

# Treatment landscape of advanced esophagus cancer

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**Abstract:** Esophageal cancer (EC) is one of the most common malignant tumors of the digestive tract worldwide. The early symptoms of EC are not obvious, so most patients with EC are already in the advanced stage when they are diagnosed. When the disease progresses to the advanced stage and the best surgical time is missed, radical surgery cannot be used for treatment, which increases the difficulty of treatment. The treatment of AEC has always been a major challenge in clinical practice. A comprehensive treatment plan based on various methods such as surgery, radiotherapy, chemotherapy, immunotherapy, targeted therapy, and traditional Chinese medicine treatment is currently the standard for the treatment of AEC. With the continuous progress and development in the treatment of AEC, the survival period and quality of life of patients with AEC have been improved. In particular, molecular targeted therapy and biological immunotherapy have brought more hope. In the future, under the premise of multidisciplinary diagnosis and treatment, combined with the individualized characteristics and tolerance of patients, the best treatment plan will be selected to further improve the quality of life of patients with AEC and prolong their survival period.

**Keywords:** Advanced esophageal cancer, treatment

## INTRODUCTION

Esophageal cancer (EC) is a malignant tumor occurring in the inner or parietal tissue of the esophagus, usually originating in epithelial cells, and is one of the common gastrointestinal tumors. Its pathogenesis is complex, involving the interaction of many factors such as lifestyle and diet, gastroesophageal reflux disease and heredity. Early EC has no obvious symptoms, and most patients are already in the advanced stage when they come for treatment, losing the best opportunity for surgery, and usually can only take palliative care. Patients with advanced esophageal cancer (AEC) are divided into two types, one is locally advanced but without distant metastasis, and the other is advanced patients with organ metastasis. For patients with AEC, treatment options are complex and patient survival is expected to be short, so decision makers need to constantly adjust their decisions to respond to changes in patient symptoms. Currently, treatment methods for AEC include surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy and multi-mode therapy. However, it should also be noted that if a single treatment is adopted, the treatment expectation is often unable to be achieved. In order to further improve the therapeutic effect, joint programs are generally adopted to carry out high-quality treatment

for AEC. This article reviews the progress of treatment methods for AEC, and provides theoretical support and practical guidance for clinical decision-making.

## SURGERY

Resection of EC is a standard method for the treatment of patients with resectable EC, especially the development of minimally invasive technology, which has the characteristics of little trauma, low complication rate and high safety, so that minimally invasive resection of EC has been widely carried out in clinic. However, for patients with locally AEC, there are more residual tumor cells with local metastasis after surgery, so there is a high recurrence rate and a high risk of metastasis. For the treatment of locally AEC, the historical trend has been from single surgical treatment to surgical combination multi-mode comprehensive treatment. On the basis of surgery, there are many combination modes, such as postoperative adjuvant therapy (postoperative chemotherapy/radiotherapy/chemoradiotherapy), and neoadjuvant therapy (neoadjuvant chemotherapy/chemoradiotherapy/immunotherapy). The recurrence rate of locally AEC is high, and patients often receive adjuvant treatment after surgery to control the residual cancer cells and reduce the chance of recurrence. Zeng et al found postoperative

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radiotherapy can significantly reduce local recurrence and improve overall survival (OS) in patients with locally advanced thoracic esophageal squamous cell carcinoma after surgery. The progression-free survival and overall survival in patients with locally advanced esophageal squamous cell carcinoma are increased by rational application of postoperative chemoradiotherapy. Adjuvant therapy can be selected according to tumor site, pathological type, gene mutation and biological behavior. With the development of comprehensive treatment mode based on surgery, neoadjuvant combined surgery has gradually become the standard treatment for patients with EC, and it is significantly better than surgery alone in terms of postoperative survival. Neoadjuvant therapy can kill part of tumor cells more effectively, reduce the risk of intraoperative spread and metastasis, facilitate complete tumor resection (no tumor remaining under the microscope, R0 resection), prolong disease-free survival, and bring survival benefits to patients. There are a lot of clinical studies on the therapeutic effects of these different treatments, the results are related to many factors such as the specific program used, the intensity of treatment and the scope of surgical resection, so there has been a lack of treatment guidelines in the sense of true evidence-based medicine for a long time.

### **RADIOTHERAPY**

Radiotherapy is one of the main treatment methods for malignant tumors. For patients with AEC who cannot undergo surgery, the current standard treatment is concurrent chemoradiotherapy. Concurrent chemoradiotherapy kills tumor cells through radiation and chemotherapy drugs, thereby eliminating or reducing tumor lesions and prolonging the survival time of patients with AEC. However, elderly patients are poorly tolerated and cannot accept concurrent chemoradiotherapy. Definite chemoradiotherapy (dCRT) is currently the only radical treatment option for locally AEC who cannot undergo surgery, and radical radiotherapy for the primary lesion and radiotherapy for metastatic lesions in AEC on the basis of systemic treatment may translate into survival benefits. Although radiotherapy techniques have been greatly improved at present, they still cannot significantly increase the survival rate of patients, and the overall therapeutic effect is not satisfactory. In clinical practice, the disease stage of patients, nutritional status, underlying diseases, irradiation range and volume, combined treatment regimens, and treatment tolerance are all important factors affecting the efficacy of dCRT for EC. From the perspective of treatment strategies, induction chemotherapy seems to have failed to bring significant survival benefits to patients, and the replacement of chemotherapy drugs has also failed to significantly improve the survival of patients, making it more difficult for dCRT to further enhance the

efficacy of patients with locally AEC. The organic combination of immunotherapy, chemotherapy, and radiotherapy is expected to become a new combination model for AEC, but research is still in the early stages and further exploration is needed in phase III clinical studies.

