American Radium Society® (ARS) Appropriate Use Criteria (AUC) for the Use of Esophageal Stents in Patients with Esophageal Cancer: Systematic Review and Guidelines

Expert Panel for Esophageal Stents:
Suzanne Russo, MD[1]; Christopher J. Anker, MD[2]; D. Chamil Codipilly, MD[3]; Gerard Abood, MD[4]; Dmitriy Akselrod, MD[5]; Christopher L. Hallemeier, MD[6]; Krishan R. Jethwa, MD, MPH[6], Zhaohui Jin, MD[7]; Ed Kim, MD[8]; Timothy Kennedy, MD[9]; Percy Lee, MD[10]; Eric D. Miller, MD, PhD[11]; Neil B. Newman, MD, MS[12]; J. Eva Selfridge, MD[13]; Navesh Sharma, DO[14]; William Small, Jr, MD[15]; Leila Tchelebi, MD[16]; Vonetta M. Williams, MD, PhD[17]; Charles B. Simone II, MD[17]

[1]Principal Author, Department of Radiation Oncology, MetroHealth, Case Western Reserve University School of Medicine, Cleveland OH
[2]Department of Radiation Oncology, University of Vermont Larner College of Medicine, Burlington, VT
[3]Department of Medicine, Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, MN
[4]Department of Surgery, Loyola University Stritch School of Medicine, Maywood, IL
[5]Division of Radiology, University of Vermont Larner College of Medicine, Burlington, VT
[6]Department of Radiation Oncology, Mayo Clinic College of Medicine, Rochester, MN
[7]Department of Medical Oncology, Mayo Clinic College of Medicine, Rochester, MN
[8]Department of Radiation Oncology, University of Washington, Seattle, WA
[9]Department of Surgery, Division of Surgical Oncology, Georgetown University, Washington D.C.
[10]Department of Radiation Oncology, City of Hope National Medical Center, Los Angeles, CA
[11]Department of Radiation Oncology, The James Cancer Hospital and Solove Research Institute, The Ohio State University, Columbus, OH
[12]Department of Radiation Oncology, University of Texas San Antonio Health Science Center, San Antonio, TX
[13]Department of Medical Oncology, University Hospitals Cleveland, Case Western Reserve University School of Medicine, Cleveland OH
[14]Department of Radiation Oncology, WellSpan Cancer Center, York PA
[15]Department of Radiation Oncology, Loyola University Stritch School of Medicine, Maywood, IL
[16]Department of Radiation Oncology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY
[17]Department of Radiation Oncology, Memorial Sloan Kettering, New York, NY

Conflict of Interest Disclosure Statement

All panelists were required to declare all conflicts of interest for the previous 36 months prior to initiating work on this document. These complete disclosure forms are retained by the American Radium Society™ in perpetuity. The ARS Appropriate Use Criteria Steering Committee reviewed the disclosures with the chair and co-chair of this document and approved participation of the panelists prior to starting development of this work. Disclosures potentially relevant to the content of this guideline are provided:

[5]Dr. Akselrod reports consulting fees from Otsuka America Pharmaceutical
[6]Dr. Jethwa reports honoraria from RadOncQuestions.com, LLC.
[7]Dr. Jin reports grants from Lilly, GlaxoSmithKline, Daiichi Sankyo/Astra Zeneca, Exelis, Elvar
[9]Dr. Lee reports honoraria from Varian Medical Systems, ViewRay, AstraZeneca; consulting fees from Varian Medical Systems, ViewRay, AstraZeneca, Genentech, Johnson & Johnson, Roche, RTOG foundation, and meeting/travel support from Radiosurgery Society.
[12]Dr. Selfridge reports drug support for clinical trials from Medpacto, Inc and Clinigen, Inc. and Industry sponsored studies from BioAtla, Arcus Biosciences, Avea, Cue Biopharma, and Pfizer; meeting/travel support Dava Oncology
[14]Dr. Small reports personal fees from Carl Zeiss.; and meeting and travel support for ACR, NRG Oncology, Carl Zeiss.

Acknowledgements

Ellie See, Talley Management Group for her attention to detail and diligence in this project.

Introduction/Background

Introduction

Approximately 22,370 new esophageal cancer (EC) cases were diagnosed in 2024[1], most presenting with dysphagia due to tumor obstructing the lumen of the esophagus. Nutritional support is an integral part of medical care for patients with EC, in both the curative and palliative settings. Esophageal stenting has the potential of palliating dysphagia, improving nutrition, allowing weight gain, obviating the need for feeding tube placement, preventing complications of esophageal obstruction such as aspiration, and improving quality of life (QoL). Potential risks associated with the use of esophageal stents include migration, bleeding, fistula formation, tracheal compression, impaction, and chest discomfort. Reintervention rates are as high as 50%, and late complications occur in up to 53%–65%.[2-4] Stent placement in the setting of chemotherapy and/or radiation therapy also contributes to the risk of complications associated with stent insertion.[5] In patients undergoing definitive or neoadjuvant chemoradiation (CRT) with curative intent, esophageal stenting has been associated with significantly increased grade $\geq$3 acute toxicities, fewer patients proceeding to esophagectomy, and worse overall survival (OS).[6,7] Furthermore, self-expanding stents (SESs) can increase radiation therapy planning target volumes (PTVs) and dose delivered to surrounding organs at risk (OARs).[8,9] In patients who had SES placed before radiation therapy, a dosimetric comparison study found that lung V5, lung V10, and heart V40 constraints were achieved more often when planning was based on pre-stent CT scans, with esophageal SES placement increasing the dose delivered to the lungs, heart, and liver.[10] While there are potential benefits to stents, clear risks are also present. We seek to investigate the balance between risks and benefits to stents for patients with malignant dysphagia in a range of clinical scenarios.

This systematic review summarizes the current evidence for the appropriate use of esophageal stents in patients with EC. The Population, Intervention, Comparator, and Outcome (PICO) questions included: (1) What are the risks/benefits of esophageal stents in patients with esophageal or Siewert I-II gastroesophageal cancer who are candidates for resection +/- neoadjuvant therapy?, (2) What are the risks/benefits of esophageal stents in patients with esophageal or Siewert I-II gastroesophageal cancer with localized disease who are not candidates for resection and are planned for definitive CRT?, (3) What are the risks/benefits of esophageal stents in patients with metastatic EC or those who are not candidates for definitive local therapy?, (4) What are the risks/benefits of esophageal stents in patients with esophageal or Siewert I-II gastroesophageal cancer with progressive obstructive symptoms following definitive CRT and/or surgery?, and (5) What are the risks/benefits of esophageal stents in patients with EC with tracheoesophageal (TE) fistula?

Methodology

This American Radium Society™ (ARS) Appropriate Use Criteria (AUC) multidisciplinary committee was comprised of all key specialties (gastrointestinal and thoracic radiation oncologists, gastroenterologists, surgical oncologists, medical oncologists, and radiologists). Using the Population, Intervention, Comparator, Outcome, Timing and Study Design (PICOTS) framework, the evidence regarding treatment outcomes was assessed using Cochrane and PRISMA 2020 methodology.[11,12] Eligible studies included prospective studies, phase II-III trials, and retrospective analyses including $\geq$ 15 patients published between 1/1/2010 – 12/3/2024 in the Ovid Medline database. Appendix A contains the database search strategy designed by a librarian-trained information specialist (CJA). Three authors independently screened the comprehensive list of articles, and one assessed the full text articles to determine the final studies included in the Summary of the Literature Review that informed our recommendations (Appendix B). Discrepancies between the reviewers were resolved by consensus. Of the 232 articles identified using the search strategy, 81 were selected for inclusion that met all inclusion criteria. Twenty-three additional studies were included through backward citation searching that significantly contributed to the literature were identified from the reference list of articles found from the search strategy. Study type and quality for these references were assessed via ARS AUC methodology. An additional 18 studies referenced outside the "Summary of Literature Review" are included to provide context, but unless they are also cited within the "Summary of Literature Review," they were not used by the committee to guide recommendations. In total, 122 references were selected for inclusion (Appendix C). The systematic review PRISMA 2020 checklist confirms the completion of essential elements (Appendix D). Well-established RAND-UCLA consensus methodology (modified Delphi) was used by the expert panel to rate the

appropriateness of the treatment options[13], with a total of 2 rounds of voting employed by the group. Categories included: (1) usually not appropriate (U, score 1-3); (2) may be appropriate (M, score 4-6); and (3) usually appropriate (A, score 7-9). The project proposal as well as this executive summary were reviewed and approved by the ARS AUC Steering Committee, which includes a librarian with expertise in systematic reviews. For further details on ARS AUC methodology guidelines, see https://www.americanradiumsociety.org/page/aucmethodology.

Patient Workup for Consideration of Esophageal Stent and Patient Selection

Both patient and tumor factors must be assessed when considering stent placement for dysphagia in the setting of malignant obstruction. When considering stent placement, patients must be fit enough for endoscopy and potentially undergo endotracheal intubation. Stenting can provide rapid relief of symptoms, but patients with a longer anticipated life expectancy (greater than 3 months) or in those where definitive surgery or curative CRT is considered may be better served by alternate therapeutic options such as feeding tube placement.[14] In patients receiving stenting, it is important to evaluate the characteristics of the tumor to select the appropriate stent. The stent must be long enough to bridge the tumor and should extend 2–4 cm beyond the margins of the stricture to minimize the chances of tumor in/overgrowth or stent migration.[15] If tolerable, fluoroscopic esophagram using barium or other contrast agents prior to stent placement can provide valuable information regarding the anatomy of the esophagus to inform stent choice and placement. Computed tomography (CT) esophagram is sometimes used as an alternative or in addition to fluoroscopic examination. Endoscopy is used to further evaluate the proximal and distal margins of the malignant stricture and luminal diameter, which must be large enough to pass the stent-introducers (typically 5-9 mm).

TE fistulas are estimated to occur in 5 to 15% of patients with EC[16], predominantly in those patients with middle third esophageal tumors. Management of TE fistulas in the setting of EC can be challenging, as patients tend to deteriorate rapidly due to contamination of the respiratory system from gastroesophageal secretions, which may lead to death from pneumonia or sepsis. The addition of flexible bronchoscopy to esophagram and endoscopy is used to evaluate for the presence of TE fistula. Contrast-enhanced CT with 3-dimensional reconstruction may also be useful in delineating the extent of the tumor and involvement of surrounding structures. Stent placement can be efficacious in the management of these fistula[17] and may require concomitant or separate airway stent placement as well[18]. Although evaluation for the presence of TE fistula typically is performed at the time of diagnosis, it is important to note that TE fistula may develop during or after treatment with chemotherapy and/or radiation therapy. Therefore, it is important to identify patients at risk for this complication for consideration of expectant management.

When considering patient selection, QoL measurements may facilitate decision making when considering treatments for dysphagia. A study by Blazeby et al.[19] demonstrated a correlation between dysphagia grade and European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 QoL questionnaire items. In this study, dysphagia grade was defined as: Grade 0: Able to eat solid food without special attention to bite size or chewing; Grade 1: Able to swallow solid food cut into pieces less than 18 mm in diameter and thoroughly chewed; Grade 2: Able to swallow semisolid food (consistency of baby food); Grade 3: Able to swallow liquids only; and Grade 4: Unable to swallow liquids or saliva. Defining the grade of dysphagia can assess patient QoL and assist in treatment decisions.

In general, indications for consideration of esophageal stents in EC patients with symptomatic dysphagia that impacts QoL include contraindication to chemotherapy and/or radiation therapy in patients who have unresectable or metastatic disease, tumor recurrence following definitive therapy (chemotherapy and/or radiation therapy +/- surgery), and management of malignant TE fistula.[15,20,21] In general, contraindications for the use of esophageal stents in patients with EC include potentially curative disease with multimodality therapy (relative), recent CRT, tumor stricture within 2 cm of the proximal esophageal sphincter, and uncorrectable coagulopathy.[15,20,21] In addition, patients in whom stent placement is being considered must be willing to adhere to a “stent diet” of soft foods.

Tumor Location and Stenting

The mid esophagus is considered the most stable and accessible location for stenting.[15] Stents should not be placed in the proximal esophagus less than 2 cm from the upper esophageal sphincter, which may result in patient discomfort while significantly increasing the risk of TE fistula formation.[15] Stents placed in the distal esophagus/gastric cardia have an increased risk of stent migration, reflux, and aspiration.[15] Endoscopic suturing of the proximal flanges of stents may mitigate stent migration.[22] Importantly, independent of stent location, palliative stenting is associated with a reintervention rate of approximately 25%–35% and requires close follow-up to maintain effective palliation.[15]

Types of Esophageal Stents

Historically, plastic stents were used for treatment of malignant esophageal obstruction but are associated with migration, food impaction, and perforation.[23] SESs are now more commonly used and are classified based on covering (partially, fully, and uncovered), metal vs. plastic, function (fully patent vs. antireflux), and biodegradability, and they are available in different diameters and lengths[15]. Compared to plastic tube insertion, metal SESs appear to provide better palliation of dysphagia, reduce recurrent dysphagia, and are associated with less migration.[24] Stent selection is based on tumor characteristics. Partially covered SESs are often used in cases of unresectable malignant obstruction to avoid tumor ingrowth, which can occur through uncovered stents resulting in recurrent dysphagia.[15] Fully covered stents are typically used to occlude malignant TE fistulas.[15]

Alternative Procedures/Therapies to Stents for Palliation of Malignant Obstruction

The optimal method of palliation for malignant obstruction in EC patients remains undefined and is not standardized. Alternatives to stent placement to facilitate nutrition in patients with potentially curative esophageal cancer include placement of feeding tubes (nasogastric, gastrostomy or jejunostomy tube, depending on the location of the cancer and potential for surgical intervention), and/or expedited initiation of neoadjuvant therapy or surgery. When there is high-grade obstruction (i.e. when a patient cannot swallow saliva), pharyngostomy drainage (to drain saliva and thereby prevent aspiration) and proceeded with feeding tube and curative or palliative intent treatment may also be considered. Esophageal dysphagia can often start to improve within a few weeks of starting neoadjuvant or definitive therapy, with noticeable relief seen after the first cycle of chemotherapy, particularly when combined with radiation therapy; however, the exact timeframe can vary depending on the individual case and the aggressiveness of the tumor.[25] For patients who are not considered candidates for potentially curative therapy and have a reasonable life expectancy, short-course external beam radiotherapy (EBRT)[26] or brachytherapy (BT)[26] may be used for palliation of dysphagia. In addition, ablative modalities such as cryotherapy[27,28], radiofrequency ablation (RFA)[29], argon plasma coagulation (APC)[30], laser therapy[31], photodynamic therapy (PDT)[32,33], and chemical ablation[34] can also be considered as alternatives to stenting, especially in patients who develop recurrence following previous radiotherapy or surgery.

Herein we describe the data evaluating the role of stents for malignant dysphagia and provide American Radium Society™ (ARS) Appropriate Use Criteria (AUC) for the Use of Esophageal Stents in Patients with Esophageal Cancer.

Summary of Literature Review

Topic 1/Use of esophageal stents in patients with esophageal or Siewert I-II gastroesophageal cancer who are candidates for resection +/- neoadjuvant therapy

Subtopic 1/ Candidates for Immediate Surgery (Variant 1)

Patients with potentially curative EC presenting with dysphagia are often diagnosed with compromised nutritional status, which has been associated with a higher operative mortality and morbidity rates than patients who maintain their weight.[35] For this reason, it is reasonable to consider stent placement prior to surgery to relieve dysphagia, increase oral intake, and improve nutritional status. A prospective study reported by Alder et al.[36] demonstrated that stent placement was safe in EC patients, permitted adequate oral feeding and improved dysphagia scores. However, stent migration occurred in 43% of patients in this study. The reported rate of stent migration ranges from

20%[37] to 60%[38] in other studies and can be associated with up to 25% stent-related clinically significant morbidity[39]. Acute stent-related morbidity includes stent migration (requiring removal or replacement), perforation (2.6%), TE fistula (5.2%), and significant bleeding (2.6%).[40] Delayed stent-related complications, including recurrent dysphagia and late occurrence of TE fistula (8%), have also been reported.[40]

Whether improvement in dysphagia correlates with improvements in nutritional status has also been investigated. Van den Berg et al.[41] demonstrated that although stent placement as a bridge to surgery resulted in improved dysphagia scores, it was also associated with decreased oral intake, weight loss, and need for additional nutritional interventions. In contrast Siddiqui et al.[42] demonstrated that albumin levels and weight increased with both stent and feeding jejunostomy, and complication rates were similar between the two procedures.

