Meta-Analysis

Safety and efficacy of esophageal stents preceding or during neoadjuvant chemotherapy for esophageal cancer: a systematic review and meta-analysis

Vinayak Nagaraja, Michael R. Cox, Guy D. Eslick

The Whiteley-Martin Research Centre, Discipline of Surgery, The Sydney Medical School Nepean, Penrith, New South Wales, Australia
Correspondence to: Associate Professor Guy D. Eslick. The Whiteley-Martin Research Centre, Discipline of Surgery, The University of Sydney Nepean Hospital, Level 5, South Block, P.O. Box 63, Penrith, NSW 2751, Australia. Email: guy.eslick@sydney.edu.au.

Background: Patients with locally advanced esophageal cancer who require neoadjuvant therapy have significant dysphagia and may severely impair nutritional status. We conducted a meta-analysis to assess the efficacy of self-expandable metal stents prior to neoadjuvant therapy.

Methods: A systematic search was conducted using MEDLINE, PubMed, EMBASE, Current Contents Connect, Cochrane library, Google Scholar, Science Direct, and Web of Science. Original data was abstracted from each study and used to calculate a pooled odd ratio (OR) and 95% confidence interval (95% CI).

Results: Only nine studies comprising of 180 patients were included for analysis. The overall procedural success rate was 95% (95% CI, 0.895-0.977). There was a substantial decrease in the dysphagia scores standard difference in means (SDM) –0.81 [standard error (SE) 0.15, 95% CI, –1.1 to –0.51], similar increase in weight SDM 0.591 (SE 0.434, 95% CI, –0.261 to 1.442) and serum albumin SDM 0.35 (SE 0.271, 95% CI, –0.181 to 0.881). The incidence of major adverse events included stent migration 32% (95% CI, 0.258-0.395) and chest discomfort 51.4% (95% CI, 0.206-0.812).

Conclusions: Placement of stents in patients with locally advanced esophageal cancer significantly improves dysphagia and allows for oral nutrition during neoadjuvant therapy. Stents appear to be effective for palliating dysphagia. Stent migration was a common occurrence; however, migration may be a sign of tumor response to neoadjuvant therapy.

Keywords: Neoadjuvant therapy; self-expandable metal stents; esophageal cancer

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Introduction

The incidence and mortality from cancer of all types in the United States has decreased during the 1991-2006 timeframe (1). However, the opposite is true for esophageal cancer. Its incidence and mortality continue to rise. In 2010, estimated new cases of esophageal cancer number 16,640 in the United States, while deaths total 14,500 (1). The United States has seen an average increase of 20.6% per year in the incidence of adenocarcinoma of the esophagus since that time (2). Esophageal cancer is a highly lethal disease in which only one-third of patients present with resectable disease. Of this select group, the average 5-year survival is only 35-45% (3). The overwhelming majority of patients have a fatal outcome, but advances in multimodality therapy appear to be improving the long term survival outcome for patients with locally advanced disease.

Most patients with advanced esophageal cancer have significant dysphagia, which contributes to weight loss and malnourishment. The majority of patients with esophageal cancer present with signs of malnutrition at the time of diagnosis as a result of both dysphagia and tumor-induced cachexia (4). Additionally, patients undergoing multimodal therapy have been shown to have significantly worse nutritional parameters than those only undergoing

resection (5). Radiation-induced esophagitis develops in 15-28% of treated patients' further aggravating dysphagia (6,7). Also, the side effects of 5-fluorouracil and cisplatin, the most common chemotherapy regimen employed to treat esophageal cancer, include nausea, vomiting, and diarrhea. Malnutrition reduces the potential response of the malignancy to chemoradiotherapy and impairs the patient's ability to tolerate the full course of treatment (8). In addition, the importance of adequate nutritional status prior to a major operation is well recognized (9).

Evidence clearly indicates that malnourished patients who undergo major operations are predisposed to infectious complications and worse postoperative outcomes (9-11). Nutritional deficiencies may also contribute to the trend of amplified perioperative morbidity and mortality among esophageal cancer patients receiving multimodal therapy compared with patients undergoing resection alone (12,13).

We hypothesized that patients treated with neoadjuvant therapy and who received removable stents would have better nutrition-related outcomes compared with those who were not stented. The objective of this study was to evaluate of the effectiveness of stents for improving the nutritional status of patients undergoing neoadjuvant therapy for esophageal cancer.

