Gong et al. Holistic Integrative Oncology (2023) 2:34
https://doi.org/10.1007/s44178-023-00054-9

Holistic Integrative Oncology

GUIDELINE

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CACA guidelines for holistic integrative management of esophageal carcinoma

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Abstract

Esophageal carcinoma (EC) is a common malignant tumor of the upper digestive tract worldwide. An analysis of the latest data from cancer centers in China showed that the incidence of EC and the number of deaths due to EC in China in 2015 were 266,000 and 188,000, respectively, ranking sixth (6.3%) and fourth (8.0%) among all malignant tumors. The early diagnosis and treatment of EC and standardized diagnosis and treatment are important tasks for EC healthcare professionals in various centers across the country. At present, the 8th edition of the EC staging system jointly released by Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) is the most recent, authoritative and widely used EC staging standard. The EC professional committee of the Chinese Anti-Cancer Association also organizes the "EC Standardization Campaign in China" every year to promote the development of EC diagnostic and treatment norms throughout the country. Since 2011, the EC Committee of the Chinese Anti-Cancer Association has published the Guidelines for Standardized Diagnosis and Treatment of EC. Considering the increasing number of EC clinical studies and the continuous progress in diagnostic and treatment technologies in recent years, the updated Guidelines will include the latest progress in the diagnosis and treatment of EC, with a goal of promoting the forward development of EC diagnosis and treatment in clinical practice.

Keywords Esophageal cancer, Clinical guideline, Holistic integrative medicine

1 Overview

Esophageal carcinoma (EC) is a common malignant tumor of the upper digestive tract worldwide, and it is also a "cancer with Chinese characteristics". EC seriously affects people's lives and health because it is associated with a long-term inability to eat and because it is at an intermediate and advanced stage when it is diagnosed. According to GLOBOCAN 2020 data released by the World Health Organization (WHO), there were approximately 604, 000 new cases of EC and 544, 000 deaths worldwide in 2020, and the morbidity and mortality of EC rank seventh (3.1%) and sixth (5.5%) among malignant tumors, respectively, with the highest morbidity in eastern Asia [1].

An analysis of the latest data from cancer centers in China showed that the incidence of EC and the number

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of deaths due to EC in China in 2015 were 266,000 and 188,000, respectively, ranking sixth (6.3%) and fourth (8.0%) among all malignant tumors [2]. According to an analysis of the continuous monitoring data from 22 cancer registries in China, from 2000 to 2015, after the standardization of the population age structure, the morbidity of EC decreased by 4.2% per year on average, showing a decreasing trend in urban areas and rural areas and in males and females, with the most significant decreasing trend in being observed in females, 5.8% per year on average. The mean age of onset of the pooled population of females, rural area residents and males also tended to be increased, with the mean age of onset being above 65 years. Among this pooled population, the proportion of women and rural area residents with EC who were over 65 years old increased significantly (from 48.7% to 65.4% in women and from 44.2% to 55.8% in rural area residents) [3].

The 2019 Global Burden of Disease Study (GBD 2019) extracted EC data from 31 provinces, municipalities directly under the central government, autonomous regions, and the Hong Kong and Macao Special Administrative Regions in China. The latest results showed that in 2019, the numbers of EC cases and deaths in China were 278,000 and 257, 000, respectively, showing increases of 60.1% and 45.7%, respectively, compared with 1990. The standardized morbidity rate decreased from 20.97/100, 000 to 13.90/100,000, and the standardized mortality rate decreased from 22.08/100, 000 to 13.15/100,000 [4].

The distribution of EC in China shows geographical differences, with EC being most common in regions near the Taihang Mountains (Henan, Hebei, Shanxi, Shandong, Anhui, and Northern Jiangsu regions). According to the EC data of Henan province in 2015, the number of new cases was estimated at 41, 000, and the number of deaths was 29,000. The morbidity of EC was 34.94/100, 000 (41.42/100,000 in males and 28.11/100, 000 in females), with a male-to-female ratio of 1.56: 1. The mortality of EC was 25.30/100,000 (31.07/100,000 in males and 19.21/100, 000 in females), with a male-to-female mortality ratio of 1.73:1.

The standardized morbidity and the standardized mortality of EC were lower in urban areas than in rural areas for both males and females. Both EC morbidity and mortality gradually increased with increasing age, peaking in the age group of 80 to 84 years [5]. The trend in EC deaths from 2006 to 2018 was evaluated in Feicheng city, Shandong province, and a crude mortality of 59.10/100, 000 was found, which increased with age, mainly after the age of 40 years, as well as a greater increase in males than in females. The average life expectancy of residents with household registration in Feicheng city from 2006 to 2018 was 76.84 years, and after the removal of the effect of EC, the life expectancy of the population increased by 0.89 years [6].

Although the morbidity and mortality of EC are greatly increasing in China, the standardized morbidity and mortality are decreasing after age standardization. The characteristics of a decreased overall burden of EC and an increasing age of onset may be related to many factors, such as the initiation of rural EC screening and early diagnosis and treatment in China, the increased life expectancy per capita, and changes in the living environments and lifestyles of residents.

According to data from the National Bureau of Statistics, China is becoming an aged society at an accelerating speed. In 1990, 2000, 2010 and 2019, the proportions of elderly individuals (over 65 years old) in China were 5.63%, 6.81%, 8.07% and 12.6%, respectively. The increasingly serious aging of the population is an important cause of the EC disease burden that China is facing. Therefore, the majority of healthcare professionals in EC treatment in China need to improve their comprehensive understanding of the etiological factors of EC and strengthen their awareness of the characteristics of EC for its early diagnosis and treatment, especially for the elderly population, which is the only way to reduce EC mortality in China.

The etiological factors of EC are various, and smoking, alcohol consumption, overeating and overdrinking, fast eating and drinking, vitamin and trace element deficiencies and preferences for pickled, mildewed, smoked, fried, dried, hard, spicy, salty and hot foods are all risk factors for EC [7]. Moreover, eating pickled food increases the effects of smoking and alcohol consumption on the pathogenesis of EC, whereas fruit intake plays a protective role in this process [8]. In addition, drinking water from unhealthy sources in areas with a high incidence of EC also deserves attention, and drinking water type and water quality are related to "ammonia nitrogen, nitrite nitrogen, nitrate nitrogen" intake in areas with a high incidence of EC [9]. Sichuan province is a high incidence area of EC, and studies have shown that EC is mainly found among rural residents who are elderly, have a low education level, have a low income and are unmarried (divorced or widowed) [10, 11]. However, not all people exposed to these risk factors develop EC, suggesting that genetic factors may play a more important role than environmental factors. The northern Henan region is also a high incidence area of EC in China, and although the environmental factors in this region are similar to those of Sichuan province, EC patients account for a small proportion of the entire population (500/100, 000) but show familial aggregation [12]. EC gene variants exist in EC families in high incidence areas, and family members tend to develop EC under the influence of environmental

factors [13]. Therefore, according to the advanced experience in global EC prevention and control and progress in domestic EC prevention and control, we should fully consider the characteristics and national conditions of EC in China; take measures to mitigate risk factors in a timely, effective and appropriate manner (for example, by promoting smoking cessation, alcohol restriction and nutritional balance in the media); and widely carry out population-based screening for EC in high-incidence areas to reduce the morbidity and mortality of EC.

The pathological types of EC mainly include squamous cell carcinoma and adenocarcinoma. Although the incidence of esophageal adenocarcinoma has increased significantly in North America and Europe in recent decades, squamous cell carcinoma is still the main pathological type of EC in China [14, 15]. The early clinical manifestations of EC are neither typical nor obvious, and the detection rate is very low. Once eating difficulties become obvious, the disease has mostly progressed to the middle and late stages, the prognosis is very poor, and the 5-year survival rate is less than 20%, which also represents an important reason for the poor prognosis of EC patients [16]. There are differences in tumor burden among the eastern, central, and western regions in China, and the medical care level is uneven in different regions, but after reviewing the development of EC diagnostic and treatment techniques over the last century, we found that China has also made great progress. Studies have shown that artificial intelligence technology can be well integrated with endoscopic diagnostic technology for EC to effectively reduce the missed diagnosis rate of precancerous lesions and help endoscopists make a more accurate diagnosis [17]. At present, clinicians at many centers have become familiar with robot-assisted EC resection. Based on a 3D field of view and a flexible and stable robotic arm, this surgical method can provide better surgical field exposure, with absolute advantages in lymph node dissection and finer operation [18]. The remote-control technology of the da Vinci robot can also effectively reduce short-term postoperative pain and improve postoperative quality of life. According to data from several medical institutions in China, the 5-year survival rate of patients with early EC after endoscopic treatment can be higher than 90%, and the 5-year survival rate of patients who receive neoadjuvant therapy combined with surgery for intermediate- and advanced-stage EC has also approached 50% [19, 20].

Therefore, the early diagnosis and treatment of EC and standardized diagnosis and treatment are important tasks for EC healthcare professionals in various centers across the country. China has a vast territory and different sanitary conditions among medical institutions at all levels, and the nonuniformity of diagnostic criteria can affect the quality of treatment. At present, the 8th edition of the EC staging system jointly released by Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) is the most recent, authoritative and widely used EC staging standard. The EC professional committee of the Chinese Anti-Cancer Association also organizes the "EC Standardization Campaign in China" every year to promote the development of EC diagnostic and treatment norms throughout the country. Since 2011, the EC Committee of the Chinese Anti-Cancer Association has published the Guidelines for Standardized Diagnosis and Treatment of EC. Considering the increasing number of EC clinical studies and the continuous progress in diagnostic and treatment technologies in recent years, the updated Guidelines will include the latest progress in the diagnosis and treatment of EC, with a goal of promoting the forward development of EC diagnosis and treatment in clinical practice.

2 Diagnosis of esophageal carcinoma

2.1 Clinical manifestations

The symptoms of early esophageal cancer (EC) are often not obvious and are easily ignored, which is the main reason why early EC is more difficult to detect. Early symptoms mainly include retrosternal discomfort, a mild choking sensation during swallowing, a foreign body sensation, a stuffy sensation, a burning sensation, mild pain in the esophageal lumen or a sensation of food stagnation after eating.

The following typical symptoms of advanced EC occur due to luminal stenosis from tumor growth and infiltration: ① progressive dysphagia, ② retrosternal pain, ③ vomiting, and ④ anemia and weight loss.

The following symptoms of advanced EC are associated with tumor compression, invasion of surrounding tissues and organs, or distant metastasis: ① the compression of the trachea can cause irritating cough and dyspnea, and cough with a choking sensation upon eating, fever, purulent sputum, etc., may occur when esophagotracheal fistula occurs, resulting in pneumonia or lung abscess; ③ the invasion of the recurrent laryngeal nerve can cause hoarseness; ② the invasion of the phrenic nerve can cause phrenic nerve palsy, resulting in dyspnea and abnormal movement of the diaphragm; ④ tumor ulceration or invasion of the great vessels can cause mediastinal infection and fatal hematemesis; ⑤ tumor distant metastasis can cause hepatomegaly, jaundice, an abdominal mass, abdominal effusion, bone pain, subcutaneous nodules and other manifestations; and ⑥ cachexia, which manifests as extreme weight loss and wasting.

2.2 Diagnostic methods

2.2.1 Laboratory examination

2.2.1.1 Blood biochemistry To date, there are no specific blood biochemical tests for EC. Liver metastasis should be considered in patients with EC who have elevated blood alkaline phosphatase, aspartate aminotransferase, lactate dehydrogenase, or bilirubin. Bone metastasis should be considered in patients with elevated blood alkaline phosphatase or serum calcium.

2.2.1.2 Serum tumor marker testing Serum carcinoembryonic antigen (CEA), squamous cell carcinoma-related antigen (SCC), tissue polypeptide antigen (TPA), and cytokeratin fragment 19 (cyfra21-1) can be used for the auxiliary diagnosis, efficacy detection, and long-term follow-up monitoring of patients with EC but cannot be used for the early diagnosis of EC.

2.2.2 Auxiliary examinations

2.2.2.1 Imaging examinations

(1) Esophagography: Esophageal and gastric barium meal X-ray fluoroscopy or radiography is the most commonly used method for the initial diagnosis of EC and gastroesophageal junction tumors. It is simple and economical, and it can clearly and visually show the location and length of EC and the degree of stenosis at the tumor site, especially for cervical EC, for which it can accurately measure the position of the upper edge of the tumor and the esophageal inlet and determine the safe surgical resection margin. At the same time, this method can accurately detect fistulas formed by the ulceration of intermediate- and advanced-stage EC tumors to surrounding structures and can help surgeons understand the condition of the stomach, the replacing organ of the esophagus, preoperatively. Double-contrast barium enema examination is more sensitive for the detection of early small lesions and can be used to help to improve the diagnostic accuracy of esophagogastric junction adenocarcinoma [21].
(2) CT examination: Contrast-enhanced CT of the neck, chest, and abdomen should be used as a routine examination for EC, mainly for EC clinical staging, resectability evaluation, the selection of a surgical approach, and postoperative follow-up. The main basis for CT diagnosis of EC is irregular thickening of the esophageal wall. The normal esophageal wall has a thickness of approximately 3 mm, and if the wall thickness exceeds 5 mm, it indicates an abnormality. CT is more accurate than B ultrasound and chest X-ray in judging distant metastases, such as liver and lung metastases. High-resolution CT can clearly show the periesophageal and abdominal lymph nodes.
(3) Ultrasonography: Ultrasonography can be used to determine whether there is metastasis in vital abdominal organs and abdominal lymph nodes and can also be used for the examination of deep cervical lymph nodes. A pathological diagnosis can be obtained with the help of lymph node puncture, which is a routine method to examine the cervical lymph nodes.
(4) MRI: MRI uses no radioactive radiation, and high tissue resolution and multidirectional and multisequence imaging can be achieved with MRI. The continuous popularization and development of high-field magnetic resonance equipment has greatly accelerated the speed of MRI scanning, allowed thin-section and multiphase dynamic contrast-enhanced scanning such as with CT, and improved the determination of the extent of lesion invasion, the relationship with surrounding organs and the detection rate of lymph node involvement.
(5) PET-CT: The role of 18F-deoxyglucose positron emission tomography (FDG-PET/CT) in staging EC is evolving. After neoadjuvant chemotherapy for EC, a reduction of more than 56% in the uptake value of 18F-FDG often indicates effective treatment, with a sensitivity of 92.9% and a specificity of 60.4%. At present, most data on the application of PET-CT in the diagnosis of EC have come from case reports of adenocarcinoma predominance in Western countries, and there is still a lack of systematic studies on squamous cell carcinoma predominance. Therefore, conditional tertiary hospitals can perform MRI and PET-CT examinations on EC and include these methods in clinical studies [22].

2.2.2.2 Cell and histopathological examination

(1) Esophageal pull-up cytology: This method can be used for large-area census monitoring in high incidence areas, and positive patients still need to undergo fiberoptic esophagoscopy for further characterization and localization. This method has been used in China for more than 40 years, but its sensitivity is 50% lower than that of endoscopic screening, and patient compliance is poor. Therefore, this method has been gradually abandoned in recent

years and switched to endoscopic screening for high-risk populations.

(2) Fiberoptic gastroscopy (esophagoscopy): Esophagoscopy is a routine and essential method in the diagnosis of EC and has gradually become the preferred examination method for patients with dysphagia symptoms. Combined esophagoscopy and CT examination is an ideal method for the diagnosis of EC and plays an important role in the qualitative localization diagnosis of EC and the selection of a surgical plan. At present, endoscopy is recommended for the early diagnosis, treatment and follow-up of EC, whereas esophagoscopy is recommended for patients with early EC with positive esophageal exfoliative cytology and negative or difficult-to-confirm X-ray examination findings.

(3) Endoscopic ultrasound (EUS): EUS is an important examination method for evaluating the clinical T staging of EC. The accuracy of EUS that is superior to that of CT examination. EUS can evaluate EC in the mucosal layer, mucosal layer, submucosal layer, muscular layer and adventitia, and it has advantages in accurately judging the degree of EC invasion [23]. In addition, EUS is also valuable in judging the chemotherapeutic effect of EC and anastomotic or esophageal bed recurrence. However, EUS is of limited help in staging locally advanced EC because it cannot see the whole picture of esophageal lesions in 15% to 30% of patients with severe esophageal strictures.

(4) Other endoscopic examination methods: In addition to conventional common endoscopy and EUS, there are many special endoscopic examinations available for the detection early and precancerous lesions that are superior to even EUS in the determination of the depth of superficial cancer invasion. Chromoendoscopy: Chromoendoscopy is mainly used for the screening of EC in populations with high incidence, and its use, including the iodine staining method and methylene blue staining method, can further improve the positive detection rate of esophagoscopy. Electronic chromoendoscopy: Electronic staining of the esophageal mucosa is realized through special optical processing. Compared with white light endoscopy, electronic chromoendoscopy can more clearly show the mucosal surface structure, microvascular shape and lesion range and can also make up for the shortcomings of adverse reactions of staining agents and the long staining time of chromoendoscopy. Magnifying endoscopy: Magnifying endoscopy is a magnification system with an adjustable focal length configured at the front end of a common endoscope that can magnify the esophageal mucosa by tens or even hundreds of times. This magnification is conducive to observing the subtle changes in the microstructure of the tissue surface and the morphological characteristics of the mucosal microvascular network. In particular, when magnifying endoscopy is combined with electronic chromoendoscopy, the display of mucosal characteristics is clearer, which can improve the accuracy of early EC diagnosis and guide the selection of treatment. Narrow band imaging: Narrow band imaging (NBI) has been widely used in clinical practice. NBI combined with magnifying endoscopy better helps to distinguish lesions from the normal mucosa and assess the depth of lesion invasion, and it has become an important means of precision in the endoscopic detection of early EC.

(5) Bronchoscopy: For EC patients for whom surgery for a lesion located above the carina is planned, bronchoscopy should be performed to determine whether the trachea and bronchi are invaded.

(6) Biopsy of the supraclavicular lymph nodes: If the supraclavicular or cervical.

(7) lymph nodes are enlarged, puncture or biopsy may be performed to determine the presence or absence of metastasis.

(8) Thoracoscopy, laparoscopy and mediastinoscopy: Thoracoscopy, laparoscopy and mediastinoscopy are effective methods to assess EC staging. Compared with noninvasive examination, thoracoscopy, laparoscopy and mediastinoscopy can more accurately determine local EC invasion and lymph node and distant metastasis. Laparoscopy is an effective method for judging abdominal metastasis of EC, and its sensitivity can reach 96%. In addition, thoracoscopy and laparoscopy can be used to determine the effect of neoadjuvant therapy in patients with progressive EC.

2.2.2.3 Combination of imaging techniques The above examination methods have their own advantages and disadvantages, and the integration and application of the two or even more methods is helpful for surgeons to make a more comprehensive diagnosis, including the pathological diagnosis, preoperative staging and judging the resectability of the tumor.

EUS-integrated CT examination provides a more complete assessment of the pretreatment staging of ECs for surgeon judgment [24, 25].

EUS-integrated PET-CT examination integrates the current state-of-the-art methods of anatomical imaging

and molecular imaging for the diagnosis of local lesions, regional lymph node involvement and distant metastasis, and is theoretically the most accurate for method EC staging diagnosis. EUS is superior to PET-CT in clinical T staging and the judgment of regional lymph node metastasis of the tumor, and PET-CT has advantages in the judgment of distant metastasis of EC [26].

2.3 Esophageal segmentation and EC classification

2.3.1 Segmentation of the esophagus

In 2017, the 8th edition of the American Joint Committee on Cancer (AJCC)/ Union for International Cancer Control (UICC) TNM staging system for esophageal and esophagogastric junction cancer was based on the location of the tumor center in the following esophagus segments to determine EC classification [27]: ① Cervical esophagus: from the hypopharynx to the thoracic inlet, that is, the level of the upper sternal notch. It is surrounded by the trachea, cervical vascular sheath, and spine. Endoscopic measurements are performed 15 to 20 cm from the upper incisors. ② Upper thoracic esophagus: from the upper thoracic inlet, inferior to the lower edge of the azygos vein (i. e., above the level of the hilum). It is adjacent anteriorly to the branches of the trachea, aortic arch, and brachiocephalic vein and posteriorly to the spine. Endoscopic measurements are performed 20 to 25 cm from the upper incisors. ③ Middle thoracic esophagus: from the lower edge of the superior azygos vein down to the lower edge of the inferior pulmonary vein (i. e., between the hilar levels). It is clamped between the two hili anteriorly, adjacent to the descending thoracic aorta on the left side, adjacent to the spine posteriorly, and free on the right side directly apposed to the pleura. Endoscopic measurements are performed 25 to 30 cm from the upper incisors. ④ Lower thoracic esophagus: superiorly from the lower edge of the inferior pulmonary vein upward and down to the esophageal junction. Endoscopic measurements are performed from 30 to 40 cm from the upper incisors.

To facilitate the classification of tumors originating from the distal esophagus and cardia, the UICC has made a clear provision: tumors involving the esophagogastric junction, with the center of the tumor ≤ 2 cm from the cardia, are staged according to the criteria for EC. If the center of the tumor is >2 cm from the cardia, it is staged according to the criteria for gastric cancer.

2.3.2 Gross classification of EC

During the development of EC, there are significant changes in morphology, and EC can be divided into two major categories, early and advanced types, according to the morphological appearance of gross specimens of the primary tumor. Early EC: including occult, erosive, plaque, and papillary types. Advanced EC: including medullary, fungoid, ulcerated, constricted, and intraluminal types.

2.3.3 EC pathological types

See Chapter X for details.

2.4 Differential diagnosis

2.4.1 Benign esophageal stricture

Esophageal scar stenosis is caused by chemical burns, reflux esophagitis, or other inflammatory lesions of the esophagus. Chemical burns are more common in children and young adults, and affected individuals generally have a history of accidental ingestion of strong acids or bases. Occasionally, esophageal scar stenosis is also seen in individuals who have attempted suicide or individuals with mental disorders with active oral administration of chemicals. Esophageal strictures caused by reflux esophagitis and other causes are generally located in the lower esophagus, often accompanied by hiatal hernia or congenital short esophagus. Esophagoscopy and biopsy are mainly used in the differential diagnosis.

2.4.2 Esophageal dysfunction

The most common esophageal dysfunction is achalasia. The main symptom is recurrent and intermittent dysphagia with a long duration of disease. The mean age of onset is generally not at an advanced age, and esophageal dysfunction often has typical findings in esophagography. It should be noted that this type of disease is likely to be complicated with EC, and gastroscopy (esophagoscopy) is helpful for differentiation.

2.4.3 Esophageal diverticula

An individual with a diverticulum in the middle esophagus often has symptoms such as dysphagia and retrosternal pain, while dysphagia is less frequent. Esophageal diverticula are associated with a risk of carcinogenesis, so missed esophageal diverticulum diagnosis should be avoided.

2.4.4 Tuberculosis of the esophagus

Esophageal tuberculosis is rare, and affected individuals may have dysphagia and imaging findings of esophageal mucosal destruction. Esophagoscopy and biopsy are needed in the differential diagnosis.

2.4.5 Other neoplasms of the esophagus

Leiomyomas are common, and affected individuals generally have mild symptoms and show a "smear sign" on X-ray examination. Esophagoscopy and EUS are needed for further differentiation, but biopsy is generally not required. Other malignant tumors of the esophagus, such

as esophageal sarcoma and esophageal melanoma, are not easily differentiated from EC through clinical manifestations, and X-ray examination and esophagoscopy are needed for the differential diagnosis.

3 Clinical staging of esophageal carcinoma

The TNM staging system for malignant tumors, jointly developed by the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC), is currently the most widely used staging standard for tumors in the world. The purpose of the TNM staging system is understanding the course of the disease, formulating a treatment plan according to the course of the disease, judging the prognosis of patients, and judging the treatment efficacy. The TNM staging system is also the basis for comparing and exchanging information between different units. Among the TNM staging systems, pathological TNM (pTNM) staging, performed by analyzing surgically resected specimens, is the "gold standard" for tumor staging. Clinical TNM (cTNM) staging is the staging of all clinical information obtained by invasive or noninvasive methods before treatment. The preoperative staging of esophageal cancer (EC) mainly determines the extent of the disease, the presence or absence of distant organ metastasis, lymph node involvement and local invasion of surrounding tissues. Accurate preoperative staging will help in the selection of a reasonable treatment plan. Patients with early EC can undergo radical surgery. Patients with advanced EC can undergo palliative surgery or receive radiotherapy or chemotherapy alone. In addition, the efficacy of different treatment options can be compared and observed.

