



Autologous esophageal mucosa with polyglycolic acid transplantation and temporary stent implantation can prevent stenosis after circumferential endoscopic submucosal dissection

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Background: This research aimed at investigating the safety and efficacy of autologous esophageal mucosa (AEM) with polyglycolic acid (PGA) transplantation and temporary stent implantation (TSI) in preventing esophageal stenosis (ES) after early esophageal cancer (EC) surgery.

Methods: Between April 2019 and October 2020, patients scheduled for circumferential endoscopic submucosal dissection (ESD) were prospectively recruited. After ESD, autologous esophageal mucosal patches (MPs) were constructed on the absorbable PGA felt. Then, the felt was structured onto a covered metal mesh stent (CMMS) and attached to the ulcer surface. The stents were removed 6–8 weeks after the operation. The occurrence of ES and adverse events was observed and analyzed.

Results: Data from 25 patients were analyzed. In total, 14 patients (56%) had no stenosis during an average follow-up of 10.2 months, and 11 patients (44%) suffered strictures at a mean interval of 63.73 days after the ESD procedure. Stent migration occurred in 2 patients. No other complications, including perforations, bleeding, or wound infections, occurred. The median of endoscopic balloon dilatation (EBD) sessions was 2.16 (range, 0–14). There showed a higher post-ESD stricture rate in patients with lesions located in the middle-lower esophagus ($P < 0.05$). More transplanted MPs may reduce the occurrence of ES.

Conclusions: AEM with PGA transplantation and TSI is a safe and effective approach of preventing ES and improving the life quality after circumferential ESD.

Keywords: Autologous esophageal mucosa (AEM); polyglycolic acid (PGA); temporary stent implantation (TSI); circumferential endoscopic submucosal dissection (ESD); stenosis

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Introduction

Endoscopic submucosal dissection (ESD) sets a standard for precancerous lesions, and early esophageal cancers (ECs) confined to the submucosa with a low risk of distant metastases (1,2).

Nevertheless, notably, the incidence of stenosis after circumferential early EC resection is very high (75% to 100%) (3,4), resulting in dysphagia, an impaired quality of life and a substantial increase in financial burden. As there are still no effective treatment methods for stenosis, some interventions are considered to be effective in preventing post ESD stenosis, including repeated endoscopic balloon dilation (EBD), oral steroids, viscous budesonide slurry, and local injection of steroids (1,5-8). Recently, several studies suggested that temporary stent placement (9), polyglycolic acid (PGA) (10), oral mucosal sheets (11), autologous skin grafting (12) and autologous esophageal mucosa (AEM) (13) may contribute to prophylactically preventing stenosis in patients with circumferential mucosal defects after ESD. However, these methods all have limitations.

For preventing esophageal stricture, we developed AEM with PGA transplantation and temporary stent implantation (TSI) (14). We designed this method based on the following considerations. First, PGA has been proved as a potential approach for reinforcing sutures and minimizing scar contracture in other medical areas. Second, AEM may play a role as punctate skin grafting in orthopedic surgery. Third, stents can support ulcers such that stenosis can be prevented. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-6987>).

Methods

Patients

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This phase I pilot investigation was ratified by the Ethics Committee of the National Cancer Center/Cancer Hospital, Chinese Medical College and Peking Union Medical College (No. 19/191-1975), and all patients had signed written informed consents. The phase I pilot investigation was carried out from April 2019 to October 2020 in National Cancer Center/Cancer Hospital, Chinese Medical College and Peking Union Medical College.

The inclusion criteria were below: (I) patients with

wholly circumferential esophageal squamous-cell carcinoma and no invasion exceeding SM1 by biopsy; (II) patients who underwent ESD; and (III) no lymph node metastases by computed tomography (CT).

The exclusion criteria were below: (I) patients with esophageal stenosis (ES) at baseline; (II) patients with coagulopathy or continuous use of anticoagulant and antiplatelet drugs; and (III) lymph node metastases by CT.

