



# Adverse events of self-expandable esophageal metallic stents in patients with long-term survival from advanced malignant disease



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**Background and Aims:** Self-expandable metallic stents are considered the best palliative treatment of dysphagia for patients with advanced esophageal cancer. Adverse events (AEs) are a major concern, especially in patients with better prognosis and longer survival. The present study aimed to evaluate the AEs of patients who survived longer than 6 months with esophageal stents in place.

**Methods:** This is a retrospective analysis of a prospectively collected database including all patients submitted to esophageal stent placement for the palliation of malignant diseases during the period from February 2009 to February 2014 at a tertiary care academic center who had stents longer than 6 months.

**Results:** Sixty-three patients were included. Mean follow-up was 10.7 months. Clinical success was achieved in all patients, and the median stent patency was 7.1 months. AEs occurred in 40 patients (63.5%), totaling 62 AEs (mean, 1.5 AEs per patient). Endoscopic management of AEs was successful in 84.5% of cases, with a mean of 1.6 reinterventions per patient. The univariate analysis revealed that performance status, age, and post-stent radiotherapy presented a trend to higher risk of AEs. The multivariate analysis revealed that only performance status was associated with AEs ( $P = .025$ ; hazard ratio, 4.1).

**Conclusions:** AEs are common in patients with long-term esophageal stenting for malignancy. However, AEs were not related to higher mortality rate, and most AEs could be successfully managed by endoscopy. Only performance status was a risk factor for AEs. Our data suggest that metallic stenting is a valid option for the treatment of malignant esophageal conditions, even when survival longer than 6 months is expected. (*Gastrointest Endosc* 2017;86:299-306.)

Abbreviations: AE, adverse event; ECOG, Eastern Cooperative Oncology Group; SEMS, self-expandable metallic stent.

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Despite recent advances in the diagnosis and treatment of esophageal cancer, more than half of malignancies involving the esophagus are inoperable at presentation because of locally advanced or metastatic disease.<sup>1</sup> The prognosis of esophageal cancer is dismal, with a 5-year survival rate below 20%.<sup>2</sup> Esophageal stenosis and esophagorespiratory fistula are frequent adverse events (AEs), usually associated with weight loss, nutritional deficiency, and low quality of life.<sup>3</sup> A variety of treatment modalities has been used to palliate dysphagia in patients with advanced esophageal tumors such as endoscopic ablation, radiotherapy, brachytherapy, endoluminal stents, and surgery.<sup>4</sup>

Self-expandable metallic stents (SEMSs) are considered the mainstay palliative treatment of dysphagia for patients with advanced esophageal cancer.<sup>5-7</sup> SEMSs provide rapid, efficient, and lifelong relief of dysphagia in most patients and are the most common palliative treatment modality performed worldwide.<sup>8,9</sup> However, migration, bleeding, fistula, and tumor or hyperplastic tissue overgrowth are common long-term AEs of definitive SEMSs and represent a major concern, especially in patients with better prognosis and longer survival.<sup>10,11</sup> The incidence of long-term esophageal stent-related AEs varies widely in the literature, with reported values ranging from 20% to 50%.<sup>12-14</sup> However, most data concerning late AE rates come from relatively small cohorts with reported median stenting times shorter than 3 months.<sup>12-14</sup>

The aim of this study was to evaluate the rate of AEs among patients who survived longer than 6 months with esophageal stents in place and the endoscopic management of these AEs. In addition, we wanted to study possible predictive factors associated with SEMS-related AEs in this clinical setting.

## Methods

We conducted a retrospective analysis of a prospectively collected database including all patients submitted to esophageal stent for palliation of malignant strictures or malignant fistulas between February 2009 and February 2014 at the Cancer Institute of the University of São Paulo. After multidisciplinary evaluation, patients were considered beyond the scope of curative surgical and oncologic treatment. For the purpose of this study, only patients who remained with the stent longer than 6 months were included in the analysis. Patients with benign stenosis or fistula because of anastomotic leakage were excluded. This study was approved by the Institutional Review Board of our institution (registration number: NP038/14).

