TRABAJOS ORIGINALES

Self-expandable metal stents are a valid option in long-term survivors of advanced esophageal cancer

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ABSTRACT

Background: self-expandable metal stents are often used for the palliative treatment of dysphagia in patients with advanced esophageal cancer and an anticipated limited survival. Due to previous reports of a high rate of adverse event when used long-term, concerns have been raised with regard to the use of self-expandable metal stents in patients with a longer survival.

Aim: assess the role of esophageal self-expandable metal stents in patients with advanced esophageal cancer that have survived longer than six months.

Methods: retrospective study of patients with advanced esophageal cancer with a self-expandable metal stent and a stent placement time greater than six months.

Results: forty-two patients were followed up for 298 days. There was a clinical improvement in all patients. However, 59% of patients experienced an adverse event. The median stent patency was 236 days. Endoscopic management was attempted in all self-expandable metal related adverse events, with a clinical success rate of 100%. However, the previously treated adverse event recurred in seven patients. Multivariate analysis showed that strictures that were traversable with an ultrathin gastroscope were associated with a higher risk of adverse events (p = 0.035).

Conclusions: long-term esophageal stenting in patients with advanced esophageal cancer is associated with a high prevalence of adverse events without an impact on mortality; most cases can be managed endoscopically.

Key words: Adverse events. Esophageal cancer. Self-expandable metal stents.

INTRODUCTION

Esophageal cancer is the eighth most common malignancy and the sixth leading cause of cancer-related death. Overall survival at one year is 40% and the five-year survival rate is 7-10% (1,2). Despite recent advances in curative treatment, more than 50% of patients with esophageal cancer have metastatic disease at the time of diagnosis, thus precluding a curative resection (3). Dysphagia is the most common symptom of incurable obstructive esophageal cancer and can be treated by esophageal stent placement.

Self-expandable metal stents (SEMS) are accepted as a palliative treatment for dysphagia in patients with advanced esophageal cancer and a predicted short-term survival (4). SEMS improve quality of life (5) by allowing the relief of dysphagia (6) and optimizing the nutritional/functional status for subsequent surgery or chemo/radiotherapy. However, they are associated with a risk of adverse events (AEs) such as hemorrhage, pain, fistula and perforation (7,8).

There are serious concerns with SEMS in patients with a survival longer than three months due to previous reports of high AE rates (20% to 50%) when they are in place for long periods of time (9). Smaller stents (10-16 mm) may be effective for controlling malignant dysphagia with fewer reported AEs (6.5% major AEs and a stent migration rate of 36% [10]). A seminal study (7) compared brachytherapy with SEMS in patients with advanced esophageal cancer. Despite a slower improvement rate (after 30 days), single-dose brachytherapy provided better long-term relief of dysphagia than SEMS placement. This was also associated with a greater dysphagia-free survival, similar overall survival and fewer AEs (21% *vs* 33%). ESGE guidelines (11) recommend brachytherapy as a valid alternative for or in addition to stent placement for esophageal cancer patients

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Dr. Rodrigues-Pinto was responsible for the study concept and design, data acquisition, analysis and interpretation of data, statistical analysis, drafting and writing of the paper. The remaining authors participated in a critical revision of the manuscript for important intellectual content.

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with malignant dysphagia. This is due to the survival advantage and a possible better quality of life. A recent meta-analysis of 623 patients reported a dysphagia free survival of 87% at three months, 67% at six months and 38% at nine months with brachytherapy (12). With regard to AEs, there was a 12% incidence of stenosis and a fistula formation rate of 8%.

The aim of this study was to assess the role of esophageal SEMS in patients with advanced esophageal cancer with an expected survival of longer than six months.

METHODS

This was a retrospective study based on the electronic medical records of 42 patients with clinical dysphagia and histologically confirmed advanced esophageal cancer referred for SEMS placement between 2011 and 2016. Only patients with the stent in place for more than six months were included (42 of 167 patients). Advanced disease included locally advanced disease (T3-T4, N0-3, M0) and metastatic disease (M1). Exclusion criteria were limited disease (Tis-T2 N0 or N1-3), evidence of tumor within 2 cm of the upper esophageal sphincter, previous upper gastrointestinal surgery or treatment with an esophageal stent for the same condition.

All stents were nitinol fully or partially covered (Hanarostent M.I.Tech Co., Inc, Seoul, South Korea), with 20 mm body diameter and 26 mm proximal and distal flares, and mounted on 18 Fr (6 mm) delivery systems. Stents were deployed under moderate or deep sedation at the discretion of the endoscopist. They were deployed over a guidewire that was placed across the lesion and distally into the stomach. Tumor length was estimated radiologically after contrast medium injection. A stent measuring 2-4 cm longer than the stricture was used to allow for a 1 to 2 cm extension above and below the proximal and distal tumor borders.

