Comparison between tunneling and standard endoscopic submucosal dissection for treatment of large esophageal superficial neoplasm

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Abstract

Background and study aims : **Endoscopic submucosal dissection (ESD) has been established as a standard endoscopic method for treating esophageal superficial neoplasms, and it can be performed using a conventional or a tunneling method. The aim of the present study was to compare the safety and efficacy of tunneling ESD (t-ESD) and standard ESD (s-ESD) for treating large esophageal superficial neoplasms and to explore the risk factors for postoperative strictures.**

Patients and methods : **Fifty-five consecutive patients with large esophageal superficial neoplasms were treated by t-ESD or s-ESD. Demographics, lesion characteristics, procedure-related parameters, and follow-up results were retrospectively collected to compare the efficacy and safety of these procedures. Multivariate analyses were conducted to determine the potential risk factors for postoperative strictures.**

Results : **Of the 55 patients, 13 underwent t-ESD and 42 underwent s-ESD. The dissection speed of t-ESD was significantly faster than that of s-ESD (7.42±1.99 min/cm² vs. 9.01±2.11 min/cm², P <0.05). En bloc resection was achieved in 98.2% (54/55) of the cases, while R0 resection was achieved in 92.7% (51/55). Curative resection was achieved in 78.2% (43/55) of the cases. Fourteen patients (25.5%) had postoperative strictures, which resolved with endoscopic dilation and/or stent insertion. Circumferential involvement of >3/4 and lesion length of >3 cm were independent risk factors for strictures.**

Conclusions : **T-ESD is a safe and effective method for treating large esophageal superficial neoplasms with a faster dissection speed than s-ESD, but postoperative strictures may be encountered for lesions involving more than three-fourths of the circumference or longer than 3 cm.** (Acta gastroenterol. belg., **2019**, 82, **469-474**).

Key words : esophageal superficial neoplasms, endoscopic submucosal tunnel dissection, endoscopic submucosal dissection, stricture.

Introduction

With the wider application of esophagogastroduodenoscopy (EGD), chromoendoscopy, and magnifying endoscopy, increasing number of esophageal carcinoma has been found in an early stage (1). Most of these early stage carcinomas can be successfully managed by endoscopic treatment, such as endoscopic mucosal resection, endoscopic piecemeal mucosal resection, and endoscopic submucosal dissection (ESD) (2). ESD is superior to the other two methods because of its ability to perform an en bloc resection regardless of the lesion size and has become the standard procedure for lesions larger than 2 cm (2).

Currently, ESD can be performed using two methods : a standard or tunneling method. Removing larger lesions by standard ESD (s-ESD) remains a challenge because it is considered a high risk and time-consuming, limiting its widespread use (3). The tunneling ESD (t-ESD) method, also called endoscopic submucosal tunnel dissection (ESTD), was first reported by Linghu in 2013 (4). The principle of this technique is to create a submucosal tunnel between the mucosa and muscularis propria layer from the oral margin and anal margin of the lesion to dissect the esophageal superficial neoplasms. Several case series have demonstrated the safety and efficacy of t-ESD for the treatment of large esophageal neoplasms (5-10) ; however, the comparison between the safety and efficacy of t-ESD and s-ESD for these lesions is rarely performed, with only one center reported to have conducted a comparison (11,12). In addition, postoperative stricture is a major concern after ESD for large esophageal neoplasms, and only a few studies have explored the risk factors (13-15). In this study, we investigated and compared the safety and efficacy of t-ESD and s-ESD for treating large esophageal superficial neoplasms and explored the risk factors for postoperative strictures.

