Palliative Approaches in Esophageal Cancer

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Esophageal cancer is a lethal malignant disease and its incidence is still increasing. Despite progress in diagnosis and therapy that has been achieved in recent years, esophageal cancer remains a devastating disease and is one of the most frequent causes of cancer-related death in the world [1–3]. Esophageal cancer is usually clinically obscure until it has reached advanced stage. Substantially more than 50% of patients with esophageal cancer present at an incurable stage. Prolonged progression-free survival is possible only in a few of them. Thus, palliation rather than cure is the treatment goal for the majority of patients [4, 5]. The primary goals of palliative treatment are relieving dysphagia, managing pain, and improving quality of life. Caring for these patients requires a multidisciplinary approach including external beam radiation therapy (EBRT), chemotherapy, endoscopic dilatation and/or stenting, photodynamic therapy, laser therapy, and palliative surgery. Dysphagia is the most common presenting symptom, often occurring secondary to intraluminal tumor growth and later secondary to treatment-induced fibrosis, postoperative

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N. F. Saba, B. F. El-Rayes (eds.), *Esophageal Cancer*,
https://doi.org/10.1007/978-3-030-29832-6_16

Table 16.1 Current palliative modalities for dysphagia associated with esophageal cancer

Endoscopic techniques	Stent placement
	Photodynamic therapy (PDT)
	Nd:YAG
	Cryotherapy
	Ablation
	Argon plasma coagulation (APC)
	Chemical injection therapy
	Dilation
	Nasoenteric feeding tube
	Percutaneous endoscopic gastrostomy (PEG)
Non-endoscopic techniques	Radiation therapy
	Brachytherapy
	External beam radiotherapy
	Chemotherapy

anastomotic stricture, or pseudo-achalasia secondary to cancer infiltration of the myenteric plexus [6]. Dysphagia often progresses rapidly to the stage when patients lose their ability to swallow liquids and even saliva, which leads to sialorrhea, aspiration, and malnutrition [7, 8].

Since most patients with incurable esophageal cancer live no longer than 6 months, the aims of palliative treatment are to relieve dysphagia promptly, maintain swallowing function, improve nutrition, and avoid serious complications. It is important to realize that treatment of incurable esophageal cancer should be individualized and based on tumor stage, medical condition, performance status, and personal willingness of the patient. In addition, both the available expertise and results of prospective, randomized studies should be taken into consideration [9, 10]. A wide range of recently developed palliative treatment modalities are available (Table 16.1).

The main options can be divided into endoscopic and non-endoscopic approaches. The current available palliative treatment techniques are equally effective for esophageal adenocarcinoma (including adenocarcinoma located in the gastrointestinal junction, the GE junction) and esophageal squamous cell carcinoma [10]. We will mainly discuss the endoscopic palliative modalities in this chapter. Non-endoscopic procedures will be mentioned in other chapters.

In recent years, the advancement of endoscopy has offered physicians a variety of nonsurgical means to palliate malignant obstruction of the esophagus. Although there are many therapeutic options, they all have some limitations. Not all methods described here can be performed at every institution. Both physician and institutional experiences often influence the selection of treatment.

Stents and Stent Placement

In the 1990s, esophageal stenting was performed using plastic stents. Stent placement at that time required extensive esophageal dilation because the stent had a diameter of 15–20 mm which couldn't pass the stricture without dilation. Although

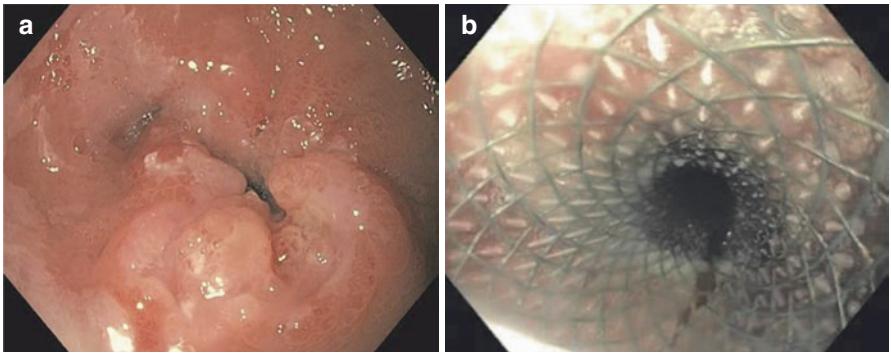

Fig. 16.1 (**a**) Middle esophageal adenocarcinoma with esophageal stricture; (**b**) partially covered metal esophageal stent placed (23 mm × 12 cm)

