CME

Role of Esophageal Stents in Benign and Malignant Diseases

Prateek Sharma, MD[1], Richard Kozarek, MD[2] and the Practice Parameters Committee of the American College of Gastroenterology

These recommendations provide an evidence-based approach to the role of esophageal stents in the management of benign and malignant diseases. These guidelines have been developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee and approved by the Board of Trustees. The following guidelines are based on a critical review of the available scientific literature on the topic identified in Medline and PubMed (January 1992–December 2008) using search terms that included stents, self-expandable metal stents, self-expandable plastic stents, esophageal cancer, esophageal adenocarcinoma, esophageal squamous cell carcinoma, esophageal stricture, perforations, anastomotic leaks, tracheoesophageal fistula, and achalasia. These guidelines are intended for use by health-care providers and apply to adult, but not pediatric, patients. As with other practice guidelines, these guidelines are not intended to replace clinical judgment but rather to provide general guidelines applicable to the majority of patients. Clinicians need to integrate recommendations with their own clinical judgment, and with individual patient circumstances, values, and preferences. They are intended to be flexible, in contrast to standards of care, which are inflexible policies designed to be followed in every case. Specific recommendations are based on relevant published information. The quality of evidence and strength of recommendations have been assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, which is a system that has been adopted by multiple national and international societies. The GRADE system is based on a sequential assessment of quality of evidence, followed by assessment of the balance between benefits vs. downsides (harms, burden, and costs) and subsequent judgment regarding the strength of recommendation.

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INTRODUCTION

This review outlines the role of esophageal stents in benign and malignant disease. The quality of evidence and strength of recommendations have been assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (**Tables 1** and **2**) (1–4). Malignant dysphagia is defined as difficulty in swallowing due to cancer resulting from a partially or completely obstructed esophageal lumen (4). Patients frequently do not recognize any symptoms until at least 50% of the luminal diameter is compromised because of the distensible nature of the esophagus, thus explaining the late presentation and poor prognosis associated with esophageal cancers. Esophageal obstruction may be either intrinsic because of esophageal cancer or extrinsic because of compression by lung cancer, lymphadenopathy, etc. The incidence of esophageal cancer continues to increase in the United States and is currently the fastest rising incidence cancer. It is estimated that there were 14,550 new cases of esophageal cancer diagnosed in 2006, with 13,770 cancer-related deaths (5). Unfortunately, the vast majority of cancers are diagnosed at a later stage wherein the cancer has invaded the submucosa and beyond with lymph node involvement or distant metastasis (6). The majority of the cases (>50%) have unresectable disease at the time of diagnosis, either because of distant metastases or unsuitable candidates for surgical resection (7), and the overall 5-year survival rate continues to be dismal (<20%) (8).

The goals of palliative therapy in patients with unresectable cancer are to ameliorate symptoms of dysphagia, treat complications, maintain oral intake, minimize hospital stay, relieve pain, eliminate reflux and regurgitation, prevent aspiration, and ultimately improve their quality of life. Various therapies have been used to palliate dysphagia in patients with esophageal carcinoma, including esophageal stenting, esophageal dilation, radiation therapy, chemotherapy, laser ablation, thermal electrocoagulation, photodynamic therapy, sclerotherapy of the tumor, and nutritional support. Esophageal stents—self-expanding metal stents (SEMSs)––have increasingly been used for palliation of malignant dysphagia and are currently the most common means of palliation. Recently, self-expandable plastic stents (SEPSs) have been used for the management of benign esophageal conditions, such as tracheoesophageal fistulas, benign esophageal strictures, esophageal perforations, and leaks. **Table 3** summarizes various conditions under

[1]Division of Gastroenterology and Hepatology, Veterans Affairs Medical Center and University of Kansas School of Medicine, Kansas City, Missouri, USA; [2]Digestive Disease Institute, Virginia Mason Medical Center, Seattle, Washington, USA. **Correspondence:** Prateek Sharma, MD, Department of Veterans Affairs Medical Center, University of Kansas School of Medicine, 4801 East Linwood Boulevard, Kansas City, Missouri 64128-2295, USA. E-mail: psharma@kumc.edu
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Table 1. Strength of recommendation using the GRADE classification and implications for patients, clinicians, and policy makers

Strong recommendations
For patients: Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be required to help individuals make decisions consistent with their values and preferences
For clinicians: Most individuals should receive the intervention. Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator
For policy makers: The recommendation can be adapted as policy in most situations
Weak recommendations
For patients: The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping individuals make decisions consistent with their values and preferences
For clinicians: Examine the evidence or a summary of the evidence yourself
For policy makers: Policy making will require substantial debates and involvement of many stakeholders

GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

Table 2. Quality of evidence—definitions and determinants

Grade	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect
	Underlying methodology: randomized controlled trials
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
	Underlying methodology: downgraded randomized controlled trials or upgraded observational studies
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
	Underlying methodology: well-done observational studies with control groups
Very low	Any estimate of effect is very uncertain
	Underlying methodology: case reports or case series

which esophageal stenting is performed. Although not provided in most reported studies, the use of a uniform dysphagia scoring system is encouraged (**Table 8**).

ESOPHAGEAL STENTS IN MALIGNANT DISEASE

The vast majority of studies evaluating SEMSs in malignant disease are uncontrolled, single, or multicenter series that have evaluated a single type of SEMSs or compared various types of commercially marketed stents. Moreover, these studies tend to combine intrinsic and extrinsic malignancies, fistulous and obstructive diseases, as well as proximal, mid, and distal esophageal lesions. There are also a few studies that have compared expandable prostheses with other forms of therapy such as brachytherapy for intrinsic malignancies.

Table 3. Conditions under which esophageal stenting has been performed

Malignant esophageal obstruction
Extrinsic esophageal compression due to primary or secondary tumors
Refractory or recurrent esophageal strictures
Tracheoesophageal fistula
Esophageal perforation or leak

Malignant strictures and fistulas

Despite attempts at earlier diagnosis, better tumor staging, neoadjuvant/multimodality therapy, improved operative technique, and better perioperative care, the 5-year survival rate for esophageal cancer in most series still approximates 20% (8). A recent Cochrane Review assessed the effectiveness of chemotherapy, best supportive care, and different chemotherapy regimens against each other in patients with metastatic carcinoma of the esophagus or gastroesophageal junction (GEJ). No survival benefit was demonstrated for chemotherapy vs. supportive care in two randomized controlled trials (RCTs). In addition, there was no consistent benefit of a specific chemotherapy regimen in 5 RCTs with a total of 1,242 patients (9). Therefore, even with initial surgical resection, a significant percentage of patients with esophageal carcinoma and those with nonluminal malignancies, such as head and neck and lung cancer, as well as mediastinal metastases will require palliation for dysphagia and/or esophago-airway fistulas.

