

Useful strategies to prevent severe stricture after endoscopic submucosal dissection for superficial esophageal neoplasm

Kaname Uno, Katsunori Iijima, Tomoyuki Koike, Tooru Shimosegawa

Kaname Uno, Katsunori Iijima, Tomoyuki Koike, Tooru Shimosegawa, Division of Gastroenterology, Tohoku University Hospital, Miyagi 981-8574, Japan

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Correspondence to: Kaname Uno MD, PhD, Division of Gastroenterology, Tohoku University Hospital, 1-1 Seiryō-cho, Aoba-ku, Sendai, Miyagi 981-8574, Japan. kaname@wa2.so-net.ne.jp
Telephone: +81-22-7177171
Fax: +81-22-7177174

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Abstract

The minimal invasiveness of endoscopic submucosal dissection (ESD) prompted us to apply this technique to large-size early esophageal squamous cell carcinoma and Barrett's adenocarcinoma, despite the limitations

in the study population and surveillance duration. A post-ESD ulceration of greater than three-fourths of esophageal circumference was advocated as an important risk factor for refractory strictures that require several sessions of dilation therapy. Most of the preoperative conditions are asymptomatic, but dilatation treatment for dysphagia associated with the stricture has potential risks of severe complications and a worsening of quality of life. Possible mechanisms of dysphasia were demonstrated based on dysmotility and pathological abnormalities at the site: (1) delayed mucosal healing; (2) severe inflammation and disorganized fibrosis with abundant extracellular matrices in the submucosa; and (3) atrophy in the muscularis proper. However, reports on the administration of anti-scarring agents, preventive dilation therapies, and regenerative medicine demonstrated limited success in stricture prevention, and there were discrepancies in the study designs and protocols of these reports. The development and consequent long-term assessments of new prophylactic technologies on the promotion of wound healing and control of the inflammatory/tumor microenvironment will require collaboration among various research fields because of the limited accuracy of preoperative staging and high-risk of local recurrence.

Key words: Esophageal stricture; Dysphasia; Endoscopic submucosal dissection

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Core tip: The number of cases of refractory post-endoscopic submucosal dissection (ESD) strictures will increase as the indications for ESD expand. Dysphagia related to the stricture is primarily treated using repeated dilatation treatments, which risk complications and a diminished quality of life. Dysmotility and inflammation-associated disorders at the site may reflect the me-

chanisms of dysphasia. However, anti-scarring agent administration, endoscopic modalities, and regenerative medicine have limited effects. The development and subsequent long-term assessment of new technologies for the prevention and control of carcinogenesis will be required based on the limited accuracy of preoperative staging and the risk of local recurrence.

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INTRODUCTION

The management of superficial esophageal neoplasms (SENs) has shifted from surgery to endoscopic treatment with recent developments in endoscopic technologies because of minimal invasiveness and positive outcomes^[1,2]. Notably, endoscopic submucosal dissection (ESD) achieves optimal histopathological staging using *en bloc* resection compared to conventional endoscopic mucosal resection (EMR)^[3-5]. Recently, ESD was successfully applied worldwide in large early esophageal squamous cell carcinoma (ESCC) and Barrett's adenocarcinoma^[6-12].

However, there are no established criteria for curability of ESD for larger-sized ESCC and Barrett's adenocarcinoma. Existing treatment guidelines state that ESCC that are limited to intraepithelial or lamina propria mucosae (LPM) with nominal lymph node metastasis are candidates for endoscopic treatment^[13], but the rates of lymph node metastases of ESCC invading the muscularis mucosae (MM) or the upper third of the submucosa (SM1) were 9% or 19%, respectively^[14]. Previous retrospective studies have demonstrated that the curability of ESD for large-sized high-grade intraepithelial neoplasms of the esophagus or superficial ESCC were equivalent to surgical resection^[7,15], which expanded the indication for endoscopic treatment of SENs^[16,17]. However, successful resection of these lesions using ESD was reported in relatively small numbers of subjects with limited-term surveillance. EMR followed by radiofrequency ablation therapy is mainly performed in patients with early stage Barrett's-associated adenocarcinoma, as an alternative to esophagectomy in Western countries with promising results^[18,19]. EMR has limitations in resectable size, which results in a higher risk of local recurrence^[13], and ESD has been used to remove large carcinomatous lesions concomitant with background Barrett's mucosa with malignant potential^[9,10,20]. However, whether it is reasonable to evaluate the curability for Barrett's adenocarcinoma that invades

SM1 using the same criteria for gastric cancer or ESCC remains controversial^[13]. Therefore, further prospective studies using large numbers of subjects and long-term surveillance are required to confirm the usefulness and safety of ESD.

Many studies have suggested that strictures after endoscopic treatment for large-sized SENs might be refractory to dilation therapy (Figure 1). The occurrence of refractory strictures after non-surgical treatments was significantly higher than the occurrence after surgery, but the overall rates of strictures after esophagogastrectomy, chemoradiation therapy (CRT), and endoscopic resection were 1.6%-25%, 3.3%-40%, and 6.0%-18%, respectively^[1,7,15,21-23]. Most strictures that occurred after endoscopic treatment were classified as complex strictures, *e.g.*, (1) a simple stricture that is a short, focal, and symmetric stenosis with a luminal diameter that allows the passage of a standard endoscope; and (2) complex strictures that are defined as having one or more of the following features: a severely narrowed luminal diameter ≤ 12 mm, length ≥ 20 mm, angulation, or asymmetry^[24,25]. Therefore, it is important to prevent severe stricture of the esophagus from occurring after endoscopic treatment. Several retrospective single-center studies identified more than three-fourths of the circumferential extent of a mucosal defect following endoscopic treatment using "(sub)circumferential resection" or pathological tumor staging deeper than the LPM as important predictors of severe stricture (Table 1). The stricture rate after esophageal (sub)circumferential ESD was reported to be 88% to 100%, which was higher than the 86% and 66% reported using CRT and EMR^[1,7,22,27-29]. The length of the stricture may also be related to its severity^[25,30,31]. Takahashi *et al.*^[25] revealed that the average length of strictures that needed more than 10 sessions of dilation was greater than strictures that required less than 10 sessions (53 mm vs 39 mm, respectively). A study at Nagasaki University Hospital showed that patients with at least two of the following risk factors might be at a higher risk to develop stricture: mucosal defect of more than three-fourths of the circumference, a longitudinal tumor diameter greater than 40 mm, or cervical location^[31]. Consequently, the length, circumference, location, and pathological depth of SENs should be taken into account when considering ESD as a treatment strategy.