Studies have compared stenting to feeding tubes. Siddiqui et al.[42] evaluated nutritional status comparing esophageal stenting (12 patients) or feeding tube placement (24 patients) in EC patients prior to receiving treatment and reported that albumin levels and weight increased with both stent and feeding jejunostomy (mean increase in weight for stent 4.4 kg vs. feeding jejunostomy 4.2 kg, P = 0.59; mean increase in serum albumin for stent 0.62 g/dL vs. feeding jejunostomy 0.44 g/dL, P = 0.05). Complication rates were similar between the two procedures in this study (stent 22% vs. feeding jejunostomy 4%, P = 0.11). Bower et al.[43] also evaluated nutritional support comparing stents (25 patients), feeding tubes (19 patients), and oral diets (14 patients). In this study, patients treated with stents had a greater mean improvement in serum albumin (stent 0.14 g/dL vs. feeding tube -0.39 g/dL vs. oral diet -0.45 g/dL, P<0.001), less percentage body weight loss (stent 1.5% vs. feeding tube 4.2% vs. oral diet 5.5%, P<0.001) and a lower rate of perioperative complications (stent 20% vs. feeding tube 47% vs. oral diet 43%). Others have reported worse QoL associated with the use of stents compared to nasogastric tube or feeding tube. Yu et al.[44] compared outcomes for patients treated with stent, nasogastric tube, or feeding tube prior to CRT and found that the use of stenting was associated with worse pain and decreased albumin and QoL when compared with the other groups. In a subgroup analysis, the stent group was associated with greater weight loss, and the nasogastric group had higher narcotic demand. These studies support the use of stents as a reasonable alternative to feeding jejunostomy for improving nutrition prior to treatment in select patients; however, the routine placement of enteral access is not necessary for EC as the risks of placing enteral access may outweigh the benefits[45].

Studies have also investigated whether stenting compromised subsequent surgery and oncologic outcomes. Mariette et al.[46] evaluated the oncologic impact of covered SESs when used as a bridge to surgery in 2,944 EC patients in a multicenter European cohort who underwent esophageal resection. Stent insertion was complicated by perforation in 5% of patients, higher mortality rates (stent 13.2% vs no stent 8.6%), a trend toward higher morbidity (stent 63.2% vs no stent 59.2%) rates, and a significant reduction in the R0 resection rate (stent 71% vs no stent 85.5%; p=0.041). Median time to recurrence (stent 6.5 vs no stent 9 months) and 3-year OS (stent 25% vs no stent 44%) were also lower for patients receiving stents.

Immediate esophagectomy should be considered (after appropriate staging and preoperative evaluation) in patients who have cT1-2N0 EC with symptomatic dysphagia and adequate nutritional status. If nutritional status is compromised enough to warrant concern for increased risk of surgical morbidity, esophageal stents or other options such as nasogastric/nasojejunal or feeding jejunostomy can be considered in a select group of patients.

Subtopic 2/ Neoadjuvant Chemo(radiation) Followed by Surgery (Variant 2)

Esophageal stenting can also serve as a bridge to neoadjuvant therapy in EC patients with symptomatic dysphagia and compromised nutritional status. Esophageal stenting may provide relief of dysphagia, leading to increased oral intake, and nutritional improvement in this setting.[36,47-49] It is important to recognize that complications from stent placement as described in “Topic 1/Subtopic 1/ Candidates for Immediate Surgery” also may negatively impact the ability to complete a prescribed course of neoadjuvant therapy.[46] A prospective study by Martin et al.[47] included patients with EC who had stent placement prior to receiving neoadjuvant therapy for EC. Stent migrations requiring replacement were reported in 5.8%, and although no esophageal erosion or perforations were reported. Approximately 25% were unable to complete the planned therapy. Of the 69% of patients who received CRT, 93% of

these patients received the planned dose of chemotherapy, and 75% received the full planned dose of radiotherapy. Of 31% of patients who received chemotherapy alone, 74% completed all prescribed chemotherapy. Langer et al.[49] also reported outcomes for EC patients who had temporary stent placement prior to neoadjuvant therapy. Although instant palliation of dysphagia was reported in 97%, stent-related complications were reported in 16% of patients and included migration (causing jejunal perforation, 3%), perforation (3%), trachea-esophageal fistula (5%), mediastinitis (3%), and bleeding (3%). A more recent study by Francis et al.[6] reported outcomes for 103 EC patients who received neoadjuvant CRT, including 28 who had stent placement prior to neoadjuvant therapy. In this study, acute grade ≥3 acute toxicities were more common in the stent vs no stent patients (71% vs. 27%; respectively; P<.01), and included esophagitis (39% vs 20%, respectively; P=.05), dehydration (29% vs 13%, respectively; P=.07), and anorexia (14% vs 5%, respectively; P=.13). The only predictor of acute toxicity was esophageal stenting (odds ratio (OR) 8.1; P<.01) on multivariate analysis. Of the 103 patients, 29% of the stent and 51% of the no-stent patients underwent esophagectomy (P=.05) and after propensity score matching, the stent patients had a worse median OS compared with the no-stent patients (11.5 vs 22.0 months; hazard ratio (HR) 2.3; P=.016).

Furthermore, the use of stents may also impact radiation therapy planning target volumes (PTVs) and dose delivered to surrounding organs at risk (OARs) for patients with EC.[8-10] A study by Francis et al.[10] demonstrating the effects stents can have on radiation dosimetry included patients who underwent radiation treatment planning prior to and following stent placement. This study found that lung V5, lung V10, and heart V40 constraints were achieved more often using plan evaluations based on pre-stent CT scans, with use of stents associated with increased radiation dose delivered to the lungs, heart, and liver nearing recommended dose-volume thresholds. Consideration of dose-volume thresholds are particularly important in EC patients receiving neoadjuvant CRT as multimodality treatments are often correlated with an increase in postoperative pulmonary complications and mortality.[50] When considering lung volume ≥ 40% receiving ≥ 10 Gy, the incidence of pneumonia and ARDS significantly increases from 8% to 35%[50], and reducing the volume of lung receiving doses > 5 Gy is significantly correlated with reduced pulmonary complications.[51] Therefore, careful consideration and multidisciplinary discussions related to risk vs. benefit of stent placement is warranted prior to radiotherapy for EC patients.

Surgical outcomes following stent placement prior to neoadjuvant therapy have also been reported. A phase II study by Brown et al.[52] included EC patients with dysphagia and weight loss who received stenting prior to neoadjuvant therapy and reported improvement in dysphagia and mild weight loss during the course of neoadjuvant therapy, although 6% of patients experienced stent migrations requiring replacement. In this study, 62.5% of patients underwent margin-negative resection without difficulty removing the stents after completion of neoadjuvant therapy, whereas 25% of patient developed progressive disease, and 12.5% of patients had a decline in performance status precluding surgery. Major perioperative complications included pulmonary embolism (6%), chyle leak (3%), and bronchial injury (3%). Kjaer et al.[53] published data from a retrospective cohort study from a prospectively maintained national database of patients with EC treated without neoadjuvant therapy that subsequently underwent R0 resection and demonstrated a detriment associated with the use of stent. Of these 63 patients who received stent as a bridge to surgery, outcomes were compared to 211 who did not receive stent. The median OS in the stent group was lower than the non-stent group (11.6 months vs. 21.3 months, respectively), as were the 2-year OS (P = 0.017) and median recurrence-free survival (9.1 months vs. 15.2 months, respectively). Similar findings were observed in a large retrospective study by Ahmed et al.[7], who reported clinical, nutritional and oncologic outcomes for 465 EC patients with dysphagia (over 9 studies). Esophageal stent use resulted in a significant improvement in mean dysphagia scores but failed to demonstrate improvements in weight, body mass index (BMI) or albumin. Furthermore, potentially curative resections were performed in only 33% of stented patients, and they were associated with reduced R0 resection and lower OS rates.

It is important to recognize that neoadjuvant therapy alone can also be considered as a palliative treatment for obstructive symptoms in EC patients.[54] Dysphagia can start to improve within a few weeks of starting neoadjuvant therapy, with noticeable relief seen after the first cycle of chemotherapy, especially when combined with radiation therapy.[25] In a study by Sunde et al.[25], EC patients with dysphagia treated with either neoadjuvant CRT (25 patients) or neoadjuvant chemotherapy alone (10 patients) reported improvements in dysphagia and appetite from baseline

to the completion of the first chemotherapy cycle, which were durable through the completion of neoadjuvant treatment. No change in body weight was observed over the course of treatment regardless of the type of neoadjuvant therapy, and there was no association between relief of dysphagia and the degree of histological response in the surgical specimen. The authors subsequently published patient-reported swallowing function as a secondary endpoint of this study. Of the 181 patients who were randomized, 87% completed the EORTC EC modules QLQ-OES24/OG25 before treatment and 73% after treatment. They reported mean dysphagia scores after neoadjuvant treatment were significantly lower after neoadjuvant chemotherapy compared to after neoadjuvant CRT (P = 0.022).[55] This study demonstrates the palliative effect of neoadjuvant therapy on dysphagia, even in the absence of stent placement. Moreover, the study implies that chemotherapy alone may be better at relieving dysphagia than CRT, which is associated with treatment-induced esophagitis driven primarily by the radiation therapy and that can often be avoided with the use of chemotherapy alone. Recent studies incorporating immunotherapy into neoadjuvant treatment strategies demonstrated similar improvements in dysphagia.[56] Expeditious treatment with neoadjuvant therapy (after complete evaluation and work-up) should be strongly considered as an alternative to stent placement for palliation of dysphagia in EC patients.

In summary, although the use of esophageal stents can be considered to palliate dysphagia and is associated with improvements in dysphagia during neoadjuvant therapy, its effect on improving patient nutritional status is less clear. Esophageal stents used in the setting of a newly diagnosed EC patient is associated with increased risks of complications and may be associated with worse oncological outcomes. Complete staging and multidisciplinary discussion[57] should direct therapy as well as supportive measures for these patients, including the use of stents. Stents should only be used with caution in patients who are being considered for potentially curative resection (+/- neoadjuvant therapy) after multidisciplinary recommendation, and other strategies of palliation and nutritional supplementation should be considered in select patients.

Topic 2/ Use of esophageal stents in patients with esophageal or Siewert I-II gastroesophageal cancer with localized disease who are not candidates for resection and are planned definitive chemoradiation (Variant 3)

In patients with localized EC who are not candidates for resection, definitive CRT is usually recommended for potential cure and long-term disease control. Because many patients with inoperable EC present with symptoms of dysphagia, weight loss, and compromised nutrition, immediate palliation with stenting may seem an attractive initial option. However, if the patient is a candidate for definitive treatment with CRT, it is important to remember that stenting may negatively impact the ability to tolerate planned treatment (as described in "Topic 1/Subtopic 2/ Neoadjuvant Chemo(radiation) Followed by Surgery").[6,10,47]

Nonetheless, some studies have evaluated the use of chemotherapy, radiotherapy, and CRT combined with stenting. One of the larger studies was a retrospective analysis reported by Burstow et al.[58] including 90 inoperable EC patients presenting with dysphagia and weight loss who were treated with esophageal stenting +/- radiation therapy +/- chemotherapy. Tumors were located in the distal (81%) or mid (19%) esophagus, with adenocarcinoma representing 68%, and squamous cell carcinoma in 32%. The median OS was 61 days for the entire group. Patients receiving chemotherapy or radiotherapy survived longer than those receiving stenting alone (152.8 days vs. 71.8 days). Lu et al.[59] evaluated the risks and benefits of using stents in the setting of CRT in patients with inoperable EC. This study reported fistula formation in 88% of patients during and after CRT following stent placement compared to 3% in patients treated with CRT without stenting. The median OS was worse for patients in the stent + CRT patients compared to the CRT group (6 months vs. 16 months, respectively; HR 5.72; 95%; confidence interval (CI) 2.15-15.21; $p < .001$).

Studies have demonstrated that CRT can be effective for improving dysphagia and improving QoL[25], with some patients showing complete response with prolonged survival.[60] A study by Valkema et al.[61] in which 131 patients who had a complete clinical response to neoadjuvant CRT were followed with active surveillance (instead of proceeding to planned surgery) were evaluated for dysphagia using EORTC QLQ-OG25 at 6, 9, 12, and 15 months

after treatment. At each time point after CRT, median dysphagia scores were 0. This study demonstrates the efficacy and durability of CRT for improving dysphagia in patients who do not undergo surgery for EC. Initial treatment with CRT or chemotherapy should be strongly considered as first-line treatment of dysphagia (instead of stenting), which can be combined with other methods of nutritional support as needed, such as feeding tubes in select patients when deemed necessary by multidisciplinary consensus.

Because the 5-year OS rate is reported to be 26% (95% CI 15%-37%) in patients with localized, non-metastatic, inoperable EC[62], it is important to consider that the use of esophageal stents used the setting of CRT is associated with increased risk of complications and may be associated with worse oncological outcomes. Palliative stents in EC patients who are candidates for definitive CRT should be carefully considered and discussed in a multidisciplinary setting.[57] Stents should only be used with caution in patients who are being treated with definitive CRT after multidisciplinary recommendations, and other strategies of palliation, such as expeditious initiation of definitive CRT, should be considered.

Many of the studies evaluating the role of esophageal stenting in the setting of inoperable EC include both patients with locally-advanced, non-metastatic disease those with incurable metastatic disease. Treatment is considered more palliative than curative in these reports; therefore, differences in outcomes are difficult to interpret when considering the two patient populations. We will delve into data reporting on the use of stents in the palliative setting (including subsets of patients with localized disease who receive CRT) in "Topic 3/ Use of esophageal stents in patients with metastatic, incurable EC or those who are not candidates for definitive local therapy" below.

Topic 3/ Use of esophageal stents in patients with metastatic, incurable esophageal cancer or those who are not candidates for definitive local therapy (Variant 4)

Palliation of dysphagia is especially important for QoL in patients with incurable EC, with the goal to provide rapid and sustained relief of symptoms. Treatment options, include stenting, short-course EBRT (+/- chemotherapy)[26] or BT[26], chemotherapy alone of ablative treatments such as cryotherapy[27,28], RFA[29], APC[30], laser therapy[31], PDT[32,33], and chemical ablation[34].

The most common treatments for palliation of dysphagia in this setting include esophageal stent placement (+/- chemotherapy) and radiotherapy (+/- chemotherapy). Treatment choice primarily depends on life-expectancy and dysphagia severity.

Subtopic 1/ Esophageal Stents

Esophageal stenting typically provides immediate relief of dysphagia and is preferred when the patient has a limited life expectancy. The use of esophageal stents has been associated with tumor ingrowth (when used as a single modality), stent migration, and reflux symptoms (especially when stents are placed across lower esophageal sphincters), and more rarely, hemorrhage, perforation and fistula formation.[15] Shenfine et al.[63] conducted a randomized study including 215 EC patients treated with stents or other palliative therapies comparing dysphagia, QoL 6 weeks following treatment, and total cost of treatment. Secondary outcome measures included treatment-associated morbidity, mortality, survival, and cost-effectiveness. In this study, there was a difference in mean dysphagia grade between treatment arms 6 weeks following treatment (P=0.046) and global QoL scores (P=0.04), with worse swallowing reported by stent-treated patients. There were no differences observed in mortality or early complication rates, but late complications were more frequent after stenting (risk ratio (RR)=2.47; 95% CI 1.88-3.04), and a survival advantage was observed for patients who did not receive stents (log-rank statistic=4.21, P=0.04). Similar results were observed in a large retrospective study by Egeland et al.[64] This study included 601 patients with incurable EC, with 270 (45%) who received endoscopic treatment for dysphagia (82% stent) and the remaining 55% treated without endoscopic intervention. The complication rate was 38% for those who received stents vs. 20% for those treated without stents (P=0.03), and 26% required repeat intervention. Worse OS was observed for patients

who received endoscopic intervention prior to treatment (HR: 2.17, 95% CI: 1.80-2.61, p < 0.001), and in the sub analysis of only patients who had an intervention were included, a survival difference was observed in favor of the non-stent group.

Non-stent palliative treatment options should be considered when patients have a reasonable life-expectancy (e.g. > 3 months).

Subtopic 2/Palliative Radiation

Radiotherapy is usually preferred for patients with a reasonable life-expectancy (e.g. > 3 months), as it is associated with more durable palliation of dysphagia compared to stent placement, although symptom relief it not immediate and may take up to 2 weeks before being noticeable.[65] Radiotherapy can be delivered via EBRT or intraluminal BT.

Palliative EBRT: Retrospective studies report that palliative EBRT results in improvement of dysphagia in >70%[66,67] when employing EBRT doses of 20 Gy in 5 fraction, 30 Gy in 10 fractions, or 39 Gy in 13 fractions, with no differences in degree of palliation or OS observed between schedules[67]. However, recurrent dysphagia is more common with the shorter courses compared to longer courses (32% vs 18%, respectively; P=0.098).[68] Using palliative fractionation regimens, median dysphagia-free survival is approximately 6 months[66,69], which is similar to the median OS indicating adequacy of the treatment. Borg et al.[70] reported results from a prospective study including treatment-naïve patients who were not candidates for curative treatment who received short-course EBRT (20 Gy in 5 fractions) followed by chemotherapy. Dysphagia was improved in 91%, with median duration of improvement 12.2 months (14.0 months for responders), and median OS 16.0 months.

