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The Impact of Self-Expanding Metallic Stent Insertion on Survival and Oncological Outcomes in Oesophageal Cancer

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Abstract

Introduction: Oesophageal cancer (OC) is an aggressive malignancy which can be temporarily managed with self-expanding metal stents (SEMS) to improve patient's dysphagia and "bridge the gap" preceding surgical resection. This study aimed to determine whether SEMS has an adverse effect on patient's oncological outcome and mean survival time through a retrospective data analysis.

Materials and methods: We retrospectively analysed 121 patients with OC who underwent curative resection between 2010 to 2015 and who underwent SEMS insertion (stent group, n=61) or not (no stent group, n=66) prior to surgical resection. Patients were then followed up in a prospective data analysis to determine survival time (months) post resection. Survival data was analysed using Kaplan-Meier analysis and statistical analysis included the Chi-Squared test (categorical data) and cox regression for hazard ratios. $P < 0.05$ was considered as significant.

Results: Mean survival time was considerably higher for patients in the non-stent group compared to the stent group (1380 days *vs* 737 days; p=0.05). This represented a 2-fold negative predictor factor on prognosis (hazard ratio = 2.28; p=0.042). These results were comparable to those receiving incomplete resections (hazard ratio= 2.32; p=0.12) (95% CI 1.208-4.68).

Conclusions: Oesophageal SEMS insertion is associated with significantly reduced mean survival time and oncological outcomes when utilised as a pre-operative 'bridge to resection'.

Keywords: Oesphageal cancer; Self-expanding metallic stents; Survival; Oncological outcomes; Tumour micro-perforation

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Introduction

Oesophageal Cancer (OC) is an aggressive malignancy with an annual incidence of around 45,900 in Europe [1]. Diagnosis is often made in the advanced stage due to a lack of widespread screening tools, delayed clinical presentation and rapid disease progression. Approximately 40-50% of patients with newly diagnosed OC are amenable to surgical resection which remains the gold standard for curative treatment [2]. However, patients continue to suffer with significant malignant dysphagia during the pre-operative stage of surgical resection, predisposing to significant; weight loss, malnutrition and reduced quality of life. Therefore, increasing enteral nutrition during the pre-operative stage via nasogastric tube or Percutaneous Endoscopic Gastrostomy (PEG) feeding can ensure adequate calorific intake in malnourished OC patients and provide an effective 'bridge to resection'. However, these treatment options are associated with significant complications such as: displacement, aspiration pneumonia and sinusitis[3]. In addition, alternative methods such as operative jejunostomy and parenteral nutrition can be utilised to enhance calorific intake but again are associated with significant drawbacks such as: risk of infection, displacement and gut bacterial translocation [4]. Nevertheless, the most important disadvantage is that these methods do not alleviate dysphagia for patients and thus have minimal impact on improving quality of life. Subsequently, research has suggested that SEMS can provide an effective method to enhance oral nutrition and relieve patient's dysphagia. SEMS placement has therefore become the standard of care for palliative management of OC to effectively alleviate patient's dysphagia with better efficacy in comparison to other treatment modalities [5]. However, recent research has shown that SEMS can negatively impact upon patient survival and oncological outcomes when used during the pre-operative period to surgical resection. It is hypothesised that SEMS insertion can cause tumour micro-perforations and tumour cell dissemination to worsen oncological outcome and survival [6]. Although published data within the literature determining the effect of SEMS insertion on survival when used as a bridge to surgical resection is incredibly sparse.

In this study, we aimed to determine whether pre-operative SEMS insertion for patients with resectable OC can adversely impact upon mean survival time using a five-year retrospective data analysis. As authors, we hypothesised that SEMS insertion will adversely impact mean survival time due to the process of stent insertion inducing shear stress and micro-perforations causing tumour cell migration and thus worsen oncological outcome.