(Sub)circumferential ESD was performed in the clinical setting in patients who were unwilling to undergo esophagectomy or patients with severe comorbidities^[13,14,31]. Thereafter, most of these patients required several sessions of dilation because of severe/refractory dysphasia, although their preoperative conditions were asymptomatic. Instead, repeated dilatation has the potential risk of tears/perforation, which results in potentially lethal complications and a

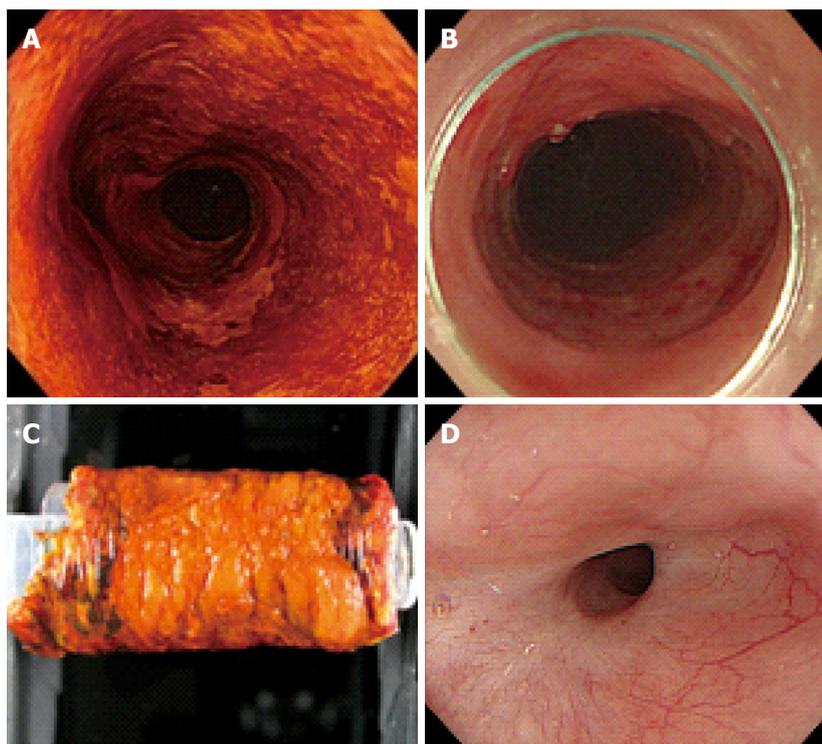


Figure 1 Representative endoscopic imaging of a stricture after circumferential endoscopic submucosal dissection for a large-sized superficial esophageal squamous cell carcinoma. A: Lugol chromoendoscopy imaging; B: Circumferential post-ESD ulceration; C: ESD specimen; D: Endoscopic imaging of post-ESD stricture 3 mo after ESD. ESD: Endoscopic submucosal dissection.

worsening of quality of life (QOL)^[32,33]. The relatively high risk of recurrence after endoscopic treatment for SENs may occur because severe strictures after ESD may mask recurrent lesions that are hidden in the blind spots of the surveillance endoscopic inspection and disturb their endoscopic treatment procedure^[20]. Therefore, the control of these refractory strictures with symptomatic dysphagia after (sub)circumferential ESD is an urgent task for broader acceptance of ESD as a treatment strategy for SEN. We review recent achievements in the preventive and treatment strategies of esophageal strictures after endoscopic resection and the mechanism of their development.

MECHANISM OF THE SYMPTOMATIC/ MECHANICAL STRICTURE AFTER ESD

We include mechanical stricture and esophageal dysmotility as major causes of post-ESD dysphasia.

First, we discuss the mechanisms of mechanical stricture development. In general, wound healing occurs by way of the following series of events: (1) induction of inflammatory response and organization of granulation tissue; (2) proliferation of epithelial cells in the border of the wound and the covering of the wound with granulation; (3) growth of subepithelial granulation; and (4) scar formation and contraction after remodeling, such as dedifferentiation from fibroblasts into fiber cells or contraction of collagen

fibers^[34]. A cascade of inflammatory cytokines and reactive oxygen species is activated immediately after injury, and inflammation continues until the process is complete^[35,36]. The following three pathological characteristics that are unique to the process of stricture formation after esophageal EMR/ESD were demonstrated: (1) delayed mucosal healing; (2) severe inflammation, which results in deeper ulceration and extensive fibrosis, in the submucosa; and (3) atrophy in the muscularis proper^[37-40]. These factors may be induced by deep thermal injury because of the electric current effect of endoscopic therapy or the prolonged loss of the esophageal epithelium as a barrier against the external environment, including exogenous material, saliva, food, microorganisms or refluxate^[29,41-43]. Our immunohistochemical study of esophageal specimens surgically obtained from patients with post-ESD strictures revealed rich collagen fibers with inflammatory cells in the submucosa and atrophic changes in the muscularis proper (Figure 2). Collagen fibers are the major components of connective tissue, which provide structural support in scars, and their disordered orientation may be associated with the elasticity and strength of esophageal tissue^[38,44]. Previous studies suggested that the atrophy of muscle fibers might originate from passive fiber atrophy or a dynamic alteration of the muscle fibers into myofibroblasts, activated fibroblasts, which are deeply associated with inflammation, and carcinogenesis. The disorganized fibrosis and the