Stent vs Palliative EBRT: Martin et al.[71] reported the results from a large retrospective database including 1,957 United States veterans with EC who received either palliative EBRT (1,593 patients) or stenting (364 patients). In that study, the incidence of treatment-related complications, including fistula, perforation, and hemorrhage, was higher for the stent group compared with the EBRT group (21.7% vs 12.4%; P<0.0010). Palliative EBRT was associated with more rapid and durable pain relief (P<.0010), and with no differences observed between the two groups regarding relief of dysphagia over time when accounting for pretreatment dysphagia scores (P=0.1029). Eldeeb et al.[72] reported survival data for 91 patients with locally advanced or metastatic EC who had been treated with either palliative EBRT, stent or both. Median OS was 169 days for patients treated with palliative EBRT alone, 119 days for treatment with stent alone, and 237 days for treatment with combined therapy. The only observed survival difference was between patients treated with stent alone vs. combined therapy (P=0.01).

Stent Combined with EBRT: Studies have reported outcomes for patients treated with stent followed by EBRT[72-77], including 2 randomized trials[73,76]. Adamson et al.[76] reported the results of a randomized trial comparing the use of stent for palliation of dysphagia in 200 EC patients compared with stent placement followed by EBRT (20 Gy in 5 fractions or 30 Gy in 10 fractions) demonstrating no additional improvements in control of dysphagia, time to first stent complication or re-intervention, or survival endpoints with the addition of EBRT. Another randomized study by Javed et al.[73] compared duration of dysphagia relief in 84 EC patients treated with stent alone (42 patients) vs. stent + EBRT (42 patients) and reported that the addition of EBRT prolonged the mean dysphagia-free survival (118.6 days vs. 96.8 days, respectively; P = 0.054). A significant improvement in all QoL parameters was reported at 1 week after stenting but declined immediately after radiotherapy. The incidence of complications was similar in the two groups. These data do not support the use of EBRT in addition to stenting for palliation of dysphagia.

Palliative CRT: The TROG 03.01 randomized trial reported by Penniment et al.[78] included 210 patients with locally advanced or metastatic EC who received either palliative CRT (111 patients) or EBRT alone (109 patients).

Median dysphagia progression-free survival (PFS) was 4.1 months (95% CI 3.5-4.8) vs. 3.4 months (3.1-4.3) in the CRT and EBRT alone groups, respectively (p=0.58), although the CRT group was associated with more than double the rates of acute toxicity, including esophagitis. Median OS was not different between the two groups (CRT 6.9 months vs. RT alone 6.7 months (P=0.88)). A prospective nonrandomized study by Akl et al.[79] using concurrent CRT with cisplatin and 5-FU in EC patients who were not candidates for surgery resulted in improvements in dysphagia in 72% of subjects with median duration of symptom relief 5 months after treatment, and median OS and PFS reported at 7 and 4 months, respectively. Both metastatic and non-metastatic inoperable patients were included in this study, and the total EBRT dose was lower (40 Gy in 22 fractions delivered with concurrent cisplatin and 5-fluorouracil (5-FU)) compared to definitive CRT doses (50.4 - 64 Gy)[62]. A retrospective study reported by Ikeda et al.[80] included 40 stage IVB EC patients who presented with dysphagia treated with palliative CRT with 2 concurrent cycles of cisplatin and 5-FU using similar radiation doses as the Akl study (40 Gy in 20 fractions). Dysphagia symptoms improved in 75% of patients, which was associated with a 95% disease control rate at the site of irradiated primary tumor. Median OS was 308 days and median PFS was 139 days. Esophageal perforation occurred in 5% of patients, but overall palliative CRT was associated with improvement of dysphagia scores and acceptable toxicity rates.

CRT has been compared to other treatment modalities in the setting of inoperable EC. A case-controlled study by Sgourakis et al.[81] reported an improvement in OS observed for patients treated with CRT compared to stent alone, chemotherapy alone, and EBRT alone. Mean patient survival for stent alone was 6.92 +/- 8.4 months; chemotherapy alone 7.8 +/- 6.6 months; EBRT alone 8.6 +/- 9.5 months, and CRT 13.5 +/- 14.7 months. Treatment modality was the only independent predictor of survival in multivariate analysis (P = 0.043). The difference in OS between stent and CRT was highly significant (P < 0.01), but when comparing CRT to chemotherapy or EBRT alone, only a trend towards a difference in OS was observed in favor of CRT (P = 0.069 and P = 0.059, respectively). Other studies comparing palliative CRT and other modalities in EC patients with dysphagia may have been limited by lack of power to evaluate survival differences.

Brachytherapy: Several prospective studies have demonstrated endoluminal BT as an effective and safe palliative treatment option for select patients with advanced EC who are not candidates for potentially curative therapy.[82-86] BT can be delivered in a single fraction (typically 12 Gy)[26,84] or over 2 to 3 fractions over the course of 2 weeks (typically 16 – 21 Gy)[82,85]. Improvements in dysphagia are reported in approximately 65% of patients undergoing BT alone[26], and treatment is fairly well tolerated, with reported complications of stricture formation in approximately 10% and fistula formation in 10% of patients receiving fractionated BT.[83] When comparing dose and fractionation schedules, patients treated with fractionated BT had an increased dysphagia-free period compared to those treated with only a single dose of BT.[87]

EBRT vs Brachytherapy: Short-course palliative EBRT is generally preferred over single-dose BT because of better clinical outcomes, lower toxicity and easier delivery. Jeene et al.[26] compared outcomes for 115 patients with incurable EC and dysphagia treated with either BT (single dose 12 Gy) or short-course palliative EBRT (20 Gy in 5 fractions). In a propensity-matched analysis, dysphagia improved in 83% after EBRT vs. 64% after BT (P = 0.048). This improvement was observed in 67% after EBRT compared with 35% after BT at 2 weeks, and the maximum effect was reached after 4 weeks in 55% and 33%, respectively. Eldeeb et at.[88] reported similar improvements in dysphagia in patients treated with either EBRT (20 – 30 Gy in 5- 10 fractions) or BT (12 Gy, single fraction) at 4 weeks (p<0.0001), and the benefit was sustained after 8 and 16 weeks in both groups.

Brachytherapy +/- EBRT: The combination of EBRT and BT has also been shown to relieve dysphagia[89] and improve QoL in patients with EC.[90] Two randomized controlled trials which compared BT and BT + EBRT reported mixed results.[86,91] The Rosenblatt et al.[86] trial which randomized 219 patients with squamous cell carcinoma EC to either BT (16 Gy in 2 fractions) or the same BT regimen followed by EBRT (30 Gy in 10 fractions) and

demonstrated better long-term improvement in dysphagia in the combination therapy group (BT + EBRT 83% vs. BT alone 67%, P<0.05). Sur et al.[91] reported no significant differences in dysphagia scores, survival, dysphagia-free survival, or adverse events for 60 patients with squamous cell EC randomized to BT (16 Gy in 2 fractions) or the same BT regimen followed by EBRT (30 Gy in 10 fractions). A retrospective study comparing EBRT alone (30 - 40.5 Gy in 10 – 15 fractions), BT (10 – 14 Gy, single fraction), or BT + EBRT demonstrated that EBRT + BT resulted in improved dysphagia-free survival scores (EBRT + BT 92% vs. EBRT alone 90% vs. BT alone 37%, respectively, P<0.01).[92] A propensity-matched study reported by Vermeulen et al.[93], demonstrated a trend toward better palliation in the combination therapy group (EBRT 30 Gy in 10 fractions + single fraction BT, 12 Gy) compared to EBRT alone (20 Gy in 5 fractions) (65% vs. 50% respectively, P=0.071), with less persistent/recurrent dysphagia observed in the combined therapy group (42% vs. 64% respectively, P=0.012). No differences in adverse events were observed between the 2 groups; however, median OS was 177 days for patients receiving EBRT + BT compared to 88 days for patients treated with BT alone.

Stent + Brachytherapy: In a prospective study reported by Bergquist et al.[94], relief of dysphagia was reported in 91% of patients treated with stent followed by BT (12 Gy, single fraction). However, other studies have demonstrated unacceptable toxicity associated with combined stent and BT, including dysphagia, vomiting and hematemesis.[95]

Stent vs Brachytherapy: In a study by Hanna et al.[96], an improvement in dysphagia was reported in 85% of patients treated with stent within the first 2 weeks following the procedure, but recurrent dysphagia was observed in 20% of patients after 10 weeks. Patients who were treated with BT (12 Gy, single fraction) experienced slower onset of palliation, with only 50% of patients reporting improvement after 2 weeks, and 90% of patients reporting relief of dysphagia after 10 weeks. This study also included 10 patients treated with EBRT and 22 patients treated with EBRT + BT which contributed to the results. Homs et al.[84]and Bergquist et al.[85] also reported longer-duration of improvement in dysphagia patients treated with BT (12 Gy, single fraction) compared to stent alone. The Homs trial[84] randomized 209 patients to stent (108 patients) or single dose BT (12 Gy; 101 patients) and found that dysphagia improved more rapidly after stent placement than after BT, but long-term relief of dysphagia was better after BT. Stent placement had more complications than BT (33% vs. 21%, respectively; P=0.02), with more late hemorrhage in the stent group (13% vs. 5%, respectively; P=0.05). Groups did not differ for persistent or recurrent dysphagia (p=0.81), or for median OS (p=0.23). Better QoL scores were associated with BT compared with stent placement.

Palliative Chemotherapy +/- Stent: Chemotherapy can be used as the first modality for palliation of dysphagia in patients with recurrent[97] or disseminated EC and may be combined with other modalities. Sunde et al.[25,55] demonstrated that (neoadjuvant) cisplatin and 5-FU chemotherapy with or without concurrent radiotherapy can relieve dysphagia in EC patients. In that study, patients received neoadjuvant chemotherapy alone and reported improvements in dysphagia and appetite following the completion of the first chemotherapy cycle that persisted throughout neoadjuvant treatment. The results of that study question whether chemotherapy alone may be better at relieving dysphagia compared to palliative EBRT or CRT, which are both associated with radiation-induced esophagitis that can be avoided with the use of chemotherapy alone. In contrast, Touchefeu et al.[98] retrospectively compared the efficacy of a chemotherapy-first approach (42 patients) with a stent-first approach (29 patients) in patients with inoperable EC and worsening dysphagia. At 4 weeks following initiation of treatment, dysphagia scores improved by 1 point in 67% of patients in the chemotherapy-first group vs. 93% in the stent-first 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). More recently, immunotherapy has been incorporated into palliative systemic therapy regimens for patients with advanced EC resulting in improved dysphagia in up to 83% of patients without additional intervention[99-101], and improved QoL when compared to chemotherapy alone[101]. A randomized trial comparing palliative systemic therapy to best supportive care in advanced EC demonstrated

superior dysphagia-free survival (14.8 months vs. 2.9 months), PFS (4.2 months vs. 2.1 months), 1-year OS (32% vs. 11%), and global and esophagus-specific QoL without a significant increase in ≥ grade 3 toxicities.[102] These results support the use of systemic therapy for palliation of dysphagia for select patients with incurable EC.

Palliative Ablation: Palliative ablation methods are rarely used but can be considered in select EC patients with dysphagia. Chemical ablation with alcohol injection has been shown to improve dysphagia and QoL, best observed after 4 treatments and may be used with other treatment modalities, but it is associated with complications such as mediastinitis, perforation and TE fistulas.[34] Thermal ablation techniques can also be considered in select patients for palliation of dysphagia and include cryotherapy[27], RFA[29], APC[30], laser therapy[31], and PDT[32], and these modalities are sometimes combined with CRT in patients with inoperable EC[103]. Ablative therapies are effective in for small, flat tumors, but are not as effective for nodular tumors, tumors longer than 5 cm, or in patients with TE fistula, or proximal or gastroesophageal junction tumors.[27,29,31,32,104] A randomized trial in 93 patients with incurable EC compared the palliative effects of APC alone, APC + PDT, and BT and found that combination treatment of dysphagia with APC and HDR or PDT was more effective at palliating dysphagia than APC alone. APC combined with HDR also resulted in fewer complications and better QoL than APC with PDT or APC alone.[105]

Table 1. Comparison of the advantages and disadvantages of stent vs EBRT vs BT when considering treatment of dysphagia in incurable EC patients.

	STENT	EBRT	BT
Onset of palliation	Rapid (~ 1 day)	1-2 weeks	1-2 weeks
Duration of palliation	Short (2-3 months)	Long (> 3months)	Long (> 3months)
Complication rate	~ 40-50%	~ 20%	~ 40-50%

In summary, single modality is recommended over combined therapy for dysphagia in the palliative setting, with radiation therapy preferred in those with a reasonable life-expectancy (e.g. > 3 months), as it is associated with lower adverse events and more durable palliation of dysphagia compared to stent placement. If the patient is fit for systemic therapy, chemotherapy alone is also considered a reasonable option and can avoid the esophagitis typically associated with radiation therapy. The use of stenting is typically considered for patients with a shorter life expectancy who need immediate palliation. Multidisciplinary discussion should guide treatment recommendations for the use of stents in EC patients who are not candidates for potentially curative therapy.[57]

Topic 4/ Use of esophageal stents in patients with esophageal or Siewert I-II gastroesophageal cancer with progressive obstructive symptoms esophageal following definitive chemoradiation and/or surgery
Subtopic 1/ Non-malignant Post-Therapy Strictures (Variant 5)
Non-malignant strictures of the esophagus occur in up to 55% of EC patients following definitive treatment with neoadjuvant therapy followed by surgery or definitive CRT.[106] Dysphagia due to stricture can reduce a patient's QoL even if the EC is cured. The standard treatment for esophageal stricture is endoscopic balloon dilation, which often requires multiple treatments to achieve success.[107] Yoda et al.[108] reported results from a large retrospective series of 122 patients treated with balloon dilation for benign strictures following definitive treatment for EC (60 surgery, 32 CRT, 30 endomucosal resection). This study demonstrated a longer time to treatment success for the CRT group compared to surgery (7 months; P=0.01), and a difference in the refractory stricture rate following dilation between the nonsurgery group (75%) and the surgery group (45%, P<0.01). For patients with benign strictures following curative treatment of ED, balloon dilation for stricture is an effective treatment strategy; however, time of relief from dysphagia is longer for patients who were treated with CRT compared to surgery.

Steroid injection is sometimes used in combination with balloon dilation in patients with benign strictures after curative treatment for EC. A randomized study reported by Hanaoka et al.[109] demonstrated an improved 6-month recurrence-free interval for those patients treated with dilation combined with steroid injection compared to those treated with dilation alone (39% vs. 16% respectively; P=0.002).

Halland et al. [110] reported a randomized study evaluating esophageal self-dilation therapy to maintain luminal patency in patients with symptomatic benign esophageal strictures that were refractory to endoscopic dilation, stenting, incisional or injectional therapies. Most patients (22 of 25 patients) were able to learn self-dilation, which involves teaching patients to pass a flexible dilator orally to keep the esophagus open. Of the patients performing self-dilation, only 50% required repeat endoscopic dilation, compared to 100% of the observational controls. Esophageal self-dilation can be utilized in refractory patients to reduce need for repeat endoscopic dilation.

Stents are rarely used in the setting of benign stricture developing after curative therapy for EC. A study by Qiu et al.[74] investigated the relationship between previous EBRT and stent use (albeit in patients with recurrent malignant obstruction following neoadjuvant CRT and surgery). In this study patients were divided into 2 groups: patients with EBRT before stent placement (RT group, n=57) and patients with no treatment before stent placement (no EBRT group, n=35). Improvement in dysphagia following stent placement was similar in both groups. Fatal complications, including gastrointestinal hemorrhage and uncontrolled pneumonia, were higher in the EBRT first group. Logistic regression analysis showed a significant interaction between prior EBRT and fatal gastrointestinal hemorrhage (relative risk (RR) 7.82, 95% CI 1.54-39.61; P=0.013). A correlation with prior radiation dose and fatal hemorrhage was observed (5.7% no EBRT, 0% < 50 Gy, 12.5% 50-60 Gy, and 44.8% > 60 Gy); however, there was no dose relationship observed with the incidence of uncontrolled pneumonia. Given the high (and sometimes fatal) complication rate, it is difficult to justify the risks of stent placement in patients without evidence of active malignancy and with alternative options.

In summary, stents are not recommended for palliation of benign post-therapy strictures in the setting of prior radiation therapy, especially in patients who have no evidence of recurrence or metastases.

