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Stricture Occurring after Endoscopic Submucosal Dissection for Esophageal and Gastric Tumors

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Endoscopic submucosal dissection (ESD) is a widely accepted treatment for early gastric and esophageal cancer. Compared to endoscopic mucosal resection, ESD has the advantage of enabling *en bloc* removal of tumors regardless of their size. However, ESD can result in a large artificial ulcer, which may lead to a considerable deformity. Circumferential mucosal defects of more than three-fourths the esophageal circumference, long longitudinal mucosal defects (>30 mm), and lesions in the upper esophagus are significant risk factors for the development of post-ESD strictures of the esophagus. In the stomach, a circumferential mucosal defects more than three-fourths in extent and longitudinal mucosal defects >5 cm are risk factors of post-ESD stricture. If scheduled early, regular endoscopic balloon dilation is effective in controlling and preventing post-ESD stricture. Moreover, intralesional steroid injections or oral steroids can achieve remission of dysphagia or reduce the need for repeated endoscopic balloon dilation. However, further study is needed to improve the prevention of stricture formation.

Key Words: Stricture; Esophagus; Stomach; Endoscopic submucosal dissection

INTRODUCTION

The number of patients with early esophageal and gastric cancer who undergo endoscopic resection is increasing because of the improvement in diagnostic techniques such as narrow-band imaging and the development of various devices,

including knives and accessories.¹ In particular, endoscopic submucosal dissection (ESD) is a useful, minimally invasive procedure for the management of early esophageal and gastric neoplasms and enables the *en bloc* resection of large lesions. Such resections cannot be achieved with conventional endoscopic mucosal resection (EMR). Moreover, ESD facilitates accurate histopathological assessment of specimens resected *en bloc* with tumor-free horizontal/vertical margins, thereby resulting in the prevention of residual disease and local recurrence.² Consequently, the risk of ESD-related complications, including potentially life-threatening perforation and postprocedural stricture, is also increasing.

The occurrence of post-ESD stricture in the esophagus

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and stomach can result in dysphagia or gastric outlet obstruction—which substantially decreases patient quality of life, requiring multiple sessions of endoscopic balloon dilation (EBD)^{3,4}—or even aspiration pneumonia.² Although strictures have been associated with the extent of the circumference and length being resected,⁵ the exact incidence of and risk factors for luminal stricture after esophageal and gastric ESD are unknown. Additionally, various effective preventive treatments have been reported, including balloon dilation, and local injection or systemic administration of steroids.^{6,7} However, no definite recommendation for the treatment and prevention of post-ESD stricture exists. In this review, we describe the incidence, risk factors, and currently available treatment modalities for strictures occurring post-ESD in the esophagus and stomach.

POST-ESD STRICTURE IN THE ESOPHAGUS

Incidence of and risk factors for post-ESD stricture

Although the incidence of post-ESD stricture in superficial esophageal neoplasms is 5% to 17% (Table 1),⁸⁻¹¹ the exact incidence remains unknown, and the risk of stricture is reportedly proportional to the extent of mucosal dissection. With large-sized superficial esophageal squamous cell neoplasms now becoming candidates for ESD, post-ESD stricture development has recently become a major and inevitable concern—in particular, regarding the long-term outcomes.

The possibility of esophageal stricture increases if a circumferential mucosal defect is more than three-fourths the esophageal circumference post-ESD (i.e., if the lesion size is greater than 60%).^{5,9-11} A Japanese study reported that postoperative strictures occurred in 90% of patients with lesions of more than three-fourths the circumferential extension.⁸ Therefore, a second-look endoscopy is performed routinely at 2 or 3 weeks post-ESD, because esophageal strictures may be evident within a few weeks post-ESD during the mucosal healing process.¹² Considering the length of longitudinal mucosal defects, a longitudinal mucosal defect >30 mm is a significant risk factor for stricture development.⁶

