Anti-reflux versus conventional self-expanding metal stents in the palliation of esophageal cancer: A systematic review and meta-analysis

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ABSTRACT

Background and study aims Self-expanding metal stents (SEMS) are an effective palliative endoscopic therapy to reduce dysphagia in esophageal cancer. Gastroesophageal reflux disease (GERD) is a relatively common complaint after non-valved conventional SEMS placement. Therefore, valved self-expanding metal stents (SEMS-V) were designed to reduce the rate of GERD symptoms. We aimed to perform a systematic review and meta-analysis comparing the two stents.

Material and methods This was a systematic review and meta-analysis including only randomized clinical trials (RCT) comparing the outcomes between SEMS-V and non-valved self-expanding metal stents (SEMS-NV) following the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. The risk of bias was assessed using the Cochrane Risk of Bias 2 tool. Data were analyzed with Review Manager Software. Quality of evidence was evaluated using Grading of Recommendations Assessment, Development, and Evaluation guidelines.

Results Ten randomized clinical trials including a total of 467 patients, 234 in the SEMS-V group and 233 in the SEMS-NV group, were included. There were no statistically significant differences regarding GERD qualitative analysis (RD –0.17; 95% CI –0.67, 0.33; P = 0.5) and quantitative analysis (SMD –0.22; 95% CI –0.53, 0.08; P = 0.15) technical success (RD –0.07; 95% CI –0.19, 0.06; P = 0.30), dysphagia improvement (RD –0.07; 95% CI –0.19, 0.06; P = 0.30), and adverse events (RD 0.07; 95% CI –0.20, 0.20; P = 0.32).

Conclusions Both SEMS-V and SEMS-NV are safe and effective in the palliation of esophageal cancer with similar rates of GERD, dysphagia relief, technical success, adverse events, stent migration, stent obstruction, bleeding, and improvement of the quality of life.
Introduction

The incidence of esophageal cancer (CA) was estimated to be more than 600,000 cases worldwide in 2020, associated with a 5-year survival rate of 19.9%, making it one of the most deadly malignancies [1, 2]. There has been an increase in the incidence of gastroesophageal junction (GEJ) cancer in young patients with Barrett’s esophagus, which is growing annually due to an increase in the incidence of obesity, which subsequently increases the risk of gastroesophageal reflux disease (GERD), a well-known risk factor for adenocarcinoma of the distal esophagus [3–5].

The cornerstone of treatment is complete resection; however, patients unfortunately present symptoms once they are at an advanced stage of their disease. For that reason, resection is not feasible in most cases, and thus, therapeutic approaches to improve the patient quality of life (QoL) are needed [6]. Self-expanding metal stents (SEMS) are widely indicated to improve dysphagia and increase calorie intake, both of which are independent causes of poor prognosis, and thus, are considered the standard of care for palliation of symptoms in this population of patients, especially in the presence of a tracheoesophageal or bronchoesophageal fistula [7, 8].

The main adverse events (AEs) that impact the QoL in patients with SEMS are post-procedure pain, dysphagia recurrence, migration, and gastroesophageal reflux disease (GERD) [9, 10]. Unfortunately, GERD occurs in about 7% of patients, due to obliteration of the lower esophageal sphincter associated with the inherent mechanism of the SEMS, and thus, it can also be associated with bronchoaspiration; a life-threatening complication, especially for these patients [10, 11]. Therefore, it has been proposed that valved SEMS (SEMS-V) could theoretically improve patient QoL by reducing GERD symptoms with the same clinical efficacy and safety as non-valved SEMS (SEMS-NV).

To evaluate the best evidence available in the literature regarding the efficacy and safety of SEMS-V compared to SEMS-NV, we performed this systematic review and meta-analysis based only on randomized clinical trials (RCT) to deliver the highest grade of evidence and recommendation.

Material and methods

Protocol registration

This study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the file number CRD42021258196 and was approved by the Ethics Committee of Hospital das Clínicas, Faculty of Medicine at The University of São Paulo. This systematic review and meta-analysis was performed in conformity with recommendations from the Cochrane Handbook of Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [12].

