Invited Review

Interventional Therapy of Esophageal Cancer

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Key Words

Arterial infusion · Electrochemical interventional therapy · Endoscopic resection · Esophageal cancer · Interstitial involvement · Stent placement

Abstract

Esophageal cancer (EC) is the fourth leading cause of cancer death in China. Despite a lot of advances in diagnosis and therapy, the survival rate of patients with EC is low. There is urgent need for a variety of methods and techniques to improve the survival time and alleviate the lesions of EC. Nowadays, alternative and less invasive approaches to the treatment of ECs are being identified. Here, we review several main interventional methods at different stages of EC, including endoscopic resection, stent placement, arterial infusion, photodynamic therapy, and radiofrequency ablation. This review will focus on the indications, methods, clinical outcomes, and complications of these methods, which may help guide the way forward.

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Introduction

Esophageal cancer (EC), which is the eighth most common cancer and the sixth most lethal cancer worldwide, remains an important global public health problem [1, 2]. EC affects more than 450,000 people worldwide, and its prevalence is expected to increase by 140% by 2025 [3, 4]. On the basis of the latest investigation, there were about 18,170 new cases and 15,450 deaths in 2014 in the United States [5]. However, developing countries made up more than 80% of total EC cases and deaths, and the cases in China account for half of worldwide EC cases [6]. Moreover, the incidence of EC is about 10 times higher in certain areas extending from Northeast China to Central and Eastern Asia than that in the United States. Adenocarcinoma and squamous cell carcinoma (SCC) are two major histologic types of EC, while small

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Fig. 1. **a** Early esophageal tumor. **b** EMR: the tumor is suctioned into the cap. **c** EMR: the tumor is completely resected.

cell carcinoma is a rare disease, accounting for 0.94–1.6% of all ECs [7, 8]. However, of all ECs, the incidence of SCC is approximately 95% in China [9], while the incidence of adenocarcinoma is relatively lower, with only about 5% per year from 2002 to 2011 [10].

Despite plenty of advances in diagnosis and therapy, the 5-year survival rate for all EC patients is about 15–20% [11]. There are a lot of obstacles when treating advanced EC, such as the distant failures and high rate of locoregional progression [12]. Currently, the treatment of EC mainly includes surgery, radiotherapy, chemotherapy and interventional therapy. However, the treatment options should be chosen according to several elements, which include cancer stage, cancer type, complications, the patient's physical status and the possible side effects. For operable patients, surgery remains the first-choice treatment for resectable EC [13]. Nevertheless, local resection is still far from satisfactory because of the high related death rate of surgery and the negative effect on quality of life following surgery [14]. Furthermore, a large portion of patients with EC are found with unresectable disease in the middle to late stage due to highly advanced disease, and even with metastases to multiple lymph nodes or distant organs. Therefore, the purposes of clinical treatment at present are to reduce dysphagia symptoms, improve the quality of life and extend the lifespan of EC patients.

Interventional treatment, including endoscopic resection (ER), stent placement, arterial infusion, photodynamic therapy (PDT), radiofrequency ablation (RFA) and so on, is among the most important methods in the treatment of EC, with excellent effect and reliable with little harm [15]. This review will provide an overview of interventional treatment in EC, with emphasis on the indications, methods, complications, and clinical outcomes of these methods.

Endoscopic Resection

Early EC is defined as a tumor limited to the mucosa with or without metastasis to lymph nodes or distant organs. ER, which includes endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), is regarded as a minimally invasive and effective therapy for the early stage of EC (fig. 1).

Endoscopic Mucosal Resection

EMR implies local excision of the dysplastic lesion. When the tumor is limited to the esophageal mucosa and the lesion size is <20 mm, EMR will be recommended as an alternative therapeutic modality. Furthermore, its results are similar to those achieved by surgery, with a good long-term survival outcome [16, 17]. According to a study in Hong Kong [17], ESD

was performed in 153 (81.8%) lesions and EMR in 34 (18.2%) lesions. The 30-day morbidity rate was 14.4%, while severe bleeding and perforations accounted for 3.2 and 4.3%, respectively. The results showed that short-term survival was very good. However, few studies have compared the long-term outcomes of ER and surgery for EC treatment. Pyo et al. [18] made this comparison for early gastric cancer, and the results demonstrated that EMR might not be inferior to surgery with respect to overall survival in patients who meet the absolute or expanded criteria. However, disease-free and recurrence-free survival might be lower after EMR than after surgery. There are still limitations to the safety and efficacy of ER. Moreover, there will be recurrence, especially when a lesion >20 mm is removed by EMR.