Sample size

Because this study was a phase I pilot study, we did not calculate the required sample size.

ESD procedure

Circumferential early EC was resected by ESD as described in a previous publication (13).

AEM with PGA transplantation and TSI

After ESD, several pieces of autologous esophageal mucosal tissue from these patients were excised by multiband mucosectomy (MBM) adopting a Duette kit (HX-20Q-1; Olympus, Tokyo, Japan) from a normal esophagus site 1 cm away from the lesion. Then, MBM was sliced into 3 to 8 mm mucosal patches (MPs). Subsequently, absorbable lines (VCP738D; Johnson & Johnson, New Brunswick, America) were used to reconstruct these pieces on the absorbable PGA felt (Neoveil, 100×50×0.15 mm; Gunze Co., Tokyo, Japan). Notably, the mucosal side was connected to the PGA felt so the submucosal side would be in contact with the ESD ulcer in each MP. The vertical and horizontal distance between each of two MPs was 1.0 cm. We measured the length of ulcer endoscopically after the resection and the suitable length of stent was chosen. Then, the felt was made onto a covered metal mesh stent (CMMS) (MTN-SE-S-20/160-A-8/650, MTN-SE-S-20/100-A-8/650, MTN-SE-S-18/120-A-8/650; Nanjing Micro Technology Co, Ltd., China). The endoscope was passed through the stent with grasping forceps through the biopsy channel to grasp the distal steel lasso loop of the stent. Eventually, the stent was positioned on the surface of the ulcer. Before stenting, a tube was placed through the mouth (MD-48618, Sumitomo bakelite Co., Ltd., Tokyo, Japan) to facilitate stent passage and protect digestive mucosa from injury. After the procedure was finished, a gastric tube was placed

