Review Article

Endoscopic management of patients with esophageal stricture in the oncology practice: a narrative review

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Abstract: Esophageal strictures are generally classified into malignant due to advanced cancer and benign strictures after treatment for esophageal cancer. Several endoscopic procedures including ablation technique and stent placement, are used for patients with malignant esophageal strictures in our oncology practice. And, there is a potential for the development of severe esophageal stricture after curative treatment including esophagectomy, radiotherapy and endoscopic resection (ER), if the esophageal cancer can be cured. The aim of this narrative review article is to introduce landmark studies about endoscopic treatment or prevention esophageal stricture in oncology and to discuss about the unsolved issue or future direction. The primary endoscopic procedure for mechanically improving benign esophageal strictures is endoscopic balloon dilation (EBD), and incision treatment or stent placement is applied for refractory cases. Regarding ER for esophageal cancer, post-intervention stricture rates are approximately 15% and the risk of stricture is associated with the lesion's size. Therefore, prophylactic treatments mainly steroid administration to prevent stricture after ER of early esophageal cancer was introduced and showed the favorable clinical outcome. Endoscopic intervention is effective and safety treatment to surgical treatment for patients with malignant and benign esophageal strictures. However, several unresolved issues remain in the endoscopic management of esophageal stricture and further development is necessary in our oncological practice.

Keywords: Endoscopy; esophageal stricture; esophageal cancer oncology; prevention

Introduction

In our oncology practice, esophageal strictures are generally classified into malignant and benign strictures. Interventions for esophageal strictures should be properly applied depending on the etiology of the stricture. Surgical intervention is a powerful tool that can achieve a rapid improvement in severe symptoms when successful. However, the indication of surgical intervention is limited because of its invasiveness, and less invasive alternatives are warranted especially for old or frail patients. Endoscopic procedures are less invasive alternatives to surgical intervention that can play an important role in improving the patient's quality of life. In this review article, we aimed to introduce landmark studies describing several endoscopic procedures for patients with malignant or benign esophageal strictures used in our oncology practice, and prophylactic treatments

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to prevent stricture after endoscopic resection (ER) of early esophageal cancer.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/aoe-20-91).

Methods

We used PubMed to search the literature using the keywords of esophageal cancer, esophageal stricture, endoscopic treatment, between 2005 and 2020. We excluded abstract only and non-English papers, and we selected articles relevant to the subject of this review article. We also added landmark studies which were collected manually.

Narrative discussion

Endoscopic intervention for malignant esophageal stricture

Malignant esophageal strictures are generally because of locally advanced esophageal cancer or esophageal luminal obstruction due to mediastinal lymph node metastasis of other cancers, and cause dysphagia, which is a serious problem. The placement of a self-expandable metallic stent (SEMS) showed a significantly favorable outcome compared to that of an old-type plastic stent in a randomized controlled trial (RCT) (1).

Accordingly, SEMS has become the standard in palliative intervention, offering rapid relief of symptoms in our practice. As stent placement is an endoscopic procedure for advanced esophageal cancer, we evaluate the following points using endoscopy with fluoroscopy guidance before the procedure: (I) width and length of the stricture, (II) location and distance from the pharyngo-esophageal or gastro-esophageal junction, and (III) presence of the fistula. We usually use an anti-reflux stent for lower esophagus or gastro-esophageal junction, and we give up for upper esophagus when the proximal end of the stricture is located at less than 2 cm from the orifice. At the placement, we generally choose, partially covered, 18 mm distal release SEMS, regardless of the presence of a fistula. We put the endoscopic marking clip at the proximal-end and the fluoroscopic marker at the distal-end of the stricture. The SEMS is gently inserted through the stricture and the appropriate position is adjusted under fluoroscopic guidance. The major disadvantage of SEMS placement is its incompatibility with radiotherapy; current guidelines from the European Society of Gastrointestinal Endoscopy (ESGE) do not recommend the use of SEMSs concurrent with or prior to external radiotherapy for esophageal cancer because of a high incidence of adverse events including perforation and severe pain (2). Severe adverse events related to SEMS placement have also been reported in patients with local failure after radiotherapy (3), and the indication of SEMSs after radiotherapy remains controversial.

