Treatment guideline of radiotherapy for Chinese esophageal carcinoma (draft)

Esophageal Carcinoma Cooperative Group of Radiation Oncology Society of Chinese Medical Association

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[Abstract] Esophageal carcinoma is one of the most common human cancers in China. Radiotherapy plays an important role in combination therapy of esophageal carcinoma. With regret, there is still no unified standard for the treatment of esophageal carcinoma in China, and there are many controversies in the treatment regimens, indications, methods and efficacy. Clinically, the clinical practice guidelines of the National Comprehensive Cancer Network (NCCN) of the United States were often consulted, but the data of them were mainly from the patients from Europe and America, and they might not be applicable for Chinese patients. In order to standardize clinical process of radiotherapy for esophageal carcinoma in China, the Esophageal Carcinoma Cooperative Group of Radiation Oncology Society of Chinese Medical Association wrote a consensus and controversies on the radiotherapy for esophageal carcinoma (draft) after years of research and discussion, We hope it be tried out and discussed with advice and valuable suggestions, in order to accelerate the process of standardization of esophageal carcinoma treatment in China.

Key words: Esophageal neoplasm, radiotherapy, guideline

Esophageal carcinoma is one of the most common human cancers. Its incidence is significantly endemic. The incidence of esophageal carcinoma in China is highest of the world, and is 20 times more than West Africa, which is a low-risk area[1]. It is estimated that about 53.8% of the esophageal carcinomas all over the world appear in China[2]. The mortality of esophageal carcinoma in China is the highest of the world, which is 31.66/100,000 for male and 15.93/100,000 for female, and the mortality in the areas with high incidence is 700 times more than that in the areas with low incidence[3]. What is more, the incidence and mortality of esophageal carcinoma ranks forth in the malignant tumor of China[4].

Domestic and abroad data have shown that[5-6] the 5-year survival rate of esophageal carcinoma patients treated with concurrent chemoradiotherapy is close to that of patients treated with surgery. As a result, radiotherapy has become one of the important treatments for esophageal carcinoma. The main reasons of failure for patients with esophageal carcinoma who have received surgery are still local and regional recurrences. Therefore, to improve the postoperative local and regional control rates of esophageal carcinoma, postoperative radiotherapy has also become one of the adjuvant treatments after surgery. However, some problems still exist in regarding the radiotherapy for esophageal carcinoma. For example, the significant difference among target delineation boundaries in radiotherapy for esophageal carcinoma and the various concurrent chemoradiotherapy regimens cause certain confusion in practical work. As a result, the accurate delineation of treatment target volume and proper treatment plan have become the primary problems in radiotherapy. We have primarily discussed the standard of radiotherapy for esophageal carcinoma through comprehensive analysis on results from domestic and abroad research.

Clinical Manifestations and Diagnosis (Omitted)

Staging

At the present time, the universally applied staging
domestically and abroad for esophageal carcinoma is TNM staging criteria based on surgery and postoperative pathology [9], but it is not applicable to patients with esophageal carcinoma who receive nonoperative treatment. In the forth National Symposium on Radiotherapy for Esophageal Carcinoma held in 2005, the clinical staging criteria for esophageal carcinoma receiving nonoperative treatment was worked out according to the length of tumor, invasion extent and metastatic condition. The criteria was modified in the fifth National Symposium on Radiotherapy for Esophageal Carcinoma held in 2009 [10], and could be tried out by oncologists.