The location of the tumor has also been associated with the occurrence of strictures. Lesions in the upper esophagus are reportedly complicated with post-ESD stricture more frequently than those in the lower esophagus (50% vs. 11%, respectively).¹⁰ This finding could be explained by the fact that the luminal diameter of the esophagus differs between the levels: the luminal diameter of the upper esophagus is smaller than that of the lower esophagus. Therefore, it would be natural that the smaller diameter is associated with a higher risk of post-ESD stricture.¹⁰ Moreover, histologic depth to m^2 with a circumferential diameter >3 cm was also associated with the occurrence of strictures.⁵

Treatment modalities for post-ESD stricture

Endoscopic balloon dilation

In the setting of benign strictures, EBD has been the treatment of choice. If scheduled early, regular EBD is effective in preventing and controlling post-ESD strictures. In association with dysphagia, post-ESD strictures can be successfully managed with EBD in a median of two sessions;⁵ however, repetitive, periodic EBD is usually needed for preventing and controlling postprocedural strictures even post-ESD.¹³ Generally, EBD using a controlled radial expansion balloon dilator is started 3 days post-ESD and performed once or twice weekly for 8 weeks. In each session, the EBD diameter is initially set at 13 to 15 mm. Greater diameters may be required when patients remain symptomatic, and the lumen is dilated to 18 mm.

However, post-ESD strictures are potentially more complex than those arising from other causes. This is a reflection of both the greater extent of the initial mucosal defects treated and the inclusion of more elderly patients, who tend to undergo minimally invasive ESD safely. Furthermore, post-ESD strictures require several dilation procedures despite the short interval before initial dilation therapy. The rate of perforation during dilation has been reportedly as high as 9.0% in the case of post-ESD strictures,¹⁴ which is slightly higher than that in the case of strictures secondary to other causes.¹⁵ Two known factors for esophageal perforation during dilation are the location of the stricture in the lower esophagus and the

Table 1. Incidence of and Risk Factors for Post-Endoscopic Submucosal Dissection Stricture in Superficial Squamous Cell Neoplasms

Author	No. of subjects	Incidence of stricture, %	Risk factors for stricture
Oyama et al. (2005) ¹⁴	102	6.9	-
Mizuta et al. (2009) ¹⁰	31	16.7	Circumferential mucosal defect >71%
Ono et al. (2009) ⁵	65	16.9	Circumferential mucosal defect >3/4 histologic depth to m^2
Repici et al. (2010) ¹¹	20	5	-
Ezoe et al. (2011) ⁶	41	-	Circumferential mucosal defect >3/4 longitudinal mucosal defect >30 mm EMR>ESD

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

need for multiple dilations.¹⁴

Endoscopic steroid injection

Although EBD has been the best treatment modality in the setting of benign esophageal stricture, additional intralesional steroid injections into corrosive or anastomotic strictures after EBD can achieve remission of dysphagia or reduce the need for repeated EBD.^{16,17} Steroids modulate wound healing through their anti-inflammatory effects by decreasing prolyl hydroxylase activity and by amplifying collagenase activity; thus, the tissue collagen content is reduced.¹⁸ Steroids inhibit fibrosis by preventing the migration and activation of inflammatory cells and fibroblasts.¹⁹ Based on these steroidal effects, the usefulness of intralesional steroid injection into benign esophageal strictures has been suggested for augmenting the effects of endoscopic dilation.^{16,17}

Because fibroblast proliferation begins 3 to 7 days after wound injury,²⁰ endoscopic steroid injection at 3 days post-ESD would suppress inflammatory cell infiltration and fibrosis effectively. A recent retrospective study demonstrated that endoscopic triamcinolone injection resulted in a decreased stricture incidence and a decreased need for EBD in patients who underwent ESD for superficial esophageal squamous cell carcinomas (Table 2).²¹ In this study, the proportion of patients developing strictures in the endoscopic triamcinolone injection group was significantly lower than that in the control group (19.0% vs. 75.0%). Furthermore, the mean number of EBD procedures required in the endoscopic triamcinolone injection group was significantly lower than that in the control group (1.7 vs. 6.6). No adverse effects, including delayed perforation or mediastinal abscess, were associated with the injection procedure.

