TOPIC HIGHLIGHT

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Prevention of esophageal strictures after endoscopic submucosal dissection

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Abstract

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have recently been accepted as less invasive methods for treating patients with early esophageal cancers such as squamous cell carcinoma and dysplasia of Barrett's esophagus. However, the large defects in the esophageal mucosa often cause severe esophageal strictures, which dramatically reduce the patient's quality of life. Although preventive endoscopic balloon dilatation can reduce dysphagia and the frequency of dilatation, other approaches are necessary to prevent esophageal strictures after ESD. This review describes several strategies for preventing esophageal strictures after ESD, with a particular focus on anti-inflammatory and tissue engineering approaches. The local injection of triamcinolone acetonide and other systemic steroid therapies are frequently used to prevent esophageal strictures after ESD. Tissue engineering approaches for preventing esophageal strictures have recently been applied in basic research studies. Scaffolds with temporary stents have been applied in five cases, and this technique has been shown to be safe and is anticipated to prevent esophageal strictures. Fabricated autologous oral mucosal epithelial cell sheets to cover the defective mucosa similarly to how commercially available skin products fabricated from epidermal cells are used for skin defects or in

cases of intractable ulcers. Fabricated autologous oral-mucosal-epithelial cell sheets have already been shown to be safe.

Core tip: Esophageal strictures after extensive endoscopic submucosal dissection (ESD) reduce quality of life. Endoscopic local injections and the oral administration of steroids are safe and effective for preventing esophageal strictures. In addition, several tissue engineering therapies have been used in attempts to overcome severe esophageal strictures. Cell-based tissue engineering therapy with fabricated autologous oral mucosal epithelial cell sheets has been used to prevent esophageal strictures after ESD in nine patients. This therapy has been shown to be safe and may be widely used in the future.

INTRODUCTION

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are accepted as less invasive treatments for early esophageal cancers, including squamous cell carcinoma and dysplasia of Barrett's esophagus (BE)[1-17]. Additionally, radiofrequency ablation has been shown to be safe and effective for treating patients with dysplasia due to BE[18-24].

The occurrence of severe esophageal strictures after endoscopic treatments for large tumors remains an unsolved problem. However, the safety and efficacy of endoscopic treatments have been technically and oncologically established for a wide range of esophageal intramucosal neoplasms and BE. Risk factors for esophageal strictures after ESD include the cervical location, a tumor size greater than 3/4 of the esophageal circumference, and a longitudinal tumor diameter of more than 40 mm[9,25-27]. Furthermore, esophageal strictures after the treatment of BE are often observed at the resection site with at least 50% of the esophageal mucosal circumference[28].

Esophageal strictures cause dysphagia, and patients are required to receive repeated balloon dilatation procedures or temporary stents. These esophageal strictures decrease the patient's quality of life, although the endoscopic treatment itself is less invasive than surgical

therapy. Moreover, the use of endoscopic balloon dilatation (EBD) to treat esophageal strictures carries the risk of perforation. Takahashi *et al*[29] reported that esophageal perforations were observed in 7 of 76 patients who received EBD for the treatment of esophageal strictures. The occurrence of strictures after esophageal ESD is more common in EBD performed after esophageal strictures (92%) than in multiple sessions of EBD performed weekly before esophageal strictures (59%)[30]. Furthermore, the duration of EBD after esophageal stricture is generally shorter in patients who undergo multiple sessions of EBD before developing esophageal strictures (29 d) than in those who undergo EBD after esophageal strictures form (78 d). Although multiple sessions of EBD before esophageal strictures can prevent esophageal strictures after ESD, such frequent dilatation treatments are problematic because of their high invasiveness and cost. Therefore, less invasive approaches are desired.

Various approaches have been used to prevent esophageal strictures after ESD and can be generally categorized as either anti-inflammatory drugs or tissue engineering technologies.

ANTI-INFLAMMATORY APPROACHES

Anti-inflammatory approaches for preventing esophageal strictures after ESD are based on the concept that subsequent strictures may be suppressed by inhibiting the infiltration of inflammatory cells, the hyperplasia of granulation, and the fibrosis of the remaining submucosal layer at the ulcer site. Anti-inflammatory treatments using steroids have recently been demonstrated to prevent esophageal strictures after ESD (Table 1). Basic research has also been conducted on several potential drugs that selectively inhibit fibrotic formation.