## Stent implantation

All procedures were done under the supervision of an anesthesiologist. Patients were placed in the supine position or left lateral decubitus. Before stent insertion, an endoscopy was performed to evaluate the tumor length

and location. When it was possible to traverse the tumor with a conventional or slim endoscope, a stiff guidewire was used to guide the stent insertion. When the tumor was not traversable and thin endoscopes were not available, a hydrophilic guidewire preloaded into a biliary catheter was used to traverse the stricture under fluoroscopic monitoring, and iodine-based dye was used to estimate tumor length (dilation was avoided). External markers or lipiodol injection in the esophageal walls was used to mark the tumor's limits. Stent length was chosen to cover at least 2 cm beyond each tumor edge.

Stents were deployed under fluoroscopic control. For tumors of the upper third close to the cricopharyngeus, endoscopic control was also used to ensure the best positioning of the proximal flare. An esophagogram with iodine-based solution was obtained immediately after stent placement to confirm the adequate flow of contrast to the stomach and to confirm fistula sealing when it was present.

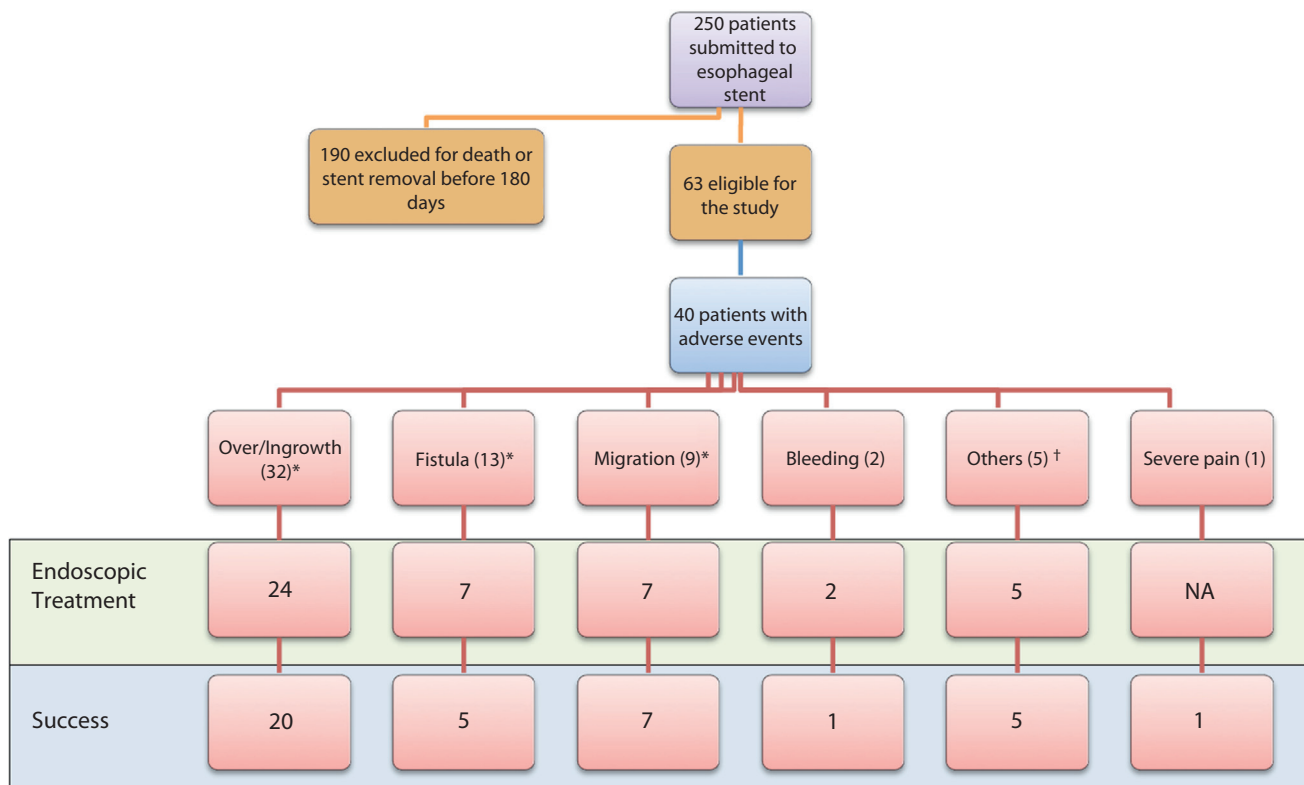
For lesions located in the proximal esophagus, we used a dedicated model of a partially covered stent with a low-profile, proximal flare shape (Choostent; MI Tech, Pyeongtaek, Korea). For lesions located in the mid-esophagus, we used a standard partially covered stent or, less often, a fully covered stent, with an 18- to 23-mm body diameter and 23- to 28-mm flare diameter (Wallflex and Ultraflex [Boston Scientific, Watertown, Mass], Evolution [Wilson Cook Medical, Letchworth, UK], Hanarostent [MI Tech], or Endoflex [Voerde, Germany]). If it was predicted that the stent would traverse the esophagogastric junction, we used a partially covered stent with an antireflux valve (Hanarostent Esophagus Valve; MI Tech).

