CLINICAL GUIDELINE

Guidelines for Radiotherapy of Esophageal Carcinoma (2020 Edition)

Branch of Radiation Oncology Therapists, Chinese Medical Association; Society of Radiation Oncology Therapy, Chinese Medical Association; Cancer Radiotherapy Committee of China Anti-Cancer Association

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1  |  SUMMARY

Esophageal carcinoma is a high-incidence malignant tumor in China, ranking sixth and fourth highest in morbidity and mortality, respectively. Radiotherapy plays an important role in the comprehensive treatment of esophageal carcinoma. Standardized diagnosis and treatment based on the suggestions of a multidisciplinary team (MDT) form its foundation. For operable esophageal carcinoma, surgery after neoadjuvant chemoradiotherapy is the standard treatment; conversely, for inoperable esophageal carcinoma, radical chemoradiotherapy is the only treatment option, and postoperative adjuvant radiotherapy can improve local control and survival rates in selected cases. Owing to the rapid technological development in radiotherapy, three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, and image guidance technology are widely used in the treatment of esophageal carcinoma. Though drugs for treating cancer have been developed rapidly, we need to explore their optimal combination with radiotherapy, including chemotherapy, targeted or immune, and radiosensitizers. Esophageal carcinoma in China differs greatly from that in European and American countries in terms of etiology, pathological type, high-incidence site, etc. Therefore, the European and American guidelines on radiotherapy for esophageal carcinoma cannot be applied in clinical practice in China. This gap was addressed when the 2019 edition of the Chinese Guidelines for Radiotherapy of Esophageal Carcinoma was formulated. In combination with suggestions for the clinical application and the latest research, the 2020 edition was launched with the hope of benefiting most patients with esophageal carcinoma.

2  |  CLINICAL MANIFESTATION

2.1  |  Symptoms

Early symptoms of esophageal carcinoma are indiscernible. There is often a sense of a foreign body in the esophagus. When swallowing hard food, there is a sense of stagnation, choking, posterior sternal burning, pinprick, or traction rubbing pain. These symptoms can be mild or severe. Typical symptoms include progressive dysphagia and the production of mucoid sputum. Persistent chest pain or back pain often suggests that the tumor has invaded the extraesophageal tissue. Invasion of the tumor into the recurrent laryngeal nerve may cause hoarseness and choking on drinking water. The compression of the cervical sympathetic ganglion may lead to Horner syndrome. Similarly, its invasion into the trachea and bronchus may cause the formation of esophagotracheal or esophagobronchial fistula, respectively; this may result in severe choking during swallowing, respiratory infection,
formation of esophagomediastinal fistula, or fever. If distant metastasis occurs, then the affected organs may exhibit symptoms.

2.2 Signs

Most patients with esophageal carcinoma display no obvious positive signs on physical examination. Special attention should be paid to the signs of distant metastasis, such as enlarged lymph nodes in the neck or supraclavicular region, liver masses, pleural effusion, and peritoneal effusion.

3 SUPPLEMENTARY EXAMINATION

3.1 Laboratory examination

3.1.1 General examination

Including blood routine, liver function and kidney function, viral serology, electrolyte, blood glucose, coagulation function, urine routine, fecal routine, etc.

3.1.2 Tumor markers

Including cytokeratin 21-1 (CYFRA21-1), carcinoembryonic antigen (CEA), and squamous cell carcinoma antigen (SCC), etc.

3.1.3 Detection of epidermal growth factor receptor (EGFR)

High expression of EGFR is an independent risk factor for the poor prognosis of esophageal carcinoma; thus, the detection of tissue EGFR expression is recommended.

3.1.4 Detection of immune-related markers

Immunotherapy is used as the second-line and above treatment for advanced esophageal carcinoma and first-line combined chemotherapy or postoperative adjuvant therapy; eligible patients should be tested for programmed death protein ligand 1 (PD-L1) and its combined positive score (CPS), tumor mutation coincidence (TMB), microsatellite instability (MSI), and mismatch repair protein loss (dMMR).

3.2 Imaging examination

3.2.1 Esophageal barium meal radiography

An important method for the diagnosis and evaluation of the curative effect on esophageal carcinoma, and low-tension double-contrast radiography is recommended. Patients who are scheduled to undergo radiotherapy should be checked for contraindications to radiotherapy, such as presence of deep ulcers.

3.2.2 CT

Chest and upper abdomen CT examination is needed before radiotherapy and during follow-up. A contrast-enhanced CT is also recommended. The scanning range can be increased according to the location (e.g., the supraclavicular area and neck) and range of lesions.

3.2.3 MRI

Can effectively complement CT in the diagnosis and evaluation of the curative effect on esophageal carcinoma. The diagnostic value of lymph node metastasis is similar or superior to that of contrast-enhanced CT. Functional MRI techniques such as diffusion-weighted imaging are helpful in the evaluation of the curative effect and prognosis.

3.2.4 Ultrasound

Mainly used for diagnosing pleural effusion, metastasis to abdominal organs, and metastasis to abdominal and cervical lymph nodes.

3.2.5 Bone scan

Not recommended as a routine primary screening method for the diagnosis of bone metastasis; a positive bone scan should be confirmed by X-ray, CT, MRI, or PET/CT.

3.2.6 PET/CT

Recommended only if necessary or conditional but not as a routine screening method.

3.3 Upper gastrointestinal endoscopy

Upper gastrointestinal endoscopy is an important method for the qualitative and localized diagnosis and treatment of esophageal carcinoma. Endoscopic biopsy is the gold standard for the diagnosis of esophageal carcinoma. Pigmented endoscopy and endoscopic ultrasonography can confirm the morphology and extent of lesions and assist in determining the clinical T and N stages. Endoscopic metal clips mark the upper and lower edges of early lesions, which can accurately assist in target localization for radiotherapy.
3.4 | Other examinations

3.4.1 | ECG

Helps screen for arrhythmias and history of myocardial infarction.

3.4.2 | Pulmonary function

Helps screen for lung volume, lung ventilation, and diffusion function.

3.4.3 | Exercise cardiopulmonary function

When the aforementioned tests cannot determine the patient’s cardiopulmonary capacity to tolerate radiotherapy, an exercise cardiopulmonary function test is recommended for further assessment.

3.4.4 | Echocardiography

Recommended for patients with a previous history of heart disease to determine any structural changes and the functional status of the heart.

4 | DIAGNOSIS

4.1 | Clinical diagnosis

Esophageal carcinoma should be clinically suspected if the patient has the aforementioned symptoms and meets one of the following criteria:

(1) Esophageal angiography reveals localized thickening of the esophageal mucosa, stiffness of the local wall, filling defect, or niche shadow.

(2) Chest CT, MRI, and PET/CT show thickening of the esophageal wall, or PET/CT displays high uptake of fluorodeoxyglucose (FDG).

(3) Upper gastrointestinal endoscopy reveals early lesions such as localized erosion of the mucosa, rough and small granular sensation, local mucosal congestion with unclear borders, small nodules, small ulcers, and small plaques. The middle- and late-stage lesions mainly exhibit nodular or cauliflower-like masses, mucosal congestion, edema, erosion or pale stiffness, easy bleeding when touched, ulcers, or varying degrees of stenosis.

The clinical diagnosis of esophageal carcinoma requires further pathological examination.

4.2 | Pathological diagnosis

Esophageal carcinoma includes two main types—SCC and adenocarcinoma—along with other rare types.

4.2.1 | Gross typing

(1) Early esophageal carcinoma: Protuberant, superficial, and depressed (ulcer) type.

(2) Advanced esophageal carcinoma: Medullary, umbrella, ulcerative, constrictive, and intraluminal type.

4.2.2 | Histological classification

The World Health Organization classification of esophageal carcinoma (2010 edition) was used (see Appendix 1).

4.2.3 | SCC

Accounts for the vast majority of esophageal carcinomas in China. According to its degree of differentiation, SCC is divided into well-differentiated, moderately differentiated, and poorly differentiated forms. There are three distinct subtypes:

(1) Verrucous carcinoma: Though this tumor is well differentiated and does not have the ability to metastasize, its occurrence in the esophagus is associated with a higher mortality rate.

(2) Spindle cell SCCs (sarcomatoid carcinomas and carcinosarcomas): Most of these show pleomorphic or spindle cell (sarcomatoid) manifestations, occasionally exhibiting focal cartilage, bone, or rhabdomyogenic differentiation. These sarcomatoid components are of epithelial origin and share the same clonal origin as that of cancer components.

(3) Basal cell-like SCC: Has a highly aggressive biological behavior, and its degree of malignancy is higher than that of common esophageal SCC.

Adenocarcinoma

More common in the lower one-third of the esophagus and occasionally originates from the ectopic gastric mucosa or the glands distributed in the lamina propria mucosae in the middle and upper esophagus.

Mucoepidermoid carcinoma

Originates in the submucosal gland in the esophagus and is similar to the mucoepidermoid carcinoma of the oral cavity in morphological characteristics and biological behavior.
Neuroendocrine tumors
Classification and diagnostic criteria are the same as those for gastrointestinal pancreatic neuroendocrine tumors.

Other malignant tumors of the esophagus
These include gastrointestinal stromal tumor, leiomyosarcoma, malignant melanoma, lymphoma, rhabdomyosarcoma, and synovial sarcoma.

5 | LOCATION AND STAGE

5.1 | Location
In their 8th edition of the 2017 TNM staging of esophageal and esophagogastric junction (EGJ) cancer, the American Joint Committee on Cancer (AJCC) and the International Union against Cancer (UICC) jointly defined the tumor location as the midpoint of the primary lesion.

5.1.1 | Cervical esophagus
Bordered superiorly by the hypopharynx and inferiorly by the thoracic inlet, which lies at the level of the sternal notch. Its endoscopic tumor length measured from the incisors is 15–20 cm.