Patients and Methods

Patients

This retrospective study was approved by the ethics committee of our hospital. Between January 2010 and December 2018, 55 patients with large esophageal superficial neoplasms were treated with t-ESD or s-ESD. The inclusion criteria for enrollment in this study were as follows : (a) esophageal superficial neoplasm diagnosed based on the results of EGD, chromoendoscopy, Lugol staining, endoscopic ultrasonography (EUS), computed tomography (CT), and biopsy ; (b) no invasion deeper than one third of the submucosal layer (sm1) and an absence of lymph node and distant metastasis as assessed by preoperative EUS or CT ; (c) presence of lesion of more than 2 cm in length and with a circumferential extent of more than one third of the esophageal circumference ; (d) provision of signed written informed

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consent to undergo a t-ESD or s-ESD procedure at our hospital. Patients who could not tolerate anesthesia and those with severe cardiopulmonary disease or blood coagulation disorders were excluded from the study. All patients were informed of possible adverse events (perforation, massive bleeding, incomplete resection, the possibility of surgery, recurrence, postoperative stricture, etc.) and other possible treatment options. Demographics, lesion characteristics, procedure-related parameters, complications, recurrence, and follow-up results were retrospectively collected to compare the efficacy and safety of t-ESD and s-ESD. Lesions were classified according to their location along the esophagus, relative to the incisor teeth : upper esophageal lesions were defined as those 15-23 cm from the incisors, middle esophageal lesions as those 24-32 cm from the incisors, and lower esophageal lesions as those >32 cm from the incisors.

Endoscopic equipment and accessories

Both t-ESD and s-ESD procedures were performed under general anesthesia using a single-channel endoscopy (GIF-Q260J ; Olympus Corp., Tokyo, Japan) with a transparent cap (D-201-11802, Olympus) attached to the front. A carbon dioxide insufflator (UCR ; Olympus) was used. Other equipment and accessories included a high-frequency generator (ICC 200 ; Erbe Elektromedizin GmbH, Tübingen, Germany), an argon plasma coagulation unit (APC300 ; Erbe), a hybrid knife (Erbe), an insulation-tip (IT) knife (KD611L ITknife2 ; Olympus), and an injection needle (NM-4L-1 ; Olympus). Submucosal injection in ESTD/t-ESD was made with a mixed solution of 100 mL saline + 5 mL 0.2% indigo carmine + 1 mg epinephrine.

The t-ESD procedure

The t-ESD was performed as previously reported (4). Briefly, the procedure had following steps : (a) determining the area of lesions using chromoendoscopy and Lugol staining ; (b) marking the margin of the lesion ; (c) submucosal injection ; (d) distal and proximal mucosal incision ; (e) creating a submucosal tunnel ending at the distal incision ; (f) lateral resection alongside the tunnel ; and (g) management of the artificial ulcer. ure 1 depicts an example of t-ESD.

The s-ESD procedure

The s-ESD was performed as previously reported (14). Briefly, the procedure had following steps : (a) determining the area of lesions using chromoendoscopy and Lugol staining ; (b) marking the margin of the lesion ; (c) submucosal injection ; (d) circumferential mucosal incision ; (e) dissection of the lesion ; (f) management of the artificial ulcer ; Figure 2 depicts an example of s-ESD.

Postoperative management

Patients were kept *nil per os* (NPO) for 24 hours, then on a liquid diet for 3 days, and returned gradually to a normal diet within 2 weeks. An intravenous proton pump inhibitor was used during the hospital stay and then orally for another 4 weeks. Postoperative observations included vital signs, recording of complaints of abdominal/chest pain, dyspnea, and abdominal distention, and an abdominal/chest examination.

Pathological evaluation

The specimens were fixed, embedded in paraffin, and then sectioned. Hematoxylin and eosin staining was performed. En bloc resection refers to a resection that results in the removal of a single piece of tissue. R0 resection is defined as histologically complete tumor removal with tumor-free lateral and basal margins. A curative resection is defined as resected neoplasia restricted to the epithelium (m1) or lamina propria (m2) but not involving the muscularis mucosa (m3), with neoplasia-free vertical and radial margins and no lymphatic or vascular invasion.

Follow-up

Surveillance endoscopy was performed at 1, 3, 6, and 12 months and annually thereafter to observe healing of the wound and check for signs of stricture and recurrence. Postoperative stricture was defined as the inability to pass an endoscope with a diameter of 9.8 mm through the stricture site after t-ESD/s-ESD.

Statistical analysis

All data were analyzed with SPSS software (version 23.0 ; IBM Corp., Armonk, NY, USA). Quantitative data were expressed as mean ± standard deviation (SD) or median and range. The Fisher's exact test and the chi-squared test were used for comparisons of categorical variables, and the Student's *t*-test was used for continuous variables. A stepwise logistic regression analysis was used for multivariate analyses to determine the risk factors for postoperative strictures. A P value <0.05 was set as the level of significance.