Methods

Study protocol

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses PRISMA guidelines where possible in performing our systematic review (14). We performed a systematic search through MEDLINE (from 1950), PubMed (from 1946), EMBASE (from 1949), Current Contents Connect (from 1998), Cochrane library, Google scholar, Science Direct, and Web of Science to May 2013. The search terms included "esophageal cancer", "neoadjuvant therapy" and "stents", which were searched as text word and as exploded medical subject headings where possible. No language restrictions were used in either the search or study selection. The reference lists of relevant articles were also searched for appropriate studies. A search for unpublished literature was not performed.

Study selection

We included studies that met the following inclusion criteria:

- Studies identifying the population of patients with esophageal cancer undergoing stent implantation prior or during neoadjuvant therapy.

Data extraction

We performed the data extraction using a standardized data extraction form, collecting information on the publication year, study design, number of cases, total sample size, population type, country, continent, mean age and clinical data. The event rate and confidence intervals (CIs) were calculated.

Statistical analysis

Pooled event rate and 95% CI were using a random effects model (15). We tested heterogeneity with Cochran's Q statistic, with $P<0.10$ indicating heterogeneity, and quantified the degree of heterogeneity using the I^2 statistic, which represents the percentage of the total variability across studies which is due to heterogeneity. I^2 values of 25%, 50% and 75% corresponded to low, moderate and high degrees of heterogeneity respectively (16). The quantified publication bias using the Egger's regression model (17), with the effect of bias assessed using the fail-safe number method. The fail-safe number was the number of studies that we would need to have missed for our observed result to be nullified to statistical non-significance at the $P<0.05$ level. Publication bias is generally regarded as a concern if the fail-safe number is less than $5n+10$, with n being the number of studies included in the meta-analysis (18). All analyses were performed with Comprehensive Meta-analysis (version 2.0), Biostat, Englwood, NJ, USA [2005].

Results

The original search strategy 418 retrieved studies (*Figure 1*). The abstracts were reviewed and after applying the inclusion and exclusion criteria, articles were selected for full-text evaluation. Of the articles selected, only nine studies (180 patients) met full criteria for analysis and are summarised in *Table 1*. The years of publication ranged from 2007 to 2012.

The overall procedural success rate was 95% (95% CI, 0.895-0.977). There was a substantial decrease in the dysphagia scores standard difference in means (SDM) –0.81 [standard error (SE) 0.15, 95% CI, –1.1 to –0.51] (*Figure 2*), similar

increase in weight SDM 0.591 (SE 0.434, 95% CI, –0.261 to 1.442) and serum albumin SDM 0.35 (SE 0.271, 95% CI, –0.181 to 0.881). The incidence of major adverse events included stent migration 32% (95% CI, 0.258-0.395) and chest discomfort 51.4% (95% CI, 0.206-0.812) (*Figure 3*).

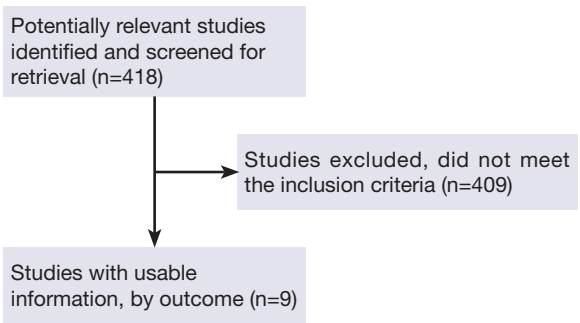

Figure 1 Flow of included studies.

Heterogeneity and publication bias

The heterogeneity of outcomes has been summarized in *Tables 2* and *3*. The reason for significant heterogeneity may be attributed to different population groups. No publication bias was detected using the Egger's regression model.