Endoscopic intralesional injections of steroids

Endoscopic intralesional injections of steroids are applied based on the concept that inflammation and fibrosis after esophageal ESD are inhibited by the direct administration of steroids to the ulcer site. The initial reports regarding steroid therapy demonstrated that intralesional injections of triamcinolone acetonide after the dilatation of benign esophageal strictures reduces the frequency of esophageal strictures in the endoscopic field[31,32]. These results are similar to findings for the injection of triamcinolone acetonide to treat keloid scars[31,33,34]. Subsequently, triamcinolone acetonide has been used to prevent esophageal strictures after ESD (Table 2). Hashimoto *et al*[35] reported that the local injection of triamcinolone acetonide into the ulcer site prevents esophageal strictures after ESD. Twenty-one patients were treated with local injections of triamcinolone acetonide at 3, 7, and 10 d after ESD. The total dose of triamcinolone acetonide was 18 to 62 mg in each injection session. The stricture rate in the patients who were given the local injection (19%, 4/21) was lower than in the control patients (75%, 15/20) ($P = 0.03$). Furthermore, the frequencies of dilatation in the patients

Table 1 Anti-inflammatory drugs for the prevention of esophageal strictures after endoscopic submucosal dissection

	Action	Administration	Advantages	Disadvantages and limitations
Clinical study				
Corticosteroids	Steroidal	Oral intake	Strongly inhibits the infiltration of inflammatory cells, the hyperplasia associated with granulation, and the fibrosis of the remaining submucosal layer	General side effects (severe infection, peptic ulcer, hyperglycemia, psychiatric symptoms, and osteoporosis) Delayed wound healing
Triamcinolone acetonide	Steroidal	Local injection	Inhibits the infiltration of inflammatory cells, the hyperplasia associated with granulation, and the fibrosis of the remaining submucosal layer	Risk of ulcer formation due to accidental injection into the muscularis Delayed wound healing
Pre-clinical study				
MMC	Inhibition of DNA synthesis	Local injection	Inhibits the proliferation and activation of fibroblasts	An effect has not been shown for the prevention of esophageal strictures, although MMC improves recurrent dysphagia or restenosis after the dilatation of esophageal strictures The risks of perforation and secondary malignancy
N-acetylcysteine	Antioxidant molecule	Oral intake	Antifibrotic effect without the inhibition of wound healing	Insufficient effect in an animal model of severe esophageal stricture

MMC: Mitomycin C.

Table 2 Intraregional triamcinolone injection for preventing esophageal strictures after endoscopic submucosal dissection

Ref.	Resection size		The methodology of triamcinolone injection					Treatment outcomes		
	Circumference[1]	Length (mm)	Injection needle	Concentration (mg/mL)	Single dose (mL)	Number of punctures (/session)	Total amounts (mg)	Sessions	The rate of strictures	The number of EBD	Observation periods
Hashimoto *et al*[35]	> 3/4	54 (28-60)	25 G, 4 mm	10	0.2	9-31	18-62	Three times[2]	19% (4/21)	1.7 (0-15)	1 yr
Hanaoka *et al*[36]	> 3/4	58 ± 11	25 G	5	0.5-1	20-40	100	Single[3]	6.60% (3/30)	0 (0-2)	2 mo

[1]The cases of whole circumferential endoscopic submucosal dissection (ESD) are excluded; [2]Three sessions of locoregional triamcinolone injection are performed at 3, 7, 10 d after ESD; [3]Only single session of locoregional triamcinolone injection is performed immediately after ESD. G: Gaze; EBD: Endoscopic balloon dilatation.

who were given a local injection (mean 1.7, range 0-15) were significantly lower than the frequency of control patients (mean 6.6, range 0-20) (*P* > 0.001). Hanaoka *et al*[36] also reported that local injection of triamcinolone prevented esophageal strictures after ESD using a single injection of triamcinolone acetonide immediately after ESD. The total dose of triamcinolone acetonide was 100 mg[36]. In Nagasaki University Hospital, 3/4-circumferential ESD cases are generally treated with this local injection therapy. Fifty mg of triamcinolone acetonide is endoscopically injected in submucosal layer 1 or 2 times for 3 wk and generally results in a satisfactory outcome. It is recommended that triamcinolone acetonide doses of approximately 18 to 100 mg are injected several times into the ulcer site in the early phase after ESD to prevent esophageal strictures. However, triamcinolone injection might be insufficient to prevent esophageal strictures for large mucosal defects because esophageal strictures can develop after the combinational treatments of dilatation and triamcinolone injection for benign esophageal strictures[31,32,37]. The patients with circumferential ESD were excluded in the clinical studies of local injections of triamcinolone[35,36]. There is also a high risk of ulcer

formation due to endoscopic local injection when the muscularis is missed during the injection[38]. Additionally, insufficient fibrosis causes the ulcer site of the esophageal wall to be fragile and leads to perforation after balloon dilatation. Isomoto *et al*[27] developed a special injection needle for injecting ulcer sites after ESD. The needle, which is 25 gauge with a length of 1.8 mm, is finer and shorter than conventional injection needles, which are usually 23 or 25 gauge in diameter and 4 mm in length, thereby avoiding deep injections into the muscularis.