Eligibility criteria

All relevant published abstracts and full-text manuscripts, regardless of language and year of publication, were included. The eligibility criteria included RCTs comparing SEMS-V versus SEMS-NV in the palliative treatment of esophageal cancer in patients over 18 years of age. The exclusion criteria were studies that were not RCTs or RCTs in which it was not possible to retrieve the required data.

Information Sources

We performed individualized searches in multiple electronic databases including MEDLINE, Embase, Cochrane, LILACS, clinicaltrials.gov, and a cross-reference search, from their inception until February 2022. The search strategy was: (Esophageal Neoplasms OR Esophageal Neoplasm OR Esophagus Neoplasm OR Esophagus Neoplasms OR Cancer of Esophagus OR Esophageal Cancers OR Esophageal Cancers AND (Prostheses and Implants OR Prosthetic Implants OR Prosthetic Implant OR Artificial Implant OR Artificial Implants OR Prostheses OR Prosthesis OR Endoprosthesis OR Endoprostheses OR Stents OR Stent).

Study selection and data collection process

Two independent researchers reviewed the title and abstract of each article after the removal of duplicated articles. Articles that were found to be relevant were selected for full-text evaluation. The final decision on choosing the studies was based on predetermined inclusion and exclusion criteria. Any disagreement on selecting the studies was resolved by consensus with a third experienced researcher.

Evaluation of bias and quality of studies

The risks of bias was assessed by the version 2 of the Cochrane Risk-of-Bias tool for Randomized Trials (RoB2) [13]. The quality of evidence, expressed in high, moderate, low, and very low, was assessed utilizing the objective criteria from the GRADE (Grading Recommendations Assessment, Development, and Evaluation) guidelines for each of the pre-specified results, and the outcomes were evaluated using the GRADEpro – Guideline Development Tool software (McMaster University, 2015; Evidence Prime, Inc., Ontario, Canada).

Data items

The following data were extracted: name of first author, year of publication, country, study design, population (number of patients), SEMS type (valved vs non-valved), and outcomes. The evaluated primary outcome was GERD qualitative and quantitative analyses. The quantitative analysis of GERD was displayed as the variation of the different reflux scores one to three months after SEMS placement. On the other hand, the secondary outcomes included technical success, dysphagia improvement, AEs, stent migration, stent obstruction, bleeding, and QoL improvement. Clinical success was defined as an improvement in patient GERD symptoms and dysphagia.
Data analysis

The data of interest extracted from the selected studies were meta-analyzed using the Review Manager (RevMan) software (Review Manager Software version 5.4 – Cochrane Collaboration) also, the interval prediction was calculated by the Comprehensive Meta-Analysis (CMA version 3) software.

For dichotomous variables, the risk difference was determined by calculating the number of events and the sample size using the Mantel Haenszel test with a 95% confidence interval [14]. For continuous variables, the mean or median with standard deviation and the total number of patients were used, employing the inverse variance test with a 95% confidence interval.

A fixed-effect was used when the heterogeneity was < 50% and a random effect when it was > 50%. Heterogeneity was calculated using the Higgins test (I²), ranging from 0% to 100%, I² values higher than 50% were considered substantial heterogeneity [14, 15]. Additionally, the prediction interval was calculated as true effects [16], and P < 0.05 was considered statistically significant.

Due to the low number of identified RCTs and the low heterogeneity between them, funnel plots were not useful to assess presence of publication bias, and therefore, were not used.

Results

Literature search results and characteristics of included studies

The initial search strategy identified 7612 records, resulting in ten studies [17–26] (Fig. 1). The 10 RCTs evaluated a total of 467 patients, 234 in the SEMS-V group, and 233 in the SEMS-NV group. The characteristics of the included studies are summarized in Table 1.