5.1.2 | Upper thoracic esophagus
Bordered superiorly by the thoracic inlet and inferiorly by the lower border of the azygos vein. Its endoscopic tumor length from the incisors is 20–25 cm.

5.1.3 | Middle thoracic esophagus
Spans from the lower edge of the azygos arch to the level of the inferior pulmonary vein. Its endoscopic tumor length from the incisors is 25–30 cm.

5.1.4 | Lower thoracic esophagus
Bordered superiorly by the lower border of the azygos vein and inferiorly by the inferior pulmonary veins. Its endoscopic tumor length from the incisors is 25–30 cm.

5.1.5 | EGJ
Endoscopic EGJ is usually defined as the first appearance of gastric folds, a theoretical landmark. Histologically, EGJ can be accurately defined as the junction of the esophageal columnar epithelium and squamous epithelium. If the midpoint of the tumor is within 2 cm of the proximal stomach, whether it invades the lower esophagus or EGJ, the tumor is staged according to the classification for esophageal carcinoma. If the tumor is beyond 2 cm of the proximal stomach, then it is staged according to the classification for gastric cancer.

5.2 | Staging
The 8th edition (2017) of AJCC/UICC staging (see Appendix 2) was used, including clinical staging (cTNM), postoperative pathological staging (pTNM), and post-neoadjuvant treatment staging (ypTNM).

6 | TREATMENT

6.1 | Principles of treatment
Based on adequate assessment of patients and tumors, the principle of comprehensive treatment based on the suggestions of MDT is recommended for reasonable application of the existing treatment methods to maximize survival rates, reduce adverse reactions, and improve quality of life.

For patients with pTis-T1aN0, endoscopic mucosal resection, endoscopic submucosal dissection (grade I recommendation), or combined radiofrequency ablation (grade II recommendation) is recommended. Resection of esophageal cancer is also feasible. Endoscopic resection combined with radiotherapy can aid in achieving a radical cure (grade II recommendation, class 2B evidence). Surgical resection is recommended for patients with a non-cervical segment of the pT1b-2N0 stage (grade I recommendation). Radical concurrent chemoradiotherapy is also feasible for stage I SCC.

For patients with locally advanced stage and resectable esophageal cancer, surgery remains the cornerstone of treatment. For patients with cT1b-2N+ or cT3-4aN0/N+, the treatment principles of SCC and adenocarcinoma are different. For patients with adenocarcinoma, neoadjuvant chemoradiotherapy is recommended (class 1A evidence) neoadjuvant chemotherapy is also feasible; for patients with adenocarcinoma who refuse surgery or have surgical contraindications, radical concurrent chemoradiotherapy (grade II recommendation) is recommended. For patients with SCC, neoadjuvant chemoradiotherapy is recommended (class 1A evidence), whereas radical concurrent chemoradiotherapy is recommended for tumors in the cervical segment and for patients who refuse surgery (class 1A evidence). The operative timing was 6–8 weeks after neoadjuvant chemoradiotherapy or 3–6 weeks after neoadjuvant chemotherapy.

For patients with locally advanced stages such as cT4bN0/N+, radical concurrent chemoradiotherapy (grade I recommendation, class 1A evidence) is recommended if the performance status (PS) score is 0–1. Radiotherapy should be carefully selected for patients with esophageal perforation or a tendency for massive hemorrhage. Radiotherapy alone is recommended for patients who cannot tolerate concurrent chemoradiotherapy. Patients with a PS score of 2 are
recommended the best supportive care or symptomatic treatment (grade I recommendation), chemotherapy alone, or palliative radiotherapy (class 2B evidence).

Regardless of whether patients with SCC received neoadjuvant chemoradiotherapy, postoperative adjuvant therapy for patients with R0 resection is controversial, and regular monitoring is required. Adjuvant radiotherapy or chemoradiotherapy may be considered for high-risk postoperative patients who have not received neoadjuvant therapy (lymph node positivity and/or stage pT3-4aN0). For patients with SCC who have received neoadjuvant chemoradiotherapy, postoperative observation or postoperative chemotherapy is recommended. For patients without neoadjuvant therapy and with negative lymph nodes, regular monitoring can be considered; however, fluorouracil-based chemoradiotherapy is feasible for high-risk pT2 (poorly differentiated, intravascular cancer emboli, nerve invasion, age <50 years) and pT3-4a stages. For lymph node-positive patients, fluorouracil-based postoperative chemoradiotherapy (class 1A evidence) or chemoradiotherapy (class 2B evidence) is recommended.

Patients who have received R1/R2 resection but not neoadjuvant chemoradiotherapy are recommended to undergo adjuvant concurrent chemoradiotherapy (class 1A evidence), sequential chemoradiotherapy (for those who cannot tolerate concurrent chemoradiotherapy, grade II recommendation, class 2B evidence), or adjuvant chemotherapy (grade III recommendation, class 3 evidence). SCC patients who received neoadjuvant chemoradiotherapy are recommended to undergo chemotherapy, optimal supportive treatment/symptomatic management, or observation (class 2B evidence). Patients with adenocarcinoma are recommended for reoperation or observation (class 2B evidence).

Chemotherapy-based combination therapy is recommended for small cell carcinomas (class 2B evidence). Radical surgery is recommended as the primary treatment for sarcomatoid carcinoma (class 2B evidence). Surgical resection is preferred for malignant melanomas (class 2B evidence). Accurate staging and evaluation of each tumor determine the treatment choice for multiple primary cancers.

For patients with local recurrence and metastasis after radiotherapy, salvage surgery or secondary chemoradiotherapy can be considered after comprehensive assessment.

6.2 | Indications of surgery

(1) Radical resection of esophageal carcinoma is suitable for patients with stage I, stage II, and partial stage III (except for the cervical segment). Patients with locally advanced disease stages are recommended to undergo neoadjuvant therapy.

(2) Salvage surgery for esophageal cancer is suitable for patients with local recurrence after radiotherapy, no distant metastasis, resectable tumors after assessment, and for those who can tolerate surgery in general.

6.3 | Radiotherapy

6.3.1 | Indications of radiotherapy

Neoadjuvant chemoradiotherapy/radiotherapy
Primarily suitable for patients with stage cT1b-2N+ or cT3-4aN0/N+.
Neoadjuvant chemoradiotherapy is grade I recommendation for patients with adenocarcinoma and non-cervical esophageal SCC.

Radical chemoradiotherapy/radiotherapy
(1) Patients with cT1b-2N+ or cT3-4aN0/N+ cervical esophageal SCC or those with non-cervical esophageal carcinoma who refused surgery.
(2) Patients with cT4bN0/N+.
(3) Patients with thoracic esophageal carcinoma with supraclavicular or retroperitoneal lymph node metastasis only.
(4) Patients who cannot tolerate surgery after preoperative chemoradiotherapy or radiotherapy evaluation.
(5) Patients with contraindications or at high risk of operation owing to old age and severe cardiopulmonary disease.

Postoperative chemoradiotherapy
(1) Patients who underwent R1 or R2 resection and did not receive preoperative chemoradiotherapy.
(2) Patients with adenocarcinoma who did not receive preoperative chemoradiotherapy and had N+ or high-risk pT2 N0 and pT3–4a N0 after R0 resection.
(3) Patients with SCC who did not receive preoperative chemoradiotherapy and had N+ or pT3–4a N0 after R0 resection.

Palliative radiotherapy
(1) After chemotherapy, the metastatic foci of patients with advanced disease are reduced or stable, and radiotherapy for primary lesions should be considered.
(2) Patients with extensive multistation lymph node metastasis who cannot receive radical radiotherapy.
(3) Patients with clinical symptoms caused by distant metastasis.
(4) To alleviate obstruction and improve the nutritional status of advanced stage patients.
(5) Patients with partially uncontrolled regional recurrence after radical treatment.

6.3.2 | Contraindications of radiotherapy

(1) Poor general condition or cachexia.
(2) Poor cardiopulmonary function or severe complications with diseases of vital organs and systems, making it difficult to tolerate radiotherapy.
(3) Massive esophageal bleeding or signs of massive hemorrhage.
(4) Esophageal fistula complicated by severe infection
6.3.3 | Planning for radiotherapy

Selection of radiotherapy technology
Conformal, intensity-modulated, and spiral tomographic intensity-modulated techniques can be employed for esophageal cancer radiotherapy. Generally, 6–8-MV X-rays are used for conformal radiotherapy, with four to five shooting fields. Anterior and posterior fields were mainly used to reduce radiation exposure to the lungs, while the lateral field avoids exposure to the spinal cord. X-ray at a dose of 6 MV is recommended for intensity adjustment of the fixed field. Generally, five to seven fields should be set up, and both shoulders should be avoided as far as possible. In general, X-ray at a dose of 6 MV and 2-arc isocentric coplanar irradiation are used in the spiral tomographic intensity-modulated technique. To reduce the radiation dose, especially the low-dose radiation volume for the lungs, two incomplete arcs can be considered, that is, transverse penetration of the lung tissue should be avoided. The spiral tomographic intensity-modulated technique can set the shielding angle at the target level to avoid transverse radiation from both sides of the lungs.

Image-guided technology
Pre-radiotherapy image guidance for esophageal cancer includes two- and three-dimensional online images. The online images should be collected before the first three to five treatments and then once a week. As bed subsidence will be introduced again after the setup of spiral tomography, it is suggested to improve the frequency of image guidance and conduct megavoltage CT (MVCT) scanning at different layers for the middle and lower segments during esophageal cancer radiotherapy. This will reduce the additional radiation dose received by a certain segment of the anatomical structure.