Endoscopic Submucosal Dissection

In order to overcome these limitations of EMR, ESD was developed. The technique of ESD with improved needle knife makes it possible to remove large lesions in the alimentary tract despite the presence or size of submucosal fibrosis, thus providing en bloc specimens for adequate pathological evaluation of lateral and deep margins [16]. However, it is still a technically difficult and time-consuming procedure associated with a higher rate of complications.

The residual mucosal defect may cause deep ulcers, esophageal wall fibrosis, proliferation of local submucosal fibrous connective tissue, acute inflammation, collagen deposition, and even esophageal stricture formation after the procedure [19]. The incidence of esophageal strictures after ESD has been extremely high at 88–100% [20–22], and the risk factors mainly include cervical location when the tumor size is >3/4 of the esophageal circumference and the diameter of a longitudinal tumor is >40 mm [23, 24]. Patients' quality of life is seriously affected due to these complications. Currently, the methods of prevention and treatment of esophageal stenosis include endoscopic autologous cell transplantation, pharmacological treatment, stent placement and endoscopic esophageal dilatation [25]. However, no single method has been widely recognized as effective in clinical practice. Experimental studies have emerged in recent years, but most of them are in the animal research stage.

To date, there are few long-term follow-up data on ESD for EC. Several reports indicated that there was a higher risk of local recurrence in patients with incomplete resection compared with complete resection during ESD.

Stent Placement

Esophageal stents have a history of more than 100 years, since Symonds discovered the benefits of the esophagus stent for the first time in 1885. Atkinson and Ferguson [26] treated inoperable malignant strictures at the cardia with fiberoptic endoscopy in 1977, and Frimberger [27] treated malignant esophageal stenoses with an expanding spiral in 1983. Later, nickel titanium alloy, stainless steel and other metal stents have been developed in recent decades [28]. The types and classifications of esophageal stents are various. According to the materials, esophageal stents can be divided into polyester plastic, silicone, stainless steel, alloy, biodegradable biomaterial scaffolds, etc.; according to the expansion mode, they are divided into expansion and memory stents; and according to whether they are coated, esophageal stents can be divided into fully/partly coated and naked stents. Moreover, there are also some other special designs of stents, such as reverse flow preventable, radioactive, recyclable, biodegradable, heating, chemotherapy drug slow release stents, and so on. At present, the main stents sold in the market include Gianturco-Rosch Z, Song, Choo, Ultraflex, Wallstent, Esophacoil, Niti-S, Flamingo, Ella, Polyflex, Niti shape memory alloy stents and Z-type stainless steel wire and so on [29].

Stent placement is suitable for unresectable EC, inducing narrow or esophageal fistula later. The procedure was confirmed by various procedures such as digital subtraction angiography, ultrasonic endoscopy and so on. The site of esophageal stent placement is 2 cm above the cricopharyngeal part in solid and narrow tumors. At present, esophageal stents are already being widely used in the treatment of esophageal stenosis or obstruction, and the effects in patients with EC are remarkable [30]. In this paper, we mainly summarize two kinds of stents, self-expandable stents and esophageal stents with iodine 125 (^{125}I) seeds, which have been used commonly in recent time.

Self-Expandable Stents

Currently, self-expandable metal stents (SEMS) and self-expandable plastic stents (SEPS) are included in the available stents for esophageal obstructions. Metal stents, made of stainless steel and alloys, are able to generate high radial forces to maintain stent patency and position with a higher degree of flexibility [31]. SEMS are available in three styles, including uncovered, partially covered or fully covered with a plastic membrane or silicone. Moreover, SEPS are always composed of polyester and silicone. It has been reported that symptom relief, survival rate and complications are the same with the use of SEPS and of SEMS. However, insertion of SEPS is technically more difficult and associated with a higher migration rate compared with SEMS. It was shown that SEMS could alleviate dysphagia rapidly in 90% of patients when they were put in place endoscopically under fluoroscopic control [7]. However, there is still debate about the first choice to different types of SEMS.

The adverse effects of stents include high obstruction recurrence as the result of tumor ingrowth, stent migration, retrosternal pain, perforation, food impaction and bronchoesophageal fistulas. It is always effective to insert a second stent for restoring luminal patency when tumor ingrowth occurs, and endoscopic clearance will be used for obstruction caused by impacted food. Stent migration is a one major complications, its occurrence varying from 4 to 36% [31, 32]. Moreover, the risk of migration will increase significantly when the stent is placed across the gastroesophageal junction [33, 34]. Some techniques of stent fixation and new stent designs preventing migration have been described [35]. Nevertheless, a double-layered SEMS embedded into the esophageal wall (named Niti-S stent) is capable of reducing migration and preventing tumor ingrowth with a structure of an outer uncovered nitinol wire mesh and an inner polyurethane layer (fig. 2). Several clinical studies have demonstrated its low migration rate [36, 37]. Experts suggested that once an esophageal stent migrates, it may cause bowel obstruction with perforation. In that case, removal of the migrated stent should be considered if possible [38].