Subtopic 2/ Malignant Obstruction Due to Tumor Recurrence (Variant 6)

Unfortunately, local tumor recurrences resulting in dysphagia are common following definitive therapy in patients with EC. Palliative esophageal stenting and/or radiation may be considered in an effort to relieve dysphagia.

Stents: In addition to the data presented by Qiu et al.[74] described in "Topic 4/Subtopic 1/ Non-malignant Post-Therapy Strictures", Iraha et al.[111] evaluated the efficacy of stent placement in patients with inoperable EC following prior radiation therapy +/- chemotherapy. Stent placement was successful in most patients, and stent-related complications included mediastinitis (10%), pneumonia (5%), and funnel phenomenon (5%), with 75% of patients treated with prior radiotherapy +/- chemotherapy reporting persistent chest pain following the procedure. Tong et al.[112] reported outcomes for 35 patients with dysphagia secondary to locoregional recurrence following esophagogastrectomy; stent placement resulted in a 98% improvement in dysphagia score. This study included patients with TE fistula from recurrent tumor. Patients who underwent stenting to repair the fistulas were associated with a 14% complication rate (stent malposition in 2 patients, and inadequate stent opening in 2 patients).

In summary, stent placement in the setting of prior radiation should be considered with caution due to increased risk of adverse events, but it may be useful for palliation of dysphagia in patients with limited life expectancy.

EBRT: EBRT/CRT can be considered in patients with recurrent malignant obstruction who were treated with surgery +/- systemic therapy without prior radiotherapy. Definitive treatment can be considered in select patients with limited locoregional recurrence and no evidence of distant disease. In patients with more advanced disease at time of recurrence or those who are not candidates for definitive CRT, palliative radiotherapy can result in improvements of dysphagia in >70%[66-68] and are associated with dysphagia-free survival of approximately 6 months.[69] Palliative regimens can also be combined with systemic therapy and have been associated with a higher rate of improvement of dysphagia (91%) with longer median duration of improvement (12.2 months).[70]

Reirradiation is sometimes used for localized EC recurrences but is associated with increased risks of stricture, perforation and fistula formation. Conservative palliative doses are typically used in this setting; however, some have used higher doses in the setting of localized recurrence in the absence of distant metastatic disease.[113,114] A study by Xu et al.[113] reported outcomes for 47 patients initially treated with EBRT ($\geq$ 50 Gy) who received reirradiation for recurrent EC associated with dysphagia. The median time to recurrence was 26 months (6-120 months), and all patients had in-field recurrences. Patients were treated with reirradiation (median dose 58 Gy; range 26-64 Gy), and sequential chemotherapy was used in 27%. Improvement in dysphagia was achieved in 57%. In the univariate analysis, an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0-1 (P = 0.014), recurrence at the local site (P = 0.048), time to recurrence >=24 months (P = 0.006) and reirradiation dose $\geq$50 Gy (P < 0.001) were associated with longer OS, but multivariate analysis demonstrated that only reirradiation dose $\geq$50 Gy was an independent factor for OS (P = 0.007). The median OS was relatively short for this cohort (17 months) and severe complications were observed in 20% of patients, with complication rates highest in patients who received reirradiation doses > 60 Gy.

In summary, EBRT or CRT are reasonable options for patients with recurrent dysphagia due to malignant obstruction after curative treatment in the setting of no prior radiation therapy. Reirradiation is associated with a high complication rate and should be regarded with, but may considered if other options are limited, especially if life-expectancy is short.

Topic 5/ Use of esophageal stents in patients with esophageal cancer with tracheoesophageal fistula

The development of TE fistula has been shown to have a negative impact on OS and is associated with recurrent aspiration and obstructive symptoms. The goals of treatment are to separate the esophagus from the respiratory tree preventing contamination, and to ensure adequate nutrition through resumption of oral intake or alternative means, such as a feeding tube. There is controversy regarding the optimal management of TE fistulas and treatment options, include surgical repair, airway stenting, chemotherapy, placement of feeding tube, and best supportive care. Lenz et al.[115] reported outcomes for 127 patients with TE fistulas treated with surgical (28%) vs. non-surgical (72%) management. Patients treated surgically survived longer than those managed with nonsurgical treatment (HR=5.6, P=0.005) and reintervention was more common with nonsurgical management (HR=2.3, P=0.03). Stent placement for management of TE fistulas can result in improvement of symptoms and performance status in many patients, but can be complicated by migration, tumor overgrowth, and recurrent fistula formation. Studies have compared outcomes for patients with EC who develop TE fistulas treated with different modalities including stents. A study by Xu et al[116]. reported a survival benefit for patients who underwent stent or feeding tube placement (+0.90 (95% CI 0.60 to 1.19) months; +0.81 (95% CI 0.47 to 1.13) months, respectively) vs. nasogastric tube; however, survival was best for the few patients who were treated with surgical repair. Herein we will discuss the use of stents for the management of TE fistulas in EC patients based on clinical presentation and whether the patient has received prior treatment for the underlying malignancy.

Subtopic 1/ Patients Presenting with TE Fistula at the Time of Diagnosis (Variant 7)

Management of TE fistula is recommended if feasible prior to definitive or other palliative treatment to avoid complications due to aspiration, especially in patients who are recommended to receive radiotherapy. In these patients, induction chemotherapy prior to definitive CRT, chemotherapy alone prior to palliative RT, or placement of an airway[28] or partially/fully covered esophageal stent should be considered to allow time for healing and palliate aspiration and dysphagia. A randomized study by Yamasaki et al. included patients with newly diagnosed T4b esophageal cancer treated with either CRT or triplet chemotherapy alone as initial therapy for conversion surgery. The 2-year OS was slightly higher in the CRT group compared to chemotherapy group (55.1% vs. 34.7%; P = -.11), and local and regional node recurrence rates were inferior for patients undergoing R0 resection treated with induction chemotherapy compared to CRT (local: 30% v. 8%, respectively, P = 0.03; regional: 37% vs. 8%, respectively, P = 0.002).[117]

Esophageal stenting is a reasonable choice to occlude the fistula, especially in those patients with esophageal stenosis without airway stenosis.[118] Combined airway and esophageal stents may also be used.[16,119] Khan et al.[120] reported outcomes from a prospective cohort of patients with EC who were treated with dual airway and esophageal stenting palliation in obstructive or fistulous lesions near the carina. There was significant improvement in both dyspnea and dysphagia after dual stenting (P<0.001). Mucus plugging, lower respiratory infection, and granulation tissue were the main complications.

Subtopic 2/ Patients Presenting with TE Fistula During Treatment with Radiation Therapy (+/- Chemotherapy)
Tracheal stenting or combined tracheal and esophageal stenting is the preferred approach in these patients and results in improvement in symptoms in most patients, allowing for completion of treatment.[16] Consideration of aggressive supportive care including alternate methods of nutritional support (e.g. placement of feeding tube) is warranted in these patients.

Subtopic 3/ Patients Presenting with TE Fistula Following Definitive CRT (+/- Surgery)
TE fistula should be suspected in patients presenting with recurrent pneumonia and/or signs of aspiration in patients who undergo potentially curative therapy for EC, regardless of remission status. For patients with no evidence of active cancer, surgical repair may be considered in select subset of patients who are healthy enough to tolerate the surgery and have small fistulas amenable to repair. In patients who received prior radiation in whom surgery is not an option, stenting may be considered with caution[16,121] as prior radiation therapy increases the rate of stent-related complications.[74] Pao et al.[122] reported esophageal perforation in 15.5% of patients who received prior definitive CRT. In this retrospective series of 129 patients, the median interval from CRT to fistula was 4.4 months (3.3-10.1), and development of fistula was associated with inferior median OS (10.0 vs. 17.2 months, P = 0.0096). T4 tumors (HR, 3.776; 95% CI, 1.383-10.308; P = 0.010) and presence of stenosis (HR, 2.601; 95% CI, 1.053-6.428; P = 0.038) at baseline were independent risk factors for inferior OS. There was a trend toward better survival for patients who underwent repair or stenting for the fistula than those only undergoing conservative treatments (median OS, 5.9 vs. 0.9 months, P = 0.058).

In summary, the use of stents for treatment of TE fistula can result in improvement of symptoms and performance status in most patients but warrant carefully consideration and close observation in patients treated with prior radiation therapy (+/- surgery or chemotherapy) as the risk of complications is high in this setting.

Conclusion:
In patients with EC, the use of stents for palliation of dysphagia or TE fistula should be carefully considered. Multidisciplinary discussions should guide the use of stents and consider clinical scenario and incorporation of treatment recommendations since the use of stents can negatively impact oncologic outcomes in some patients, and prior cancer therapies can increase the risk of stent-related complications.

Summary of Recommendations

1. The panel recommends strongly that the use of esophageal stent is usually not appropriate for the typical case of T1-2N0M0 EC associated with symptomatic dysphagia when upfront esophagectomy is planned. Stent placement may compromise surgical outcomes in these patients. Consider feeding tube placement prior to surgery if nutritional status is inadequate. [Variant 1].
2. The panel recommends that the use of esophageal stent is usually not appropriate for the typical case of locally-advanced, non-metastatic EC associated with symptomatic dysphagia when neoadjuvant/perioperative therapy and esophagectomy are planned. Stent placement has been associated with increased complications, inability to complete prescribed treatment, and compromised oncologic outcomes in these patients. Consider feeding tube placement prior to treatment if nutritional status is inadequate. [Variant 2].
3. The panel recommends strongly that the use of esophageal stent is usually not appropriate for the typical case of inoperable locally-advanced, non-metastatic EC associated with symptomatic dysphagia when curative-intent chemoradiation is planned. Stent placement has been associated with increased complications, inability to complete prescribed treatment, and compromised oncologic outcomes in these patients. Consider feeding tube placement prior to treatment if nutritional status is inadequate. [Variant 3].
4. The panel recommends that the use of esophageal stent may be appropriate for the typical case of metastatic esophageal cancer associated with symptomatic dysphagia. Stents may be appropriate in patients with a short life-expectancy with limited treatment options who would benefit from immediate palliation. Alternative methods of palliation should be considered in those patients with reasonable life expectancy in whom treatment is planned, due to associated risk of stent-related complications, especially in those receiving radiation. [Variant 4].
5. The panel recommends strongly that the use of esophageal stent is usually not appropriate for the typical case of symptomatic benign stricture following curative-intent therapy for EC. Stent placement in this setting is associated with a high risk of complications (sometimes fatal), especially in those who have received prior radiation, and should be reserved for patients who fail other therapies. Esophageal dilation is usually appropriate, and feeding tube placement may be appropriate for these patients with more severe dysphagia. [Variant 5].
6. The panel recommends that the use of esophageal stent is usually not appropriate for the typical case of local recurrence at the primary tumor site following curative-intent chemoradiation for EC associated with symptomatic dysphagia. Stent placement in the setting of prior radiation should be considered with caution due to increased risk of complications. Consider feeding tube placement prior to treatment if nutritional status is inadequate. Systemic therapy alone may be reasonable setting of prior CRT in patients as it has been shown to improve dysphagia. [Variant 6].
7. The panel recommends strongly that the use of esophageal stent is usually appropriate for the typical case of locally-advanced EC presenting with evidence of tracheoesophageal fistula. Placement of esophageal/airway stent in these patients may improve symptoms and allow for healing and nutrition. [Variant 7].

Variant Cases and Treatment Algorithm

Variant cases were developed as examples for these guidelines to illustrate practical applications of consensus recommendations. A treatment algorithm is also provided to assist in selection of patients with malignant obstruction from EC suitable for consideration of esophageal stent.

Summary of Evidence

This section summarizes the references on the evidence table.

Of the 122 references cited in the American Radium Society® Appropriate Use Criteria for Use of Esophageal Stents in Patients with Esophageal Cancer, 81 were identified through the search strategy, with 23 additional studies included through backward citation searching, identified by examining the reference lists of articles directly found through the search strategy. No studies were identified by forward citation searching and were included. 18 additional studies referenced outside the "Summary of Literature Review" are included to provide context, but unless they are also cited within the "Summary of Literature Review," they were not used by the committee to guide recommendations. In sum, the authors added 40 citations from bibliographies, websites, or books not found in the literature search.

Of the 104 references used as evidence, 104 are categorized as therapeutic references, including 17 well-designed studies (Phase II randomized and Phase III), 35 moderately well-designed studies that account for most common biases (matched cohort and Phase II studies), 50 studies with design limitations (retrospective reviews), and 2 meta-analysis studies.

Supporting Documents

For additional information on the ARS Appropriate Use Criteria methodology and other supporting documents go to http://www.americanradiumsociety.org/page/aucmethodology.

The American Radium Society™ Appropriate Use Criteria and its expert panels have developed criteria for determining appropriate procedures for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide treating and referring physicians in making decisions regarding diagnosis and treatment of cancers and related or associated conditions. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate diagnostic procedures or treatments. Only those examinations or treatments generally used for evaluation of the patient's condition are ranked. Other procedures necessary to evaluate or treat other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate procedures or treatments. Procedures, techniques, or other interventions classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment, applications, and treatment protocols should be encouraged. The ultimate decision regarding the appropriate use of any specific examination or treatment must be made by the referring physician and oncologist in light of all the circumstances presented in an individual examination.

REFERENCES:

1. https://www.cancer.org/cancer/types/esophagus-cancer/about/key-statistics.html#:~:text=The%20American%20Cancer%20Society's%20estimates,men%20and%203%2C250%20in%20women).
2. Johnson E, Enden T, Noreng HJ, et al. Survival and complications after insertion of self-expandable metal stents for malignant oesophageal stenosis. *Scand J Gastroenterol*. Mar 2006;41(3):252-6. doi:10.1080/00365520500206350
3. Homann N, Noftz MR, Klingenberg-Noftz RD, Ludwig D. Delayed complications after placement of self-expanding stents in malignant esophageal obstruction: treatment strategies and survival rate. *Dig Dis Sci*. Feb 2008;53(2):334-40. doi:10.1007/s10620-007-9862-9
4. Lowe AS, Sheridan MB. Esophageal stenting. *Semin Intervent Radiol*. Sep 2004;21(3):157-66. doi:10.1055/s-2004-860874
5. Wang MQ, Sze DY, Wang ZP, Wang ZQ, Gao YA, Dake MD. Delayed complications after esophageal stent placement for treatment of malignant esophageal obstructions and esophagorespiratory fistulas. *J Vasc Interv Radiol*. Apr 2001;12(4):465-74. doi:10.1016/s1051-0443(07)61886-7
6. Francis SR, Orton A, Thorpe C, Stoddard G, Lloyd S, Anker CJ. Toxicity and Outcomes in Patients With and Without Esophageal Stents in Locally Advanced Esophageal Cancer. *Int J Radiat Oncol Biol Phys*. Nov 15 2017;99(4):884-894. doi:10.1016/j.ijrobp.2017.06.2457
7. Ahmed O, Bolger JC, O'Neill B, Robb WB. Use of esophageal stents to relieve dysphagia during neoadjuvant therapy prior to esophageal resection: a systematic review. *Dis Esophagus*. Jan 16 2020;33(1)doi:10.1093/dote/doz090
8. Abu Dayyeh BK, Vandamme JJ, Miller RC, Baron TH. Esophageal self-expandable stent material and mesh grid density are the major determining factors of external beam radiation dose perturbation: results from a phantom model. *Endoscopy*. 2013;45(1):42-7. doi:10.1055/s-0032-1325960
9. Chen YK, Schefter TE, Newman F. Esophageal cancer patients undergoing external beam radiation after placement of self-expandable metal stents: is there a risk of radiation dose enhancement? *Gastrointest Endosc*. Jun 2011;73(6):1109-14. doi:10.1016/j.gie.2011.02.001
10. Francis SR, Anker CJ, Wang B, et al. Self-expanding stent effects on radiation dosimetry in esophageal cancer. *J Appl Clin Med Phys*. Jul 8 2013;14(4):4218. doi:10.1120/jacmp.v14i4.4218
11. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. Mar 29 2021;372:n160. doi:10.1136/bmj.n160
12. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. Mar 29 2021;372:n71. doi:10.1136/bmj.n71
13. Fitch K, Bernsein S, Aguilar M, et al. The RAND/UCLA Appropriateness Method User's Manual. Santa Monica: Rand Corporation. 2001
14. Spaander MCW, van der Bogt RD, Baron TH, et al. Esophageal stenting for benign and malignant disease: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2021. *Endoscopy*. 2021/04/30 2021;53(07):751-762. doi:10.1055/a-1475-0063
15. Martinez JC, Puc MM, Quiros RM. Esophageal stenting in the setting of malignancy. *ISRN Gastroenterol*. 2011;2011:719575. doi:10.5402/2011/719575
16. Hurtgen M, Herber SCA. Treatment of malignant tracheoesophageal fistula. *Thorac Surg Clin*. Feb 2014;24(1):117-127. doi:10.1016/j.thorsurg.2013.09.006
17. Kozarek RA, Raltz S, Brugge WR, et al. Prospective multicenter trial of esophageal Z-stent placement for malignant dysphagia and tracheoesophageal fistula. *Gastrointest Endosc*. Nov 1996;44(5):562-7. doi:10.1016/s0016-5107(96)70009-3
18. Wang H, Zhang N, Li D, et al. Airway Covered Metallic Stent Based on Different Fistula Location and Size in Malignant Tracheoesophageal Fistula. *The American Journal of the Medical Sciences*. 2015/11/01/ 2015;350(5):364-368. doi:https://doi.org/10.1097/MAJ.0000000000000565
19. Blazeby JM, Williams MH, Brookes ST, Alderson D, Farndon JR. Quality of life measurement in patients with oesophageal cancer. *Gut*. Oct 1995;37(4):505-8. doi:10.1136/gut.37.4.505

