Factors That Affect Stent-Related Complications in Patients with Malignant Obstruction of the Esophagus or Gastric Cardia

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See editorial on page 1.

Background/Aims: Self-expandable metallic stent (SEMS) placement is effective for dysphagia that results from malignant obstruction of the esophagus or gastric cardia; however, stent-related complications may be life-threatening. Thus, the goal of this study was to identify risk factors associated with complications following esophageal stenting. Methods: Of the 71 patients who underwent SEMS placement for dysphagia as a result of malignant stricture of the esophagus or gastric cardia, 53 patients with squamous cell carcinoma or adenocarcinoma, without previous SEMS placement, without a fistula, and without recurrent tumor after surgery were retrospectively identified. The occurrence of stent-related complications was used as an endpoint. Results: Stent-related complications were identified in 26 patients (49.1%), and major complications occurred in 14 patients (26.4%). The use of an Ultraflex stent (odds ratio [OR], 6.81; 95% confidence interval [CI], 1.54 to 30.00; p=0.011) and prior chemotherapy (OR, 6.13; 95% CI, 1.46 to 25.70; p=0.013) were significantly associated with stent-related complications. Moreover, the use of an Ultraflex stent (OR, 19.60; 95% CI, 2.26 to 170.00; p=0.007) and prior radiation (OR, 25.70; 95% CI, 2.37 to 280.00; p=0.008) significantly increased the risk of major complications. Conclusions: The use of an Ultraflex stent and prior radiation and/or chemotherapy may represent risk factors for complications following esophageal SEMS placement. (Gut Liver 2017;11:47-54)

Key Words: Esophageal stent; Risk factors; Complication; Radiation; Chemotherapy

INTRODUCTION

Self-expandable metallic stents (SEMS) are effective in the management of dysphagia in patients with malignant stenosis of the esophagus or gastric cardia. However, stent-related complications, such as bleeding, perforation, esophago-bronchial fistula, aspiration pneumonia, persistent pain, and gastroesophageal reflux, can occur and may be life-threatening. Previous studies have reported that the rates of mortality associated with esophageal stent placement are 3.9% to 27.2%. Therefore, it is important to select the patients with a low risk of stent-related complications.

Previous studies reported that prior radiation and/or chemotherapy increased the risk of life-threatening complications after esophageal SEMS placement, whereas another report suggested that the incidence of severe complications after SEMS placement was not affected by prior radiation and/or chemotherapy. Therefore, the relationship between prior therapy and complications after SEMS intubation remains controversial, and international consensus guidelines for the management of palliative treatment for esophageal cancer do not certify prior radiation and/or chemotherapy as contraindications for esophageal stent placement.

Several reports have been published concerning the palliation of patients with malignant dysphagia via the insertion of different types of metal stents. Siersema et al. reported that procedure-related complications were more common with the covered Gianturco-Z stent (Cook Medical, Bloomington, IN, USA) than with the covered Flamingo Wallstent or the covered Ultraflex stent (Boston Scientific, Natick, MA, USA), although May et al. found no differences in the occurrence of complications and recurrence of dysphagia among patients who received...
an uncovered Ultraflex stent, an uncovered Wallstent, or a covered Gianturco-Z stent. However, the Wallstent, Gianturco-Z stent, and Flamingo Wallstent are not commonly available or utilized in Japan. Although Verschuur et al.\textsuperscript{15} reported that there were no differences in complications among the Ultraflex stent, the Polyflex stent (Boston Scientific), and the Niti-S stent (Tae-woong Medical, Gimpo, Korea), it has been suggested that stent-related complications might differ according to the properties of each stent behavior.

Therefore, the aim of this study was to identify risk factors for complications for patients who undergo esophageal stenting for management of dysphagia due to malignant esophageal or gastric cardia stenosis.

MATERIALS AND METHODS

1. patients

Data were collected from the medical records of patients who underwent SEMS placement for malignant obstruction of the esophagus or gastric cardia at Gifu Prefectural Tajimi Hospital from January 2006 to May 2015. Exclusion criteria were unidentified tumor histology, previous metal stent placement, a fistula between the esophagus and respiratory tree, and recurrent tumor after esophagectomy or gastrectomy. All data, including age, gender, histology, tumor length, reason for palliative treatment, serum albumin, stent length, expansion rate on stent placement, location of tumor, type of stent, and prior radiation and/or chemotherapy were noted for all patients, and serum albumin at the time of decision to place esophageal SEMS was used for the analysis conducted in this study.

