



Prophylactic stenting for esophageal stricture prevention after endoscopic submucosal dissection

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Abstract

Endoscopic submucosal dissection (ESD) of superficial esophageal cancer has been increasingly used as an alternative to surgery because it is minimally invasive

and has a high rate of en bloc resection. However, a high rate of esophageal stricture is observed after ESD for large lesions, which can dramatically decrease the patient's quality of life. Stricture prevention is necessary to allow for endoscopic therapy to expand. We, herein, review the most recent evidence and discuss the role of the metallic self-expandable stent and the biodegradable stent in esophageal stricture prevention. Limited studies suggested that prophylactic stenting could reduce the stricture rate without increasing the number of complications. In addition, the number of bougie dilation procedures was significantly lower with stent placement. Esophageal stenting is a promising option for post-ESD stricture prevention. However, current evidence is too preliminary to formulate practice standards. Future studies are needed to further validate the efficacy and safety of prophylactic stenting and determine the best strategy for stricture prevention. Stent migration is the most common complication. A new stent that has advantages of a low migration rate and minimal tissue reaction will need to be developed. Therefore, randomized controlled trials with long-term follow-up periods are required before prophylactic stenting could be considered a valid option to prevent post-ESD stricture.

Key words: Biodegradable stent; Stricture prevention; Esophageal stricture; Metallic self-expandable stent; Endoscopic submucosal dissection

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Core tip: Esophageal stenting is a promising option for esophageal stricture prevention. Current evidence is too preliminary to formulate practice standards. Randomized controlled trials with long-term follow-up periods and cost-effective studies are required before prophylactic stenting could be considered a valid option to prevent post-endoscopic submucosal dissection stricture.

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INTRODUCTION

Endoscopic submucosal dissection (ESD) of superficial esophageal cancer has been increasingly used as an alternative to surgery because it is minimally invasive and has a high rate of en bloc resection. Despite these advantages, a high rate of esophageal stricture is observed after ESD for large lesions, which can dramatically decrease the patient's quality of life^[1-3]. The rate of strictures after endoscopic resection for circumferential or near-circumferential lesions can be as high as 88%^[4]. Although oral steroids were administered in one study, 45% of patients still suffered from stricture^[5]. Therefore, post-ESD esophageal stricture prevention is needed to allow for endoscopic therapy to expand. In this editorial, we discuss the use of prophylactic stenting in the prevention of post-ESD stricture and include a discussion of our future vision related to this topic. PubMed and Web of Science were searched using the following search strategy: (ESD OR endoscopic resection) AND esophageal stricture AND stent, until 31 August 2016. Studies investigating the role of stent placement after esophageal ESD were included. We searched the reference lists of the relevant studies to identify other studies on the same topic. Currently, no conclusive recommendation is evident in the literature related to the type of stent to use in stricture prevention. According to the current studies, the self-expandable metallic stent and the biodegradable stent are two potential options.

SELF-EXPANDABLE METALLIC STENTS

Temporary placement of a self-expandable metallic stent is increasingly used in practice to prevent post-ESD stricture. Ye and colleagues reported on their application of fully-covered stent placement after circumferential endoscopic resection of esophageal lesions^[6]. More information about the stent used can be found in Table 1. A total of 23 patients were included in this prospective study. During the follow-up period, 4 patients had stent migration, and 3 of those 4 patients developed esophageal strictures. The stricture rate in this study was 17.3% (4/23), which was significantly lower than the stricture rate reported in previous studies. However, only one endoscopist from a high-volume center performed the study, which raises concerns about potential bias. Because the post-ESD stricture rate could be affected by the experience and operative skills of the endoscopist, the results of this study may not be generalizable. Another limita-