Technical specifications for localization
(1) CT simulation location of esophageal cancer: The patient can be placed in the supine position on the fixed frame of the CT scanning bed, and the cervical and upper thoracic esophageal cancer can be fixed using a head-neck-and-shoulder integrated thermoplastic mask, with the arms parallel to the sides of the body. The middle and lower thoracic esophageal cancers can be fixed with a vacuum negative-pressure bag, with both hands holding the elbows in front of the forehead, legs close together, and the whole body relaxed. The scanning condition can be set as axial scanning with a layer thickness of 3 mm, and the scanning range can be set according to the lesion location and range. To manage respiratory movement, CT can be combined with technologies such as active respiratory control, four-dimensional CT, and respiratory gating. The markers of cervical and upper thoracic esophageal cancer can be placed at the mandibular level, and for middle and lower thoracic esophageal cancers they can be placed on the flat chest surface. The cross-marker line of the front part of the pelvic cavity can be added to correct the left–right deviation of the trunk when set up before treatment.

(2) MRI simulation location of esophageal cancer: Ensuring the safety of the device and patient, the location of MRI simulation should avoid contact between the coil and the body, consistently retaining body position, mark, and scanning layer thickness during the CT location process.

The position verification after the first course of radiotherapy is generally approximately 40 Gy.

Definition of the targeted area
Neoadjuvant radiotherapy/radical radiotherapy. (1) Radical radiotherapy
Gross tumor volume (GTV): This includes primary tumors (GTVp) and metastatic lymph nodes (GTVn). GTVp is a visible esophageal lesion that can be determined using a combination of imaging techniques (e.g., esophagography, contrast-enhanced CT, MRI, and/or PET/CT) and endoscopy (e.g., electronic upper gastrointestinal endoscopy and/or intravascular ultrasound). GTVn refers to metastatic lymph nodes with a diameter of ≥10 mm (parasphageal, tracheoesophageal groove ≥5 mm) as observed on CT and/or MRI or a high SUV (except inflammatory lymph nodes) as observed on PET/CT. Even if the lymph node characteristics are under these standards, those with evident necrosis, circular enhancement, enhancement to a similar degree as that of the primary lesion, and eccentric calcification are also considered as GTVn (class 2 B evidence).

Clinical target volume (CTV): According to the National Comprehensive Cancer Network (NCCN) guidelines, selective lymph node irradiation is recommended for radical radiotherapy. Involved field irradiation may be considered if the target is too large, the patient has a poor PS score, the disease stage is late, or poor cardiopulmonary function. For involved field irradiation, CTV is defined as GTVp with a 30-mm expansion superiorly and inferiorly and a 5–6-mm expansion in other directions and GTVn with a 5–6-mm expansion in all directions (adjusted when the anatomical barrier is included). For selective lymph node irradiation, in addition to the primary esophageal lesion and metastatic lymph node area, the corresponding lymph node drainage area with a high lymph node metastasis rate should also be included. The following is for reference (grouping of lymph node drainage area has been referenced from the JES 11th standard):

(i) Cervical esophageal carcinoma: bilateral 101, 102, 104, 105, and 106 rec groups
(ii) Upper thoracic esophageal carcinoma: bilateral 101, 104, 105, and 106 and partial 108 groups
(iii) Middle thoracic esophageal carcinoma: bilateral 101, 104, and 105, 106, 107, and 108; partial 110; and abdominal 1, 2, 3, and 7 groups
(iv) Lower thoracic esophageal carcinoma: 107, 108, and 110, abdominal 1, 2, 3, and 7 groups
(v) Upper crossing middle esophageal carcinoma: bilateral 101, 104, 105, 106, 107, and 108 groups
(vi) Middle crossing upper esophageal carcinoma: 105, 106, 107, and 108 and partial 110 groups
(vii) Middle crossing lower esophageal carcinoma: partial 105, 106, 107, 108, and 110 and abdominal 1, 2, 3, and 7 groups
(viii) Lower crossing middle esophageal carcinoma: 107, 108, and 110 and abdominal 1, 2, 3, and 7 groups

Planned target area (PTV): This includes CTV with a 5-mm expansion in all directions; longitudinal expansion can be up to 8 mm, and the actual margin can be determined according to the quality control data of each center.

Selective lymph node irradiation usually requires repeated localization after the first dose of prophylaxis is administered. If there is no new lesion, then only the involved field irradiation needs to be performed for radical cure during follow-up. Simultaneous integrated boost has also been studied and applied clinically and is noteworthy.

(2) Neoadjuvant radiotherapy

At present, there is no specific target area regulation for neoadjuvant chemoradiotherapy globally; hence, it is suggested that the principle of radical radiotherapy involving random radiation should be followed. When delineating the target area, the location of anastomotic stoma during subsequent surgical resection should be considered, and it should be avoided in the irradiation field to reduce the incidence of anastomotic fistula.

Postoperative radiation. The 2020 NCCN guidelines do not recommend adjuvant treatment after radical resection of esophageal SCC. However, global large-scale research, prospective stratification studies, and retrospective analyses have demonstrated that the recurrence rates of lymph node positivity and/or pT3–4a N0 stage and high-risk pT2 N0 adenocarcinoma were consistent; these results revealed that the survival rate of postoperative radiotherapy was higher than that reported in single-surgery group studies and that the recurrence rate of the radiotherapy field was significantly reduced. Therefore, postoperative radiotherapy or chemotherapy is recommended.

CTV: The bilateral supraclavicular area and superior mediastinum area include the 104, 105, 106, and 107 groups. If the lesion is in the lower esophagus with the number of lymph node metastases being ≥3 and radiotherapy alone is used, then it is recommended to include the following lymph node areas: 104, 105, 106, 107 and abdominal groups 1, 2, 3, and 7. In case of a upper thoracic esophageal carcinoma or upper resection margin ≤3 cm, anastomotic stoma should be included (class 2B evidence).

Radiotherapy plan optimization

The conformal radiotherapy plan field should follow four principles: (1) the distance from the incident plane to the center of the target area should be short; (2) avoid organs at risk; (3) the side of the beam should be parallel to the longest side of the target area; and (4) the angle between adjacent radiation beams should generally be no less than 40° (except for the supplementary small beam). In addition, the isocenter of the radiation field can generally be placed at the center of the tumor and can be slightly adjusted by considering the actual irradiation position.

Cervical and upper thoracic esophageal cancers (Figure 1): The neck, thoracic entrance, and upper thoracic esophagus largely differ in their thickness, and the depth of the esophagus is different from the body surface. If the anatomical position is deeper, then the target area dose is insufficient, and a supplementary beam should be added.

Middle and lower thoracic esophageal cancer (Figure 2): This is divided into four fields: anterior, posterior, left, and right; five fields: left anterior, right posterior, right anterior, left posterior, and anterior; or on this basis in addition to an overall conformal field with at least two beams completely avoiding the spinal cord. For patients undergoing postoperative radiotherapy, the shooting field through the thoracic stomach should be avoided. If it is unavoidable, then the weight of the beam should be minimized.

Intensity modulation scheme: Cervical and upper thoracic esophageal cancers can be distributed at equal angles. In the middle and lower thoracic esophageal cancer, the plan design is based on the principle of reducing the volume of lung irradiation, and butterfly-shaped fields along the midline of the body can be used with evenly distributed weights.

Delineation of organs at risk: This mainly includes the spinal cord, lungs, heart, liver, trachea, main bronchus, and stomach.
FIGURE 2  Conformal plan radiation beam distribution and the relative position of the tumor and spinal cord shown in the beam eye view for thoracic esophageal cancer

Note: A is the schematic diagram of the five fields of coplanar conformal radiation for middle and lower esophageal cancer. B–F are the relative positions of the gross tumor and spinal cord of the five irradiation fields in the beam eye view as well as the settings of the multi-leaf grating and collimator

(1) The dose limits for the spinal cord, lungs, heart, and liver according to QUANTEC (2012) are as follows:

The maximum doses for cervical and thoracic spinal cords are \(<45\) Gy and \(<50\) Gy.

When \(V20\) is \(<30\%\) in both the lungs, the risk of symptomatic radiation pneumonia is \(<20\%\). When the mean lung doses (MLDs) are 7, 13, 20, 24, and 27 Gy, the rates of the risk of symptomatic radiation pneumonia are 5\%, 10\%, 20\%, 30\%, and 40\%, respectively.

The risk of pericarditis is less than 15\% when the mean cardiac dose is \(<26\) Gy. When the \(V30\) of the heart is \(<46\%\), the risk of pericarditis is \(<15\%\). When \(V25\) is \(<10\%\), the risk of long-term cardiogenic death is \(<1\%\).

When the mean liver dose is \(<30–32\) Gy, the risk of radiation-induced liver disease is \(<5\%\) (in patients without previous liver diseases or hepatocellular carcinoma). When this dose is \(<28\) Gy, the risk is \(<5\%\) (in patients with previous liver diseases or hepatocellular carcinoma with Child–Pugh class A liver function; patients with hepatitis B virus reactivation are excluded).

(2) The dose tolerance limits for the trachea, main bronchus, and stomach are as follows:

Because of its proximity to the esophagus, despite the use of conformal intensity-modulated precise radiotherapy techniques, the trachea will inevitably receive high doses. There are few reports in the literature regarding a tolerable tracheal dose under routine segmentation. It is recommended that the maximum dose be \(<75\) Gy, and the hot spot dose (\(\geq110\%\) of the prescribed dose) should be avoided from overlapping with the tracheal wall in the target area.

When the stomach is irradiated, serious adverse reactions may occur, including ulcers and perforations. When the irradiated volume is one-third, two-thirds, and the whole stomach, TD5/5 values are 60, 55, and 50 Gy, respectively, and TD50/5 values are 70, 67, and 65 Gy, respectively. It is recommended that the stomach volume of 40 Gy should be \(<40\%–50\%\) of the entire thoracic stomach. The dose tolerance limit for the stomach according QUANTEC is \(D100\% <45\) Gy, corresponding to the gastric ulcer risk of \(<7\%\).

Application of special radiotherapy techniques (class 2B evidence)

Proton and heavy-ion radiotherapy. Based on existing small-scale clinical research, it is recommended that qualified centers conduct relevant clinical research and treatments carefully when treating esophageal cancer with protons and heavy ions.