Evaluation of biases and quality of studies

The studies [17–25] included in the meta-analysis presented a low risk of bias, except for the study realized by Kaduthodil et al, which had a high risk of bias (Fig. 2). The evidence quality of the evaluated outcomes was different as exposed by the GRADE illustrated in Fig. 3. In accordance with the GRADE, we exposed a maximum of seven outcomes evidence quality.

Meta-analysis

Gastroesophageal reflux disease (GERD) – qualitative evaluation

Three RCTs [20,24,25] with a total of 122 patients (59 in the SEMS-V group and 63 in the SEMS-NV group), were included in this meta-analysis showing no statistically significant difference (RD –0.17; 95% CI –0.67, 0.33; P = 0.5; I² = 93%) between the groups (Fig. 4), with a prediction interval ranging from –6.46 to 6.12 (Fig. 5). This outcome presented a very low quality of evidence (Fig. 3).

Gastroesophageal reflux disease (GERD) – quantitative evaluation

Five RCTs [17,19,22,23,26] with a total of 172 patients (81 in the SEMS-V group and 91 in the SEMS-NV group), were included in this meta-analysis showing no statistically significant difference (SMD –0.22; 95% CI –0.53, 0.08; P = 0.15; I² = 48%) between the groups (Fig. 6). This outcome presented a very low quality of evidence (Fig. 3).
Dysphagia Improvement

The meta-analysis included three RCTs [17, 20, 25] with a total of 150 patients (74 in the SEMS-V group and 76 in the SEMS-NV group) and showed no statistically significant difference (RD –0.07; 95% CI –0.19, 0.06; P=0.30; I²=0%) between SEMS-V and SEMS-NV groups for this outcome (Fig. 7). This outcome presented a moderate quality of evidence (Fig. 3).
Eight RCTs [17–21, 23–25], with a total of 364 patients (176 in the SEMS-V group and 188 in the SEMS-NV group), were included in the meta-analysis showing no statistically significant difference (RD -0.03; 95% CI -0.07, 0.01; P=0.16; I² = 0%) between groups (Fig. 8). This outcome presented a moderate quality of evidence (Fig. 3).

Adverse events

Seven RCTs [17–19, 21, 22, 24, 25] analysis with 335 patients (160 in the SEMS-V group and 175 in the SEMS-NV group) were included in this analysis. Our meta-analysis showed no statistically significant difference (RD 0.07; 95% CI -0.07, 0.20; P=0.32; I² =59%) between SEMS-V and SEMS-NV groups (Fig. 9). With a prediction interval ranging from -0.33 to 0.47 (Fig. 10). This outcome presented a low quality of evidence (Fig. 3).
Stent migration

A total of 364 patients (158 in the SEMS-V group and 188 in the SEMS-NV group) from seven RCTs [17–19, 21, 22, 24, 25] were included in this meta-analysis, showing no statistically significant difference (RD 0.07; 95% CI –0.02, 0.15; P = 0.15; I² = 0%) between SEMS-V and SEMS-NV groups (▶ Fig. 11). This outcome presented a moderate quality of evidence (▶ Fig. 3).

Stent obstruction

Six RCTs [18–22, 25], with 291 patients (138 in the SEMS-V group and 153 in the SEMS-NV group), were included in this analysis. The meta-analysis showed no statistically significant difference (RD –0.01; 95% CI –0.08, 0.05; P = 0.26; I² = 23%) between the groups (▶ Fig. 12). This outcome presented a moderate quality of evidence (▶ Fig. 3).
A total of 281 patients (133 in the SEMS-V group and 148 in the SEMS-NV group) from six RCTs [17–20, 22, 24] were included in this meta-analysis showing no statistically significant difference (RD 0.01; 95% CI –0.05, 0.06; \( P = 0.91; I^2 = 0\%\)) between the two types of SEMS (Fig. 10). This outcome presented a moderate quality of evidence. (Fig. 13).

**Bleeding**

A total of 281 patients (133 in the SEMS-V group and 148 in the SEMS-NV group) from six RCTs [17–20, 22, 24] were included in this meta-analysis showing no statistically significant difference (RD 0.01; 95% CI –0.05, 0.06; \( P = 0.91; I^2 = 0\%\)) between the two types of SEMS (Fig. 10). This outcome presented a moderate quality of evidence. (Fig. 13).