Materials and methods

Study population: We retrospectively analysed 121 patients with OC who underwent surgical resection between 2010 and 2015 at a single UK centre. The collected data included demographic parameters, details on the perioperative and surgical treatments, postoperative outcomes, histopathological analysis, and long-term outcomes. Patients were recruited according to a specific inclusion and exclusion criteria (Table 1) with any additional missing or inconsistent data excluded during recruitment stage leaving the above final sample cohort. Only patients with squamous or adenocarcinoma were included. All patients who underwent SEMS insertion were identified using a prospectively compiled database and were compared to patients who did not undergo SEMS via retrospective analysis of a prospectively maintained database.

Neoadjuvant therapy: Patients with T3 tumours and/or nodal disease received neoadjuvant chemo-radiotherapy as per national guidelines [7]. Neo-adjuvant chemo-radiotherapy was based upon standard 5-FU and platinum-based drugs in conjunction with concomitant 45Gy direct beam radiotherapy. Locally advanced tumours for which pre-operative staging suggested that R0 resection would be questionable also received neo-adjuvant treatment.

Surgical resection and self-expanding covered metallic stent insertion: Surgical technique used was standard Ivor Lewis esophagectomy in all open cases and laparoscopic technique in all other cases with primary anastomosis [3]. The indications for SEMS insertion was dysphagia for all patients. Covered SEMS were deployed in the standard manner over guidewires with the aid of radiologic imaging and endoscopic confirmation of the stent position. As the aim of the study was the determine the impact of SEMS on long term oncological outcomes, only patients who had successfully placed stents were included in the trial and the decision process surrounding the SEMS placement was not considered.

Histopathologic analysis and staging: The pre-operative TNM classification was based on endoscopic ultrasound with traditional CT scanning methods used in cases where tumour progression prevented full endoscopic ultrasound examination performed before any stenting. This was used in conjunction with positron emission tomography where metastatic disease was questioned. All patients were evaluated by a multidisciplinary team and treated with curative intent according to NICE guidelines for treatment [7]. Resection margin was considered R0 if completely resected, R1 if microscopically involving resection margins and R2 if macroscopically involving resection margins.

Outcome measures: All patients were followed up from December 2010 until death or December 2015 according to NICE guidance [7]. The primary outcome measure was to evaluate the impact of pre-operative SEMS insertion on survival time over a 5-year study period. Secondary outcome measures included R0 resection rate, TNM stage, age, tumour differential and type of operation (laparoscopic vs open) on mortality.

Statistical analysis: Quantitative variables are expressed as the mean ± SD or the median (range). Survival distributions were estimated using the adjusted Kaplan-Meier method and compared using a log-rank test. Univariate and multivariate Cox proportional hazards models were used to determine hazard ratios and their 95% CIs. All tests were 2-sided and the threshold for statistical significance was set at $p< 0.05$. Analyses were performed with SPSS software, version 19.0 (SPSS, Inc).

Table 1: Inclusion and exclusion criteria for patients.

Inclusion	Exclusion
• No distant metastatic disease	• Neo adjuvant chemo/radiotherapy
• No local invasion to unresectable structures	• Locally invasive or distant metastatic disease
• Oesophageal cancers only	• WHO performance score 4/5
• Trail by dissection	• Concurrent malignancy (primary)
• All oesophageal cancers treated with curative intent	

Table 2: Demographic data for all patients (a) and cancer patients only (b).

(a) Demographic data (all patients)	
Total patients	121
Total stents placed	13
Trial by dissection/unresectable	7
Stents for dysplasia only	12

(b) Demographic data (cancer patients only)			
	Stents (n=13)	**No stent (n=108)**	**P Value**
R1	5 (41.7%)	21 (19.4%)	0.916
	8 (60%)	70 (64%)	
	3 (20%)	36 (33.70%)	
	2 (20%)	2 (2.20%)	
	(n=10, after exclusion of trial dissections)	**(n=103, after exclusion of trial dissections)**	
T3	10 (100%)	52 (50.5%)	0.853
T2	0 (0%)	22 (20.4%)	
T1	0 (0%)	25 (23.3%)	
T0	0 (0%)	4 (3.9%)	
nodal yield (mean)	18.7	19.1	0.27
N3	4 (40%)	9 (8.7%)	0.102
N2	1 (10%)	16 (15.5%)	
N1	3 (30%)	23 (22.3%)	
N0	2 (20%)	55 (53.4%)	
Age (median)	61.6	66.9	0.119

Table 3: Mean survival times of patients with a stent and no stent (p=0.05).