Intensity-modulated proton therapy (IMPT) can reduce doses to the heart and liver better than the passive scattered proton therapy. The beam energy is 150–250 MeV, and the target delineation refers to the requirements of the relevant IMPT standards. The recommended dose of radical concurrent chemoradiation is 50.4 Gy (relative biological effectiveness; RBE) 28 times (five times/week, 36–63 Gy [RBE]). Proton therapy alone may appropriately increase the dose to 62–98 Gy (RBE). The doses to organs at risk were as follows: MLD is \(<20\) Gy, the whole lung \(V20\) is \(<30\%\), the heart \(V40\) is \(<40\%\), the liver \(V30\) is \(<30\%\), and the maximum dose to the spinal cord is \(<45\) Gy. X-ray with proton beam irradiation can be used: X-ray dose of 36 Gy (16.2–60 Gy, 1.8–2.0 Gy/f) and proton beam dose of 36 Gy (RBE) (17.5–54.5 Gy (RBE), 2.5–3.7 Gy (RBE)/time). Small-scale data show that proton radiotherapy has advantages of a high rate of symptom control and few side effects in the recurrence of esophageal cancer after radiotherapy and chemotherapy; additionally, the recommended dose is 54.0 Gy (RBE) (50.4–61.2 Gy [RBE]).

The application of heavy ions in esophageal cancer radiotherapy is limited to carbon-12 as reported in a small-scale clinical study. The Japanese Carbon Ion Radiation Oncology Research Group (J-CROS) treatment guidelines recommend neoadjuvant radiotherapy for stage II and III esophageal cancers, with a dose of 33.6 Gy (RBE)/8 f and radical radiotherapy for stage I esophageal cancer with a dose of 48–50.4 Gy/RBE/12 f. Heavy ions may cause irreversible damage to normal tissues, therefore special attention should be paid to protect normal tissues.

Afterloading intracavitary radiotherapy. Intracavitary radiotherapy for esophageal cancer is not recommended as a routine treatment but as a supplement to external radiation. If radiotherapy alone is unsuccessful and surgery is not an option, then it is recommended to use a radiation
Radiotherapy dose of 10–20 Gy. If the primary lesion recurred after radiochemotherapy, then it could be treated via afterloading combined with external irradiation (external irradiation of 40–50 Gy, afterloading 3–5 Gy/time, two to three times) or afterloading radiotherapy alone (20–40 Gy).

Radioactive seed implantation. {superscript}125I radioactive seed implantation is a type of brachytherapy and plays a role in the treatment of esophageal cancer. It is mainly used in the salvage treatment for esophageal cancer recurrence with neck and mediastinal lymph node metastasis after radiotherapy. Preoperative planning should be designed with radiotherapy treatment planning system (TPS), and a three-dimensional printed coplanar or non-coplanar template is recommended. The recommended particle activity is 0.4–0.8 mCi. The prescription dose is 100–120 Gy for those who relapsed within 6 months of radiotherapy and a dose of 120–160 Gy for those who relapsed after 6 months. Postoperative dose verification should be performed.

Palliative treatment for advanced esophageal cancer. Palliative treatment for advanced esophageal cancer consists of a covered stent with radioactive particles; it can rapidly relieve dysphagia and improve the quality of life. Compared with an ordinary stent, it can prolong esophageal patency time without increasing postoperative complications. It is suitable for older and infirm patients who refuse or cannot undergo radiotherapy or who may relapse after radiotherapy with severe dysphagia.

6.3.4 Radiotherapy dose

Neoadjuvant chemoradiotherapy: 40–50.4 Gy, conventional fractionation. At present, there is no sufficient evidence to show the difference in clinical efficacy between low-dose and high-dose neoadjuvant radiotherapies.

Radical concurrent chemoradiotherapy: 50–60 Gy, conventional fractionation. Prospective studies have shown that the differences in local control and survival rates between the low-dose and high-dose radical radiotherapy groups were not statistically significant. In contrast, retrospective studies suggested that high-dose radiotherapy improved the local control and survival rates of esophageal SCC, though it remains controversial.

Radiotherapy alone: 60–70 Gy, conventional fractionation.

Postoperative radiotherapy: R1/R2 postoperative adjuvant radiotherapy 50–60 Gy, conventional segmentation and adjuvant concurrent chemoradiotherapy with a dose of 50.4 Gy. R0 postoperative adjuvant radiotherapy with a dose of 45–50.4 Gy, conventional fractionation.

6.3.5 Prevention and treatment of radiotherapy-related complications

The most common complications of radiotherapy are radiation esophagitis, pneumonia, heart injury, and myelosuppression. Spinal cord injury rarely occurs owing to the development of precision radiotherapy (see Appendix 3 for the Radiation Therapy Oncology Group (RTOG) damage classification standards).

Radiation esophagitis

During 2–3 weeks of radiotherapy, most patients develop radiation esophagitis, and the patients mainly present with painful swallowing, increased obstruction on eating, and burning or discomfort behind the sternum. Severe cases may exhibit dehydration, malnutrition, electrolyte imbalance, or weight loss. Severe patients may display esophageal bleeding, perforation, or other life-threatening symptoms, especially those with advanced age, cervical or upper thoracic lesions, receiving concurrent chemotherapy, or accelerated hyperfractionated radiotherapy experience the symptoms earlier and in a more severe form. The treatment principles are treatment with anti-inflammatory drugs and analgesics, repair of the damaged esophageal mucosa, and nutritional support. If eating is unaffected, then it is recommended to observe temporarily, eat warm and non-stimulating semi-liquid food, and drink more water. If there is moderate to severe pain while eating, then intravenous rehydration, anti-inflammatory, hormone, acid suppression, oral gastrointestinal mucosal protective agents (e.g., sulfur saccharate), and other treatments can be administered. Oral intake of diluted lidocaine can have an anesthetic effect and reduce local pain on the mucosal surface, though it can cause allergic reactions. Radiotherapy should be discontinued when necessary.

Radiation pneumonia

Acute radiation pneumonia usually occurs within 3 months of radiotherapy, and it mainly manifests as fever (low fever), cough (irritating or dry cough), chest pain, and dyspnea. In severe cases, breathing difficulties may lead to death. However, there have been some patients with evident changes in imaging but with no clinical symptoms. There are usually no evident signs in the lungs on physical examination. Some patients can have rough breath sounds, reduced breath sounds, or dry and wet rales but nothing specific. Laboratory tests and lung function tests are also non-specific. Chest radiography or CT may show diffuse patchy increased density shadows or strip-like changes consistent with the irradiation field; these changes may not be distributed according to anatomical structures such as lung fields or lung segments. In some patients, the disease lesion can be located beyond the irradiation field and diffusely distributed in both lungs.

Owing to the lack of a specific basis, the diagnosis is mostly based on patients receiving chest radiotherapy, referring to normal lung tissue exposure volume and dose, aforementioned symptoms, lung imaging changes, no significant increase in peripheral blood neutrophils, and exclusion of other pathologies. Radiation pneumonia lacks effective treatment methods. Routine treatment includes glucocorticoids, which suppress immunity, reduce exudation, and promote the production of fibrotic factors. An adequate dose of glucocorticoids should be used immediately and for the full course of treatment. After alleviation of the clinical symptoms, the dose should be gradually reduced and then stopped. In case of co-infection, antibiotics should be used rationally, adopting symptomatic treatment, including expectorant and
appropriate oxygen inhalation. Prevention is crucial, which focuses on accurately delineating the target area, optimizes the radiotherapy plan, and minimizes the exposure dose and volume of normal lung tissue.

**Radiation heart injury**

Radiation heart injury is a collective term used to refer to a series of cardiovascular complications after radiotherapy, mainly asymptomatic myocardial ischemia (occult coronary heart disease), arrhythmia, pericarditis, angina pectoris, myocardial infarction, ischemic heart failure, and even sudden death, with a long incubation period. The diagnosis is mainly based on the long-term follow-up for cardiovascular diseases and cardiac function tests such as ECG, myocardial enzymes, echocardiography, coronary CT, cardiac IMR, and myocardial radionuclide imaging examination after radiotherapy; this excludes pathologies of coronary arteries, myocardium, pericardial disease, and arrhythmia, among others. Heart exposure volume and radiation dose are the most important influencing factors. Smoking, hypertension, dyslipidemia, obesity, and diabetes are high-risk factors, and combined chemotherapy may increase its incidence.

There are no effective and specific treatment plans for radiation-induced heart injury. Treatment principles include reducing the risk factors along with anti-inflammatory, anti-thrombotic, and nutritional myocardial therapies. Statins are currently the most effective lipid-lowering drugs. They also have anti-inflammatory, anti-thrombotic, and anti-fibrotic effects, and can reduce radiation-induced myocardial fibrosis. Angiotsin-converting enzyme inhibitors can inhibit myocardial fibrosis, and aspirin has antiplatelet aggregation effects; however, their efficacies in treating radiation-induced heart injury need to be confirmed.

**Myelosuppression**

Myelosuppression may occur in patients with esophageal cancer receiving radical radiotherapy, especially concurrent radiotherapy and chemotherapy. It is recommended that patients with a leukocyte count of <3.0 × 10^9/L or a platelet count of <80 × 10^9/L should receive pegylated recombinant human granulocyte colony-stimulating factor (G-CSF), recombinant human interleukin 11, recombinant human thrombopoietin, or other corresponding treatment.

