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Esophageal Lumen Restoration

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Abstract

Esophageal cancer is the eighth most common cancer worldwide. The prognosis for patients with esophageal cancer is poor, with published data indicating only about 12-39% of patients surviving for five years following radical treatment. As more than 50% of patients with esophageal cancer are beyond the reach of radical treatment at the time of diagnosis, palliative management becomes a fundamental approach. Several techniques for restoring the esophageal lumen have gained recognition, including mechanical methods such as esophageal dilation and stenting, as well as ablative techniques like photodynamic therapy, laser therapy, and cryotherapy. Treating patients with advanced esophageal cancer or those deemed unfit for surgery poses a significant challenge. An individualized approach to patient care requires a comprehensive understanding of various therapeutic methods. Therefore, this paper seeks to present current knowledge on available methods for alleviating esophageal obstruction in patients suffering from dysphagia due to esophageal cancer.

Keywords: Esophageal cancer; Palliative treatment; Esophageal lumen restoration; Esophageal stenting; Ablative techniques

Abbreviations

EBRT - external beam radiation therapy; MeSH - Medical Subject Headings; EUS - endoscopic ultrasound; PEG - percutaneous endoscopic gastrostomy; OTW - Over the Wire; TTS - Through the Scope; EAC - esophageal adenocarcinoma; ESCC - esophageal squamous cell carcinoma; AEs- Adverse Events; SEMS - self-expanding metal stents; SEPS - self-expanding plastic stents; BDS - biodegradable stents; ESGE - European Society of Gastrointestinal Endoscopy; PCSEMS - partially covered self-expanding metal stents; FCSEMS - fully covered self-expanding metal stents; PDT - photodynamic therapy; LT - laser therapy; APC - argon-plasma coagulation; iBT - intraluminal brachytherapy; ROS- Reactive oxygen species; PCs - Photosensitizers; 5-ALA - 5-aminolevulinic acid; CRT - chemoradiotherapy; LNSC - liquid nitrogen spray cryotherapy; CO2 - carbon dioxide; CT - computed tomography, CTH- chemotherapy; PET CT - positron emission computed tomography.

Introduction

Esophageal cancer is the eighth most common cancer worldwide and the sixth leading cause of death among cancer patients. Global estimates suggest there are approximately 600,000 new cases annually [1]. An analysis conducted by Lin et al. focuses on predicting trends in the incidence of adenocarcinoma until the year 2030. The researchers have noticed an increasing number of cases of this

disease, particularly in high-income countries. Conversely, the incidence of squamous cell carcinoma is decreasing [2]. The prognosis for patients with esophageal cancer is poor, with published data indicating only about 12-39% of patients surviving for five years following radical treatment [3, 4]. Over 50% of patients with esophageal cancer are beyond the reach of radical treatment at the time of diagnosis, with a five-year survival rate as low as 3%. Consequently, palliative management becomes a fundamental approach in such cases [5, 6].

Patients with esophageal cancer present a clinically diverse group, which significantly influences the management approach. For squamous cell carcinoma patients, direct tumor contact with the bronchial tree can lead to bronchial narrowing or esophagobronchial fistula formation. Typical predisposing factors in these patients include alcohol abuse, smoking, significant weight loss, cancer cachexia, and recurrent aspiration pneumonia. Therefore, preoperative evaluation plays a crucial role in their management. Symptoms related to respiratory dysfunction are common in this patient population.

Conversely, patients with adenocarcinoma of the esophagus and esophagogastric junction generally present with a better clinical condition. Predisposing factors associated with this condition include obesity, gastroesophageal reflux disease, and Barrett's esophagus. The presence of tumor infiltration into the stomach can significantly impede effective clearance and interventions such as stenting, owing to anatomical considerations. Thus, careful consideration and evaluation of the tumor's extent and anatomical involvement are vital in determining the most suitable treatment approach for these patients.