20. Katsanos K, Sabharwal T, Adam A. Stenting of the upper gastrointestinal tract: current status. *Cardiovasc Intervent Radiol*. Aug 2010;33(4):690-705. doi:10.1007/s00270-010-9862-6
21. Baerlocher L, Kretschmar O, Harpes P, Arbenz U, Berger F, Knirsch W. Stent implantation and balloon angioplasty for treatment of branch pulmonary artery stenosis in children. *Clin Res Cardiol*. May 2008;97(5):310-7. doi:10.1007/s00392-007-0631-8
22. Law R, Prabhu A, Fujii-Lau L, Shannon C, Singh S. Stent migration following endoscopic suture fixation of esophageal self-expandable metal stents: a systematic review and meta-analysis. *Surg Endosc*. Feb 2018;32(2):675-681. doi:10.1007/s00464-017-5720-9
23. Sharma P, Kozarek R, Practice Parameters Committee of American College of G. Role of esophageal stents in benign and malignant diseases. *Am J Gastroenterol*. Feb 2010;105(2):258-73; quiz 274. doi:10.1038/ajg.2009.684
24. Eickhoff A, Knoll M, Jakobs R, et al. Self-expanding metal stents versus plastic prostheses in the palliation of malignant dysphagia: long-term outcome of 153 consecutive patients. *J Clin Gastroenterol*. Nov-Dec 2005;39(10):877-85. doi:10.1097/01.mcg.0000180631.61819.4a
25. Sunde B, Ericson J, Kumagai K, et al. Relief of dysphagia during neoadjuvant treatment for cancer of the esophagus or gastroesophageal junction. *Dis Esophagus*. Jul 2016;29(5):442-7. doi:10.1111/dote.12352
26. Jeene PM, Vermeulen BD, Rozema T, et al. Short-Course External Beam Radiotherapy Versus Brachytherapy for Palliation of Dysphagia in Esophageal Cancer: A Matched Comparison of Two Prospective Trials. *J Thorac Oncol*. Aug 2020;15(8):1361-1368. doi:10.1016/j.jtho.2020.04.032
27. Hanada Y, Leggett CL, Iyer PG, Linn B, Mangels-Dick T, Wang KK. Spray cryotherapy prevents need for palliative stenting in patients with esophageal cancer-associated dysphagia. *Dis Esophagus*. Jan 7 2022;35(1)doi:10.1093/dote/doab051
28. Chung FT, Lin HC, Chou CL, et al. Airway ultraflex stenting in esophageal cancer with esophagorespiratory fistula. *Am J Med Sci*. Aug 2012;344(2):105-9. doi:10.1097/MAJ.0b013e3182367b6a
29. Zhang Y, Zhou M, Bai L, Han R, Lv K, Wang Z. Radiofrequency ablation combined with esophageal stent in the treatment of malignant esophageal stenosis: A single-center prospective study. *Oncol Lett*. Sep 2018;16(3):3157-3161. doi:10.3892/ol.2018.9046
30. Heindorff H, Wojdemann M, Bisgaard T, Svendsen LB. Endoscopic palliation of inoperable cancer of the oesophagus or cardia by argon electrocoagulation. *Scand J Gastroenterol*. Jan 1998;33(1):21-3. doi:10.1080/00365529850166158
31. Lightdale CJ, Zimbalist E, Winawer SJ. Outpatient management of esophageal cancer with endoscopic Nd:YAG laser. *Am J Gastroenterol*. Jan 1987;82(1):46-50.
32. Chen M, Pennathur A, Luketich JD. Role of photodynamic therapy in unresectable esophageal and lung cancer. *Lasers Surg Med*. Jun 2006;38(5):396-402. doi:10.1002/lsm.20364
33. Yoon HY, Cheon YK, Choi HJ, Shim CS. Role of photodynamic therapy in the palliation of obstructing esophageal cancer. *Korean J Intern Med*. Sep 2012;27(3):278-84. doi:10.3904/kjim.2012.27.3.278
34. Ramakrishnaiah VP, Ramkumar J, Pai D. Intratumoural injection of absolute alcohol in carcinoma of gastroesophageal junction for palliation of dysphagia. *Ecancermedicalscience*. 2014;8:395. doi:10.3332/ecancer.2014.395
35. Mariette C, De Botton ML, Piessen G. Surgery in esophageal and gastric cancer patients: what is the role for nutrition support in your daily practice? *Ann Surg Oncol*. Jul 2012;19(7):2128-34. doi:10.1245/s10434-012-2225-6
36. Adler DG, Fang J, Wong R, Wills J, Hilden K. Placement of Polyflex stents in patients with locally advanced esophageal cancer is safe and improves dysphagia during neoadjuvant therapy. *Gastrointest Endosc*. Oct 2009;70(4):614-9. doi:10.1016/j.gie.2009.01.026
37. Martin R, Duvall R, Ellis S, Scoggins CR. The use of self-expanding silicone stents in esophageal cancer care: optimal pre-, peri-, and postoperative care. *Surg Endosc*. Mar 2009;23(3):615-21. doi:10.1007/s00464-008-9851-x
38. Siddiqui AA, Loren D, Dudnick R, Kowalski T. Expandable polyester silicon-covered stent for malignant esophageal strictures before neoadjuvant chemoradiation: a pilot study. *Dig Dis Sci*. Mar 2007;52(3):823-9. doi:10.1007/s10620-006-9513-6
39. Pellen MG, Sabri S, Razack A, Gilani SQ, Jain PK. Safety and efficacy of self-expanding removable metal esophageal stents during neoadjuvant chemotherapy for resectable esophageal cancer. *Dis Esophagus*. Jan 2012;25(1):48-53. doi:10.1111/j.1442-2050.2011.01206.x

40. Nagaraja V, Cox MR, Eslick GD. Safety and efficacy of esophageal stents preceding or during neoadjuvant chemotherapy for esophageal cancer: a systematic review and meta-analysis. *J Gastrointest Oncol*. Apr 2014;5(2):119-26. doi:10.3978/j.issn.2078-6891.2014.007
41. van den Berg MW, Walter D, de Vries EM, et al. Biodegradable stent placement before neoadjuvant chemoradiotherapy as a bridge to surgery in patients with locally advanced esophageal cancer. *Gastrointest Endosc*. Nov 2014;80(5):908-13. doi:10.1016/j.gie.2014.06.004
42. Siddiqui AA, Glynn C, Loren D, Kowalski T. Self-expanding plastic esophageal stents versus jejunostomy tubes for the maintenance of nutrition during neoadjuvant chemoradiation therapy in patients with esophageal cancer: a retrospective study. *Dis Esophagus*. 2009;22(3):216-22. doi:10.1111/j.1442-2050.2008.00905.x
43. Bower M, Jones W, Vessels B, Scoggins C, Martin R. Nutritional support with endoluminal stenting during neoadjuvant therapy for esophageal malignancy. *Ann Surg Oncol*. Nov 2009;16(11):3161-8. doi:10.1245/s10434-009-0630-2
44. Yu FJ, Shih HY, Wu CY, et al. Enteral nutrition and quality of life in patients undergoing chemoradiotherapy for esophageal carcinoma: a comparison of nasogastric tube, esophageal stent, and ostomy tube feeding. *Gastrointest Endosc*. Jul 2018;88(1):21-31 e4. doi:10.1016/j.gie.2017.11.030
45. Starr B, Davis S, Ayala-Peacock D, Blackstock WA, Levine EA. Reassessment of the role of enteral tube feedings for patients with esophageal cancer. *Am Surg*. Aug 2014;80(8):752-8.
46. Mariette C, Gronnier C, Duhamel A, et al. Self-expanding covered metallic stent as a bridge to surgery in esophageal cancer: impact on oncologic outcomes. *J Am Coll Surg*. Mar 2015;220(3):287-96. doi:10.1016/j.jamcollsurg.2014.11.028
47. Martin RC, 2nd, Cannon RM, Brown RE, et al. Evaluation of quality of life following placement of self-expanding plastic stents as a bridge to surgery in patients receiving neoadjuvant therapy for esophageal cancer. *Oncologist*. Mar 2014;19(3):259-65. doi:10.1634/theoncologist.2013-0344
48. Siddiqui AA, Sarkar A, Beltz S, et al. Placement of fully covered self-expandable metal stents in patients with locally advanced esophageal cancer before neoadjuvant therapy. *Gastrointest Endosc*. Jul 2012;76(1):44-51. doi:10.1016/j.gie.2012.02.036
49. Langer FB, Schoppmann SF, Prager G, et al. Temporary placement of self-expanding oesophageal stents as bridging for neo-adjuvant therapy. *Ann Surg Oncol*. Feb 2010;17(2):470-5. doi:10.1245/s10434-009-0760-6
50. Lee HK, Vaporciyan AA, Cox JD, et al. Postoperative pulmonary complications after preoperative chemoradiation for esophageal carcinoma: correlation with pulmonary dose-volume histogram parameters. *Int J Radiat Oncol Biol Phys*. Dec 1 2003;57(5):1317-22. doi:10.1016/s0360-3016(03)01373-7
51. Wang SL, Liao Z, Vaporciyan AA, et al. Investigation of clinical and dosimetric factors associated with postoperative pulmonary complications in esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. *Int J Radiat Oncol Biol Phys*. Mar 1 2006;64(3):692-9. doi:10.1016/j.ijrobp.2005.08.002
52. Brown RE, Abbas AE, Ellis S, et al. A prospective phase II evaluation of esophageal stenting for neoadjuvant therapy for esophageal cancer: optimal performance and surgical safety. *J Am Coll Surg*. Apr 2011;212(4):582-8; discussion 588-9. doi:10.1016/j.jamcollsurg.2010.12.026
53. Kjaer DW, Nassar M, Jensen LS, Svendsen LB, Mortensen FV. A bridging stent to surgery in patients with esophageal and gastroesophageal junction cancer has a dramatic negative impact on patient survival: A retrospective cohort study through data acquired from a prospectively maintained national database. *Dis Esophagus*. Feb 1 2017;30(3):1-7. doi:10.1111/dote.12474
54. Holmen A, Jebril W, Ida S, et al. Effects of neoadjuvant therapy on health-related quality of life for patients with gastroesophageal cancer. *Eur J Surg Oncol*. Nov 2023;49(11):107008. doi:10.1016/j.ejso.2023.107008
55. Sunde B, Johnsen G, Jacobsen AB, et al. Effects of neoadjuvant chemoradiotherapy vs chemotherapy alone on the relief of dysphagia in esophageal cancer patients: secondary endpoint analysis in a randomized trial. *Dis Esophagus*. Feb 1 2019;32(2)doi:10.1093/dote/doy069
56. Ma X, Zhao W, Li B, et al. Neoadjuvant Immune Checkpoint Inhibitors Plus Chemotherapy in Locally Advanced Esophageal Squamous Cell Carcinoma: Perioperative and Survival Outcomes. *Front Oncol*. 2022;12:810898. doi:10.3389/fonc.2022.810898

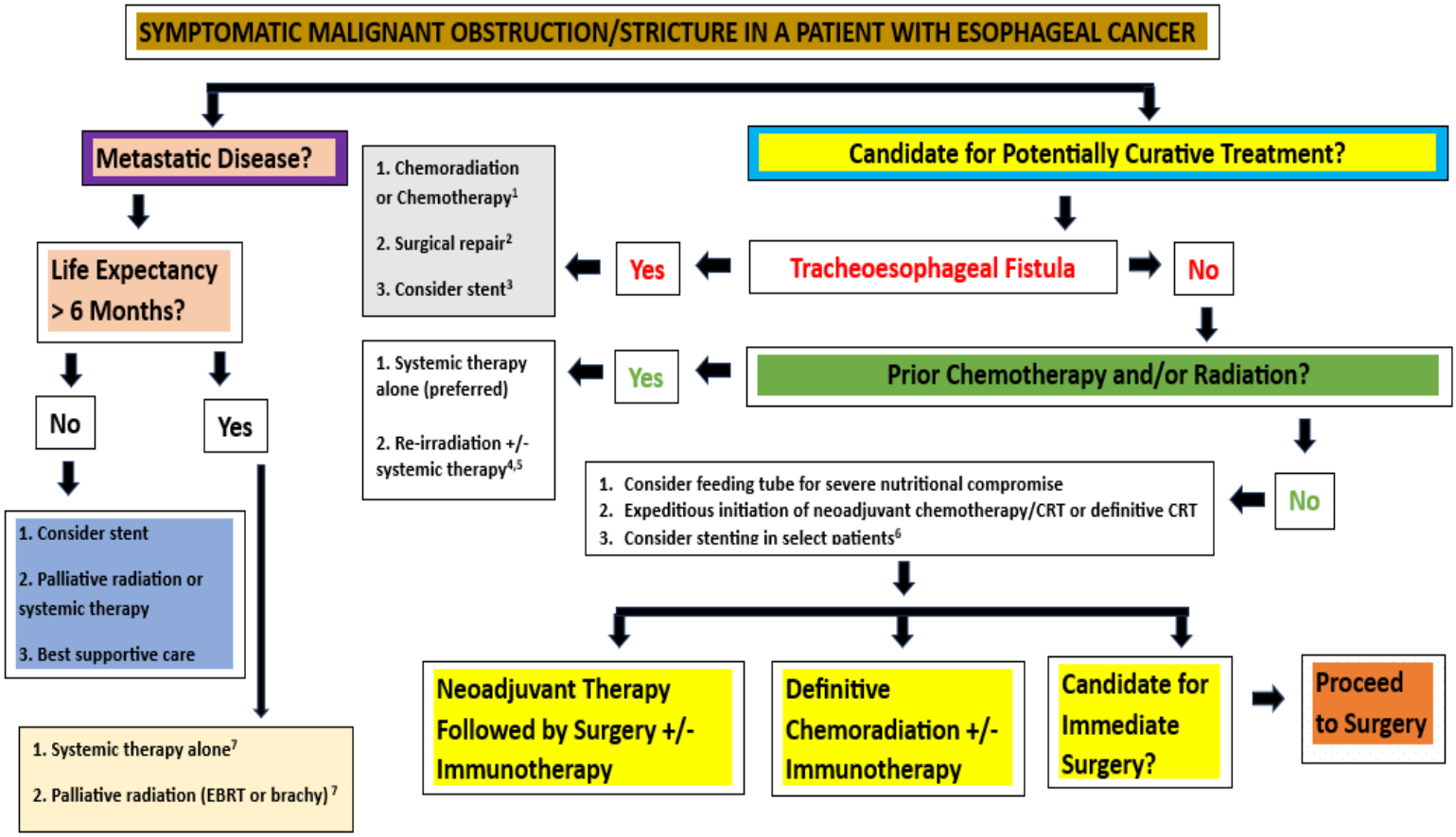
57. Vermeulen BD, Bruggeman L, Bac DJ, et al. Impact of multidisciplinary tumor board discussion on palliation of patients with esophageal or gastro-esophageal junction cancer: a population-based study. *Acta Oncol*. Apr 2020;59(4):410-416. doi:10.1080/0284186X.2020.1725240
58. Burstow M, Kelly T, Panchani S, et al. Outcome of palliative esophageal stenting for malignant dysphagia: a retrospective analysis. *Dis Esophagus*. 2009;22(6):519-25. doi:10.1111/j.1442-2050.2009.00948.x
59. Lu YF, Chung CS, Liu CY, et al. Esophageal Metal Stents with Concurrent Chemoradiation Therapy for Locally Advanced Esophageal Cancer: Safe or Not? *Oncologist*. Dec 2018;23(12):1426-1435. doi:10.1634/theoncologist.2017-0646
60. Burmeister BH, Walpole ET, Burmeister EA, et al. Feasibility of chemoradiation therapy with protracted infusion of 5-fluorouracil for esophageal cancer patients not suitable for cisplatin. *Int J Clin Oncol*. Aug 2005;10(4):256-61. doi:10.1007/s10147-005-0506-9
61. Valkema MJ, Spaander MCW, Boonstra JJ, et al. Active surveillance of oesophageal cancer after response to neoadjuvant chemoradiotherapy: dysphagia is uncommon. *Br J Surg*. Sep 6 2023;110(10):1381-1386. doi:10.1093/bjs/znad211
62. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA*. May 5 1999;281(17):1623-7. doi:10.1001/jama.281.17.1623
63. Shenfine J, McNamee P, Steen N, Bond J, Griffin SM. A randomized controlled clinical trial of palliative therapies for patients with inoperable esophageal cancer. *Am J Gastroenterol*. Jul 2009;104(7):1674-85. doi:10.1038/ajg.2009.155
64. Egeland C, Bazancir LA, Bui NH, et al. Palliation of dysphagia in patients with non-curable esophageal cancer - a retrospective Danish study from a highly specialized center. *Support Care Cancer*. Nov 2022;30(11):9029-9038. doi:10.1007/s00520-022-07316-8
65. Shridhar R, Almhanna K, Meredith KL, et al. Radiation therapy and esophageal cancer. *Cancer Control*. Apr 2013;20(2):97-110. doi:10.1177/107327481302000203
66. Murray LJ, Din OS, Kumar VS, Dixon LM, Wadsley JC. Palliative radiotherapy in patients with esophageal carcinoma: A retrospective review. *Pract Radiat Oncol*. Oct-Dec 2012;2(4):257-264. doi:10.1016/j.prro.2011.12.002
67. Walterbos NR, Fiocco M, Neelis KJ, et al. Effectiveness of several external beam radiotherapy schedules for palliation of esophageal cancer. *Clin Transl Radiat Oncol*. Jul 2019;17:24-31. doi:10.1016/j.ctro.2019.04.017
68. Olafsdottir HS, Klevebro F, Ndegwa N, Alexandersson von Dobeln G. Short-course compared to long-course palliative radiotherapy for oesophageal cancer: a single centre observational cohort study. *Radiat Oncol*. Aug 16 2021;16(1):153. doi:10.1186/s13014-021-01880-9
69. Sridharan S, Day F, Loh J, et al. Phase I trial of hypofractionated chemoradiotherapy in the palliative management of esophageal and gastro-esophageal cancer. *Radiat Oncol*. Sep 14 2022;17(1):158. doi:10.1186/s13014-022-02127-x
70. Borg D, Sundberg J, Brun E, et al. Palliative short-course hypofractionated radiotherapy followed by chemotherapy in esophageal adenocarcinoma: the phase II PALAESTRA trial. *Acta Oncol*. Feb 2020;59(2):212-218. doi:10.1080/0284186X.2019.1670861
71. Martin EJ, Bruggeman AR, Nalawade VV, et al. Palliative Radiotherapy Versus Esophageal Stent Placement in the Management of Patients With Metastatic Esophageal Cancer. *J Natl Compr Canc Netw*. May 2020;18(5):569-574. doi:10.6004/jnccn.2019.7524
72. Eldeeb H, El-Hadaad HA. Radiotherapy versus stenting in treating malignant dysphagia. *J Gastrointest Oncol*. Dec 2012;3(4):322-5. doi:10.3978/j.issn.2078-6891.2012.011
73. Javed A, Pal S, Dash NR, et al. Palliative stenting with or without radiotherapy for inoperable esophageal carcinoma: a randomized trial. *J Gastrointest Cancer*. Mar 2012;43(1):63-9. doi:10.1007/s12029-010-9206-4
74. Qiu G, Tao Y, Du X, et al. The impact of prior radiotherapy on fatal complications after self-expandable metallic stents (SEMS) for malignant dysphagia due to esophageal carcinoma. *Dis Esophagus*. Feb-Mar 2013;26(2):175-81. doi:10.1111/j.1442-2050.2012.01348.x
75. Rueth NM, Shaw D, D'Cunha J, Cho C, Maddaus MA, Andrade RS. Esophageal stenting and radiotherapy: a multimodal approach for the palliation of symptomatic malignant dysphagia. *Ann Surg Oncol*. Dec 2012;19(13):4223-8. doi:10.1245/s10434-012-2459-3