Patients received pre-emptive analgesia with morphine at a dose of 10 mg orally 3 times a day associated with a nonopioid analgesic for 14 days. On-demand simple analgesics (eg, paracetamol) to control mild pain were allowed after this period.

## Follow-up

Clinical success was defined when patients were able to resume oral intake of liquid and solid foods. For patients with malignant fistula, clinical success was defined when patients were able to tolerate liquid and solid intake without coughing or choking. Sealing of the fistula was confirmed by esophagogram performed just after stent implantation.

Follow-up time was defined from the day of stent implantation until the last clinical visit or death. After stent placement routine visits were scheduled at 1, 3, 6, 9, and 12 months, and a standard questionnaire was applied for all patients. For patients who missed the clinic appointment, contact by telephone was made for a follow-up interview. The presence of any symptoms that suggested stent malfunctioning (recurrence of dysphagia, coughing related to liquid swallowing, pain, etc) was an indication for endoscopic re-evaluation.



**Figure 1.** Study flowchart. \*Patients not submitted to endoscopic intervention were treated with nasogastric tube or gastrostomy. †Food impaction (n = 4) and GERD (n = 1). NA, Not applicable. Adverse event not amenable to endoscopic treatment.

The expected AEs were migration (stent dislodgment confirmed by endoscopy), overgrowth/ingrowth (tissue growth preventing endoscope passage), food impaction, bleeding (hematemesis and/or melena with clinical repercussion caused by tumor bleeding confirmed by endoscopy), esophageal perforation, stent-induced fistulas (compatible clinical symptoms associated with the presence of fistulous orifice detected at endoscopy), severe pain, and severe gastroesophageal reflux (heartburn or regurgitation associated with the findings of peptic erosions at endoscopy). AEs were classified into *minor* when the stent dysfunction could be managed clinically or endoscopically and no life-threatening situation was present or *major* when it was a life-threatening situation or when a major intervention such as surgery was required. AE-related death was defined as patient death caused by a stent-related AE. If an AE was adequately treated but recurred, it was considered as a new AE.

**Management of stent dysfunction**

If there was a distal dislodgment but the stent remained at the esophagus, endoscopic traction was achieved using rat-tooth forceps.<sup>15</sup> Stents that migrated into the stomach were completely removed with a rat-tooth forceps and a biliary pusher, as previously described.<sup>16</sup> Tumor ingrowth or overgrowth was

treated with argon plasma coagulation, dilation, or the combination of both. In refractory cases a second stent was placed. Stent-induced fistula was managed by placement of another stent.

**Statistical analysis**

Survival was calculated by the Kaplan-Meier method, and curves were compared by the log-rank test. Univariate analysis by Cox regression was used to explore the correlation between the predictor variables and the outcome variable (AEs). The variables with  $P \leq .1$  were included in the multivariate analysis by Cox regression. For categorical comparison of data, the  $\chi^2$  test and the Fisher exact test were used as appropriate. Statistical significance was defined as  $P \leq .05$ . Statistical modeling and tests were performed with SPSS software, version 21.0 (SPSS Statistics for Windows, Version 21.0, IBM Corp., Armonk, NY).