Systemic steroid therapy for preventing esophageal strictures after ESD

The efficacy of systemic steroid therapy for preventing esophageal strictures after ESD has been confirmed by Yamaguchi *et al*[39]. In their study, 22 patients who underwent multiple sessions of EBD before esophageal strictures were compared with 19 patients who underwent systemic steroid therapy. The stricture rate in the systemic steroid therapy group (5.3%, 1/19) was significantly lower than that in the multiple sessions of EBD before esophageal strictures group (31.8%, 7/22) (*P* < 0.0001). Furthermore, the frequency of dilatation in the systemic
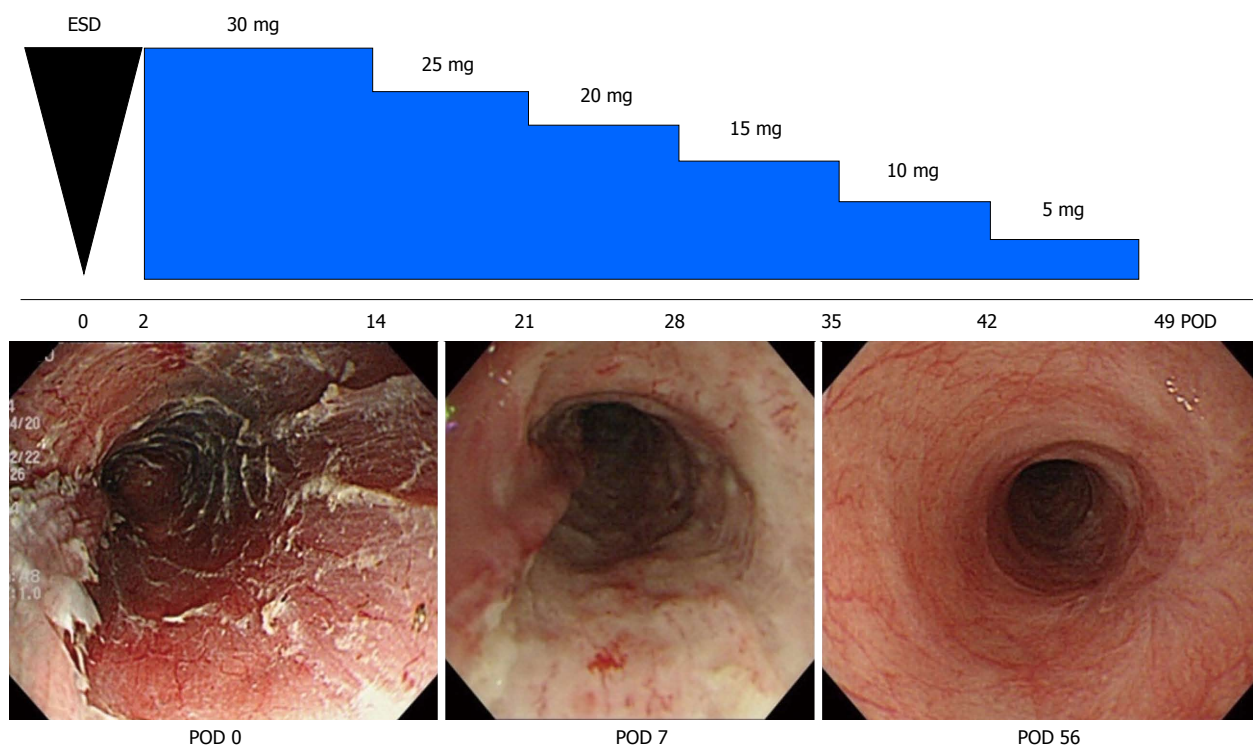
Figure 1 Systemic steroid therapy for the prevention of esophageal strictures after endoscopic submucosal dissection[83]. A 72-year-old man underwent esophageal endoscopic submucosal dissection (ESD) for early squamous cell carcinoma. Systemic steroid therapy with prednisolone was started at postoperative day 2. At postoperative day 51 following esophageal ESD, the ulcer surface was covered with a regenerative mucosa, and no esophageal stricture was present. Figures are reproduced courtesy of Shindan to Chiryo Sha, Inc. POD: Postoperative day.

