

Palliation of Dysphagia in Carcinoma Esophagus



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ABSTRACT: Esophageal carcinoma has a special place in gastrointestinal carcinomas because it contains two main types, namely, squamous cell carcinoma and adenocarcinoma. Carcinoma esophagus patients require some form of palliation because of locally advanced stage or distant metastasis, where it cannot be subjected to curable treatment with surgery and chemoradiation. Many modalities of palliation of dysphagia are available, but the procedure with least morbidity, mortality, and long-term palliation of dysphagia needs to be chosen for the patient. This study aims to discuss the recent trends in palliation of dysphagia with promising results and the most suitable therapy for palliation of dysphagia in a given patient. A total of 64 articles that were published between years 2005 and 2015 on various modes of palliation of dysphagia in carcinoma esophagus were studied, which were mainly randomized and prospective studies. Through this study, we conclude that stents are the first choice of therapy for palliation, which is safe and cost-effective, and they can be combined with either radiotherapy or chemotherapy for long-term palliation of dysphagia with good quality of life. Radiotherapy can be used as a second-line treatment modality.

KEYWORDS: carcinoma esophagus, palliation, esophageal stents, radiotherapy

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Introduction

The five-year survival rates despite advances in staging and oncologic and surgical treatment of esophageal and junctional tumors are between 10% and 15%. The majority of patients with these cancers will require some form of palliative treatment.¹ The percentage of patients with esophageal carcinoma presenting with locally advanced stage or distant metastases with tumor-related symptoms and/or poor general condition is more than 50%. These patients often present with cancer-related complications such as dysphagia, which increase as the disease progresses, leading to pain, poor nutrition, reduced performance status, and decrease in quality of life (QoL).² Surgical resection or curative chemoradiotherapy is not feasible in these patients with severe clinical symptoms as they are not fit enough to undergo such procedures. Palliation of dysphagia is also required in carcinoma esophagus patients with severe comorbidities such as, coronary artery disease, hypertension, chronic obstructive pulmonary disease, and metabolic diseases (diabetes mellitus and hypothyroidism).³

Palliation of dysphagia is required mainly under two circumstances: one, for metastatic disease, and the other for those who have undergone treatment with curative intent but

the disease recurs. Patients with inoperable esophageal cancer should receive optimum care, which includes the safest, most effective therapy and should also be cost-effective.

The palliative treatment that is selected for the patient should be based on physical characteristics and location of the tumor, the performance status and age of the patient, tumor burden, and expected survival.

Modes of palliation of dysphagia. Endoscopically delivered (bougie dilatation) rigid pulsion dilators (Savary-Gilliard) or balloon dilators, chemical energy (alcohol injection), thermal energy (Nd-YAG laser, argon beam coagulation, photodynamic therapy), and self-expanding metal stents (SEMS).

Oncologic treatment—radiotherapy and chemotherapy.

Surgical—palliative resection, bypass surgery, exclusion therapy, and nutrition.

Among the various approaches used to palliate dysphagia, esophageal stenting, radiotherapy, or a combination of both are used commonly.

Aim. The aim of this review is to study the modalities of treatment available for palliation of dysphagia in carcinoma esophagus and determine the most effective option among them.



Materials and Methods

Source of the data for the study is taken from the articles in PUBMED and Google Scholar search. The PubMed literature database was selectively searched for articles with the keywords: Palliation of dysphagia in carcinoma esophagus [MESH] or Palliation of dysphagia/Esophageal dilation or Palliation of dysphagia [MESH]/Thermal ablation and Alcohol injection therapy or Palliation of dysphagia [MESH]/Radiotherapy and Chemoradiation or Palliation of dysphagia [MESH]/SEMS. In addition, Google search and Google Scholar search was also made using key words like “Palliation of dysphagia in carcinoma esophagus”, “Alcohol injection”, “Argon plasma coagulation”, “Photodynamic therapy”, “Radiotherapy”, “Chemoradiotherapy”, and “Self-expanding metal stents”. The articles that were published during the period between 2005 and 2015 were studied for formation of an opinion. A total of 64 studies were available based on the required objective among which three studies were excluded (Fig. 1).

Thermal ablation. Ablation of esophageal carcinoma using laser thermal coagulation is relatively safe but provides only temporary relief of dysphagia. Palliation with laser ablation is used for treating polypoid lesions less than 5 cm in length or which occlude by intraluminal growth.⁴ Laser

ablation is contraindicated in the presence of tracheoesophageal fistula, in proximal esophageal lesions and lesions at lower esophagus, which are long in length or are angulated. Increase in esophageal lumen diameter after successful laser ablation helps patients tolerate a modified diet in approximately 33% of patients, while semisolid and solid diet intake is possible in around 50% of patients. Clinical improvement in dysphagia is seen few days after treatment, which recurs gradually requiring repeated sessions of therapy, usually at intervals of four to six weeks for life.⁵ For safe laser ablation, the esophageal lumen should be dilated adequately so that the laser beam is targeted starting from the distal-most margin of the esophageal growth, and when the endoscope is withdrawn, the laser ablation is then carried to the most proximal aspect of the growth.

Thermal ablative procedures are shown to be more effective when used in combination, as shown in the randomized comparison study done by Rupinski et al.⁶ The study assessed the duration of relief of dysphagia in two groups of patients where one group receives argon plasma coagulation (APC) alone and another group receives a combination therapy of APC with brachytherapy High-Dose Rate (HDR) or APC with photodynamic therapy (PDT). Among 93 patients of esophageal carcinoma, the outcome