The suggested protocol for endoscopic steroid injection is as follows.²¹ Endoscopic steroid injection begins at 3 days post-ESD, and triamcinolone acetonide (10 mg/mL) is used without further dilution. A 1-mL syringe is usually needed to manually inject triamcinolone and facilitates injection administration with consistent pressure. After shallow insertion of the needle to avoid injuring the proper muscle layer, triamcinolone is injected in aliquots of 0.2 mL into the cauterized ulcer base. Injections are performed equally (1 cm apart) in a semi-circumferential fashion. The number of injections per

session depends on the resection size. Sessions are usually conducted at 3, 7, and 10 days post-ESD for a total of three sessions.

However, some esophageal strictures are recalcitrant despite the use of intralesional steroid injection followed by endoscopic dilation.^{22,23} Moreover, the potential risks for esophageal perforation, pleural effusion, or mediastinitis are associated with local therapy.¹⁶ However, this risk seems to increase when steroids are injected directly onto the ulcer bed immediately after esophageal ESD. Hence, further study would be useful to determine the optimal timing and dose for the effective and safe action of triamcinolone.

Oral steroid administration

A recent retrospective study demonstrated that oral prednisolone reduced the need for EBD even after complete circular ESD for superficial esophageal squamous cell carcinomas (Table 2).⁷ In this study, post-ESD esophageal strictures were observed significantly more frequently in the preemptive EBD group than in the oral prednisolone group (31.8% vs. 5.3%). Additionally, the mean number of EBD sessions required in the oral prednisolone group was significantly lower than that in the control group (1.7 vs. 15.6). Oral prednisolone administration was started at a dose of 30 mg/day on day 3 post-ESD, tapered gradually (30, 30, 25, 25, 20, 15, 10, and 5 mg for 7 days each), and then discontinued after 8 weeks. In the case of oral prednisolone administration, EBD was not performed preemptively, but on demand, whenever patients reported dysphagia.

The mechanisms how systemic prednisolone controls post-ESD stricture and reduces EBD sessions remain unclear. Steroids can not only inhibit collagen synthesis but also enhance collagen breakdown; as a result, stricture formation can be inhibited.¹⁶ Furthermore, steroids possess anti-inflammatory properties.¹⁸ Because acute esophagitis with fibrosis and abundant inflammatory cell infiltration is found in histological observation of benign strictures,¹⁹ systemic steroid administration at an earlier stage (at 3 days post-ESD) can inhibit initial inflammation, which might have an additional impact on stricture prevention.

Nevertheless, steroid treatment may be associated with various adverse effects, including immunosuppression, osteopo-

Table 2. Effect of Steroids in the Prevention of Post-Endoscopic Submucosal Dissection Stricture in Superficial Squamous Cell Neoplasms

Author	Treatment methods	No. of subjects	Incidence of stricture, %	Mean no. of required endoscopic balloon dilations
Hashimoto et al. (2011) ²¹	Endoscopic triamcinolone injection	Patients 21	19.0	1.7 (0–15)
		Controls 20	75.0	6.6 (0–20)
Yamaguchi et al. (2011) ⁷	Oral prednisolone	Patients 19	5.3	1.7 (0–7)
		Controls 22	31.8	15.6 (0–48)

rosis, diabetes, peptic ulceration, psychiatric disturbances, and optical damage.²⁴ In addition, steroid administration can further increase the risk of esophageal candidiasis, to which patients with stenotic esophageal lesions are already predisposed.¹⁶ Recently, several cases of persistent esophageal stricture resistant to intralesional steroid injection were successfully managed with systemic steroid administration.²³ Systemic administration could deliver the steroid into the fibrotic tissue of the stricture more effectively compared to endoscopic injection. Therefore, oral prednisolone administration could be a novel, useful option for preventing post-ESD stricture and thus could potentially reduce the need for EBD even after complete circumferential ESD. However, further evaluation in a larger series is clearly needed before this strategy can be widely accepted in clinical settings.