### 6.3.6 Efficacy evaluation and follow-up after radiotherapy

The evaluation methods for the curative effect of radiotherapy include the following aspects:

1. **Esophageal angiography:** We used the short-term efficacy evaluation criteria of esophageal cancer radiotherapy proposed by Professor Wan Jun to evaluate the remission of the primary lesion, based on the filling defect, wave ulcer, and degree of stenosis in the esophageal lesion.
2. **CT examination:** This approach mainly involves a comparison of the changes in parameters such as length of the tumor, maximum thickness of the esophageal wall, volume of the tumor, and volume of lymph nodes before and after radiotherapy and chemoradiotherapy.
3. **Upper gastrointestinal endoscopy or ultrasound endoscopy:** Esophageal wall thickness <5 mm and negative mucosal biopsy can determine complete remission of the tumor, but sensitivity is only 50%. The sensitivity of the biopsy to detect residual tumors under endoscopic ultrasound is 75%. Ultrasound fine-needle aspiration biopsy can improve the accuracy of the assessment of complete remission of lymph nodes.
4. **MRI:** The change in apparent dispersion coefficient (ADC) values before and after radiotherapy can predict the curative effect of radiotherapy.
5. **PET/CT:** The change in SUV before and after radiotherapy can aid in the evaluation of the efficacy and prediction of prognosis (see Appendix 4 for the imaging evaluation criteria).
6. **The pathological evaluation after neoadjuvant treatment adopts the College of American Pathologists (CAP)/NCCN standards (see Appendix 5).**

Evaluation and follow-up of efficacy after neoadjuvant radiotherapy and chemotherapy: After neoadjuvant radiotherapy and chemotherapy for esophageal cancer, single-point deep biopsy or fine-needle aspiration under ultrasound endoscopy can be used to detect local residual lesions. Mucosal changes can be observed on esophageal angiography. The shrinkage proportion of the primary tumor and metastatic lymph nodes can be evaluated using CT or MRI, and distant metastases can be detected using PET/CT.

Follow-up after radical radiotherapy/radical chemoradiation/postoperative radiotherapy: Patients should be reexamined every 3 months in the first 1–2 years after the completion of radiotherapy or chemoradiotherapy, every 6 months within 2–5 years, and once a year after 5 years. The reexamination items include symptoms, physical examination, and the aforementioned auxiliary examinations, but there is currently no high-level medical evidence to suggest the best follow-up strategy.

### 6.4 Systemic therapy

#### 6.4.1 Chemotherapy

*Principles to be followed during chemotherapy for esophageal cancer*

1. Systemic chemotherapy is used for advanced esophageal squamous cell carcinoma (ESCC) and EGJ adenocarcinoma. ESCC and gastric adenocarcinoma can be used interchangeably (except if specified).
2. The choice of the treatment regimen should consider the patient’s PS score, concomitant disease, and drug toxicity.
3. Trastuzumab should be used in combination with chemotherapy in patients with unresectable or advanced EGJ adenocarcinoma overexpressing HER-2.
(4) The two-drug regimen is the first choice. A three-drug regimen can be used for patients with good PS and toxicity assessments at any time.

**Indication of chemotherapy**

**Postoperative chemotherapy/chemoradiotherapy.** For patients with (1) R1 or R2 resection; (2) R0 resection, SCC, N+ or T4aN0, or lymph node capsule invasion; (3) R0 resection, adenocarcinoma, N+ or T3-4aN0, or T2N0 with high-risk factors.

**Palliative chemotherapy.** Mainly for patients with metastatic or recurrent esophageal cancer.

**Common chemotherapy regimens.** Platinum and fluorouracil are the most commonly used drugs, and fluorouracil is interchangeable with capecitabine and S-1 depending on the need or toxicity; however, in the regimen containing irinotecan, fluorouracil cannot be replaced with capecitabine. Patients with high-risk cardiac risk factors can be treated with raltitrexed. Cisplatin is interchangeable with carboplatin and oxaliplatin, and paclitaxel is interchangeable with paclitaxel liposomes.

**Neoadjuvant chemotherapy/neoadjuvant chemoradiotherapy regimen.** The preferred options are as follows:

1. Paclitaxel + carboplatin (class 1 evidence)
   - Paclitaxel 50 mg/m² d1 and carboplatin AUC = 2 d1, QW × 5 weeks.
2. Fluorouracil + oxaliplatin (class 1 evidence)
   - Oxaliplatin 85 mg/m² d1, calcium folinate 400 mg/m² d1, fluorouracil 400 mg/m² IV d1, and 800 mg/m² CIV 24 h d1–2, Q2W, for three cycles
3. Capecitabine + oxaliplatin (class 1 evidence)
   - Capecitabine 625 mg/m² bid d1–5, for 5 weeks, oxaliplatin 85 mg/m² d1, 15, 29, and three times
4. Fluorouracil + cisplatin (class 1 evidence)
   - Cisplatin 75–100 mg/m² d1, d29, fluorouracil 750–1 000 mg/m² qd CIV d1–4, d29–32, Q5W, or cisplatin 15 mg/m² d1–5, fluorouracil 800 mg/m² qd CIV 120 h, Q3W, for two cycles.
5. Capecitabine + cisplatin (class 1 evidence)
   - Capecitabine 800 mg/m² bid d1–5, cisplatin 30 mg/m² d1, QW, for 5 weeks.
6. Fluorouracil + cisplatin (class 1 evidence)
   - Fluorouracil (fluorouracil/capecitabine/S-1 capsule) + cisplatin (class 1 evidence)
   - Fluorouracil + oxaliplatin (recommended for adenocarcinoma)
   - Paclitaxel/docetaxel + cisplatin/nedaplatin
   - Vinorelbine + cisplatin/nedaplatin
6. Fluorouracil + irinotecan
   - Modified DCF regimen (docetaxel + cisplatin + fluorouracil), DOF regimen (docetaxel + oxaliplatin + fluorouracil + calcium folinate) (class 2B evidence)
6. ECF regimen (epirubicin + cisplatin + fluorouracil; class 2B evidence)

Second-line treatments and the above options:

(1) Paclitaxel monotherapy (docetaxel/paclitaxel)
(2) Irinotecan single drug
(3) Docetaxel combined with irinotecan
(4) Raltitrexed alone or in combination with platinum (class 2B evidence)

Bone marrow safety management of radiotherapy and chemotherapy for esophageal cancer

Prophylactic use of G-CSF can reduce the degree of neutropenia after chemotherapy or concurrent chemoradiotherapy and reduce the risk of neutropenia, febrile neutropenia (FN), and infection. Among the common chemotherapy regimens for esophageal cancer, FN risk with the DCF regimen is more than 20%, and prophylactic use of G-CSF is needed. The FN risk of irinotecan + cisplatin, epirubicin + cisplatin + fluorouracil, and epirubicin + cisplatin + capecitabine is 10%–20%. When patients with neoadjuvant chemoradiotherapy receive vinorelbine + cisplatin or inoperable SSC patients receive cisplatin + paclitaxel with a radiotherapy dose >60 Gy, prophylactic use of G-CSF could be considered after comprehensive evaluation.

6.4.2 Molecular targeted therapy

Mainly suitable for unresectable locally advanced or advanced esophageal cancer and second-line and above treatment.

Anti-HER-2 therapy
HER-2 overexpression in the esophagus and EGJ adenocarcinomas require combined treatment using trastuzumab and chemotherapy.

Anti-EGFR therapy
Includes nituzumab in combination with chemotherapy or chemoradiotherapy.

Anti-angiogenesis
(1) Recombinant human endostatin combined with chemotherapy (the objective response rate of locally advanced esophageal cancer was 83.8%, of which the complete response was 56.8%).
(2) Ramucirumab alone or in combination with paclitaxel (EGJ adenocarcinoma shows class 1 evidence).
(3) Anlotinib (ESCC only).
(4) Apatinib (adenocarcinoma, class 1A evidence; SCC, class 2B evidence).  

6.4.3 Immunotherapy

Immunotherapy has an antitumor effect as the second-line and above treatments for advanced esophageal cancer (EC), and its side effects can be tolerated. Existing phase III clinical studies have shown that camrelizumab (evidence quality level 1A), pembrolizumab (evidence quality level 1A), and nivolumab can better improve overall survival and progression-free survival than chemotherapy. Pembrolizumab is recommended only for patients with a PD-L1 CPS ≥ 10. According to the results of KEYNOTE-590, pembrolizumab in combination with chemotherapy can be considered as first-line treatment. The results from CheckMate-649 indicate that nivolumab in combination with chemotherapy can be considered as first-line treatment for patients with EC or EGJ adenocarcinoma. According to the results of CheckMate-577, nivolumab combined with chemotherapy can be used as a postoperative adjuvant treatment. There is a synergistic effect of immunotherapy and radiotherapy; however, the effect of this strategy in EC needs to be further evaluated.

6.4.4 Radiosensitizers

Radiosensitizers for EC used for clinical application include nitroimidazole compounds (sodium glycididazole for injection), chemotherapy drugs (platinum, fluorouracil, and paclitaxel/paclitaxel liposome), targeted drugs (nimotuzumab), and endostatins. Sodium glycididazole for injection can improve the efficacy of radiotherapy/concurrent chemoradiotherapy, therefore it is a radiosensitizer with high efficiency and low toxicity. Drugs still in clinical trials include hypoxia-specific toxins (AQ4N) and histone deacetylase inhibitors (chidamide).

6.4.5 Nutritional support and palliative treatment

(1) Nutritional treatment
Standardized nutritional treatment can reduce weight loss and improve nutritional status and tolerance to treatment in patients with EC receiving radiotherapy. It is recommended that all patients scheduled for radiotherapy should undergo nutritional risk screening (NRS2002 scale), nutritional status assessment (PG-SGA scale), and comprehensive examination after admission. It has been suggested that patients with or at risk of malnutrition should receive standardized nutritional treatment. Oral nutrition supplements (ONS) are the first choice for enteral nutrition; if ONS alone cannot meet the nutritional needs, tube feeding (TF) should be employed. The nasogastric or nasojugal tube is the first choice for TF, but for patients who need long-term TF (>4 weeks), percutaneous endoscopic gastrostomy or jejunostomy is more suitable. Combined or complete parenteral nutrition should be used if enteral nutrition cannot be implemented or provide sufficient nutrition and energy.