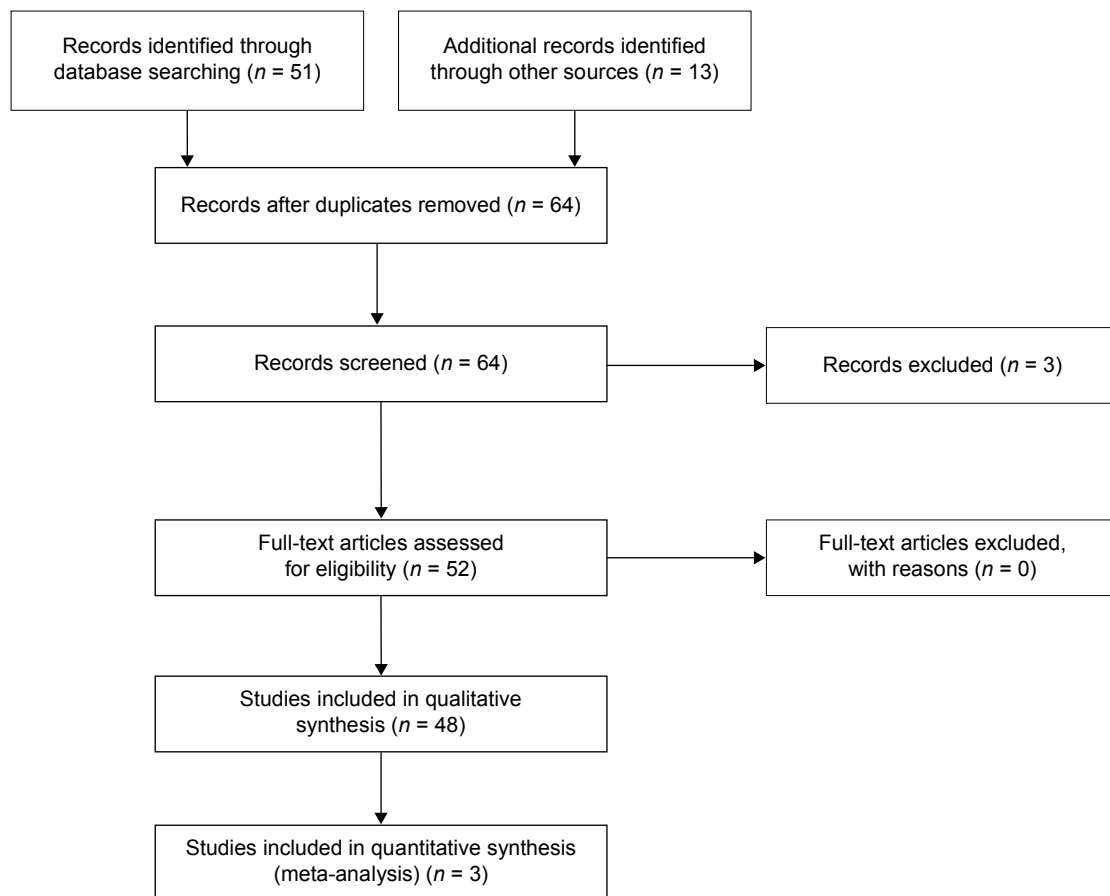


Figure 1. PRISMA (Preferred Reporting Items for Systemic review and Meta-analysis) flow diagram for the study.



studied was dysphagia relief after subjecting the patients to a combination of APC and HDR or APC and PDT or APC alone. Between the study groups, there was no significant difference in the overall survival of patients, with median time for the dysphagia to recur after therapy was 88, 59, and 35 days in the HDR, PDT, and control group, respectively. Increased sensitivity to skin was observed only in patients undergoing PDT, and fever was a major complication seen in three patients receiving PDT. The above study concluded that a combination therapy containing either APC and HDR or, APC and PDT for palliation of dysphagia is safe, better tolerated and has more efficacy compared with APC alone with a significantly better QoL after 30 days of treatment and low complication rate when HDR was used in group along with APC. The disadvantage with thermal ablative methods is the requirement of frequent reinterventions and adverse effects.

Chemical ablation therapy. Alcohol injection as a primary modality using 95%–100% ethanol is used uncommonly for palliation of dysphagia in carcinoma esophagus nowadays. However, as it is easily available, inexpensive, and easy to use, it can form a useful adjunct in the palliation of dysphagia. The mechanism of action of alcohol in palliation is that, it causes the bulky esophageal luminal lesions upon injection into them, to ulcerate, necrose, and then slough off. With endoscope over the point of obstruction, using 1 cc sclerosing needles (23G), aliquots of 6–10 cm³ of absolute alcohol are injected into the tumor circumferentially. Complications include perforation, mediastinitis, and tracheoesophageal fistula. In a study done by Ramakrishnaiah et al,⁷ alcohol was injected in 16 patients who presented with dysphagia secondary to inoperable malignant esophageal growth present at the esophagogastric junction. There was relief in dysphagia with significantly improved mean dysphagia score after alcohol injection, with improvement in QoL. There was improvement in dysphagia symptom with each session of therapy in the initial four sessions after which, no further improvement was observed. Alcohol injection can be useful in patients who are having complete esophageal luminal obstruction where passage of scope or PDT probe is not possible. Alcohol injection can help open the esophageal lumen in these patients, allowing other modalities to be used. At present, alcohol injection therapy is useful only in conditions in which other better modalities of palliation are not available and where there is a significant concern about the cost of treatment.

Radiotherapy. Radiotherapy can be delivered by brachytherapy or external beam radiotherapy (EBRT). Also, radiotherapy can be used alone or in combination with other modalities like thermal ablation, chemoradiation, or stenting in palliating dysphagia of a patient with carcinoma esophagus. Brachytherapy uses iridium-192 as isotope. The advantages of brachytherapy are that it can deliver high-dose radiation over short periods allowing palliative treatment, suitable for frail elderly patients, and it is cost-effective compared with other

modalities. The disadvantages are mainly inhomogeneity in dose distribution; hence, it is not suitable for treating bulky tumors and technically it is not feasible in patients who present with complete luminal obstruction and complete dysphagia because, for symptomatic relief to occur, there is a delay with maximum benefit seen at around six weeks after therapy. EBRT uses an external source for radiation to target tissues, which is particularly useful for bulky tumors. Modern radiotherapy employs the simple conformal radiotherapy technique, that is, shaping the radiation field to the shape of the tumor excluding adjacent tissues.

In the past 10 years, radiotherapy alone has been used less frequently as a modality of palliation of dysphagia, owing to the availability of other modalities where their combination has provided better results. At present, radiotherapy alone is used in select group of patients who are having good performance status and whose tumor is not suitable for more radical procedures because of length and position of the tumor and regional and distant spread.⁸