steroid therapy group (mean 1.7, range 0-7) was significantly lower than in the multiple sessions of EBD before esophageal strictures group (mean 15.6, range 0-48) (*P* < 0.0001). Sato *et al*[40] reported that systemic steroid therapy with EBD is also more effective than EBD alone in preventing esophageal strictures after circumferential ESD. In Nagasaki University Hospital, patients who have at least two of the following risk factors are treated with systemic steroid therapy after esophageal ESD: more than 3/4-circumferential ESD, a longitudinal tumor diameter greater than 40 mm, and cervical location. Beginning 2 d after ESD, 0.5 mg/kg prednisolone per day was administered orally for 2 wk. The dose of prednisolone was continuously reduced until the regenerative mucosa covered the artificial ulcer site of the esophageal ESD (Figure 1). However, complete healing of the esophageal mucosa generally requires 8-16 wk because steroids inhibit the activation of fibroblasts and inflammatory cells and reduce the proliferation and migration of epithelial cells. High doses of prednisolone have been associated with the possibility of developing adverse effects such as severe infections, peptic ulcers, hyperglycemia, psychiatric symptoms, and osteoporosis. However, no adverse events occurred in the clinical studies of systemic steroid therapy for preventing esophageal strictures after ESD[27,39]. Furthermore, the perforation risk of balloon dilatation after steroid therapy by either local injection or systemic administration may be higher than in multiple sessions of EBD treatment[38]. Although systemic administration of steroids prevents esophageal strictures after extensive ESD, systemic administration of steroids might not prevent esophageal strictures after a very long segmental circumferential ESD. This occurs because systemic steroid therapy does not prevent esophageal strictures after major injuries of the esophagus involving a long length of circumferential mucosal defect[41,42].

Potential drugs to target fibrotic formation

There are several studies regarding specifically preventing excessive fibrotic formation to avoid the various adverse effects of steroid therapies. The locoregional injection of mitomycin C into the esophageal stricture after ESD was shown to improve recurrent dysphagia or restenosis without serious complications in 5 patients[43]. Mitomycin C is also effective for the treatment of refractory esophageal strictures which include caustic, surgical, and peptic strictures[44]. Additionally, because mitomycin C injection has an anti-proliferative effect on fibroblasts it also prevents refractory esophageal strictures. Although the injection of mitomycin C is suggested for preventing esophageal strictures after ESD, it has poor reproducibility in an animal model[45]. Mitomycin C might cause several local adverse events such as delayed mucosal healing, ulcer formation, and perforation. In long-term studies, secondary malignancy should be examined because mitomycin induces DNA damage[46,47].

N-acetylcysteine is an antioxidant compound with antifibrotic effects that is also expected to prevent esophageal strictures. However, its efficacy is minimal in animal models of severe esophageal strictures after ESD[48].

N-acetylcysteine has been clearly shown to promote corneal wound healing better than steroid therapy. Thus, combination therapy involving N-acetylcysteine and other treatments may potentially be effective[49].

TISSUE ENGINEERING APPROACHES

Tissue engineering approaches for preventing esophageal strictures after ESD are based on the concept that transplanted materials and tissues can repair and replace damaged tissues, maintain the physiological functions of these tissues, and enhance mucosal healing. This issue is especially important because mucosal defects cause severe inflammation at artificial ulcer sites. Tissue engineering approaches for preventing esophageal strictures after ESD are divided into two groups: scaffold-based therapy and cell-based therapy.