the plastic stents were inexpensive and relatively effective at palliation of malignant esophagobronchial fistulas, the thick and stiff walls of the stent caused chest pain and poor relief from dysphagia. In addition, old plastic stents were associated with a high incidence of complications, including perforation, migration, and high procedure-related mortality [6, 11]. During the past decade or so, self-expanding metal stents (SEMS) have become available for the treatment of malignant dysphagia and have almost replaced plastic stents. SEMS can be used to treat intrinsic and extrinsic tumors that cause malignant dysphagia. They are assembled in a tightly bound unit on a delivery catheter, greatly reducing the diameter of the delivery system. After endoscopic placement of the delivery system across the stricture, SEMS are deployed under endoscopic and fluoroscopic guidance, frequently without the need for pre-dilation [7, 8]. Once in proper position, SEMS is deployed by releasing the stent from the delivery system and allowing it to expand to its maximal diameter in a few hours. They can relieve dysphagia promptly (Fig. 16.1). Placement of SEMS is a minimally invasive procedure, with a significantly smaller risk of perforation compared with placement of plastic stents [12, 13].

Currently Available Covered Metal Stents

In light of the disadvantage of re-obstruction of the original uncovered metal stents due to tumor ingrowth [14–18], the new-generation stents are covered or partially covered [19]. Generally, an ideal metal stent should have the following characteristics: an internal diameter big enough for the passage of normal diet, flexible to avoid trauma during placement, resist to migrate, and removable if necessary [10]. Although this ideal stent does not exist at this time, all available covered stents do meet some of these criteria. The frequently used covered metal stents are as follows:

The Ultraflex stent (Boston Scientific, Natick, MA, USA) consists of a knitted nitinol wire tube, and the covered version has a polyurethane layer which covers the

midsection of the stent extending to within 1.5 cm of either end of the stent. The stent has a proximal flare with two sizes: 28 mm (distal diameter 23 mm) and 23 mm (distal diameter 18 mm). It is important to remember that all these stents become 30–40% shorter after placement. The radial force of the Ultraflex stent is the lowest among the currently available metal stents. Partial obstruction of the stent can occur in stents that are sharply angled beyond the GE junction. The Wallstent (Boston Scientific) is made from a cobalt-based alloy and is formed into a tubular mesh. It is available in two designs: the Wallstent II and the Flamingo Wallstent. Stents of both designs are easy to place. The Wallstent can be repositioned during the procedure because recapture remains possible, while less than 50% of the stent is deployed. The degree of shortening after placement is about 20–30%. Both designs have a high radial force. The Wallstent II flares to 28 mm at both ends, with a diameter of 20 mm at its midsection. It is covered with a silicone polymer layer, with 2 cm left exposed at the proximal and distal ends. The Flamingo Wallstent is designed specifically for use in the distal esophagus/gastric cardia. However, it can be used in the proximal esophagus as well. The conical shape of this stent is designed to apply a variable radial force throughout the length of the stent to address anatomical differences in the distal esophagus and cardia. The stent is covered by a polyurethane layer, which is applied from the inside, extending to within 2 cm of either end of the stent. Both a large-diameter stent (proximal and distal diameters 30 and 20 mm) and a small-diameter stent (proximal and distal diameters 24 and 16 mm) are available. The Wallstent II and the Flamingo Wallstent are both very pliable, with the diameter of the stent unaffected even when angled. The Z-stent (Wilson-Cook Medical, Winston-Salem, NC, USA) with a Korean modification, the Choo stent (MI Tech, Seoul, Korea), consists of a wide "Z"-mesh of stainless steel covered over its entire length by a polyethylene layer. The Z-stent is available with or without fixing barbs in the central segment. The introduction system is more complex than that of the Wallstent and the Ultraflex stent. The stent does not shorten on release and is the least flexible of the currently available metal stents. The Z-stent flares to 25 mm at both ends with a diameter at its midsection of either 18 mm or 22 mm. Partial obstruction can also occur with Z-stents if they are sharply angled after passing across the GE junction [10].

