Approaches for stricture prevention after esophageal endoscopic resection

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Background and Aims: Endoscopic resection of extensive esophageal lesions has become more common as endoscopic resection techniques and equipment have developed. However, extensive esophageal endoscopic resections can cause postoperative esophageal strictures, which have a negative impact on the quality of life of patients. We aimed to review current treatments and innovative approaches to prevent esophageal strictures after widespread endoscopic resection of esophageal lesions.

Methods: We performed a comprehensive literature search from 2000 to 2016 using predetermined search terms to identify relevant articles and summarized their results as a narrative review.

Results: A total of 21 original articles and case series were identified. A circumferential mucosal defect involving more than three fourths of the esophageal luminal circumference was the primary risk factor for developing an esophageal stricture after endoscopic resection. Oral and injectable steroid therapy demonstrated promise in preventing post–endoscopic submucosal dissection esophageal strictures, with both strategies significantly reducing the number of required endoscopic balloon dilations. More data are needed on prophylactic self-expandable metal stents, local botulinum toxin injection, and oral tranilast as a strategy to prevent post–endoscopic submucosal dissection esophageal strictures. Although preliminary studies of tissue-shielding resection sites with polyglycolic acid sheets and fibrin glue and autologous cell sheet transplantation have demonstrated promising results, additional larger validation studies are needed.

Conclusions: Oral and locally injected/administered steroids are first-line options for the prevention of esophageal strictures, but additional innovative solutions are being developed. (Gastrointest Endosc 2017;86:779-91.)

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Endoscopic resection is globally accepted as a minimally invasive treatment for superficial esophageal dysplasia and carcinoma.[1] Endoscopic resection allows precise estimation of histology and assessment of risk factors of nodal metastasis, such as depth of invasion, lymphovascular invasion, and grade of differentiation. It is also accepted as potentially curative in patients with the negligible risk of nodal metastasis. Conventional EMR is well established for patients with both superficial esophageal adenocarcinoma and squamous cell carcinoma and is reported to give favorable long-term outcomes; serious adverse events seldom occur.[2-8]

Although wide endoscopic resection can be technically achieved by piecemeal EMR,[9-11] piecemeal resection is a significant risk factor for local recurrence after EMR of both esophageal adenocarcinoma and squamous cell carcinoma.[6,12,13] Endoscopic submucosal dissection (ESD) allows en-bloc resection of esophageal lesions regardless of size and location.[14,15] Esophageal ESD is more effective than conventional EMR in achieving

en-bloc resection and curative resection and in reducing the recurrence rate of esophageal dysplasia/neoplasia.[16,17]

ESD is gradually becoming more widely adopted as endoscopic expertise expands and new devices are developed. However, widespread esophageal endoscopic resection can lead to postoperative esophageal strictures.[18,19] It is generally diagnosed when a patient has dysphagia and a standard endoscope (9.6-11 mm in diameter) is unable to traverse the stricture.[18-23] Postoperative esophageal stricture has been reported to develop in 6% of patients who undergo EMR but increases to 11% to 20% after ESD.[18,19,22,24,25]

Retrospective studies in Japan and China have demonstrated that a mucosal defect involving greater than three fourths the luminal circumference of the esophagus after endoscopic resection is a strong risk factor for the development of a stricture.[18,19,25] Postoperative esophageal stricture developed in 66% to 100% of patients who had the risk factor.[26-29] Other risk factors include mucosal defects longer than 30 mm, which have been associated with greater severity of stenosis.[18] Some studies have reported that the depth of invasion (m2 compared with m1 in Ono et al[19] and mm/sm1 compared with Shi et al[25]) is an independent risk factor, although it is not known why a difference in histologic depth would affect postoperative stricture. In addition, deeper resections affecting the muscularis propria might have higher risk of stricture formation, but there are no data to support the hypothesis. These strictures may have a negative impact on the quality of life of patients by causing dysphagia, requiring multiple endoscopic dilations.[30] Dysphagia in association with recurrent stenosis occurred in 6.0% to 13.6% of patients who underwent extensive endoscopic resection of esophageal squamous cell carcinoma,[18,31] and 37.8% to 40.0% of those underwent complete EMR of Barrett's esophagus with neoplasia.[9,32] Endoscopic balloon dilation (EBD) was performed when patients experienced dysphagia with difficulty with some solids (dysphagia score of 2) and/or as the inability to pass an endoscope in some studies.[20,26,33] Hence, the Japanese Esophageal Society guidelines for the diagnosis and treatment of early esophageal cancer suggest that this possibility should be discussed with patients who are likely to require extensive mucosal resection exceeding three-fourths of the esophageal circumference before endoscopy and that prophylactic measures should be taken.[34]

Esophageal strictures develop after endoscopic resection by a process of healing followed by scarring of the tissue mucosal defect. Nonaka et al[35] assessed the healing process of esophageal large mucosal defects by ESD using a pig model. In this study, spindle-shaped α-smooth muscle actin–positive myofibroblasts arranged in a parallel fashion and extending horizontally were identified at the ulcer bed 1 week after the ESD and increased contributing to formation of the stenotic luminal ridge covered with the regenerated epithelium appearing 3 weeks after

ESD. They also found that the muscularis propria of the stricture site was thinned with some myocytes that seemingly showed transition to the myofibroblast layer (Figs. 1 and 2). Honda et al[36] similarly showed the submucosa was replaced with dense collagen fibers and lacked components such as esophageal glands. The muscularis propria myofiber atrophy was found to develop after the first postoperative week, eventually leading to fibrosis in a dog model.[36] These healing processes are believed to be the main cause of the esophageal stricture after endoscopic resection of large esophageal lesion.

The aims of this article were to comprehensively review approaches to prevent esophageal stricture formation after widespread endoscopic resection of esophageal lesions.