Scaffold-based therapies

Temporary scaffolds made from biodegradable materials can support tissue and protect esophageal strictures. Saito *et al*[50] reported that biodegradable stents composed of poly-L-lactic acid prevented esophageal strictures after ESD in 2 patients. Additionally, Nieponice and Badylak reported that an extracellular matrix (ECM) biologic scaffold composed of porcine-derived small intestinal submucosa, together with a temporary metallic stent, is safe and efficacious for the prevention of esophageal strictures after endoscopic resection in animal models[51-53]. Biological scaffolds have been safely used to treat five high-grade BE patients undergoing endoscopic resection[54]. Long length (8 to 13 cm) circumferential resections were performed in these patients. The esophageal strictures after endoscopic resection and were improved by only a few sessions (0 to 9) of endoscopic dilatation even though the temporary stent support prevented strictures. Surprisingly, the small perforation site healed in 18 d by covering the perforation with a biological scaffold and stent. The scaffold provides an ECM, supports strictures, and promotes cell migration. However, it may be insufficient to cover an extensive mucosal defect after esophageal ESD. The acellular scaffold of the esophageal mucosa includes key proteins required for producing a basal membrane. Additionally, the acellular scaffold of the esophageal mucosa provides a suitable environment that facilitates cell adhesion and proliferation[55]. Consequently, the risk of local recurrence after scaffold transplantation may be higher than at normal ulcer sites because the scaffold itself is also a good environment for the engraftment of unwelcome malignant cells. The transplantation of biomaterials is also associated with the risk of developing a local infection, which affects the microenvironment of wound healing. This issue is especially important for esophageal mucosal healing because both the esophageal lumen and the oral cavity are constantly exposed to microorganisms. Scaffold-based therapies currently lack sufficient clinical evidence that prevent their use for esophageal strictures and have potential risks of adverse events such as a local recurrence and infection. In the future, the development of novel materials and the advancement of biological science will help solve these problems.

Cell-based therapies

Cell-based therapies are expected to have trophic effects on the host as the transplanted cells release cytokines and growth factors and interact with other host cells. The direct injection of primary cells into the host organ has two major disadvantages, which are low viability and quick diffusion from the host sites after transplantation. Transplanted cells are difficult to engraft at the target site. As a result, there have been several in vitro attempts to engineer tissues with the ability to effectively engraft cells at the target site.

Technology of autologous oral mucosal epithelial cell sheets

In our laboratory, epithelial cell sheets of oral mucosa without any scaffold are fabricated on temperature-responsive culture inserts that are grafted with poly-N-isopropylacrylamide (PIPPAm)[56]. At 37 ℃, PIPPAm becomes hydrophobic, but below its lower critical solution temperature of 32 ℃ it is hydrophilic[57,58]. Cells attach and proliferate on the hydrophobic surface of the cell culture insert at 37 ℃. However, due to the remarkable character of PIPPAm, the cells can detach themselves from the surface when the temperature is below 32 ℃ and PIPPAm becomes hydrophilic. This behavior enables the cell sheets to be harvested without the use of enzymes and allows the cells to preserve their cell-membrane proteins and cell-to-cell junctions. Subsequently, the fabricated epithelial cell sheets can be grafted to the host organ without any adhesive materials because the ECM is deposited on the basal layer of the epithelial cell sheets and the basal side can attach to the artificial ulcer site[59]. Furthermore, the transplantation of autologous oral epithelial cell sheets to an esophageal mucosal defect has been shown to promote re-epithelization of the esophageal mucosa in a canine model[60].

Preparing autologous oral mucosal epithelial cell sheets for clinical application

