Prevention of stricture after semi-circumferential and whole circumferential esophageal endoscopic resection

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Abstract: Stricture formation after esophageal endoscopic resection (ER) worsens a patient's quality of life because it causes dysphagia and requires multiple endoscopic dilations. Numerous methods are available to prevent esophageal stricture formation after ER. For noncircumferential resections, much evidence indicates local steroid injection is the best choice and is therefore widely used in clinical practice. However, local steroid injection alone is insufficient to prevent stricture of whole circumferential resections. Accordingly, we should select oral steroid administration or combination therapy (oral steroid administration + local steroid injection) for such extensive resections. However, the stricture rate is significantly higher compared with noncircumferential resections despite these prevention methods. Steroid therapies, including local injection and oral administration, have the advantages of high effectiveness and low cost. However, concerns include the risk of steroid-related complications such as immunosuppression, diabetes onset/exacerbation, and fragility of the esophageal wall. Also, favorable outcomes of modified steroid methods such as local triamcinolone acetonide (TA) injection together with a polyglycolic acid sheet (PGA), TA-soaked PGA sheet together with a fully covered metal stent, and TA filling method have been reported. Innovative methods include tissue engineering approaches such as cell sheet transplantation and autologous mucosal transplantation. Despite the promise of these methods, further studies are required to establish their efficacies before widespread use in clinical practice.

Keywords: Endoscopic resection (ER); endoscopic submucosal dissection (ESD); esophageal cancer; stricture

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Introduction

Esophageal cancer is the eighth most common malignancy and the sixth most common cause of cancer-related mortality worldwide (1). The prognosis of esophageal cancer is very poor, with a 5-year survival rate of <20% (2). However, a favorable prognosis is expected if tumors are detected at an early stage (3,4). Endoscopic resection (ER) is a standard treatment for early-stage esophageal cancer because of its minimal invasiveness and favorable clinical outcomes (3). Endoscopic submucosal dissection (ESD) is a variation of ER, which was widely implemented approximately 20 years ago (5). Recent improvements in performing ESD enable en bloc resection of large lesions, even of whole circumferential lesions, and precise histological evaluation. Consequently, the indication for ER has gradually extended to include larger lesions that were previously treated using surgery.

Although ER is effective, extensive esophageal ER confers risk of postoperative esophageal stricture. For example, the rates of postoperative stricture without any prevention methods after semi-circumferential resection or whole circumferential resection are 50–80% and 100%, respectively; and the ranges of the required numbers of endoscopic balloon dilations (EBDs) are 6–9 and 22–33, respectively (6-12). Numerous reports demonstrate that the risk factors of post-ESD stricture are “large mucosal defect (≥5/6 or ≥7/8)” (13-16) and “longitudinal diameter of ≥50 mm” (17,18). Moreover, the stricture rate of whole circumferential resection is extremely high, even after implementation of prevention methods for stricture (8,11,13). Accordingly, it is important to avoid circumferential resection when possible.

Differences in the stricture rates after whole circumferential resection or noncircumferential resection may be explained by differences in healing. After whole circumferential resection, epithelial regeneration occurs only from the oral and anal sides of the post-ESD defect. In contrast, after noncircumferential resection, epithelial regeneration occurs from the oral and anal sides of the esophagus as well as the remaining streaky mucosa. The stricture worsens a patient’s quality of life because it causes dysphagia and requires multiple, long-term EBDs (14). To overcome such limitations of extended ESD, developing an effective preventive method for stricture is indispensable. Here we aimed to evaluate the efficacy and safety of the methods available to prevent post-ESD stricture by referring to the recent literature and our institution’s data.

Prevention methods

Prophylactic EBD

Ezoe *et al.* (15) reported the results of prophylactic EBD for post-ESD stricture formation. Stricture occurred in 59% of patients even after six (median) prophylactic EBD sessions (15). This outcome shows that prophylactic EBD is insufficient to prevent post-ESD esophageal stricture. Li *et al.* (16) recently reported the effectiveness of a novel self-help inflatable balloon to prevent post-ESD stricture in whole circumferential esophageal resection. This novel balloon was used by patients at home and was removed after the defect healed. Only one stricture occurred in eight (12.5%) patients, without complications.

Steroid therapy

Mechanism to suppress stricture formation using steroids

A process involving inflammation, cell proliferation, and tissue remodeling may represent an important component of wound healing. Collagen, which is the major fibrous connective tissue protein, is required to provide structural support in scars (19). Steroids inhibit inflammation and reduce collagen formation and fibroblast proliferation (20,21). Thus, steroids are considered the most suitable molecules for suppressing scar formation and preventing stricture after ER. Systematic reviews show that using steroids significantly reduces the stricture rate and number of EBD sessions without increasing complications (22,23).