METHODS

We performed a systematic electronic literature search of articles published in PubMed (from 2000 until December 2016) that reported on methods and techniques for the prevention of esophageal strictures after widespread endoscopic resections. Two authors (S.A. and I.O.) independently participated in the literature search, study selection, and data extraction. Disagreements were resolved through discussion with a third author (Y.S.). The search terms included "esophageal stricture or esophageal stenosis or dysphagia" and "endoscopic mucosal resection or endoscopic submucosal dissection." The search was limited to fully published original articles and case series in English and adult human studies. Case reports and animal studies were excluded. We also excluded the studies that aimed to describe treatment rather than prevention of esophageal stricture after endoscopic resection. Using a standardized data extraction form, we collected the following data from each study patient demographics, the preventative efficacy of esophageal stricture formation after endoscopic resection, and adverse events. In addition, the evidence levels of the articles were graded according to the GRADE guidelines.[37,38]

RESULTS

Among 358 articles that met the key words, we identified 21 eligible studies (stepwise endoscopic resection, 1; prophylactic balloon dilation, 1; temporary esophageal metallic stent, 2; steroid therapy, 10; oral medication other than steroid, 1; injection methods other than steroid, 1; tissue-shielding methods, 4; and cell sheet transplantation, 1). Three randomized controlled trials, 11 observational studies, and 7 case series were included; however, all studies were graded as low quality or very low quality because of small sample sizes and limitations such as lack of concealment of allocation and lack of double-blinding in randomized trials.
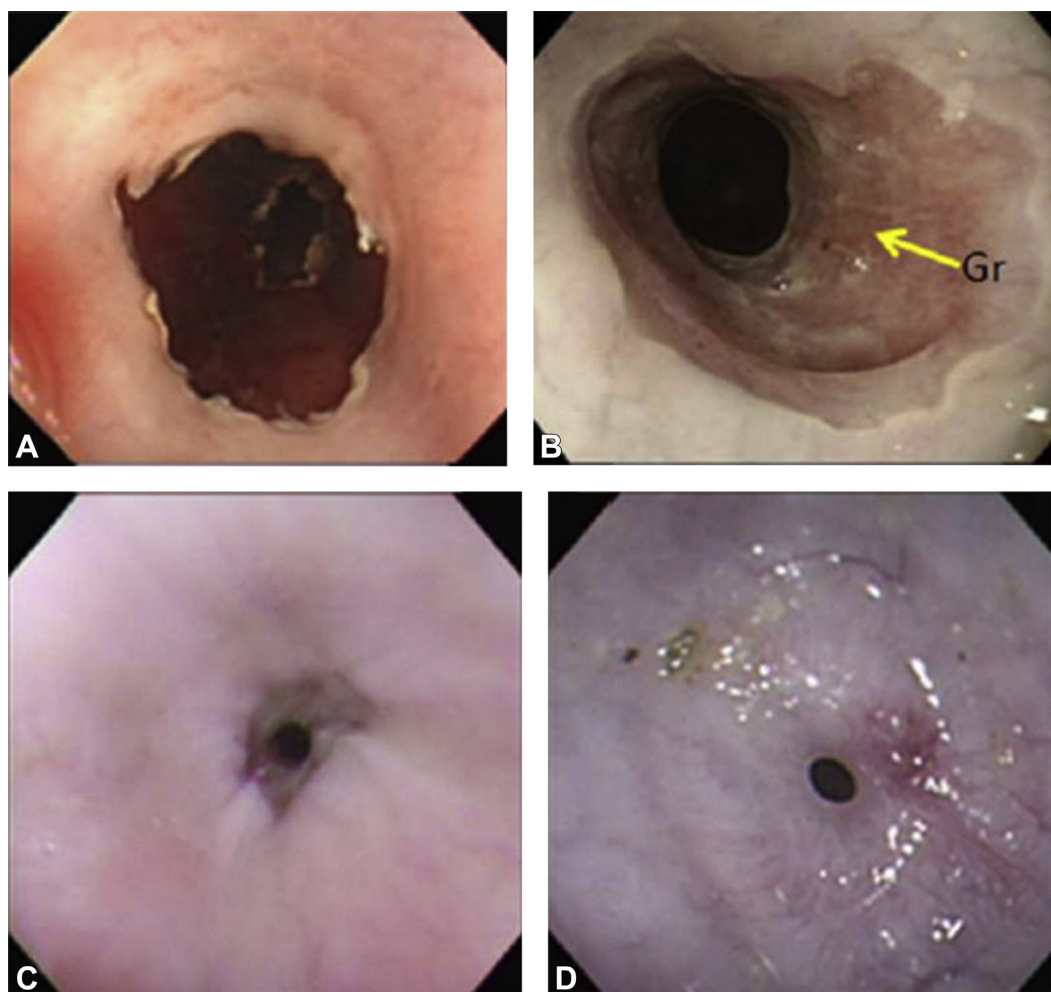
Figure 1. Endoscopic findings after esophageal endoscopic submucosal dissection (ESD) in a porcine model. **A,** A circumferential mucosal defect immediately after the ESD. **B,** One week after the ESD, the ulcer bed is mostly covered with granulation tissue (*arrow*). *Gr,* Granulation tissue. **C,** Two weeks after the ESD, the stricture of the ulcer site is remarkable. **D,** Three weeks after the ESD, the stricture shows a pinhole-like appearance, the surface of which is completely covered with the regenerated epithelium. (Licensed under CC by Nonaka et al.[35] Licensee BioMed Central Ltd 2013.)

Stepwise endoscopic resection

In the Western countries, endoscopic resection of visible nodules followed by ablation of the remaining Barrett's epithelium and endoscopic surveillance is the currently recommended standard treatment for high-grade dysplasia and intramucosal cancer in Barrett's esophagus. However, the cost of the disposable equipment, recurrence, and the risk of buried Barrett's esophagus are potential concerns. Radical endoscopic resection for complete eradication of Barrett's epithelium was initially proposed as a definitive therapy but has not been pursued further because of a high stricture rate (48%-88%) when 4 to 5 resections were performed.[39,40]

Given the background, Koutsoumpas et al[41] recently reported that stepwise complete endoscopic resection of Barrett's epithelium in short-segment Barrett's esophagus could reduce the risk of esophageal stricture to 1.1%. This method is reasonable for localized Barrett's high-grade dysplasia and adenocarcinoma.[41] However, this strategy is only applicable for short segment Barrett's esophagus and is not recommended for widespread esophageal squamous cell carcinoma because local recurrence can develop after multiple piecemeal resections, and subsequent endoscopic resection is very difficult because of fibrosis.[12]