**Quality of life**

Two RCTs [19, 22], with a total of 56 patients (25 in the SEMS-V group and 31 in the SEMS-NV group) were included in this meta-analysis showing no statistically significant difference (MD –1.00; 95% CI –14.98, 12.98; \( P = 0.89; I^2 = 0\%\)) between the groups (Fig. 14). This outcome presented a low quality of evidence.

**Discussion**

Self-expanding metal stents (SEMS) are one of the most efficient treatments for the palliation of advanced esophageal cancer [27, 28], but when placed across the cardia, they have the potential of causing gastroesophageal reflux disease (GERD) symptoms due to the obliteration of the lower esophageal sphincter. This systematic review and meta-analysis of only randomized clinical trials (RCTs) represent the most updated evidence-based data regarding the use of SEMS-NV and SEMS-V in the endoscopic palliation of esophageal cancer. Unlike the last evidence data published in 2019 [29], we attempted to use dichotomous outcomes as well for the evaluation of GERD, so...
that our meta-analysis could be more robust and reliable. We also included two more RCTs, a recent multicenter study [17], and a single-center study published in 2002 [25].

The incidence of post-procedure GERD was theoretically expected to be lower in the SEMS-V group. However, no statistically significant difference was found between both groups, as exposed in both analyses that included a total of eight studies, 294 patients, 140 in the SEMS-V group, and 154 in the SEMS-NV group, in contrast to the last meta-analysis that included four studies and performed a quantitative analysis only. Unfortunately, we could not include two studies, particularly, Coron et al [18], who performed a highly refined radiological evaluation, finding superior results in the SEMS-V group; however, the data included in the article are insufficient to calculate the SMD, and thus to be included in the meta-analysis.

The use of proton pump inhibitors (PPIs) in the SEMS-NV group was not reported in all studies, and this factor could have influenced the heterogeneity of the results. Additionally,
the qualitative analysis included a minor number of studies, but is more reliable, as the quantitative analysis has some limitations because of the combination of different scales mixed and evaluated together. Some observational studies have reported the superiority of the SEMS-V regarding GERD incidence, although they are conflicting too [30,31].

In this systematic review and meta-analysis, bothvalved and non-valved SEMS showed similar technical and clinical success rates. There was no difference in dysphagia improvement between the SEMS-V and SEMS-NV. However, only data from three RCTs were included due to the different patterns used to report their results, such as different dysphagia scores and, also, due to a lack of description of the total number of patients with dysphagia improvement. Although both types of SEMSs are associated with high rates of dysphagia improvement, recently, a novel radioactive SEMS such as the I-125 seed-loaded stent (ISS) have been developed to potentially improve the benefits. As described in two recent meta-analyses, this novel radioactive ISS provided better dysphagia improvement than conventional SEMSs and other therapies [32, 33].

In the total AE analyses, there was no difference between the two groups. Furthermore, individualized analyses were performed to evaluate stent migration, obstruction, and bleeding rates, which did not show a statistical difference between SEMS-V and SEMS-NV.

The risk of migration is considerably higher when a SEMS is placed across the gastroesophageal junction (GEJ), as it loses its natural sphincter function. Additionally, the peristalsis of the stomach may increase the risk of migration, especially with SEMS-V. Furthermore, some patients need dilation of the malignant stricture before SEMS-V placement due to the larger diameter of its delivery system when compared to SEMS-NV. Although our meta-analysis did not evaluate SEMS fixation/anchoring techniques, such as suturing, clipping, and external fixation through the nares, it is essential to know that stent fixation could potentially reduce SEMS migration [34, 35]. Only Dua et al. [17], reported that SEMS fixation was not performed, and thus, if some of the other studies used these fixation/anchoring approaches in just one of the groups, then the results may have been potentially affected.