The patients were graded according to the ability to eat and/or swallow as follows: 0=patients were able to eat normal diet; 1=patients were able to eat some solid foods; 2=patients were able to eat semi-solid foods; 3=patients were able to swallow liquids only; 4=patients were unable to swallow anything.\textsuperscript{16}

Data were retrospectively analyzed, and informed consent was obtained from all patients. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki (sixth revision, 2008), and an Institutional Review Board approved the protocol for this research project.

2. Placement of stents

During stent insertion, all patients were consciously sedated with midazolam and pentazocine. After endoscope insertion, esophagography was performed to measure tumor length. If it was impossible to pass the tumor with an endoscope, we used the cannulas for endoscopic retrograde cholangiopancreatography for wire passage. If needed, the upper and/or lower tumor margins were marked with short radio-opaque sticks attached to the surface of the patient body. The stent was expanded under fluoroscopic monitoring followed by esophagoscopy for confirmation of stent location and expansion.

Three types of stent were used (Fig. 1):

1. Partially covered or uncovered Ultraflex stents (Boston Scientific) in lengths of 10 and 15 cm, and diameters of 23 mm (proximal), 18 mm (middle), and 23 mm (distal). The partially covered stent is uncovered at both ends over a distance of 1.5 cm.

![Fig. 1. Three stent types that were used in the present study: (A) Ultraflex stent (Boston Scientific); (B) Niti-S stent (Taewoong Medical); and (C) Evolution stent (Cook Medical).]
(2) Partially covered or uncovered Niti-S stents (Taewoong Medical) in lengths of 8, 10, 12, and 15 cm, and diameters of 26 mm (proximal), 18 mm (middle), and 26 mm (distal). The partially covered stent is uncovered at both ends over a distance of 1.2 cm.

(3) Partially covered Evolution stents (Cook Medical) in lengths of 8, 10, 12.5, and 15 cm, and diameters of 25 mm (proximal), 20 mm (middle), and 25 mm (distal). The stent is uncovered at both ends over a distance of 1.5 cm.

3. Definitions

Clinical success was defined as success in reduction of more than 1 in the dysphagia score after stent placement. Expansion rate was defined as the rate of the width of the point where the stent was the narrowest to regulation diameter when the stent was deployed. Hemorrhage, perforation, fistula, aspiration pneumonia, and fever were defined as major complications, while pain and gastroesophageal reflux were defined as minor complications. Hemorrhage was defined as hematemesis and/or melena after stent placement which were considered as stent-related complications. We defined a fever over 38 degrees within 7 days after stent insertion, which might reflect micro perforation or an aspiration, as a complication. Pain (as a stent-related complication) was defined as pain that required an analgesic drug to relieve. Heartburn and/or regurgitation after stent intubation were regarded as gastroesophageal reflux. Recurrent dysphagia (including stent migration) was evaluated separately from complications in this study to focus attention on physical suffering. Patients were categorized into two groups for analysis: (1) those with some stent-related complications (complication [+]); and (2) those without any complications (complication [−]). To reveal factors affecting major complications, patients were also classified into two other groups: (1) those with some major complications (major complication [+]); and (2) those who had no major complications (major complication [−]). In univariate and multivariate analysis, patients with prior concurrent chemoradiotherapy were included as in the “prior radiation group”.

4. Statistical analysis

All data were analyzed with the Mann-Whitney U test or chi-square test, as appropriate. The survival period was evaluated using the log-rank test (Kaplan-Meier methods). Multivariate analysis was performed with a multiple logistic regression model using a stepwise selection method according to the likelihood ratio. Moreover, logistic regression was used to estimate the odds ratio (OR) and the 95% confidence interval (CI) of various possible risk factors. The p-values of <0.05 were considered to indicate statistical significance.

RESULTS

1. Patients

Among 71 patients who underwent esophageal stent placement, four patients without a tissue diagnosis, two patients with previous SEMS placement, four patients with a fistula between the esophagus and respiratory tree, and eight patients with recurrent tumor after esophagectomy or gastrectomy were excluded. Thus, 53 patients were included in the final analysis (Fig. 2).