For clinical applications, oral mucosal epithelial cell sheets must be fabricated in a cell processing center (CPC) (Figure 2)[61,62]. CPCs have separate clean rooms that meet good manufacturing practice guidelines, and various other parameters (such as aerosol, temperature, and humidity) are monitored to validate the clean environment of the CPC. To prevent possible human errors and careless mistakes during the fabrication of oral mucosal epithelial cell sheets, standard operation procedures (SOPs) for culture methods are documented and a second person always checks the document while the first operator performs the procedure in the CPC. In addition, to ensure safety and avoid possible immune reactions and unknown infections animal-derived materials are eliminated as much as
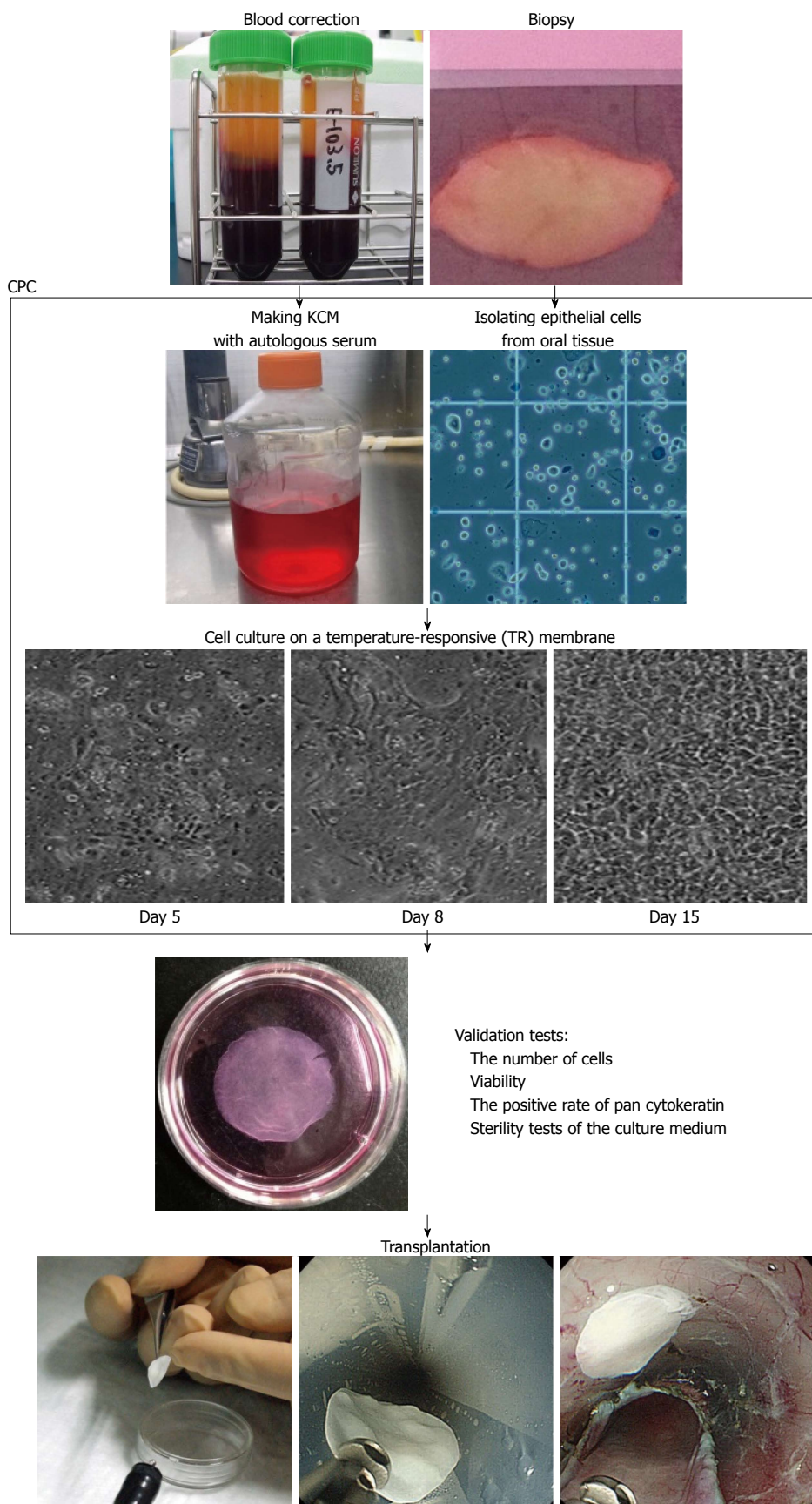
Figure 2 Protocol for the fabrication of autologous oral epithelial cell sheets for clinical application. Autologous oral epithelial cell sheets are fabricated using autologous serum and oral mucosa in the cell processing center (CPC). Isolated oral epithelial cells are cultured on a temperature-responsive membrane for 16 d. The fabricated oral epithelial cell sheets are then transplanted endoscopically after passing several validation tests. KCM: Keratinocyte culture medium.
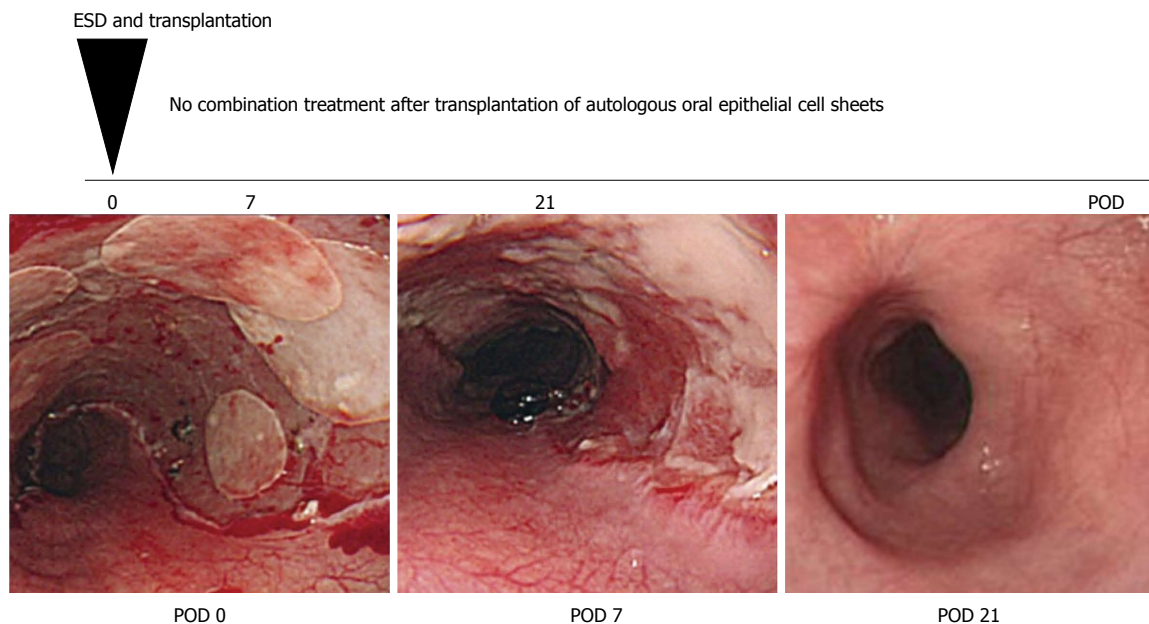
Figure 3 Transplantation of autologous oral epithelial cell sheets for the prevention of esophageal strictures after endoscopic submucosal dissection[65]. A 55-year-old man underwent esophageal endoscopic submucosal dissection (ESD) for early squamous cell carcinoma. Seven fabricated autologous oral epithelial cell sheets were transplanted immediately after esophageal ESD. At postoperative day 21, the ulcer surface after esophageal ESD was covered with a regenerative mucosa, and no esophageal stricture was present. Figures are reproduced courtesy of Elsevier. POD: Postoperative day.