The most recent version of the International EC TNM Staging Criteria is the 8th edition, published in 2017 [27]. TNM staging criteria include three key indicators: T refers to the size of the primary tumor, N refers to the involvement of regional lymph nodes, and M refers to the presence of distant metastasis. The staging factors of the 8th edition of the TNM staging criteria also include cancer cell differentiation (G), and tumor location is also an important factor in TNM staging of squamous cell carcinoma.

3.1 Primary Tumor (T) staging

Tx: primary tumor cannot be determined;
T0: no evidence of a primary tumor;
Tis: severe dysplasia, defined as no malignant cell breaking through the basement membrane;
T1: tumor invading the lamina propria, mucosa or submucosa;
T1a: tumor invading the lamina propria or mucosa;
T1b: tumor invading the submucosa;
T2: tumor invading the lamina propria;
T3: tumor invading the esophageal adventitia;
T4: tumor invading tissues and organs adjacent to the esophagus;
T4a: tumor invading the pleura, pericardium, azygos vein, diaphragm, or peritoneum;
T4b: tumor invading other adjacent tissues, such as the aorta, vertebral body, or trachea.

3.2 Regional lymph Node (N) staging

Nx: regional lymph node metastasis cannot be determined;
N0: no regional lymph node metastasis;
N1: 1–2 regional lymph node metastases;
N2: 3–6 regional lymph node metastases;
N3: ≥ 7 regional lymph node metastases.
Note: The number of metastatic lymph nodes and total number of dissected lymph nodes must be recorded.

3.3 Distant Metastasis (M) staging

M0: no distant metastasis;
M1: distant metastasis.

3.4 Grade of differentiation (G) staging

3.4.1 Adenocarcinoma G differentiation

Gx: degree of differentiation cannot be determined;
G1: well-differentiated carcinoma: > 95% of tumor cells are well-differentiated glandular tissues;
G2: moderately differentiated carcinoma: 50% ~ 95% of tumor cells are well-differentiated glandular tissues;
G3: poorly differentiated carcinoma: nests or sheets of tumor cells, < 50% with glandular formation.
Note: G3 adenocarcinoma is determined if further testing of "undifferentiated" carcinoma tissue proves it to be glandular tissue.

3.4.2 Differentiation degree of squamous cell carcinoma

Gx: degree of differentiation cannot be determined;
G1: well-differentiated, with obvious keratinized bead structure and a small number of non-keratinized basal-like cells; the tumor cells are distributed in sheets, with few mitoses;
G2: moderately differentiated, exhibiting a variety of histological appearances ranging from parakeratosis to a very low degree of keratinization to basically invisible keratinized beads;
G3: poorly differentiated, mainly nests of varying sizes composed of basaloid cells, a large number with centralized necrosis; a nest-shaped structure composed of sheets or paving-stone-like tumor cells, in which a small number of dyskeratotic cells or keratinized cells are occasionally observed.

Note: If "undifferentiated" carcinoma tissue is further tested and found to have a squamous cell component or if it is still undifferentiated carcinoma after further testing, it is classified as G3 squamous cell carcinoma.

3.5 Eighth Edition of AJCC/UICC EC TNM Staging (Tables 1, 2, 3, 4 and 5)

See Chapter XIII for the regional lymph node grouping and coding of EC.

Table 1 Pathological staging of esophageal adenocarcinoma

			N0	N1	N2	N3	M1
	Tis	0					
T1a	G1		IA	IIB	IIIA	IVA	IVB
	G2		IB				
	G3		IC				
T1b	G1		IB	IIB	IIIA	IVA	IVB
	G2						
	G3		IC				
T2	G1		IC	IIIA	IIIB	IVA	IVB
	G2						
	G3		IIA				
	T3		IIB	IIIB	IIIB	IVA	IVB
	T4a		IIIB	IIIB	IVA	IVA	IVB
	T4b		IVA	IVA	IVA	IVA	IVB

Table 2 Pathological staging of esophageal squamous cell carcinoma

			N0		N1	N2	N3	M1
			L	U/M				
	Tis	0						
T1a	G1		IA	IA	IIB	IIIA	IVA	IVB
	G2-3		IB	IB				
	T1b		IB		IIB	IIIA	IVA	IVB
T2	G1		IB	IB	IIIA	IIIB	IVA	IVB
	G2-3		IIA	IIA				
T3	G1		IIA	IIA	IIIB	IIIB	IVA	IVB
	G2-3		IIA	IIB				
	T4a		IIIB	IIIB	IIIB	IVA	IVA	IVB
	T4b		IVA	IVA	IVA	IVA	IVA	IVB

Table 3 Clinical staging of esophageal adenocarcinoma

		N0	N1	N2	N3	M1
Tis	0					
T1		I	IIA	IVA	IVA	IVB
T2		IIB	III	IVA	IVA	IVB
T3		III	III	IVA	IVA	IVB
T4a		III	III	IVA	IVA	IVB
T4b		IVA	IVA	IVA	IVA	IVB

Table 4 Clinical staging of esophageal squamous cell carcinoma

		N0	N1	N2	N3	M1
Tis	**0**					
T1		I	I	III	IVA	IVB
T2		II	II	III	IVA	IVB
T3		II	III	III	IVA	IVB
T4a		IVA	IVA	IVA	IVA	IVB
T4b		IVA	IVA	IVA	IVA	IVB

Table 5 Pathological staging after neoadjuvant therapy for EC

	N0	N1	N2	N3	M1
T0	I	IIIA	IIIB	IVA	IVB
Tis	I	IIIA	IIIB	IVA	IVB
T1	I	IIIA	IIIB	IVA	IVB
T2	I	IIIA	IIIB	IVA	IVB
T3	II	IIIB	IIIB	IVA	IVB
T4a	IIIB	IVA	IVA	IVA	IVB
T4b	IVA	IVA	IVA	IVA	IVB

4 Preoperative risk assessment of esophageal carcinoma patients

4.1 Relationship between preoperative examination and risk assessment of esophageal carcinoma patients

The purpose of preoperative examination is to learn about the condition of the patient with esophageal carcinoma (EC) and the functional status of the heart, lungs, liver, brain, kidneys and other organs. Detailed preoperative examination is not only the premise of disease evaluation but also the basis of risk evaluation. The preoperative examination of EC patients includes routine laboratory examinations, blood biochemical examinations, imaging examinations, endoscopy, cardiopulmonary function tests, and so forth. The examination methods used in EC are detailed in Chapter II: Diagnosis and Differential Diagnosis of Esophageal Carcinoma.

4.2 Preoperative risk assessment of EC patients

The preoperative risk assessment of EC patients is an important part of surgery and helps to ensure a smooth recovery. After the above examination and staging evaluations, clinicians can determine whether EC patients have surgical indications, but further comprehensive preoperative evaluation is still needed to determine whether the patient can tolerate surgery.

Detailed and comprehensive history taking is the first step in risk assessment. If the patient has a history of chronic respiratory disease (chronic obstructive pulmonary disease, emphysema, pulmonary heart disease, asthma, etc.), heart disease (angina pectoris within the past 3 months, infarction within the past 6 months, a previous history of heart failure, a history of severe arrhythmia), etc., more attention should be given to the results of cardiopulmonary function assessment. If the patient has a history of chronic hepatitis, liver cirrhosis, nephritis, renal insufficiency due to various reasons, hypertension, diabetes, cerebral hemorrhage or cerebral infarction within the past 3 months or in concurrence with any of the above diseases, attention should be given to the control of chronic diseases. If necessary, relevant departments should be consulted to assist in the evaluation, diagnosis and treatment of perioperative concurrent diseases. In addition, the history of severe chest trauma, pleurisy, thoracotomy, and thoracic chemoradiotherapy should also be taken. Furthermore, special attention also needs to be paid to eating conditions and the degree of weight loss in EC patients, and nutritional risk assessments should be carried out.

4.2.1 Cardiovascular disease risk assessment

The cardiac function evaluation methods include subjective symptom and physical sign evaluation, static electrocardiography (ECG), treadmill exercise ECG, exercise cardiopulmonary function tests (additionally with 12-lead ECG), echocardiography, radionuclide ventriculography, MRI, coronary CT angiography and cardiac catheterization ventriculography. In general, patients with grade I-II cardiac function who do not experience angina pectoris after daily activities can tolerate surgery. Patients who develop angina symptoms after daily activities or with grade III-IV cardiac function need further examination to determine the severity of the disease. For patients with severe cardiac dysfunction, coronary angiography is required to assess whether coronary stent placement or coronary artery bypass grafting is required before elective surgery. In general, surgery is not recommended for patients with a history of myocardial infarction in the past 6 months, and surgery should be postponed to at least 4 to 6 weeks later; otherwise, the risk is great.

Hypertension is classified into mild (140 ~ 159 / 90 ~ 99 mmHg), moderate (160 ~ 179 / 100 ~ 1109 mHg), and severe (≥ 180 / 110 mmHg) hypertension. Patients with mild to moderate hypertension whose blood pressure can be controlled to be within the normal range after medical treatment have less surgical risk. Patients with severe hypertension accompanied by organic lesions in the heart, brain, liver, kidneys and other organs (such as renal impairment, liver cirrhosis, and cerebral hemorrhage, etc.) have a greater risk of intraoperative and postoperative cardiovascular and cerebrovascular complications.

Patients with severe arrhythmias require appropriate management to reduce surgical risk. Severe sinus tachycardia (> 160 beats per minute) requires the correction of its underlying etiology (e. g., hypoxia, heart failure, etc.). Patients with second-degree type II or third-degree atrioventricular block, three-bundle branch block, sick sinus syndrome, and Asperger's syndrome require preoperative placement of a temporary cardiac pacemaker. Severe supraventricular and ventricular arrhythmia (> 5 beats / min) should be controlled with drugs before operation to reduce the risk of operation. Paroxysmal arrhythmia leads to a ventricular rate greater than 160 beats / min, and atrial fibrillation leads to a ventricular rate > 100 beats / min, resulting in poor ventricular filling and emptying and further leading to decreased cardiac function. Therefore, it is also necessary to control the ventricular rate to be 80 ~ 100 beats/min.

4.2.2 Respiratory disease risk assessment

The pulmonary function evaluation methods include static and dynamic methods. Static examination methods include the breath holding test, pulmonary function tests, blood gas analysis and other examinations. Dynamic examination methods include a simple stair climbing test and an exercise cardiopulmonary function test. In general, if the patient is previously healthy and has no history of vital organ disease, routine static pulmonary function evaluation methods can be performed. Surgery can generally be tolerated if pulmonary ventilation function is normal (VC% > 80%, FEV > 2.0 L, FEV1% > 70%, DLc% > 70%). In the case of mild to moderate abnormalities (VC% = 60% ~ 80%, FEV1 = 1.2–2.0 L, FEV% = 40% ~ 70%, DLc% = 40% ~ 70%), the decision should be made on a case-by-case basis, and such patients generally can tolerate esophageal surgery, but the risk of postoperative pulmonary complications will be increased. Patients with severe pulmonary dysfunction have a high risk of postoperative complications and should be carefully evaluated. Immediate surgery is generally not recommended. Active treatment of pulmonary complications and adjustment of pulmonary function are required before evaluation. If static pulmonary function test results are abnormal, further examination and evaluation can be performed, and a stair climbing test or exercise cardiopulmonary function test can be added. If a patient can climb 4 to 5 floors without rest, he or she is generally considered to be able to tolerate surgery. A simple stair climbing test can roughly reflect the cardiopulmonary function status, but it is difficult to accurately evaluate the cardiopulmonary function of patients and predict the risk after surgery. If possible, exercise cardiopulmonary function tests should also be performed. Among the cardiopulmonary function indicators of exercise, a VO2max (kg/min) of 20 mL is normal, 15 ~ 19.9 mL is mildly to moderately abnormal, and 10 ~ 14.9 mL is moderately to severely abnormal. VO2max has been shown to have a significant correlation with FEV1. Many studies have reported that patients with a VO2max (kg / min) > 20 mL can tolerate triple-incision surgery, those with a VO2max (kg/min) 15–19.9 mL can tolerate minimally invasive esophageal surgery, and those with a VO2max < 10 mL (kg/ min) cannot tolerate surgery.

4.2.3 Liver function assessment

Liver function evaluation methods include tests to measure transaminase levels, bilirubin metabolism, protein anabolism, fat catabolism and other indicators, as well as liver color ultrasound examination to evaluate the presence or absence of cirrhosis and other lesions. At present, the Child–Pugh classification is generally used for liver function assessment. Generally, the surgical risk is increased when liver function is grade B and C (> 7 points), and reoperation is recommended when hepatoprotective treatment is given first and grade A (5 ~ 6 points) is achieved.

4.2.4 Renal function assessment

Renal function evaluation methods include urological tests (urine specific gravity, urine protein, urine glucose, etc.) and renal function tests [blood urea nitrogen (BUN), creatinine (Cr), the Cr clearance rate, etc.]. Patients with mild renal impairment can generally tolerate major thoracic surgery, but for patients with moderate to severe renal impairment, it is recommended to invite relevant professional physicians for consultation and evaluation to determine whether surgical treatment can be performed.

4.2.5 Nutritional status assessment

If the patient is able to eat a semiliquid diet and weight loss is not obvious, his or her nutritional status is generally at a normal level. If the patient can eat only a liquid diet for more than two weeks, the patient's body weight will decrease, and their nutritional status will be significantly affected. At this time, preoperative nutritional status assessment should be performed. At present, the mainstream nutritional assessment scales used in China and

abroad are as follows: the Nutrition Risk Screening Score Short Form (NRS2002), the Patient-Generated Subjective Global Assessment (PG-SGA), the consensus statement of the European Society for Clinical Nutrition and Metabolism (ES-PEN 2015), and the Global Leadership Initiative on Malnutrition (GLIM). Patients with poor nutritional status should receive appropriate nutritional supplementation before surgery, including water, electrolytes, sugar, trace elements, vitamins, amino acids and fat emulsions. Reoperation after a period of time and / or parenteral nutrition support is conducive to rehabilitation.

Through the examinations discussed in the preceding two chapters and the various examinations in this chapter, evaluations can be performed after the clarification of whether EC patients can tolerate surgery, and a correct, effective and individualized integrated treatment plan can be developed on the basis of the results of these examinations.

5 Principles of surgical treatment of resectable esophageal carcinoma

5.1 Treatment principles for thoracic esophageal carcinoma and gastroesophageal junction cancer (Table 6).

5.2 Treatment principles of cervical EC (Table 7)

The T stage of the primary tumor, according to the depth of tumor invasion, can be cT1a (tumor invading the mucosal layer), cTb (tumor invading the submucosal layer), cT2 (tumor invading the lamina propria), cT3 (tumor invading the adventitial layer), cT4 (tumor invading resectable organs such as the pleura, azygos vein, diaphragm and pericardium by breaking through the adventitial layer) or cT4b (tumor invading unresectable organs such as the great vessels, spine and trachea). Preoperative T staging mainly involves chest contrast-enhanced CT, neck contrast-enhanced CT, upper gastrointestinal endoscopy, and endoscopic ultrasound. N staging refers to the evaluation of local lymph nodes, and the N stage can be cN1 (1 ~ 2 lymph node metastases), cN2 (3 ~ 6 lymph node metastases), or and cN3 (more than 7 lymph node metastases). Preoperative N stage examination methods include contrast-enhanced CT and PET-CT of the chest and abdomen. M staging refers to the evaluation of distant organ metastasis, and the M stage can be cM0 (no distant organ metastasis) or cM1 (distant organ metastasis). The M stage examination methods are contrast- enhanced CT of the chest and abdomen, PET-CT, MRI, etc.

(1) Endoscopic resection (ER) is usually selected: Before ER of Tis and T1a EC, integration and assessment should be performed in combination with an evaluation of the extent of disease (circumferential degree), tumor size, tumor differentiation,

Table 6 Treatment principles of thoracic esophageal carcinoma (EC) and gastroesophageal junction cancer

Clinical stage		Recommendations for therapeutic measure I	Recommendations for therapeutic measure II
Clinical stage 0	cTis	Endoscopic resection	
Clinical phase I	cT1a cT1b	Endoscopic resection	
Clinical stage II-III	cT1N1 cT2N0	Surgical resection	
	cT3N0 cT2-3N1 cT1b-3N2	Neoadjuvant concurrent chemotherapy + esophagectomy Neoadjuvant concurrent chemoradiotherapy + EC radical resection	Surgical resection + postoperative adjuvant therapy
Clinical stage IVA	cT4bN1-2	Neoadjuvant concurrent chemoradiotherapy; if radical resection can be achieved, surgery may be considered Neoadjuvant chemotherapy; if radical re- section can be achieved, surgical treatment may be considered	

Table 7 Treatment principles of cervical EC

Clinical stage		Therapeutic measure I	Recommendations for therapeutic measure II
Clinical stage 0	cTis	Endoscopic resection	
Clinical stage I	cT1a cT1b	Endoscopic resection	
Clinical stage II	cT1b-3, N0	Esophagectomy (Laryngectomy not required) Radical concurrent chemoradiotherapy + chemotherapy	Esophagectomy (Laryngectomy may be performed if necessary)
Clinical stage III and above	cT1b-cT2, N + or cT3-cT4a, any N	Radical concurrent chemoradiotherapy + chemotherapy	Neoadjuvant therapy + esophagectomy (Laryngectomy may be performed if necessary)

the presence or absence of vascular invasion, and the presence or absence of suspicious lymph nodes. Pathology after ER of Tis and T1a EC reveals a depth of submucosal invasion > 200 μm, lymphatic or vascular invasion, poorly differentiated or undifferentiated carcinoma, and positive vertical margins requiring additional surgical treatment, and concurrent chemoradiotherapy or radiotherapy alone is feasible in those who refuse surgery or cannot tolerate surgery.

(2) Resectable esophageal or esophagogastric junction cancer: Direct surgical treatment is usually selected for tumors invading the submucosa (T1b) or T2 EC; neoadjuvant therapy followed by surgery can be considered for patients with T2 EC or higher or for patients with Tb with multiple lymph node metastases. At present, both neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy can be used for preoperative adjuvant therapy. There is no sufficient evidence that preoperative chemoradiotherapy is superior to preoperative adjuvant chemotherapy, and preoperative adjuvant therapy should be selected on the basis of the patient's age and physical condition.

(3) Unresectable esophageal or esophagogastric junction cancer: T4b tumors involving the heart, great vessels, trachea, vertebral body or adjacent abdominal organs, including the liver, pancreas and spleen, are unresectable, and for patients with distant metastases (including nonregional lymph nodes and stage IV), the tumors are considered unresectable. There is no sufficient evidence to confirm that patients will achieve longer long-term survival after surgery than with chemoradiotherapy. Therefore, the decision to perform surgery must be based on the quality of life of patients. For patients with cervical EC without lymph node metastasis in the early stage, surgical treatment may be considered when laryngeal preservation can be fully evaluated. For patients who fail radical chemoradiotherapy, additional salvage surgery may also be considered.

(4) Optional surgical methods include Ivor-Lewis esophagogastrectomy (transabdominal + trans-right thoracic), McKeown esophagogastrectomy (trans abdominal + trans-right thoracic + cervical anastomosis), minimally invasive Ivor Lewis esophagogastrectomy (transabdominal + trans-right thoracic), minimally invasive McKeown esophagogastrectomy (transabdominal + trans-right thoracic + cervical anastomosis), mediastinoscopy + laparoscopic esophagogastrectomy + cervical anastomosis (trans abdominal + cervical anastomosis), robotic minimally invasive esophagogastrectomy, and left thoracic or thoracoabdominal incision cervical or thoracic anastomosis. Replacing organs that may be used include the stomach (preferred), colon, and jejunum.

(5) Lymph node dissection: For EC in the middle and lower thoracic regions without suspicious enlarged lymph nodes in the neck, extended thoracoabdominal two-field lymph node dissection is recommended (conventional thoracoabdominal two-field dissection + upper mediastinal dissection, especially bilateral recurrent laryngeal nerve chain lymph nodes). For EC in the upper thoracic region with suspected enlarged lymph nodes in the neck, cervical thoracoabdominal three-field lymph node dissection is recommended (double lower neck and supraclavicular + the above enlarged two-field lymph nodes). The recommended chest lymph nodes for dissection are the right pararecurrent laryngeal nerve, left pararecurrent laryngeal nerve, upper paraesophageal, parabronchial, subcarinal, middle paraesophageal region, parapulmonary region, lower paraesophageal region and supradiaphragmatic region lymph nodes. The recommended celiac lymph nodes for dissection are the right cardia, left cardia, lesser curvature, beside the left gastric artery, common hepatic trunk, periceliac lymph node and proximal splenic artery lymph nodes. For esophagogastric junction cancer, it is recommended that Siewert type I be treated based on the treatment principle for EC. Siewert type III should be treated based on the treatment principle for gastric cancer. Siewert type II treatment is controversial, and the treatment mode is currently more determined by the habits of thoracic and gastrointestinal surgeons and their proficiency with each surgical method. Patients who have not received neoadjuvant therapy before surgery should have at least 15 lymph nodes dissected when undergoing EC or esophagogastric junction cancer resection for sufficient lymph node staging.

(6) The recommended timing of surgery after neoadjuvant therapy is 4 to 8 weeks after the end of chemoradiotherapy and 3 to 6 weeks after the end of chemotherapy when the patient's physical condition permits. For those who refuse surgery or cannot tolerate surgery, radical concurrent chemoradiotherapy or radiotherapy alone can be selected.

(7) When surrounding organ involvement is suspected but cT4b is not identified, neoadjuvant therapy is recommended first, followed by secondary tumor assessment. Surgical treatment is performed for those who can undergo radical resection, and radical concurrent chemoradiotherapy can be contin-

ued for those who cannot undergo radical resection.

(8) Postoperative adjuvant therapy: Patients with R1 or R2 resection are given adjuvant radiotherapy after surgery. Patients with R0 resection are given adjuvant therapy if postoperative pathological evaluation results suggest positive lymph nodes or lymphatic and vascular invasion.

6 Robot-assisted surgery for esophageal carcinoma

After more than ten years of development, minimally invasive esophagectomy (MIE) has become the main surgical treatment for esophageal carcinoma (EC) in clinical practice. Compared with thoracotomy esophagectomy, MIE can effectively reduce the incidence of postoperative cardiac and pulmonary complications, shorten the hospital stay, reduce the cost of surgery and improve the quality of life after surgery while ensuring that the oncological effect is equivalent [28, 29]. In 2003, Horgan et al. reported the first robot-assisted esophagectomy (RAE) using a transesophageal hiatal machine. In recent years, RAE has been increasingly carried out in clinical practice [30].

6.1 Basic definitions

RAE refers to MIE performed with robotic assistance. Since esophageal resection involves multiple areas and issues such as digestive tract reconstruction and the learning curve for surgeons must be considered, the RAE currently performed also includes the following three categories:

(1) Robot-assisted abdominal operation + esophageal resection via an esophageal hiatal approach;

(2) Robot-assisted thoracic + laparoscopic or open esophagectomy: including complex robot-assisted right thoraco-abdominal median two-incision and complex robot-assisted right thoraco-abdominal median-cervical three-incision;

(3) Thoracoabdominal total robot-assisted esophagectomy: including total robot-assisted trans-right thoraco-abdominal median two-incision and total robot-assisted trans-right thoraco-abdominal median-cervical three-incision.

6.2 Indications

The indications for RAE are equivalent to those for conventional adjuvant MIE. Patients are required to be in good general condition without serious complications, and their cardiopulmonary function must be able to tolerate one-lung ventilation and thoracotomy. For surgeons with extensive experience in minimally invasive surgery for EC, the learning curve of RAE is short, and RAE can be attempted for advanced EC at the initial stage in addition to early EC.