In a study by Hanna et al,⁹ 63 patients were divided into those undergoing stenting alone and EBRT alone. In the patients who were treated initially by stenting, 85% of patients showed an improvement in dysphagia during the first 2 weeks of treatment, but recurrent dysphagia was seen in around 20% of patients after 10 weeks of treatment. After two weeks of radiotherapy, dysphagia relief was seen in only 50% of patients, indicating that radiotherapy has a slower onset of palliation; however, after 10 weeks of radiotherapy, 90% of patients were relieved of dysphagia, implying long-term efficacy of radiotherapy in palliation of dysphagia. A study by Javed et al¹⁰ assessed the duration of dysphagia relief and the overall survival in 84 patients with inoperable carcinoma esophagus, and the patients were divided into two groups, where one group received esophageal stenting alone, while another group was treated with esophageal stenting followed by EBRT. Among the 84 patients, 42 patients were subjected to esophageal stenting alone and the remaining 42 patients were given EBRT after esophageal stenting. The study concluded that after stent insertion there was a significant improvement in dysphagia score with a more sustained relief in dysphagia seen in those patients who had received EBRT after stenting than compared with those with stents alone. The overall median survival was significantly higher in patients receiving both stent and EBRT than in patients with stents alone. There was an increase in the duration of dysphagia-free period in patients receiving a combination of radiotherapy and stents; however, the QoL decreased significantly with radiotherapy after an initial one week of improvement following esophageal stent. There were no deaths related to treatment, and a similar complication rate was observed in both groups. Similar results were observed in a study conducted by Bergquist et al.¹¹

Prasad et al¹² assessed the influence of palliative radiotherapy in patients with squamous cell esophageal carcinoma



and showed that a significant number of patients had persistent chest pain and stricture of esophagus. Further prospective randomized trials are required before asserting on the efficacy and safety of combination of esophageal stenting and radiotherapy compared with either stenting or radiotherapy alone.

Chemoradiation. It is a more aggressive approach for palliation of dysphagia and long-term disease control in inoperable esophageal carcinoma. The advocacy of chemoradiation in palliation of dysphagia requires a balance between tolerance of side effects of treatment and the gain of symptom relief. The ideal chemotherapy regimen used is infusional 5-fluorouracil (5-FU) and cisplatin with concurrent EBRT. In a retrospective study by Ikeda et al,¹³ 40 patients, who presented with dysphagia secondary to carcinoma esophagus stage IVB, were given palliative chemoradiotherapy containing two courses of 5-FU and cisplatin with concurrent radiotherapy to the esophageal growth at a dosage of 40 Gy in 20 fractions. Response to palliative chemoradiotherapy was evaluated in terms of grade of dysphagia, toxicity, disease progression-free survival, and overall survival. Dysphagia scores improved in 75% of patients and 95% disease control rate was seen in the primary tumor. Other significant findings of the study were a response rate of 55%, 45% survival rate at 1 year, 308 days of median survival, and 139 days of disease progression-free survival. Major treatment-related toxicities included low hemoglobin and low neutrophil count in 23% and 20% of patients, respectively, with anorexia and nausea seen in 10% and 3% of patients, respectively. Esophageal perforation was encountered in 5% of patients undergoing chemoradiotherapy, but overall there was an improvement in dysphagia scores with a fairly long survival period associated with acceptable adverse effects. Another study by Akl et al¹⁴ using concurrent chemoradiotherapy in a prospective study containing 25 patients had shown dysphagia improvement in 72% of subjects with an overall five-month duration of relief from dysphagia after treatment. The treatment was well tolerated with common hematologic and nonhematologic toxicity being anemia and esophagitis, respectively, with a complete response seen in 72% of patients. Some studies were done using a combination of chemoradiation with stenting; one of them is a retrospective analysis done by Burstow et al,¹⁵ which showed 92.5 days of mean survival and 61 days of median survival in patients subjected to esophageal stenting for increasing dysphagia. Patients who underwent chemoradiotherapy had significantly longer survival benefit (152.8 days) compared with patients who received stents alone (71.8 days).

Esophageal stenting can act as an important bridging gap for neoadjuvant chemoradiation. The significance of this combination has been shown in a retrospective study by Siddiqui et al,¹⁶ involving 55 patients. The study has effectively shown that there is a significant improvement in dysphagia, which will allow for improvement in oral nutrition during neoadjuvant chemoradiation. In another study by Langer et al,¹⁷ 38 patients with dysphagia and loss of weight

due to advanced carcinoma esophagus who were scheduled for neoadjuvant chemoradiotherapy received prior esophageal stenting (SEMS). There was an instant relief of dysphagia seen in 37 patients (97.4%), and 20 patients (52.6%) underwent surgical resection of tumor after receiving neoadjuvant chemoradiotherapy. Stenting prior to neoadjuvant chemoradiation allows improvement of patient's nutritional status, leading to better toleration of therapy. The combination of stenting and chemoradiation is an attractive option especially in those undergoing neoadjuvant therapy, and large volume retrospective studies are required to further substantiate the usefulness of this combination.

Chemotherapy. Chemotherapy is appropriate in patients with disseminated esophageal carcinoma to palliate dysphagia with a favorable QoL, provided the patient's performance status is good. Combination chemotherapy is preferred over single-agent chemotherapy, and the most commonly used regimen is cisplatin and infusional 5-FU. Phase 3 randomized trials have shown that capecitabine and oxaliplatin have the potential to replace cisplatin and 5-FU.¹⁸ Paclitaxel and carboplatin can be used as an alternative regimen to cisplatin and 5-FU. However, Toucheffeu et al¹⁹ retrospectively compared the efficacy of chemotherapy and self-expanding metal stent in a total of 69 patients having inoperable esophageal carcinoma with progressively worsening dysphagia. Forty-two patients were included in the chemotherapy group and 29 in the esophageal stent group; it was shown that after four weeks, dysphagia scores improved by 1 point in 67% of patients in chemotherapy group vs. 93% in the stent group ($P = 0.01$), with 48% of patients in the chemotherapy group being able to eat solid food vs. 68% in the stent group ($P = 0.054$). Chemotherapy can be used as the first modality for palliation of dysphagia; however, using chemotherapy alone for palliation of dysphagia is not a feasible option, given its toxicity profile and the availability of more efficient methods of palliation.

Palliative surgery. Curative esophagectomy is a procedure with high morbidity and mortality rates of 50% and 6%, respectively, with an average duration of 14–17 days stay in hospital and additional 6 months duration for the return of physiological activity to baseline.²⁰ Since 1920s, palliative surgery has been done with a reported mortality rate of 32%, with an overall survival period below four months. Palliative surgery is not a realistic option in this era as the desired goal of palliation of dysphagia can be achieved by much safer and effective means.