Technical success was defined as a successful deployment of the stent in the correct position. Clinical success was defined as relief of dysphagia one week after stent placement. Dysphagia was assessed using the modified Takitas' dysphagia grade (13); clinical improvement was considered when grade I or grade II was achieved. AE included stent migration, stent overgrowth/ingrowth, bleeding, perforation and stent-induced fistulae. If an AE was adequately treated but recurred, it was considered as a new AE.

The study was approved by the Ethics Committee of our institution. Data with regard to baseline patient and tumor characteristics were collected; this included Eastern Cooperative Oncology Group (ECOG) score, histology of the tumor, tumor location, stent details, further treatment, technical and clinical success, AEs and mortality.

Statistical analysis

Categorical variables were described using absolute and relative frequencies and continuous variables were described as median, percentiles, minimum and maximum. Hypotheses were tested with regard to the distribution of continuous variables with a non-normal distribution using the nonparametric Mann-Whitney test. Pearson's Chi-squared and Fisher's exact tests were used for categorical comparisons of data. Kaplan-Meyer analysis was used to calculate time to an AE and survival; the curves were compared using the log-rank test. Univariate and multivariate analysis using logistic regression was used to explore the correlation between predictor variables and AEs. All significant variables evaluated in the univariate analysis were included to identify independent predictors of an AE. The results are shown as odds ratio (OR) with 95% confidence intervals (CI). All the reported p values were two-sided and p values of < 0.05 were considered to be statistically significant. All data were arranged, processed and analyzed with SPSS® v.24.0 data (Statistical Package for Social Sciences).

RESULTS

Population

Baseline demographic characteristics of all 42 patients are shown in table 1. The indication for stent placement in all patients was dysphagia due to esophageal malignancy. The median follow-up time was 298 days (183-861 days). The mortality was 93% at the end of follow-up. The majority of lesions were located at the proximal/middle esophagus (55%) and were traversable using an ultrathin gastroscope in 79% of patients. A standard upper endoscope could not be passed in any patient. Twenty-nine patients (69%) underwent further therapy (chemotherapy and/or radiotherapy) with SEMS *in situ.* However, only 14 began therapy before the development of an AE (four patients underwent further therapy after AE). The remaining eleven patients who underwent further therapy did not experience adverse events. SEMS was the only treatment in the remaining patients as the best supportive care.

Adverse events

Technical and clinical success was achieved in all patients, however, a total of 32 AEs were described in 25 patients. Fifty-nine percent of the patients (n = 25) experienced a first AE: 15 migrations, eight overgrowth/ingrowths and two stent-induced fistulae. The median stent patency (until death or stent dysfunction) was 236 days (19-513). Two AEs occurred within 30 days of stenting, seven occurred between 30 and 90 days, seven occurred between 90 and 180 days and nine, after 180 days. Endoscopic management was attempted in every SEMS-related AE. Twenty patients required a second SEMS, two had successful SEMS repositioning and one was treated with *argon plasma*; two SEMS were removed without the need for further therapy. The clinical success rate for treatment of an AE was 100%. However, the previously treated AE recurred in seven patients, four in/overgrowths and three migrations. Endoscopic management was successful in all patients. Three patients required another SEMS, one was treated with *argon plasma*, one underwent percutaneous endoscopic gastrostomy placement and two SEMS were removed without the need for further therapy.

AEs were more common when strictures were traversable using an ultrathin gastroscope (70% *vs* 22%, p = 0.01, OR 8.1 [95% CI 1.4-45.8]) and when strictures were longer (median

Table 1. *Baseline characteristic of patients with advanced esophageal cancer and a long-term survival, with a self-expandable metal stent*