Table 1 Risk factors of esophageal stricture formation after endo-therapy

Ref.	Setting	Study design	Patients (n)	Mechanical stenosis and/or symptom(dysphasia)	Risk factor	Additional therapy of chemo/radiation	Follow-up period (mo)
Ono <i>et al</i> ^[15]	Single center	Retrospective	65	Necessity of EBD	More than three-fourths of circumferential extension of mucosal defect (OR = 44.2; 95%CI: 4.4-443.6) histologic depth to the LPM cancer (OR = 14.2; 95%CI: 2.7-74.2)	Excluded	Unknown
Shi <i>et al</i> ^[26]	Single center	Retrospective	362	Failure to pass a standard endoscope (11 mm-diameter)	More than three-fourths of circumferential extension of mucosal defect (OR = 44.2, 95%CI: 4.4-443.6) depth of invasion above the LPM cancer (OR = 14.2, 95%CI: 2.7-74.2)	Excluded	41 (16-77)
Takahashi <i>et al</i> ^[25]	Single center	Retrospective	76	Failure of both symptomatic relief of dysphagia and the passage of a standard endoscope (9.2 mm or 9.0 mm-diameter) without any resistance 4-wk after the last session	More than three-fourths of the circumferential extent of mucosal defect (OR = 305.9; 95%CI: 89.387-1046.8)	Excluded	Stricture group: 30.0 (5-142) nonstricture group: 45.0 (6-174)

EBD: Endoscopic balloon dilation.

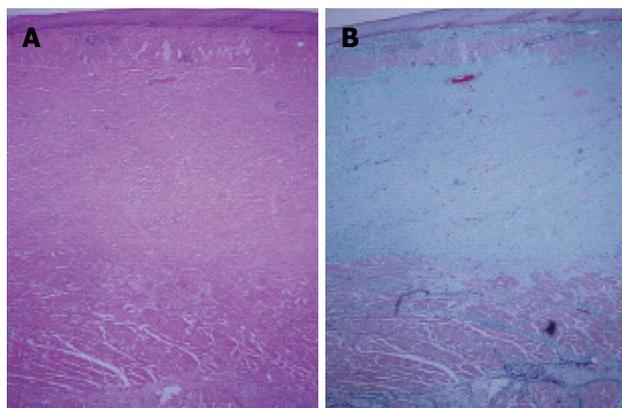


Figure 2 Representative histological findings of specimens surgically obtained from patients with post-endoscopic submucosal dissection strictures of the esophagus (magnification $\times 40$). A: Hematoxylin-Eosin staining; B: Elastica-Masson staining. These results indicated rich collagen fibers with inflammatory cells in the submucosa and atrophic changes in muscularis propria at the stricture site.

abundant production of extracellular matrices in the submucosa and atrophy in the muscularis propria are key factors in post-ESD strictures.

Second, we should consider the possible roles of esophageal dysmotility in the occurrence of symptomatic dysphagia. Previous studies also suggested that dysphagia associated with gastroesophageal reflux disease, caustic esophageal burns and mucosal damage by endoscopic photodynamic therapy may be caused by the underlying esophageal dysmotility^[45-48]. Practically, some post-ESD patients complain of sporadic dysphagia without mechanical strictures on endoscopic findings,

especially when swallowing a large mass of food. Bu *et al*^[45] demonstrated that ineffective esophageal motility after esophageal ESD was related to dysphagia symptoms using a high-resolution manometry system and a published symptomatic scoring system. These results suggested that the ESD procedure itself can induce a dysmotility related to irreversible symptomatic dysphagia without mechanical stricture. However, no study revealed the relationship between symptomatic dysphagia and esophageal dysmotility in pre- or post-ESD patients.

THERAPEUTIC STRATEGY FOR POST ESD-STRICTURES OF THE ESOPHAGUS

Endoscopic dilation therapy

Currently, endoscopic balloon dilation (EBD) is the preferred method to achieve mechanical dilation of the strictures. EBD includes possible complications of perforation, massive bleeding, and bacteremia^[24,25,32,49]. Notably, the potential risk of perforation from dilation therapies for post-EMR/ESD strictures of the esophagus is slightly higher than peptic or anastomotic strictures^[24,25,50]. We demonstrated in detail that the perforation rate in total EBD procedures for post-ESD strictures was 1.02%, which was slightly greater than the 0.4% rate that was reported in a retrospective survey for peptic strictures^[29]. Takahashi *et al*^[25] identified two independent risk factors for perforation using Maloney and Savary wire-guided bougienage, *i.e.*, multiple dilations (OR = 1.185; 95%CI: 1.038-1.353; $P = 0.012$), and location in the

