Advances in the prevention and treatment of esophageal stricture after endoscopic submucosal dissection of early esophageal cancer

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ABSTRACT

Endoscopic submucosal dissection (ESD) has become the main treatment for early esophageal cancer. While treating the disease, ESD may also cause postoperative esophageal stricture, which is a global issue that needs resolution. Various methods have been applied to resolve the problem, such as mechanical dilatation, glucocorticoids, anti-scarring drugs, and regenerative medicine; however, no standard treatment regimen exists. This article describes and evaluates the strengths and limitations of new and promising potential strategies for the treatment and prevention of esophageal strictures.

Key words: endoscopic submucosal dissection, esophageal cancer, esophageal stricture, prevention and treatment methods

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INTRODUCTION

Esophageal cancer is currently the eighth most common cancer worldwide; it ranks sixth among the causes of cancer-related deaths.[1] For patients with distant metastasis or lymph node infiltration (women are generally more resistant to metastatic spread[2]), operation, radiotherapy, and chemotherapy are usually adopted.Endoscopic submucosal dissection (ESD) is a sophisticated endoscopic technique that has been widely applied and recognized in clinical practice.[3] For patients with early esophageal cancer, ESD is a safe, effective, and feasible first-line treatment option. In contrast with traditional endoscopic mucosal resection (EMR), ESD can achieve mass resection of lesions >2 cm and deliver accurate pathological evaluation.[4–6] In recent years, endoscopic ultrasound has developed rapidly and played an important role in the treatment of pancreatic, gallbladder, and liver diseases.[7–9] Because of its unique ability to locate lesions, endoscopic ultrasound facilitates the detection, staging,

and treatment of esophageal diseases,[10-11] which is of immense significance for the determination of tumor size, margin, and internal echo structure.[12] However, postoperative esophageal stricture is a major ESD-related complication, the incidence of which is associated with the size of the lesion and the range of circumferential mucosal defects;[13] it can cause severe dysphagia and an appreciable decrease in the quality of life of patients, thus becoming a major issue to be tackled after operation. Here, we review more comprehensively recent methods for the prevention and treatment of post-ESD esophageal stricture.

ESOPHAGEAL DILATION

Endoscopic esophageal dilation

Endoscopic esophageal dilation is a common method for the prevention and treatment of post-ESD stricture; it includes balloon dilation and bougie dilation, which exhibit different modes of action. Lian et al.[14] conducted a retrospective study in which 335 patients with early esophageal cancer received ESD. Among

them, 29 patients exhibited varying degrees of dysphagia 17–45 days after ESD and received endoscopic balloon dilation (EBD) 117 times in total. Twenty-eight patients were followed up for more than 3 months after remission of dysphagia, among whom two patients were repeatedly treated with EBD owing to symptom recurrence before the end of follow-up; thus, a treatment success rate of 92.9% (26/28) was achieved. Ezoe et al.[15] revealed that, despite the fact that 60% of patients developed esophageal stricture with prophylactic balloon dilatation, the severity of the stricture was significantly reduced. However, endoscopic dilatation has limitations. Multiple dilatation procedures may induce complications such as bleeding, perforation, bacteremia, and restricture and increase the economic and mental burden on patients.

Self-help inflatable balloon

Li *et al*.[16] conducted a study on the use of a self-help inflatable balloon to prevent post-ESD stricture. Patients can operate this balloon by themselves at home, which makes the process simple and convenient; additionally, the balloon is reusable. Of the eight patients evaluated, only one patient (12.5%) developed esophageal stricture, which was relieved after three EBD procedures; none of the patients developed complications such as delayed bleeding and perforation. Further, Li *et al*.[17] studied a patient who used a self-help inflatable balloon to prevent post-ESD stricture and achieved satisfactory results. Despite the small sample size, the results indicate that a self-help inflatable balloon can be viewed as a new direction for future research.

ESOPHAGEAL STENTS

Covered metal stents

In the early days, esophageal stents were used to treat anastomotic fistula and esophageal perforation.[18] Because of their continuous dilatory effect on the esophageal wall to a certain extent, esophageal stents have also been widely applied to prevent and treat benign esophageal stricture with remarkable results.[19] Zhang *et al*.[20] studied a patient with early esophageal cancer. After ESD, a fully covered, self-expanding nitinol stent was inserted into the esophagus and removed 1 month later. The patient had mild esophageal stricture, without dysphagia or other serious complications. Yamasaki *et al*.[21] studied a patient with esophageal ulcers that were greater than half of the esophageal circumference after ESD. One month after the operation, the patient experienced dysphagia, which did not improve even after the patient received EBD four times. A fully covered, self-expandable metal stent was inserted, which relieved the symptom immediately. The stent was removed successfully 2 months later, and no stricture formed after 6 months of follow-up. Common