76. Adamson D, Byrne A, Porter C, et al. Palliative radiotherapy after oesophageal cancer stenting (ROCS): a multicentre, open-label, phase 3 randomised controlled trial. *Lancet Gastroenterol Hepatol*. Apr 2021;6(4):292-303. doi:10.1016/S2468-1253(21)00004-2
77. Machado AA, Martins BC, Josino IR, et al. Impact of radiotherapy on adverse events of self-expanding metallic stents in patients with esophageal cancer. *Dis Esophagus*. Sep 30 2023;36(10)doi:10.1093/dote/doad019
78. Penniment MG, De Ieso PB, Harvey JA, et al. Palliative chemoradiotherapy versus radiotherapy alone for dysphagia in advanced oesophageal cancer: a multicentre randomised controlled trial (TROG 03.01). *Lancet Gastroenterol Hepatol*. Feb 2018;3(2):114-124. doi:10.1016/S2468-1253(17)30363-1
79. Akl FM, Elsayed-Abd-Alkhalek S, Salah T. Palliative concurrent chemoradiotherapy in locally advanced and metastatic esophageal cancer patients with dysphagia. *Ann Palliat Med*. Jul 2013;2(3):118-23. doi:10.3978/j.issn.2224-5820.2013.05.01
80. Ikeda E, Kojima T, Kaneko K, et al. Efficacy of concurrent chemoradiotherapy as a palliative treatment in stage IVB esophageal cancer patients with dysphagia. *Jpn J Clin Oncol*. Aug 2011;41(8):964-72. doi:10.1093/jjco/hyr088
81. Sgourakis G, Gockel I, Karaliotas C, et al. Survival after chemotherapy and/or radiotherapy versus self-expanding metal stent insertion in the setting of inoperable esophageal cancer: a case-control study. *BMC Cancer*. Feb 15 2012;12:70. doi:10.1186/1471-2407-12-70
82. Sur RK, Donde B, Levin VC, Mannell A. Fractionated high dose rate intraluminal brachytherapy in palliation of advanced esophageal cancer. *Int J Radiat Oncol Biol Phys*. Jan 15 1998;40(2):447-53. doi:10.1016/s0360-3016(97)00710-4
83. Sur RK, Levin CV, Donde B, Sharma V, Miszczyk L, Nag S. Prospective randomized trial of HDR brachytherapy as a sole modality in palliation of advanced esophageal carcinoma--an International Atomic Energy Agency study. *Int J Radiat Oncol Biol Phys*. May 1 2002;53(1):127-33. doi:10.1016/s0360-3016(02)02702-5
84. Homs MY, Steyerberg EW, Eijkenboom WM, et al. Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: multicentre randomised trial. *Lancet*. Oct 23-29 2004;364(9444):1497-504. doi:10.1016/S0140-6736(04)17272-3
85. Bergquist H, Wenger U, Johnsson E, et al. Stent insertion or endoluminal brachytherapy as palliation of patients with advanced cancer of the esophagus and gastroesophageal junction. Results of a randomized, controlled clinical trial. *Dis Esophagus*. 2005;18(3):131-9. doi:10.1111/j.1442-2050.2005.00467.x
86. Rosenblatt E, Jones G, Sur RK, et al. Adding external beam to intra-luminal brachytherapy improves palliation in obstructive squamous cell oesophageal cancer: a prospective multi-centre randomized trial of the International Atomic Energy Agency. *Radiother Oncol*. Dec 2010;97(3):488-94. doi:10.1016/j.radonc.2010.09.001
87. Fuccio L, Mandolesi D, Farioli A, et al. Brachytherapy for the palliation of dysphagia owing to esophageal cancer: A systematic review and meta-analysis of prospective studies. *Radiother Oncol*. Mar 2017;122(3):332-339. doi:10.1016/j.radonc.2016.12.034
88. Eldeeb H, Reza S, Shmueli U, Logsdail G, Hinks P, Mukherjee S. External beam radiotherapy versus brachytherapy in the management of malignant oesophageal dysphagia: a retrospective study. *J BUON*. Jul-Sep 2012;17(3):508-11.
89. Laskar SG, Lewis S, Agarwal JP, Mishra S, Mehta S, Patil P. Combined brachytherapy and external beam radiation: an effective approach for palliation in esophageal cancer. *J Contemp Brachytherapy*. Dec 2015;7(6):453-61. doi:10.5114/jcb.2015.56765
90. Prasad NR, Karthigeyan M, Vikram K, Parthasarathy R, Reddy KS. Palliative radiotherapy in esophageal cancer. *Indian J Surg*. Feb 2015;77(1):34-8. doi:10.1007/s12262-013-0817-4
91. Sur R, Donde B, Falkson C, et al. Randomized prospective study comparing high-dose-rate intraluminal brachytherapy (HDRILBT) alone with HDRILBT and external beam radiotherapy in the palliation of advanced esophageal cancer. *Brachytherapy*. 2004;3(4):191-5. doi:10.1016/j.brachy.2004.09.004
92. Welsch J, Kup PG, Nieder C, et al. Survival and Symptom Relief after Palliative Radiotherapy for Esophageal Cancer. *J Cancer*. 2016;7(2):125-30. doi:10.7150/jca.13655
93. Vermeulen BD, Jeene PM, Sijben J, et al. Low-Dose Versus High-Dose Radiation Therapy for the Palliation of Dysphagia From Esophageal Cancer: A Multicenter Retrospective Cohort Study. *Pract Radiat Oncol*. Jul-Aug 2020;10(4):e255-e263. doi:10.1016/j.prro.2019.10.010

94. Bergquist H, Johnsson E, Nyman J, et al. Combined stent insertion and single high-dose brachytherapy in patients with advanced esophageal cancer--results of a prospective safety study. *Dis Esophagus*. Jul 2012;25(5):410-5. doi:10.1111/j.1442-2050.2011.01248.x
95. Hirdes MM, van Hooft JE, Wijrdeman HK, et al. Combination of biodegradable stent placement and single-dose brachytherapy is associated with an unacceptably high complication rate in the treatment of dysphagia from esophageal cancer. *Gastrointest Endosc*. Aug 2012;76(2):267-74. doi:10.1016/j.gie.2012.04.442
96. Hanna WC, Sudarshan M, Roberge D, et al. What is the optimal management of dysphagia in metastatic esophageal cancer? *Curr Oncol*. Apr 2012;19(2):e60-6. doi:10.3747/co.19.892
97. Ueda H, Kawakami H, Nonagase Y, et al. Phase II Trial of 5-Fluorouracil, Docetaxel, and Nedaplatin (UDON) Combination Therapy for Recurrent or Metastatic Esophageal Cancer. *Oncologist*. Feb 2019;24(2):163-e76. doi:10.1634/theoncologist.2018-0653
98. Touchefeu Y, Archambeaud I, Landi B, et al. Chemotherapy versus self-expanding metal stent as primary treatment of severe dysphagia from unresectable oesophageal or gastro-oesophageal junction cancer. *Dig Liver Dis*. Mar 2014;46(3):283-6. doi:10.1016/j.dld.2013.10.012
99. Nakayama Y, Ando T, Takagi H, et al. Efficacy and Safety of Immune Checkpoint Inhibitor Combination Therapy for Dysphagia in Patients with Advanced Esophageal Cancer. *J Clin Med*. Aug 15 2024;13(16)doi:10.3390/jcm13164806
100. Wu X, Li Y, Zhang K, et al. Immunotherapy with or without radiotherapy for metastatic or recurrent esophageal squamous cell carcinoma: A real-world study. *Clin Transl Radiat Oncol*. Jan 2023;38:130-137. doi:10.1016/j.ctro.2022.10.011
101. Mansoor W, Joo S, Norquist JM, et al. Health-related quality-of-life analysis from KEYNOTE-590: pembrolizumab plus chemotherapy versus chemotherapy for advanced esophageal cancer. *Oncologist*. Oct 3 2024;29(10):e1324-e1335. doi:10.1093/oncolo/oyae087
102. Noronha V, Patil VM, Menon N, et al. Phase III randomized trial comparing palliative systemic therapy to best supportive care in advanced esophageal/GEJ cancer. *Int J Cancer*. Dec 15 2024;155(12):2232-2245. doi:10.1002/ijc.35111
103. Shah T, Kushnir V, Mutha P, et al. Neoadjuvant cryotherapy improves dysphagia and may impact remission rates in advanced esophageal cancer. *Endosc Int Open*. Nov 2019;7(11):E1522-E1527. doi:10.1055/a-0957-2798
104. Eickhoff A, Jakobs R, Schilling D, et al. Prospective nonrandomized comparison of two modes of argon beamer (APC) tumor desobstruction: effectiveness of the new pulsed APC versus forced APC. *Endoscopy*. Jul 2007;39(7):637-42. doi:10.1055/s-2007-966571
105. Rupinski M, Zagorowicz E, Regula J, et al. Randomized comparison of three palliative regimens including brachytherapy, photodynamic therapy, and APC in patients with malignant dysphagia (CONSORT 1a) (Revised II). *Am J Gastroenterol*. Sep 2011;106(9):1612-20. doi:10.1038/ajg.2011.178
106. Hamer PW, Hight SC, Ward IG, Harris DL, Woodham BL, Flint RS. Stricture rate after chemoradiotherapy and radiotherapy for oesophageal squamous cell carcinoma: a 20-year experience. *ANZ J Surg*. Apr 2019;89(4):367-371. doi:10.1111/ans.14981
107. Agarwalla A, Small AJ, Mendelson AH, Scott FI, Kochman ML. Risk of recurrent or refractory strictures and outcome of endoscopic dilation for radiation-induced esophageal strictures. *Surg Endosc*. Jul 2015;29(7):1903-12. doi:10.1007/s00464-014-3883-1
108. Yoda Y, Yano T, Kaneko K, et al. Endoscopic balloon dilatation for benign fibrotic strictures after curative nonsurgical treatment for esophageal cancer. *Surg Endosc*. Oct 2012;26(10):2877-83. doi:10.1007/s00464-012-2273-9
109. Hanaoka N, Ishihara R, Motoori M, et al. Endoscopic Balloon Dilation Followed By Intralesional Steroid Injection for Anastomotic Strictures After Esophagectomy: A Randomized Controlled Trial. *Am J Gastroenterol*. Oct 2018;113(10):1468-1474. doi:10.1038/s41395-018-0253-y
110. Halland M, Prichard DO, Kahn A, Lavey CJ, Katzka DA, Alexander JA. Esophageal Self-Dilation in Benign Refractory Esophageal Strictures: Outcomes from a Randomized Controlled Trial and a Prospective Observational Study. *Dig Dis Sci*. Aug 2024;69(8):2883-2889. doi:10.1007/s10620-024-08402-z

111. Iraha Y, Murayama S, Toita T, et al. Self-expandable metallic stent placement for patients with inoperable esophageal carcinoma: investigation of the influence of prior radiotherapy and chemotherapy. *Radiat Med*. May 2006;24(4):247-52. doi:10.1007/s11604-005-1539-8
112. Tong DK, Law S, Wong KH. The use of self-expanding metallic stents (SEMS) is effective in symptom palliation from recurrent tumor after esophagogastrectomy for cancer. *Dis Esophagus*. Nov 2010;23(8):660-5. doi:10.1111/j.1442-2050.2010.01077.x
113. Xu X, Wang Z, Jiang S, Shang Y, Wu Y. Evaluating the optimal re-irradiation dose for locally recurrent esophageal squamous cell carcinoma after definitive radiotherapy. *Radiat Oncol*. Nov 4 2019;14(1):191. doi:10.1186/s13014-019-1402-1
114. Xiang G, Xu C, Chai G, et al. Re-irradiation for local primary-recurrence esophageal squamous cell carcinoma treated with IMRT/VMAT. *Radiat Oncol*. Jul 10 2023;18(1):114. doi:10.1186/s13014-023-02265-w
115. Lenz CJ, Bick BL, Katzka D, et al. Esophagorespiratory Fistulas: Survival and Outcomes of Treatment. *J Clin Gastroenterol*. Feb 2018;52(2):131-136. doi:10.1097/MCG.0000000000000751
116. Xu W, Jiang H, Liu Y, Liu X, Jiang Y. Retrospective cohort study on treatment modalities and survival time after oesophageal fistula in patients with oesophageal cancer in a regional cancer care centre in China. *BMJ Open*. Apr 12 2023;13(4):e069703. doi:10.1136/bmjopen-2022-069703
117. Yamasaki M, Miyata H, Yamashita K, et al. Chemoradiotherapy versus triplet chemotherapy as initial therapy for T4b esophageal cancer: survival results from a multicenter randomized Phase 2 trial. *Br J Cancer*. Jul 2023;129(1):54-60. doi:10.1038/s41416-023-02286-y
118. Jiao D, Yao Y, Zhang Q, Wang L, Ren J, Han X. Effectiveness and safety of a newly designed partially covered tracheal metallic Y-shaped stent for the treatment of high cervical gastro-tracheal or tracheo-esophageal fistula: A retrospective observational study. *Medicine (Baltimore)*. Mar 19 2021;100(11):e25132. doi:10.1097/MD.0000000000025132
119. Herth FJ, Peter S, Baty F, Eberhardt R, Leuppi JD, Chhajed PN. Combined airway and oesophageal stenting in malignant airway-oesophageal fistulas: a prospective study. *Eur Respir J*. Dec 2010;36(6):1370-4. doi:10.1183/09031936.00049809
120. Khan A, Hashim Z, Neyaz Z, Agarwal A, Mohindra S, Nath A. Dual Airway and Esophageal Stenting in Advanced Esophageal Cancer With Lesions Near Carina. *J Bronchology Interv Pulmonol*. Oct 2020;27(4):286-293. doi:10.1097/LBR.0000000000000672
121. Leong CK, Foo AZX, Goh KJ, et al. Airway interventions for tracheobronchial involvement in esophageal carcinoma: a retrospective cohort outcome study and algorithmic approach. *J Thorac Dis*. Jul 2022;14(7):2565-2578. doi:10.21037/jtd-22-138
122. Pao TH, Chen YY, Chang WL, et al. Esophageal fistula after definitive concurrent chemotherapy and intensity modulated radiotherapy for esophageal squamous cell carcinoma. *PLoS One*. 2021;16(5):e0251811. doi:10.1371/journal.pone.0251811