Radiotherapy

At the present time, radiotherapy is one of the main, effective and relatively safe treatment modalities for esophageal carcinoma. It has wide indications, and could be used for early-stage and advanced diseases and as locally palliative treatment for metastatic disease. Previously, the primary treatment for esophageal carcinoma was surgical excision. Currently, as the development of radiotherapy technique and comprehensive application of treatment modalities such as chemotherapy, more and more evidence showed that for operable esophageal carcinoma, concurrent chemoradiotherapy and late course accelerated hyperfractionation radiotherapy could achieve similar treatment effect to surgery. The newest edition of the Clinical Practice Guidelines of Esophageal Cancer of the United States clearly defines that for patients with early stage disease which stands for carcinoma in situ or tumor invading lamina propria (Tis/T1a), endoscopic mucosal resection or esophagectomy should be selected; surgery is only preferred for noncervical (T1b) disease which stands for tumor invading submucosa; while definitive concurrent chemoradiotherapy or preoperative chemoradiation should be the primary treatment for patients with other stage diseases such as tumors invading muscularis propria, fibrous membrane, pleura, pericardium, diaphragmatic muscle or adjacent structures. The first two types of patients are difficult to be diagnosed at early stage because they are asymptomatic or the symptoms are slight, and could only be detected in general survey by esophagoscope. As a result, these two types of patients account for only a very small proportion of the visiting patients. That is to say, most of the patients are in the latter condition, and chemotherapy should be the primary treatment for them. There is still no unified standard for the treatment of esophageal carcinoma in China, and there are many disparities in the treatment principles, target definitions and concurrent chemoradiotherapy regimen. Therefore, the Esophageal Carcinoma Cooperative Group of Radiation Oncology Society of Chinese Medical Association worked out the following radiotherapy principles for esophageal carcinoma, target definitions and concurrent chemoradiotherapy regimen after years of research and discussion, which are the references for clinical oncologists and await supplementation and perfection.

Radiotherapy principles

American and Japanese clinical practice guidelines of esophageal cancer have identified concurrent chemoradiotherapy as one of the standard treatment modalities for operable esophageal carcinoma [11,12]. Many domestic research supported this conclusion, but without evidence from multicenter strictly randomized research. There are plenty of foreign researches on preoperative neoadjuvant concurrent chemoradiotherapy. Although there is still no high grade evidence directly proving that it is superior to surgery alone, a trend has shown that preoperative concurrent chemoradiotherapy plus surgery could improve local control rate and survival [13,14], which was validated by a recent Meta analysis [15]. There is little domestic research of this kind, and Sun Yat-sen University Cancer Center has reported their results of phase II clinical trial, confirming the feasibility of neoadjuvant chemoradiotherapy plus surgery [16,17]. In addition, the only two randomized studies reported that neoadjuvant chemoradiotherapy improved survival [18,19]. Generally speaking, results of the existing research failed to show that radiotherapy after radical surgery could improve the overall survival of patients with esophageal carcinoma [20,21], but it might be beneficial for patients with stage III disease or positive lymph nodes [22,23]. As the development of tumor-targeted therapy, research on radiotherapy combined with target agents is worth expecting. Based on the results of studies mentioned above, we recommend the following treatment principles for esophageal carcinoma.

(1) Patients who are suitable for esophagectomy (stage T1–4a, N0–1, Nx, or IVA) could choose surgery or concurrent chemoradiotherapy, and studies on late course accelerated hyperfractionated radiotherapy are encouraged.

(2) Randomized controlled trials on preoperative concurrent chemoradiotherapy plus surgery should be carried out in qualified cancer centers to prove its effect on survival.

(3) Concurrent chemoradiotherapy or radiotherapy alone could be considered for patients who are unsuitable for esophagectomy (stage T4b, IVA or medically unsuitable for surgery) according to the concrete conditions (patients’ performance status score and tolerance condition, etc.). Palliative chemotherapy or supportive care could be given to patients who are intolerant to radiotherapy.

(4) Studies on radiotherapy combined with targeted
therapy are encouraged in qualified centers.

(5) Preoperative radiotherapy: surgery may not be needed in cases that response to preoperative chemoradiotherapy and surgery is more meaningful to those who do not response. Research of this kind is encouraged to carry out in qualified institutes.

(6) Postoperative radiotherapy: postoperative radiotherapy should be delivered to patients with residual lesions. For other cases, postoperative radiotherapy could be delivered in each treatment institute according to respective situations. Multicenter clinical trials are encouraged to carry out to confirm the meaning of postoperative radiotherapy.