Preemptive EBD

Prophylactic EBD may be a potentially effective approach to prevent esophageal stricture formation.[30,42] Ezoe et al[23] evaluated the efficacy and the safety of preventive EBD compared with an historical control group without EBD. This study included 41 patients with extensive mucosal defects involving three-fourths or greater of the esophageal luminal circumference. Preventative EBD was performed within 1 week after EMR/ESD and repeated until the mucosal defect was completely healed in 29 patients, whereas the remaining 12 patients who did not undergo the preventative EBD
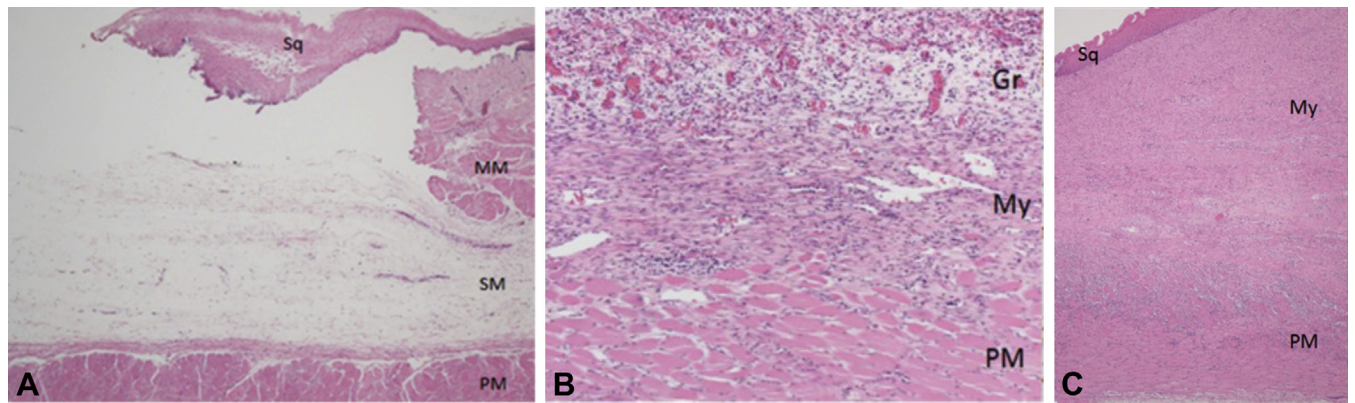
Figure 2. Histologic findings of the esophageal ulcer after esophageal endoscopic submucosal dissection (ESD). **A,** Five minutes after the ESD. A sufficient volume of the submucosal layer remains in the ulcer bed with no evidence of damage to the proper muscle (striated muscle) layer. Neither inflammatory reaction nor reparative change is noted. *Sq,* squamous epithelium; *MM,* muscularis mucosa; *SM,* submucosa; *PM,* proper muscle layer. H&E, orig. magn. ×40. **B,** One week after the ESD. In middle-power view of the ulcer bed, myofibroblastic cells (*My*) are identified and arranged in a parallel fashion and extending horizontally, forming bundles between the edematous granulation tissue of the ulcer bed surface (*Gr*) and the proper muscle layer (*PM*), partly occupying the superficial part of the PM. H&E, original magnification ×100. **C,** Three weeks after the ESD. Low-power view of the luminal ridge occupied by the thick layer of myofibroblastic cells (*My*) involving the inner layer of the PM. The ridge surface is covered with the regenerated squamous epithelium (*Sq*). H&E, original magnification ×40. (Licensed under CC by Nonaka et al.[35] Licensee BioMed Central Ltd 2013.)

were used as historical control subjects. This study concluded that preventive EBD decreased the incidence of stricture formation (59% vs 92%, $P = .04$), and also shortened time to stricture resolution (29 days vs 78 days, $P = .04$) even when strictures developed. No adverse event occurred among a total of 166 preventive EBD sessions for 29 patients; however, a perforation occurred in 1 conventional EBD session in 1 patient among a total of 189 conventional EBD sessions for 28 patients (.5% per total conventional EBD sessions, 3.6% per patient).[23] Yamaguchi et al[31] performed preemptive EBD on the third day after ESD and continued this twice weekly for 8 weeks as an historical control in their comparative study using oral prednisolone. The average number of EBD sessions required for resolving esophageal strictures was 15.6 in all lesions involving more than three-fourths of the luminal circumference and 32.7 EBD sessions in complete circumferential ESD. There were no adverse events related to EBD.[31]

These studies indicate that although preemptive EBD may be effective in decreasing the incidence and time to resolution of post-ESD esophageal strictures, they do not prevent stricture formation in most cases, and multiple sessions of EBD had to be performed, especially in patients undergoing complete circumferential ESD.[43] Multiple sessions of EBDs are associated with a substantial cost and cumulative risk of adverse events, leading to a search for alternative approaches.[44] Therefore, EBD alone was believed to be insufficient to prevent esophageal strictures after endoscopic resection, and an alternative approach is recommended.

Self-expanding endoscopic metal stents

Self-expanding endoscopic metal stent (SEMS) placement has been explored as an option to prevent and treat benign and malignant esophageal strictures.[30,45] Although SEMSs have been used to prevent post-ESD esophageal strictures, results remain inconclusive.[46] Holt et al[47] reported that prophylactic placement of fully covered SEMSs was associated with a potential risk of stent migration and delayed esophageal strictures could develop after removal of these stents. They enrolled 14 patients who had circumferential short segment Barrett esophagus and underwent complete Barrett's excision. Metal stents were inserted in 12 patients at a median of 10 days after complete Barrett's excision and were removed at a median of 7.5 weeks. Two patients underwent complete Barrett's excision and had no stent inserted because they had minimal dysphagia and no significant esophageal stricturing at the scheduled endoscopy. SEMS placement was also associated with a high risk of other adverse events, such as chest pain, which required early stent removal (25%), and stent migration (16.7%). In addition, there is currently no consensus in the literature regarding the appropriate duration of stent placement after ESD.

Recently, biodegradable esophageal stents have been developed and used in the treatment of refractory benign esophageal strictures. The prolonged dilatory effect before stent absorption and the progressive stent degradation may be a more attractive approach compared with standard SEMSs in patients undergoing extensive esophageal ESD.[48,49] However, the current evidence is insufficient to determine the relative efficacy or safety of prophylactic esophageal biodegradable stents. There is only 1 case report,[36] and there are no publications investigating their efficacy in preventing post-ESD strictures.[48] Esophageal biodegradable stents are commonly used to prevent benign esophageal strictures in Western countries; however, their efficacy has not been fully evaluated to prevent strictures after

TABLE 1. Clinical outcomes of steroid-based prevention of esophageal stricture after endoscopic resection