**RESULTS**

**Patient characteristics**

From February 2009 to February 2014, 250 patients were submitted to esophageal stent insertion and 63 patients fulfilled the inclusion criteria (Fig. 1). There was a predominance of men (74.6%), and patient mean age was 61.4 years (range, 42-79). Performance status

**TABLE 1. Patients and stents characteristics**

Characteristic	Value
Mean age, y	61.5
Gender, male/female	47/16
Tumor location	
Upper third	8
Middle third	34
Distal third	21
Histology	
Squamous cell carcinoma	51
Adenocarcinoma	10
Other	2
Indication for stent placement	
Dysphagia	49
Fistula alone	8
Dysphagia with fistula	4
Extrinsic compression	2
TNM staging	
Stage III	42
Stage IV	21
Eastern Cooperative Oncology Group scale	
0	10
1	26
2	18
3	9
Stent type	
Fully covered	7
Partially covered	56
Stent brand	
Evolution	24
Wallflex	15
Hanaro	14
Others	10
Prestent therapy	
Radiotherapy, yes/no	20/43
Chemotherapy, yes/no	44/19
Further therapy with stent in situ	
Radiotherapy, yes/no	14/49
Chemotherapy, yes/no	47/16

according to the Eastern Cooperative Oncology Group (ECOG)<sup>17</sup> was 0 (n = 10), 1 (n = 26), 2 (n = 18), and 3 (n = 9). The most common cancer was squamous cell carcinoma (80.9%), and most lesions were located in the middle esophagus (53.9%). Regarding stents placed initially, 56 were partially covered (88.8%) and 7 were fully covered. Demographic characteristics are shown in Table 1.

**TABLE 2. Time of occurrence of each adverse event (P < .005)**

Adverse events	<30 days	30-180 days	>180 days
Ingrowth/overgrowth	—	8	24
Fistula	—	6	7
Migration	4	2	3
Food impaction	1	—	3
Bleeding	—	—	2
GERD	—	1	—
Severe pain	—	1	—
Total	5	18	39

—, No event occurred in this time period.

## Follow-up

The indication for stent placement was dysphagia because of esophageal malignancy in 49 patients (77.7%), malignant fistula in 8 patients (12.6%), dysphagia associated with fistula in 4 patients (6.3%), and extrinsic compression in 2 patients (3.1%). Clinical success was achieved in all patients. The median stent patency (until death or stent dysfunction) was 7.1 months (standard deviation, ±3.8). Only 4 patients had their stent removed during the follow-up.

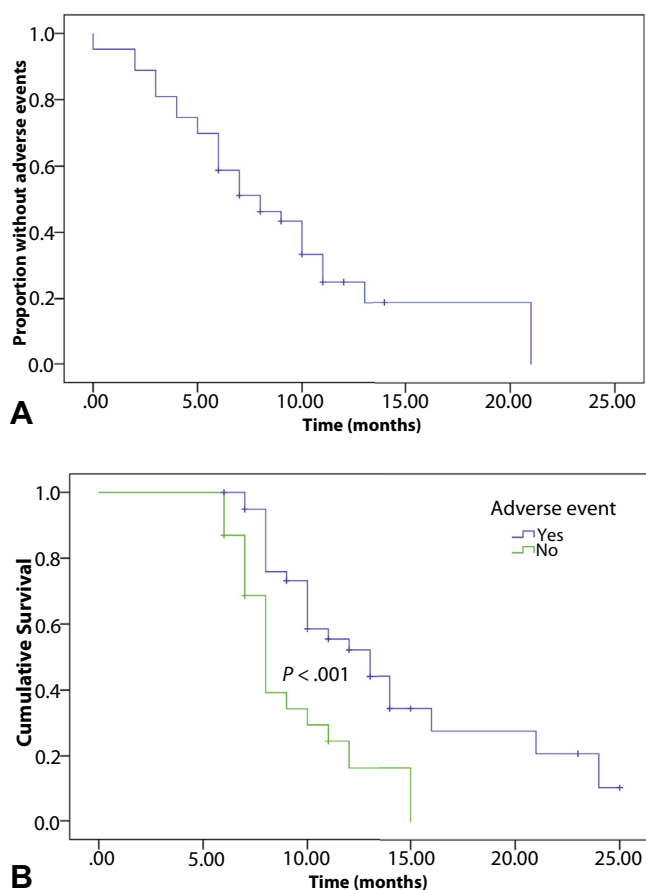
Mean follow-up time was 10.7 months (range, 6.1-25). At the end of follow-up, 37 patients (58.7%) had a functioning stent and were accepting oral intake. Twenty-six patients (41.2%) were not accepting oral intake: 20 because of cachexia and 6 because of stent dysfunction refractory to endoscopic treatment. A nasogastric tube or gastrostomy feeding was used for these patients.