Esophageal stenting. Patients who undergo esophageal stenting for palliation of dysphagia can achieve the desired goal of adequate dysphagia relief, which is usually instant, improves the patient's nutrition and QoL with a low complication rate, and has an acceptable cost of treatment. Esophageal stents have been classified in many ways as follows: (1) fully covered or partially covered based on the covering, (2) antireflux or fully patent based on the function, and (3) based on the material from which the stents are made, ie, polyvinyl,



surgical steel, or nitinol. Esophageal stenting is more commonly preferred for mid esophageal lesions; however, it can also be used for lesions at gastroesophageal junction and lesions in the proximal esophagus, provided the lesion is located away from upper esophageal sphincter by more than 2 cm.²¹ Stents impregnated with chemotherapeutic agents have shown disappointing results.²²

Stent selection is based on the tumor length, tumor bulk, tumor location, configuration of the obstructive stricture, and the presence or absence of tracheoesophageal fistula. After an esophagogram or endoscopy is done to assess the proximal and distal tumor margins, the stent is placed with its ends extending beyond the margin of growth by 2–4 cm on each side to prevent tumor overgrowth.

Selinger et al²³ studied the influence of esophageal stenting in 137 patients suffering from progressive dysphagia (86.4%) mainly due to advanced carcinoma esophagus (65%). Other indications of stenting were contraindications for surgery secondary to comorbidities (25%) and for improving the patient's nutritional status before surgery (4%). A total of 94% of patients experienced relief of dysphagia, which was significant, with 45% patients fit enough to be discharged in less than 48 hours of admission. Chest pain was seen in 13.9% of patients with hemorrhage and perforation being the major life-threatening complications seen in 5.8% of cases. Overall morbidity rate was 41.6% and the mortality rate was 24.8% at 30 days. Sundelöf et al²⁴ placed 174 stents in 149 patients who presented with dysphagia secondary to advanced esophageal carcinoma. Dysphagia improved significantly in 70% of patients with an overall morbidity rate of 26% and a mortality rate of 3%, which was procedure related. There was no effect of tumor histology, length of tumor, and location of tumor on the outcome in terms of morbidity and mortality due to procedure.

Patients having esophageal carcinoma with tracheoesophageal fistula have benefited from stent placement across fistula, which facilitates fistula closure along with relief in dysphagia. In a study by Neyaz et al,²⁵ stent effectiveness in palliation of dysphagia was studied after fluoroscopically guided stent placement. Upon clinical and radiological follow-up, a dysphagia score of 1.2 was achieved after stenting, which was 3.5 before stenting, with two patients achieving complete closure of tracheoesophageal fistula after stenting.

Patients can also be benefited from SEMS placement in cases of local recurrence after esophagogastrectomy, providing palliation of dysphagia and symptom relief from tracheoesophageal fistula. Tong et al²⁶ placed 43 esophageal stents in 35 patients who presented with dysphagia secondary to locoregional recurrence of carcinoma after prior esophagogastrectomy for carcinoma esophagus. A total of 97.6% success rate was seen after stent placement with dysphagia score, which reduced to 2.54 from a previous score of 4.66. Symptoms of tracheoesophageal fistula were successfully palliated in all patients with an immediate complication rate of 14%

among whom stent malpositioning was seen in two patients, inadequate stent opening in two patients, and stent could not be placed in one patient because of procedure failure. Forty-two days of median survival was seen mainly because of advanced disease stage, and there was no mortality secondary to procedure-related complications.

Comparison of SEMS with self-expanding plastic stents.

A disadvantage of SEMS is the problem of tumor ingrowth, which may require restenting but can be prevented using covered stents. Verschuur et al²⁷ compared the efficacy of different stent types in a randomized study containing 125 patients who presented with dysphagia secondary to advanced esophageal carcinoma. Forty-two patients had received SEMS, self-expanding plastic stents (SEPS) were placed in 41 patients, and Niti-S stents placed in 42 patients followed by monthly follow-up for six months. All patients had an improvement in median dysphagia score from initial 3 to 1 after stenting, with all three stent types having no difference in complication rate. Tumor ingrowth, stent migration, and obstruction of stent lumen by food bolus were observed in patients undergoing SEMS, SEPS, and Niti-S stent in 52%, 37%, and 31%, respectively, with stent migration being most commonly associated with SEPS and tumor ingrowth with SEMS. The choice of stent type did not have any significant impact on median survival duration.

In a meta-analysis by Yakoub et al,²⁸ uncovered and covered metal stents were compared in a study group involving 564 patients from eight studies. There was a significant decrease in the mortality rate and a reduced incidence of stent migration and perforation of esophagus in patients treated with metallic stents but, with higher chances of tumor ingrowth. The problem of tumor ingrowth was decreased with the use of covered metallic stents, but with an increased rate of stent migration.

Antireflux vs. conventional stents. Placement of SEMS in the carcinoma of lower esophagus involving cardia carries a significant risk of reflux, which can be overcome with the advent of antireflux stents. In a randomized controlled study by Power et al,²⁹ 49 patients after randomization were treated with an antireflux or a standard stent for dysphagia relief in carcinoma esophagus. European Organisation for Research and Treatment of Cancer (EORTC) questionnaire was used to assess the index of QoL in patients prior to stenting and after stenting at one week and two months. In the first week after stent insertion, tests were done to estimate the esophageal pH, and there was an improvement seen in the reflux scores, with an achievement of normal baseline pH level at the first week after stenting. Antireflux stents were associated with significantly better DeMeester scores even after two months of procedure. However, the risk of stent migration is significantly more in patients receiving antireflux stents. Schoppmeyer et al³⁰ used antireflux stents in 18 patients for palliation of dysphagia in inoperable esophageal carcinoma and showed that the mean dysphagia score improved from 2.2 to 0.6, and the study also



showed an increased rate of stent migration. Further technical improvements of antireflux stents are required for better reflux control and to reduce stent migration for its more wide range usage in palliation of dysphagia.

Economic analysis of stents. So far, the use of stents, either covered or uncovered, has been economically acceptable. In the study by Rao et al,³¹ covered and uncovered metal stents were studied using different stenting strategies and compared with respect to improvement in QoL, mortality rate secondary to stent insertion at one year, and cost-effectiveness. The study has shown that covered stents were more effective and were also less expensive.

SEMS vs. others. Even after the presence of many treatment options for the palliation of dysphagia in carcinoma esophagus, there is no single-optimum method. Many studies in the recent years have shown an improvement in the efficacy of stents with better patient acceptability, which is cost-effective and also definitely more favorable than alcohol injection, APC, and PDT because these are associated with an increased complication rate and the need for frequent reinterventions. However, the one area where the stents need further improvement is their long-term efficacy in palliation of dysphagia in which cases, radiotherapy has shown better long-term relief of dysphagia symptoms, but this difference decreases gradually after 12 months.