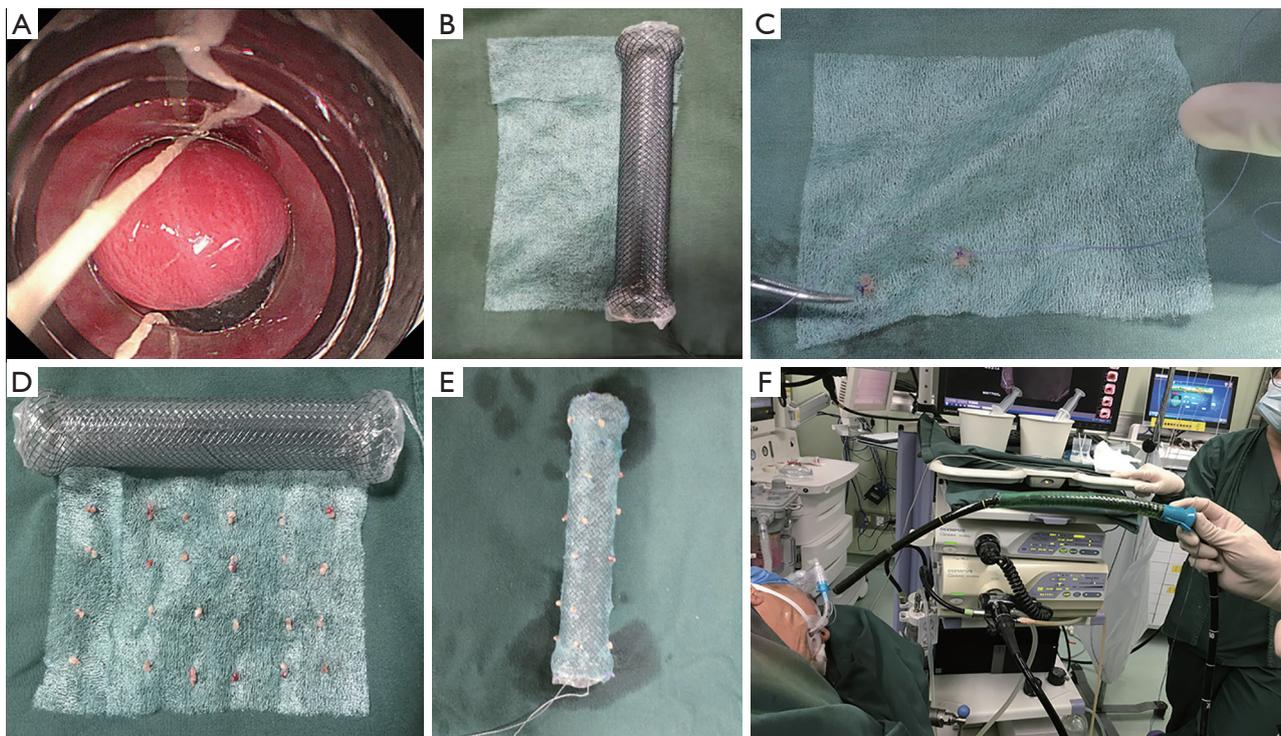


Figure 1 Autologous esophageal mucosa (AEM) with polyglycolic acid (PGA) transplantation and temporary stent implantation (TSI) surgery. (A) MBM was used to remove the AEM. (B) A suitable stent and PGA sheet were chosen. (C,D) The esophageal mucosa was sutured on PGA. (E) The PGA sheet was sutured on a completely covered esophageal stent. (F) Under direct endoscopy, the stent was placed in the esophageal defect by releasing the steel sheath grommet.

under endoscopy.

Aftercare

The patients were asked to continue fasting for the first three days after ESD and then underwent CT on the third day to determine whether there were perforations or stent migrations. On the 4th day after the operation, the patients were allowed to start a liquid diet, and on the 7th day, the gastric tube was removed. After ESD, the patient received a proton pump inhibitor (rabeprazole 20 mg; Changao, Nanjing, China) for 6 consecutive days. After that antibiotics were given 3 days q12h (Amoxicillin sodium sulbactam sodium 1.25 g; Ruiyang, Shandong, China).

Stent removal

A scheduled endoscope examination was performed once a week to confirm the position of the stent, which was removed during the 6th–8th week after the operation

depending on the patient's tolerance (*Figures 1,2*).

Stricture and follow-up

Patients were examined by endoscopy 2 weeks and 3 and 6 months after the stent removal and then annually. When the standard endoscope (GIF-H290; Olympus, Tokyo, Japan) cannot pass through the stenosis, it is defined as ES. EBD treatment was used in patients with postoperative stricture. If the patient had stenosis symptoms, they can connect our doctors and the EBD will also be done. During the EBD treatment, a special balloon (Wilson-Cook Medical Incorporated, Bloomington, Indiana, USA) 1.2–1.5 cm in size was selected on basis of the degree of ES. The duration of EBD varied among the patients with the aim to relieve dysphagia.