Author, year	Design	Intervention dosage	Inclusion (luminal circumference)	Sample size (treated/control)	Stricture rate	Mean or median number of EBD	Adverse event
Hashimoto, 2011[27]	Retrospective historical control	Triamcinolone injection 18–62 mg at days 3, 7, 10	ESD > 75% SCC	21 /20	19%/ vs 75% ($P < .001$)	mean 1.7 vs 6.6 ($P < .001$)	0
Hanaoka, 2012[26]	Prospective historical control	Triamcinolone injection 100 mg at day 0	ESD > 75% SCC	30/29	10% vs 66% ($P < .0001$)	0 vs 2 ($P < .0001$)	7% (submucosal tear, bleeding)
Takahashi, 2012[29]	Randomized controlled trial	Triamcinolone injection 10 mg/mL at day 0 (dosage was not written)	ESD > 75% SCC	16/16	62.5% vs 87.5% ($P = .22$)	mean 6.1 vs 12.5 ($P = .038$)	0.5% vs 1.0% (perforation due to EBD)
Yamaguchi, 2011[31]	Retrospective historical control	Oral prednisolone 30 mg/day tapered gradually for 8 wk	ESD 100% SCC	19/22	5.3% vs 31.8% ($P = .03$)	mean 1.7 vs 15.6 ($P < .001$)	0%
Isomoto, 2011[28]	Retrospective historical control	Oral prednisolone 30 mg/day tapered gradually for 8 wk	ESD 100% SCC	4/3	50% vs 100%	mean 3.3 vs 32.7 ($P < .05$)	0%
Sato, 2013[43]	Retrospective historical control	Oral prednisolone 30 mg/day tapered gradually for 8 wk	ESD 100% SCC and adeno	10/13 SCC 22/adeno 1	100% vs 100%	mean 13.8 vs 33.5 ($P = < .001$)	0%
Kadota, 2015[52]	Retrospective historical control	a) Triamcinolone injection 50 mg at day 0 or b) Triamcinolone injection followed by oral prednisolone 30 mg/day tapered gradually for 8 wk	ESD > 75% SCC	53/29/33 (a/b/control)	43% vs 41% vs 67% ($P < .05$, a vs control)	12.5/6/5.5 ($P < .05$)	3.8% vs. 0% vs 0% (perforation)
Mori, 2013[53]	Prospective	a) Triamcinolone injection 62-88 mg at day 0 + EBD or b) Triamcinolone gel application 100 mg at day 5, 8, 12, and 15 + EBD	ESD >75% SCC	21/29 (a/b)	81% vs 81% (at post-ESD day 60)		0%
Bahin, 2016[50]	Prospective historical control	Budesonide respules mixed with sucralose two .5 mg/2 mL twice a day for 6 wk	EMR and ESD HGD/adeno	29/75	13.8% vs 37.3% ($P = .03$)	1 vs 2 ($P = .01$)	0%

EBD, Endoscopic balloon dilation; *ESD*, endoscopic submucosal dissection; *SCC*, squamous cell carcinoma; *adeno*, adenocarcinoma; *HGD*, high-grade dysplasia.

endoscopic resection. Further investigations are warranted, including the prevention of migration.

Steroid therapy

Glucocorticoids can inhibit inflammation and reduce the formation of fibrous connective tissue. Nonaka et al[35] analyzed the time course of the healing process of esophageal mucosal defects resulting in stricture formation and its modification by local steroid injection using an animal model. This experimental study showed that esophageal stricture formation after local steroid injection was not evident, with limited appearance of the spindle-shaped myofibroblasts. After steroid injection, haphazardly arranged smooth muscle actin–positive stromal cells were noted in the granulation tissue of the ulcer site, likely explaining the reduced rates of stricture formation.

Local injection around the mucosal defect and oral therapy with steroids have been reported to prevent esophageal strictures after extensive esophageal ESD[26-29,31,43,50-53]
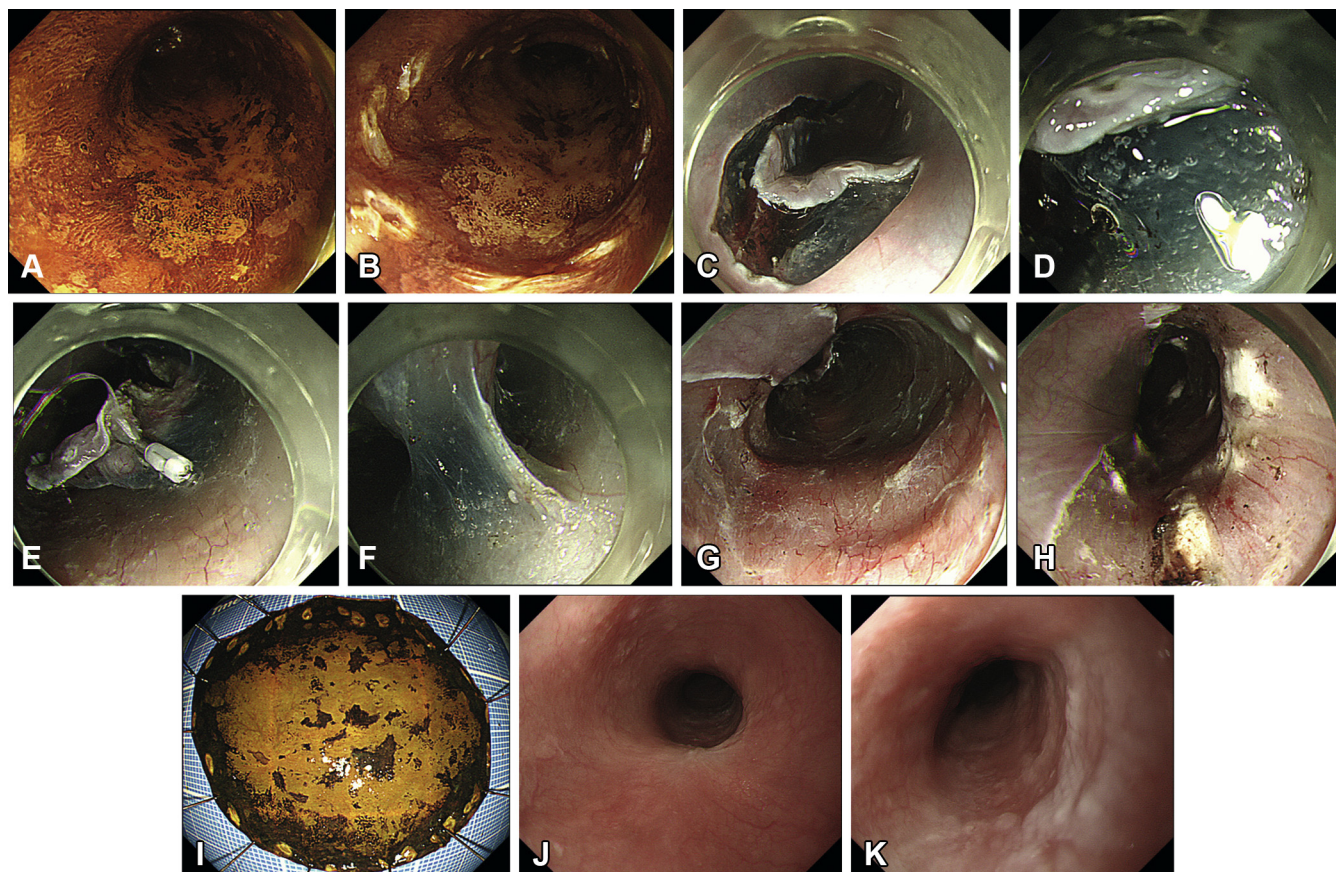
Figure 3. Endoscopic submucosal dissection (ESD) of widespread esophageal cancer followed by local triamcinolone injection. **A,** A female patient in her 70s had a widespread esophageal lesion half luminal circumference. **B,** Markings were put around the lesion before ESD. **C,** Mucosal incision of the left side. **D,** Submucosal dissection by IT knife nano device. **E,** Submucosal dissection with clip line traction. **F,** Submucosal dissection was performed with good retraction. **G,** ESD was performed and achieved en-bloc resection. Post-ESD mucosal defect was greater than three-fourths of the luminal circumference. **H,** A total of 100 mg triamcinolone was injected into the base of the mucosal defect. **I,** The resected specimen histologically revealed squamous cell carcinoma 42 mm in size, which was confined to lamina propria mucosa without lymphovascular invasion. **J** and **K,** Eight weeks after ESD. She remained asymptomatic, and a standard endoscope could traverse the scar. No endoscopic balloon dilation was required.