complications after stent placement include restricture, bleeding, and stent displacement that are related to the stent material and etiology of the disease.[19] To avoid stent displacement, the post-ESD diet should be mainly a liquid or semi-liquid, and endoscopy should be performed on a regular basis to confirm the correct position of the stent. Covered metal stent has been widely used in clinical practice, and it has been reported to be used to drain pancreatic fluid collections (PFCs).[22,23] An application named "Stent Tracker" was designed to monitor a metal stent placed for the drainage of pancreatic effusion; through this application, endoscopists can recall patients to remove the stent in time to reduce complications.[24] Therefore, whether esophageal stents can be tracked in a similar manner after insertion remains to be examined.

Biodegradable stents

Biodegradable stents (BDSs) are made of degradable synthetic polymers that decompose in the body and do not require removal. The degradation process is affected by pH, temperature, and body fluids, and the degradation products are nontoxic, partly absorbed, and partly excreted through the gastrointestinal tract.[25] Clinical studies have shown that BDSs made of poly-l-lactic acid play a pivotal role in preventing post-ESD esophageal stricture; however, stent displacement has been observed.[26] Yang *et al*.[27] conducted a prospective study by placing a silicone-covered magnesium alloy BDS into 15 rabbits with benign esophageal stricture (stent group) and compared these rabbits with six rabbits presenting simple esophageal stricture (control group). The reconstructed esophageal wall and tissue response were compared through esophagography. The diameter of the esophagus in the stent group was 9.8 ± 0.3, 9.7 ± 0.7, 9.4 ± 0.8, and 9.2 ± 0.5 mm, respectively, at the time of insertion and the first, second, and third weeks after insertion (4.9 ± 0.3 mm before insertion, $P < 0.05$). The reconstructed esophageal wall (especially in the epithelial layer and smooth muscle layer) in the stent group was significantly thinner than that in the control group ($P < 0.05$). The stent produced a good effect in rabbit models of benign esophageal stricture, without complications such as esophageal injury and stent displacement, thereby indicating a bright prospect for its application in the treatment of esophageal stricture. Pauli *et al*.[28] placed BDS made of polydioxanone into the esophagus of pigs with circumferential esophageal mucosal defects. The results suggested that the survival time of the stent group was longer than that of the control group (9.2 *vs.* 2.4 weeks, $P < 0.01$). Nevertheless, esophageal strictures of similar degree and length were found in all animals. A limitation of this stent is its high cost. Moreover, the continuous dilation exerted by the stent on the esophageal wall diminishes during degradation; thus, the use of BDS may cause stent displacement and restructure, which needs endoscopic

monitoring on a regular basis. Large-scale randomized controlled trials are required to investigate the clinical effect of BDS.

Novel detachable stents

A novel detachable stent has been recently proposed, which is formed by connecting a metal mesh with a connecting wire. The stent can be divided into three parts after the wire is detached to reduce the secondary esophageal injury caused by the radial force of the stent during removal. Shang *et al*.[29] conducted a prospective randomized controlled trial and randomly divided 18 rabbits with erosive esophageal stricture injury into three groups: detachable stent group (DS group, surgical suture connection), biodegradable stent group (BS group, polylactic acid wire connection), and the control group (without any treatment), with 6 rabbits in each group. The stricture rates, complication rates, and survival rates were similar between the DS and BS groups over 8 weeks. The differences between the DS group and the control group and between the BS group and the control group were statistically significant. After the degradation of the connection wire in the BS group, five stents moved into the stomach, and the fragments were removed using biopsy forceps. All the stents in the DS group were easily removed. Thus, the novel detachable stent exhibits good support, and it can reduce esophageal injury during removal. Such a type of stent was merely used in animal experiments; therefore, more evidence is needed to verify its effectiveness.

GLUCOCORTICOIDS

Glucocorticoids have a strong anti-inflammatory effect, and they can inhibit the synthesis, cross-linking, and fibrosis of collagen, thus inhibiting the formation of strictures. Many studies have verified their effectiveness in the prevention of post-ESD esophageal stricture through oral administration, local injection, local application of steroid gel, and local perfusion.