Pre op Stent	Mean survival time (months)			
	Estimate (months)	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
No Stent	45.372	2.42	40.614	50.131
Stent	24.24	5.127	14.19	34.29
Overall	43.45	2.336	38.87	48.029

Table 4: Oncological outcomes hazard ratios including confidence intervals.

	p Value	Hazard Ratio	95.0% CI for Exp(B)	
			Lower	Upper
Stent	0.042	2.284	1.032	5.056
Staging (TNM)	0.686	1.029	0.898	1.179
Tumour differential	0.342	1.165	0.85	1.596
Incomplete resection	0.012	2.323	1.208	4.468
Age	0.787	1.048	0.746	1.472
Operation (lap vs open)	0.553	1.123	0.766	1.645

Results

Demographic characteristics: Table 2 (a,b) shows the comparison of demographic characteristics between the two groups. The median age of the patients in the stent and non-stent groups was 61.6 and 66.9 years, respectively (p=0.119). There was however a difference between the resected histological characteristic of the specimens. In the stent group 100% of specimens were classified at T3 whereas only 50.3% of non-stent group was T3 with 20.4% classified as T2 and 23.3% shown to be T1. There was also 3.9% classified as T0. Stent patients tended to have a higher nodal classification with 40% classified as N3 (compared with 8.7% of non-stent patients). This was also noted in that 53.4% of non-stent patients had N0 disease. Tumour differentiation was however comparable between the two groups with the majority of tumours classified as moderately differentiated adenocarcinoma (stent vs non stent 61.6 and 66.9 respectively).

Kaplan – Meier curves (Figure 1) shows a significantly different predicted survival between the two groups (p=0.05). Table 3 shows that the mean survival of the non-stent group was 45.3 months (95% CI 40.6 - 50.1) compared to 24,2 months in the stent group (95% CI 14.1 - 34.2).

Secondary end points: Table 4 shows the differences between the oncological outcomes using cox regression to determine the hazard ratios for each variable. It shows that there is over a 2-fold increase in the risk of early death related to the placement of stents (95% CI 1.032-5.056) (p=0.042). This increase in early death rates was also significantly raised in the incomplete resection group which again shows over a 2-fold increase in risk of early death (95% CI 1.208-4.68). None of the other variables measured showed a significant difference.

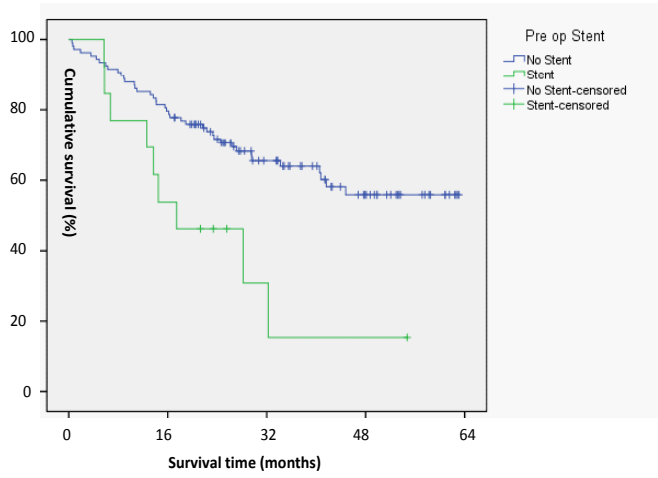

Figure 1: Kaplan-Meier curve showing the comparative survival time (months) between those who received a pre-operative stent (green line) compared to those who did not receive a stent (blue line).