(Table 1). Both approaches appear to be effective and cheaper than repeated prophylactic EBD and hence are used and considered acceptable as the current standard preventive method for esophageal strictures after esophageal resection (Fig. 3).

Some comparative studies have reported that local injection of triamcinolone at the base of the mucosal defect significantly reduced the proportion of patients developing esophageal stricture. Hashimoto et al[27] injected triamcinolone in aliquots of .2 mL (2 mg) into the cautery ulcer base 1 cm apart in a semi-circumferential fashion. Sessions were performed at 3, 7, and 10 days after ESD, and post-ESD esophageal strictures occurred significantly less frequently in the study group compared with a control group (19% vs 75%, $P < .001$). The number of required EBDs was also lower in the study group (mean, 1.7; range, 0-15) than in the control group (mean, 6.6; range, 0-20).[27] Similarly, Hanaoka et al[26] prospectively evaluated the efficacy of single sessions of intralesional triamcinolone injection

into the residual submucosal tissue of the ulcer bed in .5- to 1.0-mL increments at the ulcer base. This study also showed that the study group had a significantly lower stricture rate (10% vs 66%, $P < .0001$) and a lower number of EBD sessions needed for stricture resolution (median, 0 [range, 0–2] vs 2 [range, 0–15], $P < .0001$). Of note, both studies excluded patients who underwent complete circumferential esophageal ESD because they are likely to develop extremely severe strictures. In terms of optimal intervals of steroid injection, Wakahara et al[51] performed a randomized controlled trial comparing patients receiving weekly or biweekly intralesional triamcinolone injections. This study concluded that biweekly steroid injection of triamcinolone reduced treatment duration because the median duration of treatment was 37.0 days in the weekly group and 34.2 days in the biweekly group, although the durations were not significantly different between the 2 groups ($P = .059$). Particularly, there was a significant difference in the median duration of

treatment between the weekly and biweekly groups (42.5 days vs 29.0 days, $P = .013$) in those with mucosal defects larger than 50 mm.

Yamaguchi et al[31] also reported that oral administration of prednisolone could be effective in preventing esophageal stricture after ESD. They administered oral prednisolone at 30 mg/day on the third day post-ESD, tapered to 5 mg/day every week for 8 weeks, and then discontinued 8 weeks later. This study selected 41 patients who underwent complete circular or semicircular ESD for esophageal squamous cell carcinoma involving more than three-fourths of the lumen. Post-ESD esophageal stricture was observed significantly more frequently in the preemptive EBD group (31.8%) than in the oral prednisolone group (5.3%) ($P < .05$). The average number of EBD sessions required was 15.6 in the preemptive EBD group and 1.7 in the oral prednisolone group ($P < .001$). In addition, several other publications demonstrated that oral corticosteroids prevented esophageal stricture after esophageal ESD.[28-29,43,50,52] Among these studies, Kadota et al[52] concluded that a significant higher stricture rate (84%) was found in complete circumference defect cases regardless of prophylactic treatment compared with those in semi-circumferential. Sato et al[43] focused on only complete circumferential ESD. This study also showed that oral steroids plus EBD patients required significantly fewer EBD sessions (13.8 vs 33.5, $P < .001$) and a shorter resolution period (4.8 vs 14.2 months, $P < .005$) compared with the EBD alone group. However, it should be noted that all patients developed post-ESD stricture, and the endpoint was extended until the patients became stricture-free. Given the results of these studies, esophageal ESD involving complete luminal of the circumference followed by oral steroid therapy to prevent stricture may be clinically feasible. However, informed consent should be obtained explaining these risks, and other treatment options, such as chemoradiation, might also be considered because multiple endoscopic dilations are likely necessary even with prophylactic steroids.

The adverse effects of endoscopic steroid injection are localized and include delayed wound healing and a higher risk of perforation because of the injection needle itself (immediate) or ulceration caused by the injection (delayed).[54] Oral administration is an easier method, but the adverse events are systemic and include delayed wound healing, immune suppression, diabetes, peptic ulceration, and psychiatric disturbances. Ishida et al[55] reported a case of severe disseminated nocardiosis during oral steroid therapy for the prevention of esophageal stricture after ESD.

Wang et al conducted a meta-analysis to compare the efficacy of steroids to prevent postoperative esophageal stricture and concluded that local injection was superior to oral administration in EBD reduction. However, they reported there were various methods and doses of steroid administration.[56] Among the studies, a single session of local triamcinolone injection reported by Hanaoka et al[26]

has been commonly used and is considered acceptable as the current standard of care to prevent post-ESD esophageal strictures in Japan, because this method allows us to complete the procedure immediately after the ESD, avoid systemic adverse events, and reduce cost compared with oral prednisolone. A multicenter prospective randomized control trial (JCOG1217) is ongoing to confirm the superiority of prophylactic oral steroid administration regimen (Yamaguchi's regimen) after ESD in terms of stricture-free survival compared with endoscopic local steroid injection (Hanaoka's regimen) for patients with superficial esophageal cancer.[57]