Another endoscopic intervention for malignant esophageal stricture instead of stent placement is the ablation technique. Endoscopic ablation can damage and decrease the volume of an obstructive tumor by various devices. Photodynamic therapy (PDT), comprising the administration of a photosensitizer followed by illumination using a specific wavelength laser was initially approved as a palliative treatment for patients with symptomatic obstructive esophageal cancer by the Food and Drug Administration in the 1990's. According to a previous study on palliative PDT in 215 patients with symptomatic advanced or recurrent esophageal cancer, dysphagia improved in approximately 85% of patients (4), with a median of 2 months of dysphagia-free survival, and 4.8 months of overall survival (OS). Another retrospective study comparing multimodal palliative treatments, including PDT, stent placement, and brachytherapy revealed that the most favorable survival outcome was achieved when PDT was used as an initial endoluminal palliative treatment (5). However, the photosensitizer used in PDT requires a sunshade period of more than a month, and the dysphagia relief duration of PDT is similar to that of the sunshade period. Therefore, in consideration of the patient's quality of life, the indication of PDT as a palliative treatment may be quite limited.

Liquid nitrogen spray cryotherapy is another palliative endoscopic treatment for patients with symptomatic stricture due to advanced esophageal cancer (6). In preliminary reports, cryotherapy significantly improved the dysphagia score, without causing any severe adverse events, in inoperable esophageal cancer cases, and did not lead to serious toxicity in combination with chemoradiotherapy (CRT) (6,7). However, the two studies that assessed this were retrospective in nature and had small sample sizes; therefore, larger studies are required to clarify the efficacy and safety of cryoablation for patients with symptomatic advanced esophageal cancer in a palliative setting. Therefore, the ablation technique does not currently play a major part of our oncology practice.

### Endoscopic interventions for benign esophageal stricture after treatment for esophageal cancer

We have utilized several treatment options, including esophagectomy, radiotherapy, and endoscopic treatment, to cure patients with esophageal cancer; all these treatments involve a potential risk for the development of severe esophageal stricture even if the esophageal cancer can be cured. According to previous reports, approximately 30% of patients develop anastomotic stricture after esophagectomy (8), before treatment and 50% of patients with malignant esophageal stricture, and 10% of patients without malignant esophageal stricture before treatment develop benign esophageal stricture after radiotherapy for advanced esophageal squamous cell carcinoma (ESCC) (9). Regarding endoscopic treatments for esophageal cancer, post-intervention stricture rates are approximately 15% for ER for ESCC and 25% for PDT for high grade dysplasia in Barrett's esophagus; the risk of stricture is associated with lesion size or a history of other endoscopic interventions (10-12).