Patient characteristics are shown in Table 1. The number of patients given chemotherapy, radiation and concurrent chemoradiotherapy before stent placement was 24, three, and six, respectively. The median total radiation dose was 60 Gy (range, 10 to 66 Gy). The median time between the completion of radiation and the stent placement was 4.4 months. The median number of cycles of chemotherapy was 3.5 (range, 1 to 31). The number of patients who were treated with first-line chemotherapy, second-
The dysphagia score improved from a median 3 to 1 in most patients at 2 weeks after treatment (p<0.001) (Table 2). Stent-related complications were observed in 26 patients (49.1%), and major complications occurred in 14 (26.4%), including three (5.7%) with hemorrhage, four (7.5%) with perforation, one (1.9%) with fistula, six (11.3%) with fever, and three (5.7%) with aspiration pneumonia. Of three patients with hemorrhage, one died from active bleeding, and two required blood transfusion. In four patients with perforation, three died from mediastinitis or empyema caused by perforation, and one patient was successfully treated with another stent insertion to close the rupture. An esophago-respiratory fistula developed in one patient (1.8%), which was managed with a second stent. Regarding stent-related complications, there were no significant differences between the number of patients with prior chemotherapy or radiation alone and patients with prior concurrent chemoradiotherapy (n=18/2/5, p=0.848). The mean total radiation dose of patients with major complications was not significantly higher than that for patients without major complications (48.3 Gy vs 48.0 Gy, p=0.892).

Recurrent dysphagia occurred in 12 patients (22.6%). Tumor overgrowth was observed at the proximal end of the stent in four patients (7.5%), at the distal end in one patient (1.9%), and...
at both ends of the stent in two patients (3.8%). In one patient (1.9%) with obstruction of the lower thoracic esophagus, stent migration to the distal portion was found at the time of the endoscopy, and another stent was placed for proximal stenosis.

3. Clinical risk factors

Univariate and multivariate analyses for each risk factor when comparing the “complication (+)” group and the “complication (−)” group are shown in Table 3. Age, serum albumin, tumor length, and expansion rate were calculated as sequential values, and squamous cell carcinoma, location of tumor, use of an Ultraflex stent, prior radiation, and prior chemotherapy were used as discriminant values.

In the univariate analysis, age, use of an Ultraflex stent, and prior chemotherapy were significant predictors of complications (age, p=0.010; use of an Ultraflex stent, p=0.019; prior chemotherapy, p=0.002). In the multivariate analysis for these nine variables using a stepwise selection method by likelihood

| Variable                        | Complication (+) | Complication (−) | Univariate analysis | Multivariate analysis |
|---------------------------------|------------------|------------------|--------------------|-----------------------|
|                                 | (n=26)           | (n=27)           | p-value            | p-value OR (95% CI)   |
| Age, yr                         | 70 (51–87)       | 76 (54–94)       | 0.010              | 0.106 0.94 (0.87–1.01) |
| Serum albumin, g/dL              | 3.0±0.5          | 2.9±0.5          | 0.539              | - -                    |
| Squamous cell carcinoma          | 21 (80.8)        | 21 (77.8)        | 0.788              | - -                    |
| Tumor length, cm                 | 5.1±2.0          | 5.9±2.3          | 0.270              | - -                    |
| Expansion rate, %                | 52.6±19.6        | 60.0±17.8        | 0.135              | - -                    |
| Location of tumor                |                  |                  |                    |                       |
| Ut                              | 2 (7.7)          | 3 (11.1)         | 0.964              | - -                    |
| Mt                              | 13 (50.0)        | 12 (44.4)        | 0.897              | - -                    |
| Lt                              | 6 (23.1)         | 5 (18.5)         | 0.944              | - -                    |
| Ae+cardia                       | 5 (19.2)         | 7 (25.9)         | 0.800              | - -                    |
| Use of Ultraflex stent           | 16 (61.5)        | 7 (25.9)         | 0.019              | 0.011 6.81 (1.54–30.00) |
| Prior radiation                 | 7 (26.9)         | 2 (7.4)          | 0.127              | - -                    |
| Prior chemotherapy              | 18 (69.2)        | 6 (22.2)         | 0.002              | 0.013 6.13 (1.46–25.70) |

Data are presented as median (range), mean±SD, or number (%).