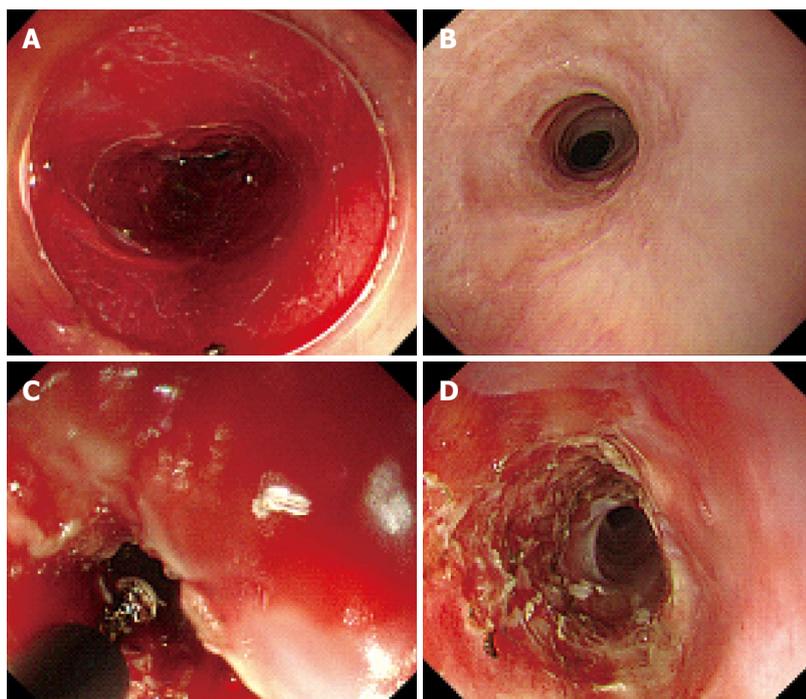


Figure 3 Representative endoscopic images of refractory strictures of the esophagus. A: Endoscopic images immediately after 10-cm long circumferential ESD; B: Images 3 mo after ESD followed by repeated EBD with steroid injection; C: ERIC procedure with IT-2 knife (Olympus, Tokyo, Japan); D: Severe stricture 1 mo after ERIC. ESD: Endoscopic submucosal dissection; ERIC: Endoscopic radial incision and cutting; EBD: Endoscopic balloon dilation.

lower esophagus, which is an area with a relative lack of muscle and/or surrounding supportive tissues (OR = 12.763; 95%CI: 1.089-149.563; $P = 0.043$)^[25]. Moreover, the dilation effect of endoscopic dilation therapies is uncertain, and suboptimal improvements in symptoms may occur. Repeated dilations can worsen scarring, which results in the recurrence of more refractory strictures^[25,51]. Therefore, a carefully planned strategy for dilation treatment is also needed for patients with strictures.

Endoscopic radial incision and cutting method

Recently, the endoscopic radial incision and cutting method (ERIC) method was developed to directly remove/slice the fibrotic tissue of a stricture using ESD-oriented devices. Minamino *et al*^[52] demonstrated the usefulness and safety of ERIC in two patients with refractory strictures of the esophagus after subcircumferential ESD followed by repeated EBD concomitant with locoregional steroid injections. However, the indication for and possible complications of this technique are uncertain because of the lack of studies using a large number of subjects and long-term surveillance. Actually, we experienced one case of stricture after a 10-cm long circumferential ESD that was too severe to be cured using repeated EBD with steroid injections followed by ERIC. It was very hard to perform the incision and slice during the procedure because the stricture was too tight to enable manipulation of the devices (Figure 3). Therefore, further studies will be required to determine the

appropriate indications for ERIC and overcome these limitations.

Stent use

Metallic esophageal stents were initially used for minimally invasive and permanent treatment of fistulas and unresectable malignant stenosis. The use of stents resulted in complications, such as granulation tissue hyperplasia, pain, stent displacement, and esophageal ulceration^[30,53,54]. Improvements in removable stents, such as temporary self-expandable metallic stents and biodegradable stents, gradually increased the use of stent implantation as a new treatment option for refractory benign esophageal strictures^[55-57].

Some studies that reported the usefulness of temporary self-expandable metallic stents for the treatment of esophageal benign stenosis noted their major advantages, including a sustained dilatation effect and ease of removal^[55,58,59]. Matsumoto *et al*^[60] reported that a patient with refractory stenosis 1 mo after ESD was cured by a 7-d implantation of a stent that caused no complications and no recurrence during the 1-mo follow-up. Wen *et al*^[61] performed a single-center randomized controlled trial (RCT) and showed that the stricture rate and number of additional dilatations during a short-term follow-up period were significantly lower in subjects treated by stent placement for 8-wk immediately after ESD than patients who were not treated with stents. However, other studies noted that the long-term treatment effect and complication rates were not as satisfactory as expected^[55,62].

Biodegradable stents were developed to overcome the drawbacks of metallic/plastic stents for benign strictures. Two case reports with short-term (up to 6 mo) surveillance demonstrated the usefulness and safety of polylactide biodegradable stents for stenosis after esophageal ESD that were greater than seven-eighth of the circumference^[63,64]. Further studies will be needed to clarify the long-term outcome, but hyperplastic regenerative changes might make it difficult to distinguish between inflammatory changes and neoplastic residues during the surveillance.

PREVENTIVE STRATEGIES FOR POST-ESD STRICTURES

No strategy for the prevention of post-ESD strictures has been established. Previous studies have reported the usefulness of the local/systemic administration of anti-scarring agents, preventive EBD, and regenerative medicine in the prevention of strictures, albeit with limited success (Table 2). A relatively small number of subjects can result in a type II error. Moreover, there are differences in study designs (basic or clinical), definitions of esophageal stricture and symptomatic dysphasia after endoscopic resection, the indication/method/devices of EBD, follow-up period after the treatment, the treatment history of additional therapies before/after endoscopic treatment, and pathological tumor staging of SENs. Notably, the circumferential extent of post-ESD ulceration can be easily affected by the extent of esophageal wall expansion due to the inflated air amount on endoscopic examination or by shrinkage of the residual mucosa after ESD. Therefore, it is difficult to make direct comparisons to clarify the best choice of prophylactic strategies for strictures. Further prospective, randomized, double-blinded, controlled investigations of a larger number of subjects are required.