6.3 Selection of surgical approach

Similar to conventional esophagectomy, RAE is mainly divided into the transesophageal hiatal approach and transthoracic approach, mainly including the right thoraco-epigastric approach (Ivor-Lewis surgery) and the left cervico-right thoraco-epigastric approach (McKeown surgery). Different surgical approaches have their own advantages and disadvantages in surgical indications, surgical procedures, intraoperative and postoperative complications, postoperative rehabilitation and oncological effects. Robot-assisted transesophageal hiatal esophagectomy is mainly used for esophageal adenocarcinoma, and it can avoid chest operation, reduce postoperative chest pain, etc., with less intraoperative bleeding, thereby shortening the postoperative hospital stay, accelerating postoperative recovery and significantly reducing the occurrence of postoperative pulmonary complications. Robot-assisted trans-esophageal hiatal esophagectomy is applied for EC patients who are not suitable for transthoracic surgery, such as those with a previous history of thoracic surgery or decreased pulmonary function [31, 32]. In traditional Ivor-Lewis surgery, due to the limitation of the device angle, manual suturing is time-consuming and laborious, and device anastomosis is mostly used. When the anastomosis effect is not satisfactory, it is difficult to achieve the exact satisfactory effect with additional sutures. Robotic technology increases the feasibility of intrathoracic esophago-gastric manual anastomosis with the help of a three-dimensional high-definition field of view, the use of an "inner wrist" device and tremor filtering, but there is no difference in the incidence rate of postoperative complications or the efficiency of lymph node dissection compared with traditional Ivor-Lewis surgery [33–38]. Robotic technology has some advantages due to the improved efficiency of lymph node dissection in McKeown surgery. Traditional superior mediastinal lymph node dissection is limited by the device and operating space, and it is difficult to expose the local area; robot-assisted surgery can clearly expose the top of the chest, and the operation process is more precise and safe. Multiple comparative studies on robotic-assisted and conventional-endoscope-assisted McKeown surgery have shown that the former can dissect more lymph nodes, especially the upper mediastinal lymph nodes [39–41]. While improving the efficiency of lymph node dissection beside the bilateral recurrent laryngeal nerves, robotic-assisted McKeown surgery does not increase the incidence of postoperative recurrent laryngeal nerve palsy.

The surgeon's experience and tumor biological characteristics should be taken into consideration when deciding which surgical approach should be adopted for RAE. The right thoracic approach is still the first choice for the surgical treatment of EC, especially for patients with esophageal squamous cell carcinoma. Robot-assisted Ivor-Lewis surgery has more operative advantages than conventional surgery, and robot-assisted McKeown surgery can achieve better results in superior mediastinal lymph node dissection.

6.4 Anesthesia and positioning

Anesthesia and surgical positioning for RAE are similar to those for conventional esophagectomy. During endotracheal intubation under general anesthesia, doctors performing McKeown surgery are more likely to select a single-lumen endotracheal tube + artificial pneumothorax, and if necessary, additional obstruction of the catheter should be carried out for one-lung ventilation, which is conducive to the exposure of the tracheoesophageal groove area and the protection of intraoperative pulmonary function [42, 43]. Ivor-Lewis surgery, on the other hand, requires the placement of a stapler and effective one-lung ventilation during thoracic procedures, so more centers choose double-lumen endotracheal tubes.

Thoracic surgical positions mainly include the left lateral and prone positions. Due to the closer proximity to the classic surgical position, many centers use the left lateral decubitus position when completing Ivor-Lewis surgery. Trugeda et al. performed Ivor-Lewis surgery with the patient lying in the prone position, with the help of gravity to better expose the esophagus, which could avoid touching the lungs and obtain a clearer bloodless field. Keown surgery in the prone or lateral prone position is mostly used to facilitate exposure of the posterior mediastinal structure, facilitate mediastinal lymph node dissection, and reduce intraoperative bleeding and postoperative pulmonary complications relative to the lateral decubitus position [44]. Abdominal surgery mostly uses the supine position, with the head in the low position, the feet in the high position, and the left side elevated, which is conducive to the mobilization of the gastroepiploic vessels and more favorable for surgeons when dealing with short gastric vessels and splenic hilar structures.

6.5 Trocar position

The position of the trocar is based on operator experience and personal preference. The trocar is generally positioned in a straight line in the chest, and the robotic arms are positioned triangularly in the abdomen and separated by a certain distance to avoid mutual conflict.

During chest operation, 3 ~ 4 robotic arms are generally placed. Doctors performing the Ivor-Lewis surgery usually set 4 robotic arms, 1 observation hole and 3 manipulating arms in a mode that is conducive to mobilizing the esophagus and completing the thoracic anastomosis. In the four-arm method at the lateral decubitus position, the observation hole is set in the 5th intercostal space of the anterior axillary line, the robotic arm is set in the 3rd intercostal space of the anterior axillary line, the 8th intercostal space of the posterior axillary line and the 10th intercostal space behind the posterior axillary line, and a robot-assisted operation hole is additionally set in the 7th intercostal space near the costal margin. The patient undergoing McKeown surgery for chest manipulation is mostly asked to lie in the prone position on their side, and the position of the trocar is overall close to the side of the spine. Chao et al. used the four-arm mode during chest operation and concluded that with the help of the third robotic arm controlled by the surgeon, good and stable exposure could be completed, and lymph node dissection was safe and easy; it was particularly noted that the dissection of lymph nodes adjacent to the left recurrent laryngeal nerve was more advantageous. Typically, a third arm is set on the left side of the manipulating arm of the left hand, which facilitates the traction of the esophagus but sometimes also conflicts with the second arm or spine. Therefore, if the patient's esophagus is globally biased to the left mediastinum, it is recommended to place the third manipulating arm on the right side of the right-hand manipulating arm while moving the other robotic arms down one intercostal space.

When the chest is operated on by the three-arm method, the observation hole is generally placed in the 6th intercostal space of the posterior axillary line, the robotic arm is placed in the 3rd intercostal space of the midaxillary line and the 9th intercostal space of the posterior axillary line, and an auxiliary operation hole is additionally set in the 5th ~ 7th intercostal space of the anterior axillary line. At the same time, a puncture esophageal suspension line can be set up in the fourth intercostal space in the interscapular region to help expose the region beside the left recurrent laryngeal nerve. The setting of the four-arm trocar is similar to a "smiling face" shape, the observation hole is placed under the umbilicus, and the three robotic arms and auxiliary operation holes are distributed on both sides of the abdomen. The observation hole in the three-arm method is placed 2 cm beside the umbilicus, two robotic arms are distributed on both sides of the observation hole in an isosceles triangle shape, and two auxiliary operation holes are set near the robotic arm in the right abdomen.

6.6 Unplanned events in RAE surgery

EC surgical procedures often involve three regions, the neck, chest, and abdomen, with many surgical steps

and highly technical requirements. Unforeseen preoperative events that occur during the surgical procedure are defined as unplanned events during the operation, including pleural adhesions, abdominal adhesions, intraoperative bleeding, airway injury, and nerve injury. Such unplanned events can affect the prognosis to varying degrees [45]. The prevention and management of common intraoperative unplanned events are as follows:

6.6.1 Thoracic and/or abdominal adhesions

A detailed preoperative history should be obtained to understand whether the patient has undergone previous thoracic and abdominal surgeries, has a history of pleurisy or has other factors that may cause severe thoracic and/or abdominal adhesions.

6.6.2 Puncture device puncturing lung tissues

Tissue rupture may occur due to the adhesion of the pleural cavity or rough puncture, and lung lacerations of varying sizes may appear. In addition to different degrees of bleeding, when the lung rupture is large or the CO2 pneumothorax tube has been connected to the puncture device, a sudden increase in blood pressure may occur due to the direct entry of high-pressure CO2 gas into the lungs. At this point, the anesthesia machine monitor will indicate that the CO2 pressure is rising rapidly.

6.6.3 Rupture of the recurrent laryngeal nerve

The left recurrent laryngeal nerve is more likely to be accidentally injured or severed because of its long course in the thoracic cavity and the narrow operating space in the upper mediastinum, and surgeons should operate with caution. Robotic arm flexibility can be utilized to complete suture reconstruction after rupture or to repair the function of the injured nerve, but the results of rupture must be monitored in long-term follow-up.

6.6.4 Tracheal injury

Tracheal injury in RAE is caused by improper use of the energy platform. In the dissection of the left recurrent laryngeal lymph nodes, an assistant is required to grasp and press the tracheal membrane to help with exposure, and excessive force can cause tracheal membrane perforation. At this time, CO2 pneumothorax should be immediately stopped; the anesthesiologist should be asked to temporarily disconnect the endotracheal tube, stop the oxygen supply of the ventilator, and maintain the state of lung collapse; and the surgeon should quickly suture the perforated site.

6.6.5 Intraoperative bleeding

The sites commonly prone to bleeding during RAE are the bronchial artery, vessels supplying the aortoesophageal region, left gastric artery and splenic artery. The surgeon should operate carefully on the basis their familiarity with the anatomical layers and should use a titanium clip or Hemo lock clamp if necessary. If hemostasis is difficult, conversion to open surgery should be decisive.

6.6.6 R2 resection

Surgeons should make an accurate judgment based on the degree primary esophageal tumor invasion and the possibility for complete resection of metastatic lymph nodes before surgery to avoid palliative surgery as much as possible. Neoadjuvant concurrent chemoradiotherapy or neoadjuvant chemotherapy combined with surgery is recommended to improve the radical resection rate of advanced EC and the therapeutic effect.

6.6.7 Intraoperative cardiopulmonary dysfunction

For patients with concurrent preoperative asthma, the history of drug allergy, arrhythmia and coronary heart disease should be obtained; a comprehensive evaluation should be performed; and an emergency plan should be formulated. When cardiopulmonary dysfunction occurs during surgery and respiratory and circulatory function is still unstable after active treatment, the operation should be terminated decisively.

Unplanned events during RAE may affect the smoothness of the operation to varying degrees and may increase the incidence of postoperative complications. Once surgeons gain sufficient experience in RAE, the incidence of unplanned events during surgery should be significantly reduced. The principles of safe, radical and minimally invasive surgery and oncology should be strictly followed to avoid the occurrence of unplanned events during surgery as much as possible. Decisive treatment should be performed, and any hazards should be minimized.

7 Endoscopic excision of esophageal carcinoma and anastomosis methods

Although diagnosis and treatment based on the discussions of a holistic integrated medicine (HIM) multidisciplinary team (MDT) have become increasingly common and recognized in terms of the improvement in treatment efficacy for esophageal carcinoma (EC), surgical resection still occupies a core position in the treatment of resectable EC. Simultaneous esophagectomy with radical lymph node dissection can significantly improve the control effect and survival of EC [46–48]. However, esophagectomy with radical lymph node dissection is one of the most invasive upper gastrointestinal (GI) procedures, and nearly half of patients undergoing thoracotomy (right laparotomy + thoracotomy) develop pulmonary complication requiring prolonged hospitalization, thus affecting their quality of life during the recovery period

[49]. Therefore, esophagectomy by thoracoscopic or laparoscopic approaches is a very attractive alternative [50]. At present, minimally invasive treatment of EC has become well known, and most centers in China can skillfully carry out minimally invasive EC surgery. With the gradual promotion of the technique, experience with this procedure is also accumulating.

7.1 Indications and contraindications for minimally invasive EC surgery

With the continuous development of minimally invasive surgical techniques, the scope of application of minimally invasive esophagectomy (MIE) are increasing, and the resection of early and mid-stage localized EC can be completed under endoscopy. ① For stage IA EC with pathological vascular invasion or tumors involving the mucosa and submucosa after early EC endoscopic submucosal dissection, endoscopic esophagectomy can be used as a supplement [51]. ② Although EC has certain tissue adhesion after neoadjuvant therapy, resection is still feasible, and there is no significant difference in terms of short-term postoperative complications or the 5-year survival rate [52, 53]. ③ MIE also has some special indications, such as for patients who cannot tolerate open surgery and as palliative surgery for advanced EC.

The contraindications for minimally invasive surgery are similar to those of open esophagectomy (OE) surgery. The contraindications for traditional OE are generally also contraindications for MIE and mainly include the inability to tolerate intraoperative anesthesia and one-lung ventilation due to cardiopulmonary insufficiency, the separation of the tumor and lymph nodes due to severe pleural adhesions, and other serious cardiopulmonary diseases. Notably, for locally advanced tumors such as T4 EC involving surrounding structures or with the development of distant metastasis, neoadjuvant therapy and downstaging can be considered, followed by the reassessment of the possibility of surgery. In addition, advanced age is not an absolute contraindication for MIE. In the evaluation and management of patients, elderly patients have also been shown to obtain a good prognosis with MIE [54]. In conclusion, MIE contraindications have decreased with the development of minimally invasive surgical techniques.

7.2 Minimally invasive surgical methods for EC

With the development of minimally invasive surgical techniques, MIE surgical methods are becoming increasingly diverse. From the earliest laparoscopy combined with a small thoracic incision to the later thoracolaparoscopy combined with a small cervical incision (gastroesophageal cervical anastomosis, McKeown MIE), thoracolaparoscopy combined with EC resection (gastroesophageal intrathoracic anastomosis, Ivor-Lewis MIE), transmediastinoscopy and robot-assisted esophagectomy (RAE) for EC resection. The surgeons should determine the best surgical method according to the specific circumstances of the tumor and the body as well as their skillfulness so that the best effect can be achieved for the patient. Here, the widely used minimally invasive procedures for EC are introduced, while robot-assisted EC resection is introduced in another chapter.

7.2.1 Thoraco-laparoscopy combined with cervical mini-incision resection of EC

In McKeown MIE, the main steps are as follows: under the condition of one-lung ventilation or ventilation combined with artificial pneumothorax, the patient is placed in the left lateral decubitus or left prone position, the esophageal mobilization is thoracoscopically completed (up to the subclavian artery plane, with downward exposure of the esophageal hiatus), and the right upper mediastinal lymph node dissection is performed. Then, the patient is changed to the prone position with the completion of laparoscopic gastric mobilization, tubular gastric creation and abdominal regional lymph node dissection. Finally, through the anterior neck incision in the left sternocleidomastoid muscle, the esophagus is dissociated and cut, and the tubular stomach is lifted to the neck and passed through a small incision for gastroesophageal anastomosis. In this operation, special attention should be given to the protection of cervical vessels and the recurrent laryngeal nerve. In addition, because the anastomotic stoma is located in the neck, the tension of the anastomotic stoma is relatively large, and the risk of postoperative anastomotic leakage is high.

7.2.2 Total thoracolaparoscopy combined with EC resection

For Ivor-Lewis MIE, the main steps are as follows: first, the patient is placed in the supine position, and the abdominal cavity is entered to examine abdominal tumor invasion and lymph node invasion. After the completion of gastric mobilization and lymph node dissection, the patient is changed to the left lateral or left prone position for thoracoscopic esophagectomy and thoracic lymph node dissection, and finally, the tubular stomach is lifted to the thoracic cavity and passed through the esophageal hiatus to complete intrathoracic gastroesophageal anastomosis. The advantages of this surgery include a lower volume of intraoperative blood loss, less tension of the intrathoracic anastomotic stoma, a better tubular stomach and a lower incidence rate of postoperative anastomosis. This conclusion has also been verified in some studies. In addition, most of the stomach may need to be removed for gastroesophageal junction tumors invading the cardia, and anastomosis can be performed in this

surgical method to ensure that the stump stomach can be anastomosed to the esophagus. However, this surgical method also has the disadvantages of a long operation time and technical difficulty in dissecting the lymph nodes next to the bilateral recurrent laryngeal nerves.

7.2.3 EC resection via cervical mediastinoscopy

A left cervical sternocleidomastoid muscle anterior margin incision is made to dissociate the cervical and middle and upper thoracic esophagus through a cervical incision using a video mediastinoscope, and after clamping the branch vessels arising from the aorta, they are cut or cauterized to the level of the inferior pulmonary vein, while the periesophageal and mediastinal lymph nodes are dissected. Subsequently, the stomach is dissociated laparoscopically, and the cardia is cut and closed. The esophagus is pulled out of the cervical incision. A tubular stomach is made and sent to the neck for esophagogastric anastomosis. This operation does not require thoracotomy, reduces postoperative pain, and facilitates recovery. However, the operation space is small, and the operation duration is very long. If the tumor has invaded the esophageal adventitia or the mediastinal lymph nodes are significantly fused, the difficulty of resection will be increased.

7.3 EC anastomosis method

At present, radical resection of EC is still the cornerstone of EC integrated therapy, and anastomotic leakage is one of the most important and lethal complications of EC surgery. A recent study showed that the incidence of anastomotic leakage was similar in the mediastinum in MIE and OE [28, 55–58]. There are various anastomosis methods for EC, including cervical / intrathoracic anastomosis, retrosternal / esophageal bed anastomosis, manual / instrumental anastomosis, and end- to-end/ end-to-side/ side-to-side anastomosis, but there is no conclusion on which anastomosis method is the best.

7.3.1 Cervical and thoracic anastomosis

During early MIE, due to the limitations of the anastomosis technique, most patients undergo cervical gastroesophageal anastomosis. Especially for patients with middle and lower esophageal cancer, cervical anastomosis increases the resected length of the normal esophagus. Although cervical anastomosis can ensure a certain oncological resection effect, it causes many postoperative complications, such as swallowing function injury, gastroesophageal reflux, and cervical anastomotic stenosis [59]. In addition, cervical anastomosis itself is associated with a higher incidence of anastomotic leakage and stenosis. After solving the technical problems of thoracoscopic gastroesophageal intrathoracic anastomosis, minimally invasive surgical methods based on upper abdominal right chest anastomosis (Ivor-Lewis) have gradually become the standard for patients with middle and lower EC and gastroesophageal junction EC. Therefore, based on the literature, intrathoracic anastomosis may have a lower incidence of anastomotic leakage than cervical anastomosis.

7.3.2 Retrosternal anastomosis with anastomosis of the esophageal bed

Studies from Fudan University Shanghai Cancer Center have shown that the reconstruction method of retrosternal anastomosis with anastomosis of the esophageal bed can significantly reduce complications [60]. The conclusion has been further confirmed by this team through anatomical modeling [61].

7.3.3 Manual anastomosis vs. device anastomosis

At present, both manual anastomosis and device anastomosis are safe and feasible.

7.3.4 End-to-end anastomosis, end-to-side anastomosis and side-to-side anastomosis

The findings from a Dutch prospective randomized trial showed that end-to-side anastomosis had a lower rate of anastomotic stenosis and anastomotic leakage than end-to-end anastomosis, while patients in whom end-to-end anastomosis was used had a lower probability of pneumonia and shorter hospital stays [62]. However, a retrospective study by Chinese scholars compared the effects of end-to-end anastomosis and end-to-side anastomosis in MIE. The results showed that there was no significant difference between the two methods in terms of anastomotic leakage, anastomotic stenosis or postoperative complications. End-to-end anastomosis was associated with a slightly lower postoperative gastric dilatation rate than end- to-side anastomosis [63]. A recent study of the Eso Benchmark database analyzed the relationship between MIE anastomosis and patient mortality, and the findings showed that the incidence of anastomotic leakage was similar between cervical anastomosis and intrathoracic anastomosis, but cervical linear end-to-end anastomosis had the lowest failure rate compared with other anastomosis methods [64]. It has been reported in the literature that the postoperative complications of side-to-side anastomosis are similar to those of end-to-side anastomosis, and side-to-side anastomosis is also a safe and effective anastomosis method [65].

In general, despite the continuous innovation and development in MIE anastomosis methods, anastomosis paths and other aspects, there are still many perspectives worth in-depth study. Given the long learning curve for this complex surgical procedure, in experienced EC

diagnosis and treatment centers, studies in this regard should be carried out as much as possible to determine the best surgical method suitable for Chinese patients for the benefit of the majority of EC patients.

8 Systematic lymph node dissection for esophageal carcinoma

8.1 Grouping criteria for lymph nodes in Esophageal Carcinoma (EC)

8.1.1 Regional lymph node stations in the 8th edition of the EC TNM staging system [27]

Group 1R: right cervical paratracheal lymph nodes, from the peritracheal region within the right supraclavicular region to the right apical region;

Group 1L: left cervical paratracheal lymph nodes, from the peritracheal region within the left supraclavicular region to the left apical region;

Group 2R: right upper paratracheal lymph nodes, from the junction of the lower edge of the brachiocephalic artery and the trachea to the right apical region;

Group 2L: left upper paratracheal lymph nodes, from the upper edge of the aortic arch to the left apical region;

Group 4R: right lower paratracheal lymph nodes, the region from the lower border of the brachiocephalic artery to the upper border of the azygos vein;

Group 4L: left lower paratracheal lymph nodes, from the upper edge of the aortic arch to the level of the carina;

Group 7: subcarinal lymph nodes, in the subcarinal region of the trachea;

Group 8U: paraesophageal lymph nodes, in the upper thoracic segment, from the pulmonary apex to the tracheal bifurcation area;

Group 8 M: paraesophageal lymph node of middle thoracic segment, the region from the tracheal bifurcation to the lower edge of the inferior pulmonary vein;

Group 8Lo: paraesophageal lymph nodes of the lower thoracic segment, from the lower edge of the inferior pulmonary vein to the esophagogastric junction;

Group 9R: right inferior pulmonary ligament lymph nodes, in the right inferior pulmonary ligament;

Group 9L: left lower pulmonary ligament lymph nodes, in the left lower pulmonary ligament;

Group 15: paradiaphragmatic lymph nodes, from the diaphragmatic dome to the diaphragmatic crus region;

Group 16: paracardial lymph nodes, immediately adjacent to the esophagogastric junction region;

Group 17: left gastric lymph nodes, area running along the left gastric artery;

Group 18: common hepatic lymph nodes, immediately adjacent to the proximal area of the common hepatic artery;

Group 19: splenic lymph nodes, immediately adjacent to the splenic artery;

Group 20: celiac trunk lymph nodes, in the celiac artery root area;

For the lymph nodes in regions VI and VII of the neck, refer to the criteria for regional lymph node stations of head and neck tumors:

Area VI: These are central lymph nodes, and the area is covered by strap muscle, where the upper boundary is the lower edge of the hyoid bone, the lower boundary is the upper edge of the sternum, the common carotid arteries (and internal jugular veins) on both sides are two boundaries, the anterior boundary is the superficial layer of deep fascia, and the posterior boundary is the deep layer of deep fascia, including prelaryngeal lymph nodes (Delphian lymph nodes), peritracheal lymph nodes, perithyroid lymph nodes, and retropharyngeal lymph nodes.

Region VII: This is the superior mediastinal region from the upper sternal border to the upper border of the aortic arch. Some scholars believe that this region is located outside the neck and does not belong to the cervical lymph node group, but the lymph nodes in this region are closely related to thyroid cancer, hypopharyngeal cancer and the metastasis of cervical EC. Therefore, this discrimination method has been generally accepted in academia.

8.1.2 Nodal stations in the Japan Esophageal Society EC staging system, version 11

The Japan Esophageal Society (JES) EC staging system is mainly aimed at esophageal squamous cell carcinoma, has certain significance for guiding surgical planning and radiotherapy target area planning and has reference value for the majority of patients with esophageal squamous cell carcinoma in China [66].

(1) Cervical lymph nodes: superficial cervical lymph node (No. 100), left cervical para esophageal lymph node (No. 101L), right cervical paraesophageal lymph node (No. 101R), deep cervical lymph node (No. 102), upper deep cervical lymph node (No. 102up), middle deep cervical lymph node (No. 102mid), retropharyngeal lymph node (No. 103), left supraclavicular lymph node (No. 104L), right supraclavicular lymph node (No. 104R).