Effect of age, sex, and comorbidities on treatment of carcinoma esophagus. Coronary artery disease, chronic obstructive pulmonary disease, hypertension, and diabetes mellitus are the four most common comorbidities encountered in clinical practice that can affect the treatment of carcinoma esophagus patients by decreasing the rate of noncancer-specific survival. It is mainly because patients with the above comorbidities

have an increased incidence of treatment-related toxicity and a high mortality rate.³² Patients with esophageal carcinoma who are above 70 years of age and who have comorbidities, two or more of the above, are generally considered to have poor survival rate. In a study by Koppert et al,³³ patients with carcinoma esophagus presenting at or above 70 years of age had a low possibility of their tumor being surgically resectable and associated with a mortality rate of 11.9% compared with 4.7% mortality rate in patients below 70 years of age. When two or more comorbidities are present, there was 11.2% mortality rate over a 30-day period. Some of these patients are not fit for surgery and are the candidates in whom palliation of dysphagia should be considered as a means to improve QoL (Table 1).

Few clinical scenarios and the most suitable palliative procedure are as follows (Fig. 2).

1. Patients with good performance score:
Stent followed by radiotherapy or, stent followed by chemoradiotherapy.
2. Patients with poor performance scores:
Stents are first choice, if stents are not available, APC or intratumoral alcohol injection can be used.
3. Patients who are having short duration of survival (<3 months) stent insertion is the preferred modality of palliation of dysphagia.
4. When chemotherapy or chemoradiotherapy is planned to be used for palliation, prior stent insertion has been shown to help increase oral intake and improve QoL within a short period in contrast to chemoradiation alone, where the mean duration for improvement in dysphagia symptom is longer.

Table 1. Merits and demerits of different modalities in palliation of dysphagia.

METHOD	ADVANTAGES	DISADVANTAGES
Alcohol injection	Inexpensive, office based	Not effective for long tumors Low efficacy
Argon plasma coagulation	Effective in short superficial tumors Less penetrating power than laser (less risk of perforation) Inexpensive, office based	Less effective with long tumor's Repeated re-intervention
Nd: YAG laser	Effective in exophytic, short tumors Office based	Repeated re-intervention Post treatment hemorrhage and perforation Not widely available
Radiotherapy		
Brachytherapy	Single treatment Successful with short tumors	No use with long tumors Esophageal lumen patency required Time lag to efficacy
External beam	Effective	Wide effect, patient fitness needed Repeated sessions of treatment
Chemotherapy	Effective with systemic disease	Gastrointestinal and hematologic toxicity Frequent monitoring
Stents	Short stay, simple Readily available Treats perforation/fistula Single treatment	Perforation, stent migration, tumor ingrowth, painful

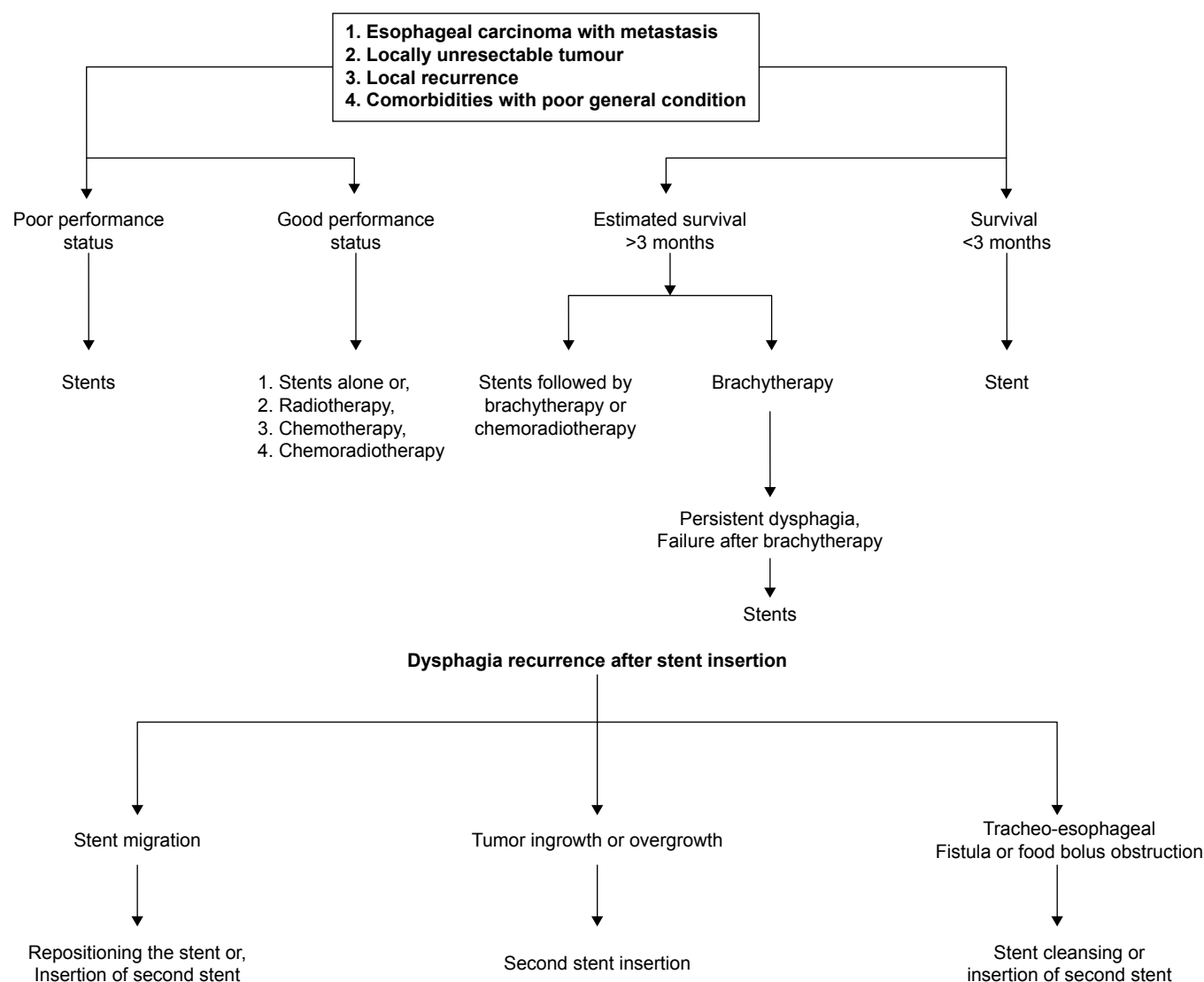


Figure 2. Treatment options for palliation of dysphagia.