TREATMENT ALGORITHM FOR THE USE OF STENTS IN PATIENTS WITH ESOPHAGEAL CANCER



[1]CRT or chemotherapy can be used as initial treatment for T4b cancers in patient who are able to tolerate, with CRT preferred as it results in better locoregional control

[2]Surgical repair may be considered in select subset of patients who are healthy enough to tolerate the surgery and have small fistulas amenable to repair

[3]Placement of an airway or partially/fully covered esophageal stent or dual airway and esophageal stents (more commonly used for patients with TE fistulas near the carina)

[4]Reirradiation is associated with a high complication rate and should be regarded with caution but may considered in well-selected patients or if other options are limited

[5]Stent placement in the setting of prior radiation therapy should be considered with caution due to increased risk of adverse events but may be useful for palliation of dysphagia in patients with limited life expectancy

[6]The use of stents in patients in the setting of a newly diagnosed EC patient who are treated with potentially curative therapy (neoadjuvant chemotherapy or CRT or definitive CRT) is associated with increased risk of complications, and may be associated with worse oncological outcomes and should be considered with caution

[7]Single modality palliation is recommended over combined therapy, with radiation therapy preferred in those with a reasonable life-expectancy (e.g. > 6 months) as it is associated with lower adverse events and more durable palliation of dysphagia compared to stent placement. Palliative brachytherapy can also be considered. If the patient is fit for systemic therapy, chemotherapy alone is also considered a reasonable option and can avoid the esophagitis typically associated with radiation therapy. The use of stenting is typically considered for patients with a shorter life expectancy who need immediate palliation

Variant 1: Symptomatic malignant obstruction in a patient with cT2N0M0 squamous cell carcinoma of the mid esophagus without evidence of tracheoesophageal fistula (Blazeby grade 1 dysphagia)

48 year-old male (former smoker; moderate daily alcohol) with a good performance status (ECOG = 1, with BMI = 24; serum albumin 3.0 g/dl) is diagnosed with a squamous cell carcinoma of the mid esophagus. He presented with progressive heartburn associated with a sense of food catching (Blazeby grade 1), resulting in an unintentional 10 lb weight loss (current weight 165 lbs) over the last 2 months. Upper endoscopy revealed a 3 cm mass from 25-28 cm from incisors starting at the level of the tracheal bifurcation and biopsy confirmed moderately differentiated squamous cell carcinoma. Flexible bronchoscopy demonstrated extrinsic compression of the trachea but no evidence of invasion or fistula. Esophagram demonstrated no evidence of aspiration. EUS demonstrated no invasion through the adventitia and no enlarged regional lymph nodes. Contrast-enhanced CT demonstrated a 3 cm circumferential mass in the mid esophagus and no enlarged lymph nodes. PET CT revealed uptake in the esophagus only and no evidence of distant disease. (cT2N0M0) He was evaluated by a multidisciplinary team and deemed fit for surgery.

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Treatment Options														
Nutrition consultation	A	0	0	0	0	1	0	4	7	4	8		S	↑
Placement of esophageal stent prior to surgery*	U	3	7	5	1	0	0	0	0	0	2		S	↑
Placement of feeding jejunostomy prior to surgery*	M	0	0	0	3	11	0	0	0	0	5		L	↑
Proceed directly to surgery*	A	0	0	0	0	1	0	7	7	1	8		S	↑

*Patient declines neoadjuvant chemotherapy or radiation

Variant Discussion:

Immediate esophagectomy can be considered (after appropriate staging and preoperative evaluation) in patients who have cT1-2N0 EC with symptomatic dysphagia and adequate nutritional status. Esophageal stents used in the setting of a newly diagnosed EC patient is associated with increased risk of complications and may be associated with worse oncological outcomes. If nutritional status is compromised enough to warrant concern for increased risk of surgical morbidity, nasogastric/nasojejunal or feeding jejunostomy are preferred over stenting and can be considered in a select group of patients.

<u>Variant 2</u>: Symptomatic malignant obstruction in a patient with cT3N1M0 adenocarcinoma of the gastroesophageal junction (Blazeby grade 2 dysphagia)

62 year-old male (former smoker; social alcohol; longstanding history of GERD) with a good performance status (ECOG = 1, with BMI = 25; serum albumin 3.4 g/dl) is diagnosed with a Siewert I adenocarcinoma of the esophagus. He presented with early satiety, progressive dysphagia to solids, and unintentional 12 lb weight loss (current weight 180 lbs) over the last 3 months. He is able to eat only pureed foods (Blazeby grade 2). Upper endoscopy revealed a near obstructing 4 cm mass from 36 to 40 cm from incisors and biopsy confirmed moderately differentiated adenocarcinoma. EUS demonstrated invasion of the adventitia and a solitary enlarged paraesophageal lymph node measuring 1.5 cm in diameter. Contrast-enhanced CT demonstrated a 4 cm circumferential mass in the distal esophagus with mild esophageal dilation proximal to the mass, and a minimally enlarged solitary paraesophageal lymph node. PET CT revealed uptake in the esophagus, regional node identified by EUS and CT, with no evidence of distant disease. (cT3N1M0) He was evaluated by a multidisciplinary team and deemed fit for definitive treatment with neoadjuvant therapy followed by surgery.

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Treatment Options														
Nutrition consultation	A	0	0	0	0	0	0	5	7	4	8		S	↑
Placement of esophageal stent prior to curative-intent therapy	U	0	4	10	0	0	0	0	0	0	3		S	↑
Placement of feeding jejunostomy prior to curative-intent therapy	M	0	0	0	3	9	2	0	0	0	5		M	↑
Proceed with neoadjuvant chemoradiation	A	0	0	0	0	0	1	10	5	0	7		S	↑
Proceed with induction chemotherapy followed by curative-intent therapy	A	0	0	0	0	1	1	8	6	0	7		M	↑
Proceed directly to surgery	U	4	6	6	0	0	0	0	0	0	2		EC	↑

<u>Variant Discussion:</u>

Although the use of esophageal stents can be considered to palliate dysphagia and is associated with improvements in dysphagia during neoadjuvant therapy, their effect on improving patient nutritional status is less clear. Esophageal stents used in the setting of a newly diagnosed EC patient is associated with increased risk of complications and may be associated with worse oncological outcomes. Complete staging and multidisciplinary discussion should direct therapy for these patients and supportive measures including the use of stents. Stents should only be used with caution in patients who are being considered for curative-intent resection (+/- neoadjuvant therapy) after multidisciplinary recommendation, and other strategies of nutritional supplementation should be considered.

<u>Variant 3</u>: Symptomatic malignant obstruction in a medically inoperable patient with cT3N2M0 adenocarcinoma of the gastroesophageal junction who is a candidate for definitive chemoradiation (Blazeby grade 2 dysphagia)

72 year-old female (never smoker or drinker; longstanding history of GERD; multiple comorbid illnesses) (ECOG = 1, with BMI = 23; serum albumin 3.3 g/dl) is diagnosed with a Siewert 2 adenocarcinoma of the gastroesophageal junction. She presented with early satiety, progressive dysphagia to solids, and unintentional 20 lb weight loss (current weight 150 lbs) over the last 2 months. She is able to eat only pureed foods (Blazeby grade 2). Upper endoscopy revealed a near obstructing 3 cm mass from 37 to 40 cm from incisors and biopsy confirmed moderately differentiated adenocarcinoma. EUS demonstrated invasion of the adventitia and 4 enlarged lesser gastric curvature lymph nodes measuring up to 2 cm in diameter. Contrast-enhanced CT demonstrated a 3 cm circumferential mass centered at the gastroesophageal junction with esophageal dilation proximal to the mass, and 4 enlarged gastrohepatic and lesser curvature lymph nodes. PET CT revealed uptake in the esophagus, regional nodes identified by EUS and CT, with no evidence of distant disease. (cT3N2M0) She was evaluated by a multidisciplinary team and deemed a poor candidate for surgery but able to tolerate chemotherapy and/or radiation.

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Treatment Options														
Nutrition consultation	A	0	0	0	0	0	0	4	5	7	8		S	↑
Placement of esophageal stent prior to curative-intent therapy	U	0	6	7	3	0	0	0	0	0	3		S	↑
Placement of feeding tube prior to curative-intent therapy	M	0	0	0	0	2	12	0	0	0	6		M	↑
Proceed with definitive chemoradiation	A	0	0	0	0	0	2	6	8	0	8		S	↑
Proceed with induction chemotherapy followed by curative-intent chemoradiation	A	0	0	0	0	0	0	14	0	0	7		M	↑

<u>Variant Discussion:</u>

For patients with localized, non-metastatic, inoperable EC, definitive CRT is associated with 5-year survival of approximately 26%. It is important to consider that the use of esophageal stents in the setting of CRT is associated with increased risk of complications and may be associated with worse oncological outcomes. Expeditious initiation of induction chemotherapy or definitive CRT can be effective in improving dysphagia and QoL, with benefits observed in some patients during the first week(s) of treatment. The use of stents in EC patients who are candidates for definitive CRT should be carefully considered and discussed in a multidisciplinary setting. Stents should only be used with caution in patients who are being treated with definitive CRT after multidisciplinary recommendations, and other strategies of palliation of dysphagia (such as expeditious initiation of CRT) and nutritional supplementation should be considered.

<u>Variant 4</u>: Symptomatic malignant obstruction in a patient with newly diagnosed metastatic adenocarcinoma of the distal esophagus who is a candidate for palliative systemic therapy and/or radiation and has a life expectancy > 6 months (with treatment) (Blazeby grade 2 dysphagia)

68 year-old male (former smoker; no alcohol; longstanding history of GERD) with a good performance status (ECOG = 1, with BMI = 24; serum albumin 3.1 g/dl) is diagnosed with metastatic adenocarcinoma of the distal esophagus. He presented with early satiety, progressive dysphagia to solids, and unintentional 20 lb weight loss (current weight 170 lbs) over the last 3 months. He is able to eat only pureed foods (Blazeby grade 2). Upper endoscopy revealed a near obstructing 5 cm mass from 34 to 39 cm from incisors and biopsy confirmed poorly differentiated adenocarcinoma. Contrast-enhanced CT demonstrated a 5 cm circumferential mass in the distal esophagus with mild esophageal dilation proximal to the mass, enlarged paraesophageal, gastrohepatic, and lesser gastric curvature lymph nodes, and diffuse liver metastases. PET CT revealed uptake in the esophagus, regional nodes, and liver without evidence of other distant disease. (Stage 4) He was evaluated by a multidisciplinary team and deemed able to tolerate chemotherapy and/or radiation.

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Treatment Options														
Nutrition consultation	A	0	0	0	0	0	0	3	5	8	9		S	↑
Placement of esophageal stent prior to systemic therapy	U	0	2	12	0	0	0	0	0	0	3		S	↑
Placement of esophageal stent prior to palliative radiation or CRT	U	0	7	6	2	1	0	0	0	0	3		S	↑
Placement of a feeding tube prior to oncologic therapy	M	0	0	0	4	6	4	0	0	0	5		M	↑
***Other endoscopic therapies prior to oncologic therapy**	U	0	5	8	1	0	0	0	0	0	3		M	↑
Brachytherapy followed by systemic therapy	M	0	0	2	3	6	3	2	0	0	5		S	↑
Palliative external beam radiation followed by systemic therapy	A	0	0	0	0	1	3	7	5	0	7		S	↑
Palliative CRT followed by systemic therapy	M	0	0	0	7	5	2	0	0	0	5		S	↑
Systemic therapy alone (with consideration of external beam radiation, brachytherapy, or endoscopic therapy if no improvement in symptoms)	A	0	0	0	0	1	3	7	5	0	7		S	↑
Best supportive care alone	U	1	11	2	0	0	0	0	0	0	2		EC	↑

***Other ablative modalities include cryotherapy, radiofrequency ablation (RFA), argon plasma coagulation (APC), laser therapy, photodynamic therapy (PDT) and chemical ablation.

<u>Variant Discussion:</u>

Single modality palliation is recommended over combined therapy for dysphagia in the palliative setting, with radiation preferred in those with a reasonable life-expectancy (e.g. > 6 months) as it is associated with lower adverse events and more durable palliation of dysphagia compared to stent placement. Palliative brachytherapy can also be considered. If the patient is fit for systemic therapy, chemotherapy alone is also considered a reasonable option and can avoid the esophagitis typically associated with radiation. The use of stenting is typically considered for patients with a shorter life expectancy who need immediate palliation. Multidisciplinary discussion should guide treatment recommendations for the use of stents in EC patients who are not candidates for curative-intent therapy.

Variant 5: Symptomatic non-malignant stricture causing obstruction in a patient who received neoadjuvant chemoradiation followed by esophagectomy without evidence of recurrence (Blazeby grade 2 dysphagia)

48 year-old female (former smoker; no alcohol) with a good performance status (ECOG = 1, with BMI = 22; serum albumin 2.9 g/dl) received neoadjuvant chemoradiation for a T3N1M0 moderately differentiated Siewert I adenocarcinoma of the esophagus followed by esophagectomy (ypT0N0) 6 months ago. She was recovering well and gaining weight, then developed progressive dysphagia to solids (Blazeby grade 2). She has lost 10 lbs over the last 2 weeks (current weight 145 lbs). Restaging contrast-enhanced CT demonstrates no evidence of locoregional recurrence or distant metastases. Upper endoscopy reveals a 2 cm stricture at the level of the anastomosis without evidence of recurrent malignancy.

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Treatment Options														
Nutrition consultation	A	0	0	0	0	0	1	2	5	8	9		EC	↑
Speech and swallowing evaluation and therapy	A	0	0	0	1	1	2	3	5	4	8		EC	↑
Initial placement of esophageal stent	U	2	4	9	1	0	0	0	0	0	3		S	↑
Initial placement of a feeding tube	M	0	0	1	10	2	1	0	0	0	4		EC	↑
Esophageal dilation	A	0	0	0	0	0	4	4	8	0	8		S	↑

Variant Discussion:

Stents are not recommended for palliation of benign post-therapy strictures in the setting of prior radiation, especially in patients who have no evidence of recurrence as they are associated with increased risk, and sometimes fatal complications especially in patients who have received prior radiation as a component of previous treatment. Balloon dilation (which often required multiple treatments to achieve success and may be combined with steroid injections) is considered a standard and effective treatment strategy for patients with benign strictures following curative treatment of EC; however, time to relief of dysphagia is longer for patients who received prior CRT compared to surgery alone.

<u>Variant 6</u>: Symptomatic malignant obstruction in a patient with local recurrence at the primary tumor site in the mid esophagus after receiving definitive chemoradiation (Blazeby grade 3 dysphagia)

65 year-old male (former smoker; former alcohol) with ECOG performance status = 1 (BMI = 22; serum albumin 3.2 g/dl) received definitive chemoradiation for a T3N2M0 moderately differentiated squamous cell carcinoma of the mid esophagus 8 months ago. He had been recovering slowly and gaining weight, then developed progressive dysphagia to solids, and some liquids (Blazeby grade 3). He has lost 10 lbs over the last 3 weeks (current weight 160 lbs). Restaging contrast-enhanced CT and PET-CT demonstrate evidence of a recurrence in the mid esophagus at the primary tumor site, without evidence of nodal or distant metastases. Upper endoscopy reveals a 3 cm obstructing mass and biopsy confirms recurrent squamous cell carcinoma. He was evaluated by a multidisciplinary team and deemed unfit for surgery.