Results

Table 1 shows the clinical characteristics of the 55 patients (13 received t-ESD and the other 42 received s-ESD). All of the patients underwent the t-ESD/s-ESD procedure successfully. Figure 1 and Figure 2 depict examples of t-ESD and s-ESD. Compared to the s-ESD group, lesions in the t-ESD group showed larger size (longitudinal diameter : 51.2 ± 13.7 mm vs. 35.9 ± 15.6 mm ; Circumferential diameter : 39.5 ± 9.2 mm vs. 25.5 ± 7.0 mm) and circumferential extension (>3/4 : 8/13

Table 1. — **Clinical features and outcomes between t-ESD and s-ESD**

	t-ESD	s-ESD	P value
Number	13	42	/
Sex, Female/male, n	4/9	12/30	NS†
Age, year	57.8 ± 8.7	58.9 ± 7.0	NS
Location of lesion Upper Middle Lower	 0 10 3	 1 28 13	NS
Longitudinal diameter (mm)	51.2 ± 13.7	35.9 ± 15.6	0.003
Circumferencial diameter (mm)	39.5 ± 9.2	25.5 ± 7.0	<0.001
Circumferencial extension, n 1/3~3/4 >3/4	 5 8	 38 4	<0.001
Macroscopic type, n IIa IIb IIc combined	 0 6 0 7	 16 19 2 5	0.009
Procedure time, minutes	148.7 ± 66.6	87.1 ± 67.5	0.006
Dissection speed, min/cm^2	7.42 ± 1.99	9.01 ± 2.11	0.020
En bloc resection, n	13/13	41/42	NS
Histological depth, n HGIN m carcinoma Sm carcinoma	 3 8 2	 17 15 10	0.032
R0 resection, n	13/13	38/42	NS
Curative resection, n	12/13	31/42	NS
Postoperative stricture, n	7/13	7/42	0.013
Follow-up time, month	31.6 ± 20.8	32.5 ± 21.7	NS

NS† : not significant ; t-ESD : tunneling endoscopic submucosal dissection ; s-ESD : standard endoscopic submucosal dissection.

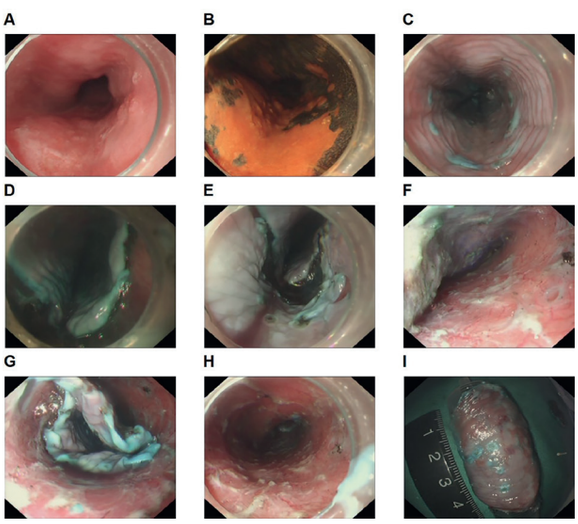

Figure 1. — Case illustration of tunneling endoscopic submucosal dissection (t-ESD). A : Esophagogastroduodenoscopy revealed rough, red mucosa. B : Lugol staining demonstrated a Lugol-negative neoplastic lesion. C : Marking the lesion. D : The anal incision. E : The oral incision. F : The submucosal tunnel. G-H : The wound after t-ESD. I : The resected specimen.