possible. In our clinical study, autologous serum is used instead of fetal bovine serum, which is commonly used for culturing cells[61]. 3T3 feeder cells are fibroblast cells obtained from mice. These cells are classified as a xenogeneic material by the Food and Drug Administration in the United States and have never been used for culture in our system. However, these feeder cells are known to promote the proliferation of various epithelial cells[63]. The fabricated oral mucosal epithelial cell sheets are required to pass all validation tests including a sterility test, a harvesting test, and a purity test prior to transplantation[64]. However, no tests for cell proliferation, migration, and attachment are included. In the future, noninvasive measurements of these test parameters will be required prior to clinical application.

Transplanting autologous oral epithelial mucosal cell sheets into artificial ulcer sites after ESD

Before transplantation of the autologous mucosal epithelial cell sheet into the artificial ulcer site after esophageal ESD, an esophageal endoscopic mucosal resection (EEMR) tube (Create Medic, Tokyo, Japan) is inserted into the patient's esophagus. The endoscopic transplantation of the autologous oral mucosal epithelial cell sheet is immediately performed after esophageal ESD using a support membrane and endoscopic forceps. The transplanted autologous oral mucosal epithelial cell sheets adhere to the ulcer site within a few minutes without suturing or any adhesive materials because the cell sheets maintain adhesive proteins on their basal side and have cell-to-cell junctions. The fabricated autologous oral mucosal epithelial cell sheet is composed of a basal layer and an apical layer. The basal layer is gently attached to the

ulcer site and this procedure requires careful handling. The transplant can be disturbed by spasm of the muscularis and by the entry balloon of the EEMR tube used to maintain the intraluminal pressure of the esophagus. Therefore, a device that facilitates transplantation of the autologous mucosal epithelial cell sheets into the ulcer site after esophageal ESD is needed.

Clinical study using autologous oral mucosal epithelial cell sheets

The safety of transplanting autologous oral mucosal epithelial cell sheets into artificial ulcer sites has been demonstrated in a phase I study[65]. The transplantation of oral mucosal epithelial cell sheets prevented esophageal strictures after ESD in 8 of 9 cases. In the eight successful cases, there was no dysphagia and strictures after esophageal ESD and no additional treatments for complications were required. Only one cases required balloon dilatation of the esophageal stricture after ESD. Additionally, mucosal healing was rapidly completed within 3 to 5 wk. This observation suggests that autologous oral epithelial cell sheets promote epithelial healing and result in the satisfactory prevention of esophageal strictures after ESD (Figure 3). In the future, a large study must be performed to confirm that autologous oral mucosal epithelial cell sheets are an effective material for the prevention of esophageal strictures after ESD.