Injection of other compounds

Botulinum toxin type A (BTX-A) has been shown to suppress collagen deposition and fibrous connective tissue formation in addition to reducing muscle contractions. It has been postulated to limit the extent of inflammatory injury and tensile forces important in the process of scar formation. Several studies have suggested the usefulness of intralesional BTX-A injections for the treatment of keloids and facial scars.[58-60] Wen et al[61] applied a topical injection of BTX-A to prevent esophageal stricture after ESD and conducted a randomized control trial in 67 patients with superficial esophageal squamous cell carcinomas. They included patients with mucosal defects that greater than one half of the circumference of the esophagus after ESD. In this study, a total of 100 units of BTX-A was diluted with 5 mL saline solution (20 units/mL). The BTX-A solution was injected in 5-mL increments into 10 separate points equally spaced along the circumference of the defect. Post-ESD strictures occurred less frequently in the BTX-A group (per-protocol analysis, 6.1%; intention to treat analysis, 11.4%) than in control group (per-protocol analysis, 32.4%; intention to treat analysis, 37.8%) ($P < .05$), and the number of required bougie dilations was significantly lower in BTX-A group (mean, 1.5; range, 0-2) than in control group (mean, 2.8; range, 0-5) ($P < .05$). No patients experienced severe adverse events. So far, only 1 small study demonstrated the favorable outcomes of BTX-A. Further investigation is required to compare the efficacy of BTX-A with other treatments.

Oral administration of other compounds

In addition to oral prednisolone, oral agent tranilast (N-[3, 4-dimethoxycinnamoyl] anthranilic acid) was reported to inhibit the release of chemical mediators from inflammatory cells and fibroblasts or to directly suppress collagen synthesis.[62] It has been used clinically not only as an antiallergic agent, but also as an agent for treating hypertrophic keloids. Uno et al[21] conducted a pilot study to evaluate the efficacy of oral agent tranilast to prevent post-ESD stricture of the esophagus. This study evaluated 31 consecutive patients who underwent ESD of superficial esophageal squamous cell carcinoma involving greater than three-fourths the luminal circumference. Patients
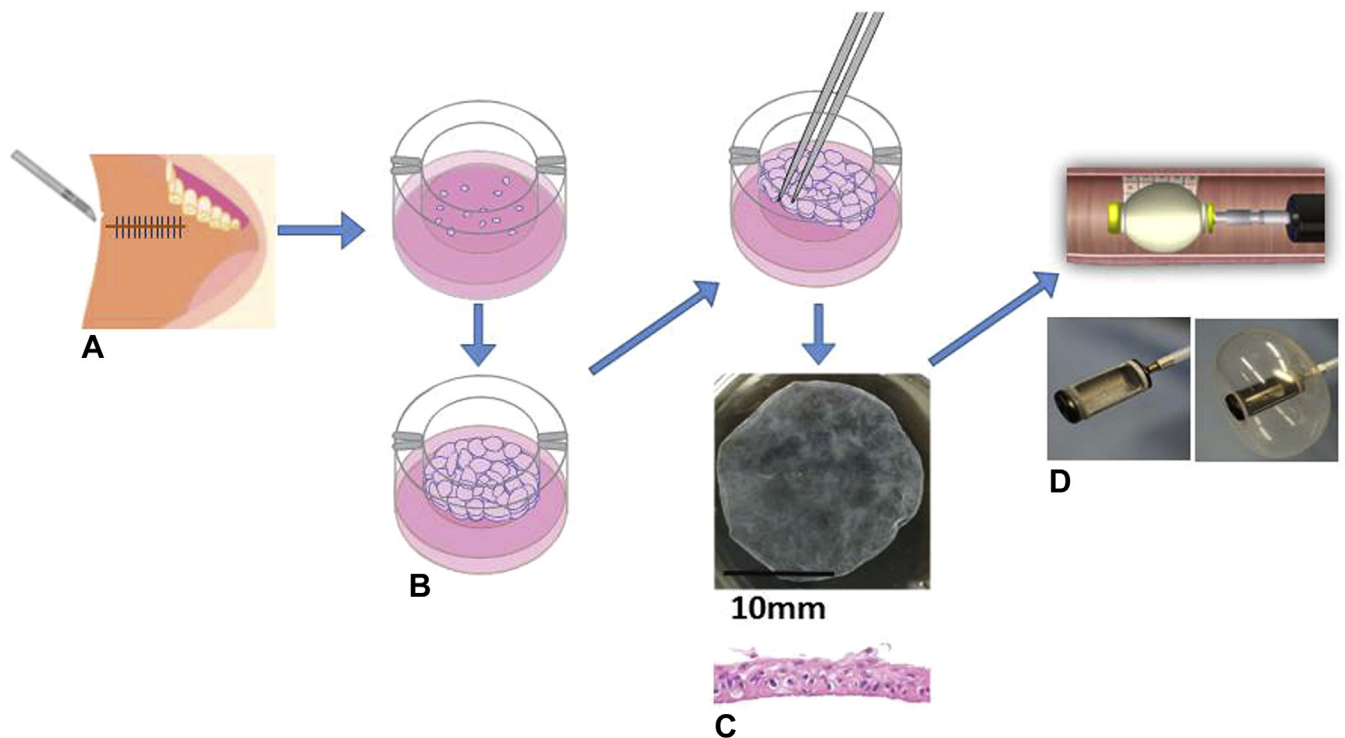
Figure 4. Epithelial cell sheet product and transplantation. **A,** Biopsy specimen of oral mucosal tissue. **B,** Seeding of isolated epithelial cells on temperature-responsive culture inserts and culture for 16 days at 37°C. **C,** Harvesting of autologous oral mucosal epithelial cell sheets by reducing temperature to 20°C. **D,** Endoscopic cell sheet transplantation using a dedicated delivery device. A cell sheet was loaded on a balloon and stored inside of the device by balloon deflation for easy delivery. Then the cell sheet could be expanded and attached to the ulcer site for transplantation by balloon inflation.

were divided into scheduled EBD with or without tranilast 300 mg/day divided in 3 doses after meals for 8 weeks. Post-ESD strictures developed in 5 of 15 patients (33.3%) in the tranilast group and in 11 of 16 patients (68.8%) in the control group (P < .05). No adverse events were observed in this study. It is possible that the adverse effects of tranilast would be fewer than that of steroids in long-term use. Further prospective studies are warranted to compare the preventative effect between oral tranilast and prednisolone and evaluate the efficacy of the combination with other methods.

Tissue-shielding methods

Polyglycolic acid (PGA; Neoveil; Gunze Co, Kyoto, Japan) is a biodegradable suture stiffener. It has been applied to cover wounds in humans in combination with fibrin glue (Bolheal; Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan). Some studies have shown that PGA sheets with fibrin glue, which was used to ensure adhesion of the sheets to the mucosal defect, could prevent scarring and contraction after head and neck surgery.[63-65] This method was also studied to prevent delayed bleeding and close perforations after endoscopic resection of duodenal and colorectal lesions[66,67] and has been applied to prevent esophageal stricture after ESD of large esophageal lesions.