Esophageal Stents with ^{125}I Seeds

In recent years, stent placement has been an option for alleviating the symptoms caused by esophageal strictures. Nevertheless, there is a high recurrence rate of neoplastic strictures following stent placement. In order to help radiotherapy, radioactive stents were developed. Among these, an esophageal stent loaded with ^{125}I seeds was designed, with a combination of advantages of immediate relief of esophageal dysphagia and radiation therapy with brachytherapy in advanced EC patients who are diagnosed with unresectable tumors due to extensive lesions, metastases, or poor medical effect [39].

^{125}I radioactive seeds were preloaded into the sheaths (4.8 mm long and 0.8 mm wide), which were attached to the outer surface of the SEMS immediately before stent insertion. Esophageal stents loaded with ^{125}I seeds were first demonstrated to be safe and feasible in a healthy rabbit model [40]. Then, esophageal stents with ^{125}I seeds were developed in clinical research. It was shown that an irradiation stent with ^{125}I can relieve dysphagia and prolong patient survival compared with controls, and no additional complications related to seed

Fig. 2. The Niti-S stent has a double-layered configuration. The inner covered layer protects against tumor ingrowth and the additional uncovered mesh helps to resist migration.

implantation were found [41, 42]. Other research also revealed that this method could help EC patients to relieve their esophageal obstruction immediately and slow down the rate of tumor growth [43, 44]. Furthermore, the study by Luo et al. [45] indicated that expandable esophageal stents loaded with ^{125}I seeds were an ideal therapeutic approach for patients with advanced EC. Overall survival was 6–20.5 months (mean 9.9 months), and all patients had improved dysphagia after stent deployment; 25 patients had a Karnofsky score ≥ 60 after the procedure compared to 11 patients before operation.

However, with the limitation of accurate measurement using in vivo dosimetry of the irradiation seeds around the stent, the calculated dose might differ from the real dose around the stent. Nevertheless, the common complications and side effects did not differ between the irradiation stent and conventional stent groups, the complaints being esophageal fistula, hemorrhage, perforation, aspiration, failure of deployment and expansion, tumor overgrowth and ingrowths, stent migration, gastroesophageal reflux, recurrent dysphagia, and pain [41]. In their research, Shen et al. [46] also indicated that ^{125}I Niti stents had the same probability of thyroid toxicity and other adverse reactions compared with ordinary stents by observing about 100 cases of clinical application.

Arterial Infusion

Arterial infusion chemotherapy is a method to treat tumors using femoral artery puncture, an esophageal artery interventional catheter with selective local infusion of chemotherapy drugs, which has achieved several theoretical advantages over conventional therapy for the treatment of unresectable malignancies.

Research showed that the target arterial infusion of verapamil combined with chemotherapy significantly improved the clinical symptoms of advanced EC. The study by Zhu et al.

Fig. 3. A case with local failure after chemoradiotherapy was treated with salvage PDT. **a** A local failure lesion limited to T1b. **b** A well-demarcated lesion after Lugol staining. **c** Deep ulceration was present 1 week after PDT. **d** Complete response was achieved and continued 1 year after PDT.

[47] included 24 patients, 23 of whom achieved partial response, which is an efficiency rate of 95.8%. When liver metastasis occurs in advanced EC, arterial infusion therapy also plays a therapeutic role. Ikebe et al. [48] reported on hepatic arterial infusion therapy with a combination regimen of low-dose *cis*-diamminedichloroplatinum and 5-fluorouracil as a multimodality therapy for liver metastases of EC. The hepatic metastases decreased markedly with no adverse effects, so hepatic arterial infusion chemotherapy can be a choice for EC when metastasis is limited to the liver. The serious complications after esophageal artery perfusion chemotherapy are few. The main complications are esophageal perforation, spinal cord injury and esophagitis. Cytotoxic drug and tissue tolerance are the main causes of esophageal perforation, so the drugs should not be strongly excitant or administered at a high dose or concentration, and the perfusion rate should not be too fast.

Arterial infusion chemotherapy also has certain limitations: (1) As EC is not a typical tumor with rich blood supply and shows individual differences, sometimes specific tumor arteries of blood supply cannot be found or introduced during the operative time. (2) Although the dosing accuracy of instantaneous blood concentration is high, it cannot long enough to maintain the effective blood drug concentration [15, 49].