(2) Thoracic lymph nodes: upper thoracic paraesophageal lymph node (No. 105), thoracic paratracheal lymph node (No. 106), paratracheal lymph node (No. 106rec), left paratracheal lymph node (No. 106recl), right paratracheal lymph node (No. 106recr), pretracheal lymph node (No. 106pre), tracheobronchial lymph node (No. 106tb), left tracheobronchial lymph node (No. 106tbl), right tracheobronchial lymph node (No. 106tbR), subcarinal lymph node (No. 107), paraesophageal lymph node

in the middle thoracic segment (No. 108), left parabronchial lymph node (No. 109 l), right parabronchial lymph node (No. 109r), paraesophageal lymph node in the lower thoracic segment (No. 110), supradiaphragmatic lymph node (No. 111), posterior mediastinal lymph node (No. 112), lymph node anterior to the thoracic aorta (No. 112aoA), lymph node posterior to the thoracic aorta (No. 112aoP), lymph node beside the inferior pulmonary ligament (No. 112pul), lymph node beside the arterial ligament (No. 113), anterior mediastinal lymph node (No. 114).

(3) Abdominal lymph nodes: cardia right lymph node (No. 1), cardia left lymph node (No. 2), lesser curvature lymph node (No. 3), lesser curvature lymph node along the left gastric artery branch (No. 3a), lesser curvature lymph node distal to the second branch of the right gastric artery (No. 3b), greater curvature lymph node along the short gastric artery (No. 4sa), greater curvature lymph node along the left gastroepiploic artery (No. 4sb), right gastroepiploic artery lymph node (No. 4d), suprapyloric lymph node (No. 5), subpyloric lymph node (No. 6), left gastric artery lymph node (No. 7), superior anterior common hepatic artery lymph node (No. 8a), lymph node posterior to the common hepatic artery (No. 8p), celiac trunk lymph node (No. 9), splenic hilar lymph node (No. 10), lymph node proximal to the splenic artery (No. 11p), lymph node distal to the splenic artery (No. 11d), hepatoduodenal ligament lymph node (No. 12), lymph node posterior to the pancreatic head (No. 13), lymph node beside the superior mesenteric artery (No. 14A), lymph node beside the superior mesenteric vein (No. 14 V), lymph node beside the middle colon artery (No. 15), paraaortic hiatal lymph node (No. 16a1), paraaortic lymph node between the celiac trunk and the left renal vein (No. 16a2), periaortic lymph node between the lower edge of the left renal vein and the upper edge of the inferior mesenteric artery (No. 16b1), abdominal periaortic lymph node between the upper edge of the inferior mesenteric artery and the bifurcation of the abdominal aorta (No. 16b2), lymph node anterior to the pancreatic head (No. 17), lymph node at the lower edge of the pancreas (No. 18), subphrenic lymph node (No. 19), lymph node beside the diaphragm and esophageal hiatus (No. 20).

8.1.3 EC thoracic lymph node grouping (Chinese standard)

In combination with the current international situation and real-world clinical observations in China, based on the AJCC / UICC standard and the JES standard, the Chinese standard for EC thoracic lymph node grouping has been proposed. The Chinese standard is more consistent with the needs of the real-world clinical situation in China and has the advantages of being simple, clear and easy to perform. With the Chinese standard, "C" indicates Chinese standard and " 2" indicates a thoracic lymph node [67, 68].

Group C201: lymph node beside the right recurrent laryngeal nerve;

Group C202: lymph node beside the left recurrent laryngeal nerve;

Group C203: upper thoracic paraesophageal lymph node;

Group C204: paratracheal lymph node;

Group C205: subcarinal lymph node;

Group C206: middle thoracic paraesophageal lymph node;

Group C207: lower thoracic paraesophageal lymph node;

Group C208: lower pulmonary ligament lymph node;

Group C209: lymph node beside the diaphragmatic muscle.

8.2 Systematic lymph node dissection

Before 2000, the main approach for EC surgical treatment in China was the left thoracic approach, but due to the presence of aortic arch occlusion and the narrow supra-arch triangle in the left chest, upper mediastinal lymph node dissection was incomplete, and the recurrence rate of lower cervical and upper mediastinal regional lymph nodes after left thoracic approach treatment for EC was as high as 30%~40%, which seriously affected the long-term survival of patients. With the progress in standardized treatment of EC and the popularization and application of minimally invasive thoracic and laparoscopic surgery for EC in China in recent years, the use of the right thoracic approach has gradually increased and become mainstream. The right thoracic approach is more thorough for thoracic lymph node dissection due to the absence of aortic arch occlusion. Compared with the left thoracic approach, complete/extended thoracic and abdominal two-field or cervical, thoracic and abdominal three-field lymph node dissection via the right thoracic approach can reduce the recurrence rate of postoperative cervical and thoracic lymph node metastasis and significantly improve the 5-year survival rate of patients [69].

Methods and principles of lymph node dissection:

(1) The surgical approach and lymph node dissection strategy need to be evaluated and judged by thoracic surgeons experienced in esophageal surgery to achieve the goal of radical resection, including the primary tumor and regional lymph nodes.

(2) The right thoracic approach should be used for the radical resection of EC, and all lymph nodes within a group should be dissected, especially the left and right lymph nodes beside the recurrent laryngeal nerve.
(3) According to the "Guidelines for Standardized Diagnosis and Treatment of Esophageal Cancer", the 8th edition of the AJCC/ UICC EC TNM staging system and the 2016 edition of the National Comprehensive Cancer Network (NCCN) Guidelines for the Diagnosis and Treatment of Esophagogastric Junction Cancer, the number of lymph nodes dissected in EC radical resection should be 11 ~ 15. However, in clinical practice, it is recommended to dissect the regional lymph nodes as thoroughly as possible to ensure that the number of dissected lymph nodes meets the requirements of ECN staging.
(4) Regarding the range of thoracic lymph node dissection in EC radical resection proposed by Chinese experts, a total of 9 groups (Groups C201-C209) of thoracic lymph nodes, as grouped by Chinese standards, should be targeted, which can meet the required number.
(5) The recommended lymph node dissection methods are as follows: if there is no suspicious metastatic lymph node in the cervical region, it is recommended to perform complete/extended two-field lymph node dissection in the chest and abdomen for esophageal cancer in the middle and lower thoracic region (conventional thoracoabdominal two-field, including regional lymph nodes in the mediastinum, especially around the bilateral recurrent laryngeal nerve chains); if there is a suspicious metastatic lymph node in the cervical region, or if esophageal cancer is located in the upper thoracic region, it is recommended to perform three-field lymph node dissection in the neck, chest and abdomen (lower neck + bilateral supraclavicular + above complete/extended two-field lymph node dissection).

9 Diagnosis and treatment for postoperative complications of esophageal carcinoma

Esophageal carcinoma (EC) surgery involves three anatomical sites, the neck, chest and abdomen, with complex surgical steps, a long operation time and great trauma to the body. EC patients are often elderly patients, have poor body function and nutritional status and are more likely to have postoperative complications. The common postoperative complications of EC are briefly summarized below.

9.1 Anastomotic leakage

9.1.1 Definition

Full-thickness gastrointestinal defects involving the esophagus, anastomosis, and local tubular stomach.

9.1.2 Grading of anastomotic leakage

9.1.2.1 Clavien–Dindo classification (Table 8)

9.1.2.2 Shanghai Chest Hospital Classification (Table 9)

9.1.3 Treatments (Table 10)

Grade I: Patients with grade I complications usually do not receive any treatment, but the fasting time is prolonged. Occasionally, the patients are asked to take cold saline orally every day to help clean the local wound surface, but there is no evidence to support that this can heal the wound surface 3 ~ 4 weeks after operation. However, endoscopic confirmation is needed.

Grade II: It is necessary to open the wound to change the dressing and for sufficient drainage and occasionally to use a local negative pressure drainage system to help clean the local would surface. Grade II complications usually resolve after 3 weeks of frequent dressing changes. Continuous local irrigation is not necessary.

Grade III: In the case of mediastinal infection, deeper drainage is needed; in most cases, the infection is formed when the anastomotic site is too low and the anastomotic stoma falls into the pleural cavity. At this time, open drainage of the cervical incision should be performed as early as possible, and if symptoms of fever and mediastinal effusion are identified, mediastinal double-cannula irrigation and drainage should be performed. If the neck wound has healed, endoscopic internal drainage may be considered.

Grade IV: Intrathoracic fistula is very difficult to treat. It takes more than a few months to ensure good drainage in the corresponding pleural cavity and then wait

Table 8 Clavien–Dindo Classification

Grade I: No drug, surgical, endoscopic or interventional therapy is required after operation, and this includes infection in wound requiring opening and a dressing change at the bedside
Grade II: Wound requiring antibiotic treatment
Grade III: Requiring surgical, endoscopic or radiological intervention
IIIa—No need for general anesthesia
IIIb—Need for general anesthesia
Grade IV: Life-threatening, requiring intensive care unit monitoring
IVa—Dysfunction of one organ
IVb—Multiple organ failure
Grade V: Death

Table 9 Shanghai Chest Hospital grading of anastomotic leakage

Grade I: No imaging signs or clinical symptoms, which can be confirmed by endoscopy, no bacteriological evidence of infection, and no effect on the discharge process
Grade II: Occurrence of anastomotic leakage confirmed by imaging or endoscopy, local infection in wound requiring opening and a dressing change
Grade III: Descending mediastinal infection requiring deep drainage (in the mediastinum)
Grade IV: Presence of pleural infection and/or airway-gastrointestinal fistula (outside the mediastinum)
Grade V: Death

Table 10 Clinical diagnosis and pathway of treatment measures for esophagogastric anastomotic leakage

Treatment measures	Grade I	Grade II	Grade III	Grade IV	Grade IV (TEF)
Local dressing change with wound opened	√	√	√	√	√
Local negative pressure drainage		√	√		
Mediastinal drainage			√	√	√
Thoracic cavity drainage				√	
Digestive tract cavity drainage + flushing				√	
Tracheal stent					√
Esophageal stent					√
Surgical repair					√
Thoracogastric removal + cervical esophagostomy				√	√

for the fistula to slowly heal. Tracheoesophageal fistula (TEF) will be described in detail later. The need for thoracogastric resection is controversial. When there is uncontrollable infection, it is clear that the anastomosis is large, or gastric necrosis is present, the resection of the thoracogastric region and two-stage colonic reconstruction should be considered. The use of stent grafts is rare, except in patients with intrathoracic fistulas and adequate chest drainage.

9.2 Necrosis of digestive organ substitute

9.2.1 Definition

Esophageal substitutes used in alimentary canal reconstruction, including the stomach, jejunum, or colon, suffer from varying degrees of ischemic necrosis.

9.2.2 Grading and treatment

Grade I: local digestive organ necrosis found endoscopically that can be treated.

with monitoring or nonsurgical treatment only;

Grade II: partial digestive organ necrosis;

Grade III: extensive digestive organ necrosis, for which the resection of digestive organ substitutes and secondary esophageal diversion are often needed.

9.3 Gastrointestinal tracheal/ Bronchial fistula

9.3.1 Definition

Gastrointestinal tracheal and bronchial fistulas are often secondary to anastomotic fistulas and gastric tube fistulas, and the erosion of the tracheal membrane by gastric juices and exudates can cause gastrointestinal tracheal and bronchial fistulas. The specific classifications, clinical manifestations and prognoses are shown in Table 11.

9.3.2 Treatment

(1) Conservative management includes jejunostomy or endoscopic placement of a duodenal feeding tube, adequate nutritional support, and waiting for the fistula to heal spontaneously.
(2) Interventional therapy: Airway interventional therapy can control aspiration in a timely manner, stimulate granulation growth, and promote fistula healing. The use of gastrointestinal stents is not supported. With the development of interventional techniques, the fistulas can be covered by an esophageal stent graft or tracheal stent graft.
(3) Surgical treatment: surgical repair is rarely performed at the early stage unless a large fistula requires the resection of the thoracogastric region. For TEF that does not heal after more than 6 months, surgical treatment may be considered. The specific situation is very complex, and the surgical plan should be determined based on the specific circumstances.

9.4 Vocal cord paralysis

Radical two-field lymph node dissection has become the standard approach for the surgical treatment of EC in

Table 11 Typing, clinical characteristics and prognosis of gastrointestinal tracheal/bronchial fistula

	Type I	Type II	Type III
Characteristics of occurrence	Descending (caustic)	Opposing small (< 1 cm)	Opposing large (≥ 1 cm)
Onset time	Late	Early	Late
Clinical manifestations	Frequent cough, low-grade fever with refractory pulmonary infection, chronic poisoning symptoms	Sudden severe cough, expectoration of digestive juice in sputum	Expectoration of digestive juice in sputum, acute poisoning symptoms
Esophageal fistula	Small	Small	Large
Location of tracheal fistula	Low (2 cm above the carina—left main)	High	Indefinite
Outcome	Exacerbation of chronic poisoning symptoms	Aspiration, acute respiratory failure, acute respiratory distress syndrome	Septic shock, respiratory failure
Development	Slow	Fast	Fast
Prognosis	Good in patients with early detection	Dangerous	Dangerous

China. Since the region beside the recurrent laryngeal nerve is the focus of dissection, related injuries are inevitable. At present, the incidence of vocal cord paralysis (VCP) is between 10 and 20% in Asian units dedicated to the dissection of lymph nodes adjacent to the recurrent laryngeal nerve. If laryngoscopy is used as the evaluation method, the number may be higher. Although vocalization recovers in 3 months-6 months for such patients, laryngoscopic verification reveals an almost permanent loss of vocal cord motor function. Therefore, how to reduce recurrent laryngeal nerve injury is a critical issue in esophageal surgery.

9.4.1 VCP causes include

(1) Intraoperative nerve traction and extrusion;
(2) Thermal injury (most common);
(3) Nerve breakage.

9.4.2 Grading

Grade I: simple tone change, which does not affect the discharge process;

Grade II: unfavorable expectoration, which requires bronchoscope-assisted sputum suction;

Grade III: confirmed recurrent laryngeal nerve injury, which requires noninvasive ventilator-assisted support;

Grade IV: recurrent laryngeal nerve injury is confirmed and the endotracheal tube cannot be removed, which requires tracheotomy.

9.4.3 Treatment after VCP

Treatment after VCP is mainly aimed at the inability to eat normally and symptomatic treatment of respiratory dysfunction. For patients with significant aspiration, feeding should be stopped immediately and changed to nutritional support with a nasoenteric tube or jejunostomy. Usually, after 2 weeks of nutritional support, the patient can be changed slowly to a semiliquid diet via tube, and after another 2 weeks, the patient can be weaned from tube feeding and eat via the mouth completely. However, patients with fixed bilateral abduction positions may not be able to eat for a long time and may require tracheotomy or even laryngectomy. For patients with postoperative stridor, tracheotomy should be performed immediately, and the patients should be slowly decannulated after 4 weeks. If early postoperative expectoration is difficult, active tracheoscopic sputum suctioning should be performed. For patients with unilateral paralysis, vocal cord injection therapy should be actively performed.

9.5 Pulmonary infection

9.5.1 Definition

Imaging-confirmed pulmonary infiltrates with or without clinical manifestations related to infection, including fever, purulent sputum, elevated white cells, positive sputum culture, and decreased oxygen partial pressure.

9.5.2 Prophylaxis and treatment

9.5.2.1 Prevention of lung infection

(1) Preoperative smoking cessation for more than 2 ~ 4 weeks and breathing training;
(2) Maintain airway patency during the surgical procedure and promptly remove tracheobronchial secretions;
(3) Postoperative cough and expectoration are encouraged after a period of time, and reasonable fluid therapy is administered.

9.5.2.2 Treatment of postoperative pulmonary infection

(1) Aerosol treatment; the effective use of expectorant measures, expectorant drugs and antibiotics; enhanced respiratory tract management; and, if necessary, sputum suction by fiberoptic bronchoscopy can be implemented.
(2) In patients with concurrent pleural effusion or empyema, perform timely drainage.
(3) The application of ventilator-assisted respiration and tracheotomy is feasible when the infection time exceeds 48 h and it is expected that weaning cannot be performed within 5 days.
(4) Anastomotic leakage, esophagotracheal fistula and other complications should be actively addressed.

9.6 Acute respiratory distress syndrome

9.6.1 Definition

The definition and diagnosis of acute respiratory distress syndrome (ARDS) mainly rely on the following important clinical features:

(1) New onset or worsening of preexisting respiratory symptoms within one week of known clinical cause;
(2) Chest X-ray or CT scan shows bilateral pulmonary infiltrates, which cannot be completely explained by pleural effusion, lobar/atelectasis or nodules;
(3) Respiratory failure cannot be fully explained by heart failure or volume overload;
(4) In the absence of relevant risk factors, objective assessment (e. g., echocardiography) is required to rule out hydrostatic hypertension pulmonary edema;
(5) Mild: positive end-expiratory pressure (PEEP) or CAPA $\geq$ 5 cmH2O, 200 mg Hg < PaO2 / FiO2 $\leq$ 300 mmHg; moderate: PEEP $\geq$ 5 cmH2O, 100 mmHg < PaO2 / FiO2 $\leq$ 200 mmHg; severe: PEEP $\geq$ 5 cmH2O, PaO2 / FiO2 $\leq$ 100 mmHg.

9.6.2 Diagnosis and treatment goals of ARDS

(1) Identify and manage potential causes: consider anti-infective therapy; consider surgical drainage of pleural effusion, intensive care, and the removal of invasive tubing in cases of catheter-related bloodstream infection;
(2) Provide supportive treatment: give adequate nutritional support; prevent stress ulcer; prevent deep venous thrombosis;
(3) Hemodynamic management: volume management strategies should help to improve lung function and reduce the duration of mechanical ventilation and intensive care;
(4) Application of lung-protective ventilation strategies to maintain oxygenation: high tidal volumes and highpressure ventilation cause the disruption of the alveolar-capillary barrier, resulting in lung volume injury and lung barotrauma. The shear force formed by the repeated opening and closing of collapsed alveoli can lead to lung biological injury (inflammatory cytokines secreted by neutrophils), causing damage to distant organs;
(5) According to the ARDS Collaborative Treatment Group, arterial oxygenation in ARDS patients can be maintained by a combination of two parameters, the oxygen concentration (FiO2) and PEEP, at PaO2 > 8 kPa or SpO2 88% ~ 95%.

9.6.3 Lung-protective ventilation strategy

(1) FiO2: PaO2 > 8 kPa can be maintained. Long-term inhalation of a high concentration of oxygen will lead to oxygen poisoning, causing lung injury;
(2) PEEP: Improve oxygenation by mechanisms such as re-expanding collapsed alveoli, improving ventilation / blood flow ratio, and reducing intrapulmonary shunting.
(3) Small tidal volume ventilation: 6 mL/kg maintenance of airway peak pressure at < 30 cmH2O according to the expected ideal body weight; permissive hypercapnia (pH > 7.1);
(4) Other options for improving hypoxemia are lung recruitment and high PEEP, prone ventilation, high-frequency oscillatory ventilation, nitric oxide inhalation, glucocorticoids, and extracorporeal membrane oxygenation.

9.7 Chylothorax

9.7.1 Definition

Chylothorax is the formation of a large amount of lymph fluid entering and retained in the thoracic cavity from a fistula of the thoracic duct or its major branches. Chylothorax generally appears on postoperative days 4 to 5 and occasionally within 24 h or 7 to 14 days. The diagnosis is mainly based on a large postoperative chest drainage volume, and when this volume is more than 600 mL/24 h, the possibility of chylothorax should be highly suspected. If milky turbid pleural effusion is aspirated by drainage or thoracentesis and confirmed to be chyle, pleural fluid can be taken for chyle testing.

9.7.2 Severity level

Mild: < 1000 mL/day;
Severe: > 1000 mL/day.

9.7.3 Prophylaxis and treatment

9.7.3.1 Preventive measures

(1) A clear understanding of the anatomy of the thoracic duct is a prerequisite to avoid the development of chylothorax. In severe cases of middle and upper thoracic tumor invasion, when dissociating the tumor and dissecting the lymph nodes during surgery, attention should be given to avoid damage to the thoracic duct, and ligation is recommended when cutting off the perithoracic tissue.
(2) Prophylactic thoracic duct ligation: If the surgeon believes that the thoracic duct was damaged during the surgical operation, the chest should be closed, and preventive ligation of the thoracic duct 5 ~ 6 cm above the diaphragm should be performed.
(3) It is emphasized that the thoracic duct should not be ligated in patients with liver cirrhosis. Because hepatic venous return is blocked during portal hypertension in cirrhosis, plasma penetrates from the sinusoidal wall into the sinoatrial space, resulting in increased hepatic lymphopoiesis and increased intralymphatic pressure. If the thoracic duct is ligated at a scope beyond the thoracic duct drainage capacity, this may result in the dilation, stasis, and rupture of the pleural lymphatic vessels, and as a result, the overflow lymph will lead to chylothorax or chyloperitoneum formation.

9.7.3.2 Treatment After the occurrence of chylothorax, conservative treatment is first attempted, and chyle output is closely observed. If the drainage volume is below 500 mL daily and gradually decreases, the observation period can last for a longer time, and there is a possibility of self-healing. If the drainage volume is more than 1000 mL per day, the observation time should not exceed 1 week. An observation time that is too long may lead to electrolyte imbalance and increase the risk of reoperation.

9.7.3.2.1 Conservative treatment

Conservative treatment involves a limited diet, including a lipid-free, high-protein, high-sugar liquid or semiliquid diet, and drinking water. Total parenteral support therapy; intravenous supplementation of protein, plasma amino acids, fat emulsion, electrolytes, vitamins and trace elements; and the correction of water and electrolyte imbalance can also be parts of a conservative treatment plan. Somatostatin has broad effects of inhibiting gastrointestinal digestive juice secretion and reducing the chylous fluid flowing through the thoracic duct. Clinically, octreotide is mostly used as a supplement to conservative treatment. Closed thoracic drainage is performed to ensure good lung expansion and thoracic cavity lavage of adhesives to prevent pleural adhesions. Conventional conservative treatment can be used in combination with positive pressure ventilation with a ventilator.

9.7.3.2.2 Surgical treatment

When conservative treatment is ineffective and the chest drainage volume is more than 1000 mL per day, the observation time should not exceed 1 week, and timely surgical treatment is needed. Surgical methods are as follows:

(1) If thoracic duct rupture can be clearly identified, direct ligation should be performed.
(2) Massive ligation should be performed on the tissues around the supradiaphragmatic thoracic duct.
(3) Treatment of recurrent chylothorax after thoracic duct ligation: Generally, after the occurrence of chylothorax, the leakage volume is small, and it can be cured after conservative treatment. If the leakage volume is large, lymphangiography is feasible to understand the anatomical variation of the thoracic duct and perform surgical ligation again.

Postoperative complications of EC are inevitable. In particular, when standardized tumor resection surgery is performed, complications are more common. However, according to the experience of our center, as long as the quality of surgery is strictly controlled and timely treatment is administered, the harm of complications is controllable.

10 Esophageal carcinoma pathological types

10.1 Esophageal carcinoma pathological types and definitions

Esophageal carcinoma (EC) is a malignant tumor derived from esophageal mucosal epithelial cells and is mainly divided into two histological types: squamous cell carcinoma and adenocarcinoma. In addition to the clinical symptoms, signs, and imaging and endoscopic examination findings, an EC diagnosis can be confirmed by cytological or histopathological examination for patients in whom the presence of cancer is identified by fiberoptic esophagoscopy, brush cytology or biopsy sample evaluation, and for patients with a clinical diagnosis of EC, the presence of extraesophageal metastatic lesions (supraclavicular lymph nodes, skin nodules, etc.) can be confirmed by biopsy sample or cytological examination [70–72].

10.1.1 Early EC

Invasive carcinoma of the esophagus confined to the mucosal layer, with or without regional lymph node metastasis.

10.1.2 Superficial EC

Invasive carcinoma of the esophagus confined to the mucosal and submucosal layers, with or without regional lymph node metastasis.

10.1.3 Progressive EC

Carcinoma of the esophagus that infiltrates the muscular layer or deeper invasive carcinoma of the esophagus.

10.1.4 Adenocarcinoma of the esophagogastric junction

The center of the tumor is located within 2 cm of the upper and 2 cm of the lower esophagogastric junction anatomically (the site where the tubular esophagus becomes the cystic stomach, which is not necessarily consistent with the squamocolumnar junction histologically).

10.2 Gross classification of EC

10.2.1 Early EC

Including occult, erosive, plaque, and papillary types.