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Treatment Options														
Nutrition consultation	A	0	0	0	0	0	1	4	4	7	8		S	↑
Placement of esophageal stent prior to salvage systemic therapy	U	0	0	13	1	0	0	0	0	0	3		S	↑
Placement of esophageal stent prior to salvage re-irradiation	U	1	6	5	4	0	0	0	0	0	3		S	↑
Placement of a feeding tube prior to salvage therapy	M	0	0	0	0	3	10	1	0	0	6		EC	↑
***Other endoscopic therapies prior to salvage therapy**	M	0	1	1	7	5	0	2	0	0	4		M	-
Proceed to systemic therapy (chemotherapy +/- immunotherapy) alone	A	0	0	0	0	0	3	5	8	0	8		S	↑
Proceed with induction systemic therapy (with consideration of re-irradiation depending on response)	M	0	0	0	5	7	2	0	0	0	5		M	↑
Consider re-irradiation														
• **External beam re-irradiation alone +/- consolidation systemic therapy**	M	0	0	0	8	4	2	0	0	0	4		M	↑
• **External beam re-irradiation with concurrent chemotherapy +/- consolidation systemic therapy**	M	1	1	1	2	8	2	1	0	0	5		M	↑
• **Brachytherapy +/- consolidation systemic therapy**	U	0	0	10	2	1	1	0	0	0	3		L	↑

*

*Other ablative modalities include cryotherapy, radiofrequency ablation (RFA), argon plasma coagulation (APC), laser therapy,

photodynamic therapy (PDT) and chemical ablation, which can also be considered as alternatives to stenting, especially in patients who develop recurrence following previous radiotherapy or surgery.

Variant Discussion:

Although EBRT or CRT is a reasonable option for patients with recurrent dysphagia due to malignant obstruction after curative treatment in the setting of no prior radiation, re-irradiation is associated with a high complication rate and should be regarded with caution but may considered if other options are limited and life-expectancy is short. Stent placement in the setting of prior radiation should be considered with caution due to increased risk of adverse events but may be useful for palliation of dysphagia in patients with limited life expectancy. Systemic therapy alone (chemotherapy +/- immunotherapy) is a reasonable consideration in the setting of prior CRT as it has been shown to improve dysphagia in a majority of patients.

Variant 7: Symptomatic malignant obstruction in a patient with cT4N1M0 squamous cell carcinoma of the mid esophagus with evidence of tracheoesophageal fistula (Blazeby grade 3 dysphagia)

67 year-old male (current heavy smoker; daily alcohol) with ECOG performance status = 2 (cachectic appearing with BMI = 19; serum albumin 2.3 g/dl) presents with admission to the hospital with pneumonia and reports progressive dysphagia to solids then liquids and coughing during eating, and an unintentional 30 lb weight loss (current weight 135 lbs) over the last 6 months. He is not able to eat solids without regurgitation and has difficulty swallowing liquids (Blazeby grade 3). Upper endoscopy revealed an obstructing friable 5 cm mass from 25-30 cm from incisors traversing the tracheal bifurcation and biopsy confirmed poorly differentiated squamous cell carcinoma. Flexible bronchoscopy demonstrated extrinsic compression and focal invasion of the trachea. Esophagram demonstrated evidence of aspiration and tracheoesophageal fistula. EUS demonstrated invasion into the trachea and a solitary 2.5 cm adjacent paraesophageal lymph node, confirmed on contrast-enhanced CT, and PET CT revealed uptake in the esophagus and adjacent node only and no evidence of distant disease. (cT4N1M0) He was evaluated by a multidisciplinary team and deemed a poor candidate for surgery at present due to compromised nutritional status and active infection.

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	SOE	SOR
		1	2	3	4	5	6	7	8	9				
Treatment Options														
Nutrition consultation	A	0	0	0	0	0	1	3	5	6	8		S	↑
Surgical repair of TE fistula prior to curative-intent therapy*	U	0	2	9	2	1	0	0	0	0	3		S	↑
Placement of stent(s) prior to curative-intent therapy**	A	0	0	1	0	1	0	6	6	0	7		S	↑
Placing the patient NPO with enteral/parenteral nutrition prior to curative-intent therapy	A	0	0	1	0	1	3	9	0	0	7		M	-

***** Surgical repair may be considered in select subset of patients who are healthy enough to tolerate the surgery and have small fistulas amenable to repair.

****** Placement of an airway or partially/fully covered esophageal stent may allow time for healing and palliate symptoms including aspiration and dysphagia.

Variant Discussion:

The optimal management of TE fistulas is complex and treatment options include surgical repair, esophageal/airway stenting, placing patient NPO with enteral/parenteral nutrition, and/or placement of feeding tube. Surgical repair may be considered in select subset of patients who are healthy enough to tolerate the surgery and have small fistulas amenable to repair however, surgery involves risks of non-healing due to malignant involvement, or delay to initiation of curative-intent treatment. Stent placement for management of TE fistulas can result in improvement of symptoms and performance status in many patients, but can be complicated by migration, tumor overgrowth, and fistula formation. Dual airway and esophageal stents are more commonly used for patients with TE fistulas near the carina due to EC and can improve both dyspnea and dysphagia as well as allow for healing and improved nutrition. When stent placement is not available, it is reasonable to consider placing the patient NPO with enteral/parenteral nutrition prior to curative-intent therapy.

Please refer to the supporting documentation for a more complete discussion of the concepts and definitions below.

Rating Categories: U Usually not appropriate; M May be appropriate; A Usually appropriate

Disagree: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

SOE: S Strong; M Moderate; L Limited; EC Expert Consensus; EO Expert Opinion

SOR: ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak

Key:

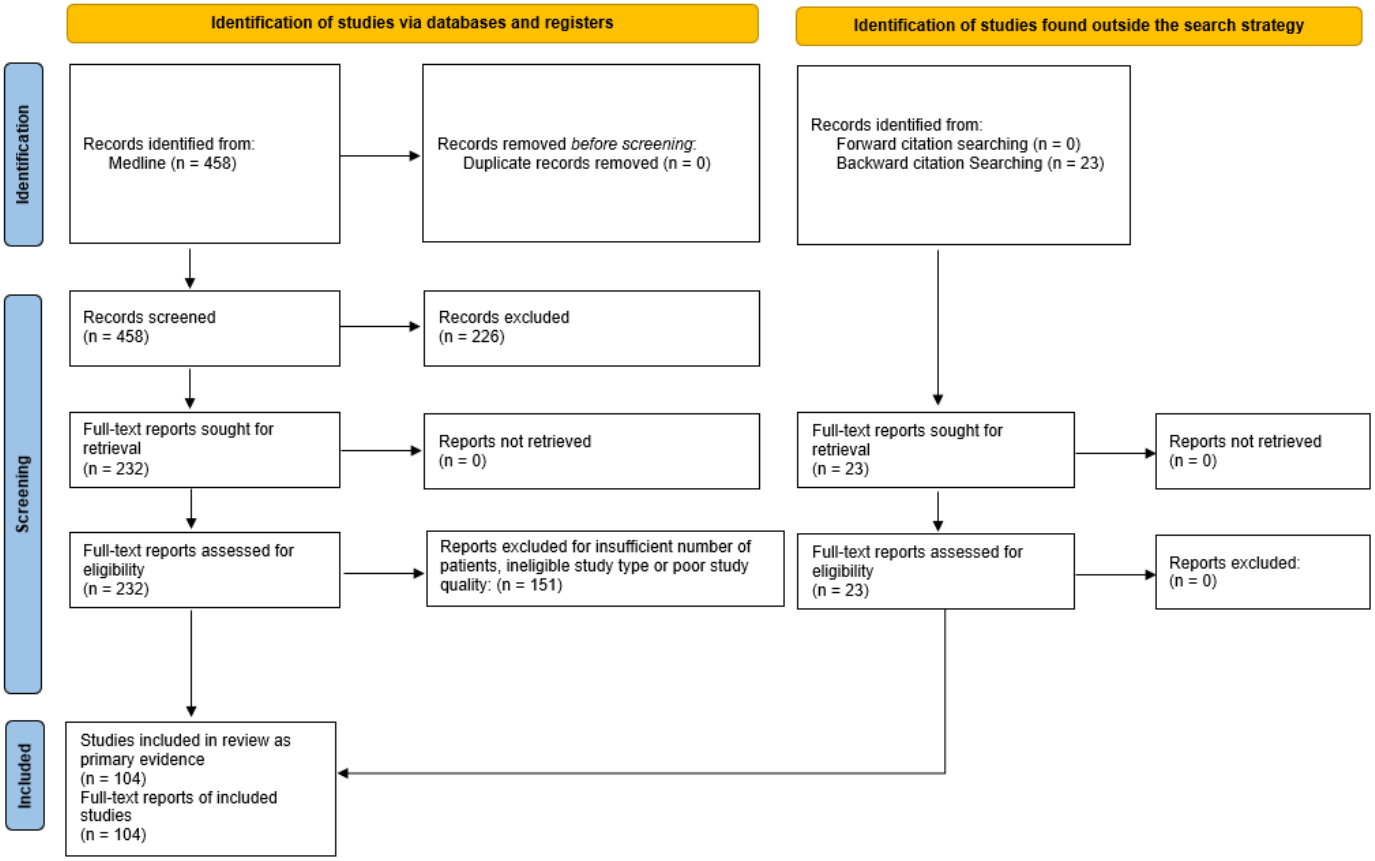
ECOG: Eastern Cooperative Oncology Group
BMI: Body mass index
lb(s): Pound(s)
EUS: Endoscopic ultrasound
CT: Computed tomography
PET-CT: Positron emission tomography-computed tomography
CRT: Chemoradiation
EC: Esophageal cancer
GERD: Gastroesophageal reflux disease
QoL: Quality of life
EBRT: External beam radiotherapy
TE: Tracheoesophageal

Appendix A: ARS AUC FOR THE USE OF ESOPHAGEAL STENTS IN PATIENTS WITH ESOPHAGEAL CANCER

Search Dates: 1/1/2010 to 12/3/2024

Database: Ovid MEDLINE(R) All
Search Strategy:
1 ("31828290" or "28864404" or "29728468").ui. (3)
2 ("33610215" or "22514498").ui. (2)
3 1 or 2 (5)
4 "23835387".ui. (1)
5 3 or 4 (6)
6 ((esophag* or oesophag* or gastroesophag* or gastro-esophag* or gastrooesophag*) adj3 (cancer* or carcinoma* or neoplas* or adenocarcinoma* or squam* or malignan* or tumor* or tumour*)).ti,ab,kf. (72245)
7 exp Esophageal Neoplasms/ (62271)
8 6 or 7 (84994)
9 5 not 8 (0)
10 (radiotherap* or radiat* or irradiat* or chemoradi* or IMRT or "intensity modulated radiation therapy" or VMAT or "volumetric modulated arc therapy" or proton*).ti,ab,kf. (1038367)
11 Radiotherapy/ or radiotherapy, conformal/ or radiotherapy, intensity-modulated/ or *radiotherapy dosage/ or *radiotherapy planning, computer-assisted/ (80124)
12 (immunotherap* or pembrolizumab* or nivolumab* or avelumab* or durvalumab* or atezolizumab* or checkpoint inhibitor* or PD-L1 inhibitor* or PD1 inhibitor* or chemo-radi* or chemoradi*).ti,ab,kf. (237953)
13 ***immunotherapy/ or *antineoplastic agent/ or *carboplatin/ or *cetuximab/ or *fluorouracil/ or *cisplatin/ or *multimodality cancer therapy/ or *radiosensitizing agent/ or *immunotherapy/ or *monoclonal antibody/ or *immunological antineoplastic agent/ or *programmed death 1 receptor/ or molecularly targeted therapy/ or vaccine/ (431791)
14 rt.fs. (218668)
15 th.fs. (2231332)
16 or/10-15 (3682919)
17 5 not 16 (0)
18 (dysphagia* or "local*" or "locoregional*" or surviv* or toxic* or esophagitis* or oesophagitis* or odynophagia* or "quality of life" or "quality-of-life" or "patient-reported-outcome*" or "patient reported outcome*").ti,ab,kf. (4216560)
19 Survival Rate/ or Disease-Free Survival/ or Survival/ or Progression-Free Survival/ or Survival Analysis/ or radiation injuries/ or Patient Reported Outcome Measures/ (454392)
20 (stent* or dysphag*).ti,ab,kf. (168927)
21 (18 or 19) and 20 (58187)
22 (stent* and (dosimetr* or ((coverage or margin) adj (target or diseas* or volume*)) or gross tumo* or GTV or clinical target volume* or CTV or planning target volume* or PTV or OAR or organ* at risk or organs*-at-risk)).ti,ab,kf. (253)
23 21 or 22 (58359)
24 5 not 23 (0)
25 8 and 16 and 23 (1989)
26 5 not 25 (0)
27 limit 25 to yr="2010 - 2025" (919)
28 limit 27 to english language (843)
29 limit 28 to "review articles" (132)
30 Meta-analys*.ti,ab,kf. or Meta-analysis/ (349418)
31 29 and 30 (14)
32 (28 not 29) or 31 (725)
33 limit 32 to ("newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)") (5)
34 (((line* or stem*) adj3 cell*) or mice* or mouse* or rat or rats or rodent* or feline* or canine* or equine* or murine* or animal* or in vivo* or "in vitro*" or "autophag*" or culture* or ELISA or bacilus* or drug screen or nano* or quasi-experimental* or ligand*).ti,ab,kf. or exp Mice/ (7881141)
35 ("Surveillance, Epidemiology, and End Results*" or SEER* or "National Cancer Database*" or NCDB).ti,ab,kf. (24785)
36 (GIST or gastrointestinal stromal* or sarcoma* or melanoma* or breast* or meningioma* or tuberculos* or pancrea* or bile duct* or periampullary* or neuroendocrine* or prostat* or gallbladder* or ACTH or gastrinoma* or cholangiocarcinoma* tuberculos* or thyroid* or bladder* or renal or testicular or seminoma* or (lung adj3 (cancer or carcinoma*)) or colon* or ovar* or reirradiat* or second-line* or second line* or reflux* or PPI or proton-pump* or pump inhibitor or gastric-acid* or acid* or gastritis* or MALT or lymphoma* or (chinese adj3 medic*) or mastalgia or radiofrequenc* or microwav* or sarcopenia or intraperitone* or splenic* or transarterial* or electroporat* or peritone* or third-line or third line or cutaneous or acupuncture* or case presentation or case report or herbal or endoscopic submucosal dissection or pylori* or herbal* or tonsil* or oropharng* or octreotid* or exercis*).ti,kf. (4176568)
37 ("case report" or "case-report" or "case-series*" or "case series*" or "narrative review" or editorial* or letter* or "response to comment*").ti,ab,kf. (828043)
38 limit 32 to (case reports or letter or editorial or clinical trial protocol) (186)
39 or/33-38 (11495399)
40 32 not 39 (458)
41 5 not 40 (0)

Appendix B: Prisma 2020[11,12] Study Selection Flow Diagram for Use of Esophageal Stents in Patients with Esophageal Cancer



Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			INTRODUCTION/BACKGROUND
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	¶2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	¶2
METHODS			METHODOLOGY
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	¶1
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	¶1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix A: Search Strategy
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	¶1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	¶1
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	¶1
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	¶1
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Appendix C: Evidence Table
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	N/A
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	N/A
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Variants 1-7 via Strength of Evidence (SOE)

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16 a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Appendix B: Flow Diagram
	16 b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Appendix B: Flow Diagram
Study characteristics	17	Cite each included study and present its characteristics.	Appendix C: Evidence Table
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Appendix C: Evidence Table
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	N/A
Results of syntheses	20 a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20 b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20 c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20 d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Variants 1-7 via Strength of Evidence (SOE) and Strength of Recommendation (SOR), & section "SUMMARY OF RECOMMENDATIONS"
DISCUSSION			
Discussion	23 a	Provide a general interpretation of the results in the context of other evidence.	SUMMARY OF LITERATURE REVIEW Topics 1 - 5
	23 b	Discuss any limitations of the evidence included in the review.	N/A
	23 c	Discuss any limitations of the review processes used.	N/A
	23 d	Discuss implications of the results for practice, policy, and future research.	N/A
OTHER INFORMATION			
Registration and protocol	24 a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24 b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24 c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Title Page
Competing interests	26	Declare any competing interests of review authors.	Title Page
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	https://www.americanradiumsociety.org/page/aucmethodology