Oral steroid administration

In the studies cited above, in which administration of oral prednisolone started at 30 mg/day, the post-ESD stricture rates were significantly lower than the controls who did not undergo stricture prevention methods (6-8). The stricture rates 10–20% were acceptable for noncircumferential resections (*Table 1*), whereas they were insufficient (27.3–100%) for whole circumferential resections (*Table 2*). When we roughly divided these reports into short-term (2–3 weeks) and intermediate long-term (6–18 weeks), there was no significant difference between the stricture rates of these groups for cases of noncircumferential resection (14–23.1% and 10–20%, respectively). Iizuka *et al.* reported a comparison of the periods of oral prednisolone administration in whole circumferential resections. They created two groups that were administered oral prednisolone for 8 weeks (original group) or 18 weeks (modified group). The post-ESD stricture rate was lower in the modified group than in the original group [36.4% (4/11) *vs.* 82% (9/11)]. However, steroid-related complications such as candida esophagitis, pneumonia, and steroid myopathy were significantly higher in the modified group (26). A meta-analysis performed by Yang *et al.* (27) found that long-term oral prednisolone administration (>12 weeks) was the most effective among nine methods for preventing postoperative stricture as follows: placebo/no treatment, long-term (≥12-weeks) oral steroids, median-term (8-weeks) oral steroids, short-term (3 weeks) oral steroids, single-dose steroid injection, multiple-dose steroid injection, topical superficial steroids, steroid injection combined with oral steroid, and prophylactic EBD (27).

These data indicate that short-term oral prednisolone administration is sufficient for noncircumferential resection and that long-term oral prednisolone is not recommended for noncircumferential resection, considering its higher risk of complications. Further investigations to determine the optimal period of oral prednisolone administration for whole circumferential resection are required to establish its benefit-to-harm ratio.

Table 1 Outcomes of oral prednisolone and local TA injection for stricture prevention methods for noncircumferential resections

Method	Stricture rate	Dose (mg) (for Method oral prednisolone)/dose per session (mg) (for Method TA injection)	Duration of intervention (weeks) (for Method oral prednisolone)/timing of intervention (for Method TA injection)	Number of EBDs, median [range]	Included cases	Ref.
Oral prednisolone	10% (4/40)	30	6–18	0 [0–14]	>3/4 circumferential resection	(17)
Oral prednisolone	14% (2/14)	30	3	6 [2–10]‡	>3/4 circumferential resection	(6)
Oral prednisolone	23.1% (3/13)	30	2	0.69 [0–3]‡	>3/4 circumferential resection	(7)
Oral prednisolone	20% (5/25)	30	8	–	>3/4 circumferential resection	(8)
TA injection	4% (1/23)	40–80	Day 0	0 [0–22]	>3/4 circumferential resection	(17)
TA injection	45% (5/11)	40	Day 0	–	>2/3 circumferential resection	(10)
TA injection	11% (13/115)	50–100	Day 0	–	>3/4 circumferential resection	(13)
TA injection	36% (17/47)	50	Days 3,7,10 or day 1 or day 0	–	>3/4 circumferential resection	(11)
TA injection	26.4% (14/53)	50.9†	Day 0	–	>2/3 circumferential resection	(24)
TA injection	17% (17/101)	80	Day 0	–	>2/3 circumferential resection	(25)
TA injection	45.7% (16/35)	Day 0: 40–100, Day 14: 16–50	Days 0,14	–	>3/4 circumferential resection	(12)
TA injection	33.3% (2/6)	40–160	Day 0	–	>3/4 circumferential resection	(8)
TA injection	22.8% (28/123)	50–150	Day 0	0 [0–13]	>3/4 circumferential resection	§

†Two cases of whole circumferential resection. ‡Mean. §The data of our institute. TA, triamcinolone acetonide; EBD, endoscopic balloon dilation.