Oral administration of steroids

The oral administration of steroids is convenient as it allows patients to take them outside the hospital. Zhou *et al*.[30] studied 23 patients who underwent ESD owing to esophageal squamous cell carcinoma and exhibited mucosal defects greater than three-quarters of the esophageal circumference. There were 13 patients in the experimental group. Oral prednisone 30 mg/d was administered from the third day after ESD and the dose was gradually decreased (30, 25, 20, 15, 10, and 5 mg, each lasting 14 days). There were 10 patients in the control group without special treatment. Upon the occurrence of dysphagia, EBD treatment was administered. The incidence of stricture was 23.1% (3/13) in the experimental group and 80%

(8/10) in the control group ($P < 0.05$); the number of EBD procedures required in the experimental group was significantly lesser than that in the control group (0.69 *vs.* 13.5 procedures, $P < 0.05$). After 12 months of follow-up, no adverse events related to the oral administration of prednisone occurred. Some researchers adopted different schemes and selected low-dose short-course treatment regimens.[31] Thirty-three patients with ESD were divided into two groups. In total, 17 patients in the experimental group took oral prednisone, whereas a total of 16 patients in the control group were treated with ESD alone. The experimental group received oral prednisone 30 mg/d from the second day after ESD; the dose was gradually decreased in the first, second, and third weeks (30, 20, and 10 mg/d, respectively), and prednisone treatment was stopped after the third week. The results revealed that both the stricture rate and the number of EBD procedures required owing to dysphagia were lower in the experimental group than in the control group, which indicates that this regimen is useful for the prevention of postoperative stricture. At present, there is no definite regimen for the dose and course of oral steroid treatment, and the systemic application of steroids may produce many side effects such as blood glucose level changes, slow wound healing, osteoporosis, and even mental illness. Moreover, the immunosuppressive effect of steroids can induce or aggravate infections, reactivate latent tuberculosis infection, and increase the risk of recurrence of tuberculosis; these effects are proportional to the dose and duration of the steroid treatment.[32]

Local injection

Local injection can decrease the effect of steroids at the systemic level and increase the steroid concentration at the injection site. Hanaoka *et al*.[33] conducted a prospective study in which 30 patients with esophageal squamous cell carcinoma underwent ESD and exhibited mucosal defects greater than three-quarters of the esophageal circumference (less than the whole circumference). Twenty-nine patients who had previously received ESD, but no steroid injections were included in the control group for historical control. The stricture rate in the study group was significantly lower than that in the control group (3/30 *vs.* 19/29, 10% *vs.* 66%, $P < 0.0001$), and the number of EBD procedures required in the study group was less than that in the control group ($P < 0.0001$). However, a retrospective study suggested that the effect of local injection was unsatisfactory in the prevention of mucosal defects greater than seven-eighths of the esophageal circumference.[34] This method has higher technical requirements, and the injection site must be the submucosa. If the muscular layer is involved, it may lead to complications such as delayed esophageal perforation. In a study by Yamashita *et al*.,[35] three pigs were subjected to ESD under general anesthesia and a 30-mm-long mucosal defect was created on the oral and anal sides of

the esophagus. Subsequently, the pigs were administered triamcinolone acetonide (TAC group) and saline (control group) by injection into the muscle layer of the artificial ulcers on the oral and anal sides, respectively. The results showed that, in the TAC group, the ulcers spread to and atrophy occurred in the muscular layer in three cases. Perforation of the esophageal wall occurred in two cases; the abscess spread to the mediastinum, and there was tissue adhesion between the esophagus and bronchus, as well as between the lungs and aorta. However, the depth of the ulcers in the control group was limited to the submucosa. Therefore, care must be taken during operation to avoid deep damage. To avoid such a consequence, a "stamping" method was utilized.[36] Specifically, the end of a catheter is placed on the surface of the muscle layer, and, subsequently, triamcinolone acetonide solution diluted with saline is injected. The injection needle is not needed during the whole process, so that the submucosal buffer layer can be created without damaging the muscle layer, thereby reducing the risk of perforation. This method is simple and easy to be implemented, and it introduces a novel strategy for avoiding the adverse event.

A new concept of "sequential steroid therapy" has been developed,[37] in which a local injection of steroids is followed by oral administration. Chu *et al*.[38] conducted a study in which mucosal defects were greater than two-thirds of the esophageal circumference after ESD. In the treatment group, 34 patients were administered a local injection of steroids immediately after ESD (concentration of 8 mg/mL, 0.5 mL per site, with a total dose of 80–120 mg) and oral steroids (30 mg/d) from the third day after ESD, the dose of which was decreased gradually (30, 30, 25, 25, 20, 15, 10, and 5 mg, 1 week at a time for 8 weeks). Nevertheless, 36 patients, in the control group, received no other treatment. The stricture rates in the treatment group and the control group were 14.7% (5/14) and 52.8% (19/36) ($P = 0.001$), respectively; the difference was statistically significant. However, a retrospective study revealed that local injection combined with oral administration was not effective in the prevention of circumferential mucosal defects in patients after ESD, with a stricture rate of 62% (16/26).[39]