New treatment modalities

Stenting

Temporary stent placement may also be a promising strategy for the prevention of post-ESD strictures. Self-expandable metal stents (SEMSs) or biodegradable stents have been used for the treatment of benign strictures such as anastomotic stricture and cicatricial stricture secondary to esophagitis.²⁵ Although recent studies reported the usefulness of SEMSs for the treatment of benign esophageal stricture,²⁶⁻²⁸ potential late-onset complications are related to long-term stent placement.²⁶⁻³⁰ Moreover, there is no removal mechanism in currently available SEMSs, which may result in difficult stent removal after long-term placement. Currently, no consensus on the appropriate duration of SEMS placement exists. In previous studies, the duration of SEMS placement varied from 3 days to several months.²⁶⁻²⁹ However, no report on SEMS placement for the treatment of post-ESD cicatricial stricture has existed until now. To overcome the difficulty in removing stents, the use of self-expanding Polyflex plastic stents (Willy Ruesch GMBH, Kernen, Germany),²⁵ fully covered retrievable SEMSs,³¹ or biodegradable stents^{32,33} has been suggested.

Thus far, the use of self-expandable removable stents for the prevention of post-ESD strictures has not been described. Reportedly, biodegradable stents have been applied for the prevention of post-EMR/ESD strictures; however, high frequen-

cies of stent migration, small numbers of patients, and short-term follow-up periods limit the usefulness of these studies.^{32,33} Thus, further evaluation of these methods is required to compare the usefulness of these stents with EBD.

Other methods under investigation

In recent years, new technologies such as autologous oral mucosal sheets¹² or extracellular matrix scaffold material¹⁴ have been suggested to manage esophageal strictures. In previous experiments, effective treatment resulting in re-epithelialization of post-ESD esophageal ulcers was shown by the transplantation of cultured autologous canine oral mucosal epithelial cell sheets,³⁵ noncultured autologous swine oral mucosal epithelial cells,³⁶ and cultured human oral mucosal epithelial cell sheets.³⁷ Recently, re-epithelialization of the esophagus post-ESD in nine patients with superficial esophageal neoplasms was promoted safely and effectively by using sutureless, endoscopic transplantation of carrier-free cell sheets composed of autologous oral mucosal epithelial cells.³⁸ Moreover, local administration of a controlled-release anti-scarring agent can prevent further esophageal stricture development post-ESD. According to a recent publication, 5-fluorouracil, which is used as an anti-scarring agent for the treatment of hypertrophic skin scars, prevented postoperative esophageal strictures in a canine model.³⁹ These methods could be used to prevent stricture formation following ESD and to improve patient quality of life. However, further study will be needed to assess the efficacy and safety of such methods for the prevention of stricture formation.

POST-ESD STRICTURE IN THE STOMACH

Incidence of and risk factors for post-ESD stricture

Perforation and bleeding are common complications of ESD in the stomach,^{40,41} and a case of extensive gastric ischemia post-ESD for early gastric cancer was found in the literature.⁴² However, reports regarding the development of strictures post-ESD for gastric neoplasm are few in number (Table 3).⁴³⁻⁴⁵ This scarcity of reports is probably because the incidence of post-ESD strictures in gastric neoplasm is very low (0.8% to 1.9%). Coda et al.⁴⁴ reported that of the post-ESD

Table 3. Incidence of and Risk Factors for Post-Endoscopic Submucosal Dissection Stricture in Gastric Neoplasms

Author	No. of subjects	Incidence of stricture, %	Risk factors for stricture
Tsunada et al. (2008) ⁴³	532	0.9	-
Coda et al. (2009) ⁴⁴	2,011	0.8	Circumferential mucosal defect >3/4 longitudinal mucosal defect >5 cm
Iizuka et al. (2010) ⁴⁵	308	1.9	Circumferential mucosal defect >3/4 located in the antrum, prepylorus, and cardia

stricture cases in the stomach, 17% occurred in the cardia and 7% occurred in the pylorus. Circumferential mucosal defects more than three-fourths in extent and longitudinal mucosal defects >5 cm were considered risk factors of post-ESD stricture. In another study, the incidence of post-ESD stricture in the cardia, antrum, and prepylorus was 4.3%, 2.0%, and 18.8%, respectively.⁴⁵ No reports have demonstrated post-ESD strictures in the body, angle, or fundus. In this study, ESD of more than three-fourths the circumference in the prepylorus, antrum, and cardia was considered a risk factor for stricture formation.