Palliative management, designed to improve the quality of life for patients, can also pave the way for further treatment. Several techniques for restoring the esophageal lumen have gained recognition, including mechanical methods such as esophageal dilation and stenting, as well as ablative techniques like photodynamic therapy, laser therapy, and cryotherapy. Non-endoscopic treatments such as external beam radiation therapy (EBRT) or brachytherapy, combined with chemotherapy, can also be considered for managing dysphagia related to esophageal cancer. These methods are often combined. The choice of the appropriate endoscopic procedure depends on the symptoms, prognosis, and individualized treatment plan of the patient. Literature suggests that certain techniques not only alleviate dysphagia but also improve overall survival [7-11].

Treating patients with advanced esophageal cancer or those deemed unfit for surgery poses a significant challenge. An individualized approach to patient care requires a comprehensive understanding of various therapeutic methods. Hence, this paper seeks to present current knowledge on available methods for alleviating esophageal obstruction in patients suffering from dysphagia due to esophageal cancer.

Materials and Methods

We conducted a systematic search using the PubMed and Google Scholar databases, covering articles published from 1985 to the present. Relevant keywords and Medical Subject Headings (MeSH) were used in our search strategy to identify studies related to the management of dysphagia in esophageal cancer. We included peer-reviewed journal articles from the specified time frame that focused on interventions, techniques, and outcomes associated with this condition.

Results and Discussion

Mechanical Methods

Esophageal Dilation

In contrast to benign strictures, where dilation may serve as a standalone treatment method [12], for esophageal cancer, it facilitates other procedures. In esophageal cancer cases, dilation serves multiple purposes, including facilitating endoscopic ultrasound (EUS) diagnostics, placement of stents or percutaneous endoscopic gastrostomy (PEG) tubes, and providing short-term relief of dysphagia before initiating chemoradiotherapy in a multimodality approach [9, 10, 13]. In terms of efficacy and safety, wire-guided dilation (OTW - Over the Wire) with flexible polyvinyl bougies is currently the most popular. Balloon (TTS - Through the Scope) dilators are used less commonly [14, 15]. Wire-guided bougie dilation, first described in the mid-1980s, has gained wide acceptance [16]. Flexible

dilators (Savary-Gilliard® or Wilson-Cook Medical Inc., Winston Salem, N.C., USA) of successive diameters are introduced through the stenosis, guided by a wire, which must be passed through the stenotic section prior to dilation. Fluoroscopic control is not mandatory [13]. It remains unclear if the "rule-of-three" applies to cancer-stenosis [12-15]. Various balloon types are available on the market. Balloon dilation (TTS) is currently mainly used to facilitate EUS completion in obstructive esophageal cancer [17]. It can also precede chemo- or chemoradiotherapy in esophageal adenocarcinoma (EAC) or squamous cell carcinoma (ESCC), and can address restenosis after these treatments [18].

Complications (Adverse Events - AEs)

Major complications of esophageal dilation include perforation (0.9 - 4.45%) and significant bleeding/haematemesis (0.06%) [18-20]. Mortality after dilation ranges from 0.81-3.1% [18-20]. Adverse events occur more frequently with dilation of malignant strictures [20].

Esophageal Stenting

Presently, three types of self-expanding stents are available for esophageal cancer treatment: self-expanding metal stents (SEMS), self-expanding plastic stents (SEPS), and biodegradable stents (BDS). SEMS and SEPS can be either uncovered or partially or fully covered. Uncovered stents have a low migration rate but a high tissue ingrowth rate, and they have been largely replaced by newer covered stents. SEMS are considered easier to place compared to SEPS [21]. Furthermore, metal stents have shown lower rates of syndrome recurrence and serious adverse events, making SEMS the recommended choice over SEPS [10]. The indications for stenting in esophageal cancer include 1) palliation of malignant dysphagia in cases of inoperable cancer, 2) sealing of tracheo- or bronchoesophageal fistula [10]. SEMS placement is preferred over laser or photodynamic therapy, but brachytherapy alone or in combination with stenting might be considered in patients with longer life expectancy [10]. The 2021 Update of the European Society of Gastrointestinal Endoscopy (ESGE) Guidelines on esophageal stenting strongly advises against using esophageal stenting as a bridge therapy prior to surgery [10]. Despite the conflicting results regarding the potential negative impact of stenting prior to multimodality treatment on outcomes such as R0 resections and overall survival, there is a higher incidence of adverse events associated with stenting, including chest discomfort, stent migration, and fistula formation. Therefore, the use of SEMS during the neoadjuvant treatment period is inadvisable [10, 21]. There is insufficient literature on the use of biodegradable stents in the context of esophageal cancer. Like other uncovered stents, BDS are prone to tissue ingrowth. More research is required to determine if BDS could serve as bridging therapy before neoadjuvant treatment [10, 14].