(2) Palliative treatment
Palliative treatments for EC mainly include analgesia, hemostasis, alleviation/relief of obstruction, psychotherapy, guidance, and education for terminal patients and their families.

6.4.6 Traditional Chinese medicine

Chemoradiotherapy is an important treatment for EC, and traditional Chinese medicine (TCM) can cure the damaged normal tissue after chemoradiotherapy. Based on TCM syndrome differentiation, anemia
and the decreases of white blood cell and platelet are caused by the deficiency of the spleen and kidney, and the main treatment is to invigorate the spleen and kidney, and nourish qi and the blood. While radiation-induced pneumonia and esophagitis are caused by heat-exposing yin, the treatment focuses on nourishment of yin, dissipation of heat, and detoxification. The clinical application of TCM is evident. Other symptoms such as dysphagia, hiccups, and vomiting can also be treated according to TCM syndrome differentiation to strengthen immunity, relieve symptoms, and improve the quality of life (evidence quality level: 2B).

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**Expert group of Chinese Guidelines for Radiotherapy of Esophageal Carcinoma (2020 Edition)**

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**REFERENCES**

1. NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers, Version 3. 2020[EB/OL]. [2020-07-31]. https://www.nccn.org/.
2. He Y, Li D, Shan B, et al. Incidence and mortality of esophagus cancer in China, 2008–2012. Chin J Cancer Res. 2019;31(3):426–434.
3. Esophageal cancer committee of China Anti Cancer Association. Guidelines for standardized diagnosis and treatment of esophageal cancer [M]. Beijing: Peking Union Medical University Press, 2011.
4. Gibault L, Metges JP, Conan-Charlet V, et al. Diffuse EGFR staining is associated with reduced overall survival in locally advanced oesophageal squamous cell cancer. Br J Cancer. 2005;93(1):107–115.
5. Tsutsui S, Saeki H, Nakashima Y, et al. Programmed death-ligand 1 expression at tumor invasive front is associated with epithelial-mesenchymal transition and poor prognosis in esophageal squamous cell carcinoma. Cancer Sci. 2017;108(6):1119–1127.
6. Bunting D, Bracey T, Fox B, Berrisford R, Wheatley S, Sanders G. Loco-regional staging accuracy in oesophageal cancer: How good are we in the modern era? Eur J Radiol. 2017;97:71–75.
7. el-Khoury GY, Dalinka MK, Alazraki N, et al. Metastatic bone disease. American College of Radiology. ACR Appropriateness Criteria. Radiology. 2000;215:283–293.
8. Minashi K, Nihei K, Mizusawa J, et al. Efficacy of endoscopic resection and selective chemoradiotherapy for stage I esophageal squamous cell carcinoma. Gastroenterology. 2019;157(2):382–390.e3.
9. Kato H, Sato A, Fukuda H, et al. A phase II trial of chemoradiotherapy for stage I esophageal squamous cell carcinoma: Japan Clinical Oncology Group Study (JCG9708). Jpn J Clin Oncol. 2009;39(10):638–643.
10. Juloori A, Tucker SL, Komaki R, et al. Influence of preoperative radiation field on postoperative leak rates in esophageal cancer patients after trimodality therapy. J Thorac Oncol. 2014;9(4):534–540.
11. Huang W, Huang Y, Sun J, et al. Atlas of the thoracic lymph nodal delineation and recommendations for lymph nodal CTV of esophageal squamous cell cancer in radiation therapy from China. Radiother Oncol. 2015;116(1):100–106.
12. Huang W, Li B, Gong H, et al. Pattern of lymph node metastases and its implication in radiotherapeutic clinical target volume in patients with thoracic esophageal squamous cell carcinoma: A report of 1077 cases. Radiother Oncol. 2010;95(2):229–233.
13. Cheng J, Kong L, Huang W, et al. Explore the radiotherapeutic clinical target volume delineation for thoracic esophageal squamous cell carcinoma from the pattern of lymphatic metastases. J Thorac Oncol. 2013;8(3):359–365.
14. Ding X, Zhang J, Li B, et al. A meta-analysis of lymph node metastasis rate for patients with thoracic esophageal cancer and its implication in delineation of clinical target volume for radiation therapy. Br J Radiol. 2012;85(1019):e1110–e1119.
15. Dong Y, Guan H, Huang W, et al. Precise delineation of clinical target volume for crossing-segments thoracic esophageal squamous cell carcinoma based on the pattern of lymph node metastases. J Thorac Dis. 2015;7(12):2313–2320.
16. Shapiro J, van Lanschot JJB, Hulshof MCCM, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090–1098.
17. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074–2084.
18. Wang YX, Yang Q, He M, et al. Recurrence regularity of stage III thoracic esophageal squamous cell carcinoma after radical operation. Chinese Journal of Radiation Oncology. 2017;39(1):48–55.
19. Chapet O, Kong FM, Quint LE, Chang AC, Ten Haken RK, Eisebruch A, Hayman JA. CT-based definition of thoracic lymph node stations: an atlas from the University of Michigan. Int J Radiat Oncol Biol Phys. 2005;63(1):170–178.

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20. Liu Q, Cai XW, Wu B, Zhu ZF, Chen HQ, Fu XL. Patterns of failure after radical surgery among patients with thoracic esophageal squamous cell carcinoma: implications for the clinical target volume design of postoperative radiotherapy. PLoS One. 2014;9(5):e97225.

21. Wong AT, Shao M, Rineer J, Lee A, Schwartz D, Schreiber D. The impact of adjuvant postoperative radiation therapy and chemotherapy on survival after esophagectomy for esophageal carcinoma. Ann Surg. 2017;265(6):1146–1151.

22. Xiao ZF, Yang ZY, Liang J, et al. Value of radiotherapy after radical surgery for esophageal carcinoma: a report of 495 patients. Ann Thorac Surg. 2003;75(2):331–336.

23. Worni M, Martin J, Gloor B, et al. Does surgery improve outcomes for esophageal squamous cell carcinoma? An analysis using the surveillance epidemiology and end results registry from 1998 to 2008. J Am Coll Surg. 2012;215(5):643–651.

24. Chen J, Zhu J, Pan J, et al. Postoperative radiotherapy improved survival of poor prognostic squamous cell carcinoma esophagus. Ann Thorac Surg. 2010;90(2):435–442.

25. Schreiber D, Rineer J, Vontgama D, et al. Impact of postoperative radiation after esophagectomy for esophageal cancer. J Thorac Oncol. 2010;5(2):244–250.

26. Shridhar R, Weber J, Hoffe SE, Almhanna K, Karl R, Meredith K. Adjuvant radiation therapy and lymphadenectomy in esophageal cancer: a SEER database analysis. J Gastrointest Surg. 2013;17(8):1339–1345.

27. Xu Y, Li J, Xu D, et al. Prognostic impact of postoperative radiation in patients undergoing radical esophagectomy for pathologic lymph node positive esophageal cancer. Radiat Oncol. 2013;8:116.

28. Zhang W, Liu X, Xiao Z, et al. Radical postoperative intensity-modulated radiotherapy improved survival in lymph node-positive or stage III thoracic esophageal squamous cell carcinoma. Oncol Res Treat. 2015;38(3):97–102.

29. Chen SB, Weng HR, Wang G, et al. The impact of adjuvant radiotherapy on radically resected T3 esophageal squamous cell carcinoma. J Cancer Res Clin Oncol. 2016;142(1):277–286.

30. Liu X, Zhang WC, Yu SF, et al. Analysis of failure mode after R0 surgery for T2-3N0M0 esophageal cancer: potential value and significance of postoperative radiotherapy. Chin J Radiat Oncol. 2015;24(1):19–24.

31. Yang J, Zhang W, Xiao Z, et al. The impact of postoperative conformal radiotherapy after radical surgery on survival and recurrence in pathologic T1N0M0 esophageal carcinoma: a propensity score-matched analysis. J Thorac Oncol. 2017;12(7):1143–1151.

32. Kirkpatrick JP, van der Kogel AJ, Schultheiss TE. Radiation dose-volume effects in the spinal cord. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S42–S49.

33. Marks LB, Yorke ED, Jackson A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S50–S19.

34. Mizumoto M, Sugahara S, Nakayama H, et al. Clinical results of proton-beam therapy for locoregionally advanced esophageal cancer. Strahlenther Onkol. 2010;186(9):482–488.

35. Xi M, Xu C, Liao Z, et al. Comparative outcomes after definitive chemoradiotherapy using proton beam therapy versus intensity modulated radiation therapy for esophageal cancer: A retrospective, single-institutional analysis. Int J Radiat Oncol Biol Phys. 2017;99(3):667–676.

36. Fernandes A, Berman AT, Mick R, et al. A prospective study of proton beam reirradiation for esophageal cancer. Int J Radiat Oncol Biol Phys. 2016;95(1):483–487.

37. Routman DM, Garant A, Lester SC, et al. A comparison of grade 4 lymphopenia with proton versus photon radiation therapy for esophageal cancer. Adv Radiat Oncol. 2019;4(1):63–69.

38. Akutsu Y, Yasuda S, Nagata M, et al. A phase I/II clinical trial of preoperative short-course carbon-ion radiotherapy for patients with squamous cell carcinoma of the esophagus. J Surg Oncol. 2012;105(8):750–755.

39. Zhu L, Jiang Y, Wang J, et al. An investigation of 125I seed permanent implantation for recurrent carcinoma in the head and neck after surgery and external beam radiotherapy. World J Surg Oncol. 2013;11:60.

40. Zhu HD, Guo JH, Mao AW, et al. Conventional stents versus stents loaded with (125)iodine seeds for the treatment of unresectable esophageal cancer: a multicentre, randomised phase 3 trial. Lancet Oncol. 2014;15(6):612–619.