tion of this study was the absence of sham control to further validate the advantage of stent placement. The only randomized controlled trial (RCT) to date to investigate this question was conducted by Wen and his colleagues^[7]. In this study, patients who had mucosal defects that exceeded 75% of the circumference of the esophagus after ESD treatment were randomized in a 1:1 fashion to either a group that received treatment with a fully-covered esophageal stent or an observation group. The study showed a significantly lower rate of stricture in the group that received stent placement compared to the observational group (18.2% vs 72.7%, respectively, $P < 0.05$). Moreover, the number of bougie dilation procedures was significantly lower in the stent placement group compared to the observational group (mean 0.45, range 0-3 vs mean 3.9, range 0-17, respectively, $P < 0.05$). In addition, complications were comparable between the two groups. Interestingly, the two patients who developed stricture in the stent group both had stent migration. The stent migration rate could be affected by the design of the stents. Different types of stents have their own characteristics. A small portion of exposed bare metal at both ends of the partially covered metallic stent helps to prevent migration. However, the granulation tissue ingrowth at the ends of the stent could lead to stent-induced strictures. In contrast, fully-covered stents do not have any exposed bare metal, but they are more prone to migration. A new stent that has advantages of both a low migration rate and minimal tissue reaction will need to be developed. Is successful stent placement without migration enough for stricture prevention? The answer may be "no". Bhat and colleagues reported a 28% stricture rate after stent removal or migration^[8]. The circumferential lesion left at the ends of the stent after stent removal is prone to forming strictures. In addition, the potential pro-inflammatory action of the implanted stent makes it unlikely to be the single best choice for esophageal stricture prevention. Although the results in previously mentioned studies are inspiring, the studies involved a small sample size and a short-term follow-up period; therefore, the results need to be confirmed in future larger trials. A recent meta-analysis conducted by Oliveira and his colleagues demonstrated that the use of preventive therapy after extensive ESD reduces the risk of stricture without increasing the number of complications^[9]. Moreover, the placement of a fully-covered stent and the use of local corticosteroid injections have the most promising results in reducing post-ESD stricture among different types of strategies. It is worth mentioning that these results were based on three small RCTs and several retrospective studies. The high degree of heterogeneity across the included studies raises additional concerns about the potential bias of this analysis. Therefore, RCTs with larger sample sizes comparing different treatment strategies are still needed to clarify this issue. In endoscopy, the

Table 1 Studies using esophageal stenting to prevent post-endoscopic submucosal dissection stricture

Ref.	Type of study	Population	Type of stent	Time of removal	Stricture rate	Stent migration rate
Ye <i>et al</i> ^[6] , 2016	Cohort	Circumferential	Fully-covered self-expandable metallic stents (CZES stent; Sigma, China)	12 wk	17.4%	17.4%
Wen <i>et al</i> ^[7] , 2014	RCT	Mucosal defect > 3/4	Fully-covered self-expandable metallic stents (CZES stent; Sigma, China)	8 wk	18.2%	18.2%
Saito <i>et al</i> ^[11] , 2008	Case report	Mucosal defect > 3/4	PLLA esophageal stent (Tanaka-Marui stent; Marui Textile Machinery Co., Japan)	Self-degradable	0	0
Saito <i>et al</i> ^[10] , 2007	Case report	Mucosal defect > 3/4	PLLA esophageal stent (Tanaka-Marui stent; Marui Textile Machinery Co., Japan)	Self-degradable	0	77.0%

RCT: Randomized controlled trial; PLLA: Poly-L-lactic acid.

advancement of a new concept could be affected by the availability and cost-effectiveness of technology. Since stents are associated with a high cost, evidence on cost-effectiveness is required in future studies.

BIODEGRADABLE STENTS

Saito *et al*^[10] reported the successful application of biodegradable stents to post-ESD esophageal stricture prevention. Despite having a high rate of early stent migration, the efficacy of stricture prevention reached 100%, but caution should be taken as the data are based on short-term follow-up case reports^[10]. This group also reported 2 cases of successful application of biodegradable stents in the prevention of re-stricture formation after balloon dilatation of post-ESD strictures^[11]. Experience in using these types of stents is learned from animal model-based experiments^[12,13]. Biodegradable stents have the potential to mitigate stent-related complications and do not require removal. The main limitations of biodegradable stents are a hyperplastic tissue reaction and stent migration. The poly-L-lactic acid (PLLA) stent and the polydioxanone stent are two types of biodegradable stents that are currently available. The PLLA-biodegradable stent has a high rate of early stent migration, which makes it unlikely to be the best choice for stricture prevention^[10,14]. Meanwhile, polydioxanone stents have a migration rate of 20%, but they could induce a severe hyperplastic tissue reaction^[15,16]. A hyperplastic tissue reaction delays the healing of the mucosa and poses a challenge when removing the stent. Moreover, it might prevent adequate surveillance for local recurrence. Although the ideal stent has not yet been developed, possible options to minimize tissue hyperplasia after biodegradable stent placement should be considered in future studies. These options include steroid injection, consumption of a drug-eluting layer, and coverage with biodegradable membranes or extracellular matrix scaffolds.

CONCLUSION

All patients with extensive esophageal ESD should receive some type of preventive treatment. Esophageal stenting is a promising option for esophageal stricture

prevention, especially when corticosteroid treatment is contraindicated in certain patients. Current evidence is too preliminary to formulate practice standards. RCTs with long-term follow-up periods are required before prophylactic esophageal stenting could be considered as a valid option to prevent post-ESD stricture.

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