Local application of steroid gel
Because local injection may cause serious complications, some studies have evaluated the effectiveness of triamcinolone acetonide gel in the prevention of post-ESD stricture. Mori *et al*.[40] randomly divided 43 patients who underwent ESD owing to early esophageal cancer into two groups. Twenty patients in the experimental group received triamcinolone acetonide gel with EBD, whereas 23 patients in the control group received local injection of steroids with EBD. There was no significant difference in the stricture rate between the two groups on the 5th, 8th, 12th, 15th, 20th, 30th, and 60th day after ESD; however, there was a difference in the number of EBD procedures required owing to esophageal stricture ($P < 0.011$). Thus, according to this study, steroid gel with EBD is superior to local injection with EBD. Nie *et al*.[41] conducted a retrospective study and divided 27 patients with post-ESD mucosal defects greater than three-quarters of the esophageal circumference into two groups. One group received local injection with oral triamcinolone acetonide ($n = 13$), whereas the other group was treated with oral hydrocortisone with aluminum phosphate gel ($n = 14$); the stricture rates for these groups were 53.8% (7/13) and 7.1% (1/14, $P < 0.05$), respectively. This new strategy may play a certain role in the prevention of postoperative stricture; however, it needs further exploration and research.

Local perfusion
Local perfusion refers to the injection of a steroid solution diluted with saline into the esophagus to induce even penetration into the ulcer surface after ESD.[42] Shibagaki *et al*.[43] conducted a prospective study. Twenty patients with early esophageal cancer were perfused twice on the first and seventh day after ESD (80 mg triamcinolone acetonide each time, 2 minutes). Endoscopy was performed every 2 weeks. If severe stricture was found, dilation was performed with balloons of 15–18 mm diameter and additional perfusion was administered. During follow-up, seven patients (7/20, 75%) developed esophageal stricture; however, the stricture was relieved without EBD in six patients with mild stricture (6/7, 85.7%). In this manner, local perfusion does produce a better preventive effect on esophageal stricture. However, there is a lack of controlled trials that examine this method; therefore, a wider range of controlled clinical studies are needed to verify its effectiveness.

ANTI-FIBROSIS OR ANTI-SCARRING DRUGS

Botulinum toxin A
Botulinum toxin A (BTX-A) is a neurotoxin that inhibits the release of acetylcholine from the presynaptic membrane, and therefore relaxes the smooth muscle. It has been reported that[44] injecting botulinum into the pyloric sphincter under the guidance of endoscopic ultrasound can treat gastroparesis caused by distal esophageal carcinoma resection. BTX-A has been used in facial surgery to inhibit scar formation,[45] thus providing a new direction for the prevention of post-ESD esophageal stricture. Wen *et al*.[46] implied that the rate of esophageal stricture and number of esophageal dilatation procedures in the group injected with BTX-A after ESD were lower than those in the untreated group. BTX-A should be injected into the deep part of

the muscle layer along the junction between the tissue with the defect and the normal tissue immediately after ESD; however, the optimal dose of injection needs to be further investigated in multicenter trials with a larger sample size.

Mitomycin C

Mitomycin C (MMC) is a widely used antineoplastic drug that inhibits cell proliferation by inhibiting DNA synthesis. Histologically, MMC can appreciably reduce the number of fibroblasts, the degree of inflammation, and the content of collagen; its inhibitory effect on the proliferation of fibroblasts is dose dependent.[47] Machida *et al*.[48] conducted a prospective study that included five patients with refractory benign esophageal stricture after ESD. Repeated treatment with EBD delivered poor results. Thus, MMC was injected into the dilated site, which relieved the symptoms of dysphagia in all patients. During the 4.8-month follow-up, there was no occurrence of restricture. Another study also confirmed that MMC could prolong the symptom-free period of dysphagia and reduce the number of dilatation procedures in patients with benign esophageal stricture.[49]

5-Fluorouracil

As one of the drugs used for combination chemotherapy, 5-fluorouracil (5-FU) has achieved positive results in the treatment of esophageal cancer;[50] additionally, 5-FU can inhibit scar formation. In an animal study conducted by Mizutani *et al*.,[51] 5-FU was encapsulated within liposomes and subsequently mixed with 2% atenolol injection to form 5-fluorouracil-liposome-collagen (5-FLC), which was injected into the ulcer immediately after ESD. The results suggested that the degrees of esophageal stricture and submucosal fibrosis in dogs treated with 5-FLC were observably lower than those in the untreated group. 5-FLC can prolong the action time of 5-FU in vitro for more than 2 weeks and can exert a stronger inhibitory effect. Current research on 5-FU is limited to animal research, and there is no definite conclusion regarding the dose. Therefore, further clinical trials are needed to confirm its practical applicability.