The first line treatment for patients with benign esophageal stricture is mechanical dilation using bougie or balloon type dilators (13). Self-dilation using an oral polyvinyl dilator is reported as an alternative method for refractory strictures at the upper to middle esophagus after surgery or radiotherapy for esophageal cancer (14). The primary endoscopic procedure for mechanically improving benign esophageal strictures utilizes through the scope balloon-type dilators (13). Endoscopic balloon dilation (EBD) is a simple technique and can be applied to various types of benign strictures after any treatment for esophageal cancer; EBD has been proved to be a safer method than the blind passage of a bougie in cases with benign esophageal strictures (15). EBD is generally indicated for patients who complain of dysphagia due to a benign stricture through which a standard sized endoscopy (≥9 mm) cannot pass (*Figure 1*). However, dysphagia did not improve in some patients even after repeating EBD, and the inability to successfully maintain a dysphagia-free status with over five dilations within a 2-week interval was previously defined as a refractory benign stricture (16). While the clinical outcomes of EBD for benign anastomotic stricture have been evaluated in several reports (17-19), little is known about the safety and efficacy of EBD for benign strictures after non-surgical treatment, including CRT and ER, for patients with ESCC. Based on this definition, we retrospectively compared the efficacy and safety of EBD between anastomotic stricture and post-non-surgical treatment stricture (20). In our study, the perforation rate of EBD among all patients was 0.3% (3/1,077), and there was no difference in safety between post-surgical and post-non-surgical treatments, including CRT