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The Glasgow prognostic score at the time of palliative esophageal stent insertion is a predictive factor of 30-day mortality and overall survival

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CONFLICTS OF INTEREST AND SOURCE OF FUNDING

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ABSTRACT

Background: Optimizing the timing of esophageal stent insertion is a challenge, partly due to difficulty predicting survival in advanced malignancy. The Glasgow prognostic score (GPS) is a validated tool for predicting survival in a number of cancers.

Goals: To assess the utility of the GPS in predicting 30-day mortality and overall survival post-esophageal stent insertion.

Study: Patients at a tertiary referral center who had received an esophageal stent for palliation of dysphagia were included if they had a measurement of albumin and C-reactive protein (CRP) in the week preceding the procedure (n=209). Patients with both an elevated CRP (>10 mg/l) and hypoalbuminemia (<35 g/l) were given a GPS score of 2 (GPS2). Patients with only one of these abnormalities were assigned as GPS1 and those with normal CRP and albumin were assigned as GPS0. Clinical and pathological parameters were also collected to assess for potential confounding factors in the survival analysis.

Results: Increasing GPS was associated with 30-day mortality; for patients with GPS0, 30-day mortality was 5% (2/43), for GPS1 it was 23% (26/114) and for GPS2 it was 33% (17/52). The adjusted hazard ratio for overall post-stent mortality was 1.6 (95% CI, 1.1 – 2.4; $P = 0.02$) for GPS1 and 2.4 (95% CI, 1.5 – 3.8; $P < 0.001$) for GPS2 patients compared with GPS0.

Conclusions: GPS is an independent prognostic factor of 30-day mortality and overall survival after esophageal stent insertion. It is a potential adjunct to clinical assessment in identifying those patients at high-risk of short-term mortality post-stent.

KEYWORDS

Esophageal cancer, stent, SEMS, survival

INTRODUCTION

Esophageal cancer is the sixth most common cause of cancer death in the UK, with 7,701 deaths in 2012, accounting for 5% of all cancer deaths [1]. Despite improved treatments, it remains a cancer that carries a poor prognosis, with a 1-year survival of 41% and a 5-year survival of 15%. The majority of patients present with incurable disease and around two-thirds are managed with palliative intent[2], most commonly for the treatment of dysphagia.

A number of palliative treatment options are available, including chemotherapy, radiotherapy, intraluminal brachytherapy, or esophageal stent insertion. Radiotherapy and brachytherapy may provide additional survival benefit over stenting, as well as a more sustained improvement in quality of life [3]. However, esophageal stenting remains a widely

accepted intervention for those patients too frail for oncological therapies, or in whom dysphagia has progressed despite treatment [4].

Optimizing the timing of esophageal stent insertion is a challenge for clinicians and patients. Side effects of esophageal stent insertion, including pain and gastro-esophageal reflux are most pronounced soon after the procedure, [5 6] and this may therefore limit the overall benefit of the intervention if the patient is nearing end-of-life care. Published data of overall median survival following esophageal stent insertion ranges from 76-145 days [7-9] and the 30-day mortality estimates vary from 10% to 25% [10 11]. As a result, developing methods of predicting survival at the time of esophageal stenting may be attractive for both patients and clinicians, in terms of aiding decision-making for this intervention.

The Glasgow prognostic score (GPS) uses a combination of serum albumin and C-reactive protein (CRP) as markers of systemic inflammation to predict survival. It is the most extensively validated inflammation-based prognostic score, and has been used to predict survival in a variety of clinical scenarios involving patients with cancer [12 13]. In esophageal cancer, its utility has been demonstrated in predicting peri-operative morbidity and survival [14], as well as predicting survival in operable disease at the time of diagnosis [15] and after neoadjuvant chemotherapy [16]. We aimed to evaluate the utility of the GPS at the time of esophageal stenting, as a means of predicting 30-day mortality and overall post-stent survival.

MATERIALS AND METHODS

Patients

From January 2009 to December 2013, patients who underwent esophageal stent placement for the palliative management of malignant dysphagia in advanced esophageal cancer at Leeds Teaching Hospitals NHS Trust were studied. Leeds is a tertiary referral center for upper gastrointestinal cancer, serving a population of 2.7 million people. Approximately 70 patients with a new diagnosis of esophageal cancer are referred to the service each year. Electronic patient records were analyzed retrospectively to identify the indications for stent insertion and a total of 329 procedures in 279 individuals were assessed. Stent placement was considered as an overall treatment modality, therefore only the first procedure was included. Patients were excluded if stenting was utilized as a bridge to curative surgery, or if the stent was placed after esophagectomy for anastomotic recurrence, leak, or fibrotic stricture.