Statistical analysis

The statistical comparison was performed by *t*-test and

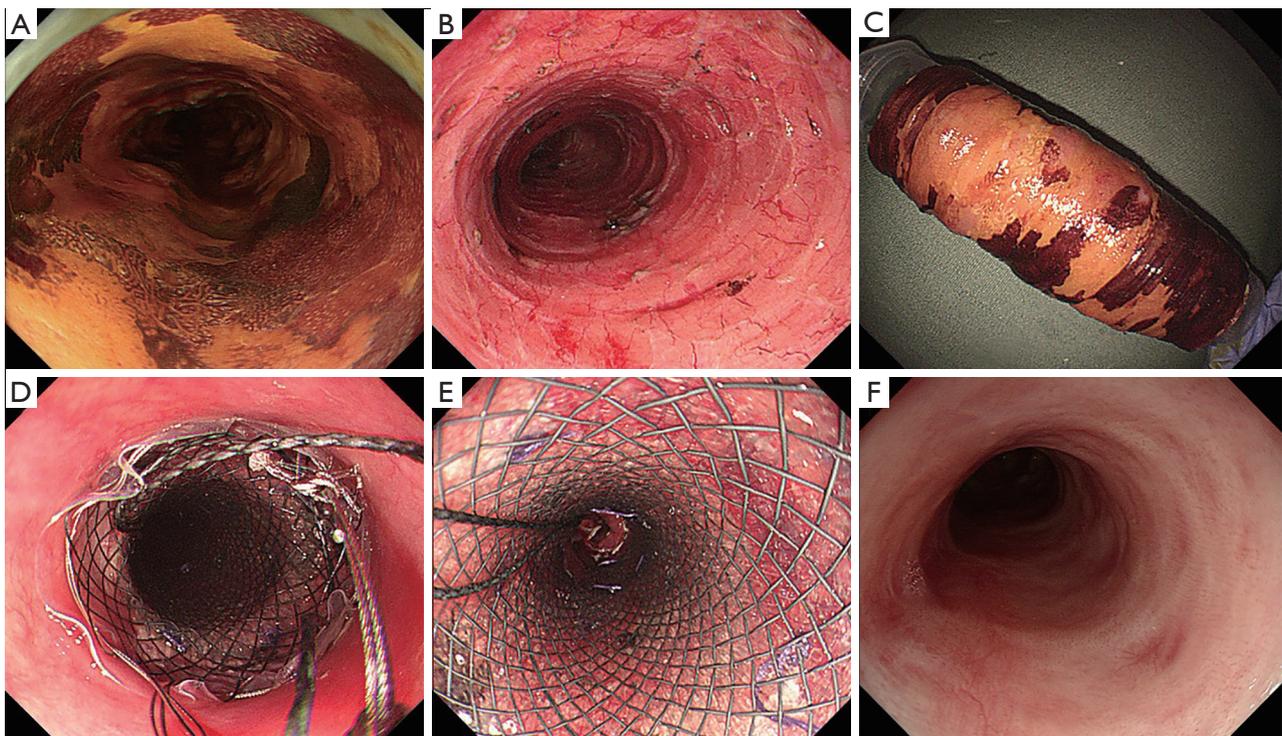


Figure 2 One case of prevention of ES was conducted with PGA AEM transplantation and TSI. (A) Lugol iodine staining showed a complete annular lesion in the esophageal lumen. (B,C) ESD caused a wholly circumferential mucosal defect. (D) The stent was placed at the site of the artificial esophageal ulcer. (E) The patient underwent a weekly endoscopy to confirm that the stent was in place. (F) No evidence of stenosis was observed 6 months after transplantation.

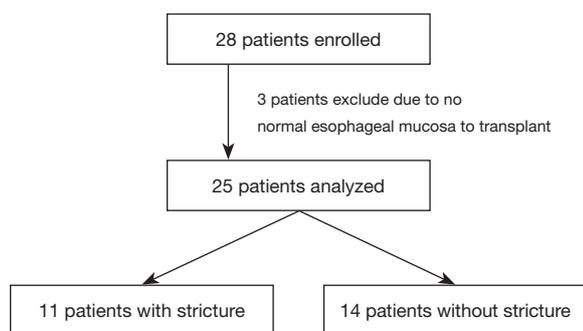


Figure 3 Flow chart of the patients included in this investigation. Of the 28 patients enrolled, twenty-five patients with ESD, followed by AEM with PGA transplantation and TSI, were evaluated endoscopically and analyzed.

the Mann-Whitney U test to analyze the parametric and nonparametric data, separately, with significance assumed at P values <0.05. The statistical calculations were conducted employing SPSS25 software (SPSS Inc., Chicago, IL, USA).

Results

Enrollment and procedures

A total of 28 patients were included in this research. However, after ESD, 3 patients did not have any normal mucosa remaining to transplant. Therefore, 25 patients underwent the complete study protocol and were included in the analysis (Figure 3, Table 1). The biopsies confirmed the esophagus squamous epithelium at the transplant site according to the histological features of a normal esophagus.