Discussion

At present, SEMS insertion has become a common procedure to treat dysphagia for OC patient's and improve their nutritional status prior to surgical resection. However, current European Society of Gastrointestinal Endoscopy (ESGE) guidelines and recent research has suggested that SEMS insertion is not only associated with significant complications (e.g. perforation), but also provides a negative prognostic impact on patient survival when utilised as a 'bridge' to surgical resection [6,8]. To our knowledge this is the first study within the United Kingdom to determine whether pre-operative SEMS insertion for patients with resectable OC can adversely impact upon mean survival time and oncological outcomes using a retrospective data analysis at a single centre Hospital. Our results demonstrate that SEMS insertion has a significant negative impact upon oncological outcomes and survival time when inserted prior to surgical resection for OC patients.

Our results are comparable with other published data within the literature, with Mariette et al [6]., demonstrating that SEMS insertion prior to surgical resection of OC produces a higher mortality and morbidity rate (13.2% *vs* 8.6% (p=0.370) and 63.2% *vs* 59.2% respectively (p=0.658). Furthermore, Kjaer et al [9]., recently demonstrated compelling evidence over a longer study period on the negative impact of SEMS insertion on patient survival for gastroesophageal junction cancer (11.6 months *vs* 21.3 months; $p<0.001$). Our results, in conjunction with compelling evidence within the literature enable us to draw concrete conclusions on the inverse proportion between SEMS insertion and survival time. Interestingly, previous articles have postulated that the timing of oesophageal stent removal and surgery may impact upon survival. Interestingly, it is important to note that the paper by Mariette et al[6]., patients had their SEMS removed immediately prior to surgical resection which may have increased mechanical shear stress and potentiate tumour cell dissemination immediately prior to surgical resection to negatively impact oncological outcomes. To that end, several authors have reported that SEMS removal 4-6 weeks after starting neoadjuvant chemotherapy can decrease fibrosis and SEMS-related complications [10,11]. Although, research in relation to optimal SEMS removal prior to surgical resection is sparse and results cannot be accurately compared.

Furthermore, the negative prognostic implications of SEMS insertion are well recognised amongst other malignant states, namely colorectal cancer. Published data has shown that SEMS insertion when utilised as a 'bridge' to resection for acute left sided colorectal cancer can negatively impact oncological outcomes with significantly greater 5-year mortality (48% *vs* 21%, $p=0.02$) [12]. Several theories exist to explain the detrimental prognostic impact of SEMS insertion on survival. One of the main recognised theories suggests that during SEMS insertion, expansive radial forces and shearing of tumour cells can induce micro-perforations of cell lumens and subsequent tumour cell dissemination. This theory has been supported with evidence to suggest that higher circulating levels of CK20 mRNA after endoscopic stenting of obstructing colonic cancer is the result of tumour cell dissemination due to mechanic force imposed upon the tumours by the stent [13].

Baseline characteristics of the stent group (Table 2) demonstrate more advanced disease state with respect to TNM and R1 resections. Therefore, it is not surprising to find that the patients attributed to the stent group had significantly reduced mean survival time in comparison to those without. However, previous research has shown that even with closely matched baseline characteristics including TNM staging, SEMS insertion has a profound negative impact on patient survival [9]. We as authors speculate that TNM stage did not prove to be a predictor of worsening oncological outcomes likely due to our small sample size. In addition, our results indicated that SEMS insertion is also associated with greater R1 resections, which again can potentiate tumour cell dissemination and has shown within our results to negatively prognosticate survival time.

Baseline nutritional status has been shown to be an independent predictive factor for increased postoperative morbidity and mortality, lower rates of respectability and survival [4]. Interestingly, these findings in conjunction with the novel findings of worsening oncological outcomes with SEMS insertion have led to researchers comparing alternative feeding methods to maintain nutritional status. The study by Won Min et al.,[14] demonstrated compelling evidence that PEG feeding offers significantly increased survival time (hazard ratio 0.557; $p=0.007$) and greater nutritional status in comparison to SEMS insertion for OC when compared during the pre-operative stage of surgical resection [14]. Therefore, our results in conjunction with novel data in the literature demonstrate promising alternative methods of feeding during pre-operative period to provide a greater impact on nutritional status and more importantly increased patient survival. This study has some limitations, mainly our small sample size that reduces our ability to confirm causality conclusions due to an under powered study. In addition, we as authors did not validate data on nutritional status and improvements in both dysphagia score and quality of life would provide prudent data in conjunction with survival time. However, our sample size is comparable with other studies in the literature and demonstrates evolving poignant data to suggest that stent placement can have a serious negative impact upon long term survival time in OC. Going forward, our recommendations would be to conduct a larger sample size to confirm our findings and also collect data on nutritional status and matched TNM staging at baseline and post SEMS insertion to confirm the causal relationship on survival time and oncological outcome.