Table 2 Outcomes of oral prednisolone and local TA injection for stricture prevention methods for whole circumferential resections

Method	Stricture rate	Dose (mg) (for Method oral prednisolone)/dose per session (mg) (for Method TA injection)	Duration of intervention (weeks) (for Method oral prednisolone)/ timing of intervention (for Method TA injection)	Number of EBD	Ref.
Oral prednisolone	27.3% (3/11)	30	6–18	Median 0 [0–14]	(17)
Oral prednisolone	100% (13/13)	30	8	Mean 13.8	(9)
Oral prednisolone	33% (1/3)	30	3	Mean 2	(6)
Oral prednisolone†	59% (13/22). ①‡9/11; ②§4/11	30	①8, ②18	Mean: ①‡19.4[0–42], ②§6.2 [0–28]	(26)
TA injection	100% (3/3)	40–80	Day 0	Median 12.8 [2–34]	(17)
TA injection	100% (5/5)	40	Day 0	Mean 10.4	(10)
TA injection	100% (6/6)	50	Days 3,7,10 or day 1 or day 0	–	(11)
TA injection	80% (4/5)	40–100	Days 0,14	Median 7 [0–1]	(12)
TA injection	100% (2/2)	50–150	Day 0	Mean 6.5 [3–10]	¶

†16 cases were also performed TA injection. ‡①The group administered OPA for 8 weeks. §②The group administered OPA for 18 weeks. ¶The data of our institute. TA, triamcinolone acetonide; EBD, endoscopic balloon dilation.

Local steroid injection

Direct, local injection of low-dose steroids was developed to suppress inflammation and fibrosis after esophageal ER as an alternative to oral administration (8,10,12,13,17,24,25). Triamcinolone acetonide (TA) was used in all studies referred to below. TA is considered the best drug for local injection because it is gradually absorbed over a few weeks. The performance of local TA injection for noncircumferential resections is favorable, although the stricture rate widely varies (4–45%) (*Table 1*). Further, local TA injection reduces the required number of EBDs to resolve post-ESD stricture (10). Studies are available that report the effects of immediate administration of one session of local TA after ESD (8,10,13,17,24,25) as well as two sessions (immediate and 14 days after ESD) (12). For example, Hashimoto *et al.* (12) reported a 45.7% (16/35 patients) stricture rate of patients administered two sessions of local TA injection for noncircumferential resections. They injected TA on days 0 and 14. These unfavorable results emphasize that it is unnecessary to inject TA more than once (12).

Other investigators determined the effects of using low- (40–50 mg) (10,11) or high-doses of TA (80–100 mg) (13,25). There is the tendency that high-dose TA is associated with lower stricture rates than low dose (*Table 1*). Each report included a few EBD cases with perforation after ESD stricture formation, although there is no difference between using low and using high doses reports (10,11,13). High-dose TA is should therefore be recommended to prevent post-ESD stricture of noncircumferential resections. Although local TA injection achieved favorable results for noncircumferential resection, its effect on whole circumferential resection cases is poor, with stricture rates ranging from 80% to 100% (*Table 2*). Therefore, oral steroid administration with an alternative treatment should be considered.

Our institution's data are provided for reference (*Tables 1,2*). We selected a single local TA injection to prevent post-ESD stricture for noncircumferential resections. We performed only one session of local TA injection immediately after ESD and adjusted the dose from 50 to 200 mg, depending on the size of the defect. Eligible patients underwent ESD between April 2014 and July 2019 for superficial esophageal neoplasms with a mucosal defect of >75% of the circumference. These patients included those who received TA injection alone to prevent postoperative stricture. The study included 123 noncircumferential resection cases and two whole circumferential resection cases. TA injection (≥100 mg) was administered to 71.2% (89/125) patients. The postoperative stricture rates were 22.8% (28/123) and 100% (2/2) for noncircumferential and whole circumferential resections, respectively.

Combination therapy (oral steroid administration + local steroid injection)

The effects of single therapy such as oral prednisolone administration or local TA injection, are insufficient for treating whole circumferential resection, therefore the efficacy of combination therapy (oral steroid administration + local steroid injection) was evaluated in some studies (*Tables 3,4*). The data show that combination therapy effectively prevents stricture for noncircumferential resection at the post-ESD stricture rate of 13% (11,28) (*Table 3*).