Iizuka et al[68] demonstrated that PGA patches measuring 15 × 7 mm were endoscopically placed onto the mucosal defect immediately after ESD followed by a fibrin glue spray. Post-ESD strictures developed in only 7.7% of patients (1/13) with esophageal mucosal defects greater than half of the luminal circumference, without any adverse events. This study concluded that the combination of PGA sheets and fibrin glue might have the potential to prevent esophageal stricture after esophageal ESD. However, delivery of the PGA patches to the surface of the mucosal defect was time-consuming because multiple intubations had to be performed to place the patches over the entire ESD defect.[68] Sakaguchi et al[69] also conducted a pilot study to investigate the efficacy of PGA sheets and fibrin glue to prevent post-ESD stricture. The clip and pull method[70] was carried out in this study. The PGA sheet was grasped by biopsy forceps and wrapped around the endoscope. The endoscope was advanced to the site of the mucosal defect; the wrapped PGA sheet was released and then anchored using endoclips. Finally, the endoscope was pulled, leaving the PGA sheet in place. This study enrolled 8 consecutive patients who underwent esophageal ESD that left a mucosal defect of more than three-fourths of the luminal circumference. The authors showed this method was technically feasible, and post-ESD stricture occurred in 37.5% of the subjects
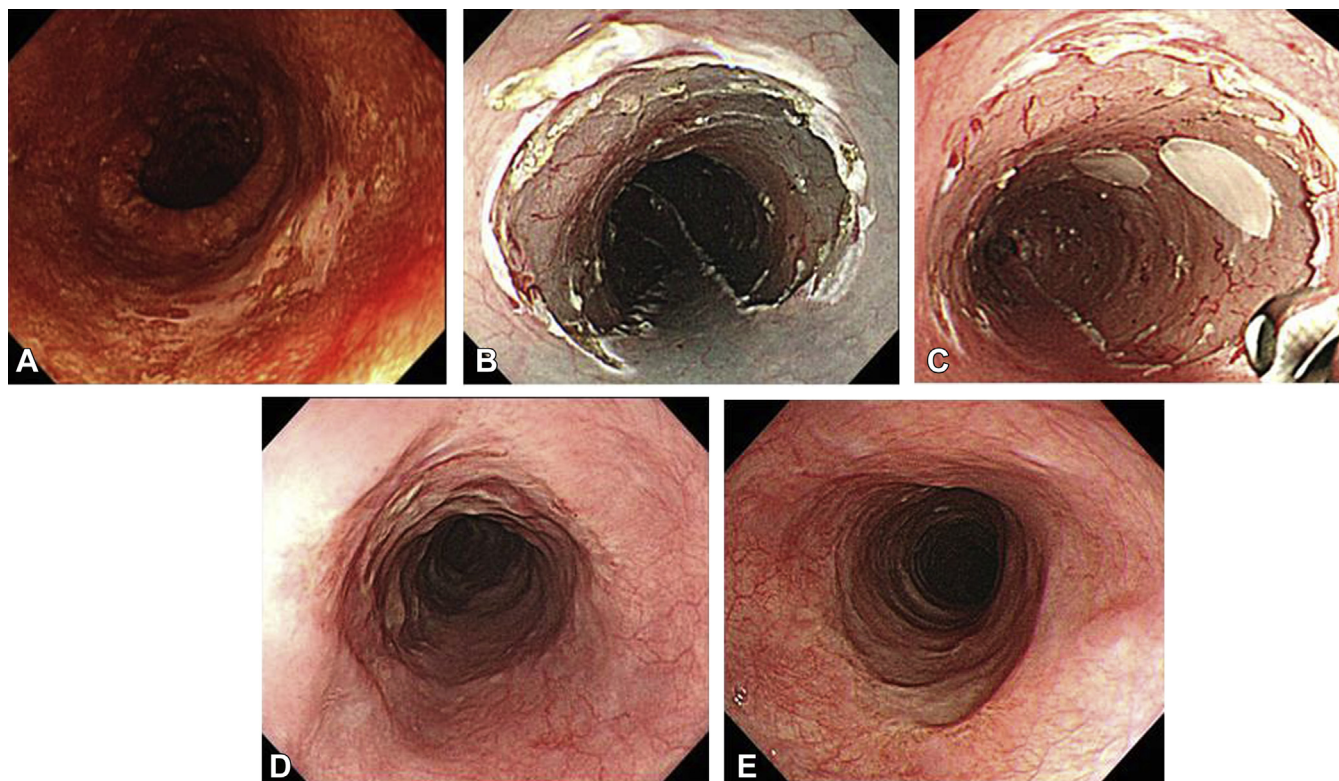
Figure 5. Endoscopic submucosal dissection (ESD) of widespread esophageal cancer followed by epithelial cell sheet transplantation. **A,** Superficial esophageal cancer located at the posterior wall of the esophagus. **B,** ESD was successfully done. Mucosal defect was seven-eighths the luminal circumference. **C,** Epithelial cell sheets were placed on the mucosal defect immediately after ESD. **D,** Two weeks after esophageal ESD. **E,** Four weeks after esophageal ESD. Stricture formation did not occur, and no dilation was required.

(3/8), and .8 ± 1.2 sessions of EBD were required in those who developed strictures after ESD.

Furthermore, the synergistic effect of combining triamcinolone injection with the PGA shielding method was also demonstrated by Sakaguchi et al.[71] They deployed PGA sheets, and fibrin glue was then instilled along the entire length of the sheet mentioned above in 15 patients who underwent endoscopic resection of over three-fourths of the circumference of the esophagus. Post-ESD esophageal stricture rate and median number of the required EBD were reported. Eleven patients (2 total circumferential, 9 semi-circumferential) were studied by this approach, after excluding 4 patients who required additional esophagostomy because of noncurative resection. Post-ESD stricture occurred in 18.2% (2/11), with a median of 0 sessions of EBD required.

Another study described the use another of tissue-shielding methods using carboxymethyl cellulose (CMC) sheets. Lua et al[72] conducted a pilot study that evaluated the efficacy of CMC sheets to prevent post-ESD esophageal stricture. This pilot study selected 7 patients who met 1 or more of the following criteria: cervical location (the area extending from the pharyngoesophageal junction to the suprasternal notch), a tumor size greater than one-half of the esophageal circumference (the size of mucosal defect greater than three-fourths of esophageal circumference),

or a longitudinal tumor diameter of more than 40 mm. After extensive esophageal ESD, the CMC sheet was pulled into an endocap with a biopsy forceps and applied on the mucosal defect. The incidence rate of postoperative stricture was 57% (4/7) and the mean number of EBD sessions was 2.8 ± 2.2 among patients who required EBD.