5. Patients with esophageal perforation secondary to esophageal carcinoma or tracheoesophageal fistula—covered self-expandable metal stents are preferred.
6. When the cost of treatment is a major concern during palliation of dysphagia, patient's undergoing SEMS insertion and/or radiotherapy, chemotherapy, and APC have not shown any significant difference in the cost of therapy between them.³⁴

Discussion

As most patients of carcinoma esophagus come to the clinician when the tumor is at a locally advanced stage with distant metastasis, palliation of the patient's symptoms, mainly of dysphagia, becomes an important objective. The more traditional methods such as esophageal dilation are no longer the primary modality in palliation of dysphagia; however, dilation can form an adjunct during esophageal stenting when dilation

can help in opening of the esophageal lumen for the passage of endoscope and placement of stent.

Thermal ablative techniques such as APC and PDT can provide symptomatic relief of dysphagia, but, because of the high complication rates such as bleeding, perforation, and the relative short-term relief in dysphagia requiring repeated reintervention, this modality is not preferred as a single first modality of palliation of dysphagia. However, thermal ablation techniques particularly in combination with radiotherapy (HDR) have been shown to be having better results with improvement in dysphagia score with a better complication profile, as shown in the study by Rupinski et al.⁶

Alcohol injection is a useful modality where the tumor is bulky and there is complete luminal obstruction, preventing scope passage beyond tumor. When initial tumor sloughing and clearing has been achieved by alcohol injection, other modalities such as thermal ablation with PDT, APC, brachytherapy, and stenting for prolonging the duration of relief of



Table 2. List of articles studied for the review article.

STUDY NAME AND ID	STUDIED MODALITY [NO. OF PATIENTS]	EFFECTIVENESS OF THE MODALITY	ENCOUNTERED ADVERSE EVENTS
PMID: 16385833 Homs MY et al	Single dose Brachytherapy versus stents [209]	Brachytherapy has long-term relief of symptoms. Brachytherapy has less complications than stents.	Late hemorrhage in stents, fistula formation [7%].
PMID: 20380272 Bona D et al	Esophageal stents	Stents are beneficial prior to chemotherapy or chemoradiotherapy.	Endoscopic reintervention in 14%.
PMCID: PMC4376823 Vishnu Prasad NR et al	External beam radiotherapy [33]	Relief of dysphagia in 90%. Improvement in quality of life.	Stricture on follow-up endoscopy [57%]. Retrosternal chest pain [26.3%].
PMID: 16770371 Tangen M et al	Esophageal stents [37]	Stent insertion is safe. Median survival 88 days.	Tumor ingrowth, death 1 patient.
PMID: 19640521 Uitdehaag MJ et al	Esophageal stents [45]	Stent placement is safe procedure.	Complications [20%]. Severe pain, hemorrhage, fever.
PMID: 19436289 Shenfine J et al	Esophageal stents [215]	Significant improvement in dysphagia scores. QOL scores low at 1 and 6 weeks post stent insertion.	Increased post procedure pain.
PMID: 18042102 Conio M et al	Esophageal stents [101] SEMS vs. SEPS	No significant different in palliation of dysphagia between 2 stent types.	Late stent migration, hemorrhage in SEPS. Intra-procedural perforation [1 SEPS, 1 SEMS].
PMID: 16960663 Wenger U et al	Antireflux stents VS conventional stents [41]	Improvement in dysphagia in both groups. No increased risk of complications with anti-reflux group.	Decrease in dyspnea after anti-reflux stent.
PMCID: PMC3908612 Vishnu Prasad NR et al	Alcohol injection [16]	Improvement in dysphagia scores. Mean dysphagia free survival 71 days.	Chest pain, perforation 1 patient, death 1 patient.
PMID: 17439590 Schoppmeyer K et al	Antireflux stents [18]	Improvement in dysphagia scores. Mean survival 54 days.	Frequent stent migration, insufficient prevention of GERD.
PMID: 24268567 Toucheffeu Y et al	Chemotherapy vs SEMS [44]	Chemotherapy a valid first option in 50% of patients.	GI and hematological toxicity.
PMID: 19054264 Kim ES et al	Covered stents and double layered stents [37]	Equal technical success and improvement in dysphagia in both types.	Stent migration and tumor overgrowth more frequently with covered stents.
PMID: 19207559 Rao C et al	Economic analysis of stents	Covered stents are cost effective than uncovered metal stents. Plastic stents are expensive than uncovered and covered metal stents.	Value of information analysis suggests that further research may not be cost-effective.
PMID: 17383456 Verschuur EM et al	Effect of stent size on recurrent dysphagia in carcinoma esophagus patients [338]	Reduced risk of recurrent dysphagia due to stent migration and tumor ingrowth.	Increased risk of hemorrhage, perforation, fistula, and fever in large diameter stents.
DOI: http://dx.doi.org/10.1016/j.gie.2011.11.036 . Meike MC Hirdes et al	Covered metal stent [48]	Effective in treating malignant dysphagia. Major complications in 30%.	Severe pain, fistula, vomiting, pneumonia.
PMID: 18594905 Yakoub D et al	Esophageal stents [911] Meta-analysis	Self-expanding metallic stents are superior to plastic stents in terms of stent insertion-related mortality, morbidity, and quality of palliation.	Covered metallic stents had significantly less tumor in-growth than the uncovered and an increased migration rate.
PMID: 20537639 Van Heel NC et al	Esophageal stents [81]	SEMS placement in recurrent esophageal cancer after surgical resection offers adequate palliation by relieving dysphagia and sealing off esophageal respiratory fistulae.	Major complications occurred in (11%). Severe pain, perforation, hemorrhage.