For whole circumferential resection, combination therapy achieved slightly better efficacy (post-ESD stricture rates, 18%–92%) than TA injection alone (11,13,28) (*Tables 2,4*) without steroid-related complications. Our institution's data are provided in these tables for comparison. We selected local TA injection alone for noncircumferential resections. Combination therapy is therefore selected for patients with semi- or whole-circumferential resection because they are predicted to have a high risk of stricture. When we administer oral prednisolone to patients who undergo whole circumferential resection, we adjust the dose according to the healing status of the esophageal ulcer. Oral prednisolone is initially administered at 30 mg/day and reduced in 5-mg biweekly increments to 20 mg. When endoscopy shows the disappearance of the white coat of the ulcer, we reduce the dose 5-mg weekly increments to 10 mg. After the ulcer forms a scar, we gradually reduce the dose and discontinue treatment. The outcomes of semi-circumferential resection are highly favorable. Thus, the postoperative stricture rate is 0% (0/8 patients). The outcome of the whole circumferential resection was better than the local TA injection alone, with a stricture rate of 40% (6/15 patients). Steroid-related complications were three cases of diabetes onset/exacerbation and one case of bacteremia. According to the literature cited here and our institution's data, we conclude therefore that combination therapy may be effective for preventing postoperative stricture of semi- or whole circumferential resection.

Modified steroid method

Several modified steroid methods more effectively prevent postoperative stricture. For example, a polyglycolic acid (PGA) sheet is a biodegradable suture reinforcement used

Table 3 Outcomes of combination therapy (oral prednisolone and local TA injection) and modified steroid method for stricture prevention methods for noncircumferential resections

Method	Stricture rate	TA dose per session (mg)	How to use TA and dose (mg)	Timing of injection	Prednisolone dose (mg)	Timing of intervention	Period of prednisolone intake (weeks)	Mean or median number of EBD	Included case	Ref.
Combination therapy	13% (2/15)	50		Days 3,7,10 or day 1 or day 0	30		8		>3/4 circumferential resection	(11)
Combination therapy	13% (3/23)	80–100		Day 0	30		8		>2/3 circumferential resection	(28)
Combination therapy	0% (0/8)	100–150		Day 0	30		7–17		>3/4 circumferential resection	†
TA injection + PGA	25% (1/4)		80			Day 0		–	>5/6 circumferential resection	(29)
TA injection + PGA	11% (1/9)		40			Day 0		Median 0 [0–20]	>3/4 circumferential resection	(30)
TA-soaked PGA + stent	0% (0/3)		Soaking the PGA, 80			Day 0 and stents were removed after 4–6 weeks		0	>3/4 circumferential resection	(31)
TA filling	5% (1/20)		Filling method, 80			Days 0, 7		Median 0 [0–3]	>3/4 circumferential resection	(32)

†The data of our institute. TA, triamcinolone acetonide; EBD, endoscopic balloon dilation; PGA, polyglycolic acid.

Table 4 Outcomes of combination therapy (oral prednisolone and local TA injection) and modified steroid method for stricture prevention methods for whole circumferential resections

Method	Stricture rate	TA dose per session (mg)	How to use TA and dose (mg)	Timing of injection	Prednisolone dose (mg)	Timing of intervention	Period of prednisolone intake (weeks)	Mean or median number of EBD	Ref.
Combination therapy	92% (11/12)	100		Day 0	30		8		(13)
Combination therapy	71.4% (10/14)	50		Days 3,7,10 or day 1 or day 0	30		8		(11)
Combination therapy	18% (2/11)†	80–100		Day 0	30		8		(28)
Combination therapy	40% (6/15)	100–200		Day 0	30		6–61		‡
TA injection + PGA	67% (4/6)		80			Day 0		–	(29)
TA injection + PGA	50% (1/2)		40			Day 0		–	(30)
TA-soaked PGA + stent	50% (3/6)		Soaking the PGA, 80			Day 0 and stents were removed after 4–6 weeks		Median 4 [0–4]	(31)

†Including >90% circumferential cases. ‡The data of our institute. TA, triamcinolone acetonide; EBD, endoscopic balloon dilation; PGA, polyglycolic acid.

for strengthening the mucosal defect that prevents scarring and relieves postoperative pain in implantation surgeries (33-35). The aim of using a PGA sheet to treat the post-ESD defect is to prevent postoperative stricture by shielding the surface of the defect from the effects of exogenous substances and suppressing subsequent organization of the granulation tissue. Further, the PGA sheet alone is effective (36,37). Using local TA injection together with a PGA sheet (29,30) achieves favorable outcomes. Thus, the ranges of post-ESD stricture rates of the noncircumferential and whole circumferential resections are 11–25% and 50–67%, respectively (*Tables 3*,*4*).

Li *et al.* (31) used a TA-soaked PGA sheet as well as a fully covered metal stent (TA-PGA+FCMS) to prevent post-ESD stricture. They immediately placed the TS-PGA+FCMS after ESD and removed all stents 4–6 weeks post-ESD. The stricture rates of the non- and whole circumferential resections are 0% (0/3 patients) and 50% (3/6 patients), respectively. There were no complications during the median follow-up period of 15.2 months (31).