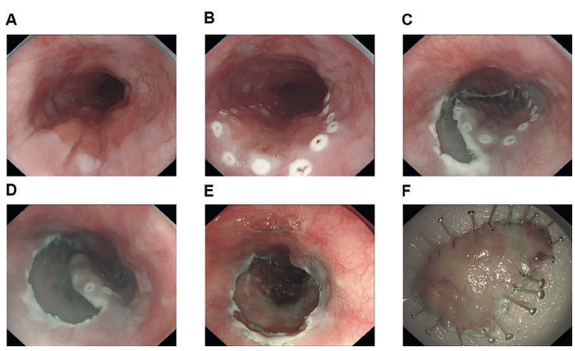

Figure 2. — Case illustration of standard endoscopic submucosal dissection (s-ESD). A : Esophagogastroduodenoscopy revealed red mucosa. B : Mark the lesion. C : Mucosal incision. D : Submucosal dissection. E : The wound after ESD. F : The resected specimen.

vs. 4/42). Also, macroscopic type and histological depth were significantly different between the two groups. En bloc resection was achieved in 98.2% of the cases while R0 resection failed in four cases in the s-ESD group. All four patients with R0 resection failure received

Table 2. — **Univariate analysis of the 55 patients underwent t-ESD or s-ESD**

	Postoperative stricture	No postoperative stricture	P value
Number	14	41	
Sex, Female/male, n	4/10	12/29	NS†
Age, year	56.9 ± 6.1	59.3 ± 7.5	NS
Location of lesion Upper Middle Lower	 0 11 3	 1 27 13	NS
Operation t-ESD s-ESD	 7 7	 6 35	0.007
Length (mm) ~3 3~	 2 12	 27 14	0.001
Circumferencial extension ~3/4 >3/4	 5 9	 38 3	< 0.001
Macroscopic type IIa IIb IIc combined	 1 8 0 5	 15 18 2 6	NS
Histological depth HGIN m carcinoma Sm carcinoma	 6 6 2	 14 17 10	NS

NS† : not significant ; t-ESD : tunneling endoscopic submucosal dissection ; s-ESD : standard endoscopic submucosal dissection ; HGIN : high-grade intraepithelial neoplasia.

Table 3. — **Risk factor selected by multivariate analysis**

	P value	Odds ratio	95% CI†
Circumferencial extension >3/4	0.002	14.550	2.639~80.221
Length >3 cm	0.038	6.758	1.111~40.866

CI† : confidence interval.

additional surgery. The curative resection rate was 92.3% (12/13) in the t-ESD group and 74.4% (31/42) in the s-ESD group. No serious bleeding or perforation occurred in the patients except for 1 in the s-ESD group with intraoperative bleeding, which was managed with electrocoagulation. Three patients with circumferential involvement received stent insertion immediately after t-ESD to prevent postoperative stricture, and the stent was removed 2, 4, and 4 weeks later, respectively. Twenty cases were identified as high-grade intraepithelial neoplasia, 34 cases of squamous cell carcinoma (from m1 to sm3), and one case of adenosquamous carcinoma (m2). Patients who received t-ESD appeared to have a higher risk of developing postoperative stricture. However, this might have been caused by the larger size of the lesions in the t-ESD group. There was no significant difference between t-ESD and s-ESD with regard to sex, age, location of lesion, rate of en bloc, R0 resection, curative resection, and follow-up time (P >0.05, Table 1). The dissection speed of t-ESD was significantly faster than that of s-ESD (7.42 ± 1.99 min/cm^2 vs. 9.01 ± 2.11 min/cm^2, P <0.05).

Fourteen patients (25.5%) had postoperative esophageal strictures with univariate analysis revealing that treating with t-ESD, lesion length >3 cm, and circumferential extension >3/4 were risk factors for postoperative strictures (Table 2), and multivariate analysis revealed that lesion length >3 cm and circumferential involvement of >3/4 were independent risk factors for postoperative strictures (Table 3). All three of the patients who received preventive stent insertion developed stricture during follow-up. Twelve of the strictures were resolved with 1-4 sessions of endoscopic dilation, and the other two needed 6 sessions of dilation and 1-2 sessions of stent insertion. No recurrence was noted during a median follow-up of 33 months (range, 3-105 months).