Tranilast

Tranilast inhibits the release of histamine and prostaglandin from mast cells to exert an anti-allergic effect, while inhibiting the release of TGF-β1, IL-1β, and PGE2 from mononuclear macrophages to inhibit the fibroblast proliferation and collagen synthesis.[52] Uno *et al*.[53] conducted a prospective study in which 31 patients underwent ESD owing to superficial squamous cell carcinoma of the esophagus and presented mucosal defects greater than three-quarters of the esophageal circumference. The experimental group was administered EBD and tranilast (300 mg/d, oral administration after

three meals), whereas the control group was administered EBD alone. The stricture rate was 33.3% (5/15) in the experimental group and 68.8% (11/16, $P < 0.05$) in the control group, and there was no adverse reaction. Some scholars believe that the long-term side effects of oral tranilast may be lower than those of oral glucocorticoids;[54] however, further prospective randomized controlled trials are needed to compare the effects of the two.

Thymosin β4Thymosin β4 (Tβ4) is a peptide containing 43 amino acids with anti-inflammatory, angiogenic, and wound-healing effects.[55] Wang *et al*.[56] divided eight Bama pigs into two groups after ESD. The experimental group was injected with Tβ4 gel (Tβ4 powder mixed with polyethylene glycol–poly lactic-co-glycolic acid gel), whereas the control group was not treated. Although all animals eventually developed esophageal stricture, the experimental group exhibited less-severe stricture and required fewer EBD procedures.

Hemostatic powder

Hemostatic powder can provide mechanical protection against physical, chemical, and microbial invasion of the exposed residual submucosa and muscle layer after ESD. Beye *et al*.[57] divided experimental pigs into two groups after ESD. Hemostatic powder was sprayed on the whole area of mucosal defects immediately after ESD and three times on the second, hfourth, and hseventh day after ESD in the experimental group, whereas the control group was not treated. The results indicated that the stricture rate in the experimental group and control group was 60% and 100%, respectively. The thickness of fibrosis, the degree of inflammatory cell infiltration, and the level of TGF-β in the experimental group were all low, demonstrating that hemostatic powder has certain anti-fibrosis properties.

N-acetylcysteine

N-acetylcysteine (NAC) exhibits an antioxidant effect, and it has been applied in the treatment of liver and pulmonary fibrosis. In an animal experiment by Barret *et al*.,[58] despite the fact that NAC produces an antioxidant effect, there were no statistically significant differences between the two groups with regard to oxidative stress, degree of esophageal inflammation and fibrosis, and the number of dilatation procedures required. Further research is needed to determine whether it is effective in the prevention of esophageal stricture in combination with other drugs.

Small interfering RNA

Small interfering RNA (siRNA) can block the carbohydrate sulfotransferase 15 (CHST15) expressed by fibroblasts, which is involved in the formation of fibrosis. Sato *et al*.[59] conducted an animal experiment in which semi-circumferential post-ESD ulcers were induced on the oral

and anal sides of the esophagus of three pigs; into one side of the ulcers, siRNA was injected. The results implied that the degrees of collagen deposition, fibroblast proliferation, and muscle fibrosis at the injection site were significantly lower than those on the other side. Despite the presence of a small post-ESD ulcer area, the experiment suggested that siRNA could prevent post-ESD esophageal stricture by inhibiting fibrosis.

WOUND PROTECTION

Polyglycolic acid

Polyglycolic acid (PGA) is an absorbable suture material that can be decomposed into nontoxic ethanol under physiological conditions for 4–6 months and eventually be converted into water and carbon dioxide. PGA combined with fibrin glue can prevent post-ESD esophageal stricture to a certain extent. Lizuka *et al*.[60] conducted a prospective study on 13 patients with mucosal defects greater than half of the esophageal circumference but less than the whole circumference. Small pieces of PGA were placed into the esophagus in stages after ESD to cover mucosal defects. The stricture rate was 7.7% (1/13) within 6 weeks, and no new stricture occurred in the next 352 days. However, when using this placement method, the endoscope needs to move in and out of the esophagus repeatedly, which not only consumes time, but also causes small pieces of PGA to fall off easily with the peristalsis of the esophageal wall, resulting in a PGA displacement rate of 60% in 2 weeks (as observed in this study). Sakaguchi *et al*.[61] adopted a new method to clamp PGA with endoscopic forceps and wrap it on the surface of the endoscope. PGA was first fixed at the anal end of the mucosal defect with endoscopic clips; subsequently, the entire defect was covered. The oral side was also fixed with the clips and eventually covered with fibrin glue. Some scholars adopted the "foam plombage" technique.[62] In this method, a foam made of nitrogen monoxide gas was sprayed into the lumen for fixing purposes and removed after 5 minutes. No complications occurred during follow-up. The mechanism of PGA remains unclear and needs to be explored through basic research.