Historically, both esophageal obstruction and fistulas were palliated with rigid prostheses under endoscopic and fluoroscopic guidance, which often required dilation to 48–54 French to allow insertion (10). Contingent upon the tumor bulk location, friability, angulation, and tightness, insertions were often traumatic and procedural complication rates were high (11,12). SEMSs were first introduced for the esophagus nearly 20 years ago, and despite a large number of retrospective and prospective series using various platforms, it was the seminal RCT by Knyrim *et al.* (13) that provided evidence that SEMSs were advantageous in the palliation of malignant dysphagia. In this randomized, prospective trial, 42 patients (39 patients with esophageal carcinoma and 3 with extrinsic obstruction) were randomized to either a 16-mm diameter conventional prosthesis or an uncovered SEMS (Wallstent). The latter prosthesis was 3 mm in diameter and 15 cm in length when constrained, and expanded to 16 mm in diameter and shortened to 10 cm in length when released and was made of stainless steel. Outcome parameters included technical success, procedural complications, dysphagia relief, reinterventions, performance status, 30-day mortality, and cost effectiveness. In this study that used general anesthesia and balloon dilation (10, 15, and 20 mm) for patients receiving plastic prostheses, prostheses or stents could be

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placed in 41 of the 42 patients. A patient with a tight cardia stricture could not be stented and underwent an endoscopic gastrostomy. There was no difference in the overall 30-day mortality between the two groups (plastic prosthesis 29% vs. SEMSs 14%, $P=0.29$), with no significant difference between the two groups in survival ($P=0.35$). Although dysphagia and Karnofsky scores (determined every 6 weeks until death) had comparable degrees of improvement with comparable reintervention rates, complications were significantly less in the SEMSs vs. the plastic prostheses patients (0 vs. 9, $P<0.001$, procedure-related mortality of 14% for plastic prostheses). Moreover, despite the initial higher costs of SEMSs, metal stents proved to be cost-effective because of decreased hospitalization stay and the absence of fatal complications. In another RCT, 31 consecutive patients with inoperable malignant esophageal stenosis were randomized to receive either a SEMS (modified Gianturco metal stent) or plastic prostheses (Atkinson tube). Although the overall complication rates were similar in both the groups, patients in the SEMSs group had better palliation of dysphagia, were discharged from hospital earlier, and survived longer (14). A retrospective review of 153 patients (45 plastic prostheses and 108 SEMSs) also showed that dysphagia score improvement, survival, and recurrent dysphagia were comparable between the two groups. However, significantly higher major complications were seen in the plastic prostheses group compared with the SEMSs group (15).

On the basis of these results, SEMSs are superior to rigid plastic prostheses in the management of unresectable obstructive esophageal cancers. The quality of evidence for this recommendation is good and the strength of recommendations is strong.

Types of stents

Multiple types of prostheses are available from various manufacturers throughout the world. Nitinol stents (alloy of nickel and titanium) and to a lesser extent, SEPSs now dominate the US market, the former because of their ability to conform to anatomical angulations and the latter for their removability (**Table 4**). The available stents differ in stent material, design, luminal diameter, radial force exerted, flexibility, and degree of shortening after use.

Self-expanding metal stents. *Partially covered vs. uncovered stents*: There is evidence that covered SEMSs fare better than uncovered stents (16–18). It should be noted that the described studies comparing covered with uncovered stents used partially covered SEMSs. The uncovered portion of the partially covered stents allows embedding and anchoring. Recently, a fully covered nitinol prosthesis has been approved by the FDA (Food and Drug Administration) (Niti-S, TaeWoong Medical, Seoul, Korea), thus allowing the option of removing the stent, but is also potentially associated with increased risk of migration. Published data on fully covered SEMSs are awaited. Recurrent dysphagia due to tumor ingrowth was the major disadvantage of uncovered SEMSs as reported by Vakil *et al.* (16) in a multicenter trial, in which 62 patients with inoperable GEJ tumors were randomized to partially covered or uncovered SEMSs of identical design. The primary outcome was the need for reintervention because of stent migration or recurrent dysphagia; secondary outcomes included dysphagia relief, functional status, and rate of complications. All patients were observed at monthly intervals until death or for 6 months. Reintervention was significantly higher in the uncovered group than in the partially covered SEMSs group (27 vs. 0%, $P=0.002$). Both stents provided comparable dysphagia relief and migration rates (uncovered 7% vs. partially covered 12%, $P=0.43$). Tumor ingrowth or obstructing mucosal hyperplasia was more common in uncovered stents compared with partially covered stents (30 vs. 3%, $P=0.005$). No differences in performance status and

Table 4a. FDA-approved SEMS currently marketed in the United States

Stent	Manufacturer	Material	Length (cm)	Diameter shaft/flare (mm)	Covering	Anti-reflux valve
Ultraflex	Boston Scientific	Nitinol	10/12/15	18/23	NC/PC	No
				23/28		
Wallflex	Boston Scientific	Nitinol	12/12/15	12/28	PC/covered	No
				23/28		
Esophageal Z	Cook	Stainless steel	8/10/12/14	18/25	PC	Yes (Dua variant)
Evolution	Cook	Nitinol	8/10/12.5/15	20/25	PC	No
Alimaxx-E	Alveolus	Nitinol	7/10/12	18/22	Covered	No
Niti-S	TaeWoong Medical	Nitinol	8/10/12/14	16/20	Covered	No
				18/23		
				20/25		
Polyflex	Boston Scientific	Polyester	9/12/15	16/20	Covered	No
				18/23		
				21/28		

FDA, Food and Drug Administration; NC, not covered; PC, partially covered; SEMS, self-expanding metal stent.

Table 4b. Selected SEMS currently available in the United States, Europe, or Asia

Stent	Manufacturer	Material	Length (cm)	Diameter shaft/flare (mm)	Covering	Anti-reflux valve	FDA approved
Ultraflex	Boston Scientific	Nitinol	10/12/15	18/23	NC/PC	No	Yes
				23/28			
Wallflex	Boston Scientific	Nitinol	12/12/15	12/28	PC/covered	No	Yes
				23/28			
Esophageal Z	Cook	Stainless steel	8/10/12/14	18/25	PC	Yes (Dua variant)	Yes
Gianturco Z	Cook	Stainless steel	8/10/12/14	18/25	PC	Yes	No
					PC; shaft bars	No	No
Evolution	Cook	Nitinol	8/10/12.5/15	20/25	PC	No	Yes
Alimaxx-E	Alveolus	Nitinol	7/10/12	18/22	Covered	No	Yes
Niti-S	TaeWoong Medical	Nitinol	8/10/12/14	16/20	Covered	No	Yes
				18/23			
				20/25			
FerX-Ella	Ella-CS	Stainless steel	9/10.5/12/13.5/15/16.5/18/ 19.5	20/36	Covered	Yes/no	No
Dostent	MI Tech	Nitinol	6/9/12	18/30	Covered	Yes/no	No
Flamingo Wallstent	Boston Scientific	Stainless steel	12/14	20/30	PC	No	No
Polyflex	Boston Scientific	Polyester	9/12/15	16/20	Covered	No	Yes
				18/23			
				21/28			

FDA, Food and Drug Administration; NC, not covered; PC, partially covered; SEMS, self-expanding metal stent.

survival were noted between the two groups. Similarly, a retrospective study compared two different types of SEMSs (uncovered and partially covered) for palliative treatment of 152 patients (uncovered 54 and partially covered 98) with inoperable malignant stenosis of the esophagus and cardia (17). Overall, 88% of patients with partially covered stents and 54% with uncovered stents were free of symptoms during follow-up ($P<0.0001$). Although the rates of stent migration were lower in the uncovered stents group (0 vs. 10%, $P=0.03$), tumor or granulation tissue ingrowth (100 vs. 53%, $P<0.0001$) and restenosis causing recurrent dysphagia (37 vs. 8%, $P<0.0001$) were significantly higher in the uncovered stents group.

Partially covered SEMSs are superior to uncovered SEMSs in the palliation of malignant dysphagia because of unresectable obstructive esophageal cancers. The quality of evidence for this recommendation is good and the strength of recommendations is strong.