Patient demographics, World Health Organization performance status and Charlson co-morbidity index were assessed from patient records. Disease characteristics including histological type, tumor site, presence of metastases, and any previous oncological therapies prior to esophageal stent insertion were recorded. The dates of diagnosis and first stent insertion were recorded, along with the date of death.

To evaluate the GPS, blood test results including serum CRP and albumin taken within a week before the stenting procedure were recorded. These had been taken as part

of routine clinical practice and patients who had not had these blood tests were excluded from the final analysis. GPS was constructed as previously described [17]; patients with both an elevated CRP (≥ 10 mg/L) and hypoalbuminemia (≤ 35 g/L) were given a score of 2 (GPS2) and patients with neither of these abnormalities were given a score of 0 (GPS0). Patients with either an elevated CRP or hypoalbuminemia were given a score of 1 (GPS1). Complete data for GPS calculation was available for 209 patients who met the inclusion criteria and these individuals were included in the final analysis (Figure 1).

The study design was approved by the Research and Innovation Directorate at Leeds Teaching Hospitals, who confirmed that since it involved routinely collected anonymized data, research ethics committee approval was not required for this retrospective study.

Esophageal Stent Insertion

At diagnosis, all patients were discussed at the regional Upper Gastrointestinal Cancer Multidisciplinary Team Meeting and operative or non-operative management options were recommended. Patients with inoperable esophageal cancer received an esophageal stent if their symptoms of dysphagia had progressed despite oncological therapies, or if stenting was the primary intervention.

All stenting procedures were performed by four experienced clinicians, under combined fluoroscopic and endoscopic guidance. The procedures were all performed

using Olympus endoscopes (Olympus Medical, Tokyo, Japan) and Niti-S double covered esophageal stents (Taewoong Medical, Gyeonggi-do, South Korea). Conscious sedation was achieved using a combination of intravenous midazolam and fentanyl.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows version 22.0 (SPSS Inc, Chicago, IL, USA). The chi-square test was used to assess the association of GPS with potential confounding clinical and pathological parameters. Univariate analysis was used to estimate a crude odds ratio (OR) for 30-day mortality post-stent insertion for the clinical and pathological variables. Multivariate logistic regression provided an estimate of the ORs for different GPS values, adjusted for these potential confounding factors.

The overall survival was defined as the time to death post-stent insertion. All patients who were alive at the time of analysis were censored. The survival of patients with different GPS values was analyzed using the Kaplan-Meier method and compared using the log-rank test. The Cox proportional hazards method was used to assess the prognostic value of GPS and other covariates in predicting overall post-stent survival. In all analyses, a P value of < 0.05 was considered statistically significant.

RESULTS

The background characteristics of the 209 patients included in the study are displayed in Table 1. There was no significant association of the GPS with any of the recorded demographic, clinical or pathological parameters. The median age of included patients was 72 years (range 36 to 99) and there were 143 (68%) men and 66 (32%) women. The ethnicity of 207 (99%) of the included patients was white, and therefore this was not included as a covariate in the subsequent analysis.

The 30-day mortality post-stent was 45/209 (22%) and the 7-day mortality was 10/209 (5%). Adverse events directly attributable to stent insertion included one patient who died of respiratory failure on the day of the procedure. Two patients suffered a perforation following stent insertion; one patient subsequently died within 30 days and the other survived for 8 months after receiving conservative management. Two patients experienced non-fatal hematemesis requiring blood transfusion.

Univariate analysis (Table 2) demonstrated a significant association of 30-day mortality with increasing GPS; for patients with GPS0, 30 day mortality was 2/43 (5%), for GPS1 it was 26/114 (23%) and for GPS2 it was 17/52 (33%). Multivariate logistic regression using the four significant predictors from univariate analysis showed that GPS was the only variable studied that was associated with 30-day mortality (Table 3). The OR for 30-day mortality for patients with GPS1 compared to GPS0 was 5.5 (95% confidence interval (CI) 1.2 – 25) and for GPS2 compared to GPS0 it was 10.0 (95% CI 2.0 – 49).

Overall survival following stent insertion is shown in Figure 2. Median post-stent survival was 92 days (95% confidence interval (CI), 73 – 111). For patients with GPS0, the median post-stent survival was 176 days (95% CI, 136 – 216), for GPS1 it was 92 days (95% CI, 75 – 108) and for GPS2 it was 37 days (95% CI, 19 – 55). Using the Mantel-Cox log-rank test, there was a significant negative correlation between increasing GPS and overall post-stent survival ($\chi^2 = 17.48$, $P < 0.001$).

Results of the multivariate analysis using the Cox proportional hazards model is shown in Table 4. There was a significant reduction in overall post-stent survival in patients with an increasing GPS. The hazard ratio (HR) for post-stent mortality was 1.6 (95% CI, 1.1 – 2.4; $P = 0.02$) for GPS1 and 2.4 (95% CI, 1.5 – 3.8; $P < 0.001$) for GPS2 patients compared with GPS0.