As mentioned previously, steroids produce a certain effect on the prevention of esophageal stricture. Some researchers have combined PGA with steroids to investigate their preventive effect of esophageal stricture. In a study by Sakaguchi *et al*.,[63] 11 patients received submucosal injection of 40 mg triamcinolone acetonide immediately after ESD, followed by shielding with PGA and fibrin glue. After 12 weeks of follow-up, the stricture rate was 18.2% (2/11) and the median number of EBD procedures was 0, which suggested that the combination could play a preventive role and reduce the requirement for EBD. Nevertheless,

randomized controlled trials with a larger sample size need to be conducted to determine whether the combined effect is greater than the single effect. Another investigator combined PGA with stent dilatation[64] in a randomized controlled trial in which 70 patients were equally divided into two groups. The experimental group was treated with PGA + stent dilatation after ESD, while the control group was treated with stent only. The results indicated that the stricture rates in the two groups were 20.5% (7/35) *vs*. 46.9% (15/35) ($P = 0.024$) and that the number of EBD procedures required was 4 *vs*. 6 ($P = 0.007$). Additionally, it has been revealed that PGA soaked with triamcinolone acetonide in combination with a fully covered metal stent (FCMS; TS-PGA + FCMS) can reduce the rate of esophageal stricture and the number of EBD procedures.[65] Thus, PGA in combination with other preventive methods is a regimen worthy of consideration. PGA with fibrin glue has a wide range of effects. Its application has been reported to result in successful treatment of esophageal perforation and muscular layer injury resulting from ESD; it can also reduce post-ESD bleeding in patients who need to keep taking anticoagulants.[66-68]

Carboxymethyl cellulose

The application of carboxymethyl cellulose (CMC) also involves covering the mucosal defect surface, and it is easy to adhere. In a pig model experiment, Tang *et al*.[69] observed that, in the CMC group, the degrees of submucosal fibrosis and muscular layer injury were lower, epithelialization was greater, and the level of TGF-β1 in the serum was lower. Lua *et al*.[70] conducted a prospective study in which they selected seven patients with post-ESD mucosal defects larger than three-quarters of the esophageal circumference. CMC was placed at the mucosal defect immediately after ESD. The incidence of esophageal stricture was 57% (4/7), the number of EBD procedures was 2.8 ± 2.2, and no adverse events occurred. However, this study did not involve a control group. Thus, further studies need to investigate the role of CMC in the prevention of esophageal stricture.

At present, the number of cases using PGA and CMC alone to prevent post-ESD stricture is limited, and their specific clinical effectiveness remains to be further explored.

ENDOSCOPIC RADIAL INCISION

Endoscopic radial incision (ERI) is aimed at patients with refractory esophageal stricture in whom the symptoms of dysphagia fail to resolve after repeated EBD treatment. An IT knife is used to radially incise the superficial muscle layer in different directions along the oral and anal sides under an endoscope; subsequently, the incision range is expanded when the endoscope can pass through.

Huang *et al*.[71] reported a 67-year-old patient with early esophageal cancer. After ESD was performed over three-quarters of the esophageal circumference, 30-day oral administration of prednisone was combined with intracavitary stent insertion to prevent post-ESD stricture. On the seventh day after stent removal, the patient developed progressive dysphagia. The effect of repeated EBD treatment was unsatisfactory; however, the symptoms resolved after ERI, and there were no complications such as fever and retrosternal pain. After a 3-month follow-up, there were still no symptoms of stricture. A recent study suggested that ERI was superior to EBD in relieving anastomotic stricture after esophagectomy.[72] Despite the fact that only a single case of post-ESD stricture has been studied and the exact number of balloon dilatation procedures required for refractory stricture remains uncertain, ERI can be viewed as a new treatment for patients with post-ESD stricture, which is particularly the case for those who have failed multiple EBD treatments.