Characteristics	n = 42
Age at SEMS placement (median; min-max)	65 (43-90)
Gender (male/female) (n)	36/6
Tumor location (n; %)	
Proximal/middle esophagus	23 (55%)
Distal esophagus/cardia	19 (45%)
Histology (n; %)	
Squamous cell carcinoma	29 (69%)
Adenocarcinoma	13 (31%)
ECOG (n; %)	
0	13 (31%)
1	9 (21%)
2	16 (38%)
3	3 (7%)
4	1 (2%)
Follow-up (days; median; min-max)	298 (183-861)
Survival at 12 months (n; %)	14 (33%)
Tumor transposable by an ultrathin gastroscope	33 (79%)
SEMS brand (n; %)	
Hanarostent	42 (100%)
SEMS type (n; %)	
Partially covered	30 (71%)
Fully covered	12 (29%)
SEMS extension (n; %)	
8 cm	1 (3%)
10 cm	7 (18%)
11 cm	2 (5%)
14 cm	11 (28%)
15 cm	18 (46%)
Further therapy with SEMS in situ (before AE development) (n = 14; %)	
Chemotherapy and radiotherapy	11 (79%)
Chemotherapy	2 (14%)
Radiotherapy	1 (7%)
Adverse events (first occurrence)	25 (59%)
Migration	15 (36%)
Overgrowth/ingrowth	8 (19%)
Stent-induced fistulae	2 (5%)

SEMS: self-expandable metal stents; ECOG: Eastern Cooperative Oncology Group Performance Status; AE: adverse event.

of 7 cm [4-14] *vs* 5 cm [2-10], p = 0.025). According to the univariate analysis, strictures traversable with an ultrathin gastroscope (OR 8.1, 95% CI [1.4-45.8], p = 0.019) and longer strictures (OR 1.5, 95% CI [1.1-2.3], p = 0.040) were associated with a higher risk of AEs. According to the logistic regression, only strictures traversable with an ultrathin gastroscope (OR 11.7, 95% CI [1.2-114.6], p = 0.035) were independently associated with a higher risk of AEs (Table 2). Patients who developed an AE tended to survive longer than patients without an AE (p = 0.065) (Fig. 1).

Migration *vs* overgrowth/ingrowth

Migration occurred in 36% of patients (n = 15), with a median stent patency of 92 days (8-210). The median follow-up time was 327 days (165-861 days). The majority of lesions were located at the distal esophagus/cardia (53%) and were traversable using an ultrathin gastroscope in 87% of patients. Eleven patients required a second SEMS, two had a successful SEMS repositioning and two SEMS were removed without the need for further therapy. Overgrowth/ingrowth occurred in 19% of patients (n = 8), with a median stent patency of 287 days (51-510). The median follow-up time was 347 days (255-648 days). The majority of lesions were located at the proximal/middle esophagus (87.5%), and all were traversable using an ultrathin gastroscope. Seven patients required a second SEMS and one was treated with *argon plasma*.

DISCUSSION

The majority of patients with esophageal cancer present with unresectable disease, with dysphagia as the primary symptom. Esophageal SEMS are commonly used for palliation with a near 100% technical and clinical success rate. Improvement in the dysphagia score of at least two points is seen within 1-2 days (14). Analysis of pooled data from RCTs and prospective and retrospective studies showed that major AEs develop in 10-21% of cases, whereas recurrent dysphagia occurs in 29-41% of cases. Stent placement-related mortality is 0-2% (11). AEs are a concern, especially in patients with a longer survival. Survival up to 19 months has been reported with modern palliative treatments (15). The use of SEMS as a valid option for the treatment of patients with advanced esophageal cancer is well known. However, there are very few reports with regard to advanced esophageal cancer patients who remain with esophageal stents for longer than six months.

All patients in our study achieved technical and clinical success after stent placement. While long-term esophageal stenting was associated with a high prevalence of AEs, this did not translate to increased mortality. In addition, most cases could be managed endoscopically. The overall dysphagia recurrence rate (migrations or overgrowth/ingrowths) was higher than previously reported, with a range of 12-49% (16,17). However, the median patient survival following stent placement was much longer than in previous published series, ranging between 61 and 209 days (18,19). We believe that the paradoxical increase in AEs with prolonged survival is related to the increase in stent placement duration. Interestingly, AEs were distributed evenly over time. We hypothesize that longer survival times and longer stent placement duration result in more AEs; the cumulative chance of AEs over time. Fortunately, most AEs can be managed endoscopically without having an impact on mortality.

Table 2. *Univariate and multivariate analysis of the risk factors for adverse events*

Risk factors	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Significant according to the univariate and multivariate analysis						
Stricture transposable by an ultrathin gastroscope	8.1	1.4-45.8	0.019	11.7	1.2-114.6	0.035
Significant according to the univariate analysis						
Lesion extension	1.5	1.1-2.3	0.040	–	–	0.05
Not significant according to the univariate and multivariate analysis						
ECOG (1-3/0)	0.5	0.1-2.2	0.391			
Stent coverage (partial/full)	2.8	0.7-11.1	0.136			
Stent length	2.9	0.7-12.5	0.157			
Lesion location	0.6	0.2-2.1	0.408			
Age	0.9	0.9-1.0	0.395			
Histological type	1.4	0.4-5.3	0.616			
Further therapy with SEMS *in situ*	3.1	0.6-6.3	0.573			

OR: odds ratio; CI: confidence interval; SEMS: self-expandable metal stents; ECOG: Eastern Cooperative Oncology Group Performance Status.