and ER. As for the treatment efficacy of EBD, EBD for post-non-surgical treatments, including CRT and ER, tended to require a significantly longer duration and a larger number of EBD procedures to achieve dysphagia-free status. Therefore, the non-surgical group comprised a significantly larger proportion of refractory cases compared to that in the post-surgery stricture group (75% *vs.* 45%, P<0.01), and post-CRT stricture comprised the largest proportion of refractory cases, with a tendency to be higher than that for post-ER stricture (86% *vs.* 66%, P=0.12). Radiotherapy generally covers a large range of esophageal primary cancers and locoregional lymph nodes, and it causes acute, as well as late, luminal and mediastinal inflammation, which can lead to severe transmural esophageal fibrosis (21). Although we could not analyze differences in the treatment efficacy of EBD in detail, another research group reported that the length and narrowness of the stricture influences the efficacy of EBD for benign esophageal stricture (22). As for refractory cases of benign esophageal stricture, steroid injection has been proven to be an effective additional treatment for EBD, based on the results of RCTs for patients with refractory peptic stricture (22) or anastomotic stricture after esophagectomy (23). Furthermore, in an RCT involving patients with anastomotic stricture after esophagectomy, the steroid injection group received injections of triamcinolone acetonide into all visible lacerations, with a total dose of 50 mg, immediately after EBD (23). Incision therapy is recommended in the UK guidelines on esophageal dilation as another interventional endoscopic procedure for EBD refractory cases (24). The radial incision and cutting (RIC) method, using an insulated tipped knife developed for