Discussion

The current standard of care is to offer neoadjuvant therapy to patients with locally advanced esophageal cancer (28). These patients receive three to six weeks of therapy before surgery (29,30). During oncologic therapy, dysphagia often increases due to mucositis and esophagitis induced by chemotherapy and radiotherapy. Others factors contributing to this include obstruction to sufficient dietary intake by luminal narrowing, anorexia and tumor cachexia. Improved baseline

Table 1 Characteristics of the studies included in the systematic review and meta-analysis

Author	Country	Year	Patients	Stent
Siddiqui *et al.* (19)	USA	2009	12	Polyflex stent
Adler *et al.* (20)	USA	2009	13	Polyflex stent
Siddiqui *et al.* (21)	USA	2007	6	Polyflex stent
Bower *et al.* (22)	USA	2009	25	Polyflex stent
Langer *et al.* (23)	Austria	2010	38	Self-expanding, plastic stents, covered metal stents
Pellen *et al.* (24)	UK	2012	16	Self-expanding removable metal stents
Siddiqui *et al.* (25)	USA	2012	55	ALIMAXX-E stent, WallFlex stent
Lopes *et al.* (26)	USA	2010	11	ALIMAXX-E, stent
Martin *et al.* (27)	USA	2009	5	Polyflex stent

Table 2 Overall odds ratio and 95% CI for patient outcomes

Outcome	Event rate	95% CI	I^2	P value
Successful placement	0.95	0.895-0.977	0	0.76
Stent migration	0.32	0.258-0.395	0	0.82
Chest discomfort	0.514	0.206-0.812	82.16	<0.0001

CI, confidence interval.

Table 3 Standard difference in means and 95% CI for patient outcomes

Outcome	Standard difference in means	Standard error	95% CI	I^2	P value
Dysphagia scores	–0.81	0.15	–1.1 to –0.51	59.72	0.01
Increase in weight	0.591	0.434	–0.261 to 1.442	86.98	<0.001
Increase in serum albumin	0.35	0.271	–0.181 to 0.881	70.68	0.01

CI, confidence interval.

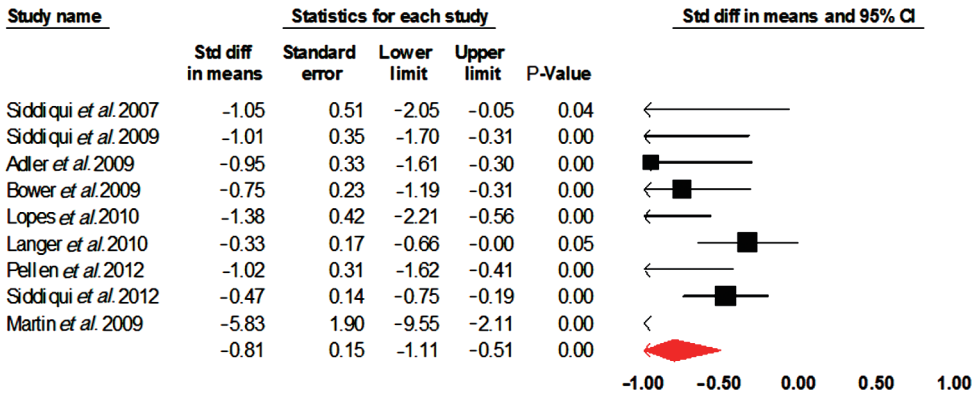

Figure 2 Dysphagia scores. CI, confidence interval.

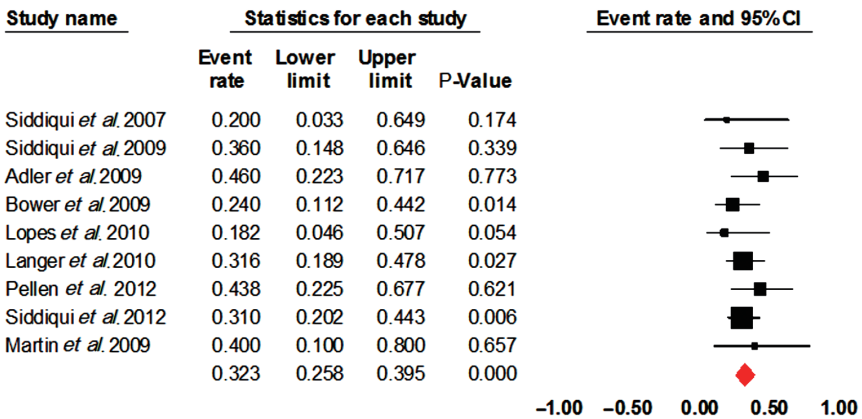

Figure 3 Stent migration. CI, confidence interval.

nutritional status independently predicts superior response to definitive chemoradiotherapy (albumin >35 g/L) and survival (BMI >18 kg/m^2) in locally advanced esophageal cancer receiving nonsurgical treatment with curative intent (31). Therefore, the need for nutritional support is increased.