Photodynamic Therapy

In recent years, PDT has been getting more attention and application in the treatment of EC because of its good selectivity and safety, especially in the setting of EC, as well as Barrett's mucosa with neoplasia or dysplasia (fig. 3) [50–53]. The photosensitizer will accumulate in the tumor, and then treatment occurs when the photosensitizer is activated by endoscopically applied laser directly to the malignant tumor. Besides, the activated photosensitizer drugs are capable of interacting with oxygen or other cellular and vascular components to stimulate a photodynamic reaction, often inducing damage or necrosis of the target tissue. Thus, the effect of treatment is often determined by the concentration of photosensitizer drug in the mucosa and the dose of light energy.

In China, PDT is approved for EC with porfimer sodium followed by 630 nm wavelength excimer dye laser irradiation. The initial descriptions of PDT, which is combined with porphyrin-based agents, dihematoporphyrin ether (DHE) with red light and hematoporphyrin derivative (HpD), have become the major forms of PDT. After further purification of the photosensitizers, several agents were released: Ps (Photofrin, USA), DHE (available in Europe under the trade name Photosan), and a second-generation form of HpD available in China under the trade name Hemporfin. A prospective randomized research by Overholt et al. [54] found that the ablation of high-grade dysplasia and the recurrence of neoplasia was 77 and 15% in the PDT group, while the rates were 39 and 29% in the omeprazole group. It is thus implied that PDT is a therapeutic method in the clinic and can ablate high-grade dysplasia and reduce the potential impact of cancer. Consistent with the research results of Overholt et al., another three studies identified PDT to have superior outcomes, satisfactory safety profiles and longer survival periods. They included 38 patients with superficial SCC, 113 consecutive patients with local failure limited to T2 without any metastases, and 93 consecutive SCC patients separately [55–57]. Nevertheless, no severe side effects, complications or therapy-related deaths were found with the method [57].

Radiofrequency Ablation

Radiofrequency waves are a kind of low-frequency and high-electric-effect magnetic waves. The polarity transformation frequency of radiofrequency is 150–1,000 kHz, which can produce a heat effect when getting into contact with the human body, causing dehydration, drying, pyknosis and necrosis of the lesion tissue to achieve a treatment effect. Moreover, the lesions can be eradicated with adjusted output power and time, with decreased injury to normal tissue and without adverse effects such as pain or stimulation of heart. Radiofrequency electrodes do not bind with the tissues or produce smoke or fire, so they have no effect on endoscopic therapy. Nowadays, RFA is a popular therapy for EC.

The use of RFA is recommended in individuals with high-grade dysplasia in Barrett's esophagus, early-stage (T1a) intramucosal cancer and selected individuals with low-grade dysplasia [58]. Furthermore RFA, which took only around 30 min to complete in the case of a 48-year-old man with an 8-cm-long circumferential squamous high-grade dysplasia over the esophagus, showed good effect in early SCC neoplasia without major adverse events [59]. Furthermore, an investigation which included 429 patients in a community practice setting revealed and verified RFA as a safe and effective treatment for Barrett's esophagus [60]. The research by Chuanqing et al. [61] indicated a significant short-term effect in relieving esophageal obstruction and improving nutrition intake by endoscopic RFA. Moreover, Matsui et al. [62] retrospectively evaluated the outcomes for pulmonary metastases from EC after RFA in 21 consecutive patients. From the initial RFA session, the rates of estimated overall survival

were 85.7, 54.8 and 38.4% at 1, 2 and 3 years, while 7.4% adverse events occurred, including pleural effusion requiring chest tube placement and pneumoderma requiring surgical intervention. In conclusion, RFA is a potential therapeutic option for patients who suffer from pulmonary metastases from EC. The main adverse reactions included persistent nausea, severe epiglottic reflex, burning pain in the chest area and pain in upper abdomen [61].

Conclusions

In summary, this review reports several approaches to interventional treatment in EC with a focus on ER, stent placement, arterial infusion, PDT and RFA. They are the regular intervention methods used in the treatment of EC, with some advantages and disadvantages. Thus, fully considering tumor location, tumor stage, the patient's age, physical and economic conditions as well as other factors will be necessary to maximize the advantages of each interventional treatment. According to organic combination and sequential treatment, the use of different interventional methods to achieve the best therapeutic effect will be an important guide and medical thought to every physician.

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Statement of Ethics

This study complied with the guidelines for human studies and animal welfare regulations.

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