Preventive EBD

Previous studies demonstrated that preventive EBD was scheduled immediately after endoscopic resection, which may be useful for the prevention of post-EMR/ESD strictures^[41]. However, patients with large-sized lesions underwent > 13 sessions of preventive EBD after sub-circumferential ESD or > 30 sessions after circumferential ESD, which worsens their QOL and increases the severity of the stricture and the occurrence of EBD-associated complications^[5,29,41,65]. Therefore, the development of new strategies to reduce the numbers of EBD sessions is needed.

Anti-inflammatory agents

The earlier administration of anti-inflammatory agents might have an impact on the initial inflammation, subsequent hyperplasia of granulation and fibrosis in the submucosa. However, the efficacy of anti-inflammatory

approaches in stricture prevention is expected^[66]. Corticosteroids possess anti-inflammatory activity^[67], inhibit collagen synthesis and enhance the breakdown of collagen fibers, thereby preventing the cross-linking of collagen fibers in the stricture formation^[68]. Nonaka *et al.*^[37] used a pig model and demonstrated that steroid injection after circumferential ESD might modify the arrangement and proliferation of spindle-shaped myofibroblasts during the healing process in a normal or near-normal way. Recently, endoscopic injection or systemic administration of steroids was primarily used in clinical studies.

Endoscopic intralesional injections of steroids:

The use of triamcinolone acetonide (TA) in the endoscopic field was proposed previously^[68-70]. Hashimoto *et al.*^[71] used TA injection into the site on the 3rd/7th/10th days after ESD at a dose of 18 to 62 mg for each session in a single-center retrospective study and demonstrated that the stricture rate in patients with TA was significantly lower than in patients without TA (19% vs 75%, respectively). In another single-center prospective study, Hanaoka *et al.*^[72] used a single local injection of 100 mg of TA immediately after ESD, which resulted in a 10% stricture rate and 0 in the median number of EBD sessions in TA subjects compared with 66% and 2%, respectively, in their historical control without TA. However, some patients who were treated using (sub)circumferential ESD followed by steroid injection with EBD still suffered from refractory strictures^[31,52,73].

The results of previous studies exhibit discrepancies^[37,38]. Some studies noted that the use of local steroid injections did not prevent strictures, but it induced serious complications, such as periesophageal abscess/perforation^[28,74,75]. Several studies suggested the following causal factors of these discrepancies. First, the delay in wound healing processes by steroid treatment exhibits bifacial effects. Instead of delayed scar formation, delayed epithelialization might facilitate bacterial infection and the subsequent extension of inflammation, which results in a worsening of the healing process and deepening of fibrotic changes^[38,49]. Second, local steroid administration may induce an excessive inhibition of fibrosis during an early phase of the healing process, which results in a weakening of the wall^[49]. Eventually, a deep ulceration and subsequent perforation can be induced by TA injection, especially when the muscle fibers are missing (Figure 4)^[75]. These changes are associated with a relatively higher risk of perforation from EBD in post-ESD patients who received steroid therapy than in patients who underwent EBD alone^[75]. Third, this method has critical/technical limitations in the certainty of drug delivery^[76]. Actually, we often encountered situations in which many of submucosal TA injections leaked out during/immediately after the injection session, which means that the injected agent may not be as evenly

Table 2 Results of previous studies on preventive strategies for esophageal stricture after endo-therapy

Ref.	Preventive strategy	Study design	n	Tumor stage	Subjects		Additional therapy of chemo/radiation	Stenosis			Dilation therapy		Outcome	
					Circumference of the mucosal defect	Tumor stage		Definition of stenosis	Dysphasia (symptom)	Dysphasia score	Indication	Device	Follow-up period	Stenosis rate
Ezoe <i>et al</i> ^[41]	Preventive EBD	Case series, retrospective	41	T1a-T1b	Subcircumference (> 3/4)	Excluded	No passage of an endoscope (φ11 mm)	Complaint of dysphagia	-	Mechanical/symptomatic	CRE balloon (four size)	Median 84 mo	59%	4.5 (0-35)
Uno <i>et al</i> ^[29]	Preventive EBD + tranilast	Case-control, prospective	31	T1a-T1b (SM1)	Subcircumference (> 3/4)	Excluded	Vomiting at least once a week + no passage of an endoscope (φ10.8 mm)	Dysphagia to regular solid meal	+	Mechanical + symptomatic	CRE balloon (15-18 mm)	24.3 ± 7.4 mo	33.30%	0.0 (0.0-1.75)
Wen <i>et al</i> ^[61]	Fully covered metallic stent	Cohort study, prospective	22	T1a-T1b (SM1)	Subcircumference (> 3/4)	Excluded	No passage of an endoscope (φ9.8 mm)	Persistent dysphagia to regular solid meal	-	Mechanical	Savary-Gilliard dilator	12 wk	18.20%	0.45 (0-3)
Hashimoto <i>et al</i> ^[71]	Local injection of steroid	Case-control, retrospective	41	T1a-T1b (SM2)	Subcircumference (> 3/4)	Included	Complaint of dysphasia/no passage of an endoscope (φ11.4 mm)	Complaint of dysphagia	-	Mechanical	CRE balloon (unclear)	Unclear	19.00%	1.7 (0-15)
Hanaoka <i>et al</i> ^[72]	Local injection of steroid	Cohort study, prospective	59	T1a-T1b	Subcircumference (> 3/4)	Included (chemotherapy)	Dysphagia to some solids/no passage of an endoscope (φ9.2 mm)	Dysphagia to some solids	+	Symptomatic	Unclear	8 wk	10%	0 (0-2)
Yamaguchi <i>et al</i> ^[65]	Systemic administration of steroid	Cohort study, retrospective	41	T1a-T1b (SM1)	Subcircumference (> 3/4)	Excluded	Unclear	Complaint of dysphagia	-	Symptomatic	CRE balloon (15-18 mm)	3 mo	5.30%	1.7 (0-7)
Sato <i>et al</i> ^[77]	Systemic administration of steroid + EBD	Cohort study, retrospective	23	T1a-T1b (SM2)	Circumference	Included	Resistance/failure to pass an endoscope (φ9.9 mm)	-	-	Mechanical	CRE balloon (15-18 mm)	No fininition	-	13.8 ± 6.9
Ohki <i>et al</i> ^[68]	Autologous oral mucosal epithelial cell sheets	Single-arm	9	Unknown	Subcircumference (> 2/3)	Unknown	No definition	-	+	Mechanical	Unclear	-	-	2.33 (0-21)
Sakaguchi <i>et al</i> ^[106]	PGA	Case series, prospective	8	T1a-T1b (SM2)	Subcircumference (> 3/4)	Unknown	Failure to pass a endoscope (φ9.8 mm)	Symptoms of dysphasia	-	Mechanical	CRE balloon (12-18 mm)	No definition	37.5% (about 28 POD)	0.8 ± 1.2
Iizuka <i>et al</i> ^[107]	PGA	Case series, prospective	15	T1a-T1b (SM2)	Subcircumference (> 1/2)	Excluded	Unclear	Unclear	-	Unclear	EBD (unclear)	6 wk	7.70%	5