Options for nutritional supplementation during neoadjuvant therapy include parenteral nutrition or enteral nutrition given via a feeding tube. Parenteral nutrition is generally avoided because of increased costs, higher rates of infectious complications, and less efficacious reversal of malnutrition (32-36). Enteral supplementation requires feeding tube placement by either an open, laparoscopic or percutaneous technique. In fact, some centers advocate routine feeding tube placement in all patients undergoing multimodal therapy (37,38). Nasogastric feeding can be poorly tolerated and unsightly for the patient. It is associated with blockage, displacement, reflux and aspiration risks, and do not palliate dysphagia.

Percutaneous endoscopic gastrostomy (PEG) mandates that the tumor be negotiable with an endoscope and even if traversable, the pull-through technique may traumatize or transfer disease from the primary tumor. In the case of PEG tube placement, the potential exists for injury to the gastroepiploic artery rendering the stomach unusable as a replacement conduit for the esophagus (39). Besides procedure-related morbidity, tube placement delays chemotherapy by 1-2 weeks to allow for resolution of local inflammation and contamination that develops at the insertion site.

Jejunostomies arguably represent the mainstay of perioperative nutritional supplementation in esophagectomy patients and may be performed radiologically or surgically. However, both pre- and postoperative jejunostomies are associated with morbidity including displacement, obstruction, tube-site infection and peritonitis (40,41).

Preoperative esophageal stenting provides a possible

alternative to address the nutritional status of patients receiving multimodal therapy. Removable self-expanding silicone stents can be placed prior to neoadjuvant therapy and later removed endoscopically or at the time of surgery (27). The overall procedural success rate was good according to our analysis.

Complications

The overall incidence of stent migration was 32%. However, the majority of them did not require stent replacement because the stent migration probably was a result of tumor shrinkage from neoadjuvant therapy (25). Additionally, all the migrations were of stents that were deployed across the gastroesophageal junction and hence were at increased risk for migration. Stent migration correlated with restoration of an esophageal lumen that allowed for adequate oral nutritional intake (25). Another advantage of preoperative esophageal stenting not all patients with locally advanced esophageal cancer will have a curative resection. Patients who do not proceed to surgery can have their stents left in place as a palliative measure.

Quality of life (QoL)

The primary aim of treatment in patients with inoperable EC is to relieve dysphagia with minimal morbidity and mortality, and thus improve their QoL. Implantation of a SEMS has become established as a treatment modality for the palliation of malignant dysphagia. SEMS relieves dysphagia rapidly and improves the nutritional status. However, in most studies, relief of dysphagia is the only aspect of health-related quality of life (HRQoL) being measured, although physical, mental and social functioning and other EC-specific aspects of HRQoL are additional important outcome measures.

A randomized clinical trial comparing SEMS with plastic endoprostheses published in 2002 by University of Glasgow and Edinburgh (42) included 50 patients suffering from dysphagia due to an inoperable EC, and measured QoL using EORTC QLQ-30, a multi-dimensional cancer-specific QoL questionnaire and an EC specific questionnaire (EORTC OES-24), allowing QoL to be measured over 26 components relating to cancer in general and EC in particular. Although the authors found no statistical significance in any of the 26 components, 21 of the 26 components showed a trend towards the metal group, five were neutral and none favored plastic stents.

Shenfine *et al.* (43) in a randomized controlled trial regarding the cost-effectiveness of palliative therapies for patients with inoperable EC studied QoL in detail using four different questionnaires including Spitzer QoL index, Karnowsky performance scale, Euroqol EQ-5D and EORTC QLQ-30. They also used proxy and self-administered questionnaires. These authors reported differences in the baseline QoL index favoring the non-SEMS group and went on to report one and six wk QoL data for the different treatment groups. Mean QoL index for the SEMS group at six wk was significantly lower than for the QoL index at baseline for the same group. The authors concluded that decreased QoL in the SEMS group at six wk, although not statistically significant, reflected the presence of pain following the intervention; the effect of pain on QoL may have significant implications for treatment with SEMS.