Discussion

In the present study, we compared the safety and efficacy of t-ESD and s-ESD for the treatment of large esophageal superficial neoplasms. The curative resection rate in the t-ESD group was 92.3% and all t-ESD cases achieved R0 resection without serious bleeding or perforation, indicating that t-ESD is effective and safe for large esophageal superficial neoplasms. Interestingly, operative time was significantly increased in the t-ESD group, which might be due to the larger size of the lesions. The dissection speed of t-ESD was still significantly faster than that of s-ESD after normalizing by the size of the lesions. Thus, we demonstrated that t-ESD is superior to s-ESD at a more efficient dissection speed for

the treatment of large esophageal superficial neoplasms. This result confirms the speculation of those who have performed t-ESD and is consistent with previous studies (11,12).

ESD has been proven to be safe and effective for treating esophageal superficial neoplasms and theoretically enables the resection of lesions regardless of their size and the severity of fibrosis (2). However, it may be difficult to perform standard esophageal ESD on large lesions due to the following two challenges : (a) because of the confined space and the thinner esophageal wall, it may be difficult to maintain a good visual field as it may be obstructed by the resected mucosa, thus consuming time and increasing the possibility of complications ; (b) in the esophagus, after circumferential incision and creation of an artificial "island", additional submucosal injection tends to dissipate easily, and sometimes it becomes difficult and hazardous to dissect the submucosal layer. The advantages of the t-ESD technique in comparison with the s-ESD procedure are as follows : (a) the mucosa of the lateral edges is stretched during submucosal dissection, which decreases the diffusion speed of the submucosal fluid, thus reducing the amount of injections required and facilitating dissection ; (b) the tunnel provides a wider space between the mucosa and muscular layers, which facilitates exposure of the lesion and avoids unintentional injury ; (c) anal incision helps determine the tunnel end and prevents excessive mucosa separation. Additionally, t-ESD may have two other potential benefits (4,16) : first, the transparent cap attached to the endoscope may have the ability to perform blunt dissection ; secondly, the gas cushion caused by insufflation may increase the distance between the mucosa and muscular layer, thus contributing to blunt dissection. Therefore, t-ESD is probably faster than s-ESD (17). and our study confirmed this speculation.

Postoperative stricture is a common concern for patients receiving t-ESD or s-ESD for large esophageal neoplasms. In a study of 40 cases of superficial esophageal cancer with near-circumferential lesions treated by ESD, Tang et al. (3), reported that the rate of postoperative stenosis was up to 45%. Several studies have demonstrated that circumferential extension of >3/4 and depth of invasion >m2 were reliable risk factors for postoperative strictures (13-15). In the present study, 14 (25.5%) cases developed esophageal stricture, and multivariate analysis revealed that circumferential involvement of >3/4 and lesion length >3 cm were independent risk factors for postoperative strictures, which is in agreement with previous studies. Several strategies have been reported for the prevention of post-ESD esophageal stricture, including oral and local steroids, preventive dilation, fully covered stent insertion, endoscopic cell and/or mucosa transplantation, etc. (7,18-24). Wen et al. (18), found that stent insertion was an effective method to prevent post-ESD esophageal stricture in cases of 75% circumferential involvement (stent vs. no stent, 18.2% vs. 72.7%, respectively), Ye et al. (7), reported a relatively low rate of post-ESD stricture in cases with stent insertion after circumferential esophageal ESD. In the present study, three patients with circumferential ESD received preventive stent insertion, however all of them encountered esophageal stricture eventually ; possible reasons might be that the stent insertion time was relatively short (2 or 4 weeks) compared with the above two studies (8 weeks or 3 months) (7,18). Management of these strictures included endoscopic dilation, stent insertion, endoscopic incision, etc., however repeated treatment is often needed (20,25-27). In the present study, twelve of the strictures were resolved with 1-4 sessions of endoscopic dilation, and the other two needed 6 sessions of dilation and 1-2 sessions of stent insertion.

Limitations of the study include its retrospective design, small sample size, and potential selection bias (for the selection of t-ESD and s-ESD), thus requiring a large scale, prospective, randomized, comparative study for further exploration.

In conclusion, this preliminary study has shown that t-ESD is a safe and effective method for the treatment of large esophageal superficial neoplasms with a faster dissection speed in comparison with s-ESD, but postoperative esophageal strictures may be encountered for lesions with more than three-fourths of the circumferential extension or lesion length >3 cm.

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Conflict of interest

All the authors have no conflict of interest related to the manuscript.

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