10.2.2 Intermediate- and advanced-stage EC including medullary, fungoid, ulcerated, constricted, and intraluminal types

10.3 Pathological types and the grading of EC

10.3.1 Histological types

The use of the 2019 version of the World Health Organization (WHO) classification of digestive system neoplasms is recommended (Table 12).

Table 12 WHO classification of digestive system tumors (2019 edition)

Histological type	ICD-O code
Squamous cell carcinoma	8070/3
Verrucous carcinoma	8051/3
Spindle cell squamous cell carcinoma	8074/3
Basal cell squamous cell carcinoma	8083/3
Adenocarcinoma	8140/3
Adenoid cystic carcinoma	8200/3
Mucoepidermoid carcinoma	8430/3
Adenosquamous carcinoma	8560/3
Anaplastic carcinoma	8020/3
Lymphoepithelioid carcinoma	8082/3
Neuroendocrine tumor	8240/3
Neuroendocrine tumor, G1	8240/3
Neuroendocrine tumor, G2	8249/3
Neuroendocrine tumor, G3	8249/3
Neuroendocrine carcinoma	8246/3
Large cell neuroendocrine carcinoma	8013/3
Small cell neuroendocrine carcinoma	8041/3
Mixed neuroendocrine-nonneuroendocrine tumor	8154/3
Compound small cell carcinoma (compound adenocarcinoma)	8045/3
Complex small cell carcinoma (complex squamous cell carcinoma)	8045/3

10.3.2 Histological grades

Squamous cell carcinoma and adenocarcinoma are classified as well differentiated, moderately differentiated, and poorly differentiated according to the degree of differentiation.

10.4 Pathological evaluation of specimens obtained in radical resection after neoadjuvant therapy

The basic characteristics of pathological changes after neoadjuvant therapy include tumor cell degeneration, regression, massive necrosis, fibrous hyperplasia, interstitial inflammatory cell infiltration, and calcium deposition. There may be only keratinization without residual cancer cells after neoadjuvant therapy for squamous cell carcinoma and large mucin lakes without residual cancer cells after neoadjuvant therapy for adenocarcinoma, which cannot be considered residual tumors.

Tumor regression grade (TRG) is an important prognostic factor. Complete tumor response (i.e., complete or almost complete tumor elimination) is the main goal of preoperative treatment, and < 10% residual tumor predicts a good prognosis. There are currently two main sets of criteria for the assessment of TRG: descriptive assessments of the relationship between residual tumor and treatment-induced fibrosis [e. g., the Mandard system, the College of American Pathologists (CAP)/National Comprehensive Cancer Network (NCCN) guidelines, etc.] and assessments of the proportion of residual tumor in the original tumor bed (e. g., Becker criteria, Japanese Esophageal Society (JES) criteria, etc.) (Table 13). The CAP / NCCN guidelines should be used for the grading of the efficacy of EC treatment.

11 Early endoscopic treatment for esophageal carcinoma

11.1 Treatment principles

Compared with traditional surgery, endoscopic resection (ER) of early EC and its precancerous lesions has the advantages of less trauma, fewer complications, rapid recovery, and low cost, and the two have equivalent efficacy, with a 5-year survival rate of more than 95%. In principle, lesions without lymph node metastasis or with a very low risk of lymph node metastasis and a low risk of residual metastasis and recurrence are eligible for ER.

11.2 Indications and contraindications

Endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) are ER methods developed in Japan for the treatment of EC. At present, there is no

Table 13 Pathological evaluation criteria after neoadjuvant therapy

CAP/NCCN criteria	Becker criteria
TRG0: No viable cancer cells	TRG1a: No residual tumor
TRG1: Single or small clusters of residual cancer cells	TRG1b: less than 10% residual tumor in tumor bed
TRG2: Residual cancer foci with interstitial fibrosis	TRG2: 10% to 50% residual tumor in tumor bed
TRG3: Regression of few or no tumor cells; a large number of residual cancer cells	TRG3: Over 50% residual tumor in tumor bed

Tumor regression grading can be used only for primary tumor assessment but not for metastatic lesion assessment. Response assessment is based on the presence of viable tumor cells. The presence of keratinized cells or mucin lakes without tumor cells after neoadjuvant therapy cannot be considered residual tumor; the presence of keratinized cells or mucin lakes without tumor cells in lymph nodes cannot be considered tumor metastasis

uniform and standardized indication for ER in China. Because the morbidity of EC and the proportion of squamous cell carcinoma are low in Europe and the United States and the use of ER techniques is quite different from that in China, the ER of early EC in China is mainly based on the Japanese guidelines.

Japanese Esophageal Society (JES) Guidelines for the Diagnosis and Treatment of Esophageal Cancer (2012 Edition): Absolute indications for ER of early EC: stage T1a EC with lesions localized in the epithelial layer or lamina propria, with a very low risk of lymph node metastasis, and ER can achieve a radical cure. Relative indications for ER: lesions infiltrating the mucosa (M3) or superficial submucosa (T1b-SM1, depth of submucosal invasion < 200 μm). A high proportion of lesions with a depth of submucosal invasion of more than 200 μm develop lymph node metastasis, and these lesions are difficult to cure with endoscopic treatment. Japan Gastroenterological Endoscopy Society ESD / EMR Guidelines for Esophageal Cancer (2017 Edition): Absolute indications for ER of early EC: for lesions with a depth of invasion not exceeding the mucosal layer (T1a) and lesions confined to the mucosal (T1a) epithelium (EP) or lamina propria mucosa (LPM), which are rarely associated with lymph node metastasis, ER is a sufficiently thorough treatment. Relative indications: lesions extending into the mucosa or slightly infiltrating the submucosa (up to 200 μm) have an increased risk of lymph node metastasis. In addition, approximately 50% of lesions showing deeper (more than 200 μm) invasion into the submucosa (T1b) are associated with metastasis, and in this case, even if they are classified as superficial carcinomas, they should be treated in the same way as advanced carcinomas. Mucosal resection covering 3/4ths of the circumference may be associated with postoperative scar stenosis. Therefore, patients should be fully informed, and precautions should be taken.

The Japan Gastroenterological Endoscopy Society developed ESD/EMR Guidelines for Esophageal Cancer ("ER Guidelines") in 2020 based on continuously updated ER scientific research evidence. These guidelines are divided into two parts: those for esophageal squamous cell carcinoma and those for esophageal adenocarcinoma.

11.2.1 ER indications for esophageal squamous cell carcinoma

The treatment strategy for superficial esophageal squamous cell carcinoma is determined based on the depth of tumor invasion, extent of disease, and metastatic condition diagnosed preoperatively. Endoscopic ultrasonography and magnifying endoscopy have higher accuracy than non-magnifying endoscopy, so it is recommended to diagnose the depth of tumor invasion by endoscopic ultrasonography or magnifying endoscopy; ER is also recommended for the clinical diagnosis of T1a EP/LPM cancer. The extent of ER is closely related to the risk of stenosis, so preoperative assessment of the extent of the disease is strongly recommended, and image-enhanced magnifying endoscopy or iodine staining is recommended to determine the extent of the disease and can clearly delineate the boundary of the lesion. However, the use of high-concentration iodine solutions may cause the detachment of the superficial epithelium, making subsequent diagnosis and treatment difficult; therefore, it is recommended to use low-concentration iodine solutions ($\leq 1\%$).

ER is a new modality for T1a-muscularis mucosa (MM)/T1b-submucosa 1 (SM1) (MM / SM1) carcinoma. If the pathological result after resection is pEP / LPM and there is no vascular invasion, it is considered a curative resection. Surgical resection or chemoradiotherapy is recommended for cT1b cancer; however, some cSM1 cancers are pathologically confirmed pT1a-mucosa (M) (pM) cancer after surgical resection, and such lesions can be treated by ER. ER can be used as a first-line treatment for non-circumferential esophageal squamous cell carcinoma preoperatively diagnosed as cT1a-MM/T1b-SM1.

For cT1a-EP / LPM superficial esophageal squamous cell carcinoma involving 50 mm in length of the esophageal circumference, ER treatment is recommended when stricture prevention measures are conditionally taken.

11.2.2 Indications for ER for esophageal adenocarcinoma

Through global consensus, the 2017 EC practice guidelines strongly recommend ER for the preoperative

diagnosis of M cancer, i. e., patients with superficial Barrett's esophageal adenocarcinoma (cM) cancer. However, resection methods differ globally. ESD is common in Japan, whereas EMR is more common in Western countries. ESD is strongly recommended over EMR for the radical treatment of superficial esophageal adenocarcinoma amenable to ER. For differentiated pDMM esophageal adenocarcinoma without vascular invasion, additional surgical resection is not recommended in patients who achieve R0 by ER.

At present, the absolute indications for the ER of early EC and precancerous lesions are more recognized in China: EC (M1, M2) with lesions localized in the epithelial layer or lamina propria and severe dysplasia of the esophageal mucosa. Relative indications for ER: the lesion infiltrates the mucosal muscular layer or superficial submucosa (M3, SM1), and no clinical evidence of lymph node metastasis is found. Lesions with a range greater than 3 / 4ths of the circumference and a high risk of stricture after resection can be regarded as relative indications for ER, but patients should be fully informed of the risks, such as postoperative stricture.

11.2.3 Contraindications

Lesions with lymph node metastasis are identified, lesions infiltrate into the deep submucosa, and the patient is in poor general condition and cannot tolerate endoscopic surgery.

11.2.4 Relative contraindications

Patients with positive nonlifting signs, patients with coagulopathy and taking anticoagulants are not suitable for surgery before coagulation correction, preoperative judgment of lesion infiltration into the submucosal deep layer, and patients refuse or are not suitable for surgery.

11.3 Treatment

11.3.1 Perioperative management

(1) Preoperative preparation: The general condition of the patient is assessed to rule out contraindications to anesthesia and endoscopic treatment. Patients taking anticoagulants should discontinue the drug for 5–7 days as appropriate before surgery, and relevant departments should be asked to assist in treatment when necessary.
(2) Postoperative treatment: fasting on the first day after the operation; the monitoring of vital signs; the observation of the presence or absence of head, neck or chest subcutaneous emphysema; and necessary laboratory and imaging examinations. If no abnormalities are identified, a completely liquid diet can be taken on the second day after surgery, followed by a soft diet for 3 consecutive days and then gradually return to a normal diet.

11.3.2 Postoperative medication

(1) First, antibiotics are used. Prophylactic use of antibiotics can be considered for patients with a large extent of resection, a long operation time, repeated submucosal injections, and a high risk of perforation. Referring to the principles of antibacterial drug use of the Ministry of Health, first-generation or second-generation cephalosporins and nitroimidazoles should be selected. Postoperative medication generally does not exceed 72 h and can be prolonged at physician discretion. Postoperative mediation protects the wound surface and hemostasis. Proton pump inhibitor (PPIs) or H2 receptor antagonists may be given for 4 to 6 weeks after surgery, and patients with a history of acid reflux or gastroesophageal reflux disease (GERD) -like symptoms require adequate and continuous PPI therapy. Mucosal protective agents and hemostatic drugs can be used as appropriate when necessary.
(2) Postoperative specimen processing: See the "Expert Consensus on Guidelines for Digestive Endoscopic Biopsy and Pathological Examination in China" (draft).
(3) Indications for additional postoperative treatment (surgery/radiotherapy/chemotherapy): submucosal invasion depth $\geq$ 200 μm, positive lymphovascular invasion, poorly differentiated or undifferentiated carcinoma, and a positive vertical resection margin. These factors need to be considered in combination with the general condition and wishes of the patient.

11.3.3 Procedure-related complications and treatment

Complications after ER of early esophageal cancer and precancerous lesions mainly include bleeding, perforation, postoperative stenosis, and infection.

11.3.3.1 Hemorrhage Intraoperative bleeding refers to local wound bleeding requiring hemostatic treatment during surgery. Delayed postoperative bleeding refers to signs such as hematemesis and melena within 30 days after surgery, with hemoglobin decreasing by more than 20 g/L.

Treatment: A small amount of intraoperative oozing can be treated by endoscopic spraying with epinephrine 0.9% NaCl solution, while a large amount of oozing can be treated with submucosal injection of epinephrine 0.9%

NaCl solution and argon plasma coagulation. Clamping with hot biopsy forceps or hemostatic clamping can be used to stop bleeding. The addition of epinephrine to submucosal injections, electrocoagulation of suspicious vessels during surgery, and the precoagulation of visible vessels after lesion resection are helpful to prevent bleeding.

11.3.3.2 Evaluation Intraoperative perforation can be detected in a timely manner. Postoperative perforation should be considered when there are signs of perforation, such as subcutaneous emphysema in the head, neck and chest, and mediastinal gas is found by abdominal X-ray or CT.

Treatment: Perforation is found during surgery. In the subsequent surgery, the amount of gas and water injected should be reduced. After the end of resection, clamping should be performed in a timely manner. After the operation, fasting, gastrointestinal decompression, intravenous use of antibiotics and supportive treatment can be recovered. When complicated by pneumothorax, negative pressure drainage should be performed. Surgery may be considered when endoscopic clamping fails or when the perforation is too large to be clamped. Conservative treatment of occult perforation can mostly recover.

11.3.3.3 Esophageal stenosis Esophageal stenosis after ER requires endoscopic treatment and is often accompanied by varying degrees of dysphagia, mostly occurring 1 month after surgery.

Management: Endoscopic esophageal dilatation is the most conventional treatment and can also be used as a preventive measure in cases of stricture. Stent placement can be an option for refractory cases, and glucocorticoids can also be used for the prevention and treatment of postoperative stenosis, but the optimal regimen needs to be explored. Regenerative medicine techniques, such as cell patches, are still in the research stage.

12 Chemotherapy for esophageal carcinoma

12.1 Chemotherapy for advanced esophageal carcinoma

Systemic chemotherapy is the standard of care for advanced unresectable or metastatic esophageal carcinoma (EC). Cisplatin combined with the 5-fluorouracil regimen (PF regimen) has been used as a standard treatment regimen in clinical practice, but large phase III randomized controlled studies are lacking to confirm its efficacy. Except for the PF regimen, the effectiveness of other single-agent chemotherapy regimens and combination regimens has not been confirmed by specific clinical studies.

12.1.1 First-line chemotherapy regimen for EC

In terms of single-agent chemotherapy, 5- fluorouracil, platinum, paclitaxel, and vinblastine drugs in combination chemotherapy regimens have been reported to have a response rate of 15% to 40% and a response rate of approximately 20% to 60% and are associated with a median survival of approximately 3 to 10 months.

Regarding the efficacy of the integrated regimen of two or three drugs, only one study compared combination therapy with monotherapy, during which the PF regimen was compared with single-agent cisplatin, with response rates of 35% vs. 19% and a median survival of 33 weeks vs. 29 weeks [73]. Because of the long-term lack of new therapeutic agents and targeted drugs, some studies have explored attempts to increase the types of chemotherapeutic drugs to prolong survival. Three phase II studies explored the safety and efficacy data of the three-drug combination regimen of taxanes, platinum, and fluorouracil [74–76]. Two studies were conducted in Japan, in which 23 patients and 34 patients were treated with docetaxel, nedaplatin and fluorouracil combination regimens, respectively. The objective response rate (ORR) was 72.7% and 47.1%, the median progression-free survival (PFS) was 6 months and 9 months, and the median overall survival (OS) was 11.2 months and 19.8 months, respectively. Another 43 patients in a Chinese study were treated with the same three-drug integrated regimen, with a complete response (CR) rate of 4.65%, a partial response (PR) rate of (58.14%), a median time to progression (TTP) of 6.7 months, and a median OS of 10.3 months. Although many attempts have been made in the first-line treatment of advanced disease, there is no clinical study to confirm the efficacy of the three-drug integrated treatment regimen. A phase III randomized controlled study, JCOG1314, of biweekly docetaxel, cisplatin, and fluorouracil combination versus cisplatin / fluorouracil was conducted in Japan in 2015, but there was no final report (Table 14).

12.1.2 Second-line chemotherapy regimen for EC

For patients with platinum- and fluoropyrimidine-resistant advanced EC, data on effective drugs are even more lacking. Most of the data are based on the fact that EC shows some response to taxanes in second-line treatment. In a phase II study, a total of 36 patients were enrolled to compare the efficacy of docetaxel combined with nedaplatin versus docetaxel alone in the second-line treatment of cisplatin- and fluorouracil-resistant cancer. The ORR in the dual-therapy group and in the monotherapy group was 52.9% and 36.8%, the median survival was 8.9 months and 7.0 months, ($P=0.544$), and the incidence of grade 3 and above adverse events (AEs) was 58.8% and 26.3%, respectively ($P=0.090$) [77].

Another multicenter randomized study led by Professor Huang Jing from the Cancer Hospital, Chinese Academy of Medical Sciences, compared irinotecan combined with tegafur versus tegafur alone in the second-line treatment of patients with platinum- or taxane-resistant esophageal squamous cell carcinoma. A total of 123 patients were enrolled, with 61 in the dual-agent group and 62 in the single-agent group. The median follow-up time was 29.2 months. The PFS was 3.8 months and 1.7 months ($P=0.006$) and the ORR was 24.6% and 9.7% in the dual-agent and single-agent groups, respectively. However, the side effects were significantly increased in the dual-agent group. The incidence of a decrease in white blood cell count (≥grade 3) was 16.4% and 0%, the incidence of a decrease in neutrophil count (≥grade 3) was 14.8% and 1.6%, and the incidence of nausea (≥grade 3) was 4.9% and 0%, respectively, in the dual-agent and single-agent groups (Table 15) [78].

12.2 Chemotherapy for localized EC

Neoadjuvant chemoradiotherapy plus surgery is currently recommended for esophageal squamous cell carcinoma. Immunotherapy alone is recommended for patients with postoperative residual disease. For patients who have not previously received any neoadjuvant therapy, the combination chemotherapy of cisplatin and fluorouracil can be administered for patients with positive lymph nodes by referring to the JCOG9204 study.

Concurrent chemoradiotherapy is always the standard treatment modality for patients with locally advanced unresectable disease. With the increase in chemotherapeutic agents, new combinations of combination regimens have also emerged. In 2019, there was a phase III randomized controlled study in China that compared the efficacy and safety of radiotherapy combined with the PF regimen or combined with the TF (paclitaxel combined with fluorouracil) regimen [79]. A total of 436 patients were included and randomized in a 1: 1 ratio into the radiotherapy + PF regimen and radiotherapy + TF regimen groups, with a 3-year OS of 51.8% and 55.4% and a 3-year PFS of 45.5% and 43.7%, respectively. There were no significant differences between the two groups in terms of OS or TTP. However, treatment-related side effects varied.

In addition, CRTCOESC was another Chinese study that evaluated the efficacy and safety of the X regimen (capecitabine) vs. the XE + LOX regimen (capecitabine combined with oxaliplatin) vs. the PF regimen as a radical chemoradiotherapy regimen. A total of 244 patients were included and divided into three groups in a 1: 1: 1 ratio, and the 2-year OS was 63.8%, 61.5%, and 62.5% ($P=0.973$); the median OS was 39.7 months, 40 months and 34 months ($P=0.703$); the CR rate was 43.8%, 41.4%, and 42.4% ($P=0.964$); and the incidence of grade 3 or higher AEs was 26.5%, 33.8% and 49.3% ($P=0.0193$), respectively, for the X, XE + LOX, and PF regimens. No differences in the OS, PFS, or pathological CR (pCR) rates were observed between capecitabine plus chemotherapy and the doublet combination, but the overall incidence of AEs was markedly reduced.

Another study of concurrent chemoradiotherapy in China compared the efficacy and safety of three regimens of concurrent chemoradiotherapy: paclitaxel + cisplatin, paclitaxel + carboplatin, and paclitaxel + fluorouracil. A total of 321 patients were included and randomly divided into the paclitaxel + cisplatin, paclitaxel + carboplatin, and paclitaxel + fluorouracil groups in a 1: 1: 1 ratio; the 3-year OS rates of the three groups were 59.5%, 59.5%, and 58.2%, respectively ($P=0.839$). In terms of adverse reactions, neutropenia, thrombocytopenia, vomiting, and asthenia were significantly higher in the paclitaxel + cisplatin group than in the other two groups, while the incidences of esophagitis and pneumonia were higher in the paclitaxel + fluorouracil group than in the other two groups.

Taken together, the results of these studies combined with those of the 5010 study and CROSS study show that there are many options for concurrent chemoradiotherapy, as shown in Table 16 [20, 80].

Table 14 EC first-line chemotherapy regimens

Protocol	Response rate (%)
Cisplatin 100 mg/m2 D1, Fluorouracil 1000 mg/m2 D1-5, Q3w	35
Cisplatin 70 mg/m2 D1, fluorouracil 1000 mg/m2 D1-5, Q3w	35.9
Nedaplatin 90 mg/m2, fluorouracil 800 mg/m2 D1-5, Q4w	39.5
Doxorubicin 30 mg/m2 D1, cisplatin 14 mg/m2 D1-5, fluorouracil 700 mg/m2 D1-5, Q4w	43.9
Docetaxel 30 ~ 40 mg/m2 D1 to D15, cisplatin 80 mg/m2 D1, fluorouracil 800 mg/m2 D1-5, Q4w	62
Docetaxel 60 mg D1, nedaplatin 70 mg D1, fluorouracil 800 mg/m2 D1-5, Q3w	47.1
Docetaxel 35 mg D1 D15, nedaplatin 90 mg D1, fluorouracil 800 mg/m2 D1-5, Q4w	72.7

Table 15 EC second-line chemotherapy regimens

1. Paclitaxel 80 mg/m2 D1 D8 to D15, Q4w docetaxel 60–75 mg/m2 D1, Q3w
2. Irinotecan 150 ~ 180 mg/m2 D1, Q2w
3. Tegafur 80 ~ 120 mg/d D1-14, Q3w
4. Irinotecan + tegafur irinotecan 160 mg/m2 D1, tegafur 80–120 mg/d D1-10, Q3w

13 Radiotherapy for esophageal carcinoma

13.1 Esophageal carcinoma radical radiotherapy

13.1.1 Indications [79, 81–83]

(1) Radical concurrent chemoradiotherapy is recommended for patients with pT1b-2N0 stage noncervical disease who cannot tolerate or refuse surgery.
(2) For patients with cT1b-2N+or cT3- 4aN0 / N+esophageal carcinoma (EC), an Eastern Cooperative Oncology Group (ECOG) performance score (PS) score of 0 ~ 1, cervical segment EC and those who refuse surgery or have surgical contraindications, radical concurrent chemoradiotherapy is recommended.
(3) For patients with cT4bN0 / N+EC and PS scores of 0 ~ 1, radical concurrent chemoradiotherapy is recommended. For patients with a tendency for esophageal perforation or massive hemorrhage, radiotherapy should be carefully selected. For patients who cannot tolerate concurrent chemoradiotherapy, radiotherapy alone or sequential chemoradiotherapy is recommended. In N+patients, complete resection of metastatic lymph nodes is difficult (invasion of surrounding organs), and radical concurrent chemoradiotherapy is recommended.

13.1.2 Contraindications

(1) The general condition of the patient is poor, with cachexia;
(2) Poor cardiopulmonary function, comorbid serious diseases of vital organ systems, or an inability to tolerate radiotherapy;
(3) Patients with signs of massive esophageal bleeding or warning signs of massive esophageal bleeding;
(4) Esophageal fistula complicated with severe infection.

13.1.3 Coordination in terms of chemotherapy

The standard nonsurgical treatment of locally advanced EC is concurrent chemoradiotherapy, and induction chemotherapy prior to radical chemoradiotherapy does not improve survival [79, 81, 82, 84, 85]. Commonly used regimens for concurrent chemotherapy include platinum combined with fluorouracil or paclitaxel combined with platinum in a dual-therapy regimen. According to the patient's tolerance, capecitabine and tegafur can be used to replace fluorouracil, and carboplatin, oxaliplatin or nedaplatin can be used to replace cisplatin.

Commonly used regimens for radical chemoradiotherapy: fluorouracil+cisplatin, cisplatin 75 ~ 100 mg / m^2 d1, fluorouracil 750 ~ 1000 mg / m^2 qd CIV 96 h, Q4W, concurrent radiotherapy for 2 cycles, followed by 2 cycles of paclitaxel+carboplatin/ chemotherapy, paclitaxel 50 mg/m^2 d1, carboplatin AUC = 2 (cisplatin 25 mg/ m^2) d1, QW for 5 weeks.