Shibagaki *et al.* (32) conducted a prospective multicenter study of the TA filling method. This procedure maintains a saline solution of TA in the esophagus for a certain time with upper endoscopy to infiltrate the ulcer with TA. They performed this method immediately after ESD, on day 7 post-ESD, and when mild stenosis allowing endoscope passage was found. This study included 20 cases of semi-circumferential (>3/4) resections, and the 5% (1/20) stricture rate is favorable. Furthermore, only three sessions of EBD were required. The authors emphasize that this method does not require injection, which obviously eliminates complications associated with the injection (32).

These reports showed impressive results for preventing postoperative stricture. However, they include small numbers of cases, and some used expensive materials such as PGA sheets and FCMS. Thus, further investigations of more patients and determination of the cost-to-benefit ratio are required to sufficiently evaluate these methods.

Adverse events associated with steroid therapy

Possible adverse events associated with oral steroid administration include immunosuppression, diabetes onset/exacerbation, psychiatric disorders, osteoporosis, and peptic ulcer. Further, there is increased risk of infectious diseases such as pneumonia, candida esophagitis, and pneumocystis pneumonia (26,38). Prophylactic use of antibacterials for pneumocystis pneumonia is advised for patients administered steroids at doses >20 mg for longer than one month (39). There is one report of disseminated nocardiosis during oral steroid administration aimed to prevent postoperative stricture (40).

The findings of animal studies raise the concern that local steroid injection may cause atrophy of the muscularis propria and fragility of the esophagus (41,42). Further, a recent animal study found that esophageal perforations and abscesses in the mediastinum form 28 days after TA injection into the muscle layer of esophageal ulcers (43). Furthermore, there is one case report of delayed perforation after local TA injection into the wound following EBD for post-ESD stricture, which is likely explained by the injection of TA into the muscularis propria (44). Another study found that the perforation rate of EBD for post-ESD stricture is higher in patients treated with local TA injection (45.4%, 5/11) than without (14.3%, 1/7) (45). These findings suggest that we should avoid TA injection into the muscular layer and consider the fragility of the esophagus, which can be addressed using a small-caliber balloon or low inflation pressure.

Selection of oral or injectable steroids

Oral steroid administration and local TA injection confer favorable effects that prevent post-ESD stricture of noncircumferential resections (*Table 1*). Wang *et al.* conducted a network meta-analysis that did not detect a significant difference between the efficacies of oral and local steroid injection for noncircumferential resections (22). Given similar efficacies, local TA injection is simpler than administering oral steroids because the former can be immediately completed after ESD. Furthermore, after oral steroid administration, outpatient care is required to control the steroid dose and to monitor complications such as diabetes onset/exacerbation. The efficacy and convenience of the procedures support the conclusion that local TA injection is better for noncircumferential resection (*Table 1*).

Some investigators maintain that local TA injection requires a high level of skill. However, this is not difficult for endoscopists who perform esophageal ESD for large lesions. A multicenter randomized controlled trial (JCOG1217), designed to compare the efficacies of prophylactic oral steroid administration and local TA injection for patients with noncircumferential lesions is ongoing in Japan (46). The results of this study may provide important information regarding the selection of these two steroid therapies. In summary, the results of the studies reviewed in this section support the conclusion that for whole circumferential resections, the effect of local TA injection alone is insufficient (*Table 2*). Oral steroid administration and combination therapies are the most widely used methods, although insufficient data are available to unequivocally establish their efficacies and safety (*Tables 2,4*). Further investigations regarding the effects and adverse events associated with these treatments are therefore required.

Other therapies and tissue engineering

Other therapies

Botulinum toxin type A (47) and the PGA sheet alone (36,37) serve to prevent post-ESD stricture. However, the outcomes of these treatments are not favorable compared with steroid therapy. Furthermore, high cost limits the use of the PGA sheet. Retrievable, fully covered metal stents achieve favorable results (48,49), with stricture rates ranging from 17% to 57% for whole circumferential resections. However, the use of metallic esophageal stents to prevent benign post-ESD esophageal strictures is controversial because of the associated risks of adverse events such as bleeding, esophageal perforation, and stent migration (50). Biodegradable esophageal stents overcome this limitation (51,52) and are under evaluation for clinical application in Japan.