endoscopic submucosal dissection (ESD), has been shown to be an effective procedure for EBD refractory anatomical stricture (25). The RIC procedure comprises a radial incision of the stricture and slicing of the fibrotic tissue between the longitudinal incision, and the application of ESD. Currently, an RCT comparing EBD and RIC for patients with an EBD refractory anatomical stricture of 2 cm or shorter is being conducted in Japan (26). Moreover, RIC has been reported as a technically feasible procedure for stricture due to non-surgical treatments, including CRT and ESD (*Figure 2*) (27,28). However, the durability of
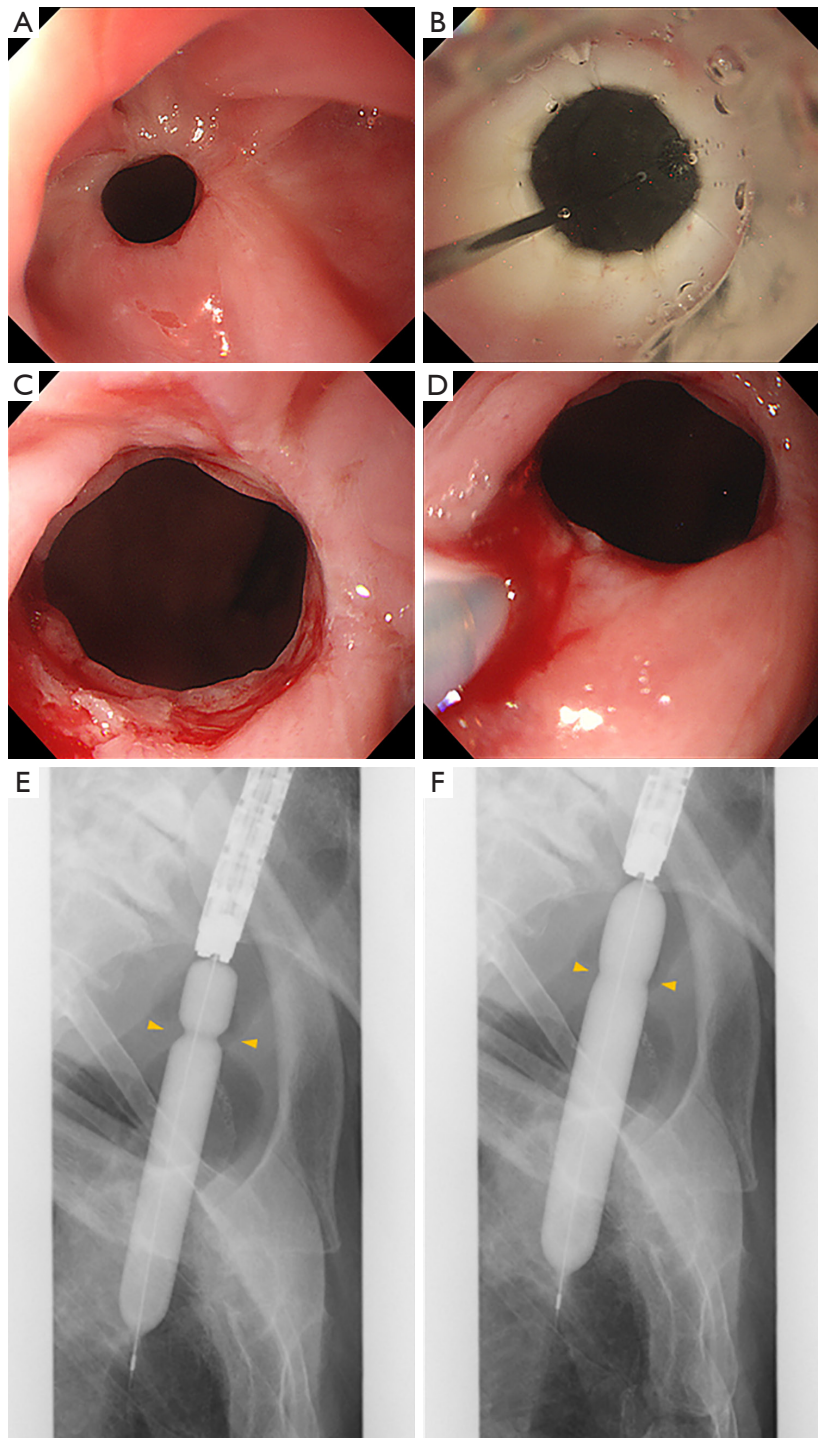
Figure 1 Endoscopic balloon dilatation and steroid injection for anastomotic strictures after esophagectomy. (A) Endoscopic view of an esophagogastric anastomotic stricture after esophagectomy. The diameter of the stricture was about 5 mm. (B) Dilating with EBD (12–15 mm E-dive™ NIPRO, Japan). (C) Endoscopic view of the anastomotic strictures just after EBD. (D) Injection of steroid to the lacerations. (E,F) Confirmation of the position and shape of balloon under fluoroscopy during EBD (E: pre-BD, F: post-BD). Yellow allow: waist of the balloon.
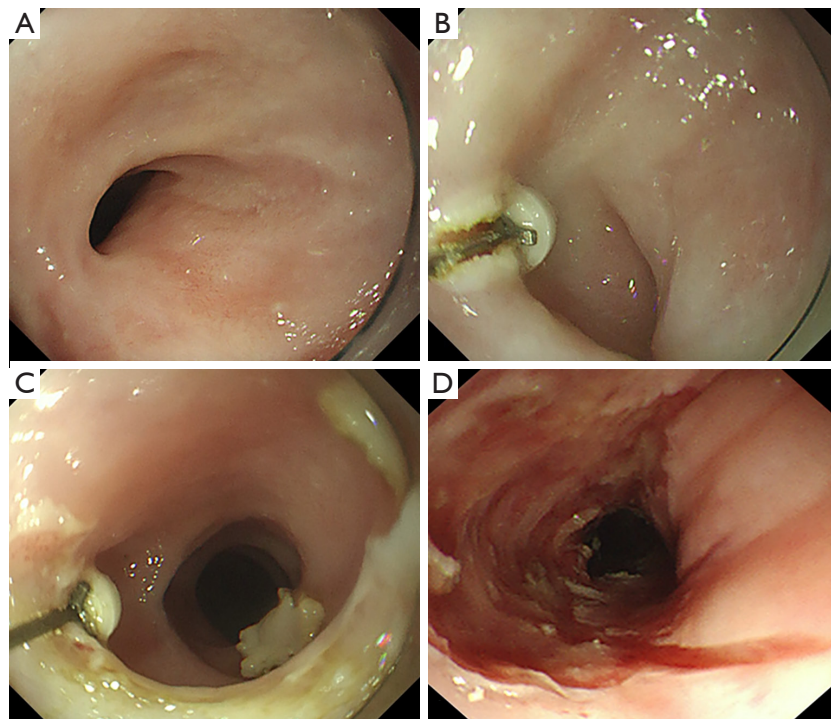
Figure 2 Radial incision and cutting (RIC) method for refractory benign esophageal stricture after endoscopic submucosal dissection (ESD) for esophageal squamous cell carcinoma. (A) Endoscopic view of refractory stricture after ESD. The diameter of the stricture was less than 5 mm and the length was longer than 3 cm. (B) Initial radial incision using electric knife for ESD (IT knife-2, Olympus, Tokyo) into stricture. (C) Slicing the fibrotic tissue longitudinal incision. (D) Endoscopic view after the completion of RIC method for stricture.