Furthermore, it is important to evaluate the possibility of tumoral bleeding or bleeding caused by the procedure itself after SEMS placement. Regarding the diameter of the release mechanism, the two SEMS models are not similar. Although, SEMS-V could have had a bigger impact on bleeding after SEMS placement we found no statistically significant differences between the groups.

In terms of SEMS obstruction, it was expected that the valved model would be associated with more obstruction because of the shorter length and diameter. Finally, the size of the SEMS-V could affect migration or obstruction [36–38]. Another important AE related to SEMS use is aspiration pneumonia, as these patients generally have an additional risk of reflux associated with narcotic use or involvement of periesophageal nerves by the tumor. In theory, the SEMS-V may protect from aspiration, but the low incidence of this AE did not allow us to evaluate for this outcome. On the other hand, as the GERD results were similar between groups, in theory, the aspiration rates would be expected to be similar in both groups.

Endoscopic palliation therapies must prioritize the evaluation of Health-Related Quality of Life (HRQL) [39, 40]. Three studies evaluated QoL [17,19,22]. However, our qualitative analysis regarding QoL only included two studies that utilized the same score (QLQ-C30) [19,22]. The most recent RCT included the GERD-HRQL scale [17]; although it is reliable, it is a different score, and thus, we could not include it in the meta-analysis due to other methods applied to measure it. Furthermore, it is important to note that after SEMS deployment, there was an almost immediate increase in patient QoL. However, the difference between the groups was not statistically significant.

Despite this being a systematic review and meta-analysis including only RCTs (level of evidence 1A) and carefully following the PRISMA guidelines, our study has some limitations. First, there was significant variability in the parameters and measurement scales utilized for some of the outcomes, including some essential outcomes such as dysphagia improvement, GERD, and QoL. For example, for GERD, some studies utilized simple clinical scores, while others used other diagnostic tools, such as an upper endoscopy or Ph study, to confirm or quantify GERD. However, to overcome this limitation, we used dichotomous variables to elevate its reliability, thus reducing bias. Particularly with GERD, we presented a quantitative analysis but with similar results as the qualitative analysis. Second, there was a limited number of patients (minimum of 36 and a maximum of 65 patients) per included RCT, which may potentially reduce the power of our analysis; thus, the results of our analysis may represent an insufficient sample size, as illustrated by the width of the confidence intervals of the outcomes, particularly, on the primary outcomes. However, advanced esophageal cancer in the distal esophagus with adequate criteria to utilize SEMS-V is not common, thus making it challenging to perform a large RCT. Third, the different models of SEMS used in each study could have affected the outcomes since there is a wide variety of anti-reflux mechanisms, delivery systems, and models. Furthermore, included in the RCTs, there were differences between the groups’ SEMS length and diameter. Finally, the size and extension of the tumor were not correlated to the outcomes of our analysis, as they were not described in the included studies.

In summary, SEMS is a cornerstone treatment in endoscopic palliation of advanced esophageal cancer. Regarding SEMS-V, they have similar technical and clinical success rates when compared to the SEMS-NV, although there is a lack of statistical significance, thus, the demand for more RCTs is warranted. Therefore, we cannot recommend the best approach and the decision about the type of SEMS to be utilized should be individualized, taking into consideration anatomy, local expertise, resource availability, and patient preference.
Conclusions
Outcomes with SEMS-V and SEMS-NV for endoscopic palliation of advanced esophageal cancer are similar in terms of technical success, dysphagia relief, post-stent GERD, AEs, stent migration, stent obstruction, bleeding, and QoL.

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The study was approved by the Research Ethics Committee of the Hospital das Clínicas – University of São Paulo School of Medicine.

Competing interests
Dr. Diego Hourneaux De Moura is an advisory board member for Bar-iTek. Dr. Sanchéz-Luna is the recipient of the 2021 American Society for Gastrointestinal Endoscopy (ASGE) Endoscopic Training Award by the ASGE and Fujifilm. Dr. Eduardo Guimaraes Hourneaux De Moura is a consultant for Olympus and Boston Scientific.

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