Overall outcomes

All 25 patients successfully underwent a combination of circumferential ESD, AEM with PGA transplantation and TSI. Stent removal was conducted in 2 patients with complaints of thoracalgia during the 3rd and 4th weeks after ESD. In our study, we found that the PGA sheet and absorbable line can be absorbed totally in 6 weeks. Even in the cases we have to remove the stents in 3 or 4 weeks, the

Table 1 Demographic features of patients and lesions

Case No.	Age (y)	Gender	Endoscopic morphology	IPCL type	Position of the lesion	Longitudinal length of ulcer(mm)	Length of stent (mm)	Histological depth
1	53	Male	Ila+Iib	B2	Middle-lower	120	120	SM2
2	60	Male	Iib	B1	Middle	80	100	SM1
3	69	Male	Iib	B1	Upper-middle	110	120	M2
4	71	Male	Iib	B2	Middle-lower	90	100	SM2
5	74	Female	Iib	B1	Middle	70	100	M1
6	62	Female	Ila+Iib	B2	Upper-middle	100	120	M3
7	60	Female	Iib	B1	Middle	90	120	M2
8	57	Male	Iib	B1	Upper-middle	120	120	M1
9	65	Female	Ila	B1	Middle-lower	90	100	M2
10	70	Female	Iib	B1	Upper-middle	100	120	M2
11	51	Male	Iib	B2	Middle-lower	100	120	M3
12	53	Male	Ila+Iib	B2	Middle	140	140	SM2
13	61	Male	Ila	B2	lower	80	100	SM2
14	69	Female	Ila+Iib	B1	Middle	80	100	SM1
15	65	Female	Ila+Iib	B1	Middle-lower	100	120	M3
16	85	Male	Iib	B1	Middle-lower	80	100	M2
17	72	Female	Iib	B1-B2	Upper-middle	140	140	M2
18	63	Male	Iib	B1-B2	Upper-middle	90	120	M3
19	64	Male	Iib	B1-B2	Middle-lower	90	100	M3
20	65	Female	Iib	B1-B2	Middle-lower	80	100	SM1
21	56	Male	Iib	B1-B2	Middle-lower	110	140	SM2
22	75	Male	Iib	B1	Middle-lower	70	100	M2
23	75	Male	Ila+Iib	B2	Middle-lower	120	120	M1
24	71	Female	Iib	B2	Middle	90	120	M3
25	62	Male	Ila+Iib	B1	Middle-lower	120	120	SM1

IPCL, Intraepithelial papillary capillary loops.

PGA sheet and absorbable line were absorbed partly which were enough to let the mucosa separate from the stent. So when we remove the stent, there were no difficulties. Stent migration occurred in 2 patients. The stents fell into the stomach. We pulled them back to esophagus and adjusted the position of the stent during the follow-up endoscopy. One of the 2 patients experienced the stent migration twice so we remove his stent on the 5th week when the stent migration happened the second time. No other complications, including bleeding, wound infections,

or perforations, occurred. The demographic characteristics and lesion features of 25 patients are exhibited (*Table 1*). *En bloc* resection was achieved in each lesion. Regarding the tumor invasion depth and pathology, 3 intramucosal invasive carcinomas were limited to the epithelial layer, 7 intramucosal invasive carcinomas were limited to the lamina propria mucosa membrane, 6 intramucosal invasive carcinomas were limited to the muscularis mucosa membrane, and 9 invasive carcinomas were limited to the submucosa. The average ulcer longitudinal length was 98.00

Table 2 Clinical outcomes of autologous esophageal mucosa with polyglycolic acid transplantation and temporary stent implantation

Case No.	Time of stent removal (week)	Stricture	Time of stricture after ESD (day)	Times of dilation	Number of MPs	Follow-up, mo
1	8	-	-	0	8	18
2	8	+	84	3	8	17
3	8	+	49	14	8	17
4	8	+	77	3	10	17
5	3	+	42	2	10	17
6	8	+	63	5	12	15
7	8	-	-	0	20	14
8	8	+	120	4	20	13
9	8	-	-	0	19	13
10	8	-	-	0	24	13
11	8	-	-	0	18	12
12	7	+	56	4	15	11
13	7	-	-	0	16	9
14	6	+	49	4	16	11
15	6	-	-	0	24	10
16	4	+	42	7	20	10
17	6	-	-	0	32	9
18	7	+		6	26	8
19	6	-	-	0	18	4
20	6	+	56	2	20	4
21	6	-	-	0	24	4
22	6	-	-	0	20	3
23	6	-	-	0	28	2
24	6	-	-	0	24	2
25	5	-	-	0	24	2