PMID: 17185082 Ross WA et al	Stents [97]	SEMS fall short of an ideal palliative method, because complications that require additional intervention are frequent. Treatment of choice for TEF.	Major complications [37%]. Hematemesis, stent migration.
PMID: 22284093 Hirdes MIM et al	Covered metal stent [28]	Effective in malignant dysphagia.	Major complications [30%]. Severe pain, bleeding, fistula, pneumonia. Stent migration and tumor overgrowth [5%].
PMCID: PMC3168502 Juan Carlos Martinez et al	Stents [review]	Instant dysphagia relief in 96% patients. Stents are the first line of treatment in palliation of dysphagia.	Delayed complication 53% [stent migration, tumor ingrowth—over growth].
PMID: 19636630 Bower M et al	Esophageal stents during neoadjuvant setting [25]	Esophageal stenting improves preoperative nutrition and tolerance of neoadjuvant chemoradiotherapy.	Stent migration 24%.
PMID: 15717937 Shenfine J et al	Cost effectiveness of palliative therapies [217]	No difference in cost or effectiveness between SEMs and non-SEMS therapies. 18-mm SEMs had equal effectiveness to, but less pain than, 24-mm SEMs. Bipolar electrocoagulation and ethanol tumor necrosis are poor in primary palliation.	
PMID: 19821338 Sreedharan A et al	Different modalities in palliation of dysphagia [2542]	SEMS insertion is safer than plastic stents. Brachytherapy is a suitable alternative. Thermal and chemical ablation give comparable dysphagia palliation but have an increased rate of re-interventions and adverse effects.	
PMCID: PMC3533211 Pierre Hindy et al	Esophageal stents review	SEMS are safer and cost-effective than the plastic stents.	Use of biodegradable stents has complications of migration, stricture recurrence, and tissue ingrowth.
PMID: 21295300 Parker RK et al	Stents for proximal esophageal cancer [151]	SEMSs effectively palliate dysphagia in proximal esophageal carcinoma.	Complication and survival rates are comparable to those of distal carcinoma patients.
PMID: 17033441 Szegedi L et al	Self-expanding plastic stents [69]	Safe and effective in improving the quality of life.	Tumoral overgrowth and of stent migration.
PMID: 16208111 Eickhoff A et al	SEMS vs SEPS [153]	Metal stents are safer and associated with prolonged improvement of dysphagia score.	Plastic stents associated with more complications than metal stents.
PMID:19636630 Bower M et al	Nutritional support in endoluminal stenting during neoadjuvant therapy [25]	Stenting in the neoadjuvant setting improves preoperative nutrition and tolerance of neoadjuvant chemoradiotherapy.	Stent migration (24%).
PMID: 21505346 Gray RT et al	SEMS and impact of nutritional factors on survival [53]	Invasive nutritional support before SEMs insertion is associated with poor prognosis.	
PMID: 16763332 Maroju NK et al	SEMS [30]	Safe and effective treatment modality for palliation of dysphagia.	Pain most common complication.
PMID: 17466213 Wilkes EA et al	SEMS [98]	Direct-vision SEMs placement as a safe and efficacious than under fluoroscopy guidance.	
PMID: 25354795 Dai Y et al	Different interventions used in palliation of dysphagia [3684]	SEMS is safe and effective. Brachytherapy is effective alternative. Combination of SEMs and brachytherapy is preferable.	
PMID: 17900325 Verschuur EM et al	Stents [125]	SEMS, SEPS are safe and effective.	Stent migration in SEPS, tumor ingrowth in SEMs.
PMID: 19302213 Burstow M et al	Stents [126]	No significant difference in complications or survival between endoscopic or radiologic methods to deploy SEMs. Adjuvant chemoradiation improved survival.	Hemorrhage, pneumonia, exhaustion, perforation, and sepsis.

(Continued)



Table 2. (Continued)

STUDY NAME AND ID	STUDIED MODALITY [NO. OF PATIENTS]	EFFECTIVENESS OF THE MODALITY	ENCOUNTERED ADVERSE EVENTS
PMID: 24390360 Mezes P et al	Double layered metal stents [56]	Device is safe and effective. Migration rate is zero in patients who do not receive chemoradiotherapy.	Tissue overgrowth, stent migration.
DOI: 10.1111/j.1442-2050.2008.00837.x. Cho SH et al	Chemoradiotherapy [31]	Improvement of dysphagia in 21 (76%) patients. Median progression-free survival and overall survival 10.6 ± 0.6 months.	Neutropenia most common. Asthenia, vomiting.
DOI:10.1111/j.1442-2050.2009.00958.x. Frobe Ana et al	Brachytherapy [30]	Significant improvement in dysphagia. Median survival 165 days.	Acute toxicity 13%.
DOI: http://dx.doi.org/10.1016/j.surg.2006.03.930 . StéphaneLeclaire et al	Stent insertion and impact of nutrition on survival [120]	Dysphagia scores decreased in 89.1% of patients. Serum albumin level, BMI < 18 kg/m ² , and WHO performance index >2 at SEMS insertion are independent predictive factors of 30-day mortality.	
PMID: 19473211 Madhusudhan C et al	Stents [33]	Significant improvement in dysphagia in lower third esophageal malignancy.	Tumor ingrowth, stent migration.
PMID: 20835926 Javed A et al	Stent with or without radiotherapy [84]	Dysphagia relief was more sustained after radiotherapy. Radiotherapy following stenting prolonged the mean dysphagia-free survival.	QOL significantly declined immediately after radiotherapy.
PMID: 17033441 Szegedi L et al	Stents [69]	Self-expandable plastic stents in palliation of esophageal cancer are safe and effective.	Tumor ingrowth, stent migration.
PMID: 17190756 Sundelof M et al	Stents [149]	Self-expanding metal stents is safe, provides immediate improvement of dysphagia.	Tumor ingrowth, stent migration.
DOI: 10.1245/s10434-012-2459-3. Natasha M Rueth et al	Stents and radiotherapy [45]	Patients with RT after stent placement have longer median survival compared to those without RT.	Stent migration.
DOI: 10.1245/s10434-007-9679-y. Simon K et al	Concurrent Chemoradiotherapy (CRT) or Stenting [72]	CRT significantly improved 5-year survival.	
PMID: 22726465 Siddiqui AA et al	Stent placement before neo adjuvant therapy [55]	Improvement in dysphagia and allows oral nutrition during neoadjuvant therapy.	Chest pain, stent migration [31%].
PMID: 17301645 Conigliaro R et al	Stents [60]	Plastic and metal stents have similar efficacy in palliation of dysphagia.	Stent migration, tumor ingrowth.
PMID: 17354135 Neyaz K	Stents [22]	Fluoroscopic placement of self-expandable metallic stents is a safe and effective.	Food impaction, tumor overgrowth.
PMID: 21670770 Rupinski M et al	Brachytherapy, APC, PDT [93]	Palliative combination treatment of dysphagia with APC and HDR or PDT was significantly more efficient than APC alone, and was safe and well tolerated.	Fever in PDT patients.
PMID: 25083306 Nagaraja V et al	Stents with neo adjuvant therapy [180]	Stents significantly improves dysphagia and allows for oral nutrition during neoadjuvant therapy.	Stent migration.
PMID: 16958397 Iraha Y et al	Influence of radiotherapy and chemotherapy on stent placement [19]	Prior irradiation or chemotherapy increases risk of persistent chest pain after stent placement.	Pneumonia, mediastinitis.
PMID: 19202963 Molnarova A	Different modalities	Brachytherapy and stents have longer benefit. Stents provide fastest relief of dysphagia.	Esophageal perforation, bleeding, stent migration, tumor ingrowth [30%].