Complications

The reported rate of major adverse events (AE) is 18-21% [10]. The most frequent early AEs include reflux (9.3%), severe pain (8.7%), bleeding (7.6%), perforation (0.9%), and airway obstruction (0.4%) [10, 13]. Delayed complications occur in up to 53-65% of patients. The most common delayed complications are reflux (15%), severe pain (15%), tissue ingrowth/stent occlusion (3-18% for partially or fully covered stents - PCSEMS, FCSEMS), stent migration (0-20%), and tracheo-bronchoesophageal fistula (3.4-10%) [10, 21]. The reintervention rate can reach up to 50% [21].

The mortality rate associated with esophageal stenting in cancer ranges between 0.4% and 7% [13, 21].

To date, the use of PCSEMS or FCSEMS has not been shown to affect the rate of complications. Likewise, the placement of stents with or without an anti-reflux mechanism does not impact reflux [10, 14].

Ablative methods

Ablative methods include: photodynamic therapy (PDT), laser therapy (LT), argon-plasma coagulation (APC), brachytherapy (iBT), and spray/liquid nitrogen cryoablation.

Photodynamic Therapy (PDT)

Photodynamic Therapy (PDT) is based on the chemical destruction of tumor tissue mediated by singlet molecular oxygen. Reactive oxygen species (ROS) are generated while irradiating the tumor site with light of an appropriate wavelength in the presence of a photosensitizer [22, 23]. ROS lead to tissue necrosis, cellular apoptosis, and vascular obstruction. Photosensitizers (PSs) are molecules with a greater affinity for cancer than for healthy cells. They can be administered orally or intravenously. There are three generations of photosensitizers [23]. The first generation consists of porphyrin/hematoporphyrin and their derivatives. The second generation includes porphyrins, chlorophyll derivatives, and dyes. The third generation comprises a combination of first- and second-generation molecules combined with antibodies and nanoparticles. PSs differ in the wavelength needed to activate them as well as in the depth of induced necrosis.

First-generation PSs, such as Porfimer sodium (Photofrin), temoporfin/mTHPC (Foscan), and 5-aminolevulinic acid (5-ALA), are activated by red light energy (excimer dye laser). They absorb light at 630 nm, 652 nm, and 635 nm, respectively. The depth of necrosis reaches 7 mm, 5-10 mm, and 2 mm, respectively [23]. Talaporfin sodium (Laserphyrin), a second-generation PS, causes deeper necrosis up to the muscularis propria, as it absorbs light at a longer wavelength (664 nm) emitted by a diode laser [24].

Indications for PDT include:

- Mucosal or submucosal esophageal cancer.
- Tumor size within 2x2 cm.
- Tumors smaller than half the circumference of the lumen.
- Tumors that are difficult to resect endoscopically [22, 25].

PDT, especially when using the second generation of PS—Talaporfin—can be applied as salvage therapy in nonsurgical patients with local recurrence after chemoradiotherapy (CRT) or radiotherapy (RT) [25-27].

Complications

The most important complication observed in photodynamic therapy (PDT) is skin hypersensitivity to light, which occurs in approximately 6-32% of patients [22-27]. To prevent this, patients should adhere to long-term sun protection measures: 4-6 weeks for first-generation photosensitizers and 2 weeks for Talaporfin [24, 26, 27]. Less common complications include perforation (2.3%) and stenosis (7.7-24%). Additionally, there has been a reported case of fatal esophageal-aortic fistula [22, 25]. Fever, chest pain, and photosensitivity are common side effects, regardless of the photosensitizer used. However, serious complications such as perforation or stenosis are more likely to occur after salvage therapy, particularly with first-generation photosensitizers [22, 23, 25].