Comparison of Different Types of Metal Stents

With the wide availability of different metal stents on the market, it is important to investigate which stent offers the most optimal palliation for malignant dysphagia. Several retrospective or prospective studies compared the outcome of different types of metal stents.

One retrospective study compared the uncovered Ultraflex, the covered and uncovered versions of the Wallstent, and the covered Z-stent on 96 patients. There were no differences in the outcome and complication rate among the different stent types [20]. Covered versions of the Wallstent and the Ultraflex stent were compared in another retrospective trial, showing a higher early complication rate with the

Wallstent but a higher re-intervention rate with the Ultraflex stent [9, 21]. In a prospective study, 100 patients were randomized into 1 of 3 types of covered metal stents, Ultraflex stent, Flamingo Wallstent, and Z-stent. No significant differences were found in dysphagia improvement, the occurrence of complications, or recurrent dysphagia, although there was a trend toward more complications with Z-stent (Ultraflex stent 8/34 (24%) and Flamingo Wallstent 6/33 (18%) than Z-stent 12/33 (36%); $P = 0.23$) [22]. In another prospective trial, the Ultraflex stent and the Flamingo Wallstent were compared in patients with distal esophageal cancer. The two types of stents were equally effective in the palliation of dysphagia in this patient group, and the complication rate associated with their use was also comparable (Ultraflex stent 7/31 (23%) and Flamingo Wallstent 5/22 (23%)) [9, 23].

We can conclude that there are only slight differences between the most frequently used types of stents. The choice of stent should therefore depend on the location and anatomy of the malignant stricture as well as the specific characteristics of the stent.

The Efficacy and Complications of Self-Expanding Mental Stent

Generally, the technical success rate for placement of metal stents is close to 100%. Almost all patients experience rapid improvement of dysphagia within a few days. The dysphagia grade usually improves from a median of 3 (able to drink liquids only) to a median of 1 (able to eat most solid foods). Limitations to successful placement include severe pain during procedure; extensive tumor growth in the stomach; failure of the stent to release from the introduction system, as can occur with Ultraflex stents; and immediate stent migration when the stent has been placed too distally. Procedure-related complications after metal stent placement mainly consist of perforation, aspiration pneumonia, fever, bleeding, and severe chest pain and occur in 5–15% of patients. Minor complications are mild retrosternal pain and gastroesophageal reflux, which are reported in 10–20% of patients. Delayed complications and recurrent dysphagia following stent placement are an important problem and occur in 30–45% of patients. This includes hemorrhage, fistula formation, stent migration, tumor over- or ingrowth, and food bolus obstruction. Treatment of fistula formation, stent migration, and tumor overgrowth or ingrowth mostly consists of placement of a second stent. This is an effective treatment and improves dysphagia scores [9, 24].

Stent Placement for Esophagorespiratory Fistulas

Esophagorespiratory fistula is a dreaded complication of esophageal cancer, which can lead to aspiration and respiratory failure, and occurs in 5% of all cases. It may also arise secondary to lung cancer and trachea and larynx cancer and have high morbidity and mortality rates because of comorbid conditions such as aspiration pneumonia [6, 25]. Placement of a covered metal stent is the choice of treatment for esophagorespiratory

fistula. Complete sealing of a fistula is established in more than 90% of patients with no significant difference between the currently available covered metal stents. Moreover, dysphagia scores improve significantly as well. The complication rate (early and late complications) varies between 10% and 30% [26–30].