REGENERATIVE MEDICINE

Extracellular matrix scaffold
The formation of an extracellular matrix (ECM) scaffold is a decellularization process that retains the ECM while removing resident cells in the tissue, thus greatly reducing its immunogenicity. Compared with artificial stents, ECM scaffolds exhibit better histocompatibility, reduce inflammation, and promote ulcer healing.[73] Nieponice *et al*.[74] used pig bladder to construct a tubular stent that matched the cervical esophageal structure of dogs through mechanical delamination, decellularization, and immersion and washing. They placed it into the esophagus of five dogs that had undergone a complete cycle of EMR (UBM-ECM group), whereas five other dogs treated with EMR alone formed the control group. The results showed that esophageal stricture occurred in three dogs in the control group, while no stricture occurred in the UBM-ECM group. Histological results showed that the UBM-ECM group exhibited a continuous and intact mucosal layer, no inflammatory cells in the reconstructed segment, and close to normal esophageal tissue, implying that the ECM scaffold could improve esophageal wall reconstruction to a certain extent. Badylak *et al*.[75] revealed that ECM scaffolds derived from porcine small intestine could also prevent esophageal stricture; these ECM scaffolds were completely replaced by mature esophageal squamous epithelium 4 months after the operation. However, it has also been suggested that the preventive effect of ECM scaffolds on post-EMR esophageal stricture is unsatisfactory.[76]

Autologous cell suspension
The application of an autologous cell suspension involves the use of cells extracted from autologous fat, skin, and oral tissue to form a cell suspension; this suspension is then injected into the mucosal defect site through an endoscope. Several animal experiments showed that[77–79] adipose-derived stromal cells from dogs, skin keratinocytes from sheep, and oral keratinocytes from pigs all play a role in inhibiting fibrosis and reducing the rate of esophageal stricture. Such research is limited to animals, and the cell survival rate and utilization rate remain low; these aspects need to be improved in further studies.

Cell sheet
In comparison with endoscopic injection of autologous cell suspension, cell sheets can contain more cells and reduce the risk of bleeding and perforation during injection. Their therapeutic effect stems from three biological activities: (1) promoting keratinization and migration of epithelial cells, (2) preventing inflammatory immune cells from infiltrating into the wound, and (3) inhibiting fibrosis.[80] In a previous study,[81] mucosal tissue samples were obtained from the oral cavity of nine patients, cultured into cell sheets, and placed into the esophagus after ESD. During follow-up, none of the patients exhibited stricture-related symptoms, and the cell sheets promoted re-epithelialization of the esophagus. Yamaguchi *et al*.[82] conducted a study that included 10 patients with superficial esophageal squamous cell carcinoma who had undergone ESD with mucosal defects greater than three-quarters of the esophageal circumference. Autologous oral mucosal epithelial cells were collected 16 days before the ESD, and autologous serum was used as a culture medium for the cell sheet culture. The sheets were successfully placed in all patients; the incidence of esophageal stricture was 40%, the median number of EBD procedures required for four patients with stricture was 1.5, and no transplantation-related complications occurred. The investigators compared the serum in the medium before transplantation with the initial serum and found that the levels of cytokines, chemokines, and vascular endothelial growth factor increased appreciably, thus speculating that this may be one of the reasons why cell sheets can promote epithelialization. In an animal study,[83] an adipose-derived stromal cell sheet was moved to the surface of the esophagus after circumferential ESD. On the 28th day after ESD, there was marked fibrosis on the esophageal wall in the control group, while regeneration of the epithelium increased and the healing was significantly improved in the placement group.

Conditioned medium gel
Mizushima *et al*.[84] conducted a study in which the conditioned medium (CM) from human amniotic membrane–derived bone marrow mesenchymal stem cells was mixed with 5% CMC to form a CM gel. The incidence of esophageal stricture was lower in the group whose wounds were covered with CM gel and also in the oral CM

gel group than in the control group (local steroid injection). The CM gel group exhibited a low degree of neutrophil and macrophage infiltration and fibroblast count. Therefore, it can be predicted that CM gel has a preventive effect on esophageal stricture, and oral administration is easily accepted, thus indicating a promising prospect.

Cell-derived structures exhibit a better promotion of tissue reconstruction and reduction of inflammation than non-cellular structures.[85] Although the abovementioned methods have achieved certain results in the prevention of esophageal stricture, they have not been widely promoted in clinical practice because of their complicated practical application, difficult technical requirements, and high cost. Therefore, numerous clinical trials are needed to optimize their feasibility.

AUTOLOGOUS TISSUE TRANSPLANTATION

Transplantation of gastric mucosa
Hochberger *et al*.[86] reported the case of a patient with cervical esophageal squamous cell carcinoma. First, the esophageal lesion was dissected through ESD; the mucosal defect was 10 cm in size. Next, the gastric mucosa, which was 9 cm long and 4–6 cm wide, was dissected from the anterior wall of the gastric antrum through ESD. The gastric mucosa was divided into three small pieces attached to the esophageal mucosal defect and fixed with clips and a stent; the stent was removed 20 days later. Within 5 months, strictures recurred in the uppermost 1-cm area where the gastric mucosa was not placed; however, the remaining areas grew well. After 32 months of follow-up, no complications remained.