Table 16 Concurrent chemoradiotherapy for locally advanced EC

Norvinblastine 25 mg/m2 D1 to D8 D22 D29; cisplatin 75 mg// m2 D1 D22
cisplatin 25 mg/m2 D1 to D2; fluorouracil 1000 mg/m2 D1 to D5 Q3w, 2 cycles
Paclitaxel 175 mg/m2 D1; fluorouracil 1800 mg/m2 72 h, Q4w, 2 cycles
Paclitaxel 50 mg/m2 D1; fluorouracil 300 mg/m2 D1, Qw, 5 cycles
Paclitaxel 175 mg/m2 D1; cisplatin 25 mg/m2 D1-3, Q4w, 2 cycles
Paclitaxel 50 mg/m2 D1; carboplatin AUC 2, Qw, 6 cycles

13.1.4 Irradiated target area [86–88]

Gross tumor target volume (GTV): including primary tumor (GTVp) and metastatic lymph nodes (GTVnd). GTVp is an esophageal lesion and is determined based on imaging (contrast-enhanced CT, MRI, upper gastrointestinal radiography, and PET-CT) and endoscopic ultrasonography. GTVnd is radiologically visible metastatic lymph nodes, including lymph nodes with a short diameter 10 mm (paraesophageal, tracheoesophageal groove 5 mm) or lymph nodes with significant necrosis, ring enhancement, and clustering.

Clinical target volume (CTV): According to the National Comprehensive Cancer Network (NCCN) guidelines, field irradiation is recommended for radical radiotherapy. Studies have shown that there was no significant difference in survival between the selected field and involved field irradiation groups based on further pretreatment examinations; therefore, for patients with an excessive tumor range, a poor PS score, advanced-stage disease and poor cardiopulmonary function, involved field irradiation is recommended. When the involved field is irradiated, the CTV is defined as 5 ~ 6 mm expansion in the anteroposterior, left and right directions of the GTVp; 30 mm expansion in the superior and inferior directions; and 5 ~ 6 mm expansion in all directions of the GTVn (which needs to be appropriately adjusted according to the anatomical barrier after the expansion). During prophylactic lymph node radiotherapy, in addition to the primary esophageal lesion and metastatic lymph node area, irradiation of the upper mediastinum and supraclavicular lymphatic drainage area is recommended for those with lesions in the cervical and upper thoracic segments, and irradiation of the left gastric lymphatic drainage area is recommended for those with lesions in the lower thoracic segment.

Planned target volume (PTV): 5 mm expansion in all directions of the CTV and 8 ~ 10 mm expansion in the longitudinal direction (the actual expansion distance can

be determined according to the quality control data of each center).

13.1.5 Radiotherapy dose [82, 89, 90]

Radical concurrent chemoradiotherapy: 50 ~ 60 Gy, conventional fractionation, a single dose of 1.8 ~ 2.0 Gy, total fractionation times of 25 ~ 30 times. Prospective studies have shown that there were no significant differences in the local control rate and survival rate between the standard-dose versus high-dose radical radiotherapy group and the concurrent boost high-dose group. The findings from some retrospective studies and meta-analyses suggest that high-dose radiotherapy might improve the local control rate and survival rate of esophageal squamous cell carcinoma. For patients receiving radical chemoradiotherapy who receive adequate chemotherapy during radiotherapy, a standard dose is recommended for the radiotherapy dose, and high-dose radiotherapy can be used for patients receiving radiotherapy alone, with a radiotherapy dose of 60 ~ 70 Gy in conventional fractionation.

13.1.6 Radiation techniques [91, 92]

Intensity-modulated radiotherapy (IMRT) and helical tomographic intensity-modulated techniques [volumetric modulated arc therapy (V-MAT) and tomography (TO-MO)] can be selected for EC radiotherapy, and 6 MV X-rays are recommended. During treatment, it is recommended to perform cone-beam CT (CBCT)-based position verification before each treatment for the first 3 ~ 5 times and then carry out acquisition once a week.

Intensity-modulated proton beam therapy (IMPT) can better reduce the dose delivered to the lungs, heart and liver than passive scattered proton therapy (PSPT) and IMRT, but whether it can improve survival is still under further study.

13.2 EC Preoperative radiotherapy

13.2.1 Indications [20, 93, 94]

For patients with cT1b-2N + or cT3-4aN0/N + and a PS score of 0 ~ 1, neoadjuvant chemoradiotherapy is recommended for patients with adenocarcinoma, and neoadjuvant chemotherapy is also feasible. Neoadjuvant chemoradiotherapy is recommended for patients with squamous cell carcinoma; the timing of surgery is 6 ~ 8 weeks after the end of neoadjuvant chemoradiotherapy or 3 ~ 6 weeks after the end of neoadjuvant chemotherapy. For patients who do not achieve a pCR after neoadjuvant chemoradiotherapy, maintenance therapy with nivolumab is recommended.

13.2.2 Preoperative chemoradiotherapy regimen for EC [20, 93]

Commonly used regimens for concurrent chemotherapy during radiotherapy: paclitaxel + carboplatin, paclitaxel 50 mg/m2 d1, carboplatin AUC = 2 d1, QW, for 5 weeks; cisplatin + fluorouracil (capecitabine, tegafur), 75 ~ 100 mg/m2d1, 29, fluorouracil 750 ~ 1000 mg/m2qd d1 ~ 4, d29 ~ 32, Q4 W, for a total of 2 cycles.

13.2.3 Irradiation target area and dose [20, 93]

At present, there is no international provision on the radiotherapy target area specifically for neoadjuvant chemoradiotherapy, and it is recommended to be based on the principles of radical radiotherapy irradiation. The location of the anastomotic stoma during subsequent surgical resection should be considered when the target area is delineated, and the position of the anastomotic stoma in the radiation field should be avoided as much as possible, thereby reducing the incidence of anastomotic leakage.

The dose of preoperative neoadjuvant chemoradiotherapy is generally 40 ~ 50.4 Gy, conventional fractionation, 1.8 ~ 2.0 Gy / time, for a total of 20 ~ 28 times.

13.3 Postoperative radiotherapy for EC

13.3.1 Indications [95–97]

For patients with squamous cell carcinoma, the NCCN guidelines do not recommend adjuvant therapy after radical resection, but according to the recurrence rate results reported worldwide, especially in a large number of domestic cases (mostly based on left thoracotomy and two-field lymph node dissection), prospective stratified studies and retrospective analyses of many cases, postoperative radiotherapy or chemoradiotherapy can be considered for patients with positive postoperative lymph nodes and / or pT3-4aN0 stage EC who do not receive neoadjuvant therapy. Especially for patients with postoperative N2 ~ 3, postoperative concurrent or sequential chemoradiotherapy can reduce the locoregional recurrence rate and improve the survival rate. In terms of adenocarcinoma, fluorouracil-based chemoradiotherapy is feasible for patients with high-risk pT2 (poorly differentiated, vascular tumor thrombus, nerve invasion, < 50 years of age) and patients with pT3-4a without neoadjuvant therapy. For lymph-node-positive patients, fluoropyrimidine-based postoperative chemotherapy or chemoradiotherapy is recommended.

Concurrent chemoradiotherapy or sequential chemoradiotherapy is recommended for patients who do not receive neoadjuvant chemoradiotherapy after R1 / R2 resection (suitable for patients who cannot tolerate concurrent chemoradiotherapy).

13.3.2 Irradiated target area

Postoperative radiotherapy CTV: The radiation field design is controversial. Radiation to the bilateral supraclavicular regions and superior mediastinal region, that is,

groups 104, 105, 106, and 107 groups, is recommended. If patients have lower EC and ≥ 3 lymph node metastases, when single radiotherapy is used, it is recommended to include lymph node areas 104, 105, 106, and 107 and abdominal groups 1, 2, 3, and 7. If patients have upper thoracic EC or the upper resection margin measures ≤ 3 cm in size, it is recommended to include the anastomotic stoma. The radiation dose to the thorax and stomach or mediastinum and stomach of patients should be considered for the extent of the postoperative radiotherapy target area and in whether concurrent chemotherapy is performed, especially for patients at the stage after right thoracotomy.

13.3.3 Radiotherapy dose

Postoperative radiotherapy: R1/R2 postoperative adjuvant radiotherapy 50 ~ 60 Gy, conventional fractionation; when the radiotherapy dose is determined, there is a need to consider the highest dose point of the thorax and stomach to reduce the occurrence of postoperative bleeding and fistula. The dose of adjuvant concurrent chemoradiotherapy is 50.4 Gy, and the dose of R0 postoperative adjuvant radiochemotherapy is 45 ~ 50.4 Gy, conventional fractionation.

13.3.4 Integration of postoperative radiotherapy and chemotherapy [98]

Retrospective studies have shown that postoperative chemoradiotherapy can improve the survival rate of patients with positive lymph nodes, especially N2 ~ 3. The commonly used chemotherapy regimen is similar to the chemotherapy regimen in EC radical chemoradiotherapy. In general, for elderly and frail patients who cannot tolerate concurrent chemoradiotherapy, sequential chemoradiotherapy or chemotherapy with tegafur during radiotherapy can be used.

13.4 Palliative radiotherapy for EC

Palliative radiotherapy for EC is commonly used in the following patients:

(1) For patients with advanced lesions with reduced or stable metastases after chemotherapy, radiotherapy of the primary tumor may be considered.
(2) Patients with clinical symptoms caused by distant metastasis can receive palliative radiotherapy.
(3) Patients with advanced disease need the treatment of esophageal obstruction and the improvement of nutritional status.

13.5 Normal tissues

Normal tissue delineation and dose limitation are based on the QUANTEC criteria. The delineation scope of the main normal tissues mainly includes the spinal cord, lungs, heart, liver, trachea, stomach, thyroid gland and small intestine (if within the radiation field range).

The following dose limitations for normal tissues are recommended: cervical spinal cord, ≤ 45 Gy; thoracic spinal cord, ≤ 50 Gy; lungs V20 ≤ 30% and mean dose (MLD) < 20 Gy; cardiac tissue, mean dose < 26 Gy, V30 < 40%, and V40 < 30%; in patients without previous liver disease or hepatocellular carcinoma, a mean liver dose < 30 Gy; in patients with Child–Pugh A liver function with previous liver disease or hepatocellular carcinoma, a mean liver dose < 28 Gy; trachea, maximum dose ≤ 70 Gy, and measures should be taken to prevent hotspot dosing (≥ 110% of prescribed dose) into the tracheal wall; for patients with serious adverse reactions after gastric irradiation, including ulcers and perforations, the gastric volume of patients receiving 40 Gy should be less than 40% ~ 50% of all doses to the thorax and stomach, and the maximum dose generally should not exceed 54 Gy.

13.6 Common toxicities of radiotherapy

The most common acute toxicities of radiotherapy include radiation esophagitis, pneumonia, cardiac injury and bone marrow suppression. Spinal cord injury rarely occurs due to the development of accurate radiotherapy. Common late reaction injuries include pulmonary fibrosis, esophageal stenosis and perforation, and cardiac injury.

13.6.1 Radiation esophagitis

At 2 to 3 weeks of radiotherapy, most patients will experience radiation esophagitis, mainly manifesting as swallowing pain; patients with severe cases can experience dehydration, malnutrition, electrolyte imbalance or weight loss. The principle of treatment is anti-inflammation, analgesia, the repair of the damaged esophageal mucosa and nutritional support therapy, and for patients with severe cases, nasogastric tube placement can be considered for nutritional support therapy.

13.6.2 Radiation pneumonitis

Acute radiation pneumonitis usually occurs within 3 months after the start of radiotherapy and mainly manifests as fever, cough, dyspnea, etc.; in patients with severe cases, death often occurs due to dyspnea. Glucocorticoids should be used as early as possible, in adequate doses and throughout the entire course of treatment, and the doses should be gradually reduced to discontinuation after clinical symptoms are significantly improved. The main way to manage radiation pneumonitis is prevention, mainly by accurately delineating the target area, optimizing the radiotherapy plan, and minimizing the dose and volume to normal lung tissue. Especially for patients with

chronic lung diseases, interstitial pneumonia, diabetes or receiving multiple cycles of chemotherapy or combined immunotherapy before radiotherapy, the dose and volume to normal lung tissue should be strictly controlled.

13.6.3 Radiation-induced cardiac injury

Radiation-induced cardiac injury is a collective term for a series of cardiovascular complications after radiotherapy, mainly including asymptomatic myocardial ischemia, arrhythmia, pericarditis, myocardial infarction, and ischemic heart failure, with a long latency period. There are currently no effective or specific treatment options for radiation-induced cardiac injury.

14 Neoadjuvant therapy for esophageal carcinoma

14.1 Indications for neoadjuvant therapy

Neoadjuvant therapy is recommended for esophageal carcinoma (EC) patients who also meet the following indications: locally advanced EC (cT1b-cT2N + M0 or cT3- cT4aany N M0); resectable or marginally resectable esophageal or esophagogastric junction cancer; and willingness to undergo surgery and ability to tolerate chemoradiotherapy toxicity.

(1) Resectable esophageal or esophagogastric junction cancer: For tumors invading the submucosa (T1b) or deeper, surgical treatment is usually selected. Although multiple and multistation lymph node metastases are relative contraindications to surgery, T1- T3 tumors can also be resected in cases of regional lymph node metastases (N+), at which time factors such as patient age and physical condition should be considered. T4a tumors involving the pleura, pericardium, or diaphragm are resectable.
(2) Resectable EC or junction cancer at the margin: For patients with suspected involvement of the surrounding organs but cT4b is not identified, neoadjuvant therapy is recommended first, followed by secondary tumor assessment. Surgical treatment is performed for those who can undergo radical resection, and radical concurrent chemoradiotherapy can be continued for those who cannot undergo radical resection.

14.2 Selection of neoadjuvant therapy (Table 17)

14.3 Neoadjuvant therapy regimens

14.3.1 Chemotherapy regimen

14.3.1.1 Squamous cell carcinoma

Preoperative chemotherapy regimen:

(1) Cisplatin	80 mg/m2	i.v.d	d1 (or divided into 3 ~ 5 days)
paclitaxel	150 ~ 175 mg/m2	i.v.d	d1
(or docetaxel	60 ~ 75 mg/m2	i.v.d	d1)
(2)Cisplatin	75 mg/m2	i.v.d	d1 (or divided into 3 ~ 5 days)
paclitaxel	135 mg/m2	i.v.d	d1
Fluorouracil	4 g/m2	civ 120 h	d1)
(3)Fluorouracil	5 g/m2	civ 120 h	d1
Cisplatin	80 mg/m2	i.v.d	d1 (or divided into 3 ~ 5 days)

Repeat every 3 ~ 4 weeks, 2 ~ 3 courses before surgery, and 3 ~ 4 weeks after chemotherapy surgery.

Concurrent chemotherapy regimen:

(1)Fluorouracil	500 mg/m2	i.v.d	d1 ~ 5
Cisplatin	25 mg/m2	i.v.d	d1 ~ 4
(2)Cisplatin	25 mg/m2	i.v.d	d1 ~ 4
Vinorelbine	25 mg/m2	i.v.d	d1, d8
(3)Cisplatin	25 mg/m2	i.v.d	d1 ~ 4
paclitaxel	175 mg/m2	i.v.d	d1
(or docetaxel	75 mg/m2	i.v.d	d1)

Repeat every 3 to 4 weeks for 2 courses, concurrently with radiotherapy.

14.3.1.2 Adenocarcinoma

Perioperative chemotherapy regimen:

(1)Fluorouracil	2600 mg/m2	civ 24 h	d1
Leucovorin	200 mg/m2	i.v.d	d1
Oxaliplatin	85 mg/m2	i.v.d	d1
Docetaxel	50 mg/m2	i.v.d	d1

Repeat every 2 weeks for 4 courses before and after surgery.

(2)Oxaliplatin	85 mg/m2	i.v.d	d1
Leucovorin	400 mg/m2	i.v.d	d1
Fluorouracil	400 mg/m2	i.v. push	d1
Fluorouracil	1200 mg/m2	civ 24 h	d1 ~ 2

Repeat every 2 weeks for 3 courses before and after surgery.

(3)Oxaliplatin	130 mg/m2	i.v.d	d1
Capecitabine	1000 mg/m2	P.O. BID	d1 ~ 14

Repeat every 3 weeks for 3 courses before and after surgery.

Table 17 Selection of neoadjuvant therapy for EC

Squamous cell carcinoma	Resectable	Neoadjuvant concurrent chemoradiotherapy[a]	Neoadjuvant chemotherapy[b]
	Resectable margin	Evaluate the possibility of surgery after neoadjuvant concurrent chemoradiotherapy, and if radical resection can be achieved, surgical treatment is feasible	Evaluate the possibility of surgery after neoadjuvant chemotherapy, and if radical resection can be achieved, surgical treatment is feasible
Adenocarcinoma	Resectable	Neoadjuvant concurrent chemoradiotherapy[c] or perioperative chemotherapy[d]	
	Resectable margin	Neoadjuvant concurrent chemoradiotherapy or evaluate the possibility of surgery after neoadjuvant chemotherapy, and if radical resection can be achieved, surgical treatment is feasible	

[a] In hospitals with the proper conditions, preoperative neoadjuvant concurrent chemoradiotherapy is recommend- ed. Concurrent chemoradiation prior to EC is a more well-proven treatment and can therefore be recommended as a routine treatment. Previous studies have confirmed that for operable tumors, the treatment paradigm of preoperative chemo- radiotherapy combined with surgery could achieve a significant survival benefit over surgery alone [93, 99–101]. For esophageal squamous cell carcinoma, a prospective, multicenter randomized controlled phase clinical trial (study) confirmed that the integrated treatment mode of preoperative chemoradiotherapy combined with surgery improved overall survival and prolonged tumor-free survival compared with surgery alone, while there was no significant difference in perioperative mortality or the incidence rate of most postoperative complications between the two groups [20]

[b] Data on whether the long-term survival benefit of preoperative concurrent chemoradiotherapy is superior to that of preoperative chemotherapy are inconclusive, but the findings from most studies suggest that integrated chemoradiotherapy can improve the locoregional control rate and radical surgical resection rate [100, 101]

[c] For esophageal adenocarcinoma, the efficacy of neoadjuvant concurrent chemoradiotherapy has also been effectively confirmed. A randomized controlled phase III clinical study (CROSS study) comparing the effects of preoperative chemoradiotherapy combined with surgery and surgery alone showed that the integrated treatment mode of preoperative chemoradiotherapy combined with surgery could effectively increase the R0-resection rate and prolong overall survival and progression-free survival compared with surgery alone [80, 93]

[d] For perioperative chemotherapy, Cunningham MAGIC et al. compared the efficacy of chemotherapy combined with surgery and surgery alone. The results showed that there was no significant difference in the incidence rate of postoperative complications between the two groups. Perioperative chemotherapy could reduce the risk of death and prolong progression-free survival [102]

Concurrent chemotherapy regimen:

(1)Paclitaxel	50 mg/m2	i.v.d	d1
Carboplatin	AUC = 2	i.v.d	d1

Repeat for 5 weeks.

(2)Oxaliplatin	85 mg/m2	i.v.d	d1
Leucovorin	400 mg/m2	i.v.d	d1
Fluorouracil	400 mg/m2	i.v. push	d1
Fluorouracil	800 mg/m2	civ 24 h	d1 ~ 2

Repeat every 2 weeks for 3 courses, concurrently during radiotherapy.

(3)Oxaliplatin	85 mg/m2	i.v.d	d1, 15, 29
Capecitabine	625 mg/m2	P.O. BID	d1 ~ 5

Repeat for 5 weeks.

Preoperative chemotherapy regimen:

Fluorouracil	1000 mg/m2	civ 24 h	d1 ~ 4
Cisplatin	80 mg/m2	i.v.d	d1

Repeat every 3 weeks for 2 cycles.

14.3.2 Radiotherapy program

Studies have confirmed that concurrent chemoradiotherapy is more effective than radiotherapy alone in terms of tumor down-staging, the R0 resection rate, and the pathological response rate [103, 104]. Therefore, a radiation-alone regimen is selected only if the patient cannot tolerate concurrent chemoradiotherapy.

14.3.2.1 Preoperative radiotherapy dose DT40 ~ 50 Gy: The dose of 40 ~ 41.4 Gy is currently being used in two phase III prospective studies, and there is no sufficient evidence to show whether there is a difference in the clinical efficacy between low-dose and high-dose neoadjuvant radiotherapy [93, 105].

14.3.2.2 Radiotherapy Accurate radiotherapy techniques, such as three-dimensional conformal radiotherapy (3DCRT), conformal intensity-modulated radiotherapy (IMRT), and proton radiotherapy can be used. Several dosimetric studies and large retrospective clinical studies have confirmed that IMRT has advantages in terms of dose distribution in the target area and the protection of normal organs compared with 3DCRT, especially in terms of the protection of the heart and lungs, and it can reduce the incidence of cardiopulmonary complications and may improve survival. Therefore, IMRT has gradually replaced 3DCRT as the mainstream technique for EC radiotherapy in recent years. The findings from a prospective phase II randomized controlled study

showed that proton therapy could further reduce the incidence of radiotherapy complications compared with IMRT.

14.3.2.3 Target definition The gross tumor volume (GTV) includes the primary esophageal tumor (GTVp) and the positive lymph nodes (GTVn). The clinical target volume (CTV) includes subclinical lesions (normal esophagus 3 cm above and below the GTVp) and 0.5 ~ 1.0 cm outward expansion of the GTVn in all directions. Whether to perform selective lymphatic drainage area irradiation is currently controversial. In addition, the location of the anastomotic stoma during subsequent surgical resection should be considered when the target area is delineated, and the position of the anastomotic stoma in the radiation field should be avoided as much as possible, thereby reducing the incidence of anastomotic leakage.

14.3.3 Selection of surgical methods

The recommended timing of surgery after neoadjuvant therapy is 6 to 8 weeks after the end of chemoradiotherapy and 3 to 6 weeks after the end of chemotherapy when the patient's physical condition permits.

14.3.3.1 Selection of surgical method for EC Recommended surgical methods: McKeown surgery (transabdominal + trans-right thoracic + cervical anastomosis), Ivor-Lewis surgery (transabdominal + trans-right thoracic surgery), assisted McKeown/Ivor-Lewis surgery, and robot-assisted McKeown / Ivor- Lewis if available.

14.3.3.2 Extent of lymph node dissection

(1) Squamous cell carcinoma: It is recommended to perform total mediastinal lymph node and abdominal field lymph node dissection: Thorax-in clinical practice, the thoracic lymph nodes should be dissected as thoroughly as possible to ensure that the number of dissected lymph nodes meets the requirements of ECN staging. The recommended dissection range includes the lymph nodes beside the right recurrent laryngeal nerve (group C201), lymph nodes beside the left recurrent laryngeal nerve (group C202), lymph nodes beside the upper thoracic esophagus (group C203), paratracheal lymph nodes (group C204), subcarinal lymph nodes (group C205), middle thoracic paraesophageal lymph nodes (group C206), lower thoracic paraesophageal lymph nodes (group C207), lower pulmonary ligament lymph nodes (group C208), and paradiaphragmatic lymph nodes (group C209). ("C" represents the Chinese standard, and "2" represents thoracic lymph nodes) [106]. Abdomen-down to the upper margin of the pancreas, up to the diaphragmatic hiatus, left to the ligament of the spleen and stomach, right to the root of the hepatogastric ligament and right gastric artery.
(2) Adenocarcinoma: Recommended dissection range: Thorax–the recommended dissection range is from the upper boundary to the plane of the carina, including the subcarinal lymph nodes (group C205), middle thoracic paraesophageal lymph nodes (group C206), lower thoracic paraesophageal lymph nodes (group C207), lower pulmonary ligament lymph nodes (group C208), and paradiaphragmatic lymph nodes (group C209). Abdomen-down to the upper margin of the pancreas, up to the diaphragmatic hiatus, left to the ligament of the spleen and stomach, right to the root of the hepatogastric ligament and right gastric artery.