41. Cooper JS, Guo MD, Hershkovic 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. JAMA. 1999;281(17):1623–1627.

42. Noordman BJ, Spaander MCV, Valkema R, et al. Detection of residual disease after neoadjuvant chemoradiotherapy for esophageal cancer (preSANO): a prospective multicentre, diagnostic cohort study. Lancet Oncol. 2018;19(7):965–974.

43. Noordman BJ, Wijhoven BPL, Lagarde SM, et al. Neoadjuvant chemoradiotherapy plus surgery versus active surveillance for esophageal cancer: a stepped-wedge cluster randomised trial. BMC Cancer. 2018;18(1):142.

44. Wainberg ZA, Lin LS, DiCarlo B, et al. Phase II trial of modified FOLFOX6 and erlotinib in patients with metastatic or advanced adenocarcinoma of the oesophagus and gastro-oesophageal junction. Br J Cancer. 2011;105(6):760–765.

45. Doi T, Piha-Paul SA, Jalal S, et al. Safety and antitumor activity of the anti-programmed death-1 antibody pembrolizumab in patients with advanced esophageal carcinoma. J Clin Oncol. 2018;36(1):61–67.

46. Kudo T, Hamamoto Y, Kato K, et al. Nivolumab treatment for esophageal squamous-cell carcinoma: an open-label, multicentre, phase 2 trial. Lancet Oncol. 2017;18(5):631–639.

47. Huang J, Xu B, Mo H, et al. Safety, activity, and biomarkers of SHR-1210, an anti-CD-1 antibody, for patients with advanced esophageal carcinoma. Clin Cancer Res. 2018;24(6):1296–1304.

48. Janjigian YY, Bendell J, Calvo E, et al. CheckMate-032 study: Efficacy and safety of nivolumab and ipilimumab in patients with metastatic esophagogastric cancer. J Clin Oncol. 2018;36(28):2836–2844.

49. Alisina M, Moehler M, Lorenzen S. Immunotherapy of esophageal cancer: Current status, many trials and innovative strategies. Oncol Res Treat. 2018;41(5):266–271.

50. Meindl-Beinker NM, Betge J, Gutting T, et al. A multicenter open-label phase II trial to evaluate nivolumab and ipilimumab for 2nd line therapy in elderly patients with advanced esophageal squamous cell cancer (RAMONA). BMC Cancer. 2019;19(1):231.

51. Ralph C, Elkord E, Burt DJ, et al. Modulation of lymphocyte regulation for cancer therapy: a phase II trial of tretemeliumab in advanced gastric and esophageal adenocarcinoma. Clin Cancer Res. 2010;16(5):1662–1672.

52. FDA Approves New Monotherapy Indication for Merck’s KEYTRUDA® (pembrolizumab)[EB/OL]. [2019-07-31]. https://www.mrknewsroom.com/news-release/prescription-medicine-news/fda-approves-new-monotherapy-indication-mercks-keytruda-pemb.

53. Wang H, Mu X, He H, et al. Cancer radiosensitizers. Trends Pharmacol Sci. 2018;39(1):24–48.

54. Kang M, Quan XF. Clinical study of radiosensitizers for esophageal cancer. Int J Oncol. 2015;42(12):932–935.

55. Deng JY, Wang CY, Zhao XL. Research progress of paclitaxel (PTX) in concurrent chemoradiotherapy of esophageal cancer. Fudan Journal (Medical Edition). 2014;41(5):697–700.

56. Ruhstaller T, Pless M, Dietrich D, et al. Cetuximab in combination with chemoradiotherapy before surgery in patients with resectable, locally advanced esophageal carcinoma: a prospective, multicenter phase IB/II Trial (SAKK 75/06). J Clin Oncol. 2011;29(6):626–631.

57. Li W, Chen P, Zhang N, Song T, Wu S. Endostatin and oxaliplatin-based chemoradiotherapy for inoperable esophageal squamous cell
carcinoma: Results of a phase II study. Oncologist. 2019;24(4):461–e136.
58. 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. Lancet Oncol. 2014;15(11):1224–1235.
59. Qin SB, Wang YD, Yang JQ, et al. Radiosensitization effect of sodium glycididazole on thoracic esophageal squamous cell carcinoma: a phase III multicenter randomized controlled study. Chin J Radiat Oncol. 2012;21(5):426–429.
60. Steward WP, Middleton M, Benghiat A, et al. The use of pharmacokinetic and pharmacodynamic end points to determine the dose of AQ4N, a novel hypoxic cell cytotoxin, given with fractionated radiotherapy in a phase I study. Ann Oncol. 2007;18(6):1098–1103.
61. Gong LJ, Xie JN, Zhu S, et al. Application of multifunctional nano materials in tumor radiosensitization. Acta Physicochemical, 2018; 34 (2): 140–167.
62. Lu JH, Li T. Nutritional therapy for patients with esophageal cancer after radiotherapy. J Tumor Metab Nutr. 2017; 4 (2): 144–148.
63. Lyu J, Li T, Xie C, et al. China Society for Nutritional Oncology. Enteral nutrition in esophageal cancer patients treated with radiotherapy: a Chinese expert consensus 2018. Future Oncol. 2019;15(5):517–531.
64. Xu YJ, Cheng JC, Lee JM, Huang PM, Huang GH, Chen CC. A walk-and-eat intervention improves outcomes for patients with esophageal cancer undergoing neoadjuvant chemoradiotherapy. Oncologist. 2015;20(10):1216–1222.
65. Lu JH, Li T, Zhu GY, et al. Effects of enteral nutrition on nutritional status, adverse reactions and short-term efficacy in patients with esophageal cancer undergoing concurrent chemoradiotherapy: a prospective, multicenter, randomized controlled clinical study (nct02399306). Chin J Radiat Oncol. 2018;27 (1): 44–48.
66. 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. Cancer. 2013;119(18):3343–3353.
67. Checkmate-649, a phase 3 trial evaluating opdivo (nivolumab) plus chemotherapy vs. chemotherapy, meets primary endpoints demonstrating superior overall survival and progression-free survival in first-line treatment of gastric and esophageal cancers [EB/OL]. [2020-08-11]. https://news.bms.com/press-release/corporatefinancial-news/checkmate-649-phase-3-trial-evaluating-opdivo-nivolumab-plus-c.
68. Merck’s KEYTRUDA® (pembrolizumab) in combination with chemotherapy significantly improved overall survival and progression-free survival compared with chemotherapy in locally advanced or first-line metastatic esophageal cancer [EB/OL]. [2020-08-19]. https://www.merck.com/news/mercks-keytruda-pembrolizumab-in-combination-with-chemotherapy-significantly-improved-overall-survival-and-progression-free-survival-compared-with-chemotherapy-in-locally-advanced-or/.
69. Opdivo (nivolumab) demonstrated superior disease-free survival in patients with resected esophageal or gastroesophageal junction cancer compared to placebo in the adjuvant setting [EB/OL]. [2020-9-21]. https://news.bms.com/news/details/2020/Opdivo-nivolumab-Demonstrated-Superior-Disease-Free-Survival-in-Patients-with-Resected-Esophageal-or-Gastroesophageal-Junction-Cancer-Compared-to-Placebo-in-the-Adjuvant-Setting/default.aspx.

APPENDIX 1

WORLD HEALTH ORGANIZATION CRITERIA FOR ESOPHAGEAL CANCER (2010 EDITION)

| T category                                                                 |
|---------------------------------------------------------------------------|
| T0: Tumor cannot be assessed                                               |
| T1: Tumor invades the lamina propria, muscularis mucosae, or submucosa     |
| T1a: Tumor invades the lamina propria or muscularis mucosae               |
| T1b: Tumor invades the submucosa                                           |
| T2: Tumor invades the muscularis propria                                  |
| T3: Tumor invades the adventitia                                           |
| T4: Tumor invades the adjacent structures                                 |
| T4a: Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum |
| T4b: Tumor invades other adjacent structures, such as the aorta, vertebral body, or trachea |

| N category                                                                 |
|---------------------------------------------------------------------------|
| Nx: Regional lymph nodes cannot be assessed                                |
| N0: No regional lymph node metastasis                                      |
| N1: Metastasis in 1–2 regional lymph nodes                                 |
| N2: Metastasis in 3–6 regional lymph nodes                                 |
| N3: Metastasis in ≥7 regional lymph nodes                                  |

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Note:
1. At least 15 lymph nodes need to be removed. The number of metastatic lymph nodes must be recorded together with the total number of lymph nodes removed.
2. Metastases to the mediastinum 3, 5, 6, supraclavicular areas of the bilateral common carotid artery and retroperitoneal lymph node metastasis are M1.

### 3. M category

**M0:** No distant metastasis

**M1:** Distant metastasis

### 4. Adenocarcinoma G category

Gx: Differentiation cannot be assessed

**G1:** Well differentiated, with >95% of the tumor composed of well-formed glands

**G2:** Moderately differentiated, with 50–95% of the tumor showing glandular formation

**G3:** Poorly differentiated, with tumors composed of nests and sheets of cells and <50% of the tumor showing glandular formation

*If further testing of “undifferentiated” cancers reveals a glandular component, categorize as adenocarcinoma G3.

### 5. Squamous cell carcinoma G category

Gx: Differentiation cannot be assessed

**G1:** Well differentiated, with prominent keratinization with pearl formation and a minor component of non-keratinizing basal-like cells, tumor cells arranged in sheets, and low mitotic counts

**G2:** Moderately differentiated, with variable histologic features ranging from parakeratotic to poorly keratinizing lesions and pearl formation generally absent

**G3:** Poorly differentiated, consisting predominantly of basal-like cells forming large and small nests with frequent central necrosis and with nests consisting of sheets or pavement-like arrangements of tumor cells that are occasionally punctuated by small numbers of parakeratotic or keratinizing cells

*Basal cell-like squamous cell carcinoma, spindle cell squamous cell carcinoma, small cell carcinoma, large cell neuroendocrine carcinoma, and undifferentiated carcinoma are staged according to poorly differentiated squamous cell carcinoma. Mixed cancers with mixed squamous cell components (such as adenosquamous cell carcinoma) and unknown histological types are staged according to squamous cell carcinoma.