New Stent Designs

New stent designs focus on two aspects, changing of configuration and optimization of materials. For example, metal stents with an anti-reflux mechanism have been developed to prevent gastroesophageal reflux of distal esophageal cancer. The design of completely covered stents, like the Polyflex stent and the Niti-S stent, might be able to overcome ingrowth of tumoral tissue. Further, the Niti-S stent with a double-layer configuration, consisting of an inner polyurethane layer to prevent tumor ingrowth and an outer uncovered nitinol wire tube to allow the mesh to embed itself in the esophageal wall, has been designed to reduce stent migration.

A recently reported cause of recurrent dysphagia is the ingrowth and overgrowth of non-tumoral, inflammatory tissue, over and through the uncovered meshes at the ends of partially covered stents [31]. So, in addition to progressive tumor growth, benign tissue is also able to cause stent obstruction. Therefore, stents made with biodegradable materials, such as magnesium alloy or polymerid, may relieve obstruction and degrade after a period of time [32]. Relative studies are still on the way and further comparative studies are needed [33].

Laser Therapy: Nd:YAG Laser

Treatment of obstructing esophageal cancer with the high-power neodymium-yttrium-aluminum-garnet (Nd:YAG) laser is another relatively safe but often temporary palliation for dysphagia. Nd:YAG laser therapy delivers an intense beam of light that heats and vaporizes tumor tissue, thereby restoring patency to the esophageal lumen. Dysphagia relief occurs often immediately, and successful tumor recanalization can be achieved in more than 90% of appropriately selected patients. Tumors that are relatively short in length (<6 cm), exophytic, and located in the mid esophagus are most amenable to laser ablation. It is not recommended for tumors in submucosa, tumors causing extrinsic compression, and tumors with angulation. It is less effective for cancer of the proximal esophagus or gastroesophageal junction. However, many patients (70–95%) require multiple treatment sessions and are usually reassessed at 4–6 weekly intervals [34, 35].

Laser therapy offers similar dysphagia relief to esophageal stents. An early study suggested that laser therapy was associated with fewer complications than esophageal stenting [36]. A limitation of this retrospective study was that many of the patients in the stenting group received a plastic endoprosthesis rather than SEMS. A prospective randomized study subsequently concluded that laser therapy carried a higher risk of fistula formation, bleeding, and need for repeating intervention when compared to esophageal stents [19]. Therefore, this therapy is not widely utilized.

Photodynamic Therapy (PDT)

PDT, a non-thermal tissue ablative technique, involves intravenous injection of a photosensitizing agent that is preferentially taken up by neoplastic cells, followed by endoscopic application of laser therapy to the malignant stricture. Porphyrin compounds, such as porfimer sodium, have been the most commonly used photosensitizers for the palliation of malignant dysphagia. PDT with porfimer, a hematoporphyrin derivative, is thought to have a direct toxic effect on malignant cell via the production of singlet oxygen, which damages the microvasculature of the tumor and renders it ischemic [37]. Porfimer preferentially accumulates in malignant tissue after intravenous injection. The area is then exposed to an endoscopically placed low-powered laser diffuser with monochrome light (630 nm), which initiates a photochemical reaction resulting in tumor necrosis. The malignant tissue can be treated repeatedly to provide optimal tissue ablation [6].

PDT appears to be effective at palliating dysphagia, but its widespread acceptance is limited by the high cost of the photosensitizing agent and the requirement for patients to avoid sunlight for several weeks to avoid skin phototoxicity [38, 39]. Furthermore, patients require repeating intervention within a mean interval of 2 months. Major complications, including perforation, fistula formation, and strictures, have been reported in up to 30% of patients [38].