lumen patency with the RIC method is limited, especially in long anatomical strictures or in strictures after non-surgical treatments, including ESD and CRT, for esophageal cancer (25,28).

Stent placement for refractory benign esophageal stricture

The guidelines of the ESGE do not recommend the use of SEMS as a first-line treatment for refractory esophageal stricture because of the potential of adverse events (2). In addition, SEMS placement should be considered when other treatments, including dilation with or without steroid injection and incision therapy, have failed, and stents should usually be removed at a maximum of 3 months. However, there are no indication criteria for stent placement for refractory benign stricture. A fully covered SEMS has been developed and is favored for benign strictures because of its improved removability due to decreased stent-induced hyperplastic granulation of embedded mucosa into the mesh of the stent. According to the results of a retrospective study, fully covered stent placement was successful in most patients, and removal was easily performed (29). However, the migration rate of fully covered SEMS is approximately 30%, which is one of the most important weaknesses of this type of stent (*Figure 3*) (30). A biodegradable stent (SX-ELLA Stent Esophageal Degradable BD; ELLA-CS, Hradec Kralove, Czech Republic), made of polydioxanone, is degraded by hydrolysis; therefore, there is no need for it to be removed from patients with benign strictures. This biodegradable stent maintains its radial forces for 6–8 weeks and disintegrates within 8–12 weeks in cases of esophageal stricture (31). The improvement in dysphagia in patients with refractory benign esophageal stricture due to esophagectomy or ESD for esophageal cancer is approximately 40–60% at 12 weeks after placement (32,33). According to the results of a multi-institutional RCT comparing standard dilation, including bougie or EBD, to biodegradable stents for patients with recurrent benign esophageal stricture, patients treated with biodegradable stents required significantly fewer dilations within 3 months, and median time to the first dilation of recurrent stricture was significantly longer, compared to that with conventional
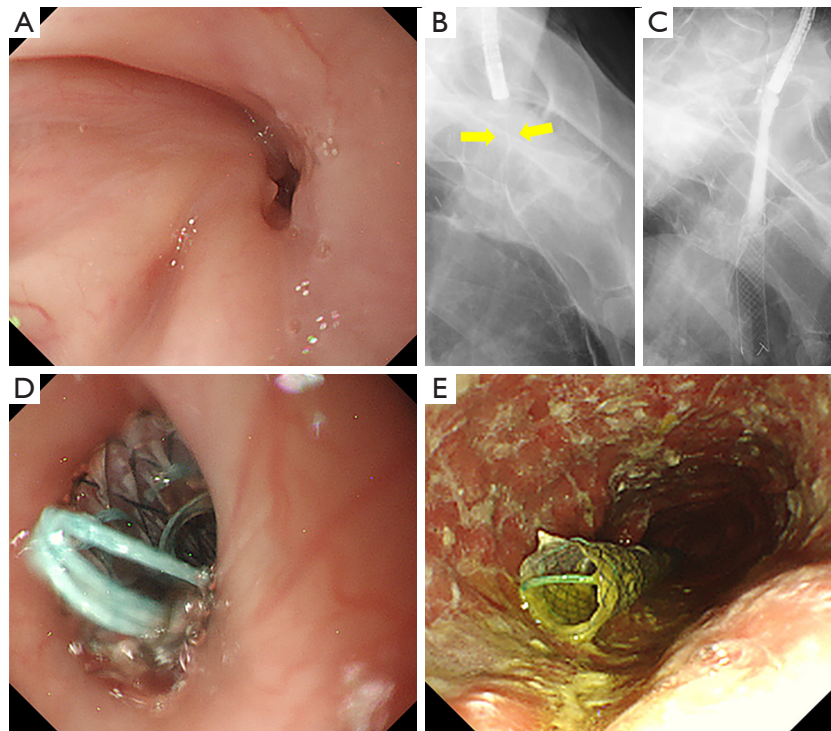
Figure 3 Fully covered self expandable metallic stent (SEMS) placement for refractory benign stricture after esophagectomy and radiotherapy. (A) Endoscopic view of a refractory benign stricture after esophagectomy and radiotherapy. (B) Fluoroscopic view of a stricture with a diameter of less than 3 mm and length of 4 cm (at the yellow arrows). Patient could not drink water smoothly. (C) Fluoroscopic view of a stricture after placement of fully covered SEMS (Niti-S Slicone covered Esophageal stent CONIO 12 mm, TaeWoong Medical Co., Ltd., Korea). (D) Endoscopic view of a stricture after placement of fully covered SEMS. The dysphagia of the patient was dramatically improved after placement of stent, and he could eat semi-solid food smoothly. (E) The fully covered SEMS was migrated into the reconstructive stomach roll one week after placement.

dilation (34). However, there was no difference in the number of endoscopic dilations for recurrent stricture at 6 months, and the long-term benefits of treatment with a biodegradable stent was not clarified in patients with refractory benign esophageal stricture. Furthermore, the incidence of esophago-respiratory fistula with biodegradable stent placement in patients after radiotherapy for esophageal cancer has been reported (32,33). Therefore, careful patient selection is necessary, as well as a better understanding of the benefit of a temporal reduction in repeated EBD and the risk of perforation in patients after radiotherapy.

Preventive methods against stricture after ER for wide-spread superficial esophageal cancer

ER is currently accepted as the standard of care for patients with superficial esophageal cancer worldwide.