Comparison between various SEMSs: Prospective RCTs have compared various stent types in the palliation of malignant esophageal diseases (**Table 5**). In a prospective RCT, Sabharwal *et al.* (18) compared rates of complications (perforation, migration, severe gastroesophageal reflux, bleeding, and restenosis due to tumor ingrowth) with improvement in dysphagia in 53 patients with inoperable distal esophageal cancer randomized to a Flamingo Wallstent; Ultraflex stent (Boston Scientific, Natick, MA). The two stents were equally effective in the palliation of dysphagia (mean dysphagia score: Ultraflex 1.0 vs. Flamingo Wallstent 0.9, $P>0.1$) with comparable rates of complications between the two groups. In another RCT, Siersema *et al.* (19) compared the partially covered Flamingo Wallstent, Ultraflex, and Gianturco Z stents (William Cook, Bloomington, IN) in 100 consecutive patients with gastroesophageal carcinoma. Technical success, dysphagia scores, performance status, mortality rates, survival, complication rates, and incidence of recurrent dysphagia were compared between the three groups. Dysphagia improved in all patient groups ($P<0.001$) with no difference in the degree of improvement between the three groups. There were no statistically significant differences in the major complication rates between the three groups (Ultraflex stent 24%, Flamingo Wallstent 18%, and Gianturco Z stent 36%, $P=0.23$). The incidence of recurrent dysphagia was also similar across the three groups ($P=0.13$), related to tumor overgrowth or migration in the majority of cases. Thus, all three stents afforded comparable dysphagia relief, although stent migration was associated with the use of small-diameter stents within the esophagus. Retrospective studies that compared outcomes of different types of SEMSs have also been published. May *et al.* compared the uncovered Ultraflex, partially covered and uncovered Wallstent, and partially covered Z stent in 96 patients with inoperable esophageal cancers. The improvement in the degree of dysphagia and complication rates was similar across the different stent groups (20). Finally, although there are no formal cost-effectiveness data,

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Table 5. Select studies comparing various SEMS/SEPS for malignant dysphagia

Author (reference)	Study type (*n*)	Stent type (*n*)	Technical success	Dysphagia relief	Complications	Survival
Vakil *et al.* (16)	RCT (62)	Covered (32)/uncovered (30) Ultraflex	Comparable	Comparable	Tumor ingrowth 3 vs. 30% (*P*=0.005)	Comparable (life-table analysis, log-rank test=0.378)
Sabharwal *et al.* (18)	RCT (53)	Flamingo Wallstent (22)/Ultraflex (31)	Comparable	Comparable	Comparable 23% Flamingo 19% Ultraflex	Not specified Mean: 96.5/97.1 days
Siersema *et al.* (19)	RCT (100)	Ultraflex (34)/Flamingo Wallstent (33)/Gianturco Z (33)	Comparable	Comparable	Comparable 23% Ultraflex 18% Wallstent 36% Z Stent (*P*=0.23)	Not specified Median: 104/113/110 days
Conio *et al.* (21)	RCT (101)	Polyflex (47)/Ultraflex (54)	Comparable	Comparable	Higher with Polyflex, 48 vs. 33% (OR 2.3 (95% CI: 1.2–2.4))	Comparable Median: 134/122 days

CI, confidence interval; OR, odds ratio; RCT, randomized controlled trial; SEMS, self-expanding metal stent; SEPS, self-expandable plastic stent.

as the differences in cost among the available stent types are relatively small; this is unlikely to determine the type of stent to be used in the palliation of malignant dysphagia.

Minor differences in efficacy and complication rates exist between the available SEMSs, and on the basis of the above data, the use of one brand of SEMSs over the other cannot be recommended. The quality of evidence for this recommendation is moderate and the strength of recommendation is strong.

Self-expanding plastic stents

SEPSs have also been shown to be safe and effective in the palliation of malignant dysphagia (21–27). In a case series of 33 patients with malignant dysphagia (27 esophageal and 6 GEJ cancers) who underwent SEPS placement, improvement in dysphagia was noted in all patients (23). Stent occlusion as a result of tumor overgrowth occurred at a rate of 12.1%, the stent migration rate was 6%, and the overall reintervention rate was 21.1%. A prospective multicenter case series reported on the experience with SEPSs in 60 patients with unresectable esophageal and GEJ cancers (22). SEPSs were placed successfully in 59 of 60 patients with an improvement in the mean dysphagia score from 2.8 to 1.0 ($P<0.001$). Early minor complications occurred in 32% of patients (e.g., chest pain, incomplete stent usage, fever, gastroesophageal reflux symptoms) and major complications in 22%, including 2 deaths caused by massive hemorrhage. Overall, the stent migration rate was 20% and tumor overgrowth was observed in 13.6% of the patients. Another large case series using SEPSs for palliation of malignant dysphagia in 66 patients showed a high technical success rate for placement, achieving improvement in dysphagia scores (25). The migration rate was 4.5% and no tumor ingrowth was reported.

A recent, prospective trial randomized 101 patients with unresectable esophageal carcinoma (82 squamous cell cancer and 19 adenocarcinoma) to SEPSs (Polyflex, Boston Scientific, Natick, MA; $n=47$) or partially covered SEMSs (Ultraflex, $n=54$); the investigators were successful in placing stents in 98 and 100% of patients, respectively (21). Patients with GEJ cancers were excluded from this study. There was comparable dysphagia relief between the two groups, but a significantly higher complication rate (hemorrhage, tumor or hyperplastic overgrowth, migration, and food impaction) was noted (odds ratio 2.3, 95% confidence interval (95% CI): 1.2–4.4) in patients treated with SEPSs. The median survival was 134 days in the SEPSs group compared with 122 days in the SEMSs group ($P=$NS). In another RCT, 125 patients with malignant dysphagia due to inoperable esophageal or gastric cardia cancers were randomized to treatment with a partially covered SEMS (Ultraflex, $n=42$), SEPS (Polyflex, $n=41$), or a modified nitinol stent (Niti-S, $n=42$) (28). The primary outcome of the study was recurrent dysphagia (either from tissue ingrowth or overgrowth, stent migration, or food obstruction). Secondary outcomes included technical and functional outcomes (dysphagia scores, performance status), complications, and survival. Overall, recurrent dysphagia occurred more frequently in patients with Ultraflex stents ($P=0.03$). Although not statistically significant, tissue ingrowth or overgrowth occurred more frequently in the partially covered SEMSs (Ultraflex) group. Patients also had higher rates of food obstruction ($P<0.01$) compared with those of the other two groups. However, stent migration (SEPSs, $n=12$ (29%); Ultraflex, $n=7$ (17%); Niti-S, $n=5$ (12%); $P=0.01$) and technical difficulties in stent placement ($P=0.008$) were significantly higher for the SEPSs group. No differences were noted in the degree of improvement in dysphagia, performance status, complication rates, or survival across the three groups. On the basis of the technical difficulties and high stent migration rates, the investigators concluded that the SEPS was the least preferable stent in this patient group.

The use of SEMSs is associated with significantly fewer complications than SEPSs when inserted for malignant dysphagia. The quality of evidence for this recommendation is moderate and the strength of recommendation is strong.

Location of malignancy. There is continuing debate about the advisability of SEMS placement for proximal esophageal cancer

and the need for an anti-reflux component in SEMSs that cross the GEJ. The use of stents close to the upper esophageal sphincter in patients with cervical strictures may be limited by patient intolerance due to pain and globus sensation, as well as an increased risk of complications (tracheoesophageal fistula and aspiration pneumonia). Although the majority of prospective studies have excluded patients with high cervical strictures, retrospective series have demonstrated the feasibility of proximal esophageal stent placement with effective palliation (29–31). The largest retrospective series from Rotterdam reviewed 104 patients (66 primary esophageal carcinoma and 38 recurrent cancer after gastric tube interposition) with a malignant stricture within 8 cm of the upper esophageal sphincter (29). Overall, 24 (23%) patients also had a tracheoesophageal fistula. The procedure was technically successful in 96% of patients, and the dysphagia score improved from a mean of 3 to 1. Fistula sealing was achieved in 19 of 24 patients (79%). Complications were noted in a third of the patients, major complications in 21%. Recurrent dysphagia occurred in 29 (28%) patients and was mainly caused by tissue ingrowth or overgrowth ($n=10$), food bolus obstruction ($n=7$), stent migration ($n=3$), or other reasons ($n=11$; persistent fistula, $n=5$; difficulty in swallowing, $n=4$; and dislocation of the stent, $n=2$). Although transient post-procedural pain was common, persistent globus sensation was noted in only 8% of patients, but none of these patients required stent retrieval. In addition, a smaller series has also been reported using a modified nitinol prostheses (Niti-S stent, TaeWoong Medical) with comparable results (32). If placed, it is frequently recommended that a distance of 2 cm below the upper esophageal sphincter should be maintained while placing a stent.