Cryotherapy

During cryoablation, liquid nitrogen or carbon dioxide at super cold temperatures (−76 to −158 °C) is sprayed directly on the tumor for 20–40 s. The tissue is then allowed to thaw before spraying again for 20–40 s. Typically, 2–4 freeze-thaw cycles of liquid nitrogen or 4–8 freeze-thaw cycles of carbon dioxide are administered. These freeze-thaw cycles cause intracellular disruption and ischemia, which leads to ablation of tumor tissue (thermal ablation) (Fig. 16.2). High-quality data has demonstrated the safety and effectiveness of this

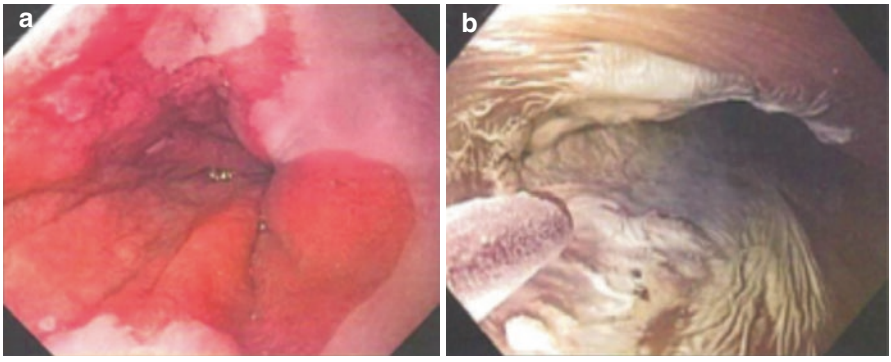

Fig. 16.2 Cryotherapy of esophageal cancer and Barrett's esophagus. (**a**) Before cryotherapy. (**b**) Immediately after therapy

technology in Barrett's esophagus and early esophageal cancer. The published literature on the efficacy of this modality for esophageal cancer palliation is primarily from smaller case series [40], and long-term survival has been reported [41]. Further research is necessary to clarify the role of cryoablation in esophageal cancer palliation.

Argon Plasma Coagulation

Argon plasma coagulation (APC) is an ablative endoscopic technique. A type of monopolar electrocautery, APC causes tissue coagulation, desiccation, and destruction via the transfer of energy from the APC probe to the malignant tissue in the form of ionized, electrically conductive argon gas ("plasma"). The APC probe produces a plasma arc that destroys tissue to a depth of approximately 2–3 mm and is most useful in superficial lesions [42].

Several studies have assessed its effectiveness in the palliation of malignant dysphagia. In one retrospective study of 32 patients, recanalization was achieved in 89% of patients [43]. A separate report of 83 patients found a similar recanalization rate of 86% [44]. Most of these patients required multiple sessions to maintain patency, averaging five to six sessions per patient, usually at an interval of 3–4 weeks. Perforation was seen in 1–1.8% of procedures, a rate comparable to that seen in other modalities [45, 46]. Argon plasma coagulation seems to be a safe and easy alternative to laser treatment. Further prospective trials are needed for comparison [42].

Radiofrequency Ablation (RFA)

With the advent of radiofrequency (RF), radiofrequency ablation (RFA) has been reported widely in recent decades. The energy of the radiofrequency current can radiate off solid tumors by electromagnetic waves [47, 48]. Due to its precise orientation, smaller trauma, and less pain, RFA has become increasingly recommended as a new option for esophageal tumors, which in part averts both pain and poor life quality in advanced patients [49]. In clinical practice, the endoscopic RFA can not only ablate tumors in the esophagus directly but also can further offer space for the stent extension by ablating ingrowth tumor, therefore keeping the stent patent for a longer time [50] (Fig. 16.3).