Innovations of ESD have resolved the technical limitations of endoscopic mucosal resection (EMR), and enabled the removal of whole lesions *en bloc*, regardless of size or concomitance with fibrosis (35). However, postoperative stricture is known to be an adverse event of ESD, and a mucosal defect with a circumferential extension of three-quarters or more has been reported as a predictive factor for esophageal stricture after ESD (36). Therefore, a sufficient explanation of the risk of severe stricture with such lesions must be provided to patients prior to ESD. Additionally, esophageal cancer practice guidelines released by the Japan Esophageal Society advocate for preventive treatments against strictures (37). Preventive EBD has been reported as an effective approach to prevent post-ESD stricture for defects with a circumferential extension of three-quarters or more after ESD for esophageal cancer (38). However, since the reporting of favorable results for preventive steroid
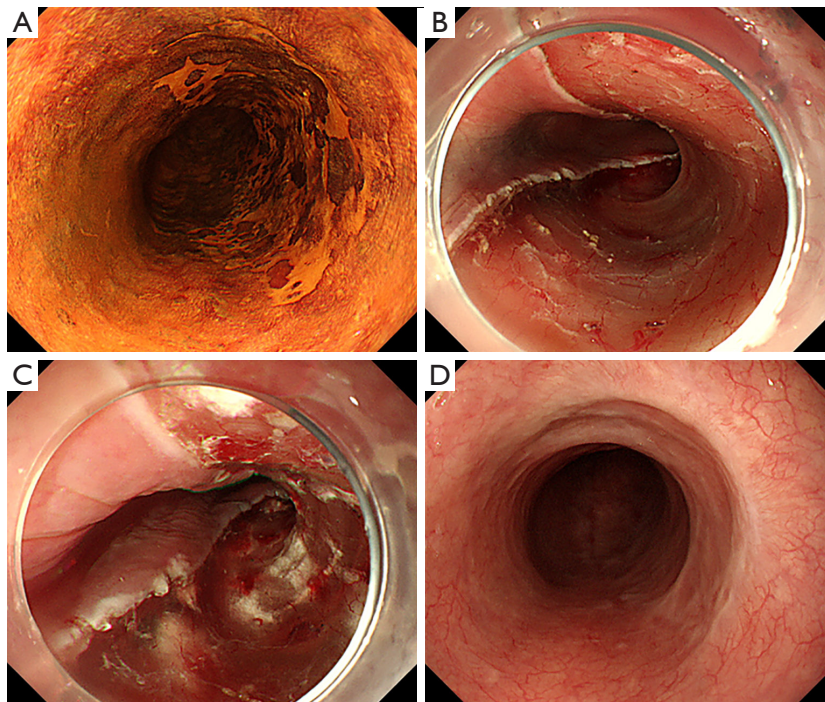
Figure 4 A case who underwent endoscopic resection for large superficial esophageal squamous cell carcinoma. (A) Endoscopic view of the tumor after Lugol's staining. The tumor spread to about 3/5 of the circumference of the esophageal lumen. (B) Endoscopic view of the ulcer bed immediately after ESD. The mucosal defect after ESD was about 3/4 of the circumference of the esophageal lumen. (C) Endoscopic view of the ulcer bed immediately after steroid injection. (D) Endoscopic view on the 6 months after ESD. The complete epithelialization was shown and esophageal strictures was not occurred. ESD, endoscopic submucosal dissection.

administration after esophageal ESD, interventions using steroids have become the standard of care for stricture prevention. Oral steroid administration, local injection into the mucosal defect after ESD, or a combination of both routes is supported by several published papers (*Figure 4*) (39-42), and an RCT, conducted in Japan, has compared oral administration to local steroid injection (43). In the prospective trial conducted by Hanaoka *et al.*, the single session of the steroid injection was performed just after ESD, a 1:1 dilution of triamcinolone acetonide and normal saline was used for the injection. For each puncture, 0.5 mL of solution was used, and total amount of 5mlwas injected into the residual thin submucosal layer at the post-ESD ulcer margin or bed. Moreover, there were no cases of perforation due to the local injection of the steroid (41).

Although prophylactic steroid treatment shows favorable outcomes in cases with a subtotal circumference mucosal defect after ESD, stricture prevention is currently difficult in cases with a total circumference mucosal defect, especially 5 cm or longer in length, even with combined oral and local steroid administration (44,45).