### **CHEMOTHERAPY**

Chemotherapy, a common cancer treatment method, may cause adverse reactions such as gastrointestinal reactions, loss of appetite, nausea and vomiting during the treatment process, which can affect the patient's quality of life and treatment effectiveness. For patients with tolerable AEC, chemotherapy can be used as a palliative measure to alleviate symptoms and improve the quality of life of patients. However, the response rate (RR) of monotherapy for AEC is 15% to 30%, with almost no complete remission, and the duration of its effect is relatively short (generally less than 4 months). Therefore, this has promoted extensive research on combined medication to improve the effective rate. At present, the combined chemotherapy regimens for AEC can mainly be divided into two categories: those containing cisplatin and those without cisplatin. At present, there is no standard chemotherapy regimen for AEC. It is believed that with the in-depth research on EC and the continuous emergence of new drugs, more patients will benefit and the long-term survival rate of advanced patients will be improved.

### **IMMUNOTHERAPY**

Tumor immunotherapy achieves the goal of treating cancer by enhancing the attack ability of the patient's own immune cells against cancer cells. Immunotherapy has shown great potential in the treatment of cancer. With the continuous deepening of research, it has been discovered that compared to radiotherapy and chemotherapy, immunotherapy can not only inhibit the proliferation of malignant tumor cells and accelerate their disappearance, but also reduce adverse reactions for patients, with higher safety. At present, the drugs mainly used for immunotherapy in clinical practice for patients with AEC are camrelizumab, sintilimab and pembrolizumab. Although immunotherapy is gradually being used in the treatment of AEC and has achieved good clinical efficacy, the adverse reactions caused by immunotherapy and its negative impact on clinical efficacy have become increasingly prominent, becoming an important topic that scholars in the industry are constantly exploring.

### **MOLECULAR TARGETED THERAPY**

Molecular targeted therapy is a treatment method that designs corresponding therapeutic drugs at the cellular and molecular level based on clearly

identified carcinogenic sites. Once these drugs enter the body, they can specifically select carcinogenic sites to bind and take effect, causing specific necrosis of tumor cells and having less impact on normal tissues. In recent years, with the rapid development of molecular oncology, targeted therapy has become a vital force in tumor treatment. With the continuous in-depth development of molecular biology and pathology in tumorigenesis, development and metastasis, molecular targeted drugs for EC have been widely applied. Currently, for the epidermal growth factor receptor (EGFR) and the proto-oncogene human epidermal growth factor receptor-2 (HER2), vascular endothelial growth factor (VEGF), and cyclooxygenase-2 (COX-2) molecular targets have achieved certain therapeutic effects in the treatment of AEC. Other targeted therapeutic drugs for EC include cyclin-dependent kinase (CDK) inhibitors, mTOR inhibitors, matrix metalloproteinases (MMPs) inhibitors, ubiquitin-proteasome inhibitors, farnesyl transferase inhibitors, etc. The efficacy of these targeted drugs still requires a large number of clinical trials to be confirmed. The signal transduction involved in the occurrence and development of EC is a complex network system involving multiple factors, and there are still many potential targets to be discovered. With the discovery of more and more targets, the combination of multiple targets and the integration of targeted drugs with radiotherapy and chemotherapy will be the focus and trend of targeted therapy for EC in the future.

#### **OTHER TREATMENT METHODS**

Progressive dysphagia caused by malignant esophageal obstruction is the main symptom of AEC, and esophageal stent implantation is the best treatment for alleviating malignant esophageal obstruction caused by AEC. At present, various esophageal stents such as self-expanding stents, absorbable stents, 3D-printed stents, drug-eluting stents, and anti-reflux stents have been developed for palliative treatment of AEC, and their effectiveness has been verified in clinical or animal experiments. Esophageal stents combined with the currently emerging internal irradiation therapy, photodynamic therapy, photothermal therapy and immune checkpoint therapy are expected to achieve in situ treatment of tumors. However, with the development of various new types of stents, how to select stents to achieve better clinical prognosis remains to be studied. Photodynamic therapy is a new treatment for malignant tumors, which involves injecting photosensitizers (a drug that needs to be activated at a specific wavelength) into patients, and then irradiating the lesion with a specific wavelength of laser to generate singlet oxygen and free radicals, damaging subcellular structures and causing necrosis of tumor tissue. In addition, there are some treatment methods, such as Chinese medicine treatment, laser

therapy, dilation therapy and supportive therapy, etc. No matter which method is adopted, a large amount of clinical data support is required. We still need to continuously explore the differences of these methods in the treatment of patients with AEC, make full use of their advantages and avoid their shortcomings, so that their application in patients with AEC can be broader and more precise.

#### **CONCLUSION**

At present, for locally advanced resectable EC, surgical treatment methods mainly include simple surgery and neoadjuvant therapy combined with surgery. For unresectable AEC, radical radiotherapy and chemotherapy, combined immunotherapy, targeted therapy and multidisciplinary treatment are often carried out. The prognosis of patients receiving different treatments is different, and clinicians' understanding of them is often not comprehensive enough. The treatment of AEC still poses considerable challenges, and more clinical trials need to be established to standardize the comprehensive treatment system. Clinicians should follow the principle of multidisciplinary comprehensive treatment and make a comprehensive consideration based on the patient's wishes, physical condition, etc., to select the best treatment method. With the advent of the era of precision medicine, it has become possible to bring good news to patients with AEC by conducting individualized treatment through multi-disciplinary collaboration and the combination of multiple methods.

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