### 6. Squamous cell carcinoma L category

Lx: Location unknown

**Upper:** Cervical esophagus to the lower border of the azygos vein

**Middle:** Lower border of the azygos vein to the lower border of the inferior pulmonary vein

**Lower:** Lower border of the inferior pulmonary vein to the stomach, including the esophagogastric junction

Note: This staging is not applicable to non-epithelial tumors such as lymphoma, sarcoma, gastrointestinal stromal tumor, and melanoma. Neuroendocrine tumors (NETs) of the esophagus are extremely rare.

### TABLE B.1 Post-neoadjuvant pathologic stage groups (ypTNM): adenocarcinoma and squamous cell carcinoma

| ypT | ypN | ypM |
|-----|-----|-----|
| T0  | N0  | M0  |
| T0s | N0  | M0  |
| T1  | N0  | M0  |
| T2  | N0  | M0  |
| T3  | N0  | M0  |
| T4a  | N0  | M0  |
| T4b  | N0  | M0  |

### TABLE B.2 Pathologic stage groups (pTNM): squamous cell carcinoma

| pT  | pN  | pM  |
|-----|-----|-----|
| Tis | N0  | M0  |
| T1a | N1  | M1  |
| T1b | N1  | M1  |
| T2  | N1  | M1  |
| T3  | N1  | M1  |
| T4a  | N1  | M1  |
| T4b  | N1  | M1  |

### TABLE B.3 Pathologic stage groups (pTNM): adenocarcinoma

| pT  | pN  | pM  |
|-----|-----|-----|
| Tis | N0  | M0  |
| T1a | N1  | M1  |
| T1b | N1  | M1  |
| T2  | N1  | M1  |
| T3  | N1  | M1  |
| T4a  | N1  | M1  |
| T4b  | N1  | M1  |
TABLE B.4  Clinical stage groups (cTNM): squamous cell carcinoma

|     | N₀ | N₁ | N₂ | N₃ | M₁ |
|-----|----|----|----|----|----|
| Tis | 0  |    |    |    |    |
| T₁  | I  | I  | III| IV A| IV B|
| T₂  | II | II | III| IV A| IV B|
| T₃  | II | III| III| IV A| IV B|
| T₄a | IV A| IV A| IV A| IV A| IV B|
| T₄b | IV A| IV A| IV A| IV A| IV B|

TABLE B.5  Clinical stage groups (cTNM): adenocarcinoma

|     | N₀ | N₁ | N₂ | N₃ | M₁ |
|-----|----|----|----|----|----|
| Tis | 0  |    |    |    |    |
| T₁  | I  | II A| IV A| IV A| IV B|
| T₂  | II B| III| IV A| IV A| IV B|
| T₃  | III| III| IV A| IV A| IV B|
| T₄a | IV A| IV A| IV A| IV A| IV B|
| T₄b | IV A| IV A| IV A| IV A| IV B|

APPENDIX 3
RADIATION THERAPY ONCOLOGY GROUP CLASSIFICATION FOR ACUTE RADIATION-INDUCED INJURIES TO THE LUNG, ESOPHAGUS, HEART, AND SPINAL CORD INJURIES (QUANTEC 2012)

1. Acute radiation-induced lung injury
   - Level 0: No change
   - Level 1: Mild dry cough or difficulty in breathing when fatigued
   - Level 2: Persistent cough requiring narcotic cough suppressant or dyspnea on slight movement but not at rest

   Level 3: Severe cough, no response to narcotic cough suppressants, dyspnea at rest, clinical or imaging evidence of acute radiation pneumonia, intermittent oxygen, or possible need for steroid therapy
   - Level 4: Severe respiratory insufficiency or continuous oxygen or assisted ventilation
   - Level 5: Lethality

2. Acute radiation-induced esophageal injury
   - Level 0: No change
   - Level 1: Mild dysphagia requiring topical anesthesia or analgesics or soft food
   - Level 2: Moderate dysphagia requiring an anesthetic or fluid
   - Level 3: Severe dysphagia, dehydration, or weight loss requiring tube feeding
   - Level 4: Complete obstruction, ulcer, or perforation
   - Level 5: Lethality

3. Acute radiation-induced cardiac injury
   - Level 0: No change
   - Level 1: No symptoms, objective changes in ECG; or pericardial abnormalities, and no other evidence of heart disease
   - Level 2: Symptoms with objective changes in ECG and imaging, congestive heart failure, or pericardial disease; does not require special treatment
   - Level 3: Congestive heart failure, angina pectoris, and pericardial disease responding to treatment
   - Level 4: Congestive heart failure, angina pectoris, pericardial disease, and arrhythmia; non-surgical treatment ineffective
   - Level 5: Lethality

4. Acute radiation-induced spinal cord injury
   - Level 0: No change
   - Level 1: Mild L’Hermitte’s syndrome
   - Level 2: Severe L’Hermitte’s syndrome
APPENDIX 4
EVALUATION CRITERIA FOR THE EFFICACY OF RADIOTHERAPY AND CHEMOTHERAPY

1. World Health Organization criteria (1981) change in sum of products
   - Complete response (CR): Disappearance; confirmed at 4 weeks
   - Partial response (PR): 50% decrease; confirmed at 4 weeks
   - Stable disease (SD): Met neither the PR nor PD criteria
   - Progressive disease (PD): 25% increase; no CR, PR, or SD documented before an increase in the severity of the disease

2. RECIST criteria (2000) change in the sum of the longest diameters
   - CR: Disappearance
   - PR: 30% decrease
   - PD: 20% increase; no CR, PR, or SD documented before an increase in the severity of the disease
   - SD: Met neither the PR nor PD criteria

APPENDIX 5
PATHOLOGICAL ASSESSMENT OF COLLEGE OF AMERICAN PATHOLOGISTS/NCCN CRITERIA AFTER NEOADJUVANT THERAPY

| Diagnostic criteria                                      | Tumor regression grade |
|---------------------------------------------------------|------------------------|
| No residual viable cancer cells                         | 0 (complete response)  |
| Single or small clusters of residual cancer cells       | 1 (moderate response)  |
| Residual cancer foci with interstitial fibrosis         | 2 (mild response)      |
| Minimal or no tumor cells regression; a large number of residual cancer cells | 3 (minimal response) |

Note. (1) Tumor regression grade can be evaluated only for the primary tumor, not applicable to the evaluation of metastatic lesions.
(2) The efficacy evaluation is based on the survival of tumor cells. The appearance of a keratinous or mucus lake without cancer cells after neoadjuvant treatment cannot be considered as a residual tumor. The appearance of a keratinous or mucous lake without cancer cells in lymph nodes cannot be considered as tumor metastasis.

APPENDIX 6
GENERAL CONDITION SCORE

1. Karnofsky score

| Karnofsky score | Description                                    |
|----------------|-----------------------------------------------|
| 100            | Normal, no signs or symptoms; no evidence of disease |
| 90             | Able to carry on normal activity; minor symptoms and signs of disease |
| 80             | Normal activity with effort; some symptoms or signs of disease |
| 70             | Cares for self; unable to carry on normal activity or to do active work |
| 60             | Able to care for most of his personal needs, requires occasional assistance, unable to do active work |
| 50             | Requires considerable assistance and medical care |
| 40             | Unable to care for self; requires special care and assistance |
| 30             | Severely disabled; hospital admission is indicated although not very sick |
| 20             | Very sick; completely lost self-care ability, needs hospitalization and active supportive treatment |
| 10             | Moribund; fatal processes progressing rapidly |
| 0              | Dead                                          |
### 2. ECOG score

| Score | Description |
|-------|-------------|
| 0     | Normal activity |
| 1     | Minor symptoms of disease, able to care for self and carry out light work |
| 2     | Able to tolerate tumor symptoms and care for self, but spend less than 50% of the time in bed during the day |
| 3     | Severe symptoms of disease, spend more than 50% of the time in bed during the day, capable of getting up and limited self-care |
| 4     | Completely disabled; totally confined to bed |
| 5     | Dead |

### APPENDIX 7

#### TERMS AND DEFINITIONS

1. **Esophageal cancer**

   Esophageal cancer refers to the cancer of the esophageal epithelium from the hypopharynx to the esophagus–gastric junction.

1.1. **Squamous cell carcinoma of the esophagus**

   Squamous cell carcinoma of the esophagus refers to a malignant epithelial tumor differentiated from esophageal squamous cells.

1.2. **Adenocarcinoma of esophagus**

   Adenocarcinoma of the esophagus refers to the glandular tubular differentiated malignant epithelial tumor originating from Barrett’s esophageal mucosa in the inferior third of the esophagus and, occasionally, originates from the ectopic gastric mucosa of the upper esophagus or submucosal glands.

2. **Early-stage esophageal cancer**

   Early-stage esophageal cancer refers to the tumor confined to the mucosal layer and submucosa of the esophagus, without lymph node metastasis, including carcinoma in situ/severe dysplasia, intramucosal and submucosal carcinomas.

3. **Barrett esophagus**

   Barrett esophagus refers to the stratified squamous epithelium of the inferior esophagus being replaced by the simple columnar epithelium.

4. **Precancerous diseases and precancerous lesions of the esophagus**

   Precancerous diseases include chronic esophagitis, Barrett’s esophagitis, esophageal leukoplakia, esophageal diverticulum, esophageal achalasia, reflux esophagitis, and benign stenosis of the esophagus.

   Precancerous lesions refer to squamous epithelial dysplasia, including mild, moderate, and severe dysplasia, also called intraepithelial neoplasia, which is divided into low- and high-grade intraepithelial neoplasia. Among them, severe dysplasia and high-grade intraepithelial neoplasia are associated with Tis.