Several other interesting methods have been reported as prophylactic treatments for the prevention of severe stricture after ESD. For example, shielding by polyglycolic acid sheets applied to mucosa defects just after ESD shows a similar favorable outcome to that achieved with steroid administration, in terms of stricture prevention (46). Furthermore, combined treatment with polyglycolic acid sheets, steroid injection, and temporary stent placement has shown comparable favorable efficacy (47,48). The pathological mechanism and process of post-ESD stricture have been examined in large animal models; inflammatory cell invasion at the ulcer bed occurs in the acute phase a few days after ESD, followed by fibrous tissue hyperplasia accompanied by angiogenesis at one week after ESD (49). Moreover, at the time of complete epithelialization of ulceration at one month after ESD, atrophy and fibrosis of the muscularis propria remains, causing severe stricture, with fibrotic scarring, after ESD (49,50). Steroid administration can play an important role in this post-ESD modification process by reducing acute inflammation (50).

Additionally, preventive approaches using tissue engineering and regenerative medicine or molecular targeting for fibrosis have been in animal models (51-53), some of which have been further evaluated in clinical studies. For example, endoscopic transplantation of tissue- engineered autologous oral mucosal epithelial cell sheets after ESD for esophageal cancer has been evaluated in clinical study (54). The technique of endoscopic transplantation into a post-ESD ulcer has been shown to be feasible, with re-epithelialization confirmed within a month, no patient experienced dysphagia and stricture, with the exception of cases with a full circumference mucosal defect. Interestingly, another method for transplanting gastric mucosa into post-ESD esophageal ulcer after circumferential ESD for ESCC was clinically successful in preventing stricture and reported as a case report (55). However, at present, interventions using tissue engineering and regenerative medicine have not been introduced to our practice as prophylactic procedures for the prevention of esophageal stricture at present because of their insufficient effect whole-circumference mucosal defects and inconvenient complicated procedural steps, with high costs. In addition, shielding with specific materials for mucosal defects is technically challenging, therefore, innovative devices that can easily access into the lumen and apply the sheets to the esophageal wall should are needed.

Summary, future perspective and conclusions

At present, endoscopic treatment is the first choice of care for patients with esophageal stricture, regardless of its etiology; however, there are several new modalities (other than stent placement) that we have used in our practice. In order to expand the use of endoscopic approaches in the treatment of esophageal stricture in our oncology practice, there are several unmet issues that must be resolved, with further development. First, the poor compatibility between radiotherapy and stent placement in patients with malignant and benign esophageal strictures has not been resolved. Because of esophageal pain due to the stiffness of the stent and a high risk of perforation, it is difficult to define the indication criteria of stent placement as a palliative treatment for patients after radiotherapy. Second, no definitive prophylactic treatment to prevent stricture after total-circumference ESD for early esophageal cancer has been determined. Therefore, while ESD can control the oncological outcome of patients with intramucosal esophageal cancer less invasively, controversy remains regarding the indication for patients with total-circumference ESD for esophageal cancer because of the

risk of esophageal stricture. Finally, there are only a few high-quality clinical studies that support the treatment utility in the field of palliative endoscopic treatment for patients with esophageal stricture. Currently, new therapies must be shown to be superior to conventional treatments in RCTs to be accepted into treatment guidelines. While it is difficult to determine hard endpoints that can be objectively quantified in clinical studies to evaluate the patient's quality of life, innovation efforts should be made continuously for effective and safe endoscopic treatments for patients with esophageal stricture, and high-quality clinical studies should be conducted to clarify its utility in oncology practice.

In conclusion, endoscopic intervention is a highly favored alternative treatment to surgical intervention for patients with malignant and benign esophageal strictures. However, several unresolved issues remain in the endoscopic management of esophageal stricture in oncology practice; therefore, new treatments and management methods are necessary, especially for patients with esophageal stricture after radiotherapy.

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