Yes	Yes	No	25	14.9/894
ME	4	Yes	Yes	Yes	No	14	7.4/446
SS	1	Yes	Yes	Yes	No	19	16.2/871
SS	2	No	Yes	Yes	Yes	23	20.5/1231
SS	3	No	Yes	Yes	No	38	18.6/1118
SS	4	Yes	Yes	Yes	No	16	12.2/724
YM	1	No	Yes	Yes	No	22	18.7/1123
YM	2	Yes	Yes	Yes	No	21	11.1/667
YM	3	Yes	Yes	No	Yes	16	13.0/781
YM	4	No	Yes	Yes	No	13	13.6/817
TH	1	No	Yes	Yes	Yes	19	22.6/1358
TH	2	Yes	Yes	Yes	Yes	17	19.3/1156
TH	3	Yes	Yes	Yes	No	19	14.5/871
TH	4	No	Yes	Yes	Yes	13	17.3/1038

ESD: endoscopic submucosal dissection.

Table 2. Comparison of technical outcomes of ESD between the ESD-T and ESD-N groups.

	All (n=16)	ESD-T (n=8)	ESD-N (n=8)	p
Dissection time, minutes, median, (IQR)	14.5 (11.8-18.7)	12.5 (10.2-14.5)	18.0 (14.6-19.2)	0.040
En bloc resection, n (%)	16 (100)	8 (100)	8 (100)	---
Complete resection, n (%)	14 (87.5)	7 (87.5)	7 (87.5)	>0.99
Injection, mL, Median, (IQR)	19 (16-22)	18.0 (16.38-19.5)	20.5 (15.25-23.5)	0.562
Perforation, n (%)	6 (37.5)	3 (37.5)	3 (37.5)	>0.99

p value was calculated using the Fisher's exact test for categorical data.
p value was calculated using Mann-Whitney U test for continuous data with non-normal distribution.
*significant value.
ESD: endoscopic submucosal dissection; IQR: interquartile range; ESD-T: endoscopic submucosal dissection with traction; ESD-N: endoscopic submucosal dissection with non-traction

Table 3. Comparison between the early phase and late phase of learning on the technical outcomes of ESD.

	All (n=16)	Early phase (n=8)	Late phase (n=8)	p
Dissection time, mL, median, (IQR)	14.5 (11.8-18.7)	16.6 (11.2-19.6)	14.1 (12.8-15.5)	0.495
En bloc resection, n (%)	16 (100)	8 (100)	8 (100)	---
Complete resection, n (%)	14 (87.5)	7 (87.5)	7 (87.5)	>0.99
Injection, mL, median, (IQR)	19 (16-22)	20.0 (18.5-22)	16.25 (13.75-20.5)	0.225
Perforation, n (%)	6 (37.5)	4 (50.0)	2 (25.0)	0.608

p value was calculated using the Fisher's exact test for categorical data.
p value was calculated using Mann-Whitney U test for continuous data with non-normal distribution.
ESD: endoscopic submucosal dissection; IQR: interquartile range.

ESD-T and ESD-N (18.0 mL *versus* 20.5 mL, respectively, p=0.526).

Comparison of technical outcomes according to the procedure phase

There were no significant differences between the two groups for all technical outcomes when comparing the early and the late phases of learning (Table 3). Although the number of cases in which perforation occurred decreased from four to two between the early and late phases of learning, this difference was not statistically significant.

DISCUSSION

To our knowledge, this is the first study to evaluate the usefulness of clip-with-thread traction for ESD in a model of artificial submucosal fibrosis. Our main finding was that traction decreased the time of ESD when compared to non-traction, without an effect on the rate of perforation. The decrease in procedure duration would be beneficial for the application of ESD in the treatment of recurrent esophageal cancer after dCRT, which is often complicated by submucosal fibrosis.

The incidence of esophageal carcinoma has been increasing worldwide (16), with surgery and CRT being increasingly considered as definitive treatments for locally advanced esophageal SCC (17-19). The 5-year survival rate for SCC is estimated to be between 13% and 27%, however the local recurrence after CRT is still a significant clinical problem (17). Although salvage surgery is the standard treatment for recurrent lesions, it is associated with a high rate of morbidity and perioperative risk (20-22). Endoscopic treatment, especially salvage ESD, has been advocated for the treatment of recurrent lesions localized to the surface of the esophagus as a means of lowering the risk of perioperative mortality and to improve the quality of life (5-7). However, dCRT applied to the esophageal wall results in submucosal fibrosis, which increases the difficulty of ESD. In fact, previous studies identified ulcerative scarring and submucosal fibrosis to be significant factors that increase the technical difficulty of gastric ESD (23,24). If ESD is to be adopted as the standard treatment for recurrent lesions, then reducing the difficulty of ESD in the presence of fibrosis is paramount.