Laser Therapy (LT)

Laser therapy involves the delivery of energy using the Nd:YAG laser directly to the tumor tissue. The laser is introduced through the gastroscope, positioned 1 to 2 cm above the obstructing tumor, resulting in heating, burns, and vaporization [14]. The effectiveness of this method in restoring esophageal patency is reported to reach 80% [14, 28]. However, multiple treatment sessions (2-6) are often necessary [29, 30]. It is important to consider that patients with a longer life expectancy will likely require a repeat procedure in 4-12 weeks [14, 28].

Complications

The most common complication of laser therapy for esophageal obstruction is re-occlusion of the esophagus. Isolated cases of tracheoesophageal fistulae have been reported [14, 29, 30].

Argon Plasma Coagulation (APC)

Argon plasma coagulation (APC) is a technique used to deliver energy through electrically conductive argon gas, resulting in coagulation and destruction of neoplastic tissue. It is classified as a form of monopolar electrocautery [14, 31, 32]. During the procedure, catheters are inserted through endoscopes, providing either an axial, side fire conical, or circumferential beam [32]. The depth of tissue destruction achieved with APC typically ranges from 2-3 mm [14]. It is noteworthy that 26-100% of patients require a minimum of two procedures to achieve esophageal recanalization [31, 32].

Cryoablation

Cryotherapy is a therapeutic approach that involves the freezing of tissue using endoscopically delivered liquid nitrogen (LNSC - liquid nitrogen spray cryotherapy) or compressed carbon dioxide. The freezing process induces the formation of water crystals within the cells, causing damage to the cell membrane and protein denaturation. Subsequently, osmotic dehydration of the cells occurs, leading to cell death. In low-pressure nitrogen spray cryotherapy, the surrounding temperature is reduced to -196 degrees Celsius, while compressed CO2 achieves a temperature of -78 degrees Celsius. Gas venting is necessary in both methods, with rates of 6-8 l/20 seconds for nitrogen and 6-8 l/min for CO2. It is important to note that a sudden increase in gas volume within the gastrointestinal tract can potentially cause perforation [11]. The precise mechanism of action of cryotherapy in palliative therapy is not fully elucidated. It is believed to involve direct damage to superficial layers, likely through the activation of cytochrome-C from damaged mitochondria. Additionally, cryotherapy has an impact on the deeper matrix of the tumor tissue, and an autoimmune effect is also postulated [11]. The dosage and duration of cryotherapy have not been standardized adequately. Typically, three freezing cycles lasting 20-40 seconds each are applied, with a thawing interval of at least 45 seconds between cycles. The procedure often necessitates repetition with a 4-6 week interval [7, 11, 14].

Complications

Complications of cryotherapy include chest pain, bleeding, and perforation [11]. Additionally, there is a risk of developing esophageal stricture, which occurs in approximately 13% of cases. This risk is particularly elevated in patients who have undergone previous interventions such as endoscopic resection, radiotherapy, or photodynamic therapy (PDT) [7, 11, 14].

Brachytherapy

Indications for palliative intraluminal brachytherapy (iBT), as outlined by the American Brachytherapy Society, include the following [33]:

- Unresectable local disease progression/recurrence after definitive radiation treatment.
- Adeno- or squamous cancers of the thoracic esophagus with distant metastases.
- Stenosis.
- Dysphagia.
- Tumor hemorrhage.
- Alternative to stent placement.

Brachytherapy is administered endoscopically under sedation. Adequate positioning of the applicator requires a minimum of 10 mm of esophageal lumen, occasionally necessitating a separate dilation session to achieve the desired diameter [33]. The use of 3D CT-based treatment planning is recommended as it offers advantages over the applicator-based approach. This method allows for precise calculation of the dose, taking into account the local anatomical relations of the tumor and aiding in the sparing of organs at risk of irradiation [33]. The success rate in alleviating dysphagia ranges from 48% to 73%, and the median time to restenosis has been reported to be 4.2 months [14].

Complications

Complications of brachytherapy include fistula formation, which has been reported in 5-6% of patients. Additionally, approximately 15% of patients develop strictures as a result of the treatment [14].