Sahlgrenska University Hospital (44) in their randomized controlled clinical trial published in 2005, compared endoluminal brachytherapy with endoscopic stent placement for newly diagnosed patients with advanced EC or gastroesophageal junction cancer, with a primary outcome being the detailed evaluation of HRQoL. Sixty-five patients eligible for the study were enrolled; 34 were randomized to stent treatment and 31 to brachytherapy. The authors assessed dysphagia improvement as a part of disease-specific HRQoL questionnaire EORTC OES-23 and found a statistically significant improvement in dysphagia grade, ability to swallow saliva, choking and coughing compared to baseline scores. There was no improvement in these outcomes for patients treated with brachytherapy. In an interim inter-group analysis at one mo a significant improvement in dysphagia scale favored the SEMS group. At three mo, some of the dysphagia-related parameters continued to show clinical improvement in the SEMS group but these did not achieve statistical significance. In the brachytherapy group, clinically significant improvements were noted in some of the parameters related to dysphagia at three mo and these were maintained at six mo. However, these data did not achieve statistical significance. General health QoL was measured using the EORTC QLQ-30 scale. In the stent group all functional scales and single symptom scales deteriorated compared to mean scores at inclusion. The largest deterioration was found for social function, followed by pain, role function and insomnia. In the brachytherapy group, a clinically relevant deterioration was found for most variables on the function and single symptom scales with physical function, global QoL and pain scales reaching statistical significance.

Madhusudhan *et al.* (45) in their prospective study

assessed the QoL using EORTC QLQ-C30 (version 3) and EORTC QLQ-OES 18 questionnaires before stenting, and at one, four and eight wk following placement of the stent. The results showed significant improvement following stenting. The general health scale and function scores increased significantly. Most symptom scores, except pain, showed improvement. The pain score deteriorated at one wk, as initial expansion of SEMS following its placement led to an increase in pain sensation. Over a period of two mo, the pain scores decreased to baseline values. The financial strain scores also showed a significant improvement. The studies did not specifically address the influence of stents on patient QoL; although anecdotally we have extrapolated that improved swallowing will result in improved QoL. Improvement of dysphagia is likely a result of stent placement along with decreased tumor burden from neoadjuvant therapy. A generous decrease in the dysphagia scores SDM –0.81 was observed in our investigation.

Other applications of stent implantation in perioperative and postoperative care of the carcinoma of the esophagus

Removable self-expanding silicone stents have previously demonstrated utility for relieving dysphagia from benign strictures and from both resectable and unresectable malignant disease (27,46-49). University Medical Centre Utrecht (50) performed a pooled analysis regarding placement of fully covered and partially covered SEMS (FSEMS and PSEMS) and SEPS for treating benign esophageal ruptures and anastomotic leaks. Twenty-five studies, including 267 patients with complete follow-up on outcome, were identified. Clinical success was achieved in 85% of patients and was not different between stent types (SEPS 84%, FSEMS 85% and PSEMS 86%, P=0.97). Time of stent placement was longest for SEPS (eight weeks) followed by FSEMS and PSEMS (both six weeks). In total, 65 (34%) patients had a stent-related complication. Stent migration occurred more often with SEPS [n=47 (31%)] and FSEMS [n=7 (26%)] than with PSEMS [n=2 (12%), P≤0.001], whereas there was no significant difference in tissue in- and overgrowth between PSEMS [12% *vs.* 7% (FSEMS) and 3% (SEPS), P=0.68].

Martin *et al.* (51) compared early esophageal stenting *vs.* repeated dilation in esophagectomy strictures. The median number of dilatations were 2 (range, 1 to 3) for the 18 stent patients, with all stents placed for three months' duration, and 4 dilations (range, 2 to 12 dilations) in 24 patients treated solely with dilatation. An evaluation of median, high and low total charges, net revenue, and direct margin demonstrated that the use of a removable stent after one failed dilation was more cost-efficient than repeated dilations.

In conclusion, self-expanding stents are a safe and effective method for endoscopic improvement of dysphagia in patients with malignant esophageal strictures receiving neoadjuvant therapy. The stents represent a new, alternative and cost-effective therapy for maintaining adequate oral nutrition. The QoL benefits gained by restoring the patient's ability to eat and enjoy food is admirable.

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