In this study, artificial fibrosis was created at the center of the mock lesion by thread suturing. A blue transparent layer in the submucosal layer did not appear in the fibrotic part during the ESD procedure. Therefore, these lesions were classified as severe fibrosis (F2) (25). The fibrosis remained during the dissection of the entire fibrotic area even after some of the thread was broken due to the cross-suturing technique. Therefore, mock lesions comparable to actual fibrotic lesions were reproduced in this study.

The efficacy of various methods of applying traction to assist gastric ESD has previously been reported (8). However, the efficacy of traction for salvage ESD for recurrent lesions with submucosal fibrosis has not been previously evaluated. The difficulty of performing ESD in the presence of submucosal fibrosis is increased in the esophagus when compared to the gastrointestinal tract, as the former is substantially narrower than the latter and, thus, any additional equipment can easily interfere with the endoscope. The clip-with-thread is a low-profile method to easily apply traction to the lesion prior to resection.
We provide preliminary evidence regarding the suitability of this method of traction for esophageal ESD, as previously reported for conventional esophageal ESD (11,26). Notably, we found a significant decrease in procedure time with applied traction. This may indicate possible effectiveness of clip-with-thread traction in reducing the difficulty of salvage ESD for esophageal lesions with submucosal fi-

brosis. Furthermore, we found no difference in technical outcomes between the early and late phases of learning.

Perforation is a severe adverse event of ESD, leading to the risk of death. The wall of the esophagus is thinner than that of the gastrointestinal tract, which increases the risk for perforation during ESD. A previous randomized controlled trial provided evidence that clip traction using dental floss can reduce the risk of perforation during ESD for gastric neoplasms (13). It was suggested that traction decreased the risk of perforating the gastric wall by securing the field of view of the lesion during ESD. Previous reports of esophageal ESD assisted with traction also reported a lower rate of perforation compared to no traction (11,26). However, in our study, there was no difference in the rate of perforation between ESD-T and ESD-N. Traction is not effective in lowering the rate of perforation during ESD, which may have resulted from the tougher submucosal fibrosis created by suturing compared to what is naturally formed during dCRT. Our *ex vivo* pig models actually had severe esophageal fibrosis (F2) with a high risk of procedure-related perforation. Whereas in clinical practice we might consider stopping the procedure when we realize that there is a high risk of perforation, in an animal model there is no need to do so. This explains the higher rate of perforation in the present study. Of note, we identified a non-significant trend toward a lower rate of perforation from the early to the late phase of learning as one case of perforation still occurred with ESD-T in the late phase of learning. This difference in the rate of perforation may reflect an advantage of accumulated training in performing the procedure using the pig model. The problem of perforation is an important issue that will need to be addressed if the use of salvage ESD is to become the treatment of choice. Clip-with-thread traction did not resolve the problem of perforation during ESD for lesions with submucosal fibrosis. Additional devices or new methods are needed to perform ESD safely for the treatment of recurrent lesions after dCRT.

This study has some limitations which should be acknowledged. Firstly, this is a basic research study in an *ex vivo* pig model. In the absence of blood circulation, we could not evaluate the effect of bleeding during ESD performed with traction. This is an important issue to consider as recurrent lesions after CRT are normally highly vascularized. Also, the lesions used in our study were not pathological and, therefore, the application of these methods in the treatment of early esophageal carcinoma with submucosal fibrosis in humans remains to be clarified. Further studies will be required, especially by improving animal models with esophageal submucosal fibrosis that are more similar to clinical situations. Secondly, this study was non-blinded and non-randomized as the individual operator knew if clip-with-thread traction was involved in the ESD procedure. This might affect the treatment outcomes, especially procedure time. Lastly, we did not create lesions in the cervical or upper thoracic regions of the esophagus, which might be more difficult to resect. Studies in humans are needed to fully characterize the efficacy of traction assistance during esophageal ESD in all sections of the esophagus.

In conclusion, clip-with-thread traction is an effective method to assist esophageal ESD of lesions with submucosal fibrosis in an *ex vivo* pig model. As such, this traction technique could be useful for ESD treatment of locally recurrent esophageal carcinoma after CRT, cases that are normally complicated by submucosal fibrosis. Further evaluation in humans is warranted.

Ethics Committee Approval: Ethics committee approval was received for this study from the Institutional Animal Care and Use Committee Statement, Institutional Review Board and Ethical Committee.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.E., Y.M.; Design - M.E., Y.M.; Supervision - Y.O.; Data Analysis and/or Interpretation - S.S., S.T., T.H., W.M., Y.H.; Writing Manuscript - M.E., Y.M.; Critical Review - M.E., Y.M.

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