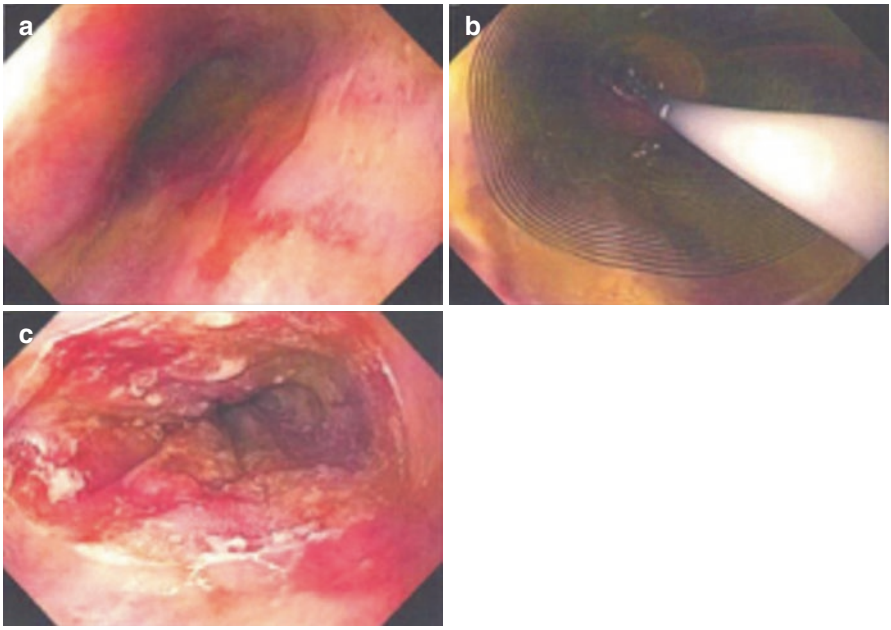

Fig. 16.3 Radiofrequency ablation of esophageal cancer and Barrett's esophagus. (**a**) Before therapy, (**b**) during therapy, (**c**) immediately after therapy

Dilatation

The normal functional lumen diameter of the esophagus in adults is 25 mm. If it decreases to 13 mm, symptoms of dysphagia to solid and regular diet appear. Esophageal dilation is generally used for benign or postoperative strictures and not recommended for malignant stricture. But in some special situations, dilatation might provide temporary relief. Endoscopically directed balloon dilatation or wire-guided polyvinyl bougies can bring temporary relief of dysphagia until more definitive treatment is given. Several sessions with balloon, Savary, and Maloney dilators can safely dilate most malignant strictures up to 17 mm. The relief duration obtained from dilatation is short; repeated dilatation is required in 1–2 weeks. Dilatation of malignant stricture should only be used as a preliminary modality before endoscopic tumor ablation or placement of an enteral feeding tube prior to chemoradiation therapy [6, 51–53].

Alcohol Injection

Direct injection of pure ethanol into malignant tissue is the simplest and least expensive technique that can recanalize an obstructed esophagus. Alcohol injected under endoscopic visualization can cause tissue fixation, tumor ulceration, and necrosis. It

has proved to be an effective modality in the relief of malignant dysphagia. Like laser therapy, alcohol injection is best suited for treating exophytic bulky lesions at all levels of the esophagus.

Significant relief of dysphagia was demonstrated in two uncontrolled trials [54]. In a randomized, controlled trial comparing neodymium-yttrium-aluminum-garnet (Nd:YAG) laser with ethanol injection, the dysphagia-free interval was 37 days and 30 days, respectively. An improvement in the dysphagia score of at least two points was noted in 88% of the laser group and 78% of the ethanol group, with no difference in median survival [34]. In one of the largest studies, 36 patients underwent alcohol injection therapy for palliation of dysphagia. The mean number of treatments required to "recanalize" the esophagus was 1.8, and the mean volume of alcohol injected per session was 7.8 milliliter (mL). All patients reported fever and chest pain for 12–24 h after the procedure. Dysphagia improved in 81% of patients. Seven of the 36 patients had no subjective improvement despite objective evidence of esophageal patency [7].

Despite this technique relying on readily available and inexpensive materials and capability by nearly all endoscopists, this procedure has not gained widespread use in the United States since it is performed simply by injection of ethanol in aliquots of 0.5–1.0 mL into protuberant portions of neoplastic tissue. Excessively firm or fibrotic tumors may lead to difficulties with injection. On the other hand, if tumors are too soft, without much resistance to alcohol injection, it may be difficult to estimate the amount of alcohol delivered. Thus, when using alcohol injection, dosimetry can be inaccurate [7].

In summary, there are a number of palliative modalities for advanced-stage esophageal cancer. Stent placement, RFA, APC, and cryotherapy are commonly used. Selection depends on patients' condition and expertise.

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