OR, odds ratio; CI, confidence interval; Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus; Ae, abdominal esophagus.

| Variable                        | Major complication (+) | Major complication (−) | Univariate analysis | Multivariate analysis |
|---------------------------------|------------------------|------------------------|--------------------|-----------------------|
|                                 | (n=14)                 | (n=39)                 | p-value            | p-value OR (95% CI)   |
| Age, yr                         | 71 (51–81)             | 75 (54–94)             | 0.183              | - -                   |
| Serum albumin, g/dL              | 3.0±0.6                | 2.9±0.5                | 0.709              | - -                   |
| Squamous cell carcinoma          | 12 (85.7)              | 30 (76.9)              | 0.755              | - -                   |
| Tumor length, cm                 | 5.5±2.0                | 5.5±2.3                | 0.840              | - -                   |
| Expansion rate, %                | 51.7±21.6              | 58.1±17.8              | 0.234              | - -                   |
| Location of tumor                |                        |                        |                    |                       |
| Ut                              | 2 (14.3)               | 3 (7.7)                | 0.848              | - -                   |
| Mt                              | 7 (50.0)               | 18 (46.2)              | 0.948              | - -                   |
| Lt                              | 4 (28.6)               | 7 (17.9)               | 0.648              | - -                   |
| Ae+Cardia                       | 1 (7.1)                | 11 (28.2)              | 0.214              | - -                   |
| Use of Ultraflex stent           | 11 (78.6)              | 12 (30.8)              | 0.005              | 0.007 19.60 (2.26–170.00) |
| Prior radiation                 | 6 (42.9)               | 3 (7.7)                | 0.010              | 0.008 25.70 (2.37–280.00) |
| Prior chemotherapy              | 10 (71.4)              | 14 (35.9)              | 0.048              | - -                   |

Data are presented as median (range), mean±SD, or number (%).

OR, odds ratio; CI, confidence interval; Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus; Ae, abdominal esophagus.
ratio, use of an Ultraflex stent (OR, 6.81; 95% CI, 1.54 to 30.00; p=0.011) and prior chemotherapy (OR, 6.13; 95% CI, 1.46 to 25.70; p=0.013) were significantly associated with stent-related complications.

Univariate and multivariate analyses to compare the “major complication (+)” group and “major complication (−)” group are shown in Table 4. Use of an Ultraflex stent, prior radiation, and prior chemotherapy significantly increased the risk of major complications in the univariate analysis (use of an Ultraflex stent, p=0.005; prior radiation, p=0.010; prior chemotherapy, p=0.048). The multivariate analysis showed that factors increasing the risk of major complications were the use of an Ultraflex stent (OR, 19.60; 95% CI, 2.26 to 170.00; p=0.007) and prior radiation (OR, 25.70; 95% CI, 2.37 to 280.00; p=0.008).

DISCUSSION

The use of SEMS in the management of inoperable malignant stricture of the esophagus and gastric cardia is well established, and endoscopic placement of SEMS has become the first-line palliative option for dysphagia. For this purpose, we expected that the esophageal SEMS would relieve dysphagia, prevent recurrent dysphagia, and have few complications.

In our study, approximately 50% of patients who underwent esophageal stent placement suffered complications. Fourteen patients (26.4%) had major complications, and four patients (7.5%) died due to severe complications (i.e., hemorrhage and perforation) (Table 2). This study demonstrated that the use of an Ultraflex stent and prior chemotherapy were independent predictors of complications after esophageal SEMS insertion and that major complications after SEMS placement were significantly associated with the use of an Ultraflex stent and prior radiation.

Although some previous studies have reported that anticancer drug-eluting stents and stents loaded with radioactive material are more effective for patients with unresectable esophageal cancer when compared with conventional stents, there were no differences in the efficacy of SEMS to relieve dysphagia between the types of the conventional stent. Therefore, the difference on efficacy has little impact on the clinicians’ selection of the specific type of SEMS. Recurrent dysphagia due to tumor overgrowth or ingrowth, food bolus impaction, and stent migration occurs in about 20% to 40% of patients after SEMS placement, and these complications require reintervention. Previous studies reported that recurrent dysphagia occurred more frequently with Ultraflex stents than with Polylflex stents or Niti-S stents, although Polylflex stents were associated with a high rate of stent migration. Therefore, placement of plastic stents (i.e., Polylflex stents) is not recommended because of the high rates of complications. Thus, we consider it important to choose a stent with a lower risk of restenosis and fewer stent-related complications. The finding from the present study that the use of an Ultraflex stent is a predictor of stent-related complications might influence clinicians to select alternate stents.