**Target volume of radiotherapy**

(1) GTV (gross tumor volume) is tumor extension visible in imaging, including primary tumor and enlarged lymph nodes. The commonly used imaging examine methods at present include endoscope, esophagogram, CT, MRI, PET-CT, and so on. Complementary effect exists between each imaging examination method, and could significantly improve the accuracy and sensitivity when judging the gross tumor volume. As a result, results of various imaging examinations should be consulted when defining GTV.

(2) CTV (clinical target volume) refers to the range of sub-clinical lesions. There is still no internationally unified opinion or high grade evidence based medical evidence on the definition of this range. Gao et al. carried out screening on esophageal carcinoma specimens using serial section technique, and defined the distribution range of sub-clinical radiotherapy: the microscopic infiltration ranges were < 3 cm superior and inferior along the vertical axis of esophagus in 94% of the patients with esophageal carcinoma. Therefore, we recommend extended margin of 3 cm along the vertical axis of GTV and of 0.5 cm surrounding the sections. After extension, adjustment should be made according to anatomic barriers. In principle, anatomic barriers should not be exceeded, unless there is evidence proving that the disease has broken through them.

(3) CTVnd (clinical target volume-node) refers to the lymphatic drainage districts of esophageal carcinoma. There is no high grade evidence identifying the range of lymphatic drainage districts in prophylactic radiation for esophageal carcinoma. At the present time, the range of surgical lymphadenectomy is usually consulted when defining the prophylactic radiation districts. Results of Radiation Therapy Oncology Group (RTOG) study showed that the main reason of the failure in radiotherapy for esophageal carcinoma was local failure. One prospective study carried out in Tumor Hospital of Fudan University delivered radiotherapy alone for esophageal squamous cell carcinoma with three dimensional conformal radiotherapy technique, and only tumor and positive lymph nodes were radiated, without selective lymph nodes districts radiation. Analysis on treatment failure types showed that the out-field recurrence rate of isolated lymph nodes without tumor progression and distant metastasis was only 8%. Therefore, it was concluded that selective prophylactic radiation to lymph nodes districts was unnecessary. Considering that radiotherapy is different to surgery, and prophylactic radiation is no longer delivered in the radiotherapy principles of lung cancer, a British study concluded that it was reasonable to deliver radical chemoradiotherapy without prophylactic lymph nodes radiation. A group of research data from postoperative radiotherapy carried out by Hebei Medical University compared the results of radiotherapy to the prophylactic district identified according to the surgical lymphadenectomy range (extended field) and the enlarged lymph node district alone (involved field). The results showed that there was no statistical significance in one year survival rate between the two groups, while the treatment related toxicities of the former was significantly higher than those of the latter.

As a result, in radiotherapy for esophageal carcinoma, it seems to be more rational to define CTVnd as including only the districts where enlarged lymph nodes locate (involved field) other than the radiation field identified according to surgical lymphadenectomy range (extended field). However, strict clinical trials are still needed for verification.

(4) ITV (internal target volume): the esophagus movement range has not been referred to in foreign treatment standards. Two latest papers reported that the movement range of esophagus in all directions was 0.5 cm in upper part, 0.6–0.7 cm in middle part, and 0.8–0.9 cm in lower part, lacking of longitudinal movement range.

(5) PTV (planning target volume): extended margin of 0.5–1.0 cm to CTV (selected according to the measured results in each institutes).

**Radiotherapy regimen**

(1) Concurrent chemoradiotherapy: results of many randomized research have shown that concurrent chemoradiotherapy was more beneficial to radiotherapy alone in esophageal carcinoma. As a result, concurrent chemoradiotherapy has become standard treatment for patients with inoperable esophageal carcinoma. However, there are still no consensuses on the dosage of radiotherapy or chemotherapy in treatment regimen.