There were 2 cases of extrinsic esophageal compression caused by metastatic breast cancer and lung cancer. The first patient had 3 episodes of overgrowth and ingrowth. All episodes were endoscopically managed with success, and the patient survived 25 months with a patent stent. The patient with lung cancer had 2 episodes of overgrowth, both successfully treated by endoscopy. Dysphagia recurred 12.8 months after stent placement, when a nasogastric tube was placed; the patient died 10 days later.

## Adverse events

AEs occurred in 40 patients (63.5%). Sixteen patients had more than 1 AE, and 5 patients had recurrence of a previously treated AE (4 patients with recurrence of ingrowth/overgrowth and 1 patient with recurrence of migration). There were a total of 62 AEs, with a mean of 1.5 AEs per patient. Five AEs occurred within 30 days of stenting, 18 occurred between 30 and 180 days, and 39 occurred after 180 days (P = .042). Table 2 shows the occurrence of each AE according to 3 different periods of time. Figure 2A shows the likelihood of AE occurrence with time.

Most AEs (n = 47, 75.8%) were minor and included severe pain (1), severe reflux (1), migration (9), ingrowth/



**Figure 2.** A, Likelihood of adverse event occurrence with time. B, Survival curves of patients with and without adverse events.

overgrowth (32), and food impaction (4). There were 15 major AEs: 13 esophageal fistulas and 2 bleedings. Endoscopic treatment was attempted in 9 of 15 major AEs, with success in 6. Three major AEs were fatal: 2 patients had esophagorespiratory fistulas and died from pulmonary sepsis and 1 died because of tumor bleeding. Figure 1 summarizes AEs and endoscopic interventions.

### Management of stent dysfunction

Endoscopic management was not attempted in every stent-related AE. When patients were considered too ill (usually because of cachexia) to be submitted to an endoscopic intervention, they were palliated with a nasoenteral tube or a gastrostomy. Twenty-six patients of our cohort advanced to this situation. The mean time to cessation of endoscopy efforts for these patients was 8.3 months. When endoscopic treatment was attempted, the success rate was 84.5% and the mean number of reinterventions per patient was 1.6 (range, 0-10). One patient with severe pain required opioid analgesia (morphine) for 4 months after stent placement.

The management of the 3 most common AEs are briefly described as follows. Thirty-two patients were

managed for ingrowth or overgrowth: 11 were treated with argon plasma coagulation and/or dilation, 13 patients required a second stent, and 8 received palliative care (nasoenteral tube). For the 13 patients with stent-induced fistula, 7 received a second SEMS (6 with clinical success) and 6 received palliative care (nasoenteral tube or gastrostomy). Finally, 9 patients experienced migration. Five had their stents successfully repositioned with endoscopy, 2 had their stents completely removed and received a second stent, and 2 received palliative care (nasoenteral tube).

### Risk factors for AEs

The univariate analysis showed that ECOG status, age, and radiotherapy after stent placement presented a trend to higher risk of AEs. However, on multivariate analysis only ECOG status was associated with AEs (hazard ratio, 4.1; 95% confidence interval, 1.339-12.105). There was no statistically significant correlation between AE and chemotherapy, stent features, duration of stenting, or tumor characteristics (Table 3). Patients submitted to chemotherapy before stenting did not present higher migration rate (13.6% vs 10.5%,  $P > .999$ ). Patients submitted to radiotherapy before stenting did not present higher migration (10% vs 14%,  $P > .999$ ) or “de novo” fistula rates (25% vs 18.6%,  $P = .739$ ). Patients who presented AEs survived longer than patients without AEs (Fig. 2B).