ESD, endoscopic submucosal dissection; MPs, mucosal patches.

mm. On basis of the mucosal defect size and the normal esophagus length, the number of MPs varies between 8 and 32. The clinical results of the new operations are exhibited (Table 2). In total, 14 patients had no stenosis during an average follow-up of 10.2 months, and 11 patients suffered strictures at a mean interval of 63.73 days after the course. EBDs average was 2.16. One of the 11 patients suffered stricture before stent removal. The stenosis occurred in the anal side of the ulcer where had severe tissue proliferation. We advised all the cases of SM invasion to ask the radiotherapy doctor and thoracic surgeon for advice. One

of the patients underwent additional surgery 9 months after ESD and he did not suffer from stricture before the surgery. Besides, 1 case of SM invasion underwent radiotherapy 4 months after ESD, and he had no stenosis.

Comparison of groups with or without stricture

The features of the patients with or without stricture are exhibited (Table 3). No significant difference existed in age, gender, longitudinal length of ulceration or length of stent between the two groups, while the patients without stricture

Table 3 Characteristics and clinical results of patients with or without stricture

Characteristic	Patients with stenosis (n=11)	Patients without stenosis (n=14)	P value
Age, mean ± SD, y	66.18±8.83	64.29±7.72	0.573
Gender, n			0.742
Male	7	8	
Female	4	6	
Lesion location, n			0.030
Upper-middle	4	2	
Middle	5	2	
Middle-lower	2	10	
Longitudinal length of ulceration, mean ± SD, mm	94.55±21.15	100.00±16.64	0.477
Length of stent, mean ± SD, mm	110.91±13.75	117.14±13.26	0.263
Invasion depth			0.165
T1a	7	9	
T1b	4	5	
No. of mucosal patches, mean ± SD	15.00±5.95	21.36±5.76	0.013

had more transplanted MPs ($P<0.05$), and the patients with lesions located in the middle-lower esophagus had a lower chance of developing post-ESD stricture ($P<0.05$).

Discussion

ES incidence after resecting wholly circumferential lesions varies between 88% and 100% (1,2). In the past few years, multiple approaches have been designed to prevent postoperative strictures. Sato *et al.* reported an average of 33.5 dilatations in patients after circumferential esophageal ESD and 13.8 dilatations in patients after circumferential esophageal ESD with the administration of after-dilatation steroids (15). In our hospital, the mean incidence of strictures and EBD number in patients after circumferential esophageal ESD with no specific treatment were 98.21% and 10.16%, respectively. More EBD operations result in heavier economic burdens to patients. The outcomes demonstrate that autologous esophageal mucosal transplantation can not only clearly lessen the incidence of stenosis but also remarkably reduce the mean time of the EBD operation.

As for the method to choose the suitable length of stent, many researchers suggest that that approximately 2 cm of the stent extended beyond both the top and bottom borders of the mucosal defect to reduce stent migration (9). But longer stent will cause more serious thoracalgia to the

patient, especially the patients whose proximal border of ulcer within 22 cm to the incisors. In our study, we found that the stent can be effective as long as the stent can cover the ulcer. On the other hand, if the ulcer was within 10 cm and the distance of proximal border from the incisors was longer than 22 cm, we would prefer the stent longer than the ulcer to reduce stent migration.