Transplantation of esophageal mucosa
Liao *et al*.[87] studied nine patients with early esophageal cancer who underwent ESD. EMR was used to obtain normal esophageal mucosa tissue away from the esophageal lesions. The tissue was cut into small 10-mm pieces, attached to the four quadrants of the ulcer surface with clips, and subsequently fixed with covered metal stents, which were removed 7 days later. The results showed that the survival rate of the transplanted tissue was 96.5%. Eight patients developed postoperative esophageal strictures after 24.7 days on an average, which were resolved after an average

Table 1: Comparison of current common methods			
Methods	**References**	**Advantages**	**Disadvantages**
Esophageal dilation	Ezoe *et al*.[15] Li *et al*.[16] Yamasaki *et al*.[21]	The time required to relieve stricture is short	Repeated in a short time, stricture is easy to replapse Perforation, hemorrhage may occur The high cost
Esophageal stents	Wen *et al*.[19] Yamasaki *et al*.[21]	Provide continuous expansion tension The low cost	Chest pain, granulation tissue hyperplasia, and stent displacement are easy to occur
Glucocorticoids	Zhou *et al*.[30] Patil and Jadhav[32] Yamashita *et al*.[35] Kadota *et al*.[39] Shibagaki *et al*.[42]	Helps prevent refractory narrowing Inhibition of fibroblast proliferation and collagen synthesis	Systemic side effects：immune suppression, infection, optical damage, psychiatric disturbance, diabetes, peptic ulceration, and osteoporosis Secondary infection：activation of latent TB foci and reinfection of *Mycobacterium tuberculosis* Local injection is prone to esophageal perforation and formation of esophageal abscess
Anti-fibrosis or anti-scarring drugs	Wu *et al*.[47] Zhang *et al*.[49] Suzawa *et al*.[52] Uno *et al*.[53] Beye *et al*.[57]	Inhibit the production of cytokines, limit the inflammatory response, and, to a greater extent, inhibit the activation of myofibroblasts and collagen synthesis Reduce the rate of stent displacement by inhibiting esophageal peristalsis Less systemic side effects	Less sample size
Regenerative medicine	Wu *et al*.[47] Wang *et al*.[56] Nieponice *et al*.[74] Badylak *et al*.[75] Chian *et al*.[83]	Promotes epithelialization and mucosal functional reconstruction Releases biochemical components that promote angiogenesis, cell migration, and proliferation	Complex cell culture Unstable technology and high cost Less sample size
Autologous tissue transplantation	Liao *et al*.[87] Chai *et al*.[88]	Physical and chemical components of the natural extracellular matrix Tissue accessibility	Less sample size Lack of control group

of 2.7 EBD procedures. During 16.8 months of follow-up, eight patients showed no symptoms of dysphagia (one of them died 15 months after the operation). However, it remains to be considered whether unnecessary stricture will occur in the normal esophageal mucosa owing to a large resection range.

Skin transplantation

Chai *et al.*[88] conducted a study that included eight patients who underwent complete circular endoscopic submucosal tunnel dissection (ccESTD). Skin grafts were collected from the lateral right thigh, used to cover the surface of an FCMS, placed into the esophagus, and fixed with clips. The stent was removed 4 weeks later. No adverse events such as perforation, infection, and stent displacement occurred in this process. Biopsy confirmed the presence of keratinized squamous epithelium at the transplantation site. No stricture was found in five patients during the median follow-up period of 7 months, whereas strictures were found in three patients after stent removal, which were resolved after EBD.

The above three methods have introduced new approaches for the prevention of esophageal stricture; however, the number of related experiments is small, the sample sizes are small, and there is a lack of controls. Thus, randomized controlled studies on a larger scale are needed to investigate the applicability of these approaches.

CONCLUSION

Owing to the extensive development of endoscopic technology, post-ESD stricture is an inevitable problem for which early prevention and treatment is particularly important. A variety of methods have been proven effective in the prevention and treatment of stricture through experiments; however, they all exhibit advantages and disadvantages (Table 1). For example, it is more convenient for patients to use self-help inflatable balloon or oral administration of steroids. However, some tissue engineering methods have been limited to animal research, and they have not been widely used and popularized in clinical practice. Esophageal strictures in some patients have not been well resolved with certain methods. Multicenter, large-sample randomized controlled trials are needed on a larger scale to examine whether the formulation of individualized regimens according to the condition of each patient or the combined application of certain methods will be more effective. The most reasonable, simplest, and most effective solution is expected to be determined through these efforts.

Conflict of Interests

There is no conflict of interests.

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