Development of a prediction model of adverse events after stent placement for esophageal cancer

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Background and Aims: Self-expandable metal stent (SEMS) positioning is the recommended method for palliation of dysphagia from esophageal cancer, although it is not adverse event–free. The present study was aimed at identifying predictors for adverse events and at proposing a statistical model to predict them.

Methods: We performed a retrospective analysis of a prospectively collected database. All patients who underwent SEMS placement for stricture due to esophageal cancer between 2002 and 2011 in a tertiary-care center were identified. Multivariable regression analysis in the presence of competing risk events was used to identify factors associated with SEMS-related adverse events and to build a prediction model.

Results: A total of 267 patients were included. According to the competing risk regression analysis, only 2 variables were significantly associated with the risk of SEMS-related adverse events: prior chemoradiotherapy (CRT), yielding a hazard ratio (HR) of 1.687 (95% confidence interval [CI], 1.076-2.644), and the SEMS length (HR 0.884; 95% CI, 0.798-0.980) for every 10-mm length increase. Based on the estimated probability curves, after 4 months from SEMS placement, the probability of an adverse event in patients who did receive prior CRT was 50.9% compared with 34.4% in those who did not receive prior therapy, which was reduced to 9.2% and 15.1%, respectively, if a 180 mm-length stent was used. The ability of the predictive model to differentiate between patients who did and did not experience the adverse event was moderate (c-index: 0.617).

Conclusion: The rate of SEMS-related adverse events was higher in patients with previous CRT and lower in patients receiving longer stents. Both factors were used to build an accurate predictive model. (Gastrointest Endosc 2016;83:746-52.)

Esophageal cancer is the eighth most common cancer worldwide.[1] In 2012, the global incidences of esophageal adenocarcinoma and squamous cell carcinoma were 0.7 and 5.2 per 100,000 participants, respectively.[2] Despite many advances in diagnosis and treatment, the prognosis for esophageal cancer is still poor, with a reported 5-year survival rate ranging from 15% to 20%.[3] Furthermore, the majority of patients present with inoperable disease at diagnosis, requiring palliative treatments to relieve dysphagia and to re-establish an acceptable quality of life.

Self-expandable metal stent (SEMS) placement is the recommended method for palliation of dysphagia and fistulae secondary to esophageal cancer, because of its immediate and durable efficacy.[4] However, life-threatening adverse events may occur after SEMS placement, such as perforation, massive bleeding, or aspiration pneumonia.[5,6]

A stratification of patients with cancer-related dysphagia according to the risk of developing SEMS-related adverse events would be of great importance because it would allow specific tailoring of the best palliative strategy. Therefore, the recognition of independent predictors of SEMS-related adverse events is crucial. Several studies have investigated this issue, without achieving a definite conclusion.[6-15]

Abbreviations: SEMS, self-expandable metal stent; CRT, chemoradiotherapy.

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The present study was aimed at disclosing predictors of SEMS-related adverse events in patients with dysphagia caused by esophageal cancer and at proposing a predictive model for identifying patients at higher risk of developing stent-related adverse events.

METHODS

Study design and patient selection

This study represents a retrospective analysis of a prospectively collected database. The SEMS database of Veneto Oncology Institute in Padua, Italy, which serves as a tertiary-care referral center for esophageal diseases, was reviewed. All patients who consecutively underwent covered or partially covered SEMS placement for stricture caused by esophageal cancer between 2002 and 2011 were identified. Only patients for whom SEMS placement was technically and clinically successful and for whom follow-up data were available were included. Technical success was achieved when an adequate deployment and positioning of the stent at the site of the stricture was obtained. Clinical success was intended as an improvement of at least 1 grade in the dysphagia score after SEMS placement. Dysphagia score is routinely assessed and recorded at the study center according to the score proposed by Ogilvie et al.[16]

The study was approved by the ethics committee, and written informed consent for the procedure and data acquisition were obtained from all patients.

Endoscopic SEMS placement

All endoscopic procedures were performed with patients under deep sedation. Before SEMS placement, endoscopy was routinely performed, and the lesion was inspected with a standard or pediatric video endoscope. Proximal and distal tumor margins were identified and the tumor length evaluated. Dilation was performed when it was required to allow passage of the endoscope or insertion of the SEMS. A guidewire was left in situ, and the stent was advanced over it and deployed under endoscopic view. A stent at least 4 cm longer than the stricture was used in order to allow for at least a 2-cm extension above and below the proximal and distal tumor margins. The following types of covered or partially covered SEMSs were used over the study period: Ultraflex stent and Flamingo Wallstent (Boston Scientific, Natick, Mass); Choostent (M.I. Tech, Seoul, Korea); Hanarostent (M.I. Tech), Deltamed (Italy), Song stent (Sooho Medi-Tec, Seoul, Korea).

Data collection

The following data were extracted for each patient: age, sex, length and site of the lesion, lesion histology, cancer stage (according to the National Comprehensive Cancer Network Guideline; www.nccn.org),[17] type of stent inserted (covered or partially covered), stent diameter and length, presence of concomitant esophageal fistula at the time of SEMS placement, type of previous chemotherapy and/or radiotherapy (chemoradiotherapy, CRT), Karnofsky score,[18] length of follow-up, patient status at the end of follow-up, type of adverse event, interval between SEMS placement and the development of any SEMS-related adverse event. For the purpose of our study, only major adverse events, that is, adverse events for which a repeated endoscopic intervention or hospitalization was required, were included in the analyses. Early and late adverse events were defined when they occurred within and after 30 days of SEMS placement, respectively.

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD) or median and interquartile range when not normally distributed. Categorical variables are reported as proportion. At univariate analysis, comparisons were made by using the Mann-Whitney U test and the Fisher exact test, as appropriate. The occurrence of SEMS-related adverse events may be influenced by several factors; hence, a multivariable regression analysis in the presence of competing risk events according to the semiparametric proportional hazards model proposed by Fine and Gray[19] was carried out. All clinically and potentially relevant covariates were included in the analysis (age, site and length of the lesion, Karnofsky score, histology and cancer stage, prior CRT, stent length and diameter). The aim of the analysis was to estimate the cumulative incidence of adverse events, with death without an adverse event as a competing risk event, considering the effect on adverse events of predictive factors and covariates.

The multivariate model was used to build up the predictive rule to be applied in the clinical field. The predictive accuracy of the estimated model was assessed by means of calibration, which refers to whether the predicted risks from the prognostic model agreed with the observed risks. Furthermore, the model's ability to discriminate between those participants who experienced the outcome of interest against those who did not was evaluated by the c-index.[20] Wolbers et al[20] formally defined a cause-specific concordance index $[C_1(t)]$ in the presence of competing risks: the index $[C_1(t)]$ quantifies the ability of the model to correctly rank events of interest up to time t and to discriminate them from competing events.

The competing risk analysis was performed by using R,[21] with the package cmprsk.[22]

RESULTS

Between 2002 and 2011, 356 patients with dysphagia caused by esophageal cancer were treated with SEMS placement; 89 cases were excluded because they did not fulfill the inclusion criteria. Therefore, 267 patients were