Many researchers have focused on steroid therapy to decrease stricture. Two observational investigations reported the efficacy of systemic (oral) steroids in decreasing the incidence of post-ESD stenosis (16,17). A systematic review identified that high-dose steroids can result in gastrointestinal ulcer, osteoporosis, immunosuppression, hyperglycemia, and even systemic infection (18). A systematic review exhibited a steroid injection was better than systemic (oral) steroids (19). Nevertheless, in some patients, intractable stenosis still occurs after local injection of steroids. Hanaoka *et al.* (20) and Nagami *et al.* (21) reported that even after a prophylactic steroid injection, $>3/4$ or $>5/6$ circumferential mucosal defect were independent risk factors for refractory strictures even after prophylactic steroid injections. Therefore, many studies reported different methods to prevent the post-ESD strictures of circumferential mucosal defect.

In 2015, Sakaguchi *et al.* reported that PGA sheets reduced stenosis incidence in 37.5% of patients with mucosal defects

of over 3/4 of the esophageal circumference (22). However, a limitation of this method is that the PGA is easy to shift, and whether PGA is useful for patients after wholly circumferential esophageal ESD is unclear. Ohki *et al.* transplanted tissue-engineered autologous oral mucosal epithelial cell sheets by endoscopy (11). However, it is still technically difficult and costly to transplant tissue-engineered autologous oral mucosal epithelial cell sheets. Additionally, the only wholly circumferential patient in his study experienced structure and 21 dilations. Recently, some researchers have reported that the autologous gastric mucosa (23) or skin (12) transplantation could prevent strictures. However, gastric antral mucosa, which can secrete gastric acid, may result in undesired symptoms, such as chest pain or even observable ulcerations. Theoretically, skin tissues may be unfavorable because of sweat secretion. Liao *et al.* reported that autologous esophageal mucosal transplantation can lessen the mean number of dilatation sessions needed (13). A research study by Chai *et al.* published in 2018 showed PGA sheets plus esophageal stent placement could lessen ES occurrence in patients with a circumferential lesion range to 42.86% (6/14) (24). However, the number of patients with circumferential lesions in that study was only 14, and the follow-up period was only 3 months. Actually, we applied PGA sheets plus esophageal stent placement in 3 patients with complete circular ESD with no remaining normal mucosa to transplant. Severe strictures occurred in these 3 patients.

In our study, we creatively combined temporary stent insertion, AEM and PGA transplantation to prevent strictures of circumferential mucosal defect. Furthermore, in this study, we found that more esophageal mucosal patch transplantation lowers the risk of post-ESD strictures for circumferential lesions. Besides, circumferential lesions situated in the upper-middle esophagus have a higher risk of post-ESD strictures.

For the circumferential lesions situated in the upper-middle esophagus, there are few researches just focused on the upper-middle esophagus stenosis. The researches of EBD, oral steroids, local injection of steroids, oral mucosal sheets, autologous skin grafting and AEM (1,5,6,9-13) all include the cases of upper-middle esophagus. So comprehensive approaches should be considered for the circumferential lesions situated in the upper-middle esophagus. In our study, these cases were treated by EBD when they had strictures after stent removal.

Some restrictions still exist in our investigation. For starters, this investigation was a small sample single-center research. Secondly, this investigation was a single-arm

research, and hence, selection bias is possible because we designed this study as a phase I study. In the near future, we aim to conduct a prospective, multicenter, single-arm phase II study. Third, as few patients undergo complete circular ESD, we did not establish a control group in which a stent alone or a stent plus a PGA sheet were employed for preventing post-ESD stenosis. However, as far as we know, this study is the first report on preventing ES after ESD by AEM combined with PGA transplantation and TSI.

In conclusion, our preliminary research shows that the operation of an AEM with PGA transplantation and TSI is feasible and effective in reducing strictures and promoting the life quality after circumferential ESD.

Conclusions

AEM with PGA transplantation and TSI is a safe and effective approach of preventing esophageal stricture and improving the quality of life after circumferential ESD.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-6987>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the National Cancer Center/Cancer Hospital, Chinese Medical College and Peking Union Medical College (No. 19/191-1975), and informed consent was taken from all individual participants.

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