PGA: Polyglycolic acid; ESD: Endoscopic submucosal dissection; EBD: Endoscopic balloon dilation.

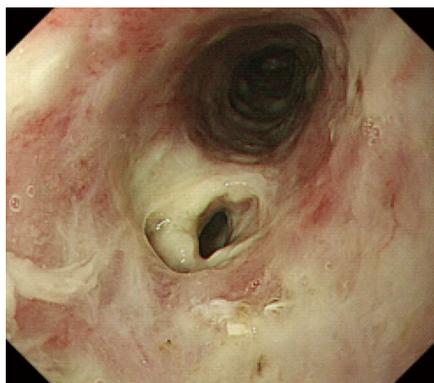


Figure 4 Representative image of esophageal perforation 2 d after local injection of triamcinolone acetonide for endoscopic submucosal dissection ulceration.

distributed as we intended. Therefore, it can be difficult to measure/establish the precise/optimal amount of the drug that was actually delivered because no studies used tracing modalities for the injected drugs. Further studies are needed to establish a stable drug delivery system and define the optimal dose, duration, and timing of steroid administration for stricture prevention.

Systemic steroid therapy: Yamaguchi *et al*^[65] demonstrated the efficacy of systemic steroid therapy for stricture prevention. Oral prednisolone was initiated 2 d after ESD at a dose of 30 mg/d, and the dose was gradually tapered in decrements of 5 mg/d every 2 wk for 1 mo followed by decrements of 5 mg/d every week for the next 4 wk for 8 wk after ESD. A comparison of the stricture rate of 19 patients with systemic steroid therapy with 22 patients with preventive EBD alone revealed that the rate in the former group was significantly lower than that in the latter group (5.3% vs 31.8%, respectively). Sato *et al*^[77] also reported that early, rather than late, administration of systemic steroid therapy concomitant with therapeutic EBD was more effective than therapeutic EBD alone in the prevention of esophageal strictures after circumferential ESD. However, we should consider that there were only limited effects of steroids on stricture prevention, especially after long-length (sub)circumferential ESD or circumferential ESD, before extrapolating these results from study settings to practical clinical settings^[73,78]. We should also pay careful attention to the adverse effects of systemic administration, such as immune suppression, psychiatric disturbances, diabetes, and peptic ulceration^[65]. One case report described that systemic steroid therapy after esophageal ESD may have caused disseminated nocardiosis^[79].

Potential drugs to target fibrotic formation: Machida *et al*^[80] demonstrated that local injection of mitomycin C (MMC) into the site improved recurrent

dysphagia or re-stenosis without serious complications in 5 patients. MMC has an anti-proliferative effect on fibroblasts in strictures, but the reproducibility of these results was poor^[76,81]. In contrast, MMC may cause critical adverse events, such as delayed mucosal healing, ulcer formation, perforation, and secondary malignancy^[82,83].

N-acetylcysteine (NAC) is also expected to prevent esophageal strictures because of the efficacy of NAC against pulmonary fibrosis and restructuring after EBD for intestinal strictures of Crohn's disease or coronary angioplasty^[84-86]. NAC is an antioxidant compound with antifibrotic effects, which primarily occur through the inhibition of transforming growth factor- β signaling, and anti-inflammatory effects that occur via the down-regulation of tumor necrosis factor- α , interleukin-6 and interleukin-8 synthesis^[87-90]. Barret *et al*^[91] demonstrated that the systemic administration of NAC after circumferential ESD did not exhibit a significant benefit on the occurrence of esophageal fibrosis and subsequent esophageal stricture one month after ESD in a pig model, which had the special condition of continuous acid aggression in the esophagus, compared to other models^[91]. We performed a prospective, stratified-randomized, open-label trial in humans and demonstrated the efficacy and safety of preventive EBD combined with the commercially available oral agent NAC Tranilast for the prevention of esophageal strictures after 5 circumferential or 26 near-circumferential ESD cases (Figure 5). We demonstrated that the percentage of post-ESD strictures and the median numbers of additional EBD sessions and published dysphagia score 16 and 24 wk after ESD in subjects with preventive EBD concomitant with Tranilast intake were significantly lower than patients without Tranilast intake (33.3%, 0.0%, 0.0%, 0.0%, vs 68.8%, 4.0%, 5.0%, 3.0%, respectively)^[29]. A previous study suggested that combination therapy involving NAC and other treatments may exhibit synergy effects^[92], and we are currently performing a randomized controlled trial to elucidate the synergistic effect of NAC on the preventive effect of oral steroid administration.