There are discordant data, in turn, using stents with anti-reflux capabilities across the GEJ. Dua *et al.* (33) demonstrated an improvement in reflux in patients with GEJ malignancy after placement of a modified Z stent (polyurethane coating of the metallic Z stent extended beyond its lower end to form a windsock-type valve to prevent reflux). These results were confirmed in an RCT by Laasch *et al.* (34) in which 3 of 25 patients (12%) with the anti-reflux Z stents placed across the GEJ had demonstrable reflux compared with 24 of 25 patients (96%) treated with a standard open Flamingo Wallstent ($P<0.001$). There were no differences in the degree of dysphagia improvement or complications between the two groups. Another study also demonstrated gastroesophageal reflux in five of eight patients after conventional SEMS placement, whereas none of the six patients with an anti-reflux stent placement had reflux (all patients with GEJ malignancy) (35). Shim *et al.* randomized 36 patients to receive the Hanarostent (MI Tech Co. Ltd. Incheon, South Korea) with a S-shaped anti-reflux valve, the Dostent (MI Tech Co. Ltd. Incheon, South Korea) with a tricuspid anti-reflux valve, or a standard open SEMS. The fraction of the total recording time during which intraesophageal pH was <4 was 3%, using the Hanarostent, compared with 29% in the Dostent group and 15% in the standard open SEMSs group ($P<0.001$) (36). However, these encouraging results were not reproduced in other studies. An RCT by Wenger *et al.* (37) compared an anti-reflux stent with a standard open SEMS in 41 patients with inoperable distal esophageal or cardia cancers. No significant difference in esophageal reflux symptoms was noted between the two groups. In another RCT involving 30 patients with distal esophageal or gastric cardia cancer, patients were randomized to receive either a stent with a windsock-type anti-reflux valve (FerX-Ella, ELLA-CS, s.r.o., Hradec Kralove, Czech Republic; $n=15$) or a standard open SEMS of the same design without the valve ($n=15$) (38). Gastroesophageal reflux was assessed 2 weeks after the treatment using a standardized questionnaire and by 24-h pH monitoring. Reflux symptoms were reported by 25% of patients treated with an anti-reflux stent compared with 14% with an open stent. Although not statistically significant, 24-h pH monitoring showed increased esophageal acid exposure with the anti-reflux stent.

Given the conflicting results, the routine use of SEMSs with anti-reflux valve in the management of malignant dysphagia due to distal esophageal and gastric cardia malignancy for reducing gastroesophageal reflux cannot be recommended. The quality of evidence is low and the strength of recommendation is weak.

The use of SEMSs in proximal malignancy, in contrast, should be considered contingent upon proximity to the upper esophageal sphincter and tolerance. The quality of the evidence is moderate and the strength of recommendations is strong.

Fistula closure. Malignant esophageal fistulas usually develop because of the infiltration of esophageal carcinoma into the respiratory tract (trachea or bronchi) and rarely between the esophagus and aorta, mediastinum or pleura. Lung and mediastinal cancers may additionally cause tracheoesophageal fistulas as can pressure necrosis due to stents and radiation therapy. There are multiple prospective case series using SEMSs for esophago-airway fistulas reporting occlusion rates of 70–100% and complication rates between 10 and 30% (39–48). In the largest series to date, Shin *et al.* (49) successfully placed SEMSs in 61 patients with esophagorespiratory fistulas, successfully sealing off the fistula in 49 patients (80%), although 10 patients also required concomitant airway prostheses. During follow-up, approximately a third of patients had recurrence of fistulas, eight of whom had successful re-treatment with SEMSs. The overall mean survival was 3 months (1–56 weeks), but was significantly longer in patients with successful fistula closure compared with those with incomplete closure (15.1 vs. 6.2 weeks; $P<0.05$).

The endoscopic placement of covered SEMSs is the treatment of choice for malignant esophageal fistulas. The quality of the evidence for malignant fistula closure with SEMSs is moderate and the strength of the recommendation is strong (given the paucity of alternatives).

APPLICATION OF SEMSS WITH CHEMOTHERAPY AND/OR IRRADIATION FOR PALLIATION OF MALIGNANT DYSPHAGIA

Similar to studies using SEMSs for GEJ cancers, data regarding their use in the context of concomitant irradiation are discordant and limited. A majority of the series have been retrospective, using various SEMSs. For instance, in a survey of 200 patients with GEJ malignancies, Homs *et al.* (50) reported that previous

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chemo-irradiation increased the incidence of retrosternal pain, but did not affect the rate of complications or overall outcomes after SEMS placement. Other smaller retrospective series have demonstrated an increased rate of stent migration, bleeding, and fistulization in patients treated with SEMSs with previous chemo-radiation (35,51,52). Similarly, a large retrospective study of 116 patients showed that previous chemo-radiation was an independent predictor of post-procedural major stent complications (odds ratio 5.59 (95% CI: 1.7–18.1)) (53). In a more recent comparative study, 47 patients with esophageal malignancy had covered, retrievable nitinol stents placed 1 week before initiating irradiation (54). The stents were then electively removed at week 4 (group A, $n=24$) or removed in the event of complications (group B, $n=23$). Successful stent placement and improved dysphagia scores were noted in both groups. Although more number of complications were noted in group B patients (severe pain, granulation tissue formation, migration, fistula development, hematemesis), these were not statistically significant. However, the number of patients who required related reinterventions was significantly higher in group B than in group A ($P=0.03$). These results suggested that the short-term placement of a fully covered SEMS, followed by removal during irradiation therapy might be of some benefit in esophageal malignancy. Another small, retrospective series demonstrated that SEPSs improved the speed of oral alimentation without significant side effects in patients undergoing chemo-radiation for malignant dysphagia (55).

On the basis of these limited data, SEMSs in conjunction with chemo-irradiation cannot be routinely recommended. The quality of evidence for the use of SEMSs in this scenario is low and the strength of the recommendation is weak.

COMPARISON OF SEMSS WITH OTHER TREATMENT MODALITIES

There are some studies evaluating the use of laser therapy (with or without concomitant irradiation) vs. plastic or expandable stents. In a retrospective review of 125 patients with malignant dysphagia, the initial success rates for dysphagia relief were comparable, but the early complication rates were 5-fold higher with expandable or conventional stenting ($P<0.001$), including an 8–10-fold higher rate of major complications ($P<0.001$) (56). An additional study described 39 patients with unresectable esophageal cancer randomly allocated to ND:YAG laser with brachytherapy ($n=21$) or SEMS placement ($n=18$) (57). There was a higher rate of fistula formation, bleeding, need for re-treatment, and costs in the laser/brachytherapy group compared with the SEMSs group, but with no significant difference in the mean survival between the two groups.

A multicenter RCT compared the outcomes of stent placement and brachytherapy in 209 patients with inoperable esophageal carcinoma (58). Patients were randomized to receive SEMSs ($n=108$) or single-dose (12 Gy) brachytherapy ($n=101$). Dysphagia improved (primary outcome) more rapidly after stent placement than after brachytherapy, but long-term dysphagia relief was better after brachytherapy. For secondary outcomes, the SEMSs group had more complications than did the brachytherapy group (33 vs. 21%, $P=0.02$), but with no difference in the frequency of persistent or recurrent dysphagia or median survival. Quality-of-life scores favored brachytherapy, whereas total medical costs were similar across the two groups. Subsequently, on the basis of predicted survival, the same group of investigators developed a prognostic model for identification of patients with esophageal cancer in whom SEMS placement would be preferable to brachytherapy (59). Using data obtained from the above-described multicenter RCT ($n=209$) and a consecutive series ($n=396$), tumor length, performance scores, and the presence of metastases were identified as significant prognostic factors for survival. Using a simple score that also included age and gender, patients could be divided into poor, intermediate, or relatively good prognosis groups. For patients in the poor prognosis group, the difference in dysphagia-adjusted survival (alive with no or mild dysphagia) was numerically higher in the SEMSs group than in the brachytherapy group (77 vs. 54 days, $P=0.16$). For patients in other prognostic groups, brachytherapy resulted in better dysphagia-adjusted survival (relatively good prognosis: 138 vs. 104 days, $P=0.17$, intermediate: 98 vs. 68 days, $P=0.09$). Despite the evidence in favor of brachytherapy for patients with high performance status, the ease of SEMS insertion as first-line therapy and the need for SEMS rescue in a significant number of patients initially treated with irradiation have limited the application of brachytherapy in the United States. In addition, this method of local radiotherapy is unavailable in the majority of hospitals in the United States. Furthermore, this scoring system has not yet been validated, precluding its use in clinical practice in the selection of palliative treatment for patients with inoperable esophageal cancer.