Notes: ① Radical resection requires R0 resection (no residual cancer macroscopically or microscopically); ② the safe resection margin is not less than 5 cm; ③ intraoperative R2 resection, with metal clip labeling, should be performed for patients with residual tumor; ④ the stomach is the first choice for the reconstructed organs, and the colon or jejunum can be considered if the stomach cannot be used; ⑤ intraoperative establishment of a nutritional channel, including nasojejunal feeding tube or jejunostomy.

15 Immunotherapy and target therapy for esophageal carcinoma

15.1 EC Immunotherapy

Programmed death-1 (PD-1) is an immuno- suppressive transmembrane protein expressed on active T lymphocytes. The binding of PD-1 to PD-L1 and PD-L2 on the tumor surface can inhibit the activation of T cells, and the tumors can then achieve immune escape. Blocking the PD-1 / PD-L1 pathway can reactivate the killing effect of the immune system on tumor cells. In recent years, PD-1/PD-L1 monoclonal antibodies developed based on this mechanism have been indicated for melanoma, lung cancer and other tumors, and a large amount of clinical study evidence has also confirmed that PD-1 monoclonal antibodies have great potential in the treatment of esophageal carcinoma (EC).

15.1.1 EC neoadjuvant immunotherapy

At present, according to the results of the CROSS and NEOCRTEC5010 clinical studies, neoadjuvant chemoradiotherapy has become the standard treatment for

locally advanced operable EC, but the treatment of EC in China is still based on postoperative adjuvant therapy, and the adoption rate of neoadjuvant chemoradiotherapy is only 22% [107–109]. At the same time, the results of the CROSS and NEOCRTEC5010 clinical studies showed that the overall recurrence rate among EC patients receiving neoadjuvant chemoradiotherapy was 30%~50%, mainly distant metastasis, which remains to be further improved. The current use of immune checkpoint inhibitors has been moved forward, bringing new combinations and treatment modalities for EC neoadjuvant therapy. Currently available evidence includes the following:

(1) The PALACE-1 study included a total of 20 patients with esophageal squamous cell carcinoma who received neoadjuvant chemoradiotherapy (chemotherapy regimen was paclitaxel + carboplatin) integrated with pembrolizumab. The incidence of grade 3 or higher adverse reactions during neoadjuvant therapy was 65%. Except for one patient whose disease progressed during treatment, a total of 18 patients underwent surgery. The median interval between the last treatment and surgery was 42.5 days. A total of 10 (56%) patients achieved a pathological complete response (pCR) in both the primary tumor and lymph nodes. The major pathological response (mPR) rate of the primary tumor was 89%. The R0 resection rate was 94% [110].
(2) A total of 28 patients with locally advanced esophageal squamous cell carcinoma were included in a Korean phase II study of preoperative neoadjuvant chemoradiotherapy combined with pembrolizumab (NCT02844075). The pCR rate of the primary tumor was 46.1%, and the one-year survival rate was 82.1%. The common adverse reactions were neutropenia (50%) and elevated liver transaminases (30.8%). However, two patients died of severe lung injury after the operation.
(3) In the NICE study, a phase II clinical study of neoadjuvant therapy with camrelizumab combined with albumin-bound paclitaxel and carboplatin for locally advanced thoracic esophageal squamous cell carcinoma with multistation lymph node metastasis, the postoperative pCR rate was 45.4%. The pT0 was 54.5% (6 / 11), the imaging response was 90.9%, and the R0 resection rate was 100%. Common grade 3~4 adverse reactions included neutropenia (8 / 11) and thrombocytopenia (2/11).
(4) The results of a clinical study (NCT03917966) of camrelizumab combined with docetaxel and nedaplatin in neoadjuvant therapy for locally advanced esophageal squamous cell carcinoma showed that the pCR rate was 31.82% and the mPR rate was 68%.
(5) In the NIC-ESCC2019 study, a multi-center, open-label, single-arm, phase II study to assess integrated chemotherapy with camrelizumab as neoadjuvant therapy for resectable locally advanced esophageal squamous cell carcinoma, 56 patients were enrolled. Fifty-one patients underwent surgical resection. Eighteen patients (35.3%) achieved a pCR, 12 patients (23.5%) had an mPR, and 21 patients (41.2%) had an incomplete pathological response (IPR). In these small-sample-size phase II clinical studies, neoadjuvant chemotherapy combined with immunotherapy has shown a high pCR rate and safety, but there are no large-sample-size phase III clinical study results, and a number of clinical trials of neoadjuvant immunotherapy are ongoing.

Postoperative adjuvant immunotherapy for EC has also made great progress. Check-Mate 577 is a phase III, randomized, global multicenter, double-blind clinical study to evaluate the efficacy of adjuvant therapy with nivolumab in patients with EC and gastroesophageal junction cancer who did not achieve a pCR after neoadjuvant chemoradiotherapy. The results showed that patients who received neoadjuvant chemoradiotherapy but did not achieve a pCR received postoperative nivolumab, which reduced the risk of recurrence by 31%, and this regimen is recommended by the National Comprehensive Cancer Network (NCCN) EC guidelines [94, 111]. Other clinical studies of postoperative adjuvant immunotherapy are still ongoing.

15.1.2 Immunotherapy for late-stage EC

At present, a number of multicenter, phase III, randomized controlled clinical trials (KEYNOTE-590, Checkmate-648, ES-CORT-1st, ORIENT-15, JUPITER-06) have been performed on the efficacy and safety of immunotherapy combined with chemotherapy compared with chemotherapy alone in the treatment of advanced esophageal squamous cell carcinoma. The findings from these studies have shown that PD-1 monoclonal antibody integrated chemotherapy was superior to chemotherapy alone in terms of survival and efficacy and could reduce the risk of death by 30%~40%. This clinical study evidence indicates a role of immunotherapy combined with chemotherapy in the first-line treatment of advanced EC [112, 113]. The Food and Drug Administration (FDA) is currently accelerating the approval of pembrolizumab and camrelizumab for first-line treatment of recurrent or metastatic esophageal squamous cell carcinoma. In addition, the results of a phase II clinical study of first-line chemotherapy combined with immunotherapy for advanced esophageal squamous cell carcinoma in China,

including tislelizumab combined with chemotherapy, camrelizumab combined with apatinib and chemotherapy, preliminarily showed good clinical efficacy [114, 115].

In the second-line immunotherapy of advanced esophageal squamous cell carcinoma, the results of the KEYNOTE-181 study suggested that pembrolizumab could significantly prolong the survival time of patients compared with chemotherapy in the population with PD-L1 CPS ≥ 10. The results of the AT TRACTION-3 study suggested that nivolumab was superior to chemotherapy in the second-line treatment of esophageal squamous cell carcinoma. In addition, the results of the ESCORT study in Chinese patients with esophageal squamous cell carcinoma also confirmed that camrelizumab significantly prolonged the survival time compared with docetaxel or irinotecan. According to the above high-grade clinical study evidence, in 2020, the US FDA approved pembrolizumab as the standard second-line treatment for patients with PD-L1-positive advanced esophageal squamous cell carcinoma. The US NCCN guidelines preferentially recommend nivolumab for first-line and second-line treatment of esophageal squamous cell carcinoma. In 2020, the Chinese Society of Clinical Oncology (CSCO) guidelines also recommended multiple PD-1 monoclonal antibodies for second-line and beyond treatment of esophageal squamous cell carcinoma [116–118].

Second-line immunotherapy for advanced EC brings a significant survival benefit to patients. It is worth noting that the response rate of immunotherapy alone is 10% ~ 20%, and the response rate of immunotherapy combined with chemotherapy is 60% ~ 70%, yet most of the population still cannot obtain long-term survival benefit from immunotherapy. Therefore, the timing of immunotherapy, population screening and the immunotherapy compared with chemotherapy method still need to be further explored. In addition, with the breakthrough of immunotherapy in advanced EC, approximately 50% of responding patients will develop acquired resistance in the future. Exploring the EC resistance microenvironment and developing strategies to reverse immune resistance will be issues that need to be addressed in future clinical and translational research.

15.2 EC targeted therapy

At present, the targets of advanced esophageal squamous cell carcinoma include EG- FR, HER2, VEGFR, etc., but the relevant clinical research progress is slow, and most drugs fail. Among EGFR-related drugs, cetuximab or panitumumab combined with first-line chemotherapy did not achieve a significant survival advantage in patients with esophageal squamous cell carcinoma. Translational studies have found that for patients with esophageal squamous cell carcinoma with high EGFR expression, the survival benefit of cetuximab was more significant [119–121]. In addition, the results of a phase II clinical study showed that the response rate of nimotuzumab combined with cisplatin and paclitaxel chemotherapy in patients with esophageal squamous cell carcinoma was up to 51.8%, and the median survival time was 14 months, suggesting that nimotuzumab had certain therapeutic potential in esophageal squamous cell carcinoma, and relevant phase III clinical studies are also ongoing [122].

In addition to monoclonal antibodies, the academic community has also explored the treatment of EC with EGFR small-molecule inhibitors, but gefitinib has shown no survival benefit compared with second-line chemotherapy in the treatment of EC. In patients with advanced esophageal squamous cell carcinoma with high EGFR expression or gene amplification, the response rate to icotinib was 16.7%, but the therapeutic effect still needs to be further explored [123, 124].

For antiangiogenic drugs, studies have explored the second-line use of anlotinib or apatinib for esophageal squamous cell carcinoma, but the response rate of monotherapy was only 5% ~ 10%, and the improvement in survival time was limited [125–127].

For HER2-positive advanced esophageal adenocarcinoma, according to the treatment regimen of gastric adenocarcinoma, trastuzumab integrated chemotherapy was used for the first-line treatment of metastatic esophageal adenocarcinoma. In addition, integrated treatment combined with lapatinib for the treatment of HER2-positive esophageal adenocarcinoma has shown a significant effect [128, 129]. In the second-line treatment of locally advanced or metastatic adenocarcinoma of the esophagus, ramucirumab can be used as a single-agent treatment or in combination with chemotherapy [130, 131].

16 Supportive care for esophageal carcinoma

16.1 Nutritional diagnosis

(1) Esophageal carcinoma (EC) is the malignant tumor with the highest risk of malnutrition. It is recommended that the Nutrition Risk Screening 2002 (NRS 2002) scale be used to evaluate and comprehensively measure the nutritional status of all confirmed EC patients during diagnosis, after admission, in the perioperative period and during radiotherapy [132].

(2) For EC patients determined to be at risk during nutritional screening, further nutritional assessment using the Patient-Generated Subjective Global Assessment (PG-SGA) scale is recommended to be implemented by nurses, physicians, and dietitians.

(3) For patients with good nutritional status but expected nutritional risk, regular nutritional assessment should be performed, and nutritional intervention should be given if necessary [133].
(4) On the basis of nutritional assessment findings, for malnourished patients, especially those with severe malnutrition, it is recommended to further comprehensively determine the nutrition of patients in terms of their stress level, inflammatory response, energy expenditure level, metabolic status, organ function, body composition, and cardiac status [134].

16.2 Indications for nutritional therapy

Following the "five-step" principle, nutrition education is first chosen, followed by oral nutritional supplementation, total enteral nutrition, partial parenteral nutrition, and total parenteral nutrition.

16.2.1 Surgical patients

Patients with at least one of the following conditions should receive nutritional therapy for 7 to 14 days before surgery: weight loss ≥ 10% within 6 months, a body mass index (BMI) < 18.5 kg/m2, a subjective global assessment (SGA) score of grade C or a serum albumin content less than 30 g/L in the absence of liver and kidney dysfunction [135]. Postoperative nutritional therapy is recommended for all patients who benefit from preoperative nutritional therapy, malnourished patients, patients who are unable to eat by mouth after surgery, or patients who have an oral intake of less than 60% of their energy requirements within 1 week after surgery [136].

16.2.2 Chemoradiation patients

For EC patients scheduled for chemoradiotherapy, it is recommended to standardize and individualize the nutritional therapy path according to the PG-SGA score before chemoradiotherapy, the PG-SGA score and acute chemoradiotherapy toxicity grade during chemoradiotherapy, and the PG-SGA score and late chemoradiotherapy toxicity grade after chemoradiotherapy [137].

16.3 Nutritional therapy path

Enteral nutrition support should be considered as much as possible in both surgical and nonsurgical (chemoradiotherapy) patients as long as they have or partially have gastrointestinal digestion and absorption function. In patients with inadequate nutrient and energy intake due to partial or complete gastrointestinal functional failure, contraindications to enteral nutrition, and an inability to implement enteral nutrition, enteral nutrition combined with partial parenteral nutrition or total parenteral nutrition is recommended [132, 138, 139].

16.4 Nutritional therapy access

16.4.1 Enteral nutritional access

Oral nutritional supplement (ONS) administration is the preferred mode of enteral nutrition for EC patients.

Following the "four-step" principle, ONSs are preferred for patients with normal gastro-intestinal function. In patients with moderate-severe swallowing obstruction, weight loss of more than 5% within one month, a BMI < 18.5 kg / m2, a PG-SGA ≥ 4 points, food intake of less than 60% of the requirement for more than 3 ~ 5 days, and the presence of digestive absorption function, when the patient's nutritional needs cannot be met (intake of less than 60% of the target requirement for 3 ~ 5 days) or ONS administration cannot be implemented, nasogastric (intestinal) tube, endoscopic gastrostomy (jejunostomy) and surgical gastrostomy (jejunostomy) can be selected in turn to provide enteral nutrition [140].

Tube feeding nutrition is recommended for patients with moderate-severe dysphagia, severe chemoradiotherapy esophageal mucositis and other factors affecting peroral food intake. Nasogastric feeding is recommended if the estimated duration of tube feeding is ≤ 30 days. If long-term tube feeding is expected (> 30 days), tube feeding given by percutaneous puncture and fistulization is recommended. Surgical gastrostomy (jejunostomy) can be used for patients who cannot receive percutaneous endoscopic gastrostomy (jejunostomy) due to severe esophageal stenosis [138].

16.4.2 Parenteral nutrition access

If the enteral nutrition of EC patients cannot completely meet normal needs or patients have contraindications, enteral nutrition combined with partial parenteral nutrition or total parenteral nutrition is recommended. Parenteral nutrition access is divided into peripheral vein and central vein paths. The choice of venous access requires a comprehensive consideration of factors such as the patient's condition, the osmotic pressure of the parenteral nutrition solution, the expected duration of use, vascular conditions, and the care environment [137].

16.5 Nutrients

16.5.1 Energy

The patient's weight and nutritional intake should be checked regularly to determine whether their energy requirements have been met. The energy supply proportions of nutrients in patients in a nontumor-bearing state is as follows: carbohydrates, 50% ~ 55%; fats, 25% ~ 30%; and proteins, 15% ~ 20%. The energy requirements of EC patients vary with tumor stage, general condition, treatment modalities and adverse reactions. When accurate and individualized measurements are not possible, an

energy requirement of 25 to 30 kcal/ (kg· d) is generally recommended [134].

16.5.2 Carbohydrates, fats and proteins

It is recommended to reduce carbohydrates; appropriately increase the energy supply proportion of fats; and provide an enteral nutritional formula with high in proteins and fats (rich in omega-3 polyunsaturated fatty acids) and low in carbohydrates. For general patients, the recommended target amount of protein should be greater than 1.0 g/ (kg· d). For patients undergoing EC surgery and chemoradiotherapy, the target intake of protein is recommended to be increased to 1.5 to 2.0 g/ (kg· d) [141].

16.5.3 Immunonutrients

Immunotrophins mainly include glutamine, nucleotides, arginine, omega-3 polyunsaturated fatty acids, and branched-chain amino acids. Immunotrophins can improve nutrition-related endpoints in EC patients, but it is uncertain whether they have a positive effect on clinical outcomes [141].

16.6 Improving appetite

Glucocorticoids, progestogens, N-3 fatty acids, etc., can be used to improve appetite in cancer patients with anorexia, but attention should be given to side effects [137].

16.7 Maintenance of swallowing function

Screening and management of dysphagia is recommended, and patients should be instructed on how to maintain normal swallowing function during enteral nutrition [138].

16.8 Exercise

In addition to aerobic exercise, it is recommended to add individualized resistance training.

16.9 Home nutrition therapy

Physicians should select and establish appropriate nutritional access for patients, develop nutritional programs, monitor nutritional complications and manage the nutritional process [134, 140].

16.10 Efficacy evaluation

(1) During and after EC treatment, clinicians/dietitians should regularly evaluate the efficacy of nutritional therapy, including rapid response indicators, medium response indicators and slow response indicators, to provide the basis for the adjustment of nutritional therapy.

(2) During EC radiotherapy, the nutrition regimen should be dynamically adjusted. The adjustment is mainly based on the changes in the nutritional status (especially body weight), swallowing obstruction, swallowing pain, food intake and dietary structure of the patients. Adjustments can include the method of enteral nutrition, nutritional requirements and the proportion of nutrients.

Abbreviations

EC	Esophageal carcinoma
UICC	Union for International Cancer Control
AJCC	American Joint Committee on Cancer
WHO	World Health Organization
GBD 2019	2019 Global Burden of Disease Study
CEA	Serum carcinoembryonic antigen
SCC	Squamous cell carcinoma-related antigen
TPA	Tissue polypeptide antigen
cyfra21-1	Cytokeratin fragment 19
EUS	Endoscopic ultrasound
NBI	Narrow band imaging
pTNM	Pathological TNM
cTNM	Clinical TNM
ECG	Static electrocardiography
NRS2002	The Nutrition Risk Screening Score Short Form
PG-SGA	The Patient-Generated Subjective Global Assessment
ES-PEN 2015	The consensus statement of the European Society for Clinical Nutrition and Metabolism
GLIM	The Global Leadership Initiative on Malnutrition
MIE	Minimally invasive esophagectomy
RAE	Robot-assisted esophagectomy
ARDS	Acute respiratory distress syndrome
ESD	Endoscopic submucosal dissection
EMR	Endoscopic mucosal resection
JES	Japanese Esophageal Society
ORR	Objective response rate
PFS	Progression-free survival
CR	Complete response
TTP	Progression

Acknowledgements

We thank all the medical staff battling against esophageal cancer along with patients and all the researchers exploring the way to fight this disastrous disease.

Authors' contributions

Professor Yousheng Mao conceived the manuscript under the valuable advice and guidance of Professor Daiming Fan. Members of China Anti-Cancer Association (CACA) Esophageal Cancer Committee drafted and approved the manuscript for publication. The author(s) read and approved the final manuscript.

Funding

This work was supported by China Anti-Cancer Association (CACA).

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Consent for publication bas been obtained from all authors of this manuscript.

Competing interests
The authors have no conflicts of interest to declare.

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Received: 14 July 2023 Accepted: 9 August 2023

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries[J]. CA Cancer J Clin. 2021;71(3):209–49.
2. Sung KX, Zheng RS, Zhang SW, et al. Analysis of the incidence and mortality of malignant tumors in China in 2015[J]. China Oncology. 2019;28(01):1–11.
3. Zhou JC, Zheng RS, Zhang SW, et al. Trends in the incidence and age of esophageal cancer in cancer registration areas in China from 2000 to 2015[J]. Chin J Cancer Prev Treat. 2020;27(18):1437–42.
4. Chen F, Wang YQ. Analysis of the disease burden and changing trend of esophageal cancer in China from 1990 to 2019[J]. China Oncology. 2021;30(06):401–7.
5. Zhang LY, Chen Q, Liu SZ, et al. Estimation of esophageal cancer incidence and death in Henan Province in 2015[J]. Cancer Prevention and Treatment. 2019;32(11):978–83.
6. Yang J, Zhang N, Gao DQ, et al. Analysis of death trend and life expectancy of esophageal cancer in Feicheng city, Shandong Province from 2006 to 2018[J]. China Oncology. 2020;29(12):939–45.
7. Song WP, Wang Y, Xie JY, et al. Correlation between dietary factors and esophageal cancer in Chinese[J]. Journal of Clinical and Pathology. 2021;41(08):1915–24.
8. Chen WL, Huang LP, Han HH, et al. A case-control study on the relationship between pickled food intake combined with smoking, drinking and the incidence of esophageal cancer[J]. Chinese Public Health. 2018;34(05):643–6.
9. Huang H, Wang Y, Jiang KY, et al. Investigation and analysis of dietary status of rural residents in high-incidence areas of esophageal cancer[J]. Mod Oncol. 2018;26(22):3667–70.
10. Xiong XY, Tian D, Hou XY, et al. Investigation and analysis of the cognition of esophageal cancer among rural residents in high-incidence areas of esophageal cancer[J]. Chin J Thorac Surg. 2018;5(01):37–41.
11. He Q, Jing YH, Huang HR, et al. Analysis of exposure levels and aggregation of risk factors for esophageal cancer in rural residents in southern counties of Sichuan Province[J]. Chin J Cancer Prev Treat. 2019;26(22):1675–80.
12. Yang ES, Zhao BS, Liu SG, et al. Analysis of the role of genetic factors in esophageal cancer in northern Henan[J]. Mod Oncol. 2018;26(21):3418–21.
13. Pan EC, Sun ZM, He Y, et al. Relationship between familial inheritance and the risk of esophageal cancer among residents in high-incidence areas of esophageal cancer along the Huaihe River[J]. Mod Prev Med. 2016;43(14):2524–6.
14. Uhlenhopp DJ, Then EO, Sunkara T, et al. Epidemiology of esophageal cancer: update in global trends, etiology and risk factors[J]. Clin J Gastroenterol. 2020;13(6):1010–21.
15. Liang H, Fan JH, Qiao YL. Epidemiology, etiology, and prevention of esophageal squamous cell carcinoma in China[J]. Cancer Biol Med. 2017;14(1):33–41.
16. Thrift AP. Global burden and epidemiology of Barrett oesophagus and oesophageal cancer[J]. Nat Rev Gastroenterol Hepatol. 2021;18(6):432–43.
17. Chen LH, Li T. Application progress of artificial intelligence in endoscopy of esophageal cancer[J]. Esophageal Dis. 2021;3(02):106–10.
18. Li G, Shen X, Alaiguha, et al. Systematic review and meta-analysis of the clinical effect of Da Vinci robot-assisted esophagectomy and thoracoscopic laparoscopy combined with esophagectomy for esophagectomy[J]. Chin Thorac Cardiovasc Clin J Surg. 2021:1(1):1–8.
19. Zeng Y, Liang W, Liu J, et al. Endoscopic Treatment Versus Esophagectomy for Early-Stage Esophageal Cancer: a Population-Based Study Using Propensity Score Matching[J]. J Gastrointest Surg. 2017;21(12):1977–83.
20. Yang H, Liu H, Chen Y, et al. Long-term Efficacy of Neoadjuvant Chemoradiotherapy Plus Surgery for the Treatment of Locally Advanced Esophageal Squamous Cell Carcinoma: The NEOCRTEC5010 Randomized Clinical Trial[J]. JAMA Surg. 2021;156(8):721–9.
21. Ueyama T, Kawamoto K, Yamada Y, et al. Early esophageal carcinoma. Evaluation of the depth of invasion based on double-contrast esophagography[J]. Acta Radiol. 1998;39(2):133–7.
22. Miyata H, Yamasaki M, Takahashi T, et al. Determinants of response to neoadjuvant chemotherapy for esophageal cancer using 18F-fluorodeoxiglucose positron emission tomography (18F-FDG-PET)[J]. Ann Surg Oncol. 2014;21(2):575–82.
23. Choi J, Kim SG, Kim JS, et al. Comparison of endoscopic ultrasonography (EUS), positron emission tomography (PET), and computed tomography (CT) in the preoperative locoregional staging of resectable esophageal cancer[J]. Surg Endosc. 2010;24(6):1380–6.
24. Noble F, Bailey D, Tung K, et al. Impact of integrated PET/CT in the staging of oesophageal cancer: a UK population-based cohort study[J]. Clin Radiol. 2009;64(7):699–705.