Conclusion

Our study supports growing evidence within the literature that oesophageal SEMS insertion should not be recommended as a clinical 'bridge' to surgical resection for patients with OC due to the significant negative impact upon oncological outcomes and survival time. However, more robust randomised controlled trials with larger samples are needed to exemplify this causality.

References

1. Ferlay J, Steliarova-Foucher E,Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. Eur J Cancer. 2013; 49(6): 1374-403.

2. Hirdes MM, Vieggaar FP andSiersema PD. Stent placement for esophageal strictures: an update. Expert Rev Med Devices. 2011; 8(6): 733-55.

3. Park RH, Allison MC, Land J, Spence E, Morris AJ, Danesh BJ, et al. Randomised comparison of percutaneous endoscopic gastrostomy and nasogastric tube feeding in patients with persisting neurological dysphagia. BMJ. 1992; 304(6839): 1406-9.

4. Mariette C, De Botton ML andPiessen G. Surgery in esophageal and gastric cancer patients: what is the role for nutrition support in your daily practice? Ann surg Oncol. 2012; 19(7): 2128-34.

5. Spaander MC, Baron TH,Siersema PD, Fuccio L, Schumacher B, Escorsell À, et al. Esophageal stenting for benign and malignant disease: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2016; 48(10): 939-48.

6. Mariette C, Gronnier C, Duhamel A, Mabrut JY, Bail JP, Carrere N, et al. Self-expanding covered metallic stent as a bridge to surgery in esophageal cancer: impact on oncological outcomes. J Am Coll Surg. 2015; 220(3): 287-96.

7. National Institute for Health and Care Excellence. Oesophago-gastric cancer: assessment and management in adults. London: NICE; 2018.

8. Spaander MC, Baron TH,Siersema PD, Fuccio L, Schumacher B, Escorsell À, et al. Esophageal stenting for benign and malignant disease: European society of gastrointestinal endoscopy (ESGE) clinical guideline. Endoscopy. 2016; 48(10): 939-48.

9. Kjaer DW, Nassar M, Svendsen LB, Mortensen FV and Jensen LS. A bridging stent to surgery in patients with esophageal and gastroesophageal junction cancer has dramatic negative impact on patient survival: A retrospective cohort study through data acquired from prospectively maintained national database. Dis Esophagus. 2017; 30(3): 1-7.

10. Park JH, Song HY, Park JY, Kim JH, Kim YH, Kim JH, et al. Temporary stent placement with concurrent chemoradiation therapy in patientswith unresectable oesophageal cancinoma: is there an optimal time for stent removal? Eur Radiol. 2013; 23(7): 1940-5.

11. Park JH, Song HY, Kim YH, Kim SB, Kim JH and Shin JH. Prelimary results of temporary placement of retrievable expandable metallic stents during preoperative neoadjuvant chemoradiotherapy in patients with resectableesophageal cancer. J VascInterv Radiol. 2015; 26(6): 883-8.

12. Sabbagh C, Browet F, Diouf M, Cosse C, Brehant O, Bartoli E, et al. Is stenting as “a bridge to surgery” an oncologically safe strategy for the management of acute, left-sided, malignant, colonic obstruction? A comparative study with a propensity score analysis. Ann Surg. 2013; 258(1): 107-15.

13. Maruthachalam K, Lash GE, Horgan AF and Shenton BK. Tumour cell dissemination following endoscopic stent insertion. Br J Surg. 2007; 94(9): 1151-4.

14. Min YW, Jang EY, Jung JH, Lee H, Min BH, Lee JH, et al. Comparison between gastrostomy feeding and self-expandable metal stent insertion for patients with esophageal cancer and dysphagia. PLoS One. 2017; 12(6): e0179522.