### DISCUSSION

Metallic esophageal stenting is the most common palliative intervention for malignant dysphagia and malignant esophageal fistula.<sup>2</sup> In spite of being an efficient and safe method and providing rapid relief of dysphagia, AEs may occur in up to half of the patients in some series.<sup>14</sup> This is a concern, especially in patients with longer survival. It is important to point out that with modern palliative treatment for squamous cell carcinoma, survival can reach up to 19 months.<sup>18</sup> In this study we present data related only to patients who remained with esophageal stents in place for longer than 6 months. Most data available in the literature include patients with a shorter time of stenting or a heterogeneous cohort of patients with benign and malignant conditions.<sup>12,19,20</sup>

The overall AE rate in our cohort was 63.5%. Thirty-four of 63 patients (53.9%) had to undergo endoscopic reintervention (mean, 1.6 reinterventions per patient). In spite of the high incidence of AEs, 75.8% were minor and 84.8% of all AEs could be managed clinically or endoscopically with success. Most AEs occurred after 180 days, and the median survival of patients with AEs was longer than patients without AEs (13.2 vs 7.9 months,  $P < .001$ ). We believe that patients who survived longer had more time to

**TABLE 3. Univariate and multivariate analysis by Cox regression of the risk factors for adverse events**

Variables	Univariate			Multivariate		
	Hazard ratio	95% CI	P value	HR	95% CI	P value
Age	.958	.913-1.004	.075	.961	.916-1.007	.095
Histologic type (extra esophageal/SCC)	3.140	.743-13.438	.123			
Histologic type (adenocarcinoma/SCC)	1.114	.505-2.457	.788			
Tumor location (distal/upper)	2.036	.586-7.068	.263			
Tumor location (middle/upper)	1.441	.427-4.866	.557			
Tumor extension	.971	.852-1.105	.653			
Fistula (yes/no)	1.786	.806-3.959	.153			
TNM staging	1.466	.757-2.842	.257			
Eastern Cooperative Oncology Group (1-3/0)	4.115	1.339-12.105	.010	3.672	1.177-11.456	.025
Chemotherapy before stent (yes/no)	.937	.479-1.834	.850			
Chemotherapy after stent (yes/no)	.483	.144-1.616	.238			
Radiotherapy before stent (yes/no)	.989	.498-1.964	.974			
Radiotherapy after stent (yes/no)	1.833	.937-3.587	.077	1.229	.598-2.526	.574
Stent brand (others/ Evolution)	1.055	.352-3.163	.923			
Stent brand (others/ Wallflex)	1.454	.448-4.725	.533			
Stent brand (others/ Hanarostent)	.444	.129-1.525	.197			
Stent caliber	1.089	.958-1.238	.193			
Stent length	1.031	.894-1.189	.671			
Coverage (partial/full)	1.591	.487-5.197	.445			
Transcardiac (no/yes)	1.293	.652-2.562	.462			
Duration of stenting	.999	.997-1.002	.543			

CI, Confidence interval; SCC, squamous cell carcinoma.

experience AEs. These findings indicate a cumulative chance of AEs with long-time stenting, without impact on mortality. Homann et al<sup>14</sup> analyzed 133 patients with esophageal SEMSs and found an overall incidence of delayed AEs of 53.4%. However, the cut-off definition for delayed AEs was only 4 weeks. In support of our results, the authors found that the median survival in patients submitted to endoscopic therapy was longer than in patients who did not require reintervention.

AE rate in our cohort was higher than those reported in other studies.<sup>12,14,19</sup> Schoppmann et al<sup>12</sup> retrospectively evaluated the safety and efficacy of 70 patients with long-term esophageal stenting (>120 days) for various indications. The overall AE rate was 30%, and endoscopic reintervention was necessary in 17.1% of patients. However, their cohort included patients with benign stenosis and postoperative leakage, and 60% of stents were placed in a temporary intention. Moreover, it is not clear how many patients underwent stent removal. The higher AE rate in our study probably reflects our cohort that included only palliative patients with advanced disease who remained stented at least more than 180 days.

The impact of chemoradiation on the esophageal SEMS results is contradictory in the literature. Some studies

report longer survival for patients palliated with esophageal SEMSs who also received chemotherapy and/or radiotherapy compared with those treated with stent alone. Moreover, radiation therapy could prolong overall stent patency.<sup>1,11</sup> However, some evidence supports adjuvant therapy increasing stent-related AEs, especially migration.<sup>2,21</sup> In our study we found a trend to higher AE rates in patients submitted to radiotherapy, albeit not statistically significant ( $P = .08$ ).