25. Williams RN, Ubhi SS, Sutton CD, et al. The early use of PET-CT alters the management of patients with esophageal cancer[J]. J Gastrointest Surg. 2009;13(5):868–73.
26. Walker AJ, Spier BJ, Perlman SB, et al. Integrated PET/CT fusion imaging and endoscopic ultrasound in the pre-operative staging and evaluation of esophageal cancer[J]. Mol Imaging Biol. 2011;13(1):166–71.
27. Rice TW, Ishwaran H, Ferguson MK, et al. Cancer of the esophagus and esophagogastric junction: an eighth edition staging primer[J]. J Thorac Oncol. 2017;12(1):36–42.
28. Biere SS, van Berge HM, Maas KW, et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial[J]. Lancet. 2012;379(9829):1887–92.
29. Straatman J, van der Wielen N, Cuesta MA, et al. Minimally invasive versus open esophageal resection: three-year follow-up of the previously reported randomized controlled trial: the TIME trial[J]. Ann Surg. 2017;266(2):232–6.
30. Horgan S, Berger RA, Elli EF, et al. Robotic-assisted minimally invasive transhiatal esophagectomy[J]. Am Surg. 2003;69(7):624–6.
31. Orringer MB, Marshall B, Chang AC, et al. Two thousand transhiatal esophagectomies: changing trends, lessons learned[J]. Ann Surg. 2007;246(3):363–72. 372-374.
32. Hulscher JB, Tijssen JG, Obertop H, et al. Transthoracic versus transhiatal resection for carcinoma of the esophagus: a meta-analysis[J]. Ann Thorac Surg. 2001;72(1):306–13.
33. Han DP, Xiang J, Gao TT, et al. Comparison of short-term efficacy between robotic-assisted and traditional Ivor-Lewis radical esophagectomy[J]. Chin J Minim Invasive Surg. 2016;16(05):404–7.
34. Wang WP, Chen LQ, Zhang HL, et al. Modified Intrathoracic Esophagogastrostomy with Minimally Invasive Robot-Assisted Ivor-Lewis Esophagectomy for Cancer[J]. Dig Surg. 2019;36(3):218–25.
35. Zhang YJ, Han Y, Xiang J, et al. Application of robotic minimally invasive Ivor-Lewis radical resection for esophageal cancer[J]. Chin J Thorac Cardiovasc Surg. 2018;25(09):735–41.
36. Hodari A, Park KU, Lace B, et al. Robot-Assisted Minimally Invasive Ivor Lewis Esophagectomy With Real-Time Perfusion Assessment[J]. Ann Thorac Surg. 2015;100(3):947–52.
37. Cerfolio RJ, Bryant AS, Hawn MT. Technical aspects and early results of robotic esophagectomy with chest anastomosis[J]. J Thorac Cardiovasc Surg. 2013;145(1):90–6.
38. Zhang Y, Xiang J, Han Y, et al. Initial experience of robot-assisted Ivor-Lewis esophagectomy: 61 consecutive cases from a single Chinese institution[J]. Dis Esophagus. 2018;31(12):1–8.
39. Deng HY, Huang WX, Li G, et al. Comparison of short-term outcomes between robot-assisted minimally invasive esophagectomy and video-assisted minimally invasive esophagectomy in treating middle thoracic esophageal cancer[J]. Dis Esophagus. 2018;31(8):1–7.
40. Chao YK, Hsieh MJ, Liu YH, et al. Lymph node evaluation in robot-assisted versus video-assisted thoracoscopic esophagectomy for esophageal squamous cell carcinoma: a propensity-matched analysis[J]. World J Surg. 2018;42(2):590–8.
41. Park S, Hwang Y, Lee HJ, et al. Comparison of robot-assisted esophagectomy and thoracoscopic esophagectomy in esophageal squamous cell carcinoma[J]. J Thorac Dis. 2016;8(10):2853–61.
42. Palanivelu C, Prakash A, Senthilkumar R, et al. Minimally invasive esophagectomy: thoracoscopic mobilization of the esophagus and mediastinal lymphadenectomy in prone position–experience of 130 patients[J]. J Am Coll Surg. 2006;203(1):7–16.
43. Markar SR, Wiggins T, Antonowicz S, et al. Minimally invasive esophagectomy: lateral decubitus vs. prone positioning; systematic review and pooled analysis[J]. Surg Oncol. 2015;24(3):212–9.
44. Professional Committee of Esophageal Cancer of China Anti-Cancer Association. Recommendations of Chinese clinical experts for robot-assisted esophagectomy (2019 edition)[J]. Chin J Surg. 2019;57(09):E1.
45. Guo X, Ye B, Yang Y, et al. Impact of unplanned events on early postoperative results of minimally invasive esophagectomy[J]. Thorac Cancer. 2018;9(1):94–8.
46. Akiyama H, Tsurumaru M, Udagawa H, et al. Radical lymph node dissection for cancer of the thoracic esophagus[J]. Ann Surg. 1994;220(3):364–72. 372-373.
47. Ando N, Ozawa S, Kitagawa Y, et al. Improvement in the results of surgical treatment of advanced squamous esophageal carcinoma during 15 consecutive years[J]. Ann Surg. 2000;232(2):225–32.
48. Nishihira T, Hirayama K, Mori S. A prospective randomized trial of extended cervical and superior mediastinal lymphadenectomy for carcinoma of the thoracic esophagus[J]. Am J Surg. 1998;175(1):47–51.
49. Hulscher JB, van Sandick JW, de Boer AG, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus[J]. N Engl J Med. 2002;347(21):1662–9.
50. Takeuchi H, Kawakubo H, Kitagawa Y. Current status of minimally invasive esophagectomy for patients with esophageal cancer[J]. Gen Thorac Cardiovasc Surg. 2013;61(9):513–21.
51. Booka E, Takeuchi H, Kikuchi H, et al. Recent advances in thoracoscopic esophagectomy for esophageal cancer[J]. Asian J Endosc Surg. 2019;12(1):19–29.
52. Ben-David K, Rossidis G, Zlotecki RA, et al. Minimally invasive esophagectomy is safe and effective following neoadjuvant chemoradiation therapy[J]. Ann Surg Oncol. 2011;18(12):3324–9.
53. Holscher AH, Demeester TR, Schmidt H, et al. Propensity score-matched comparison between open and minimal invasive hybrid esophagectomy for esophageal adenocarcinoma[J]. Langenbecks Arch Surg. 2020;405(4):521–32.
54. Sugita Y, Nakamura T, Sawada R, et al. Safety and feasibility of minimally invasive esophagectomy for elderly esophageal cancer patients[J]. Dis Esophagus. 2021;34(3):1–7.
55. Sihag S, Kosinski AS, Gaissert HA, et al. Minimally invasive versus open esophagectomy for esophageal cancer: a comparison of early surgical outcomes from The Society of Thoracic Surgeons National Database[J]. Ann Thorac Surg. 2016;101(4):1281–8. 1288-1289.
56. Noble F, Kelly JJ, Bailey IS, et al. A prospective comparison of totally minimally invasive versus open Ivor Lewis esophagectomy[J]. Dis Esophagus. 2013;26(3):263–71.
57. Tapias LF, Mathisen DJ, Wright CD, et al. Outcomes with open and minimally invasive ivor lewis esophagectomy after neoadjuvant therapy[J]. Ann Thorac Surg. 2016;101(3):1097–103.
58. Dolan JP, Kaur T, Diggs BS, et al. Impact of comorbidity on outcomes and overall survival after open and minimally invasive esophagectomy for locally advanced esophageal cancer[J]. Surg Endosc. 2013;27(11):4094–103.
59. Biere SS, Maas KW, Cuesta MA, et al. Cervical or thoracic anastomosis after esophagectomy for cancer: a systematic review and meta-analysis[J]. Dig Surg. 2011;28(1):29–35.
60. Chen H, Lu JJ, Zhou J, et al. Anterior versus posterior routes of reconstruction after esophagectomy: a comparative anatomic study[J]. Ann Thorac Surg. 2009;87(2):400–4.
61. Hu H, Ye T, Tan D, et al. Is anterior mediastinum route a shorter choice for esophageal reconstruction? A comparative anatomic study[J]. Eur J Cardiothorac Surg. 2011;40(6):1466–9.
62. Nederlof N, Tilanus HW, Tran TC, et al. End-to-end versus end-to-side esophagogastrostomy after esophageal cancer resection: a prospective randomized study[J]. Ann Surg. 2011;254(2):226–33.
63. Mao CY, Yang YS, Yuan Y, et al. End-to-End Versus End-to-Side Hand-Sewn Anastomosis for Minimally Invasive McKeown Esophagectomy[J]. Ann Surg Oncol. 2019;26(12):4062–9.
64. Schroder W, Raptis DA, Schmidt HM, et al. Anastomotic Techniques and Associated Morbidity in Total Minimally Invasive Transthoracic Esophagectomy: Results From the EsoBenchmark Database[J]. Ann Surg. 2019;270(5):820–6.
65. Zhang H, Wang Z, Zheng Y, et al. Robotic Side-to-Side and End-to-Side Stapled Esophagogastric Anastomosis of Ivor Lewis Esophagectomy for Cancer[J]. World J Surg. 2019;43(12):3074–82.
66. Japanese Classification of Esophageal Cancer. 11th Edition: part I[J]. Esophagus. 2017;14(1):1–36.
67. Ye X, Zhao Y, You B, et al. The interpretation of the Chinese expert consensus on mediastinal lymph node dissection in esophagectomy for esophageal cancer (2017 edition)[J]. Zhonghua Wei Chang Wai Ke Za Zhi. 2018;21(9):976–82.
68. Li H, Fang W, Yu Z, et al. Chinese expert consensus on mediastinal lymph node dissection in esophagectomy for esophageal cancer (2017 edition)[J]. J Thorac Dis. 2018;10(4):2481–9.

69. Udagawa H, Ueno M, Shinohara H, et al. The importance of grouping of lymph node stations and rationale of three-field lymphoadenectomy for thoracic esophageal cancer[J]. J Surg Oncol. 2012;106(6):742–7.
70. Wang P, Xie J, Wang L, et al. Expert consensus on the norms of digestive endoscopy biopsy and pathological examination in China (draft)[J]. Chin J Digestion. 2014;34(09):577–81.
71. Zhou PH, Cai MP, Yao LQ, et al. Expert consensus on endoscopic submucosal dissection for gastrointestinal mucosal lesions[J]. Chin J Gastrointes Surg. 2012;10:1083–6.
72. Ma D, Yang F, Liao Z, et al. Expert consensus on early esophageal cancer screening and endoscopic diagnosis and treatment in China (2014, Beijing)[J]. Gastroenterology. 2015;20(04):220–40.
73. Bleiberg H, Conroy T, Paillot B, et al. Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced squamous cell oesophageal cancer[J]. Eur J Cancer. 1997;33(8):1216–20.
74. 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[J]. Oncologist. 2019;24(2):163–76.
75. Miyazaki T, Ojima H, Fukuchi M, et al. Phase II study of docetaxel, nedaplatin, and 5-fluorouracil combined chemotherapy for advanced esophageal cancer[J]. Ann Surg Oncol. 2015;22(11):3653–8.
76. Guo JF, Zhang B, Wu F, et al. A phase II trial of docetaxel plus nedaplatin and 5-fluorouracil in treating advanced esophageal carcinoma[J]. Chin J Cancer. 2010;29(3):321–4.
77. Yajima S, Suzuki T, Nanami T, et al. Randomized Phase II Study to Comparing Docetaxel/Nedaplatin versus Docetaxel for 5-Fluorouracil/Cisplatin Resistant Esophageal Squamous Cell Carcinoma[J]. Ann Thorac Cardiovasc Surg. 2021;27(4):219–24.
78. Huang J, Xu B, Liu Y, et al. Irinotecan plus S-1 versus S-1 in patients with previously treated recurrent or metastatic esophageal cancer (ESWN 01): a prospective randomized, multicenter, open-labeled phase 3 trial[J]. Cancer Commun (Lond). 2019;39(1):16.
79. Chen Y, Ye J, Zhu Z, et al. Comparing paclitaxel plus fluorouracil versus cisplatin plus fluorouracil in chemoradiotherapy for locally advanced esophageal squamous cell cancer: a randomized, multicenter, phase III clinical trial[J]. J Clin Oncol. 2019;37(20):1695–703.
80. Shapiro J, van Lanschot J, Hulshof M, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial[J]. Lancet Oncol. 2015;16(9):1090–8.
81. 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[J]. JAMA. 1999;281(17):1623–7.
82. Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94–05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy[J]. J Clin Oncol. 2002;20(5):1167–74.
83. Guideline for Radiation Therapy of Esophageal Cancer in China (2019 Edition) [J]. Int J Oncol. 2019;07:385–98
84. Conroy T, Galais MP, Raoul JL, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial[J]. Lancet Oncol. 2014;15(3):305–14.
85. Liu S, Luo L, Zhao L, et al. Induction chemotherapy followed by definitive chemoradiotherapy versus chemoradiotherapy alone in esophageal squamous cell carcinoma: a randomized phase II trial[J]. Nat Commun. 2021;12(1):4014.
86. Gao XS, Qiao X, Wu F, et al. Pathological analysis of clinical target volume margin for radiotherapy in patients with esophageal and gastroesophageal junction carcinoma[J]. Int J Radiat Oncol Biol Phys. 2007;67(2):389–96.
87. Lyu J, Yisikandaer A, Li T, et al. Comparison between the effects of elective nodal irradiation and involved-field irradiation on long-term survival in thoracic esophageal squamous cell carcinoma patients: A prospective, multicenter, randomized, controlled study in China[J]. Cancer Med. 2020;9(20):7460–8.
88. Zhu H, Rivin DCE, Ye J, et al. Involved-Field Irradiation in Definitive Chemoradiotherapy for Locoregional Esophageal Squamous Cell Carcinoma: Results From the ESO-Shanghai 1 Trial[J]. Int J Radiat Oncol Biol Phys. 2021;110(5):1396–406.
89. Xu YJ, Zhu WG, Liao ZX, et al. A multicenter randomized prospective study of concurrent chemoradiation with 60 Gy versus 50 Gy for inoperable esophageal squamous cell carcinoma][J. Zhonghua Yi Xue Za Zhi. 2020;100(23):1783–8.
90. Hulshof M, Geijsen ED, Rozema T, et al. Randomized Study on Dose Escalation in Definitive Chemoradiation for Patients With Locally Advanced Esophageal Cancer (ARTDECO Study)[J]. J Clin Oncol. 2021;39(25):2816–24.
91. Lin SH, Wang L, Myles B, et al. Propensity score-based comparison of long-term outcomes with 3-dimensional conformal radiotherapy vs intensity-modulated radiotherapy for esophageal cancer[J]. Int J Radiat Oncol Biol Phys. 2012;84(5):1078–85.
92. Wang X, Hobbs B, Gandhi SJ, et al. Current status and application of proton therapy for esophageal cancer[J]. Radiother Oncol. 2021;164:27–36.
93. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer[J]. N Engl J Med. 2012;366(22):2074–84.
94. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer[J]. N Engl J Med. 2021;384(13):1191–203.
95. Deng W, Yang J, Ni W, et al. Postoperative Radiotherapy in Pathological T2–3N0M0 Thoracic Esophageal Squamous Cell Carcinoma: Interim Report of a Prospective, Phase III, Randomized Controlled Study[J]. Oncologist. 2020;25(4):e701–8.
96. Ni W, Yu S, Xiao Z, et al. Postoperative adjuvant therapy versus surgery alone for stage IIB-III esophageal squamous cell carcinoma: a phase III randomized controlled trial[J]. Oncologist. 2021;26(12):e2151–60.
97. Yang J, Zhang W, Xiao Z, et al. The impact of postoperative conformal radiotherapy after radical surgery on survival and recurrence in pathologic T3N0M0 esophageal carcinoma: a propensity score-matched analysis[J]. J Thorac Oncol. 2017;12(7):1143–51.
98. Chen J, Pan J, Liu J, et al. Postoperative radiation therapy with or without concurrent chemotherapy for node-positive thoracic esophageal squamous cell carcinoma[J]. Int J Radiat Oncol Biol Phys. 2013;86(4):671–7.
99. Bedenne L, Michel P, Bouche O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102[J]. J Clin Oncol. 2007;25(10):1160–8.
100. Zhang ZX, Gu XZ, Yin WB, et al. Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of adenocarcinoma of gastric cardia (AGC)–report on 370 patients[J]. Int J Radiat Oncol Biol Phys. 1998;42(5):929–34.
101. Stahl M, Walz MK, Stuschke M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction[J]. J Clin Oncol. 2009;27(6):851–6.
102. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer[J]. N Engl J Med. 2006;355(1):11–20.
103. Klevebro F, Alexandersson VDG, Wang N, et al. A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction[J]. Ann Oncol. 2016;27(4):660–7.
104. Herskovic A, Martz K, Al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus[J]. N Engl J Med. 1992;326(24):1593–8.
105. Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781[J]. J Clin Oncol. 2008;26(7):1086–92.
106. Li H, Fang WT, Yu ZT, et al. Chinese expert consensus on thoracic lymph node dissection in radical esophagectomy for esophageal cancer (2017 edition) [J]. Chin J Digest Surg. 2017;16(11):1087–90.
107. Romero D. Genetics: Oesophageal cancer - not all alike[J]. Nat Rev Clin Oncol. 2017;14(3):138.
108. Ntziachristos P, Lim JS, Sage J, et al. From fly wings to targeted cancer therapies: a centennial for notch signaling[J]. Cancer Cell. 2014;25(3):318–34.

109. Mao YS, Gao SG, Wang Q, et al. Big data analysis of clinical epidemiological characteristics and surgical treatment of esophageal cancer in China[J]. Chin J Oncol. 2020;03:228–9.
110. Li C, Zhao S, Zheng Y, et al. Preoperative pembrolizumab combined with chemoradiotherapy for oesophageal squamous cell carcinoma (PALACE-1)[J]. Eur J Cancer. 2021;144:232–41.
111. Nie Y, Liao J, Zhao X, et al. Detection of multiple gene hypermethylation in the development of esophageal squamous cell carcinoma[J]. Carcinogenesis. 2002;23(10):1713–20.
112. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study[J]. Lancet. 2021;398(10302):759–71.
113. Luo H, Lu J, Bai Y, et al. Effect of Camrelizumab vs Placebo Added to Chemotherapy on Survival and Progression-Free Survival in Patients With Advanced or Metastatic Esophageal Squamous Cell Carcinoma: The ESCORT-1st Randomized Clinical Trial[J]. JAMA. 2021;326(10):916–25.
114. Xu J, Bai Y, Xu N, et al. Tislelizumab Plus Chemotherapy as First-line Treatment for Advanced Esophageal Squamous Cell Carcinoma and Gastric/Gastroesophageal Junction Adenocarcinoma[J]. Clin Cancer Res. 2020;26(17):4542–50.
115. Zhang B, Qi L, Wang X, et al. Phase II clinical trial using camrelizumab combined with apatinib and chemotherapy as the first-line treatment of advanced esophageal squamous cell carcinoma[J]. Cancer Commun (Lond). 2020;40(12):711–20.
116. Kojima T, Shah MA, Muro K, et al. Randomized Phase III KEYNOTE-181 Study of Pembrolizumab Versus Chemotherapy in Advanced Esophageal Cancer[J]. J Clin Oncol. 2020;38(35):4138–48.
117. Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial[J]. Lancet Oncol. 2019;20(11):1506–17.
118. Huang J, Xu J, Chen Y, et al. Camrelizumab versus investigator's choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (ESCORT): a multicentre, randomised, open-label, phase 3 study[J]. Lancet Oncol. 2020;21(6):832–42.
119. Moehler M, Maderer A, Thuss-Patience PC, et al. Cisplatin and 5-fluorouracil with or without epidermal growth factor receptor inhibition panitumumab for patients with non-resectable, advanced or metastatic oesophageal squamous cell cancer: a prospective, open-label, randomised phase III AIO/EORTC trial (POWER)[J]. Ann Oncol. 2020;31(2):228–35.
120. Lorenzen S, Schuster T, Porschen R, et al. Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie[J]. Ann Oncol. 2009;20(10):1667–73.
121. Huang ZH, Ma XW, Zhang J, et al. Cetuximab for esophageal cancer: an updated meta-analysis of randomized controlled trials[J]. BMC Cancer. 2018;18(1):1170.
122. Lu M, Wang X, Shen L, et al. Nimotuzumab plus paclitaxel and cisplatin as the first line treatment for advanced esophageal squamous cell cancer: a single centre prospective phase II trial[J]. Cancer Sci. 2016;107(4):486–90.
123. Dutton SJ, Ferry DR, Blazeby JM, et al. Gefitinib for oesophageal cancer progressing after chemotherapy (COG): a phase 3, multicentre, double-blind, placebo-controlled randomised trial[J]. Lancet Oncol. 2014;15(8):894–904.
124. Huang J, Fan Q, Lu P, et al. Icotinib in patients with pretreated advanced esophageal squamous cell carcinoma with EGFR overexpression or EGFR gene amplification: a single-arm, multicenter phase 2 study[J]. J Thorac Oncol. 2016;11(6):910–7.
125. Huang J, Xiao J, Fang W, et al. Anlotinib for previously treated advanced or metastatic esophageal squamous cell carcinoma: A double-blind randomized phase 2 trial[J]. Cancer Med. 2021;10(5):1681–9.
126. Yanwei L, Feng H, Ren P, et al. Safety and efficacy of apatinib monotherapy for unresectable, metastatic esophageal cancer: a single-arm, open-label, phase II study[J]. Oncologist. 2020;25(10):e1464–72.
127. Chu L, Chen Y, Liu Q, et al. A phase II study of apatinib in patients with chemotherapy-refractory esophageal squamous cell carcinoma (ESO-Shanghai 11)[J]. Oncologist. 2021;26(6):e925–35.
128. Bang YJ, van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial[J]. Lancet. 2010;376(9742):687–97.
129. Hecht JR, Bang YJ, Qin SK, et al. Lapatinib in combination with capecitabine plus oxaliplatin in human epidermal growth factor receptor 2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma: TRIO-013/LOGiC–a randomized phase III trial[J]. J Clin Oncol. 2016;34(5):443–51.
130. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial[J]. Lancet. 2014;383(9911):31–9.
131. Wilke H, Muro K, van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial[J]. Lancet Oncol. 2014;15(11):1224–35.
132. Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients[J]. Clin Nutr. 2017;36(1):11–48.
133. Quyen TC, Angkatavanich J, Thuan TV, et al. Nutrition assessment and its relationship with performance and Glasgow prognostic scores in Vietnamese patients with esophageal cancer[J]. Asia Pac J Clin Nutr. 2017;26(1):49–58.
134. Chen MJ, Wu IC, Chen YJ, et al. Nutrition therapy in esophageal cancer-Consensus statement of the Gastroenterological Society of Taiwan[J]. Dis Esophagus. 2018;31(8):1–9.
135. Yu ZT. Perioperative nutritional therapy for esophageal cancer[J]. Electron J Tumor Metab Nutr. 2015;2(2):19–22.
136. Ma XH, Yang H, Wang JJ, et al. Nutritional status and correction analysis at different perioperative periods in patients with esophageal cancer[J]. Electron J Tumor Metab Nutr. 2018;5(03):274–8.
137. Li T, Lv JH, Lang JY, et al. Expert consensus on nutritional therapy for patients with malignant tumor radiotherapy[J]. Electron J Tumor Metab Nutr. 2018;5(04):358–65.
138. Arends J, Bodoky G, Bozzetti F, et al. ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology[J]. Clin Nutr. 2006;25(2):245–59.
139. Wang G, Chen H, Liu J, et al. A comparison of postoperative early enteral nutrition with delayed enteral nutrition in patients with esophageal cancer[J]. Nutrients. 2015;7(6):4308–17.
140. Lyu J, Li T, Xie C, et al. Enteral nutrition in esophageal cancer patients treated with radiotherapy: a Chinese expert consensus 2018[J]. Future Oncol. 2019;15(5):517–31.
141. Fietkau R, Lewitzki V, Kuhnt T, et al. A disease-specific enteral nutrition formula improves nutritional status and functional performance in patients with head and neck and esophageal cancer undergoing chemoradiotherapy: results of a randomized, controlled, multicenter trial[J]. Cancer. 2013;119(18):3343–53.

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