Tissue engineering

Tissue engineering is based on the theory that transplanted materials can replace damaged tissues and promote scarless wound healing (53). Tissue engineering approaches for preventing post-ESD stricture are classified into cell-based and scaffold-based therapies.

Cell-based therapy

Cell-based therapies are expected to improve the wound healing because the transplanted cells produce cytokines and growth factors in cooperation with other cells. In animal models, direct injection of autologous buccal keratinocytes (54) and transplanted adipose tissue-derived stromal cell sheets (55) suppress stricture formation after ER. Ohki *et al.* (56) endoscopically transplanted autologous oral mucosal epithelial cell sheets onto the post-ESD defect of ≥1/2 in 9 patients. Complete re-epithelialization was observed after a median of 3.5 weeks, and post-ESD stricture occurred in one patient who had undergone whole circumferential resection (53,56). When the same methods were used by Yamaguchi *et al.*, 10 patients with a mucosal defect of >5/6 or whole circumferential defect, the stricture rate was 40% with a median number of EBD sessions =0 (range, 0–7) without complications (57). Although these methods show promising efficacy, their extremely high cost requires detailed benefit-to-cost analyses.

Scaffold-based therapy and extracellular matrix (ECM) scaffolds

ECM scaffolds are produced using materials such as the submucosal tissue of the small intestinal or urinary bladder (58), which may stimulate the growth of epithelial cells to improve wound healing (59). In a porcine model, an acellular dermal matrix (ADM) patch graft, a type of ECM scaffold, was applied to the hemi-circumferential defect after ESD. The stricture rate was 0% (0/7 pigs) in the ADM group and 42.8% (3/7 pigs) in the ESD-only control group (60). However, there are conflicting results for the efficacies of ECM scaffolds used to treat patients (61-63). Furthermore, there are concerns about the potential risk of local recurrence or local infection because ECM scaffolds provide a favorable environment for the engraftment of cancer cells and bacteria.

Autologous mucosal transplantation

Liu *et al.* recently showed that mucosal transplantation of pigs may be suitable method for preventing stricture after large ER (64). In this study, two submucosal tunnels in the esophagus involved one-third of the width of the esophageal circumference. The mucosal roofs of both tunnels were removed in group A and only the left in group B. All pigs (6/6) in group A developed esophageal stricture, whereas animals (0/6) in group B did not. Histological examination showed inflammation and fibrous hyperplasia of the submucosal layer in both groups. These findings indicate that submucosal fragments in group B contributed to the prevention of stricture and support the validity of mucosal transplantation to prevent stricture.

Mucosal transplantation is used to prevent post-ESD stricture in patients by transplanting autologous gastric mucosa to the esophagus. A patient who underwent a circumferential resection from the hypopharynx to the cervical esophagus received an autologous gastric mucosal transplant, which was harvested from the gastric antrum using ESD. The transplanted gastric mucosa was fixed to the esophageal defect using an uncovered metal stent for 20 days. Six months after ESD, the defect was covered by the implanted gastric mucosa without stricture (65).

Liao *et al.* reported the effectiveness of esophageal mucosal transplantation to prevent stricture formation after whole circumferential resections. EMR was used to harvest several pieces of normal autologous esophageal mucosa, which were fixed to the post-ESD defect using clips and a covered stent that was removed 7 days after the procedure. Although the stricture formation rate was high (8/9 patients), the required number of EBD sessions was small (mean =2.7, range, 0–6) (66). This outcome was more favorable than those reported by others (*Table 2*).

Although these methods are unique and are expected to be effective, problems remain that must be overcome before applying them to clinical practice. These methods include invasive procedures such as resection of normal mucosal tissue and stent insertion. Furthermore, an important concern is the risk of recurrent cancer caused by the implanted esophageal mucosa because the esophageal mucosal tissues of patients with esophageal cancer patients are highly carcinogenic according to the cancerization theory (67).

Conclusions

Steroid therapy remains the mainstay of preventive treatment for stricture. Our review supports the conclusion that local steroid injection is the preferable method for noncircumferential resection because of its efficacy, lower rate of complications, and convenience. However, the risk of stricture associated with whole circumferential resection is high, irrespective of preventive methods. Therefore, whole circumferential resection should be primarily avoided whenever possible, although when it is unavoidable, oral steroid administration or combination therapy with oral steroids and local steroid injection may represent the most effective strategies.

Despite previous research and development, the efficacy of current practice to prevent stricture after ESD is unsatisfactory. To improve this situation, innovative methods are being developed. Prospective large-scale studies are required to determine the efficacies of these methods.

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