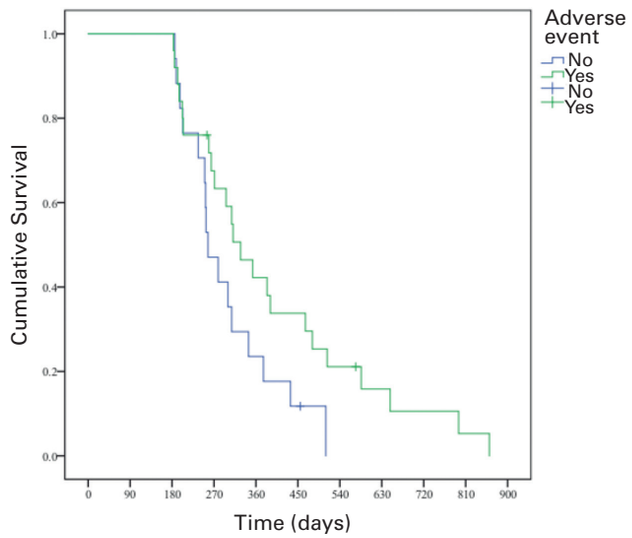

Fig. 1. *Kaplan-Meier survival curves of patients with and without adverse events.*

Strictures traversable with an ultrathin gastroscope were a risk factor for AEs in our study. The explanation may be similar to that of Siersema et al. (20), as larger stents are less likely to migrate although they are associated with a higher risk of major AEs. A tighter stricture may allow a better apposition of the stent in the lesion and mucosa, thus decreasing the risk of migration, which was the main AE in this study. A total of two patients experienced major AEs, both were fistula formation; However, all were managed endoscopically. Although some data showed an increased risk of AEs in patients who received chemotherapy and/or radiotherapy after SEMS placement (21), this may be due to some tumor regression/shrinkage. This was not observed in our study, as stent migration occurred only in seven patients while under further treatments.

Migration was the main AE in this study. It tended to occur in more distal strictures, whereas overgrowth/ingrowth mainly occurred in proximal/middle strictures. Although migration may be attributable to some tumor regression or milder strictures at baseline, overgrowth/ingrowth mainly derives from progressive disease. This is reflected by the shorter stent patency in the first group (92 *vs* 287 days). Both AEs are extremely different in clinical practice. However, no baseline/stent characteristics were a risk factor for each of these AEs individually. The majority of patients in our study had squamous cell carcinoma that involved the proximal/mid esophagus. In the West, the majority of patients have adenocarcinomas involving the distal esophagus. Therefore, stents often need to traverse the gastroesophageal junction, resulting in intractable reflux. The prevalence and classification of AEs might therefore differ significantly in this population, limiting the generalization to Western populations. Even though several anti-migration features have been reported, the results are mixed (22). Perhaps the use of techniques such as suturing, which lasts longer than the first few days, can be used. This reduces the risk of migration while the uncovered flanges of the stent are not embedded in the esophageal wall, which may be important in patients with a higher risk of stent migration (23). Similar data with a high rate of AEs (63.5%) at 10.7 months of follow-up were reported in a recent study by Medeiros et al. (24). A higher mortality rate was not reported in this study and the majority of AEs were managed endoscopically.

The limitations of our study include its retrospective nature and the fact that the results derived from a single, tertiary center, with a possible selection bias that may preclude the generalization to the community practice. Pain and reflux/regurgitation are also common AEs after SEMS placement that are not mentioned in this paper and are easily missed in a retrospective study. Quality of life after SEMS placement is also not mentioned in the paper due to the retrospective study design; this data was not available for all patients. Nevertheless, we present the second

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biggest cohort of patients with advanced esophageal cancer who underwent SEMS placement with palliative intentions, with a stent placement time greater than six months. Only patients with dysphagia and esophageal cancer were included and the follow-up period was longer than that of the study by Medeiros et al. (24).

We believe our study provides a valuable insight into the natural history of chronic indwelling esophageal SEMS in this subset of patients and allows the assessment of the true impact of esophageal stenting in long-term palliation of dysphagia. Our data suggest that SEMS may be a valid option for the treatment of patients with advanced esophageal cancer and an expected survival of longer than six months. Especially in centers where brachytherapy is not available.

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