The use of brachytherapy as the primary modality for management of malignant dysphagia due to inoperable esophageal cancer cannot be recommended. The quality of evidence for use of brachytherapy for this indication is moderate and the strength of recommendation is weak.

COMPLICATIONS

Complications caused by stent placement in esophageal malignancies can be myriad and multiple and are contingent upon tumor location (30–32), the presence or absence of a fistula or tumor shelf (38,44,49), use of concomitant chemo-irradiation (53), tumor vascularity (64), as well as the diameter and design of the prosthesis itself (**Table 6**) (13,16,18,19,21,22,60–65). They include inadequate expansion with increased post-procedural dysphagia, variable throat or chest pain, prosthesis migration with or without subsequent bowel obstruction, esophageal erosions with bleeding or fistulization, and significant reflux when placed across the GEJ. Other complications include stent-related perforation and tumor ingrowth or overgrowth, as well as benign obstruction by elicitation of granulation tissue. Complications approximate 30–35% in most series and increase as the intensity and duration of follow-up increases. Complications also seem to be higher with SEPS (Polyflex) (21,28), European Z stents (which have mid-shaft barbs) (19), if the stent crosses the GEJ (if reflux post

Table 6. Complications of esophageal self-expandable metal stents

Immediate (at the time of placement)
Aspiration
Airway compromise
Malposition
Delivery system entrapment
Stent dislodgement
Perforation
Early (up to 1 week after stent placement)
Bleeding
Chest pain
Nausea
Late (beyond 1 week of successful stent placement)
Recurrent dysphagia due to reobstruction from tumor or food impaction
Migration
Tracheoesophageal fistula
Bleeding
Gastroesophageal reflux disease/aspiration

Adapted from Baron (65).

prosthesis is defined as a complication) (33,34,36), and arguably higher in patients undergoing concomitant irradiation (53,54). In a retrospective review, 338 patients with malignant dysphagia from esophageal or gastric cardia cancer were treated with three different types of SEMSs (Ultraflex ($n=153$), Gianturco Z stent ($n=89$), or Flamingo Wallstent ($n=96$)) (63). In all, 265 small-diameter and 73 large-diameter stents were used, and both stent types were associated with a comparable dysphagia relief. There was an increased risk of major complications (hemorrhage, perforation, fistula, and fever) with the large-diameter Gianturco Z stents compared with smaller-diameter prostheses (40 vs. 20% complication rate, adjusted hazard rate 5.03, 95% CI: 1.33–19.11), but not in patients with a large-diameter Ultraflex or Flamingo Wallstent. Even with small-diameter Gianturco Z stents, minor complications, particularly pain, were more common in patients who had undergone previous irradiation or chemotherapy. On the other hand, dysphagia from bolus impaction, tissue overgrowth, and stent migration occurred more frequently in patients with small-diameter stents than in those with large-diameter stents (Ultraflex 42 vs. 13%, hazard rate 0.16 (95% CI: 0.04–0.74); Gianturco Z 27 vs. 10%, hazard rate 0.97 (95% CI: 0.11–8.67); Flamingo Wallstent 37 vs. 15%, hazard rate 0.4 (95% CI: 0.03–4.79)).

A recent study by Homann *et al.* (64) reported delayed complications in 71 of 133 stented patients (53.4%) with a quarter of patients experiencing multiple complications. Recurrent dysphagia related to tumor ingrowth (22%), overgrowth (15%), stent migration (9%), and food bolus obstruction (21%) were the most common complications, followed by the development of esophago-airway fistulas (9%). Successfully retreated patients had a significantly longer life expectancy (222±26 vs. 86±14 days, $P<0.001$) than did those not undergoing reintervention. In an additional retrospective review of 97 patients with SEMS placement, dysphagia improved in 86% and tracheoesophageal fistula symptoms in 90% of the patients (66). Minor complications (pain, nausea, vomiting, reflux) were noted in 47% of the patients and major complications (hematemesis, severe emesis, stent migration, tumor overgrowth, new stricture formation, food impaction, procedure-related death) in 37%. Major complications were significantly more common in female patients ($P=0.008$) and in those with adenocarcinoma ($P=0.03$), but not related to previous chemo-irradiation, age, stricture length, and location.

Multiple complications caused by stent placement in esophageal malignancies have been described and range from 30 to 50% in most series. They are contingent upon tumor location, the presence or absence of a fistula or tumor shelf, use of concomitant chemo-irradiation, tumor vascularity, and the diameter and design of the prosthesis itself. The quality of the evidence that increased stent diameter associated with increased complications is moderate and the strength of evidence is high. The quality of evidence and the strength of evidence that other stricture characteristics are associated with higher complications are moderate and recommendation for SEMS placement is, nevertheless, high.

ESOPHAGEAL STENTS IN BENIGN DISEASE

The ideal stent characteristics for effective management of benign esophageal lesions are as follows: the stent should be easily retrievable or repositioned, technically easy to place, designed to have a small-caliber delivery device with minimal shortening on usage, have low migration rates, and finally, insertion and removal should be associated with minimal complications (4,67).

SEMSs in benign esophageal strictures

Although SEMSs are highly effective in the palliation of malignant esophageal strictures, several limitations preclude the routine use of partially covered stents in the management of benign esophageal disorders. A significant limitation of SEMSs is the difficulty in removing them after placement because of tissue embedment that occurs in the uncovered portion, rendering stent removal difficult and traumatic. Data regarding the use of SEMSs in benign conditions are in the form of case series and case reports. SEMSs placed for benign disease are associated with significant complications, such as high migration rates, bleeding, fistula, erosion into vital structures, recurrent strictures, and death (4,68–74). New stricture formation is believed to be due to fibrosis resulting from mechanical injury of the stent on the esophageal wall or due to ingrowth of the granulation tissue either through the mesh or at either end of the stent. Stent migration is more likely to occur with covered as opposed to uncovered stents because of the lack of traction on the esophageal wall.

In a retrospective analysis using partially covered SEMSs for benign indications that included eight patients with esophageal stent placement, half of the patients had major complications.

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Two patients developed strictures above the stent, one patient developed distal stent migration, and one patient died because of exsanguination as a result of erosion into the aorta (74). In a case series of three patients who had SEMSs placed for benign esophageal strictures, all three developed further strictures above the stents, one complicated by a tracheo-esophageal fistula and two stents in one patient migrated distally into the stomach (68). In one report, stent migration occurred in 7 of 12 patients (58%), and new stricture formation was seen in 50% of the patients (73). In another case series that reported the use of partially covered SEMSs in 10 patients with severe esophageal benign strictures, stent migration was seen in 3 patients with new strictures seen in 2 patients (69). A review of 29 patients in whom partially covered SEMSs were placed for benign esophageal strictures, new stricture formation was seen in 41%, stent migration in 31%, chest pain or reflux in 21%, tracheo-esophageal fistula in 6%, and anemia in 3% of the patients (72). Thus, the overall major complication rates associated with SEMSs from the available uncontrolled data may be as high as 80% (72).