Migration was the third most common AE in this series. The efficacy of antimigration measures is always a matter of debate.<sup>15</sup> To minimize the risk of migration, we prefer a partially covered stent in the palliative setting. Curiously, all 9 patients who experienced stent migration had a partially covered stent, and none of the patients with fully covered stent presented this AE. Suture and Ovesco clipping would be our preference, but they are not yet available in our country. Standard clips seem too fragile to keep the stent in place, although it is a simple and low-cost technique that could be applied to patients at risk for migration. In our practice, when we judge that there is a higher risk of migration (eg, stenting for malignant fistula without stenosis), we use a temporary external fixation method with a modified Shim's technique as

previously described by our group.<sup>22</sup> We are not sure about the use of antimigration measures in a routine fashion. From the available antimigration techniques, only suturing seems to last longer than the first few days, which would be the period of higher risk of migration because the uncovered flanges of the stent would not be embedded in the esophageal wall. From the 4 migration episodes during the first 30 days observed in the present series, 2 occurred in a patient with achalasia and dilated esophagus that did not accommodate the stent. Excluding this uncommon situation, we had 2 migrations before 30 days in 62 patients, or a 3.2% 30-day migration rate. This finding could argue against the routine use of antimigration measures.

In a retrospective study of patients with malignant strictures submitted to SEMS placement, Fuccio et al<sup>23</sup> demonstrated that longer stents protected against the occurrence of AEs. This finding was not confirmed in our study. Other stent features and tumor characteristics were also not related to AEs. On the other hand, poor performance status (ECOG) was associated with increased AEs. We hypothesize that poor performance status could be associated with neoplasia that present a more aggressive biologic behavior that could theoretically explain a higher rate of tumor ingrowth, overgrowth, fistulization, and bleeding.

Alternative therapies like intraluminal brachytherapy have emerged in recent years. The relief of dysphagia is delayed when compared with SEMS insertion, but better improvement in dysphagia and lower AE rates were identified with brachytherapy treatment.<sup>2</sup> In a review the authors found strong evidence to support the use of intraluminal brachytherapy in the symptomatic treatment of patients with advanced esophageal cancer in a palliative setting, suggesting brachytherapy as the treatment of choice in patients with a life expectancy greater than 3 months.<sup>24</sup> However, this procedure is not widely available and requires dedicated logistics and experienced professionals. Stent insertion combined with single-dose brachytherapy has been reported and seems to be feasible and safe, besides providing a longer dysphagia-free period and longer survival.<sup>25-27</sup>

The main drawback of long endoscopic stenting is dysphagia recurrence, through ingrowth/overgrowth, migration, fistula, or food impaction. Nevertheless, endoscopic reinterventions are efficient, safe, and acceptable. McManus et al<sup>10</sup> evaluated a population of 165 patients who received a metallic stent, most (n = 132) because of esophageal cancer, and aimed to determine the rate of reintervention and effectiveness of the various intervention modalities. They found an AE rate of 26.6% with a total of 75 reinterventions (mean, 1.7 per patient) and a success rate of 68%. Survival after first reintervention was comparable with that after initial stenting (median 9.8 weeks and 14.3 weeks, respectively). In our series we found a similar

reintervention rate per patient (1.6), although endoscopic reintervention was more efficient with 84.5% of success. Restenting was performed in 23 patients: 13 for ingrowth/overgrowth, 7 for fistulas, 2 for migrations, and 1 for severe reflux. The patient with severe reflux received an antireflux valve stent. A combination of methods (argon plasma coagulation, dilation, foreign body removal) was applied to treat other patients. No surgery was required to treat stent-related AEs. It is possible to infer that an early endoscopic approach for stent-related AEs can improve the quality of life in patients with advanced gastroesophageal tumors palliated with SEMSs, as has been previously exposed.<sup>14</sup>

Our study had some limitations, mainly because of its retrospective design and single-center study. Also, we did not apply a quality of life questionnaire. However, in our study we present a significant number of patients who were treated with palliative intentions submitted to esophageal SEMSs, followed for longer than other series, allowing us to have a broad picture of the long-term effects of esophageal stents in the palliative treatment of malignant dysphagia.

In conclusion, our data demonstrate that long-term esophageal stenting in patients with malignant disease involving the esophagus is related to a relatively high prevalence of AEs. However, AE was not related to higher mortality rate, and most cases were minor events that could be managed endoscopically. Fatal AEs were uncommon. Performance status was the only predictive factor for AEs. Our data suggest that metallic stenting is a valid option for the treatment of malignant esophageal conditions, even when survival longer than 6 months is expected.

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