The recommended concurrent chemoradiotherapy regimen in the Clinical Practice Guidelines of Esophageal Cancer of the United States is: radiotherapy of 50.4 Gy in 28 fractions within 5.5 weeks, DDP 75 mg/m² d1, 5-FU 1000 mg/m² d1–d4, 28 days a cycle for 4 cycles. The
recommended concurrent chemoradiotherapy regimen in the Clinical Practice Guidelines of Esophageal Cancer of Japan[10] is: radiotherapy of 60 Gy in 30 fractions within 42 days, DDP 70 mg/m² d1, d29, 5-FU 700 mg/m² d1–d4 and d29–d32. Results of the dose escalating research on PF regimen in concurrent chemoradiotherapy by Lin et al.[13] showed that when radiotherapy of 60 Gy in 30 fractions within 42 days was delivered to patients from North China, the maximum tolerance dose of chemotherapy was DDP 52.5 mg/m² d1, 5-FU 700 mg/m² d1–d5, 28 days a cycle for 4 cycles. The recommended concurrent chemoradiotherapy regimen for esophageal carcinoma in the first Radiation Oncology Accurate Therapy Meeting[16] was: radiotherapy of 60 Gy in 30 fractions within 42 days, DDP 25–30 mg/m² for 3–5 days, 5-FU 450–500 mg/m² for 5 days (continuous intravenous infusion was recommended), 28 days a cycle for 2 cycles, 3–4 cycles of consolidate chemotherapy 1–3 months later.

Currently, the standard chemotherapy regimen in concurrent chemoradiotherapy for esophageal carcinoma is 5-FU/DDP (Category 1 evidence), but the chemoradiotherapy dosage which is suitable for Chinese still awaits multicenter randomized controlled trials.

(2) Late course accelerated hyperfractionated radiotherapy: results of domestic randomized grouping research showed that late course accelerated hyperfractionated radiotherapy could improve the survival rate of esophageal carcinoma. However, the acute treatment related toxicities also increased. For the present, there is still no result of multicenter randomized controlled trials with large sample sizes and the same enrolled criteria in China, and this task still awaits completion.


**Dose constraint for organs at risk**

Dose to bilateral lungs: average dose of ≤ 13 Gy, V20 ≤ 30% of bilateral lungs, V30 ≤ 20% of bilateral lungs. Dose to the spinal cord: average dose of 9–21 Gy, dose to 0 volume ≤ 45 Gy within 6 weeks, ≤ 40 Gy when chemotherapy is concurrently used. Dose to the heart: V25 ≤ 50%, V40 < 30%. There are plenty of research achievements of lung cancer on this field which are renewed rapidly, and relevant up-to-date research results could be consulted simultaneously.

**Follow-up after radiotherapy**

(1) For patients without symptom: the first month after radiotherapy, once every four months in the first year, once every six months in the second year, once every year thereafter to at least five years.

(2) Examine items: blood routine, biochemistry test, upper gastroenterography and/or esophagoscopy, chest X-ray films/chest computed tomography (CT). Pathologic examination and positron emission tomography (PET)/CT scan could be carried out if recurrence or metastasis is clinically suspected.

(3) Patients with symptoms should be followed up according to clinical requirement.

To sum up, as one of the most effective treatment modalities for esophageal carcinoma, radiotherapy plays an irreplaceable role in the treatment of esophageal carcinoma. Lots of controversies exist in fields such as the selection of comprehensive treatment regimens and target delineation, concurrent chemotherapy regimen and dosage, and so on. However, as the emergence of more and more high-grade evidence based clinical evidences, we have got plenty of consensuses on radiotherapy for esophageal carcinoma. We hope that multicenter randomized controlled clinical trials which are well designed and with large sample sizes according to that these consensuses could be carried out actively by professionals to verify and update their consensus continually, and more data could be put forward to solve the existing disputes, in order to accelerate the course of standardization of radiotherapy for esophageal carcinoma in China.

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**Reference**


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