On the basis of this prohibitive rate of complications, partially covered SEMSs in their current form are not recommended or FDA approved for benign esophageal conditions. The quality of evidence for the use of SEMSs for benign esophageal strictures is very low and the strength of recommendation is strong.

SEPSs in benign esophageal strictures

Recently, SEPSs have been increasingly used in the treatment of benign esophageal diseases that include esophageal strictures, fistulas, perforation, and anastomotic leaks. There are several advantages of SEPSs over SEMSs in the treatment of benign esophageal lesions, including the option of retrieval, limited local tissue reaction while providing alleviation of dysphagia and possibly lower costs (4,67,75–80). The stent is made of polyester netting embedded in a silicone membrane, creating a polyester mesh outer cover with a smooth silicone inner lining that is present for the entire length of the stent. The proximal end of the stent is flared in an attempt to prevent distal migration, whereas the middle and distal portions are of the same diameter. The tips of the polyester mesh at the proximal and distal ends of the stent are protected with silicone to avoid impaction or tissue damage. Barium is incorporated into the stent at its proximal end, distal end, and midpoint to assist fluoroscopic placement, whereas colored reference markings at the proximal and distal ends are useful during endoscopic positioning. Stents are placed endoscopically, often with the assistance of fluoroscopy and assembly is necessary before the procedure is conducted. Similar to SEMSs, the stent should cover the entire length of the stricture with an additional 1–2 cm above and below the stricture. Owing to the diameter of the stent delivery device (12–14 mm), dilation of the stricture may be necessary to assist with passage. Retrieval and/or repositioning can be accomplished endoscopically with foreign-body forceps or a standard polypectomy snare.

There are several case series and reports describing the placement of SEPSs in the management of benign esophageal disorders (**Table 7**). In a prospective study that evaluated the use of SEPSs in the treatment of benign esophageal conditions in 21 patients (17 esophageal strictures and 4 anastomotic leaks), temporary SEPS placement was curative (i.e., patients were symptom free with improvement in dysphagia scores) in 17 of 21 (81%) patients, especially in those with caustic and hyperplastic strictures and anastomotic fistula (76). Similarly, another case series reported on the efficacy of SEPSs in the management of esophageal strictures in 15 patients. Stent placement was successful in all patients, and with the stent *in situ* dysphagia completely resolved in all patients. Long-term resolution during a mean follow-up of 22.7 months was achieved in 80% of the patients (81). In another case series, SEPSs were placed in 39 patients: 13 patients with benign indications (esophageal strictures ($n=6$); esophageal fistula, leaks, perforation ($n=7$)). The stents were successfully used in all patients and clinical success defined by dysphagia relief and the ability to resume oral feeding was achieved in 69.2% of the patients (82). However, recent reports have tempered the initial enthusiasm regarding the use of SEPSs in the management of refractory esophageal strictures. A small case series of five patients with refractory esophageal strictures (three patients with benign esophageal strictures) who underwent SEPS placement reported a high complication rate, which included migration, esophageal perforation, and ulceration (83). A retrospective case series of 30 patients who underwent SEPS placement for benign esophageal disorders reported a high rate of stent migration (62.1%) with a disappointingly low rate (17%) of long-term improvement after stent removal. In addition, repeat stenting was required in 55% of the patients (75). Another prospective case series of 40 patients with refractory benign esophageal strictures who underwent SEPS placement (with subsequent removal in 4 weeks) showed that at median follow-up of 53 weeks, only 30% patients were dysphagia free (84). Complications included migration (22%), severe chest pain (11%), bleeding (8%), perforation (5.5%), and a single mortality caused by massive bleeding. A recent study compared esophageal stenting (SEPS) plus dilation with repeated dilation in patients with benign and postoperative anastomotic esophageal strictures (85). In all, 18 patients underwent SEPS placement and 24 were treated with standard repeated dilations without stents. Both groups showed a significant improvement in their dysphagia scores (SEPS: pre-therapy score 2.3, post-SEPS placement 1.2; dilation: pre-therapy 2.4, post-dilation 2.1, $P=0.02$). The SEPSs group required a lower median number of dilations compared with the dilation-alone group (2 vs. 4, $P=0.01$). Stent migration occurred in one patient and one patient required reintervention because of impacted food bolus. Although a formal cost-effectiveness analysis was not conducted, the median total charges, total direct costs, and insurance payments in the SEPSs plus dilation group were about twice the cost of dilation alone. If a single dilation was spared, the costs were equivalent, and if more than one dilation was spared, then SEPSs plus dilation was more cost efficient.

Overall, for benign esophageal strictures, success rates of SEPSs in the reported literature range from 17 to 95%. The etiology of clinical failures in various studies includes recurrence of strictures after stent removal, incomplete sealing of fistulas, leaks or perforations, and recurrent migrations. There are several issues

Table 7. Clinical series evaluating self-expandable plastic stents for benign esophageal diseases

Author (reference)	Type of study	Year	Number of patients (benign indications)	Indications	Technical success (%)	Clinical success (%)	Complications
Dua *et al.* (84)	Case series	2008	40	Esophageal strictures	95	30	Migration: 8/40 (20%)
							Bleeding: 3/40 (8%)
							Perforation: 2/40 (5.5%)
							Fistula: 1/40 (2.7%)
							Mortality: 1/40 (2.5%)
Holm *et al.* (75)	Case series	2008	30	Esophageal strictures	96.60	17	Migration: 18/29 (62.1%)
							Restenting: 16/29 (55.1%)
							Others: tracheal compression (3 procedures), aspiration pneumonia (2 procedures), pneumomediastinum (1 procedure)
Garcia-Cano *et al.* (77)	Case series	2008	4	Esophageal strictures	100	80	Migration: 3/4 (75%)
							Restenting: 4/4 (100%)
Pennathur *et al.* (78)	Case series	2008	38 (30)	Esophageal strictures ($n=25$)	NA	NA	Migration: 28/38 (73%)[a]
				Esophageal leak ($n=8$)			Persistent fistula or leak: 5/13 (38%)
				Tracheoesophageal fistula ($n=5$)			Restenting: 31/38 (81.5%)
							Others: reflux (4 patients), food impaction (3 patients)
Barthel *et al.* (79)	Case series	2008	8	Esophageal strictures	100	12.50	Migration: 11/13 (85%)
							Restenting: 4/8 (50%)
							Chest pain: 8/8 (100%)
Karbowski *et al.* (108)	Case series	2008	30 (20)	Esophageal strictures ($n=12$)	100	90	Migration: 5/20 (25%)
				Benign fistula ($n=2$)			Restenting: 54%
				Perforation and leak ($n=4$)			
				Others ($n=2$)			
Martin *et al.* (85)	Case–control	2008	18	Esophageal strictures	100	94	Migration: 1/18 (5%)
							Food bolus impaction: 1/18 (5%)
Ott *et al.* (107)	Case series	2007	35 (13)	Esophageal strictures ($n=1$)	100	Strictures: 95[a]	Migration: 37%
				Esophageal fistula, leak, perforations ($n=7$)		Others: 50[a]	Reintervention: 42.9%
Freeman *et al.* (109)	Case series	2007	17	Esophageal perforations	100	94	Migration: 3/17 (17.6%)
Fukumoto *et al.* (80)	Case series	2007	4	Esophageal leak post bariatric surgery	100	75	Migration: 2/4 (50%)
Triester *et al.* (83)	Case series	2006	5 (3)	Esophageal stricture	100	0	Migration: 1/3 (33.3%)
							Perforation: 1/3 (33.3%)
							Esophageal ulceration: 1/3 (33.3%)