In our study, hemorrhage and perforation were the two critical complications. There are several possible reasons for hemorrhage. First, esophageal SEMS contact and damage the mucosa and the tumor. Second, if the tumor has infiltrated a large artery, such as the aorta, pressure from SEMS on the esophageal wall can lead to arterial rupture and massive and lethal bleeding. Metallic stent placement exerts constant pressure on the esophageal wall and the tumor, which can increase the risk of local necrosis, an inflammatory reaction with increased fibrotic activity and degeneration of the muscular layers. Such changes in the esophageal wall and the tumor, which may cause bleeding and perforation, are related to the properties of stents. In coronary artery stenting, the axial force, in other words, the force required to keep the stent straight after bending is the main predictor of severe adverse cardiac events and restenosis. The Ultraflex stent has a higher radial force and a lower axial force than the Niti-S stent or Evolution stent. In our study, patients treated with Ultraflex stents were at higher risk of stent-related complications than those treated with other stents (i.e., Niti-S stent or Evolution stent). This result might be because of the radial force resulting from stent expansion is associated with tissue damage caused by embedding of the stent in the esophageal wall. In addition, in contrast to the coronary artery, the esophagus is very straight, and the axial force, which might produce injury to the esophageal wall due to poor fit within the lumen, has a lower impact on damage to the esophageal wall than does the radial force.

Moreover, prior radiation therapy was also found to be a significant predictor of major complications in both the univariate and multivariate analyses (Table 4). Although radiation therapy to the esophagus has acute and late toxicity, the late effects of radiation are believed to be due to inflammation and scar formation within the esophageal musculature. Histologic study has shown epithelial thickening, chronic inflammation, submucosal or muscularis fibrosis, and vasculitis, which may lead to local hypoxemia. The late effects of radiation therapy are seen 3 or more months after completion of radiation therapy, with a median time to onset of 6 months. In our study, the median time from prior radiation to the esophageal SEMS insertion was approximately 4 months, and two-thirds of patients with prior radiation suffered major complications. This finding supports the idea that the late effects of esophageal radiation therapy have an important role in the occurrence of severe stent-related complications. The esophageal toxicity of radiation therapy is recognized as dose-dependent. Therefore, it is possible that the relationship between prior radiation and stent-related complications is also dose-dependent. Our series cannot confirm this hypothesis, as there was no significant difference in the dose of radiation between patients with prior radiation who developed major complications after stent insertion and patients who did
not develop major complications. One reason for this result may be that patients with unresectable esophageal cancer are often treated with standard-dose radiation in Japan, so it is difficult to compare them with patients who receive radiation therapy using different doses of radiation therapy. It has been also reported that severe esophageal toxicity is significantly increased when chemotherapy is given concurrently with radiation when compared with sequential chemoradiation or radiation alone. Chemotherapy is delivered to shrink the tumor alone or to improve the efficacy of radiation-induced tumor necrosis. Therefore, chemotherapy can lead to tissue damage followed by esophageal wall atrophy, and such changes might increase the risk of stent-related complications. However, there were no significant difference in term of complications between the number of patients with prior concurrent chemoradiation and patients with prior radiation or chemotherapy alone.

This study has several potential limitations. First, it was a retrospective study performed in a single institution; a prospective, multicenter trial would be of benefit to validate our results. Second, nine of 23 Ultraflex stents (39.1%) were uncovered and only one of 30 other stents (3.3%) was uncovered. It is possible that this has an influence on complication rates. However, Vakil et al. reported that there was no difference in complications of esophageal stent placement, except tumor ingrowth, between the number of patients with covered stent and patients with uncovered stent, so that it likely did not affect the stent-related complications whether to use covered stent or not. Third, patients with prior concurrent chemoradiation, which might be associated with a greater risk of adverse reactions than prior radiation and chemotherapy alone, were included as in the “prior radiation group.” Regardless, this assessment may be appropriate, because significant relations between prior chemotherapy or radiation and complications still exist after multivariate analysis accounts for the effect of confounders.

In conclusion, our results of the clinical research seem to indicate that use of the Ultraflex stent and prior radiation and/or chemotherapy are risk factors for stent-related complications in patients with malignant obstruction of the esophagus and gastric cardia. A prospective, multicenter trial would be of benefit to validate our results.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

Author contributions: Conception and design: Hiroyasu Iwasaki, Takashi Mizushima; Acquisition of data: Hiroyasu Iwasaki, Yuta Suzuki, Shigeki Fukusada, Kenta Kachi, Takanori Ozeki, Kaiki Anbe; Analysis and interpretation of data: Hiroyasu Iwasaki, Takashi Mizushima, Hironobu Tsukamoto, Fumihiro Okumura; Drafting the article: Hiroyasu Iwasaki; Revising the article critically for important intellectual content: Takashi Mizushima; Making the decision to submit for publication: Takashi Joh, Hi-toshi Sano.

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