Combined Methods

There are several possibilities for combining the methods described above. Esophageal dilation and each ablative method can be supplemented with radiotherapy or radiochemotherapy. Intraluminal brachytherapy can be used as initial treatment (boost) to external beam radiotherapy (EBRT) or as salvage treatment in case of tumor recurrence after radical EBRT [33]. A specific method of combined therapy is the use of stents coated with radioactive iodine-125. This combination of stenting and brachytherapy has resulted in an extension of the dysphagia-free period, although it comes with a higher risk of massive bleeding in patients previously treated with external beam radiotherapy [8, 34, 35]. Each case of failure of ablative therapy may indicate the need for esophageal prosthetics. However, esophageal prosthesis placement is contraindicated prior to planned external beam radiotherapy [9, 10].

Discussion

The most prevalent method for treating dysphagia in esophageal cancer is stent placement [12-14]. The implementation of a stent in a single procedure offers the fastest restoration of oral feeding capability [14, 32, 33]. Self-expandable metal stents (SEMS) possess a technical edge over plastic stents (SEPS) concerning ease of placement. They also exhibit a better complication profile (lower rates of granulation tissue ingrowth and migration) [21]. According to the European Society of Gastrointestinal Endoscopy (ESGE) guidelines, SEMS are preferred over photodynamic therapy (PDT) and laser therapy (LT). The quick relief of dysphagia with SEMS indicates their use, particularly in patients with advanced-stage disease and a short estimated survival time (<3 months) [9, 10]. For patients with a longer estimated survival time, ablative methods should be considered [11, 14, 32, 33]. It should be highlighted that due to the high complication rate, stent placement is not recommended as a bridging therapy before surgery or planned radiotherapy [9, 10] Chemoradiotherapy reduces the degree of dysphagia; however, its effect may only become evident several weeks after the first dose [7]. Intraluminal brachytherapy (iBT) also exhibits delayed action, but its efficacy in maintaining esophageal patency is longer-lasting compared to SEMS. Nonetheless, the insertion of an isotope catheter during the iBT procedure necessitates a minimum esophageal lumen diameter of 10 mm. If the stricture is narrower, esophageal dilation is required, which also improves dysphagia [33]. Brachytherapy, both as an exclusive treatment for malignant dysphagia and salvage therapy in recurrent cancer after radical EBRT, seems to be an overlooked and underutilized option. The limited availability of this method may be the reason for its underutilization [14, 33].

Another method necessitating prior esophageal clearance is cryoablation with liquid nitrogen spray cryotherapy (LNSC). Clearance is crucial to introduce a ventilation tube into the stomach, which prevents perforation due to the sudden introduction of a significant volume of gas into the gastrointestinal tract. Although data on cryoablation are limited, it appears to be a promising method. A report by Dhaliwal et al., which compares the results of combining LNSC with chemotherapy to exclusive chemotherapy use, is particularly intriguing. The survival in the LNSC+CTH group compared to the CTH group was 19.2 vs 9.5 months, respectively [11]. The mechanism behind these results is unknown. The authors suggest that improvement in the nutritional status of patients who underwent LNSC may be one of the contributing factors. They also propose a mechanism involving an autoimmune response to tumor tissues located deeper than the freezing zone [11]. Similar observations were made by Guo, J. H. et al., evaluating the use of LNSC before chemoradiotherapy. Assessing the clinical response to neoadjuvant treatment with liquid nitrogen cryoablation and chemoradiotherapy, a complete clinical response (based on endoscopy biopsies and PET CT) was observed in 56% of patients. This result contrasts with the 29% complete pathological response rate reported in the seminal study by van Hagen et al. [7, 36]. However, it is crucial to acknowledge the difference in evaluating treatment response between clinical and pathological responses in these two studies. Furthermore, studies on the application of liquid nitrogen cryoablation have been conducted on small patient cohorts, mostly focusing on early-stage tumors (T1, T2) [7, 11, 14].

Conclusion

The authors wish to emphasize that daily practice, often influenced by economic factors and the availability of specific methods, has led to the widespread use of esophageal stenting. Instances of stenting prior to surgical procedures or radiotherapy are frequently observed. Stents are primarily placed in patients with a relatively good prognosis, while the potential of ablative methods is often overlooked. Therefore, there is a need to enhance organizational efforts and conduct further research aimed at expanding the use of ablative methods for the management of malignant esophageal obstruction.

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