Table 7 continued on following page

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Table 7. Continued

Author (reference)	Type of study	Year	Number of patients (benign indications)	Indications	Technical success (%)	Clinical success (%)	Complications
Radecke *et al.* (82)	Case series	2005	39 (13)	Esophageal strictures (*n*=6)	100	69.2[a]	Migration: 8/39 (20.5)[a]
				Esophageal fistula, leak, perforations (*n*=7)			Restenting: 14/39 (35.8%)
							Bleeding: 3/39 (7.7%)
							Others: mediastinal emphysema (*n*=1), tracheal compression (*n*=1)
Langer *et al.* (116)	Case series	2005	24	Anastomotic esophageal leaks	91.60	88.80	Migration: 9/24 (37.5%)
							Perforation: 2/24 (8.3%)
							Food bolus impaction: 1/24 (4.1%)
Schubert *et al.* (115)	Case series	2005	12	Anastomotic esophageal leaks	100	91.60	Migration: 2/12 (16.6%)
Repici *et al.* (81)	Case series	2004	15	Esophageal strictures	100	80	Migration: 1/15 (6.6%)
Evrard *et al.* (76)	Case series	2004	21	Esophageal strictures (*n*=17)	100	80	Migration: 12/21 (57.1%)
				Esophageal fistula (*n*=4)			Restenting: 5/21 (23.8%)
							Others: epiglottic stenosis (*n*=1) tracheal compression (*n*=1)
Gelbman *et al.* (115)	Case series	2004	9	Anastomotic esophageal leaks (*n*=5)	100	66	Migration: 2/9 (22.2%)
				Esophageal perforations (*n*=4)			
Hunerbein *et al.* (114)	Case series	2004	9	Anastomotic esophageal leaks	100	88.80	Migration: 2/9 (22.2%)
Costamagna *et al.* (24)	Case series	2003	16 (2)	Esophageal strictures	75	100[a]	Migration: 3/16 (18.7%)[a]

NA, not applicable.
[a]Unable to separate data between benign and malignant indications.

with regard to the available data on the management of benign esophageal strictures using SEPSs. Most studies do not provide a uniform dysphagia scoring system (**Table 8**). The use of a validated dysphagia score is essential in understanding the impact of SEPS placement. Similarly, definitions of technical and clinical success have varied among studies precluding an accurate comparison between patients across studies, a critical element in understanding the true impact of the endoscopic intervention. Definitions of clinical success ranged from immediate improvement of dysphagia, long-term improvement in symptoms, to dysphagia relief with the ability to resume oral feeding. Most studies do not provide information on stricture length or diameter at the time of stent placement, details regarding management of the pathology before stent placement, and previous attempts at endoscopic therapy (dilation, needle–knife techniques, steroid injection), and acid-suppressive therapy. This makes it difficult to ascertain with certainty the degree to which physicians have attempted to ameliorate strictures. A standardized definition of refractory and recurrent strictures has not been used uniformly in all studies. A definition of refractory and recurrent strictures has been proposed recently. This defines a stricture as an anatomical restriction because of

Table 8. Dysphagia scoring scale

0—Able to consume a normal diet
1—Dysphagia with certain solid foods
2—Able to swallow semi-solid soft foods
3—Able to swallow liquids only
4—Unable to swallow saliva (complete dysphagia)

cicatricial luminal compromise or fibrosis that results in the clinical symptom of dysphagia in the absence of endoscopic evidence of inflammation. This may occur as the result of either an inability to successfully dilate the anatomical stenosis to a diameter of 14 mm over 5 sessions at 2 weekly intervals (refractory) or as a result of the inability to maintain a satisfactory luminal diameter for 4 weeks once the target diameter of 14 mm has been achieved (recurrent) (86). Alterations to the design of the SEPS may decrease migration rate, but careful selection of patients and a better understanding of the pathophysiology and expected clinical response of the stricture to the endoprosthetics are required.

Complications of SEPSs in benign indications

Complications associated with SEPSs are similar to those associated with SEMSs. These may be classified as immediate, early, and late (65). Immediate complications include aspiration, airway compromise, malposition, stent dislodgement, and perforation. Early complications include bleeding, chest pain, nausea, and patient intolerance. Late complications include stricture recurrence or development of new strictures, esophageal perforation, esophageal ulceration, bleeding, gastroesophageal reflux, food impaction, and pneumomediastinum. However, stent migration, the need for repeat stenting, and stent failure are the three main late complications. The need for repeat stenting ranged from 24 to 100% of the cases reported. Stent migration is the most common complication with frequency ranging from 7 to 75% of the cases. Overall, the rate of migration of SEPSs seems to be higher than that of partially covered SEMSs. In most instances, the stents were removed endoscopically and anecdotal reports on the use of endoscopic clips to secure the stent to the mucosa are disappointing. The presence of short strictures and proximal and distal strictures are some of the factors that may promote stent migration (75,76,82). In addition, the risk of fatal bleeding from SEPS placement needs to be emphasized.

On the basis of these results and lack of success, SEPSs cannot be routinely recommended in treating refractory benign esophageal strictures until there is significant improvement in the design. The quality of evidence for the use of SEPSs is very low and the strength of recommendation is weak.

Retrievable self-expandable metallic and biodegradable stents in benign esophageal strictures

Fully covered retrievable SEMSs have been developed for malignant esophageal strictures and have been occasionally used off label for benign stenoses. FDA-approved fully covered SEMSs include the Niti-S (TaeWoong) and the covered Wallflex (Boston Scientific, Natick, MA) The Niti-S prosthesis has been available in Asia and Europe for several years. It is composed of a single thread of 0.2 mm nitinol wire shaped with wider-diameter proximal and distal ends in a dumbbell configuration and completely covered in polyurethane. Nylon loops are hooked inside each bend at the proximal end with two nylon monofilaments passing through each loop to create a drawstring to aid in removal. A stent retrieval system has been specifically designed for stent removal. An initial study using the prototype in 21 patients (5 benign refractory strictures) reported dysphagia relief in all benign cases and electively removed 8 weeks later from 4 patients with migration observed in 1 patient. Stricture recurrence was observed in two of the five patients (40%) (87). In a larger series of 25 patients with benign esophageal strictures using different designs, the same investigators reported that only five patients (20%) reached the end point of keeping the stent in place for 8 weeks before elective removal. New stricture formation was seen in 48% of the patients and one patient developed a small esophago-bronchial fistula (88). Thus, significant limitations exist with this stent, mainly new stricture formation and migration, which preclude the widespread use of this stent in the management of benign esophageal strictures. At the time of preparation of these guidelines, there were no published data regarding the risks, benefits, and outcomes of patients treated with a fully covered Wallflex stent.

Recently, the Alveolus esophageal stent system was introduced and is approved by the FDA for maintaining esophageal lumen patency in esophageal strictures caused by intrinsic and/or extrinsic malignant tumors and for occlusion of esophageal fistulas. This nitinol stent is fully covered internally, allowing the outer portion to adhere to the esophageal wall. In an animal study using eight Yucatan pigs, the Alveolus stent at the end of 4 weeks resulted in minimal tissue response in the esophagus and was endoscopically removed easily and atraumatically (89). The efficacy in the treatment of refractory benign esophageal strictures in nine patients has been reported in an abstract form. A total of 13 stents were placed in 9 patients, and the mean dysphagia score at 12 weeks was significantly better than the pre-stenting scores (90). In another recent report, 19 Alveolus stents were placed in 7 patients (anastomotic leak 5, perforation 1, and tracheoesophageal fistula 1). The stent successfully occluded the leak or fistula in four of the seven patients (57%) (91). Long-term prospective data collected from RCTs are required to determine whether the Alveolus stent has a beneficial role in benign esophageal diseases.

There has been some interest in the use of biodegradable stents in the treatment of benign esophageal conditions, which could potentially decrease the need for reinterventions to remove the stent. In a single case series from Japan, 13 patients (caustic stricture 2, postsurgical resection of esophageal cancer 4, esophageal cancer post-endoscopic submucosal dissection 7) with benign esophageal stenosis were treated with a biodegradable stent constructed with poly-L-lactic acid monofilaments. Stent migration was seen in 77% of the cases within 10–21 days of placement and the stents remained in position in 3 cases. No symptoms of restenosis were observed and further endoscopic therapies were not required. The same investigators reported encouraging results in two patients with esophageal strictures after endoscopic submucosal dissection of early esophageal cancer (92). Further studies using these types of stents are awaited.