Treatment modalities for post-ESD stricture

Endoscopic balloon dilation

Balloon dilation is considered to be useful for the treatment of post-ESD stricture. Coda et al.⁴⁴ reported that stricture-related symptoms were completely resolved in all patients as a result of EBD. The median number of dilations in patients with post-ESD strictures following cardiac and pyloric resections was 5 and 9, respectively. The median period from ESD to the diagnosis of post-ESD stricture was 22 days in cases of cardiac resection and 27 days in cases of pyloric resection. There were no complications after any of the balloon dilations. The authors indicated that it was advisable to start balloon dilation before the stricture actually developed.

In a case series of five patients with post-ESD stricture, one patient required surgery because of a severe stricture that could not be resolved by balloon dilation, and two patients required emergency surgery because of perforations caused by balloon dilation.⁴³ This case series stressed the importance of starting the dilation in the early stage of the healing process post-ESD.

In another report on six cases of symptomatic strictures, EBD was successful and all patients experienced relief from stricture symptoms.⁴⁵ One case was complicated by perforation, although the patient recovered following conservative treatment. The number of balloon dilations was 1 to 7 (average, 2.8), and the duration between relief from stricture symptoms and the initial dilation ranged from 1 to 5 months (average, 2.5).

Local steroid injection

Several studies recommended the use of oral steroids or endoscopic steroid injections in cases of post-ESD esophageal strictures.^{7,16,17,19,21-23} In a previous study, the presence of granulation tissue over the ulcer floor led to contraction and deformity of the ulcer.⁴⁶ During the healing process of post-ESD gastric ulcers, ulcer granulation and contraction as well as regenerative mucosa extension toward the center of the ulcer

led to protruded granulation tissue formation. Steroids can modulate the process of wound healing in a post-ESD ulcer through their anti-inflammatory effects. The local injection of steroids into the post-ESD ulcer promotes the formation of flat and abundant granulation tissue without fibrotic contraction. Consequently, the formation of granulation tissue prevents convergence around the ulcer edge toward the center, thus avoiding gastric deformity.

A recent study suggested that local injection of triamcinolone into the artificial ulcer may prevent post-ESD gastric deformity.⁴⁷ At 5 and 12 days post-ESD, triamcinolone was injected in sites 5 mm apart in three straight lines, which quadrisected the post-ESD ulcer across its maximum diameter. Measurements of clip-to-clip distance and ulcer diameter were recorded at 5, 12, 30, and 60 days post-ESD. The total doses of triamcinolone per session ranged from 40 to 72 mg. Local triamcinolone injection did not alter the clip-to-clip distance at 60 days post-ESD, and flat granulation tissue formation over the ulcer was followed by regenerative mucosa formation without any gastric deformity. No patient experienced triamcinolone injection-associated complications. The local injection of triamcinolone into a post-ESD ulcer promotes granulation tissue formation at an early stage of the healing process, thus leading to gastric mucosa regeneration without mucosal convergence or gastric deformity.

New treatment modalities

A recent report described the use of a biodegradable esophageal stent in patients with post-ESD esophageal strictures, which may be beneficial in preventing post-ESD strictures in patients with cardiac or pyloric resections.³⁵ Temporary insertion of the removable stent could be another treatment modality if dilation is not effective.

CONCLUSIONS

The incidence of post-ESD strictures in esophageal neoplasms is 5% to 17%. In the esophagus, circumferential mucosal defects of more than three-fourths the esophageal circumference, longitudinal mucosal defects >3 cm, and lesions located in the upper esophagus are risk factors for stricture development. Thus far, EBD has been the treatment of choice for esophageal strictures. However, intralesional steroid injection or oral steroid administration has been reported to promote remission of dysphagia or reduce the need for repeated EBD. The incidence of post-ESD strictures in gastric neoplasm is 0.8% to 1.9%. In the stomach, circumferential mucosal defects of more than three-fourths in extent and longitudinal mucosal defects >5 cm are risk factors for post-ESD stricture. Although local steroid injection can also be helpful

in preventing and treating post-ESD strictures in the stomach, early EBD has proven effective for their control and prevention. Furthermore, temporary stent placement may also be a promising strategy for preventing post-ESD stricture in the upper gastrointestinal tract.

Conflicts of Interest

The authors have no financial conflicts of interest.

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