These tissue-shielding methods have the potential to prevent esophageal strictures after ESD without adverse events. However, the precise cellular mechanisms of both PGA and CMC sheets by which these happen remain unknown, although it has been speculated that the PGA sheet and fibrin glue protect the ESD site from stimulation by oral indigenous bacteria, decreasing the inflammatory response and potentially the ensuing cicatrization.[64] Indeed, some studies have reported that CMC sheets reduced scar formation and enhanced the healing process in other organs.[73]

Although promising, this approach has been tested in only small studies and needs further evaluation. Also, none of these studies used a control group to precisely understand the therapeutic benefit of the intervention. The tissue-shielding compounds do not appear to prevent all strictures, with strictures continuing to occur in some patients. Furthermore, both sheets can be easily disturbed by subsequent oral intake of food. Larger clinical studies and additional technical improvements

TABLE 2. Advantages and limitations of currently available methods of prevention of esophageal stricture after esophageal stricture

	Current availability	Advantage	Limitation
Stepwise resection	Good	Technically easy and safe	Local recurrence Difficulty in additional endoscopic resection
Preemptive balloon dilation	Good	Widely used	High failure rate Inferior to steroid treatment
Self-expandable metal stents	Good	Widely used	Limited efficacy
Local steroid injection	Good	Superior to balloon dilation alone Single session No concern of systemic adverse event	Potential risk of perforation
Oral steroid medication	Good	Superior to balloon dilation alone Noninvasive	Systemic adverse events Long administration period
Local botulinum toxin injection	Fair	Superior to balloon dilation alone Single session	Small number of literature
Oral tranilast	Good	No concern of systemic adverse event	Small number of literature
Tissue shielding method	Fair	Noninvasive No adverse event	Time-consuming Difficult application
Cell sheet transplantation	Poor	Noninvasive No adverse event	Time-consuming Extremely high medical cost

focused on ensuring adherence of these sheets to the ESD site are warranted to confirm the preventive effect of shielding methods on esophageal stricture formation.

Autologous cell sheet transplantation

Previously, many animal studies of esophageal tissue engineering have been conducted using isolated esophageal cells.[74-77] However, harvesting an adequate number of cells from biopsy specimens was challenging, leading to use of endoscopic resection to harvest sufficient cells. However, endoscopic resection is associated with risks of bleeding and perforation. Thus, Ohki et al[78] used oral mucosal epithelial cells as the cell source instead of esophageal epithelial cells, because both were squamous epithelium. They created an oral epithelial cell sheet and transplanted it endoscopically over an esophageal ESD defect in a canine model. The transplanted cell sheets could successfully adhere to and survive on the underlying muscle layers, accelerating wound healing and preventing esophageal stricture.[79] Despite its novelty, this tissue-engineering method can be challenging to apply clinically, given that this method requires 3T3 cells, derived from mice and fetal bovine serum to culture the cell sheets. Also, concerns have arisen regarding bovine spongiform encephalopathy.

In this context, new tissue-engineered cell sheets without xenogeneic materials were developed by Murakami et al.[80] They developed temperature-responsive culture inserts and demonstrated that tissue-engineered epithelial cell sheet grafts could be fabricated from the inserts and autologous serum, without the need for 3T3 cell feeder layers and fetal bovine serum. Thereafter, Ohki

et al[81] developed a procedure involving the endoscopic transplantation of cultured autologous oral mucosal epithelial cell sheets to the base of the esophageal endoscopic resection site. They described the methods as follows (Fig. 4). First, biopsy specimens were taken from the patient's buccal mucosa. Second, oral epithelial cells were isolated from the tissue by proteolytic enzyme treatment. Third, epithelial cells were then seeded onto temperature-responsive culture inserts, which have a unique multifunctional system varying by temperature.[82] Surfaces of the culture dishes were covalently linked with a temperature-responsive polymer and became hydrophobic at 37°C, which allowed for attachment of the cultured cells. The epithelial cells were cultured with autologous serum for 16 days at 37°C. After the cells became confluent, the temperature was reduced to 20°C, which caused the surfaces to become hydrophilic. The cell sheets (23 mm in diameter) then detached and were harvested as consecutive cells without the use of protein enzymes. Fourth, autologous oral mucosal epithelial cell sheets on a support membrane were transplanted with endoscopic forceps or a dedicated delivery device onto the mucosal defect of the esophagus through an esophageal EMR tube (Create Medic Co, Yokohama, Japan) immediately after ESD. Autologous cell sheets were successfully transplanted to mucosal defects using an endoscope successfully in 10 patients. Complete re-epithelialization occurred within a median time of 3 weeks. No patients developed dysphagia, stricture, or other adverse events after the procedure, except for 1 patient who underwent full circumferential ESD (Fig. 5).[81,83]

The advantages of using oral mucosal cells are that they are easy to harvest, the harvesting methods are minimally

invasive, and the methods of removal do not cause perforation. Although the process of cell sheet transplantation takes at least 10 minutes for each cell sheet, a novel device has been developed to reduce transplantation time.[84] Although at this time the cost of cell sheet production is expensive, these applications of regenerative medicine can offer innovative solutions to prevent post-ESD esophageal strictures in the future. In addition, cell sheet transplantation is not commercially and clinically available. It is still investigational and performed in only a few limited Japanese institutions. Additional studies need to be done to achieve widespread use of this method.

CONCLUSIONS

Although the evidence level was still insufficient, corticosteroid therapy, particularly local triamcinolone injection, is currently the most commonly applied strategy to prevent esophageal strictures after extensive endoscopic resection (Table 2). The preponderance of evidence is suggestive of a beneficial effect of steroids (administered by local injection or orally) in reducing either the incidence of strictures or the severity of resulting strictures (by reducing the number of dilations needed for stricture resolution). The results of a multicenter prospective randomized control trial (JCOG1217) that aims to compare the preventive efficacy of local triamcinolone injection and oral prednisolone medication will help to rigorously evaluate appropriate methods to reduce esophageal stricture formation and the number of required EBD. Other injection materials such as BTX-A may be potential candidates to prevent post-ESD strictures. Tissue-shielding methods with PGA sheets and fibrin glue and autologous cell sheet transplantation are novel strategies to prevent post-ESD stricture. Preliminary studies have demonstrated promising results without any adverse events; however, several issues, such as endoscopic delivery, cost-effectiveness, and widespread use, need to be resolved by larger prospective studies.

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