Patients who had received prior chemo-radiotherapy have a shorter overall post-stent survival, with a HR for mortality of 1.7 (95% CI, 1.1 – 2.7; $P = 0.02$). However, considering survival from the date of diagnosis the median survival in patients receiving palliative chemo-radiotherapy was 372 days (95% CI, 270 – 473) compared with 120 days (95% CI, 71 – 169) for patients who did not receive any oncological therapy. A shorter overall post-stent survival was also seen in patients with greater co-morbidity (Charlson score > 7, HR = 1.7 (95% CI, 1.0 – 3.0; $P = 0.05$)) but the association with metastatic disease did not reach statistical significance (HR = 1.4 (95% CI, 0.9 – 2.0; $P = 0.07$).

DISCUSSION

This study, involving 209 patients with advanced esophageal cancer undergoing esophageal stenting for palliation of malignant dysphagia, revealed that GPS is an independent prognostic factor of 30-day mortality and overall survival after esophageal stent insertion. A significant increase in the OR for 30-day mortality and the HR for post-stent mortality was seen with increasing GPS.

Overall post-stent mortality was also associated with increasing co-morbidity and metastatic disease, but these factors were not shown to be significant in predicting 30-day mortality after multivariate logistic regression. These findings demonstrate the potential value of using GPS to assist decision-making about esophageal stenting, when predicting short-term mortality may be helpful. Previous chemo-radiotherapy therapy was associated with increased risk of post-stent mortality, but additional analysis showed that overall survival from diagnosis in this group was significantly longer than the group that had stenting as the only intervention. These data are insufficient to derive a causal relationship of prior chemo-radiotherapy with post-stent survival. The increased post-stent survival in patients receiving no oncological therapy may be explained by a lead-time bias, since these patients are stented earlier in the course of their disease. There remains some uncertainty over the impact on prior chemo-radiotherapy on outcomes following stenting [18] [19].

The study's strengths include the homogeneity of the sample, since it included only those patients with inoperable disease who were receiving a stent for palliation of dysphagia. It also benefits from the use of the same stent and the same experienced endoscopists throughout. No patients were lost to follow-up and the availability of detailed clinical data allowed for adjustment for potential confounding factors.

The limitations of the study include its retrospective design and a prospective study would be required for validation of the GPS in this setting. This study examined all-cause mortality and the impact of procedure-related mortality is uncertain. For example the development of aspiration pneumonia may be a complication of both malignant esophageal obstruction as well as the stenting procedure itself. Systemic inflammation is associated with advanced malignancy as well as infection, and this study does not distinguish between these. In practice, therefore, it may be necessary to exclude infection as a cause of raised CRP when using GPS for prognosis.

The ethnicity of the patient group was almost exclusively white, which may impact on the generalizability of the findings to other populations. However, since esophageal cancer histology was accounted for in the analysis, the potential confounder of race on survival through its association with histology will have been minimized.

Previous studies have used the GPS at the time of diagnosis of esophageal cancer and prior to esophagectomy in operable disease, in order to predict 30-day mortality and overall survival. This study is the first, to our knowledge, that has measured GPS at the

time of palliative esophageal stent insertion. Whereas previously a significant association of GPS with peri-operative mortality has not been seen [14], this study highlights the potential role of GPS in a population with more advanced disease, in order to identify those patients with a higher predicted short-term mortality. This principle has been demonstrated using similar inflammation-based scoring systems to successfully predict short-term mortality in percutaneous endoscopic gastrostomy insertion [20 21].

GPS is simple to measure, routinely available and well-standardized. The high 30-day mortality rate post-esophageal stent insertion requires careful consideration when optimizing the palliative management of patients with inoperable esophageal cancer. This study has implications for future practice, because it shows that GPS is a potential adjunct to clinical assessment in identifying those patients at high-risk of short-term mortality post-stent. By identifying these patients, decision-making about the timing and appropriateness of an esophageal stent can be tailored to an individual's priorities about potential symptom improvement with a stent, along with potential side-effects and complications, which may be more pronounced immediately following stent insertion.

Survival analysis alone, however, is insufficient to assist patients and clinicians when making decisions about the optimal timing and appropriateness of esophageal stent insertion. For patients approaching end-of-life care, an individual assessment of the importance of potential dysphagia improvement by stent insertion must be weighed against procedural risk and adverse events.

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FIGURE LEGENDS

Figure 1. Selection of patients meeting inclusion criteria for post-stent survival analysis.

Figure 2. Kaplan-Meier plots of overall post-stent survival in relation to GPS.