Regenerative medicine approaches

Tissue engineering approaches and scaffold-based therapy/cell-based therapy are based on the concept that transplanted tissue with/without supportive materials can induce early repair and replace damaged tissues.

Cell-based therapies: Transplanted cells are expected to induce an early repair of wounds through their interaction with the host tissue, but their efficacies were demonstrated in only some animal studies. Sakurai *et al*^[93] demonstrated the effect of autologous keratinocyte implantation in the prevention of scar formation 2 wk after EMR, but there was no significant difference in inflammatory

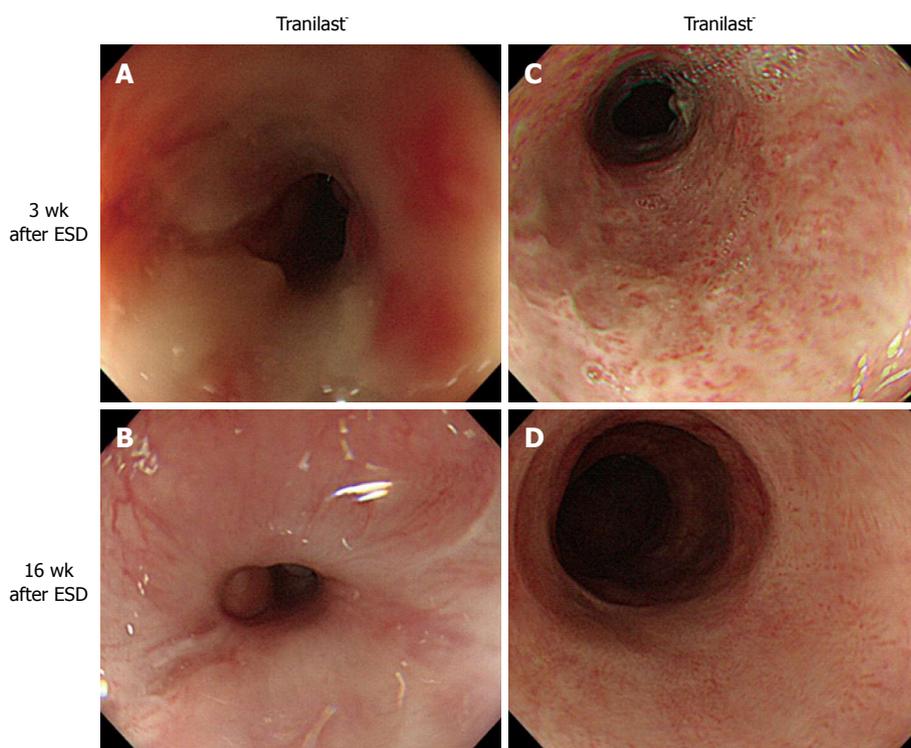


Figure 5 Representative image of the ulcer healing process after circumferential endoscopic submucosal dissection of the esophagus. A: 3 wk after ESD of patient without Tranilast intake; B: 16 wk after ESD of patient without Tranilast intake; C: 3 wk after ESD of patient with Tranilast intake; D: 16 wk after ESD of patient with Tranilast intake. ESD: Endoscopic submucosal dissection.

cell infiltration^[93]. Zuercher *et al*^[33] demonstrated that stricture formation with circumferential transmural fibrosis 6 mo after a 6-cm long circumferential EMR of sheep esophagus was inhibited by the injection of autologous keratinocytes into the sites. The further development of regenerative medicine will be achieved by the use of adipose-derived stem cells (ADSCs), which are easily obtained from adipose tissue, for the targeted prevention of esophageal strictures. ADSCs exhibit biological features that are similar to those of bone marrow-derived stem cells, which enhance early wound healing through humoral factor secretion, differentiation into multiple cell-types, suppression of inflammatory cells, and the promotion of angiogenesis^[94-96]. Honda *et al*^[39] demonstrated that local injection of autologous ADSCs after post-EMR ulceration prevented esophageal strictures in a canine model, but no investigations of surface markers, multi-potentiality, or cell proliferation during the healing process were performed.

However, other studies noted possible difficulties in the engraftment of transplanted cells at the site because of their low viability and difficulty in confirming their injection into the targeted site. Whether the injected cells can really form a regenerating epithelial layer or facilitate epithelial cells of the ulcer edge to cover the site remains unclear because of the difficulty in tracing the cells.

Technology of autologous oral mucosal epithelial cell sheets:

A breakthrough system for epithelial cell sheets on temperature-responsive culture inserts was developed at Tokyo Women's Medical University^[97], and the cell membrane proteins and cell-to-cell junctions in these sheets can be directly grafted to the site without suturing or the use of any adhesive materials. Sheet transplantation to mucosal defects immediately after ESD promoted re-epithelization in an animal/clinical model^[40,43,98,99]. Transplantation of cell sheets prevented esophageal strictures after hemi-circumferential to sub-circumferential ESD in 8 of 9 cases in a clinical study, and mucosal healing was rapidly completed within 3 to 5 wk. Only one case required 21 sessions of EBD^[98]. These results suggested that cell sheets promote epithelial healing and prevent stricture formation. However, the transplantation of these sheets may be disturbed by esophageal wall motion, the passage of intakes, or gravity, depending on the location of the site. Therefore, further studies of the development of devices that facilitate stable sheet transplantation are warranted to confirm the usefulness and safety of this therapy.