Further long-term prospective data obtained from controlled trials are awaited before retrievable self-expandable metallic and biodegradable stents can be recommended for the management of benign esophageal lesions.

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Esophageal stents in the management of esophageal perforations, leaks, and fistulas

Spontaneous or iatrogenic esophageal perforations, esophageal fistula, and disruption of esophageal anastomosis are potentially life-threatening events that are associated with high morbidity and mortality rates (93–95). Successful management of perforations depends on early/immediate diagnosis and prompt intervention to prevent fulminant mediastinitis. The classic surgical treatment options include repair, esophagectomy, or cervical exclusion along with clearance of mediastinal and peritoneal contamination, infection, and inflammation by successful drainage. Despite major advances in surgery, the mortality rate remains high (96). Primary closure and mediastinal drainage within 24 h of the injury have been shown to improve survival (97). However, after a delayed diagnosis, surgery involves high morbidity and mortality, particularly in patients with mediastinal and pleural contamination. In addition, in elderly and debilitated patients, anastomotic disruption after esophagectomy and perforation associated with invasive esophageal cancer are markers of a poor outcome. Surgical mortality equals that of conservative management in these groups of patients (98). In recent years, the placement of esophageal stents has been described as a promising modality in the management of these conditions. This is performed under direct visualization of the pathology under conscious sedation, thus eliminating the risks associated with anesthesia and also avoids extensive dissection associated with surgical option. As in the management of esophageal strictures, the literature on stenting in these situations is also limited to case reports and case series.

The use of esophageal stents in the management of spontaneous esophageal perforations (Boerhaave's syndrome) has been described in several case reports (99–102). Results have been mixed and complications included bleeding, stent-related strictures, tissue ingrowth, fistula formation, and migration. A case series of three patients with Boerhaave's syndrome who were treated with SEMS (Song and Niti-S stents) reported favorable outcomes (i.e., closure of the perforation). Stents were placed between 4 and 30 days of the event and removed without any difficulty 2–6 months later (101). A similar favorable response was seen in a patient with Boerhaave's syndrome who underwent SEPS placement (102).

Esophageal stenting has also been reported in the management of perforations secondary to endoscopic therapies such as esophageal dilation, tumor resection, and secondary to external blunt and sharp trauma. Successful experiences with esophageal stent placement in these situations especially in perforations smaller than 50–70% of the circumference have been reported. In one case series, 11 consecutive patients who presented with traumatic nonmalignant esophageal perforations and diagnosis was delayed by >24 h were managed by SEMS placement. Pleural cavities were drained with thoracostomy drains and antibiotics were administered. Stents were placed at a median of 60 h after the onset of symptoms. The stents completely sealed the perforation in 9 of 11 patients, whereas 2 patients still required esophagectomy because of inadequate closure of perforation and incomplete drainage. In seven patients, the stents were retrieved endoscopically (103). In another case series of three patients with iatrogenic esophageal perforations, successful closure of the perforation was reported in all three cases using SEMSs; however, stent migration was reported in all three cases and esophageal stricture in one (104). In another prospective study, partially covered SEMSs were used in 22 consecutive patients with esophageal perforations or rupture (13 benign etiologies). Successful closure of the lesion was achieved in 12 of 13 benign cases, and all stents were retrieved with no complications after 3 weeks (105). A recent retrospective study compared outcomes in 15 consecutive patients with benign spontaneous and iatrogenic esophageal perforations treated with SEMSs; one group underwent stent placement with an average time delay of 45 min (group 1) and the other at 123 h (group 2). Treatment was successful in all patients in group 1, whereas one patient in group 2 died of pneumonia and the majority had their hospital course complicated by sepsis and multiorgan failure. Immediate insertion of stent placement enabled an excellent outcome with minimal morbidity in this group of patients and even in patients with delayed diagnosis, sealing with SEMSs achieved good outcomes compared with surgery (106). Recently, placement of SEPSs has also been described in the management of esophageal perforations (82,107–109). A prospective case series described the use of SEPSs in 17 patients with iatrogenic esophageal perforations at a tertiary care medical center. Leak occlusion as confirmed by an esophagogram was achieved in 16 patients (94%), but stent migration was observed in 3 patients (17.6%) (109).

A case series of three patients with postoperative anastomotic leaks treated with SEMSs reported clinical success in all three patients (110). Similarly, another recent case series described the management of six patients with postoperative anastomotic leaks using SEMSs. Leaks were successfully closed in all patients and oral feeding was resumed on day 2. Stent migration was observed in two patients (111).

The use of SEMSs in temporary sealing of acquired benign tracheoesophageal fistulas was described in a case series of 12 mechanically ventilated patients. Stent placement was successful in all patients and fistula occlusion was achieved in every case. No stent migration was reported and fistulas remained sealed until death or upon decision for removal. Nine patients died because of the primary disease and three patients were referred for surgery, before which the stents were removed easily (112). In a case series of 19 patients with anastomotic leaks after esophagectomy, the initial 10 patients were treated by re-exploration or conservative means, whereas the next 9 patients received a large-diameter SEPS a median of 8 days after resection. Leak occlusion was established in eight of nine patients (89%). The mean time to stent removal was 4 weeks and stent placement led to earlier oral intake and a shorter hospital stay (113). In another study, SEPSs were placed in nine patients with anastomotic leaks after esophageal resection or perforation. The leaks were completely sealed in seven of nine patients (78%). Stent migration was observed in 33% of the cases (115). Finally, a case series of 12 patients with esophageal anastomotic leaks who were treated with large-diameter SEPS along with perianastomotic mediastinal drainage by chest drains, complete closure of the leakage was achieved in 11 of 12 patients (91.6%) (115). These investigators suggested that for patients with small

leaks (<30% of circumference) endoscopic fibrin glue injection or clipping should be performed, in patients with 30–70% circumferential dehiscence stent placement should be considered, and finally for patients with >70% dehiscence, surgery is recommended. However, these recommendations have not been validated in prospective trials. In another study, 24 patients with esophageal anastomotic leaks underwent SEPS placement. Stent placement was successful in 22 of 24 patients and clinical success was achieved in 16 of 22 patients (72%) (116).

In conclusion, in selected cases, SEMSs and SEPSs can be considered in the treatment of esophageal perforation. However, the quality of evidence for the use of esophageal stenting in the management of esophageal perforations, leaks and fistulas is very low and the strength of recommendation is weak.

CONCLUSIONS

Esophageal stenting using SEMSs is currently the most common means of palliation of malignant dysphagia. SEMSs are clearly superior to rigid plastic prostheses in the management of unresectable obstructive esophageal cancers, and covered SEMSs are preferred to uncovered SEMS mainly because of lower rates of tumor ingrowth. There are minor differences in the efficacy and complication rates between the various available SEMSs, and hence one brand of SEMSs over the other cannot be recommended. It seems that SEPSs when used for malignant dysphagia are associated with significantly higher complication rate than SEMSs. Future research should focus on the development of stents associated with low migration rates and less tumoral/nontumoral overgrowth that ultimately decrease reintervention rates. In addition, there has been increasing interest in the use of SEPSs in the management of benign esophageal conditions, such as benign refractory esophageal strictures, tracheoesophageal fistulas, esophageal perforations, and leaks. Data on the use of SEPSs in the management of benign refractory esophageal strictures have been mixed. Until there is a significant improvement in the design, SEPSs cannot be routinely recommended for this indication. The use of self-expandable stents for the management of anastomotic leaks and perforations seems promising. Long-term prospective data obtained from controlled trials on the use of retrievable SEMSs and biodegradable stents in the management of benign esophageal lesions are eagerly awaited.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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