Future topics for standardizing treatments using epithelial cell sheets

Cell-based therapy using autologous oral mucosal epithelial cell sheets has several disadvantages compared with scaffold-based therapy and anti-inflammatory drug

therapy. First, a CPC is necessary to culture the oral epithelial cells. Thus, the operating cost is high and is currently estimated to be at least 20000 to 30000 USD per case. Thus, fabricating oral mucosal epithelial cell sheets in a CPC in every hospital will be technically and financially difficult. One alternative is ready-made oral mucosal epithelial cell sheets that can be transported in a suitable environment from a production site to the hospital where the transplantation will be performed. Second, the fabrication of autologous oral mucosal epithelial cell sheets requires the patient's own tissues and serum. Although autologous oral epithelial cell sheets have been successfully fabricated, it is difficult to maintain consistent fabrication quality and quantity because individual differences can affect cell proliferation and differentiation. Third, possible bacterial and fungal contamination during the culture of oral mucosal epithelial cell sheets is the most common factor leading to failure, which may be a disappointment to patients who have provided their own tissues. Fourth, multiple neoplasms in the oral and throat areas are sometimes observed in patients with esophageal cancer so harvesting tissues from the premalignant region in the oral mucosa must also be avoided because the transplantation of multipotent cancer cells may cause local recurrence[66,67]. Translational research studies aimed at improving these disadvantages are currently in progress in our laboratory.

Epidermal cells are expected to be suitable substitutes for oral mucosal epithelial cells. Epidermal cells have characteristics similar to esophageal and oral mucosal epithelial cells because these cells are classified as squamous cells. Furthermore, epidermal cells are frequently cultured for the production of cutaneous medical devices that are already used in clinics[68-72]. The risk of contamination with malignant cells is lower in the skin than in the oral mucosa, and the epidermis is composed of keratinocytes. Additionally, in a swine model, cell sheets made from autologous epidermal cells have been shown to prevent esophageal strictures after ESD as effectively as oral mucosal epithelial cell sheets[73].

The capability of fabricating cell sheets in serum-free medium is essential to reduce the variation between individual differences and to standardize cell culture procedures. Specifically, the addition of an IL-1 receptor antagonist has been found to be beneficial for fabricating cell sheets in serum-free medium[74].

Adipose-derived stem cells

Adipose-derived stem cells (ADSCs) are similar to bone marrow-derived stem cells. ADSCs have the following biological features: growth factor secretion, capacity to differentiate into multiple cell types, ability to suppress inflammatory cells, ability to promote angiogenesis and enhanced of wound healing[75-77]. Additionally, ADSCs can be obtained easily from adipose tissue. Cell therapies using ADSCs have been performed to repair bone defects, treat complex perianal fistulas in Crohn's disease, and alleviate severe steroid-resistant graft-*vs*-host disease[78-80].

Cell-based therapy using ADSCs is also expected to prevent esophageal strictures after ESD. The local injection of autologous ADSCs after esophageal EMR has also been found to prevent esophageal strictures in a canine model[81]. This result is insufficient evidence for concluding that ADSCs prevent esophageal strictures after ESD because no evaluations of the surface markers, multipotentiality, and proliferation of the injected cells have been performed.

Future prospects of treatments using tissue engineering for esophageal stricture therapy

Tissue engineering approaches have great potential for treating various damaged tissues and organs. Currently, treatments using tissue engineering must include safety and quality controls and require careful observations after transplantation. Esophageal tissue engineering will be developed and become available in the near future because transplanted engineered tissues can be noninvasively observed by endoscopy and because unexpected complications such as local infections, immunological responses, and tumorigenesis are easily managed.

The replacement of mucosal structures with a basal membrane after esophageal ESD may be a novel tissue engineering therapy for the prevention of esophageal strictures after ESD. Therefore, sufficient numbers of cells and biomaterials in basal membranes are necessary to overcome severe esophageal strictures after ESD.

Tissue engineering approaches will also provide a treatment for refractory esophageal strictures. Patch esophagoplasty using biologic scaffolds for refractory esophageal strictures has already been performed in 4 patients[82]. Various treatments using tissue engineering for refractory esophageal strictures will be performed in the near future.

CONCLUSION

This review reports several strategies for preventing esophageal strictures after extensive ESD with a focus on anti-inflammatory, scaffold-based, and cell-based treatments. Anti-inflammatory treatments, which are mainly local and systemic steroid therapies, have shown positive outcomes in small comparative clinical studies. However, the clinical evidence of scaffold-based and cell-based treatments is still insufficient, and their efficacy needs to be confirmed in comparative studies because they are potentially new technologies for tissue engineering and novel treatment strategies for wound healing. To establish a truly minimally invasive treatment using endoscopic surgery, improvements to all of these methods are needed. Nonetheless, these three strategies will eventually become available as a combined therapy in the future.

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