Scaffold-based therapies:

Temporary scaffolds developed from biodegradable materials may provide key proteins to establish a microenvironment that is suitable to facilitate cell adhesion and migration/

proliferation, which results in early wound repair^[100].

Previous studies have suggested that the extracellular matrix plays an important role in the prevention of strictures. Badylak *et al*^[101] found that stents combined with extracellular matrix and autologous muscle tissues enabled the reconstruction of esophageal structures and the recovery of function without stricture formation in a canine model. Nieponice *et al*^[102] demonstrated that implantation of a temporary stent wrapped with an extracellular matrix biological scaffold composed of porcine-derived small intestinal submucosa macroscopically/microscopically prevented esophageal stenosis even after a long-length circumferential EMR of the esophagus in another canine model.

Commercially available biological scaffold sheets composed of polyglycolic acid (PGA), poly-L-lactic acid (PLLA), or human amniotic membrane (AM) are expected to minimize scar contracture in various clinical fields^[64,103,104]. PGA/PLLA are widely used as biodegradable suture materials because they are synthetic compounds that are completely degraded into nontoxic products in physiological conditions^[104]. A recent case-series/report applied PGA sheets for the prevention of post-ESD stricture^[105-107]. Sakaguchi *et al*^[106] demonstrated that the use of sheets after ESD with mucosal defects of more than three-quarters of the esophageal circumference resulted in a stricture rate of 37.5% 4 wk after ESD. Iizuka *et al*^[107] demonstrated a stricture rate of 7.7% 6 wk after ESD with more than half of the mucosal defects. Saito *et al*^[64] demonstrated the usefulness of biological scaffolds composed of PLLA as temporary stent supports for stricture prevention in 2 cases. AM grafts, which consist of an avascular stroma and a monostratified cylinder cell epithelium with very few antigens^[108], are used clinically in the field of ophthalmology. However, Barret *et al*^[108-110] demonstrated that AM grafts had only limited benefit in preventing strictures in a swine model. More recently, Schomisch *et al*^[111] revealed that no commercially available biological mesh with stent prevented esophageal stricture after 5-10-cm long circumferential ESD in a swine model. Therefore, the usefulness of 'clinically available' biological scaffold sheets in stricture prevention remains controversial.

Technical difficulties in the delivery of cell sheets to the esophageal wall also remain. Delivery using over-the-scope applications using clips or through-the-scope applications using dilation balloons or temporary self-expandable stents are time-consuming, and hole defects after ESD remain uncovered by the sheets in some cases. Instead, the patched sheets easily drop off, probably due to peristaltic esophageal wall motions or gravity depending on the anatomical location. Uno *et al*^[29] and Iizuka *et al*^[107] demonstrated that the sheets remained in place 1 wk after ESD in 86.7% of the patients and 2 wk after ESD in 40% of the patients, although a much longer time was needed for complete healing. Moreover, these sheets exhibit

potential adverse events, such as local recurrences and infections, because the scaffold itself provides a good environment for the engraftment of malignant cells or microorganisms in the esophageal lumen and oral cavity.

Therefore, these biological scaffold-based approaches that target the control of the tissue microenvironment will shed new light on the development of new technologies for the prevention of strictures. However, sufficiently stable and firm covering technologies without adverse effects have not been developed.

PERSPECTIVE

Previous studies have suggested that each of these preventive strategies might reduce the risk of esophageal stricture after (sub)circumferential ESD from 88%-100% to 5.3%-59%. However, these strategies have a reduced or no effect on prevention in some cases, such as circumferential mucosal defects after ESD and sub-circumferential mucosal defects of a longitudinal length longer than 50 mm (Table 2).

Further studies using a combination of the published strategies, rather than a single strategy, are warranted as the first step to overcome this issue. The establishment of accurate, consistent, and safe methods to deliver agents through an endoscope is one of the most important topics in this field. Recent developments in stent technologies, such as recyclable covered stents, drug-eluting stents, anti-displacement stents, and biodegradable stents, promote future improvements in stents with an adherent substance that contains release agents/nanoparticles, which may enable a more reliable and feasible drug delivery system.

Another approach is the development of transplanting engineered tissues. The rationale for this idea is that tissue engineering approaches have the ability to create a temporary mechanical barrier and promote epithelial re-growth because of their anti-inflammatory and anti-fibrotic properties. Future prospects in tissue engineering approaches have great potential to cause damaged tissues to exhibit (near-) normal physiological functions. However, there remain concerns about possible complications from the existing technologies, such as local infection, immunological responses, and tumorigenesis, remain because some previous studies included patients with large-sized SENs in which the pathological assessment of the ESD specimens revealed submucosal invasion or positive vertical margins. Myofibroblasts are a major component of the microenvironment, and these cells might play a central role in the wound healing process and the development of carcinogenesis. Therefore, further works that focus on the control of fibroblast activity, such as stable wound-covering stent/cell sheets with biological agents/nanoparticles with anti-fibrotic activity, could provide a big step in the

development of new modalities.

CONCLUSION

We reviewed the recent achievements in preventive strategies for post-ESD strictures of the esophagus, which demonstrated only limited success. The limitations of preoperative staging accuracy and the relatively high risk of local recurrence during the surveillance support the establishment of preventive strategies as an urgent task to maintain prognosis and improve QOL. Therefore, the strengthening of the unity of knowledge of the biological/physiological mechanisms of post-ESD strictures in various research fields, such as basic/clinical medical research, nanotechnology, and medical engineering, is required to establish new strategies to promote wound healing and control the tumor/inflammatory microenvironment in carcinogenesis. After the efficacy and safety of these new strategies are confirmed in long-term careful assessments, (sub)circumferential ESD of the esophagus will be accepted more broadly as the major treatment strategy for SENs.

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