PMID: 22161968 Thumbs A et al	Stents [143]	SEMS is an appropriate palliative treatment.	Stent migration, tumor ingrowth [11.9%].
PMID: 20069308 Eisharkawy AA et al	Stents [124]	SEMS is a reliable, effective, simple and safe method for palliation.	Stent migration, tumor ingrowth [33%].
PMID: 18766117 Weber A et al	SEMS vs Polyethylene stents [154]	SEMS have longer patency rate than polyethylene stents.	
PMID: 19191854 Xinopoulos D et al	Stents [23]	SEPS placement is an effective and safe palliative treatment.	Tumor ingrowth overgrowth, stent migration.
PMID: 17177084 Ott C et al	Stents [35]	Safe and cost effective treatment for palliation of dysphagia.	Stent migration most common.
PMID: 17958720 Power et al	Anti-reflux stents VS conventional stents [43]	Comparable relief from dysphagia. Anti-reflux stents controlled symptomatic and physiological reflux.	Stent migration common.
PMID: 19859771 Langer et al	Neoadjuvant therapy after stent placement [38]	Instant dysphagia relief, enables adequate oral nutrition during neo-adjuvant therapy.	Jejunal perforation, re-intervention, bleeding.
PMID: 19473204 Eroglu A et al	Stents [170]	Significant improvement in dysphagia. Less frequent re-intervention.	
PMID: 20545971 Tong DK et al	Stents [35]	SEMS in patients with recurrent tumor after esophagogastrectomy is safe and effective.	Stent malposition, tumor ingrowth.
PMID: 21742654 Ikeda E et al	Concurrent chemoradiotherapy [20]	Improvement in dysphagia score [75%]. Improved oral intake to no longer needing the support [85%].	Esophageal perforation [5%], Hematotoxicity.
PMID: 25842093 Aki FM et al	Concurrent chemoradiotherapy [25]	Effective and well tolerated treatment for dysphagia.	Anemia [80%], esophagitis.



dysphagia can be utilized. Alcohol injection therapy is used nowadays mainly when other superior modalities are not available or when there are concerns about the cost of therapy when involving radiotherapy and stenting.

Radiotherapy that can be delivered in the form of brachytherapy or EBRT in the palliation of dysphagia can provide long-term symptomatic relief of dysphagia, less complication rate, and better QoL.³⁵ Past 10 years have shown less use of radiotherapy alone as a first modality of palliation of dysphagia owing to the availability of SEMS, where their combination have provided better results.³⁶ Brachytherapy in combination with stents has been shown to provide instant relief of dysphagia which is long-lasting with better survival rates. Studies (before 2005) have shown an increased rate of complications when radiotherapy is combined with stent placement, mainly formation or worsening of esophageal fistula, massive hematemesis, stent migration, and chest pain; however, recent study by Javed et al¹⁰ has shown no significant difference in major or minor complications. At present, radiotherapy alone is useful in selected group of patients with good performance status whose tumor is not suitable for more radical procedures because of length and position of the tumor and regional and distant spread.

Chemoradiation using 5-FU and cisplatin is a more aggressive approach for long-term disease control, which is beneficial for those patients with good performance status and with minimal comorbidities.³⁷ Infusional 5-FU and cisplatin with concurrent radiotherapy (EBRT) is used as an alternative to stenting.³⁸ This combination is effective as neoadjuvant chemoradiation for patients with dysphagia where studies have shown them to be effective in improving dysphagia scores and QoL with some patients showing complete response with prolonged survival.³⁹ In some studies,^{40,41} esophageal stenting has been shown to be an important bridging therapy, where it allows early relief of dysphagia, leading to oral intake, nutritional improvement, and better tolerance of chemoradiation therapy.

Esophageal stenting has emerged as the first-line therapy for the relief of dysphagia in patients with carcinoma esophagus because of early onset in improvement of dysphagia, which is safe, easily available, and a cost-effective procedure.⁴² Self-expanding metal stents either covered or uncovered are used most commonly for mid esophageal carcinoma, and they can also be used for lower or upper esophageal carcinoma.^{43,44} Esophageal stenting has been associated with most common complications of tumor ingrowth, stent migration, and reflux symptoms when stents are placed across lower esophageal sphincter, and major complications such as hemorrhage and esophageal perforation. The two most commonly used stent types are SEMS and SEPS. Studies have shown that these stent types are equal in efficacy for relieving the symptom of dysphagia but differ in their complications, where SEMS is most commonly associated with tumor ingrowth and SEPS is associated with stent migration; however, SEPS stents prevent

tumor ingrowth and SEMS stents prevent stent migration.^{45–47} Overall metallic stents are associated with decreased procedure-related morbidity and mortality with respect to decreased incidence of stent migration, esophageal perforation, but high chance of tumor ingrowth. It is observed that there is no significant difference in stent-related mortality and morbidity between both metallic and plastic stents.^{48,49} The introduction of antireflux stents to prevent reflux in cases of lower esophageal carcinoma has shown good results but are associated with stent migration in some patients.⁵⁰ Stents have a definite superiority as compared with other modalities of palliation but the area where stents lag behind is long-term efficacy, in which case radiotherapy alone or in combination has shown to be giving better long-term dysphagia-free period; however, further randomized studies are required to justify the combination of stents and radiation therapy. The shortcomings of our study are that articles published between years 2005 and 2015 were selected for the study and articles published only in English journals were included (Table 2).

Conclusion

Based on the profile of recent studies on the palliation of dysphagia in carcinoma esophagus, it is clear that stents are the first choice of therapy with less complication and cost-effectiveness with radiotherapy as an effective alternative. Combination of one or more modalities of therapy has shown to be beneficial in terms of long-term symptom relief with the combination of stents and radiotherapy being the most promising. However, further randomized studies are required with the combination of stents and radiation to make it a more feasible option.

Author Contributions

Conceived the concepts: VPNR, SM, GSS, SK, SC. Analyzed the data: VPNR, SM, GSS. Wrote the first draft of the manuscript: SM, GSS, VPNR. Contributed to the writing of the manuscript: SK, SC. Agree with manuscript results and conclusions: VPNR, SM, GSS, SK, SC. Jointly developed the structure and arguments for the paper: VPNR, SM. Made critical revisions and approved final version: VPNR, SM, GSS, SK, SC. All authors reviewed and approved of the final manuscript.

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